The Effect of Oral Contraceptives on Bone Mass and Stress Fractures in Female Runners

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ABSTRACT

COBB, K. L., L. K. BACHRACH, M. SOWERS, J. NIEVES, G. A. GREENDALE, K. K. KENT, B. W. BROWN, K. PETTIT, D. M. HARPER, and J. L. KELSEY. The Effect of Oral Contraceptives on Bone Mass and Stress Fractures in Female Runners. *Med. Sci. Sports Exerc.*, Vol. 39, No. 9, pp. 1464–1473, 2007. **Purpose:** To determine the effect of oral contraceptives (OC) on bone mass and stress fracture incidence in young female distance runners. **Methods:** One hundred fifty competitive female runners ages 18–26 yr were randomly assigned to OC (30 μg of ethinyl estradiol and 0.3 mg of norgestrel) or control (no intervention) for 2 yr. Bone mineral density (BMD) and content (BMC) were measured yearly by dual x-ray absorptiometry. Stress fractures were confirmed by x-ray, magnetic resonance imaging, or bone scan. **Results:** Randomization to OC was unrelated to changes in BMD or BMC in oligo/amenorrheic (N = 50) or eumenorrheic runners (N = 100). However, treatment-received analyses (which considered actual OC use) showed that oligo/amenorrheic runners who used OC gained about 1% per year in spine BMD ($P < 0.005$) and whole-body BMC ($P < 0.005$), amounts similar to those for runners who regained periods spontaneously and significantly greater than those for runners who remained oligo/amenorrheic ($P < 0.05$). Dietary calcium intake and weight gain independently predicted bone mass gains in oligo/amenorrheic runners. Randomization to OC was not significantly related to stress fracture incidence, but the direction of the effect was protective in both menstrual groups (hazard ratio [95% CI]: 0.57 [0.18, 1.83]), and the effect became stronger in treatment-received analyses. The trial's statistical power was reduced by higher-than-anticipated noncompliance. **Conclusion:** OC may reduce the risk for stress fractures in female runners, but our data are inconclusive. Oligo/amenorrheic athletes with low bone mass should be advised to increase dietary calcium and take steps to resume normal menses, including weight gain; they may benefit from OC, but the evidence is inconclusive. **Key Words:** RANDOMIZED TRIAL, AMENORRHEA, FEMALE ATHLETE TRIAD, BONE DENSITY, CALCIUM

Female athletes with amenorrhea or oligomenorrhea have reduced bone mineral density (BMD) for their age (4,5,9,24,30). Physicians have conventionally treated amenorrheic athletes with hormone therapy or oral contraceptives (OC) (12), but these treatments are controversial (17). Athletic amenorrhea is strongly related to disordered eating and caloric restriction (5,7,28), and exogenous estrogens may be ineffective at improving BMD in the absence of improved nutrition and weight gain (7,9,30). Indeed, in nonathletic women with clinically apparent anorexia nervosa, randomized trials have found no effect for hormone therapy or OC on bone (for a review of these trials, see Liu and Lebrun (19)). In amenorrheic athletes, one longitudinal study found modest skeletal benefits for hormone therapy (6), but two small randomized trials found no benefit (11,24). Longitudinal studies have also found small to modest skeletal benefits for OC (4,22,25), and one randomized trial found that OC use reduced bone turnover in amenorrheic athletes, but no randomized trials have evaluated the impact of OC on BMD in this population.

The effect of OC on the BMD of eumenorrheic athletes is also unknown. Some eumenorrheic athletes have subclinical menstrual irregularities (e.g., anovulatory cycles) that are associated with an increased risk of bone loss (21), and, hypothetically, OC might benefit this subgroup. Alternatively, eumenorrheic athletes may be similar to nonathletic premenopausal women, for whom OC have little effect on bone (19). Lastly, OC use could be detrimental to bone health in exercising women with normal menstrual cycles. Studies from two research groups found that physically

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active women who used low-dose OC (< 50 μg of ethinyl estradiol) had reduced BMD compared with physically active women who did not use OC (14,15,26) or inactive women (26). To our knowledge, there have been no randomized trials of OC use and BMD in eumenorrheic female athletes.

OC use may also protect against stress fractures in athletes, by affecting bone quality, bone turnover, or a combination of these (2), but results of previous studies are mixed. One cross-sectional and one case–control study linked OC use to a decrease in stress fracture risk (1,20), but two prospective cohort studies, in athletes (3) and female military recruits (23), found no association. There have been no randomized trials to test this hypothesis.

We conducted a randomized trial to test the effect of OC use on bone mass and stress fracture incidence in female runners. We chose to focus on running to reduce heterogeneity otherwise introduced by multiple sports, and because runners have a high frequency of both amenorrhea and stress fractures.

MATERIALS AND METHODS

Participants and recruitment. The study recruited 150 competitive female runners from intercollegiate cross-country teams, postcollegiate running clubs, and road races, mainly in the geographic areas of Palo Alto, CA, Los Angeles, CA, Ann Arbor, MI, West Haverstraw, NY, and Boston, MA. Recruitment took place between August 1998 and September 2003. To be eligible, women had to be 18–26 yr old, run at least 40 miles per week during peak training times, and compete in running races. Women were excluded if they had used OC, other hormone therapy, or other hormonal contraception within 6 months before entering the study; were unwilling to be randomized to take OC or not to take them for 2 yr; or had any medical contraindications to OC use. All women were required to visit a study physician or student health service staff member before enrollment in the study, to rule out contraindications to OC use. Details of the study and testing procedures were explained to each subject, and written informed consent was obtained. The protocol was approved by the institutional review boards of Stanford University, the University of California–Los Angeles, the University of Michigan, the Helen Hayes Hospital, the Massachusetts General Hospital, the U.S. Army Medical Research and Materiel Command, and the colleges from which participants were recruited.

Randomization and intervention. Eligible women were randomly assigned to receive OC or no intervention for an intended 2 yr, stratified according to clinical site. An independent investigator who was not otherwise affiliated with the study performed the randomization using a random-number table. Those assigned to take OC received the prescription from a study physician or student health service staff member. The OC active ingredients were 30 μg of ethinyl estradiol and 0.3 mg of norgestrel (Lo/Ovral, Wyeth Ayerst, 28-d pack). No placebo was used, and neither the athletes nor prescribing physician were blinded to treatment assignment, because it would be unethical to have women unsure of their contraceptive status.

Data collection and follow-up. At baseline, participants visited one of the clinical sites for bone, body composition, and physical measurements. Bone mineral density (BMD), bone mineral content (BMC), and body composition were measured by dual-energy x-ray absorptiometry (see below). Height and weight were measured using standard stadiometers and balance-beam scales, respectively (Stanford University: Harpenden stadiometer/Healthometer scale; University of California–Los Angeles: Healthometer; University of Michigan: Healthometer; Helen Hayes Hospital: Measurement Concepts stadiometer/Detecto scale; Massachusetts General Hospital: Healthometer). Participants also filled out questionnaires on menstrual history, previous use of OC, injury and stress fracture history, training regimen, diet, eating attitudes, and eating behaviors, as previously described (5). Women were classified as amenorrheic, oligomenorrheic, or eumenorrheic according to the number of menses they reported having in the previous 12 months (5). Amenorrhea was defined as zero to three cycles in the past year, oligomenorrhea was defined as four to nine cycles in the past year, and eumenorrhea was defined as 10 or more cycles in the past year (5). Participants were asked to return to the same clinical site 1 yr and 2 yr later to repeat these measurements and questionnaires.

There were 124 participants (83%) who attended at least one of these follow-up appointments, and 96 (64%) participants attended both, at an average of 14.4 months (median: 13.1 months) and 26.6 months (median: 25.4 months), respectively, after baseline. Three additional women provided information on stress fracture occurrence (for an average of 7.9 months after baseline) but did not return for any clinical visits. Baseline characteristics of the 23 participants with no follow-up data were similar to those with follow-up data, except that they were more likely to have a history of stress fracture before baseline (52 vs 32%, $P = 0.05$).

Between clinic visits, participants filled out a monthly calendar on which they recorded menstrual bleeding, use of OC pills, and the occurrence of stress fractures.

Ascertainment of compliance. Women in the treatment group were asked to report whether and when they discontinued taking the study medication. Treatment compliance was also monitored through return of used pill packs, monthly calendars, and yearly questionnaires. If a woman reported having discontinued treatment, she was contacted by a study investigator to determine whether and when OC were discontinued, and why. Similarly, women in the control group were asked to contact us if they were planning to start an OC. If so, they were encouraged to take the study pill (Lo/Ovral, Wyeth-Ayerst) or a pill with a

similar dose of estrogen. Compliance was also monitored on monthly calendars and yearly questionnaires. If a woman reported having started OC, she was contacted by a study investigator to get the date of starting the OC, as well as the formulation and the reason for starting them. Among women in the control group who took the OC, the majority took Lo/Ovral or Ortho Tri-Cyclen (Ortho-McNeil Pharmaceutical, Inc.; 35 μg of ethinyl estradiol). The trends seemed similar with both formulations, but numbers were too small to make firm conclusions, so we combined them into a single OC group for all secondary analyses.

Ascertainment of outcomes: BMD and content. At baseline and at each follow-up visit, BMD ($g \cdot cm^{-2}$) and BMC (g) at the left proximal femur, lumbar spine, and whole body were estimated by dual-energy x-ray absorptiometry (DXA, Hologic QDR 4500A at 4 sites and QDR 2000W at 1, site). The coefficient of variation for measuring BMD at the hip and spine in the same person after leaving and then returning to the measuring table on the same day was 2% or less at each of the clinical sites (Stanford University: 0.9% for the lumbar spine, 0.6% for the total hip; University of California–Los Angeles: 1.4% spine, 2.2% femoral neck; University of Michigan: 1.0% spine, 0.9% femoral neck; Helen Hayes Hospital: 1.2% spine, 1.4% hip; Massachusetts General Hospital: 1.0% spine, 1.4% hip). For most of the periods of data collection, machines were cross-calibrated using a circulating Hologic anthropomorphic spine phantom, and each site maintained a quality-assurance program.

Ascertainment of outcomes: stress fractures. Participants were asked to record the occurrence of a possible stress fracture on a monthly calendar and to report their occurrence to the coordinating center immediately. Participants were also queried periodically about the occurrence of stress fractures by e-mail, phone, and on their questionnaires. Fractures had to be confirmed by x-ray, bone scan, or magnetic resonance imaging to be counted in this study. All self-reported stress fractures were, in fact, confirmed. The study paid for the imaging as needed. We included stress fractures that occurred up to 1 month after the final follow-up visit.

Statistical design and analysis. We calculated that we would need 150 subjects (75 per group) to attain 80% power to detect differences in changes in BMD and stress fracture incidence between the OC group and the control group, assuming a 20% annual rate of stress fractures in the control group (3), a threefold difference in stress fracture incidence (1,20), and a half-SD difference in changes in BMD, and accounting for anticipated losses to follow-up and noncompliance (we anticipated that 5% of subjects would be lost to follow-up, 20% of treated subjects would discontinue OC, and 5% of control subjects would begin OC).

Statistical analyses were performed using the SAS statistical package, version 9.1 (SAS Institute, Cary, NC). Means were compared between groups using a *t*-test for normally distributed variables and a Wilcoxon sum–rank test for nonnormally distributed variables. Proportions were compared using a chi-square test or a Fisher's exact test, in the case of small cells. For graphing, changes in BMD, BMC, and weight were expressed as annualized percentages of change since baseline.

All primary outcomes were analyzed according to the intention-to-treat principle. Linear mixed-effects models were used to determine the effect of OC on changes in BMD and BMC over time. As initially planned, all BMD and BMC analyses were stratified according to baseline menstrual status. Cox proportional hazards models were used to determine the effect of OC on stress fracture incidence. Potential effect modifiers of the relationship

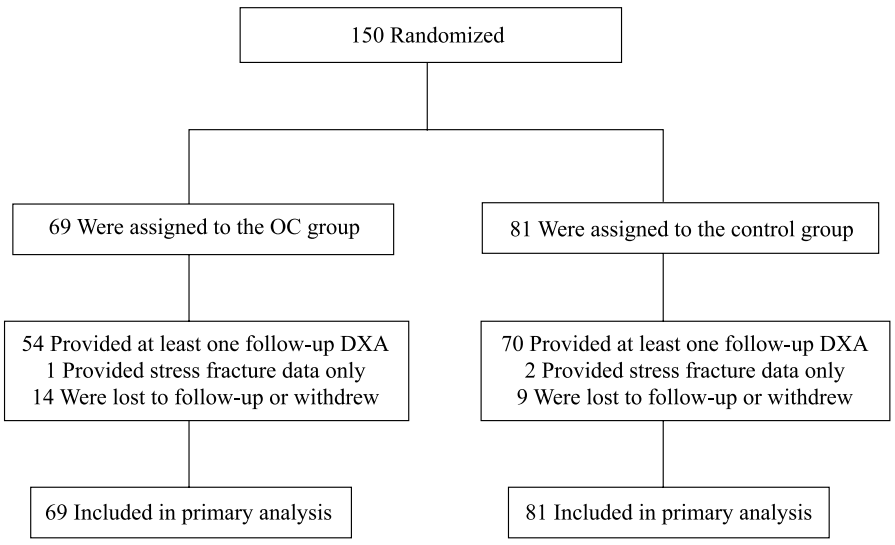

FIGURE 1—Flow of participants through the trial.

TABLE 1. Mean ± SD or percentage (number) with selected characteristic at baseline, by treatment randomization.

	Treatment Randomization	
	Oral Contraceptives (*N* = 69)	Control (*N* = 81)
Age (yr)	22.3 ± 2.7	21.9 ± 2.6
Race/ethnicity		
White	82.6% (57)	82.7% (67)
Asian/Pacific Islander	4.4% (3)	9.9% (8)
Hispanic	7.3% (5)	3.7% (3)
Black	2.9% (2)	0% (0)
Other	2.9% (2)	3.7% (3)
Clinical site		
Stanford	53.6% (37)	43.2% (37)
Boston	17.4% (12)	21.0% (17)
Los Angeles	15.9% (11)	21.0% (17)
New York	10.1% (7)	8.6% (7)
Michigan	2.9% (2)	6.2% (5)
Hip BMD ($g \cdot cm^{-2}$)	0.986 ± 0.119	0.975 ± 0.114
Spine BMD ($g \cdot cm^{-2}$)	0.979 ± 0.098	0.985 ± 0.112
Whole-body bone mineral content (g)	2171 ± 312	2146 ± 279
History of one or more stress fractures	36.2% (25)	33.3% (27)
Age at menarche (yr)	13.1 ± 1.4	13.0 ± 1.5
Total lifetime menstrual periods (no. of cycles)	69 ± 28	67 ± 30
Menses in past year (no. of cycles)	9.4 ± 3.8	9.5 ± 3.1
Irregular menses		
Amenorrhea[a]	11.6% (8)	6.2% (5)
Oligomenorrhea[b]	18.8% (13)	29.6% (24)
Ever used oral contraceptives	43.5% (30)	40.7% (33)
Height (cm)	165.9 ± 6.6	165.4 ± 6.1
Weight (kg)	58.2 ± 7.3	58.1 ± 6.6
Body mass index ($kg \cdot m^{-2}$)	21.1 ± 1.9	21.3 ± 2.0
Body fat (%)	22.7 ± 5.2	23.3 ± 5.4
Daily caloric intake ($kcal \cdot d^{-1}$)	2250 ± 893	2302 ± 988
Dietary calcium intake ($mg \cdot d^{-1}$)	1394 ± 829	1412 ± 670
Total eating disorder inventory score[c]	14.7 ± 14.7	10.6 ± 11.8
Age started running competitively (yr)	14.1 ± 3.8	14.3 ± 3.3
Average distance run per week, past year (miles)	34.8 ± 10.5	34.8 ± 11.4

[a] Zero to three menstrual periods in the year before baseline; [b] four to nine menstrual periods in the year before baseline; [c] total eating disorder inventory score, which can range from 0 to 69, is the sum of the scores from the anorexia, bulimia, and body dissatisfaction subscales from Garner and Olmstead (10).

between OC and bone mass or OC and stress fractures were evaluated by stratifying the model (for categorical variables) or by including an interaction term (for both categorical and continuous variables).

Secondary analyses were performed on the 127 women who provided follow-up data. Per-protocol analyses excluded women from the analysis at the time they switched groups. Treatment-received analyses grouped women according to their actual use of OC, or they modeled OC use as a time-dependent variable (allowing OC status to change at the dates of starting and stopping OC). BMD and BMC changes were analyzed by mixed models, and stress fracture data were analyzed by Cox proportional hazards models. In mixed models with changes in BMD or BMC as the outcome, calcium intake was adjusted for energy intake by the residual method (27).

RESULTS

Baseline characteristics. One-hundred fifty women were randomized to receive OC or no intervention (Fig. 1). By chance, 69 women were assigned to the OC group, and 81 were assigned to the control group. The groups were well balanced on age, race/ethnicity, BMD, stress fracture history, menstrual history, weight and body composition, dietary factors, and training factors (Table 1). Amenorrhea was more common in the OC group, and oligomenorrhea was more common in the control group, but these differences were not statistically significant, and the groups were similar in the total proportion of athletes with menstrual irregularity (amenorrhea or oligomenorrhea).

At baseline, amenorrheic women had the lowest BMD on average (spine: 0.932 $g \cdot cm^{-2}$; hip: 0.937 $g \cdot cm^{-2}$), oligomenorrheic women had intermediate values (spine: 0.967; hip: 0.972 $g \cdot cm^{-2}$), and eumenorrheic women had the highest BMD (spine: 0.995 $g \cdot cm^{-2}$; hip: 0.988 $g \cdot cm^{-2}$). However, these differences did not quite reach statistical significance.

Retention and adherence. Twenty-three participants (15%) withdrew or were lost to follow-up after baseline (Fig. 1). Reasons for withdrawing included geographic relocation, pregnancy, illness, and lack of time. Of the remaining 127 participants, 42 (33%) switched groups during the study—25.5% of the treatment group discontinued OC after an average of 5.4 months of use, and 38.9% of the control group started taking them at an average of 11.3 months into the study (Table 2). Four women in the control group and one woman in the treatment group switched groups twice. In decreasing order of frequency, the reasons women gave for stopping OC included fear of weight gain or perceived weight gain, side effects (irritability, abdominal symptoms, nausea, fatigue, or unspecified), and fear of detriment to athletic performance. In decreasing order of frequency, the reasons control women gave for starting OC included regulating periods, alleviating menstrual symptoms and cramps, preventing pregnancy, treating acne, and treating allergies.

Women who stopped taking OC had significantly lower percent body fat, fewer menstrual periods per year, and more disordered eating than women who adhered to OC (Table 2). Amenorrheic women were the least likely to comply with taking OC: of eight amenorrheic women who were assigned to OC, only one took them through the entire study (of the remaining seven, two were lost to follow-up, five discontinued OC within 2 months, and one discontinued OC after 1.5 yr). In the control group, women who self-initiated OC use were less likely than control adherent women to have a history of stress fractures before baseline.

Primary analysis: BMC and BMD. The effect of OC on bone mass was similar across the clinical sites, so we combined the data from the sites, retaining site as a

TABLE 2. Selected follow-up measures and baseline characteristics according to intervention adherence (where follow-up data were available).

	Adherence			
	Adherent to Treatment (*N* = 41)	Switched from Treatment to Control (*N* = 14)	Adherent to Control (*N* = 44)	Switched from Control to Treatment (*N* = 28)
Follow-up measure				
Time in study (months)	24.2 ± 4.7	24.7 ± 8.5	24.0 ± 6.4	25.6 ± 8.3
Time switched groups (months into study)	—	5.4 ± 5.6	—	11.3 ± 10.3
Oral contraceptive use (months)	24.2 ± 4.7	5.4 ± 5.6	0	14.4 ± 9.1
Baseline characteristic				
Age (yr)	22.0 ± 2.7	22.2 ± 2.8	22.1 ± 2.6	21.9 ± 2.8
Hip BMD ($g \cdot cm^{-2}$)	0.994 ± 0.132	0.962 ± 0.088	0.991 ± 0.115	0.977 ± 0.108
Spine BMD ($g \cdot cm^{-2}$)	0.984 ± 0.104	0.960 ± 0.103	1.00 ± 0.115	0.985 ± 0.109
Whole-body bone mineral content (g)	2157 ± 340	2192 ± 226	2166 ± 243	2181 ± 330
History of one or more stress fractures	34.2% (14)	28.6% (4)	38.6% (17)	17.9% (5)*
Menses in past year (no. of cycles)	10.8 ± 2.3	6.3 ± 5.1**	9.6 ± 2.9	9.4 ± 3.4
Irregular menses[a]				
Amenorrhea	2.4% (1)	35.7% (5)***	4.6% (2)	7.1%(2)
Oligomenorrhea	14.6% (6)	21.4% (3)	36.4% (16)	25.0% (7)
Weight (kg)	58.6 ± 7.6	57.2 ± 5.4	58.5 ± 6.4	58.4 ± 6.6
Body fat (%)	23.7 ± 4.8	19.5 ± 6.1†	23.6 ± 5.5	23.0 ± 5.1
Total eating disorder inventory score[b]	10.9 ± 11.2	17.4 ± 16.2	12.0 ± 12.4	10.0 ± 11.9
Evidence of prior or current disordered eating[c]	26.8% (11)	57.1% (8)‡	31.8% (14)	32.1% (9)

* $P = 0.06$, differs from control adherent group, chi-square test; ** $P < 0.005$, differs from treatment adherent group, Wilcoxon sum–rank test; *** $P < 0.005$, differs from treatment adherent group, Fisher's exact test; † $P < 0.05$, differs from treatment adherent group, *t*-test; ‡ $P < 0.05$, differs from treatment adherent group, chi-square test.
[a] Amenorrhea was defined as zero to three periods in the year before baseline; oligomenorrhea was defined as four to nine periods in the year before baseline; [b] total eating disorder inventory (EDI) score, which can range from 0 to 69, is the sum of the scores from the body dissatisfaction, anorexia, and bulimia subscales, Garner and Olmstead (10); [c] women were considered to have evidence of prior or current disordered eating if they scored in the top quartile of the EDI questionnaire (≥ 23) anytime during the study or had a history of anorexia nervosa or bulimia nervosa.

covariate in all models. Results for spine and hip BMD were similar to results for spine and hip BMC; for comparability with previous studies, we report the BMD results for these sites.

We found that randomization to OC had no effect on changes in BMC or BMD, with one exception: in the oligomenorrheic group, total hip BMD was significantly reduced ($P = 0.04$) in the OC group compared with the control group (Table 3). This finding may be the result of chance, attributable to multiple comparisons and small numbers. After correction for multiple comparisons with a Hochberg correction (16), this difference was no longer statistically significant at the 0.05 level.

Regardless of treatment assignment, bone changes were strongly related to initial menstrual status. Overall, the amenorrheic and oligomenorrheic groups had significant increases in spine BMD and whole-body BMC, with the largest gains occurring in the amenorrheic group. Eumenorrheic women had a small but significant increase in whole-body BMC (6.4 ± 2.6 $g \cdot yr^{-1}$, $P < 0.05$) but no changes in hip or spine BMD.

We found no interactions between randomization status and age, BMD, weight, weight changes, body composition, disordered eating, calcium intake, or miles run per week with respect to bone outcomes.

Secondary analyses: BMC and BMD. One hundred twenty-four women had at least one follow-up DXA and

TABLE 3. Annual rate of change in spine and hip bone mineral density (BMD) and whole-body bone mineral content (BMC) by treatment randomization, stratified on initial menstrual status.

	Whole-Body BMC ($g \cdot yr^{-1}$ ± SE)	Spine BMD ($g \cdot cm^{-2} \cdot yr^{-1}$ ± SE)	Total Hip BMD ($g \cdot cm^{-2} \cdot yr^{-1}$ ± SE)
Amenorrheic[a]			
Treatment (*N* = 8)	16.1 ± 10.3	0.0197 ± 0.0036*	0.0050 ± 0.0040
Control (*N* = 5)	28.9 ± 9.9**	0.0138 ± 0.0049**	0.0052 ± 0.0054
Treatment vs control	−12.8 ± 12.4	0.0060 ± 0.0061	−0.0002 ± 0.0067
Oligomenorrheic[b]			
Treatment (*N* = 13)	23.2 ± 10.4**	0.0019 ± 0.0037	−0.0096 ± 0.0033***
Control (*N* = 24)	15.3 ± 7.4**	0.0076 ± 0.0026***	0.0012 ± 0.0023
Treatment vs control	8.1 ± 12.8	−0.0056 ± 0.0045	−0.01076 ± 0.0041**
Eumenorrheic			
Treatment (*N* = 48)	9.9 ± 3.9**	0.0022 ± 0.0019	0.0013 ± 0.0017
Control (*N* = 52)	3.7 ± 3.4	0.0002 ± 0.0016	−0.0023 ± 0.0015
Treatment vs control	6.2 ± 5.2	0.0020 ± 0.0025	0.0035 ± 0.0022

Rate of change was determined from linear mixed models, adjusted for age and clinical site.
[a] Amenorrhea was defined as zero to three periods in the year before baseline; [b] oligomenorrhea was defined as four to nine periods in the year before baseline.
* $P < 0.0001$, rate of change differs from 0; ** $P < 0.05$, rate of change differs from 0; *** $P < 0.01$, rate of change differs from 0.

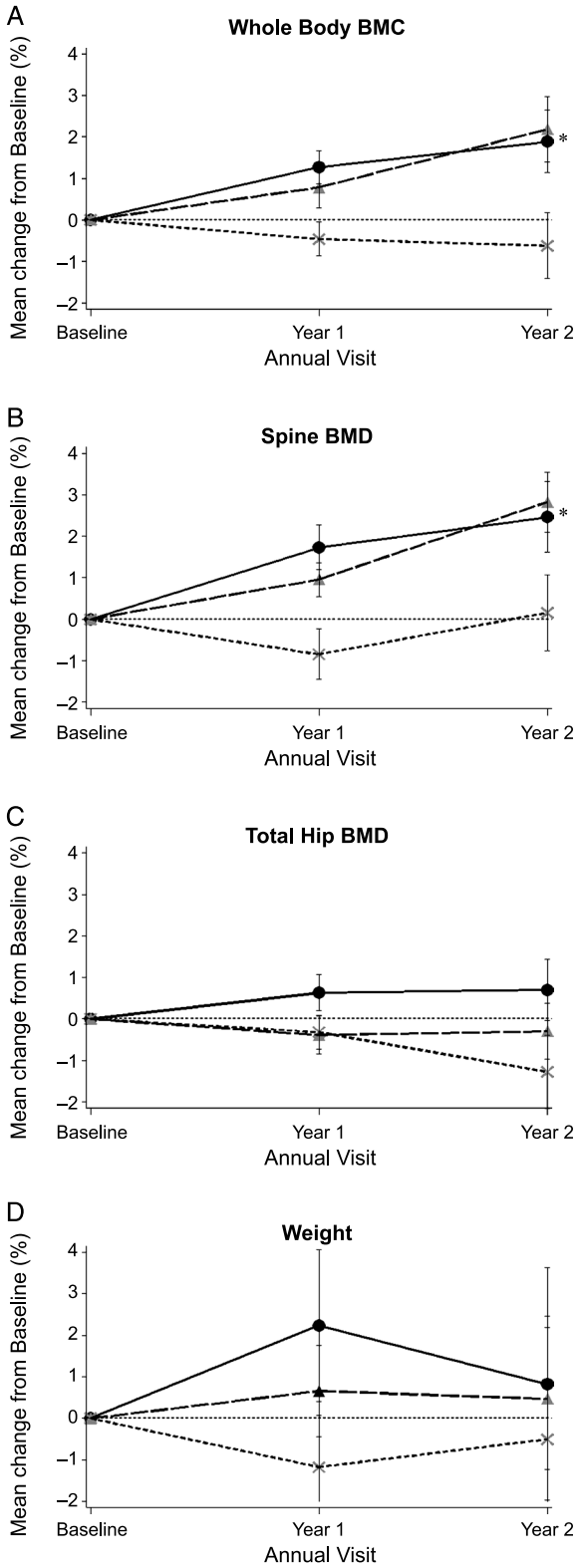

FIGURE 2—Annualized mean percent change in whole-body bone mineral content (BMC), spine and hip bone mineral density (BMD), and weight among oligo/amenorrheic women according to follow-up menstrual status (graph displays mean ± one standard error of the mean). ● Used oral contraceptives for at least 6 months ($N = 16$); ▲ spontaneously regained menses ($N = 14$); x, remained oligo/amenorrheic ($N = 11$). * $P < 0.05$, different than women who remained oligo/amenorrheic, mixed models.

were included in secondary analyses. We combined the amenorrheic and oligomenorrheic groups for these analyses because the groups gave similar results when analyzed separately, but the amenorrheic group was too small ($N = 10$) to yield precise estimates in multivariate analyses.

Per-protocol and treatment-received analyses gave similar results to the intention-to-treat analysis (data not shown), except that we did not find a negative effect of OC on hip BMD in oligo/amenorrheic women. For treatment-received analyses, we classified women as being in the OC group if they had used OC for at least 6 months during the study. We used a cutoff of 6 months because it may take this long for OC to affect BMD. We repeated all analyses using an alternate cutoff of 3 months or modeling OC use as a time-dependent variable, and we found similar results (data not shown).

Fourteen of the oligo/amenorrheic women (4 amenorrheic and 10 oligomenorrheic) regained their periods spontaneously (had 10 or more periods in the year before their final measurement) without the help of OC. When we divided oligo/amenorrheic women into those who had used OC (for at least 6 months), those who regained their periods spontaneously, and those whose cycles never normalized, we found that OC users gained significantly more whole-body BMC and spine BMD than women who remained oligo/amenorrheic (Fig. 2, Table 4). The gain in bone mass among OC users did not differ statistically from women who regained periods spontaneously. On average, both groups gained about 1% per year in whole-body BMC and spine BMD, whereas women who remained oligo/amenorrheic neither gained nor lost bone. Average weight gain was (nonsignificantly) higher in the OC group than the other two groups during the first year of the study (Fig. 2), but adjustment for weight changes did not remove the effect of OC (Table 4). Adjustment for changes in body composition gave similar results (data not shown).

In oligo/amenorrheic women, weight gain independently predicted gains in spine BMD and whole-body BMC, and it showed a trend at the hip ($P < 0.10$). Gains in fat mass also independently predicted gains in spine and hip BMD and whole-body BMC, but gains in lean mass predicted gains only in whole-body BMC (data not shown). Changes in fat mass and weight were highly correlated ($r = 0.84$, $P < 0.0001$), so we chose to include weight in the final model, because it is a more clinically accessible measure. Higher dietary calcium intake also predicted gains in whole-body BMC and hip BMD in oligo/amenorrheic women.

In eumenorrheic women, weight gain was not associated with bone changes, but dietary calcium intake was associated with increases in hip BMD ($P < 0.05$) and showed a trend for whole-body BMC ($P < 0.10$) (Table 4).

Primary analysis: stress fractures. Eighteen runners had at least one stress fracture during the study in the tibia, foot, femur, or pelvis (Table 5). Six occurred in the group randomized to OC (5.8 per woman-year) and 12 in the group randomized to control (9.2 per woman-year)

TABLE 4. Treatment-received analyses: adjusted annual rates of change in whole-body bone mineral content (BMC) and spine and hip bone mineral density (BMD) among women with at least one follow-up DXA measurement, stratified on initial menstrual status.

	Whole-Body BMC ($g \cdot yr^{-1} \pm SE$)	Spine BMD ($g \cdot cm^{-2} \cdot yr^{-1} \pm SE$)	Total Hip BMD ($g \cdot cm^{-2} \cdot yr^{-1} \pm SE$)
Oligo/amenorrheic[a] ($N = 41$)			
Used oral contraceptives for at least 6 months ($N = 16$) vs remained oligo/amenorrheic ($N = 11$)	26.8 ± 11.3*	0.0103 ± 0.0043*	0.0068 ± 0.0043
Regained periods spontaneously ($N = 14$) vs remained oligo/amenorrheic ($N = 11$)	34.9 ± 11.5*	0.0113 ± 0.0043*	0.0035 ± 0.0043
Baseline calcium intake (per 1-SD increase)[b]	10.6 ± 4.9*	0.0020 ± 0.0018	0.0048 ± 0.0017*
Weight change (per 5-kg increase)	21.3 ± 8.8*	0.0126 ± 0.0033**	0.0063 ± 0.0033***
Eumenorrheic ($N = 83$)			
Used oral contraceptives for at least 6 months ($N = 50$) vs did not use oral contraceptives for at least 6 months ($N = 33$)	5.9 ± 5.6	0.0027 ± 0.0027	0.0034 ± 0.0024
Baseline calcium intake (per 1-SD increase)[b]	4.9± 2.7***	0.0020 ± 0.0013	0.0027 ± 0.0011*
Weight change (per 5-kg increase)	−3.6 ± 10.3	0.0060 ± 0.0049	0.0060 ± 0.0043

Annual rates of change are estimated from linear mixed models, adjusted for clinical site, age, baseline weight, and all other predictors shown in the table.
[a] Oligo/amenorrhea was defined as zero to nine menses in the year before baseline; [b] baseline calcium intake is adjusted for caloric intake using the residual method (27). A 1-SD increase was about 550 mg of calcium in this population.
* $P < 0.05$, rate of change differs from 0; ** $P < 0.001$, rate of change differs from 0; *** $P < 0.10$, rate of change differs from 0.

(Table 6). After adjusting for baseline menstrual status, clinical site, age, prior stress fracture, and spine BMD (the latter two variables were strongly related to fracture risk) in a Cox proportional hazards model, we found that randomization to OC yielded a nonsignificant 43% decrease in the rate of stress fracture. This effect was similar across the different clinical sites and across baseline menstrual groups; the hazard ratio (95% CI) for eumenorrheic women was 0.56 (0.14, 2.22), and for oligo/amenorrheic women it was 0.60 (0.06, 5.83).

Women who were oligo/amenorrheic at baseline were not at increased risk of fracture compared with women who were eumenorrheic at baseline (HR: 1.20); however, the majority of oligo/amenorrheic women regained menstrual regularity during the trial. A small group of women who remained oligo/amenorrheic ($N = 11$) or became so during the study ($N = 2$) had nonsignificant increases in fracture risk (HR [95% CI]: 2.71 [0.70, 10.60]).

We did not find interactions between randomization status and age, low BMD, weight, weight changes, body composition, past menstrual irregularity, disordered eating, calcium intake, or miles run per week with respect to stress fractures, though we had limited statistical power to detect interactions.

Four women had a second stress fracture during the study (three in the control group and one in the treatment group), but this was too small a number to evaluate statistically.

Secondary analyses: stress fractures. When we excluded nonadherent women from our analysis on the date at which they switched groups, OC seemed more protective, but this did not reach statistical significance (Table 6). We then modeled OC use as a time-dependent variable to ensure that we were only counting OC treatment that occurred before each fracture. When women were taking OC (and had been on them at least a month), OC use seemed to be significantly protective (HR [95% CI]: 0.23 [0.06, 0.86]). However, four fractures occurred in the control group within the first 3 months of the study, and it is unclear whether these fractures can be attributed to anything other than chance. Excluding these fractures by requiring OC use of at least 3 months reduced the magnitude of the effect slightly and also reduced our statistical power (HR [95% CI]: 0.40 [0.11, 1.50]).

TABLE 5. Distribution of stress fractures by site and mode of diagnosis.

Site of Fracture	Diagnostic Test	Number
Tibia	Bone scan	9
Tibia	X-ray	1
Foot	X-ray	3
Foot	Bone scan	1
Foot	MRI	1
Femur	MRI	2
Pelvis	X-ray	1

Four women had two stress fractures during the study; only their first stress fractures are included in this table.

Adverse events. There were no serious adverse events in the trial. Five women discontinued OC, citing irritability, abdominal symptoms, nausea, fatigue, or unspecified side effects.

DISCUSSION

We found that randomization to OC had no effect on BMD or BMC in oligo/amenorrheic or eumenorrheic female runners, and it yielded a 43% reduction (not statistically significant) in the rate of stress fractures across menstrual groups. The trial's statistical power was diminished by noncompliance: 38.9% of women in the control group started taking OC, and 25.5% of women in the treatment group stopped taking them (among those with follow-up data). Additionally, power was reduced because 38% of oligo/amenorrheic runners in the control group resumed normal menses spontaneously. We confirm the difficulties of doing a definitive trial of OC in female athletes (11).

Contrary to previous reports (14,15,26), we did not find that use of low-dose OC was detrimental to BMD levels in eumenorrheic female athletes. Some of these previous reports were cross-sectional studies (14,15), which cannot establish the direction of causality and may be confounded by reasons for use of OC. Because of our choice of study population, we cannot rule out a negative effect of OC use for inactive women who begin an exercise program (26) or for athletes younger than 18 (14).

TABLE 6. Effect of oral contraceptives on stress fracture incidence, according to type of analysis.

Analysis	Oral Contraceptives (*N* = 69)	Control (*N* = 81)	Hazard Ratio (95% CI)[a]
Intention-to-treat analysis			
Number of fractures	6	12	
Time to fracture or censoring in months (mean ± SD)	18.1 ± 11.4	19.4 ± 11.2	
Rate of fracture, per 100 women-years	5.8	9.2	
			0.57 (0.18, 1.83)
Per-protocol analysis[b]			
Number of fractures	5	11	
Time to fracture or censoring in months (mean ± SD)	14.6 ± 11.5	14.7 ± 11.3	
Rate of fracture, per 100 women-years	6.0	11.1	
			0.40 (0.11, 1.49)
Treatment–received analyses			
Took oral contraceptives ≥ 1 month and still taking them[c]			0.23 (0.06, 0.86)*
Took oral contraceptives ≥ 3 months and still taking them[d]			0.42 (0.11, 1.57)

[a] Adjusted by Cox proportional hazards model for age, clinical site, baseline menstrual status, baseline spine BMD, and prior fracture. The hazard ratios are for the oral contraceptive group compared with the control group.
[b] This analysis censors women who switched groups at the time of switching.
[c] Time-dependent variable that considers a woman to be in the oral contraceptive group only after she has taken them for at least 1 month and has not stopped taking them.
[d] Time-dependent variable that considers a woman to be in the oral contraceptive group only after she has taken them for at least 3 months and has not stopped taking them.
* $P < 0.05$.

In our treatment-received analyses, we found that oligo/amenorrheic runners who took OC for at least 6 months gained more spine BMD and whole-body BMC than did runners who remained oligo/amenorrheic, and this association was independent of changes in weight or body composition. The magnitude of the effect—approximately 1% annual gains—was similar to that of regaining periods spontaneously or gaining 5 kg. However, we cannot conclude that OC per se caused these gains. Women who dropped out of the OC group were more likely to be amenorrheic and have disordered eating—two factors that predispose to continued bone loss or lack of bone growth. Oligo/amenorrheic runners who adhered to or started on OC may have been concerned about their bone health and, thus, actively trying to improve it in other ways not discernible in this study.

Results of previous studies of estrogen supplementation and BMD in amenorrheic athletes have been mixed and may be complicated by the use of different formulations and doses of hormones. Longitudinal cohort studies of OC (30–35 μg of ethinyl estradiol (4,22,25)) or hormone therapy (0.625 mg of conjugated estrogen or a 50-μg estradiol patch (6)) have found small to modest positive effects on BMD in amenorrheic athletes, but these studies may be confounded by other factors associated with the choice to take hormones. Two randomized trials failed to find an effect of hormone therapy (Premarin/Provera and 2 mg of estradiol/1 mg of estriol, respectively) in 24 amenorrheic ballet dancers (24) and 34 oligo/amenorrheic runners (11). However, similar to our findings with OC, the latter trial did find a significant benefit for using hormones compared with remaining oligo/amenorrheic in treatment-received analyses.

Our results confirm previous findings that spontaneous recovery of menses benefits the skeleton (8,11,18). In our study, it was unclear why some runners spontaneously resumed normal menses and others did not, and the reasons are likely heterogeneous. Previous researchers have found that decreased training, increased caloric intake, and weight gain predict spontaneous resumption of menses (8,18). We found that, on average, women who spontaneously regained menses had a trend toward higher caloric intake than did women who remained oligo/amenorrheic, but this translated to only slightly higher average gains in weight and fat mass. We speculate that small improvements in energy balance and eating patterns may normalize menstrual periods without substantial weight gain.

We confirm previous findings that weight gain is an important independent predictor of bone mass gain in oligo/amenorrheic athletes (18); weight gain was associated with increases in whole-body BMC, spine BMD, and hip BMD. Fat mass gains were more predictive of changes in BMD and BMC than were lean mass gains.

Dietary calcium intake (controlled for energy intake) predicted gains in whole-body BMC and hip BMD in both oligo/amenorrheic and eumenorrheic athletes, with a stronger effect in oligo/amenorrheic women. We found no effect for calcium supplementation, but this variable was imprecisely measured, and use of supplements was sporadic in this population. One previous cross-sectional study found a relationship between dietary calcium intake and BMD (29), but these estimates were not adjusted for energy intake. We believe the present study is the first longitudinal study to show that dietary calcium intake is important for continued skeletal mineralization in young adult female runners.

Whole-body BMC significantly increased during the course of the study in all menstrual groups, thereby indicating continued skeletal mineralization in this age group. Amenorrheic and oligomenorrheic women who recovered their periods (through OC or spontaneously) gained whole-body BMC and spine BMD (but not hip BMD) at a faster rate than did eumenorrheic women. This is promising in that it suggests a catch-up effect, whereby previously amenorrheic and oligomenorrheic athletes with reduced BMD can gain bone in the third decade of life (9).

This is the first randomized trial to test whether OC can protect young female athletes against stress fractures. Our results are inconclusive, but they show a trend toward

protection. In our intention-to-treat analysis, there was a nonsignificant 43% reduction in stress fracture incidence among women randomized to OC. The magnitude of the effect was similar in eumenorrheic and oligo/amenorrheic runners. Follow-up, but not baseline, menstrual irregularity was associated with a nonsignificant increase in fracture risk.

The effect of OC on stress fractures became stronger in both per-protocol and treatment-received analyses. In our treatment-received analysis, women were significantly protected against fractures (by 77%) whenever they were taking OC, though this estimate was weakened when we excluded fractures that occurred early in the trial (58% reduction in risk, $P = 0.20$). Our finding may be attributable to chance or bias. We found that women who switched from the control group to OC use were less likely to have a history of stress fractures before joining the study. Thus, the type of woman runner who is willing to continue on or who chooses to take OC may be less prone to fracture for other reasons.

OC may protect against stress fractures by suppressing bone turnover (25). During bone remodeling, bone resorption precedes bone formation, temporarily leaving skeletal sites weakened and more vulnerable to fracture (2). OC may also protect against fracture through cumulative effects on BMD (2), but we found no evidence of this in our trial. Finally, OC may be acting on some other aspect of bone quality that affects fracture risk.

Our findings are consistent with two previous observational studies that found protective effects of similar magnitude. In a case–control study by Myburgh et al. (20), current use of OC was associated with a 76% reduction in the odds of stress fracture; in a cross-sectional study by Barrow and Saha (1), having used OC at any time (for at least 1 yr) was associated with a 59% reduction in risk of ever having had a fracture. Our findings differ from two prospective cohort studies that reported no benefit for OC in track and field athletes and female military recruits (3,23).

Even if OC confer benefit, women at the highest risk of severe bone deficits and stress fractures may be unwilling to take them. The amenorrheic women in our study had the lowest BMD and were the least willing to take OC; only one of eight amenorrheic women assigned to OC took them for the entire study period. Women with disordered eating, considered the precipitating factor in the female athlete triad, were also less likely to continue taking OC, possibly driven by fear of weight gain.

Our study highlights the difficulty of conducting a randomized trial of OC use in this population. Recruitment for this study took more than 5 yr. Women have strong personal preferences regarding OC use and are reluctant to leave this decision to chance.

Even though this is the largest randomized trial yet of OC in female athletes (and the largest in oligo/amenorrheic athletes), the trial was likely underpowered for both BMD and stress fracture outcomes, similar to the findings of Gibson et al. (11). Our original sample size calculations greatly underestimated the number of women in the control group who would switch to OC during the trial, and we did not account for the women in the oligo/amenorrheic group who would spontaneously regain periods and, thus, obscure our ability to see effects. Despite our best efforts, 15% of the study sample provided no follow-up data, which was slightly higher than initially anticipated. The rate of stress fracture in the control group was also lower than anticipated. On the basis of our results, we estimate that we actually had only 20% power to detect an effect of OC on stress fractures in our intention-to-treat analysis. We estimate that 900 runners would be required for 80% power to detect an effect of OC on stress fractures in a 2-yr trial of female runners of any menstrual status. From our study, it is unclear whether an adequately powered trial for the effect of OC on BMD (in oligo/amenorrheic athletes) is even possible; effects may be completely obscured regardless of sample size because of the high rates of women switching groups or spontaneously regaining menses. On the basis of their data, Gibson et al. (11) previously have estimated that 1150 oligo/amenorheic athletes would be needed; given the difficulties that we had recruiting for a trial of 150 runners of any menstrual status, we believe it would be extremely difficult to enroll this many oligo/amenorrheic athletes.

We used an oral contraceptive with 30 μg of ethinyl estradiol and 0.3 mg of norgestrel. We cannot rule out that different dosages, different routes of administration of hormones, or a different ratio of estrogen to progestin might have more beneficial effects on the skeleton. For example, isolated case reports in amenorrheic women suggest that transdermal estrogen may confer more benefits to bone than would oral estrogen (13,30).

We did not use a placebo control, because of ethical considerations and the high probability of unblinding; most women would have figured out whether they were on an OC by the timing of their menstrual cycles. We did not measure serum hormone concentrations or markers of bone turnover, which may have added information to the study, because these measurements were outside of the study's scope and resources. Because of our lack of hormone data, we cannot rule out that some cases of menstrual irregularity were caused by mechanisms other than hypothalamic suppression; such cases could have contributed to our failure to find an effect for OC. We did not have data on the severity of stress fracture injury, which may have limited our ability to see effects. We included stress fractures from multiple skeletal sites in our analysis; because OC may differentially affect different skeletal sites, this may also have obscured our ability to see effects. Finally, our results may not apply to athletes in other sports, because only runners were considered.

In summary, we found that OC use is not detrimental to BMD or BMC in female runners and may protect against stress fractures. Our data suggest that oligo/amenorrheic athletes with low BMD should be advised

to gain weight, increase dietary calcium intake, and consider taking OC if they are unable to establish regular menses on their own. However, we underscore that no clinical trials (including our own) have definitively shown that hormone therapy or OC increase (or prevent loss of) BMD or BMC in this group. We conclude that it will be difficult to conduct a randomized trial that definitively answers this question.

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