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Medically assisted reproduction and mental health: a 24-year longitudinal analysis using Finnish register data

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Condensation: Remaining childless after undergoing Medically Assisted Reproduction is associated with persistently higher psychotropic purchases than having a live birth after Medically Assisted Reproduction or naturally.

Short Title: Medically Assisted Reproduction and mental health in Finland.

AJOG at a Glance:

- Why was this study conducted?

The number of women relying on medically assisted reproduction (MAR) to conceive has grown rapidly, yet our knowledge about their mental health as they undergo MAR treatments is limited.

- What are the key findings?

Women who did not have a live birth after undergoing MAR treatments purchased more psychotropic medication than women who gave birth after conceiving naturally or through MAR. Differences did not attenuate over time, even when adjusting for socio-demographic characteristics. Women who conceived naturally and through MAR had very similar psychotropic use from three years before conception to four years after, and over the long term.

- What does this study add to what is already known?

Similarities in psychotropic purchases of women who had a live birth, whether naturally or through MAR suggest that the higher psychotropic use among women who remained childless after undergoing MAR is likely to be driven more by involuntary childlessness than by treatment-related stress.

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Abstract

Background: Medically assisted reproduction (MAR) can negatively impact women's mental health, particularly when the treatments do not result in a live birth. While the number of women relying on MAR to conceive has grown rapidly, our knowledge about the mental health effects before, during, and after treatment is limited.

Objective: To understand the long-term association between medically assisted reproduction and mental health outcomes for women before, during and after their treatments, and according to whether the treatment resulted in a live birth or not.

Study Design: Using Finnish register data for the period 1995-2018 we estimated the probability of psychotropic purchases (antidepressants, anxiolytics, hypnotics and sedatives) for three groups of women who: 1) gave birth after natural conception (NC), 2) gave birth after MAR treatments (MAR+), or 3) underwent MAR but remained childless (MAR-). We followed women for up to 12 years before and 12 years after the reference date which corresponded to the conception date for women who had a first live birth either after a natural or a MAR conception, or the date of the last MAR treatment for women with no live birth by the end of 2017. We estimated linear probability models before and after the adjustment for socio-demographic characteristics.

Results: The results show that women who did not have a live birth after undergoing MAR treatments purchased more psychotropics than women who gave birth after conceiving naturally or through MAR, and that these differences did not attenuate over time. 12 years after the reference date 17.73% (95% CI: 16.82-18.63) of MAR- women purchased psychotropics, versus 11.11% of NC (95% CI: 10.98-11.26) and 12.17% (95% CI: 11.65-12.69) of MAR+ women. In addition, women who conceived naturally and through MAR had very similar psychotropic use patterns

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from three years before conception to four years after, and over the long term. Adjustment for women's socio-demographic characteristics did not change the results.

Conclusions: The similarities in psychotropic purchases of women who had a live birth, whether naturally or through MAR, suggest that the higher psychotropic use among women who remained childless after undergoing MAR were likely driven more by involuntary childlessness than by treatment-related stress. The results highlight the importance of counselling for women undergoing MAR treatments, especially if their attempts to conceive are unsuccessful.

Keywords: fertility treatments, mental health, psychotropic purchases, involuntary childlessness, subfertility.

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Introduction:

As childbearing is increasingly postponed and infertility treatments are becoming more widely available, the number of women relying on medically assisted reproduction (MAR) – which includes techniques such as ovulation induction, artificial insemination, and assisted reproductive technology (ART; including in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI)) – to conceive has grown rapidly across the globe.[1] Between 1997 and 2016, IVF procedures have increased 5.3-fold in Europe and 4.6-fold in the United States.[2]

Previous studies have suggested that MAR treatments can negatively affect women's psychological wellbeing and cause psychological distress, anxiety, and depression[3–5]. The mental health burden is higher for women whose treatments do not result in a live birth[6–8]. While some studies have found that women's psychological wellbeing improves as they adjust to subfertility and/or childlessness[6,9–11], others have reported long-term negative effects.[12,13]

However, evidence about women's mental health as they undergo MAR treatments is limited. The few existing longitudinal studies on this topic[3,4,6,7] have limitations. First, the beginning of the follow-up period is often around the time the MAR treatments started; i.e., when the women were already struggling with subfertility. This approach makes it difficult to determine the extent to which the mental health levels of women who undergo MAR diverge from their pre-treatment levels. Second, they tend to use small and non-representative samples collected in MAR treatment clinics, which are subject to self-reporting and recall bias.[3,4] Finally, none of these studies directly documents differences between women who conceive naturally, women who conceive through MAR, and women who remain childless after MAR treatments.

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In this study, we analyse the use of psychotropic medication among women who underwent MAR to conceive and compare it to that of women who conceived naturally with a long-term perspective. A key contribution is that we compare women who had a live birth after MAR to women who underwent MAR but remained childless. We expand on the existing literature by investigating women's psychotropic purchases both before and after the date of conception or the last treatment cycle using population register data from Finland, and a significantly larger observation window than prior studies.

Materials and Methods:

Study population:

All women in Finnish administrative registers who were born between 1950-1995, were childless in 1995, and gave birth to their first child (either after natural conception or MAR) between ages 20 and 45 in 1996-2016 or underwent MAR treatments in 1995-2016 but were childless in 2017.

Reference date:

We set as reference date the conception date (estimated as birthdate minus gestational age) for women who had a first live birth either after a natural or a MAR conception, or the date of the last MAR treatment for women with no live birth by the end of 2017.

Outcome:

Psychotropics medication are commonly used to treat depression, anxiety, insomnia and other related mental health problems.[14,15] Information about psychotropic purchases prescribed in the public and private sectors was gathered from the National Prescription Register between January 1995 and December 2018. In Finland, all psychotropic medication is prescribed by clinical doctors,

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and residents are entitled to reimbursement for medication expenses, usually provided directly at pharmacies. The prescription register includes information on the purchase date and medication type, classified according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System (WHO, 2013). We included all purchases of antidepressants (ATC codes N06A), anxiolytics (ATC codes N05B), and hypnotics and sedatives (ATC codes N05C).

We divided our follow-up period into six-month intervals before and after the reference date. For each interval, the outcome variable takes a value of one if a woman purchased psychotropics, and of zero otherwise.

MAR treatments:

We identified women undergoing MAR treatments between 1995 and 2016 using administrative data from the prescription, healthcare, and birth registers.

To identify MAR treatments in the prescription register, we updated Hemminki et al.'s[16] algorithm by including two drugs introduced after 2000 and some restrictions on stand-alone treatments (more information in Appendix 1). We identified children conceived through MAR by combining each woman's purchases of fertility drugs with her child's birthdate (retrieved from the Finnish Medical Birth Register). We excluded purchases of drugs used in infertility treatment when also plausibly used to treat other medical conditions, such as cancer. The healthcare register contains information on dates and types of MAR procedures in the public sector. We identified children conceived through MAR by combining the dates of MAR procedures with the child's birthdate. Finally, to complement this information, we identified in the birth register children born after MAR treatments from 2004 onwards.

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Our three groups of interest are women who had their first live birth after 1) a natural conception (NC) or 2) a MAR conception (MAR+), and 3) women who remained childless after MAR treatments (MAR-). Women who conceived after MAR treatments could be identified from any of the three sources, and women who underwent MAR treatments not resulting in a live birth were identified using the procedure and/or drug registers. We assumed a woman conceived naturally if none of the data sources indicated that her child was conceived through MAR.

Treatment length:

We defined treatment length as the time between the first and last MAR treatment, and created a binary variable that takes a value of one for women who underwent treatments for over two years, and of zero otherwise. The two-year threshold was chosen based on the average treatment length (1.98 years) in our sample. For cases in which MAR treatment was identified only through the birth register (11.5% of MAR+ women) – which does not provide information on treatment length – we imputed the first treatment date using age-specific average times between the start of MAR treatments and conception.

Period of observation:

Data on psychotropic purchases from 1995 to 2018, together with data on MAR treatments between 1995 and 2016, allowed us to follow women for up to 12 years before and after the reference date, resulting in an unbalanced panel with a total of 48 six-month intervals (24 years), and a median follow-up of 35 intervals (18 years) (appendix Table 2A).

Exclusions:

We excluded from the sample women who were under age 20 or over age 45 at the reference date. We excluded women with triplets, which is associated with more distress.[17] We censored

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psychotropic purchases that occurred before women reached age 18. Furthermore, we censored women who were living abroad in any given year, as medication purchases are recorded only for women residing in Finland. Finally, we excluded observations with missing values in the covariates (0.07%). This results in a sample of 575,921 women. Of them, 97.73% had a first birth in 1996-2016 (5.89% after MAR), and 2.27% remained childless after undergoing MAR treatments.

Statistical analysis:

We estimated Generalized Estimating Equation linear models using the six-month intervals as repeated panel observations and robust standard errors with exchangeable correlation structure. We modelled changes in psychotropic purchases by interacting the three groups of interest (women who had a live birth after a natural or a MAR conception, and women who remained childless after MAR treatments) with the six-month period variable (time-varying), which resulted in 96 coefficients representing the probability of psychotropic use for MAR+ and MAR- against NC women for each period.

We estimated two models. In Model 1, we adjusted for calendar year to control for increasing psychotropic use over time[18], and for age, because, on average, psychotropic use increases with age[19] and women who undergo MAR are older than women who conceive naturally.[20] Since women who undergo MAR treatments are, on average, socio-economically advantaged[21], Model 2 additionally controls for time-varying socio-demographic factors: household income decile (categorical), cohabitation status (binary), as well as hospital district of residence (categorical). As psychotropic purchases may be affected by the transition to a higher-parity birth, Model 2 also adjusts for the transition to a second- and third- or higher-order birth (binary). To investigate whether treatment duration moderated the association between MAR treatments and psychotropic

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purchases, we estimated Model 1 interacting the period variable with a variable that identified the three interest groups and their treatment length, resulting in five categories: NC, MAR+ above two years, MAR+ below two years, MAR- above two years, and MAR- below two years.

All analyses were conducted in Stata 16. The study was exempt from IRB approval as it was not necessary given prior institutional approval of the overall project (European Research Council grant #803958).

Results:

Table 1 shows that 33.4% of women purchased psychotropics in at least one six-month period during the 24-year follow-up, with 15% having purchased at least once in the 12 years before the first conception or last MAR cycle, and 27.3% in the following 12 years. Psychotropic use differed across the three groups: 14.5% and 18.9% of NC and MAR+ women, respectively, purchased psychotropics before they conceived their first child, versus 25% of MAR-.

We observed substantial differences across groups over time (Figure 1). Differences in psychotropic purchases between women who underwent MAR treatments and women who conceived naturally emerged as early as 9-10 years before conception or last treatment cycle, with the latter being more likely to purchase psychotropics (MAR-: 3.25% (95% CI:2.71-3.79); MAR+: 2.51% (95% CI:2.27-2.75)) than the former (1.48% (95% CI:1.14-1.58)).

Five years before conception or the last cycle, the psychotropic purchases of women undergoing MAR diverged (Figure 1). The share of women taking psychotropics remained at 4.86% for MAR+ women (95% CI:4.59-5.13), but increased to 6.45% (up 16.02% from the previous year) among MAR- women.

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Women who had a child either through MAR or naturally had similar levels of psychotropic use from three years before conception to four years after. Nonetheless, while the probability of purchasing psychotropics decreased gradually from two years before conception onwards among MAR+ women, no shift occurred among NC women until right before conception. Conversely, women who remained childless after MAR increased their psychotropic use sharply after the last MAR cycle. This resulted in a large gap in psychotropic purchases around the reference date, with 9.82% (95% CI:9.29-10.36) of MAR- women purchasing psychotropics versus 2.83% (95% CI: 2.78-2.88) of NC women and 2.49% (95% CI:2.31-2.66) of MAR+ women. The psychotropic purchases of both NC and MAR+ women increased immediately following childbirth, which resulted in an attenuation of the differences between NC, MAR+, and MAR- groups. From six years after the reference date onwards, the gap in psychotropic purchases between childbearing and childless women remained relatively stable. The gap never fully attenuated, as 12 years after the reference date, women who underwent unsuccessful MAR treatments were 45.69% and 59.48% more likely to purchase psychotropics than women who delivered a live birth through MAR or naturally, respectively.

To illustrate the fluctuations in psychotropic purchases among women who underwent MAR treatments and either gave birth or remained childless, Figure 2 shows the ratio of predicted margins estimated using the delta method for these women relative to women who conceived naturally. The figure shows a clear peak in psychotropic purchases among MAR- women.

When adjusting for socio-demographic characteristics in Model 2, differences in psychotropic purchases across groups remained consistent with Model 1 (appendix Figure 1A). We re-estimated all models excluding women who underwent fertility treatments but conceived naturally, and the results held (appendix Figure 2A).

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Lengthier MAR treatments were associated with higher psychotropic purchases regardless of the treatment result (Figure 3 and appendix Table 4A). For example, women undergoing lengthier treatments were 37.28% (MAR+) and 32.47% (MAR-) more likely to purchase psychotropics around the date of conception or last cycle than their counterparts undergoing shorter treatments, and these differences shrank after the reference date. Nonetheless, the results were consistent with those of Model 1: women who had a child following MAR had lower psychotropic use than women who underwent MAR and remained childless.

Comment:

Principal Findings:

The results show that psychotropic use was higher among women who remained childless after MAR than among women who conceived naturally or through MAR. This pattern persisted over the long term, in line with the findings of other studies.[3,5,10,12,13] Adjustment for socio-demographic characteristics did not change the pattern of results.

However, while women who conceived via MAR had higher psychotropic use than women who conceived naturally at the beginning of the observation window, their psychotropic use was similar from three years before to four years after conception, and the differences over the longer term remained small, and were unlikely to be clinically relevant.

Results in the context of what is known:

While the finding of similarities in long-term psychotropic use between women who conceived naturally and through MAR is consistent with previous studies[5,22], in this study, we were able to significantly extend the observation window, and thus to provide further evidence about the mental wellbeing of this growing population group.

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Our results significantly deepen the understanding of the link between MAR and mental health in three ways. First, we showed that differences between women for whom MAR treatments did not result in a live birth and women who delivered a live birth either naturally or through MAR arose as early as five years before the date of conception or last MAR cycle, with the former increasing their psychotropic uptake more than the latter. A possible explanation for the emergence of this gap well before women ended MAR treatments is that the former may have already received a diagnosis of subfertility and started the infertility treatment process. There is evidence that the start of infertility treatments are related to increased levels of depression and anxiety.[22,23]

Second, we showed there was a sharp increase in psychotropic purchases following the last failed treatment cycle, which could have been driven by the grief women felt when they realised that they were unlikely to have a biological child.[13] Although this stark increase could also be related to women breaking up with their partner and suspending treatment[24], adjusting for partnership status in the analyses did not alter the results. By contrast, women who had a live birth either naturally or after undergoing MAR treatments reduced their psychotropic purchases when trying to conceive and whilst pregnant. The reasons for this could be twofold: On the one hand, the decrease and slow return to pre-conception psychotropic purchase levels (around 36 months) could be related to a temporary increase in subjective wellbeing around the time of first birth.[25] On the other, pregnant women may decrease their psychotropic uptake during pregnancy or postpartum because medications may have negative side effects[26] even though some medications are safe to use during this period.[27–29]

Third, while the psychotropic purchases of the two MAR groups were similar at the beginning of the observation window, they started diverging from around six years before conception or the last MAR cycle, and the differences never fully attenuated during follow-up. The stark increase in

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psychotropic uptake that occurred around the last treatment date for women who remained childless could suggest that their worse mental health outcomes were driven more by involuntary childlessness than by treatment-related stress. The analyses on the moderating role of the MAR treatment length further supported this hypothesis. Within the MAR+ and MAR- groups, women who underwent MAR for 2+ years had higher psychotropic use at the beginning and end of the follow-up period. However, the differences became smaller over the longer term, as the purchases of women who underwent longer MAR processes in both the MAR+ and MAR- groups tended to converge with those of their counterparts who underwent shorter MAR processes; i.e., childbearing status was more important in determining women's psychotropic purchases than MAR treatment length. The results reinforce the hypothesis that higher psychotropic purchases were associated with unintended childlessness after undergoing MAR treatments, while the moderating effect of the length of the MAR process was small.

Clinical implications:

In light of the increasing use of MAR treatments, the results of this study underscore the importance of offering counselling to women undergoing MAR treatments, particularly if their attempts to conceive through MAR are unsuccessful. The provision of psychological support and counselling during the MAR process may reduce the likelihood of women ending treatments prematurely because of stress; better prepare women for the potential failure of treatments; and help women deal with the grieving process if their desire to have a child is unfulfilled.[13] However more evidence is needed to determine whether and to what extent such psychological support is effective.

Research Implications:

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We found that involuntary childlessness has associated mental health costs, yet more work is necessary to establish what are the mechanisms underlying this association. Moreover, the results show that the estimation of the MAR effect on mental health is sensitive to when it is measured during the MAR process i.e. could be over or underestimated depending on how the baseline and follow up are defined with respect to conception/last MAR cycle.

Strengths and limitations:

This study has several strengths. First, the use of a large and nationally representative register allowed us to investigate the association between MAR treatments and psychotropic purchases free of self-reporting biases, and to investigate this association before, upon, and after the conception date (or the last cycle date for unsuccessful MAR cases) in six-months intervals. Second, the long follow-up allowed us to observe psychotropic purchases when women were most likely not yet struggling with infertility or MAR treatments. Third, we identified and compared women who had a live birth naturally or after MAR to women who underwent MAR but whose treatments did not result in a live birth, which is relevant for understanding how MAR treatments and their outcomes affect women's mental health. Finally, by focusing on psychotropics, which are widely used to treat depression and anxiety in women of reproductive ages, we were able to observe common psychiatric disorders, and not only the more acute or severe cases (e.g., psychiatric hospitalisations).

The study also has limitations. First, the analysis focused on Finland, a context with subsidised medical care and medication costs, which could limit the generalisability of our findings to other settings. However, in contexts where MAR treatments are not as well subsidised as in Finland, the association between psychotropic uptake and MAR treatments could be even stronger because of higher levels of stress related to income loss. Second, although the analysis of psychotropic

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purchases allows us to observe women who suffer from common psychiatric disorders, there are other non-pharmacological interventions such as therapy and counselling which we are not considering. Thirdly, we were unable to establish whether the association between MAR treatments and psychotropic purchases was causal given that subfertility is associated with higher levels of stress[3–5], but using psychotropics is also associated with infertility.[30,31] Nevertheless, additional analyses (see appendix figure 3A) demonstrate that our main results remain similar when excluding all women who had purchased psychotropics before the reference date, suggesting that our conclusions are unlikely to be primarily related to an underlying higher propensity to use psychotropic medications among women who undergo MAR and remain childless. Fourth, whilst the use of administrative registers has many advantages, they do not provide information on the causes of infertility or cases of abnormal pregnancies. Finally, we are unable to account for the role of pregnancy loss because registry data record only those that require hospitalization. Nevertheless, it is unlikely results are driven by miscarriages since we do not observe differences in psychotropic uptake before the reference date between MAR+ and NC women even though the former experience, on average, a higher number of miscarriages because they suffer from subfertility.

Conclusions:

The similarities in the psychotropic purchases of women who had a live birth, whether naturally or through MAR, suggest that the higher psychotropic use among women who remained childless after undergoing MAR were likely driven more by involuntary childlessness than by treatment-related stress. The results highlight the importance of counselling for women undergoing MAR treatments, especially if their attempts to conceive are unsuccessful.

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Tables:

Table 1: Psychotropic purchases before and after conception or last MAR treatment

	NC		MAR+		MAR-		Total	
Psychotropic purchases:	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD
Before conception or last cycle date	14.48	35.19	18.85	39.11	25	43.3	14.98	35.68
After conception or last cycle date	27.04	44.42	27.87	44.84	37.9	48.52	27.33	44.57
Before and/or after conception or last cycle date	32.93	47	36.15	48.04	45.24	49.77	33.4	47.16
Number of observations	528,913		33,942		13,066		575,921	

Note: NC refers to women who conceived naturally, MAR+ to women who conceived after MAR treatments, and MAR- to women who underwent MAR treatments and remained childless.

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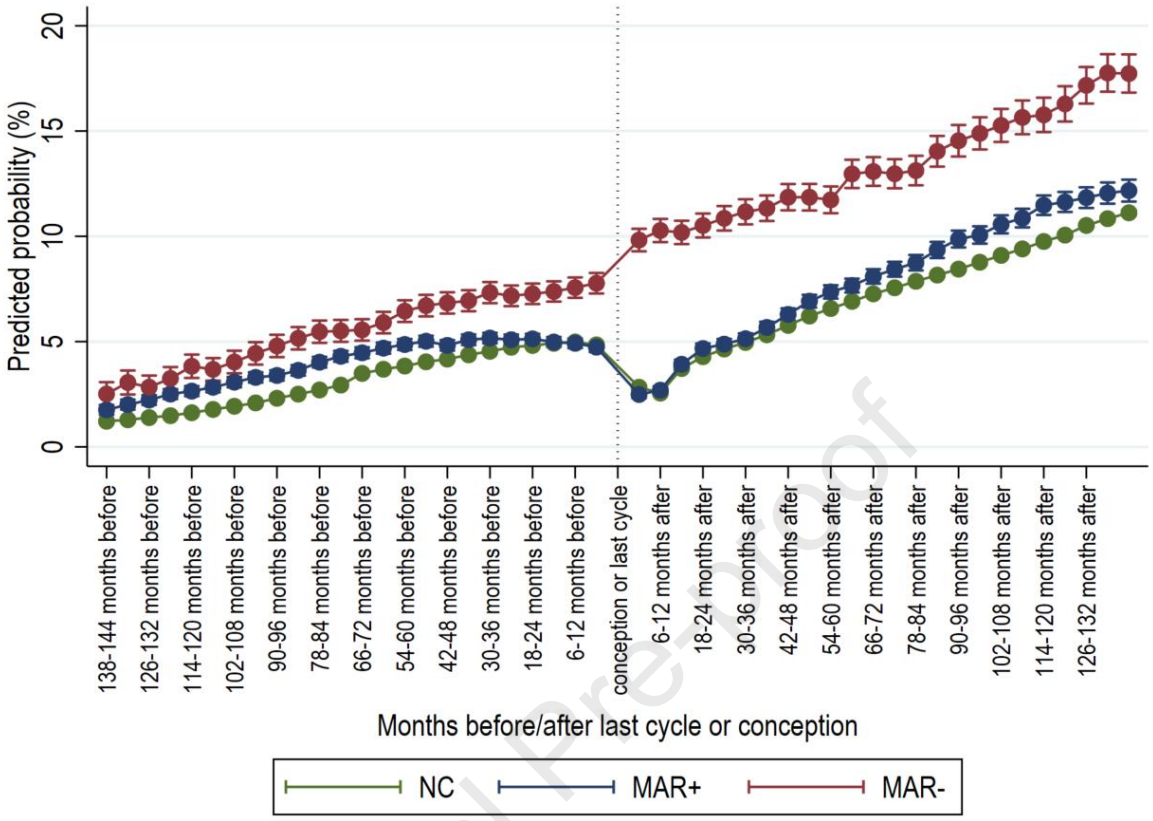
Figure 1: Predicted probabilities of purchasing psychotropics before and after the reference date, by group (Model 1)



Note: NC refers to women who conceived naturally, MAR+ to women who conceived after MAR treatments, and MAR- to women who underwent MAR treatments but did not deliver a live birth by the end of 2017. Model 1 adjusts for calendar year and age.

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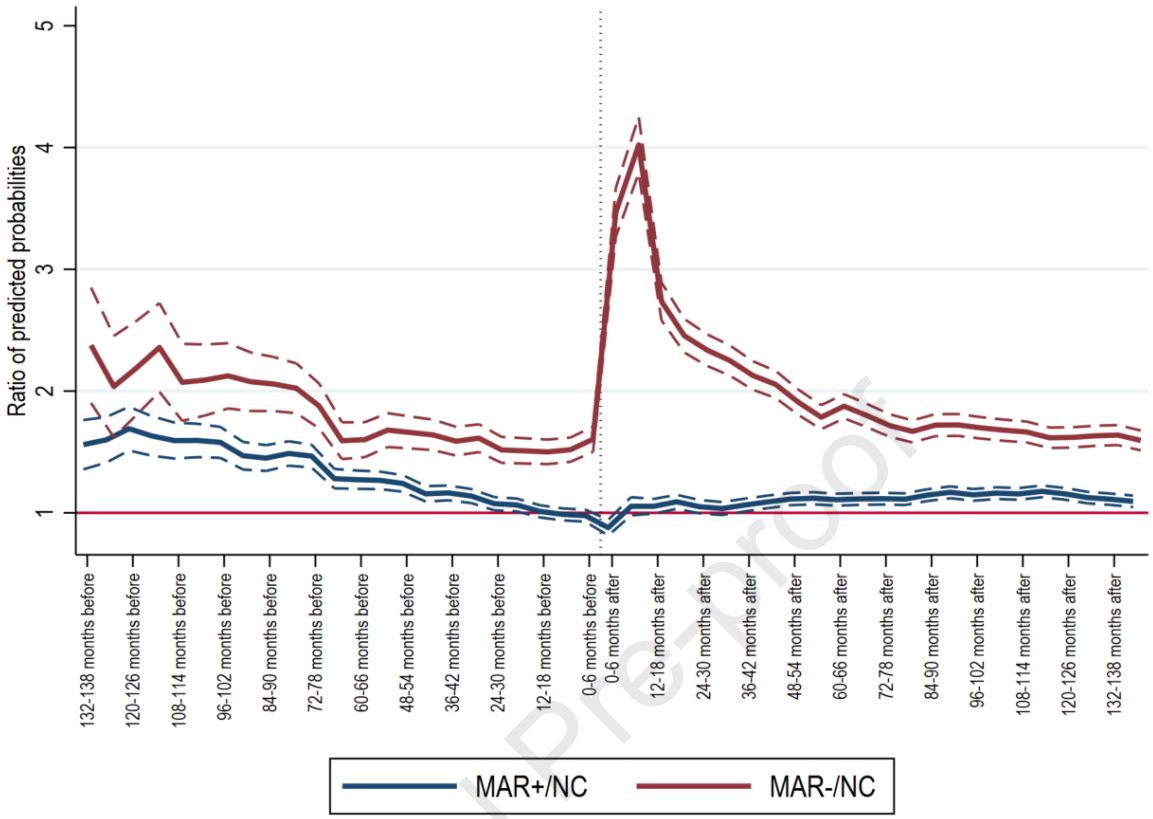
Figure 2: Ratio of predicted probability of purchasing psychotropics before and after the reference date, estimated after Model 1



Note: NC refers to women who conceived naturally, MAR+ to women who conceived after MAR treatments, and MAR- to women who underwent MAR treatments but did not deliver a live birth by the end of 2017. Ratios calculated after the estimation of Model 1. Horizontal red line in y=1 represents equal predicted probabilities between each of the MAR and NC groups.

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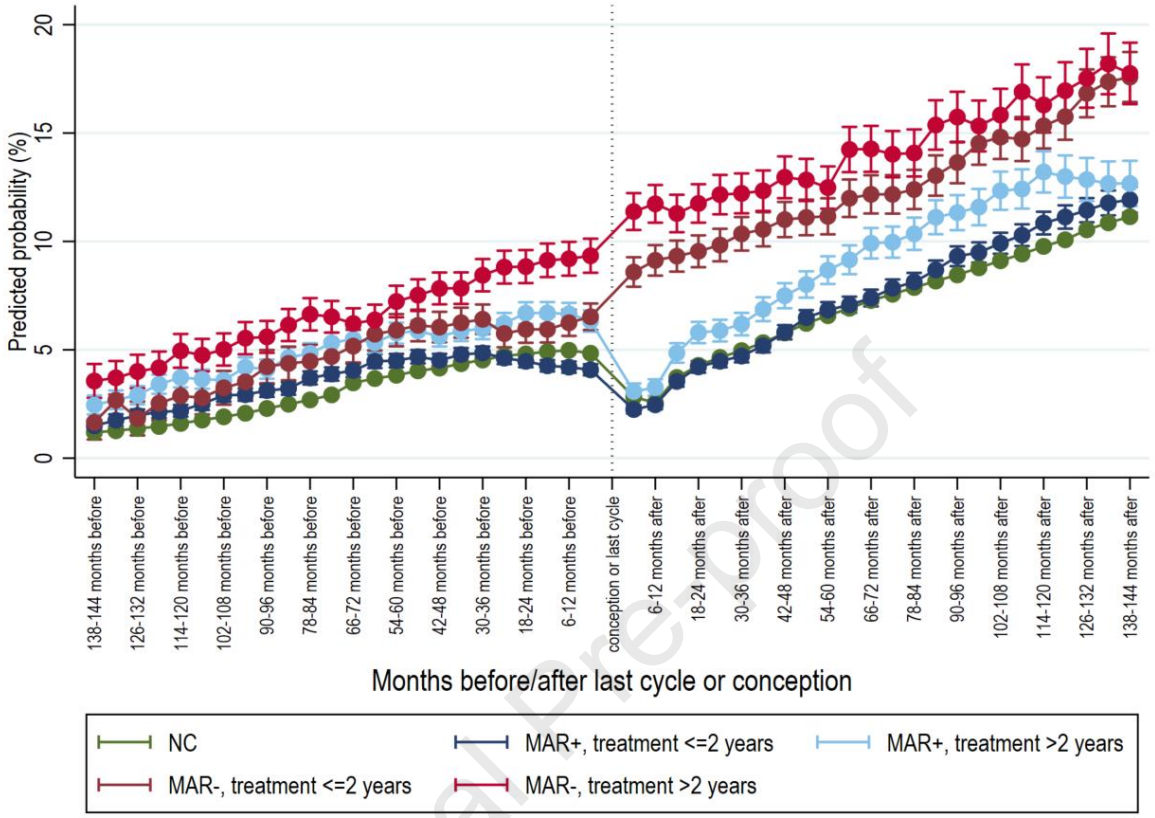
Figure 3: Predicted probability of purchasing psychotropics before and after the reference date, by group and length of treatment (Model 1)



Note: NC refers to women who conceived naturally, MAR+ to women who conceived after MAR treatments, and MAR- to women who underwent MAR treatments but were childless by the end of 2017.

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