Dietary fatty acid intakes and the risk of ovulatory infertility

Jorge E Chavarro, Janet W Rich-Edwards, Bernard A Rosner, and Walter C Willett

ABSTRACT
Background: Pharmacologic activation of the peroxisome proliferator-activated receptor γ (PPAR-γ) improves ovulatory function in women with polycystic ovary syndrome, and specific dietary fatty acids can affect PPAR-γ activity.

Objective: The objective of the study was to assess whether the intakes of total fat, cholesterol, and major types of fatty acids affect the risk of ovulatory infertility.

Design: We conducted a prospective cohort study of 18,555 married, premenopausal women without a history of infertility who attempted a pregnancy or became pregnant between 1991 and 1999. Diet was assessed twice during follow-up by using a food-frequency questionnaire.

Results: During follow-up, 438 incidents of ovulatory infertility were reported. In logistic regression analyses, intakes of total fat, cholesterol, and most types of fatty acids were not related to ovulatory infertility. Each 2% increase in the intake of energy from trans unsaturated fats, as opposed to that from carbohydrates, was associated with a 73% greater risk of ovulatory infertility after adjustment for known and suspected risk factors for this condition [relative risk (RR) = 1.79; 95% CI: 1.11, 2.89]. Obtaining 2% of energy from trans fats rather than from n−6 polyunsaturated fats was associated with a similar increase in the risk of ovulatory infertility (RR = 1.73; 95% CI: 1.11, 2.69). In addition, obtaining 2% of energy from trans fats rather than from monounsaturated fats was associated with a more than doubled risk of ovulatory infertility (RR = 2.31; 95% CI: 1.09, 4.87).

Conclusion: Trans Unsaturated fats may increase the risk of ovulatory infertility when consumed instead of carbohydrates or unsaturated fats commonly found in nonhydrogenated vegetable oils. Am J Clin Nutr 2007;85:231–7.

KEY WORDS Diet, dietary fatty acids, infertility, ovulation, reproductive medicine, nutritional epidemiology

INTRODUCTION
Infertility, defined as the inability to conceive after 12 mo of unprotected intercourse (1), is a common problem affecting 10–15% of couples (2). More than 7 million women in the United States have an impaired ability to bear children (3), and, by 2025, as many as 7.7 million women are expected to face this problem (4). Assisted reproduction technologies have been developed to overcome infertility, but their costs (5–7) make them a less-than-ideal option for tackling infertility at a population level (8). Thus, identifying modifiable risk factors to prevent infertility is important.

The role of diet and other modifiable lifestyle practices in infertility is largely unexplored. However, considerable evidence suggests that dietary factors affecting insulin sensitivity may have an important role in the etiology of some forms of infertility. Factors known to increase insulin resistance, such as increased body weight and decreased physical activity, have been associated with an increased risk of infertility due to ovulatory dysfunction (9, 10). In addition, biochemical markers of sustained hyperglycemia, such as high concentrations of glycated hemoglobin, have been prospectively linked to decreased fertility (11). Moreover, in clinical trials of insulin sensitizers, including those that activate the peroxisome proliferator–activated receptor γ (PPAR-γ), these medications have improved reproductive metabolic profiles and ovulatory function in women with polycystic ovary syndrome (PCOS; 12–17).

Specific dietary unsaturated fatty acids can bind PPAR-γ (18), but their effects appear to differ for cis and trans isomers (19). Higher intake of cis unsaturated fatty acids (commonly found in nonhydrogenated vegetable oils and salad dressings) has been associated with lower concentrations of inflammatory markers (20, 21) and risk of type 2 diabetes (22), as well as with improved metabolic and endocrine characteristics in women with PCOS (23). Conversely, the consumption of trans fats (commonly found in commercially fried and baked products) instead of other macronutrients has been associated with greater inflammation (21, 24), insulin resistance (25), and risk of type 2 diabetes (22). Thus, we decided to test the hypotheses that trans unsaturated fatty acids (TFAs) increase the risk of ovulatory infertility whereas polyunsaturated fatty acids (PUFAs) reduce this risk.

SUBJECTS AND METHODS
Subjects
The Nurses’ Health Study II is a prospective cohort study of 116,671 female registered nurses who were 24–42 y old at study inception in 1989. The current study is a prospective analysis of...
incident ovulatory infertility among married women who provided dietary information as part of their participation in the Nurses’ Health Study II. 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. Every 2 y, participants were asked if they had tried for >1 y to become pregnant and to indicate whether their inability to conceive was cause by tubal blockage, ovulatory disorder, endometriosis, cervical mucus factor, or spousal factor or was not found, was not investigated, or was due to another condition. In a validation study of women who reported ovulatory infertility in 1989, self-reported ovulatory infertility was confirmed by review of medical records in 95% of the cases (9). Participants were also asked if they became pregnant—including pregnancies resulting in live births, miscarriages, or induced abortions—during the preceding 2-y period. With this information, we reconstructed a cohort of women who were trying to become pregnant. Only married women [whose pregnancies are more likely to be intentional than those of unmarried women (3)] 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 2-y period in which they reported a pregnancy or a failed pregnancy attempt, and they 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.

Type 2 diabetes has been associated with the intake of some fatty acids (22) and may affect ovulatory function. Of the 1987 women diagnosed with type 2 diabetes through 1999, 886 were unmarried, 408 had a history of infertility, 308 had undergone sterilization, 256 had reached menopause, 116 did not become pregnant or attempt a pregnancy during follow-up, and 3 did not have dietary data; thus, 10 diabetic women remained who met the selection criteria. Because this small number of diabetic subjects would preclude meaningful statistical adjustment for diabetes, these 10 women with diabetes were excluded from analysis. After exclusions, we identified 18 555 women without a history of infertility who tried to become pregnant or became pregnant between 1991 and 1999.

Women who met the selection criteria and reported infertility due to ovulatory disorder during follow-up, including those reporting multiple infertility diagnoses, were considered cases. All other events (pregnancies—whether resulting in live births, miscarriages, or induced abortions—and infertility due to other causes) were considered noncases.

Dietary assessment

Dietary information was collected in 1991 and 1995 by using a semiquantitative food-frequency questionnaire (FFQ) with 133 and 142 food items, respectively. Participants were asked to report how often during the previous year, on average, they had consumed each of the foods and beverages included in the FFQ. The questionnaire had 9 options for frequency of intake, ranging from never or <1 time/mo to ≥6 times/d. Nutrient intakes were estimated by summing the nutrient contribution of all food items in the questionnaire and taking into consideration the brand and type of margarine and the types of fat used in cooking and baking. The nutrient contents of each food and specified portion size were obtained from a nutrient database derived from the US Department of Agriculture (26) 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 nonenergy-bearing nutrient intakes, these intakes were adjusted for total energy intake with the use of the nutrient residual method (27).

The FFQ has been previously found to be reproducible and valid for the measurement of fat intake. In a validation study, the deattenuated correlation coefficients between FFQ estimates of nutrient intakes and the estimated intake from the average of repeated dietary records were 0.68 for saturated fatty acids (SFAs), 0.48 for PUFAs, and 0.58 for monounsaturated fatty acids (MUFA) (28). In another study, the correlation between calculated trans unsaturated fat intake from FFQ and TFAs in subcutaneous fat aspirates was 0.51 (29).

To determine whether recent or long-term diet was more relevant in the pathogenesis of ovulatory infertility, we defined dietary intakes in 2 ways. First, we used the most recent intakes, whereby the 1991 diet was used for the 1991–1995 follow-up period and the 1995 diet was assigned to the 1995–1999 follow-up. Second, in separate analyses we calculated cumulative averaged intakes to represent long-term diet. Specifically, the 1991 intakes were used to represent diet during the 1991–1995 follow-up period and the average of the 1991 and 1995 intakes was used for the 1995–1999 period.

Assessment of covariates

We collected information about nondietary covariates known or suspected to be related to ovulatory infertility including age, body mass index (BMI), parity, smoking and physical activity. Data were updated as follow-up questionnaires became available. In addition, we identified women with phenotypical features of PCOS: hyperandrogenism (defined as a history of physician-diagnosed severe teenage acne or use of isotretinoin during adolescence and a history of physician-diagnosed hirsutism) and a lifetime pattern of long menstrual cycles (≥40 d at ages 18–22 y and in 1993).

Statistical analysis

The relative risk of infertility according to dietary fat intake was estimated by using proportional hazards regression. Participants contributed 2 person-years of follow-up for each eligible pregnancy or pregnancy attempt. Because dates of ovulatory infertility diagnosis were not available, all events within each 2-y period were coded as having occurred simultaneously, and the exact method of handling ties (30) was used to account for this.

To assess the shape of the relation between the intake of specific types of fat and ovulatory infertility, we modeled these exposure in 3 ways. First, we divided women into 5 groups by quintile of the percentage of energy obtained from each type of fat. In these models, the relative risk (RR) was computed as the rate of infertility in a specific quintile of intake compared with that in the lowest quintile. Tests for linear trend were conducted by using the median values of intake in each category as a continuous variable. With the available sample size and number of cases, the statistical power to detect significant associations was >80% when the RR comparing extreme quintiles of fatty acid intake was >1.54 or <0.57. Second, we modeled fat intake as a continuous variable by using a linear term to achieve maximum
analyses were performed by using SAS software (version 8.2; SAS Institute, Cary, NC). Analyses were performed by using SAS software (version 8.2; SAS Institute, Cary, NC). Analyses were performed by using SAS software (version 8.2; SAS Institute, Cary, NC).

Results
During 8 y of follow-up, 26,971 eligible pregnancies or pregnancy attempts were identified in 18,555 women, infertility from any cause was reported for the first time by 3430 women, of whom 2165 underwent an investigation of the cause of infertility, and 438 were incident ovulatory infertility cases. As compared with women with lower total fat intake, women with a higher intake of total fat were younger and consumed less alcohol (Table 1); they also were heavier, less physically active, more likely to smoke, and more likely to report use of oral contraception at the beginning of the mailing cycle in which they entered the study. Moreover, women with higher fat intake were less likely to use multiple vitamin supplements and to be nulliparous than were those with lower fat intake. The associations between individual characteristics and intakes of specific types of fat were similar to those described for total fat intake.

We initially explored the relation between recent dietary fat intake and ovulatory infertility. In age and energy-adjusted analyses in which dietary fat was modeled by quintiles of intake (Table 2), total fat intake was inversely related to the risk of ovulatory infertility (RRQ5 versus Q1 = 0.80; 95% CI: 0.60, 1.06; P for trend = 0.02). This association appeared to be driven by intake of SFAs (RRQ5 versus Q1 = 0.69; 95% CI: 0.52, 0.94; P for trend < 0.01) and MUFAs (RRQ5 versus Q1 = 0.82; 95% CI: 0.62, 1.08; P for trend = 0.03). After adjustment for potential confounders, these associations were considerably weaker and no longer significant. Simultaneous introduction of all major types of fat and protein intake into the multivariate adjusted models did not change the results for SFAs or MUFAs. However, a weak nonsignificant trend toward increasing risk of ovulatory infertility with increasing TFA intake was observed. Intakes of cholesterol and PUFAs were unrelated to ovulatory infertility in these analyses.

Recent fat intake was subsequently modeled as a continuous variable (Table 3). When each of the types of fat was analyzed separately (to estimate the effect of the isocaloric substitution of fat for the average macronutrient mixture in the study population), total fat intake and intakes of saturated and MUFAs were...
TABLE 2
Relative risks (95% CIs) of ovulatory infertility by quintile (Q) of recent dietary fat intake

<table>
<thead>
<tr>
<th>Type of fat</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P for trend²</th>
</tr>
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<tbody>
<tr>
<td>Total fat</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (% of calories)</td>
<td>23.5</td>
<td>27.8</td>
<td>30.6</td>
<td>33.4</td>
<td>37.5</td>
<td></td>
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<tr>
<td>Case/noncases (n)</td>
<td>111/5283</td>
<td>95/5300</td>
<td>78/5316</td>
<td>67/5327</td>
<td>87/5307</td>
<td></td>
</tr>
<tr>
<td>Age- and energy-adjusted†</td>
<td>1.00 (referent)</td>
<td>0.87 (0.66, 1.15)</td>
<td>0.73 (0.55, 0.98)</td>
<td>0.63 (0.46, 0.86)</td>
<td>0.80 (0.60, 1.06)</td>
<td>0.02</td>
</tr>
<tr>
<td>Multivariate-adjusted 1ª</td>
<td>1.00 (referent)</td>
<td>0.97 (0.74, 1.29)</td>
<td>0.87 (0.65, 1.18)</td>
<td>0.72 (0.53, 1.00)</td>
<td>0.90 (0.66, 1.21)</td>
<td>0.18</td>
</tr>
<tr>
<td>Cholesterol</td>
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<td></td>
<td></td>
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<tr>
<td>Median intake (mg)</td>
<td>162</td>
<td>202</td>
<td>230</td>
<td>262</td>
<td>314</td>
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<tr>
<td>Case/noncases (n)</td>
<td>103/5330</td>
<td>82/5188</td>
<td>81/5459</td>
<td>81/5204</td>
<td>91/5352</td>
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</tr>
<tr>
<td>Age- and energy-adjusted‡</td>
<td>1.00 (referent)</td>
<td>0.84 (0.63, 1.12)</td>
<td>0.80 (0.60, 1.07)</td>
<td>0.86 (0.64, 1.15)</td>
<td>0.89 (0.67, 1.18)</td>
<td>0.53</td>
</tr>
<tr>
<td>Multivariate-adjusted 1ª</td>
<td>1.00 (referent)</td>
<td>0.89 (0.66, 1.20)</td>
<td>0.86 (0.64, 1.16)</td>
<td>0.92 (0.68, 1.24)</td>
<td>0.94 (0.70, 1.26)</td>
<td>0.77</td>
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<tr>
<td>Saturated fat</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (% of calories)</td>
<td>8.0</td>
<td>9.8</td>
<td>11.0</td>
<td>12.2</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>Case/noncases (n)</td>
<td>11/5282</td>
<td>102/5294</td>
<td>81/5313</td>
<td>69/5325</td>
<td>75/5319</td>
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</tr>
<tr>
<td>Age- and energy-adjusted‡</td>
<td>1.00 (referent)</td>
<td>0.96 (0.73, 1.25)</td>
<td>0.76 (0.57, 1.01)</td>
<td>0.64 (0.47, 0.88)</td>
<td>0.69 (0.52, 0.94)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Multivariate-adjusted 1ª</td>
<td>1.00 (referent)</td>
<td>1.11 (0.84, 1.47)</td>
<td>0.91 (0.67, 1.23)</td>
<td>0.76 (0.56, 1.05)</td>
<td>0.82 (0.59, 1.13)</td>
<td>0.06</td>
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<td>Monounsaturated fat</td>
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<td></td>
</tr>
<tr>
<td>Median intake (% of calories)</td>
<td>8.6</td>
<td>10.4</td>
<td>11.6</td>
<td>12.8</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>Case/noncases (n)</td>
<td>112/5282</td>
<td>95/5299</td>
<td>73/5321</td>
<td>68/5327</td>
<td>90/5304</td>
<td></td>
</tr>
<tr>
<td>Age- and energy-adjusted‡</td>
<td>1.00 (referent)</td>
<td>0.87 (0.66, 1.15)</td>
<td>0.68 (0.50, 0.91)</td>
<td>0.64 (0.47, 0.87)</td>
<td>0.82 (0.62, 1.08)</td>
<td>0.03</td>
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<tr>
<td>Multivariate-adjusted 1ª</td>
<td>1.00 (referent)</td>
<td>0.95 (0.72, 1.26)</td>
<td>0.79 (0.59, 1.08)</td>
<td>0.74 (0.54, 1.01)</td>
<td>0.90 (0.66, 1.21)</td>
<td>0.23</td>
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<tr>
<td>Polyunsaturated fat</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (% of calories)</td>
<td>3.8</td>
<td>4.5</td>
<td>5.1</td>
<td>5.8</td>
<td>6.9</td>
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<tr>
<td>Case/noncases (n)</td>
<td>94/5299</td>
<td>90/5306</td>
<td>84/5310</td>
<td>78/5317</td>
<td>92/5301</td>
<td></td>
</tr>
<tr>
<td>Age- and energy-adjusted‡</td>
<td>1.00 (referent)</td>
<td>0.99 (0.74, 1.32)</td>
<td>0.93 (0.69, 1.25)</td>
<td>0.87 (0.64, 1.18)</td>
<td>1.01 (0.75, 1.35)</td>
<td>0.87</td>
</tr>
<tr>
<td>Multivariate-adjusted 1ª</td>
<td>1.00 (referent)</td>
<td>1.03 (0.77, 1.38)</td>
<td>0.96 (0.71, 1.30)</td>
<td>0.87 (0.63, 1.19)</td>
<td>0.99 (0.63, 1.19)</td>
<td>0.70</td>
</tr>
<tr>
<td>trans Unsaturated fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (% of calories)</td>
<td>0.9</td>
<td>1.2</td>
<td>1.4</td>
<td>1.7</td>
<td>2.3</td>
<td></td>
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<tr>
<td>Case/noncases (n)</td>
<td>108/5286</td>
<td>75/5320</td>
<td>80/5314</td>
<td>84/5310</td>
<td>91/5303</td>
<td></td>
</tr>
<tr>
<td>Age- and energy-adjusted‡</td>
<td>1.00 (referent)</td>
<td>0.69 (0.51, 1.93)</td>
<td>0.76 (0.56, 1.01)</td>
<td>0.81 (0.60, 1.08)</td>
<td>0.86 (0.64, 1.14)</td>
<td>0.74</td>
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<td>Multivariate-adjusted 1ª</td>
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<td>0.79 (0.59, 1.07)</td>
<td>0.92 (0.68, 1.24)</td>
<td>0.94 (0.70, 1.27)</td>
<td>0.90 (0.72, 1.34)</td>
<td>0.74</td>
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<tr>
<td>Multivariate-adjusted 2ª</td>
<td>1.00 (referent)</td>
<td>0.87 (0.64, 1.20)</td>
<td>1.11 (0.79, 1.55)</td>
<td>1.21 (0.85, 1.73)</td>
<td>1.31 (0.88, 1.95)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

1 n = 26,971.
2 Calculated with median intake of fat in each quintile as a continuous variable.
3 Model stratified by age (1-y intervals) and calendar time (four 2-y intervals) and adjusted for total energy intake (continuous).
4 Age- and energy-adjusted model further adjusted for BMI (<20, 20–24.9, 25–29.9, ≥30, or missing), parity (0, 1, ≥2, or missing), smoking history (never; previously 1–4, 5–14, 15–24, or ≥25 cigarettes/d or unknown amount; or current 1–4, 5–14, 15–24, or ≥25 cigarettes/d or unknown amount), physical activity (<3, 3–8, 9–17.9, 18–26.9, 27–41.9, or ≥42 MET-h/wk or missing), contraceptive use (current user; never user; past user 0–23, 24–47, 48–71, 72–95, 96–119, or ≥120 mo ago or missing), use of multivitamins (yes or no), intake of alcohol (no intake or <2, 2–4.9, or ≥5 g/d), coffee (<1 serving/mo, 1 serving/mo, 2–6 servings/week, 1 serving/week, 2–3 servings/week, or ≥4 servings/week), and quintiles of retinol, iron, and α-carotene intakes.
5 Multivariate-adjusted model 1 plus quintiles of intake for the remaining types of fat (saturated, monounsaturated, polyunsaturated, and trans fat) and quintiles of protein intake.

Inversely related to the risk of infertility in age- and energy-adjusted models but unrelated to infertility in multivariate-adjusted models. When the intakes of protein and all major types of fat were simultaneously included in the models (to estimate the effect of the isocaloric substitution of fat for carbohydrates), intake of TFAs was positively associated with risk of ovulatory infertility. A 2% increase in energy intake from TFAs was associated with a 94% greater risk of ovulatory infertility (95% CI: 22%, 208%) in age- and energy-adjusted analyses. This association remained significant after adjustment for potential confounders, although the estimated risk increase was somewhat lower (Table 3). Adjustment for BMI, parity, use of oral contraceptives, and intakes of alcohol and iron produced the largest changes in the association between TFAs and ovulatory infertility. Intakes of SFAs, MUFAs, total PUFAs, n-3 PUFAs, and n-6 PUFAs were not associated with ovulatory infertility.
We used the regression coefficients from this multivariate model to estimate the effect of the isocaloric substitution of one type of fat for another and found that eating TFAs instead of carbohydrates, MUFAs, or n-6 PUFAs was associated with a significantly greater risk of ovulatory infertility (RR = 1.79; 95% CI: 1.11, 2.89; P = 0.02).

Because the results of the models simulating nutrient substitutions rely on an assumption of a linear relation between fat intakes and ovulatory infertility, we evaluated that assumption. No evidence was found for a nonlinear relation between the intake of SFAs (P = 0.32), MUFAs (P = 0.83), PUFAs (P = 0.21), or TFAs (P = 0.35) and ovulatory infertility. Similarly, there was no evidence of differences in the associations between intake of fatty acids and ovulatory infertility by levels of age, BMI, menstrual cycle length, hyperandrogenism, parity, oral contraceptive use, smoking or multivitamin use (BMI, menstrual cycle length, hyperandrogenism, parity, oral intake of fatty acids and ovulatory infertility by levels of age, there was no evidence of differences in the associations between

<table>
<thead>
<tr>
<th>Substitution for the average mixture of other energy sources</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fat (5% of energy)</td>
<td>0.74 (0.61, 0.91)</td>
<td>&lt;0.01</td>
<td>0.84 (0.68, 1.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>Monounsaturated fat (5% of energy)</td>
<td>0.78 (0.64, 0.95)</td>
<td>0.01</td>
<td>0.86 (0.70, 1.05)</td>
<td>0.14</td>
</tr>
<tr>
<td>Polyunsaturated fat (5% of energy)</td>
<td>1.01 (0.69, 1.47)</td>
<td>0.96</td>
<td>0.94 (0.65, 1.37)</td>
<td>0.76</td>
</tr>
<tr>
<td>trans Unsaturated fat (2% of energy)</td>
<td>0.99 (0.71, 1.39)</td>
<td>0.97</td>
<td>1.09 (0.77, 1.54)</td>
<td>0.61</td>
</tr>
<tr>
<td>Total fat intake (5% of energy)</td>
<td>0.90 (0.83, 0.98)</td>
<td>0.02</td>
<td>0.94 (0.86, 1.03)</td>
<td>0.17</td>
</tr>
<tr>
<td>Substitution for carbohydrates</td>
<td>0.77 (0.55, 1.07)</td>
<td>0.12</td>
<td>0.86 (0.61, 1.20)</td>
<td>0.38</td>
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<tr>
<td>Monounsaturated fat (5% of energy)</td>
<td>0.68 (0.45, 1.03)</td>
<td>0.07</td>
<td>0.75 (0.49, 1.13)</td>
<td>0.17</td>
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<tr>
<td>Polyunsaturated fat (5% of energy)</td>
<td>1.31 (0.83, 2.08)</td>
<td>0.25</td>
<td>1.09 (0.69, 1.73)</td>
<td>0.70</td>
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<tr>
<td>trans Unsaturated fat (2% of energy)</td>
<td>1.94 (1.22, 3.08)</td>
<td>&lt;0.01</td>
<td>1.73 (1.09, 2.73)</td>
<td>0.02</td>
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<tr>
<td>Total fat intake (5% of energy)</td>
<td>0.89 (0.82, 0.97)</td>
<td>0.01</td>
<td>0.93 (0.85, 1.02)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

1 n = 26,971.
2 Models are stratified by age (1-y intervals) and calendar time (four 2-y intervals) and adjusted for total energy intake (continuous), BMI (≤20, 20–24.9, 25–29.9, ≥30, or missing), parity (0, 1, ≥2, or missing), smoking history (never; previously 1–4, 5–14, 15–24, or ≥25 cigarettes/d or unknown amount; current 1–4, 5–14, 15–24, or ≥25 cigarettes/d or unknown amount), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, 27–41.9, or ≥42 MET-h/wk or missing), contraceptive use (current user; never user; past user 0–23, 24–47, 48–71, 72–95, 96–119, or ≥120 mo ago or missing), use of multivitamins (yes or no), intake of alcohol (no intake or <2, 2–4.9, or ≥5 g/d), coffee (<1 serving/mo, 1 serving/mo, 2–6 servings/wk, 1 serving/d, 2–3 servings/d, or ≥4 servings/d), and quintiles of retinol, iron, and α-carotene intakes.
3 From separate models including linear terms for each type of fat and total energy intake as predictors.
4 From a single model including linear terms for all types of fat (saturated, monounsaturated, polyunsaturated, and trans unsaturated), protein intake, and total energy intake as predictors.
5 Total fat was entered into a different model not including the specific types of fat.

The analyses exploring the association between cumulative averaged fat intakes and ovulatory infertility showed similar results, albeit slightly attenuated. The multivariate-adjusted RRs for the estimated isocaloric substitution of fat for carbohydrates were 0.84 for SFAs (5% of energy; 95% CI: 0.59, 1.20), 0.77 for MUFAs (5% of energy; 95% CI: 0.49, 1.22), 1.11 for total PUFAs (5% of energy; 95% CI: 0.69, 1.79), 1.40 for n−3 PUFAs (1% of energy; 95% CI: 0.64, 3.05), 0.99 for n−6 PUFAs (1% of energy; 95% CI: 0.87, 1.12) and 1.67 for TFAs (2% of energy; 95% CI: 1.04, 2.69).

**DISCUSSION**

We examined the association between the intakes of different types of fat and ovulatory infertility and found that consuming TFAs instead of carbohydrates, MUFAs, or n−6 PUFAs was associated with a greater risk of this disease. The results did not differ according to a woman’s age, parity, past use of oral contraception, smoking, BMI, or menstrual cycle length or the presence of clinical manifestations of excess androgens. Although the association between fat intake and the risk of infertility has not, to our knowledge, previously been examined in humans, studies of women with PCOS suggested that this association would resemble that between fat intake and insulin resistance. A randomized trial in which 782 women with PCOS were assigned to a daily intake of 150, 300, or 600 mg/d of troglitazone or placebo for a total of 44 wk documented dose-dependent improvements in signs of ovulatory dysfunction, such as ovulation rate and pregnancy rates, as well as in clinical and biochemical signs of hyperandrogenemia (13). Similar results
have been observed in trials involving other pharmacologic ac-

tivators of PPAR-γ (14–16). These results support our finding re-
garding the associations between the intake of trans fats and ovulatory infertility because, at levels of usual human consump-
tion, TFAs have been found to down-regulate PPAR-γ expres-
sion in vivo by ≈40% (33). The intake of TFAs has also been
associated with greater insulin resistance (25), risk of type 2
diabetes (22), and concentrations of inflammatory markers (21,
24), which may adversely affect ovulatory function (34). These
mechanisms could explain the observed association between
the intake of TFAs and the risk of ovulatory infertility, although
alternative mechanisms cannot be ruled out.

Intake of PUFAs was not protective of ovulatory infertility in
the entire group of women. However, a strong inverse association
was noted in women with high iron intake, and mechanisms that
could explain this interaction have been described. The activity
of Δ-6 desaturase (an enzyme that participates in the conversion
of linoleic acid into arachidonic acid and of α-linolenic acid into
eicosapentaenoic acid and docosahexaenoic acid) is significantly
impaired in persons with low serum iron concentrations (35), and
iron is an important functional component of this enzyme (36).
Because arachidonic acid and eicosapentaenoic acid bind
PPAR-γ more efficiently than do PUFAs with shorter chain
lengths (37), the observed interaction would be expected if
women with low iron intakes had impairments in this metabolic
pathway, whereas women with a high iron intake could endog-

enously produce long-chain PUFAs more efficiently through this
pathway. In addition, iron is a known oxidant, and oxidated
metabolites of PUFAs are more potent ligands of PPAR-γ than
are PUFAs themselves (38). It is tempting to conclude that the
mechanism described above explains the observed effect modi-
fication, especially after adjustment for the high prevalence of
depleted iron stores observed among young women in national
surveys (21%) (39). Nevertheless, this interaction should be in-
terpreted with caution, given that the intake of heme iron has been
associated with a greater risk of outcomes related with insulin
resistance (40) and that multiple tests for effect modification
were conducted, which makes it possible that this finding was
due to chance.

We observed inverse associations between the estimated iso-
caloric substitutions of total fat and saturated fat for the average
mixture of other energy sources and risk of ovulatory infertility
in age- and energy-adjusted models but not in multivariate-
adjusted models. Disturbances of menstrual cycles that could be
causal intermediates for ovulatory infertility, such as secondary
amenorrhea, increased menstrual cycle length, and increased
follicular phase length, were previously associated in smaller
studies (41–45) with low intakes of total fat or saturated fat.
However, some of these studies did not consider differences in
total energy intake or other subject characteristics as alternative
explanations for their findings (43, 44), and feeding studies made
simultaneous changes in intakes of protein (42) and the ratios of
saturated to monounsaturated to polyunsaturated fats (41, 45),
which limited the ability of the investigators to draw conclusions
regarding intakes of specific types of fat.

Strengths of the current study include its prospective nature:
diet was collected 2–4 y before events were reported, which
made it unlikely that results were affected by a subject’s fertility
status at the time of dietary report. The use of previously vali-
dated questionnaires of dietary intake and outcome assessment is
also a strength of the current study. The most important limitation
is that the subjects are not a cohort of women known to be
planning to become pregnant. Cases, who were clearly attempt-
ing to conceive, may have been more health-conscious than the
pregnancy noncases, who may have conceived accidentally.
However, TFA intake is inversely associated with markers of
health consciousness, and thus increased health consciousness of
cases is more likely to have caused an inverse association, rather
than the positive association between TFAs and ovulatory infer-

tility we observed. Moreover, we simulated a cohort of preg-
nancy planners in our study by including only married women
and by including in the noncase group women who were diag-

nosed with infertility from other causes. These steps made it less
likely that pregnancy intention would affect our results. Another
limitation was that selection bias might have been introduced by
including only clinically recognizable outcomes of a pregnancy
attempt in the study. However, pregnancy attempts with clini-
cally nonrecognizable outcomes, such as early pregnancy losses,
are likely to have been identified as infertility of unknown eti-
ology or to be due to other causes, thus minimizing any potential
selection bias. In addition, any bias present is unlikely to be any
more influential than that introduced by design into traditional
case-control studies of infertility or retrospective time-to-
pregnancy studies, both of which have been useful in identifying
risk factors for infertility. Because the current study was obser-
vational, we cannot completely rule out the possibility that our
findings may be due in part to unmeasured confounders of the
associations. Nevertheless, our results were statistically adjusted
for numerous recognized risk factors for infertility and several
other factors associated with ovulatory infertility in this popula-
tion. Finally, because the study included only 438 ovulatory
infertility cases, our statistical power to detect a significant as-

sociation in categorical analyses based on quintiles of intake was
limited (≈40% in the trans fatty acids analysis). However, we
complemented those analyses with more powerful analyses us-
ing fat intakes as continuous variables, and those analyses
showed that some of the hypothesized relations were significant.

In conclusion, our data suggest that dietary trans fatty acids
increase the risk of ovulatory infertility when they replace car-
bohydrates or the unsaturated fats that are commonly found in
vegetable oils. Given that these associations have not previously
been reported, our findings should be reproduced, preferably in
large prospective studies and randomized trials involving cou-
ples known to be planning a pregnancy. Because replacing trans
fats with nonhydrogenated vegetable oils is likely to reduce the
risk of coronary heart disease (46) and type 2 diabetes (22),
women planning to become pregnant should consider this strat-
egy; it could reduce their risk of infertility as well.

All authors were responsible for the study concept and design; WCW
obtained funding and collected data; JEC analyzed the data and drafted the
manuscript; BAR provided statistical support; and all authors critically re-
viewed and revised the manuscript. None of the authors had a personal or
financial conflict of interest.

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