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ORIGINAL ARTICLE *Infertility*

Male alcohol consumption and fecundability

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STUDY QUESTION: Does male alcohol consumption affect fecundability?

SUMMARY ANSWER: In data pooled across Danish and North American preconception cohort studies, we found little evidence of an association between male alcohol consumption and reduced fecundability.

WHAT IS KNOWN ALREADY: Experimental and clinical studies have shown that alcohol affects male reproductive physiology, mainly by altering male reproductive hormones and spermatogenesis. However, few epidemiologic studies have examined the association between alcohol consumption and male fertility.

STUDY DESIGN, SIZE, DURATION: Data were collected from two ongoing prospective preconception cohort studies: the Danish 'SnartForaeldre' (SF) study (662 couples) and the North American 'Pregnancy Study Online' (PRESTO) (2017 couples). Participants included in the current analysis were enrolled from August 2011 through June 2019 (SF) and from June 2013 through June 2019 (PRESTO).

PARTICIPANTS/MATERIALS, SETTING, METHODS: Eligible men were aged ≥18 years in SF and ≥21 years in PRESTO, in a stable relationship with a female partner and not using contraception or receiving fertility treatment. In both cohorts, alcohol consumption/serving size was self-reported as number of beers (330 mL/12 oz.), glasses of white or red wine (120 mL/4 oz. each), dessert wine (50 mL/2 oz.) and spirits (20 mL/1.5 oz.). Overall alcohol consumption was categorized as none, 1–5, 6–13 and ≥14 standard servings per week. Total menstrual cycles at risk were calculated using data from female partners' follow-up questionnaires, which were completed every 8 weeks until self-reported pregnancy or 12 menstrual cycles, whichever came first. Analyses were restricted to couples that had been trying to conceive for ≤6 cycles at study entry. Proportional probability regression models were used to compute fecundability ratios (FRs) and 95% confidence interval (CIs). We adjusted for male and female age, female partner's alcohol consumption, intercourse frequency, previous history of fathering a child, race/ethnicity, education, BMI, smoking and consumption of sugar-sweetened beverages and caffeine.

MAIN RESULTS AND THE ROLE OF CHANCE: The cumulative proportion of couples who conceived during 12 cycles of follow-up were 1727 (64.5%). The median (interquartile range) of total male alcohol consumption was 4.5 (2.0–7.8) and 4.1 (1.0–8.6) standard servings per week in the SF and PRESTO cohorts, respectively. In pooled analyses, adjusted FRs for male alcohol consumption of 1–5, 6–13 and ≥14 standard servings per week compared with no alcohol consumption were 1.02 (95% CI: 0.90–1.17), 1.10 (95% CI: 0.96–1.27) and 0.98 (95% CI: 0.81–1.18), respectively. For SF, adjusted FRs of 1–5, 6–13 and ≥14 standard servings per week compared with no alcohol consumption were 0.97 (95% CI: 0.73–1.28), 0.81 (95% CI: 0.60–1.10) and 0.82 (95% CI: 0.51–1.30), respectively. For PRESTO, adjusted FRs of 1–5, 6–13 and ≥14 standard servings per week compared with no alcohol consumption were 1.02 (95% CI: 0.88–1.18), 1.20 (95% CI: 1.03–1.40) and 1.03 (95% CI: 0.84–1.26), respectively.

LIMITATIONS, REASONS FOR CAUTION: Male alcohol consumption was ascertained at baseline only, and we did not distinguish between regular and binge drinking. In addition, we had insufficient numbers to study the effects of specific types of alcoholic beverages. As always, residual confounding by unmeasured factors, such as dietary factors and mental health, cannot be ruled out. Comorbidities thought to play a role in the reproductive setting (i.e. cancer, metabolic syndrome) were not considered in this study; however, the prevalence of cancer and diabetes was low in this age group. Findings for the highest categories of alcohol consumption (6–13 and ≥14 servings/week) were not consistent across the two cohorts.

WIDER IMPLICATIONS OF THE FINDINGS: Despite little evidence of an association between male alcohol consumption and reduced fecundability in the pooled analysis, data from the Danish cohort might indicate a weak association between reduced fecundability and consumption of six or more servings per week.

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Key words: alcohol / fecundability / time to pregnancy / male fertility / infertility

Introduction

In developed countries, infertility affects up to 15% of couples (Slama *et al*., 2012, Thoma *et al*., 2013). The distress experienced by infertile couples and the increasing demand for ART (Kupka *et al*., 2014) have led to a greater focus on elucidating modifiable risk factors for infertility. In Western nations, a decline in sperm count has been observed over the last 40 years (Levine *et al*., 2017), and male factors contribute to infertility in approximately 50% of all cases (Irvine *et al*., 1998).

Potential modifiable risk factors for male infertility include lifestyle factors such as smoking (Soares and Melo, 2008; Harlev *et al*., 2015), obesity (Wise *et al*., 2010; Sundaram *et al*., 2017) and intake of sugar-sweetened beverages (Hatch *et al*., 2018); the impact of alcohol consumption is less clear. Alcohol consumption is a habitual part of daily life for a large proportion of males of reproductive age (WHO, 2014). In several countries, official guidelines recommend that men limit their consumption of alcohol to a maximum of 14 drinks per week, with no distinction made for men actively trying to conceive (Danish National Board of Health, 2015; The U.S. Department of Health and Human Services and the U.S. Department of Agriculture, 2015).

Previous studies have shown that alcohol affects the male reproductive system by altering the regulation of the hypothalamic–pituitary–gonadal (HPG) axis and spermatogenesis. Most studies of healthy young men have found higher alcohol consumption to be positively associated with testosterone levels and inversely associated with sex hormone-binding globulin levels (Shiels *et al*., 2009; Hansen *et al*., 2012; Jensen *et al*., 2014a; Jensen *et al*., 2014b). In contrast, decreased testosterone levels, and elevated levels of FSH and LH have been observed among alcoholic men, indicating that alcohol abuse may impair the HPG axis or cause Leydig-cell damage (Emanuele, 1998; Muthusami and Chinnaswamy, 2005; Maneesh *et al*., 2006).

Alcohol consumption also has been inversely associated with total sperm count, sperm concentration and percentage of morphologically normal sperm (Emanuele, 1998; Muthusami and Chinnaswamy, 2005; La Vignera *et al*., 2013; Jensen *et al*., 2014; Borges *et al*., 2018). Other studies have reported a positive association between moderate male alcohol consumption and semen quality (Ricci *et al*., 2018).

One cohort study found that male alcohol consumption was associated with shorter time to pregnancy (TTP) (Florack *et al*., 1994), whereas two other cohort studies found a weak association with longer TTP (Curtis *et al*., 1997; Olsen *et al*., 1997). Thus, the extent to which male alcohol consumption influences TTP is unclear. In the present study, we examined the association between male alcohol consumption and couples' TTP in two prospective cohort studies of Danish and North American couples.

Materials and Methods

Study population

The SnartForaeldre (Soon Parents) study is an ongoing prospective cohort study of Danish pregnancy planners (Mikkelsen *et al*., 2009). The study was launched in August 2011. Participants are recruited primarily through web-based advertising (Christensen *et al*., 2017). Participants complete a screening questionnaire at the study website (http://snartforaeldre.dk), which confirms eligibility and ascertains how long they had tried to conceive before study entry. Eligible men and women are invited to complete a baseline questionnaire and are encouraged to invite their partner to take part in the study. Couples are linked by means of an email invitation sent to the partner or by their home address as registered in the Danish Civil Registration System on the date of study entry (Frank, 2000).

The Pregnancy Study Online (PRESTO) is similar in design to SnartForaeldre (Wise *et al*., 2015). It has recruited pregnancy planners from the USA and Canada since June 2013. Eligible women complete baseline and follow-up questionnaires at the study website (http://presto.bu.edu). After enrollment, female participants are given the option to invite their male partners to complete a one-time baseline questionnaire. PRESTO received non-financial support from Swiss Precision Technologies, Sandstone Diagnostics, FertilityFriend.com and Kindara.

In both cohorts, inclusion criteria are being in a stable relationship with a partner of the opposite sex and not using any contraception or receiving fertility treatment. SnartForaeldre recruits females aged 18–49 years and males aged ≥18 years, whereas PRESTO recruits females aged 21–45 years and males aged ≥21 years. Reasons for exclusion are shown in Fig. 1. Couples who had tried to conceive for >6 months at study entry are excluded to reduce bias related to changes in behavior due to subfertility. Male and female baseline questionnaires elicit socio-demographic data, information on behavioral and lifestyle factors and reproductive and medical history. Female follow-up questionnaires are completed bimonthly for up to 12 months or until reported pregnancy. These questionnaires update data on pregnancy status and lifestyle factors that vary over time.

Assessment of male alcohol exposure

On baseline questionnaires, men in both cohorts reported their average weekly alcohol consumption during the previous month as bottles of beer (330 mL/12 ounces), glasses of white and red wine (120 mL/4 ounces each), dessert wine (50 mL/2 ounces) and spirits (20 mL/1.5 ounces). Help buttons in the questionnaires instruct respondents on

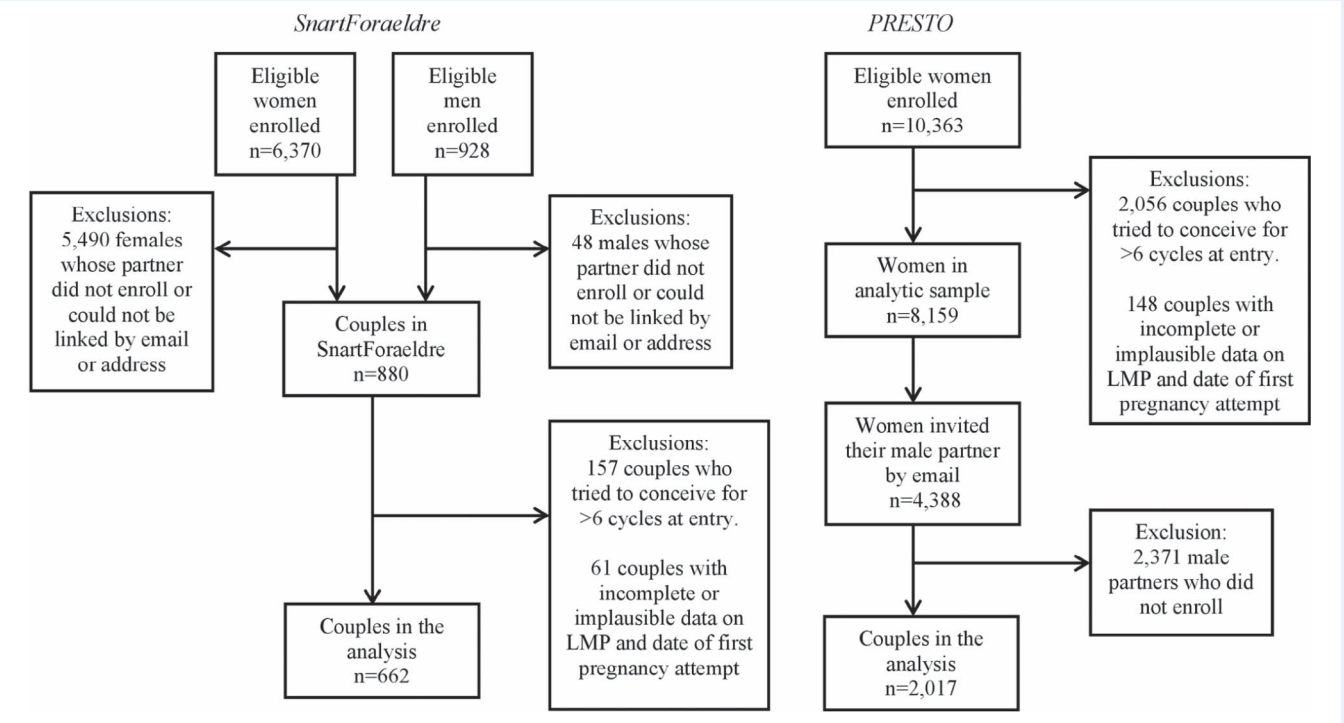

Figure 1 Flow chart of participants in SnartForaeldre and PRESTO. SnartForaeldre: the Danish study, PRESTO: the North American Pregnancy Study Online, LMP: last menstrual period.

how to assess the number of average weekly servings and to report 'no intake' if they drank less than one drink per week. To standardize alcohol consumption across cohorts and types of beverages, we calculated total weekly alcohol consumption in standard servings (12 grams of alcohol per serving) by summing the amount of alcohol in grams from each type of beverage consumed and dividing by 12. In PRESTO, ounces were converted to milliliters (1 oz. = 29.57 mL). We assumed that a bottle of beer (330 mL), one glass of red wine or white wine (120 mL), dessert wine (50 mL) and spirits (20 mL) each contain 11.6, 12, 8 and 7 g of alcohol, respectively (National Food Institute, 2016).

Total weekly alcohol consumption was categorized as none, 1–5, 6–13 and ≥14 standard servings.

Assessment of pregnancies and cycles at risk

On each follow-up questionnaire, women reported the date of their last menstrual period (LMP) and their pregnancy status. TTP was estimated as the number of menstrual cycles during which a couple tried to achieve pregnancy and included the time trying to conceive, both before study entry and during follow-up. Total menstrual cycles at risk, rounded to the nearest whole number, were calculated as follows: cycles of attempt time at study entry + (((LMP date from most recent follow-up questionnaire − date of baseline questionnaire completion) / cycle length) + 1) (Wise *et al.*, 2010).

Assessment of covariates

The male baseline questionnaire collected data on age, education, hours per week of employment, previous conception with a female partner, smoking, physical activity, height and weight, consumption of sugar-sweetened beverages, intake of multivitamins and caffeine and history of disease (migraine, asthma, hay fever, depression, anxiety, hypertension, diabetes, sexually transmitted infections and infections in the male reproductive organs). Female questionnaires elicited data on age, alcohol consumption, household income, pregnancy attempt time before study entry and timing and frequency of intercourse. We estimated total metabolic equivalents (METs) by multiplying the average number of physically active hours per week by METs for various activities. In SnartForaeldre, we estimated METs from walking, moderate exercise and vigorous exercise using the short-form International Physical Activity Questionnaire (Craig *et al.*, 2003), whereas in PRESTO METs of various activities were estimated using the Compendium of Physical Activities (Ainsworth *et al.*, 2000). We used baseline data on height and weight to calculate BMI as weight (kg)/height $(m)^2$. Identical covariates were examined in both cohorts, except for race/ethnicity (obtained only in PRESTO) and education (ascertained differently in each cohort but harmonized into a single variable (Wise *et al.*, 2017)).

Data analysis

We performed a pooled analysis with harmonized data and parallel analyses in each cohort for the August 2011–June 2019 (SnartForaeldre) and June 2013–June 2019 (PRESTO) study periods. We used proportional probability regression models to compute fecundability ratios (FRs) with 95% confidence intervals (CIs) (Weinberg *et al.*, 1989). The FR represents the per-cycle probability of conception comparing exposed men with unexposed men; a FR below 1 indicates reduced fecundability. To account for left truncation (attempt time at study entry ranged from 0–6 cycles), we analyzed risk sets restricted

to observed menstrual cycles (Schisterman *et al*., 2013). For example, if a couple had tried to conceive for 4 cycles at study entry and reported pregnancy after 8 cycles, they would have contributed Cycles 5 through 8 (four cycles) to the analysis (Wise *et al*., 2010). We right-censored couples who were lost to follow-up (9.6%), stopped trying to conceive (1.9%), started fertility treatment (7.6%) or reached 12 cycles of attempted pregnancy (12.6%). We compared baseline characteristics for those with and without complete follow-up (i.e. couples who responded only to the baseline questionnaire or who stopped responding to follow-up questionnaires before study completion). Most males were invited by their female partners. To evaluate the possibility of differential male participation, we compared characteristics (age, smoking status and BMI) between male participants and non-participants as reported by their female partners.

In the multivariate regression analysis, we adjusted for male and female age (continuous), female alcohol consumption in standard servings (continuous), frequency of intercourse (<1, 1, 2–3, ≥4 times/week), history of previously fathering a child (yes/no), education (≤12, 13–15, 16, ≥17 years), BMI (continuous), smoking (regular, occasional, former, never), sugar-sweetened beverage consumption (continuous), caffeine consumption (continuous) and study cohort (SnartForaeldre/PRESTO). PRESTO models were adjusted additionally for race/ethnicity (non-Hispanic white/other). We selected potential confounders based on the literature and on directed acyclic graphs. We used multiple imputations to impute missing exposure, covariate and outcome data. Couples who completed only the baseline questionnaire (6.7%) were assigned 1 cycle of follow-up, and their pregnancy status was imputed. We generated five imputed datasets, analyzed each dataset and subsequently combined the results across the imputed datasets (Sterne *et al*., 2009). We also used restricted cubic splines to assess the presence of a non-linear association between male alcohol intake and fecundability.

To assess whether reverse causation could explain our results, we stratified our analysis by pregnancy attempt time at enrollment (≤2 versus 3–6 cycles). Furthermore, we stratified results according to male BMI (<25 versus ≥25 kg/m^2), history of previously fathering a child (yes versus no), female age (<30 versus ≥30 years) and gravidity (yes versus no), as those factors potentially modify the association between male alcohol intake and fecundability (Collins *et al*., 1995; Wang *et al*., 2008). In secondary analyses, we estimated FRs for alcohol consumption of 14–20 and ≥21 standard servings per week.

Ethics approvals

Study protocols were approved by the Danish Data Protection Agency (2016-051-000001, # 431) and the Institutional Review Board at Boston Medical Center. Participants provided informed consent online.

Results

Participant characteristics

Overall, 1727 (64.5%) of the 2679 participating couples conceived during follow-up. SnartForaeldre couples (N = 662) contributed 2475 menstrual cycles at risk and 450 pregnancies (68.0%), and PRESTO couples (N = 2017) contributed 7969 menstrual cycles at risk and 1277 pregnancies (63.3%). The median (interquartile range) of total male alcohol consumption was 4.5 (2.0–7.8) standard servings per week in SnartForaeldre and 4.1 (1.0–8.6) in PRESTO. The proportion of non-drinkers was 11.0% in SnartForaeldre and 20.4% in PRESTO. The proportions of male participants drinking ≥14 standard serving per week were 7.7% in SnartForaeldre and 13.9% in PRESTO. More men consumed beer (76.6%) than wine (48.7%) or spirits (43.7%). In total, 1598 (59.6%) men consumed a combination of two or more alcoholic beverages. Fewer men consumed only beer, wine or spirits (18.9, 2.6 and 3.4%, respectively).

Couples in SnartForaeldre and PRESTO had many similar characteristics, as shown in Table I. However, SnartForaeldre couples had a higher frequency of male physical activity, male sexually transmitted infections and infection in male reproductive organs than PRESTO couples. At the same time, men in PRESTO worked more hours per week, had a higher BMI and were more likely to consume soft drinks than men in SnartForaeldre. In both cohorts, caffeine consumption, regular smoking, female alcohol consumption and shorter attempt time at study entry were positively associated with male alcohol consumption, and men who previously had fathered a child were more likely to be non-drinkers. History of chronic disease ranged from 1.7% for diabetes to 12.3% for asthma and was not meaningfully associated with male alcohol consumption (data not shown). Overall, baseline characteristics were similar for couples with complete versus incomplete follow-up, except for couples lost to follow-up who were more likely to have shorter education, have lower income and be smokers (data not shown). Non-participating men were similar to participating men according to age and BMI, but more likely to be smokers (data not shown).

Alcohol consumption and fecundability

In pooled analyses, adjusted FRs for 1–5, 6–13 and ≥14 standard servings per week compared with no alcohol consumption were 1.02 (95% CI: 0.90–1.17), 1.10 (95% CI: 0.96–1.27) and 0.98 (95% CI: 0.81–1.18), respectively (Table II). In cohort-stratified analyses, FRs in SnartForaeldre for 1–5, 6–13 and ≥14 standard servings per week compared with no alcohol consumption were 0.97 (95% CI: 0.73–1.28), 0.81 (95% CI: 0.60–1.10) and 0.82 (95% CI: 0.51–1.30), respectively. In PRESTO, FRs for 1–5, 6–13 and ≥14 standard servings per week compared with no alcohol consumption were 1.02 (95% CI: 0.88–1.18), 1.20 (95% CI: 1.03–1.40) and 1.03 (95% CI: 0.84–1.26), respectively. Similarly, the restricted cubic spline curve indicated little association between lower levels of alcohol consumption and fecundability (Fig. 2). Starting at approximately 8.5 servings weekly, the spline curves show an inverse association between male alcohol consumption and fecundability in SnartForaeldre, but not in PRESTO.

In the pooled analysis (Table III), the relation between alcohol consumption and fecundability was similar across strata of attempt time at study entry, BMI and history of previously fathering a child. When we stratified by female age (<30 versus ≥30 years) and gravidity (yes versus no), alcohol consumption was slightly associated with decreased fecundability among older females and previous gravidity, though estimates were imprecise. In secondary analyses of the pooled data, in which we used a finer categorization of alcohol consumption, FRs for 14–20 and ≥21 standard servings per week compared with no alcohol consumption were 0.97 (95% CI: 0.79–1.21) and 0.99 (95% CI: 0.78–1.26), respectively.

Table I Baseline characteristics of 2679 males, by level of alcohol intake in standard servings/week.

Characteristics	Total	SNARTFORAELDRE (*N* = 662)				PRESTO (*N* = 2017)			
		None[a]	1–5	6–13	≥14	None[a]	1–5	6–13	≥14
No. of men (%)	2679	73 (11.0)	303 (45.8)	235 (35.5)	51 (7.7)	411 (20.4)	712 (35.3)	614 (30.4)	280 (13.9)
Age, median years	31	30	30	31	31	30	31	31	32
Partner's age, median years	29	28	29	29	29	29	29	30	29.5
Partner's median alcohol intake, servings/week (IQR)	2 (0–4)	0 (0–2)	1 (0–3)	2.5 (1–4.5)	4 (1–7)	0 (0–1)	1 (0–3)	3 (2–5)	5 (2–8.5)
Educational level <16 years, *N* (%)	841 (31.4)	17 (23.3)	90 (29.7)	60 (25.5)	13 (25.5)	182 (44.3)	234 (32.9)	141 (23.0)	104 (37.1)
Median hours per week of employment	40	37	37	37	37	40	40	42	41.5
Household income (SF/PRESTO) <24 999 DKK monthly/ <50 000 USD annual, *N* (%)	444 (16.6)	15 (20.5)	47 (15.5)	25 (10.6)	8 (15.7)	117 (28.5)	127 (17.8)	63 (10.3)	42 (15.0)
BMI, median kg/m^2	26.2	25.2	24.7	24.8	24.7	27.5	27.2	26.1	27.1
Physical activity, median MET hours/week	29	33	37.2	33	31.1	22.8	28.4	30.4	26.9
Previously fathered a child, *N* (%)	1170 (43.7)	42 (57.5)	107 (35.3)	83 (35.3)	21 (41.2)	216 (52.6)	322 (45.2)	252 (41.0)	127 (45.4)
Frequency of intercourse ≥2 times/week, *N* (%)	1664 (62.1)	42 (57.5)	201 (66.3)	148 (63.0)	31 (60.8)	242 (58.9)	444 (62.4)	378 (61.6)	178 (63.6)
Timing of intercourse[b], *N* (%)	2044 (76.3)	55 (75.3)	227 (74.9)	175 (74.5)	32 (62.7)	311 (75.7)	539 (75.7)	490 (79.8)	215 (76.8)
Attempt time >2 months at study entry, *N* (%)	825 (30.8)	31 (42.5)	103 (34.0)	72 (30.6)	14 (27.5)	143 (34.8)	213 (29.9)	171 (27.9)	78 (27.9)
Regular smoking, *N* (%)	182 (6.8)	*	18 (5.9)	17 (7.2)	*	29 (7.1)	32 (4.5)	33 (5.4)	45 (16.1)
Multivitamin use, *N* (%)	878 (32.8)	25 (34.2)	87 (28.7)	67 (28.5)	14 (27.5)	138 (33.6)	234 (32.9)	213 (34.7)	100 (35.7)
Softdrinks[c] >1 serving/week, *N* (%)	1371 (51.2)	28 (38.4)	83 (27.4)	77 (32.8)	24 (47.1)	269 (65.5)	406 (57.0)	311 (50.7)	173 (61.8)
Caffeine consumption >150 mg/day, *N* (%)	1397 (52.1)	27 (37.0)	181 (59.7)	155 (66.0)	43 (84.3)	129 (31.4)	327 (45.9)	350 (57.0)	185 (66.1)
History of sexually transmitted infection and/or infection in male reproductive organs, *N* (%)	353 (13.2)	24 (32.9)	83 (27.4)	77 (32.8)	12 (23.5)	27 (6.6)	47 (6.6)	58 (9.4)	25 (8.9)
Asthma and/or hayfever, *N* (%)	523 (19.5)	17 (23.3)	81 (26.7)	56 (23.8)	9 (17.6)	67 (16.3)	127 (17.8)	125 (20.4)	41 (14.6)
Depression and/or anxiety, *N* (%)	380 (14.2)	*	25 (8.3)	19 (8.1)	*	67 (16.3)	109 (15.3)	92 (15.0)	50 (17.9)
Non-Hispanic white, *N* (%)	-	-	-	-	-	344 (83.7)	582 (81.7)	542 (88.3)	257 (91.8)

[a]Includes drinkers who reported drinking <1 drink per week.
[b]Having intercourse at the time of highest probability of conception.
[c]Includes sugar-sweetened soda intake and juice.
*Low numbers. The precise numbers cannot be shown, according to the guidelines of Statistics Denmark.
SnartForaeldre: Danish study, PRESTO: North American Pregnancy Study Online, MET: metabolic equivalents, IQR = interquartile range.

Table II Couples' fecundability by male alcohol consumption.

Servings/week	Pregnancies	Cycles	Fecundability ratio (FR: 95% CI) Unadjusted FR	Adjusted FR*
SnartForaeldre and PRESTO, *N* = 2679				
None	292	1906	(Reference)	(Reference)
1–5	651	3975	1.03 (0.91–1.17)	1.02 (0.90–1.17)
6–13	578	3217	1.11 (0.97–1.26)	1.10 (0.96–1.27)
≥14	206	1346	0.95 (0.80–1.12)	0.98 (0.81–1.18)
SnartForaeldre, *N* = 662				
None	51	256	(reference)	(reference)
1–5	216	1087	0.93 (0.71–1.22)	0.97 (0.73–1.28)
6–13	153	940	0.80 (0.60–1.07)	0.81 (0.60–1.10)
≥14	30	192	0.75 (0.49–1.14)	0.82 (0.51–1.30)
PRESTO, *N* = 2017				
None	241	1650	(Reference)	(Reference)
1–5	435	2888	1.01 (0.87–1.17)	1.02 (0.88–1.18)
6–13	425	2277	1.19 (1.03–1.37)	1.20 (1.03–1.40)
≥14	176	1154	0.99 (0.83–1.18)	1.03 (0.84–1.26)

*Adjusted for male and female age, female alcohol intake (continuous), frequency of intercourse, previously fathered a child, education, BMI, smoking, consumption of sugar-sweetened beverages and caffeine. There was further adjustment for race/ethnicity in PRESTO and study cohort in pooled analysis.

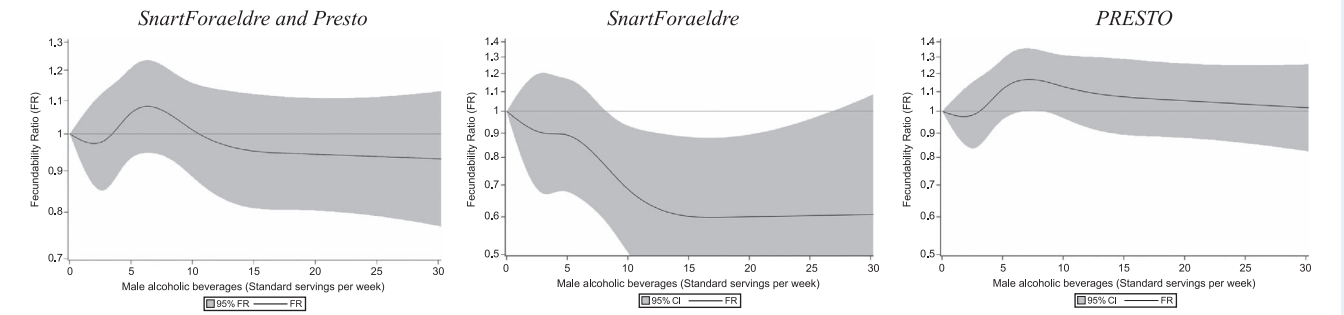

Figure 2 Association between male alcohol consumption and fecundability, examined using restricted cubic splines. Curves were adjusted for male and female age, female alcohol intake (continuous), frequency of intercourse, previously fathered a child, education, BMI, smoking, consumption of sugar-sweetened beverages and consumption of caffeine. PRESTO analyses were adjusted further for race/ethnicity. Five knots were located at 0, 3, 5, 10 and 18. CI: confidence interval.

Discussion

Key findings

In these prospective preconception cohort analyses, we found little evidence of a consistent association between male alcohol consumption and fecundability in pooled analyses. In SnartForaeldre, consumption of 6–13 and ≥14 servings per week were associated with slightly reduced fecundability; however, the estimates were imprecise. Clinically, this finding indicates a slightly lower probability of conception in each menstrual cycle among couples in which the male partner consumed 6–13 or ≥14 servings per week compared with no alcohol intake. The restricted cubic spline analyses also indicated reduced fecundability with heavier alcohol consumption among men in SnartForaeldre, but not in PRESTO or both cohorts combined.

Although we used the same methods in SnartForaeldre and PRESTO overall, it is possible that minor differences, such as in the measure of drinks per week or unmeasured confounding by other behavioral factors, could have affected study-specific estimates. In pooled analyses, no appreciable association was observed for heavier alcohol consumption (14–20 and ≥21 standard servings per week) compared with no alcohol consumption.

Overall, there was limited variation in the amount of alcohol consumed, with most men consuming ≤14 drinks per week. Despite our relatively large study population compared with previous studies, results were imprecise in some stratified analyses.

Table III Male alcohol intake and couples' fecundability, stratified by pregnancy attempt time at entry, male BMI, history of previously fathering a child, female age and gravidity (cohort = 2679).

	Alcohol intake, servings per week							
	None	**1–5**	**6–13**	**≥14**	**None**	**1–5**	**6–13**	**≥14**
	≤2 cycles of attempt at study entry				**3–6 cycles of attempt at study entry**			
Pregnancies, *n*	207	492	429	153	85	159	149	53
Cycles, *n*	1212	2736	2352	1032	694	1239	864	314
Adjusted FR (95% CI)	(Ref)	1.06 (0.91–1.23)	1.09 (0.92–1.28)	0.97 (0.78–1.20)	(Ref)	0.90 (0.70–1.16)	1.14 (0.87–1.50)	1.09 (0.76–1.57)
	Male BMI <25kg/m²				**Male BMI ≥25kg/m²**			
Pregnancies, *n*	107	246	251	67	185	405	327	139
Cycles, *n*	647	1521	1346	454	1259	2454	1871	892
Adjusted FR (95% CI)	(Ref)	0.94 (0.76–1.17)	1.03 (0.83–1.29)	0.87 (0.64–1.19)	(Ref)	1.07 (0.91–1.26)	1.14 (0.95–1.37)	1.04 (0.82–1.31)
	Previously fathered a child				**Did not previously father a child**			
Pregnancies, *n*	157	285	249	90	135	366	329	116
Cycles, *n*	924	1519	1120	558	982	2456	2097	788
Adjusted FR (95% CI)	(Ref)	0.96 (0.81–1.15)	1.10 (0.91–1.34)	0.90 (0.69–1.17)	(Ref)	1.08 (0.89–1.31)	1.11 (0.91–1.36)	1.08 (0.84–1.40)
	Female age <30 years				**Female age ≥30 years**			
Pregnancies, *n*	160	364	281	103	132	287	297	103
Cycles, *n*	1092	2108	1515	647	814	1867	1702	699
Adjusted FR (95% CI)	(Ref)	1.15 (0.96–1.38)	1.18 (0.97–1.43)	1.06 (0.83–1.37)	(Ref)	0.83 (0.69–1.00)	0.96 (0.78–1.17)	0.85 (0.65–1.12)
	Gravidity ≥1				**Nulli-gravidity**			
Pregnancies, *n*	160	285	247	83	132	366	331	123
Cycles, *n*	907	1571	1168	494	999	2404	2049	852
Adjusted FR (95% CI)	(Ref)	0.89 (0.74–1.07)	0.99 (0.82–1.20)	0.85 (0.65–1.12)	(Ref)	1.16 (0.96–1.41)	1.22 (0.99–1.51)	1.12 (0.86–1.44)

Previous studies

The association between semen quality and fecundability has been shown to be approximately linear up to a concentration of 40 mill/Ml. Above this concentration elevated sperm counts do not markedly increase fecundability (Bonde *et al*., 1998). Therefore, the predictive value of semen quality for fecundability may be limited. This limitation may explain why some studies (Emanuele, 1998; Muthusami and Chinnaswamy, 2005; La Vignera *et al*., 2013; Jensen *et al*., 2014a; Borges, al., 2018) found an association between alcohol consumption and semen quality, whereas the association between alcohol consumption and fecundability was less evident.

Our findings are fairly consistent with previous studies that showed no or weak associations between male alcohol consumption and fecundability. A retrospective European multicenter study found that male alcohol consumption was slightly associated with prolonged TTP, when odds for subfecundity (TTP >9.5 months) for male alcohol consumption of 0–7 drinks per week were compared with ≥22 drinks per week (odds ratio (OR) = 1.3, 95% CI: 0.9–1.7) (Olsen *et al*., 1997). Another retrospective cohort study found little association between male alcohol consumption and TTP (FRs comparing 0.1–2, 2.1–6 and >6 ounces per week with no alcohol consumption were 1.05 (95% CI: 0.96–1.15) 1.02 (95% CI: 0.90–1.10) and 0.95 (95% CI: 0.83–1.09), respectively). However, heavier drinking of more than 10 glasses of beer or 6 glasses of liquor per week was associated with reduced fecundability (FR = 0.88 (95% CI: 0.75–1.02) and FR = 0.87 (95% CI: 0.71–1.06), respectively) (Curtis *et al*., 1997). Another prospective cohort study found that male alcohol consumption was positively associated with fecundability when ≥10 drinks per week were consumed compared with <5 drinks per week (OR = 1.6, 95% CI: 1.0–2.4) (Florack *et al*., 1994). In that study, 259 females with unrestricted pregnancy attempt time at study entry (21.6% had been trying to conceive for >1 year) were interviewed about their male partner's alcohol intake. In contrast, men in our study reported their own alcohol intake and couples were enrolled in the preconception period, with 80.7% of couples enrolled within their first 3 cycles of pregnancy attempt.

Strengths and limitations

Our study population included the entire spectrum of fertility, from highly fertile to subfertile couples. However, we studied only pregnancy planners, which may overestimate TTP since unintended pregnancies are more likely to occur among highly fertile couples and alcohol consumers (Oulman *et al*., 2015). To address potential misclassification due to changes in alcohol consumption resulting from subfertility, we limited the study population to couples who had tried to conceive for ≤6 cycles at study entry.

Although the study population included self-selected couples recruited via the Internet, it seems unlikely that the association between male alcohol intake and fecundability differs between Internet users and nonusers. Participants in our study may be more health-conscious than non-participants (e.g. men are more likely to be non-smokers), but that should not influence the validity of the internal comparisons within the cohorts. Previous validation studies have shown that even when characteristics (such as age or smoking) differ between study participants and non-participants, well-established perinatal associations are not biased by self-selection (Nilsen *et al*., 2009; Hatch *et al*., 2016). Cohort retention was 88.8% after 12 months of follow-up, and overall we found similar baseline characteristics, including alcohol consumption, for couples with complete follow-up compared with couples lost to follow-up.

We collected detailed information on covariates and adjusted for potential confounders, but we cannot entirely rule out the possibility of residual confounding. In addition, we did not distinguish between regular and binge drinking (defined as at least five drinks per occasion) (National Institute on Alcohol Abuse and Alcoholism, 2004). Also, except for caffeine and sugar-sweetened beverages, we did not include information on male dietary habits or metabolic factors, e.g. lipid status, body fat or blood sugar level, which may have confounded or mediated the association between male alcohol intake and fecundability (Salas-Huetos *et al*., 2017; Sundaram *et al*., 2017; Maresch *et al*., 2018; Sedes *et al*., 2018). Male health and history of chronic disease, including cancer, are other potential confounders, which have been associated with low semen quality in some studies (Eisenberg *et al*., 2015; Ventimiglia *et al*., 2015). However, the prevalence of chronic disease among male participants was low and approximately equally distributed across levels of alcohol consumption in our cohorts.

Self-reported alcohol consumption was not validated. If alcohol intake was inaccurately reported, it was most likely underreported (Høyer *et al*., 1995; Ekholm, 2004). Although inaccuracies in self-reported alcohol intake would be independent of prospectively collected information on pregnancy status, such non-differential misclassification could explain the weak associations observed in our study. Finally, we examined alcohol intake at baseline only, which could have potentially biased our results if male alcohol intake changed with increasing pregnancy attempt time. However, studies of males and females in general populations have reported monthly stability in alcohol consumption over time for low to moderate drinkers, particularly when follow-up is short (Kerr *et al*., 2002; Knott *et al*., 2017).

In summary, we found little evidence in the combined cohorts of an association between male alcohol consumption and fecundability in couples. Data from only the Danish cohort indicate that consumption of six or more servings of alcohol per week may be weakly associated with reduced fecundability, but the estimates were imprecise.

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Authors' roles

E.E.H., K.J.R., L.A.W., H.T.S. and E.E.M. designed the study. S.H. took the lead on writing the manuscript. A.H.R. and A.K.W. conducted the statistical analyses. All authors interpreted the results and critically revised the article for publication. All authors approved the final manuscript.

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Conflict of interest

Dr Wise serves as a consultant on uterine leiomyomata for AbbVie.com. All other authors declare no conflict of interest.

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