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Protein intake and ovulatory infertility

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Abstract

Objective—To evaluate whether intake of protein from animal and vegetable origin is associated with ovulatory infertility.

Study Design—18,555 married women without a history of infertility were followed as they attempted a pregnancy or became pregnant during an eight year period. Dietary assessments were related to the incidence of ovulatory infertility.

Results—During follow-up, 438 women reported ovulatory infertility. The multivariate-adjusted relative risk [RR] (95% CI; P, trend) of ovulatory infertility comparing the highest to the lowest quintile of animal protein intake was 1.39 (1.01 – 1.90; 0.03). The corresponding RR (95% CI; P, trend) for vegetable protein intake was 0.78 (0.54 – 1.12; 0.07). Further, consuming 5% of total energy intake as vegetable protein rather than as animal protein was associated with a more than 50% lower risk of ovulatory infertility (P = 0.007).

Conclusions—Replacing animal sources of protein with vegetable sources of protein may reduce ovulatory infertility risk.

Keywords

Infertility; ovulation; protein; diet; epidemiology

INTRODUCTION

Infertility is a common condition affecting as many as one of every six couples during their reproductive lifetime [1]. Although assisted reproductive technologies are available to treat infertility, their large costs [2] make it important to consider alternative approaches. Thus, the identification of modifiable risk factors for infertility is important.

How nutritional factors might influence fertility is largely an unexplored field. Although there is a substantial body of literature documenting how fertility is affected by underweight

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and excess weight [3], very little is known about how dietary composition influences fertility. Much evidence indicates that insulin sensitivity, which can be affected by diet [4], is an important determinant of ovulatory function and fertility [5, 6]. The amount and sources of protein in diet have been found to influence insulin sensitivity [7–10], yet high-protein, low-calorie diets have been found not to influence reproductive parameters beyond their effects on weight loss in women with polycystic ovary syndrome (PCOS) [11, 12]. However, it is not currently known whether the amount or source of dietary protein affects ovulatory function or fertility among healthy women not in weight loss diets. To address these issues we prospectively evaluated whether the intakes of protein from animal and vegetable sources and specific protein-rich foods were related to the risk of ovulatory infertility in a cohort of healthy women.

MATERIALS AND METHODS

The Nurses' Health Study II (NHS II) is a prospective cohort started in 1989 when over 116,000 female registered nurses completed a mailed baseline questionnaire. Participants have been followed since then with mailed questionnaires every two years. Here we present a prospective analysis of incident ovulatory infertility among participants of this cohort. The study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Follow-up for the current analysis started in 1991, when diet was first measured, and concluded in 1999. Every two years participants were asked if they had tried to become pregnant for more than 1 year without success since the previous questionnaire administration, and to indicate whether their inability to conceive was caused by tubal blockage, ovulatory disorder, endometriosis, cervical mucous factor, male factor, was not found, was not investigated or was due to another reason. In a validation sub-study, self-reported diagnosis of ovulatory infertility was confirmed by review of medical records in 95% of the cases [13]. Women were also asked if they became pregnant during the preceding two-year period, including pregnancies resulting in miscarriages or induced abortions. Using this information we simulated a cohort of women attempting to become pregnant. Only married women, with available dietary information and without a history of infertility, were eligible to enter the analysis. These women contributed information to the analysis during each two-year period in which they reported a pregnancy or a failed pregnancy attempt, and were followed until they reported an infertility event from any cause, reached menopause or underwent a sterilization procedure (themselves or their partner), whichever came first. Ten diabetic women met these criteria. Since the small number of diabetics would preclude meaningful statistical adjustment or exploration of modification of the associations by diabetes, diabetic women were excluded from the analysis. After exclusions, we identified 18,555 women without a history of infertility who tried to become pregnant or became pregnant during the 8-year follow-up period. Women entered the analysis when they reported their first pregnancy or failed pregnancy attempt: 14,336 entered the analysis in 1991, 2,686 entered in 1993, 796 entered in 1995 and 737 entered in 1997.

Women who reported infertility due to ovulatory disorder were considered cases. All other events (pregnancies – resulting in live births, miscarriages or induced abortions – and infertility due to other causes) were considered non-cases.

Dietary assessment

Dietary information was collected in 1991 and 1995 using a validated food-frequency questionnaire (FFQ) with more than 130 food items [14, 15]. The FFQ has been previously found to validly estimate nutrient intakes up to four years in the past [16]. Participants were asked to report how often, on average, they consumed each of the foods and beverages included in the FFQ during the previous year. The questionnaire offered nine options for

frequency of intake, ranging from never or less than once per month to six or more times per day. Nutrient intakes were estimated by summing the nutrient contribution of all food items in the questionnaire. The nutrient content of each food and specified portion size was obtained from a nutrient database derived from the US Department of Agriculture [17] and additional information obtained from food manufacturers. The percentage of energy contributed by each energy-bearing nutrient was calculated as the intake of energy from each nutrient divided by total energy intake. To reduce extraneous variation in non-energy-bearing nutrient intakes, these were adjusted for total energy intake using the nutrient residual method [18].

Statistical analyses

The relative risk, (calculated as an odds ratio) of ovulatory infertility in relation to protein and meat was estimated using logistic regression. The odds ratio is a good estimate of the relative risk because of the low frequency of infertility due to ovulation problems (1.6% of all events). The generalized estimating equation approach [19] with an exchangeable working correlation structure, was used to account for the within-person correlation in outcomes at different time periods. We divided women into five groups according to quintiles of total, animal and vegetable protein intake. In these models, the relative risk was computed as the risk of infertility in a specific quintile of cumulative averaged intake compared to the risk in the lowest quintile. Tests for linear trend were conducted by using the median values of intake in each category as a continuous variable. The relative risk associated with increasing protein intake by a specific percentage of calories was estimated using protein intake as a continuous variable. Similarly, the relative risk associated with a 1-serving per day increase in consumption of specific protein-rich foods was estimated by modeling the intake of these foods as a continuous variable.

All models were adjusted for total energy intake, age and calendar time at the beginning of each questionnaire cycle. Multivariate models included additional terms for body mass index (wt (kg)/ht^2 (m)) (BMI), parity, smoking history, physical activity, history of oral contraceptive use and dietary factors found to be related to infertility in preliminary analyses (use of multivitamins and intakes of alcohol, coffee, retinol, iron and specific fatty acids) [20, 21]. Values of the dietary and non-dietary variables were updated as new data became available from follow-up questionnaires. In a second set of multivariate models we simultaneously included terms for the percentages of energy derived from specific types of protein and fat. The coefficients from this model have the interpretation of substituting a specific percent of energy from protein with the same amount of energy from carbohydrates. We estimated the effects of substituting one type of protein for another as the difference between their regression coefficients in the same model and calculated the 95% confidence intervals using the estimates of the covariance between the regression coefficients [22].

Lastly, we examined whether the association between protein intake and ovulatory infertility was modified by participant characteristics (age, parity and BMI), or a history of long menstrual cycles (>40 days between ages 18 to 22 and during adulthood), by introducing cross-product terms between protein and the variable of interest. All *P* values were two sided. Analyses were performed in SAS version 9.1.

RESULTS

During 8 years of follow-up, 26,971 eligible pregnancies and pregnancy attempts were accrued among 18,555 women. Of these events, 3,430 (12.7% of all events) were incident reports of infertility, of which 2,165 were of women who underwent medical investigation for infertility and 438 (1.6% of all events, 20.2% of investigated infertility cases) were incident reports of ovulatory infertility. Ovulatory infertility cases were more likely to report

manifestations of PCOS (menstrual cycles >40 days or clinical signs of excess androgens) than women reporting infertility due to other causes (OR [95% CI] = 4.00 [2.87 – 5.57]) or women who became pregnant during follow-up (OR [95% CI] = 4. 41 [3. 33 –5.83]).

At baseline, women who consumed more animal protein, also consumed more saturated fat, less alcohol and coffee, and were slightly younger, heavier, less physically active and more likely to be parous (Table I). Women who consumed more vegetable protein consumed more coffee and less saturated, monounsaturated and *trans* fat, were slightly older, leaner and more physically active, were less likely to smoke, be recent users of oral contraceptives or experience long menstrual cycles and more likely to be nulliparous. Protein intake was unrelated to use of multivitamins.

Total protein intake, as well was the intakes of animal and vegetable protein were unrelated to ovulatory infertility in age and energy-adjusted analyses (Table II). After adjusting for potential confounders (particularly for intake of specific fatty acids, parity and BMI) women in the highest quintile of total protein intake had a 41% greater risk of ovulatory infertility than women in the lowest quintile of intake (95% CI: 4% – 91%). The association between animal protein intake and ovulatory infertility closely resembled the association for total protein intake. Conversely, there was a suggestion of an inverse association between vegetable protein intake and ovulatory infertility (P, trend = 0.07).

We then examined the association between specific protein-rich foods and ovulatory infertility (Table III). In multivariate-adjusted analyses, meat intake was positively associated with ovulatory infertility. Adding one serving of meat (red meats, chicken, turkey, processed meats and fish) per day, while holding calories, constant was associated with a 32% greater risk of ovulatory infertility (p = 0.01). This increased risk was due mostly to intake of chicken and turkey, the most important protein source in this population, and to a lesser extent to the intake of red meats. Intakes of processed meats, fish and eggs were unrelated to ovulatory infertility. Consuming foods rich in vegetable protein was related to modest decreases in the risk of ovulatory infertility, but none of these associations reached statistical significance.

Next, we estimated the effect that consuming protein instead of other energy sources would have on the risk of developing ovulatory infertility (Table IV). Consuming 5% of total energy intake as animal protein instead of as carbohydrates was associated with 19% greater risk of ovulatory infertility (p = 0.03). In contrast, consuming 5% of energy as vegetable protein rather than as carbohydrates was associated with a 43% lower risk of ovulatory infertility (p = 0.05). Furthermore, consuming 5% of energy as vegetable protein as opposed to as animal protein was associated with a more than 50% lower risk of ovulatory infertility (RR [95% CI; *p*] = 0.48 [0.28 – 0.81; 0.007]). When these analyses were repeated excluding women who used oral contraceptives within two years of the event, the results were essentially the same for animal protein and stronger for vegetable protein. The multivariate-adjusted relative risk (95% CI) of ovulatory infertility associated with increasing protein intake by 5% at the expense of carbohydrates was 1.18 (1.00 – 1.39) for animal protein and 0.50 (0.27 – 0.92) for vegetable protein. The corresponding RR (95% CI) for increasing vegetable protein intake by 5% at the expense of animal protein was 0.42 (0.24 – 0.76).

Lastly, we assessed the possibility that the association between protein intake and ovulatory infertility could differ according to levels of personal characteristics including age, BMI, parity and menstrual cycle length. The associations between animal and vegetable protein intake did not differ according to menstrual cycle length (p, interaction = 0.14 and 0.99, respectively), BMI (p, interaction = 0.30 and 0.22) or parity (p, interaction = 0.39 and 0.78). However, the association between vegetable protein intake and ovulatory infertility was

different according to age levels (p, interaction = 0.05). For women 32 years of age or younger consuming 5% of energy as vegetable protein rather than as carbohydrates was unrelated to ovulatory infertility whereas for women over 32 years this nutrient substitution was associated a more than 50% lower risk of ovulatory infertility (RR [95% CI; *p*] = 0.48 [0.27 – 0.86; 0.01). Similarly, consuming 5% of energy as vegetable protein instead of as animal protein was associated with a lower risk among women above 32 years (RR [95% CI; *p*] = 0.27 [0.14 – 0.51; <0.001]) but not among younger women (RR [95% CI; *p*] = 0.95 [0.50 – 1.78; 0.87]).

COMMENT

We prospectively evaluated the association between protein intake and ovulatory infertility in a cohort of healthy women and found that consuming animal protein was associated with an increased risk of this condition. Further, we found that consuming vegetable protein instead of carbohydrates or animal protein was associated with a substantially lower risk of ovulatory infertility. This association was particularly strong among women older than 32 years although there is no clear explanation as to why age might modify the association between protein intake and ovulatory infertility.

Two previous studies have examined the role of protein intake in reproductive function. Both were small randomized trials comparing the effects on reproductive function of low protein (15% of energy) vs. high protein (30% of energy) diets for weight loss among overweight women with PCOS [11, 12]. The protein content of diet had no effect on reproductive function in these studies, although there were some improvements in menstrual cyclicity [12] and reductions in circulating androgens [11] as a result of improved insulin sensitivity due to weight loss. It is not clear, however, whether the amount of dietary protein in a weight maintenance diet influences reproductive function. Given that insulin sensitivity and glucose homeostasis influence reproductive function and fertility in women [5, 6] any effects dietary protein may have on these factors could also influence fertility. Replacing carbohydrates with protein appears to improve markers of insulin sensitivity in type 2 diabetics [8] but has also increased insulin resistance in animal models [9]. Unfortunately, these later studies did not record changes in reproductive function nor did they specify the food sources used to increase protein intake, thus limiting their usefulness in the interpretation of our results.

In our study, consumption of protein from animal sources, including chicken and red meats, was associated with an increased risk of infertility due to anovulation while consuming protein from vegetable sources appeared to have the opposite effect. These findings are in agreement with previous studies measuring the effect of diet on ovulatory function in animals. Increasing vegetable (soy) protein intake has been found to increase ovulation rates in pigs [23]. Also, protein intake may affect insulin and glucose response differently, depending on the protein source. In diabetics, the postprandial insulin response to vegetable (soy) protein and egg protein is lower than that to red meat and turkey protein [7]. Similarly, in normal subjects the postprandial insulin response to vegetable protein is lower than that to animal protein [24]. Further, cod and soy protein have been found to improve insulin sensitivity when compared to casein in rodent models [10]. A differential effect of various protein sources on insulin sensitivity could be a mechanism explaining our findings.

Another possible mechanism underlying the observed associations could be a differential effect of animal and vegetable protein on circulating IGF-I levels. Elevated levels of free IGF-I may be involved in the development of PCOS [25, 26], the most common cause of anovulation. Holmes and colleagues found that, in women, animal protein intake was positively associated with IGF-I levels while vegetable protein intake was not related to this

hormone [27]. However, in a similar study conducted in men, both animal and vegetable protein intake were positively associated with blood IGF-I levels and to the ratio of IGF-I to its binding protein [28]. Whether differential effects of animal and vegetable protein on IGF-I levels could explain our findings deserves further consideration.

Strengths of our study include the use of previously validated questionnaires for dietary and outcome assessment. Also, dietary information was collected two to four years before events were reported making it unlikely that our results are affected by fertility status at the time information on diet was collected. A potential limitation of our study is that it was not a cohort of women known to be planning a pregnancy. While cases were clearly trying to conceive, some pregnancy non-cases may have conceived accidentally. However, we simulated a cohort of pregnancy planners by restricting the study to married women, whose pregnancies are more likely to be intentional [29], and by considering women diagnosed with infertility from other causes as non-cases. In addition, when the analyses were restricted to non-users of oral contraception at the last questionnaire before reporting pregnancy or infertility, the results were similar or stronger than those using the entire cohort. This makes it less likely that pregnancy planning affected our results. Imperfect measurement is also of concern in this study. In the case of diet, within-person errors, mostly due to normal variation of diet not captured by the FFQ, tend to bias the associations towards the null. Misclassification of our study outcome, either because women are incorrectly classified as cases or non-cases or because among cases not all women share the same underlying pathology, will also tend to bias the association towards the null. Thus, improved dietary assessment and case characterization would be expected to result in stronger associations than we observed. We cannot completely exclude the possibility that our findings are due to unmeasured factors related both to protein intake and ovulatory infertility. However, statistically accounting for a variety of known and suspected risk factors for infertility in our analyses had a minimal impact on our results, with the exception of adjustment for intake of fatty acids, parity and BMI. Lastly, because multiple statistical tests were performed it is possible that the statistical significance of some results is overestimated.

In summary, our findings suggest that replacing animal sources of protein, in particular chicken and red meats, with vegetable sources of protein may reduce the risk of infertility due to anovulation. Since this is, to our knowledge, the first report of this relationship in humans, these results should be confirmed. It is also important to clarify which biological mechanisms are responsible for this association.

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Table I

Baseline* characteristics of the study population by quintiles of animal and vegetable protein intake.

	Animal Protein				Vegetable Protein			
	Q1†	Q3	Q5	p	Q1	Q3	Q5	p
Age, years	32.9	32.5	32.4	<0.001	31.9	32.4	33.6	<0.001
Saturated fat intake, g/day	20.1	22.7	23.4	<0.001	24.8	22.6	18.5	<0.001
Monounsaturated fat intake, g/day	22.2	23.6	23.7	<0.001	24.7	23.7	20.8	<0.001
Polyunsaturated fat intake, g/day	10.7	10.8	10.6	0.003	10.2	10.9	10.8	<0.001
Trans unsaturated fat intake, g/day	3.1	3.2	2.9	<0.001	3.4	3.2	2.5	<0.001
Alcohol intake, g/day	3.6	2.7	2.2	<0.001	2.8	2.9	2.8	0.54
Coffee intake ≥ 2 cups/day. %	25	23	22	<0.001	19	25	27	<0.001
Multivitamin use, %	56	57	54	0.19	55	56	59	<0.001
Current smoker, %	8	7	7	0.63	10	7	5	<0.001
Body Mass Index, kg/m^2	23.0	23.8	24.7	<0.001	24.4	23.9	23.2	<0.001
Physical activity, METs/week	23.4	20.6	20.9	<0.001	18.0	20.9	26.6	<0.001
Cycles ≥ 40 days ‡, %	3	3	3	0.71	4	3	3	0.03
Nulliparous, %	28	21	24	<0.001	22	22	29	<0.001
Oral contraceptive use at the beginning of the mailing cycle, %	17	16	17	0.33	18	17	14	<0.001

*Baseline refers to the year of entry into the study for each individual. See methods section for further explanation. Values are presented as means for continuous variables and proportions for categorical variables.

†Q1, Q3 and Q5 refer to quintiles 1 (lowest), 3 and 5 (highest), respectively, of the distributions of animal and vegetable protein.

‡Cycles >40 days between ages 18 to 22 and during adulthood.

Table II

Relative risks and 95% confidence intervals for ovulatory infertility by quintiles of cumulative averaged protein intake.

	Quintile of Intake					
	1	2	3	4	5	P, trend *
Total Protein						
Median Intake (% of calories)	15.4	17.6	19.1	20.7	23.1	
Cases / non-cases	88 / 5,306	72 / 5,322	78 / 5,316	84 / 5,311	116 / 5,278	
Age and energy adjusted RR †	1.00 (referent)	0.81 (0.59–1.11)	0.87 (0.64–1.18)	0.91 (0.68–1.24)	1.22 (0.92–1.62)	0.11
Multivariate adjusted RR ‡	1.00 (referent)	0.93 (0.68–1.28)	1.04 (0.76–1.43)	1.04 (0.76–1.44)	1.41 (1.04–1.91)	0.02
Animal Protein						
Median Intake (% of calories)	10.2	12.5	14.1	15.9	18.5	
Cases / non-cases	88 / 5,306	75 / 5,319	79 / 5,316	87 / 5,308	109 / 5,284	
Age and energy adjusted RR †	1.00 (referent)	0.87 (0.64–1.18)	0.90 (0.66–1.22)	0.97 (0.72–1.31)	1.17 (0.88–1.56)	0.20
Multivariate adjusted RR ‡	1.00 (referent)	0.98 (0.71–1.34)	1.05 (0.76–1.44)	1.13 (0.82–1.55)	1.39 (1.01–1.90)	0.03
Vegetable Protein						
Median Intake (% of calories)	3.7	4.4	4.9	5.4	6.3	
Cases / non-cases	89 / 5,305	92 / 5,302	92 / 5,303	75 / 5,319	90 /5,304	
Age and energy adjusted RR †	1.00 (referent)	1.04 (0.77–1.39)	1.02 (0.76–1.37)	0.82 (0.60–1.12)	0.96 (0.71–1.30)	0.47
Multivariate adjusted RR ‡	1.00 (referent)	1.03 (0.76–1.40)	0.99 (0.72–1.35)	0.74 (0.53–1.05)	0.78 (0.54–1.12)	0.07

* Calculated with median protein intake in each quintile as a continuous variable.

† Adjusted for age (continuous), calendar time (4 two-year intervals) and total energy intake (continuous).

‡ Age and energy adjusted model further adjusted for body mass index (<20, 20–24.9, 25–29.9, ≥30 and missing), parity (0, 1, ≥2 and missing), smoking history (never, past 1–4 cig/day, past 5–14 cig/day, past 15–24 cig/day, past ≥ 25 cig/day or unknown amount, current 1–4 cig/day, current 5–14 cig/day, current 15–24 cig/day and current ≥ 25 cig/day or unknown amount), physical activity (<3 MET-h/wk, 3–8.9 MET-h/wk, 9–17.9 MET-h/wk, 18–26.9 MET-h/wk, 27–41.9 MET-h/wk, ≥ 42 MET-h/wk and missing), oral contraceptive use (current user, never user, past user 0–23 months ago, past user 24–47 months ago, past user 48–71 months ago, past user 72–95 months ago, past user 96–119 months ago, past user ≥ 120 months ago and missing), frequency of multivitamin use (non-users, ≤2 tablets/week, 3 to 5 tablets/week, ≥6 tablets/week and missing), intake of alcohol (no intake, < 2 g/day, 2–4.9 g/day, ≥ 5 g/day), coffee (<1 serving/month, 1 serving/month, 2–6 servings/week, 1 serving/day, 2–3 servings/day, ≥ 4 servings/day), quintiles of intake of retinol and iron and linear terms for intake of saturated, mono-unsaturated, poly-unsaturated and *trans* fatty acids.

Table III

Relative risks (95% CIs) of ovulatory infertility associated with increasing the intake of specific protein-rich foods by 1 serving/day.

Food	Age and energy-adjusted *		Multivariate-adjusted †	
	RR (95% CI)	*p*	RR (95% CI)	*p*
All meats	1.20 (0.99 – 1.45)	0.07	1.32 (1.08 – 1.62)	0.01
Red Meats ‡	0.91 (0.65 – 1.26)	0.56	1.42 (0.98 – 2.06)	0.06
Chicken or turkey	1.85 (1.44 – 2.38)	<0.001	1.53 (1.12 – 2.09)	0.01
Processed meats §	0.77 (0.47 – 1.27)	0.31	1.04 (0.67 – 1.62)	0.85
Fish	1.36 (0.88 – 2.11)	0.17	1.04 (0.64 – 1.70)	0.86
Eggs	0.89 (0.80 – 0.99)	0.03	0.97 (0.87 – 1.08)	0.57
Tofu or soybeans	0.95 (0.85 – 1.06)	0.35	0.90 (0.79 – 1.03)	0.14
Peas or lima beans	0.90 (0.82 – 0.98)	0.02	0.96 (0.88 – 1.05)	0.39
Beans or lentils	0.94 (0.86 – 1.03)	0.20	0.92 (0.84 – 1.01)	0.09
Peanuts	0.92 (0.80 – 1.07)	0.28	0.89 (0.76 – 1.04)	0.16
Other nuts	1.02 (0.90 – 1.15)	0.73	0.98 (0.86 – 1.13)	0.83
Peanut butter	0.90 (0.83 – 0.98)	0.01	0.99 (0.91 – 1.07)	0.75

* Adjusted for age (continuous), calendar time (4 two-year intervals) and total energy intake (continuous).

† Age and energy adjusted model further adjusted for body mass index (<20, 20–24.9, 25–29.9, ≥30 and missing), parity (0, 1, ≥2 and missing), smoking history (never, past 1–4 cig/day, past 5–14 cig/day, past 15–24 cig/day, past ≥ 25 cig/day or unknown amount, current 1–4 cig/day, current 5–14 cig/day, current 15–24 cig/day and current ≥ 25 cig/day or unknown amount), physical activity (<3 MET-h/wk, 3–8.9 MET-h/wk, 9–17.9 MET-h/wk, 18–26.9 MET-h/wk, 27–41.9 MET-h/wk, ≥ 42 MET-h/wk and missing), oral contraceptive use (current user, never user, past user 0–23 months ago, past user 24–47 months ago, past user 48–71 months ago, past user 72–95 months ago, past user 96–119 months ago, past user ≥ 120 months ago and missing), frequency of multivitamin use (non-users, ≤2 tablets/week, 3 to 5 tablets/week, ≥6 tablets/week and missing), intake of alcohol (no intake, < 2 g/day, 2–4.9 g/day, ≥ 5 g/day), coffee (<1 serving/month, 1 serving/month, 2–6 servings/week, 1 serving/day, 2–3 servings/day, ≥ 4 servings/day), quintiles of intake of retinol and iron and linear terms for intake of saturated, mono-unsaturated, poly-unsaturated and *trans* fatty acids.

‡ Includes beef, pork and lamb consumed as hamburger, mixed dish and main dish

§ Includes hot dogs, bacon and other processed meats (e.g. salami, bologna, etc.)

Table IV

Relative risks (RRs) of ovulatory infertility associated with the specified isocaloric substitution of protein

	Age and energy-adjusted		Multivariate adjusted *	
	RR (95% CI)	*p*	RR (95% CI)	*p*
Substitution for the average mixture of other energy sources †				
Animal Protein (5% of energy)	1.18 (1.01, 1.37)	0.03	1.19 (1.03, 1.38)	0.02
Vegetable Protein (5% of energy)	0.73 (0.47, 1.13)	0.15	0.64 (0.40, 1.03)	0.07
Total Protein (5% of energy) §	1.17 (0.99, 1.38)	0.06	1.18 (1.01, 1.38)	0.04
Substitution for carbohydrates ‡				
Animal Protein (5% of energy)	1.20 (1.02, 1.40)	0.03	1.19 (1.02, 1.39)	0.03
Vegetable Protein (5% of energy)	0.52 (0.30, 0.91)	0.02	0.57 (0.32, 1.00)	0.05
Total Protein (5% of energy) §	1.22 (1.04, 1.44)	0.02	1.22 (1.04, 1.43)	0.01

* Adjusted for age (continuous), calendar time (4 two-year intervals) and total energy intake (continuous), body mass index (<20, 20–24.9, 25–29.9, ≥30 and missing), parity (0, 1, ≥2 and missing), smoking history (never, past 1–4 cig/day, past 5–14 cig/day, past 15–24 cig/day, past ≥ 25 cig/day or unknown amount, current 1–4 cig/day, current 5–14 cig/day, current 15–24 cig/day and current ≥ 25 cig/day or unknown amount), physical activity (<3 MET-h/wk, 3–8.9 MET-h/wk, 9–17.9 MET-h/wk, 18–26.9 MET-h/wk, 27–41.9 MET-h/wk, ≥ 42 MET-h/wk and missing), oral contraceptive use (current user, never user, past user 0–23 months ago, past user 24–47 months ago, past user 48–71 months ago, past user 72–95 months ago, past user 96–119 months ago, past user ≥ 120 months ago and missing), frequency of multivitamin use (non-users, ≤2 tablets/week, 3 to 5 tablets/week, ≥6 tablets/week and missing), intake of alcohol (no intake, < 2 g/day, 2–4.9 g/day, ≥ 5 g/day), coffee (<1 serving/month, 1 serving/month, 2–6 servings/week, 1 serving/day, 2–3 servings/day, ≥ 4 servings/day) and quintiles of intake of retinol and iron.

† From separate models including linear terms for each type of protein and total energy intake as predictors.

‡ From a single model including as predictors linear terms for intakes of animal and vegetable protein, major types of fatty acids (saturated, mono-unsaturated, poly-unsaturated and *trans*-unsaturated) and total energy.

§ Total protein was entered into a different model not including the specific types of protein.