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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: 12/05/2022
To: "Kevin Young Xu" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1863

RE: Manuscript Number ONG-22-1863

Pregnant versus Non-Pregnant Reproductive-Age Women with Opioid Use Disorder: A Comparison of Medication Initiation and Treatment Discontinuation

Dear Dr. Xu:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 12/27/2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* Figures 1-3: Please submit the current figure files as-is unless changes have been requested by the Statistical Editor.

REVIEWER COMMENTS:

Reviewer #1: The authors are to be commended at reviewing the association of pregnancy with MOUD initiation and continuation, when compared with non-pregnant individuals. I have a few comments regarding the piece:

- Throughout the text, please use gender-inclusive language (e.g., "pregnant person" instead of "pregnant woman")

METHODS
- line 65 - While the authors do note the time period, it occurs to me that multiple states (e.g., Alabama, Tennessee) were not providing MOUD, especially during the same period in which these states were forcibly incarcerating pregnant people with OUD and having them undergo detoxification (see https://www.amnesty.org/en/documents/amr51/6203/2017/en/ and https://pubmed.ncbi.nlm.nih.gov/26996987/). I'm curious if the authors were able to exclude these sites from analysis, as these areas are known to be some of the hardest hit by the opioid epidemic.

- line 95 - Given the prerequisite for medical coverage for 6 months prior to the treatment episode, I am concerned about the overall generalizability of the data, given the association of OUD with low SES and poor insurance coverage

(https://jamanetwork.com/journals/jama/fullarticle/2722771 and https://pubmed.ncbi.nlm.nih.gov/35123114/). Can the authors specify that these data are limited by the inclusion criteria, namely continuous insurance coverage 6 months prior to the treatment episode?

- line 126 - the limitation of race/ethnicity data to those only insured by a government payor is a notable limitation in the data, as recent CDC data demonstrate that while non-Hispanic White individuals still constitute the majority of OUD-related deaths in the U.S., the rate of deaths associated with OUD have sharply increased among non-Hispanic Black people (https://www.cdc.gov/media/releases/2022/s0719-overdose-rates-vs.html)

- lines 136-7- if self-reported race is dependent upon insurance payor in the dataset, shouldn't the regression analysis adjust for an interaction factor constituted by race and insurance payor? The same could be said about co-occurring SUDs and comorbid psychiatric conditions, as those tend to be associated with one another. Not sure if the authors performed an interaction analysis before creating the regression model, but would want to ensure that these covariates are not treated as if they are wholly independent from one another.

RESULTS
- lines 170-2 - I'm struck by the relatively high proportion of non-MOUD use and, when MOUD is employed, buprenorphine. The former finding is concerning, especially given the recommendations for universal initiation of MOUD during pregnancy - acknowledging the historical timeframe in which the authors are evaluating initiation. The logistical difficulties of an X-waiver, replete with case load caps, have been demonstrated in the literature for pregnant (https://pubmed.ncbi.nlm.nih.gov/33345932/) and non-pregnant people (https://pubmed.ncbi.nlm.nih.gov/23702611/); furthermore, the latter study notes the association of certain forms of MOUD with race and SES, which has been replicated in qualitative data surrounding management of OUD (e.g., https://anthrosource.onlinelibrary.wiley.com/doi/abs/10.1111/j.2153-9588.2012.01098.x). The extant literature and the findings presented in this paper need to be reconciled with one another, as I'm a bit concerned about the overall generalizability of the data. Furthermore, the authors do not account for prioritization of treatment access for pregnant people by state - even though prioritization of treatment and criminalization of substance use during pregnancy tend to go hand in hand (https://www.sciencedirect.com/science/article/abs/pii/S1049386722001086#!). If possible, I would want to interrogate these findings further to see if there is a geospatial relationship between receipt of MOUD (Y/N) and subtype of MOUD (methadone v. buprenorphine-containing compound), as location of residence may be a mediator.

- line 180 - it's unclear in the methods section that the authors are creating multiple models for analysis. Please clarify this before presenting the data.

- line 201 - in the methods, the authors state that they are going to generate "mortality ratios", but present the data as hazard ratios. Though used interchangeably with survival analyses, the terminology will confuse a reader not savvy with these methodologies. Please update the methods to state that hazard ratios were generated.

CONCLUSION
- line 211 - While behavioral change and health systems resources are part of the picture, it would be remiss to not acknowledge the punitive legal landscape for pregnant people who use substances. Treatment during pregnancy can reduce the likelihood for termination of parental custody in states where substance use during pregnancy is criminalized or seen as a form of chemical endangerment. See, for example, https://pubmed.ncbi.nlm.nih.gov/31055757/ and https://onlinelibrary.wiley.com/doi/pdf/10.1002/hec.4518. Furthermore, the authors were conducting their analyses during time points in which pregnant women were actively being incarcerated for SUD during pregnancy (see previously cited Amnesty International documents). Therefore, this is a critical contextual factor and one that bears on any discussion of limitations of the study.

- line 217 - the authors should cite Hendree et al N Eng J Med 2010 for rates of discontinuation for buprenorphine, which were noted to be higher when compared to methadone (https://pubmed.ncbi.nlm.nih.gov/21142534/)

- line 231 - would also add to the list incarceration, especially given the relationship between carcerality, pregnancy, and access (or lack thereof) to treatment options. See https://www.ucpress.edu/book/9780520293212/getting-wrecked and https://www.ucpress.edu/book/9780520288683/jailcare

Reviewer #2:

Obstetrics and Gynecology
Manuscript #ONG-22-1863

"Pregnant versus non-pregnant reproductive-age women with opioid use disorder: a comparison of medication initiation and treatment discontinuation"

General:

This manuscript describes a retrospective cohort study of pregnant and non-pregnant patients initiated on medical therapy for opioid use disorder (MOUD), with comparison of time from initiation to discontinuation based on pharmacy prescriptions.

1. The primary finding of the article is that patients who initiate MOUD during pregnancy have a longer duration of continuation, with the inference is that MOUD s self-discontinued; however, do the authors have any data regarding discontinuation as per formal medical directive (i.e. ("treatment completion")?

2. The definition of pregnancy status is not clearly stated: was this "enrolled in prenatal care" within the most recent 210 days or actual deliveries? Lines 105-106 reference using delivery date to extrapolate conception timing?

3. Patients who initiated therapy in the third trimester were excluded from analysis; could the authors clarify the rationale for this decision?

4. Were the authors able to identify "initial MOUD treatment" versus "previous MOUD treatment" from the data set? (i.e., for how many patients did this represent true first MOUD exposure?)

5. Did any patients transition from psychosocial therapy to MOUD during the study interval?

6. In pregnant patients who discontinued MOUD therapy, how often did this occur antepartum versus postpartum?

7. Do the authors have any data regarding lactation rates?

Reviewer #3: The paper is a retrospective cohort study in the IBM MarketScan Databases examining the association of pregnant status with treatment initiation and discontinuation of medication for opioid use disorder (MOUD). While there are multiple published studies supporting improvements in pregnancy outcomes with MOUD, which has now become the standard of care, there are few studies examining who is receiving such therapy and treatment retention/discontinuation rates. The key finding of this paper is that pregnant status was significantly associated with increased MOUD initiation and improved retention in the indicated population. The paper concisely addresses a timely topic, with both its strengths and weaknesses clearly delineated in the discussion. Please consider the following comments:

1. While the requirement of six months of pharmacy and medical coverage is logical for statistical analysis (line 95), how does it alter real life interpretations and implications of the data? Can this six month requirement/limitation be elaborated upon in the discussion further than is briefly mentioned (line 233, 236)?

2. Significant attention was given to the differences between usage of methadone, buprenorphine alone, and combination product by pregnant and non-pregnant people. These results were not significantly touched on later in the paper. Consider discussing the findings or indicating that there is nothing worth noting to discuss, given that the data was presented in such a way as to anticipate significant discussion.

3. Lines 216 and 244 indicate "systems" and "structures" that contribute to discontinuation of MOUD, but these are not appreciably discussed in the paper. While one strength of the paper is how succinct it is, greater weight could be given to the argument regarding the poor state of the healthcare system (patients not getting standard of care) and the insidious tenacity of treatment discontinuation if more detail was given to these ideas.

STATISTICAL EDITOR COMMENTS:

Table 1: Should statistically compare the two cohorts, they appear to be statistically different in several characteristics.

Fig 2: Should include a column of unadjusted ORs for contrast with the aORs. Also, since Medicaid enrollees comprised ~ 2/3 of all participants, it is no surprise that their aORs are statistically indistinguishable. Should also show results for non-medicaid participants (pregnant vs non-pregnant) for buprenorphine and methadone initiation.

Fig 3: For both 3A and 3B, should include the counts for the N remaining in each group at the indication times along the x-axes. Should also indicate in Results the median (IQR) follow-up for each cohort in order to show the reader that censoring was equivalent for the two groups.

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Sincerely,

Jason D. Wright, MD
Editor-in-Chief

The Editors of Obstetrics & Gynecology

December 26, 2022

Dear Editors,

We are writing to resubmit our manuscript entitled " Pregnant versus Non-Pregnant Reproductive-Age People with Opioid Use Disorder: A Comparison of Medication Initiation and Treatment Discontinuation" to Obstetrics and Gynecology.

Attached is the updated manuscript, along with a detailed response letter. We thank the reviewer for their generous comments regarding our manuscript. We hope that you find our revisions satisfactory and the manuscript much improved.

Thank you in advance for evaluating this manuscript for publication in your journal.

RESPONSE TO REVIEWER COMMENTS
ONG-22-1863

Reviewer #1

1)	Comment:	The authors are to be commended at reviewing the association of pregnancy with MOUD initiation and continuation, when compared with non-pregnant individuals.
	Response:	We thank the reviewer for these generous comments.
2)	Comment:	Throughout the text, please use gender-inclusive language (e.g., "pregnant person" instead of "pregnant woman")
	Response:	We revised our manuscript to use the term “pregnant people” in lieu of “pregnant women.”
3)	Comment:	line 65 - While the authors do note the time period, it occurs to me that multiple states (e.g., Alabama, Tennessee) were not providing MOUD, especially during the same period in which these states were forcibly incarcerating pregnant people with OUD and having them undergo detoxification (see . I'm curious if the authors were able to exclude these sites from analysis, as these areas are known to be some of the hardest hit by the opioid epidemic.
	Response:	The reviewer raises an excellent point. There is substantial heterogeneity across states providing (and not providing) MOUD. Amid the ongoing overdose epidemic, research is needed to evaluate such heterogeneity. Unfortunately, the proprietary IBM MarketScan multi-state Medicaid claims data does not contain data at the state level. We have added additional description to our limitations that ***“Importantly, we are unable to address state-by-state heterogeneity in MOUD initiation, an important factor to consider given differential prioritization of treatment access for pregnancy (and criminalization of substance use during pregnancy) tends to vary by state (White et al. 2022).” (page 10 line 23)***
4)	Comment:	line 95 - Given the prerequisite for medical coverage for 6 months prior to the treatment episode, I am concerned about the overall generalizability of the data, given the association of OUD with low SES and poor insurance coverage (jamanetwork.com/journals/jama/fullarticle/2722771). Can the authors specify that these data are limited by the inclusion criteria, namely continuous insurance coverage 6 months prior to the treatment episode?
	Response:	The reviewer’s concern is an important one. This 6-month requirement was built into our data pull, and we are unfortunately unable to access people with shorter periods of insurance coverage. We have revised our limitations section to be more direct in noting this shortcoming of our methods: “***Given the association of OUD with low SES and poor insurance coverage (Patrick et al.), it is a significant limitation that we only*** **include people with 6 months of insurance coverage prior to MOUD initiation, excluding populations at especially high risk of poor OUD outcome” (page 11, line 8)**
5)	Comment:	line 126 - the limitation of race/ethnicity data to those only insured by a government payor is a notable limitation in the data, as recent CDC data demonstrate that while non-Hispanic White individuals still constitute the majority of OUD-related deaths in the U.S., the rate of deaths associated with OUD have sharply increased among non-Hispanic Black people (https://www.cdc.gov/media/releases/2022/s0719-overdose-rates-vs.html)
	Response:	This is an important comment that resonates with us. On re-read of the manuscript, we agree that we need to be more **direct** in emphasizing the limitation of race/ethnicity data only being available for those insured by government payor. In initial version of the manuscript that we submitted, this limitation was regrettably mentioned only in passing, and we believe this deserves more space in the revised draft. We have thus added the following: “***We are also limited by an absence of race/ethnicity data for commercial insurance claims and limited detail for race/ethnicity for Medicaid, which is an important limitation given sharply increasing rates of death among non-Hispanic Black people with OUD (CDC data 2022)…” (page 10, line 26)***
6)	Comment:	lines 136-7- if self-reported race is dependent upon insurance payor in the dataset, shouldn't the regression analysis adjust for an interaction factor constituted by race and insurance payor?
	Response:	We regret that our language was unclear with regards to the race and insurance data. What we intended to say was that racial data is **only** available among people who were Medicaid

		enrollees, whereas commercial insurance regretfully does not provide data on race/ethnicity. We have revised our eTables 3 and 4 in the Supplement (adding "***Excluding commercial enrollees, as race/ethnicity data is only available among Medicaid enrollees"),*** as well as Table 1 (***adding "among Medicaid enrollees" for the race label),*** to emphasize that the racial data is only among Medicaid enrollees, which was not made clear in our initial draft.
7)	Comment:	The same could be said about co-occurring SUDs and comorbid psychiatric conditions, as those tend to be associated with one another. Not sure if the authors performed an interaction analysis before creating the regression model, but would want to ensure that these covariates are not treated as if they are wholly independent from one another.
	Response:	We thank the reviewer for this point. We conducted collinearity diagnostics but regretfully did not indicate this in our methods. In our revised draft, we described in the methods that "***we computed variance inflation factors (VIF) to evaluate for multicollinearity, finding no significant collinearity among covariates using a highly conservative threshold of <2.0."*** **(page 6, line 17)**
8)	Comment:	- lines 170-2 - I'm struck by the relatively high proportion of non-MOUD use and, when MOUD is employed, buprenorphine. The former finding is concerning, especially given the recommendations for universal initiation of MOUD during pregnancy - acknowledging the historical timeframe in which the authors are evaluating initiation. The logistical difficulties of an X-waiver, replete with case load caps, have been demonstrated in the literature for pregnant (https://pubmed.ncbi.nlm.nih.gov/33345932/) and non-pregnant people); furthermore, the latter study notes the association of certain forms of MOUD with race and SES, which has been replicated in qualitative data surrounding management of OUD (e.g., https://pubmed.ncbi.nlm.nih.gov/23702611/). The extant literature and the findings presented in this paper need to be reconciled with one another, as I'm a bit concerned about the overall generalizability of the data.
	Response:	Our study provides the first multi-state estimate of MOUD initiation among reproductive-age women with OUD in the U.S., and we echo the reviewer's comments that the low MOUD initiation rates were surprising. One explanation for this may be substantial heterogeneity by state/region in terms of MOUD access in pregnant people, especially among people with public insurance. We agree that these estimates may not be generalizable to all communities in the U.S., and we have emphasized this limitation in our Discussion section. Existing studies have also found much heterogeneity in OTP and buprenorphine-waivered providers accepting Medicaid; for instance, per the Patrick et al. 2019, it was reported that OTPs accepting Medicaid range from a high of 88% in Massachusetts to a low of 8% in Tennessee. In summary, this topic area will need rigorous, multi-state studies – using datasets that allow us to categorize participants by state and region – in order to provide a more comprehensive picture of MOUD initiation/retention. We added description in our discussion: "our study also shows that in both pregnant and non-pregnant people with OUD, the majority of individuals do not receive the standard of care, MOUD, **which supports studies illustrating the myriad logistical barriers experienced by patients attempting to access MOUD such as case load caps, X-waiver logistical difficulties, prohibitive costs, geographic inaccessibility, and long wait times (Bedrick et al., 2020)**" **(page 10, line 2)** In the limitations, we also added a reference to Dr. Hansen and colleagues' seminal work on disparities in buprenorphine and methadone treatment by race: "**We are also limited by an absence of race/ethnicity data for commercial insurance claims and limited detail for race/ethnicity for Medicaid, which is an important limitation given sharply increasing rates of death among non-Hispanic Black people with OUD(** ***CDC data 2022*****) *and racial disparities in the type of MOUD received by patients.(Hansen et al. 2013)" (page 11, line 2)***
9)	Comment:	The authors do not account for prioritization of treatment access for pregnant people by state, even though prioritization of treatment and criminalization of substance use during pregnancy tend to go hand in hand (sciencedirect.com/science/article/pii/S1049386722001086). If possible, I would want to interrogate these findings further to see if there is a geospatial relationship between receipt of MOUD (Y/N) and subtype of MOUD (methadone v. buprenorphine-containing compound), as location of residence may be a mediator.
	Response:	This is an important point raised by the reviewer. We unfortunately do not have state-by-state data, and we acknowledged this in the limitations: ***"Importantly, we are unable to address***

		state-by-state heterogeneity in MOUD initiation, an important factor to consider given differential prioritization of treatment access for pregnancy (and criminalization of substance use during pregnancy) tends to vary by state (White et al. 2022)" (page 10, line 23)
10)	Comment:	line 180 - it's unclear in the methods section that the authors are creating multiple models for analysis. Please clarify this before presenting the data.
	Response:	We agree with the reviewer that it is unclear that we are creating multiple models and have edited the methods section to improve readability: "**In addition to multivariate models adjusting for insurance, age, and comorbidities, we estimated separate models among Medicaid enrollees adjusting for race, age, and comorbidities (as racial data was only available for Medicaid enrollees)." (page 6, line 25)**
11)	Comment:	line 201 - in the methods, the authors state that they are going to generate "mortality ratios", but present the data as hazard ratios. Though used interchangeably with survival analyses, the terminology will confuse a reader not savvy with these methodologies. Please update the methods to state that hazard ratios were generated.
	Response:	The reviewer's point is well taken, and we have updated the methods to state that hazard ratios were generated, not mortality ratios: "**with adjusted hazard ratios obtained after controlling for covariates and accounting for multiple episodes per person (page 6, line 23)**
12)	Comment:	- line 211 - While behavioral change and health systems resources are part of the picture, it would be remiss to not acknowledge the punitive legal landscape for pregnant people who use substances. Treatment during pregnancy can reduce the likelihood for termination of parental custody in states where substance use during pregnancy is criminalized or seen as a form of chemical endangerment. See, for example, https://pubmed.ncbi.nlm.nih.gov/31055757/ and https://onlinelibrary.wiley.com/doi/pdf/10.1002/hec.4518. Furthermore, the authors were conducting their analyses during time points in which pregnant women were actively being incarcerated for SUD during pregnancy (see previously cited Amnesty International documents). Therefore, this is a critical contextual factor and one that bears on any discussion of limitations of the study.
	Response:	We thank the reviewer for this insightful suggestion. We have added a section to our Discussion stating that "***Our analysis was conducted over time periods in which many pregnant women were incarcerated for OUD; this is important to consider given the punitive legal landscape for pregnant people who use substances in the U.S. (Sue 2019, Sufrin 2017), such that OUD is stigmatized and criminalized (Meinhofer et al. 2022; Premkumar et al. 2020)*** **" (line 11, line 6)** this is a study of Medicaid and private payers , therefore it is unlikely that incarcerated women would be part of the sample.
13)	Comment:	line 217 - the authors should cite Hendree et al N Eng J Med 2010 for rates of discontinuation for buprenorphine, which were noted to be higher when compared to methadone (https://pubmed.ncbi.nlm.nih.gov/21142534)
	Response:	Absolutely- We have added the citation to Dr. Jones' seminal paper: "**Unfortunately, among individuals who do receive MOUD, MOUD treatment discontinuation remains high, with more than one-half discontinuing methadone and approximately one-half discontinuing buprenorphine 180 days into treatment, *higher rates in this observational dataset than in the MOTHER trial sample (33% buprenorphine, 18% methadone) (Jones et al., 2010)" (page 10, line 5)***
14)	Comment:	Line 231 - would also add to the list incarceration, especially given the relationship between carcerality, pregnancy, and access (or lack thereof) to treatment options. See https://www.ucpress.edu/book/9780520293212/getting-wrecked and https://www.ucpress.edu/book/9780520288683/jailcare-
	Response:	This is indeed important to include. Multi-level health services research impacting multiple aspects of intersectionality (i.e., spanning carceral treatment systems, pregnancy, lack of access) are needed, and we have added a reference to Dr. Kim Sue and Dr. Carolyn Sufrin's excellent books (both which happen to among the first author's favorite non-fiction books). ***"Our analysis was conducted over time periods in which many pregnant women were***

		incarcerated for OUD; this is important to consider given the punitive legal landscape for pregnant people who use substances in the U.S.(Sue 2019, Sufrin 2017)…" (page 11, line 6)

Reviewer #2

1)	Comment:	The primary finding of the article is that patients who initiate MOUD during pregnancy have a longer duration of continuation, with the inference is that MOUD s self-discontinued; however, do the authors have any data regarding discontinuation as per formal medical directive (i.e. ("treatment completion")?
	Response:	This is a thought-provoking comment raised by the reviewer. While many will assume that discontinuation of MOUD equates "self-discontinuation," we cannot infer this based on administrative claims data, as patients may be discontinuing by formal medical directive, forced detox, etc. This comment reminds us that research is needed to dive into the mechanisms of treatment "discontinuation", which is all too often overlooked. We have added: "**The specific reasons for MOUD treatment discontinuation—ranging from self-discontinuation to discontinuation by formal medical directive—cannot be inferred from this analysis and warrant further investigation." (page 10, line 13)**
2)	Comment:	The definition of pregnancy status is not clearly stated: was this "enrolled in prenatal care" within the most recent 210 days or actual deliveries? Lines 105-106 reference using delivery date to extrapolate conception timing?
	Response:	We thank the reviewer for this helpful critique. We have revised our definition of pregnancy status to improve readability, describing that we were using delivery date to extrapolate conception timing in line with established methods: **"The primary predictor variable was pregnant status (derived from delivery codes) in the 210 days prior to and including the time of OUD treatment initiation. (page 5, line 6)**
3)	Comment:	Patients who initiated therapy in the third trimester were excluded from analysis; could the authors clarify the rationale for this decision?
	Response:	We sought to assess people who were pregnant while receiving MOUD. Amid our objective to assess the association between pregnancy and MOUD utilization, pregnancy was our exposure variable, and to decrease heterogeneity in the ***amount*** of exposure, we excluded people who delivered (i.e., or were no longer pregnant) shortly after treatment initiation. We have added clarifying language in our methods: "**As pregnancy was our exposure variable, we sought to decrease heterogeneity in the amount of exposure and thus excluded people..." (page 4, line 12)**
4)	Comment:	**Were the authors able to identify "initial MOUD treatment" versus "previous MOUD treatment" from the data set? (i.e., for how many patients did this represent true first MOUD exposure?)**
	Response:	We cannot rule out the possibility of prior MOUD exposure. For example, a person's "first" MOUD initiation may indeed have been preceded with prior MOUD exposure while on a different insurance plan, which cannot be captured in the IBM MarketScan dataset. However, we conducted sensitivity analyses using ***first*** observed episode showing consistent results whether we were taking into account each person's first episode or including all episodes in their analyses, which suggests that our observed effects are likely consistent regardless of whether it is a person's initial MOUD treatment or subsequent MOUD treatment.

Adjusted Logistic Regression Models for the Association Between Pregnancy and MOUD Initiation.

Buprenorphine	Odds Ratio	95% Confidence Limits		P-value
Among all individuals Model 1, Pregnant v Not-Pregnant Status, Among all Treatment Episodes, n=155,771 episodes	1 57	1.44	1.70	<.0001
Excluding commercial enrollees , as race/ethnicity data is only available among Medicaid enrollees Model 2, Pregnant v Not-Pregnant Status, Among All Treatment Episodes, n=155,771 episodes	1.66	1.52	1.81	<.0001
Among all individuals Model 3, Pregnant v Not-Pregnant Status, One Episode Per Person (First Episode), n=101,772 episodes	1 50	1.37	1.63	<.0001

Excluding commercial enrollees , as race/ethnicity data is only available among Medicaid enrollees Model 4, Pregnant v Not-Pregnant Status, One Episode Per Person (First Episode), n=101,772 episodes	1 57	1.43	1.72	<.0001

Methadone	Odds Ratio	95% Confidence Limits		P-value
Among all individuals Model 1, Pregnant v Not-Pregnant Status, Among all Treatment Episodes, n=155,771 episodes	2.04	1 82	2.27	<.0001
Excluding commercial enrollees , as race/ethnicity data is only available among Medicaid enrollees Model 2, Pregnant v Not-Pregnant Status, Among All Treatment Episodes, n=155,771 episodes	2.01	1.79	2.26	<.0001
Among all individuals Model 3, Pregnant v Not-Pregnant Status, One Episode Per Person (First Episode), n=101,772 episodes	1.97	1.76	2.22	<.0001
Excluding commercial enrollees , as race/ethnicity data is only available among Medicaid enrollees Model 4, Pregnant v Not-Pregnant Status, One Episode Per Person (First Episode), n=101,772 episodes	1.96	1.74	2.21	<.0001

Among all individuals
Models 1, 3: Logis ic regression models controlling for age, insurance status, co-occurring substance use disorders (alcohol, cannabis, sedative, stimulant, tobacco), co-occurring anxiety disorders, co-occurring psychotic disorders, co-occurring mood (bipolar, major depression) disorders

Excluding commercial enrollees , as race/ethnicity data is only available among Medicaid enrollees
Models 2, 4:Logis ic regression models controlling for age, race (**among Medicaid**), co-occurring substance use disorders (alcohol, cannabis, sedative, stimulant, tobacco), co-occurring anxiety disorders, co-occurring psychotic disorders, co-occurring mood (bipolar, major depression) disorders

Adjusted Cox Regression Models for the Associa ion Between Pregnancy and MOUD Discontinuation.

Buprenorphine	Hazard Ratio	95% Confidence Limits		P-value
Among all individuals Model 1, Pregnant v Not-Pregnant Status, Among all Treatment Episodes, n=155,771 episodes	0.71	0.67	0.76	<.0001
Excluding commercial enrollees , as race/ethnicity data is only available among Medicaid enrollees Model 2, Pregnant v Not-Pregnant Status, Among All Treatment Episodes, n=155,771 episodes	0.71	0.66	0.77	<.0001
Among all individuals Model 3, Pregnant v Not-Pregnant Status, One Episode Per Person (First Episode) , n=101,772 episodes	0.68	0.63	0.73	<.0001
Excluding commercial enrollees , as race/ethnicity data is only available among Medicaid enrollees Model 4, Pregnant v Not-Pregnant Status, One Episode Per Person (First Episode), n=101,772 episodes	0.61	0.56	0.67	<.0001

Methadone	Hazard Ratio	95% Confidence Limits		P-value
Among all individuals Model 1, Pregnant v Not-Pregnant Status, Among all Treatment Episodes, n=155,771 episodes	0.68	0.61	0.75	< 0001
Excluding commercial enrollees , as race/ethnicity data is only available among Medicaid enrollees Model 2, Pregnant v Not-Pregnant Status, Among All Treatment Episodes, n=155,771 episodes	0.66	0.59	0.73	< 0001
Among all individuals Model 3, Pregnant v Not-Pregnant Status, One Episode Per Person (First Episode) , n=101,772 episodes	0.50	0.44	0.57	< 0001
Excluding commercial enrollees , as race/ethnicity data is only available among Medicaid enrollees Model 4, Pregnant v Not-Pregnant Status, One Episode Per Person (First Episode), n=101,772 episodes	0.48	0.42	0.55	< 0001

Among all individuals
Models 1, 3: Logis ic regression models controlling for age, insurance status, co-occurring substance use disorders (alcohol, cannabis, sedative, stimulant, tobacco), co-occurring anxiety disorders, co-occurring psychotic disorders, co-occurring mood (bipolar, major depression) disorders

Excluding commercial enrollees , as race/ethnicity data is only available among Medicaid enrollees
Models 2, 4:Logis ic regression models controlling for age, race (**among Medicaid**), co-occurring substance use disorders (alcohol, cannabis, sedative, stimulant, tobacco), co-occurring anxiety disorders, co-occurring psychotic disorders, co-occurring mood (bipolar, major depression) disorders

		While writing our response to this excellent comment, we realized we did not make it clear that our analyses that limited observations to one treatment episode per person were focusing on each person's ***first*** episode, and the revised manuscript makes this clearer: "**we conducted sensitivity analyses: 1) limiting observations to one treatment episode per person (<u>each person's first episode</u>), and 2) limiting observations to one pregnancy per person." (page 7, line 2)**
5)	Comment:	**Did any patients transition from psychosocial therapy to MOUD during the study interval?**
	Response:	Overall, approximately 26% of people receiving MOUD had co-occurring claims for psychosocial treatment; these episodes were counted as MOUD, as opposed to psychosocial treatment. The specific directionality (i.e., whether people were transitioning from psychosocial therapy to MOUD during the episode or whether psychosocial therapy was coinciding with MOUD simultaneously) cannot be inferred from our data. The psychosocial treatment without MOUD category in the study focuses **solely** on people receiving psychosocial treatment without MOUD (to identify people NOT receiving the standard of care), as opposed to psychosocial treatment with MOUD (standard of care). Importantly, because our analysis was conducted at the treatment <u>episode</u> level, as opposed to the individual level, we were able to include individual people multiple times in our analysis. For instance, if a person had psychosocial treatment during one episode AND buprenorphine during another episode, they would contribute data to both the psychosocial AND buprenorphine groups; during the psychosocial treatment episode, we would assess whether the person was pregnant, and for the buprenorphine treatment episode, we would assess again whether the person was pregnant.
6)	Comment:	**Do the authors have any data regarding lactation rates?**
	Response:	This is a very intriguing question—definitely a topic worthy of in-depth research. Unfortunately, our dataset does not have information regarding lactation rates.

<u>Reviewer 3</u>

1)	Comment:	The paper is a retrospective cohort study in the IBM MarketScan Databases examining the association of pregnant status with treatment initiation and discontinuation of medication for opioid use disorder (MOUD). While there are multiple published studies supporting improvements in pregnancy outcomes with MOUD, which has now become the standard of care, there are few studies examining who is receiving such therapy and treatment retention/discontinuation rates. The key finding of this paper is that pregnant status was significantly associated with increased MOUD initiation and improved retention in the indicated population. The paper concisely addresses a timely topic, with both its strengths and weaknesses clearly delineated in the discussion.
	Response:	We thank the reviewer for these helpful comments.
2)	Comment:	While the requirement of six months of pharmacy and medical coverage is logical for statistical analysis (line 95), how does it alter real life interpretations and implications of the data? Can this six month requirement/limitation be elaborated upon in the discussion further than is briefly mentioned (line 233, 236)?
	Response:	The inclusion of 6 months of pharmacy and medical coverage is used to provide a period for baseline covariate assessments. We agree with the reviewer that, while this is logical from a statistical analysis standpoint, it is an important shortcoming of our research. Many of our patients with OUD do not have insurance coverage to begin with, and others do not have stable insurance coverage for 6 months. This leads us to infer that our results constitute a "best case scenario," as it is plausible that people without 6 months of insurance coverage will have even lower MOUD initiation and retention rates. We have added additional content in our Discussion addressing this issue: **"*<u>Given the association of OUD with low SES and poor insurance coverage (Patrick et al.), it is a significant limitation that we only…" (page 11, line 8)</u>***
3)	Comment:	Significant attention was given to the differences between usage of methadone, buprenorphine alone, and combination product by pregnant and non-pregnant people. These results were not significantly touched on later in the paper. Consider discussing the findings or indicating that there is nothing worth noting to discuss, given that the data was presented in such a way as to anticipate significant discussion.

	Response:	We have removed the data on the mono product vs combination product, as we agree it goes beyond the scope of this paper and may hinder the readability of our discussion. .
4)	Comment:	Lines 216 and 244 indicate "systems" and "structures" that contribute to discontinuation of MOUD, but these are not appreciably discussed in the paper. While one strength of the paper is how succinct it is, greater weight could be given to the argument regarding the poor state of the healthcare system (patients not getting standard of care) and the insidious tenacity of treatment discontinuation if more detail was given to these ideas.
	Response:	We agree that the discussion could be strengthened with more commentary on the poor state of the healthcare system. Together with Reviewer 1's comments on the intersection of carcerality, access, and pregnancy, we have added a description of: "***Our analysis was conducted over time periods in which many pregnant women were incarcerated for OUD; this is important to consider given the punitive legal landscape for pregnant people who use substances in the U.S…" (page 11, line 7)***

Statistical Editor

1)	Comment:	**Should statistically compare the two cohorts, they appear to be statistically different in several characteristics.**
	Response:	We have computed univariate tests comparing the two cohorts, and the associated effect sizes and p-values have been added to the revised manuscript. We added to the Methods: **"First, we used chi-square tests to compute descriptive statistics for Medicaid status, race, and co-occurring SUDs, and comorbid psychiatric disorders by pregnant status. The Wilcoxon-sum rank test was used to compute univariate statistics for age by pregnant status." (page 6, line 10)**
2)	Comment:	**Fig 2: Should include a column of unadjusted ORs for contrast with the aORs. Also, since Medicaid enrollees comprised ~ 2/3 of all participants, it is no surprise that their aORs are statistically indistinguishable. Should also show results for non-medicaid participants (pregnant vs non-pregnant) for buprenorphine and methadone initiation.**
	Response:	-We have added a column of unadjusted ORs for contrast with the aORs in the text of our manuscript, as well as in the Supplementary Information (eTables 3 and 4 have been broken into eTable 3a and eTable 4a for unadjusted findings and eTable 3b and 4b for adjusted findings). -The reviewer's point about including the results for non-Medicaid participants separately is well taken. However, results for non-Medicaid vs Medicaid participants (pregnant vs non-pregnant) for buprenorphine and methadone initiation are currently part of a separate manuscript that provides an in-depth analysis on insurance- and racial disparities in MOUD initiation and retention. Because we cannot publish the same data twice, we are unable to add the non-Medicaid vs Medicaid results to this present manuscript. We will gladly share this data with interested readers until the insurance and racial disparities manuscript is published and in press.
3)	Comment:	**For both 3A and 3B, should include the counts for the N remaining in each group at the indication times along the x-axes. Should also indicate in Results the median (IQR) follow-up for each cohort in order to show the reader that censoring was equivalent for the two groups.**
	Response:	-We have included counts for the N remaining in each group at the indication times along the x-axes in the updated draft. We have also indicated in the results the median (IQR) follow-up for each cohort.