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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 2,135 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.

Keywords

caffeine; soda; fertility; time-to-pregnancy; preconception cohort

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1.1 INTRODUCTION¹

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

1.2 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.

¹BMI=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

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, 3,072 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, 2,135 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/m²), 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/m²), 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 hours/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.

We conducted sensitivity analyses adding caffeine from medications (for both sexes) and food sources (females only) to caffeine from beverages only. Caffeine intake from medications was ascertained using a series of questions on the male and female baseline questionnaires about specific types of medication use in the past month. We calculated caffeine intake from medications by multiplying the frequency of each caffeine-containing medication by the caffeine content of that medication (25). Caffeine intake from foods was ascertained from the female DHQ II.

Less than 1% of observations were missing for each of the individual beverages. We created five imputed data sets using PROC MI to impute missing values for exposures and covariates (32). To combine coefficient and standard error estimates from the five data sets, we used PROC MIANALYZE (32).

1.3 RESULTS

The 2,135 women in the analysis of female caffeine intake and fecundability contributed 9,653 cycles and 1,318 pregnancies. At baseline, median female intake of caffeine from beverages was 109.2 mg/day (interquartile range (IQR): 28.6-162.6; range 0-1,473.6 mg/day). On average, 62.6%, 17.9%, 17.2% and 2.3% of female caffeine intakes were from coffee, tea, soda, and energy drinks, respectively. Over follow-up, 9.7% of women decreased, 4.5% increased, and 85.8% stayed in the same category of caffeine intake.

The analysis of male caffeine intake and fecundability included 662 males whose female partners contributed 2,778 cycles and 447 pregnancies. Median male caffeine intake was 147.9 mg/day (IQR: 61.4-258.3; range: 0-999.4 mg/day). On average, 63.1%, 9.9%, 20.1%, and 6.8% of male caffeine intakes were from coffee, tea, soda, and energy drinks, respectively.

After controlling for age, we found that males and females who consumed ≥ 300 mg/day of caffeine were more likely to be White/non-Hispanic and less likely to have a college degree (Table 1). Male and female caffeine intakes were positively associated with ever smoking, current alcohol intake, and hours/week working, and were inversely associated with sleep duration; these associations were independent of age.

Female caffeine intake was not appreciably associated with fecundability. Compared with <100 mg/day of caffeine, FRs for 100-199, 200-299 and ≥ 300 mg/day of caffeine were 0.99 (95% CI=0.88-1.10), 0.93 (95% CI=0.78-1.11), and 0.90 (95% CI=0.69-1.18), respectively (Table 2). The results using baseline caffeine were similar except for the highest category of caffeine (FR=1.15, 95% CI=0.90-1.48). Male caffeine intake was non-monotonically associated with fecundability. Compared with <100 mg/day of caffeine, FRs for 100-199, 200-299, and ≥ 300 mg/day were 1.09 (95% CI=0.89-1.35), 1.12 (95% CI=0.88-1.47), and 0.72 (95% CI=0.54-0.96), respectively (Table 3).

Among females, caffeinated coffee intake showed little association with fecundability (Table 2, Figure 1). Black tea, but not green tea, was associated with a slight decrease in fecundability (FR for 2 vs. 0 cups/day black tea=0.89, 95% CI=0.53-1.48). The restricted cubic spline model predicting fecundability from caffeinated tea showed a monotonic decrease in fecundability from 1.5 to 3 cups/day, indicating a dose-response relation (Figure 1). Caffeinated soda intake showed a non-monotonic association with fecundability (1 and 2 vs. 0 cans/day: FR=0.76, 95% CI=0.57-1.01 and FR=1.09, 95% CI=0.66-1.79, respectively). The restricted cubic spline model showed a decrease in fecundability from 0 to 1 sodas/day, but no substantial change with higher consumption (Figure 1). There was no substantial relation between energy drink intake and fecundability, although few women drank these beverages. Results for female consumption of individual beverages at baseline were similar to the time-varying results. Decaffeinated coffee (FR for 1 vs. 0 cups/day=0.69, 95% CI=0.48-1.01) and herbal/decaffeinated tea (FR for 1 vs. 0 cups/day=0.82, 95% CI=0.65-1.03) were associated with slightly decreased fecundability, whereas decaffeinated soda (FR for >0 vs. 0 cans/day=0.94, 95% CI=0.81-1.09) was not.

Male caffeinated soda intake showed an inverse dose-response relation with fecundability (1 and 2 vs. 0 cans/day: FR=0.77, 95% CI=0.56-1.05 and FR=0.72, 95% CI=0.46-1.11, respectively) (Table 3). The restricted cubic spline model shown in Figure 2 confirms an inverse dose-response relation between caffeinated soda intake and fecundability. Male energy drink intake was also associated with reduced fecundability (1 vs. 0 cans/day: FR=0.46, 95% CI=0.21-0.98), whereas caffeinated coffee, black tea, and green tea were not. Decaffeinated coffee (>0 vs. 0 cups/day: FR=0.73, 95% CI=0.46-1.17) and herbal/decaffeinated tea (1 vs. 0 cups/day: FR=0.64, 95% CI=0.32-1.31) were associated with slightly decreased fecundability, whereas decaffeinated soda was not (>0 vs. 0 cans/day: FR=0.90, 95% CI=0.70-1.16).

Adjusting female analyses for male caffeine intake and vice versa did not substantially alter the results. Models in which we estimated caffeine from beverages, food sources, and medications were nearly identical to the beverage-only results (data not shown).

When restricting the models to couples attempting pregnancy for <3 cycles at enrollment, FRs for female and male intake of caffeine, coffee, and caffeinated tea were similar to the main analysis, and FRs for caffeinated soda intake were farther from the null. We found no consistent evidence that the relation of caffeinated beverage intake and fecundability was stronger among women or men who were ever smokers or who consumed >3 alcoholic drinks per week (data not shown). There were no substantial differences in the findings when restricting to nulliparous women; among women 30 years of age, the results for both male and female soda intake were dampened, but confidence intervals were wide.

1.4 DISCUSSION

In this preconception cohort study, female caffeine intake was not appreciably associated with fecundability, but male caffeine intake was non-monotonically inversely associated with fecundability. The latter finding appeared to be driven primarily by intake of caffeinated soda and energy drinks, for which we found some evidence of an association

with reduced fecundability among males. Tea consumption was associated with reduced fecundability among females but increased fecundability among males, and coffee intake had little association with fecundability in either sex. Energy drink intake was related to lower fecundability among males, but not females.

The lack of association between caffeine intake and fecundability agrees with some (7-10) but not all (11-13) prior prospective studies. In a prospective cohort study of 104 pregnancy planners, women who consumed $>3,150$ vs. $3,150$ mg/month of caffeine had 50% lower fecundability. When the analysis included women who conceived in the first 3 months of follow-up, results were attenuated ($FR=0.80$) and more closely resembled those from the present study (12). Two preconception cohort studies of Danish and Dutch couples found strong inverse associations between female (11) and male (11, 13) caffeine intake and fecundability, but caffeine levels were much higher than those in the present analysis, making comparison with our results difficult. It is possible that an effect on fecundability exists at very high levels, but we were not able to observe it in our cohort due to lower caffeine intake.

The observed association between female caffeinated soda intake and reduced fecundability agrees with prior studies (7, 9, 10, 22). Wilcox et al. reported a 50% lower chance of conception for every 1 caffeinated soft drink consumed per day (22). Other studies found that sugar-sweetened and diet sodas are associated with increased risk of ovulatory infertility (7), reduced overall fecundability (9), and increased risk of metabolic syndrome and impaired fasting glucose (38), which can affect ovulation and risk of polycystic ovarian syndrome. These findings indicate that sugar or other ingredients in soda could be responsible for the association with fecundability.

Our finding of a possible association between male soda intake and fecundability agrees with two cross-sectional studies of semen quality in reproductive-age men. Sugar-sweetened beverage intake was inversely associated with progressive sperm motility in the Rochester Young Men's Study (21). Likewise, Danish men who consumed ≥ 2 sodas/day had lower sperm concentration and total sperm count than men who drank 0 sodas/day (14).

To our knowledge, no other study has examined the association between energy drink consumption and fecundability. We found little association between female energy drink intake and fecundability, but a 57% reduction in fecundability among males who consumed 1 vs. 0 energy drinks/day. However, consumption of energy drinks was low. Energy drinks also contain many ingredients besides caffeine and sugar (39), introducing the potential for confounding by other compounds.

The observed reduced fecundability among female tea drinkers and decaffeinated beverage drinkers of both sexes may be due to an adverse biologic effect of compounds in tea, including catechins and tannins, on fecundability; however, these findings may also be the result of residual confounding or chance. Choice of beverage types may be linked to other lifestyle habits or prior health issues that could affect fertility. For instance, tea and decaffeinated coffee are viewed as healthy alternatives to caffeinated coffee. Although we

controlled for many sociodemographic and lifestyle factors, other dietary, environmental, lifestyle, or genetic factors could confound the relation of beverage intake and fecundability.

We calculated caffeine separately for individual sodas and energy drinks, resulting in improved assessment of caffeine intake compared with other studies. However, we did not have specific information on serving size or proportion consumed, and did not collect daily diary or 24-hour recall data, which provide more precise estimates of caffeine intake (40). Caffeine content differs based on brewing method, type of coffee bean or tea leaf, or batch of soda (41), but we had to rely on standard caffeine concentration values. We found that foods and medications accounted for 12% and 1% of total caffeine intake, respectively, but results including these caffeine sources did not differ substantially from the beverage results. Even if caffeine were measured perfectly, it would not necessarily be highly correlated with circulating caffeine levels, as genetic polymorphisms in the CYP1A2 and NAT2 genes lead to considerable individual variation in caffeine metabolism (42). Misclassification of caffeine is likely non-differential with respect to time-to-pregnancy, and is therefore expected to result in bias towards the null in the extreme categories.

We accounted for changes in beverage intake over follow-up, but could not account for changes in intake that occurred before study entry. However, when our analyses were restricted to couples who had attempted conception for <3 cycles at enrollment, results were similar, indicating that reverse causation is unlikely. A final limitation of our data is that we did not assess caffeine intake over time among males and therefore could not assess the relation between time-varying male caffeine intake and fecundability.

Although those lost to follow-up had some demographic and lifestyle differences compared with those who experienced a study endpoint, caffeine intake was similar in the two groups. Therefore, differential loss to follow-up is unlikely to be an important source of bias.

Strengths of the study include the enrollment of pregnancy planners during the preconception period and the prospective evaluation of the entire range of the fertility spectrum. We collected detailed information on caffeine over time for females, allowing us to capture behavioral changes that can occur throughout the pregnancy attempt. Lastly, this is one of the only studies to enroll both partners, allowing us to examine joint effects of male and female exposure and to better control for confounding by partner caffeine intake.

In summary, our results suggest that caffeine intake among males but not females may be associated with reduced fecundability, and that fecundability varied by individual beverage type. Specifically, we observed some evidence of an inverse relation between intake of soda and energy drinks among males and fecundability. However, the observed results may be affected by chance, residual confounding, and non-differential exposure misclassification.

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REFERENCES

- Schliep KC, Schisterman EF, Mumford SL, Pollack AZ, Zhang C, Ye A, et al. Caffeinated beverage intake and reproductive hormones among premenopausal women in the BioCycle Study. *Am J Clin Nutr*. 2012; 95(2):488–97. [PubMed: 22237060]
- Kotsopoulos J, Eliassen AH, Missmer SA, Hankinson SE, Tworoger SS. Relationship between caffeine intake and plasma sex hormone concentrations in premenopausal and postmenopausal women. *Cancer*. 2009; 115(12):2765–74. [PubMed: 19384973]
- Lawson CC, LeMasters GK, Levin LS, Liu JH. Pregnancy hormone metabolite patterns, pregnancy symptoms, and coffee consumption. *Am J Epidemiol*. 2002; 156(5):428–37. [PubMed: 12196312]
- Fenster L, Quale C, Waller K, Windham GC, Elkin EP, Benowitz N, et al. Caffeine consumption and menstrual function. *Am J Epidemiol*. 1999; 149(6):550–7. [PubMed: 10084244]
- Kapidaki M, Roupa Z, Sparos L, Tzonou A, Olsen J, Trichopoulos D. Coffee intake and other factors in relation to multiple deliveries: a study in Greece. *Epidemiology*. 1995; 6(3):294–8. [PubMed: 7619939]
- Kinney A, Kline J, Kelly A, Reuss ML, Levin B. Smoking, alcohol and caffeine in relation to ovarian age during the reproductive years. *Hum Reprod*. 2007; 22(4):1175–85. [PubMed: 17261576]
- Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Caffeinated and alcoholic beverage intake in relation to ovulatory disorder infertility. *Epidemiology*. 2009; 20(3):374–81. [PubMed: 19279491]
- Hakim RB, Gray RH, Zacur H. Alcohol and caffeine consumption and decreased fertility. *Fertil Steril*. 1998; 70(4):632–7. [PubMed: 9797089]
- Hatch EE, Wise LA, Mikkelsen EM, Christensen T, Riis AH, Sorensen HT, et al. Caffeinated beverage and soda consumption and time to pregnancy. *Epidemiology*. 2012; 23(3):393–401. [PubMed: 22407137]
- Caan B, Quesenberry CP Jr, Coates AO. Differences in fertility associated with caffeinated beverage consumption. *Am J Public Health*. 1998; 88(2):270–4. [PubMed: 9491020]
- Jensen TK, Henriksen TB, Hjollund NH, Scheike T, Kolstad H, Giwercman A, et al. Caffeine intake and fecundability: a follow-up study among 430 Danish couples planning their first pregnancy. *Reprod Toxicol*. 1998; 12(3):289–95. [PubMed: 9628552]
- Wilcox A, Weinberg C, Baird D. Caffeinated beverages and decreased fertility. *Lancet*. 1988; 2(8626-8627):1453–6. [PubMed: 2904572]
- Florack EI, Zielhuis GA, Rolland R. Cigarette smoking, alcohol consumption, and caffeine intake and fecundability. *Prev Med*. 1994; 23(2):175–80. [PubMed: 8047523]
- Jensen TK, Swan SH, Skakkebaek NE, Rasmussen S, Jorgensen N. Caffeine intake and semen quality in a population of 2,554 young Danish men. *Am J Epidemiol*. 2010; 171(8):883–91. [PubMed: 20338976]
- Ramlau-Hansen CH, Thulstrup AM, Bonde JP, Olsen J, Bech BH. Semen quality according to prenatal coffee and present caffeine exposure: two decades of follow-up of a pregnancy cohort. *Hum Reprod*. 2008; 23(12):2799–805. [PubMed: 18757446]
- Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*. 2010; 33(11):2477–83. [PubMed: 20693348]
- Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr*. 2006; 84(2):274–88. [PubMed: 16895873]
- Wise LA, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis A, Hatch EE. An internet-based prospective study of body size and time-to-pregnancy. *Hum Reprod*. 2010; 25(1):253–64. [PubMed: 19828554]
- Cao XL, Corriveau J, Popovic S. Sources of low concentrations of bisphenol A in canned beverage products. *J Food Prot*. 2010; 73(8):1548–51. [PubMed: 20819371]

20. Mok-Lin E, Ehrlich S, Williams PL, Petrozza J, Wright DL, Calafat AM, et al. Urinary bisphenol A concentrations and ovarian response among women undergoing IVF. *Int J Androl*. 2010; 33(2): 385–93. [PubMed: 20002217]
21. Chiu YH, Afeiche MC, Gaskins AJ, Williams PL, Mendiola J, Jorgensen N, et al. Sugar-sweetened beverage intake in relation to semen quality and reproductive hormone levels in young men. *Hum Reprod*. 2014; 29(7):1575–84. [PubMed: 24812311]
22. Wilcox AJ, Weinberg CR. Tea and fertility. *Lancet*. 1991; 337(8750):1159–60. [PubMed: 1674032]
23. Peaslee MH, Einhellig FA. Reduced fecundity in mice on tannic acid diet. *Comp Gen Pharmacol*. 1973; 4(16):393–7. [PubMed: 4788789]
24. Ly C, Yockell-Lelievre J, Ferraro ZM, Arnason JT, Ferrier J, Gruslin A. The effects of dietary polyphenols on reproductive health and early development. *Hum Reprod Update*. 2015; 21(2): 228–48. [PubMed: 25376587]
25. Somogyi, L. Caffeine intake by the U.S. population: Food and Drug Administration. Oakridge National Laboratory; 2010. Available from: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofFood/CFSAN/CFSANFOIAElectronicReadingRoom/UCM333191.pdf> [2015 27 July]
26. Garriguet, D. Beverage consumption of Canadian adults. Statistics Canada; Ottawa, Canada: 2008.
27. Wise LA, Rothman KJ, Mikkelsen EM, Stanford JB, Wesselink AK, McKinnon C, et al. Design and Conduct of an Internet-Based Preconception Cohort Study in North America: Pregnancy Study Online. *Paediatr Perinat Epidemiol*. 2015; 29(4):360–71. [PubMed: 26111445]
28. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires : the Eating at America's Table Study. *Am J Epidemiol*. 2001; 154(12):1089–99. [PubMed: 11744511]
29. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983; 24(4):385–96. [PubMed: 6668417]
30. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989; 8(5):551–61. [PubMed: 2657958]
31. Lum KJ, Sundaram R, Buck Louis GM. Women's lifestyle behaviors while trying to become pregnant: evidence supporting preconception guidance. *Am J Obstet Gynecol*. 2011; 205(3):203, e1–7. [PubMed: 21658667]
32. SAS Institute. SAS/Stat 9.3 user's guide. SAS Institute; Cary, NC: 2008.
33. Pazaris, M.; Hertzmark, E.; Spiegelman, D. [2016 17 March] The SAS TABLE1 Macros. 2013. Available from: <https://cdn1.sph.harvard.edu/wp-content/uploads/sites/271/2013/11/table1.pdf>
34. Schisterman EF, Cole SR, Ye A, Platt RW. Accuracy loss due to selection bias in cohort studies with left truncation. *Paediatr Perinat Epidemiol*. 2013; 27(5):491–502. [PubMed: 23930785]
35. Howards PP, Hertz-Picciotto I, Poole C. Conditions for bias from differential left truncation. *Am J Epidemiol*. 2007; 165(4):444–52. [PubMed: 17150983]
36. Olsen J. Cigarette smoking, tea and coffee drinking, and subfecundity. *Am J Epidemiol*. 1991; 133(7):734–9. [PubMed: 2018028]
37. Bolumar F, Olsen J, Rebagliato M, Bisanti L. Caffeine intake and delayed conception: a European multicenter study on infertility and subfecundity. European Study Group on Infertility Subfecundity. *Am J Epidemiol*. 1997; 145(4):324–34. [PubMed: 9054236]
38. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, et al. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation*. 2007; 116(5):480–8. [PubMed: 17646581]
39. Seifert SM, Schaechter JL, Hershorin ER, Lipshultz SE. Health effects of energy drinks on children, adolescents, and young adults. *Pediatrics*. 2011; 127(3):511–28. [PubMed: 21321035]
40. Schliep KC, Schisterman EF, Mumford SL, Perkins NJ, Ye A, Pollack AZ, et al. Validation of different instruments for caffeine measurement among premenopausal women in the BioCycle study. *Am J Epidemiol*. 2013; 177(7):690–9. [PubMed: 23462965]
41. Bracken MB, Triche E, Grosso L, Hellenbrand K, Belanger K, Leaderer BP. Heterogeneity in assessing self-reports of caffeine exposure: implications for studies of health effects. *Epidemiology*. 2002; 13(2):165–71. [PubMed: 11880757]

42. Grosso LM, Bracken MB. Caffeine metabolism, genetics, and perinatal outcomes: a review of exposure assessment considerations during pregnancy. *Ann Epidemiol.* 2005; 15(6):460–6. [PubMed: 15967394]

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Highlights

- Our results do not indicate an important association between male or female caffeine intake and couple fecundity.
- However, male intake of soda and female intake of caffeinated tea were associated with reduced fecundability.
- Male energy drink intake was associated with reduced fecundability, but the number consuming energy drinks was small.

Figure 1.

Association between daily intake of caffeinated coffee, tea, and soda and fecundability, fit by restricted cubic splines, among female pregnancy planners in PRESTO, 2013-16. The solid line represents the FR, and the dotted lines represent the upper and lower bounds of the 95% CI. The reference level for the FR is 0 servings/day. The curves are adjusted for age, race/ethnicity, education, BMI, smoking history, alcohol intake, intercourse frequency, doing something to improve chances of conception, average nightly sleep, perceived stress scale score, average work time, and other caffeinated beverages. The splines are trimmed at the 99th percentile and have 3 knot points each, located at the 50th, 75th, and 90th percentiles.

Figure 2.

Association between daily intake of caffeinated coffee, tea, and soda and fecundability, fit by restricted cubic splines, among male pregnancy planners in PRESTO, 2013-16. The solid line represents the FR, and the dotted lines represent the upper and lower bounds of the 95% CI. The reference level for the FR is 0 servings/day. The curves are adjusted for age, race/ethnicity, education, BMI, smoking history, alcohol intake, intercourse frequency, doing something to improve chances of conception, average nightly sleep, average work time, and other caffeinated beverages. The splines are trimmed at the 99th percentile and have 3 knot points each, located at the 50th, 75th, and 90th percentiles.

Table 1

Selected characteristics^a of 2135 female and 662 male pregnancy planners according to caffeine intake at baseline, PRESTO, 2013-16.

	Female caffeine intake (mg/day)				Male caffeine intake (mg/day)			
	<100	100-199	200-299	300	<100	100-199	200-299	300
Total N	1045	733	249	108	226	204	130	102
Age at baseline (years)	29.4	30.5	30.8	30.1	30.7	31.8	32.9	33.0
Partner's age at baseline (years)	32.0	31.9	32.1	32.0	29.9	30.2	30.0	29.7
Non-white (%)	16.5	13.3	10.6	9.0	16.1	13.0	12.3	5.0
Household income <\$50,000 (%)	18.3	14.8	16.3	19.8	16.8	15.4	12.2	19.7
Education <college degree (%)	20.0	20.8	21.4	29.5	24.9	25.0	24.7	28.6
BMI (kg/m ²)	26.2	26.4	26.6	28.2	27.7	27.4	26.9	28.2
Physical activity (MET-hours/week)	34.9	35.6	37.6	30.4	37.7	40.6	36.5	38.5
Multivitamin intake (%)	82.8	84.7	82.4	81.0	--	--	--	--
Ever smoker (%)	17.2	26.2	37.6	53.2	14.7	28.5	34.8	39.7
Alcohol intake (drinks/week)	2.5	4.1	4.8	5.2	4.1	6.1	8.2	9.2
Perceived stress scale score (mean)	15.2	15.3	15.8	16.9	--	--	--	--
Parous (%)	30.6	26.0	31.1	39.6	--	--	--	--
Intercourse frequency (%)								
<1 time/week	19.1	21.1	21.0	29.1	18.7	16.7	17.8	18.6
4 times/week	16.1	15.1	11.4	14.8	16.7	14.9	14.1	9.9
Doing something to improve chances of conception ^b	74.7	75.1	73.0	70.4	78.1	74.9	81.9	74.1
Last method of contraception (%)								
Hormonal	39.4	37.6	40.7	37.9	--	--	--	--
Barrier	39.6	44.0	35.6	39.0	--	--	--	--
<7 hours/night of sleep (%)	20.7	18.4	25.0	35.2	27.2	36.2	36.4	37.9
50 hours/week of work (%)	10.0	10.5	13.9	12.0	28.0	33.2	32.1	43.2

^aWith the exception of age, all characteristics are standardized to age at baseline. The characteristics under female caffeine intake are specific to females (i.e. age at baseline indicates female age); the characteristics under male caffeine intake are specific to males (i.e. age at baseline indicates male age).

^bDoing something to improve chances of conception includes checking basal body temperature, monitoring cervical fluid, use of ovulation kits or electronic fertility monitors, charting menstrual cycles, counting days since LMP, or feeling for changes in cervical position.

Table 2

Adjusted fecundability ratios for caffeinated beverage intake among 2135 female pregnancy planners, PRESTO, 2013-16.

Exposure	Baseline Beverage Data			Time-Varying Beverage Data		
	No. of Pregnancies	No. of Cycles	Adjusted ^d FR (95% CI)	No. of Pregnancies	No. of Cycles	Adjusted ^d FR (95% CI)
Caffeine (mg/day)						
<100	642	4698	Reference	691	4915	Reference
100-199	466	3298	1.06 (0.94, 1.18)	443	3223	0.99 (0.88, 1.10)
200-299	147	1159	0.98 (0.83, 1.17)	131	1021	0.93 (0.78, 1.11)
300	63	498	1.15 (0.90, 1.48)	53	494	0.90 (0.69, 1.18)
Regular coffee (cups/day) ^b						
0	436	3271	Reference	489	3364	Reference
<1	363	2946	0.97 (0.85, 1.10)	338	3007	0.82 (0.72, 0.94)
1	406	2523	1.21 (1.06, 1.37)	394	2428	1.09 (0.96, 1.24)
2	113	913	1.02 (0.84, 1.25)	97	854	0.84 (0.68, 1.03)
Black tea (cups/day) ^b						
0	942	7026	Reference	964	7078	Reference
<1	291	1933	1.08 (0.96, 1.22)	272	1916	1.07 (0.93, 1.23)
1	61	442	1.06 (0.83, 1.34)	62	428	1.16 (0.88, 1.52)
2	24	250	0.85 (0.58, 1.25)	20	231	0.89 (0.53, 1.48)
Green tea (cups/day) ^b						
0	981	7271	Reference	1006	7422	Reference
<1	287	2018	1.03 (0.92, 1.17)	268	1891	1.06 (0.92, 1.22)
1	50	364	0.98 (0.76, 1.28)	42	340	0.97 (0.72, 1.32)
Caffeinated soda (cans/day) ^b						
0	712	4802	Reference	6787	5530	Reference
<1	501	3836	0.95 (0.86, 1.06)	407	3118	0.98 (0.84, 1.16)
1	73	725	0.85 (0.68, 1.07)	87	641	0.76 (0.57, 1.01)
>2	32	290	0.92 (0.66, 1.28)	37	364	1.09 (0.66, 1.79)
Energy drinks (servings/day) ^b						
0	1226	8838	Reference	1232	8892	Reference

Exposure	Baseline Beverage Data			Time-Varying Beverage Data		
	No. of Pregnancies	No. of Cycles	Adjusted ^a FR (95% CI)	No. of Pregnancies	No. of Cycles	Adjusted ^a FR (95% CI)
>0	92	815	0.93 (0.76, 1.14)	86	761	0.95 (0.77, 1.17)

^a Adjusted for age, race/ethnicity, education, BMI, smoking history, alcohol intake, intercourse frequency, doing something to improve chances of conception, average nightly sleep, perceived stress scale score, and average work time.

^b Additionally adjusted for other caffeinated beverages.

Table 3

Adjusted fecundability ratios for baseline caffeine intake among 662 male pregnancy planners, PRESTO, 2013-16.

Exposure	No. of Pregnancies	No. of Cycles	Adjusted ^a FR (95% CI)
Caffeine (mg/day)			
<100	147	959	Reference
100-199	144	808	1.09 (0.89, 1.35)
200-299	95	509	1.12 (0.88, 1.42)
300	61	502	0.72 (0.54, 0.96)
Regular coffee (cups/day) ^b			
0	120	831	Reference
<1	106	602	1.17 (0.91, 1.50)
1	126	711	1.11 (0.88, 1.41)
2	95	634	0.88 (0.68, 1.14)
Black tea (cups/day) ^b			
0	352	2231	Reference
<1	67	389	0.97 (0.76, 1.23)
1	28	158	0.99 (0.70, 1.41)
Green tea (cups/day) ^b			
0	381	2340	Reference
<1	51	370	0.81 (0.62, 1.07)
1	15	68	1.33 (0.83, 2.13)
Caffeinated soda (cans/day) ^b			
0	179	1025	Reference
<1	201	1173	0.97 (0.80, 1.16)
1	46	382	0.77 (0.56, 1.05)
2	21	198	0.72 (0.46, 1.11)
Energy drinks (servings/day) ^b			
0	370	2237	Reference
<1	70	441	0.99 (0.78, 1.26)
1	7	100	0.46 (0.21, 0.98)

^aAdjusted for age, race, education, BMI, smoking history, intercourse frequency, doing something to improve chances of conception, sleep duration, and average work time.

^bAdditionally adjusted for other caffeinated beverages.