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Caffeine and caffeinated beverage consumption and fecundability in a preconception cohort

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ABSTRACT

Caffeine is an adenosine receptor antagonist that may influence fertility by affecting ovulation, menstrual characteristics, or sperm quality. We studied the association between female and male preconception caffeine intake and fecundability in a North American prospective cohort study of 2135 pregnancy planners. Frequency of caffeinated beverage intake was self-reported at baseline. Outcome data were updated every 8 weeks until reported pregnancy; censoring occurred at 12 months. Adjusted fecundability ratios (FR) and 95% confidence intervals (CI) were estimated using proportional probabilities regression. Total caffeine intake among males, but not females, was associated with fecundability (FR for ≥300 vs. <100 mg/day caffeine among males = 0.72, 95% CI = 0.54–0.96), although the association was not monotonic. With respect to individual beverages, caffeinated tea intake was associated with slight reductions in fecundability among females, and caffeinated soda and energy drink intake were associated with reduced fecundability among males.

1. Introduction

Caffeine is an adenosine receptor antagonist and stimulant of the central nervous system that has short-term physiologic effects in the human body. Caffeine intake may lower luteal phase levels of estrogen and progesterone [1–3] and increase risk of short menstrual cycles (<25 days) [4], but has also been found to stimulate ovulation [5] and to have little effect on ovarian aging [6]. The relation of female caffeine intake and fertility has been studied extensively, with inconsistent findings. Some prospective epidemiologic studies have found little relation between female caffeine intake and fertility [7–10], whereas others have reported inverse [11,12] or positive [13] associations. Evidence among men is more limited, but cross-sectional studies have shown that caffeine intake is associated with reduced sperm concentration, total sperm count [14] and higher testosterone levels [15]. In prospective studies, male caffeine intake has been associated with reduced fecundability [11,13].

Some caffeinated beverages could affect fertility through mechanisms that do not involve caffeine. Soda intake, for instance, could cause subfertility through increased risk of insulin resistance, metabolic syndrome and weight gain [16–18], or through exposure to chemical contaminants in soda cans (e.g. bisphenol A) [19,20]. Male soda intake has been shown to deleteriously affect sperm characteristics [14,21], whereas female soda intake has been associated with reduced fecundability in most [7,9,10,22] but not all [13] prospective cohort studies. Animal studies have shown that polyphenols such as catechins and tannins, which are present in certain teas, may harm fertility [23,24]. Prospective cohort studies, however, have found tea intake to be either beneficial for [9,10,13] or unrelated to [7,22] fertility.

Given the high intake of caffeinated beverages in North America [25,26], thorough examination of the reproductive health effects of these beverages is of great public health importance. In a cohort of North American pregnancy planners, we prospectively evaluated

Abbreviations: BMI, body mass index; CI, confidence interval; DHQ, dietary health questionnaire; FR, fecundability ratio; IQR, interquartile range; LMP, last menstrual period; PSS-10, perceived stress scale; PRESTO, Pregnancy Study Online.

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the association of female and male caffeine, coffee, tea, soda, and energy drink intake with fecundability.

2. Methods

Pregnancy Study Online (PRESTO) is an internet-based, preconception cohort study of pregnancy planners. Study methods have been described elsewhere [27]. Women age 21–45 years, residing in the U.S. or Canada, in a stable relationship with a male partner, and not using contraception or fertility treatment were eligible for participation. Female participants completed an online baseline questionnaire on demographics, lifestyle, medical history, and medication use. They completed follow-up questionnaires every 8 weeks for up to 12 months to ascertain pregnancy status and updated exposure information. Women also completed the National Cancer Institute's Dietary Health Questionnaire (DHQ) II [28], an internet-based food frequency questionnaire.

After completing the baseline questionnaire, women were given the option to invite their male partners to participate. Males age 21 years and older were eligible. Fifty-seven percent of females chose to invite their male partner; 50% of invited males participated by completing a baseline questionnaire similar to that for females. This study was approved by the Institutional Review Board at Boston University Medical Center, and informed consent was obtained from all participants.

Over 33 months of recruitment, 3072 women completed the baseline questionnaire. We excluded women without follow-up data (n = 508), with implausible or insufficient last menstrual period (LMP) or attempt start date (n = 89), or who had been attempting conception for >6 cycles at baseline (n = 340). After exclusions, 2135 women remained for analysis of female caffeine intake and fecundability. Analysis of male caffeine intake and fecundability was further restricted to couples with male participation (n = 662).

Compared with women who reached a study endpoint or were censored at 12 cycles, women lost to follow-up (n = 207) were heavier (body mass index [BMI] 27.6 vs. 26.3 kg/m^2), less educated (4.8 vs. 2.0% without college degree), more likely to be current smokers (6.3 vs. 4.9%) and less likely to self-identify as White/non-Hispanic (81.6 vs. 86.2%), but were similar with respect to age (29.9 vs. 30.0 years) and caffeine intake (119.7 vs. 116.8 mg/day).

On female and male baseline questionnaires and female follow-up questionnaires, participants were asked if, in the past month, they had consumed caffeinated and decaffeinated coffee; black, green, white, or herbal/decaffeinated tea; soda (from a list of 13 brands); or energy drinks (from a list of 10 brands). Participants were asked for the approximate number of 8-ounce cups (for coffee and tea), 12-ounce cans (for soda) or cans or bottles (for energy drinks) consumed per week. Space was provided to specify additional brands of soda and energy drinks that were not listed.

At baseline, women reported their LMP date, usual cycle length, and number of cycles attempting conception. At each follow-up, they reported their LMP date and any pregnancies occurring since last follow-up. Total cycles at risk were calculated as follows: (cycles of attempt at study entry) + (((LMP from most recent follow-up questionnaire – date of baseline questionnaire completion)/usual cycle length) + 1). Women contributed cycles to the analysis from baseline until self-reported conception, loss to follow-up, withdrawal, initiation of fertility treatment, or 12 cycles, whichever came first.

At baseline, men and women reported their age, race/ethnicity, education, household income, vitamin intake, height, weight, smoking history, physical activity, alcohol consumption, intercourse frequency, average sleep duration, and average hours per week of work. Women additionally reported their gravidity, parity, stress levels via the perceived stress scale (PSS-10) [29], last method of contraception, and whether or not the couple was doing something to improve their chances of conception (including timing intercourse, use of ovulation predictor kits, etc.). Information on physical activity, alcohol consumption, and intercourse frequency was collected on follow-up questionnaires; these female covariates were updated over time in the analysis.

We calculated caffeine intake separately for each sex. We assigned a value for caffeine content per serving to each individual beverage (135 mg for coffee, 5.6 mg for decaffeinated coffee, 40 mg for black tea, 20 mg for green tea, 15 mg for white tea, 23–69 mg for individual brands of soda, and 48–280 mg for individual type of energy drinks) [25], and summed caffeine across all beverages. We also analyzed the association between fecundability and intake of caffeinated and decaffeinated coffee; black, green, and herbal/decaffeinated tea; caffeinated and decaffeinated soda; and energy drinks. In statistical analyses, we categorized caffeine (<100, 100–199, 200–299, ≥300 mg/day) based on prior studies. We categorized individual caffeinated beverages based on the natural categories in the data set that correspond to whole number of beverages per week. We fit restricted cubic splines to describe the trend in the data while allowing for non-linear associations [30].

Among females, we updated information on beverage intake throughout follow-up. Our primary analysis focused on time-varying intake of caffeine and caffeinated beverages, as women may reduce caffeine consumption while attempting pregnancy and the mechanism through which caffeine may affect fertility is likely short-acting [12,31]. Secondary analyses examined the association between baseline intake and fecundability. Male exposures were not updated over time.

All statistical analyses were conducted using SAS version 9.3 [32]. Descriptive analyses of covariates, stratified by male and female caffeine intake, were standardized by age using a SAS macro [33]. We ran proportional probabilities regression models to estimate fecundability ratios (FR) and 95% confidence intervals (CI), which measure the per-cycle probability of conception in each exposure category compared with the reference category. This model incorporates the baseline decline in fecundability over time and allows for left truncation due to delayed entry into the risk set [34,35].

Potential confounders were selected *a priori* based on the literature and an assessment of a causal graph. Results for female caffeine intake and fecundability were adjusted for female age (<25, 25–29, 30–34, ≥35 years), race/ethnicity (non-white, white), education (<college degree, college degree, graduate school), BMI (<25, 25–29, 30–34, ≥35 kg/m^2), smoking history (never, former, current), alcohol intake (<1, 1–6, 7–13, ≥14 drinks/week), intercourse frequency (<1, 1–3, ≥4 times/week), doing something to improve chances of conception, PSS-10 score (<10, 10–19, 20–29, ≥30), sleep duration (<7, 7–8, ≥9 h/night), and work time (<30, 30–49, ≥50 hours/week). Results for male caffeine intake and fecundability were adjusted for male versions of the same variables (except for the PSS-10, which was not assessed in males). Caffeinated beverages were mutually adjusted for other each other in multivariable models. Decaffeinated beverages were adjusted for the caffeinated counterpart of that beverage. We conducted a sensitivity analysis adjusting female caffeine intake for male caffeine intake, and vice versa.

We assessed the hypothesis that caffeine intake may interact with other behaviors [36,37] by stratifying models by smoking history and alcohol intake. In addition, we assessed reverse causation (subfertility influencing a reduction in caffeine intake) by restricting models to couples who had attempted pregnancy for <3 cycles at baseline. We also assessed the extent to which results differed in the potentially less-fertile subgroups of nulliparous women and women ≥30 years of age.