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This is a two-year randomized trial of the effects of oral contraceptives on bone mass and stress fracture incidence among 150 female competitive distance runners in the age range 18-25 years. The Coordinating Center is a t Stanford University and bone mass is being measured at five sites: Massachusetts General Hospital, University of California Los Angeles, University of Michigan, Stanford University/Palo Alto VA Medical Center, and Helen Hayes Hospital in West Haverstraw NY. Athletes were recruited from the areas around these five clinical sites. To date, over all five clinical sites, 152 have been randomized. Final results of the study will not be available until 2005.

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(5) INTRODUCTION

Highly trained female athletes may experience loss of menses because of their participation in intense physical activity. Previous cross-sectional research has shown that women with exercise-induced menstrual irregularities have a significantly higher frequency of stress fractures and low bone mass than normally menstruating controls. Longitudinal studies suggest that these women are losing bone mass over time. Low serum estrogen levels are believed to be a principal cause of the bone loss. If so, re-establishing normal estrogen levels in these women should prevent or retard bone loss and decrease the incidence of stress fracture. This study is a two-year randomized trial of the effect of oral contraceptives on bone mass and stress fracture incidence among 150 female cross country runners in the age range 18-25 years. The Coordinating Center is at Stanford University and bone mass is being measured at five sites: the Massachusetts General Hospital, the University of California Los Angeles, the University of Michigan, Stanford University/Palo Alto VA Medical Center, and the Helen Hayes Hospital in West Haverstraw, NY. Athletes are being recruited from the areas around these five clinical sites.

(6) BODY

Below we summarize (a) our progress through year 5, (b) the status of recruitment as of the end of year 5, and (c) our plans for completing the study.

<u>(a) Progress through year 5 (excluding recruitment, which will be described under [b] below):</u>

As of the time of this writing (October 2003), 152 runners have been randomized, 93 have completed their first year follow-up visits, and 58 have had both follow-up visits and have thus completed the study protocol. 15 have withdrawn from the study, and 10 are missing or not

responding. During year 5 specifically, 25 new runners were recruited and randomized, 19 attended their first follow-up visit, and 12 completed the study.

During year 4, we published the first manuscript, Disordered Eating, Menstrual Irregularity, and Bone Mineral Density in Female Runners, in *Medicine and Science in Sports and Exercise*. A copy of this publication is attached.

(b) Recruitment through year 5:

Recruitment has been completed.

(c) Plans for completing the study: Now that we have completed recruitment, we need about two more years to complete the study. (This is two and a half years beyond the scheduled date of termination.) We expect to complete the study by September 2005. This means with 152 enrolled minus the 25 lost to follow up and the 58 who are completed with the study, there are 69 participants left. Forty-nine of those participants need two more bone density appointments and 20 need only one more. Of the 49 who still need two more tests, 25 were recruited this year, several are currently scheduling their appointments, and several are abroad and will schedule when they return. At present we have funding until September 2004, and we will have to seek a small amount of additional funds for partial salary support for an additional year.

(7) KEY RESEARCH ACCOMPLISHMENTS:

- Attached is a manuscript describing some baseline results from the first 91 subjects. We found that (a) disordered eating is strongly related to menstrual irregularity, (b) menstrual irregularity is associated with low bone mineral density independent of body weight and

body composition, and (c) disordered eating is associated with low bone mineral density in the absence of menstrual irregularity.

- Since the submission of this manuscript for publication, we have analyzed baseline data from an additional 30 subjects. The trends that were observed for the first 91 participants were maintained when data from the additional 30 participants were added to the analyses. Additionally, differences between the amenorrheic and oligomenorrheic groups are now becoming apparent. Disordered eating and low bone mineral density are more strongly associated with amenorrhea than with oligomenorrhea.
- Also attached is an abstract from another paper that is currently being prepared. The paper concluded that: (a) disordered eating and fiber intake are positively associated and fat intake negatively associated with risk of oligomenorrhea and/or amenorrhea, (b) BMD is not influenced strongly by any one particular nutrient, and (c) dietary interventions to treat the female athlete triad should focus on restoring regular menstrual cycles, as normal menstrual functioning is strongly associated with adequate BMD.

(8) REPORTABLE OUTCOMES: When examined at baseline, one runner had a slightly abnormal Pap test. This abnormality was reported to all concerned IRBs, but was not deemed by the examining physician or several consultants to be a reason for exclusion from the study.

(9) CONCLUSIONS: We will have no firm conclusions to report on the primary hypothesis of the study until the end of the trial. However, in preparing interim data for our Medical Monitor, we can report that oral contraceptive use may be beneficial to spine bone mineral density in oligo/amenorrheic runners. We can also report that resumption of regular menses among the oligo/amenorrheic runners (either spontaneous resumption or due to oral contraceptives) is associated with gains in spine bone mineral density and, to a lesser extent, with gains in hip and

whole body bone mineral density. In addition, we observed that oral contraceptive use appears to bring about small gains in both lean and fat mass in young women runners.

(10) REFERENCES: None

(11) APPENDICES: Please see attached publication and abstract.

Disordered Eating, Menstrual Irregularity, and Bone Mineral Density in Female Runners

KRISTIN L. COBB[1], LAURA K. BACHRACH[2], GAIL GREENDALE[3], ROBERT MARCUS[4], ROBERT M. NEER[5], JERI NIEVES[6], MARY FRAN SOWERS[7], BYRON W. BROWN, JR.[1], GEETHA GOPALAKRISHNAN[1], CRYSTAL LUETTERS[1], HEATHER K. TANNER[1], BRIDGET WARD[1], and JENNIFER L. KELSEY[1]

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ABSTRACT

COBB, K. L., L. K. BACHRACH, G. GREENDALE, R. MARCUS, R. M. NEER, J. NIEVES, M. F. SOWERS, B. W. BROWN, JR., G. GOPALAKRISHNAN, C. LUETTERS, H. K. TANNER, B. WARD, and J. L. KELSEY. Disordered Eating, Menstrual Irregularity, and Bone Mineral Density in Female Runners. *Med. Sci. Sports Exerc.*, Vol. 35, No. 5, pp. 711–719, 2003. **Purpose:** To examine the relationships between disordered eating, menstrual irregularity, and low bone mineral density (BMD) in young female runners. **Methods:** Subjects were 91 competitive female distance runners aged 18–26 yr. Disordered eating was measured by the Eating Disorder Inventory (EDI). Menstrual irregularity was defined as oligo/amenorrhea (0–9 menses per year). BMD was measured by dual x-ray absorptiometry. **Results:** An elevated score on the EDI (highest quartile) was associated with oligo/amenorrhea, after adjusting for percent body fat, age, miles run per week, age at menarche, and dietary fat, (OR [95% CI]: 4.6 [1.1–18.6]). Oligo/amenorrheic runners had lower BMD than eumenorrheic runners at the spine (−5%), hip (−6%), and whole body (−3%), even after accounting for weight, percent body fat, EDI score, and age at menarche. Eumenorrheic runners with elevated EDI scores had lower BMD than eumenorrheic runners with normal EDI scores at the spine (−11%), with trends at the hip (−5%), and whole body (−5%), after adjusting for differences in weight and percent body fat. Runners with both an elevated EDI score and oligo/amenorrhea had no further reduction in BMD than runners with only one of these risk factors. **Conclusion:** In young competitive female distance runners, (i) disordered eating is strongly related to menstrual irregularity, (ii) menstrual irregularity is associated with low BMD, and (iii) disordered eating is associated with low BMD in the absence of menstrual irregularity. **Key Words:** FEMALE ATHLETES, LONG DISTANCE, OSTEOPENIA, OSTEOPOROSIS, AMENORRHEA, OLIGOMENORRHEA, EATING ATTITUDES, EATING DISORDER INVENTORY, FEMALE ATHLETE TRIAD

The "female athlete triad" (33) is the combination of disordered eating, menstrual irregularity, and osteoporosis/osteopenia seen in young female athletes. Disordered eating, which affects as many as two thirds of young female athletes (33), consists of restrictive eating behaviors that do not necessarily reach the level of a clinical eating disorder (2). Women athletes with disordered eating may limit their caloric and/or fat intakes but maintain high training levels, often resulting in a state of chronic energy deficit. Among other adverse consequences, energy imbalance has been linked to depressed estrogen levels, metabolic disturbances, and amenorrhea or oligomenorrhea (2,7,26,34,49,50). Amenorrheic/oligomenorrheic athletes on average have lower bone mineral density (BMD) than eumenorrheic controls (6,7,9,20,22–24,26,28,29,32,34,37–39,46,48,49). This bone deficit may be related to an increased incidence of stress fractures (1,10,30) and may be only partially reversible (16,18,21) putting women at risk for life-long health consequences.

The existence of the female athlete triad is implicit in studies that established a relationship between eating behaviors and menstrual irregularity (2,7,26,34,39,49,50) and those that established a relationship between menstrual irregularity and low BMD (6,7,9,20,22–24,26,28,29,32,34,37–39,45,47,48). How-

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ever, few studies have actually measured menstruation, diet, and BMD simultaneously (7,23,26,34,39), and these studies were conducted, largely, before the female athlete triad was recognized as a distinct syndrome. Therefore, the female athlete triad has yet to be explored as a triad, and the complex relationships among all three components have yet to be established.

In this article, we examine eating attitudes and patterns, menstrual status, and BMD in a group of 91 competitive female distance runners, using data collected at the baseline examination of a randomized controlled trial. We examine the etiology of menstrual irregularity in this population, specifically as it relates to diet and eating behaviors. We address the question of whether low body weight can explain the differences in BMD between eumenorrheic and oligo/amenorrheic athletes, as several researchers have suggested (6,32,45,48) or if menstrual irregularity is associated with BMD independently of low weight. Finally, we examine the relationship between disordered eating and BMD independent from menstrual irregularity, a link that has not been well studied in female athletes.

MATERIALS AND METHODS

We analyzed the baseline cross-sectional data from 91 competitive female long-distance runners, aged 18–25 yr, who enrolled in a randomized controlled trial to examine the effect of oral contraceptives on BMD in female runners.

Subjects. Women were recruited from intercollegiate cross-country teams, postcollegiate running clubs, and road-race participants in the geographic areas of Palo Alto, CA; Los Angeles, CA; Ann Arbor, MI; West Haverstraw, NY; and Boston, MA. To be eligible, women had to run at least 40 miles·wk^{-1} during peak training times, and they had to compete in running races. Additionally, because the women were recruited as part of a randomized trial of oral contraceptives, they could not have used oral contraceptives or other hormonal contraception within 6 months before entering the study; they had to be willing to be randomized to take oral contraceptives or not to take them; and they could have no medical contraindications to oral contraceptive use. All women were required to visit a study physician or student health service staff member before enrollment in the study. Details of the study and testing procedures were explained to each subject, and a written, informed consent was obtained. The experimental 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, and Massachusetts General Hospital.

Questionnaire. A self-administered questionnaire was used to assess training regimen and menstrual history. Women were asked to record the number of miles they ran per week during each competitive season (fall cross-country, winter track, spring track) and the off-season (summer) in the past 12 months. From this information, an average number of miles run per week was calculated for the year before study enrollment.

Women reported the number of menses in the previous 12 months and were classified, accordingly, as eumenorrheic (10 or more cycles in the past year), oligomenorrheic (4–9 menstrual cycles per year), or amenorrheic (fewer than 4 cycles in the past year) (40). Menstrual irregularity has been defined as 0–9 menses per year in previous studies of young women runners (1,28,30,39), and we used that definition here. Both oligomenorrheic and amenorrheic athletes have previously been found to have lower serum estradiol concentrations (24,39,42) and to have lower BMD than eumenorrheic athletes (6,24,38,39,42). In our study population, amenorrheic and oligomenorrheic athletes were similar in BMD, EDI scores, and past menstrual irregularity, justifying their combination into a single group. Women recorded their age at menarche and indicated whether they had had 0, 1–3, 4–9, or 10–13 menses during each year after menarche. Total lifetime menses was calculated using the midpoint of each of these categories. The total number of past years of amenorrhea was calculated by summing the number of years for which women checked "0" or "1–3" periods, excluding the year of menarche and the current year. Past oligomenorrheic years were calculated similarly, except using the category "4–9" periods.

Diet and eating behaviors. An expanded version of the 97-item National Cancer Institute Health Habits and History food frequency questionnaire (4) was used to estimate usual nutrient intake during the prior 6 months. We modified the questionnaire to accommodate the special diets of college-aged female athletes by adding low-fat and nonfat versions of certain foods, vegetarian and vegan foods, ethnic foods, and sports nutrition products (such as Gatorade and Power Bars). The nutrient contents of the added foods were obtained from the U.S. Department of Agriculture Nutrient Database for Standard Reference, release 14 (http://www.nal.usda.gov/fnic/foodcomp), and from food labels. Total intakes of energy, protein, fat, carbohydrates, calcium, phosphorous, iron, fiber, and vitamin C were calculated.

Three subscales (drive for thinness, bulimic tendencies, and body dissatisfaction) of the Eating Disorder Inventory (EDI) were used to screen for subclinical eating disorders (2,12,13). Athletes with subclinical eating disorders have previously been shown to have significantly elevated scores on these three subscales of the EDI (2,11,13,35). Responses on each EDI subscale were scored separately and also totaled.

Physical and bone measurements. At each of the five clinical assessment sites, height and weight were measured using standard stadiometers and balance-beam scales, respectively. Body mass index was calculated as kilograms per square meter.

BMD (g·cm^{-2}) at the left proximal femur, spine, and whole body, and body composition (lean body mass and fat mass) were measured by dual energy x-ray absorptiometry (DXA; QDR 4500A, Hologic). The coefficient of variation for these machines is less than 1.0% for all bone sites (http://www.hologic.com/prod-bd/pdf/spec-4500.pdf). Machines were cross-calibrated using a circulating Hologic anthropomorphic spine phantom. Each site maintained a

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TABLE 1. Mean ± 1 SEM for selected physical and reproductive characteristics, and training variables, by menstrual group.

Characteristic	Menstrual Group	
	Eumenorrheic (N = 58)	Oligo/Amenorrheic* (N = 33)
Age (yr)	21.7 ± 0.3	21.8 ± 0.5
Weight (lb)	129.1 ± 1.9	128.1 ± 2.7
Height (inches)	65.1 ± 0.3	65.4 ± 0.5
BMI (kg·m^{-2})	21.5 ± 0.2	21.1 ± 0.3
Body fat (%)	23.9 ± 0.6	22.7 ± 1.0
Menses in past year (no. cycles)	11.5 ± 0.1	5.0 ± 0.5†
Menarche (age in yr)	12.6 ± 0.2	13.8 ± 0.2‡
Total lifetime menstrual periods (no. cycles)	89.5 ± 4.4	49.5 ± 4.0‡
Started running (age in yr)	14.5 ± 0.5	14.7 ± 0.7
Amount of running (miles·wk^{-1} in past 12 months)	33.0 ± 1.2	39.0 ± 2.2§

* Oligo/amenorrhea was defined as 0–9 menses over the past 12 months.
† $P < 0.0001$, Wilcoxon signed rank test.
‡ $P < 0.0001$, t-test.
§ $P < 0.05$, t-test.

standard quality assurance program. All women were asked to refrain from heavy physical activity 24 h before screening to minimize the effect of fluctuations in hydration status on body composition measurements.

Statistical analyses. Statistical analyses were performed using the SAS statistical package, version 6.12 (SAS Institute, Cary, NC). Means were compared between groups using t-tests for normally distributed variables and the Wilcoxon signed rank test for nonnormally distributed variables. Tukey's multiple comparisons test was used to compare mean BMD across more than two groups. ANCOVA was used to control for age, weight, and body composition.

The relationships between oligo/amenorrhea and training, diet, and physical characteristics were assessed by multiple logistic regression. Multiple linear regression was used to examine the effects of menstrual group and EDI score on BMD when considering EDI score as a continuous variable.

RESULTS

Thirty-six percent of the study sample met criteria for abnormal menses; 26% were oligomenorrheic and 10% were amenorrheic during the past year. Oligo/amenorrheic women were similar to eumenorrheic women in age, weight, height, and body composition (Table 1). The oligo/amenorrheic women had menarche a mean of 1.2 yr later and had had an average of 45% fewer menstrual periods in their lifetime than eumenorrheic women. They also ran an average of 18% more miles per week than eumenorrheic women.

Disordered eating and menstrual irregularity. The women were divided into two groups (normal EDI/elevated EDI) by their total scores on three subscales of the EDI. Women in the highest quartile of total EDI were classified as having elevated EDI scores compared with women in the lowest three quartiles. Women in the elevated EDI group had EDI values comparable to those previously published for patients with anorexia nervosa (12) on the drive for thinness and body dissatisfaction subscales (Table 2). Athletes with elevated EDI scores reported 19% lower daily caloric intakes compared with women with normal EDI scores (Table 2) and reported that they obtained 25% fewer of those calories from fat. The groups were similar in consumption of other nutrients. Although the elevated EDI group had a somewhat lower daily calcium intake, this was proportional to their lower energy intake. Both groups, on average, consumed

TABLE 2. Mean ± 1 SEM for selected diet and nutrition characteristics by eating disorder inventory (EDI) group and, for comparison, a previously published anorectic group.

Characteristic	EDI Group (This Study)		
	Normal EDI (N = 67)	Elevated EDI* (N = 23)	Anorectics (Previously Published)† (N = 155)
EDI scores*			
Drive for thinness subscale (0–21)	1.6 ± 0.3	16.3 ± 0.8‡	13.8 ± 0.5
Bulimia subscale (0–21)	0.8 ± 0.2	3.2 ± 0.7‡	8.1 ± 0.5
Body dissatisfaction subscale (0–27)	3.6 ± 0.5	16.0 ± 1.2‡	15.5 ± 0.6
Total (0–69)	6.0 ± 0.8	35.6 ± 1.8‡	37.4 ± 0.9
Daily nutrient intake			
Calories (kcal·d^{-1})	2346 ± 112	1904 ± 148§	
Fat (% of total calories)	18.7 ± 0.8	14.0 ± 1.0‖	
Protein (% of total calories)	16.4 ± 0.3	16.0 ± 0.8	
Calcium (mg)	1467 ± 96	1300 ± 147	
Fiber (g)	30.6 ± 2.5	26.4 ± 2.2	
Vitamin C (mg)	291 ± 23	247 ± 23	
Iron (mg)	23.6 ± 2.3	20.0 ± 1.9	

* EDI score is the total score from three subscales of the Eating Disorder Inventory (EDI), Garner and Olmstead (12). Elevated scores are defined as the highest quartile (≥23). One subject is missing EDI scores; therefore, she was removed from all analyses involving EDI.
† Average scores for anorexia nervosa patients as published by Garner and Olmstead (12).
‡ Elevated EDI group vs normal EDI group, $P < 0.0001$, Wilcoxon signed rank test.
§ Elevated EDI group vs normal EDI group, $P < 0.05$, t-test.
‖ Elevated EDI group vs normal EDI group, $P < 0.01$, t-test.

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TABLE 3. Mean ± 1 SEM for selected diet and nutrition characteristics by menstrual group.

Characteristic	Menstrual Group: Eumenorrheic (N = 58)	Menstrual Group: Oligo/Amenorrheic (N = 33)
EDI scores*		
Drive for thinness subscale (0–21)	3.3 ± 0.7	9.3 ± 1.4†
Bulimia subscale (0–21)	0.9 ± 0.2	2.3 ± 0.5‡
Body dissatisfaction subscale (0–27)	5.4 ± 0.8	9.3 ± 1.5‡
total (0–69)	9.6 ± 1.5	20.9 ± 3.0†
Daily nutrient intake		
Calories (kcal·d^{-1})	2241 ± 121	2219 ± 147
Fat (% of total calories)	18.7 ± 0.9	15.3 ± 1.0§
Protein (% of total calories)	16.3 ± 0.4	16.3 ± 0.5
Calcium (mg)	1418 ± 106	1437 ± 123
Fiber (g)	28.1 ± 2.2	32.0 ± 3.7
Vitamin C (mg)	283 ± 23	274 ± 28
Iron (mg)	22.2 ± 2.6	23.6 ± 2.1

* EDI score is the total score from three subscales of the Eating Disorder Inventory (EDI), Garner and Olmstead (12).
† Oligo/amenorrheic vs eumenorrheic, $P < 0.005$, Wilcoxon signed rank test.
‡ Oligo/amenorrheic vs eumenorrheic, $P < 0.05$, Wilcoxon signed rank test.
§ Eumenorrheic vs oligo/amenorrheic, $P < 0.05$, t-test.

greater than 1200 mg of calcium per day, which is the U.S. recommended daily allowance for this age group.

Of 23 women with elevated EDI scores, 65% had oligo/amenorrhea, whereas only 25% of 67 women with normal EDI scores did. Though each of the three EDI subscales scores was higher in the oligo/amenorrheic group, the drive for thinness EDI subscale had the strongest association with oligo/amenorrhea (Table 3). Oligo/amenorrheic athletes and eumenorrheic athletes were similar in daily nutrient profiles, though oligo/amenorrheic athletes reported a lower percentage of their calories from fat (Table 3).

Table 4 shows odds ratios for several factors associated with oligo/amenorrhea. Being in the top quartile of EDI score conferred fourfold-increased odds of oligo/amenorrhea. Every 1-yr increase in age at menarche was associated with a more than twofold increase in the odds of oligo/amenorrhea. Odds of oligo/amenorrhea were also increased with greater miles run per week and were decreased with a higher percent body fat and with a higher percent fat intake, but the confidence intervals for these associations included one. Total energy intake was not associated with menstrual disturbances.

EDI score and percent fat intake were modestly negatively correlated (Spearman rank correlation coefficient: r = −0.34) and reduced fat intake may lie in the causal pathway between elevated EDI and oligo/amenorrhea. If dietary fat is removed from the logistic regression model, the OR for elevated EDI score increases from 4.6 to 6.7 (1.8, 25.6), suggesting that low fat intake accounts for some of the association between elevated EDI and menstrual irregularity. EDI score was not correlated with miles run per week (Spearman rank correlation coefficient: r = 0.01), so increased training, though related to oligo/amenorrhea, does not mediate the relationship between elevated EDI scores and oligo/amenorrhea.

TABLE 4. Odds ratios (and 95% confidence intervals) for the association between selected characteristics and oligomenorrhea/amenenorrhea.*

Characteristic	Odds Ratios (95% CI)
Elevated EDI score (≥23 vs <23)	4.56 (1.12, 18.61)
Menarche (each 1 yr later)	2.45 (1.46, 4.11)
Miles per week (every 10 miles)	1.64 (0.96, 2.79)
Dietary fat (every 5% of total calories)	0.61 (0.36, 1.03)
Body fat (every 5%)	0.56 (0.30, 1.07)

* Adjusted for age and each of the other variables in the table by multiple logistic regression.

TABLE 5. Observed and adjusted* spine, hip, and whole body bone mineral density (BMD, g·cm^{-2} ± 1 SEM), by menstrual group.

	Menstrual Group: Eumenorrheic (N = 58)	Menstrual Group: Oligo/Amenorrheic† (N = 33)
Spine BMD		
Observed	1.01 ± 0.013	0.94 ± 0.018‡
Adjusted*	1.00 ± 0.013	0.95 ± 0.019§
Total hip BMD		
Observed	1.00 ± 0.015	0.95 ± 0.020§
Adjusted*	1.00 ± 0.014	0.94 ± 0.020§
Whole body BMD		
Observed	1.12 ± 0.011	1.08 ± 0.015§
Adjusted*	1.11 ± 0.010	1.08 ± 0.015

* Adjusted for age, body weight, percent body fat, EDI score, and age at menarche by analysis of covariance.
† Oligo/amenorrhea was defined as 0–9 menses over the past 12 months.
‡ Eumenorrheic vs oligo/amenorrheic, $P < 0.005$, t-test.
§ Eumenorrheic vs oligo/amenorrheic, $P < 0.05$, t-test.

Menstrual irregularity and BMD. BMD was 5%, 6%, and 3% lower at the lumbar spine, total hip, and whole body, respectively, in oligo/amenorrheic women compared with eumenorrheic women, after adjustment for weight, percent body fat, EDI score, and age at menarche (Table 5). Adjusted and unadjusted BMD values were similar (Table 5); thus, although weight was strongly correlated with BMD at all skeletal sites (the Pearson correlation coefficients were whole body: r = 0.43; hip: r = 0.40; and spine: r = 0.38), lower weight did not account for the association between menstrual irregularity and low BMD in this study population.

Disordered eating and BMD. There were no differences in BMD between women with elevated EDI scores and women with normal EDI scores before adjusting for body size. However, women with elevated EDI scores were heavier (138.5 ± 3.2 lb) and had a higher percent body fat (25.7 ± 1.1%) than those with normal EDI scores (125.8 ± 1.7 lb; 22.8 ± 0.6%). Based on multiple linear regression, we would expect the women with elevated EDI to have 0.038 g·cm^{-2} greater BMD at the spine and hip and 0.028 g·cm^{-2} greater BMD at the whole body due to their higher weight (correcting for their higher percent body fat). Once we adjusted for body weight and composition, women with elevated EDI scores had significantly lower BMD compared with women with normal EDI scores at the spine (−6%), with trends at the hip (−3%) and whole body (−4%).

Menstrual status modified the effect of EDI score on adjusted BMD (Table 6). Among eumenorrheic women, those with elevated EDI scores had significantly lower spine BMD and nonsignificant trends for lower hip and whole body BMD compared with women with normal EDI scores (Table 6). These differences were not attributable to past menstrual history, which was similar in the two groups. Among oligo/amenorrheic women, however, there were no trends for lower BMD among women with elevated EDI compared with women with normal EDI.

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TABLE 6. Observed and adjusted* spine, hip, and whole body bone mineral density ($g \cdot cm^{-2} \pm 1$ SEM) by combined menstrual and eating disorder inventory (EDI) groups.

	Group			
	1	2	3	4
EDI score group†	Normal	Normal	Elevated	Elevated
Menstruation	Eumenorrhea	Oligo/amenorrhea‡	Eumenorrhea	Oligo/amenorrhea
N	50	17	8	15
Mean weight (lb ± SE)	126.3 ± 1.8	123.5 ± 4.3	146.4 ± 5.7	133.4 ± 3.2
Spine BMD ($g \cdot cm^{-2} \pm$ SE)				
Observed	1.02 ± 0.015	0.90 ± 0.024§	0.97 ± 0.027	0.97 ± 0.025
Adjusted*	1.02 ± 0.014	0.93 ± 0.024§	0.91 ± 0.036|	0.96 ± 0.025**
Total hip BMD ($g \cdot cm^{-2} \pm$ SE)				
Observed	1.00 ± 0.016	0.91 ± 0.038|	1.00 ± 0.023	0.98 ± 0.032
Adjusted*	1.01 ± 0.015	0.93 ± 0.027|	0.96 ± 0.040	0.96 ± 0.027
Whole-body BMD ($g \cdot cm^{-2} \pm$ SE)				
Observed	1.12 ± 0.013	1.07 ± 0.018	1.12 ± 0.029	1.09 ± 0.016
Adjusted*	1.13 ± 0.010	1.08 ± 0.019	1.07 ± 0.028	1.08 ± 0.020

* Adjusted for body weight, percent body fat, age, and age at menarche by analysis of covariance.
† EDI score is the total score from three subscales of the Eating Disorder Inventory (EDI), Garner and Olmstead (12). Elevated scores are defined as the highest quartile (≥23). One subject is missing EDI score; therefore, she was removed from all analyses involving EDI.
‡ Oligo/amenorrhea was defined as 0–9 menses over the past 12 months.
§ Group 1 vs group 2, $P < 0.005$, Tukey's test for comparing multiple group means.
| Group 1 vs group 2; group 1 vs group 3, $P < 0.05$, Tukey's.
** Group 1 vs group 4, $P < 0.10$, Tukey's.

Multiple linear regression analysis confirmed the significant interactions between menstrual irregularity and total EDI score (0–69) on BMD at all skeletal sites (Fig. 1). Among eumenorrheic runners, EDI score is inversely related to BMD. However, among oligo/amenorrheic women, BMD is not related to EDI score. Similarly, among women with low EDI scores, oligo/amenorrheic women had lower BMD than eumenorrheic women, but, among women with high EDI scores, menstrual irregularity was not related to BMD.

DISCUSSION

This study confirms the existence and significance of the "female athlete triad," a syndrome composed of three interrelated conditions: disordered eating, menstrual irregularity, and osteopenia/osteoporosis (33). (i) We confirm that disordered eating in female runners is correlated with oligo/amenorrhea; (ii) we demonstrate that the association between oligo/amenorrhea and low BMD in female runners is independent of body weight and body composition; and (iii) we provide novel evidence that disordered eating is associated with low BMD in eumenorrheic women runners.

The women in our study who were in the highest quartile of total EDI score had similar values on two EDI subscales to patients with diagnosed anorexia nervosa (12); they also had similar or slightly higher EDI scores than women athletes with established subclinical eating disorders (2,11,13,35). The EDI measures only attitudes about food and body size. However, we verified that elevated scores on the EDI translated to actual eating practices; women with elevated EDI scores reported lower total energy intakes (by approximately 19% d^{-1}) and lower percent fat intakes (by approximately 25% d^{-1}) than women with normal EDI scores. None of the 91 women in our study indicated that she was dieting to lose weight (data not shown), suggesting that this observed dietary restriction

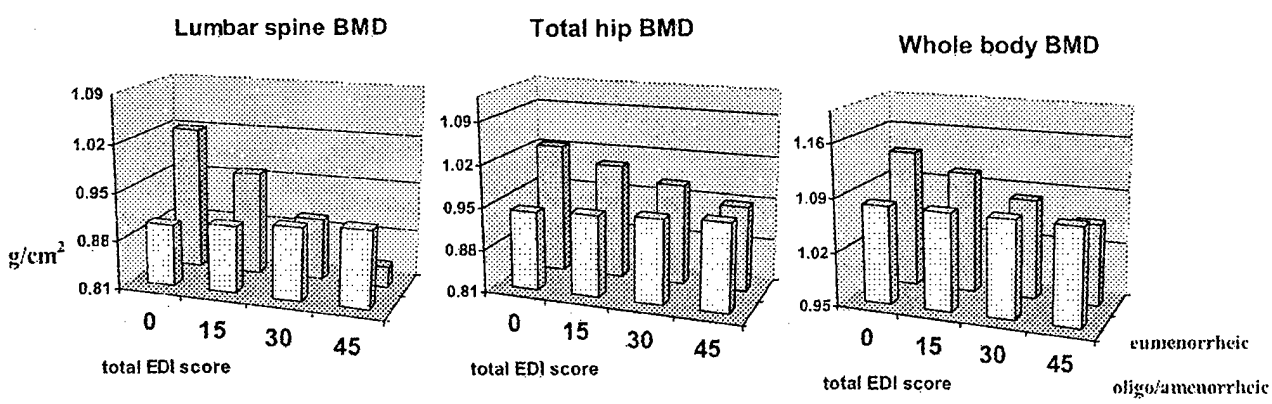

FIGURE 1—Mean BMD ($g \cdot cm^{-2}$) at the spine, hip, and whole body by menstrual status and varying levels of total EDI score (from multiple linear regression). The means are based on the following multiple linear regression results (adjusted for age, weight, and percent body fat). Regression coefficients (standard error)—menstrual status −0.12 (0.33), EDI score (0–69) −0.004 (0.001), interaction: menstrual status × EDI score +0.0043 (0.002); menstrual status −0.089 (0.036), EDI score (0–69) −0.002 (0.001), interaction: menstrual status × EDI score +0.002 (0.002); menstrual status −0.060 (0.025), EDI score (0–69) −0.002 (0.001), interaction: menstrual status × EDI score +0.002 (0.001). (Menstrual status equals 1 if the woman is oligo/amenorrheic and 0 if the woman is eumenorrheic.)

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represents long-term, chronic restriction, rather than temporary attempts to lose weight.

Women with elevated EDI scores had a fourfold increase in risk for oligo/amenorrhea, when controlling for other factors. Chronic energy deficit has previously been implicated in the etiology of athletic amenorrhea (2,7,8,19,25,26,31,34,44,46, 49,50). Menstruation requires a small amount of energy, and halting menstruation may be an adaptive energy-conservation mechanism. In our study, the caloric restriction of the elevated EDI group did not appear to explain their excess oligo/amenorrhea. Rather, our data suggest that the development of oligo/amenorrhea in these women may have been mediated in part by a reduction of dietary fat intake. Though dietary fat, independent of total energy intake, has previously been shown to influence the menstrual cycle in nonathletic women (15,27), this association has not previously been demonstrated in female athletes and needs verification in further studies. We speculate that women with disordered eating may have more aberrant patterns of eating, such as binging and fasting cycles; although total energy intake may not be altered, these patterns have potential to alter metabolic pathways, hormone levels, and, ultimately, menstruation (3,5,14).

We found that oligo/amenorrheic runners ran more miles per week than eumenorrheic runners. Therefore, although energy intake was not associated with menstrual irregularity, oligo/amenorrheic runners may have had greater energy imbalance due to a higher energy expenditure. Energy imbalance may cause hypothalamic dysfunction, which disrupts both menses and bone remodeling (50).

We confirm previous research that shows that delayed menarche is a strong predictor of later menstrual irregularity (6,9,29,34). Delayed menarche was correlated with menstrual irregularity in both women who initiated training before menarche ($N = 22$) and women who started training after menarche ($N = 69$); thus, prior training does not explain the delay in menarche in the oligo/amenorrheic runners. This finding suggests that some women may be predisposed to menstrual irregularity, which may account for the existence of a subset of women with low total EDI scores (6.8 ± 1.8) and putatively sufficient caloric intake (2443 ± 210) who still lost their periods. Alternatively, disordered eating patterns may have developed premenarche and pretraining in certain women which contributed to a delay in the onset of menarche and has subsequently continued to disrupt the menses. Our data were insufficient to evaluate this hypothesis.

We confirm numerous reports of reduced BMD in oligo/amenorrheic female athletes, with the largest and most consistent effects having been demonstrated at the lumbar spine. The BMD differences between oligo/amenorrheic and eumenorrheic women that we observed were not attributable to differences in body weight, body composition, or EDI score. The magnitude of the difference was important; 6% of the oligo/amenorrheic young women had spine BMD values that would be considered osteoporotic, that is, a BMD value less than 2.5 SD below young adult BMD (17) (<0.772 $g \cdot cm^{-2}$ as measured with the Hologic densitometer). Forty-eight percent were osteopenic at the spine, a BMD between −1 SD and −2.5 SD below the young adult value (0.772–0.937 $g \cdot cm^{-2}$). In contrast, none of the eumenorrheic athletes were classified as being osteoporotic and only 26% were classified as being osteopenic based on spine BMD values.

Women with elevated EDI scores had low BMD for their weight. We attempted to determine whether low BMD among women with elevated EDI scores was due to oligo/amenorrhea or whether the disordered eating had an independent effect on bone. Eight women with high EDI scores were currently eumenorrheic and had no history of amenorrhea or delayed menarche. BMD was significantly lower at the spine and was lower at the hip and whole body in this subgroup compared to eumenorrheic women with normal EDI, after adjusting for weight, body composition, age, and age at menarche. Eumenorrheic women with elevated EDI were heavier and had more body fat than all other subgroups; they also started running at a later age (18.3 ± 1.3 yr). Possibly, this group was resistant to loss of menses despite their aberrant eating because their menstrual cycles were established before they started running and/or because they were not as thin (41). It is also possible that these women have subclinical menstrual abnormalities, such as anovulatory cycles and shortened luteal phase, which have been associated with spinal bone density losses (36).

In our study population, having both disordered eating and oligo/amenorrhea was no more detrimental for bone than having either disorder alone. The numbers in some of our groups were small, however, and this observation should be verified in further studies. That there was no excess risk suggests that the two disorders share causal pathways. Both oligo/amenorrhea and disordered eating have been associated with low serum estrogen concentrations (25,49,50), which would be expected to have an adverse effect on BMD. Accordingly, disordered eating may result in estrogen deficiency or other sex hormone changes, which then may lead both to bone loss and menstrual irregularity. Menstrual irregularity and disordered eating may also contribute to bone loss, or lack of bone formation, through metabolic changes (49).

Figure 2 summarizes risk factors for low BMD and menstrual irregularity, as well as possible pathways connecting elements of the female athlete triad. Disordered eating may decrease menstruation and BMD through estrogen deficiency and through alterations of other metabolic pathways (43). Low weight is an established independent risk factor for low BMD; in this study population, women weighing less than 115 lb had fivefold-increased odds of being osteopenic at any skeletal site (OR [95% CI]: 5.3 [1.6–17.0]). Some previous studies also found an association between low weight and oligo/amenorrhea (26,6,32,45), though this study did not. Menstrual irregularity may be related to low BMD through mechanisms other than reduced estrogen (36,49). Training factors and delayed menarche have direct influences on the menstrual cycle and on BMD.

It is difficult to explain why the athletes with elevated EDI scores were heavier than the women with low EDI scores even though they reported lower energy and fat intakes. We would expect women with subclinical eating disorders to have lower weight and body fat, but this was not the case in our study. Possibly, heavier women are more prone to eating disorders

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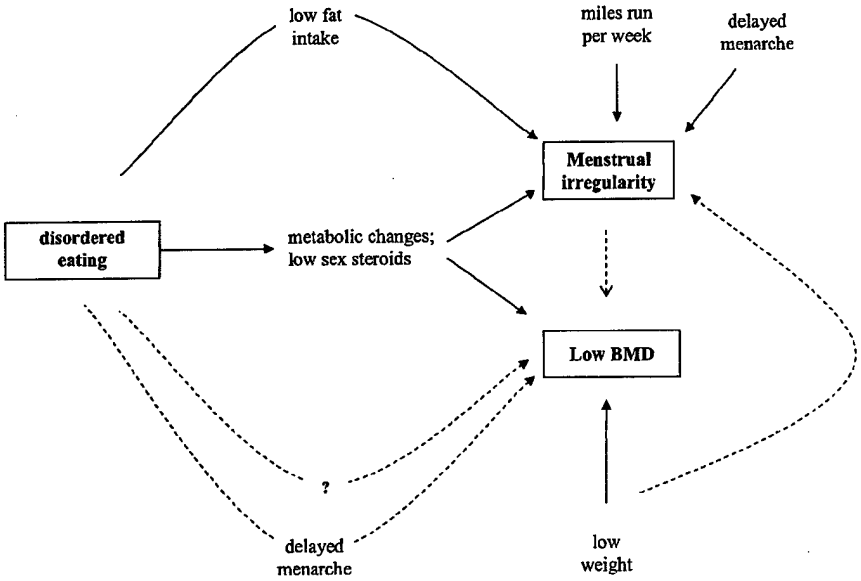

FIGURE 2—Proposed pathways among disordered eating, menstrual irregularity, and low BMD. *Solid lines* represent associations suggested by the current study; *dashed lines* represent associations suggested by previous studies.

because they are more dissatisfied with their natural body type. Some of these athletes with higher EDI scores may have had bulimic behaviors that could have explained the higher weights. Alternatively, the EDI scale may identify women in the early stages of an eating disorder but may miss women in the later stages, when they have already lost weight. We speculate that some of the women in the thinnest subgroup, the oligo/amenorrheic women with low EDI scores, may have had eating disorders but may be in denial and/or may currently be satisfied with their bodies because they have succeeded in reaching a low weight. We further recognize that the division of the population into normal EDI/elevated EDI is simplistic. There is a continuum of disordered eating behavior, but we have artificially imposed a division on that continuum. However, multiple linear regression analysis, in which we treat EDI as a continuous variable, confirms our categorical data results.

Our results are limited by the fact that menstrual status, training history, and diet were assessed by subject recall. We recognize that recall menstrual histories cannot be as accurate as those obtained by prospective record keeping. However, we believe that these menstrual histories were reasonably accurate, as the subjects were young, had short histories to recall, and, as competitive athletes, tend to be aware of their overall health. Many competitive runners keep detailed logs of their training and their miles run per week, which may have helped to minimize recall errors on the training section of our questionnaire. Finally, we recognize the limitations of food frequency questionnaires but note that the questionnaire that was employed was specifically modified to accommodate the special diets of college-aged female athletes. Prospective studies are needed confirm and further explore our findings.

Additionally, we may have missed women with subclinical menstrual abnormalities, such as anovulatory cycles and shortened luteal phase, because we assessed menstrual irregularity by questionnaire rather than laboratory testing. Measurement of serum hormone levels would have provided additional information about the role of sex hormones. Accurate measurements of energy expenditure using doubly labeled water would have helped us to assess the role of energy balance in menstrual irregularity and low BMD. However, such measurements were outside of the scope and resources of the present study.

A further limitation of our findings is that eating attitudes and body image perception may influence the reporting of food intake (8). We cannot rule out the possibility that women with aberrant attitudes about body and food systematically underreport intake. As they are hyperconscious about their food intake, they may report what they think they should be eating rather than what they actually eat. Food frequency questionnaires, despite other limitations, may help minimize this tendency, as the total amounts of daily food, calories, and fat being reported are not readily quantifiable to the athlete.

In conclusion, we provide evidence that confirms the female athlete triad. We also conclude that the female athlete triad may be more hidden than previously realized. The women in this study were not excessively lean; indeed, amenorrheic women averaged more than 22% body fat and women with elevated EDI scores averaged more than 25% body fat. Thus, those with the triad may not be readily discernible to a coach or a physician. However, both amenorrhea and disordered eating significantly affect bone, even in the absence of the other. Because there is a high prevalence of osteopenia in this population that may have serious life-long consequences, we recommend that all competitive women endurance athletes, particularly those in sanctioned collegiate programs, receive screening for eating disorders and menstrual irregularity and education about the female athlete triad.

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Abstract

Background: Women who participate in endurance activities often experience the female athlete triad, a condition characterized by disordered eating, menstrual irregularities, and low bone mineral density (BMD).

Objective: This investigation examines the nutritional factors and eating behaviors associated with menstrual irregularity and low bone mineral density in young female distance runners

Design: This study is a cross-sectional analysis of 136 competitive female distance runners, aged 18-25 years. An expanded version of the 97-item National Cancer Institute Health Habits and History food frequency questionnaire was used to estimate usual nutrient intake. Disordered eating was measured by the Eating Disorder Inventory (EDI). Menstrual irregularity was classified as amenorrhea (0-3 menses per year) or oligomenorrhea (4-9 menses per year). Bone mineral density was measured by dual x-ray absorptiometry (DXA).

Results: Scoring in the highest quartile on the EDI conferred more than a 15-fold increase in risk of amenorrhea [OR=15.53 (95% CI: 3.26,73.88)], and more than a five-fold increase in risk of oligomenorrhea [OR=5.87(95% CI: 2.11,16.33)], after adjustment for age, age at menarche, and body mass index (BMI). Every 10-gram increase in fiber intake, also adjusted for total caloric intake, was associated with an 89% higher risk of amenorrhea [OR=1.89 (95% CI: 1.13, 3.15)], while every 5% increase in total calories from dietary fat decreased risk of amenorrhea by 52%[OR=0.48 (95% CI: 0.25,0.92)]. Every 5% increase in percent of total calories from fat also decreased risk oligomenorrhea by 31% [OR=0.69 (95% CI: 0.48,0.99)].

None of the energy-adjusted nutrient intakes explained more than 2% of the variance in BMD at the spine, hip, and whole body. However, in oligo/amenorrheic women, being in the top quartile of energy-adjusted calcium intake was associated with lower BMD at all three skeletal

sites. Being in the top quartile of energy-adjusted protein intake was also associated with a trend toward decreased BMD in oligo/amenorrheic women, and, to a lesser extent, in eumenorrheic women

Conclusions: We confirm the inter-relatedness of disordered eating and menstrual irregularities in young female distance runners. While disordered eating and fiber intake were associated with an increased risk and percent dietary fat with a decreased risk of oligomenorrhea and/or amenorrhea, BMD was not influenced strongly by one particular nutrient. Dietary interventions to treat the female athlete triad should focus on restoring regular menstrual cycle, as normal menstrual functioning is strongly associated with adequate BMD.