

**Title:** A prospective cohort study of COVID-19 vaccination, SARS-CoV-2 infection, and fertility

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**Running Head:** COVID-19 and fertility

## ABSTRACT

Some reproductive-aged individuals remain unvaccinated against COVID-19 due to concerns about potential adverse effects on fertility. We examined the associations of COVID-19 vaccination and SARS-CoV-2 infection with fertility among couples trying to conceive spontaneously using data from an internet-based preconception cohort study. We enrolled 2,126 self-identified females residing in the U.S. or Canada during December 2020-September 2021 and followed them through November 2021. Participants completed questionnaires every 8 weeks on sociodemographics, lifestyle, medical factors, and partner information. We fit proportional probabilities regression models to estimate associations between self-reported COVID-19 vaccination and SARS-CoV-2 infection in both partners with fecundability, the per-cycle probability of conception, adjusting for potential confounders. COVID-19 vaccination was not appreciably associated with fecundability in either partner (female FR=1.08, 95% CI: 0.95, 1.23; male FR=0.95, 95% CI: 0.83, 1.10). Female SARS-CoV-2 infection was not strongly associated with fecundability (FR=1.07, 95% CI: 0.87, 1.31). Male infection was associated with a transient reduction in fecundability (FR=0.82, 95% CI: 0.47, 1.45 for infection within 60 days; FR=1.16, 95% CI: 0.92, 1.47 for infection >60 days). These findings indicate that male SARS-CoV-2 infection may be associated with a short-term decline in fertility and that COVID-19 vaccination does not impair fertility in either partner.

**Key words:** COVID-19; fecundability; fertility; preconception; prospective cohort; SARS-CoV-2; vaccination

## INTRODUCTION

The three COVID-19 vaccines approved by the United States (U.S.) Food and Drug Administration have shown high efficacy in reducing the occurrence of SARS-CoV-2 infection and severe COVID-19 disease.<sup>1-3</sup> As of November 20, 2021, 71% of U.S. adults had received two doses of Pfizer-BioNTech<sup>®</sup> (BioNTech, Mainz, Germany; Fosun Pharma, Shanghai, China; Pfizer, New York, NY) or Moderna<sup>®</sup> (Moderna Therapeutics, Cambridge, MA) vaccines or one dose of the Johnson & Johnson<sup>®</sup> (Janssen Pharmaceutical Companies, Beerse, Belgium) vaccine, with 82% having received at least one dose of any vaccine.<sup>4</sup> Vaccination rates were lower among reproductive-aged adults, with approximately 60% of adults aged 18-39 years fully vaccinated.<sup>4</sup> Safety is an important factor in individual decision-making. Concern about possible side effects is a top reported reason for remaining unvaccinated<sup>5</sup> and, among reproductive-aged adults, there is particular concern about the potential effects of vaccination on fertility.<sup>6-8</sup>

The hypothesis that COVID-19 vaccination may impair female fertility originated with a blog post that claimed the similarity between a SARS-CoV-2 surface glycoprotein and syncytin-1 (an envelope protein essential for formation of the placenta<sup>9</sup>) could lead to development of anti-syncytin-1 antibodies that would impair placental function. However, three studies have demonstrated the absence of anti-syncytin-1 antibodies after mRNA vaccination.<sup>10-12</sup> Anecdotal reports of menstrual cycle irregularities after vaccination have also contributed to concerns about the vaccine's potential effect on fertility.<sup>13</sup> Data on the association between COVID-19

vaccination and fertility are still limited, but do not indicate a harmful association. Although pregnant individuals were ineligible for the initial COVID-19 vaccine trials, the rate of unintended pregnancies occurring during the trials did not differ substantially between vaccinated and control groups.<sup>14-16</sup> In clinical trials for the AstraZeneca vaccine (ChAdOx1 nCoV-19), fertility rates were similar in participants who received the vaccine (n=50 pregnancies) vs. the placebo (n=43 pregnancies).<sup>17</sup> In three separate studies of female patients undergoing *in vitro* fertilization, no meaningful association was found between COVID-19 vaccination status and implantation rates,<sup>18</sup> stimulation characteristics,<sup>19</sup> embryological outcomes,<sup>19</sup> or ovarian follicular function.<sup>20</sup>

Likewise, a limited number of studies have evaluated the association of COVID-19 vaccination on male fertility. Two studies in couples undergoing fertility treatments<sup>19,21</sup> and one in the general population<sup>22</sup> found no appreciable difference in semen volume, sperm concentration, or motility measures before and after COVID-19 vaccination.

In contrast to data on COVID-19 vaccination, which do not indicate adverse associations with fertility, infection with SARS-CoV-2 has been associated with reproductive dysfunction.<sup>23</sup> Recent SARS-CoV-2 infection has been associated with poor sperm quality, including abnormal morphology, decreased concentration, lower motility, and increased DNA fragmentation;<sup>24-31</sup> these findings may result from COVID-19 disease-associated fever and inflammation.<sup>32,33</sup> SARS-CoV-2 infection has also been associated with impaired Leydig cell function<sup>34</sup> and dysregulation of the hypothalamic-pituitary-gonadal axis.<sup>35</sup> Some reports suggest that female patients with SARS-CoV-2 infection experience menstrual cycle changes, including irregular

cycles, decreased menstrual volume, and prolonged menstrual cycles,<sup>36,37</sup> although these studies lacked an uninfected comparison group. Studies of patients undergoing fertility treatment report that SARS-CoV-2 infection is largely unrelated to treatment outcomes.<sup>38,39</sup> However, in an observational study among reproductive-aged females, recent SARS-CoV-2 infection was associated with lower concentrations of anti-Müllerian hormone and higher concentrations of testosterone and prolactin.<sup>40</sup>

Here, we examine the associations of female and male COVID-19 vaccination and SARS-CoV-2 infection with fecundability, the per-cycle probability of conception, in a North American prospective cohort study of couples trying to conceive.

## METHODS

### *Study design and participants*

Pregnancy Study Online (PRESTO) is an internet-based prospective preconception cohort study of couples residing in the U.S. and Canada.<sup>41</sup> Enrollment began in June 2013 and is ongoing. Eligible participants identified as female, were aged 21-45 years, and were trying to conceive without use of fertility treatment. Participation involved completion of a baseline questionnaire on sociodemographics, lifestyle, and reproductive and medical histories; follow-up questionnaires every 8 weeks for up to 12 months; and additional questionnaires in pregnancy and postpartum. Female participants were given the option to invite their male partners to complete a baseline questionnaire; eligible partners were aged  $\geq 21$  years. The institutional review board at Boston University Medical Campus approved the study. All participants provided informed consent.

### *Assessment of COVID-19 vaccination*

On female and male baseline questionnaires and female follow-up and early pregnancy questionnaires, we asked, “Have you ever received a COVID-19 vaccination?” and, if “yes,” participants reported the vaccine brand (“Moderna,” “Pfizer,” “Johnson & Johnson,” or “Other,” with a text box to enter the brand) and dates of first and second doses. Beginning in June 2021, we also asked female participants on all questionnaires if their partners had received a COVID-19 vaccination, as well as the dates of vaccination and vaccine brand.

### *Assessment of SARS-CoV-2 infection*

On female and male baseline questionnaires and female follow-up and early pregnancy questionnaires, we asked participants if they had ever tested positive for SARS-CoV-2, and if so, the date they tested positive. On female questionnaires, we asked if their partners had ever tested positive for SARS-CoV-2, and if so, the date they tested positive. For both vaccination and infection, we prioritized male partner data from the male baseline questionnaire (available for 25% of couples); otherwise, we relied on female report of male exposures.

### *Assessment of fecundability*

We collected menstrual cycle information on the baseline and follow-up questionnaires. At baseline, participants reported how long they had been trying to conceive (in menstrual cycles), their last menstrual period (LMP) date, typical menstrual cycle length, and whether their cycles were regular (*i.e.*, can usually predict date of next period within a few days). On follow-up questionnaires, we asked for number of cycles since previous questionnaire, LMP dates for each

cycle, and length of the most recent cycle. On follow-up questionnaires, participants also reported whether they were currently pregnant, had initiated fertility treatment, or had experienced any pregnancy losses since their previous questionnaire. Those who conceived reported how the pregnancy was confirmed (*e.g.*, urine test, blood test, ultrasound). We asked non-pregnant participants if they were still trying to conceive.

For each menstrual cycle during follow-up, we identified the first day of menses. If participants did not provide information on number and dates of cycles since the previous questionnaire, we estimated LMP date(s) that occurred between questionnaires using information on time between reported LMP dates, length of the most recent menstrual cycle, and typical cycle length.<sup>42</sup>

### *Exclusions*

In this analysis, we included PRESTO participants who enrolled between December 14, 2020 (when COVID-19 vaccines first became available in U.S.) and September 22, 2021 (Web Figure 1; n=2,679). We followed participants through November 11, 2021. We excluded 91 individuals with implausible baseline dates for LMP. We restricted to those who had been trying to conceive for  $\leq 6$  cycles at enrollment to reduce the potential for reverse causation, which could occur if fertility concerns influence decisions about vaccination. The final analytic sample included 2,126 couples. Analyses of male partner vaccination and fecundability were restricted to the 1,369 couples for whom these data were available from either partner.

### *Statistical analysis*

We used the Andersen-Gill data structure, with one observation per menstrual cycle, to account for left truncation due to delayed entry and to update exposure status over time. For analysis of vaccination, we compared participants who had received at least one dose of vaccine by the first day of each menstrual cycle with participants who had not received any vaccine doses. In secondary analyses, we compared participants who had received a full vaccine regimen (defined as two doses of Pfizer-BioNTech or Moderna or one dose of Johnson & Johnson) with participants who had not received any vaccine doses. For analysis of SARS-CoV-2 infection, we compared participants who had ever tested positive for SARS-CoV-2 by the first day of the menstrual cycle with those who had never tested positive. We fit proportional probabilities regression models (*i.e.*, log-binomial models adjusting for cycle number at risk) to estimate fecundability ratios (FRs) and 95% confidence intervals (CIs). The FR represents the per-cycle probability of conception comparing exposed and unexposed individuals. We followed couples until pregnancy (regardless of outcome) or the occurrence of a censoring event (*i.e.*, initiation of fertility treatment, cessation of pregnancy attempt, loss to follow-up, or 12 cycles of pregnancy attempt), whichever came first. To examine the association between time since vaccination or infection with fecundability, we fit restricted cubic splines.

In multivariable-adjusted models, we adjusted for the following female baseline variables: age (years), educational attainment ( $\leq$ high school, some college, college degree, graduate school), household income (<50,000, 50,000-99,999, 100,000-149,999,  $\geq$ 150,000 USD), current smoker, private health insurance, hours/week of work, rotating shift work, night shift work, body mass index, intercourse frequency (<1, 1-3,  $\geq$ 4 times/week), doing something to improve chances of conception (*e.g.*, timing intercourse, measuring basal body temperature), sleep duration (<6, 6-8,



≥9 hours/night), 10-item Perceived Stress Scale score,<sup>43</sup> Major Depression Inventory score,<sup>44</sup> Pap smear in past three years, history of self-reported infertility, parity (parous vs. nulliparous), irregular menstrual cycles, menstrual cycle length (<25, 25-31, ≥32 days), geographic region of residence (Northeastern U.S., Southern U.S., Midwestern U.S., Western U.S., Canada), last method of contraception (oral contraceptive pills, other hormonal methods, barrier/natural methods), occupation in the health care industry (defined based on United States Census Industry codes 8190 [Hospitals], 8180 [Other health care services], 8170 [Home health care services], 8080 [Offices of other health practitioners], 8070 [Offices of optometrists], 8090 [Outpatient care centers], 8270 [Nursing care facilities], 8290 [Residential care facilities, without nurses], 7970 [Offices of physicians] and 7980 [Offices of dentists]) and race/ethnicity (non-Hispanic white, non-Hispanic Black, non-Hispanic Asian, non-Hispanic other race, Hispanic). To account for expanding vaccine eligibility over time, we also adjusted for time since December 14, 2020 (days), as well as time squared and cubed. For analyses of vaccination, we adjusted for history of SARS-CoV-2 infection; for analyses of SARS-CoV-2 infection, we adjusted for history of COVID-19 vaccination.

We also fit models adjusting for confounding using fine stratification by propensity score.<sup>45,46</sup> Use of propensity scores to control confounding is as effective as stratification or regression modeling, and offers the ability to improve validity by excluding individuals who are outside the mutual range of propensity scores for exposed and unexposed.<sup>47</sup> We fit a logistic regression model of cycle-specific vaccination status (or infection status) regressed on covariates to calculate propensity scores (*i.e.*, predicted probabilities of exposure). The propensity score models included the following variables that are either associated with both exposure and

outcome or outcome only: age, educational attainment, household income, current smoker, private health insurance, rotating shift work, night shift work, body mass index, intercourse frequency, doing something to improve chances of conception, sleep duration, 10-item Perceived Stress Scale score, Major Depression Inventory score, Pap smear in the past three years, history of infertility, parity, irregular menstrual cycles, menstrual cycle length, geographic region of residence, last method of contraception, occupation in health care industry, race/ethnicity, time since December 14, 2020, time squared, and time cubed, and tested positive for SARS-CoV-2 (or COVID-19 vaccination, as appropriate). After developing the propensity score model, we excluded individuals who were outside the overlapping range of propensity scores for exposed and unexposed. We then divided the data set into 50 strata of propensity scores based on the distribution of propensity scores in exposed individuals and developed weighted regression models to derive an adjusted exposure association. Exposed individuals were assigned weights of 1; unexposed individuals were assigned weights as follows:

$$\text{Unexposed weights} = \frac{N \text{ exposed in stratum} / N \text{ total exposed}}{N \text{ unexposed in stratum} / N \text{ total unexposed}}$$

This weighting scheme generates a pseudo-population in which confounder balance is achieved within each stratum, and thus, in the population overall. We then calculated the marginal measures of association in the weighted population to estimate the average treatment effect among the treated.

In sensitivity analyses, we defined vaccination date as dose date plus 14 days to assess the association with a full immune response to the dose. We also stratified by vaccination brand, country of residence (U.S. vs. Canada), occupation in health care industry, and calendar time at risk (December 2020-March 2021 vs. April 2021-November 2021). To assess potential for

reverse causation, we stratified by attempt time at study entry (<3 vs. 3-6 cycles) and restricted to participants without a history of infertility. Finally, for vaccination analyses, we restricted to participants who never tested positive for SARS-CoV-2 to control for potential confounding by infection.

We used multiple imputation with fully conditional specification to impute missing data. We generated 20 imputed datasets and combined estimates across analytic datasets. Missingness was generally low: no participants were missing vaccination status or brand, and covariate missingness ranged from 0% (age) to 2% (household income).

## RESULTS

Most female participants in our analysis had high educational attainment (83% with  $\geq 16$  years), high household income (57% with income  $\geq \$100,000$  USD/year) and private health insurance (employment-based or purchased privately; 86%). Most participants self-identified as non-Hispanic white (85%). A large proportion worked in the health care industry (25%). Around 37% had a previous live birth, and 9% reported a history of infertility.

Vaccination prevalence was similar among female and male participants. Seventy-three and 74% had received at least one dose of COVID-19 vaccine by the LMP date of the final observed cycle, respectively. Vaccinated individuals were more likely to have higher education and income, reside in the U.S., work in the health care industry, and perform night or rotating shift work, and were less likely to be parous, report history of infertility, and have irregular menstrual

cycles than unvaccinated individuals (Table 1). We observed few differences in participant characteristics by vaccine brand (Web Table 1).

COVID-19 vaccination was not appreciably associated with fecundability in either partner (Table 2). Female participants who received at least one dose of vaccine before a given menstrual cycle had 1.08 times the probability of conceiving during that cycle compared with unvaccinated participants (95% CI: 0.95, 1.23). The corresponding adjusted FR for female receipt of a full vaccine regimen (two doses of Pfizer-BioNTech or Moderna, or one dose of Johnson & Johnson) before a given menstrual cycle was 1.07 (95% CI: 0.93, 1.23). For male partners, the adjusted FR for at least one dose was 0.95 (95% CI: 0.83, 1.10) and for a full vaccine regimen was 1.00 (95% CI: 0.86, 1.17). The FR for couples where both partners had received at least one dose compared with couples where neither partner had received any doses was 0.97 (95% CI: 0.82, 1.16).

Findings were similar after adjustment for potential confounders using fine stratification on propensity scores (Table 2). After trimming non-overlapping propensity scores and re-weighting across 50 propensity score strata, the distribution of propensity scores was similar across exposure groups (Web Figure 2), and we achieved reasonable balance of covariates by exposure status (Web Figure 3).

Figures 1 and 2 present FRs and 95% CIs for several sensitivity analyses comparing individuals who had received at least one dose of vaccine with unvaccinated individuals. For both partners, when we compared individuals who received their vaccine dose at least 14 days before the first

day of their cycle with unvaccinated individuals, results were similar to the main analysis. We did not observe any substantial variation in FRs by vaccine brand, country of residence, occupation in the health care industry, or calendar time at risk. FRs were similar when we stratified by attempt time at study entry and when we restricted to individuals with no history of infertility. FRs were also similar among individuals who had never tested positive for SARS-CoV-2. We observed little variation in fecundability by time since vaccination in female or male partners (Figure 3).

By the final observed LMP date in the study, 7.2% of female and 7.8% of male participants had a history of a positive test for SARS-CoV-2 infection. Overall, history of testing positive for SARS-CoV-2 in either partner was not strongly associated with fecundability (adjusted FR for female partner=1.07; 95% CI: 0.87, 1.31; adjusted FR for male partner=1.07; 95% CI: 0.88, 1.31; Table 2). However, restricted cubic spline analyses showed that among male partners, recent infection was associated with a transient reduction in fecundability (Figure 4): men who reported testing positive for SARS-CoV-2 within 60 days of a given cycle had reduced fecundability compared with men who never tested positive or who tested positive at least 60 days prior. FRs for male partner infection 0-30 and 0-60 days post-infection were 0.20 (95% CI: 0.03, 1.39; 41 exposed cycles) and 0.82 (95% CI: 0.47, 1.45; 99 exposed cycles), respectively. Male partner infection at least 60 days ago was not associated with reduced fecundability (FR=1.16, 95% CI: 0.92, 1.47). Among female partners, SARS-CoV-2 infection was not appreciably associated with fecundability regardless of time since infection.

## DISCUSSION

High-quality data on the risks and benefits of vaccination are essential for informed COVID-19 vaccine decision-making. In this prospective cohort study of couples trying to conceive, we found no meaningful association between COVID-19 vaccination in either partner with fecundability. This adds to the evidence from animal studies,<sup>48</sup> studies of humans undergoing fertility treatment,<sup>18-20</sup> and the COVID-19 vaccine trials,<sup>14-17</sup> none of which found an association between COVID-19 vaccination and lower fertility. Similarly, several studies have documented no appreciable association between COVID-19 vaccination and miscarriage risk.<sup>49-52</sup> In terms of benefits, vaccination is highly effective at preventing SARS-CoV-2 infection and severe COVID-19 disease.<sup>1-3</sup> Here, we also show that SARS-CoV-2 infection among male partners was associated with a short-term decline in fertility that may be avoidable by vaccination. Therefore, given the known risks of SARS-CoV-2 infection during pregnancy to maternal and fetal health,<sup>53-56</sup> and the evidence presented herein of no harmful association with fertility, our results support promotion of COVID-19 vaccination during the preconception period.

One hypothesized mechanism by which COVID-19 vaccination could influence female fertility is via changes in menstrual cycles. Although our study and others have shown no adverse associations of female COVID-19 vaccination on fertility,<sup>14-20</sup> anecdotal reports of menstrual changes and vaginal bleeding after vaccination have contributed to skepticism of vaccine safety and concerns about fertility. An association between COVID-19 vaccination and menstrual irregularities could theoretically arise through mechanisms involving immunological influences on hormone levels<sup>57</sup> or through immune cells in the lining of the uterus.<sup>58</sup> Some previous vaccines have been associated with short-term menstrual changes, including the typhoid,<sup>59</sup> hepatitis B,<sup>60</sup> and human papilloma virus<sup>61</sup> vaccines. To date, no prospective study has examined

the association between COVID-19 vaccination and menstruation. Two retrospective reports<sup>62,63</sup> show that high proportions of menstruating adults report irregular cycles and heavy bleeds post-vaccination, and that breakthrough bleeding was common among individuals taking gender-affirming hormones or long-acting reversible contraception and among post-menopausal individuals. However, these studies were likely enriched with individuals who noticed a change in their cycles and so cannot be used to estimate associations with menstruation. Results from our study indicate that even if vaccines do have short-term effects on menstruation, there is likely little or no subsequent effect on fertility.

In our study, vaccinated participants were trying to conceive between 0 and 11 months after vaccination (mean=3.5 months). Therefore, at this time, we cannot draw conclusions about long-term effects of vaccination on fertility. There are two possible sources of long-term effects of vaccination: the components of the vaccine and the immune response to vaccination.

Components of the vaccine have documented safety profiles,<sup>1-3</sup> and any potential allergic reactions attributable to vaccine ingredients would be observed within approximately 15-30 minutes of vaccination.<sup>64</sup> The innate (rapid, non-specific) phase of the immune response takes place over several days and triggers the adaptive phase (slower, highly specific), which occurs over several weeks.<sup>65</sup> Beyond this point, antibody concentrations plateau or slowly decline, and the risk of severe immunization-related complications drops dramatically. Enrollment in PRESTO is ongoing, and we will continue to monitor long-term associations of COVID-19 vaccination and fecundability; however, it is unlikely that adverse effects on fertility could arise many months after vaccination.

Our finding of a short-term decline in fertility after male SARS-CoV-2 infection is consistent with several studies indicating short-term declines in sperm quality after SARS-CoV-2 infection.<sup>24-30</sup> Fever is a known determinant of impaired spermatogenesis, and effects on sperm concentration, motility, and morphology can persist for 3-4 months (*i.e.*, the duration of spermatogenesis).<sup>33</sup> Fever is one of the most common symptoms of SARS-CoV-2 infection;<sup>32</sup> therefore, fever could explain our finding of an acute decline in fertility among men with recent SARS-CoV-2 infection. Although fever is also a side effect of vaccination, it is much less common than for infection.<sup>14-16</sup> The fertility decline could also be related to immune response and inflammation in the testes and epididymis, which have been observed in hospitalized COVID-19 patients.<sup>27</sup> Erectile dysfunction is also more common among males following SARS-CoV-2 infection.<sup>66</sup> Due to a lack of data on COVID-19 symptoms or disease severity, we could not assess this hypothesis. Regardless, we did not observe any association between SARS-CoV-2 infection and fecundability that persisted beyond 60 days.

We adjusted for a broad range of sociodemographic, lifestyle, medical, occupational, and reproductive factors that could confound the association between COVID-19 vaccination or SARS-CoV-2 infection and fecundability. We adjusted for confounding using traditional regression modeling as well as propensity score stratification. As in any non-experimental study, uncontrolled confounding is possible.

Loss to follow-up was low in our cohort (82% completed at least one questionnaire, and of those, only 3% were subsequently lost to follow-up) and was similar by vaccination status. Therefore, it is unlikely that differential loss to follow-up was an important source of bias.



We relied on self-report to assess COVID-19 vaccination status, which may have resulted in some misclassification. In addition, for couples in which the male partner did not complete his questionnaire, we relied on female report of male vaccination status. We expect that any misclassification was infrequent and non-differential with respect to fecundability. Validation studies of influenza vaccination in the past year found 97% agreement between vaccination status based on self-report and medical records.<sup>67</sup> Because length of the recall interval was shorter for COVID-19 vaccination in this study and recipients received vaccination cards, we anticipate little exposure misclassification.

We assessed history of SARS-CoV-2 infection by asking participants if they had ever tested positive for SARS-CoV-2. We also relied on female report of male infection for nearly 75% of couples. Underestimation of the true incidence of SARS-CoV-2 infection is probable because most participants were likely not testing regularly throughout the follow-up period. Given the high specificity of antigen and PCR tests for SARS-CoV-2,<sup>68</sup> we anticipate that our exposure definition had very high specificity but potentially low sensitivity. If misclassification of SARS-CoV-2 infection was unrelated to fecundability, there should be minimal to no bias in relative measures of association.<sup>69</sup>

We calculated fecundability using self-reported information on LMP dates, typical menstrual cycle length, and pregnancy status. We also estimated LMP dates that occurred between follow-up questionnaires. To the extent that any of these variables were ascertained with error, outcome misclassification may have occurred. In previous work from this cohort, LMP dates

prospectively-reported on a menstrual charting app and retrospectively-reported on follow-up questionnaires were within 1 day for 93% of participants.<sup>41</sup> Because we did not have daily urinary measures of human chorionic gonadotropin, we likely missed some conceptions ending in early loss. However, 96% of the cohort used home pregnancy tests, and the median weeks' gestation at pregnancy detection was 4.0 (interquartile range: 3.7-4.4), indicating that participants are testing early for pregnancy.

Several features of PRESTO make it an ideal setting in which to assess the relation of COVID-19 vaccination and SARS-CoV-2 infection with fertility. Recruitment of couples trying to conceive without use of fertility treatment is challenging, given that individuals often do not publicize their intentions or interact with health care providers. Our study has successfully recruited couples during preconception using advertising on social media, with internet-based data collection and follow-up.<sup>41</sup> Our internet-based methods allowed us to continue enrolling couples throughout the COVID-19 pandemic, as participation required no face-to-face interaction with study staff. We prospectively followed couples every two months and collected time-varying data on COVID-19 vaccination and SARS-CoV-2 infection. Finally, our cohort is more geographically and socioeconomically diverse than most other preconception cohorts<sup>70</sup> and represents the largest study on these associations to date.

Our study was limited to pregnancy planners enrolled through the internet. Although both pregnancy planning status and internet access are related to sociodemographic characteristics such as income and education, we do not expect our associations to vary by these characteristics.

Thus, these results may generalize to the broader population of pregnancy planners in North America.

In summary, we found no adverse association between COVID-19 vaccination and fertility and a short-term decrease in fertility after male partner SARS-CoV-2 infection. These results can be used to guide informed decision-making around COVID-19 vaccination among reproductive-aged individuals, particularly those who are trying to conceive now or in the future.

ORIGINAL UNEDITED MANUSCRIPT

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Table 1. Distribution of female baseline characteristics by COVID-19 vaccination status and history of infection with SARS-CoV-2,<sup>a</sup> Pregnancy Study Online, December 2020–November 2021.

Characteristic	COVID-19 Vaccination				SARS-CoV-2 Infection			
	No (n=897)		Yes (n=1,229)		No (n=1,963)		Yes (n=163)	
	%	Mean	%	Mean	%	Mean	%	Mean
Age (years)		30.2		31.2		30.8		30.5
Attempt time at study entry (cycles)		2.2		1.8		2.0		1.9
Educational attainment (years)								
≤12	5.6		1.4		3.2		4.0	
13-15	20.1		8.8		13.5		14.1	
16	33.2		31.4		32.3		29.1	
≥17	41.2		58.5		51.0		52.8	
Household income (USD/year)								
<\$50,000	17.0		9.1		12.5		13.0	
\$50,000-\$99,999	35.4		27.9		30.3		37.1	
\$100,000-\$149,999	26.9		30.6		29.3		23.1	
≥\$150,000	20.7		32.4		27.9		26.8	
Race/ethnicity								
Hispanic	7.4		6.8		6.7		8.8	
Non-Hispanic white	83.5		85.6		84.9		83.1	
Non-Hispanic Black	4.0		1.8		2.6		4.9	
Non-Hispanic Asian	2.8		3.0		3.1		1.4	
Non-Hispanic mixed/other race	2.3		2.8		2.8		1.8	
Geographic region of residence								
Northeastern U.S.	14.5		18.3		16.5		18.5	
Southern U.S.	25.2		23.0		23.5		28.9	
Midwestern U.S.	19.6		21.7		20.3		27.9	
Western U.S.	15.4		21.4		18.7		20.4	
Canada	25.3		15.7		20.9		4.3	
Current smoker	5.3		3.2		4.1		3.8	
Received ≥1 dose of COVID-19 vaccine					57.8		57.8	
Ever tested positive for SARS-CoV-2	7.7		7.8					

Partner received $\geq 1$ dose of COVID-19 vaccine	8.7	77.7	56.5	61.0	
Partner ever tested positive for SARS-CoV-2	8.2	8.9	4.1	62.0	
Private health insurance	81.1	89.9	85.4	93.3	
Work duration (hours/week)		31.5	36.1	34.0	35.7
Rotating shift work	11.0	13.3	12.3	13.4	
Night shift work	10.2	11.6	11.1	10.5	
Occupation in health care industry <sup>b</sup>	16.8	30.4	24.2	34.3	
Body mass index <sup>c</sup>					
<25	43.8	48.5	46.5	46.1	
25-29	24.6	23.5	24.2	20.9	
$\geq 30$	31.6	28.0	29.3	33.1	
Intercourse <1 time/week	24.1	28.0	26.4	24.7	
Intercourse $\geq 4$ times/week	14.7	8.6	11.1	12.2	
Doing something to improve chances of conception	86.4	81.7	84.0	81.9	
Sleep duration <6 hours/night	4.5	4.0	4.2	4.7	
Perceived Stress Scale-10 score		17.4	16.1	16.7	16.7
Major Depression Inventory score		12.7	11.1	11.7	11.9
Pap smear in past three years	89.7	91.9	91.3	87.5	
History of infertility	11.4	6.5	8.6	10.5	
Parous	40.9	33.6	37.2	30.4	
Irregular menstrual cycles	16.3	12.6	14.3	14.9	
Typical menstrual cycle length (days)		30.3	29.9	30.0	30.7
Hormonal last method of contraception, %	29.2	29.8	29.4	32.6	

COVID-19=coronavirus disease 2019; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; USD=United States dollars

<sup>a</sup> Vaccination status defined by at least one dose of vaccine by the LMP date of the final observed cycle. Infection history defined as self-report of testing positive for SARS-CoV-2 by the LMP date of the final observed cycle.

<sup>b</sup> Occupation in health care industry defined based on United States Census Industry codes 8190 (Hospitals), 8180 (Other health care services), 8170 (Home health care services), 8080 (Offices of other health practitioners), 8070 (Offices of optometrists), 8090 (Outpatient care centers), 8270 (Nursing care facilities), 8290 (Residential care facilities, without nurses), 7970 (Offices of physicians) and 7980 (Offices of dentists).

<sup>c</sup> Weight (kg)/height (m)<sup>2</sup>

Table 2. Association between COVID-19 vaccination, SARS-CoV-2 infection, and fecundability,<sup>a</sup> Pregnancy Study Online, December 2020–November 2021.

Exposure	No. of cycles	No. of pregnancies	Unadjusted		Adjusted <sup>b</sup>		Adjusted <sup>c</sup>		
			FR	95% CI	FR	95% CI	FR	95% CI	
Female COVID-19 vaccination status									
Unvaccinated	2,844	539	1.00	Referent	1.00	Referent	1.00	Referent	
First dose	3,675	676	1.06	0.95, 1.18	1.08	0.95, 1.23	1.09	0.92, 1.30	
Second dose <sup>d</sup>	3,144	565	1.05	0.94, 1.17	1.07	0.93, 1.23	1.13	0.93, 1.39	
Female SARS-CoV-2 infection <sup>e</sup>									
Never	6,063	85	1.00	Referent	1.00	Referent	1.00	Referent	
Ever	456	1,130	0.99	0.81, 1.22	1.07	0.87, 1.31	0.99	0.80, 1.23	
Male COVID-19 vaccination status									
Unvaccinated	2,418	432	1.00	Referent	1.00	Referent	1.00	Referent	
First dose	2,486	408	0.98	0.86, 1.11	0.95	0.83, 1.10	1.05	0.87, 1.25	
Second dose <sup>d</sup>	2,140	352	0.99	0.87, 1.13	1.00	0.86, 1.17	0.95	0.78, 1.15	
Male SARS-CoV-2 infection <sup>e</sup>									
Never	5,977	1,112	1.00	Referent	1.00	Referent	1.00	Referent	
Ever	542	103	1.03	0.85, 1.24	1.07	0.88, 1.31	1.06	0.84, 1.34	

CI=confidence interval; COVID-19=coronavirus disease 2019; FR=fecundability ratio; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2;

<sup>a</sup> Fecundability is the per-cycle probability of conception. FRs >1 indicate an exposure associated with improved fecundability (or shorter time-to-pregnancy), whereas FRs <1 indicate an exposure associated with reduced fecundability (or longer time-to-pregnancy).

<sup>b</sup> Adjusted for female age, educational attainment, household income, current smoker, private health insurance, hours/week of work, rotating shift work, night shift work, body mass index, intercourse frequency, doing something to improve chances of conception, sleep duration, Perceived Stress Scale score, Major Depression Inventory score, Pap smear in past three years, history of infertility, parity, irregular menstrual cycles, menstrual cycle length, geographic region of residence, last method of contraception, occupation in health care industry, race/ethnicity, and days since 12/14/2020. Analysis of COVID-19 vaccination status was adjusted for ever having tested positive for SARS-CoV-2 and analysis of SARS-CoV-2 infection was adjusted for COVID-19 vaccination.

<sup>c</sup> Propensity scores were developed to predict the odds of vaccination (see Appendix). We adjusted for propensity score using fine stratification weighting and calculated the Mantel-Haenszel summary FR

<sup>d</sup> Individuals included in “second dose” are also included in “first dose.” Those who received the Johnson & Johnson vaccine are included in the sample of “first dose” and “second dose”.

<sup>e</sup> SARS-CoV-2 infection defined as self-report of ever testing positive for SARS-CoV-2.

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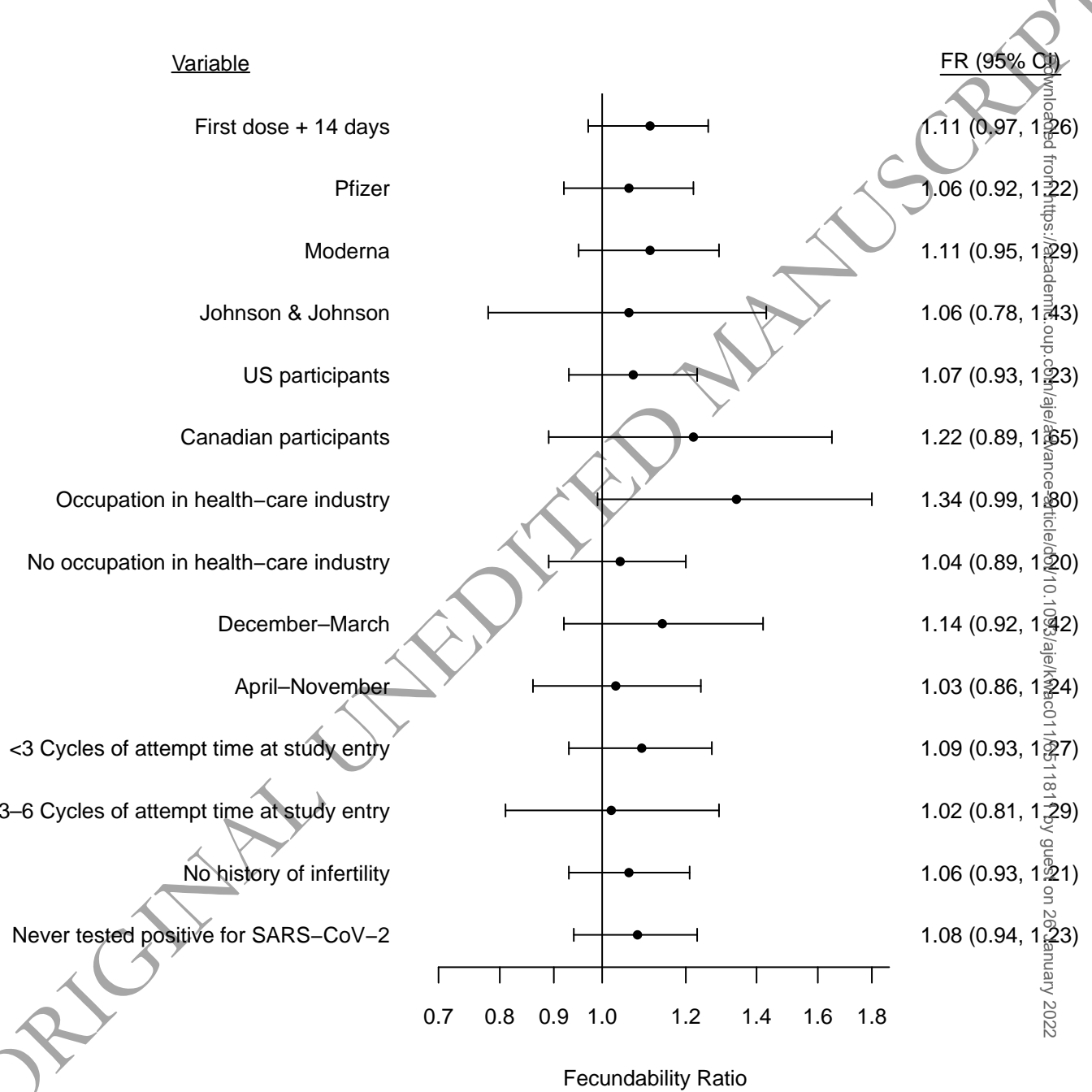
Figure 1. Association between female partner receipt of COVID-19 vaccine by first day of menses and fecundability, stratified by selected variables, Pregnancy Study Online, December 2020–November 2021. The reference group comprises individuals who were unvaccinated as of the first day of menses. Estimates are adjusted for age, educational attainment, household income, current smoker, private health insurance, hours/week of work, rotating shift work, night shift work, body mass index, intercourse frequency, doing something to improve chances of conception, sleep duration, Perceived Stress Scale score, Major Depression Inventory score, Pap smear in past three years, history of infertility, parity, irregular menstrual cycles, menstrual cycle length, geographic region of residence, last method of contraception, occupation in health care industry, race/ethnicity, days since 12/14/2020, and ever tested positive for SARS-CoV-2. The x-axis is plotted on the natural log-scale. CI=confidence interval; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2

Figure 2. Association between male partner receipt of COVID-19 vaccine by first day of menses of the female partner and fecundability, stratified by selected variables, Pregnancy Study Online, December 2020–November 2021. The reference group comprises individuals who were unvaccinated as of the first day of menses of the female partner. Estimates are adjusted for age, educational attainment, household income, current smoker, private health insurance, hours/week of work, rotating shift work, night shift work, body mass index, intercourse frequency, doing something to improve chances of conception, sleep duration, Perceived Stress Scale score, Major Depression Inventory score, Pap smear in past three years, history of infertility, parity, irregular menstrual cycles, menstrual cycle length, geographic region of residence, last method of contraception, occupation in health care industry, race/ethnicity, days since 12/14/2020, and ever tested positive for SARS-CoV-2. The x-axis is plotted on the natural log-scale. CI=confidence interval; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2

Figure 3. Association between time since female (left) and male (right) partner COVID-19 vaccination and fecundability, fit using restricted cubic splines, Pregnancy Study Online, December 2020–November 2021. The black solid line represents the fecundability ratio, the gray shaded area represents the 95% confidence band, and the black dotted line represents the reference fecundability ratio of 1.0. The splines have knots at 30, 60, 90, and 120 days. The reference group comprises unvaccinated individuals and individuals who were vaccinated at least 180 days ago. Splines are adjusted for age, educational attainment, household income, current smoker, private health insurance, hours/week of work, rotating shift work, night shift work, body mass index, intercourse frequency, doing something to improve chances of conception, sleep duration, Perceived Stress Scale score, Major Depression Inventory score, Pap smear in past three years, history of infertility, parity, irregular menstrual cycles, menstrual cycle length, geographic region of residence, last method of contraception, occupation in health care industry, race/ethnicity, days since 12/14/2020, and ever tested positive for SARS-CoV-2.

Figure 4. Association between time since female (left) and male (right) partner SARS-CoV-2 infection and fecundability, fit using restricted cubic splines, Pregnancy Study Online, December 2020-November 2021. The black solid line represents the fecundability ratio, the gray shaded area represents the 95% confidence band, and the black dotted line represents the reference fecundability ratio of 1.0. The splines have knots at 30, 60, 90, and 120 days. The reference group comprises individuals who have never tested positive for SARS-CoV-2 and who tested positive at least 180 days ago. Splines are adjusted for age, educational attainment, household income, current smoker, private health insurance, hours/week of work, rotating shift work, night shift work, body mass index, intercourse frequency, doing something to improve chances of conception, sleep duration, Perceived Stress Scale score, Major Depression Inventory score, Pap smear in past three years, history of infertility, parity, irregular menstrual cycles, menstrual cycle length, geographic region of residence, last method of contraception, occupation in health care industry, race/ethnicity, days since 12/14/2020, and received COVID-19 vaccination.

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Variable

FR (95% CI)

First dose + 14 days

0.99 (0.86, 1.15)

Pfizer

1.00 (0.84, 1.17)

Moderna

0.97 (0.80, 1.17)

Johnson & Johnson

1.02 (0.73, 1.44)

US participants

0.97 (0.84, 1.12)

Canadian participants

1.09 (0.74, 1.62)

December–March

1.23 (0.91, 1.67)

April–November

0.98 (0.83, 1.14)

<3 Cycles of attempt time at study entry

1.02 (0.87, 1.20)

3–6 Cycles of attempt time at study entry

0.86 (0.61, 1.22)

No history of infertility

0.96 (0.83, 1.12)

Never tested positive for SARS–CoV–2

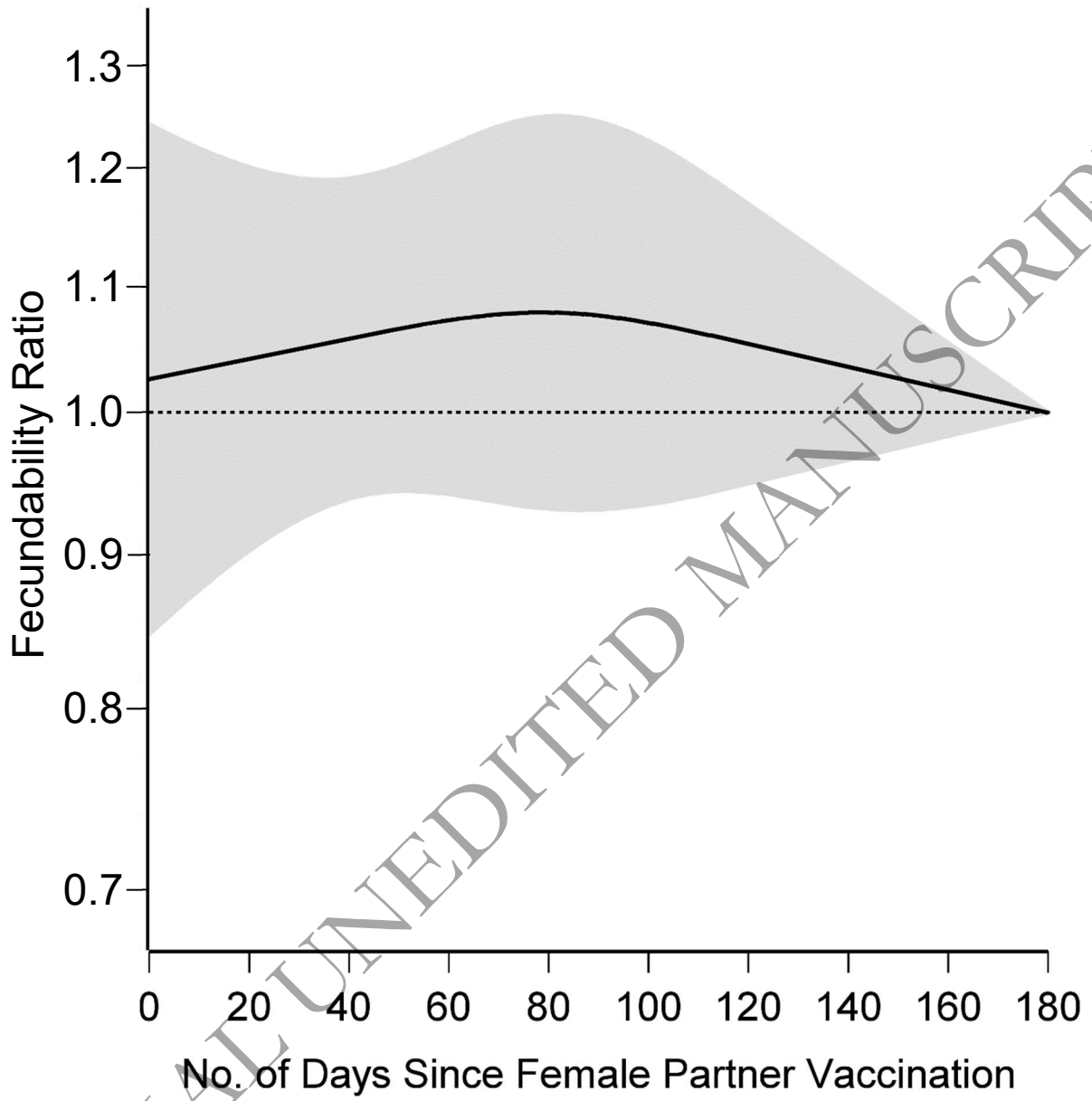
0.97 (0.83, 1.13)

0.6 0.7 0.8 0.9 1.0 1.2 1.4 1.6 1.8

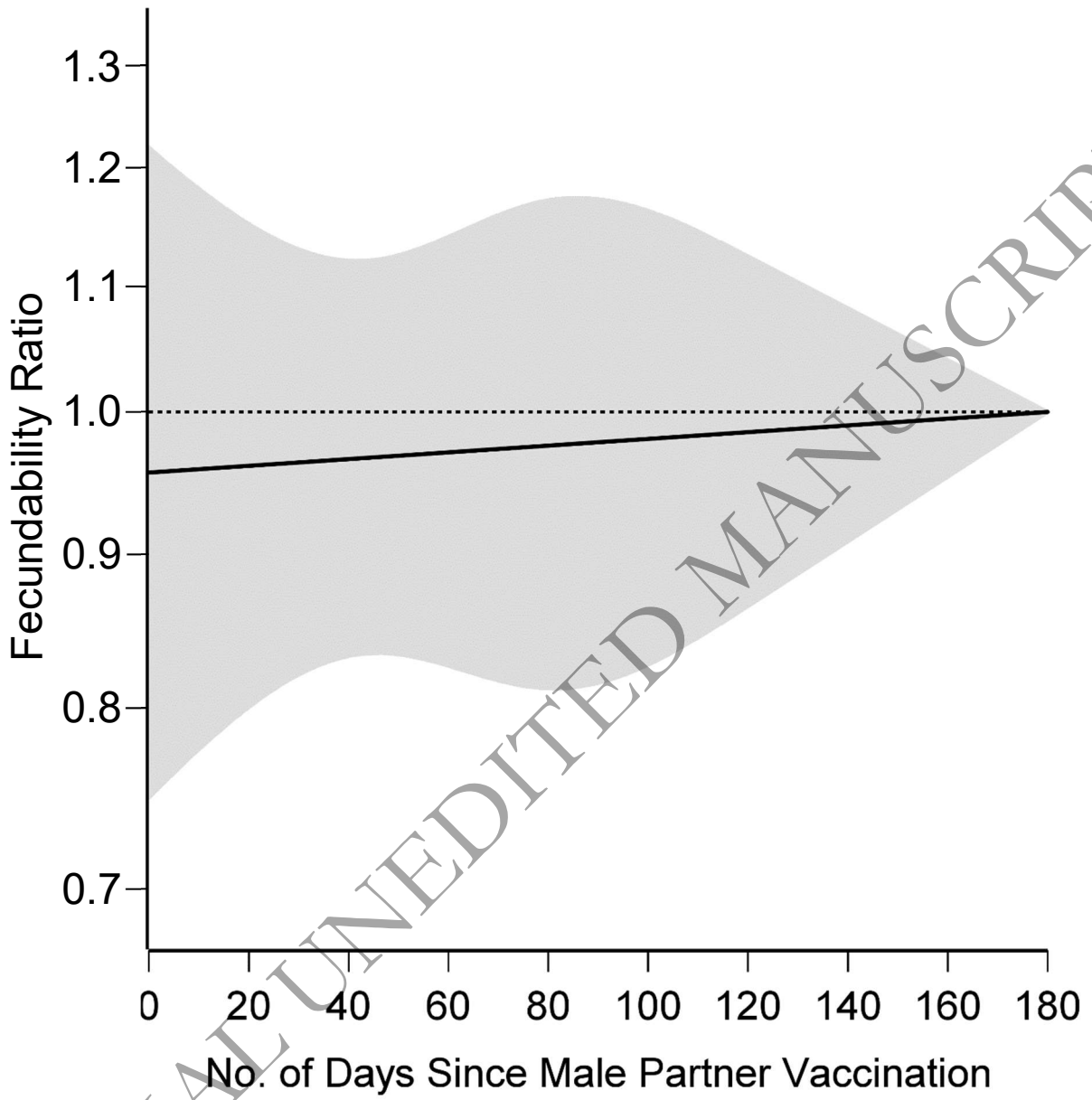
Fecundability Ratio

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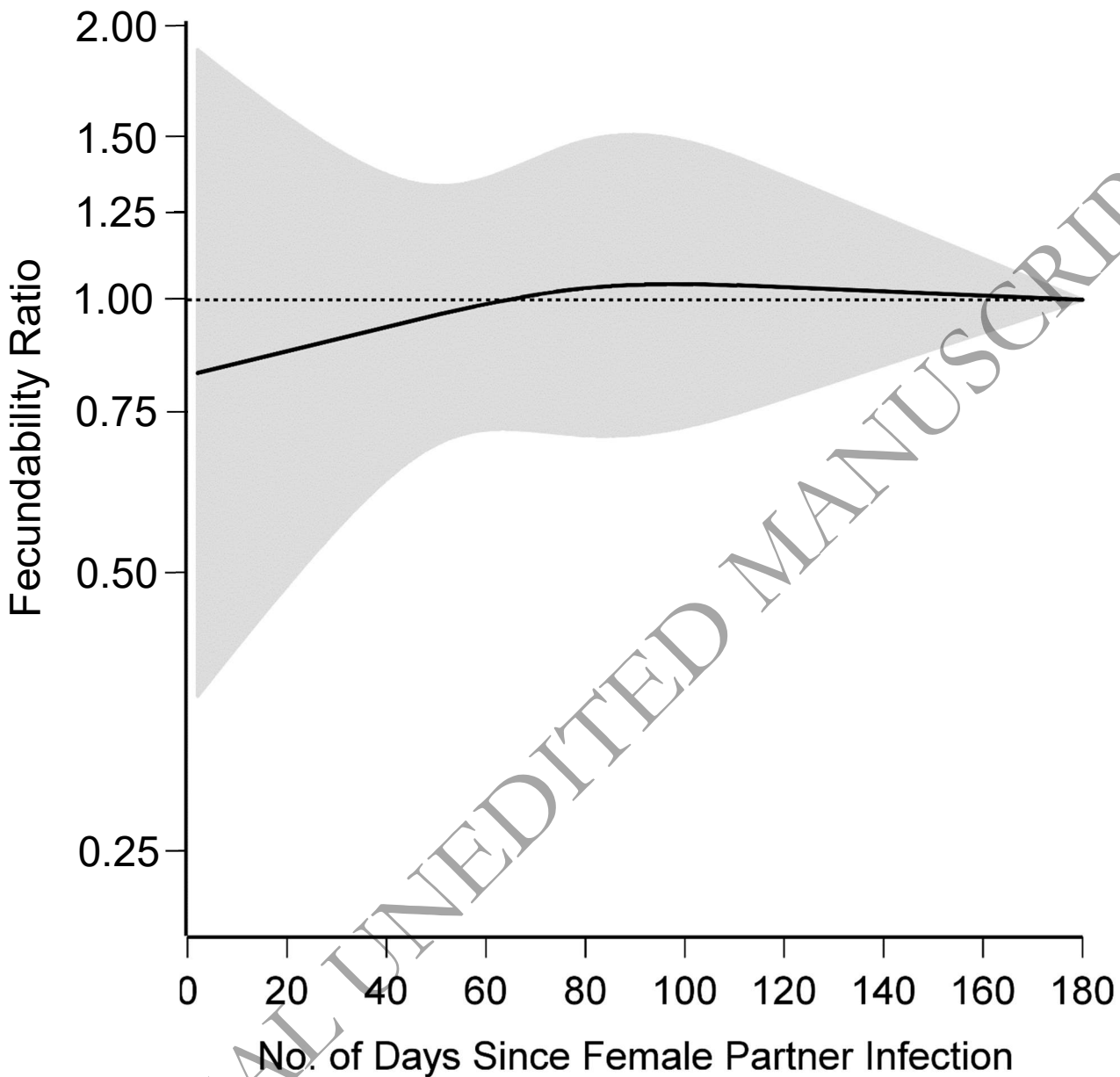




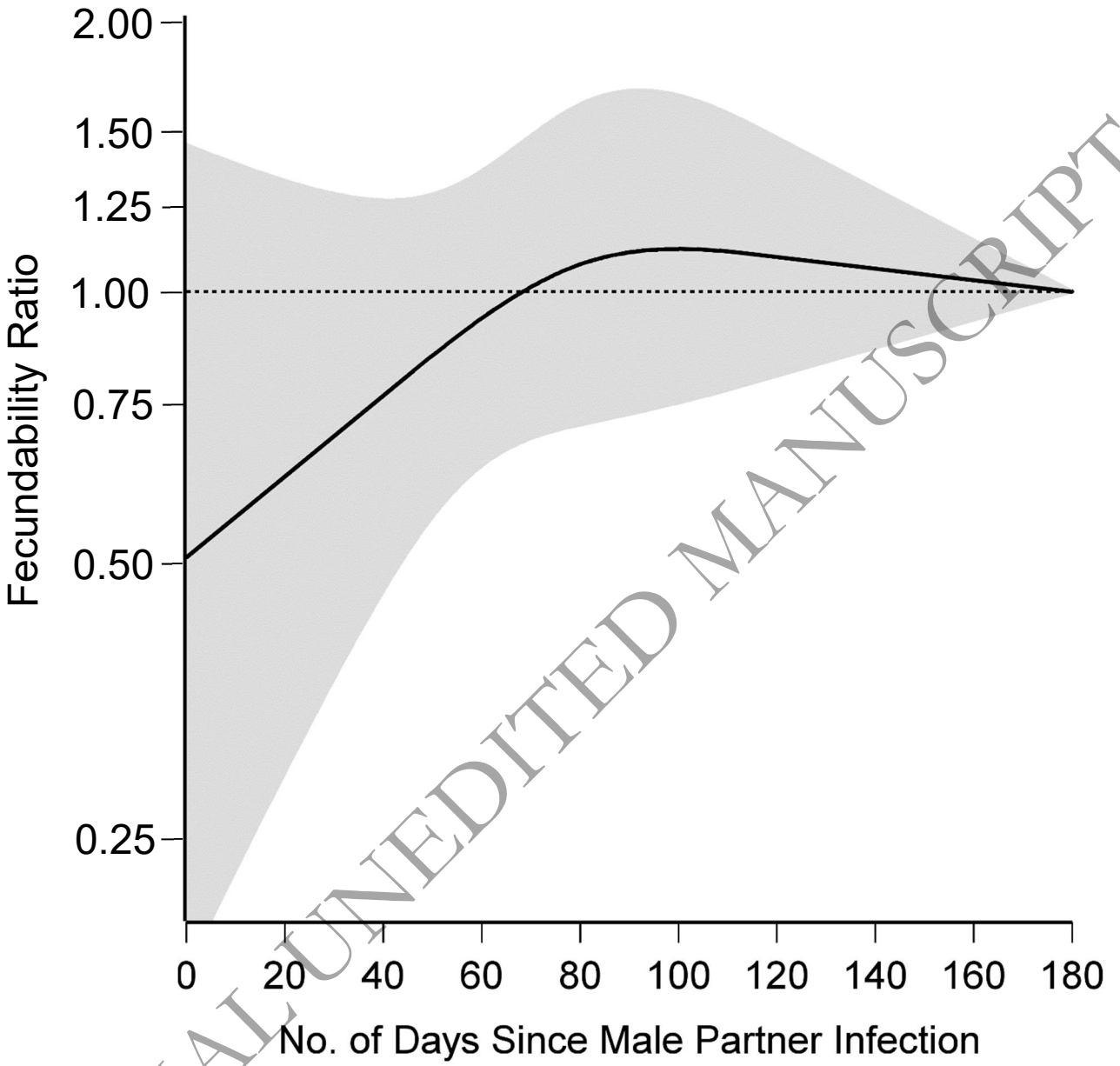
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