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The association between preconception maternal beverage intake and IVF outcomes

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Abstract

Objective—To study whether maternal intake of beverage type affect IVF outcomes

Design—A prospective study

Setting—Tertiary, University-affiliated center.

Patient (s)—340 women undergoing IVF from 2014 through 2016 for infertility as well as for pre-genetic diagnosis for autosomal recessive diseases were enrolled during ovarian stimulation and completed a questionnaire describing their usual beverage consumption .

Intervention(s)—none

Main Outcome Measure (s)—IVF outcomes were abstracted from medical records. Total caffeine intake was estimated by summing the caffeine content for specific beverages multiplied by frequency of intake. Associations between specific types of beverages and IVF outcomes were analyzed using Poisson and logistic regression models adjusting for possible confounders.

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Result (s)—Higher intake of sugared soda was associated with lower total, mature, and fertilized oocytes and top quality embryos following ovarian stimulation. Women who consumed sugared soda had, on average, 1.1 fewer oocytes retrieved, 1.2 fewer mature oocytes retrieved, 0.6 fewer fertilized oocytes and 0.6 fewer top quality embryos compared to women who did not consume sugared soda. Furthermore, compared to women who did not drink sugared soda, the adjusted difference in percent of cycles resulting in live birth for women consuming 0.1–1 cups/day and >1 cup/day were −12% and −16%, respectively (p-trend=0.01). No associations were found between consumption of coffee, caffeine or diet sodas and IVF outcome.

Conclusion (s)—Sugared beverages, independently of their caffeine content, may be a bigger threat to reproductive success than caffeine and caffeinated beverages without added sugar.

Keywords

IVF; caffeinated beverages; non-caffeinated beverages; sugared soda

Introduction

Up to 10% of reproductive aged couples suffer from infertility (1) with more than 600,000 IVF cycles performed in Europe in 2011 (2) and more than 140,000 IVF cycles performed in the USA in 2014 (www.sartcorsonline.com). Despite the relative increase in pregnancy rates with time, overall success rates of IVF remain relatively low. To date, the best characterized predictors of IVF success are unmodifiable (i.e., patient age), hence the need to investigate potentially modifiable factors, one example of which is type of beverages consumed (3–5).

Among the most popular beverages consumed by reproductive aged women are caffeinated drinks, sugared sodas, and diet sodas. Caffeine is a stimulant of the central nervous system (6). While increased caffeine consumption is associated with lower estrogen levels in the luteal phase (7–9), the effects of caffeinated beverages on fecundity are still inconsistent (6, 10–13). Intake of sugared soda has been linked to weight gain as well as a rapid increase in circulating insulin and insulin-like growth factor 1 (IGF-1) levels and insulin resistance due to their high glycemic content (14). Moreover, soda drinkers are potentially exposed to higher levels of endocrine disruptors chemicals such as bisphenol A, which migrate from the coating of soda cans into the liquid (15).

Most studies to date have evaluated the effects of caffeine, sugared sodas and diet beverages either on time to conception or risk of fetal loss and the results are still conflicting (16–20). However, the effects of these beverages on intermediate IVF cycle outcomes (i.e., number of oocytes retrieved, oocyte maturation, fertilization and day 3 embryo quality) as well as clinical IVF outcomes (positive beta-hCG, clinical pregnancy rates, spontaneous abortions and live births) have been less well studied (21–23).

In the most recent study on this topic, Abadia and colleagues found no association between low to moderate caffeine intake (<200mg/day) and IVF outcomes in a prospective cohort on infertile women in the USA (24). They also found no associations with any of the specific caffeinate beverages. However, due to the low soda consumption in that cohort, the study was unable to assess whether consumption of these beverages is related with ART outcomes.

The aim of the current study was to evaluate the associations between preconception drinking habits of women with fresh IVF cycle outcomes in a prospective cohort of women from outside the USA consuming much higher levels of caffeine (mainly instant coffee) and sodas (both full calorie and diet).

Methods

Study Design

From January 2014 through August 2016, 359 women undergoing a fresh IVF cycle at a tertiary university affiliated hospital were recruited into a study on environmental exposures and fertility. Cryopreserved cycles were excluded from our analysis. The study was approved by our local IRB and all patients signed informed consents. Participants were enrolled during ovarian stimulation and followed through one fresh IVF cycle. For the analysis of intermediate IVF outcomes, exclusion criteria included women with missing embryology (n=3) or exposure (n=2) information, women who froze their oocytes (n=11), women using egg donors (n=1), and women missing information on oocyte retrieval (n=2). Thus, the final dataset consisted of 340 women. For the analysis of clinical IVF outcomes, we further excluded one woman who was lost to follow-up after identification of a clinical pregnancy, bringing the final analytic sample to 339 women.

Exposure Assessment

Women reported their usual intake of caffeinated and non-caffeinated beverages on the first day of stimulation and/or on the day of oocyte retrieval. The questionnaire specifically asked women, “Do you drink any of the following 14 beverages: filtered coffee, instant coffee, boiled black coffee, mud coffee, decaffeinated coffee, cappuccino, espresso, caffeinated tea, herbal tea, chocolate drinks, caffeinated soda, caffeinated diet sodas, non-caffeinated diet sodas, and energy drinks and, if so, in what quantity (in cups)”. Women were also provided with information on converting common serving sizes to cups (e.g. 1 mug = 2 cups). Total caffeine intake was estimated by summing the caffeine content for each specific beverage multiplied by their frequency of intake. We assumed the following caffeine concentrations for each caffeinated beverage: filtered coffee, 95 mg/cup; instant coffee, 63 mg/cup; boiled black and mud coffee, 115 mg/cup; decaffeinated coffee, 2 mg/cup; cappuccino, 64 mg/cup; espresso, 64 mg/shot; caffeinated tea, 26 mg/cup; chocolate drinks, 5 mg/cup; caffeinated sodas, 16 mg/cup; and energy drinks, 111 mg/cup.

Covariate Assessment

Height and weight, measured at the start of the IVF cycle by a trained nurse, were used to calculate body mass index (BMI) (kg/m^2). A woman’s age, smoking status, number of previous pregnancies and deliveries, duration of infertility, and IVF attempt number were abstracted from patients’ medical records. On the same questionnaire as the beverages, women also provided information on their country/region of birth, years of education, smoking history, and field of employment.

Outcome Assessment

Patients were treated with controlled ovarian stimulation using one of three protocols (GnRH antagonist, GnRH agonist suppressive protocol or GnRH agonist flare-up protocol) as clinically indicated. Patients were monitored during gonadotropin stimulation for serum estradiol, follicle size measurements and counts, and endometrial thickness through 2 days before oocyte retrieval. Human chorionic gonadotropin (hCG) was administered approximately 36 hours before the scheduled oocyte retrieval procedure to induce oocyte maturation. Women received conventional insemination or intracytoplasmic sperm injection (ICSI) as clinically indicated. Embryologists classified oocytes as germinal vesicle, metaphase I, metaphase II (MII) or degenerated. Embryologists determined fertilization 16 to 18 hours after insemination as the number of oocytes with two pronuclei. The resulting embryos were assessed for cell number, symmetry and fragmentation (25). Top quality embryos were considered to be embryos with 7–8 cells on day 3 (or in cases of day 2 transfer, 4 cells) and <10% fragmentation. Positive β-hCG (i.e., successful implantation) was defined as a serum β-hCG level > 25 mIU/mL typically measured 14 days after oocyte retrieval. Embryos were scheduled for transfer on day 3 in non-PGD patients. In cases that day 3 was a holiday, transfers were performed on day 2 (n=12 cycles). For PGD patients, embryos were biopsied on day 3 and transferred on day 4. Clinical pregnancy was defined as the presence of an intrauterine gestational sac and fetal heartbeat confirmed by ultrasound by 7 weeks of gestation, and live birth as the delivery of a live neonate on or after 24 weeks gestation. All clinical information was abstracted from medical records.

Statistical Analysis

Women were stratified into quartiles of total caffeine intake and categories of beverage consumption based on the distribution of consumption in the population. Descriptive statistics, calculated for demographic and reproductive characteristics in the entire cohort and by quartile of total caffeine intake, were presented as mean (standard deviation) or number of women (%). For continuous and categorical variables, ANOVA and chi-square tests were used, respectively, to test for associations across categories of total caffeine intake.

To evaluate the association between caffeine and beverage intake and number of total oocytes, mature oocytes, fertilized oocytes, and top quality embryos (all count data), we used a multivariable Poisson regression with log link. Adjusted marginal mean counts for each quartile or category were obtained. For the clinical outcomes, we used a multivariable logistic regression model to derive the adjusted proportion of initiated cycles resulting in implantation, clinical pregnancy, and live birth for each quartile or category. Risk of pregnancy loss was evaluated among women with an implantation and was defined as any loss of pregnancy prior to live birth. To test associations between caffeine and beverage intake and pregnancy loss, we used a Poisson regression with log link and present results as risk ratios (95% CIs). Tests for trend were conducted across quartiles or categories using the median level of intake in each category as a continuous variable in the regression models.

Confounding was evaluated using prior knowledge and descriptive statistics from our cohort. Variables retained in the final multivariable models were age, BMI, smoking status, and

country of origin. Specific beverages also were further adjusted for coffee, caffeinated tea, herbal tea, sugared soda, and energy drink intakes. To test for potential effect modification by PGD, we included a cross-product term in the final multivariable model. All analyses were conducted using SAS Software package 9.4 (Cary NC).

Results

Between January 2014 and August 2016, 340 women who underwent ovarian stimulation for a fresh IVF cycle completed questionnaires on their recent consumption of coffee, tea, hot chocolate, soda, and energy drinks. The women were 31.5 ± 4.0 years and had a BMI of 23.4 ± 4.5 kg/m^2 (Table 1). Their primary reason for undergoing IVF was preimplantation genetic diagnosis for autosomal recessive disorders (n=129 women, 37.9%) followed by male factor infertility (33.8%), unexplained infertility (16.8%), and known female factors (i.e., anovulation or endometriosis) (11.5%). The majority (62.4%) of women was undergoing their first IVF cycle, 20.9% were undergoing their second IVF cycle, and 16.8% were undergoing their third IVF cycle. There were no differences regarding the number of embryos transferred, the number of top quality embryo transferred and the day of transfer across the quartiles of caffeine intake. The mean ± SD caffeine intake of women in our cohort was 163.5 ± 125.3 mg/day which corresponds to about 2.5 cups of instant coffee per day. Women with higher caffeine intake were, on average, slightly older and more likely to be current smokers (Table 1); all other demographic and reproductive characteristics were similar across quartiles of caffeine intake.

There were no associations between total caffeine intake and number of total or mature oocytes, fertilized oocytes, or top quality embryos (Table 2). Similarly, total coffee intake was not associated with these outcomes. Higher consumption of instant coffee was associated with a slightly lower number of fertilized oocytes. However, none of the other coffee beverages were related to this or other oocyte or embryo outcomes. On the other hand, women with higher caffeinated tea intake had a lower number of total (P-trend=0.001) and mature oocytes (P-trend=0.003) and a lower number of fertilized oocytes (P-trend=0.05). In contrast, herbal tea intake, was associated with higher total and mature oocyte yield (P-trend=0.001 and 0.02, respectively).

Intake of sugared soda, but not of diet soda, was associated with lower total and mature oocytes, fertilized oocytes, and top quality embryos. Women who consumed sugared soda had, on average, 1.1 fewer oocytes retrieved, 1.2 fewer mature oocytes retrieved, and 0.6 fewer fertilized oocytes compared to women who did not consume sugared soda (p for trend=0.002, <0.001, and 0.01, respectively). Similarly, inverse associations were seen for these same outcomes comparing energy drink consumers to non-consumers (p-value for comparisons=<0.001, <0.001. and 0.005, respectively).

Among the 339 women who were included in analysis of clinical outcomes, 283 (83.5%) had an embryo transfer, 116 (34.2%) had positive β-hCG 14 days after embryo transfer, 102 (30.1%) had a clinical pregnancy, and 83 (24.5%) had a live birth. Total caffeine intake was not associated with probability of positive β-hCG, clinical pregnancy, or live birth following IVF (Table 3). Of all the beverages examined, only sugared soda intake was related to

clinical outcomes. Higher intake of sugared sodas was inversely associated with clinical pregnancy (P-trend=0.01) and live birth (P-trend=0.01). Specifically, compared to women who reported no sugared soda intake (0 cups/day), the adjusted difference in percent of cycles resulting in live birth for women consuming 0.1–1 cups/day and >1 cup/day were −12% and −16%, respectively (p-trend=0.01). When the analysis was restricted to only women who underwent embryo transfer, this association strengthened (Supplemental Table 1). The adjusted differences in percent of transfers resulting in live birth for women consuming s0.1–1 cups/day and >1 cup/day compared to non-consumers were −15% and −19%, respectively (p-trend=0.01). Among women with implantation, the risk of pregnancy loss prior to delivery was 3.51 (95% CI 1.46, 8.45) times higher among women consuming >1 cup/day of sugared soda compared to women consuming no sugared soda (P-trend=0.02).

There was no evidence of effect modification by PGD for the association between caffeine and sugared soda and live birth (p-value for interaction=0.43 and 0.85, respectively).

Discussion

In our prospective cohort of women undergoing IVF we found that higher preconception intake of sugared sodas was associated with a lower number of total and mature oocytes retrieved, a lower number of fertilized oocytes as well as a lower proportion of cycles resulting in clinical pregnancy and live birth. Intake of caffeinated tea and energy drinks was also associated with poorer oocyte and embryo outcomes but these associations did not translate into poorer clinical outcomes. Contrary to our hypothesis, however, intake of caffeine, coffee, specific caffeinated beverages, or diet sodas, failed to show consistent associations with any of the outcomes examined.

Regarding our initial hypotheses that caffeine and/or the increased glycemic impact of sugar in beverages might alter IVF outcomes, the one most supported by our data is the second one pertaining to sugar. This proposed mechanism not only fits with the sugar soda findings, but also explains the results regarding energy drinks, which often contain high levels of either sucrose or high-fructose corn syrup. Moreover, it is possible that a high proportion of women add sugar to their caffeinated tea which might explain why we also found a similar inverse association with this beverage and intermediate IVF outcomes.

Consumption of sugared soda has been linked to abnormal markers of glycemic control such as insulin resistance, metabolic syndrome and type 2 diabetes (26–29). Insulin resistance is a situation in which the responsiveness of the body to the hormone insulin is diminished, resulting in metabolic dysregulation (30, 31). Insulin resistance can alter the maternal metabolic environment and follicular fluid microenvironment, leading to lower quality oocytes and embryos (9, 11, 32). In mice, this condition leads to altered mitochondrial function and abnormal spindle formation (33). Interestingly, another marker of abnormal glycemic control, glycosylated hemoglobin (HbA1C), which increases in diabetes, was previously reported to be associated with reduced fertility (34).

We found that the proportion of cycles resulting in clinical pregnancy and live birth was lower among women who consumed higher levels of sugared sodas compared with those

who drank lower levels of these beverages. Although to the best of our knowledge, the only other study that has investigated the association between female intake of sugared sodas IVF outcomes found no association between usual intake of soda in the year prior to infertility treatment and probability of live birth (24). However, this study did not distinguish between diet and sugared soda and was limited by a low number of high soda consumers (only 8.3% reported consuming >=1 one serving of any type of soda while in our study 27.9% of women reported consuming >=1 one cup of any type of soda). This previous study also only focused on sub-fertile women undergoing ART for infertility treatment as compared to our cohort which also included women undergoing ART for PGD. Taken together, these differences in study population could help explain some of our seemingly discrepant findings. In contrast, and more in line with our current findings, a previous study among women conceiving spontaneously showed that women who consumed high levels of sugar sweetened beverages had decreased fecundity. Specifically, among 3628 women planning a pregnancy in Denmark the adjusted fecundability ratios were 0.89 (0.80–0.98), 0.85 (0.71–1.02), 0.84 (0.57–1.25), and 0.48 (0.21–1.13) for < 1, 1, 2, and 3+ servings per day, respectively, compared with none (16). This inverse association with fecundity, however, was not confirmed in a more recent prospective study among 2135 North American pregnancy planners (11). Moreover, in this same cohort of women, there was no link between pre-pregnancy soda consumption and pregnancy loss (35).

In contrast with our hypothesis, we failed to find an association between caffeine consumption and number of total, mature, or fertilized oocytes or embryo quality. Also, pre-conception caffeine intake was not associated with implantation, clinical pregnancy, or live birth. Our results are in line with a previous study of 221 women undergoing IVF, in which no associations were observed for between recent caffeine intake and IVF outcomes (23). A lack of association between current consumption of caffeine and number of oocytes retrieved, fertilization rate, implantation rate, or live birth rate was also reported by Choi et al., who evaluated 2,474 women undergoing 4,716 IVF treatment cycles from 1994 to 2003 (21, 22). A third study among 619 women undergoing IVF also found no significant associations between current caffeine intake and pregnancy rate, despite having a median caffeine intake of 455.8 mg/day (21). Finally, the most recent study on caffeine intake and IVF outcomes (n=300 women, 493 IVF cycles) found no association between usual caffeine intake over the previous year and intermediate or clinical outcomes of IVF (24).

Our study was subject to some limitations. Although women reported their intake of specific beverages (in cups), there is still likely error in their self-report as information on serving size and amount consumed was limited. Furthermore, the brewing method for the specific coffee types was not collected which could impact the quantity of caffeine in a given serving size. However, misclassification of beverage intake is unlikely to be linked with IVF outcome given the prospective nature of our study and would therefore tend to attenuate our associations towards the null. We also lacked information regarding the beverage habits during the pregnancy and it is possible that patients change their drinking beverage habits through pregnancy, especially by decreasing their caffeine and diet soda consumption. Beverage consumption could also be correlated with other diet and lifestyle factors as well as dietary consumption that were not assessed and that may confound the relation with

fertility. Thus, we cannot exclude the possibility that the lack of association seen in our data is an artifact produced by unmeasured factors.

Finally, given the sample size of our study, our results cannot rule out modest effect sizes, which we were underpowered to detect.

Despite the above limitations, our analysis had several important strengths. First, collection of prospective data from relatively large number of women undergoing IVF enables us to get accurate data regarding their usual drinking habits before oocyte retrieval. Second, in order to generalize our results, we included also fertile women, undergoing IVF for preimplantation genetic diagnosis. Moreover, our cohort included a wide range of caffeine intake, which allowed us to examine more relevant levels of exposure given the high intake of caffeine by reproductive aged women in many countries (36, 37). Last, all patients underwent their IVF treatment in the same program, enabling standardization of the laboratory conditions and limiting possible inter-observer variations.

In conclusion, pre-pregnancy consumption of sugared sodas seems to have the most detrimental impact on IVF outcomes compared to other commonly consumed beverages. Given our findings, it is possible that sugar, rather than the caffeine, is a stronger reproductive toxicant. Although we failed to find an association between caffeine consumption and IVF outcomes, these results should to be interpreted with caution and deserve further evaluation, including measurement of urinary caffeine metabolites to assess the accurate level of exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS medicine. 2012; 9:e1001356. [PubMed: 23271957]
2. Kupka MS, D'Hooghe T, Ferraretti AP, de Mouzon J, Erb K, Castilla JA, et al. Assisted reproductive technology in Europe, 2011: results generated from European registers by ESHRE. Human reproduction. 2016; 31:233–48. [PubMed: 26740578]
3. Gormack AA, Peek JC, Derraik JG, Gluckman PD, Young NL, Cutfield WS. Many women undergoing fertility treatment make poor lifestyle choices that may affect treatment outcome. Human reproduction. 2015; 30:1617–24. [PubMed: 25924654]
4. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Hum Reprod Update. 2007; 13:209–23. [PubMed: 17208948]

5. Hornstein MD. Lifestyle and IVF Outcomes. Reproductive sciences. 2016; 23:1626–9. [PubMed: 27609400]
6. 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; 12:289–95. [PubMed: 9628552]
7. 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; 115:2765–74. [PubMed: 19384973]
8. Sisti JS, Hankinson SE, Caporaso NE, Gu F, Tamimi RM, Rosner B, et al. Caffeine, Coffee, and Tea Intake and Urinary Estrogens and Estrogen Metabolites in Premenopausal Women. Cancer Epidemiol Biomarkers Prev. 2015; 24:1174–83. [PubMed: 26063478]
9. 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; 95:488–97. [PubMed: 22237060]
10. Stanton CK, Gray RH. Effects of caffeine consumption on delayed conception. American journal of epidemiology. 1995; 142:1322–9. [PubMed: 7503053]
11. Wesselink AK, Wise LA, Rothman KJ, Hahn KA, Mikkelsen EM, Mahalingaiah S, et al. Caffeine and caffeinated beverage consumption and fecundability in a preconception cohort. Reproductive toxicology. 2016; 62:39–45. [PubMed: 27112524]
12. Wilcox A, Weinberg C, Baird D. Caffeinated beverages and decreased fertility. Lancet. 1988; 2:1453–6. [PubMed: 2904572]
13. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Caffeinated and alcoholic beverage intake in relation to ovulatory disorder infertility. Epidemiology. 2009; 20:374–81. [PubMed: 19279491]
14. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. Jama. 2002; 287:2414–23. [PubMed: 11988062]
15. Cao XL, Corriveau J, Popovic S. Sources of low concentrations of bisphenol A in canned beverage products. Journal of food protection. 2010; 73:1548–51. [PubMed: 20819371]
16. 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; 23:393–401. [PubMed: 22407137]
17. Gaskins AJ, Rich-Edwards JW, Williams PL, Toth TL, Missmer SA, Chavarro JE. Pre-pregnancy caffeine and caffeinated beverage intake and risk of spontaneous abortion. European journal of nutrition. 2016
18. Buck Louis GM, Sapra KJ, Schisterman EF, Lynch CD, Maisog JM, Grantz KL, et al. Lifestyle and pregnancy loss in a contemporary cohort of women recruited before conception: The LIFE Study. Fertility and sterility. 2016; 106:180–8. [PubMed: 27016456]
19. Cnattingius S, Signorello LB, Anneren G, Clausson B, Ekbom A, Ljunger E, et al. Caffeine intake and the risk of first-trimester spontaneous abortion. N Engl J Med. 2000; 343:1839–45. [PubMed: 11117975]
20. Klebanoff MA, Levine RJ, DerSimonian R, Clemens JD, Wilkins DG. Maternal serum paraxanthine, a caffeine metabolite, and the risk of spontaneous abortion. The New England journal of medicine. 1999; 341:1639–44. [PubMed: 10572151]
21. Al-Saleh I, El-Doush I, Grisellhi B, Coskun S. The effect of caffeine consumption on the success rate of pregnancy as well various performance parameters of in-vitro fertilization treatment. Medical science monitor : international medical journal of experimental and clinical research. 2010; 16:CR598–605. [PubMed: 21119578]
22. Choi JH, Ryan LM, Cramer DW, Hornstein MD, Missmer SA. Effects of Caffeine Consumption by Women and Men on the Outcome of In Vitro Fertilization. Journal of caffeine research. 2011; 1:29–34. [PubMed: 24761261]
23. Klonoff-Cohen H, Bleha J, Lam-Kruglick P. A prospective study of the effects of female and male caffeine consumption on the reproductive endpoints of IVF and gamete intra-Fallopian transfer. Hum Reprod. 2002; 17:1746–54. [PubMed: 12093834]

24. Abadia L, Chiu YH, Williams PL, Toth TL, Souter I, Hauser R, et al. The association between pre-treatment maternal alcohol and caffeine intake and outcomes of assisted reproduction in a prospectively followed cohort. Hum Reprod. 2017 In Press.
25. Machtinger R, Racowsky C. Morphological systems of human embryo assessment and clinical evidence. Reproductive biomedicine online. 2013; 26:210–21. [PubMed: 23352813]
26. Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. Bmj. 2015; 351:h3576. [PubMed: 26199070]
27. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. Circulation. 2008; 117:754–61. [PubMed: 18212291]
28. Mayans L. Metabolic Syndrome: Insulin Resistance and Prediabetes. FP essentials. 2015; 435:11–6. [PubMed: 26280340]
29. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. Jama. 2004; 292:927–34. [PubMed: 15328324]
30. Ma J, Jacques PF, Meigs JB, Fox CS, Rogers GT, Smith CE, et al. Sugar-Sweetened Beverage but Not Diet Soda Consumption Is Positively Associated with Progression of Insulin Resistance and Prediabetes. The Journal of nutrition. 2016; 146:2544–50. [PubMed: 27934644]
31. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. American journal of physiology Endocrinology and metabolism. 2008; 294:E15–26. [PubMed: 17957034]
32. Cardozo E, Pavone ME, Hirshfeld-Cytron JE. Metabolic syndrome and oocyte quality. Trends in endocrinology and metabolism: TEM. 2011; 22:103–9. [PubMed: 21277789]
33. Ou XH, Li S, Wang ZB, Li M, Quan S, Xing F, et al. Maternal insulin resistance causes oxidative stress and mitochondrial dysfunction in mouse oocytes. Human reproduction. 2012; 27:2130–45. [PubMed: 22556376]
34. Hjollund NH, Jensen TK, Bonde JP, Henriksen TB, Andersson AM, Skakkebaek NE. Is glycosylated haemoglobin a marker of fertility? A follow-up study of first-pregnancy planners. Human reproduction. 1999; 14:1478–82. [PubMed: 10357963]
35. Hahn KA, Wise LA, Rothman KJ, Mikkelsen EM, Brogly SB, Sorensen HT, et al. Caffeine and caffeinated beverage consumption and risk of spontaneous abortion. Hum Reprod. 2015
36. Fulgoni VL 3rd, Keast DR, Lieberman HR. Trends in intake and sources of caffeine in the diets of US adults: 2001–2010. Am J Clin Nutr. 2015
37. Rudolph E, Faerbinger A, Koenig J. Caffeine intake from all sources in adolescents and young adults in Austria. Eur J Clin Nutr. 2014; 68:793–8. [PubMed: 24690592]

Table 1

Demographic and reproductive characteristics by quartiles of caffeine intake.

		Quartile of Caffeine Intake (range, mg/day)				
	Total Cohort	**Q1 (0–70)**	**Q2 (71–141)**	**Q3 (142–230)**	**Q4 (231–816)**	
Number of Women	**340**	**84**	**86**	**87**	**84**	**p-value[1]**
Age[2], yrs	31.5 (4.0)	31.2 (4.2)	30.7 (4.0)	31.9 (4.3)	32.2 (3.4)	0.06
BMI, kg/m^2	23.4 (4.5)	23.2 (4.9)	23.1 (3.7)	23.3 (4.9)	24.0 (4.5)	0.56
Current Smoker, n (%)	61 (17.9)	5 (6.0)	19 (22.1)	14 (16.1)	23 (27.7)	0.002
Native Born, n (%)	256 (75.3)	68 (81.0)	70 (81.4)	60 (69.0)	58 (69.9)	0.10
Years of Education	15.4 (2.7)	15.1 (2.8)	15.1 (2.8)	15.8 (2.6)	15.5 (2.9)	0.33
Type of Work, n (%)						0.72
Education	59 (17.4)	16 (19.1)	11 (12.8)	20 (23.0)	12 (14.5)	
Healthcare	37 (10.9)	8 (9.5)	11 (12.8)	11 (12.6)	7 (8.4)	
Office work	161 (47.4)	38 (45.2)	45 (52.3)	37 (42.5)	41 (49.4)	
Other	83 (24.4)	22 (26.2)	19 (22.1)	19 (21.8)	23 (27.7)	
Gravidity, n (%)						0.25
0	145 (42.7)	35 (41.7)	35 (40.7)	44 (50.6)	31 (37.4)	
1	102 (30.0)	24 (28.6)	31 (36.1)	25 (28.7)	22 (26.5)	
≥2	93 (27.4)	25 (29.8)	20 (23.3)	18 (20.7)	30 (36.1)	
Parity, n (%)						0.61
0	208 (61.2)	50 (59.6)	54 (62.8)	58 (66.7)	46 (55.4)	
1	96 (28.2)	23 (27.4)	25 (29.1)	23 (26.4)	25 (30.1)	
≥2	36 (10.6)	11 (13.1)	7 (8.1)	6 (6.9)	12 (14.5)	
Years of Infertility	1.4 (1.8)	1.3 (1.7)	1.3 (1.5)	1.3 (1.8)	1.7 (2.2)	0.45
Previous IVF Attempts, n (%)						0.08
0	212 (62.4)	48 (57.1)	56 (65.1)	62 (71.3)	46 (55.4)	
1	71 (20.9)	25 (29.8)	17 (19.8)	12 (13.8)	17 (20.5)	
≥2	57 (16.8)	11 (13.1)	13 (15.1)	13 (14.9)	20 (24.1)	
Infertility Diagnosis, n (%)						0.38
Male	115 (33.8)	30 (35.7)	32 (37.2)	29 (33.3)	24 (28.9)	
Female	39 (11.5)	10 (11.9)	6 (7.0)	10 (11.5)	13 (15.7)	

		Quartile of Caffeine Intake (range, mg/day)				
	Total Cohort	**Q1 (0–70)**	**Q2 (71–141)**	**Q3 (142–230)**	**Q4 (231–816)**	
Number of Women	**340**	**84**	**86**	**87**	**84**	**p-value[1]**
Unexplained	57 (16.8)	9 (10.7)	12 (14.0)	17 (19.5)	19 (22.9)	
PGD	129 (37.9)	35 (41.7)	36 (41.9)	31 (35.6)	27 (32.5)	
Antagonist Protocol, n (%)	330 (97.1)	80 (95.2)	85 (98.8)	84 (96.6)	81 (97.6)	0.55
FSH Ampules	25.8 (17.8)	25.6 (20.8)	23.7 (11.1)	26.5 (16.1)	27.4 (21.7)	0.57
Embryo Transfer Day, n (%)						0.16
2	12 (3.5)	3 (3.6)	6 (7.0)	0 (0.0)	3 (3.6)	
3	199 (58.5)	46 (54.8)	44 (51.2)	56 (64.4)	53 (63.9)	
4[3]	129 (37.9)	35 (41.7)	36 (41.9)	31 (35.6)	27 (32.5)	
Number of Embryos Transferred, n (%)						0.63
0	53 (15.6)	11 (13.1)	16 (18.6)	18 (20.7)	8 (9.6)	
1	114 (33.5)	29 (34.5)	30 (34.8)	29 (33.3)	26 (31.3)	
2	159 (46.8)	40 (47.6)	38 (44.2)	37 (42.5)	44 (53.0)	
3–4	14 (4.2)	4 (4.8)	2 (2.3)	3 (3.5)	5 (6.0)	
≥1 Top Quality Embryos Transferred, n (%)	236 (69.4)	64 (76.2)	57 (66.3)	56 (64.4)	59 (71.1)	0.34

[1] Differences across categories were tested using an ANOVA test for continuous variables and a Chi Square test for categorical variables

[2] Data are presented as mean (standard deviation) or number of women (%) unless otherwise specified.

[3] All day 4 embryo transfers were PGD cycles.

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Table 2

Associations between beverage intake and intermediate outcomes of *in vitro* fertilization (n=340 women/cycles).

		Adjusted Mean (95% CI)[1]			
Beverage Intake (Range)	**N**	**Total Oocytes**	**Mature Oocytes[2]**	**Fertilized Oocytes[2]**	**Top Quality Embryos**
Total Caffeine Intake					
Q1 (0–70 mg/day)	84	10.7 (10.0, 11.4)	8.4 (7.8, 9.1)	6.0 (5.5, 6.6)	2.7 (2.4, 3.1)
Q2 (71–141 mg/day)	86	10.2 (9.6, 11.0)	7.8 (7.2, 8.4)	5.2 (4.8, 5.8) *	2.4 (2.1, 2.8)
Q3 (142–230 mg/day)	87	9.8 (9.1, 10.4)	7.5 (6.9, 8.1) *	5.5 (5.1, 6.0)	2.4 (2.1, 2.7)
Q4 (231–816 mg/day)	83	9.9 (9.3, 10.7)	7.7 (7.1, 8.3)	5.4 (5.0, 6.0)	2.6 (2.2, 2.9)
P-trend[2]		0.13	0.11	0.21	0.69
Total Coffee					
0 cup/day	70	11.1 (10.2, 11.8)	8.8 (8.1, 9.5)	6.4 (5.8, 7.0)	2.6 (2.3, 3.1)
0.1–1 cups/day	70	8.8 (8.1, 9.5) *	6.8 (6.3, 7.5) *	4.8 (4.4, 5.4) *	2.4 (2.0, 2.8)
1.1–2 cups/day	92	10.2 (9.6, 10.9)	8.1 (7.5, 8.7)	5.4 (4.9, 5.9) *	2.4 (2.1, 2.8)
2.1–3 cups/day	52	10.2 (9.3, 11.1)	7.1 (6.4, 7.8) *	5.5 (4.9, 6.2)	2.5 (2.1, 3.0)
3.1–10 cups/day	56	10.0 (9.2, 10.9)	7.8 (7.1, 8.6)	5.5 (4.9, 6.2) *	2.5 (2.1, 3.0)
P-trend		0.64	0.14	0.24	0.79
Instant Coffee					
0 cup/day	115	10.8 (10.2, 11.5)	8.4 (7.8, 8.9)	6.1 (5.7, 6.6)	2.8 (2.5, 3.1)
0.1–1 cups/day	73	9.6 (8.9, 10.3) *	7.5 (6.9, 8.1) *	5.1 (4.6, 5.7) *	2.5 (2.1, 2.9)
1.1–2 cups/day	85	9.3 (8.7, 10.0) *	7.2 (6.7, 7.8) *	5.0 (4.6, 5.5) *	2.1 (1.8, 2.4) *
2.1–10 cups/day	67	10.1 (9.4, 10.9)	7.8 (7.1, 8.5)	5.5 (5.0, 6.1)	2.6 (2.2, 3.0)
P-trend		0.06	0.10	0.04	0.18
Filtered Coffee					
0 cup/day	325	10.0 (9.7, 10.4)	7.7 (7.4, 8.1)	5.5 (5.3, 5.8)	2.5 (2.3, 2.7)
0.1–2 cups/day	15	10.2 (8.6, 12.0)	8.3 (6.9, 10.0)	5.6 (4.4, 7.0)	2.0 (1.4, 2.9)
Boiled or Mud Coffee					
0 cup/day	317	9.9 (9.6, 10.3)	7.7 (7.4, 8.0)	5.5 (5.3, 5.8)	2.5 (2.3, 2.6)
0.1–5 cups/day	23	11.3 (10.0, 12.8) *	8.4 (7.3, 9.7)	5.6 (4.7, 6.6)	2.8 (2.2, 3.6)

		Adjusted Mean (95% CI)[1]			
Beverage Intake (Range)	**N**	**Total Oocytes**	**Mature Oocytes[2]**	**Fertilized Oocytes[2]**	**Top Quality Embryos**
Cappuccino					
0 cup/day	281	9.9 (9.6, 10.3)	7.8 (7.5, 8.1)	5.5 (5.3, 5.8)	2.5 (2.3, 2.7)
0.1–4 cups/day	59	10.4 (9.6, 11.3)	7.6 (6.9, 8.3)	5.4 (4.8, 6.1)	2.5 (2.1, 3.0)
Espresso					
0 cup/day	315	10.1 (9.7, 10.4)	7.8 (7.5, 8.1)	5.5 (5.2, 5.8)	2.5 (2.3, 2.6)
0.1–4 cups/day	25	9.4 (8.3, 10.7)	7.1 (6.1, 8.2)	5.9 (5.0, 6.9)	2.7 (2.1, 3.5)
Decaffeinated Coffee					
0 cup/day	324	10.0 (9.7, 10.4)	7.8 (7.5, 8.1)	5.5 (5.3, 5.8)	2.5 (2.3, 2.7)
0.1–3 cups/day	16	9.9 (8.5, 11.5)	6.8 (5.7, 8.2)	4.9 (3.9, 6.1)	2.5 (1.8, 3.4)
Caffeinated Tea					
0 cup/day	168	10.3 (9.8, 10.8)	8.0 (7.5, 8.4)	5.8 (5.4, 6.2)	2.6 (2.3, 2.8)
0.1–1 cups/day	111	10.1 (9.5, 10.7)	7.9 (7.4, 8.5)	5.7 (5.3, 6.2)	2.5 (2.2, 2.8)
1.1–8 cups/day	61	9.2 (8.5, 10.0) *	6.9 (6.3, 7.6) *	4.5 (4.0, 5.0) *	2.2 (1.9, 2.6) *
P-trend		0.03	0.03	0.002	0.15
Herbal Tea					
0 cup/day	242	9.7 (9.3, 10.1)	7.6 (7.2, 7.9)	5.4 (5.1, 5.7)	2.5 (2.3, 2.7)
0.1–1 cups/day	66	10.5 (9.7, 11.3)	8.0 (7.3, 8.7)	5.6 (5.1, 6.3)	2.5 (2.1, 2.9)
1.1–6 cups/day	32	11.6 (10.4, 12.8) *	8.8 (7.9, 10.0) *	6.1 (5.3, 7.0)	2.1 (1.7, 2.7)
P-trend		0.001	0.02	0.11	0.23
Hot Chocolate					
0 cup/day	295	9.9 (9.6, 10.3)	7.7 (7.4, 8.0)	5.4 (5.2, 5.7)	2.4 (2.2, 2.6)
0.1–5 cups/day	45	10.7 (9.8, 11.7)	8.1 (7.3, 9.0)	6.0 (5.3, 6.8)	3.0 (2.6, 3.6) *
Sugared Soda					
0 cup/day	243	10.4 (10.0, 10.9)	8.1 (7.8, 8.5)	5.8 (5.5, 6.1)	2.6 (2.4, 2.8)
0.1–1 cups/day	60	8.9 (8.2, 9.7) *	6.9 (6.3, 7.6) *	4.7 (4.2, 5.3) *	2.4 (2.0, 2.8)
1.1–10 cups/day	37	9.3 (8.3, 10.3) *	6.9 (6.1, 7.8) *	5.2 (4.5, 6.0)	2.0 (1.6, 2.5) *
P-trend		0.002	<0.001	0.01	0.03
Diet Soda					
0 cup/day	249	10.1 (9.7, 10.5)	7.7 (7.4, 8.1)	5.5 (5.2, 5.8)	2.4 (2.2, 2.6)

		Adjusted Mean (95% CI)[1]			
Beverage Intake (Range)	**N**	**Total Oocytes**	**Mature Oocytes[2]**	**Fertilized Oocytes[2]**	**Top Quality Embryos**
0.1–1 cups/day	40	10.0 (9.1, 11.1)	8.2 (7.3, 9.2)	5.7 (5.0, 6.5)	3.0 (2.5, 3.6) *
1.1–15 cups/day	51	9.7 (8.8, 10.6)	7.7 (6.9, 8.5)	5.6 (4.9, 6.3)	2.3 (1.9, 2.8)
P-trend		0.42	0.78	0.66	0.82
Energy Drink					
0 cup/day	320	10.4 (10.0, 10.7)	8.0 (7.7, 8.3)	5.6 (5.4, 5.9)	2.5 (2.4, 2.7)
0.1–2 cups/day	20	6.0 (5.0, 7.2) *	5.1 (4.2, 6.3) *	4.0 (3.2, 5.0) *	1.9 (1.4, 2.7)

Models were run using Poisson regression with log link. All data are presented as adjusted mean counts.

[1] Total caffeine and caffeinated beverages were adjusted for intake age, BMI, smoking status, and country of origin. Specific beverages were further adjusted for coffee, caffeinated tea, herbal tea, sugared soda, and energy drink intake.

[2] For one patient, the embryologist dropped a dish with oocytes and as a result the exact number of mature/fertilized oocytes is missing.

[3] P-trend was calculated by using the median value in each category as a continuous variable in the multivariable model.

* Indicates p-value is <0.05 for that specific category compared to lowest category or non-drinkers.

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Table 3

Associations between beverage intake and clinical outcomes of *in vitro* fertilization (n=339 women/completed cycles).

		Adjusted Proportions (95% CI)		
Beverage Intake (Range)	**N**	**positive b-hCG**	**Clinical Pregnancy**	**Live Birth**
Total Caffeine Intake				
Q1 (0–70 mg/day)	84	0.36 (0.26, 0.47)	0.33 (0.24, 0.44)	0.33 (0.24, 0.44)
Q2 (71–141 mg/day)	86	0.30 (0.22, 0.41)	0.25 (0.17, 0.35)	0.20 (0.13, 0.30)
Q3 (142–230 mg/day)	86	0.35 (0.26, 0.46)	0.31 (0.22, 0.41)	0.23 (0.15, 0.33)
Q4 (231–816 mg/day)	83	0.35 (0.25, 0.46)	0.31 (0.22, 0.42)	0.22 (0.14, 0.32)
P-trend[2]		0.47	0.94	0.18
Total Coffee				
0 cup/day	70	0.35 (0.24, 0.47)	0.33 (0.23, 0.45)	0.32 (0.22, 0.44)
0.1–1 cups/day	70	0.33 (0.23, 0.45)	0.24 (0.15, 0.36)	0.19 (0.12, 0.31)
1.1–2 cups/day	92	0.33 (0.24, 0.43)	0.28 (0.20, 0.38)	0.23 (0.15, 0.33)
2.1–3 cups/day	51	0.38 (0.25, 0.52)	0.31 (0.20, 0.46)	0.22 (0.12, 0.35)
3.1–10 cups/day	56	0.32 (0.21, 0.45)	0.31 (0.20, 0.45)	0.22 (0.13, 0.35)
P-trend		0.89	0.89	0.32
Instant Coffee				
0 cup/day	115	0.32 (0.24, 0.42)	0.28 (0.21, 0.37)	0.24 (0.17, 0.33)
0.1–1 cups/day	73	0.37 (0.27, 0.49)	0.32 (0.22, 0.44)	0.25 (0.16, 0.36)
1.1–2 cups/day	84	0.36 (0.26, 0.47)	0.29 (0.21, 0.40)	0.23 (0.15, 0.34)
2.1–10 cups/day	67	0.30 (0.20, 0.42)	0.28 (0.19, 0.40)	0.23 (0.14, 0.34)
P-trend		0.78	0.96	0.82
Filtered Coffee				
0 cup/day	324	0.33 (0.28, 0.38)	0.29 (0.24, 0.34)	0.23 (0.19, 0.28)
0.1–2 cups/day	15	0.54 (0.30, 0.77)	0.46 (0.23, 0.71)	0.32 (0.13, 0.59)
Boiled or Mud Coffee				
0 cup/day	316	0.34 (0.29, 0.39)	0.29 (0.24, 0.35)	0.24 (0.19, 0.29)
0.1–5 cups/day	23	0.34 (0.18, 0.56)	0.29 (0.14, 0.51)	0.21 (0.09, 0.42)
Cappuccino				
0 cup/day	281	0.34 (0.28, 0.40)	0.30 (0.24, 0.35)	0.24 (0.19, 0.29)

		Adjusted Proportions (95% CI)		
Beverage Intake (Range)	**N**	**positive b-hCG**	**Clinical Pregnancy**	**Live Birth**
0.1–4 cups/day	58	0.34 (0.22, 0.47)	0.28 (0.18, 0.41)	0.22 (0.13, 0.35)
Espresso				
0 cup/day	314	0.33 (0.28, 0.39)	0.29 (0.24, 0.34)	0.24 (0.19, 0.29)
0.1–4 cups/day	25	0.42 (0.24, 0.62)	0.36 (0.20, 0.57)	0.24 (0.12, 0.45)
Decaffeinated Coffee				
0 cup/day	323	0.34 (0.29, 0.39)	0.29 (0.25, 0.35)	0.24 (0.20, 0.29)
0.1–3 cups/day	16	0.33 (0.15, 0.59)	0.26 (0.10, 0.53)	0.12 (0.03, 0.39)
Caffeinated Tea				
0 cup/day	168	0.36 (0.28, 0.43)	0.30 (0.23, 0.37)	0.22 (0.17, 0.30)
0.1–1 cups/day	111	0.29 (0.21, 0.38)	0.26 (0.18, 0.35)	0.22 (0.15, 0.31)
1.1–8 cups/day	60	0.38 (0.26, 0.51)	0.35 (0.23, 0.48)	0.30 (0.19, 0.43)
P-trend		0.98	0.70	0.35
Herbal Tea				
0 cup/day	242	0.37 (0.31, 0.43)	0.32 (0.26, 0.38)	0.26 (0.21, 0.32)
0.1–1 cups/day	65	0.25 (0.16, 0.37)	0.21 (0.13, 0.33)	0.15 (0.08, 0.26)
1.1–6 cups/day	32	0.31 (0.17, 0.48)	0.27 (0.14, 0.44)	0.23 (0.12, 0.40)
P-trend		0.18	0.20	0.24
Hot Chocolate				
0 cup/day	294	0.33 (0.28, 0.39)	0.28 (0.23, 0.33)	0.22 (0.17, 0.27)
0.1–5 cups/day	45	0.39 (0.25, 0.54)	0.40 (0.26, 0.55)	0.36 (0.23, 0.52)
Sugared Soda				
0 cup/day	242	0.38 (0.32, 0.44)	0.35 (0.29, 0.41)	0.28 (0.23 0.34)
0.1–1 cups/day	60	0.21 (0.13, 0.33) *	0.16 (0.09,0 0.28) *	0.16 (0.09 0.27)
1.1–10 cups/day	37	0.28 (0.16, 0.45)	0.20 (0.10, 0.37)	0.12 (0.05 0.27) *
P-trend		0.06	0.01	0.01
Diet Soda				
0 cup/day	248	0.33 (0.28, 0.40)	0.29 (0.24, 0.35)	0.22 (0.17, 0.28)
0.1–1 cups/day	40	0.41 (0.26, 0.57)	0.38 (0.24, 0.55)	0.32 (0.19, 0.48)
1.1–15 cups/day	51	0.31 (0.19, 0.46)	0.23 (0.14, 0.37)	0.23 (0.13, 0.38)
P-trend		0.97	0.68	0.63

		Adjusted Proportions (95% CI)		
Beverage Intake (Range)	**N**	**positive b-hCG**	**Clinical Pregnancy**	**Live Birth**
Energy Drink				
0 cup/day	319	0.34 (0.29, 0.39)	0.29 (0.24, 0.35)	0.24 (0.19, 0.29)
0.1–2 cups/day	20	0.34 (0.16, 0.59)	0.31 (0.13, 0.56)	0.23 (0.09, 0.49)

Models were run using logistic regression. All data are presented as adjusted mean proportions.

[1]Total caffeine and caffeinated beverages were adjusted for intake age, BMI, smoking status, and country of origin. Specific beverages were further adjusted for coffee, caffeinated tea, herbal tea, sugared soda, and energy drink intake.

[2]P-trend was calculated by using the median value in each category as a continuous variable in the multivariable model.

*Indicates p-value is <0.05 for that specific category compared to lowest category or non-drinkers.