Male alcohol intake and couples' fecundability: A prospective cohort study

Research year report

Sidse Høyer

Health, Aarhus University

Department of Clinical Epidemiology, Aarhus University Hospital

SUPERVISORS AND COLLABORATORS

Ellen M. Mikkelsen, MPH, PhD, senior researcher (main supervisor)
Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

Anders H. Riis, MSc, biostatistician, external lecturer (co-supervisor)
Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

Gunnar Toft, PhD, DMSc, associate professor (co-supervisor)
Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

Lauren Wise, professor (collaborator)
Department of Epidemiology, Boston University, USA

Elisabeth E. Hatch, professor (collaborator)
Department of Epidemiology, Boston University, USA

Kathryn A. McInerney, PhD (collaborator)
Department of Epidemiology, Boston University, USA

PREFACE

This report is based on a study conducted during my one year of research at Department of Clinical Epidemiology, Aarhus University Hospital.

My first meeting with my three supervisors feels like yesterday. Ignorantly, I asked them whether this research project could possibly extend over one year – it could for sure!
A special thanks to my main supervisor Ellen M. Mikkelsen who opened my eyes to the field of epidemiology and provided excellent guidance through the process. Also, I must express my thanks to Anders H. Riis for his invaluable statistical expertise and patience, and to Gunnar Toft for sharing his extensive knowledge in epidemiology and male reproduction. After all our supervision meetings, I felt optimistically guided in the right direction.

During my research year, I had the pleasure of a two-month research stay at Department of Epidemiology, Boston University. I am deeply grateful for the extreme hospitality and great supervision of our collaborators Kenneth Rothman, Elisabeth E. Hatch, Lauren Wise, Kathryn A. McInerney and Amelia Wesselink.

Finally, I thank my colleagues at Department of Clinical Epidemiology for creating a friendly working environment. I am especially grateful to Tina Christensen for our partnership in participant recruitment and to my fellow research year students for being there in every sense.

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ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
CPR	Civil Registration Number
FR	Fecundability ratio
FSH	Follicle stimulating hormone
HPG	Hypothalamic-pituitary-gonadal
IQR	Interquartile range
LH	Luteinizing hormone
LMP	Last menstrual period
MET	Metabolic equivalent
PRESTO	Pregnancy Study Online
SF	SnartForaeldre
TTP	Time to pregnancy
WHO	World Health Organization

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ABSTRACT

Background: Experimental and clinical studies have shown that alcohol affects male reproductive function, mainly by altering spermatogenesis and hormonal regulation. Few epidemiologic studies have examined the association between alcohol consumption and male fertility, and most have collected retrospective information on alcohol intake and time to pregnancy.

Objective: To examine the effects of male alcohol intake on couples' fecundability.

Methods: Data were collected from two ongoing prospective preconception cohort studies: The Danish "SnartForaeldre" (SF) study and the North American "Pregnancy Study Online" (PRESTO), which included 291 and 1,125 couples, respectively. Eligible men were aged ≥18 years in SF and ≥21 years in PRESTO, in a stable relationship with a female partner, and not using birth control or fertility treatment. In SF and PRESTO, alcohol intake was self-reported as the 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.). The overall intake was categorized as none, 1-5, 6-13 and ≥14 standard servings per week. Total menstrual cycles at risk were calculated by female follow-up questionnaires completed every 8 weeks until pregnancy or for up to 12 menstrual cycles. Analyses were restricted to couples who had been trying to conceive for ≤6 cycles at study entry. A proportional probabilities regression model was used to compute the fecundability ratio (FR) and 95% confidence interval (CI). We adjusted for male and female age, female alcohol intake, intercourse frequency, previous conception, race, education, BMI, smoking, and consumption of sugar sweetened-beverages and caffeine.

Results: 919 (64.9%) couples conceived during follow-up. FRs for male alcohol intake of 1-5, 6-13 and ≥14 servings per week compared with no alcohol consumption were 0.91 (95% CI: 0.76-1.09), 1.09 (95% CI: 0.72-1.24), and 0.90 (95% CI: 0.70-1.15), respectively.

Conclusion: We found little evidence of an association between moderate male alcohol intake and couples' fecundability.

DANSK RESUMÉ

Baggrund: Tidligere studier har vist, at alkohol påvirker den mandlige reproduktion. Få epidemiologiske studier har imidlertid undersøgt sammenhængen mellem alkoholforbrug og mandlig fertilitet, og de fleste har indsamlet retrospektiv information om alkoholforbrug og den tid det tager at blive gravid.

Formål: At undersøge sammenhængen mellem mandligt alkoholforbrug og fekundabilitet, målt som den tid det tager for par at blive gravide.

Metoder: Data blev indsamlet fra to prospektive kohortestudier: Det danske "SnartForaeldre" (SF) studie og det nordamerikanske "Pregnancy Study Online" (PRESTO), der inkluderede hhv. 291 og 1.125 par. Inklusionskriterierne for de deltagende par var, at de planlagde graviditet, var i et fast forhold, ikke anvendte prævention og ikke var i fertilitetsbehandling. Alkoholindtaget var selvrapporteret i SF og PRESTO som antal øl (330 ml/12 ounce), antal glas hvidvin eller rødvin (120 ml/4 ounce), dessertvin (50 ml/2 ounce) og spiritus (20 ml/1,5 ounce). Det samlede alkoholindtag blev kategoriseret som ingen, 1-5, 6-13 og ≥14 standard genstande om ugen. Det totale antal menstruationscyklusser i studietiden blev beregnet ud fra follow-up spørgeskemaer til de kvindelige partnere, som blev udfyldt hver anden måned indtil graviditet eller i op til 12 måneder. Analysen blev begrænset til par, som havde forsøgt at blive gravide i ≤6 cyklusser ved studiets start. Fekundabilitetsratio (FR) og 95% konfidensinterval blev udregnet på baggrund af en proportionel sandsynlig regressionsmodel, justeret for mænd og kvinders alder og samlejehyppighed, kvinders alkoholforbrug samt mænds uddannelse, rygning, BMI, race, tidligere befrugtning af en kvinde, samt forbrug af sukker- og koffeinholdige drikkevarer.

Resultater: 919 (64,9%) par blev gravide i løbet af follow-up perioden. Den justeret FR for mandligt alkoholforbrug på 1-5, 6-13 og ≥14 genstande per uge var henholdsvis 0.91 (95% CI: 0.76-1.09), 1.09 (95% CI: 0.72-1.24) og 0.90 (95% CI: 0.70-1.15), sammenlignet med intet alkoholindtag.

Konklusion: Et moderat alkoholforbrug blandt mænd var ikke associeret med den tid, det tager par at blive gravide.

MANUSCRIPT

Introduction

In developed countries, infertility affects up to 20% of couples[1, 2] with male causes contributing to approximately 50% of all cases[3, 4]. Considerable distress among infertile couples and increasing demand for assisted reproductive technologies[5] has led to greater focus on the etiology of infertility.

Well-known risk factors for male infertility include lifestyle factors such as smoking[6] and obesity[7], whereas the impact of alcohol remains unclear. Alcohol consumption is a habitual part of daily life for a large proportion of males at reproductive age[8, 9]. In Denmark, 23% of men aged 16-34 years have an alcohol intake of ≥14 drinks per week[9], and 28% of American men aged 18-34 years reported binge drinking (at least five drinks per occasion) during the preceding month[10]. In several countries, the official guidelines recommend a maximum alcohol intake for men of 14 drinks per week, with no distinction for male pregnancy planners[11-13].

Previous studies have shown that alcohol affects the male reproductive system by altering the regulation of the hypothalamic-pituitary-gonadal (HPG) axis and the spermatogenesis. Most studies on healthy young men have found higher alcohol intake to be positively associated with testosterone levels and inversely associated with the level of sex-hormone-binding-globulin[14-17]. In contrast, decreased testosterone levels has been reported mainly in alcoholic men, indicating that heavy alcohol abuse may impair the HPG-axis or cause Leydig-cell damage[18-20]. Furthermore, elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels have been seen in alcoholic men[20], whereas other studies found no such association[14, 15, 17] or even an inverse association between alcohol intake and the level of FSH and LH[18, 19]. In rat studies, a high ethanol diet induced atrophic seminiferous tubules and damages to the testicular germinal epithelium, which prevents spermatozoa from maturing and ultimately results in aspermia[21, 22]. Also, alcohol consumption has been inversely associated with total sperm count, sperm concentration and percentage of morphologically normal sperm[14, 18, 20, 23]. Two epidemiologic studies showed no or only weak relation between male alcohol consumption and couples' time to pregnancy (TTP)[24, 25]. However, these studies collected retrospective information on alcohol intake and TTP, which may have introduced potential for differential misclassification. Thus, the extent to which alcohol

influences male fertility is unclear. In the present study, we examined the association between male alcohol intake and couples' TTP in two prospective cohorts of Danish and North American couples.

Methods

Study population

The SnartForaeldre (Soon Parents) study is an ongoing prospective cohort study of Danish pregnancy planners[26]. The study was launched in August 2011 and participants were recruited through online and offline advertising[27]. Participants completed a screening questionnaire at the study website http://snartforaeldre.dk, which confirmed eligibility and provided information on how long a couple had tried to conceive before study entry. Eligible participants were invited to complete a baseline questionnaire and follow-up questionnaires and encouraged to invite their partner to the study. Couples were linked via email invitation of the partner or by their home address as registered in the Danish Civil Registration System at the date of study entry[28].

Pregnancy Study Online (PRESTO) is similar in design to SnartForaeldre[29], and has recruited pregnancy planners from the United States and Canada since June 2013. Eligible women completed baseline and follow-up questionnaires at the study website http://presto.bu.edu. After enrollment, female participants were given the option to invite their male partners to complete a one-time baseline questionnaire.

In both cohorts, the inclusion criteria were being in a stable relationship with a partner of the opposite sex and not using any contraception or fertility treatment. In SnartForaeldre we recruited females, aged 18-49 years and males aged ≥18 years, whereas in PRESTO we recruited females aged 21-45 years and males aged ≥21 years. We excluded participants as illustrated in the flow chart in Figure 1 and further excluded couples who had tried to conceive for >6 months at study entry, in order to avoid misclassifying behavioral factors due to subfertility. Baseline questionnaires obtained information on socio-demographic data, behavioral and lifestyle factors, and reproductive and medical history. Follow-up questionnaires were completed bimonthly for up to 12 months or until reported pregnancy, updating data on pregnancy status and lifestyle factors that vary over time. Study protocols were approved by the Danish Data Protection Agency and the Institutional Review Board at Boston Medical Center.

Assessment of male alcohol exposure

On baseline questionnaires, men reported their average weekly alcohol intake during the past month in SnartForaeldre and PRESTO as bottles of beer (330 ml/12 ounce), glasses of white and red wine (120 ml/4 ounce each), dessert wine (50 ml/2 ounce) and spirits (20 ml/1.5 ounce). Help buttons in the questionnaires instructed respondents on how to assess the average weekly servings and to report "no intake" if they drank less than one unit per week. We calculated total weekly alcohol consumption in standard servings (12 grams of alcohol in each) by summing the amount of alcohol in grams from each type of beverage and dividing by 12. The 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 months trying to achieve pregnancy divided by menstrual cycle length, and included the time trying to conceive both before study entry and during follow-up time. Total number of menstrual cycles at risk was calculated using the following formula: Cycles of attempt time at study entry + (((LMP date from most recent follow-up questionnaire – date of baseline questionnaire completion)/cycle length) + 1). One cycle was added to the formula to account for the fact that the average woman was in her mid-cycle when completing the baseline questionnaire[30].

Assessment of covariates

The male baseline questionnaire collected data on age, education, job hours per week, previous conception with a female partner, smoking, physical activity, height and weight, consumption of soft drinks, multivitamins and caffeine, history of sexually transmitted infections and infection of the male reproductive organs. Female questionnaires provided 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 metabolic equivalents. In SnartForaeldre, we estimated

metabolic equivalents from walking activity, moderate activity and vigorous exercise using the short-form International Physical Activity Questionnaire[31], whereas metabolic equivalents of various activities were estimated using the Compendium of Physical Activities in PRESTO[32]. We used baseline data on height and weight to calculate body mass index (BMI) as: weight (kg)/height $(m)^2$. Identical covariates were examined in the two cohorts, except for race/ethnicity (obtained only in PRESTO) and education (reported differently in each cohort).

Data analysis

We performed 1) a pooled analysis with harmonized data and 2) parallel analyses of the two cohorts for the study periods of August 2011-April 2017 (SnartForaeldre) and June 2013-June 2017 (PRESTO). We used a variant of Cox-regression, discrete-time proportional probabilities regression, to compute fecundability ratios (FR) with 95% confidence intervals (CIs)[33]. The FR represents the per-cycle probability of conception among couples where exposed men are compared with unexposed men; a FR below one indicates a reduced fertility. To account for left truncation (couples had tried to conceive for a range of 0-6 cycles at study entry), we analyzed risk sets for observed menstrual cycles only[34]. For example, if a couple had tried to conceive for four cycles at study entry and reported pregnancy after eight cycles, they would contribute cycles 5 through 8 (four cycles) to the analysis[30]. Right censoring occurred when couples were lost to follow-up (13.7%), started fertility treatment (8.1%), stopped trying to conceive (1.1%), or reached 12 cycles of pregnancy attempt (12.1%).

In the multivariate regression analysis, we adjusted for male and female age (continuous), female alcohol intake in standard servings (continuous), frequency of intercourse (<1, 1, 2-3, ≥4 times/week), previous conception (yes/no), education (<3, 3, 3-4, <4 years), body mass index (continuous), smoking (regular, occasional, former, never), consumption of sugar-sweetened beverages (continuous), consumption of caffeine (continuous) and study (SnartForaeldre/PRESTO). In addition, PRESTO models were adjusted for race (non-Hispanic white or other). We selected potential confounders based on literature and directed acyclic graphs. We used multiple imputation to impute missing exposure, covariate, and outcome data. One follow-up cycle of pregnancy status was imputed for couples who had completed only baseline questionnaire (5.4%). We generated five imputed dataset, analyzed each dataset, and subsequently combined the results across the imputed datasets[35].

To assess whether reverse causation could explain our results, we stratified by pregnancy attempt time at enrollment (≤2 vs. 3-6 cycles). Furthermore, we stratified according to BMI (<25 vs. ≥25 kg/m^2), timing of intercourse (yes/no) and previous conception (yes/no). In secondary analyses, we estimated FR for alcohol consumption of ≥21 standard servings per week. Analyses were conducted using Stata version 14.2 and SAS version 9.4.

Results

In total, 919 (64.9%) of the 1,416 included couples conceived during follow-up. SnartForaeldre couples (291) contributed 1,123 menstrual cycles at risk and 201 pregnancies, and PRESTO couples (1,125) contributed 4,663 menstrual cycles at risk and 718 pregnancies. The median (IQR) of total male alcohol intake was 4.5 (2-8) and 4.2 (1-9) standard servings per week, while the proportion of non-drinkers was 19% and 21% for SnartForaeldre and PRESTO, respectively. More men consumed beer (77.4%) than wine (49.2%) or spirits (42.2%). In total, 840 (59.3%) men consumed a combination of two or more alcoholic beverages, whereas fewer men consumed only beer, wine or spirits (19.7%, 2.6% and 2.9%, respectively).

Couples in SnartForaeldre and PRESTO were similar according to a large number of characteristics (Table 1). However, couples in SnartForaeldre had a higher frequency of intercourse, male physical activity, and male sexually transmitted disease or infection in male reproductive organs compared to couples in PRESTO. On the other hand, PRESTO couples were slightly older, men 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 and female alcohol intake were positively associated with male alcohol intake. Furthermore, alcohol intake for males in PRESTO was positively associated with regular smoking and inversely associated with household income <50,000 UDS annually and pregnancy attempt time at study entry of >2 months.

In the pooled analysis, adjusted FRs for 1-5, 6-13 and ≥14 drinks per week compared with no alcohol were 0.91 (95% CI: 0.76-1.09), 1.09 (95% CI: 0.90-1.31) and 0.90 (95% CI: 0.70-1.15), respectively (Table 2). FRs for ≥14 drinks per week compared with no alcohol intake were 0.76 (95% CI: 0.39-1.47) for SnartForaeldre and 0.95 (95% CI: 0.72-1.24) for PRESTO.

In the stratified analyses, the association between male alcohol intake and fecundability became stronger among men with a BMI of <25 (reduced FR) and couples who did not time their

intercourse (increased FR). Furthermore, relative to men drinking no alcohol, consuming ≥14 drinks per week was associated with decreased fecundability among men who had previously fathered a child and couples who timed their intercourse (Table 3). Adjusted FRs for 14-20 and ≥21 drinks per week compared with no alcohol intake were 0.89 (95% CI: 0.67-1.19) and 0.90 (95% CI: 0.66-1.24), respectively.

Discussion

In this prospective cohort study, overall alcohol consumption was weakly associated with fecundability in both pooled and parallel analyses. In SnartForaeldre, the results indicated a dose-response relationship, though the estimates were imprecise. Overall, we used the same methods in SnartForaeldre and PRESTO, but we cannot rule out the possibility that minor differences, e.g. in the measure of standard servings, could have affected the study specific estimates. Only weak association was observed for both ≥14 and ≥21 drinks per week compared to no alcohol intake. Alcohol consumption was not associated with decreased fecundability among couples with 3-6 cycles of attempt time at study entry, thus reverse causation is unlikely. The stronger inverse association among men with a BMI of <25 in relation to men with a BMI of ≥25 may be explained by a lower alcohol tolerance due to a smaller distribution of alcohol in the body tissue[36].

Our findings of male alcohol intake are fairly consistent with previous studies that have shown no or weak effects on couples' fecundability. A retrospective European multicenter study found male alcohol intake to be slightly associated with increased fecundability, when comparing male alcohol intake of 0-7 drinks per week with 8-21 and ≥22 drinks per week (OR=1.0, 95% CI: 0.8-1.2 and OR=1.3, 95% CI: 0.9-1.7, respectively)[24]. Another retrospective study found no association between alcohol consumption and TTP, comparing no alcohol with 0.1-2, 2.1-6 and >6 ounces per week (FR=1.05, 95% CI: 0.96-1.15, FR=1.02, 95% CI: 0.90-1.10 and FR=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 suggested reduced fecundability (FR= 0.88, 95% CI: 0.75-1.02 and FR=0.87, 95% CI: 0.71-1.06, respectively)[25]. Another prospective study found male alcohol intake to be positively associated with fecundability when consuming ≥10 drinks per week compared to <5 drinks per week (OR=1.6, 95% CI: 1.0-2.4)[37]. In this study, 259 females with unrestricted pregnancy attempt time at study entry 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 81.1% of couples enrolled within their first 3 cycles of pregnancy attempt.

Some further methodological explanations must be taken into account when considering our findings. Our study population includes 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 most likely to occur among the highly fertile couples. To address this problem – and the potential misclassification caused by over time change in alcohol intake due to subfertility – we limited the study population to couples who had tried to conceive for ≤6 cycles at study entry. Furthermore, the study population includes self-selected couples, recruited via the Internet. It seems unlikely that the association between male alcohol intake and couples fecundability would differ for Internet users and nonusers, and thus affect the validity of our study findings. Previous validation studies have shown that even when characteristics (such as age or smoking) differ between study participants and non-participants, well-known perinatal associations are not biased as a result of self-selection[38, 39]. Cohort retention was 86.3%, and we found similar baseline characteristics, including alcohol consumption, for couples with complete follow-up and couples who were lost to follow-up.

We collected detailed information on covariates and adjusted for well-known potential confounders, but we cannot rule out the possibility of residual confounding, e.g. roughly categorization in the questionnaires. In addition, we did not distinguish between regular and binge drinking, nor did we collect information on male dietary habits, which may have confounded the association between male alcohol intake and fecundability[14, 40]. Furthermore, the self-reported alcohol consumption was not validated. If alcohol intake was imprecisely reported it is most likely underreported[41, 42]. However, this would be independent of the prospectively collected information on pregnancy status, which would result in non-differential misclassification. Finally, we examined alcohol intake at baseline only, which could potentially result in bias if male alcohol intake decreased due to difficulties with conception. However, studies have reported monthly stability in alcohol consumption over time for low to moderate drinkers and when follow-up time is short[43, 44].

Conclusion

In summary, we observed no detrimental effect of moderate male alcohol intake on couples' fecundability. Also, male alcohol intake of ≥14 drinks per week was only weakly associated with a prolonged time to pregnancy, and the estimates were imprecise. Additional insight into the biological mechanisms of heavy male alcohol intake and binge drinking in relation to fecundability is of major public health interest. Improved understanding of the impact of alcohol and other lifestyle factors on fertility is substantial in the counseling of couples who are planning a pregnancy.

SUPPLEMENTARY

Background

Male infertility

Clinically, infertility is defined as the inability to conceive after one year of regular unprotected intercourse. However, fertility is a matter of probability on a continuous scale so the definition of infertility is somewhat arbitrary[45]. This is one of the challenges when studying human fertility. Another challenge when studying this topic is that infertility characterizes a couple and not only one person.

To archive a pregnancy several conditions must be fulfilled: 1) The female must produce a normal oocyte; 2) male semen must be of acceptable quality; 3) the sperm must reach the oocyte and be able to fertilize it; 4) the fertilized oocyte must implant in the uterus[46]. Usually, clinicians can detect if one or more of these conditions fail. However, 30% of infertility cases have no explanation[47]. Infertility is often considered a female disorder, though male infertility is equally prevalent and contributes to approximately 50% of all cases with known explanation[48]. The reasons for male infertility include varicocele, birth defects, like cryptorchidism, and infectious diseases, including adult mumps and HIV. Lifestyle factors such as smoking and obesity have been associated with male infertility, whereas the impact of alcohol is controversial.

Researchers have several ways to examine the etiology of male infertility. One is by studying male semen characteristics, which involves measures of semen volume, sperm concentration, motility and morphology. WHO provided reference values for "normal" semen parameters[49], where sperm concentration and the non-motile sperm proportion seem to be the best predictors of male fertility[50]. However, the association between semen measures and fertility is not dichotomous and a decrease in sperm quality does not necessarily result in loss of fertility[50]. Another way of examining male infertility is by studying fecundability, which is the probability of conception in one menstrual cycle. Fecundability incorporates all the male and female biological pathways from conception to time of clinically recognized pregnancy. However, fecundability cannot be measured directly, but must be determined indirectly through the study of time-to-pregnancy.

Methodological considerations

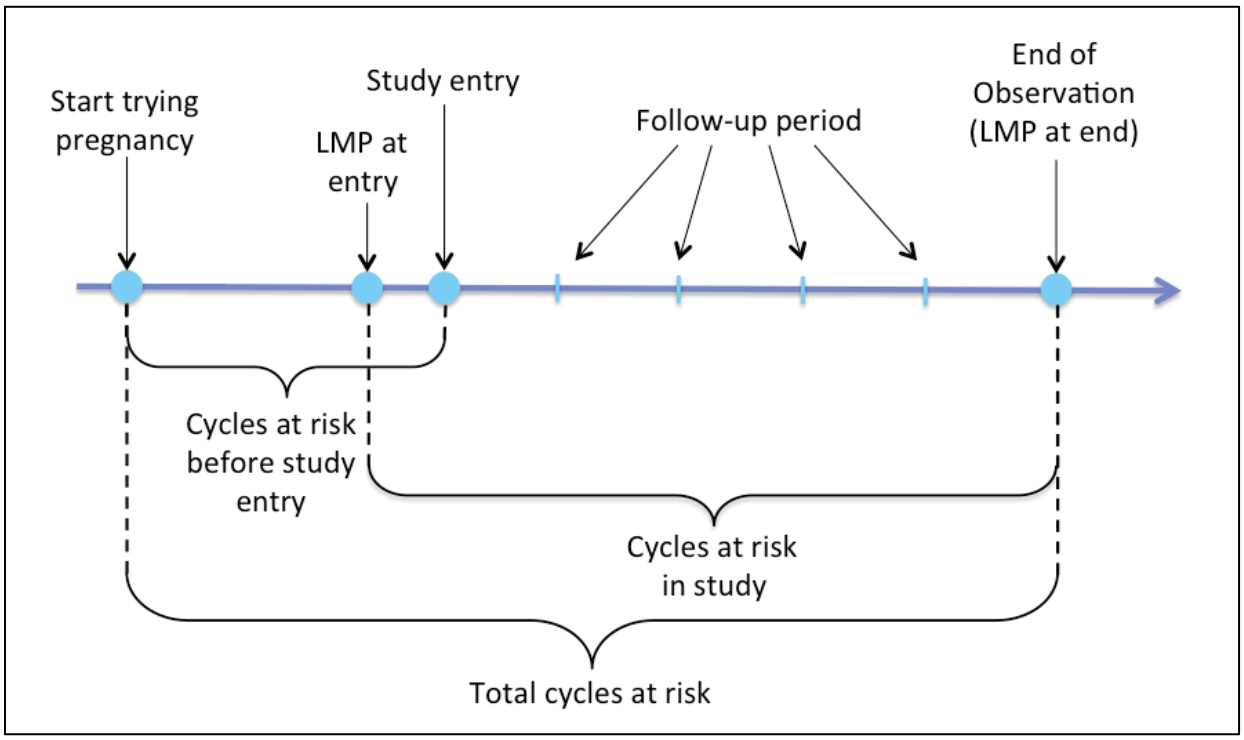
Study design

In order to examine the association between male alcohol intake and fecundability, we used data from two prospective cohort studies. In cohort studies, groups of people defined by exposure differences are followed over time to evaluate the incidence of the event of interest[51]. The fact that our study is a *prospective* cohort study means that the cohort was assembled and classified by exposure in the present, and followed into the future. Another option is the *retrospective* cohort study, where the cohort is identified from records in the past and followed from that time up to the present. Compared to the classical prospective cohort study, retrospective cohort studies are often easier to conduct, cheaper, and quicker. However, these studies may lack information that is not recorded in the past or they may be prone to recall bias if relying on individual reports of former exposures[51].

In cohort studies, we cannot ignore the risk of confounding. In randomized controlled trials, we can minimize the influence of both known and unknown confounders because study participants are allocated randomly into intervention groups differing by exposure. It is possible to apply our exposure of male alcohol intake to randomized groups of couples and follow their time-to-pregnancy over a 12 months period. However, this would be costly, time consuming, and unethical.

Time-to-event analysis

With a survival-analytic method we studied time-to-pregnancy (TTP), which is the time interval from the onset of unprotected intercourse to a clinically recognized pregnancy, usually measured as number of months or menstrual cycles[45]. TTP studies have proven useful when examining the effect of various exposures on fertility[52]. In our study, we calculated total number of menstrual cycles at risk from A) Screening questionnaire, where females report how many cycles they have tried to conceive before study entry, B) Baseline questionnaire, where females report the date of their last menstrual period (LMP) and their usual menstrual cycle length, and C) Follow-up questionnaires, where females report their LMP date and pregnancy status (including miscarriage, abortion and ectopic pregnancy) since last completed questionnaire. Couples contributed cycles at risk (**supplemental figure 1**) until pregnancy, 12 cycles, use of fertility treatment, or loss to follow-up, whichever came first.



Supplemental figure 1 Overview of cycles at risk and study structure.

We used dynamic cohorts with delayed entry (couples can enter the study after having tried to conceive for one or more cycles), where only observed cycles were analyzed. For example, if a couple had tried to conceive for 3 cycles before study entry and report pregnancy after 6 cycles, they would contribute cycle 4 to 6 to the analysis. To estimate the probability of conception, where each menstrual cycle is an opportunity for conception, we used a discrete time proportional probabilities model. This model analyses discrete probabilities, unlike the continuous Cox survival model that analyses probabilities as a smooth hazard function[33]. Furthermore, this model controls for a declining fecundability over time, by adjusting for the cycle number at risk (e.g. all pregnancies in cycle 1 are analyzed by the correct likelihood). Mean fecundability is highest in the first cycle, whereas it declines after additional cycles of trying. This reflects a gradual accumulation of infertile couples among those who have still not conceived[45].

Missing values

In our study populations, the proportion of missing data on male alcohol intake ranged from 0.3% (1/291) for beer to 5.5% (16/291) for dessert wine in SnartForaeldre and from 0.0% (0/1,125) for white wine to 0.2% (2/1,125) for liquor in PRESTO.

Missing data can be classified as 1) missing completely at random (MCAR), where the reason for missing data is independent of observed and unobserved data, 2) missing at random (MAR), where the reason for data being missing depends on observed data only or 3) missing not at random (MNAR), where the reason for data being missing depends on unobserved data, conditional of observed data[53]. For example, in our study of alcohol intake, data are MAR if well-educated men are more likely to report their alcohol intake, but MNAR if men with higher alcohol intake are more likely to report their alcohol consumption than other men of the same educational level.

Multiple imputation is a statistical method that handles missing data, by using the observed data to estimate a set of plausible values for those missing. This method generates multiple complete datasets, each dataset is analyzed individually, and the estimates are combined into an overall estimate[53]. Usually, multiple imputation is used under the assumption of data being MAR. In our study, we used multiple imputation to impute exposure, covariate, and outcome data to estimate fecundability and an appropriate variance using completed data [54].

Additional strengths and limitations

We can never know the true value of fecundability and a casual relationship between male alcohol intake and couples' time-to-pregnancy cannot be proven. However, we can get closer to estimating a casual association by considering whether our results can be explained by systematic or random error.

Systematic error

Systematic error, also called bias, is introduced by an inaccuracy at any stage leading to results that are systematically different from the truth[51]. Typically, a systematic error remains constant and is not reduced by increasing the sample size. There are three broad categories of systematic error:

selection bias, information bias, and confounding. In the following, these terms are described in relation to the present study.

Selection bias

Selection bias occurs when the association between exposure and outcome differs for study participants and non-participants[55]. This type of bias can be introduced by selection criteria or when factors related to both exposure and outcome determine study participation and/or loss to follow-up[38].

Our study was restricted to pregnancy planners, self-selected via the study websites. The exclusion of unplanned pregnancies, which tend to occur among the most fertile couples, could potentially have left an overrepresented proportion of subfertile couples in our study[45]. Furthermore, our study cohort may have included more health-conscious couples, who may have a lower alcohol intake compared to the general population. However, the overrepresentation of subfertile couples and couples where men have a lower alcohol intake will not cause selection bias in itself. Selection bias occurs if male alcohol intake has a different impact on couples' fecundability in the general population compared to couples in our study. For example, if male alcohol intake had a greater impact on pregnancy planners (less fertile couples), this would cause and overestimation of the association between male alcohol intake and couples fecundability.

In the attempt to minimize selection bias, we restricted the analysis to couples who had tried to conceive for less than 6 cycles at study entry, and hence, considered to have a higher fecundability. Furthermore, nearly 80% of pregnancies in Denmark are planned[56], so our study cohort of Danish pregnancy planners may not be a particularly selected group compared to the general Danish population. However, in countries like the United States, up to 50% of pregnancies are unintended[57], which may indicate planned pregnancies as a marker of lower fecundability.

Our recruitment method, involving enrollment of participants through the Internet, may raise concern for selection bias if Internet-users diverged from non-users in the association between male alcohol intake and couples' TTP. A previous validation study of "Snart-Gravid" (a study before SnartForaeldre, where only females enrolled) examined the associations between maternal characteristics and pregnancy outcomes, e.g. smoking and low birth weight, from self-reporting vs. records from the Danish Medical Birth Registry[38]. Well-known exposure-outcome associations

were similar among study participants and the general population of Danish women giving birth. This suggests that the recruitment of participant through the Internet - and the inclusion criteria in general – did not introduce significant selection bias. Since the "Snart-Gravid" study is so similar to SnartForaeldre, this validation study indicates that selection bias may not have influenced our results among Danish pregnancy planners.

Finally, selection bias could occur if those couples with partial follow-up (13.7%) diverged in the association between male alcohol intake and fecundability compared to couples with complete follow-up. We compared baseline characteristics of couples with partial and complete follow-up and found no major differences between the two groups. Thus, selection bias due to loss to follow up is unlikely a major problem in this study.

Information bias

Another systematic error is information bias, where the exposure, covariate or outcome information of study participants is erroneous – it is misclassified[55]. If misclassification of a variable (e.g. exposure) differs in relation to other study variables (e.g. outcome), it is *differential*. In contrast, if misclassification of a variable is unrelated to other study variables, it is *non-differential*. Non-differential misclassification of a dichotomous exposure is expected to bias the association towards the null value, whereas non-dichotomous exposures may be biased either towards or away from the null value[55].

In our study, we collected data on TTP prospectively every other month, so recall bias does not seem to be a major problem. At study entry, women report the numbers of cycles they have already tried to conceive, which could have created some misclassification. In addition, we examined male alcohol intake at baseline only, though this exposure ideally should have been measured in every cycle. If male alcohol intake changed over time, because couples were having trouble conceiving, this could bias the result. Men in SnartForaeldre did in fact complete follow-up questionnaires with updated reports on their alcohol intake. Still, we found no overall detrimental effect on fecundability and the estimates became more imprecise when using updated alcohol intake: Adjusted FRs for 1-5, 6-13 and ≥14 standard servings per week were 1.00 (95% CI: 0.64-1.58), 1.01 (95% CI: 0.55-1.83) and 1.44 (95% CI: 0.65-3.17), respectively.

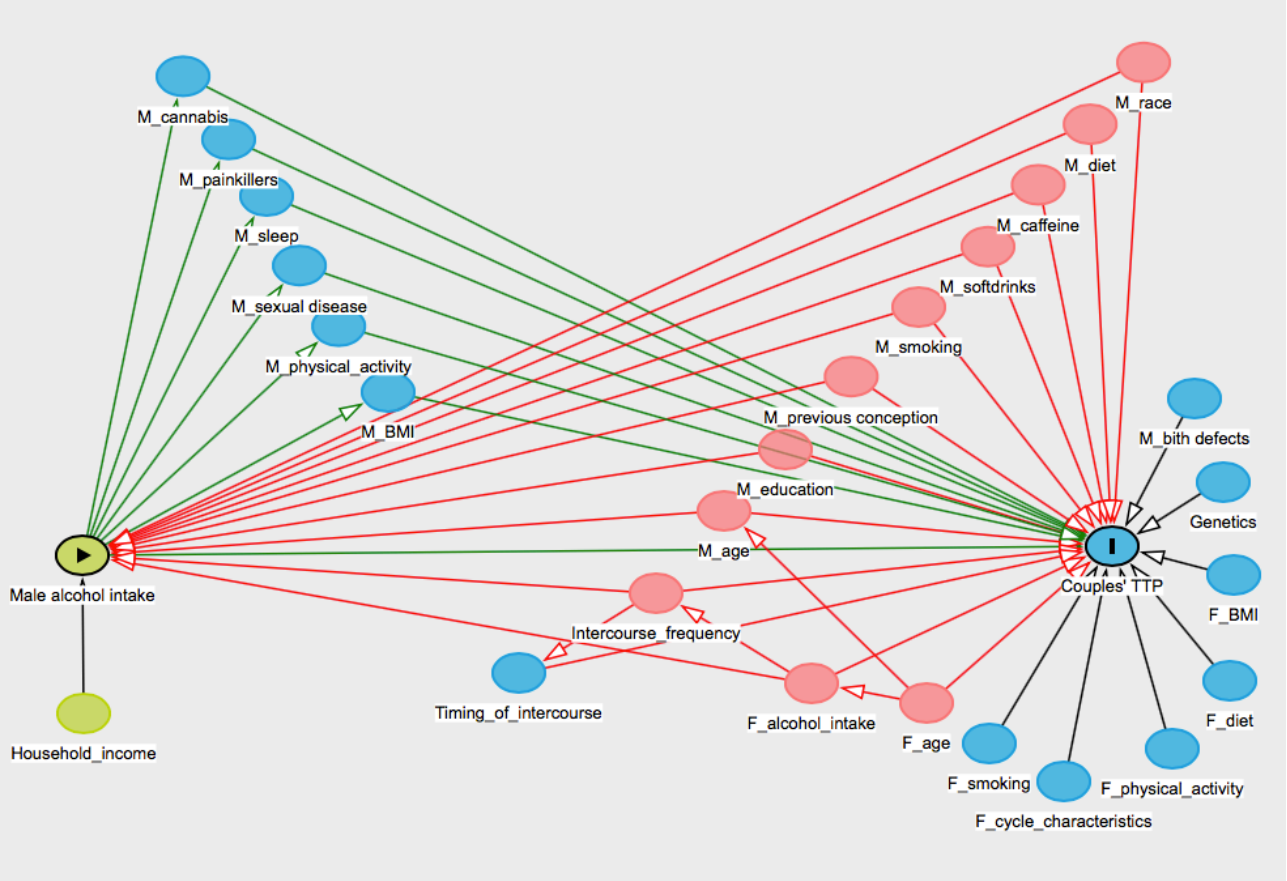
In addition, self-reported male alcohol intake may not be reported accurately, and could be underreported[41, 42]. We assessed male alcohol intake (and other covariates) before the occurrence of a pregnancy, which makes differential misclassification unlikely. However, men and women did not necessarily enroll at the same time. For example, women may enroll a few months before male enrollment, and thus reports in the male baseline questionnaire could potentially be biased by the influence of current pregnancy status. In total, 36 (12.4%) men in SnartForaeldre and 113 (10.0%) men in PRESTO completed the baseline questionnaire at least one month after their female partner, whereas 11 (3.8%) men in SnartForaeldre and 59 (5.2%) men in PRESTO completed the baseline questionnaire more than 3 months after their partner. However, if men reported inaccurately or chanced their lifestyle due to current pregnancy status, this is unlikely to be consistent in one direction and thereby cause differential misclassification.

Confounding

Confounding is a confusion of effects – that is the exposure-outcome association is mixed with another variable, resulting in bias. The confounding variable must be associated with the exposure *and* the outcome of interest, while not being a part of the casual chain from exposure to outcome[51]. Confounding can be minimized by methods within study design (e.g. randomization, matching, restriction) and statistical analysis (e.g. stratification, standardizing, adjustment).

In our study, we used a multivariable adjustment in which the effect of several variables is considered simultaneously. In this way the effect of one variable – male alcohol intake – can be determined. We considered a wide range of potential confounders as illustrated in the direct acyclic graph (**Supplemental figure 2**).

For example, male age may confound the association between male alcohol intake and couples' fecundability, but when *conditioning* on male age, it cannot drive the exposure-outcome association. However, when adjusting for potential confounders it is important to keep in mind that residual confounding (within-stratum confounding) may still persist. In our study, it is possible that a rough categorization of the variables in the questionnaire may have caused some residual confounding. Also, some variables may not be taken into account, either because they were not measured (e.g. male diet) or because the importance was unknown.



Supplemental figure 2 An example of a direct acyclic graph of the association between male alcohol intake and couples' TTP. Blue nodes are ancestors of couples' TTP, green node is ancestor of male alcohol intake and red nodes are ancestors of male alcohol intake *and* couples' TTP. Green arrows are casual paths and red arrows are biased paths.

Random error

If a sample is selected without bias, it may still misrepresent the underlying population due to chance[51]. This variability in data, called random error, can never be eliminated, but by increasing the sample size it can be reduced. In order to describe the extent of random error, we used 95% confidence intervals to estimate the precision of the effect measurements. In our study, we included a fairly large study population (1,416 couples). However, some subgroups were smaller, which may have resulted in greater random error, illustrated by the wider CIs.

External validity

External validity (also called generalizability) is the degree to which the study results can hold true in other settings, e.g. to other populations, geographical places and time periods. The baseline characteristics of our cohort – including male alcohol intake – may not be completely generalizable

to the general Danish or American population of pregnancy planners. However, whether the characteristics of a study population is representative for the general population, is not as important as the representativeness of the underlying biological effect[55, 58]. In other words, is it more important to evaluate whether the *association* between male alcohol intake and couples' fecundability is generalizable to the general population. It is unlikely that the biologic association would differ for study participants and non-participants and furthermore we assume a high internal validity in our study. Therefore, it is very likely that the biologic association we measured is generalizable to the general population of Danish and American pregnancy planners. Also, our results may well apply to other societies comparable to Denmark and North America, where the proportion of pregnancy planners is high.

Perspectives

The overall number of assisted reproductive technology cycles has increased year by year[5]. Furthermore, impaired fertility has physiological, psychological and economic costs for those couples affected. Thus, knowledge about factors that impair fertility is of major public health interest and substantial in the counseling of couples who are planning a pregnancy.

Our study adds the evidence that moderate male alcohol intake does not seem to prolong time to pregnancy for couples who are attempting to conceive. Though the biological mechanisms are still somewhat unclear, several studies have found alcohol to affect the male reproductive system – either by direct impact on spermatogenesis or indirectly through the regulation of the HPG-axis. However, even if moderate alcohol intake would cause a decrease in sperm quality, it does not necessarily cause a detectable effect on couples' fecundability. Nevertheless, a substantial decrease in sperm concentration, for example, would be recognized as a cause of prolonged time to pregnancy. It is possible that our methods were not sensitive enough to detect more discrete reductions in fecundability[45].

The exact biological affects of alcohol on couples fecundability remains unclear, thus it is too early to make recommendations for male pregnancy planners. Further insight into the impact of heavy alcohol drinking and binge drinking on couples fecundability is needed.

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TABLES AND FIGURE

Figure 1: Flow chart of included participants in SnartForaeldre and PRESTO

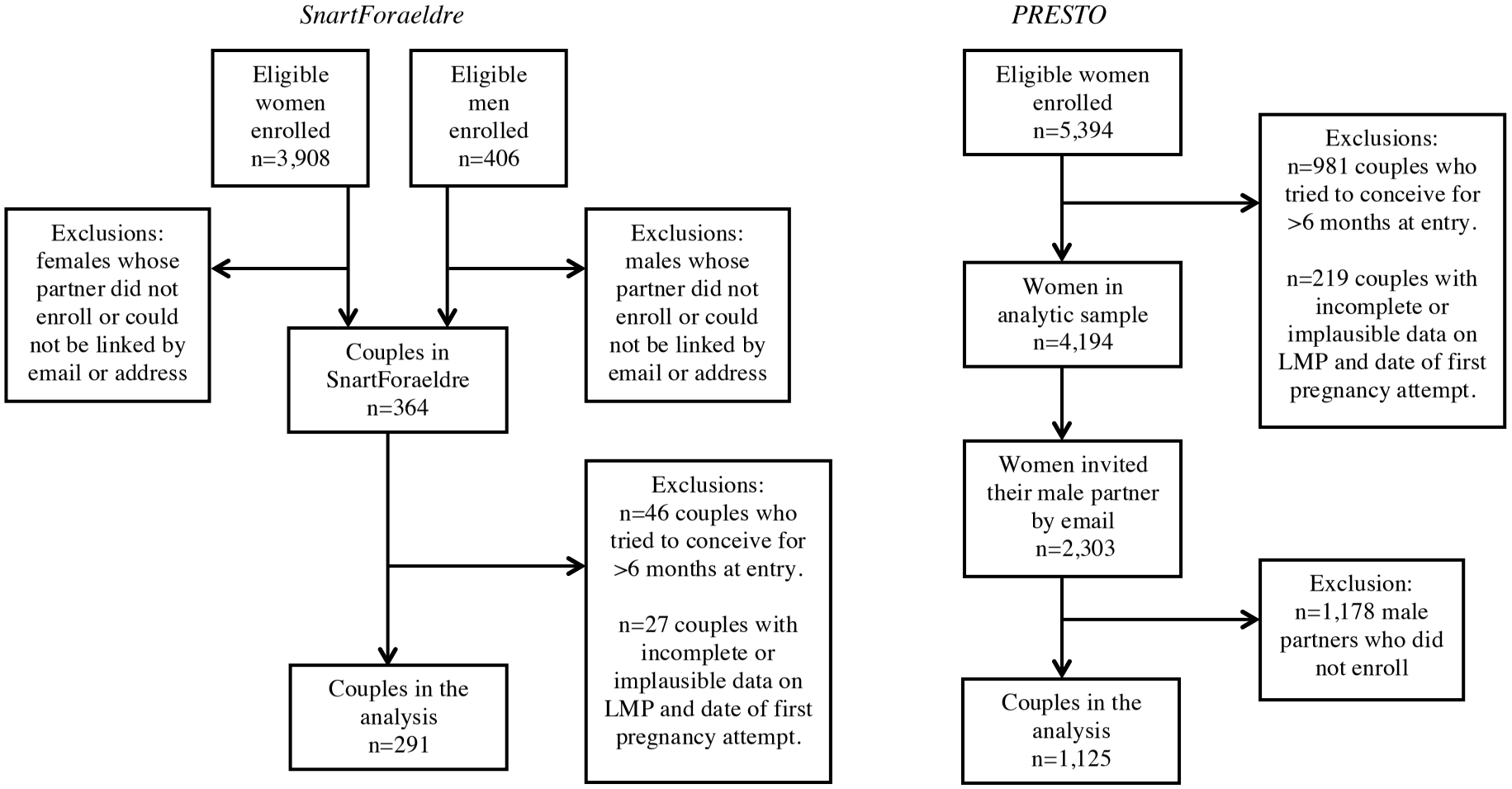

Table 1: Baseline characteristics of 1,416 males, by level of alcohol intake in standard servings/week

Characteristics	Total	SNARTFORAELDRE				PRESTO			
		None	1-5	6-13	≥14	None	1-5	6-13	≥14
No. of men (%)	1,416 (100%)	34 (11.7)	132 (45.4)	100 (34.4)	25 (8.6)	218 (19.4)	390 (34.7)	362 (32.2)	155 (13.8)
Age, median years	31	29	30	29.5	30	30	31	32	32
Partner's age, median years	29	27	28	29	27	29	29	30	30
Partner's median alcohol intake, servings/week (IQR)	2 (0-4)	0 (0-2)	1 (0-2)	3 (1-5)	4 (1-7)	0 (0-1)	1 (0-3)	3 (2-6)	5 (2-9)
Educational level <16 years, N (%)	413 (29.7)	9 (26.5)	46 (34.9)	29 (29.0)	9 (36.0)	81 (37.2)	117 (30.0)	75 (20.7)	47 (30.3)
Median job hours per week	40	37	37	37	37	40	40	45	44
Household income (SF/PRESTO) <24,999 DKK monthly/<50,000 USD annual, N (%)	246 (17.4)	7 (20.6)	29 (22.0)	17 (17.0)	8 (32.0)	66 (30.3)	69 (17.7)	32 (8.8)	18 (11.6)
Body Mass Index, median kg/m2	26.0	25.6	24.8	24.2	24.7	26.8	26.6	25.9	27.0
Physical activity, median MET hours/week	29.8	36.8	45.4	38.6	24.0	22.6	28.2	32.1	26.5
Conceived with previous or current partner, N (%)	607 (42.9)	20 (58.8)	49 (37.1)	38 (38.0)	9 (36.0)	106 (48.6)	168 (43.1)	145 (40.1)	72 (46.5)
Frequency of intercourse ≥4 times/week, N (%)	246 (17.4)	10 (29.4)	32 (24.2)	22 (22.0)	11 (44.0)	42 (19.3)	60 (15.4)	41 (11.3)	28 (18.1)
Timing of intercourse, N (%)	1,069 (75.5)	25 (73.5)	99 (75.0)	71 (71.0)	18 (72.0)	175 (80.3)	288 (73.9)	273 (75.4)	120 (77.4)
Attempt time >2 months at study entry, N (%)	434 (30.7)	11 (32.4)	37 (28.0)	24 (24.0)	9 (36.0)	84 (38.5)	127 (32.6)	101 (27.9)	41 (26.5)
Regular smoking, N (%)	85 (6.0)	*	9 (6.8)	8 (8.0)	*	9 (4.1)	14 (3.6)	18 (5.0)	22 (14.2)
Multivitamin consumption, N (%)	465 (32.8)	11 (32.4)	30 (22.7)	28 (28.0)	9 (36.0)	77 (35.3)	132 (33.9)	128 (35.4)	50 (32.3)
Soft drinks >1 serving/week, N (%)	714 (50.4)	12 (35.3)	41 (31.1)	39 (39.0)	15 (60.0)	132 (60.6)	210 (53.9)	171 (47.2)	94 (60.7)
Caffeine consumption >150 mg/day, N (%)	709 (50.1)	13 (38.2)	68 (51.5)	56 (56.0)	19 (76.0)	63 (28.9)	168 (43.1)	211 (58.3)	111 (71.6)
History of sexually transmitted infection and/or infection in male reproductive organs, N (%)	165 (11.7)	8 (23.5)	32 (24.2)	30 (30.0)	8 (32.0)	16 (7.3)	28 (7.2)	30 (8.3)	13 (8.4)
Non-Hispanic white, N (%)	-	-	-	-	-	185 (84.9)	323 (82.8)	330 (91.2)	142 (91.6)

* Numbers ≤3. The precise numbers cannot be shown, according to guidelines of Statistics Denmark

Table 2: Couples' fecundability by male alcohol consumption

			Fecundability ratio (95% CI)	
Servings/week	Pregnancies	Cycles	Unadjusted FR	Adjusted FR*
SnartForaeldre and PRESTO, N=1,416				
None	155	979	(reference)	(reference)
1-5	319	2187	0.92 (0.77-1.09)	0.91 (0.76-1.09)
6-13	327	1814	1.10 (0.92-1.31)	1.09 (0.90-1.31)
≥14	118	806	0.88 (0.70-1.09)	0.90 (0.70-1.15)
SnartForaeldre, N=291				
None	24	111	(reference)	(reference)
1-5	94	498	0.94 (0.62-1.43)	0.98 (0.63-1.51)
6-13	68	408	0.87 (0.57-1.34)	0.94 (0.59-1.52)
≥14	15	106	0.70 (0.38-1.29)	0.76 (0.39-1.47)
PRESTO, N=1,125				
None	131	868	(reference)	(reference)
1-5	225	1689	0.88 (0.72-1.07)	0.89 (0.73-1.09)
6-13	259	1406	1.14 (0.94-1.38)	1.16 (0.94-1.43)
≥14	103	700	0.90 (0.71-1.14)	0.95 (0.72-1.24)

* Adjusted for male and female age, female alcohol intake, frequency of intercourse, previous conception, education, BMI, smoking, consumption of sugar-sweetened beverages and caffeine. Furthermore adjusted for race (in PRESTO) and study (in pooled analysis).

Table 3: Male alcohol intake and couples' fecundability, stratified by pregnancy attempt time at entry, BMI, timing of intercourse and previous conception, cohort=1,416

	Alcohol intake, servings per week			
	None	1-5	6-13	≥14
≤2 cycles of attempt at study entry				
Pregnancies, n	108	244	247	88
Cycles, n	591	1480	1337	643
Adjusted FR (95% CI)	(Reference)	0.95 (0.77-1.17)	1.07 (0.86-1.33)	0.86 (0.64-1.14)
3-6 cycles of attempt at study entry*				
Pregnancies, n	47	75	80	30
Cycles, n	388	707	477	163
Adjusted FR (95% CI)	(Reference)	0.82 (0.57-1.16)	1.12 (0.76-1.64)	1.09 (0.67-1.78)
BMI <25				
Pregnancies, n	62	115	148	37
Cycles, n	324	808	852	278
Adjusted FR (95% CI)	(Reference)	0.79 (0.59-1.07)	0.90 (0.68-1.21)	0.74 (0.48-1.12)
BMI ≥25				
Pregnancies, n	93	204	179	81
Cycles, n	655	1379	962	528
Adjusted FR (95% CI)	(Reference)	1.02 (0.81-1.29)	1.29 (1.01-1.65)	1.06 (0.77-1.45)
No timing of intercourse*				
Pregnancies, n	28	79	82	34
Cycles, n	217	616	515	197
Adjusted FR (95% CI)	(Reference)	1.12 (0.74-1.69)	1.24 (0.81-1.90)	1.35 (0.79-2.32)
Timing of intercourse				
Pregnancies, n	127	240	245	84
Cycles, n	762	1571	1299	609
Adjusted FR (95% CI)	(Reference)	0.87 (0.72-1.07)	1.09 (0.88-1.35)	0.78 (0.59-1.04)
No previous conception				
Pregnancies, n	71	172	187	66
Cycles, n	517	1355	1177	454
Adjusted FR (95% CI)	(Reference)	0.96 (0.74-1.26)	1.12 (0.85-1.49)	1.02 (0.71-1.46)
Previous conception				
Pregnancies, n	84	147	140	52
Cycles, n	462	832	637	352
Adjusted FR (95% CI)	(Reference)	0.87 (0.68-1.11)	1.07 (0.82-1.39)	0.82 (0.57-1.19)

*Not adjusted for previous conception and race.

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