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Title: Infertility treatment and new-onset maternal mental illness: population-based cohort study
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Reviewer 1
General comments (author response in bold)

This is an excellent paper on a very important topic Post partum mental health disorders are one of the most serious in the psychiatric population and early identification of patients at risk is very important. This paper is very well done looking at a large cohort of women and identifying the risks to post partum mental health disorders associated with subfertility . The strengths and limitations of using administrative health data are well discussed.
We thank the reviewer for this positive review.

Reviewer 2: John Fahey
Institution: Reproductive Care Program of Nova Scotia, Nova Scotia Department of Health and Wellness
General comments (author response in bold)

Merely assembling the dataset must have been a substantial undertaking and doing so deserves our thanks. The process of drawing valid and interesting conclusions from it was undertaken with care and vigour so I do not have a myriad of suggested improvements. Those I do have are simply enumerated below:

1) At the very least, a sentence or two of discussion could be addressed to the possibility of a temporal trend in infertility, diagnoses of mental health disorders (particularly the outpatient ones that constitute the bulk of your findings), or, as I suspect, both. Ideally, a table or quick trend analysis would also be included.
We have now generated two figures: one demonstrating annual rates of subfertility and infertility treatments per year, along with the proportion of spontaneously conceived births; and a figure plotting outpatient and severe mental health outcomes over time, according to fertility status. While the proportion who use of infertility treatment increased slightly over time, mental health outcomes remained overall constant with little variability between groups, other than a trend towards reduced mental illness in the group with subfertility but no treatment. These figures are in the Appendix and mentioned in the Results section, pages 8-9.

2) More attention should be paid in your discussion to the fact that the results from the severe-illness subgroup are inconclusive at best and occasionally contradictory to your main findings.
It is correct that in our analyses of severe mental health outcomes, absolute rates of severe mental health outcomes were slightly higher among the spontaneous group, however the direction of the effect changed after adjustment, suggesting the presence of negative or reverse confounding. The same pattern was true when evaluating only outpatient mental health outcomes.

This is elaborated in Interpretation page 11 onward: "IVF, typically characterized by repeated rounds of high dose ovarian stimulation and intense hormonal fluctuations, has been postulated to contribute to increased peripartum mood disorders,[26] although not consistently so.[27] One prior systematic review found that women who use IVF are not at higher risk of postpartum depression except those with multiple gestation.[27] The authors of this review noted that the sample sizes of included studies were small and did not use appropriate comparison groups, indicating the need for more rigorous investigation into this topic. IVF-treated individuals in our cohort experienced a low absolute rate of postpartum mental illness; in particular they experienced the lowest rate of severe mental illness requiring hospitalization or ED visit when compared with other exposure groups. In contrast, adjusted analyses demonstrate that IVF-treated people experience higher relative risk of a composite postpartum mental illness when compared with spontaneous births, indicating the presence of "reverse confounding". In our cohort, IVF-treated women were socially advantaged, resided in higher income neighborhoods, and thus able to afford the cost of IVF therapy.[16,17] Second, IVF necessitates closer medical follow-up, and in some cases, more intense screening for "readiness" for pregnancy, including both physical and mental health fitness.[29] Therefore, after adjustment for maternal age and social determinants of health, there may exist an underlying predisposition towards adverse postpartum mental health – mostly mood and anxiety disorders identified in the outpatient setting – among recipients of IVF."

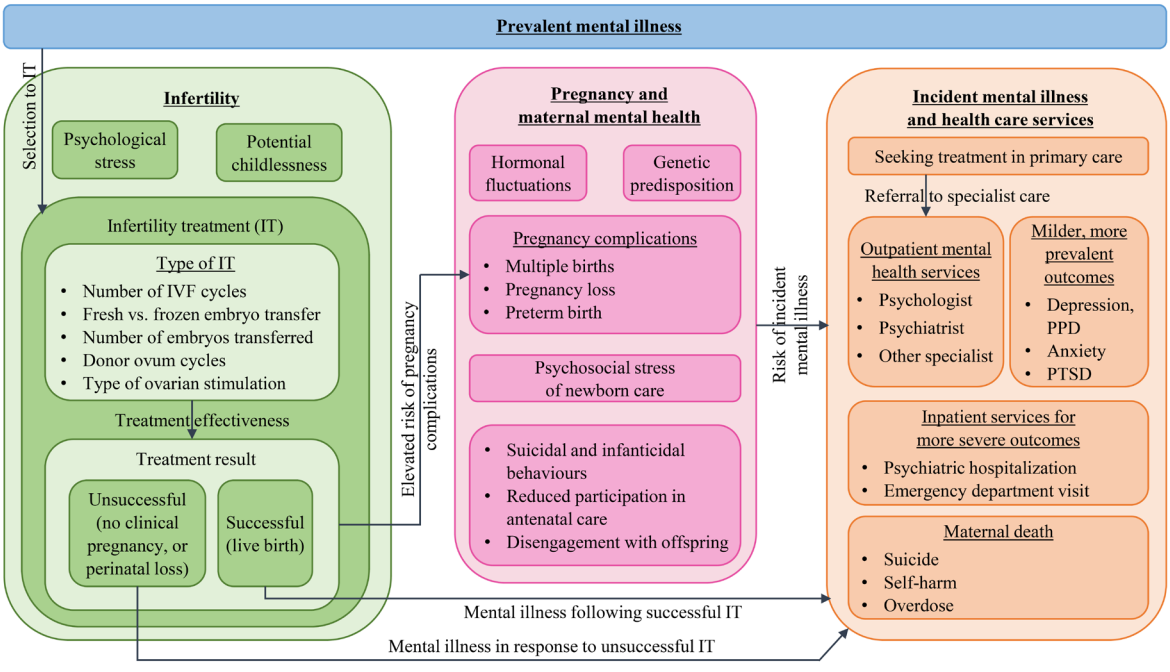
3) Additionally, consideration should also be made for the possibility that those women who are at higher risk for infertility, a priori, are also at higher risk of a mental health diagnosis.
Indeed, reproductive conditions that are associated with infertility (i.e., Polycystic Ovary Syndrome (PCOS), and endometriosis) have been previously associated with mental illness. This is mentioned in Interpretation page 12-13 "IUI-assisted conception is often required among women with polycystic ovarian syndrome,[33] and 15% of women in the non-invasive infertility group were obese. Both obesity and polycystic ovarian syndrome are independent risk factors for mood and anxiety disorders.[34]
We chose to remove persons with prior mental illness from our main analysis, which includes individuals with PCOS and endometriosis. Furthermore, our aim was to globally assess for any association between subfertility and infertility treatment, regardless of reason for treatment. Therefore we don't see this as introducing bias, and our interpretation indicates only that being subfertile or having infertility treatment might identify persons at risk for significant postpartum mental illness. We did not claim to know the mechanism of this association with our data.

4) The exacerbation results are equally important, I would argue, though not always consistent with the main findings. The truth is often messy and the reader is done a disservice by glossing over this fact. Another sentence or two of discussion is merited at the very least.
We agree with the reviewer that exacerbations are important. The aRRs for our composite outcome (1.10) were not materially different than our main results (1.13), and were also affected by "reverse confounding." We have added the following to the Interpretation, page 11 "The magnitude of associations between

infertility treatment and any exacerbation was similar to that found for de novo events in adjusted analyses, however infertility and its treatment seemed to protect against severe mental illness in these individuals." and page 13 "Among people with pre-existing mental health conditions, the fact that exacerbations of severe mental illness was lower in subfertile groups suggests the possibility that at least part of the stress of infertility is alleviated by being pregnant. Indeed some reports have indicated greater feelings of "hopefulness" when infertile individuals initiate treatment[35]."

5) While I applaud your having eschewed p-values, the multitude of confidence intervals similarly give rise to the issue of multiple comparisons. If you've chosen to ignore that issue, remind the reader of its existence so they can come to their own conclusion on how it might impact how they interpret your results.
To our knowledge, Bonferroni or similar statistical techniques to adjust for multiple comparisons apply to the use of p-values and typically in the field of genetics when numerous pairwise comparisons are being made, which was not the case in our study. We specifically use confidence intervals for any finding in order to provide the greatest transparency about the uncertainty surrounding each estimate.

6) You separate effect modifiers and confounders in your analysis. An eFigure including a DAG would be very helpful in the exposition of which is which and why.
We used substantive knowledge to develop our models. Our general conceptual framework is provided below. We will allow the editor to decide if this should be published as part of the supplement.



IT, infertility treatment; PPD, postpartum depression; PTSD, posttraumatic stress disorder

7) While arguably outside the scope of this paper, I cannot help but think that modest additional effort might have allowed you to include age/SES matched controls of non-

pregnant women, allowing exploration of another whole set of even more-interesting questions.
We agree that comparison with non-pregnant population is outside the scope of this paper. Our objective was to evaluate the role of mode of conception on new onset maternal mental illness.

8) DBF's contribution to authorship is included twice. On page 16, line 28, I'd replace "costs" by "cost".
These typographical errors have been corrected.