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Dietary Fat, Fiber, and Carbohydrate Intake and Endogenous Hormone Levels in Premenopausal Women

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Abstract The authors conducted a cross-sectional study to investigate the associations of fat, fiber, and carbohydrate intake with endogenous estrogen, androgen, and insulin-like growth factor (IGF) levels among 595 premenopausal women. Overall, no significant associations were found between dietary intake of these macronutrients and plasma sex steroid hormone levels. Dietary fat intake was inversely associated with IGF-I and IGF-binding protein 3 (IGFBP-3) levels. When substituting 5% of energy from total fat for the equivalent amount of energy from carbohydrate or protein intake, the plasma levels of IGF-I and IGFBP-3 were 2.8% (95% confidence interval [CI] 0.3, 5.3) and 1.6% (95% CI 0.4, 2.8) lower, respectively. Animal fat, saturated fat, and monounsaturated fat intakes also were inversely associated with IGFBP-3 levels ($P<0.05$). Carbohydrates were positively associated with plasma IGF-I level. When substituting 5% of energy from carbohydrates for the equivalent amount of energy from fat or protein intake, the plasma IGF-I level was 2.0% (95% CI 0.1, 3.9%) higher. No independent associations between fiber intake and hormone levels were observed. The results suggest that a low-fat/high-fiber or carbohydrate diet is not associated with endogenous levels of sex steroid hormones, but it may modestly increase IGF-I and IGFBP-3 levels among premenopausal women.

Keywords Gonadal steroid hormones · Insulin-like growth factor I · Insulin-like growth factor binding protein 3 · Dietary fats · Dietary fiber · Dietary carbohydrates

Abbreviations

BMI	Body mass index
CI	Confidence interval
DHEA	Dehydroepiandrosterone
DHEAS	DHEA sulfate
FFQ	Food frequency questionnaire
IGF	Insulin-like growth factor
IGFBP	IGF-binding protein
NHS	Nurses' health study
SHBG	Sex hormone binding globulin

Endogenous sex hormone levels play an important role in the etiology of endometrial [1–4], breast [5–12], and ovarian [13, 14] cancers. Insulin-like growth factors (IGFs) are important in regulating cell proliferation, differentiation, apoptosis, and transformation, and IGF binding proteins (IGFBPs) can enhance or inhibit the effect of IGFs [15–18]. Circulating levels of IGF-I and IGFBP-3 have been associated with risk of prostate [19–23], breast [24–28], colorectal [29, 30], and lung cancer [22, 25, 31–33] in some but not all studies.

Although some epidemiological studies have suggested that dietary fat or fiber may be related to the risk of

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endometrial [34–37], ovarian[38–41], and colon[42–44] cancers, the evidence has not been consistent. A primary mechanism by which these factors might influence risk is through the modulation of hormone levels. A low-fat/high-fiber diet is thought to reduce plasma estrogen levels by increasing the fecal excretion of estrogens [45, 46]. Energy and protein intakes appear to increase IGF levels [47], but little is known about the effect of dietary fat, fiber, or carbohydrates on the IGF axis, and results from previous studies are inconsistent[48–51].

Data from dietary fat and fiber in relation to sex hormone and IGF levels among premenopausal women are particularly limited. To investigate the relationship of dietary fat and fiber intake with endogenous hormone levels, we conducted a cross-sectional study among premenopausal participants in the Nurses' Health Study (NHS) II cohort, for whom blood samples were timed according to the menstrual cycle.

Materials and Methods

Study Population

The NHS II is a prospective cohort study established in 1989, when 116,671 registered nurses in 14 states, 25–42 years of age at that time, completed a baseline questionnaire about their medical histories and lifestyles. Subsequent questionnaires requesting updated information on risk factors and medical events have been mailed every 2 years. The follow-up rate in this cohort between 1989 and 2003 was over 95% of potential person-years.

From 1996 to 1999, the NHSII participants meeting the following criteria were invited to send us a blood sample, timed within the menstrual cycle: (a) still having menstrual periods, (b) had not used oral contraceptives or other hormones in the past 6 months, (c) had not been pregnant or lactating in the previous 6 months, and (d) had no prior cancer diagnosis. These women provided an initial 15-ml blood sample drawn on the third to fifth day of their menstrual cycle (follicular blood draw) and a second 30-ml blood sample drawn 7–9 days before the anticipated start of their next cycle (luteal blood draw). To accurately determine when in the luteal phase the second blood was collected, women were asked to mail us a follow-up postcard documenting when their next menstrual cycle began. A total of 19,092 women provided timed blood samples. The women who did not meet the criteria above or declined to give a timed blood sample were asked to provide a one-time 30-ml untimed blood sample. In total, 11,090 women provided the untimed samples. Menopausal status was ascertained via questionnaire at the time of blood collection.

Follicular samples were placed in a refrigerator for 8–24 h and then aliquoted by the participant and frozen until the luteal blood collection. Both the follicular and luteal blood samples were shipped via overnight courier and with an ice-pack to our laboratory where the luteal blood sample was processed and aliquoted into plasma, red blood cell, and white blood cell components. The untimed samples were processed and stored in a similar manner. We previously showed that hormone levels are stable in whole blood processed in this manner [52].

Women included in this analysis are the premenopausal controls of a nested case–control study of breast cancer (n=482) (detailed in [53–56]) and the subjects of a previously published study to assess hormone reproducibility over time in premenopausal women (n=113) [57]. We used the first blood sample provided in this study. Among these 595 women, 502 had both follicular and luteal samples, two had only luteal samples, and 93 had untimed samples.

Assessment of Intake of Fat, Fiber, and Carbohydrates

A semi-quantitative food frequency questionnaire (FFQ) was collected in 1991 and every 4 years since (1995, 1999, and 2003). The questionnaire queried average intake over the last year of 133 foods, with frequency of intake ranging from never or almost never to ≥6 times per day. The validity of FFQs similar to those used in the NHS II cohort has been described elsewhere [58–60]. In the NHS cohort, the correlation coefficients between energy-adjusted total fat, fiber, and carbohydrates from FFQs and the average of four 1-week diet records at 3-month intervals were 0.53, 0.58, and 0.61, respectively. For saturated and polyunsaturated fats, the coefficients were 0.59 and 0.48 [59]. A previous study done in the NHS cohort also showed that plasma triglyceride levels across the categories of energy intake were comparable to those found in an intervention study, providing objective evidence that the FFQs used in this study are sensitive to dietary fat [61].

The calculation of dietary intake was based on the USDA database [62]. We evaluated total fat, animal fat, vegetable fat, specific fatty acids (saturated fat, monounsaturated fat, polyunsaturated fat, and trans fat), total fiber, fiber from cereals, vegetables, fruits, cruciferous vegetables, and legumes, and carbohydrates. Average dietary intake, calculated using data from the 1995 and 1999 FFQs (the dietary questionnaires collected closest in time to the blood draw), was used in the analyses to reduce measurement error.

Laboratory Assays

Samples were assayed in three batches. Estradiol, estrone, estrone sulfate, and testosterone were measured at Quest

Diagnostics (San Juan Capistrano, CA) by radioimmunoassay following extraction and celite column chromatography. Progesterone, androstenedione, sex hormone binding globulin (SHBG), dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEAS) were measured at the Royal Marsden Hospital (London, UK) by radioimmunoassay (SHBG was measured using IMMULITE Diagnostic Products), and IGF-I and IGFBP-3 were measured at the Lady Davis Research Institute, M. Pollak's Laboratory (Montreal, CA) by ELISA (Diagnostic Systems Laboratory, TX). Different hormones were measured in follicular, luteal, and untimed samples. (Appendix 1). In each batch, we included replicate plasma samples to assess laboratory precision. All between-batch coefficients of variation were less than 10%, except for follicular estradiol (12%), SHBG (13%), and progesterone (14%).

Data Analyses

Since estrogen levels fluctuate during the menstrual cycle, follicular and luteal hormone levels were analyzed separately, and only women with timed samples were included in these analyses. Because levels of SHBG, androgens, and IGFs fluctuate only modestly [57], we used both timed and untimed samples in these analyses. For women with both follicular and luteal hormone values (i.e., for SHBG, androstenedione, and testosterone), we used their average hormone level. We identified statistical outliers based on the generalized extreme studentized deviate many-outlier detection approach [63]. Two to four observations were deleted for luteal estradiol, luteal free estradiol, luteal estrone, and luteal progesterone. Also, in the analyses of luteal estrogens and progesterone, anovulatory women (luteal progesterone <400 ng/dl) were excluded (n=53).

The associations between dietary fiber and percentage of energy from fat and carbohydrate intakes and hormone levels were assessed by linear regression. Statistical analyses were performed with SAS software (SAS Institute, Cary, NC) using PROC MIXED procedure. The independent variables, types of dietary fat, fiber, and carbohydrates, were continuous. The robust variance was used to ensure valid inference even if the regression residuals were not normally distributed. The difference in plasma hormone levels was modeled on the natural logarithm scale. Solving $(1-e^{-\beta\Delta})\times 100$, where β is the estimated regression slope and Δ is the specified incremental difference in macronutrient intake, represents the percentage difference in that hormone level. The mean hormone levels across the quintiles of nutrients intake were computed to show the absolute difference in plasma hormone levels.

The covariates included in the regression model were age, fasting status, laboratory batch, luteal day (for luteal levels), time of day of blood draw, body mass index (BMI) at age 18, BMI at blood collection, smoking status, parity, and level of physical activity in 1997, total energy and alcohol intakes (average of 1995 and 1999 FFQs), age at menarche, and height (see Table 3 for variable definitions). In the multivariate models, the coefficients for fat and carbohydrates can be interpreted as substitution of a percentage of energy from fat/carbohydrates for an equal percentage from other sources of energy.

Results

After exclusions, 595 premenopausal women were included in the analysis. The mean age at blood draw was 43.4, and mean BMI was 25.2 kg/m^2 in 1997 (see Table 1). Of the women included in the analysis, 69.9% never smoked and ever smokers smoked an average of 10.1 pack-years. The average intake of total energy per day was 1,842 kcal, 29.1% of which was from fat, 51.3% from carbohydrates, and 18.1% from protein. On average, these women consumed 20 g of dietary fiber and 4.2 g of alcohol. Median plasma hormone levels and their 10th–90th ranges are shown in Table 2.

In Table 3, we present the geometric means of hormones across categories of percentage energy from fat adjusted to the mean levels of the covariates, as well as the estimated percentage difference in plasma hormone levels from substituting 5% of energy from total fat for the equivalent amount of energy from carbohydrate or protein. Unadjusted and multivariable adjusted models had similar results, so only results of multivariable models are shown. Overall, we found no significant association between

Table 1 Characteristics of women included in the study

Characteristic	Mean (SD)
Age at blood draw, years	43.4 (3.9)
BMI at 18, kg/m^2	21.0 (2.7)
BMI in 1997, kg/m^2	25.2 (5.7)
Parity among parous women	2.3 (0.9)
Ever-smoked,%	30.1 (45.9)
Pack-years among smokers	10.1 (7.7)
Energy intake, kcal/day[a]	1842 (496)
Alcohol intake, g/day[a]	4.2 (6.6)
Fiber intake energy-adjusted, g/day[a]	20.2 (5.8)
Percentage of energy from protein,%[a]	18.1 (2.8)
Percentage of energy from fat,%[a]	29.1 (5.6)
Percentage of energy from carbohydrate,%[a]	51.3 (6.8)

[a] Average of 1995 and 1999 reported intake

Table 2 Plasma hormone levels

	Number	Median	10th–90th Percentile
Estradiol (pg/ml)			
Follicular	460	46.0	21.0, 98.0
Luteal	408	125	79.0, 203
Free estradiol (pg/ml)			
Follicular	436	0.6	0.3, 1.1
Luteal	399	1.6	0.9, 2.6
Estrone (pg/ml)			
Follicular	464	40.0	25.0, 63.0
Luteal	442	80.0	50.0, 124
Estrone sulfate (pg/ml)			
Follicular	449	667	291, 1514
Luteal	402	1478	573, 3,235
Progesterone (ng/ml)	447	1509	740, 2,639
SHBG[a] (nmol/l)	593	63.1	31.5, 109
Androstenedione[a] (ng/ml)	593	106	63.0, 176
Testosterone[a] (ng/ml)	588	24.0	14.5, 37.0
Free testosterone[a] (ng/ml)	588	0.2	0.1, 0.4
DHEA[b] (ng/dl)	477	642	344, 1133
DHEA sulfate[b] (μg/dl)	477	79.5	39.1, 142
IGF-I[b] (ng/ml)	595	245	147, 349
IGFBP-3[b] (ng/ml)	595	4,769	3,297, 5,911

[a] Average of follicular and luteal timed values for women with both

[b] Concatenation of luteal values and untimed values

percentage energy from total fat and plasma levels of estrogens, progesterone, SHBG, or androgens. Although there was no linear relationship between total fat and plasma follicular levels, levels of follicular estradiol were significantly higher among the first category (percentage of energy from total fat ≤20%) versus all other categories (P=0.01). A higher percentage of energy from total fat was related to modestly lower levels of IGF-I and IGFBP-3, but not the IGF-I/IGFBP-3 ratio. For a 5% increase in energy from total fat intake, plasma IGF-I levels were 2.8% lower (95% confidence interval [CI] 0.3%, 5.3%) and plasma IGFBP-3 levels 1.6% lower (95% CI 0.4%, 2.8%). We also found that IGF-I levels among those with ≤20% of energy from total fat were significantly higher than levels in all other categories (P<0.01).

We also estimated the percentage difference in plasma hormone levels from substituting 1% of energy from specific types of fat for the equivalent amount of energy from other sources as replacement (Table 4). As observed with total fat, most hormone levels were not related with any fat type. Saturated fat was inversely associated with IGF-I levels (1.2% decrease; 95% CI 0, 2.4%). IGFBP-3 also was inversely associated with intakes of animal fat, saturated fat, and monounsaturated fat. For a 1% increase in energy from animal fat, saturated fat, and monounsaturated fat, plasma IGFBP-3 levels decreased 0.4% (95% CI 0.1,% 0.7%), 0.8% (95% CI 0.2%, 1.4%), and 0.6% (95% CI 0.1%, 1.2%), respectively. Similarly, we did not find significant associations between intake of fat types and the IGF-I/IGFBP-3 ratio.

Overall, the percentage of energy from carbohydrates was not related to estrogen, progesterone, androgen, or SHBG levels (Table 5). We observed a significant positive relationship between percentage of energy from carbohydrates and IGF-I levels. With substitution of 5% of energy from carbohydrates for the equivalent amount of energy from fat or protein, plasma IGF-I levels increased by 2.0% (95% CI 0.1, 3.9%).

We also observed no substantial difference in mean hormone values across categories of total fiber intake (Table 6). Similarly, we did not find significant relationships between levels of any hormone and total fiber intake, except for androstenedione. A 5-g increment of total fiber intake was related to a 3.0% decrease in androstenedione levels (95% CI 0.1%, 5.9%). Also, we did not find significant associations between plasma hormone levels

Table 3 Geometric means across categories of percentage of energy from total fat and estimated percentage difference in plasma hormone levels from substituting 5% of energy from total fat for the equivalent amount of energy from carbohydrate or protein intake

N (range)	% Energy from total fat					% Difference in hormone levels	
	≤20%	20.1–25%	25.1–30%	30.1–35%	>35%		
	15–25	70–114	143–215	100–148	63–90		
	Geometric means					Estimate	95% CI
Estradiol (pg/ml)							
Follicular	61.3	40.4	50.1	46.6	43.1	−1.1	−5.7, 3.2
Luteal	128	122	116	124	118	−0.1	−0.8, 0.5
Free estradiol (pg/ml)							
Follicular	0.7	0.5	0.6	0.6	0.5	−1.0	−5.5, 3.3
Luteal	1.6	1.5	1.5	1.5	1.4	−0.3	−1.0, 0.3
Estrone (pg/ml)							
Follicular	39.0	37.5	41.8	38.9	41.7	1.3	−1.9, 4.5
Luteal	75.4	75.8	74.6	75.2	75.4	−0.1	−0.7, 0.5
Estrone sulfate (pg/ml)							
Follicular	752	619	679	697	666	0.8	−4.5, 5.8
Luteal	1,336	1,401	1,332	1,322	1,368	−0.0	−1.2, 1.1
Progesterone (ng/ml)	1,229	1,369	1,350	1,484	1,176	−0.3	−1.0, 0.5
SHBG (nmol/l)	65.1	57.0	60.3	62.2	64.7	2.2	−1.0, 5.3
Androstenedione (ng/ml)	105.1	97.5	103.3	106.5	109.6	2.6	−0.4, 5.4
Testosterone (ng/ml)	24.1	21.8	23.8	23.4	24.6	1.6	−1.2, 4.3
Free testosterone (ng/ml)	0.2	0.2	0.2	0.2	0.2	0.1	−3.0, 3.1
DHEA (ng/dl)	587	626	645	650	634	1.5	−2.1, 4.9
DHEA sulfate (μg/dl)	66.1	75.4	77.9	78.0	77.2	1.3	−2.9, 5.3
IGF-I (ng/ml)	275	229	237	229	220	−2.8	−5.3, −0.3*
IGFBP-3 (ng/ml)	4,655	4,622	4,644	4,585	4,399	−1.6	−2.8, −0.4*
IGF-I/IGFBP-3	0.06	0.05	0.05	0.05	0.05	−1.1	−3.2, 0.9

[a] Adjusted for age at blood draw (continuous), fasting status [<8, ≥8 h], laboratory batch, day of luteal blood draw (for luteal hormones, 3–7, 8–28 days, missing/untimed sample), smoking status (pack years, never, 1–10, 11–20, 20+years], BMI in 1997 (continuous), BMI at age 18 (continuous), total energy intake (average of 1995 and 1999, continuous), alcohol intake (average of 1995 and 1999, continuous), parity (nulliparity, 1 and age at first birth <25, 1 and age at first birth≥25, 2 and age at first birth <25, 2 and age at first birth≥25, 3+ and age at first birth <25, 3+ and age at first birth≥25], age at menarche [<12, 12, >12], and height (continuous).

*$P<0.05$

and fiber from cereals, fiber from vegetables, fiber from fruits, fiber from cruciferous vegetables, and fiber from legumes (data not shown).

Discussion

In this cross-sectional study among premenopausal women, we did not find significant associations between dietary fat, fiber, or carbohydrates and plasma levels of estrogens, progesterone, androgens, or SHBG. However, we observed modest but significant inverse associations between the percentage of energy from dietary fat and plasma levels of both IGF-I and IGFBP-3 and a positive association between the percentage of energy from carbohydrates and plasma IGF-I levels.

Results from the few prior studies of premenopausal women have been inconsistent, although differences in study design (e.g., the intervention used, hormones measured) complicate comparisons. In a meta-analysis of ten intervention studies conducted among premenopausal women, subjects changed from a high-fat (29–46% of fat in calories) to a low-fat (12–25% of fat calories) diet typically for 2 or 3 months, and overall a statistically significant 7.4% reduction in serum estradiol level was observed [64]. However, only one of the ten

Table 4 Estimated percentage difference in plasma hormone levels from substituting 1% of energy from types of fat for the equivalent amount of energy from other sources as replacement

	% Difference in hormone levels									
	Animal fat		Vegetable fat		Saturated fat		Monounsaturated fat		Polyunsaturated fat	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Estradiol (pg/ml)										
Follicular	−0.4	−1.5, 0.7	0.1	−1.4, 1.5	−0.1	−2.3, 2.0	−0.5	−2.6, 1.6	−1.8	−5.9, 2.3
Luteal	0.1	−0.8, 0.9	−0.5	−1.5, 0.5	0.1	−1.7, 1.7	−0.4	−2.0, 1.1	−1.0	−4.0, 1.8
Free estradiol (pg/ml)										
Follicular	0.1	−1.2, 1.0	−0.4	−1.8, 1.1	−0.3	−2.4, 1.7	−0.4	−2.6, 1.7	−1.1	−5.0, 2.7
Luteal	−0.1	−1.0, 0.7	−0.8	−1.8, 0.3	−0.6	−2.3, 1.0	−0.9	−2.5, 0.6	−1.0	−4.1, 2.1
Estrone (pg/ml)										
Follicular	0.2	−0.6, 1.0	0.4	−0.6, 1.4	0.4	−1.2, 2.0	0.6	−0.9, 2.1	1.1	−1.7, 3.8
Luteal	−0.1	−0.8, 0.7	−0.1	−1.0, 0.8	−0.3	−1.8, 1.1	−0.0	−1.3, 1.2	−0.4	−3.2, 2.4
Estrone sulfate (pg/ml)										
Follicular	0.1	−1.2, 1.3	0.3	−1.4, 2.0	−0.1	−2.5, 2.3	0.7	−1.7, 3.1	0.6	−4.2, 5.2
Luteal	0.0	−1.5, 1.4	−0.0	−2.1, 2.1	−0.8	−3.6, 2.0	0.2	−2.5, 2.9	1.8	−4.0, 7.2
Progesterone (ng/ml)	0.1	−0.8, 1.0	−0.9	−2.2, 0.4	−0.2	−2.0, 1.6	−0.8	−2.5, 0.9	−1.0	−4.5, 2.4
SHBG (nmol/l)	0.2	−0.6, 1.0	0.8	−0.2, 1.7	1.1	−0.5, 2.6	1.2	−0.2, 2.7	−0.0	−2.9, 2.7
Androstenedione (ng/ml)	0.5	−0.2, 1.2	0.5	−0.4, 1.4	1.3	−0.2, 2.7	0.7	−0.6, 2.1	1.9	−0.6, 4.4
Testosterone (ng/ml)	0.4	−0.3, 1.1	0.1	−0.8, 1.0	1.1	−0.3, 2.4	0.4	−1.0, 1.6	0.4	−2.0, 2.7
Free testosterone (ng/ml)	0.3	−0.5, 1.0	−0.4	−1.4, 0.6	0.4	−1.4, 1.8	−0.5	−2.0, 0.9	0.5	−2.2, 3.2
DHEA (ng/dl)	0.5	−0.4, 1.3	−0.0	−1.1, 1.0	0.8	−0.9, 2.5	0.3	−1.3, 1.9	1.0	−2.5, 4.4
DHEA sulfate (μg/dl)	0.6	−0.4, 1.6	−0.4	−1.8, 0.9	0.5	−1.5, 2.4	0.5	−1.4, 2.4	0.6	−3.8, 4.7
IGF-I (ng/ml)	−0.5	−1.1, 0.1	−0.5	−1.3, 0.2	−1.2	−2.4, 0.0*	−1.0	−2.1, 0.0	−1.9	−4.1, 0.4
IGFBP-3 (ng/ml)	−0.4	−0.7, −0.1*	−0.2	−0.5, 0.2	−0.8	−1.4, −0.2*	−0.6	−1.2, −0.1*	−0.8	−1.9, 0.3
IGF-I/IGFBP-3	−0.1	−0.6, 0.4	0.4	−1.0, 0.3	−0.4	−1.4, 0.6	−0.4	−1.3, 0.5	−1.0	−3.0, 0.9

[a] Adjusted for age at blood draw (continuous), fasting status (<8, ≥8 h), laboratory batch, day of luteal blood draw (for luteal hormones, 3–7, 8–28 days, missing/untimed sample), smoking status (pack years, never, 1–10, 11–20, 20+years), BMI in 1997 (continuous), BMI at age 18 (continuous), total energy intake (average of 1995 and 1999, continuous), alcohol intake (average of 1995 and 1999, continuous), parity (nulliparity, 1 and age at first birth <25, 1 and age at first birth≥25, 2 and age at first birth <25, 2 and age at first birth≥25, 3+ and age at first birth <25, 3+ and age at first birth≥25], age at menarche [<12, 12, >12], and height (continuous)

*$P<0.05$

Table 5 Geometric means across categories of percentage of energy from carbohydrates and estimated percentage difference in plasma hormone levels from substituting 5% of energy from carbohydrates for the equivalent amount of energy from fat or protein intake

N (range)	% Energy from total carbohydrate					% Difference in hormone levels	
	≤40%	40.1–45%	45.1–50%	50.1–55%	>55%		
	21–27	44–65	93–139	128–195	109–166		
	Geometric means					Estimate	95%CI
Estradiol (pg/ml)							
Follicular	44.1	40.8	48.0	47.6	46.4	1.7	−2.1, 5.3
Luteal	124	128	113	116	124	0.6	−2.1, 3.2
Free estradiol (pg/ml)							
Follicular	0.6	0.5	0.6	0.6	0.6	0.7	−3.1, 4.3
Luteal	1.6	1.5	1.4	1.5	1.6	1.1	−1.5, 3.7
Estrone (pg/ml)							
Follicular	39.2	38.6	41.3	41.1	38.7	−0.5	−3.3, 2.3
Luteal	72.7	77.5	72.2	77.0	74.6	0.8	−1.6, 3.1
Estrone sulfate (pg/ml)							
Follicular	644	614	696	692	659	0.3	−4.3, 4.7
Luteal	1,345	1,332	1,198	1,419	1,393	2.0	−2.9, 6.6
Progesterone (ng/ml)	1,174	1,317	1,361	1,343	1,330	0.4	−2.8, 3.4
SHBG (nmol/l)	56.3	69.2	60.8	60.1	60.0	−0.9	−3.6, 1.7
Androstenedione (ng/ml)	101	108	106	106	99	−1.6	−4.1, 0.8
Testosterone (ng/ml)	20.6	25.8	23.6	23.4	22.9	−0.6	−2.9, 1.7
Free testosterone (ng/ml)	0.2	0.2	0.2	0.2	0.2	0.0	−2.6, 2.6
DHEA (ng/dl)	612	659	635	665	606	−1.1	−4.2, 1.9
DHEA sulfate (μg/dl)	65.6	80.5	77.9	79.2	73.6	−0.7	−4.4, 2.9
IGF-I (ng/ml)	211	230	225	238	237	2.0	0.1, 3.9*
IGFBP-3 (ng/ml)	4,456	4,484	4,533	4,668	4,599	1.0	−0.0, 1.9
IGF-I/IGFBP-3	0.05	0.05	0.05	0.05	0.05	1.1	−0.7, 2.8

Adjusted for age at blood draw (continuous), fasting status (<8, ≥8 h), laboratory batch, day of luteal blood draw (for luteal hormones, 3–7, 8–28 days, missing/untimed sample), smoking status (pack years, never, 1–10, 11–20, 20+years], BMI in 1997 (continuous), BMI at age 18 (continuous), total energy intake (average of 1995 and 1999, continuous), alcohol intake (average of 1995 and 1999, continuous), parity (nulliparity, 1 and age at first birth <25, 1 and age at first birth≥25, 2 and age at first birth <25, 2 and age at first birth≥25, 3+ and age at first birth <25, 3+ and age at first birth≥25), age at menarche (<12, 12, >12), and height (continuous)

*$P<0.05$

studies had a simultaneous control group [65]. In one 2-month intervention study with 62 women, a significant reduction was observed in luteal estradiol and estrone levels among wheat-bran but not oat- or corn-bran supplements groups [66]. However, two other dietary intervention studies (using a 12-month low-fat/high-fiber intervention among 213 women [67] or a 2-month replacement of saturated fat with polyunsaturated fat among 14 women[68]) found no influence of diet change on blood estrogen levels in the luteal [67, 68] or follicular [68] phases. Several cross-sectional studies found significant positive associations between total and monounsaturated fat intakes and follicular estrone levels [69] or inverse associations between the ratio of polyunsaturated to saturated fat (P/S) and estradiol and estrone during the luteal phase [70] or higher follicular plasma estrogen levels among high-fat/low-fiber group [71]. In other studies, no significant associations were observed between dietary fiber intakes and estrogen levels during the follicular [69, 70] or luteal [68, 70] phases. Cumulatively, no strong consistent associations have been observed, and weak to moderate effects remain uncertain; our study, which is substantially larger than previous cross-sectional studies, suggests there is little, if any, association between these macronutrients and premenopausal estrogens. The significantly higher levels of follicular estradiol among

Table 6 Geometric means across categories of total fiber and estimated percentage difference in plasma hormone levels from 5-g increment of total fiber

N (range)	Total fiber				% Difference in hormone levels	
	≤15 g	15.1–20 g	20.1–25 g	>25.1 g		
	73–97	151–230	105–164	64–101		
	Geometric means				Estimate	95%CI
Estradiol (pg/ml)						
Follicular	46.1	47.6	45.6	45.3	−1.7	−6.3, 2.7
Luteal	117	124	119	118	0.2	−3.4, 3.7
Free estradiol (pg/ml)						
Follicular	0.6	0.6	0.6	0.6	−0.6	−4.6, 3.2
Luteal	1.4	1.6	1.5	1.4	0.4	−3.2, 3.8
Estrone (pg/ml)						
Follicular	39.8	41.7	39.8	37.3	−2.0	−4.8, 0.8
Luteal	72.5	74.8	79.6	74.0	1.4	−1.5, 4.2
Estrone sulfate (pg/ml)						
Follicular	682	705	669	597	−1.5	−6.8, 3.6
Luteal	1,340	1,319	1,465	1,312	2.5	−2.8, 7.6
Progesterone (ng/ml)	1,289	1,375	1,324	1,291	−1.0	−5.3, 3.0
SHBG (nmol/l)	62.7	61.7	59.3	60.7	−1.4	−4.6, 1.7
Androstenedione (ng/ml)	105	108	103	97.2	−3.0	−5.9, −0.1*
Testosterone (ng/ml)	23.1	24.5	22.6	22.7	−1.4	−4.2, 1.3
Free testosterone (ng/ml)	0.2	0.2	0.2	0.2	−0.5	−3.8, 2.6
DHEA (ng/dl)	594	684	631	594	−1.6	−5.8, 2.4
DHEA sulfate (μg/dl)	72.3	81.2	76.9	71.4	−0.9	−5.2, 3.3
IGF-I (ng/ml)	223	232	233	243	1.9	−0.4, 4.2
IGFBP-3 (ng/ml)	4,416	4,570	4,702	4,610	1.3	0.0, 2.5
IGF-I/IGFBP-3	0.05	0.05	0.05	0.05	0.7	−1.3, 2.6

Adjusted for age at blood draw (continuous), fasting status (<8, ≥8 h], laboratory batch, day of luteal blood draw (for luteal hormones, 3–7, 8–28 days, missing/untimed sample), smoking status (pack years, never, 1–10, 11–20, 20+years], BMI in 1997 (continuous), BMI at age 18 (continuous), total energy intake (average of 1995 and 1999, continuous), alcohol intake (average of 1995 and 1999, continuous), parity (nulliparity, 1 and age at first birth <25, 1 and age at first birth≥25, 2 and age at first birth <25, 2 and age at first birth≥25, 3+ and age at first birth <25, 3+ and age at first birth≥25], age at menarche [<12, 12, >12], and height (continuous)

*$P<0.05$

those with the lowest percent energy from fat suggested a threshold effect, but we need to be careful in interpreting these data as there were only 20 participants in this category of intake.

Fewer studies have been done to investigate the associations between diet and endogenous levels of SHBG, androgens, or progesterone. A 2-month intervention study reported a significant reduction in follicular androstenedione and an increase in luteal testosterone levels after a low-fat/high-fiber intervention [72]. Previous intervention studies also found no significant change in blood SHBG after a 2-month high-fiber intervention [66, 72] or in luteal progesterone levels after either a low-fat/high-fiber [67] or bran supplement [66] intervention. Several cross-sectional studies found higher SHBG levels with increased monounsaturated fat intake [69] or in the high-fat/low-fiber intake group [71]. Other studies also reported significant positive associations between P/S intakes with DHEAS [70] or an inverse association between dietary fibers with serum luteal levels of androstenedione among premenopausal women [73]. However, in these studies, no differences were found in plasma testosterone levels between groups [71], and no significant associations of fat and fiber intake with androgens or SHBG [70] or fiber with androgen, SHBG, or progesterone [73]. Similarly, we observed no association between fat/fiber and plasma androgens or progesterone.

We found modest but significant associations between plasma IGF-I levels and both total fat (inverse association) and carbohydrates (positive association). Since the percentage of energy from total fat and from carbohydrates is highly correlated (Spearman correlation coefficient is −0.86), it is hard to distinguish the effect of fat versus carbohydrates. The inverse association between total fat and IGF-I is consistent with a previous intervention study which found that IGF-I levels rose significantly after an intervention to reduce total fat intake [74]. However, in other intervention studies, IGF-I levels did not change [75–77] after a low-fat/high-fiber diet intervention. Previous cross-sectional studies reported positive [49] or no [51, 78] associations between fat intake and IGF-I levels. The significant but modest inverse associations between intakes of total fat, animal fat, saturated fat, and monounsaturated fat and plasma IGFBP-3 observed in our study are supported by some previous cross-sectional studies in which IGFBP-3 levels were inversely related to fat intakes [48–50] but not another large cross-sectional study including 2,109, women which found no significant associations with dietary fat intake [51]. Our findings did not appear to be due to total energy or to protein intake, since neither of them was significant in our multivariate models. Residual confounding by known confounders also is unlikely since the results did not change substantially after multivariable adjustment. The modest positive association between carbohydrates and plasma IGF-I is inconsistent with the few prior cross-sectional studies which found no association among premenopausal women [78] or an inverse association among healthy adults ages 30 to 84 years old [49].

The strengths of our study include its relatively large sample size, generally low laboratory CVs, and evaluation of a large number of hormones with careful timing by menstrual cycle phase. Our study also had several potential limitations. The women in our study are well-nourished, and the average intake of fiber and percent energy from fat per day were 20.2 g/day and 29.1%, which were less extreme than those in a few prior studies [66, 70]. If there are associations between diet and endogenous hormone levels and the associations are non-linear (a possibility suggested by our findings on fat intake and follicular estradiol), our study might not have a sufficient number of subjects in the effect range. But we previously reported an inverse association between fat intakes and plasma sex steroid hormone levels among postmenopausal women [61], and associations of both total fat [79] and fiber [80] with disease risk. Error in our diet assessment is also a concern, although our use of two FFQs collected 4 years apart should dampen this error. Finally, although the intraclass correlation coefficients (ICC) for IGFs and androgens were quite high (range from 0.59 to 0.89 over up to 3 years), the ICC for estrogens and progesterone were lower [57]. Although we controlled for day of luteal blood draw, the possible associations could be attenuated due to that source of within-person variability. Finally, we made a large number of comparisons in this analysis, and we cannot rule out the possibility of observing several associations by chance.

In conclusion, our results suggest that a low-fat/high-fiber and carbohydrate diet within the range of intake generally observed in the USA is not importantly associated with endogenous levels of sex steroid hormones but may modestly increase IGF-I and IGFBP-3 levels among premenopausal women. Further large studies are needed to investigate the relationships between dietary intakes and endogenous hormone levels throughout the menstrual cycle.

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Conflict of Interest The authors declare that they have no conflict of interest.

Appendix 1: Hormones measured during menstrual cycle

	Follicular	Luteal	Untimed
Estradiol	X	X	
Estrone	X	X	
Estrone Sulfate		X	
Progesterone		X	
SHBG	X	X	X
Androstenedione	X	X	X
Testosterone	X	X	X
DHEA		X	X
DHEAS		X	X
IGF-I		X	X
IGFBP-3		X	X

X denotes hormones measured

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