Preconception alcohol consumption and risk of miscarriage in over 4.5 million Chinese women aged 20–49 years

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ABSTRACT

Objective To assess the impact of preconception alcohol consumption on risk of miscarriage incidence, and further evaluate the association between maternal periconception drinking abstinence and miscarriage.

Methods We performed a population-based, retrospective cohort study in China between 1 January 2013 and 31 December 2016. Alcohol intake and potential confounding factors were reported in standard questionnaires. Participants who became pregnant were recontacted for pregnancy outcome information within 1 year. A total 4 531 680 women with available data on preconception alcohol intake and miscarriage were included in the final analyses. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results The prevalence of miscarriage was 2.70% among 4 531 680 women. Compared with non-drinkers, the adjusted OR of miscarriage was 1.06 (95% CI 1.02 to 1.10) and 1.59 (95% CI 1.15 to 2.20) in maternal occasional drinkers and regular drinkers, respectively. Compared with couples in which neither the male nor the female consumed alcohol, the adjusted OR for miscarriage among women was 1.09 (95% CI 1.07 to 1.10), 1.13 (95% CI 1.06 to 1.21) and 1.12 (95% CI 1.07 to 1.17) in the couples in which only the female drank alcohol, only the male drank alcohol, and both drank alcohol, respectively. The adjusted OR was 0.58 (95% CI 0.51 to 0.65) in women with alcohol abstinence compared with alcohol drinkers.

Conclusions Preconception alcohol consumption was associated with higher odds of miscarriage, and an increasing risk was found with paternal and maternal alcohol drinking. Periconception alcohol abstinence was inversely associated with miscarriage.

Key messages

- Pre-pregnancy alcohol consumption was associated with higher odds of miscarriage, and an increasing risk of miscarriage was found with paternal and maternal alcohol consumption.
- The study demonstrates a clear impact of alcohol intake in both partners on the risk of miscarriage, besides its association with maternal and paternal alcohol intake, considered separately.
- Identification of alcohol intake before pregnancy, modification of drinking behaviour, and even quitting drinking altogether are critical factors in miscarriage prevention.

INTRODUCTION

Prenatal alcohol consumption is a potential risk factor for many adverse pregnancy outcomes.[1–3] It is associated with fetal growth restriction, preterm birth, small for gestational age, stillbirth and miscarriage.[4–8] Public health guidance notes that no amount of alcohol during pregnancy is known to be safe.[9] Numerous studies have established the adverse consequences of alcohol consumption during pregnancy on miscarriage,[10–16] yet few studies focus on pre-pregnancy alcohol intake, and the association between pre-pregnancy alcohol intake and miscarriage remains conflicting. Chiodo *et al* reported that

preconception alcohol consumption was directly associated with pregnancy loss,[12] while Rossi found a slight protective association between alcohol drinking prior to pregnancy and lower risk of miscarriage.[16] However, most of the previous studies were case–control studies designed with small sample sizes, and they failed to find significant associations between alcohol drinking and miscarriage.[17–19]

Genetic anomalies are known to play a critical role in many spontaneously aborted embryos, with 35%–75% exhibiting chromosomal abnormalities.[7] Previous studies have suggested that alcohol consumption was not only associated with aneuploidy in sperm cells[20] but was also found to increase the numbers of morphologically abnormal sperm[21] and further interfere with conception. Thus, it appears that paternal alcohol consumption before pregnancy might be a risk factor for miscarriage. Besides, alcohol intake has wide-ranging effects on cellular stress, as well as on hormonal and nutrient signalling pathways, which may affect the development and metabolism of the early embryo, with high doses associated with reduced placental weight, the development of pre-eclampsia, placental abruption and miscarriage.[10 22]Nevertheless, little attention has been paid to the influence of paternal alcohol drinking, and the combined effects of female and male alcohol intakes on risk of miscarriage are still unclear.[7 11 23]

Therefore, we conducted a large, population-based, retrospective cohort study to assess the impact of preconception alcohol consumption on risk of miscarriage incidence, and to further explore the association between maternal periconception alcohol abstinence and the risk of miscarriage.

METHODS

Study participants and study design

A population-based, retrospective cohort study was conducted in China among couples aged 20–49 years who were planning a pregnancy within the next 6 months between 1 January 2013 and 31 December 2016, based on data collected by the National Free Pre-Pregnancy Checkups Project (NFPCP). NFPCP is a national preconception healthcare service launched by the National Health Commission and the Ministry of Finance of the People's Republic of China to provide free health examinations before conception and follow-up of pregnancy outcomes throughout China. Previously published articles have included detailed information on the project-related design, organisation and implementation of NFPCP,[24] and a flow diagram for the design of the NFPCP is included in online supplemental figure 1. Women in this study were participants in the NFPCP. The analyses included 6 817 494 Chinese women aged 20–49 years, and were conducted between 1 January 2013 and 1 December 2016. After the removal of women with missing information on alcohol intake and delivery date, a total

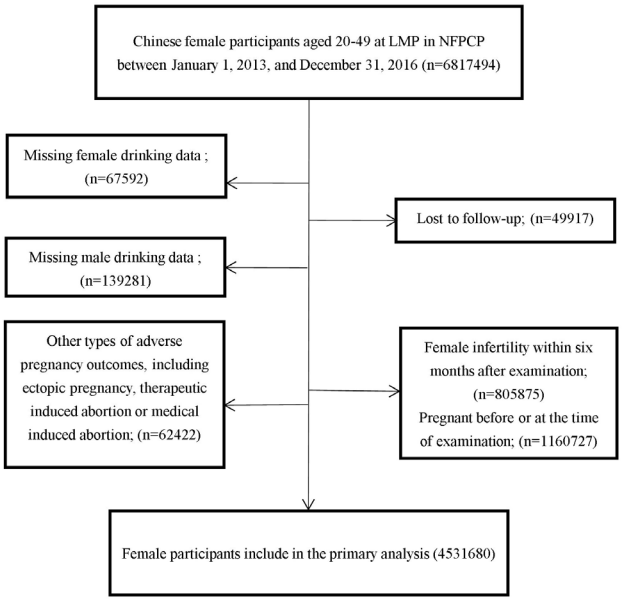

Figure 1 Flowchart of the study population. LMP, last menstrual period; NFPCP, National Free Pre-Pregnancy Checkups Project.

4 531 680 women with available data on preconception alcohol intake and miscarriage were included in the final analyses after considering the exclusion criteria outlined in figure 1. The Institutional Research Review Board at the National Research Institute for Family Planning, Beijing, China approved this study. Written informed consent of all NFPCP participants was obtained.

Patient and public involvement

Patients and members of the public were not directly involved in the design of this study.

Data collection and alcohol assessment

Face-to-face interviews, medical examinations and follow-up investigations were conducted by healthcare professionals using a standard questionnaire which contained a pre-pregnancy examination chart (both male and female) and several follow-up charts to collect baseline information on demographics, socioeconomic factors, lifestyle, as well as pregnancy outcomes.

During the pre-pregnancy physical examination, maternal and paternal alcohol consumption information was collected by trained health professionals (doctors, nurses) using separate questionnaires for women and their partners. The couples were (individually) asked "Do you drink alcohol? If yes, how often do you drink, occasionally or frequently?" at the preconception health examination to identify their alcohol drinking status. Drinking was defined as drinking once per week on average at the time of examination (regardless of the type of drinking, such as white wine, liquor, beer, red wine, yellow rice wine, etc.). Occasionally drinking and frequently drinking were identified as drinking 1–2 times and 3+ times per week, respectively. According to the drinking

status of the couples, we classified 4 531 680 couples into four groups: (1) neither maternal nor paternal drinking (neither-drinker), (2) only maternal drinking (maternal-only), (3) only paternal drinking (paternal-only) and (4) both drinking (both drinkers).

After the preconception stage, the early pregnancy follow-up interview was conducted by telephone. If a woman was not pregnant by the first follow-up telephone interview, repeated telephone inquiries were conducted within a 3-month period. Repeated telephone inquiries were conducted subsequently within the next 3-month period until 1 year after the preconception examination, if the woman did not get pregnant at the first follow-up interview. For pregnant women the questions "Did you drink?" and "Have you quit drinking?" were asked to ascertain their alcohol drinking status in the first trimester. If they replied "No" to the second question, changes in alcohol consumption (reducing, remaining the same, or increasing) during early pregnancy were recorded, and compared with the amount of drinking before conception. Information about the last menstrual period (LMP), symptoms during pregnancy, toxic or harmful substances exposure, and diet or lifestyle changes in the first trimester of pregnancy was also collected during the follow-up interview.

In the final stage, the participants who had become pregnant were recontacted for pregnancy outcome information within 1 year after the completion of the first follow-up survey. The follow-up chart of pregnancy outcome documented miscarriage, low birth weight, induced labour, ectopic pregnancy, birth defects, preterm birth, or stillbirth as adverse pregnancy outcomes, and collected self-reported information from the women on their delivery experience and vital newborn information such as the delivery date, birth weight and gender. If the participants had an abortion or experienced other gestational problems, especially adverse pregnancy outcomes occurring during the early pregnancy period, they were encouraged to report by telephone, and then a pregnancy outcome follow-up interview was conducted by a member of the research staff.

Outcome assessment

Miscarriage was defined as pregnancy loss occurring before the 28th week of gestation. In the current study, the gestational age (in weeks) was calculated as the time difference between the self-reported first day of the LMP during the early pregnancy follow-up and the time of delivery in the pregnancy outcome follow-up interview.

Statistical analysis

The age-adjusted and multivariable-adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) of miscarriage associated with the couples' alcohol consumption (non-drinker, drinker including occasional drinking or regular drinking), alcohol drinking status of the couples (neither-drinker, paternal-only, maternal-only or both drinkers) and the periconception alcohol consumption change (non-drinker, kept drinking or quit drinking) were estimated by logistic regression models separately, using the neither-drinker and the non-drinker group as the reference group, respectively. The data in the two logistic regression models were adjusted for potential confounding variables which were significant in the univariate analyses, including maternal age at LMP (from 20 to 50 years in 5-year intervals); maternal education level (primary school or below, high school or above); area of residence (rural, urban); preconception body mass index (BMI) (≤18.5, 18.6–23.9, 24.0–27.9 or ≥28.0 kg/m^2); Han Chinese ethnicity (yes, no); parity (primipara, multiparity); maternal cigarette smoking (yes, no); maternal passive cigarette smoking (yes, no); history of adverse pregnancy outcomes (yes, no); uterine diseases (yes, no); periconception drinking cessation (yes, no); history of recurrent miscarriage (0, 1, ≥2); and alcohol consumption of male and female (yes, no). History of adverse pregnancy outcomes was defined as history of preterm birth, later fetal death, miscarriage or abortion in previous pregnancies. Finally, we also investigated the possible effects of periconception maternal drinking cessation on miscarriage. The term 'periconception' indicates that drinking cessation occurs either before conception or during early pregnancy.

All statistical analyses were performed using R (version 3.5.0; https://www.r-project.org/) with the "reshape2 (version 1.4.3)" and "speedglm (version 0.3–2)" packages. All statistical tests were two-sided, and p values <0.05 were considered statistically significant.

RESULTS

Among 4 531 680 women aged 20 to 49 years recruited between 1 January 2013 and 31 December 2016 the prevalence of miscarriage is 2.70%. The baseline characteristics of female participants in the four groups before conception are presented in table 1. The females of the couples in the both drinkers group were more likely to be older, urban inhabitants, with a lower BMI, higher educational attainment, have exposure to secondhand smoke and have a history of adverse pregnancy outcomes compared with the neither-drinker group (table 1).

According to the alcohol drinking status of women, the incidence of miscarriage was 2.68% and 3.27% in the non-drinker and drinker groups, respectively. In the drinkers, the corresponding incidence was 3.25% and 5.65% in the occasional drinking and regular drinking groups, respectively. Using the non-drinker group as the reference group, the adjusted ORs of miscarriage were 1.06 (95% CI 1.03 to 1.10), 1.06 (95% CI 1.02 to 1.10) and 1.59 (95% CI 1.15 to 2.20) among maternal

Table 1 Characteristics of female participants before pregnancy according to the drinking status of the couples (n=4 531 680)

Variable	Neither-drinker (n=3 251 769)	Paternal-only (n=1 162 477)	Maternal-only (n=31 192)	Both drinkers (n=86 199)	P value*
Maternal age at LMP (years) (mean±SD)	26.22±4.10	26.53±4.18	26.75±4.12	26.91±4.08	<0.001†
Parity (primipara) (n (%))	2 046 847 (62.95)	701 469 (60.34)	22 555 (72.31)	62 230 (72.19)	<0.001
Education (high school or above) (n (%))	494 119 (15.20)	245 142 (21.09)	11 044 (35.41)	34 505 (40.03)	<0.001
Han ethnicity (n (%))	2 984 056 (91.77)	1 072 440 (92.25)	28 658 (91.88)	78 601 (91.19)	<0.001
Rural inhabitants (n (%))	3 036 219 (93.97)	1 034 485 (88.99)	24 435 (78.34)	63 497 (73.66)	<0.001
BMI (kg/m^2) (mean±SD)	21.33±2.86	21.29±2.98	21.00±2.93	20.94±2.89	<0.001†
Smoker (n (%))	3290 (0.10)	2369 (0.20)	1003 (3.22)	2494 (2.89)	<0.001
Secondhand smoker, n (%)	189 109 (5.82)	224 891 (19.35)	17 868 (57.28)	54 481 (63.20)	<0.001
History of adverse pregnancy outcomes (n (%))	421 125 (12.95)	258 332 (22.22)	7949 (25.48)	24 161 (28.03)	<0.001

*Multiple comparison with Bonferroni-adjusted p value <0.05, compared with neither-drinker.
†The Kruskal–Wallis H test was used to examine the differences in baseline characteristics among above four groups. Other characteristics used the χ^2 test.
BMI, body mass index; LMP, last menstrual period; SD, standard deviation.

drinkers, maternal occasional drinkers and maternal regular drinkers, respectively. The corresponding ORs of miscarriage were 1.08 (95% CI 1.07 to 1.10), 1.08 (95% CI 1.06 to 1.09) and 1.27 (95% CI 1.21 to 1.34) among women in the above groups classified as paternal drinkers, paternal occasional drinkers and paternal regular drinkers. Besides, compared with the reference group (neither-drinker), the adjusted OR for miscarriage among women was 1.09 (95% CI 1.07 to 1.10), 1.13 (95% CI 1.06 to 1.21) and 1.12 (95% CI 1.07 to 1.17) in the paternal-only, maternal-only and both drinkers, respectively (table 2).

We also summarised the associations between the periconception maternal changes in alcohol consumption behaviour and risk of miscarriage. The incidence of miscarriage was 1.81% and 3.11% in the quit drinking and kept drinking groups, respectively. Compared with those who kept drinking, the adjusted OR for miscarriage was 0.58 (95% CI 0.51 to 0.65) in women who quit drinking (table 3).

Table 2 Adjusted odds ratios of miscarriage according to pre-pregnancy maternal/paternal/couple drinking status (n=4 531 680)

Drinking status	Miscarriage n/N (%)	Age-adjusted OR* (95% CI)	Multivariable-adjusted OR (95% CI)
Maternal			
Non-drinker	118 130/4 414 289 (2.68)	1	1
Drinker	3834/117 391 (3.27)	1.18 (1.15 to 1.22)	1.06 (1.03 to 1.10)†
Occasional drinking	3792/116 647 (3.25)	1.18 (1.14 to 1.22)	1.06 (1.02 to 1.10)†
Regular drinking	42/744 (5.65)	1.97 (1.44 to 2.69)	1.59 (1.15 to 2.20)†
Paternal			
Non-drinker	84 680/3 282 961 (2.58)	1	1
Drinker	37 284/1 248 719 (2.99)	1.14 (1.13 to 1.15)	1.08 (1.07 to 1.10)‡
Occasional drinking	35 679/1 210 953 (2.95)	1.13 (1.11 to 1.14)	1.08 (1.06 to 1.09)‡
Regular drinking	1605/37 766 (4.25)	1.46 (1.38 to 1.53)	1.27 (1.21 to 1.34)‡
Couple			
Neither-drinker	83 681/3 251 769 (2.57)	1	1
Paternal-only	34 449/1 162 520 (2.96)	1.13 (1.12 to 1.16)	1.09 (1.07 to 1.10)§
Maternal-only	999/31 192 (3.20)	1.20 (1.12 to 1.27)	1.13 (1.06 to 1.21)§
Both drinkers	2835/86 199 (3.29)	1.22 (1.17 to 1.26)	1.12 (1.07 to 1.17)§

*ORs were adjusted by maternal age at LMP (last menstrual period).
†ORs were adjusted by maternal age at LMP, maternal education, area of residence, preconception BMI, Han Chinese ethnicity, parity, uterus disease, periconception maternal drinking cessation, history of recurrent miscarriage, paternal drinking, smoking, passive smoking, history of adverse pregnancy outcomes.
‡ORs were adjusted by paternal age at LMP, maternal education, area of residence, preconception BMI, Han Chinese ethnicity, parity, uterus disease, periconception maternal drinking cessation, history of recurrent miscarriage, maternal drinking, smoking, passive smoking, history of adverse pregnancy outcomes.
§ORs were adjusted by maternal and paternal age at LMP, maternal education, area of residence, preconception BMI, Han Chinese ethnicity, parity, uterus disease, periconception maternal drinking cessation, history of recurrent miscarriage, smoking, passive smoking, history of adverse pregnancy outcomes.
BMI, body mass index; CI, confidence interval; LMP, last menstrual period; OR, odds ratio.

The population attributable fraction (PAF) (%) of preconception maternal and paternal drinking for miscarriage was 0.55 (95% CI 0.45 to 0.65) and 4.06 (95% CI 3.70 to 4.41), respectively (online supplemental table 1).

DISCUSSION

In this large, retrospective cohort study we found a significant positive association between pre-pregnancy alcohol intake and miscarriage. This study also shows a clear impact of alcohol intake in both partners on the risk of miscarriage, besides its association with maternal and paternal alcohol intake, considered separately. In addition, our study demonstrates that identification of pre-pregnancy alcohol consumption and subsequent alcohol cessation reduces the risk of miscarriage.

Although the consequences of alcohol intake during pregnancy are well known, only a few studies have focused on pre-pregnancy alcohol consumption. In previous studies using measures of pre-pregnancy alcohol exposures, Chiodo *et al* conducted a cohort study of 302 African-American women which found a slightly increased risk,[12] but most studies failed to find significant associations between pre-pregnancy alcohol consumption and risk of miscarriage, contrary to the findings in our study. This inconsistency in findings may be due to the other studies' case–control design and small sample size.[17–19] The PAF results show that if the frequency of couple alcohol drinking, maternal alcohol drinking and paternal alcohol drinking decreased, this could prevent the proportion of miscarriage by 4.27%, 0.55% and 4.06%, respectively.

Additionally, compared with non-drinkers, the occasional drinkers and regular drinkers had higher odds of miscarriage. The current results are consistent with studies that also reported significant increases in miscarriage related to the frequency of drinking.[10 25] Our findings replicate previous study results which have found an association between paternal alcohol consumption during pregnancy and miscarriage.[7 11] Only a case–control study that used retrospective data from 161 Helsinki women found that paternal alcohol consumption does not increase the risk of miscarriage, and such inconsistencies might be attributed to the small sample size and cross-sectional study design. It is known that approximately 60% of miscarriages are associated with chromosomal defects in the ova, which is determined by maternal and paternal genes.[26] Paternal factors, such as alcohol abuse, may gain significance, particularly because ethanol induces chromosomal aberrations in animals.[27] Thus, it is suggested that paternal alcohol consumption before pregnancy might be a risk factor for miscarriage.

To date, many previous studies have discussed the impact of alcohol consumption on miscarriage by considering male and female alcohol intake separately; however, concerns about their combined effects on the risk of miscarriage, especially prior to pregnancy, were seldom considered.[7] In the current study, the combined effects of couples' alcohol intake on the risk of miscarriage was further investigated. Thus, instead of focusing on maternal drinking alone, attention should be paid to paternal drinking and/or couple drinking, which both increase the risk of miscarriage, and there should be more guidelines on safe drinking levels for couples who are trying for a pregnancy.

Moreover, our study is the first to successfully detect the protective effect of periconception drinking cessation behaviour on miscarriage incidence. The US Centres for Disease Control and Prevention recommends that all women who are planning a pregnancy or who are not using reliable contraception abstain from alcohol use.[28] Abstinence from alcohol is often considered critical in decreasing the risk of adverse pregnancy outcomes. It is suggested that maternal and child healthcare providers should carefully monitor their pregnant patients and their partners' alcohol drinking, and that women should abstain from alcohol as soon as possible after conception, and ideally even during the preconception period. Further research should pay more attention to improving clinical practice guidelines related to pre-pregnancy alcohol use among women of childbearing age.

Animal models have shown that alcohol may increase the risk of resorptions and fetal death, which may include alcohol-induced chromosomal defects through pathophysiological mechanisms.[29] Alcohol could increase the production of prostaglandins, including prostaglandins in the E series (PGE), and increase the excretion of prostaglandins and thromboxane in humans.[30] Prostaglandins could activate cyclic adenosine monophosphate (cAMP) and suppress the rate of cell division, and an increased level of PGE2

Table 3 Adjusted odds ratios of miscarriage according to periconception maternal drinking status

Drinking status	Miscarriage n/N (%)	Age-adjusted OR* (95% CI)	Multivariable-adjusted OR† (95% CI)
Kept drinking	402/12 929 (3.11)	1	1
Quit drinking	826/45 619 (1.81)	0.57 (0.51 to 0.64)	0.58 (0.51 to 0.65)

*ORs were adjusted by maternal age at LMP.
†ORs were adjusted by maternal age at LMP, maternal education, area of residence, preconception body mass index, Han Chinese ethnicity, parity, uterus disease, history of recurrent miscarriage, smoking, passive smoking, history of adverse pregnancy outcomes.
CI, confidence interval; LMP, last menstrual period; OR, odds ratio.

and PGF2a may possibly increase the risk of adverse outcomes including miscarriage.[31]

The findings of the current study are drawn from a large-scale cohort study, which ensured the statistical power of the analysis, and also permitted consideration of important potential confounders omitted in other analyses. It is also the first study to investigate the combined effects of male and female pre-pregnancy alcohol intake as well as the effect of quitting drinking on miscarriage.

Some limitations should be borne in mind when interpreting these study results. First, self-reported alcohol intake may underestimate true consumption, and thus could further understate the effect of drinking frequency on drinking and miscarriage. Second, some previous studies have reported a dose–response-like association between the number of drinks consumed and the risk of miscarriage;[10 32] however, we were unable to assess the relationship between volume and type of alcohol intake and the effect on miscarriage due to limited data availability. Third, the notion of miscarriage was not precisely defined, as it would have been in medical data. Finally, there could be a misclassification of miscarriage and induced abortion, as the latter could be intentionally reported as miscarriage on account of social desirability.

CONCLUSIONS

Our results indicate that pre-pregnancy alcohol consumption is associated with higher odds of miscarriage, and an increasing risk of miscarriage is found with paternal and maternal alcohol consumption. Alcohol abstinence during periconception was inversely associated with miscarriage. Identification of alcohol intake before pregnancy, modification of drinking behaviour, and even alcohol abstinence are critical for the prevention of miscarriage.

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Contributors YY and XM conceived the study, provided overall guidance and revised the manuscript. JC, TG and YY have full access to data in the study and take responsibility for data integrity and the accuracy of data analysis. JC and YY designed and supervised the study. TG and QX led the data collection. TG analysed the data and interpreted the results. TG and YD searched the literature and drafted the manuscript. LJ, JZ, ZP, YH, YW, YaZ, HZ, QW, HS, YipingZ and DY collected the data. YD, TG and YY revised the manuscript. All authors contributed to the critical revisions of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval This study was approved by the Institutional Research Review Board at the National Health and Family Planning Commission, now known as the National Health Commission (IRB-201001).

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