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ORIGINAL ARTICLE *Infertility*

The association between pre-treatment maternal alcohol and caffeine intake and outcomes of assisted reproduction in a prospectively followed cohort

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STUDY QUESTION: Is pre-treatment alcohol and caffeine intake associated with infertility treatment outcomes among women undergoing ART?

SUMMARY ANSWER: Low to moderate alcohol and caffeine intakes in the year prior to infertility treatment were not related to ART outcomes.

WHAT IS KNOWN ALREADY: Alcohol and caffeine intake have been found to be associated with infertility in some studies. Nevertheless, data on their relation with outcomes of infertility treatments are scarce and inconsistent.

STUDY DESIGN, SIZE, DURATION: We included 300 women (493 ART cycles) from the Environment and Reproductive Health Study, an ongoing cohort study (2006–2016).

PARTICIPANTS/MATERIALS, SETTING, METHODS: Pre-treatment intakes of alcohol and caffeine were assessed retrospectively using a validated food frequency questionnaire. Intermediate and clinical endpoints of ART were abstracted from electronic medical records. Generalized linear mixed models with random intercepts to account for multiple ART cycles per woman were used to evaluate the association with ART outcomes adjusting for age, BMI, smoking status, infertility diagnosis, protocol type, race, dietary patterns, and calories, vitamin B12 and folate intake.

MAIN RESULTS AND THE ROLE OF CHANCE: Median (range) pre-treatment alcohol and caffeine intakes were 5.6 (0.0–85.8) g/day and 124.9 (0.3–642.2) mg/day, respectively. The adjusted percentage of initiated cycles resulting in live birth (95% CI) for women in increasing categories of pre-treatment alcohol intake was 34% (20, 52%) for non-consumers, 46% (36, 57%) for 0.1–6 g/day, 41% (29, 53%) for 6.1–12 g/day, 42% (31, 55%) for 12.1–24 g/day, and 41% (22, 63%) for >24 g/day (P, trend = 0.87). The adjusted percentage of cycles resulting in live birth (95% CI) for women in increasing categories of caffeine intake was 46% (36–57%) for <50 mg/day, 44% (29, 60%) for 50.1–100 mg/day, 42% (31, 53%) for 100.1–200 mg/day, 40% (28, 53%) for 200.1–300 mg/day and 40% (21, 63%) for >300 mg/day (P, trend = 0.34). When specific types of alcoholic and caffeinated beverages were evaluated, no relations with ART treatment outcomes were observed.

LIMITATIONS, REASONS FOR CAUTION: Residual confounding by other diet and lifestyle factors cannot be ruled out owing to the observational nature of this study. It is also unclear how generalizable these results are to women who are conceiving without the assistance of ART.

WIDER IMPLICATIONS OF THE FINDINGS: Our results provide reassurance that low to moderate intakes of alcohol (e.g. ≤12 g/day) and caffeine (e.g. <200 mg/day) in the year prior to infertility treatment initiation do not have an adverse effect on intermediate or clinical outcomes of ART.

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Introduction

Infertility affects ~15–25% of couples trying to achieve pregnancy in western countries (Slama *et al.*, 2012; Thoma *et al.*, 2013). Treatment using ART is common for couples facing difficulties conceiving. In the USA, over 190 000 ART cycles were performed in 2013 resulting in the birth of ~2% of all children nationwide (Sunderam *et al.*, 2015). Despite these impressive numbers, success rates for ART have remained steady for approximately a decade (Wright *et al.*, 2006; Sunderam *et al.*, 2015), making it important to identify potentially modifiable predictors of successful treatment.

Among potentially modifiable lifestyle factors, alcohol and caffeine intake have received substantial attention as potential risk factors for infertility and pregnancy loss (Bolumar *et al.*, 1997; Olsen *et al.*, 1997; Bailey and Sokol, 2011; Greenwood *et al.*, 2014). While some studies from the general population suggest that consumption of alcohol can reduce fecundability (Grodstein *et al.*, 1994; Hakim *et al.*, 1998; Greenlee *et al.*, 2003), others have failed to prove so (Curtis *et al.*, 1997; Olsen *et al.*, 1997; Juhl *et al.*, 2001; Mikkelsen *et al.*, 2016). Similarly, while several studies have reported that caffeine intake may reduce the ability to achieve pregnancy (Wilcox *et al.*, 1988; Christianson *et al.*, 1989; Williams *et al.*, 1990; Grodstein *et al.*, 1993), many others have failed to show such associations (Joesoef *et al.*, 1990; Florack *et al.*, 1994; Alderete *et al.*, 1995).

Few studies have specifically evaluated how alcohol and caffeine intake may influence infertility treatment outcomes, and results of studies addressing pre-treatment alcohol intake are largely conflicting. Alcohol intake in the year prior to IVF treatment was negatively associated with the number of oocytes retrieved but was not associated with probability of live birth (Klonoff-Cohen *et al.*, 2003). Current alcohol consumption prior to IVF, however, was related to lower peak estradiol levels (Rossi *et al.*, 2011), lower embryo quality (Wdowiak *et al.*, 2014) and greater odds of failed fertilization (Rossi *et al.*, 2011) suggesting a strong detrimental impact of recent alcohol intake on IVF outcomes. However, the most recent prospective cohort found no association between alcohol consumption during Days 4–10 of the treatment cycle and IVF outcomes (Firns *et al.*, 2015). Of three studies investigating caffeine intake and ART outcomes, one small study (n = 221 couples) observed an association with live birth when comparing women consuming >2–50 and >50 versus <2 mg/day of caffeine in the year prior to IVF (Klonoff-Cohen *et al.*, 2002), while two other studies found no association between caffeine intake consumed just before (Choi *et al.*, 2011) or during IVF treatment (Al-Saleh *et al.*, 2010) and IVF outcomes. Given the equivocal findings in the literature, we evaluated the relationship of pre-treatment intakes of alcohol and caffeine with ART outcomes among women attending a fertility center.

Materials and Methods

Study population

Participants were women enrolled in the Environment and Reproductive Health (EARTH) Study, an ongoing prospective cohort study started in 2006 aimed at identifying determinants of fertility among couples presenting to the Massachusetts General Hospital (MGH) Fertility Center (Boston, MA). All women who meet eligibility requirements (age 18–45 years at enrollment and no planned use of donor gametes at enrollment) are approached by research staff and invited to participate in the study. Approximately 60% of those contacted by the research nurses participate in the study. The study was approved by the Human Subject Committees of the Harvard T.H. Chan School of Public Health and Massachusetts General Hospital (MGH). Written informed consent was obtained from all participants.

Patient involvement

No patients were involved in the study design or implementation of the study or the outcome measures, nor in setting the research question. No patients were asked advice on the interpretation or writing up of results. Selected results of the EARTH study are disseminated to participants through yearly newsletters.

Alcohol and caffeine assessment

Diet was assessed before ART treatment initiation using a validated food frequency questionnaire (FFQ) (Rimm *et al.*, 1992; Yuan *et al.*, 2017). In brief, participants were asked to report how often, on average, they consumed 131 foods and beverages during the previous year using nine categories of intake frequency, ranging from less than one per month to six or more per day. Multivitamin and supplement users were also asked to specify the brand of the multivitamin or supplement, the dose, and frequency of use. Nutrient intakes were estimated by summing the nutrient contribution of all food and supplement items (U.S. Department of Agriculture, 2012).

Total alcohol intake was estimated from intake of regular beer, light beer, red wine, white wine, and liquor over the previous year. The estimated alcohol content of each beverage was 11.3 g per bottle or can of light beer (355 mL), 12.8 g per can of regular beer (355 mL), 11.0 g per 5-ounce glass of wine (118 mL), and 14.0 g per shot of liquor (44 mL). Specific caffeine-containing items were caffeinated coffee (137 mg caffeine/cup, 237 mL) and tea (47 mg caffeine/cup, 237 mL), caffeinated sodas (46 mg caffeine/bottle or can, 355 mL) and chocolate (7 mg caffeine/1 oz serving, 28 g). We calculated the total intake of alcohol and

caffeine by summing the alcohol/caffeine content for specific items multiplied by weights proportional to the frequency of use of each item. In a separate population, high correlations were found between alcoholic and caffeinated beverage intake assessed with the FFQ and four 1-week diet records (beer, $r = 0.87$; wine, 0.85; liquor, 0.80; coffee: 0.78, tea: 0.93, soda: 0.84) (Salvini *et al.*, 1989; Rimm *et al.*, 1992). These high correlations were also confirmed in a more recent validation of the FFQ ($r = 0.77$ for alcohol and $r = 0.76$ for caffeine) (Yuan *et al.*, 2017).

The majority of women only completed one FFQ, however, some women completed a second FFQ if they re-enrolled ($n = 13$). In these cases, the cycles initiated subsequent to the receipt of the second FFQ were assigned to this FFQ.

Covariate assessment

Height and weight were measured at enrollment by a trained research nurse to calculate BMI (kg/m^2). The research nurses also administered a brief questionnaire to collect data on demographics, medical history and selected lifestyle factors. Participants also completed a detailed take-home questionnaire with additional questions on reproductive health, medical history and lifestyle factors.

We used two data-derived dietary patterns, constructed using principle components analysis, to describe and adjust for general patterns of food consumption (Gaskins *et al.*, 2012), which may confound the relationship between alcohol and caffeine intake and IVF outcomes. The Prudent pattern was characterized by intakes of fish, fruits, vegetables, nuts and legumes and the Western pattern was characterized by high intakes of red and processed meat, butter, refined grains and sweets. Women received a score for each dietary pattern, with higher scores indicating higher adherence.

ART outcome assessment

Oral contraceptives were given as pre-treatment for a period of 2–5 weeks to suppress ovulation prior to participants' ART cycle, unless contraindicated. On Day 3 of induced menses, patients began controlled ovarian stimulation using one of three protocols as clinically indicated: luteal-phase GnRH-agonist protocol using low-, regular- or high-dose leuprolide with pituitary desensitization beginning in the luteal phase; follicular-phase GnRH-agonist/Flare protocol, in which leuprolide started on Day 2 of the follicular phase at 20 units and decreased to five units on Day 5; or GnRH-antagonist protocol, in which GnRH-antagonist began when the lead follicle reached 14 mm in size and/or estradiol levels were ≥1000 pg/mL. Patients were monitored during gonadotrophin stimulation for serum estradiol, follicle size measurements and counts, and endometrial thickness through 2 days before oocyte retrieval. HCG was administered ~36 h before the scheduled oocyte retrieval procedure to induce oocyte maturation.

Couples underwent ART with conventional IVF or ICSI as clinically indicated. Embryologists classified oocytes as germinal vesicle, metaphase I, metaphase II (MII) or degenerated. Embryologists determined fertilization rate 17–20 h after insemination as the number of oocytes with two pronuclei divided by the number of MII oocytes inseminated or injected. The resulting embryos were monitored for cell number and morphological quality (1 for best, 5 for worst) on Days 2 and 3. For analysis we classified embryos as best quality if they had four cells on Day 2, eight cells on Day 3, and a morphologic quality score of one or two on Days 2 and 3. We defined successful implantation as a serum β-hCG level >6 mIU/mL typically measured 17 days (range: 15–20 days) after oocyte retrieval, clinical pregnancy as the presence of an intrauterine gestational sac confirmed by ultrasound at 6 weeks of gestation, and live birth as the birth of a neonate on or after 24 weeks gestation. All clinical information (including infertility diagnoses) was abstracted from electronic medical records. Diet and clinical information was only merged in the final stages of the study by linking the two datasets using the study participant's unique identification.

Statistical analysis

Women were divided into categories according to their pre-treatment alcohol and caffeine intake based on the average amount of alcohol and caffeine in a standard serving (12 g and 100 mg, respectively) (Mitchell *et al.*, 2014; DeSalvo *et al.*, 2016), the recommended intakes from relevant guidelines (e.g. United States Department of Agriculture for alcohol: ≤1 serving/day and The American Congress of Obstetrics and Gynecology (ACOG) for caffeine: <200 mg/day) (ACOG, 2010), and the range of consumption in our population. Descriptive statistics were calculated for demographic, dietary and reproductive characteristics by categories of alcohol and caffeine intake. For continuous variables, Kruskal Wallis tests were used to test for associations across categories of alcohol and caffeine intake. For categorical variables, chi-square tests (or Fisher's exact tests when the expected cell count was <5) were used to test the associations across categories of alcohol and caffeine intake.

We used multivariable generalized linear mixed models to evaluate the association of alcohol and caffeine intake with treatment outcomes, with a random intercept to account for multiple ART cycles per woman. A normal distribution and identity link were specified for continuous outcomes (estradiol levels, endometrial thickness); a Poisson distribution and log link function for count outcomes (number of total and MII oocytes retrieved); and binomial distribution and logit link function for proportions (fertilization, embryo quality measures and clinical outcomes). Tests for trend were conducted across categories using the median alcohol and caffeine intake in each category as a continuous variable in the regression models. In addition to the categorical analyses, we also assessed the association between alcohol and caffeine intake and ART outcomes where intakes were modeled as continuous variables.

To account for potential confounders, multivariable models included terms for age, race, BMI, infertility diagnosis, calories intake, folate and vitamin B12 intakes, which were previously related to treatment outcomes in this population (Gaskins *et al.*, 2014), smoking status, and overall food choices as captured by the Prudent and Western dietary patterns. Sensitivity analyses were conducted among the subgroup of women for whom male partner diet data were available to account for potential confounding by male partner intakes of alcohol and caffeine. We also conducted a sensitivity analysis restricting to women who had no record of prior infertility treatment at MGH in order to account for potential confounding due to changes of lifestyle habits after undergoing a previous infertility treatment. We tested the interaction of caffeine and alcohol consumption's association with live birth by BMI (<25 versus ≥25), smoking (ever versus never) and age (<35 versus ≥35 years) as these are the variables most strongly related to IVF outcomes. Effect modification was tested by introducing cross-product terms between levels of alcohol and caffeine intake and the potential modifiers. For all results we present the marginal means obtained using the GLIMMIX procedure and LSMEANS statement; the most frequent category for categorical variables was used as reference for estimation of marginal means (Searle *et al.*, 1980). All analyses were conducted using SAS 9.4 (Cary, NC). A value of $P < 0.05$ was considered significant.

Results

In total, 399 women who completed at least one ART cycle between 2007 and 2015 were eligible for this analysis. Among these, 91 women (23%) were excluded because they had not completed a FFQ and eight women (2%) were excluded because they had started their ART cycle prior to FFQ assessment. Women who were excluded were more likely to be diagnosed with diminished ovarian reserve (16.8 versus 7.6%) or endometriosis (12.6 versus 4.6%) and were more likely to have ART cycles that failed prior to embryo transfer (15.8 versus

8.2%). All other characteristics were similar to the women included in our analysis.

The 300 women we included were mostly white (84%) with mean age 35.2 years. One-third (33%) were overweight or obese (BMI ≥ 25 kg/m^2). The median (range) pre-treatment alcohol and caffeine intake was 5.6 (0.0–85.8) g/day and 103.8 (0.8–642.2) mg/day, respectively. The majority were low caffeine and alcohol consumers, with 75% consuming <200 mg/day of caffeine and 70% consuming ≤12 g/day of alcohol. Alcohol and caffeine intakes within women were moderately correlated ($\rho = 0.31$). In addition, female and male partner intake of caffeine ($\rho = 0.15$) and alcohol ($\rho = 0.51$) had slight to moderate correlations within a couple. On average, women with higher pre-treatment caffeine intakes were more likely to be white, current smokers, have higher BMIs, and consume more calories, alcohol and vitamin B12 (Table I). Women with higher pre-treatment alcohol intakes, were older on average, had higher caffeine and calorie intakes, higher Prudent and Western dietary pattern scores, and were more likely to be in a couple diagnosed with male factor infertility and have a partner who had ever smoked.

Of the 493 initiated cycles, 285 (58%) resulted in implantation, 252 (51%) resulted in clinical pregnancy, and 202 (41%) resulted in live birth. After adjusting for potential confounders, the adjusted percentage of initiated cycles resulting in live birth (95% CI) for women in increasing categories of pre-treatment alcohol intake was 34% (20–52%) for non-consumers, 46% (36–57%) for 0.1–6 g/day, 41% (29–53%) for 6.1–12 g/day, 42% (31–55%) for 12.1–24 g/day and 41% (22–63%) for >24 g/day (*P*, trend = 0.87) (Table II). The adjusted percentage of cycles resulting in live birth (95% CI) for women in increasing categories of caffeine intake was 46% (36–57%) for <50 mg/day, 44% (29–60%) for 50.1–100 mg/day, 42% (31–53%) for 100.1–200 mg/day, 40% (28–53%) for 200.1–300 mg/day and 40% (21–63%) for >300 mg/day (*P*, trend = 0.34).

We found no relation between pre-treatment intakes of caffeine and alcohol and markers of response to ovarian stimulation (Table III), fertilization (Table IV) or markers of embryo quality (Supplementary Table SI). We also found no relations between pre-treatment intake of specific types of alcoholic, caffeinated, and decaffeinated beverages with ART treatment outcomes (Supplementary Table SII).

In sensitivity analyses restricted to women who never received infertility treatment at MGH, we found a marginally significant positive relation, albeit not entirely linear, between pre-treatment alcohol intake and live birth (*P*-trend = 0.10); however, the association with caffeine and live birth remained non-significant (Supplementary Table SIII). Similar results were obtained when we restricted the analysis to women who were not current smokers or to cycles with an embryo transfer and when models were further adjusted for male partner intakes of alcohol and caffeine. Results were also similar when alcohol and caffeine intakes were modeled as continuous variables. Finally, there were no associations between pre-treatment intakes of caffeine and alcohol and pregnancy loss (defined as an implantation that did not end in live birth).

The association of caffeine consumption with live birth was not modified by BMI, age, or smoking (*P*, interaction = 0.96, 0.48 and 0.89, respectively). The association with alcohol consumption and live birth was also not modified by BMI, age or smoking (*P*, interaction = 0.64, 0.26 and 0.79, respectively).

Discussion

In this prospective study of 300 women undergoing infertility treatment, pre-treatment intake of alcohol and caffeine over the previous year were not related to the probability of live birth following ART. This lack of association persisted in various sensitivity analyses including those with additional adjustment for male caffeine and alcohol intakes. Similarly, we found no evidence of an association between intakes of alcohol or caffeine with intermediate ART endpoints. These findings suggest that low to moderate consumption of alcohol (≤12 g/day) and caffeine (<200 mg/day) in the year prior to infertility treatment may not affect ART outcomes.

Some studies from the general population suggest that women with moderate to heavy consumption of alcohol are more likely to develop infertility and experience decreases in fecundability (Grodstein *et al.*, 1994; Hakim *et al.*, 1998; Greenlee *et al.*, 2003). However, many other studies have shown that moderate alcohol intake does not influence fecundity as measured by time to pregnancy (Curtis *et al.*, 1997; Olsen *et al.*, 1997; Juhl *et al.*, 2001; Mikkelsen *et al.*, 2016). The first prospective cohort study on alcohol and IVF outcomes reported that higher maternal alcohol consumption during the year prior to IVF was negatively associated with oocyte retrieval; however, similar to our study they found no association with other IVF outcomes, including live birth (Klonoff-Cohen *et al.*, 2003). In that study it was only when they assessed alcohol intake in the month or week prior to IVF treatment that they found significant associations between higher alcohol intake and decreased risk of becoming pregnant and increased risk of miscarriage (Klonoff-Cohen *et al.*, 2003). In a cohort study of 2545 couples whose alcohol intake was assessed at the start of their IVF cycle (Rossi *et al.*, 2011), women who consumed >50 g of alcohol per week had significantly lower peak estradiol levels and greater odds of failed fertilization. Moreover, women who consumed ≥4 alcoholic drinks per week had a 16% lower chance of live birth compared to women consuming less (Rossi *et al.*, 2011). Finally, in a prospective cohort study ($n = 152$ women) which assessed alcohol intake between Days 4 and 10 of the treatment cycle, there was no relationship between female alcohol consumption and IVF outcomes such as oocyte production or fertilization rate (Firns *et al.*, 2015). There are many potential reasons for the discrepant results across studies. First and foremost there were differences in the timing of alcohol assessment. Most of the previous studies that have found detrimental effects of alcohol on IVF outcomes have evaluated current or short-term alcohol intake. If alcohol has a critical window of exposure immediately prior to IVF treatment then this could explain the different results observed in those studies as compared to ours.

Several studies evaluating the effects of caffeine on fecundability have reported that caffeine intake may reduce the ability to achieve pregnancy (Wilcox *et al.*, 1988; Christianson *et al.*, 1989; Williams *et al.*, 1990; Grodstein *et al.*, 1993), whereas others have not shown any associations (Joesoef *et al.*, 1990; Florack *et al.*, 1994; Alderete *et al.*, 1995). The first study ($n = 221$ couples) found no associations between caffeine intake in the year prior to the start of IVF and oocyte retrieval, fertilization, embryo transfer or implantation rates (Klonoff-Cohen *et al.*, 2002). However, they found that women with usual caffeine intakes of 2–50 and >50 mg/day had an adjusted odds ratio (95% CI) of not achieving a live birth of 3.1 (1.1–9.7) and 3.9 (1.3–11.6) respectively, compared to women consuming <2 mg/day. The second study that evaluated the

Table I Baseline characteristics of 300 women (313 unique FFQs) in the EARTH study (2007–2015) according to alcohol and caffeine intakes.

	Categories of alcohol intake (g/day)					Categories of caffeine intake (mg/day)				
Median	0.0	2.34	8.67	15.46	32.37	11.9	65.3	123.9	252.0	370.6
Range	32	0.1, 6.0	6.1, 12.0	12.1, 24.0	24.1, 85.8	0.31, 50	50.1, 100	100.1, 200	200.1, 300	300.1, 642
Unique FFQs, *N*	54	127	63	72	19	93	48	99	56	17
Cycles, *N*		195	106	106	32	156	65	151	93	28
Baseline characteristics										
Age, years Mean ± SD	34.4 ± 4.9	35.6 ± 4.4	34.2 ± 5.6	34.9 ± 3.1	37.9 ± 3.4	35.3 ± 4.0	35.7 ± 4.8	34.4 ± 5.3	35.3 ± 3.6	36.6 ± 3.3
White/Caucasian, *N* (%)	23 (71.9)	103 (81.1)	59 (93.7)	63 (87.5)	16 (84.2)	74 (79.6)	33 (68.8)	88 (88.9)	52 (92.9)	17 (100.0)
BMI, kg/m^2 Mean ± SD	24.3 ± 5.4	24.2 ± 4.2	23.9 ± 3.4	23.8 ± 4.0	25.2 ± 3.8	23.5 ± 4.2	24.5 ± 3.7	23.8 ± 4.1	24.9 ± 3.9	25.8 ± 5.3
Smoking status, *N* (%)										
Never smoker	26 (81.3)	96 (75.6)	44 (69.8)	48 (66.7)	10 (52.6)	75 (80.7)	38 (79.2)	69 (69.7)	35 (62.5)	7 (41.2)
Former smoker	6 (18.8)	29 (22.8)	19 (30.2)	20 (27.8)	8 (42.1)	18 (19.4)	10 (20.8)	29 (29.3)	17 (30.4)	8 (47.1)
Current smoker	0 (0.0)	2 (1.6)	0 (0.0)	4 (5.6)	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.0)	4 (7.1)	2 (11.8)
College degree or higher, *N* (%)	27 (87.1)	114 (91.2)	57 (91.9)	64 (92.8)	16 (88.9)	85 (92.4)	41 (91.1)	88 (90.7)	50 (92.6)	14 (82.4)
Dietary characteristics										
Caffeine intake, mg/day Mean ± SD	78.1 ± 72.9	102.1 ± 108.6	159.3 ± 127.4	136.6 ± 86.0	192.3 ± 102.4	19.3 ± 14.7	73.0 ± 16.1	128.8 ± 23.7	252.3 ± 26.3	401.0 ± 106.5
Alcohol intake, g/day Mean ± SD	0.0 ± 0.0	2.5 ± 1.6	8.8 ± 1.7	16.1 ± 2.7	38.5 ± 16.9	4.5 ± 5.1	7.7 ± 9.9	11.8 ± 13.1	10.8 ± 10.9	11.5 ± 8.1
Calorie intake, kcal/day Mean ± SD	1604.7 ± 571.5	1682.5 ± 608.4	1858.6 ± 558.3	1901.9 ± 587.5	2235.5 ± 572.1	1712.4 ± 604.4	1671.5 ± 551.0	1871.0 ± 673.4	1786.9 ± 504.8	2162.6 ± 464.5
Dietary folate equivalents, mcg/day Mean ± SD	1530.3 ± 660.3	1887.2 ± 888.0	1844.2 ± 819.7	1846.2 ± 800.0	1602.1 ± 673.2	1795.1 ± 850.2	1957.4 ± 976.5	1744.2 ± 721.8	1770.0 ± 748.9	2088.3 ± 1006.7
Vitamin B12, mcg/day Mean ± SD	9.9 ± 3.9	34.4 ± 97.6	46.3 ± 121.7	28.6 ± 83.5	37.3 ± 113.9	32.0 ± 88.9	54.8 ± 139.0	17.1 ± 51.2	29.7 ± 93.5	82.6 ± 161.2
Prudent pattern score Mean ± SD	−0.55 ± 0.82	−0. 21 ± 0.93	0.12 ± 1.01	0.16 ± 1.07	0.44 ± 0.99	−0.19 ± 0.92	−0.24 ± 0.77	0.15 ± 1.18	−0.09 ± 1.00	0.15 ± 0.76
Western pattern score Mean ± SD	−0.04 ± 0.88	−0.16 ± 0.95	0.02 ± 0.80	0.10 ± 0.96	0.54 ± 1.15	−0.08 ± 0.96	−0.07 ± 0.94	0.01 ± 0.91	0.04 ± 0.92	0.27 ± 1.09
Partner characteristics										
Age, years Mean ± SD	35.7 ± 4.4	36.5 ± 4.7	37.2 ± 6.5	36.5 ± 3.7	38.0 ± 6.2	37.6 ± 5.5	36.5 ± 6.3	35.6 ± 4.3	36.5 ± 4.3	38.2 ± 3.9
BMI, kg/m^2 Mean ± SD	26.9 ± 3.4	27.5 ± 4.4	26.7 ± 3.5	26.6 ± 3.8	28.4 ± 2.6	26.8 ± 4.0	26.9 ± 3.3	26.9 ± 4.1	27.9 ± 4.0	28.4 ± 3.9
Ever smoker, *N* (%)	8 (42.1)	15 (20.3)	15 (38.5)	15 (36.6)	7 (63.6)	12 (22.6)	11 (36.7)	17 (28.8)	18 (51.4)	2 (28.6)
Caffeine intake, mg/day Mean ± SD	224.4 ± 174.1	194.9 ± 124.8	216.4 ± 126.5	176.1 ± 112.4	225.2 ± 125.8	168.2 ± 127.4	229.9 ± 153.5	199.4 ± 134.0	219.6 ± 199.0	219.6 ± 116.4
Alcohol intake, g/day Mean ± SD	6.0 ± 9.4	10.7 ± 10.0	16.9 ± 9.8	22.0 ± 14.4	21.9 ± 13.6	11.8 ± 10.8	15.5 ± 11.7	15.5 ± 11.8	17.0 ± 15.4	17.0 ± 15.5
Reproductive characteristics										
Initial infertility diagnosis, *N* (%)										
Male factor	12 (37.5)	43 (33.9)	17 (27.0)	21 (29.2)	9 (47.4)	29 (31.2)	20 (41.7)	30 (30.3)	18 (32.1)	5 (29.4)
Diminished ovarian reserve	2 (6.2)	14 (11.0)	4 (6.3)	2 (2.8)	1 (5.3)	8 (8.6)	6 (12.5)	5 (5.0)	1 (1.8)	3 (17.6)
Endometriosis	5 (15.6)	4 (3.1)	1 (1.6)	2 (2.8)	2 (10.5)	6 (6.4)	2 (4.2)	2 (2.0)	4 (7.1)	0 (0.0)
Ovulatory	2 (6.2)	11 (8.7)	5 (9.7)	11 (15.3)	0 (0.0)	5 (5.4)	6 (15.5)	11 (11.1)	5 (8.9)	2 (11.8)
Tubal	4 (12.5)	6 (4.7)	3 (4.8)	9 (12.5)	2 (10.5)	6 (6.4)	3 (6.2)	8 (8.1)	6 (10.7)	1 (6.0)
Uterine	0 (0.0)	0 (0.0)	3 (4.8)	1 (1.4)	1 (5.3)	0 (0.0)	0 (0.0)	3 (3.0)	0 (0.0)	2 (1.8)
Unexplained	7 (21.9)	49 (38.6)	30 (47.6)	26 (36.1)	4 (21.1)	39 (41.9)	11 (22.9)	40 (40.4)	22 (39.3)	4 (23.5)
Initial treatment protocol, *N* (%)										

Antagonist	6 (18.7)	13 (10.2)	5 (7.9)	9 (12.5)	3 (15.8)	14 (15.1)	3 (6.3)	8 (8.1)	8 (14.3)	3 (17.7)
Flare	3 (9.4)	15 (11.8)	5 (7.9)	8 (11.1)	4 (21.1)	11 (11.8)	7 (14.6)	9 (9.1)	6 (10.7)	2 (11.8)
Luteal phase agonist	23 (71.9)	99 (78.0)	53 (84.1)	55 (76.4)	12 (63.2)	68 (73.1)	38 (79.2)	82 (82.8)	42 (75.0)	12 (70.6)
Day three FSH, IU/L mean ± SD	7.31 ± 2.15	7.49 ± 3.12	7.21 ± 2.28	6.85 ± 1.89	7.84 ± 2.07	7.42 ± 2.50	7.81 ± 3.44	6.99 ± 2.53	7.14 ± 1.78	7.28 ± 2.37
Previous IVF at MGH, *N* (%)	12 (37.5)	30 (23.6)	18 (28.6)	14 (19.4)	3 (15.8)	26 (28.0)	15 (31.2)	23 (23.2)	10 (17.9)	3 (17.6)
Previous IUI at MGH, *N* (%)	11 (34.4)	53 (41.7)	24 (38.1)	31 (43.1)	3 (15.8)	42 (45.2)	20 (41.7)	38 (38.4)	18 (32.1)	4 (25.5)

EARTH: Environment and Reproductive Health; FFQ: Food Frequency Questionnaire; MGH: Massachusetts General Hospital.

association between caffeine and IVF (Choi *et al.*, 2011) did so in a much larger population of women (n = 2474 couples and 4716 cycles) and found that current caffeine consumption prior to IVF treatment was associated with lower peak estradiol level but was not associated with number of oocytes retrieved, fertilization rate, implantation rate, or live birth rate. Moreover, the range of caffeine intake compared in this population (i.e. none versus 0–114, 115–200, and >201 mg/day) was more similar to that reported in our study. The third study (Al-Saleh *et al.*, 2010) focused on caffeine and IVF outcomes in 619 Saudi Arabian women and found no significant associations between current caffeine intake and pregnancy rate, despite having a median caffeine intake of 455.8 mg/day, which is almost six times higher than the intake of women in our study. Taken together with our results, the evidence on pre-treatment caffeine intake and infertility treatment outcomes suggests that moderate caffeine intake is not associated with lower success of ART.

There are limitations of the present study that need to be considered when interpreting our results. First, caffeine and alcohol consumption are lifestyle choices that can be correlated with several other factors. Thus, we cannot exclude the possibility that the lack of association seen in our data is an artifact produced by unmeasured confounding. However, we have controlled for many plausible confounders. Second, it is difficult to quantify the exact amount of caffeine and alcohol in beverages. Although, we used a validated questionnaire, there is still likely error in women's self-report as information on serving size and amount consumed was limited. Furthermore, the brewing method for coffee was not collected which could impact the quantity of caffeine in a given serving size (Bunker and McWilliams, 1979) as well as the metabolic effects of caffeinated beverages themselves (Jee *et al.*, 2001; Cai *et al.*, 2012). However, misclassification of alcohol, caffeine, and beverage intake is unlikely to depend on IVF outcome given the prospective nature of our study. While this type of non-differential misclassification would tend to attenuate associations towards the null, it is hard to determine whether the null associations we observed are due to measurement error or due to a lack of true biological effect. It is also important to acknowledge that our FFQ assesses average intake over the previous year and that participants enrolling in this study might have made changes to their alcohol or caffeine intake, such as reducing alcohol and caffeine intakes. While our FFQ might capture these changes in diet habits (if patients tended to base their reports on the past 3 months as opposed to the last year (Fowke *et al.*, 2004)), if short-term alcohol or caffeine consumption is related to fertility potential then our study would not capture these associations. We also do not have information on diet, including caffeine and alcohol intake, during pregnancy. The majority of our women were also relatively low caffeine and alcohol consumers, with 75% consuming <200 mg/day of caffeine and 70% consuming ≤12 g/day of alcohol, making our study's findings likely not generalizable to women with higher alcohol and caffeine intakes. Due to the slightly higher exclusion of women failing early in their IVF cycles, there is also a possibility for selection bias if the excluded women had higher or lower caffeine/alcohol intakes than the included population. However, given that the FFQs were filled out anonymously and that questions about beverage consumption started on the 13th page of the FFQ, we believe it is unlikely that women who failed to complete the FFQ had differential caffeine or alcohol intakes. Finally, given the sample size of our study, our results cannot rule out modest effect sizes, which we were underpowered to detect.

Strengths of our study include its prospective design with complete follow-up and our ability to adjust for a wide range of potential

Table II Adjusted probabilities of implantation, clinical pregnancy and live birth following ART by alcohol and caffeine intake in 300 women (313 unique FFQs, 493 ART cycles) from the EARTH Study.

Categories, range	Number of unique FFQs/cycles	Adjusted proportions (95% CI)[a]		
		Implantation	Clinical pregnancy	Live birth
Alcohol intake, g/day				
0.0	32/54	0.53 (0.36–0.69)	0.48 (0.32–0.64)	0.34 (0.20–0.52)
0.1–6.0	127/195	0.66 (0.56–0.75)	0.59 (0.49–0.68)	0.46 (0.36–0.57)
6.1–12.0	63/106	0.66 (0.54–0.76)	0.53 (0.41–0.65)	0.41 (0.29–0.53)
12.1–24.0	72/106	0.62 (0.50–0.74)	0.53 (0.41–0.65)	0.42 (0.31–0.55)
24.1–85.8	19/32	0.62 (0.41–0.80)	0.49 (0.29–0.70)	0.41 (0.22–0.63)
P-trend[b]		0.95	0.51	0.87
Caffeine intake, mg/day				
0.3–50	93/156	0.68 (0.57–0.77)	0.59 (0.48–0.69)	0.46 (0.36–0.57)
50.1–100	48/65	0.69 (0.53–0.81)	0.63 (0.47–0.76)	0.44 (0.29–0.60)
101.1–200	99/151	0.64 (0.53–0.74)	0.52 (0.41–0.62)	0.42 (0.31–0.53)
200.1–300	56/93	0.59 (0.45–0.71)	0.51 (0.39–0.64)	0.40 (0.28–0.53)
300.1–642	17/28	0.52 (0.30–0.73)	0.48 (0.27–0.69)	0.40 (0.21–0.63)
P-trend[b]		0.08	0.16	0.34

[a]Data are presented as predictive marginal means adjusted for age, BMI, infertility diagnosis, race, smoking status, alcohol, caffeine, calories, folate and Vitamin B12 intake and dietary patterns, with continuous covariates at their mean level and categorical measures estimated at their reference level.
[b]Tests for trend were performed using the median level of caffeine and alcohol intake in each group as a continuous variable in the model.

Table III Adjusted mean peak estradiol concentrations, mature oocyte count and endometrial thickness on the day of embryo transfer following ART, by alcohol and caffeine intake in 279 women (290 unique FFQs, 389 fresh ART cycles with egg retrieval) from the EARTH Study.

Categories, range	Number of unique FFQs /cycles	Adjusted means (95% CI)[a]		
		E_2 trigger levels, pmol/L	Endometrial thickness, mm	MII phase oocytes count, *n*
Alcohol intake, g/day				
0.0	30/38	2243 (1446–3040)	10.2 (8.2–12.2)	9.8 (8.1–12.0)
0.1–6.0	115/151	2052 (1584–2519)	10.3 (9.2–11.5)	9.6 (8.5–10.8)
6.1–12.0	59/83	2048 (1502–2594)	10.3 (8.9–11.7)	9.2 (8.0–10.6)
12.1–24.0	69/91	2024 (1471–2577)	10.4 (8.9–11.8)	9.8 (8.5–11.3)
24.1–85.8	17/26	2022 (1039–3005)	10.2 (7.7–12.7)	10.4 (8.2–13.3)
P-trend[b]		0.59	0.93	0.53
Caffeine intake, mg/day				
0.3–50	88/128	2112 (1607–2616)	10.1 (8.8–11.4)	9.1 (8.0–10.3)
50.1–100	39/47	1841 (1130–2552)	10.0 (8.2–11.8)	9.4 (7.9–11.2)
101.1–200	94/120	2043 (1554–2531)	10.4 (9.2–11.7)	9.8 (8.7–11.1)
200.1–300	53/71	2063 (1462–2663)	10.5 (9.0–12.1)	10.1 (8.7–11.7)
300.1–642	16/23	2061 (1056–3066)	10.7 (8.1–13.2)	10.3 (8.1–13.3)
P-trend[b]		0.93	0.16	0.16

MII: metaphase II; E_2: estradiol.
[a]Data are presented as predictive marginal means adjusted for age, BMI, infertility diagnosis, race, smoking status, alcohol, caffeine, calories, folate and Vitamin B12 intake and dietary patterns, with continuous covariates at their mean level and categorical measures estimated at their reference level.
[b]Tests for trend were performed using the median level of caffeine and alcohol intake in each group as a continuous variable in the model.

Table IV Adjusted mean fertilization rate following ART by alcohol and caffeine intake in 279 women (290 unique FFQs, 389 fresh ART cycles with egg retrieval) from the EARTH Study.

Categories, range	Number of unique FFQs/cycles	Adjusted proportions (95% CI)[a]		
		IVF cycles (n = 181)	ICSI cycles (n = 208)	Combined cycles (n = 389)
Alcohol intake, g/day				
0.0	30/38	0.69 (0.55–0.80)	0.64 (0.48–0.77)	0.63 (0.53–0.71)
0.1–6.0	115/151	0.63 (0.55–0.70)	0.77 (0.68–0.84)	0.68 (0.63–0.73)
6.1–12.0	59/83	0.76 (0.67–0.84)	0.74 (0.64–0.82)	0.73 (0.66–0.78)
12.1–24.0	69/91	0.63 (0.54–0.72)	0.77 (0.68–0.84)	0.69 (0.63–0.75)
24.1–85.8	17/26	0.69 (0.51–0.83)	0.79 (0.65–0.89)	0.74 (0.64–0.82)
P-trend[b]		0.79	0.24	0.18
Caffeine intake, mg/day				
0.3–50	88/128	0.67 (0.59–0.75)	0.75 (0.65–0.82)	0.70 (0.64–0.75)
50.1–100	39/47	0.65 (0.52–0.76)	0.66 (0.51–0.78)	0.64 (0.55–0.71)
101.1–200	94/120	0.65 (0.56–0.73)	0.76 (0.67–0.82)	0.69 (0.64–0.74)
200.1–300	53/71	0.68 (0.58–0.77)	0.77 (0.66–0.85)	0.71 (0.64–0.77)
300.1–642	16/23	0.68 (0.47–0.84)	0.84 (0.72–0.92)	0.77 (0.67–0.85)
P-trend[b]		0.86	0.13	0.23

[a]Data are presented as predictive marginal means adjusted for age, BMI, infertility diagnosis, race, smoking status, alcohol, caffeine, calories, folate and Vitamin B12 intake and dietary patterns, with continuous covariates at their mean level and categorical measures estimated at their reference level.
[b]Tests for trend were performed using the median level of caffeine and alcohol intake in each group as a continuous variable in the model.

confounding factors. We also had information on male partner diet, intake of specific caffeinated and alcoholic beverages, and many other dietary factors such as dietary patterns, which previous studies have not included. In regards to generalizability of our study, the average alcohol consumption for American women of reproductive age is 0.5 servings/day (White *et al.*, 2015) and 146 mg/day of caffeine (Mitchell *et al.*, 2014), which is comparable to the mean alcohol and caffeine intake of our population (0.7 servings/day of alcohol and 124.9 mg/day of caffeine) suggesting that our study population's drinking habits may resemble that of US women.

In conclusion, we found that pre-treatment maternal intake of alcohol and caffeine in the year prior to infertility treatment was not associated with outcomes of ART. Furthermore, none of the specific types of caffeinated or alcoholic beverages were associated with outcomes of ART. Our results provide reassurance that low to moderate intakes of alcohol and caffeine over the year prior to infertility treatment initiation do not have an adverse effect on intermediate or clinical outcomes of ART. Future research is needed to clarify the relationship between short-term alcohol and caffeine consumption and ART outcomes.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

L.A. and A.J.G. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. R.H. and J.E.C. were responsible of the study concept and design. The acquisition, analysis and interpretation of data was conducted L.A., Y.H.C., T.L.T., I.S., R.H., J.E.C. and A.J.G. Statistical analysis was handled by L.A., Y.H.C., P.L.W. and A.J.G. L.A. and A.J.G. drafted the article. The critical revision of the article for important intellectual content was conducted by L.A., Y.H.C., P.L.W., T.L.T., I.S., R.H., J.E.C. and A.J.G.

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Conflict of interest

None.

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