Journal Pre-proof

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

Alice Goisis, PhD, Maria Palma, M.Sc, Niina Metsä-Simola, PhD, Reija Klemetti, PhD, Pekka Martikainen, PhD, Mikko Myrskylä, PhD, Alina Pelikh, PhD, Marco Tosi, PhD, Hanna Remes, PhD

Please cite this article as: Goisis A, Palma M, Metsä-Simola N, Klemetti R, Martikainen P, Myrskylä M, Pelikh A, Tosi M, Remes H, Medically assisted reproduction and mental health: a 24-year longitudinal analysis using Finnish register data, *American Journal of Obstetrics and Gynecology* (2022), doi: https://doi.org/10.1016/j.ajog.2022.10.041.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1   **Medically assisted reproduction and mental health: a 24-year longitudinal analysis using**

2   **Finnish register data**

3   **Corresponding author**

4   Alice GOISIS [1] PhD

5   55-59 Gordon Square, WC1H 0NU

6   Centre for Longitudinal Studies

7   University College London

8   England, United Kingdom.

9   Email: a.goisis@ucl.ac.uk

10

11   **Co-authors**

12   Maria PALMA[1], M.Sc.

13   Niina METSÄ-SIMOLA[2], PhD

14   Reija KLEMETTI[3], PhD

15   Pekka MARTIKAINEN[2,4], PhD

16   Mikko MYRSKYLÄ[2,4], PhD

17   Alina PELIKH[1], PhD

18   Marco TOSI[5], PhD

19   Hanna REMES[2], PhD

20

21   1. Centre for Longitudinal Studies, Social Research Institute, University College London,

22   London, United Kingdom

23   2. Population Research Unit, Faculty of Social Sciences, University of Helsinki, Helsinki,

24   Finland

25   3. National Institute for Health and Welfare Finland

26   4. Laboratory of Population Health, Max Planck Institute for Demographic Research, Rostock,

27   Germany

28   5. Department of Statistical Sciences, University of Padua.

38   **Data Sharing:** Researchers may apply for permission from Statistics Finland to use the data. After

39   permission has been granted, data will be available in the remote access system provided by the

40   register holders. The code used in the analyses of this paper may then be uploaded to the remote

41   access system by contacting the authors.

42   **Abstract word count:** 316 words

43   **Main text word count:** 3,285 words

44

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.

67 **Abstract**

68 **Background:** Medically assisted reproduction (MAR) can negatively impact women's mental

69 health, particularly when the treatments do not result in a live birth. While the number of women

70 relying on MAR to conceive has grown rapidly, our knowledge about the mental health effects

71 before, during, and after treatment is limited.

72 **Objective:** To understand the long-term association between medically assisted reproduction and

73 mental health outcomes for women before, during and after their treatments, and according to

74 whether the treatment resulted in a live birth or not.

75 **Study Design:** Using Finnish register data for the period 1995-2018 we estimated the probability

76 of psychotropic purchases (antidepressants, anxiolytics, hypnotics and sedatives) for three groups

77 of women who: 1) gave birth after natural conception (NC), 2) gave birth after MAR treatments

78 (MAR+), or 3) underwent MAR but remained childless (MAR-). We followed women for up to

79 12 years before and 12 years after the reference date which corresponded to the conception date

80 for women who had a first live birth either after a natural or a MAR conception, or the date of the

81 last MAR treatment for women with no live birth by the end of 2017. We estimated linear

82 probability models before and after the adjustment for socio-demographic characteristics.

83 **Results:** The results show that women who did not have a live birth after undergoing MAR

84 treatments purchased more psychotropics than women who gave birth after conceiving naturally

85 or through MAR, and that these differences did not attenuate over time. 12 years after the reference

86 date 17.73% (95% CI: 16.82-18.63) of MAR- women purchased psychotropics, versus 11.11% of

87 NC (95% CI: 10.98-11.26) and 12.17% (95% CI: 11.65-12.69) of MAR+ women. In addition,

88 women who conceived naturally and through MAR had very similar psychotropic use patterns

89 from three years before conception to four years after, and over the long term. Adjustment for

90 women's socio-demographic characteristics did not change the results.

91 **Conclusions:** The similarities in psychotropic purchases of women who had a live birth, whether

92 naturally or through MAR, suggest that the higher psychotropic use among women who remained

93 childless after undergoing MAR were likely driven more by involuntary childlessness than by

94 treatment-related stress. The results highlight the importance of counselling for women undergoing

95 MAR treatments, especially if their attempts to conceive are unsuccessful.

98

99

100

101

102

103

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.

125   In this study, we analyse the use of psychotropic medication among women who underwent MAR

126   to conceive and compare it to that of women who conceived naturally with a long-term perspective.

127   A key contribution is that we compare women who had a live birth after MAR to women who

128   underwent MAR but remained childless. We expand on the existing literature by investigating

129   women's psychotropic purchases both before and after the date of conception or the last treatment

130   cycle using population register data from Finland, and a significantly larger observation window

131   than prior studies.

132   **Materials and Methods:**

133   **Study population:**

134   All women in Finnish administrative registers who were born between 1950-1995, were childless

135   in 1995, and gave birth to their first child (either after natural conception or MAR) between ages

136   20 and 45 in 1996-2016 or underwent MAR treatments in 1995-2016 but were childless in 2017.

137   **Reference date:**

138   We set as reference date the conception date (estimated as birthdate minus gestational age) for

139   women who had a first live birth either after a natural or a MAR conception, or the date of the last

140   MAR treatment for women with no live birth by the end of 2017.

141   **Outcome:**

142   Psychotropics medication are commonly used to treat depression, anxiety, insomnia and other

143   related mental health problems.[14,15] Information about psychotropic purchases prescribed in the

144   public and private sectors was gathered from the National Prescription Register between January

145   1995 and December 2018. In Finland, all psychotropic medication is prescribed by clinical doctors,

146 and residents are entitled to reimbursement for medication expenses, usually provided directly at

147 pharmacies. The prescription register includes information on the purchase date and medication

148 type, classified according to the World Health Organization's Anatomical Therapeutic Chemical

149 (ATC) Classification System (WHO, 2013). We included all purchases of antidepressants (ATC

150 codes N06A), anxiolytics (ATC codes N05B), and hypnotics and sedatives (ATC codes N05C).

151 We divided our follow-up period into six-month intervals before and after the reference date. For

152 each interval, the outcome variable takes a value of one if a woman purchased psychotropics, and

153 of zero otherwise.

154 **MAR treatments:**

155 We identified women undergoing MAR treatments between 1995 and 2016 using administrative

156 data from the prescription, healthcare, and birth registers.

157 To identify MAR treatments in the prescription register, we updated Hemminki et al.'s[16] algorithm

158 by including two drugs introduced after 2000 and some restrictions on stand-alone treatments

159 (more information in Appendix 1). We identified children conceived through MAR by combining

160 each woman's purchases of fertility drugs with her child's birthdate (retrieved from the Finnish

161 Medical Birth Register). We excluded purchases of drugs used in infertility treatment when also

162 plausibly used to treat other medical conditions, such as cancer. The healthcare register contains

163 information on dates and types of MAR procedures in the public sector. We identified children

164 conceived through MAR by combining the dates of MAR procedures with the child's birthdate.

165 Finally, to complement this information, we identified in the birth register children born after MAR

166 treatments from 2004 onwards.

167   Our three groups of interest are women who had their first live birth after 1) a natural conception

168   (NC) or 2) a MAR conception (MAR+), and 3) women who remained childless after MAR

169   treatments (MAR-). Women who conceived after MAR treatments could be identified from any of

170   the three sources, and women who underwent MAR treatments not resulting in a live birth were

171   identified using the procedure and/or drug registers. We assumed a woman conceived naturally if

172   none of the data sources indicated that her child was conceived through MAR.

173   **Treatment length:**

174   We defined treatment length as the time between the first and last MAR treatment, and created a

175   binary variable that takes a value of one for women who underwent treatments for over two years,

176   and of zero otherwise. The two-year threshold was chosen based on the average treatment length

177   (1.98 years) in our sample. For cases in which MAR treatment was identified only through the

178   birth register (11.5% of MAR+ women) – which does not provide information on treatment length

179   – we imputed the first treatment date using age-specific average times between the start of MAR

180   treatments and conception.

181   **Period of observation:**

182   Data on psychotropic purchases from 1995 to 2018, together with data on MAR treatments

183   between 1995 and 2016, allowed us to follow women for up to 12 years before and after the

184   reference date, resulting in an unbalanced panel with a total of 48 six-month intervals (24 years),

185   and a median follow-up of 35 intervals (18 years) (appendix Table 2A).

186   **Exclusions:**

187   We excluded from the sample women who were under age 20 or over age 45 at the reference date.

188   We excluded women with triplets, which is associated with more distress.[17] We censored

189 psychotropic purchases that occurred before women reached age 18. Furthermore, we censored

190 women who were living abroad in any given year, as medication purchases are recorded only for

191 women residing in Finland. Finally, we excluded observations with missing values in the

192 covariates (0.07%). This results in a sample of 575,921 women. Of them, 97.73% had a first birth

193 in 1996-2016 (5.89% after MAR), and 2.27% remained childless after undergoing MAR

194 treatments.

195 **Statistical analysis:**

196 We estimated Generalized Estimating Equation linear models using the six-month intervals as

197 repeated panel observations and robust standard errors with exchangeable correlation structure.

198 We modelled changes in psychotropic purchases by interacting the three groups of interest (women

199 who had a live birth after a natural or a MAR conception, and women who remained childless after

200 MAR treatments) with the six-month period variable (time-varying), which resulted in 96

201 coefficients representing the probability of psychotropic use for MAR+ and MAR- against NC

202 women for each period.

203 We estimated two models. In Model 1, we adjusted for calendar year to control for increasing

204 psychotropic use over time[18], and for age, because, on average, psychotropic use increases with

205 age[19] and women who undergo MAR are older than women who conceive naturally.[20] Since

206 women who undergo MAR treatments are, on average, socio-economically advantaged[21], Model

207 2 additionally controls for time-varying socio-demographic factors: household income decile

208 (categorical), cohabitation status (binary), as well as hospital district of residence (categorical). As

209 psychotropic purchases may be affected by the transition to a higher-parity birth, Model 2 also

210 adjusts for the transition to a second- and third- or higher-order birth (binary). To investigate

211 whether treatment duration moderated the association between MAR treatments and psychotropic

212 purchases, we estimated Model 1 interacting the period variable with a variable that identified the

213 three interest groups and their treatment length, resulting in five categories: NC, MAR+ above two

214 years, MAR+ below two years, MAR- above two years, and MAR- below two years.

215 All analyses were conducted in Stata 16. The study was exempt from IRB approval as it was not

216 necessary given prior institutional approval of the overall project (European Research Council

217 grant #803958).

218 **Results:**

219 Table 1 shows that 33.4% of women purchased psychotropics in at least one six-month period

220 during the 24-year follow-up, with 15% having purchased at least once in the 12 years before the

221 first conception or last MAR cycle, and 27.3% in the following 12 years. Psychotropic use differed

222 across the three groups: 14.5% and 18.9% of NC and MAR+ women, respectively, purchased

223 psychotropics before they conceived their first child, versus 25% of MAR-.

224 We observed substantial differences across groups over time (Figure 1). Differences in

225 psychotropic purchases between women who underwent MAR treatments and women who

226 conceived naturally emerged as early as 9-10 years before conception or last treatment cycle, with

227 the latter being more likely to purchase psychotropics (MAR-: 3.25% (95% CI:2.71-3.79); MAR+:

228 2.51% (95% CI:2.27-2.75)) than the former (1.48% (95% CI:1.14-1.58)).

229 Five years before conception or the last cycle, the psychotropic purchases of women undergoing

230 MAR diverged (Figure 1). The share of women taking psychotropics remained at 4.86% for MAR+

231 women (95% CI:4.59-5.13), but increased to 6.45% (up 16.02% from the previous year) among

232 MAR- women.

233   Women who had a child either through MAR or naturally had similar levels of psychotropic use

234   from three years before conception to four years after. Nonetheless, while the probability of

235   purchasing psychotropics decreased gradually from two years before conception onwards among

236   MAR+ women, no shift occurred among NC women until right before conception. Conversely,

237   women who remained childless after MAR increased their psychotropic use sharply after the last

238   MAR cycle. This resulted in a large gap in psychotropic purchases around the reference date, with

239   9.82% (95% CI:9.29-10.36) of MAR- women purchasing psychotropics versus 2.83% (95% CI:

240   2.78-2.88) of NC women and 2.49% (95% CI:2.31-2.66) of MAR+ women. The psychotropic

241   purchases of both NC and MAR+ women increased immediately following childbirth, which

242   resulted in an attenuation of the differences between NC, MAR+, and MAR- groups. From six

243   years after the reference date onwards, the gap in psychotropic purchases between childbearing

244   and childless women remained relatively stable. The gap never fully attenuated, as 12 years after

245   the reference date, women who underwent unsuccessful MAR treatments were 45.69% and

246   59.48% more likely to purchase psychotropics than women who delivered a live birth through

247   MAR or naturally, respectively.

248   To illustrate the fluctuations in psychotropic purchases among women who underwent MAR

249   treatments and either gave birth or remained childless, Figure 2 shows the ratio of predicted

250   margins estimated using the delta method for these women relative to women who conceived

251   naturally. The figure shows a clear peak in psychotropic purchases among MAR- women.

252   When adjusting for socio-demographic characteristics in Model 2, differences in psychotropic

253   purchases across groups remained consistent with Model 1 (appendix Figure 1A). We re-estimated

254   all models excluding women who underwent fertility treatments but conceived naturally, and the

255   results held (appendix Figure 2A).

256   Lengthier MAR treatments were associated with higher psychotropic purchases regardless of the

257   treatment result (Figure 3 and appendix Table 4A). For example, women undergoing lengthier

258   treatments were 37.28% (MAR+) and 32.47% (MAR-) more likely to purchase psychotropics

259   around the date of conception or last cycle than their counterparts undergoing shorter treatments,

260   and these differences shrank after the reference date. Nonetheless, the results were consistent with

261   those of Model 1: women who had a child following MAR had lower psychotropic use than women

262   who underwent MAR and remained childless.

263   **Comment:**

264   Principal Findings:

265   The results show that psychotropic use was higher among women who remained childless after

266   MAR than among women who conceived naturally or through MAR. This pattern persisted over

267   the long term, in line with the findings of other studies.[3,5,10,12,13] Adjustment for socio-demographic

268   characteristics did not change the pattern of results.

269   However, while women who conceived via MAR had higher psychotropic use than women who

270   conceived naturally at the beginning of the observation window, their psychotropic use was similar

271   from three years before to four years after conception, and the differences over the longer term

272   remained small, and were unlikely to be clinically relevant.

273   Results in the context of what is known:

274   While the finding of similarities in long-term psychotropic use between women who conceived

275   naturally and through MAR is consistent with previous studies[5,22], in this study, we were able to

276   significantly extend the observation window, and thus to provide further evidence about the mental

277   wellbeing of this growing population group.

278 Our results significantly deepen the understanding of the link between MAR and mental health in

279 three ways. First, we showed that differences between women for whom MAR treatments did not

280 result in a live birth and women who delivered a live birth either naturally or through MAR arose

281 as early as five years before the date of conception or last MAR cycle, with the former increasing

282 their psychotropic uptake more than the latter. A possible explanation for the emergence of this

283 gap well before women ended MAR treatments is that the former may have already received a

284 diagnosis of subfertility and started the infertility treatment process. There is evidence that the start

285 of infertility treatments are related to increased levels of depression and anxiety.[22,23]

286 Second, we showed there was a sharp increase in psychotropic purchases following the last failed

287 treatment cycle, which could have been driven by the grief women felt when they realised that

288 they were unlikely to have a biological child.[13] Although this stark increase could also be related

289 to women breaking up with their partner and suspending treatment[24], adjusting for partnership

290 status in the analyses did not alter the results. By contrast, women who had a live birth either

291 naturally or after undergoing MAR treatments reduced their psychotropic purchases when trying

292 to conceive and whilst pregnant. The reasons for this could be twofold: On the one hand, the

293 decrease and slow return to pre-conception psychotropic purchase levels (around 36 months) could

294 be related to a temporary increase in subjective wellbeing around the time of first birth.[25] On the

295 other, pregnant women may decrease their psychotropic uptake during pregnancy or postpartum

296 because medications may have negative side effects[26] even though some medications are safe to

297 use during this period.[27–29]

298 Third, while the psychotropic purchases of the two MAR groups were similar at the beginning of

299 the observation window, they started diverging from around six years before conception or the last

300 MAR cycle, and the differences never fully attenuated during follow-up. The stark increase in

301 psychotropic uptake that occurred around the last treatment date for women who remained

302 childless could suggest that their worse mental health outcomes were driven more by involuntary

303 childlessness than by treatment-related stress. The analyses on the moderating role of the MAR

304 treatment length further supported this hypothesis. Within the MAR+ and MAR- groups, women

305 who underwent MAR for 2+ years had higher psychotropic use at the beginning and end of the

306 follow-up period. However, the differences became smaller over the longer term, as the purchases

307 of women who underwent longer MAR processes in both the MAR+ and MAR- groups tended to

308 converge with those of their counterparts who underwent shorter MAR processes; i.e., childbearing

309 status was more important in determining women's psychotropic purchases than MAR treatment

310 length. The results reinforce the hypothesis that higher psychotropic purchases were associated

311 with unintended childlessness after undergoing MAR treatments, while the moderating effect of

312 the length of the MAR process was small.

313 Clinical implications:

314 In light of the increasing use of MAR treatments, the results of this study underscore the

315 importance of offering counselling to women undergoing MAR treatments, particularly if their

316 attempts to conceive through MAR are unsuccessful. The provision of psychological support and

317 counselling during the MAR process may reduce the likelihood of women ending treatments

318 prematurely because of stress; better prepare women for the potential failure of treatments; and

319 help women deal with the grieving process if their desire to have a child is unfulfilled.[13] However

320 more evidence is needed to determine whether and to what extent such psychological support is

321 effective.

322 Research Implications:

323   We found that involuntary childlessness has associated mental health costs, yet more work is

324   necessary to establish what are the mechanisms underlying this association. Moreover, the results

325   show that the estimation of the MAR effect on mental health is sensitive to when it is measured

326   during the MAR process i.e. could be over or underestimated depending on how the baseline and

327   follow up are defined with respect to conception/last MAR cycle.

328   <u>Strengths and limitations:</u>

329   This study has several strengths. First, the use of a large and nationally representative register

330   allowed us to investigate the association between MAR treatments and psychotropic purchases

331   free of self-reporting biases, and to investigate this association before, upon, and after the

332   conception date (or the last cycle date for unsuccessful MAR cases) in six-months intervals.

333   Second, the long follow-up allowed us to observe psychotropic purchases when women were most

334   likely not yet struggling with infertility or MAR treatments. Third, we identified and compared

335   women who had a live birth naturally or after MAR to women who underwent MAR but whose

336   treatments did not result in a live birth, which is relevant for understanding how MAR treatments

337   and their outcomes affect women's mental health. Finally, by focusing on psychotropics, which

338   are widely used to treat depression and anxiety in women of reproductive ages, we were able to

339   observe common psychiatric disorders, and not only the more acute or severe cases (e.g.,

340   psychiatric hospitalisations).

341   The study also has limitations. First, the analysis focused on Finland, a context with subsidised

342   medical care and medication costs, which could limit the generalisability of our findings to other

343   settings. However, in contexts where MAR treatments are not as well subsidised as in Finland, the

344   association between psychotropic uptake and MAR treatments could be even stronger because of

345   higher levels of stress related to income loss. Second, although the analysis of psychotropic

346   purchases allows us to observe women who suffer from common psychiatric disorders, there are

347   other non-pharmacological interventions such as therapy and counselling which we are not

348   considering. Thirdly, we were unable to establish whether the association between MAR

349   treatments and psychotropic purchases was causal given that subfertility is associated with higher

350   levels of stress[3–5], but using psychotropics is also associated with infertility.[30,31] Nevertheless,

351   additional analyses (see appendix figure 3A) demonstrate that our main results remain similar

352   when excluding all women who had purchased psychotropics before the reference date, suggesting

353   that our conclusions are unlikely to be primarily related to an underlying higher propensity to use

354   psychotropic medications among women who undergo MAR and remain childless. Fourth, whilst

355   the use of administrative registers has many advantages, they do not provide information on the

356   causes of infertility or cases of abnormal pregnancies. Finally, we are unable to account for the

357   role of pregnancy loss because registry data record only those that require hospitalization.

358   Nevertheless, it is unlikely results are driven by miscarriages since we do not observe differences

359   in psychotropic uptake before the reference date between MAR+ and NC women even though the

360   former experience, on average, a higher number of miscarriages because they suffer from

361   subfertility.

362   Conclusions:

363   The similarities in the psychotropic purchases of women who had a live birth, whether naturally

364   or through MAR, suggest that the higher psychotropic use among women who remained childless

365   after undergoing MAR were likely driven more by involuntary childlessness than by treatment-

366   related stress. The results highlight the importance of counselling for women undergoing MAR

367   treatments, especially if their attempts to conceive are unsuccessful.

368

369

References

1. De Geyter C, Calhaz-Jorge C, Kupka MS, et al. ART in Europe, 2015: results generated from European registries by ESHRE. *Hum Reprod Open*. 2020;2020(1). doi:10.1093/hropen/hoz038

2. De Geyter C, Wyns C, Calhaz-Jorge C, et al. 20 years of the European IVF-monitoring Consortium registry: what have we learned? A comparison with registries from two other regions. *Hum Reprod*. 2020;35(12):2832-2849. doi:10.1093/humrep/deaa250

3. Hogström L, Johansson M, Janson PO, et al. Quality of life after adopting compared with childbirth with or without assisted reproduction. *Acta Obstet Gynecol Scand*. 2012;91(9):1077-1085. doi:https://doi.org/10.1111/j.1600-0412.2012.01491.x

4. Vahratian A, Smith YR, Dorman M, Flynn HA. Longitudinal depressive symptoms and state anxiety among women using assisted reproductive technology. *Fertil Steril*. 2011;95(3):1192-1194. doi:10.1016/j.fertnstert.2010.09.063

5. Vikström J, Josefsson A, Bladh M, Sydsjö G. Mental health in women 20–23 years after IVF treatment: a Swedish cross-sectional study. *BMJ Open*. 2015;5(10):e009426. doi:10.1136/bmjopen-2015-009426

6. Yli-Kuha AN, Gissler M, Klemetti R, Luoto R, Koivisto E, Hemminki E. Psychiatric disorders leading to hospitalization before and after infertility treatments. *Hum Reprod*. 2010;25(8):2018-2023. doi:10.1093/humrep/deq164

7. Klemetti R, Raitanen J, Sihvo S, Saarni S, Koponen P. Infertility, mental disorders and well-being--a nationwide survey. *Acta Obstet Gynecol Scand*. 2010;89(5):677-682. doi:10.3109/00016341003623746

8. Gameiro S, Finnigan A. Long-term adjustment to unmet parenthood goals following ART: a systematic review and meta-analysis. *Hum Reprod Update*. 2017;23(3):322-337. doi:10.1093/humupd/dmx001

9. Baldur-Felskov B, Kjaer SK, Albieri V, et al. Psychiatric disorders in women with fertility problems: results from a large Danish register-based cohort study. *Hum Reprod*. 2013;28(3):683-690. doi:10.1093/humrep/des422

10. Johansson M, Adolfsson A, Berg M, et al. Gender perspective on quality of life, comparisons between groups 4–5.5 years after unsuccessful or successful IVF treatment. *Acta Obstet Gynecol Scand*. 2010;89(5):683-691. doi:https://doi.org/10.3109/00016341003657892

11. Milazzo A, Mnatzaganian G, Elshaug AG, Hemphill SA, Hiller JE, Group AHS. Depression and anxiety outcomes associated with failed assisted reproductive technologies: a systematic review and meta-analysis. *PloS One*. 2016;11(11):e0165805.

405 12. Agerbo E, Mortensen PB, Munk-Olsen T. Childlessness, parental mortality and psychiatric
406   illness: a natural experiment based on in vitro fertility treatment and adoption. *J Epidemiol*
407   *Community Health*. 2013;67(4):374-376. doi:10.1136/jech-2012-201387

408 13. Gameiro S, van den Belt-Dusebout AW, Bleiker E, Braat D, van Leeuwen FE, Verhaak
409   CM. Do children make you happier? Sustained child-wish and mental health in women 11–
410   17 years after fertility treatment. *Hum Reprod*. 2014;29(10):2238-2246.
411   doi:10.1093/humrep/deu178

412 14. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the
413   pharmacological treatment of anxiety disorders: recommendations from the British
414   Association for Psychopharmacology. *J Psychopharmacol (Oxf)*. 2005;19(6):567-596.

415 15. Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating
416   depressive disorders with antidepressants: a revision of the 2000 British Association for
417   Psychopharmacology guidelines. *J Psychopharmacol (Oxf)*. 2008;22(4):343-396.

418 16. Hemminki E, Klemetti R, Rinta-Paavola M, Martikainen J. Identifying exposures of in vitro
419   fertilization from drug reimbursement files: a case study from Finland. *Med Inform Internet*
420   *Med*. 2003;28(4):279-289. doi:10.1080/14639230310001621666

421 17. Garel M, Blondel B. Assessment at 1 year of the psychological consequences of having
422   triplets. *Hum Reprod*. 1992;7(5):729-732.

423 18. Metsä-Simola N, Martikainen P. Divorce and changes in the prevalence of psychotropic
424   medication use: A register-based longitudinal study among middle-aged Finns. *Soc Sci*
425   *Med*. 2013;94:71-80. doi:10.1016/j.socscimed.2013.06.027

426 19. Kessler RC, Demler O, Frank RG, et al. Prevalence and treatment of mental disorders, 1990
427   to 2003. *N Engl J Med*. 2005;352(24):2515-2523. doi:10.1056/NEJMsa043266

428 20. Chambers GM, Hoang VP, Sullivan EA, et al. The impact of consumer affordability on
429   access to assisted reproductive technologies and embryo transfer practices: An international
430   analysis. *Fertil Steril*. 2014;101(1):191-198.e4. doi:10.1016/j.fertnstert.2013.09.005

431 21. Goisis A, Håberg SE, Hanevik HI, Magnus MC, Kravdal Ø. The demographics of assisted
432   reproductive technology births in a Nordic country. *Hum Reprod*. 2020;35(6):1441-1450.
433   doi:10.1093/humrep/deaa055

434 22. Verhaak CM, Smeenk JMJ, Evers AWM, Kremer J a. M, Kraaimaat FW, Braat DDM.
435   Women's emotional adjustment to IVF: a systematic review of 25 years of research. *Hum*
436   *Reprod Update*. 2007;13(1):27-36. doi:10.1093/humupd/dml040

437 23. Knoll N, Schwarzer R, Pfüller B, Kienle R. Transmission of Depressive Symptoms. *Eur*
438   *Psychol*. 2009;14(1):7-17. doi:10.1027/1016-9040.14.1.7

439   24. Olivius C, Friden B, Borg G, Bergh C. Why do couples discontinue in vitro fertilization
440   treatment? a cohort study. *Fertil Steril*. 2004;81(2):258-261.
441   doi:10.1016/j.fertnstert.2003.06.029

442   25. Myrskylä M, Margolis R. Happiness: Before and after the kids. *Demography*.
443   2014;51(5):1843-1866.

444   26. Marchocki Z, Russell NE, Donoghue KO. Selective serotonin reuptake inhibitors and
445   pregnancy: A review of maternal, fetal and neonatal risks and benefits. *Obstet Med*.
446   2013;6(4):155-158. doi:10.1177/1753495X13495194

447   27. Jimenez-Solem E, Andersen JT, Petersen M, et al. Prevalence of Antidepressant Use during
448   Pregnancy in Denmark, a Nation-Wide Cohort Study. *PLOS ONE*. 2013;8(4):e63034.
449   doi:10.1371/journal.pone.0063034

450   28. Marchesi C, Ossola P, Amerio A, Daniel BD, Tonna M, De Panfilis C. Clinical
451   management of perinatal anxiety disorders: A systematic review. *J Affect Disord*.
452   2016;190:543-550. doi:10.1016/j.jad.2015.11.004

453   29. Zoega H, Kieler H, Nørgaard M, et al. Use of SSRI and SNRI Antidepressants during
454   Pregnancy: A Population-Based Study from Denmark, Iceland, Norway and Sweden. *PLOS
455   ONE*. 2015;10(12):e0144474. doi:10.1371/journal.pone.0144474

456   30. Casilla-Lennon MM, Meltzer-Brody S, Steiner AZ. The effect of antidepressants on
457   fertility. *Am J Obstet Gynecol*. 2016;215(3):314.e1-314.e5. doi:10.1016/j.ajog.2016.01.170

458   31. Cesta CE, Viktorin A, Olsson H, et al. Depression, anxiety, and antidepressant treatment in
459   women: association with in vitro fertilization outcome. *Fertil Steril*. 2016;105(6):1594-
460   1602.e3. doi:10.1016/j.fertnstert.2016.01.036

461

462

463 **Tables:**

464

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

Psychotropic purchases:	NC		MAR+		MAR-		Total	
	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	

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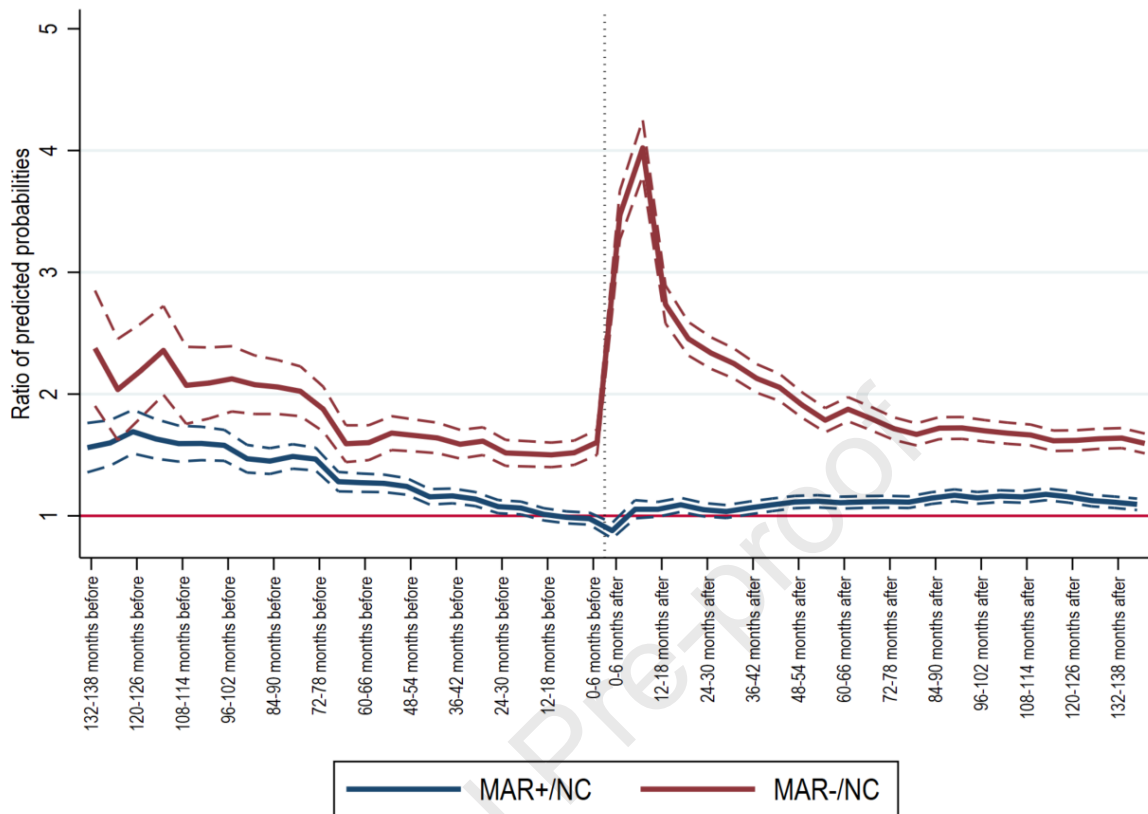467 treatments, and MAR- to women who underwent MAR treatments and remained childless.

468

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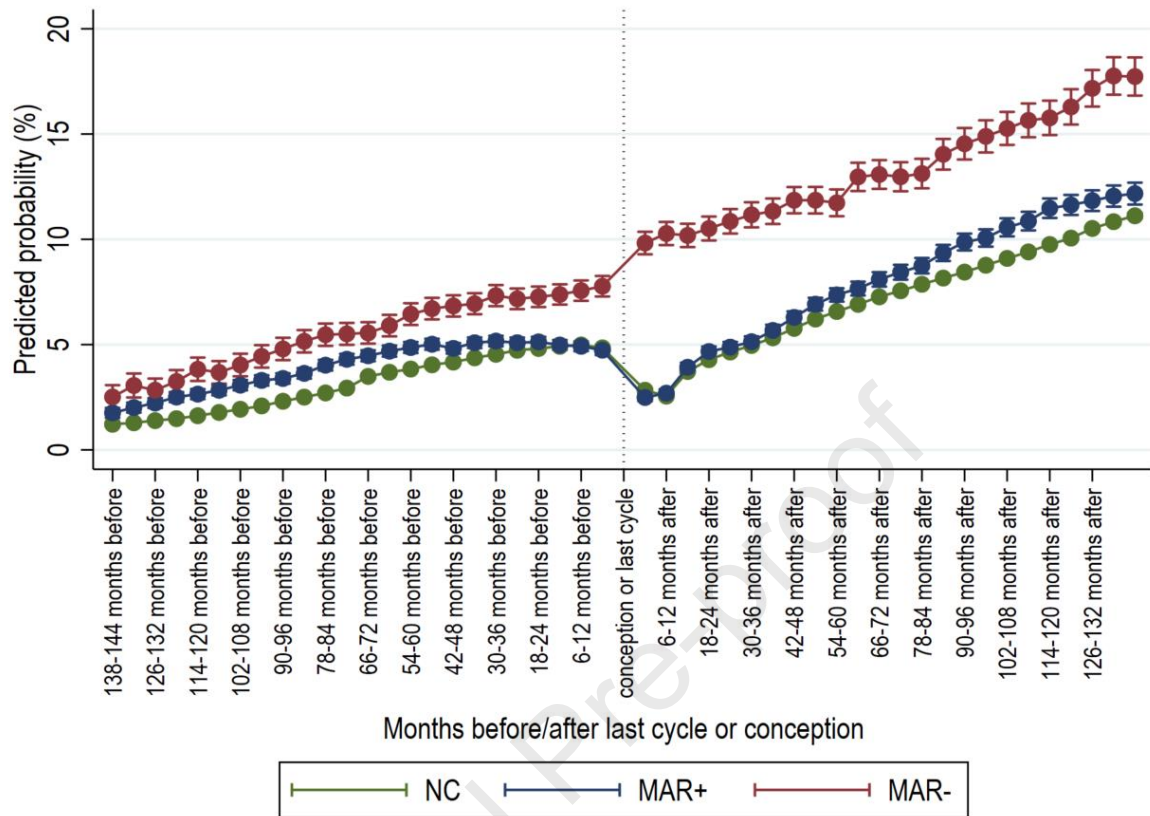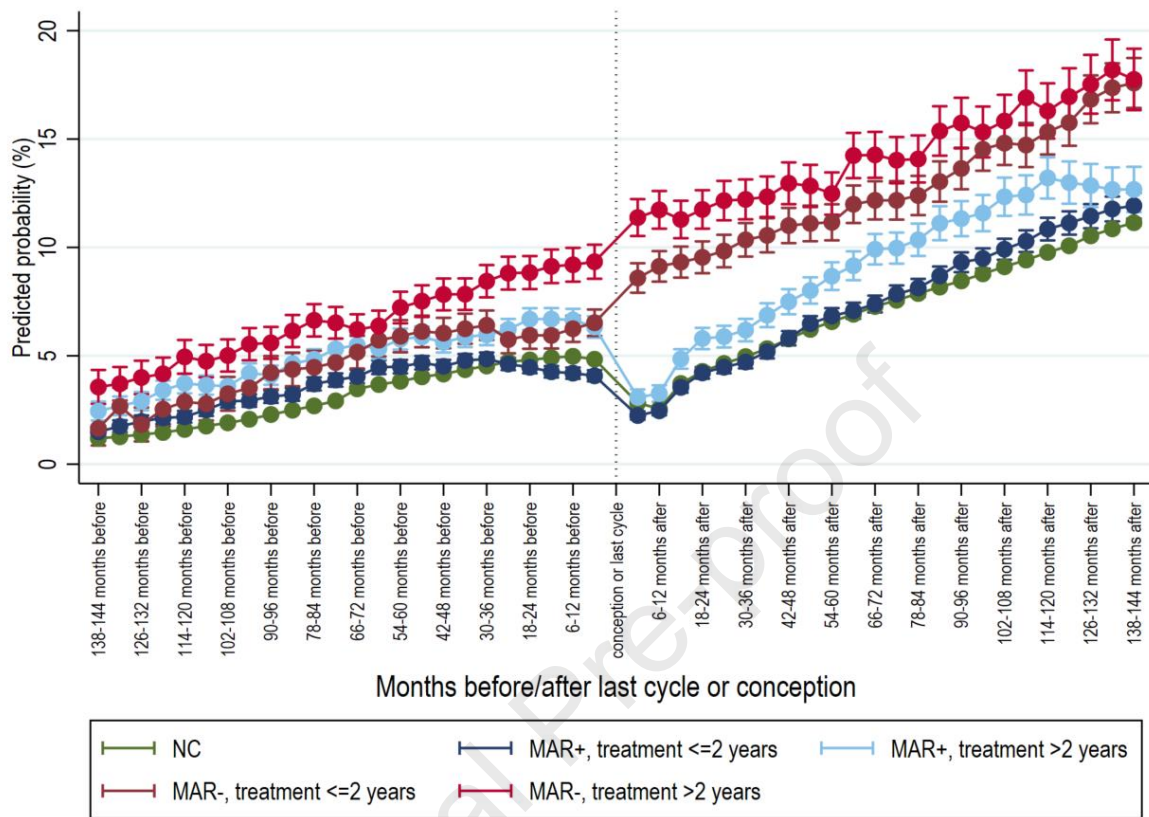

Note: NC refers to women who conceived naturally, MAR+ to women who conceived after MAR treatments, and MAR- to women who underwent MAR treatments but did not deliver a live birth by the end of 2017. Model 1 adjusts for calendar year and age.

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.

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.