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Caffeinated and alcoholic beverage intake in relation to ovulatory disorder infertility

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Abstract

Background—Many studies have examined whether caffeine, alcohol, or specific beverages containing these affect fertility in women. However most of these studies have retrospectively collected information on alcohol and caffeine intake, making the results susceptible to biases.

Methods—We followed 18,555 married women without a history of infertility for 8 years as they attempted to become (or became) pregnant. Diet was measured twice during this period and prospectively related to the incidence of ovulatory disorder infertility.

Results—There were 438 incident report of ovulatory disorder infertility during follow-up. Intakes of alcohol and caffeine were unrelated to the risk of ovulatory disorder infertility. The multivariate-adjusted relative risk (RR), 95% confidence interval (CI), *P* for trend comparing the highest to lowest categories of intake were 1.11 (0.76–1.64; 0.78) for alcohol and 0.86 (0.61–1.20; 0.44) for total caffeine. However, intake of caffeinated soft drinks was positively related to ovulatory disorder infertility. The multivariate-adjusted RR 95% CI, and *P* for trend comparing the highest to lowest categories of caffeinated soft drink consumption were 1.47 (1.09–1.98; 0.01). Similar associations were observed for noncaffeinated, sugared, diet and total soft drinks.

Conclusions—Our findings do not support the hypothesis that alcohol and caffeine impair ovulation to the point of decreasing fertility. The association between soft drinks and ovulatory disorder infertility appears not to be attributable to their caffeine or sugar content, and deserves further investigation.

INTRODUCTION

No aspects of diet have been studied as much as caffeine and alcohol intake as potential disruptors of human fertility. To date, 28 studies have investigated whether these substances affect fertility in women.^{1–28} Results across studies are inconsistent, with studies showing deleterious effects of caffeine^{2,3,5–8,12,13,18,20} and alcohol^{10,17,22,25–28} on fertility, and

nearly as many studies showing no association^{1,4,9,11,14–17,19–21,23} or even improved fertility with consumption of certain caffeinated or alcoholic beverages.^{9,15,24} One potential explanation for these inconsistencies is the fact that most of the studies are retrospective, and thus subject to recall and other types of bias.

Although clear pathophysiologic mechanisms for the purported effects of caffeine and alcohol on fertility have not been elucidated, both substances have been suggested to affect ovulation.²⁹ However, caffeine and alcohol intake have both been linked to improved insulin sensitivity,^{30–33} which in turn has been related to improved ovulatory function in women with polycystic ovary syndrome.³⁴ Polycystic ovary syndrome is the most common cause of anovulation in women of reproductive age, and the most common cause of infertility due to ovulation disorders.^{35–39} Moreover, neither caffeine nor alcohol intake is related to biologic markers of ovarian aging.⁴⁰ To investigate these associations, we prospectively evaluated whether intake of alcohol, caffeine, or specific alcoholic and caffeinated beverages were associated with the risk of infertility due to ovulatory disorders in a large group of apparently healthy women.

METHODS

Study Population

The Nurses' Health Study II started in 1989 when more than 116,000 female registered nurses ages 24–42 completed and returned a mailed baseline questionnaire. These women have been followed every 2 years since then with mailed questionnaires. Diet was first measured in 1991 and has been updated every 4 years. Our study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Follow-up for the current analysis started in 1991 and concluded in 1999. Further follow-up was not performed because of the low number of women in this cohort who attempted to become or became pregnant after 1999. On biennial questionnaires participants were asked whether they had tried to become pregnant for more than 1 year without success since the previous questionnaire administration, and whether their inability to conceive was caused by tubal blockage, ovulatory disorder, endometriosis, cervical mucus factor, spousal factor, or reasons. (Other options were no investigation of causes, and no cause discovered.) In a validation substudy, self-reported diagnosis of ovulatory disorder infertility was confirmed by review of medical records in 95% of the cases.⁴¹ In each follow-up questionnaire, women were asked if they became pregnant during the preceding 2-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 (defined as a report of infertility in any preceding questionnaire), were eligible to enter the analysis. These women contributed information to the analysis during each 2-year period in which they reported a pregnancy or a failed pregnancy attempt, and were followed until they reported infertility from any cause, reached menopause, or underwent a sterilization procedure (themselves or their partner), whichever came first.

Ten diabetic women met these criteria. Insulin resistance and hyperinsulinemia, hallmark characteristics of type 2 diabetes, may affect ovulatory function^{42,43} and have been associated with intake of alcohol and caffeine.^{30,32} Because 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, there were 18,555 women without a history of infertility who tried to become pregnant or became pregnant during the 8-year follow-up period.

Women who met the selection criteria and reported infertility due to ovulatory disorder were considered cases, and all other reports (infertility due to any other cause and pregnancies – including those terminating in live births, miscarriage, or elective abortion) were considered noncases. If a pregnancy and infertility were reported in the same follow-up questionnaire it was assumed that infertility preceded the pregnancy and the woman was counted as a case.

Dietary Assessment

Dietary information was collected in 1991 and 1995 using a food-frequency questionnaire (FFQ) with more than 130 food items, including 14 caffeinated or alcoholic beverages (eAppendix, <http://links.lww.com>). 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 9 options for frequency of intake, ranging from never or less than once per month to 6 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 Agriculture⁴⁴ and additional information obtained from food manufacturers. To reduce extraneous variation in nutrient intakes, these were adjusted for total energy intake using the nutrient residual method.⁴⁵

The FFQ has been previously found to provide valid and reproducible estimates of intake of caffeinated and alcoholic beverages.⁴⁶ As a measure of validity the de-attenuated correlation coefficients between estimated intake from the average of 4 prospectively collected 1-week diet records and from the FFQ were 0.78 for coffee, 0.93 for tea, 0.94 for beer, 0.90 for wine, 0.84 for spirits, 0.84 for cola carbonated beverages, and 0.36 for noncola carbonated beverages. As a measure of reproducibility the correlation coefficients between levels of consumption collected with FFQs 1 year apart were 0.75 for coffee, 0.86 for tea, 0.93 for beer, 0.76 for wine, 0.74 for spirits, 0.80 for cola carbonated beverages, and 0.81 for noncola carbonated beverages.⁴⁶

Statistical Analyses

Relative risks relating intakes of caffeine, alcohol, and specific beverages to the incidence of ovulatory disorder infertility were estimated using logistic regression. The generalized estimating equation approach⁴⁷ with an exchangeable working correlation structure was used to account for the within-person correlation in outcomes at different time periods. We first divided women into groups according to their intake frequency of alcohol and specific beverages, and into quintiles according to their intake of caffeine. Tests for linear trend were conducted using the median values of intake in each category as a continuous variable.

Analyses were performed using the most recent intakes (assigning the 1991 diet to events reported in 1993 and 1995 and the 1995 diet to events reported in 1997 and 1999) and cumulative averaged intakes, (assigning the 1991 diet to events reported in 1993, and the average of the 1991 and 1995 diets to the remainder of the follow-up period). The results from these 2 methods were nearly identical. Because cumulative averaged intakes reduce measurement error due to within-person random variation over time,⁴⁸ only results using this method are presented.

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 parity, body mass index ($\text{wt [kg]/ht}^2 [\text{m}^2]$) (BMI), smoking history, physical activity, history of oral contraceptive use, and a summary diet score that incorporated multiple dietary factors previously found to be related to infertility due to ovulation disorders in this population.⁴⁹ Multivariate models for alcohol and alcoholic beverages were also adjusted for caffeine

intake. Similarly, multivariate models for caffeine and caffeinated beverages included terms for alcohol intake. Values of the dietary and nondietary variables were updated as new data became available from follow-up questionnaires.

Last, we examined whether the association between caffeine, alcohol, or specific beverage intake and infertility was modified by age, parity, or smoking status. This was done by introducing cross-product terms between specific beverage intakes and the variable of interest. All *P* values were 2 sided. Analyses were performed in SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

During 8 years of follow-up there were 26,971 pregnancies and pregnancy attempts accrued among 18,555 women. Of these, 3430 (13% of all events) were incident reports of infertility, of which 2165 were of women who underwent medical investigation for infertility. Twenty percent of investigated infertility cases (438, or 2% of all events) were incident reports of ovulatory disorder infertility. Ovulatory disorder infertility cases were more likely to report additional manifestations of polycystic ovary syndrome (menstrual cycles >40 days and clinical signs of excess androgens) than women reporting infertility due to other causes (odds ratio [OR] = 4.2; confidence interval [CI] = 3.0–5.8) or women who became pregnant during follow-up (4.4; 3.4–5.9).

At baseline, women with higher intakes of caffeine or alcohol were older; had a lower intake of animal protein, carbohydrates, and iron; were less likely to use multivitamins; were more physically active; and more likely to be smokers, nulliparous, and recent users of oral contraception (Table 1). In addition, women with higher alcohol intakes had a lower intake of saturated fat and a lower BMI, whereas women with higher caffeine intakes had higher intakes of all types of fats.

Intake of alcohol and specific alcoholic beverages was positively related to ovulatory disorder infertility risk in age- and energy-adjusted analyses (Table 2). Women consuming 10 g or more of alcohol per day (approximately >1 drink/day) had nearly 50% greater risk of ovulatory infertility than women who did not drink any alcohol. Among the alcoholic beverages the association was strongest for intake of spirits. However, after adjusting for other factors (particularly parity) all of these associations disappeared.

Caffeine intake was unrelated to the risk of infertility due to ovulation disorders, as were coffee (the main source of caffeine in this population), decaffeinated coffee, and tea (Table 3). Intake of caffeinated soft drinks, however, was associated with a higher risk of ovulatory disorder infertility among women consuming at least 2 or more caffeinated soft drinks per day. In multivariate-adjusted analyses, women consuming 2 or more caffeinated soft drinks per day had a 47% greater risk of ovulatory infertility than women who consumed less than 1 caffeinated soft drink per week.

Because the analyses suggested that caffeinated soft drinks, but not other caffeinated beverages, might affect fertility, we recategorized coffee and caffeine intake to allow more extreme comparisons in an attempt to rule out the possibility that a true association had been distorted by collapsing a high-risk group (caffeinated soft drink users) together with a low-risk group (coffee drinkers) into the prespecified levels of coffee and caffeine intake. Performing these more extreme comparisons suggested the presence of an inverse association between coffee intake and ovulatory infertility risk. The multivariate-adjusted RR comparing women consuming coffee more than 4 times per day to women consuming coffee less than once weekly was 0.45 (0.21–0.97) with a statistically significant linear trend (*P* for trend = 0.05). Similarly, the multivariate-adjusted RR comparing women in the top

5% of the caffeine distribution (median intake 654 mg/day) with women in the bottom 5% (median intake 3 mg/day) was 0.51 (0.27–0.98) although a clear dose–response relationship was not apparent (Fig. 1).

We also included caffeine and caffeinated soft drinks in the same multivariate model to examine whether caffeine was responsible for the observed association of these soft drinks with ovulatory infertility. The association between caffeinated soft drinks and ovulatory infertility became stronger in this multivariate model that included additional terms for caffeine intake. The relative risk comparing women consuming these beverages twice or more per day with women consuming them once or less than once per week was 1.60 (1.15–2.22) (P for trend = 0.003). The RR for increasing quintiles of caffeine intake in the same model were 1.00, 0.91 (0.65–1.26), 0.82 (0.58–1.15), 0.91 (0.65–1.28), and 0.73 (0.51–1.05) (P for trend = 0.13).

To examine alternative explanations for these findings, we also examined the associations of noncaffeinated, sugared, diet, and all soft drinks combined, and fructose intake with ovulatory infertility risk. The RR comparing women consuming these beverages twice daily with those consuming them once or less each week was 1.31 (0.90–1.90; P for trend = 0.34) for noncaffeinated soft drinks; 1.54 (1.14–2.10; P for trend = 0.02) for sugared soft drinks; 1.41 (1.07–1.85; 0.01) for diet soft drinks and 1.33 (0.94 – 1.87; 0.02) for all soft drinks combined. Fructose intake was unrelated to ovulatory infertility risk. The RR for increasing quintiles of fructose intake were 1.03 (0.76–1.38); 1.10 (0.82–1.49); 0.92 (0.67–1.26); and 1.03 (0.76–1.41) (P for trend = 0.96).

Last, tests for interaction did not reveal significant differences in the association of these dietary factors with ovulatory infertility risk for women older or younger than 35 years of age, for nulliparous or parous women, or for current smokers or nonsmokers (P , interaction > 0.05 in all cases).

DISCUSSION

We prospectively examined the relation between the intake of alcoholic and caffeinated beverages and risk of infertility due to ovulation disorders. Only the consumption of 2 or more soft drinks per day was associated with this infertility after accounting for multiple potential confounders. The association between high consumption of soft drinks and ovulatory disorder infertility did not appear to depend on the caffeine content of these beverages. Further, there was no evidence that an association between caffeine, alcohol, or sodas and ovulatory infertility was restricted to subgroups of women defined by age, parity, or smoking status, as has been the case in some previous studies.^{6,12,18,26}

We found a positive association between alcohol intake of approximately 1 drink or more per day and ovulatory disorder infertility in age-adjusted analyses. This association disappeared after accounting for parity and other factors. Alcohol drinking at lower levels was unrelated to ovulatory infertility in all analyses. To date, 16 studies have examined the association between alcohol intake and fertility in women,^{1,9,10,14,15,17,19–28} many of them reporting deleterious effects of alcohol. However, only 5 of these studies have been prospective.^{9,17,22,26,27} Among the prospective studies, 2 reported decreased fecundability,^{17,22} 1 reported a higher risk of infertility,²⁷ 1 found a positive relation between alcohol and infertility among women older than 30 years of age but also a similarly strong inverse association among younger women,²⁶ and 1 found no association between alcohol intake and fecundability.⁹ Only 1 previous study has examined alcohol intake in relation to specific infertility diagnoses and found alcohol to be associated with a higher risk of infertility due to ovulatory factor or endometriosis.¹⁰ Our results are not in agreement

with this report. When our results are considered with those of all other prospective studies, there is an evenly divided field between null and positive studies. Clearly, more large prospective studies are necessary to clarify the role of moderate alcohol consumption on human fertility.

We did not observe a positive association between intake of caffeine, coffee, tea, or decaffeinated coffee and risk of ovulatory infertility. Indeed, supplementary analyses suggested a lower, rather than increased, risk of ovulation-related infertility with very high levels of coffee consumption, although these findings were based on only 7 cases and could be the result of chance. Ten of the 17 studies conducted to date have found a relation between coffee or caffeine intake and decreased fertility.^{2,3,5-8,12,13,18,20} Most of these studies are retrospective.^{3,5-8,12,13,20} When only the 5 prospective studies are considered, 2 reported decreased fecundability^{2,22} and 3 showed either no association^{16,17} or slightly improved fertility.⁹ Leviton and Cowan⁵⁰ have described how retrospective studies and studies of lower methodologic quality are more likely to report a relation between caffeine intake and impaired reproduction (including decreased fertility) than prospective studies. Furthermore, a positive association between prepregnancy coffee drinking and a higher rate of dizygotic twin pregnancies has been described,⁵¹ suggesting that caffeine may, if anything, stimulate ovulation rather than suppress it. Our results are in agreement with the majority of prospective epidemiologic studies conducted to date that suggest no association between caffeine intake and reduced fertility.

Soft drinks were the only beverages positively related to ovulatory infertility. Our analyses suggested that neither caffeine nor fructose was responsible for this association. Extreme comparisons of caffeine and coffee intake (coffee being the most important source of caffeine in this population) suggested no association or an inverse association with ovulatory disorder infertility. Also, including caffeine intake in the same multivariate model with caffeinated sodas made the association between caffeinated sodas and ovulatory disorder infertility stronger, rather than weaker as would be expected if caffeine explained part of the association. In addition, noncaffeinated soft drinks showed a similar relation to this condition, albeit slightly weaker. Similarly, intakes of both sugared and diet soft drinks were positively related to ovulatory infertility and fructose intake was unrelated to this condition. The lack of specificity for a particular type of beverage suggests that this could be a chance finding. Alternatively, this association could be due to soft drink components common to all types of soft drinks or a dietary pattern in which soft drinks (regardless of type) are preferably consumed, which could not be accounted for in this analysis. In support of the later hypotheses, others have previously reported that intakes of caffeinated, decaffeinated, sugared, and diet soft drinks have similar relations to the incidence of impaired fasting glucose and metabolic syndrome;⁵² a very relevant finding given the role of insulin sensitivity on ovulation and the pathogenesis of polycystic ovary syndrome. In addition, the notion that the relation between soft drinks and infertility is independent of caffeine is further supported by previous studies. For example, Wilcox and colleagues⁵³ reported that an increase of 1 caffeinated soft drink per day was associated with a 50% lower chance of conception each month after accounting for coffee consumption and other relevant variables, and concluded that this association exceeded what would be expected, based on data on coffee and fecundability from the same study, if caffeine were responsible for the association. Also, Hatch and Bracken⁸ reported a stronger association between soft drinks and delayed conception than between coffee and this outcome at lower levels of caffeine intake from sodas. Both studies were conducted in the United States, where coffee is the main contributor to intake of caffeine. Further research is needed to confirm these findings and to identify what components of soft drinks explain their association with decreased fertility.

The limitations of our study need to be considered. First, in assembling the cohort we assumed that the pregnancies included in the analysis were planned. Although cases and women reporting infertility due to other causes were clearly attempting to conceive, some pregnancy noncases may have conceived accidentally, potentially distorting the results. However, we studied a group who, based on their educational and demographic characteristics, was likely to plan a pregnancy⁵⁴ and further restricted the study to married women, whose pregnancies are also more likely to be intentional than those of unmarried women.⁵⁴ In addition, we included in the noncase group women diagnosed with infertility from other causes, making it less likely that pregnancy intention affected our findings. As a related issue, we did not collect data on male partner exposures. However, male exposures are unlikely to have a large effect on their partner's fertility^{25,55} and thus their influence on our results is probably minimal. Moreover, any effect of male exposures on female fertility can be accounted for in part by adjusting for the same factor in women, as we did for smoking and other lifestyle characteristics because spouses often share environmental exposures and lifestyle practices^{56,57} and are likely to change a health-related behavior when their spouse changes it.^{58,59} Second, the possibility that our findings may be due in part to unmeasured confounding cannot be completely ruled out. Nevertheless, we considered the potential confounding effects of many variables associated with caffeine or alcohol intake and ovulatory infertility, as well as of recognized risk factors for infertility, and found that only statistical adjustment for parity had important impact on the results. Third, our dietary data referred to a period up to 4 years before the reported pregnancy or failed attempt, potentially misclassifying the true exposure to these beverages around the periconceptional period and attenuating the results toward the null. Last, because we examined only the association of caffeinated and alcoholic beverage intake with ovulation-related infertility, we cannot rule out the possibility that these drinks impair fertility by affecting other aspects of reproductive function.

In summary, our results do not support the notion that consuming alcohol or caffeine in moderation affects ovulatory function to the point of increasing the frequency of infertility due to ovulation disorders. Consistent with previous reports,^{8,53} these data also suggest that soft drinks may be a risk factor for infertility and that this relation is independent of their caffeine content. Because a randomized trial of moderate caffeine or alcohol consumption in relation to fertility may be judged as unethical, further large prospective observational studies, preferably in populations with different patterns of alcohol and caffeine use, are necessary to determine whether moderate consumption of these substances affects fertility in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Table 1

Baseline Characteristics of the Study Population According to Intakes of Alcohol and Caffeine^a

	Alcohol (g/d)					
	0	0.1–1.9	2–4.9	5–9.9	≥ 10	
Age, y	32.3	32.6	32.6	33.0	33.5	
Caffeine, mg/d	138	187	212	247	269	
Saturated fat, g/d	22.5	22.3	23.2	22.0	21.6	
Monounsaturated fat, g/d	23.4	23.2	23.4	23.3	23.0	
Polyunsaturated fat, g/d	10.7	10.8	10.8	10.8	10.6	
<i>Trans</i> unsaturated fat, g/d	3.2	3.1	3.1	3.1	2.9	
Animal protein, g/d	64.7	65.2	64.0	62.1	61.0	
Vegetable protein, g/d	22.1	22.5	22.5	22.7	22.0	
Total carbohydrates, g/d	232	230	227	223	211	
Iron, g/d	38.1	31.6	30.2	27.9	23.7	
Multivitamin use, %	60	55	54	53	51	
Current smoker, %	5	7	9	9	16	
Body mass index, kg/m ²	24.5	23.8	23.5	23.0	23.2	
Physical activity, METs/wk	18.2	21.6	23.8	25.3	26.1	
Cycles ≥ 40 d, %	4	3	3	3	2	
Nulliparous, %	17	22	27	32	37	
Oral contraceptive use at the beginning of the mailing cycle, %	13	17	19	19	23	

	Caffeine (mg/d)					
	≤ 30	31–82	83–160	161–332	≥ 333	
Age, y	32.3	31.9	32.4	32.8	33.4	
Alcohol, g/d	1.3	1.9	2.7	3.5	4.5	
Saturated fat, g/d	21.8	22.1	22.2	22.4	22.8	
Monounsaturated fat, g/d	22.6	23.1	23.3	23.7	23.9	
Polyunsaturated fat, g/d	10.6	10.5	10.7	10.9	11.0	
<i>Trans</i> unsaturated fat, g/d	2.9	3.1	3.1	3.2	3.2	
Animal protein, g/d	65.8	63.7	63.8	63.4	63.7	
Vegetable protein, g/d	23.0	21.7	22.2	22.3	22.5	

	Caffeine (mg/d)				
	≤ 30	31–82	83–160	161–332	≥ 333
Total carbohydrates, g/d	233	233	229	226	222
Iron, g/d	41.2	36.4	32.6	29.8	26.1
Multivitamin use, %	63	61	57	54	47
Current smoker, %	2	3	5	8	17
Body mass index, kg/m ²	23.6	24.0	24.0	24.1	23.9
Physical activity, METs/wk	20.8	20.6	21.7	22.0	22.0
Cycles ≥ 40 d, %	4	3	3	3	3
Nulliparous, %	20	22	24	25	26
Oral contraceptive use at the beginning of the mailing cycle, %	11	17	18	19	18

^aValues are presented as age-standardized means and proportions.

Table 2
Relative Risks (95% CIs) for Ovulatory Disorder Infertility by Intake Levels of Alcoholic Beverages

Alcohol						<i>P</i> , trend ^a
	Intake range (g/d)	0	0.1–1.9	2–4.9	5–9.9	≥10
Median intake (g/d)		0	1	3	6.8	13.2
Cases/noncases		157/10,580	107/6355	82/4988	54/2831	38/1779
Age and energy adjusted ^b		1.00	1.09 (0.85–1.40)	1.08 (0.82–1.41)	1.26 (0.92–1.72)	1.47 (1.02–2.10)
+ Parity		1.00	0.99 (0.77–1.27)	0.85 (0.65–1.12)	0.90 (0.65–1.24)	0.90 (0.63–1.29)
Multivariate adjusted ^c		1.00	1.00 (0.77–1.30)	0.91 (0.68–1.22)	1.03 (0.74–1.45)	1.11 (0.76–1.64)
Alcoholic Beverages		< 1/mo	1–3/mo	1/wk	≥2/wk	
Beer						
Cases/noncases		268/16,254	74/4817	38/2621	58/2841	
Age and energy adjusted ^b		1.00	0.92 (0.71–1.20)	0.87 (0.62–1.23)	1.24 (0.93–1.66)	0.16
Multivariate adjusted ^c		1.00	0.88 (0.67–1.15)	0.79 (0.56–1.12)	1.07 (0.79–1.46)	0.61
Wine						
Cases/noncases		231/14,996	131/7218	37/2277	39/2042	
Age and energy adjusted ^b		1.00	1.18 (0.95–1.46)	1.05 (0.74–1.50)	1.24 (0.88–1.75)	0.27
Multivariate adjusted ^c		1.00	1.04 (0.83–1.31)	0.88 (0.61–1.27)	1.00 (0.69–1.43)	0.86
Spirits						
Cases/noncases		346/22,269	63/3008	29/1256		
Age and energy adjusted ^b		1.00	1.36 (1.04–1.79)	1.52 (1.03–2.23)		0.01
Multivariate adjusted ^c		1.00	1.09 (0.82–1.44)	1.14 (0.76–1.69)		0.45

^a Calculated with median intake in each group as a continuous variable.

^b Adjusted for age (continuous), calendar time (4 2-year intervals), and total energy intake (continuous).

^c 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/d, past 5–14 cig/d, past 15–24 cig/d, past ≥ 25 cig/d or unknown amount, current 1–4 cig/d, current 5–14 cig/d, current ≥ 25 cig/d 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 mo ago, past user 24–47 mo ago, past user 48–71 mo ago, past user 72–95 mo ago, past user 96–119 months ago, past user ≥ 120 mo ago, and missing), and dietary quality score (quintiles) and caffeine intake (quintiles).

Table 3
Relative Risks (95% CIs) for Ovulatory Disorder Infertility by Intake Levels of Caffeinated Beverages

										<i>P</i> , trend ^a
Caffeine										
Intake range (mg/d)	≤30	31–82	83–160	161–332	≥333					
Median intake (mg/d)	13	53	125	214	416					
Cases/noncases	80/5274	87/5335	88/5334	102/5282	81/5308					
Age and energy adjusted ^b	1.00	1.11 (0.81–1.50)	1.12 (0.82–1.51)	1.26 (0.94–1.70)	0.98 (0.72–1.34)					0.84
Multivariate adjusted ^c	1.00	0.97 (0.71–1.32)	0.95 (0.69–1.30)	1.07 (0.78–1.47)	0.86 (0.61–1.20)					0.44
Caffeinated Beverages	<1/wk	1/wk	2–6/wk	1/d	≥2/d					
Coffee										
Cases/noncases	226/12,846	13/1166	45/2860	75/4155	79/5506					
Age and energy adjusted ^b	1.00	0.64 (0.37–1.12)	0.87 (0.63–1.20)	1.01 (0.77–1.31)	0.83 (0.64–1.07)					0.23
Multivariate adjusted ^c	1.00	0.68 (0.39–1.20)	0.86 (0.62–1.20)	0.99 (0.75–1.30)	0.80 (0.60–1.06)					0.17
Decaffeinated coffee										
Cases/noncases	351/19,785	17/1603	32/2567	38/2578						
Age and energy adjusted ^b	1.00	0.62 (0.38–1.01)	0.71 (0.49–1.02)	0.88 (0.62–1.24)						0.15
Multivariate adjusted ^c	1.00	0.61 (0.37–1.01)	0.76 (0.52–1.10)	0.98 (0.70–1.40)						0.46
Tea										
Cases/noncases	222/13,063	39/2708	75/4663	62/3437	40/2662					
Age and energy adjusted ^b	1.00	0.86 (0.61–1.21)	0.95 (0.73–1.24)	1.11 (0.84–1.48)	0.93 (0.66–1.31)					0.85
Multivariate adjusted ^c	1.00	0.80 (0.56–1.14)	0.90 (0.69–1.18)	1.08 (0.81–1.44)	0.96 (0.68–1.36)					0.98
Caffeinated soft drinks										
Cases/noncases	147/10,662	41/3267	110/6263	64/3516	76/2825					
Age and energy adjusted ^b	1.00	0.91 (0.64–1.29)	1.26 (0.99–1.62)	1.32 (0.98–1.78)	1.97 (1.48–2.61)					<0.001
Multivariate adjusted ^c	1.00	0.87 (0.61–1.23)	1.12 (0.87–1.44)	1.07 (0.79–1.46)	1.47 (1.09–1.98)					0.01

^a Calculated with median intake in each group as a continuous variable.

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

^c 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/d, past 5–14 cig/d, past 15–24 cig/d, past ≥ 25 cig/d or unknown amount, current 1–4 cig/d, current 5–14 cig/d, current 15–24 cig/d and current ≥25 cig/d 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 mo ago, past user 24–47 mo ago, past user 48–71 mo ago, past user 72–95 mo ago, past user 96–119 months ago, past user ≥ 120 mo ago, and missing), and dietary quality score (quintiles) and caffeine intake (quintiles) and alcohol intake (no intake, < 2 g/d, 2–4.9 g/d, 5–9.9 g/d, ≥10 g/d).