UNIVERSITY OF COPENHAGEN
FACULTY OR DEPARTMENT

PhD Thesis

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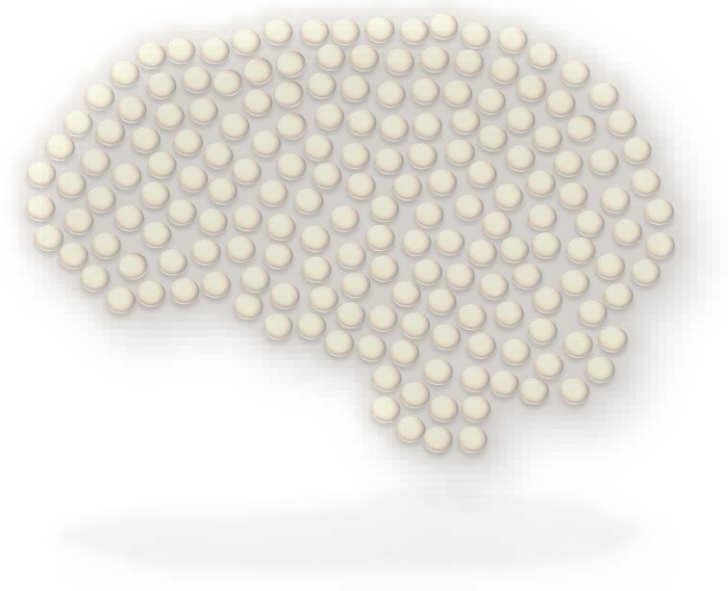

Hormonal contributions to depressive episodes in women

Insights from register-based cohort studies from Denmark

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This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on February 23, 2024.

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Table of contents

List of studies

I. Association between intrauterine system hormone dose and depression risk

Søren Vinther Larsen, Anders Pretzmann Mikkelsen, Brice Ozenne, Trine Munk-Olsen, Øjvind Lidegaard, Vibe Gedso Frokjaer

Submitted November, 2023 and revised and resubmitted February, 2024.

II. Depression associated with hormonal contraceptive use as a risk indicator for postpartum depression

Søren Vinther Larsen, Anders Pretzmann Mikkelsen, Øjvind Lidegaard, Vibe Gedso Frokjaer

Published in JAMA Psychiatry, 2023, doi: 10.1001/jamapsychiatry.2023.0807.

III. Postpartum hormonal contraceptive use and risk of depression

Søren Vinther Larsen, Brice Ozenne, Anders Pretzmann Mikkelsen, Xiaoqin Liu, Kathrine Bang Madsen, Trine Munk-Olsen, Øjvind Lidegaard, Vibe Gedso Frokjaer

Manuscript in prep.

Related studies not included in this thesis:

1. **Larsen SV**, Mikkelsen AP, Madsen KB, Liu X, Munk-Olsen T, Frokjaer VG, Lidegaard Ø, *Postpartum hormonal contraceptive use in Denmark during 1997-2021*, In press in MedRxiv.
2. Johansson T, **Larsen SV**, Bui M, Ek WE, Karlsson T, Johansson Å, *Population-based cohort study of oral contraceptive use and risk of depression*, Epidemiol. Psychiatr. Sci., Volume 32, 2023, e39. doi: https://doi.org/10.1017/S2045796023000525
3. Jensen KHR, McCulloch DEW, Olsen AS, Bruzzone SEP, **Larsen SV**, Fisher PM, Frokjaer VG, *Effects of an Oral Contraceptive on Dynamic Brain States and Network Modularity in a Serial Single-Subject Study*, Front. Neurosci., 14 June 2022 | https://doi.org/10.3389/fnins.2022.855582
4. **Larsen SV**, Ozenne B, Köhler-Forsberg K, Poulsen AS, Dam VH, Svarer C, Knudsen GM, Jørgensen MB, Frokjaer VG, *The Impact of Hormonal Contraceptive Use on Serotonergic Neurotransmission and Antidepressant Treatment Response: Results From the NeuroPharm 1 Study*, Front. Endocrinol., 11 March 2022 | https://doi.org/10.3389/fendo.2022.799675

Acknowledgement

I would like to express my heartfelt gratitude to my supervisor, Vibe Gedsø Frøkjær, for her helpful guidance and support. Thank you for entrusting me with responsibilities that allowed me to develop as a researcher. Thank you for being an inspiration, for showing me enthusiasm and spirit every day, for trusting in me, and for supporting me in pursuing my ideas.

Thank you to my co-supervisors, Øjvind Lidegaard, for giving me the opportunity to work in the research field of epidemiology and for your ongoing mentorship and support, and Annamaria Giraldi, for guidance and inspiration, for sharing your wisdom and critical mind.

I would like to express my deepest gratitude to Anders Mikkelsen and Brice Ozenne. Anders, I cannot thank you enough for your assistance in navigating the national registers and for your readiness to provide guidance whenever needed. Brice, your guidance in statistics has been incredibly valuable to me and I am deeply thankful for your patience and dedication in helping and educating me in statistics.

Thank you, Trine Munk Olsen, for hosting me during my secondment in Aarhus, and for being an inspiration. Thank you, Xiaoqin Liu and Kathrine Bank-Madsen for sharing your expertise in epidemiology.

I am deeply grateful to Lone Freyr and Emilie Henriksen for assisting me in the Pill Project, for always being helpful, and for being so kind. Thank you, Arafat Nasser, for always being supportive, for assisting with the biological samples, and for all our great conversations. Thank you, Annika Rasmussen, Mette Clausen, Anna Kauffmann, and Mette Hochheim for all your efforts with the Pill Project. It has been the best support I could have wished for. I would not have succeeded without you. Thank you to the radiochemistry unit and all the rest of the colleagues, collaborators, and participants who have contributed to the Pill Project. In particular, Kristoffer Brendstrup-Brix, Kristian Jensen, Malene Ravn Aarestrup, Malthe Andersen, Anders Spanggaard, Svitlana Olsen, Gerda Thomsen, Claus Svarer, and Patrick Fisher, your contributions have been invaluable. A special thanks to Dorthe Givard, Peter Jensen, and Birgit Tang for making every day easier, we would be lost without you, and to Gitte Moos Knudsen, for your support and trust and for making it all possible.

Thank you to the whole NRU for being the best workplace, to my office mates for making every day more fun, Drummond McCulloch, Clara Madsen, Sara Marie Larsen, Ruben Dörfel, Nakul Raval, Gjertrud Laurell, and Annette Johansen. Annette, for sharing and listening to ideas and thoughts within and outside research. Stinne Høgh for sharing the journey, both ups and downs, and for being a great travel companion. Thank you to other colleagues, I have had the privilege of working with during my time at NRU, including, but not restricted to Silvia Bruzzone, Maja Marstrand-Jørgensen, Kristian Larsen, Miriam Navarro, Sidsel Andersen, Giske Opheim, and Sanjay Aripaka. Thank you to current and past students for giving NRU such an energetic atmosphere. For having inspired me from the beginning of my research journey, and for having created the best possible atmosphere at NRU, a special thanks to Kristin Köhler-Forsberg, Martin Korsbak, Camilla Borgsted, Cheng Ip, Vincent Beliveau, Lene Donovan, Sofia Armand, Asbjørn Poulsen, Ida Marie Brandt, Emily Beaman, and Vibeke Dam.

I want to express my gratitude to my family and friends for their enduring patience. Especially, I want to extend my heartfelt thanks to my partner, Siri, for your patience and understanding throughout this journey. Your encouragement has been my strength, and I am immensely grateful for your unwavering support.

Funding

The studies included in this thesis were funded by The Independent Research Fund Denmark (grant identifier: 0134-00278B and 7025-00111B). The Independent Research Fund Denmark had no role in designing, analyzing, interpreting, or writing of the studies.

Summary

Depression is twice as common in women compared to men with a lifetime prevalence of 17-21%. This may be attributed to a combination of social, psychological, and biological factors. Some evidence points to hormonal contributions to depressive episodes across women's reproductive lives, particularly, some phases associated with significant hormonal fluctuations are linked to an increased appearance of depressive symptoms such as in the premenstrual, postpartum, and the perimenopausal phase. Additionally, emerging evidence links the use of hormonal contraception to an increased risk of depression. Our understanding of how changes in the hormonal milieu can contribute to depressive episodes and whether it is the same women who are at risk across different reproductive events remains unknown.

This thesis aimed to use cohort studies based on Danish national health registry data to investigate the link between progestin exposure and depression risk, to determine if depressive episodes across different reproductive events are linked, and if hormonal contraceptive use in the postpartum period is linked to an increased risk of depression. In all studies, hormonal contraceptive exposure started when a prescription was filled, while depression was identified either through filled prescriptions of antidepressant medication recorded in the National Prescription Register or through hospital diagnoses of depression in the National Patient Register.

Study I compared the 1-year risk of depression in first-time users of three different hormonal intrauterine systems with different progestin release dosages; low, medium, and high levonorgestrel-release dose. Study II investigated if prior depression associated with hormonal contraceptive initiation was associated with an increased risk of postpartum depression relative to prior depression not associated with hormonal contraceptive initiation. Study III investigated if hormonal contraceptive initiation postpartum was associated with an increased risk of depression within 12 months after delivery.

The studies showed evidence of an association between the progestin-release dose in intrauterine systems and the risk of depression such that a higher dose was associated with a higher risk of depression and an association between postpartum hormonal contraceptive use and depression risk. Additionally, it showed that depression linked to hormonal contraceptive use may indicate postpartum depression susceptibility. Such insights are important to be conveyed at contraceptive counseling to establish awareness of potential side effects. Moreover, it could aid in identifying women who are more vulnerable to hormonal fluctuations, which may inform future prevention and treatment strategies for depression.

Dansk resumé

Depression er dobbelt så hyppig hos kvinder end den er hos mænd med en livstidsrisiko på 17-21%. Dette skyldes formentlig en kombination af sociale, psykologiske, og biologiske faktorer. Evidens peger på et potentielt hormonbidrag til nogle depressive episoder på tværs af kvinders reproduktive alder. Særligt nogle faser, der er koblet til hormonelle fluktuationer, er forbundet med en øget risiko for depression, såsom i den præmenstruelle fase, i efterfødselsperioden samt i overgangsalderen. Derudover tyder mere og mere evidens på, at der kan være en sammenhæng mellem brugen af hormonel prævention og udvikling af depression. Vores forståelse for, hvordan hormonændringer kan bidrage til udvikling af depressive episoder, og om det er de samme kvinder, der udvikler depression på tværs af de forskellige reproduktive begivenheder, er fortsat uklart.

Formålet med denne afhandling var at bruge kohortestudier baseret på de danske sundhedsregistre til at undersøge koblingen mellem hormoneksponering og risikoen for udvikling af depression, om depressive episoder er forbundne på tværs af reproduktive begivenheder, samt om opstart på hormonel prævention i efterfødselsperioden øger risikoen for depression. I alle studierne blev brugen af hormonel prævention registreret, når en recept blev indløst på et apotek, og en depressiv episode enten ved indløst recept på antidepressiv medicin eller ved tildeling af en hospitalsdiagnose med depression registeret i hhv. Lægemiddelstatistikregisteret og Landspatientregisteret.

Studie I sammenlignede risikoen for depression efter et år hos førstegangsbrugere af tre forskellige typer af hormonspiraler med forskellige frigivelsesdosis; lav-, mellem-, og høj levonorgestrel frigivelsesdosis. Studie II bestemte, om tidligere depression i forbindelse med opstart på hormonel prævention var forbundet med en øget risiko for fødselsdepression i forhold til at have en tidligere depression, der ikke opstod i forbindelse med opstart på hormonel prævention. Studie III bestemte, om opstart på hormonel prævention i efterfødselsperioden var forbundet med en forhøjet risiko for udvikling af depression inden for 12 måneder efter fødslen.

Studierne viste evidens for en forbindelse mellem hormonspiralernes hormonmængde og risiko for depression, således at en højere mængde var forbundet med en højere risiko, og at opstart på hormonel prævention i efterfødselsperioden øgede risikoen for depression. Derudover viste de, at depression forbundet til opstart på hormonel prævention indikerede en højere risiko for udvikling af fødselsdepression. Denne viden er vigtigt i formidlingen om bivirkninger ved præventionsrådgivningen. Derudover, kan denne viden potentielt hjælpe med at identificere de kvinder, der har en større risiko for at udvikle en fødselsdepression, hvilket kan være med til at understøtte fremtidige behandlings- og forebyggelsesstrategier ved depression.

Abbreviations

5-HT4R	Serotonin 4 receptor
ALLO	Allopregnanolone
ATC	Anatomical Therapeutic Chemical
CHC	Combined hormonal contraception
CI	Confidence interval
COC	Combined oral contraception
GABA	Gamma-aminobutyric acid
HC	Hormonal contraception
HPG	axis: hypothalamic-pituitary-gonadal axis
HR	Hazard ratio
ICD-8	International Classification of Diseases version 8
ICD-10	International Classification of Diseases version 10
LNG	Levonorgestrel
LNG-IUS	Levonorgestrel-releasing intrauterine system
OR	Odds ratio
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome
PPD	Postpartum depression
POC	Progestogen-only contraception
POP	Progestogen-only pill.

1. Background

An estimated 5% of the global population suffers from depression (Ferrari et al. 2013). In 2019, it ranked the second-highest disorder measured in years lived with disability and 13th highest on disability-adjusted life-years (GBD 2019 Mental Disorders Collaborators 2022). This trend was particularly pronounced in adolescents and young adults, where it ranked as the second-highest (Abbafati et al. 2020). It is projected by the World Health Organization that depression will be the leading cause of disease burden worldwide by 2030 (World Health Organization 2011). Epidemiological evidence across both high and low-income countries shows that about twice as many women develop depression compared to men, with a lifetime prevalence estimated at 17-21% in women vs. 10-13% in men (Kessler et al. 1993; Kuehner 2017; Pedersen et al. 2014). The reason for this is not well understood and likely involves an interplay between multiple factors, including environmental, psychological, and biological (Kuehner 2017). Understanding the causes behind such sex differences could enhance our understanding of depression pathophysiology, potentially leading to relevant patient stratifications and the development of targeted prevention and treatment strategies.

The scope of this thesis is to illuminate potential hormonal contributions to depressive episodes in women across the reproductive lifespan. Specifically, it will focus on the role of exogenous hormone exposure, in the form of hormonal contraceptive use, in relation to the development of depressive episodes.

1.1 Hormonal Contributions to Depressive Episodes

The higher incidence of depression in women compared to men is not observed before puberty, as similar or even higher rates are observed in prepubertal boys compared to prepubertal girls (Douglas and Scott 2014; Hankin et al. 2015). The incidence drastically changes between 10-15 years of age following advancing pubertal stages in pubertal girls (Patton et al. 2008). Here, the depression incidence increases to twice that in boys, which lasts through adulthood (Kessler et al. 1993; Salk, Hyde, and Abramson 2017). Across women's reproductive lives, depressive episodes coincide with reproductive events including the emergence of depressive symptoms in the premenstrual phase of the menstrual cycle, in relation to pregnancy and childbirth, and during the perimenopausal transition (Altemus, Sarvaiya, and Neill Epperson 2014).

The pubertal transition involves the maturation or the re-activation of the hypothalamic-pituitary-gonadal (HPG) axis resulting in irregular hormonal fluctuations around the menarche (Diaz, Laufer, and Breech 2006). During the menstrual cycle, luteinization

hormone, follicular stimulating hormone, estradiol, and progesterone follow a cyclic pattern orchestrated by feedback loops in the HPG axis. The menstrual cycle is divided into a follicular phase with low progesterone and increasing estradiol and follicular stimulating hormone levels culminating in a luteinization hormone surge triggering ovulation. This is followed by the luteal phase where progesterone and estradiol levels increase and subsequently drop to baseline levels resulting in the onset of menstruation (**Figure 1**) (Draper et al. 2018).

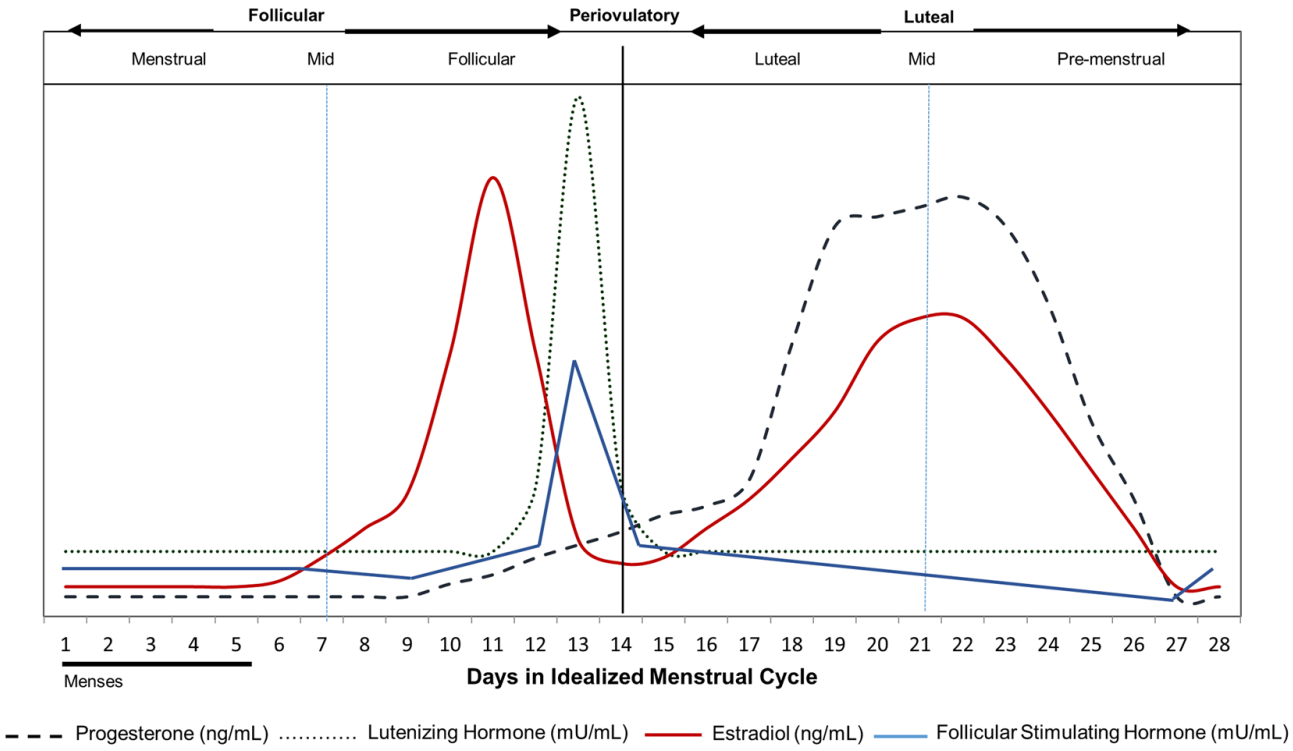

Figure 1. Hormones across the menstrual cycle. From Draper, C.F., Duisters, K., Weger, B. et al. Sci Rep 8, 14568, 2018 (14) (http://creativecommons.org/licenses/by/4.0/).

Some women are sensitive to the hormonal changes across the menstrual cycle to an extent recognized as premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD). These are disorders characterized by repeated emergence of physical symptoms such as menstrual cramps, bloating, and breast tenderness, but also affective symptoms such as mood lability and depressive symptoms in the late luteal phase lasting until the early follicular phase causing severe daily life disability (Hantsoo and Epperson 2015). An estimated 3-8% is suffering from PMDD, but even as many as 13-18% may experience a degree of debilitating premenstrual symptoms (Halbreich et al. 2003). In an experimental setting, it has been shown that women meeting diagnostic criteria for PMS are reactive to pharmacological hormone manipulation; downregulation of endogenous hormones decreased mood symptoms, which reappeared after re-

introduction of both estradiol and progesterone, separately. This was not the case for women not meeting PMS criteria (Schmidt et al. 1998).

An estimated 13% of women develop a depressive episode in the postpartum period (O'Hara and Swain 1996), and some already develop depression during pregnancy (Bennett et al. 2004). During pregnancy and especially at the end of pregnancy, progesterone and estrogen levels reach 10- to a 1000-fold higher level than outside pregnancy (Reshef and Taylor 2000). The transition following delivery includes a sudden hormonal withdrawal within hours after delivery and it is hypothesized that these abrupt hormonal transitions can contribute to the development of depressive episodes in some women (Schiller, Meltzer-Brody, and Rubinow 2015). This is supported by a study showing that women with a history of PPD were sensitive to pharmacologically-induced withdrawal of estradiol and progesterone resulting in the emergence of depressive symptoms, which was apparent in the women with no prior PPD (Bloch et al. 2000). Accordingly, estradiol treatment after childbirth has been suggested as a promising treatment or even as prophylaxis for PPD (Gregoire et al. 1996; Høgh et al. 2021; Sichel et al. 1995).

The perimenopausal transition has an average length of 4 years and involves irregular hormonal fluctuations and irregular menstrual cycles, which are linked to physical and affective symptoms such as vasomotor symptoms, sleep disturbances, and mood lability (Santoro et al. 2021). Evidence supports that women have a 2-4 times increased risk of incident depression during this transition and the development of depressive symptoms has been correlated with the magnitude of fluctuation in estradiol levels (Bromberger et al. 2011; Cohen et al. 2006; Freeman et al. 2004, 2006; de Kruif, Spijker, and Molendijk 2016). Estradiol plus intermittent micronized progesterone has shown promising treatment and prophylactic effects for perimenopausal depression (Gordon et al. 2018; De Novaes Soares et al. 2001), however, due to an increased risk of thromboembolic events and breast cancer, it is not used in general preventive strategies (Rossouw et al. 2002).

More recent evidence has shed light on the potential role of exposure to synthetic hormones in the form of hormonal contraception (HC) and the risk of developing depression. This will be addressed in sections 1.4 and 1.5.

1.2 Hormonal Contraception

The first HC was approved for contraceptive purposes in 1961 by the Food and Drug Administration (Dhont 2010). HC played a significant role in advancing women's rights by promoting sexual liberation and by empowering women to take control over family planning and

by avoiding unwanted pregnancies and dangerous illegal abortions (Dhont 2010). Furthermore, HC use has beneficial effects on various gynaecological disorders such as polycystic ovarian syndrome (Teede et al. 2018), endometrioses (Harada et al. 2008), dysmenorrhea (Davis et al. 2005), and menorrhagia (Lethaby et al. 2019). However, it also carries side effects such as nausea, breast tenderness, and elevated risk of thromboembolic events (Dhont 2010). This led to a substantial reduction in hormone content in the following decades after its release.

Today, HC exists in different formulations and with different methods of administration. All HC contain synthetic progesterone and some are combined with estrogen either in the form of estradiol or estestrol or the synthetic ethinylestradiol (Cooper, Patel, and Mahdy 2023). They can be divided into those administered orally, i.e., the combined oral contraceptives (COC) and progestogen-only pills (POP), and non-orally in the form of combined non-oral contraceptives (CNOC) and progestogen-non-oral contraceptives (PNOC). COC is further categorized into generations dependent on the progestogen content in 1^{st}-4^{th} and non-classified generations (Kristensen and Lidegaard 2021). CNOC includes the patch and the vaginal ring, and PNOC includes depot injection, the implant, and the levonorgestrel-releasing intrauterine system (LNG-IUS).

The mechanism of action of HC depends on the hormonal content (Rivera, Yacobson, and Grimes 1999); the estrogen and the progestogen provide negative feedback on the release of the gonadotrophin-releasing hormone from the hypothalamus, which inhibits the release of the follicular stimulating hormone and the luteinization hormone from the pituitary gland resulting in inhibition of the maturation of dominant follicle and ovulation. In addition, the estrogen has proliferative effects on the endothelium, reducing the risk of breakthrough bleeding, while the progestogen thins the endothelium lining and thickens the cervical mucus, preventing sperm penetration and implantation of the oocyte. LNG-IUS mainly works through these local mechanisms, however, it may still show anovulatory effects, especially during the early treatment period (Apter et al. 2014).

1.3 Prevalence of Hormonal Contraceptive Use

More than a quarter of a billion worldwide use HC (United Nations Department of Economic and Social Affairs 2022). The type most frequently used depends largely on the country; implants and injections are frequently used in countries with low sociodemographic index and oral contraceptives in countries with high index whereas patches and rings are rarely used across most countries (Haakenstad et al. 2022). In the Nordic countries, 30-40% of women in the reproductive age use HC (Lindh et al. 2017). In 2013, COC was the most commonly used form,

followed by LNG-IUS (Lindh et al. 2017). COC was predominantly used by younger women, while the utilization of POP and LNG-IUS increased with increasing age. In Denmark, more and more are using PNOC, especially the LNG-IUS, and since 2010 there has been a shift from 3rd and 4th to 2nd generation COC due to the discovery of a higher risk of thromboembolic events in the former two (**Figure 2**) (Lidegaard et al. 2011).

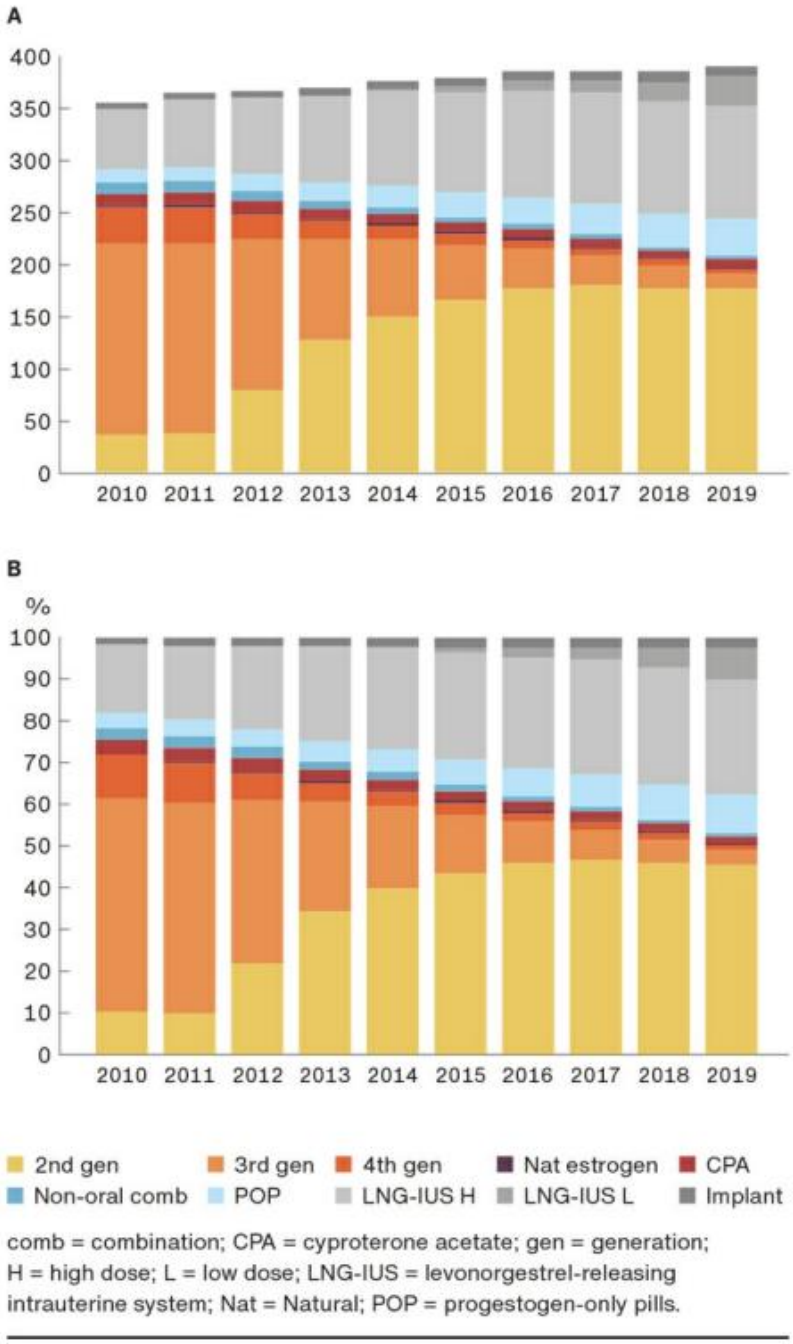

Figure 2. "Absolute (A) and relative (B) defined daily doses per 1,000 per day of ten different hormonal contraceptive types from 2010-2019 in women aged 15-49 years". From Kristensen, S.I.P., Lidegaard Ø., Dan Med J 2021;68(6):A08200599 (Kristensen and Lidegaard 2021) (https://creativecommons.org/licenses/by-nc-nd/4.0/deed.da).

Women start to use HC earlier and earlier in Denmark coinciding with the pubertal transition and as many as 85% have used it at 20 years of age (Løkkegaard and Nielsen 2014). Childbirth marks another reproductive event whereafter many women start HC; as many as 40% of women in Denmark initiate HC within the first year after giving birth (in press). Through the last 20 years, mothers have started earlier and earlier on HC after giving birth and more and more are starting on progestogen-only contraceptives (POC) instead of COC making up two-thirds of HC types used in 2021 in the postpartum period (**Figure 3**). This is in line with recommendations from the World Health Organization stating that POC is the preferred choice over combined hormonal contraception (CHC) due to the increased risk of thromboembolic events in the postpartum period and due to the putative negative effect CHC may have on lactation (World Health Organization 2010).

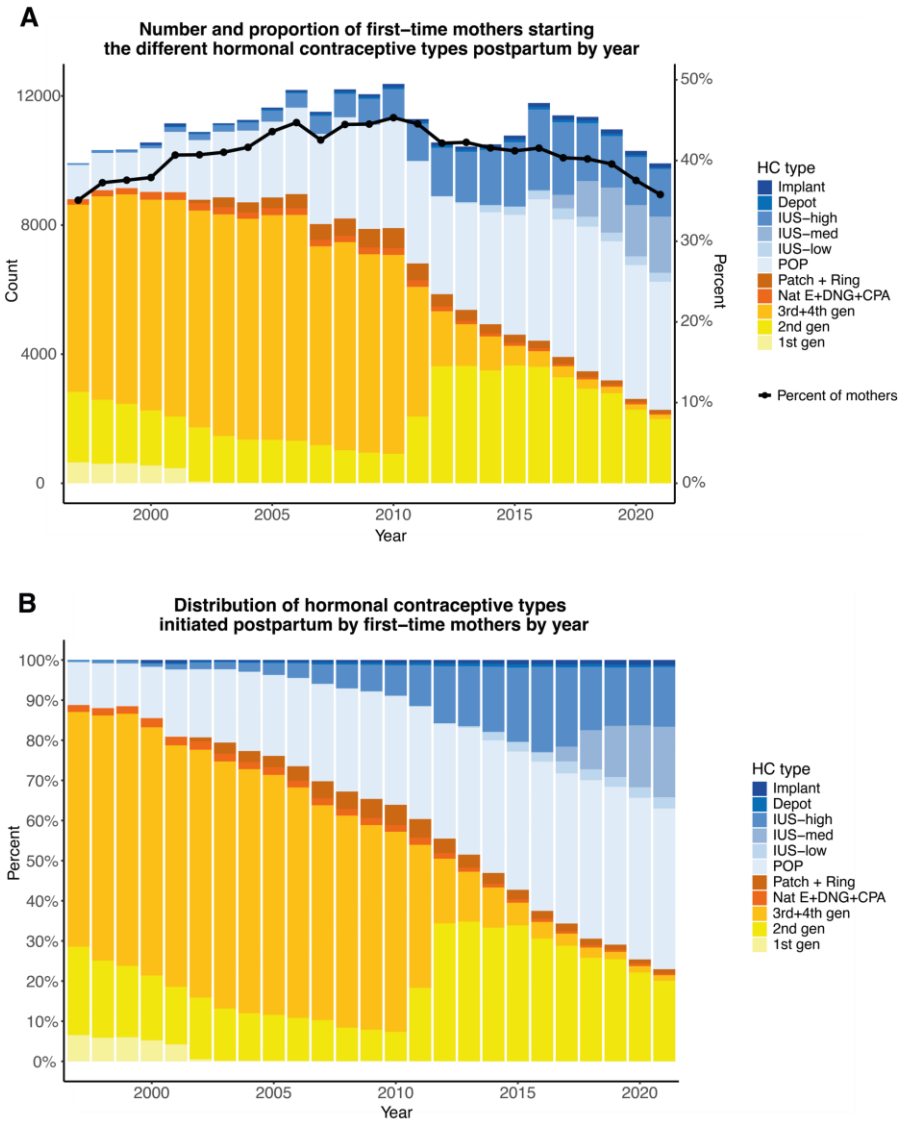

Figure 3. Initiation of different hormonal contraceptive types within 12 months postpartum in Denmark from 1997 to 2021. From Larsen SV et al 2024, Postpartum hormonal contraceptive use in Denmark during 1997-2021, In press in MedRxiv (https://creativecommons.org/licenses/by/4.0/).

1.4 Hormonal Contraception and Risk of Depression

The link between HC use and depressive symptoms traces back to the 1960s-70s, a period when the hormonal content was higher compared to modern HC formulations (Slap, 1981). The reduction in hormonal content in the following decades may have reduced the extent of mood symptoms (Brace & McCauley, 1997; Deijen et al., 1992). Nevertheless, mood symptoms persist as a significant contributor to early discontinuation; as many as 30% of users discontinue HC use within the first six months, with a considerable portion attributing their discontinuation to side effects. Mood symptoms and decreased sexual desire are among the most frequently reported reasons for discontinuation (Daniels & Mosher, 2013; Hines et al., 2023; Larsson et al., 1997; Martell et al., 2023; Rosenberg & Waugh, 1998; Sanders et al., 2001). However, the debate over whether HC can induce depressive episodes persists due to inconsistent study findings. More research, including large prospective studies involving incident users, is needed to elucidate this link (Fruzzetti & Fidecicchi, 2020; Kraft et al., 2024; Robakis et al., 2019; Schaffir et al., 2016).

Randomized, placebo-controlled studies have shown no clear evidence between HC use and depression, but they are likely underpowered and susceptible to healthy user bias (de Wit, de Vries, de Boer, Scheper, Fokkema, Schoevers, et al., 2021). Among the largest of these studies is a Swedish study on 332 women randomized 1:1 to three months of COC containing 150 µg LNG plus 30 µg ethinylestradiol or placebo. This study found no significant difference in depressive symptoms, as measured by the Beck Depression Inventory. However, it did observe a reduction in psychological general well-being, as measured by the Psychological General Well-Being Index. The decrease in general well-being was attributed to an increase in depressed mood, less positive well-being, and reduced self-control and vitality (Zethraeus et al., 2017). Another Swedish study, involving 202 women randomized to three months of either COC containing 1.5 mg estradiol plus 2.5 mg nomegestrol acetate or placebo, found increased anxiety, irritability, and mood lability in the intermenstrual phase, while fewer depressive symptoms were reported in the premenstrual phase. This was driven by the women who reported previous experience of mood symptoms related to HC use. The study found no significant difference in the proportions experiencing mood deterioration between the COC (24.1%) and the placebo group (17.0%) (Lundin et al., 2018). In a comparative study, 1821 women were randomized to LNG-IUS and 937 to copper-IUS. More women in the LNG-IUS group (2.5%) reported depressive mood symptoms as a side effect than in the copper-IUS group (0.4%) after three months, while there was no difference at the 5-year follow-up. However, the discontinuation rate, due to depression, was higher in the LNG-IUS group (three per 100 women-years) than in the copper-IUS group (zero per 100 women-years) (Andersson et al., 1994).

Within the last decade, nationwide register-based studies from the Nordic Countries, studying 700,000-1,000,000 women, have been published. These studies have demonstrated that HC use is associated with an increased risk of starting antidepressant medication, receiving a depression diagnosis, and even committing suicidal attempts and suicide (Edwards et al., 2020; Lindberg et al., 2012; Lundin et al., 2022; Skovlund et al., 2016; Zettermark et al., 2018). Specifically, a study found that HC use was associated with a 40-50% higher risk of depression after six months of use (Skovlund et al., 2016). Some studies found this to be the case only for POC and CNOC (Lindberg et al., 2012; Lundin et al., 2022). Two studies have even shown protective effects associated with COC use (Lindberg et al., 2012; Lundin et al., 2022). A Danish study found that the risk peaked six months after starting HC use (Skovlund et al., 2016), and a recent study, utilizing data from the UK Biobank, found that COC use was associated with the highest risk of depression within two years of initiation, followed by a subsequent decline (Johansson et al., 2023). Notably, there is no observed risk of depression in the time before HC initiation, but it increases shortly after initiation (Costa-Ramón et al., 2023; Skovlund et al., 2016). The increased risk has been most pronounced in adolescents (De Wit et al., 2020; Lindberg et al., 2012; Skovlund et al., 2016; Zettermark et al., 2018), and studies have demonstrated that initiation in adolescence can predict lasting vulnerability into early adulthood (Anderl et al., 2020, 2022). Risk behaviors, related to early sexual debut and health-seeking behavior, have been suggested to confound such observational findings (Ditch et al., 2020; McKetta & Keyes, 2019). One study attempted to account for such confounders by including sister pairs, aiming to adjust for any potential confounders clustered within the family. However, this approach did not explain the association (Johansson et al., 2023). Other studies accounted for early sexual debut; one study found it to diminish the association (McKetta & Keyes, 2019), while two other studies found it not to affect the association (Anderl et al., 2020; Johansson et al., 2023). Another study accounted for risk behaviors around the time of HC initiation, including having an abortion, use of emergency contraception, visits to the hospital due to alcohol abuse or intoxication, and having a screening for sexually transmitted diseases. The study concluded that such events did not explain the association (Costa-Ramón et al., 2023). Furthermore, they also assessed whether general practitioners' prescription tendencies regarding HC could confound such findings. They found that prescription tendencies were not associated with mental health outcomes for similar-aged boys assigned to the same general practitioner, nor did it relate to the tendency to refer to hospitalizations for ambulatory care (Costa-Ramón et al., 2023).

1.5 Potential Mechanism Linking Hormonal Contraception with Depression

The underlying biology behind a potential link between HC use and the development of depressive symptoms remains unknown. Current evidence primarily stems from research on the effects of endogenous hormones on brain biology together with relatively few, but emergent studies on direct HC effects on the brain (Lewis et al., 2019; Porcu et al., 2019; Song et al., 2023). Estradiol and progesterone exert their effect through interaction with nuclear receptors and membrane-bound G-protein-coupled receptors that are abundant throughout the brain. The hormones modulate brain neurotransmission through key signaling pathway systems such as the serotonin, noradrenaline, dopamine, and glutamatergic and gamma-aminobutyric acid (GABA)-ergic systems, all of which overlap in anatomical distribution with the sex steroid receptors (**Figure 4**) (Barth et al., 2015). Sex steroids are thought to affect mood and behavior by modulating these neurotransmitter systems, as they play integral roles in various aspects of emotional regulation, motivational behavior, and stress- and fear-related behavior (Barth et al., 2015).

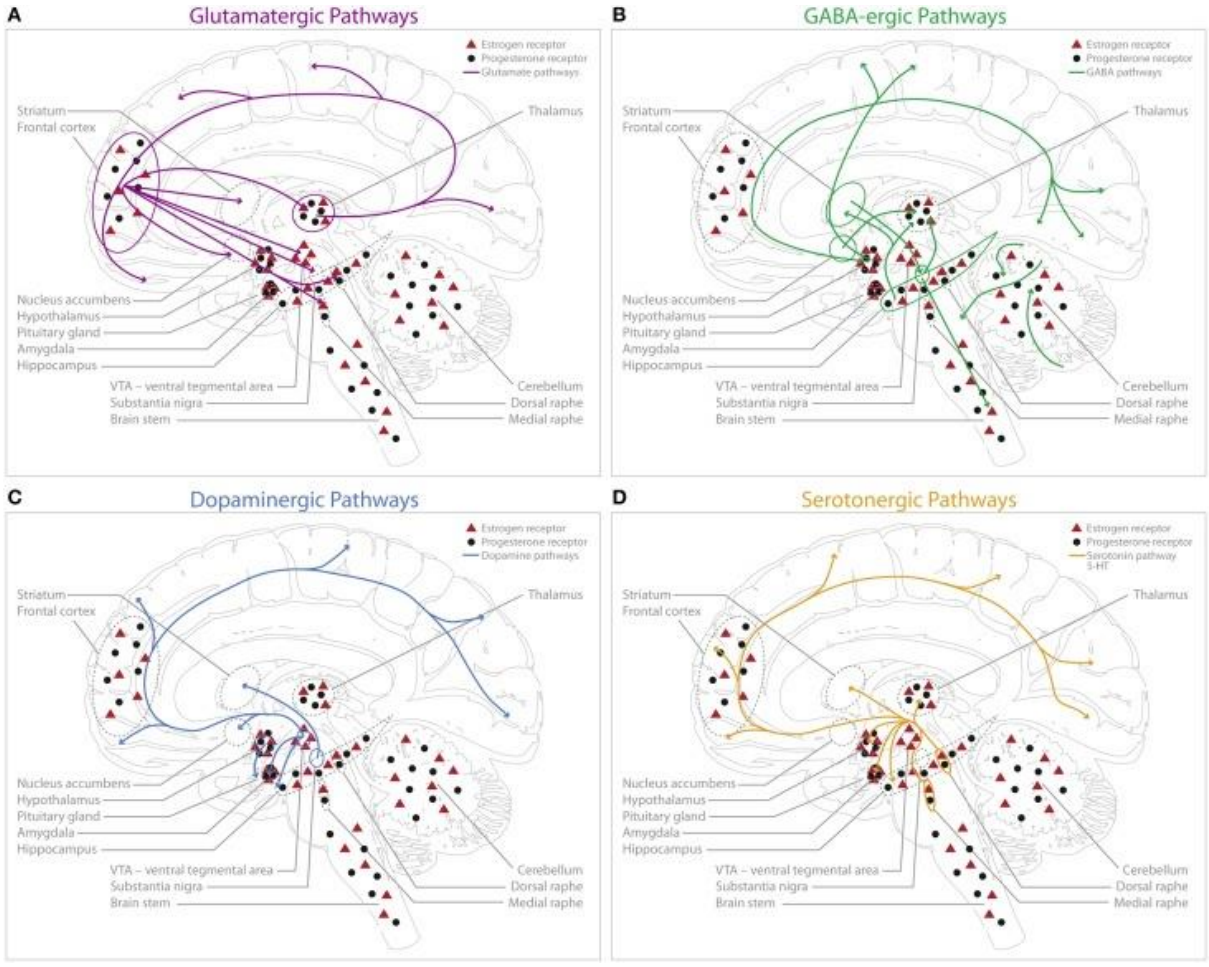

Figure 4. Distribution of estrogen and progesterone receptors and the glutamergic (A), GABAergic (B); dopaminergic (C), and serotonergic (D) brain systems in the human brain. From © Barth, Villringer and Sacher. Frontiers in Neuroscience, volume 9, 2015- doi: 10.3389/fnins.2015.00037 (Barth, Villringer, and Sacher 2015) (https://creativecommons.org/licenses/by/4.0/).

The synthetic estradiol and progestogen have different receptor affinity profiles than the endogenous hormones, including different affinities for other steroid receptors such as the androgen, glucocorticoid, and mineralocorticoid receptors, and thus may affect brain biology differently (Pletzer et al., 2023). Preclinical studies have investigated the effect of HC steroids on the brain's monoamine systems (Porcu et al., 2019). A study found reduced serotonin levels in the rat brain and identified the progestogen component as the driver for these effects (Shetty & Gaitonde, 1980). Contrarily, another study found increased serotonin levels (Daabees et al., 1981). In humans, the effects on the monoaminergic system have been studied by use of positron emission tomography imaging. Here, we have shown that oral contraceptive use is associated with a reduced level of serotonin 4 receptors (5-HT4R) globally in the brain (**Figure 5**) (Larsen et al., 2020).

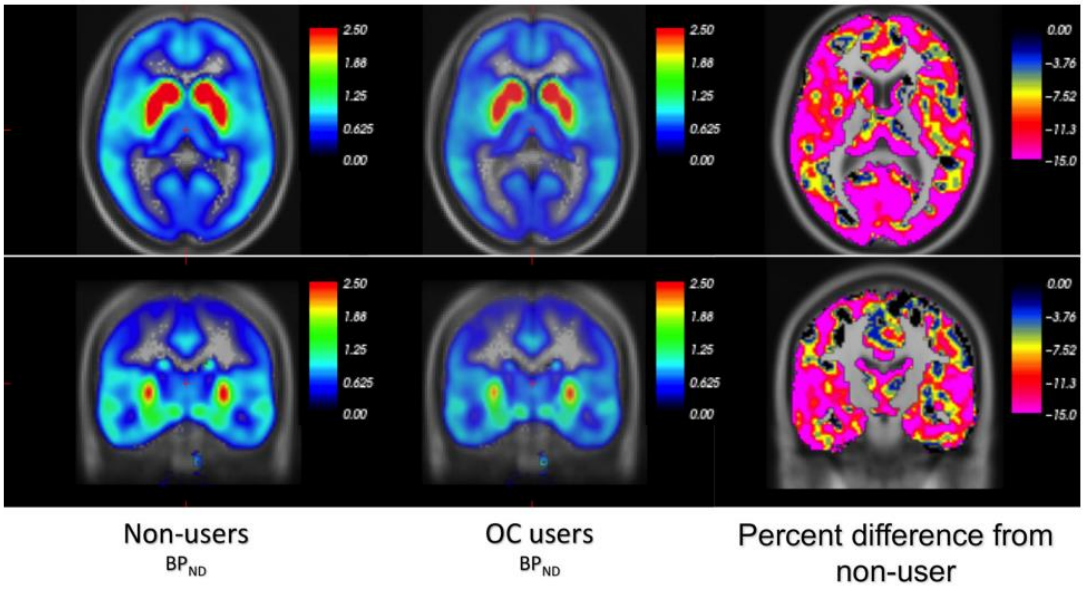

Figure 5. Difference in serotonin 4 receptor binding potential (BP_{ND}) in women using oral contraception (OC) vs. non-users. From Larsen et al, Acta Psychiatr Scand 2020 ;142(4):294-306. doi: 10.1111/acps.13211 (Larsen et al. 2020) (http://creativecommons.org/licenses/by-nc-nd/4.0/).

This difference was similar in magnitude and direction as observed in depressed individuals relative to non-depressed controls (Köhler-Forsberg et al. 2023), where the lower level of 5-HT4R in depressed individuals was associated with higher levels of reported anxiety (Köhler-Forsberg et al., 2022). The role of the 5-HT4R has also been elucidated in rodents, where 5-HT4R stimulation has shown anxiolytic-like and antidepressant-like effects (Faye et al., 2020; Mendez-David et al., 2014) and prophylactic effects against stress (Chen et al., 2020). Further, emerging evidence points to the serotonin system playing an important role in motivational and reward-related behavior (Courtiol et al., 2021). Accordingly, the 5-HT4R in the striatum, the key

hub associated with reward processing, may play an important role for motivational behavior both in the healthy and in the depressed state. In a healthy cohort of women, we observed that the lower 5-HT4R levels were associated with a lower striatal activation during a monetary reward paradigm (Poulsen et al., 2019). In the depressed cohort of women, we observed that a lower striatal 5-HT4R level was associated with lower sexual drive and desire in the women (Rasmussen et al., 2023)

Motivation- and reward-related behavior is often linked to dopaminergic brain biology (Bromberg-Martin et al., 2010), which may as well be sensitive to hormonal contraceptive steroids. Studies have shown reduced dopamine levels in the rat brain after administration of contraceptive steroids (Dey et al., 1991; Schmider et al., 1997; Shetty & Gaitonde, 1980), potentially due to a larger dopamine turnover (Algeri et al., 1976; Jori & Dolfini, 1976). The mechanism behind these changes in the brain's dopamine levels is not fully understood, but evidence suggests it could involve the regulation of monoamine oxidases (Marchi & Cugurra, 1974; Shetty & Gaitonde, 1980), the main enzyme for dopamine degradation, or decreased synthesis because of lower tyrosine hydroxylase expression (Simone et al., 2015). In contrast, human positron emission tomography studies show no evidence of an HC effect on dopamine release (Smith et al., 2019; Taylor et al., 2023), or even higher striatal dopamine synthesis capacity than in naturally cycling women (Taylor et al., 2023).

Studies on reward-related brain activity have shown that women using COC exhibit increased regional brain activity associated with monetary rewards (Bonenberger et al., 2013), and decreased activity in response to erotic stimuli compared to follicular women (Abler et al., 2013), but no difference in value-based decision-making (Lewis et al., 2022). Additionally, follicular women tend to show enhanced rating of attractiveness and increased activity in reward-associated brain regions compared to COC users when administered oxytocin (Scheele et al., 2016). This difference may be attributed to higher baseline oxytocin levels in COC users (Garforth et al., 2020), potentially resulting in reduced sensitivity to oxytocin fluctuations and decreased vigilance towards romantic stimuli.

Several studies have explored how HC may affect brain reactivity to emotional stimuli and its implications for emotional regulation and associated learning. An electroencephalography study found increased emotional reactivity during negative emotional arousal in LNG-IUS users compared to natural cycling women, where the triggered brain responses reflected an increased attention allocation to the negative stimuli (Zelionkaitė et al., 2024). Functional magnetic resonance imaging studies show inconsistent brain activation patterns in relation to emotional stimuli; however, they have consistently implicated effects on

the emotional brain circuits, including the amygdala, a key region for evaluating and processing emotional stimuli (Šimić et al., 2021). One study found reduced activity of the amygdala in relation to both positive and negative arousing stimuli in women using oral contraceptives compared to naturally cycling women (Petersen & Cahill, 2014). A randomized, placebo-controlled, double-blinded study on women, with prior mood symptoms related to HC, found altered brain activity in response to angry and fearful expressions, accompanied by depressive mood and fatigue (Gingnell et al., 2013). This altered activity included a lack of reduced amygdala reactivity over time, potentially reflecting a lack of habituation to the fearful stimuli.

A lack of habituation to fearful stimuli may have implications for fear learning and extinction processes, and this may happen due to altered stress hormone responses (Bierwirth & Stockhorst, 2022; Giustino & Maren, 2018; Merz & Wolf, 2022; Nostadt et al., 2023). Emotional stimulation of amygdala activity has been linked to an interplay between increased noradrenalin and cortisol levels (van Stegeren et al., 2007). Hence altered amygdala activation related to oral contraceptive use may be tied to reduced noradrenalin levels observed in the rat brain after oral contraceptive administration (Dey et al., 1991; Jori & Dolfini, 1976; Shetty & Gaitonde, 1980), or to blunted stress hormone responses including blunted cortisol (Gervasio et al., 2022; Hertel et al., 2017; Høgsted et al., 2021) and noradrenalin reactivity in humans on oral contraception (Nielsen et al., 2013; Otterstetter et al., 1999). For instance, blunted noradrenalin reactivity has been shown to potentially affect emotional memory consolidation in COC users (Nielsen et al., 2013). A randomized, placebo-controlled study found that COC moderated the effect of cortisol on fear learning, which was accompanied by lower amygdala activation in COC users compared to natural cycling women (Merz et al., 2012). In clinical settings, the effects of cortisol dynamics have shown to be important in exposure therapy, where cortisol administration has shown promising augmentation effects; however, this may be impeded by COC use (Raeder et al., 2023). Such a mechanism may explain some of the emerging evidence that COC use can reduce the extinction of intrusive memories after watching a traumatic film (Maslahati et al., 2023) and reduce the effect of exposure therapy for arachnophobia (Graham et al., 2018; Raeder et al., 2019).

Changes in neuroplasticity within emotion and fear-processing brain structures are other suggested mechanisms by which HC use may affect associated learning and emotional regulation. Brain structure changes occur in response to fluctuating levels of estradiol and progesterone throughout the menstrual cycle (Zsido et al., 2023), and this may apply to HC use as well. For example, studies have shown that HC use is associated with lower levels in the prefrontal cortex areas (Brouillard et al., 2023; Petersen et al., 2015, 2021), which may be linked

to poor extinction memory (Milad et al., 2005), potentially due to diminished top-down control of amygdala activity (Albaugh et al., 2019). Although few longitudinal studies have been conducted on the structural effects of HC use, one pre-post quasi-study found a decreased gray matter volume in the left amygdala/anterior parahippocampal gyrus after three months of COC use and found it to be predictive of change in positive affect (Lisofsky et al., 2016). These structural effects may contribute to altered emotional regulation, such as decreased positive affect observed in oral contraceptive users in response to emotional stimuli (Jarva & Oinonen, 2007).

Altogether, emerging evidence indicates that HC use can affect important brain biology considered important for mood and behavior, which give us a mechanistic understanding of how HC can be related to depression, however, despite more than 60 years with HC, this research is still it its early phase.

1.6 Knowledge Gaps

1.6.1 Motivation for Study I

Despite more than 60 years with HC, we are still uncertain of how HC affects the brain and how such effects are linked to behavior and mood disorders. This is complicated by the many different HC types differing by administration method and hormonal content (Kraft et al., 2024). Of the synthetic steroids used in HC in Denmark today, LNG is the one used by most women. It is contained in the most frequently used 2nd generation COC brand and LNG-IUS. LNG-IUS does not contain any estrogen component and is administered in the intrauterine cavity, making it less prone to potential inter-individual variability due to absorption and first-pass metabolism (Fotherby, 1996). Since 2017, women in Denmark have been able to choose between three different LNG-IUS; a low-dose containing a total amount of 13.5 mg LNG and an initial-release dose of 14 μg/day (Bayer Group, 2014); a medium-dose containing 19.5 mg LNG and an initial release dose of 17.5 μg/day (Bayer HealthCare Pharmaceuticals Inc, 2016); and a high-dose containing 52 mg LNG and an initial release dose of 21 μg/day (Bayer HealthCare Pharmaceuticals Inc, 2000). The availability of three different dosages administrated in the same way makes the LNG-IUS an ideal candidate to study the dose-response relationship between LNG exposure and the risk of depression. Furthermore, the ability to compare such risks between users of different LNG-IUS dosages, rather than to a non-user group, minimizes the risk

of potential confounders related to HC use, including potential surveillance bias and bias related to health-seeking behavior.

1.6.2 Motivation for Study II

Whether it is the same women at risk of developing depressive episodes across the different reproductive stages, i.e., PMDD, PPD, and depression in the perimenopause, remains unknown. Such knowledge could provide further evidence for the role of hormonal contributions to depressive episodes in women. Current evidence is based on retrospective studies with a high risk of recall and confirmation bias (Cao et al., 2020). HC provides an alternative model to the endogenous hormone fluctuations in relation to the menstrual cycle, postpartum period, and during perimenopause. In contrast to menstrual cycle phases and the perimenopausal transition, HC initiation and deliveries are well-defined events recorded in national health registers. Therefore, they provide suitable candidates for studying the link between depressive episodes with potential hormonal contributions across women's reproductive lives.

1.6.3 Motivation for Study III

As the postpartum period is already a time of heightened risk of depressive episodes, and as mothers have just gone through abrupt hormonal changes in relation to pregnancy and delivery, we know little about whether starting HC postpartum adds to the risk of depression in this period of women's lives (Ti & Curtis, 2019). As four out of ten women initiate HC in the postpartum period, this is a highly relevant clinical question. Furthermore, focusing solely on a population of new mothers, who share more similarities in terms of life circumstances compared to populations across a broad spectrum of lifetime periods typically utilized in prior large-scale observational studies on this topic, offers an alternative and potentially more homogenous population for investigating the association between HC use and depression risk.

Therefore, with the advantage of accessing health data, contained in national registers from Denmark, on a nationwide population, we are able to consider and apply these design considerations to investigate the potential link between exposure to hormonal contraception and depression risk. Furthermore, this allows us to examine potential evidence of a subpopulation more susceptible to hormonal changes across women's reproductive lives.

2. Objectives

The overall aim of this thesis was to investigate the role of hormonal exposure in the development of depressive episodes across the reproductive life in women. Specifically, it concerned the role of hormonal contraceptive use in the development of depressive episodes both outside and in relation to the postpartum period and how episodes with potential hormonal contribution may be linked. The objectives for each of the studies are presented below.

2.1 Study I

The objective of this study was to evaluate and compare the 1-year risk of depression in first-time users of LNG-IUS between the three different LNG dosages; low-, medium-, or high-dose LNG.

2.2 Study II

The objective of this study was to investigate if previous depression associated with initiation of HC use was associated with an increased risk of postpartum depression compared to prior depression unrelated to initiation of HC use.

2.3 Study III

The objective of this study was to evaluate the 1-year postpartum risk of depression in first-time mothers exposed vs. non-exposed to HC in the postpartum period. The secondary objectives were to determine this risk stratified on age group and HC type.

3. Methods

3.1 Data Sources

The studies were based on Danish national health registry data, which were linked via unique the personal identification number. The registers used were the Danish Civil Registration system (Pedersen 2011), the National Prescription Register (Wallach Kildemoes, Toft Sørensen, and Hallas 2011), the Danish National Patient Registry (Lynge, Sandegaard, and Rebolj 2011), The Psychiatric Central Register (Mors, Perto, and Mortensen 2011), the Danish Medical Birth Register (Knudsen and Olsen 1998), and Statistics Denmark (Statistics Denmark. n.d.). The variables and codes from each register used across all the studies are presented in **Table 1**. The data were provided by the Danish e-health Authority and hosted by Statistics Denmark.

3.2 Ethics and Approvals

Approval for conducting the studies was obtained from the Danish Data Protection Agency (journal-nr. Pactius-2020-217 and "Privacy", 2022) and the National Data Health Board. In Denmark, no ethics approval or informed consent is needed for register-based studies.

3.3 Study Designs

Studies I-III were all observational cohort studies. Study I followed women for up to 12 months from when they first filled a prescription for an LNG-IUS. The second and third study followed women from when they had their first live birth and until 6 or 12 months postpartum, respectively. For all studies, the follow-up time ended if one of the following events happened before the end of the follow-up time; an outcome event, death, emigration, or end of study period. The study period for Study I was 1995-2022, for Study II 1995-2017, and Study III was 1997-2022.

Table 1. Overview of registers, variables, and codes

Registers	Variables	Codes
Danish Civil Registration System (data since 1968)		
	Date of birth, immigration, emigration, kinship, civil status	
Demographic Registers of Statistics Denmark		
	Educational degree	
Danish Medical Birth Register (complete data since 1973)		
	Twin birth, stillbirth, gestational age, smoking status	
Danish National Patient Register (complete data since 1977)		
	Postpartum/perinatal depression	ICD-8: 296.09, 296.29, 298.09, 300.49, 301.19 ICD-10: F32-34, F38, F39, F530
	Instrument-assisted and caesarean delivery	ICD-10: O81, O82 NCSP-D: KMAE, KMAF0-2, KMAG03, KMAG13, KMCA
	Preeclampsia/eclampsia	ICD-8: 637, ICD-10: O11, O14-15
	Pre-gestational/gestational diabetes	ICD-8: 249-250 ICD-10: E10-14, O24
	Breast cancer	ICD-8: 174, 233 ICD-10: C50
	Liver tumor	ICD.8: 155, 197.7-8,211.5, 230.5 ICD-10: C22, D015B, D134, D376A, C787
Medical indications for HC use	Polycystic ovary syndrome	ICD-8: 256.9 ICD-10: E282
	Endometriosis	ICD-8: 625.3 ICD-10: N80
	Premenstrual syndrome	ICD-10: N943
	Dysmenorrhea	ICD-8: 626.3 ICD-10: N944-946
	Menorrhagia	ICD-8: 626.2 ICD-10: N92
	Leiomyoma	ICD-8: 218 ICD-10: D25
	Hirsutism	ICD-10: L680
	Acne	ICD-8: 706.1 ICD-10: L70
The Psychiatric Central Register (complete data since 1969 on hospital admission and 1995 on outpatient contacts)		
	Mental disorders	ICD-8: 300.0-315.0 (except 302.0 and 302.3) ICD-10: F00-F99
	Depression	ICD-8: 296.09, 296.29, 298.09, 300.49, 301.19 ICD-10: DF32-34, DF38, DF39
Danish Prescription Register (complete data since 1995)		
Hormonal contraception	COC	ATC: G03AA* (except for G03AA13) and G03AB*
	Patch	ATC: G03AA13
	Vaginal ring	ATC: G02BB01
	POP	ATC: G03AC* (except for G03AC06 and G03AC08)
	LNG-IUS	ATC: G02BA03
	Implant	ATC: G03AC06
	Depot injections	ATC: G03AC08
	Antidepressant medication	ATC: N06A*
	Psychotropic medicine	ATC: N05* and N06*
	IVF-treatment	ATC: G03G*, G03DA04, H01CC01, H01CC02, L02AE01

ATC: Anatomical Therapeutic Chemical Classification system; ICD-8: International Classification of Disease and Health Related Problems, 8th revision; ICD-10: 10th revision, NCSP-D: Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures – Denmark. The table is modified from Study 1-III (Appendix 1-III).

3.4 Study Populations

The study population for Study I counted all women between 15 and 44 years of age who filled a prescription for an LNG-IUS for the first time between January 1, 2000, through 2022. The years between 1995 and 2000 were used as a 'wash-out' period to ensure that exposure and outcome were incident events. Accordingly, women were excluded if they had immigrated or emigrated after turning 15 years or if they were known with any psychiatric disorder (ICD8-codes: 209-315, ICD-10 codes: F00-F99) or had ever used any psychotropic medication (ATC codes starting with N05 and N06) before initiating an LNG-IUS.

For Study II and Study III, the study population counted all first-time mothers between 1996 through 2017 and 1997 through 2022, respectively. Mothers were excluded if the first delivery was a stillbirth or multiple birth. In addition, for Study II, the study population only included those who were maximally 16 years of age in 1995 to ensure sufficient medical history to establish the exposure groups outlined in section 3.5. Accordingly, women were also excluded 1) if they immigrated or emigrated before turning 16 years of age, 2) if they had never used HC before giving birth to ensure that they had been tested for HC sensitivity 3) if they received a depression diagnosis or were treated with antidepressant medication before 1996 to ensure sufficient prescription history to determine the exposure group, or within 12 months before delivery to exclude ongoing depressive episodes. For Study III, women were excluded if they had received a depression diagnosis or filled a prescription for antidepressant medication within 24 months before their delivery or if they were known with a diagnosis of breast cancer or liver tumor.

3.5 Exposures

The exposure of interest across Study I and III concerned exposure to HC, which was defined to start on the day an HC prescription was filled. Study I included first-time use of an LNG-IUS (ATC code G02AB03) with one of three different LNG dosages; low- (total LNG content of 13.5 mg; initial release dose of 14 µg/day), medium- (total LNG content of 19.5mg; initial release dose of 17.5 µg/day), or high-dose (total LNG content of 52 mg; initial release dose of 21 µg/day). For Study III, the primary exposure included first-time use of any HC (ATC codes G03AA*, G03AB*, G03AC*, G02BA03, G02BB01) in the postpartum period and secondary, the HC type categorized based on whether it was administrated orally or not and whether it was a CHC or POC, resulting in the following secondary exposure categories; COC, CNOC, PNOC, and POP.

For Study II, the exposure was prior depression either associated or not associated with the initiation of HC use. Depression was defined as having received a depression diagnosis at an in- or outpatient psychiatric clinic (ICD-8 codes: 296.09, 296.29, 298.09, 300.49, 301.19 and ICD-10 codes: DF32-34, DF38, DF39) or having filled a prescription for an antidepressant medication (ATC codes starting with N06A). HC-associated depression was defined as a depression registered within 6 months after a new HC exposure and contrarily a non-HC-associated depression was a depression registered outside this time-window. A new HC exposure was defined as either first-time HC use, switch of HC type, or restart of HC use. A prescription length was determined by the defined daily dose per package multiplied by the number of packages purchased on a day. A restart was only registered if this followed a break of a minimum of 6 months to ensure that the depressive episode was not related to the former HC period. Further, this was also to ensure that potential small gaps in prescriptions would not be registered as a restart, as such small gaps likely relate to a degree of uncertainty about the timing of initiation of the redeemed prescription; the small gaps can be due to delayed initiation of the first prescription and due to accumulation of pills over time as prescriptions were filled before the duration of a former prescription. Depressive episodes were distinguished by a minimum of 30-day treatment gaps in antidepressant treatment, by 6 months between depression discharge diagnoses. Last, women with no prior depression were categorized as a third group, which enabled a comparison between the size of the estimated risk to that of having no prior depression.

3.6 Outcomes

The outcome of interest for Study I was incident depression within 12 months after starting the use of an LNG-IUS. For Study II, it was the development of a depressive episode within 6 months postpartum, and for Study III within 12 months postpartum. A depressive episode was defined as the start of antidepressant medication (ATC codes starting with N06A) or receiving a hospital discharge diagnosis of depression (ICD-8 codes: 296.09, 296.29, 298.09, 300.49, 301.19, ICD-10 codes: DF32-34, DF38, DF39, DF530).

3.7 Covariates

Various covariates were considered potential confounders across the studies; this included age or maternal age (below 20 years and hereafter in 5-year bands or grouped hereafter as 20-29 years and 30 years and above), calendar period (in 5-year calendar periods), educational level (defined

as below high school, high school or vocational education, or bachelor degree or above), and familial history of depression (Study II) or just any psychiatric disorder (Study I and III) defined as having a parent with any such diagnosis.

In addition, in Study I, postpartum LNG-IUS use, i.e. within 6 months after delivery, and the following medical indications with bleeding abnormalities were considered as potential confounders as they may have been an indication for prescribing a high-dose LNG-IUS. This included menorrhagia, leiomyoma, polycystic ovarian syndrome, dysmenorrhea, and endometriosis.

In Study II and III, having any medical indication for HC use was considered a covariate, which included a diagnosis of polycystic ovary syndrome, endometriosis, premenstrual syndrome, dysmenorrhea, heavy menstrual bleeding, hirsutism, or acne. Additionally, these were also adjusted for civil status and potential obstetric risk factors for postpartum depression including preterm birth, instrument-assisted- or cesarean delivery, pre-eclampsia/eclampsia, and pre-gestational- or gestational diabetes. Last, having a prior major psychiatric disorder was accounted for in Study II (i.e., organic mental disorders, mental and behavioral disorders due to substance use, schizophrenia, bipolar disorder, eating disorders, and mental retardation) or just any prior psychiatric disorder or prior use of psychotropic drugs was adjusted for in Study III. Study III also included in vitro fertilization treatment as a potential confounder as it is assumed that those women are less likely to start HC use postpartum.

3.8 Data Analysis and Statistics

Study I and III used time-to-event analyses with the use of Cox proportional hazard models with time-on-study as the underlying time scale. Women were followed for 12 months from either first use of an LNG-IUS (Study I) or from first delivery (Study III) or until an event, death, emigration, or December 31, 2022, whichever came first. The models were adjusted for the mentioned covariates in section 3.6. For Study I, women were considered exposed during the whole follow-up period, but for Study III, women started as non-exposed and switched to be exposed on the day they filled an HC prescription, hence the model included a time-varying exposure. Even if women discontinued or switched HC type during follow-up, they were still considered exposed to the first type for the rest of the follow-up time. As relatively many women who discontinue HC because of side effects such as mood deterioration, including such a transition of the exposure would violate the assumption of the Cox regression model stating that shift of exposure is unrelated to the probability of developing depression afterward (Dewey,

Clayton, and Hills 1995). With the relatively short follow-up time of only 12 months and as a diagnosis of depression or the start of antidepressant treatment may happen with some delay from symptom debut, this was considered the optimal strategy. The rest of the covariates were evaluated at the time of initiation for Study I and at the first delivery for Study II and III and were considered constant throughout the follow-up time. In Study III, secondary analyses were conducted where age-stratified and HC type-stratified effects were evaluated.

In addition, marginal effects models were implemented in Study I and III to compute a more intuitive summary of the HC effect in the form of average causal effects compared to the hazard ratios (HR), as it is not an easy summary to comprehend and to apply in a real-world setting (George, Stead, and Ganti 2020; Keil et al. 2014). Instead, from the marginal effect models, the 12-month risks in the form of absolute risks, relative risks, and risk differences were generated by using the G-formula estimator with inputs from the cause-specific Cox regression models by use of the riskRegression package in R (Ozenne et al. 2017). However, as study III had a time-varying exposure, it required some additional steps, which involved using a multistate Markov Cox model by use of the *RiskIDM* function (https://rdrr.io/github/bozenne/butils/src/R/riskIDM.R). This considered all the possible states a mother could be in, i.e., "No HC", "HC" and "Depression" state as illustrated in **Figure 6A**. In **Figure 6B**, a state existed for each of the HC types. In these multistate models, all women started in "No HC" and could stay here or transition to the absorbing state "Depression" or to "HC" or any of the HC types and either stay here or transition further to the "Depression" state. The multistate Markov Cox model consisted of two Cox regression models, one computing the transition intensity from "No HC" to "HC" and the other from each of these to the "Depression" state.

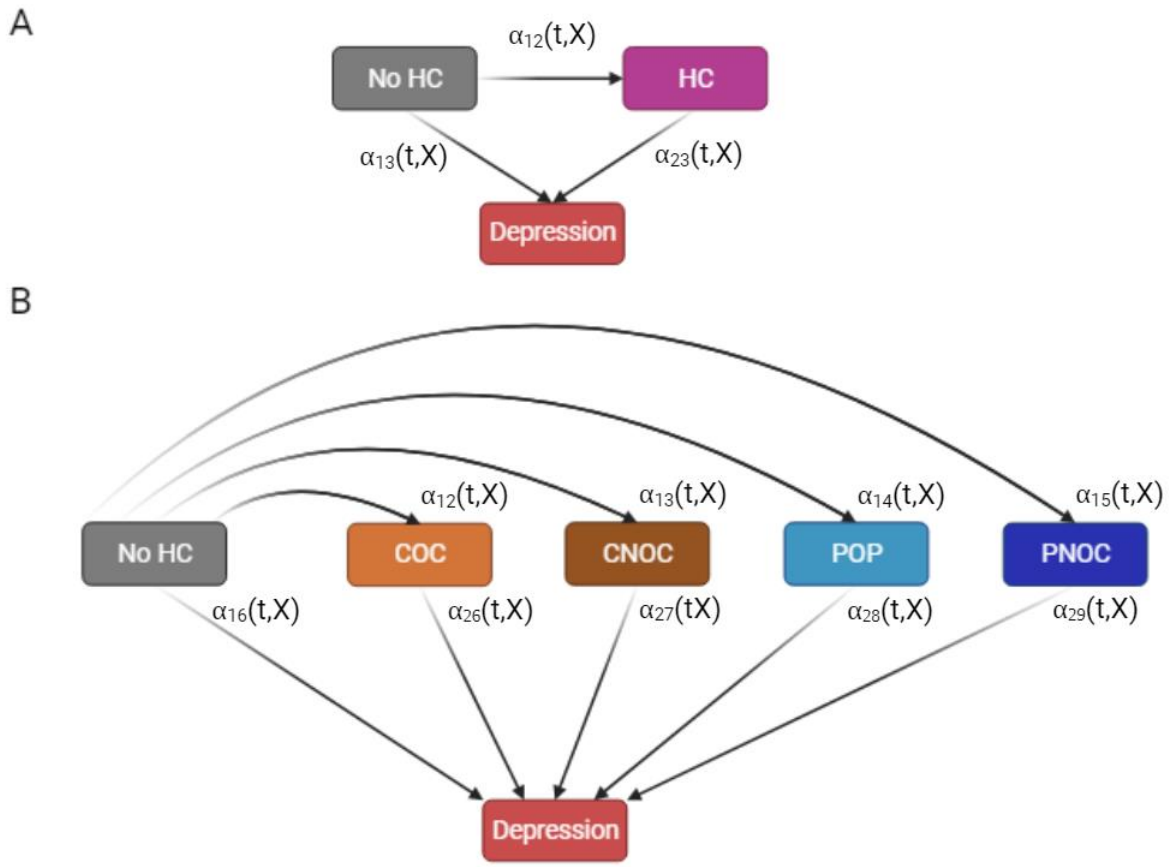

Figure 6. These are the multistate models used in study III, where **A)** illustrates the three possible states "No HC", "HC", and "Depression" used in the model with the primary exposure definition. Between each state exists a transition intensity (denoted by α_{12}, α_{13}, α_{23}). All women started in "No HC" and could transition to "HC" or the absorbing state "Depression" either directly or via "HC". **B)** Illustrates the possible states in the model with the secondary exposure definition counting the different HC types. Once a HC type was initiated, the mothers could not transition to another HC type or transition back to "No HC". The transition intensity from any of the HC types to depression was generated as a constant fraction of the transition intensity from "No HC" to "Depression".

HC, hormonal contraceptive. COC, combined oral contraceptive. CNOC, combined non-oral contraceptive. POP, progesterone-only pill. PNOC, progesterone-only non-oral contraceptive. Figure is adapted and caption modified from Study III (Appendix III).

For Study III, the average causal effects are presented as the absolute risk and risk difference between the hypothetical scenario had no one transitioned to "HC" compared to the observed 12-month risk in the population with the observed transition intensity to "HC". To establish the risk in the hypothetical scenario had nobody started HC, the transition intensity from "No HC" to "HC" was set to zero. The G-formula was now used to obtain the average risk by using the outlined steps to obtain the risk for each individual with their given covariate status and average the risk across the whole population (Cortese and Andersen 2010).

For Study I, the average causal effect represents the risk or risk difference/ratio between the hypothetical scenario had all started medium-dose or high-dose LNG-IUS compared to the hypothetical scenario had all started low-dose LNG-IUS (Keil et al. 2014).

In Study II, a logistic regression model was used to compute the odd ratio (OR) of developing a depressive episode in the postpartum period between those with a history of HC-associated depression or no history of depression compared to those with a history of non-HC-associated depression. Due to the rare disease assumption, the OR was interpreted as relative risks (Greenland and Thomas 1982).

For each study, the estimated effects are presented with a 95% confidence interval and the null hypothesis was rejected if this did not overlap with 1.00 for OR, HR, or RR, and if it did not overlap with zero for absolute risk differences. All analyses were conducted in R (R Core Team 2022).

3.8.1 Sensitivity Analyses

Additional analyses were conducted in each study to assess whether design choices had potential implications for the findings and interpretation hereof. In each study, the main analysis was repeated while only adjusting for either no other covariates or just age and calendar period to ensure against overfitting and for potentially adjusting for intermediate variables (Ananth and Schisterman 2017; Schisterman, Cole, and Platf 2009). In addition, in Study I, the model was adjusted for menorrhagia as a prescription indication for LNG-IUS use to account for potential confounding by indication. For Study III, other additional covariates were added to the model to control for potential confounding in the form of immigrant status, smoking status, and highest obtained educational level by parents. The latter was used to potentially better assess socioeconomic status as for the young mothers their educational level might not mirror this sufficiently if they had not yet obtained their full educational potential.

In Study I, depression was redefined as depression diagnosis and filled antidepressant medication, separately. Further, only prescriptions not specifically addressed for

other indications than depression were used, unless depression was confirmed by diagnosis. To estimate the potential strength of an association of an unmeasured confounder to explain away the estimated association, E-values were estimated (Van Der Weele and Ding 2017).

In Study II, we also conducted an analysis on perinatal depression, i.e., when the outcome of depression happens was measured not only during the postpartum phase but also during the last trimester of the pregnancy as some women already developed depressive symptoms during this phase (Bennett et al. 2004). Last, we repeated the analysis while only considering the first depressive episode for defining the exposure category.

In Study III, the PNOC exposure group was redefined to only include LNG-IUS as implants, as well as depot injections, may have some confounding by indication. Further, the follow-up time was redefined to 1) start 28 days later than the HC was prescribed to address that they might not have started on the day they filled the prescription, 2) to end when a subsequent pregnancy was registered.

3.8.2 Missing Data

Missing data was observed in all studies, which was handled by imputing to either a separate group or to imputed values by performing multiple imputations via logistic regression for binary variables and polytomous logistic regression for categorical variables via the Multivariate Imputation by Chained Equations (mice) package in R (Buuren and Groothuis-Oudshoorn 2011).

3.8.3 Model Control

To test whether the proportional hazard assumption was violated in Study I and III, the correlation between the Schoenfeld residuals and time was numerically tested for the covariates with the *survival*-package and graphical inspected for the exposures by using the *timereg*-package (Therneau 2023; Torben Martinussen & Thomas H. Scheike 2006). For the covariates where this was the case, the model was stratified on these, and if it concerned the exposure of interest, this was handled by using a flexible parametric survival model where the HR was visualized as a function of time, and by relaxing the transition intensities from “No HC” and “HC” to “Depression” state in the multistate Markov Cox regression model.

4. Results

A summary of the results from Study I-III is presented in sections 4.1-4.3, however, for all details, see the result sections and supplementary material for each study in Appendix I-III.

4.1 Study I

In Study I, we investigated the risk of depression in first-time users of three different LNG-IUS dosages. Out of 149,238 first-time users of LNG-IUS between 2000-2022, 14.8% filled a prescription for low-dose, 32% for medium-dose, and 53.2% for high-dose LNG-IUS (**Table 2**). Notably, high-dose LNG-IUS users were generally older, and fewer were nulliparous.

Table 2. Demographics and clinical profiles

Profiles	**Exposure**					
	Low-dose LNG-IUS		**Medium-dose LNG-IUS**		**High-dose LNG-IUS**	
	No.	**(%)**	**No.**	**(%)**	**No.**	**(%)**
Total	22,029	(14.8)	47,712	(32.0)	79,459	(53.3)
Age						
15-19	6,362	(28.9)	10,498	(22.0)	3,839	(4.8)
20-24	9,707	(44.1)	17,175	(36.0)	10,799	(13.6)
25-29	4,173	(18.9)	9,282	(19.5)	21,675	(27.3)
30-34	1,403	(6.4)	6,429	(13.5)	27,681	(34.8)
35-39	357	(1.6)	3,348	(7.0)	12,847	(16.2)
40-44	27	(0.1)	980	(2.1)	2,618	(3.3)
Calendar period						
2000-2004	0	(0.0)	0	(0.0)	419	(0.5)
2005-2009	0	(0.0)	0	(0.0)	4799	(6.0)
2010-2014	2,009	(9.1)	0	(0.0)	22,858	(28.8)
2015-2019	14,296	(64.9)	14,603	(30.6)	34,727	(43.7)
2020-2022	5,724	(26.0)	33,109	(69.4)	16,656	(21.0)
Educational level[a]						
Below high school	6.374	(28.9)	10,484	(22.0)	9,358	(11.8)
High school/ vocational education	10,274	(46.6)	21,506	(45.1)	30,783	(38.7)
Bachelor degree or above	5,368	(24.4)	15,706	(32.9)	39,252	(49.4)
Postpartum initiation	1,355	(6.2)	7,135	(15.0)	28,404	(35.7)
Nulliparous	19,765	(89.7)	33,311	(69.8)	14,216	(17.9)
Parental history of mental disorder	3,044	(13.8)	6,930	(14.5)	10,223	(12.9)
Endometriosis	68	(0.3)	186	(0.4)	1,273	(1.6)
Polycystic ovarian syndrome	104	(0.5)	372	(0.8)	1,268	(1.6)
Dysmenorrhea	162	(0.7)	314	(0.7)	747	(0.9)
Leiomyoma	12	(0.1)	54	(0.1)	242	(0.3)
Menorrhagia	327	(1.5)	694	(1.5)	2,442	(3.1)
Menorrhagia as prescription indication[b]	753	(3.4)	2,926	(6.1)	8.658	(10.9)
Previous HC use						
None	2,582	(11.7)	4,742	(9.9)	2,166	(2.7)
1 type	15,257	(69.3)	32,871	(68.9)	52,671	(66.3)
2 types	3,778	(17.2)	9,232	(19.3)	21,718	(27.3)
3 or more types	412	(1.9)	867	(1.8)	2,904	(3.7)

[a]0.1%, 0.0%, 0.1% had missing information about education level among low-, medium-, and high-dose LNG-IUS users.

[b]11.5%, 4.7%, and 12.0% had missing prescription indication among low-, medium-, and high-dose LNG-IUS users.

HC; hormonal contraceptive. LNG-IUS; levonorgestrel-releasing intrauterine system. Table and caption are modified from Study I (Appendix I).

The 12-month risk of depression was 1.21% (95% CI, 1.06;1.36) for low-dose, 1.46% (1.33;1.59) for medium-dose, and 1.84% (1.72;1.96) for high-dose LNG-IUS users (**Figure 6**). Compared to low-dose LNG-IUS use, this corresponded to a RR of depression of 1.21 (1.03;1.39) and 1.52 (1.30;1.74) for medium- and high-dose LNG-IUS users, respectively. Compared to medium-dose, the RR was 1.26 (1.10;1.41) for high-dose LNG-IUS use.

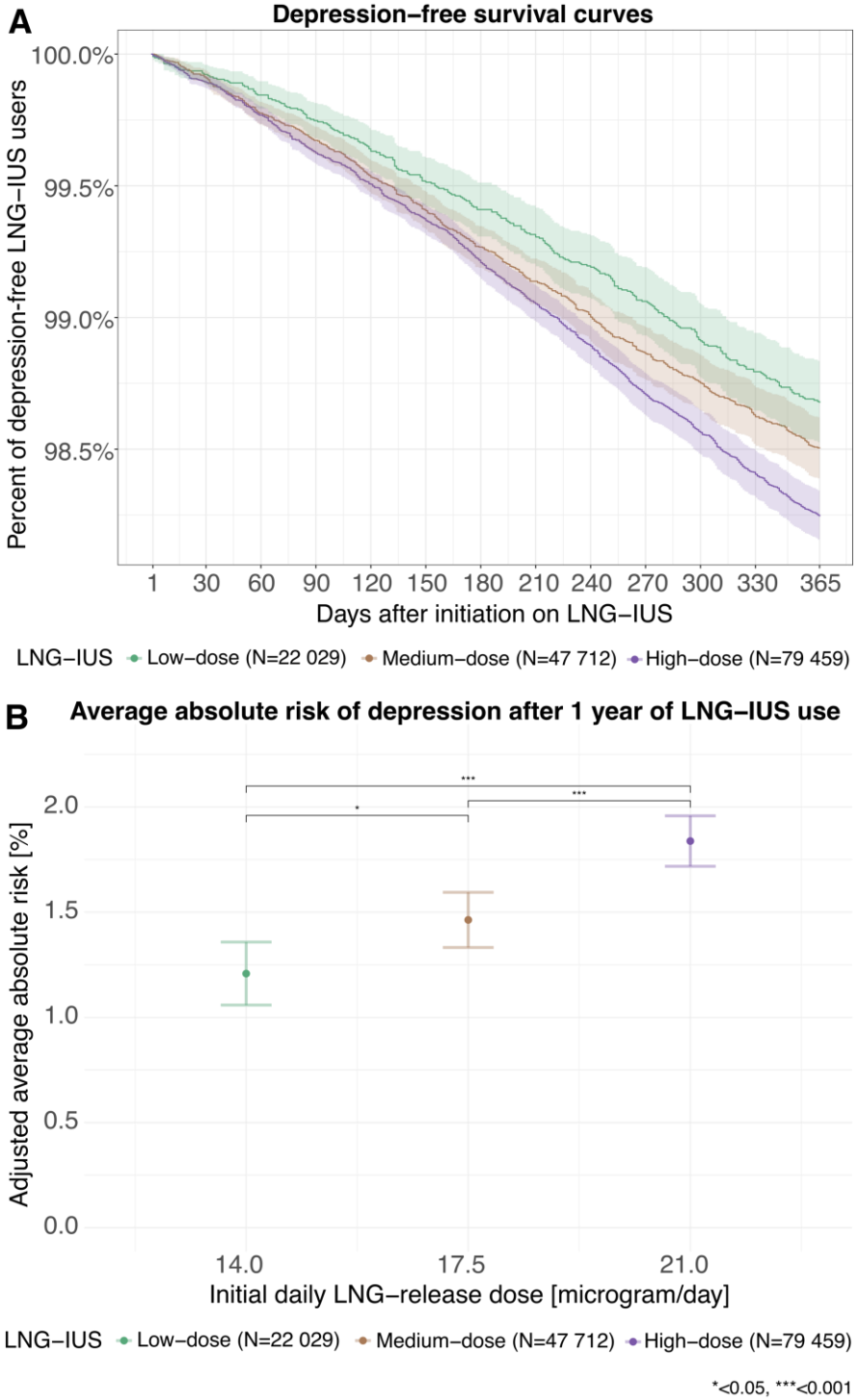

Figure 6. A) 12-months depression-free survival curves for first-time users of low-, medium-, and high-dose LNG-IUS users. **B)** 12-months absolute risks of incident depression for first-time users of low-, medium-, and high-dose LNG-IUS users. LNG-IUS; levonorgestrel-releasing intrauterine system. Figures are adapted and caption modified from Study I (Appendix I).

When the outcome was depression diagnosis, the RR were 1.41 (0.95;1.86) and 1.24 (0.86;1.62), and when it was filled prescriptions for antidepressant medication, they were 1.61 (1.36;1.86) and 1.25 (1.05-1.45) in high- and medium- compared to low-dose LNG-IUS users. If prescriptions for other indications than depression were excluded unless depression was confirmed by diagnosis, they were 1.73 (1.38;2.08) and 1.18 (0.93;1.43), and when prescriptions with missing indication were included, they were 1.74 (1.43;2.05) and 1.26 (1.02;1.50) in high- and medium- compared to low-dose LNG-IUS users.

Twice as many women using high-dose LNG-IUS (3.1%) were known with a menorrhagia diagnosis compared to women using low- (1.5%) and medium-dose LNG-IUS (1.5%). Menorrhagia could be a potential confounder as only high-dose LNG-IUS is approved for treating such (Bayer HealthCare Pharmaceuticals Inc 2000). As women may be treated for menorrhagia without necessarily receiving a diagnosis at the hospital, we likely miss a proportion of these. This was mitigated by including information on prescription indications for LNG-IUS. Here, 10.9% of high-dose LNG-IUS users were known with such an indication (**Table 1**). However, the effect of adjusting for menorrhagia diagnoses and prescription indication had little impact on the estimated risk as shown in **Figure 7**.

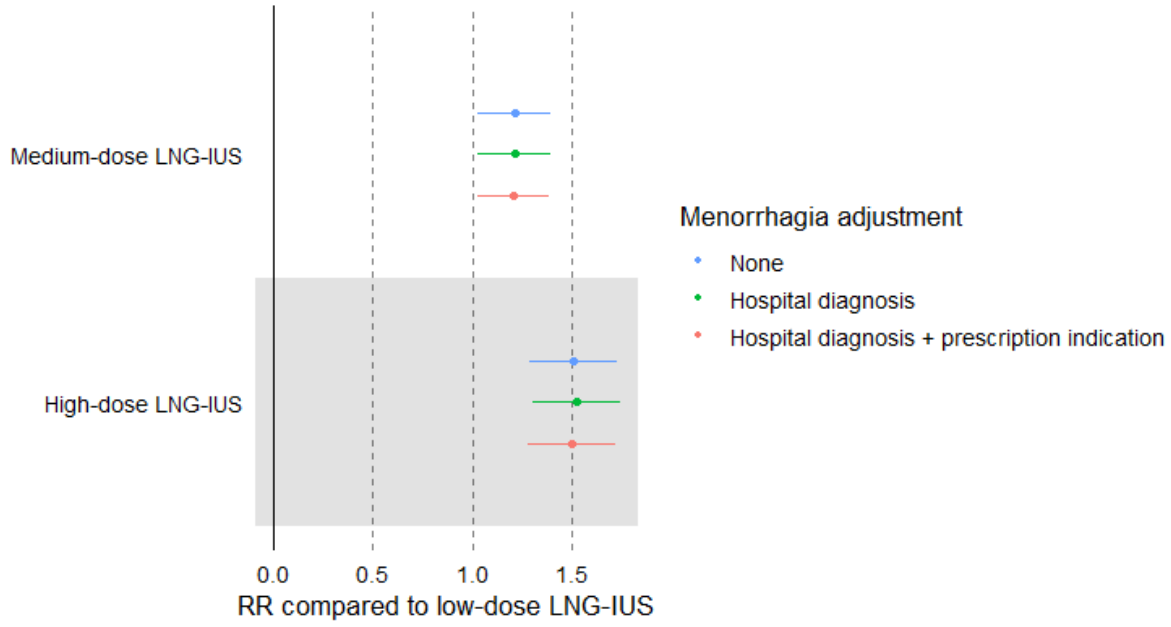

Figure 7. Relative risk of depression compared to low-dose LNG-IUS dependent on adjustment for menorrhagia information. LNG-IUS; levonorgestrel-releasing intrauterine system.

E-values based on the RRs for high- and medium- relative to low-dose LNG-IUS use were estimated to be 2.41 (with a lower border of 1.92) and 1.71 (with a lower border of 1.21). In comparison, the RRs for menorrhagia diagnosis and prescription indication were 1.52 and 1.19.

4.2 Study II

In Study II, we investigated if prior depression associated with HC initiation was associated with an increased risk of PPD compared to prior depression not associated with HC initiation. Of 188,648 first-time mothers, 5,722 (3.0%) and 18,431 (9.8%) had developed a depressive episode before their pregnancy in relation to and not in relation to HC initiation, respectively. The demographics and clinical profiles are presented in **Table 3**.

Table 3. Demographics and clinical profiles

Profiles	**Exposure**		
	Non-HC-related depression	**HC-related depression**	**No depression**
No. (%)	18,431 (9.8)	5,722 (3.0)	164,495 (87.2)
Maternal age at delivery, no. (%)			
<20	415 (2.3)	191 (3.3)	9,880 (6.0)
20-24	5,221 (28.3)	1,830 (32.0)	49,885 (30.3)
25-29	8,656 (47.0)	2,527 (44.2)	77,738 (47.3)
30-34	3,721 (20.2)	1,059 (18.5)	25,171 (15.3)
35-39	418 (2.3)	115 (2.0)	1,821 (1.1)
Educational level, no. (%)			
Below high school	5,571 (30.2)	2,143 (37.5)	37,035 (22.5)
High school/vocational education	7,735 (42.0)	2,174 (38.0)	66,645 (40.5)
Bachelor degree or above	5,125 (27.8)	1,405 (24.6)	60,815 (37.0)
Married, no. (%)	8,402 (45.6)	2,344 (41.0)	87,862 (53.4)
Familial disposition for depression, no. (%)	2,020 (11.0)	761 (13.3)	11,172 (6.8)
Other major psychiatric disorder, no. (%)	2,224 (12.1)	934 (16.3)	2,750 (1.7)
BMI[a], no. (%)			
<18.5	955 (5.2)	353 (6.2)	6,996 (4.3)
18.5 - 24.9	10,135 (55.0)	3,184 (55.6)	94,627 (57.5)
25.0-29.9	3,806 (20.6)	1,143 (20.0)	30,527 (18.6)
≥30.0	2,717 (14.7)	798 (13.9)	16,952 (10.3)
Smokers[b], no. (%)	4,352 (23.6)	1,515 (26.5)	27,451 (16.7)
(Pre-)gestational diabetes, no. (%)	765 (4.2)	210 (3.7)	4,080 (2.5)
Eclampsia/preeclampsia, no. (%)	927 (5.0)	265 (4.6)	7,194 (4.4)
Preterm birth[c], no. (%)	1,189 (6.5)	389 (6.8)	10,148 (6.2)
Instrument-assisted delivery, no. (%)	2,324 (12.6)	740 (12.9)	22,431 (13.6)
Cesarean section, no. (%)	4,003 (21.7)	1,238 (21.6)	29,470 (17.9)
Medical indication for HC, no. (%)	1,413 (7.7)	552 (9.6)	7,163 (4.4)
Age at first depression, mean (SD)	21.5 (3.6)	20.3 (3.4)	-
Age at exposure-defining episode. mean (SD)	21.5 (3.6)	21.2 (3.6)	-
Number of depressive episodes, no. (%)			
0	-	-	164,495 (100.0)
1	11,319 (61.4)	2,101 (36.7)	-
2	3,832 (20.8)	1,359 (23.8)	-
3	1,667 (9.0)	833 (14.6)	-
≥4	1,613 (8.8)	1,429 (25.0)	-

[a]4.4%, 4.3%, and 9.4% of the first-time mothers with a history of non-HC-related depression, HC-related depression, and no depression had unknown BMI. [b]Correspondingly, 2.3%, 2.2%, and 2.4% had unknown smoking status, and [c]0.6%, 0.6% and 0.6% had unknown gestational age from each exposure group, respectively.

BMI, Body Mass Index; HC, hormonal contraceptive. From © 2023 Larsen SV et al. JAMA Psychiatry (S. V. Larsen et al. 2023)

The mothers with HC-associated and non-HC-associated depression were roughly comparable in terms of age, educational level, BMI, and obstetric risk factors for postpartum depression. On the other hand, women with HC-associated depression tended to be more often known with other psychiatric disorders, having a parent with a depression history, and also had more depressive episodes than mothers with non-HC-associated depression.

Of all the first-time mothers, 2,457 (1.3%) developed a depressive episode in the postpartum period, which counted 297 (5.2%), 682 (3.7%), and 1,478 (0.9%) of mothers with a history of HC-associated depression, non-HC-associated depression, and no history of depression, respectively. This resulted in an adjusted OR of 1.35 (1.17;1.56) for mothers with HC-associated compared to mothers with non-HC-associated depression (**Figure 8**). If depressive episodes in the third trimester were included (i.e., perinatal depression) the adjusted OR was 1.41 (1.23;1.60). In comparison, mothers with no depression had an adjusted OR of 0.25 (0.23;0.27) and 0.23 (95% CI, 0.2;0.25) compared to mothers with non-HC-associated depression for postpartum and perinatal depression, respectively.

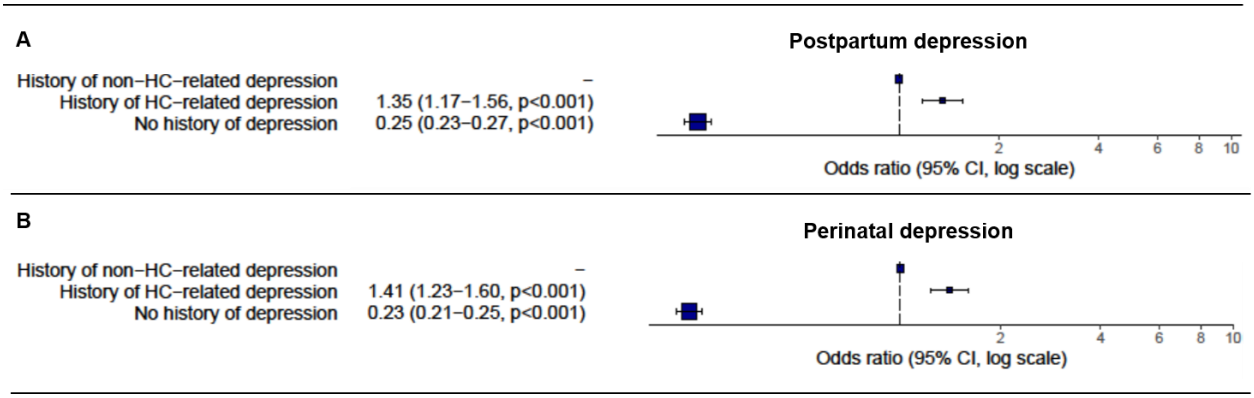

Figure 8. Forest plot of the ORs for (A) postpartum depression and (B) perinatal depression adjusted for women with history of depression associated vs. not associated with HC initiation. From © 2023 Larsen SV et al. JAMA Psychiatry (S. V. Larsen et al. 2023) (https://creativecommons.org/licenses/by/4.0/)

When only the first depressive episode was used to distinguish the exposure category, 3,792 (2.0%) women had a prior HC-associated depression, and 20,361 (10.8%) with non-HC-associated depression. These groups had a more comparable number of prior depressive episodes with 44.4% and 44.6% with more than one episode in each group, respectively. Based only on such a categorization, the adjusted OR of postpartum depression was now 1.19 (95% CI, 1.00-1.40), and for perinatal depression 1.18 (1.01;1.38) for mothers with HC-associated vs. non-HC-associated depression.

4.3 Study III

The study population counted 610,038 first-time mothers, of which 248,274 (40.7%) initiated an HC within 12 months after delivery. Most of these started on COC (23.6%), second most on POP (10.9%), third most on PNOC (5.3%), and least started on CNOC (0.9%). The demographics and clinical profiles are shown in **Table 4**.

Table 4. Characteristics and clinical profiles of mothers using and not using hormonal contraception postpartum

	Exposure, No. (%)	
Profile	**Non-users**	**HC users**
	No. (%)	**No. (%)**
Total	361,764 (59.3)	248,274 (40.7)
Maternal age, y		
<20	6429 (1.8)	8426 (3.4)
20-29	194,036 (53.6)	171,993 (69.3)
≥30	161,299 (44.6)	67,855 (27.3)
Educational level[a]		
Below high school	47,370 (13.1)	42,448 (17.1)
High school/vocational education	123,022 (34.0)	103,969 (41.9)
Bachelor degree or above	187,427 (51.8)	100,777 (40.6)
Highest educational level of parents[b]		
Below high school	50,562 (14.0)	40,258 (16.2)
High school/vocational education	145,299 (40.2)	120,518 (48.5)
Bachelor degree or above	129,051 (35.7)	77,059 (31.0)
Familial disposition for mental disorder	36,852 (10.2)	27,869 (11.2)
History of mental disorder	65,720 (18.2)	44,382 (17.9)
Immigrant or descendant of immigrant	55,378 (15.3)	18,606 (7.5)
Civil status[c]	140,647 (38.9)	70,553 (28.4)
Smoking status[d]	40,006 (11.1)	39,414 (15.9)
Medical indication for HC	19,062 (5.3)	10,161 (4.1)
IVF treatment	64,073 (17.7)	14,260 (5.7)
(Pre-)gestational diabetes	11,634 (3.2)	6677 (2.7)
Eclampsia/preeclampsia	15,895 (4.4)	11,376 (4.6)
Preterm birth[e]	21,206 (5.9)	15,608 (6.3)
Instrument-assisted delivery	121,217 (33.5)	83,346 (33.6)

[a]0.4% and 1.1% had missing information among mothers initiating HC and not initiating HC postpartum, respectively. [b]4.2% and 10.2% had missing information among mothers initiating HC and not initiating HC postpartum, respectively. [c]0.1%, and 0.2% had missing information among mothers initiating HC and not initiating HC postpartum, respectively. [d]6.9% and 8.6% had missing information among mothers initiating HC and not initiating HC postpartum, respectively. [e]0.7% and 1.3% had missing information among mothers initiating HC and not initiating HC postpartum, respectively. HC; hormonal contraception. The Table and caption are modified from Study III (Appendix IIII).

HC users were younger and accordingly had lower educational level than non-users, which was driven by younger COC and CNOC users. The proportion with a history of mental disorders did not differ remarkably between HC users and non-users, but more non-oral HC users were known with a history of mental disorders. About twice as many non-users were immigrants or descendants hereof and approximately three times as many had used IVF-treatment compared to HC users.

The 12-month cumulative incidence of depression was 1.5% resulting in a crude incidence rate of 16 per 1,000 person-years for all the first-time mothers. This was 21 and 14 per 1,000 person-years for HC users and non-users, respectively. HC use was associated with depression with an adjusted HR of 1.49 (1.42;1.56) compared to no use. This was 1.72 (1.63;1.82) for COC use, 1.97 (1.65;2.37) for CNOC use, and 1.40 (1.25;1.56)) for PNOC use. When PNOC users only counted those using LNG-IUS, the HR was 1.27 (1.12;1.44). Only adjusting for age and calendar year or by additionally adjusting for immigration status, highest education level of parents, and smoking status only changed the estimates to some degree, which was most pronounced for CNOC and COC (**Figure 9**).

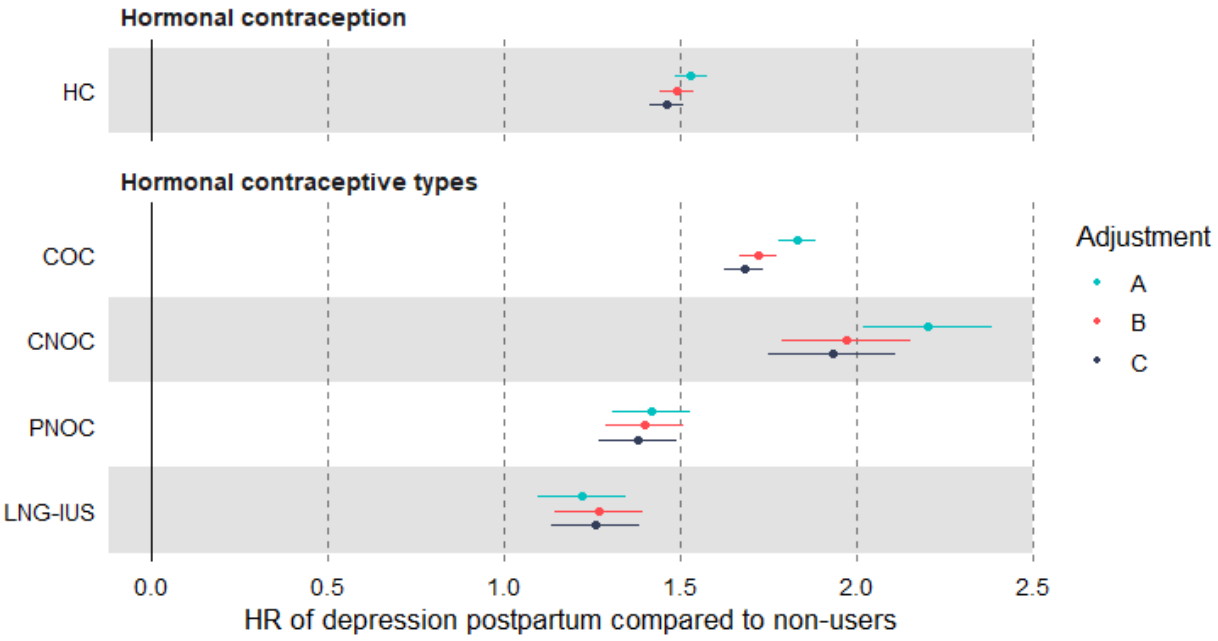

Figure 9. The instantaneous risk of depression postpartum in HC users compared to non-users dependent on type and covariate adjustment set. (**A**) was adjusted for age and calendar year. (**B**) (main analysis) was additionally adjusted for educational level, civil status, history of mental disorder, parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes. (**C**) was additionally adjusted for immigration status, smoking status, and parental educational level.
Missing values in adjustment (B) were handled by imputing to separate groups for educational level, civil status and preterm delivery status. For adjustment (C), they were handed by performing multiple imputations using polytomous logistic regression for educational level and parental education level and logistic regression for civil status, preterm delivery, and smoking status based on the listed covariates and outcome with 10 iterations and 5 imputations.
The HR for POP violated the non-proportional hazard assumption, hence the time-varying HR is shown in Figure 6. HC, hormonal contraceptive. HR, adjusted hazard ratio. COC, combined oral contraceptive. CNOC, combined non-oral contraceptive. HC, hormonal contraception. POP, progestogen-only pill. PNOC, progestogen-only non-oral contraceptive. LNG-IUS, levonorgestrel-releasing intrauterine system. Caption is modified from Study III (Appendix III)

The proportional hazard assumption for POP use on the instantaneous depression risk was violated. Therefore, to estimate the time-varying HR, we used a flexible parametric model where we varied the degrees of freedom for the baseline hazard function. With three degrees of freedom or more, the model fits appeared similar (**Figure 10**), with a limited indication of improvement beyond 3 degrees of freedom, as evidenced by the lowest Bayesian Information Criterion (BIC) value observed for this model. Consequently, based on this model, **Figure 11** illustrates the baseline hazard and the time-varying HR for POP use. The instantaneous risk was reduced early postpartum among POP users, but hereafter increased to a HR above 1 about 8 months postpartum reaching approximately 1.2 at 12 months postpartum.

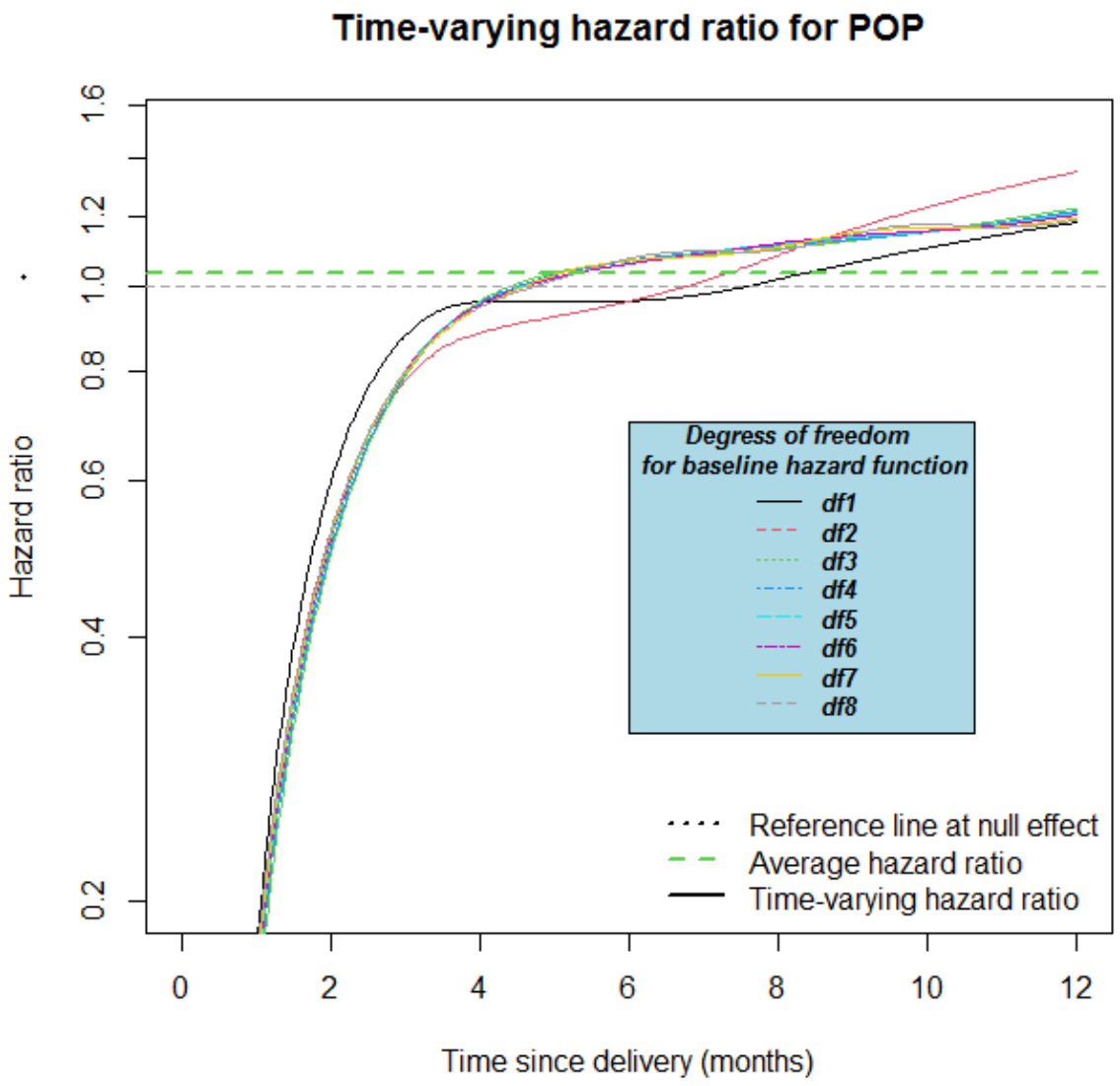

Figure 10. Time-varying hazard ratio for depression postpartum for POP users compared to non-users from a flexible parametric model where degrees of freedom for the baseline hazard function varied from 1 to 8. There was no evidence of a better fit of the data after 3 degrees of freedom.

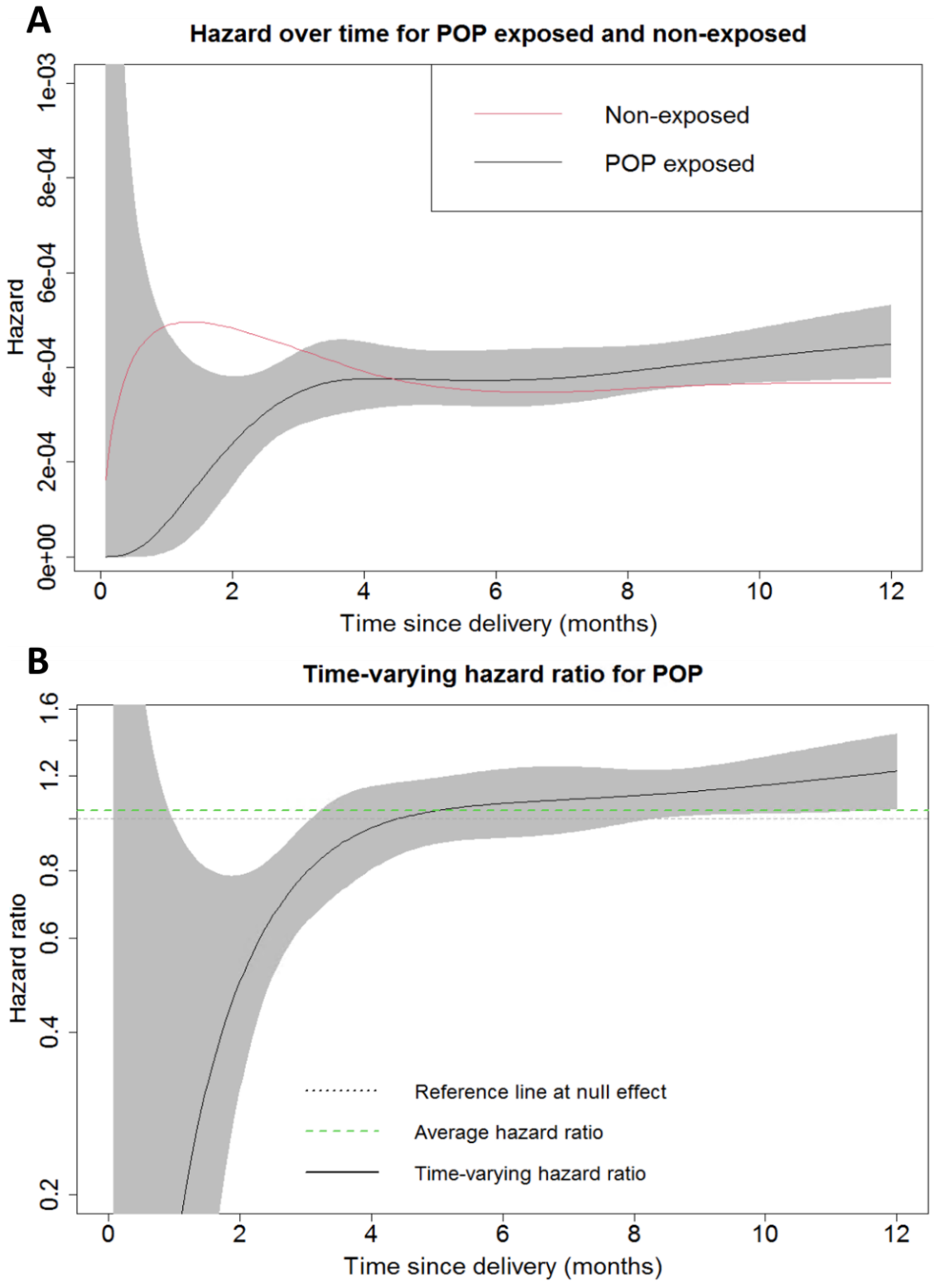

Figure 11. A) Time-varying hazard for developing depression in the postpartum period for mothers exposed to progestogen-only pill (POP) (solid black line with 95% confidence interval) and non-exposed (solid red line) across the postpartum period. **B**) The time-varying hazard ratio (HR) (the solid line with 95% confidence interval) for developing depression in the postpartum period for women starting on progesterone-only pills (POP) compared to non-exposed. The dotted gray line shows the HR=1 and the dotted green line shows the estimated HR assuming proportional hazard. Figures are adapted and caption modified from Study III (Appendix IIII).

The corresponding 12-month average absolute risks between the population with the observed HC initiation compared to the hypothetical scenario had nobody started HC were 1.37% (1.34;1.41) and 1.55% (1.52;1.58), respectively (**Figure 12A**). This resulted in an absolute risk difference of 0.18% (0.16;0.20) (**Figure 12B**). Correspondingly, if all HC users had started COC, it was 1.63% (1.59;1.67), CNOC 1.72% (1.59;1.85), POP 1.38% (1.34;1.42), PNOC 1.51% (1.45;1.57) (**Figure 12C),** and specifically LNG-IUS 1.45% (1.39;1.51). The corresponding absolute risk differences are shown in **Figure 12D**.

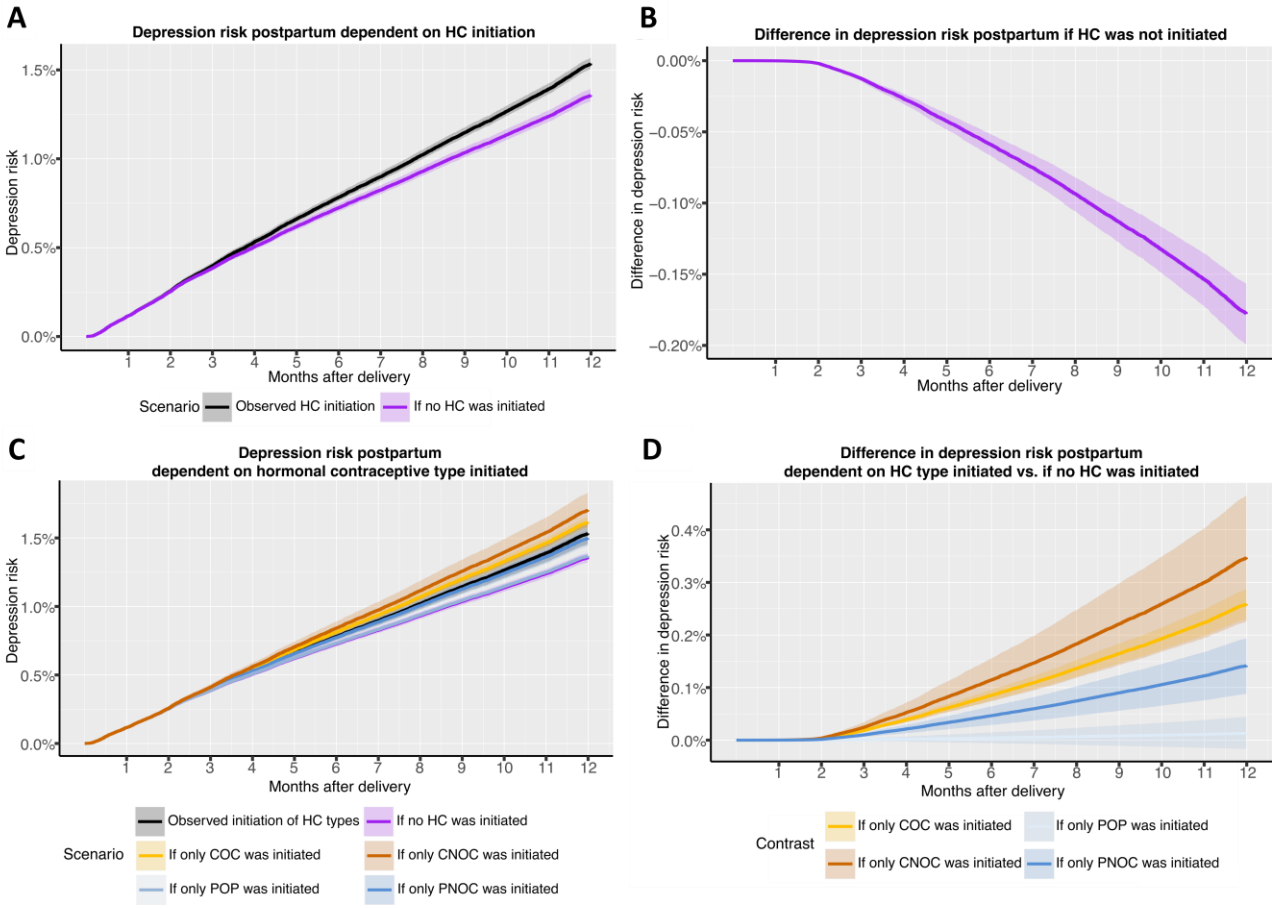

Figure 12. Risk curves for depression postpartum. **A**) The 12-months average absolute risk of depression with 95% confidence intervals for the observed HC initiation vs. the hypothetical scenario had nobody initiated HC. **B**) The 12-months average absolute risk difference of depression with 95% confidence interval between the observed HC initiation vs. the hypothetical scenario had nobody initiated HC. **C**) The 12-months average absolute risk of depression with 95% confidence intervals for the hypothetical scenarios had all HC users initiated either combined oral contraception (COC), combined non-oral contraception (CNOC), progestogen-only pill (POP), or progestogen-only non-oral contraception (PNOC) vs. the hypothetical scenario had nobody initiated HC. **D**) The 12-months average absolute risk difference of depression with 95% confidence interval between the hypothetical scenarios had all HC users initiated either COC, CNOC, POP, or PNOC vs. the hypothetical scenario had nobody initiated HC. HC, hormonal contraceptive. aHR, adjusted hazard ratio. COC, combined oral contraceptive. CNOC, combined non-oral contraceptive. POP, progesterone-only pill. PNOC, progesterone-only non-oral contraceptive. IUS, intrauterine system. Figures are adapted and caption modified from Study III (Appendix IIII).

The HR for mothers younger than 20 years was 1.63 (1.24;1.47), between 20-29 years 1.55 (1.46-1.64), and for mothers aged 30 or older 1.35 1.34;1.47).

The results of the Cox regression models stratified on the covariates, which showed evidence of violating the proportional hazard assumption, showed similar findings (**Figure 13)**, except that the HR for mothers younger than 20 years decreased considerably to 1.33.

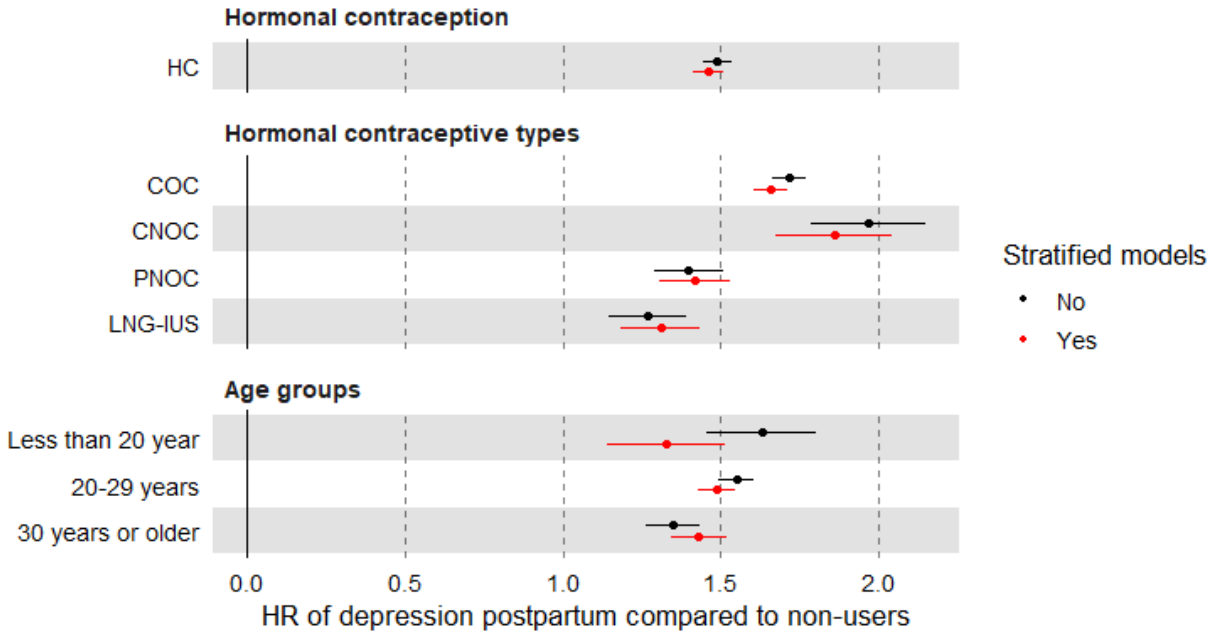

Figure 13. Black dots show the results of the main models which were not stratified on any covariates. The models were adjusted for age group, calendar period, educational level, civil status, history of mental disorder; parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes, parental educational level, immigration status, and smoking status. In red dots are the results of the models stratified on the covariates showing evidence of violating the proportional hazard assumption, which included age group, calendar period, educational level, civil status, and IVF-treatment.
Missing values were handled by imputing to a separate group educational level (0.2% missing data), immigration status (0.1% missing data), cohabitant status (0.1% missing data), and preterm delivery status (0.1% missing data).

5. Discussion

The overall aim of this thesis was to illuminate the potential link between hormonal contraceptive exposure and the risk of developing depressive episodes. Additionally, it aimed to explore how this potential link could serve as a model for further investigating how depressive episodes with potential hormonal contributions may be linked across women's reproductive lives.

5.1 Main Findings

In Study I, the use of LNG-IUS with a higher initial LNG-release dose was associated with a higher risk of developing depression. Specifically, the 12-month risk of depression for low-, medium-, and high-dose LNG-IUS use was 1.21%, 1.46%, and 1.84%. The corresponding increase in relative risk was 21% and 52% in medium- and high- compared to low-dose LNG-IUS use and 26% for high- compared to medium-dose LNG-IUS use. These results were somewhat consistent when investigated based on depression diagnosis and antidepressant prescription, separately, and after adjusting for medical indications for the use of higher LNG-IUs dose, including diagnosis or prescription indication for menorrhagia. These findings support a positive dose-response association between progestin exposure and the risk of developing depression.

In Study II, a history of HC-associated depression was associated with an increased risk of developing PPD compared to women with prior depression not associated with HC initiation. This was also supported by a sensitivity analysis, where the exposure was defined based on the first depressive episode, albeit with lower estimates (1.19 vs. 1.40). These findings provide some evidence supporting that some women are more susceptible to hormonal effects and that such susceptibility may persistent across their reproductive lives. Such information may be useful to identify women at risk of developing PPD, as HC-associated depression may indicate PPD susceptibility.

In Study III, HC initiation postpartum was associated with a 1.49 times higher risk of depression within 12 months after delivery. For the observed population of first-time mothers during 1997-2022, this resulted in an increase in 12-month depression risk from 1.37% to 1.55%. The higher risk was consistent across age groups and COC, CNOC, and PCOC. However, the evidence related to POP exposure was less clear. A time-varying HR showed reduced risk early

postpartum, which increased across the postpartum period to reach an increased risk 8 to 12 months postpartum. These findings were supported by a sensitivity analysis accounting for additional potential confounders such as immigrant and smoking status, as well as parents' educational level. This raises the question of whether routine HC initiation postpartum may increase the risk of depression during this period when women are already more susceptible to developing a depressive episode.

5.2 In the Context of Existing Knowledge

5.2.1 Study I

Studies investigating the link between LNG-IUS and mental health have shown inconsistent results (Bürger et al. 2021). However, until recently, studies investigating the association between HC use and depression did not compare between different LNG-IUS dosages, but compared the risk among all LNG-IUS dosages altogether with non-exposed. Large observational studies have shown a 40-60% increased risk of depression associated with LNG-IUS use (C. Lundin et al. 2022; Skovlund et al. 2016; Stenhammar et al. 2023). When compared to copper-IUS use, the instantaneous risk was 17% higher in LNG-IUS users over approximately 4 years of follow-up time and by 21% over approximately 3 years of follow-up time (Slattery et al. 2018). A longer follow-up time can be problematic due to a built-in selection bias, i.e., frailty or early depletion of susceptible women, making the exposure appear less harmful at later times. The reported hazard ratio, estimated from a Cox model, can be viewed as some average of the hazard ratios over time and is therefore subject to this selection bias, which may bias toward the null (Hernán 2010). Before the initiation of Study I, only one study had previously compared the risk of starting antidepressant medication after the start of medium- and high-dose LNG-IUS. This study found a 13% increased 2-year risk in high-dose compared to low-dose LNG-IUS (Roland et al. 2023). Another study was recently published that investigated the risk of initiating antidepressant medication between the three types of LNG-IUS (Skovlund et al. 2024). With 1-year follow-up, the estimated incidences were 14.0, 18.6, and 34.8 per 1000 person-years in low-, medium-, and high-dose LNG-IUS users. These risks are not far from those observed in Study I; however, they did not detect any difference between low- and medium-dose LNG-IUS, possibly due to a population size approximately three times smaller. In addition, Study I did not include women with a history of any mental disorder or use of psychotropic drugs. A separate analysis conducted on this subset showed higher risk across all types (4.80%, 5.22%, and 5.91%

in low-, medium-, and high-dose LNG-IUS users), but attenuated relative risks of 1.09 and 1.23 associated with medium and high- compared to low-dose LNG-IUS. Hence including women with prior mental disorders may affect outcome estimates. This may be due to a healthy user bias or to a relatively higher influence of other risk factors in such a population.

5.2.2 Study II

Prior studies have attempted to investigate whether depressive episodes with a potential hormonal contribution across women's reproductive lives are linked. However, most of these studies are based on retrospective diagnoses and the lack use of proper diagnostic assessments, increasing the risk of recall and confirmation bias (Cao et al. 2020). A meta-analysis showed that these studies supported a link between PMS and PPD, such that women with PMS had twice the likelihood of developing PPD compared to women without PMS. However, the meta-analysis also concluded that the quality of these studies was low (Cao et al. 2020). Other studies have also observed a similar link between PMS and PPD to the emergence of perimenopausal depressive symptoms (Payne, Palmer, and Joffe 2009). A few studies have directly addressed the link between PMS/PMDD, PPD, and depression in perimenopause with depressive symptoms related to oral contraceptive use. One of the studies, involving 1286 women, asked participants to fill out a questionnaire within the first three days after childbirth. The questionnaire included the Edinburgh Postnatal Depression Scale to assess postpartum depressive symptoms (of which 7% scored ≥10, potentially indicating PPD) and questions regarding prior emotional reactivity to oral contraceptive use. The study showed no association between mood symptoms related to childbirth and oral contraceptive use (Bloch et al. 2006). However, when this was investigated in the high-risk and low-risk groups for PPD, they found an association between PPD and prior emotional reactivity to oral contraceptive use (Bloch et al. 2005). Another study, involving 72 women with an ongoing depressive episode, assessed mood symptoms across different reproductive events and found no association between these events and mood symptoms related to oral contraceptive use. However, it was also noted that only 50 women had previously tried oral contraception (Gregory, Masand, and Yohai 2000). A third study found that 70% of 57 women with PMS reported prior side effects to oral contraception, compared to 39% of 22 women without PMS (Dennerstein, Morse, and Varnavides 1988). Finally, a menopausal clinic assessed women for psychological distress. Among 86 women scoring high on psychological distress, compared to 42 women scoring low on psychological distress, those with high distress were more likely to have experienced prior oral contraceptive dysphoria (Stewart and Vigod

2016). These studies are limited by their small sample sizes and by a high risk of recall and confirmation bias, so they should be interpreted with caution.

5.2.3 Study III

Only a few studies have previously investigated whether HC initiation after childbirth is associated with an increased risk of depression, and they showed conflicting results (Ti and Curtis 2019). Two randomized studies with depot injections both found a higher degree of depressive symptoms in women receiving depot injections compared to those receiving placebo and/or copper-IUS (Lawrie et al. 1998; Singata-Madliki, Hofmeyr, and Lawrie 2016). On the contrary, two retrospective observational studies found no increased risk (Drake et al. 2020; Tsai and Schaffir 2010). One prospective study, which followed women through pregnancy and half a year postpartum, found increased levels of depressive symptoms in women using HC compared to non-users, despite no difference in mental symptoms during pregnancy (Nilsson and Almgren 1968).

Reports of PPD as adverse effects to the US Food and Drug Administration Adverse Event Reporting System are rare. However, they have shown a potential association between PPD and HC use, particularly with LNG-IUS and implants (Horibe et al. 2018). Further, a study including 75,528 women, registered in the US military medical system, who were either active or retired from military service, or related to one who was, found that 42% initiated HC within 12 months postpartum, mostly on POP (63%) and LNG-IUS (10%) (Roberts and Hansen 2017). In contrast to Study III, this study followed women for 12 months or until the expected discontinuation time based on the date of prescription and the prescribed amount, resulting in an average follow-up time of 9 months, which included only 4 months for POP users. Similarly to Study III, they observed a short time from delivery until initiation of POP, which was shorter than for the other HC types. They found considerably higher rates of depression (5%) and prescriptions of antidepressants (8%) than in Study III. They showed an associated increased risk of initiating antidepressants with the use of implants (HR of 1.2) and vaginal rings (HR of 1.5), an associated decreased risk with POP use (HR of 0.6), and no associated risk with COC and LNG-IUS use. A lower risk for a diagnosis of depression was associated with POP (HR of 0.6) and LNG-IUS use (HR of 0.7). The reduced risk associated with POP use mirrors the reduced risk in POP users early postpartum in Study III. However, in contrast to Study III, they were unable to replicate the finding that the risk increased across the postpartum period, reaching an increased risk at 8-12 months postpartum, due to the short follow-up time. As speculated in Appendix III, this time-varying instantaneous risk may be explained by a mismatch between the

day of filling a prescription and the day of actual starting. This might especially be the case for POP, for which prescriptions were filled early coinciding with the 8-week postpartum visit at the general practitioner, and for which many did not make a refill. This could indicate that they never initiated or that they initiated much later than expected. A study has shown that many women intend to start POP early postpartum by receiving a POP prescription, but they had either not started or already discontinued it at three and six months postpartum (Uhm et al. 2020). The higher risk related to COC use compared to POC use contrasts with some findings, although not conclusive, outside the postpartum period (Kraft et al. 2024). It may be explained by the fact that more mothers using CHC are not breastfeeding, as is it not recommended to use CHC while breastfeeding (Sundhedsstyrelsen 2022). Although the direction is unclear, breastfeeding has been associated with a lower risk of PPD (Pope and Mazmanian 2016). A potential mechanism involving downstream positive modulation of oxytocin on stress response and sleep has been suggested (Pope and Mazmanian 2016), but it may as well be that PPD women are more likely to discontinue breastfeeding. Hence, such a distinction between exposure groups may introduce as bias.

5.2.4 Hormonal Contributions to Depressive Episodes across Study I-III

In Study II, about 3% of first-time mothers were known to have had a depression developed in relation to HC initiation. This corresponded to approximately one out of every four women with prior depression before their first delivery. In addition, one out of every 10 PPD cases among first-time mothers was recorded with such a predisposition. Importantly, the precise number of women who developed depression with a potential HC contribution remains unknown. The risk of PPD was about 40% higher in first-time mothers with such a predisposition compared to the general predisposition for depression. Correspondingly, the absolute risk increase was only 1.5 percentage points from 3.7% to 5.2%, such that, despite a history of depression associated with HC initiation, most did not develop PPD. In Study I and III, the risk of depression was about 50% higher associated with high-dose vs. low-dose LNG-IUS and with postpartum HC exposure vs. unexposed. However, the corresponding absolute risk differences were only 0.63 and 0.15 percentage points, respectively. This implies that, at the population level, the number of depressive episodes with a potential hormonal contribution is likely small, at least those episodes leading to medical treatment or hospital referral. This emphasizes that the risk of developing a depressive episode across women's reproductive lives is influenced by many other factors, and potential hormonal contributions may only constitute a relatively small fraction.

The underlying mechanism for hormonal contributions to depressive episodes is not fully understood, and whether the same mechanisms underpin the episodes across different reproductive events remains to be clarified. It is hypothesized that downstream susceptibility to hormonal fluctuations is involved, including postpartum estradiol withdrawal (Schiller, Meltzer-Brody, and Rubinow 2015), premenstrual progesterone/ALLO and/or estradiol withdrawal (Hantsoo and Epperson 2015), and perimenopausal estradiol fluctuations (Freeman et al. 2006). Depressive episodes related to HC use have been speculated to result from exposure to synthetic progestogens (Pletzer, Winkler-Crepaz, and Maria Hillerer 2023; Sundström-Poromaa et al. 2020), as well as from the withdrawal of endogenous hormones (Graham and Milad 2013). Even withdrawal of the synthetic steroids during the pill break has been shown to be linked to mood symptoms (Noachtar, Frokjaer, and Pletzer 2023), and the blunted endogenous hormone state obtained from continuous COC use may also have mood-stabilizing effects for women with PMDD/PMS (de Wit, de Vries, de Boer, Scheper, Fokkema, Janssen, et al. 2021).

Some evidence indicates that susceptibility originates at the gene or gene expression level and a different gene disposition may exist for mood symptoms related to oral contraceptive use compared to that associated with other mental symptomatology (Kendler et al. 1988). Additionally, evidence suggests involvement of the estrogen receptor alfa in PMDD (Huo et al. 2007), the estrogen receptor beta in both PMDD and perimenopausal mood symptoms (Takeo et al. 2005), and polymorphism of the serotonin 1A receptor in PMDD (Dhingra et al. 2007). The serotonin 1A receptor is also shown to be dysregulated across the menstrual phase in women with PMDD (Jovanovic et al. 2006). Furthermore, one study has indicated that epigenetic markers during late pregnancy, involving estrogen receptor signaling, show promising predictive accuracy for PPD (D. Mehta et al. 2014). These findings were partly replicated in another study, which linked these markers to both induced mood symptoms and changes in brain serotonin transporter levels following a pharmacological hormone manipulation with a gonadotropin-releasing hormone agonist (Divya Mehta et al. 2019). Additionally, an increased brain serotonin transporter level has been observed during the premenstrual phase in women with PMDD compared to those without PMDD (Sacher et al. 2023). This observation may suggest a premenstrual decrease of synaptic serotonin availability, potentially explaining the rapid response achieved by selective serotonin reuptake inhibitors in the treatment of PMDD (Steinberg et al. 2012), thereby enabling efficient cyclic treatment during the menstrual cycle (Reilly et al. 2023).

Monoamine oxidase brain levels, which have been shown to be increased in depression (Meyer et al. 2009; Moriguchi et al. 2019), have been associated with both the

postpartum and the perimenopausal transition states. It is upregulated during the perimenopausal state compared to both the premenopausal and postmenopausal states (Rekkas et al. 2014). Based on rodent studies, it is suggested that early estradiol treatment, rather than late treatment, may improve mood symptoms during perimenopause; only early treatment improved depressive-like behavior and this was associated with a downregulation of monoamine oxidase (Hou et al. 2019). This may mirror the potential time window of vulnerability related to the perimenopausal transition. Additionally, the postpartum period has been linked to increased levels of monoamine oxidase (Sacher et al. 2010), which have been correlated with the level of postpartum mood lability (Sacher et al. 2015). The increased monoamine oxidase is speculated to be related to the significant decrease in estradiol levels following childbirth, as estradiol has been shown to downregulate monoamine oxidase levels, likely via downstream effects of estrogen receptor beta activation (Hou et al. 2019). The duration of increased monoamine oxidase levels remains unknown, but it is known that the postpartum window of vulnerability can last several months (Munk-Olsen et al. 2006). Research on the effect of HC steroids on monoamine oxidase is limited and has shown conflicting results (Marchi and Cugurra 1974; Shetty and Gaitonde 1980; Tandon et al. 1983). When HC is initiated, especially those inhibiting ovulation as their primary mode of action, the endogenous hormone levels are kept low for a longer period after delivery. Further, ethinylestradiol has relatively little affinity for estrogen receptor beta compared to endogenous estradiol, but high affinity for estradiol receptor alfa (Escande et al. 2006), upon which stimulation may instead increase monoamine oxidase A levels (Bertotto et al. 2019; Hou et al. 2019). Together, yet speculative, such downregulated endogenous estradiol and potential direct effects of ethinylestradiol could increase the length of the window of vulnerability by maintaining high levels of monoamine oxidase. This raises the clinically relevant question of whether there is any time window of vulnerability related to HC-associated depression in the postpartum period, i.e., if the depression risk associated with HC initiation depends on the timing of initiation in the postpartum period. This is a research question we will pursue in follow-up analyses in Study III.

The GABAergic neurotransmission is another neurotransmitter system suggested to be influenced by hormonal transitions (Gilfarb and Leuner 2022). It has been suggested that women with PMDD/PMS and PPD have a dysregulated GABA(A) receptor plasticity in response to fluctuating hormone levels, or specifically ALLO levels (Hantsoo and Payne 2023; MacKenzie and Maguire 2014; Maguire and Mody 2008). The receptor plasticity involves a compensatory regulation of different receptor subunits making it adaptive to fluctuating hormone levels (MacKenzie and Maguire 2014). However, dysregulation may lead to a difference in

sensitivity to ALLO (Timby et al. 2016). New GABA-modulating treatments, such as brexanolone and zuranolone for PPD (Deligiannidis et al. 2021; Meltzer-Brody et al. 2018), and sepranolone for PMDD, are emerging (Torbjörn Bäckström et al. 2021). Rodent work indicates that HC steroids induce changes in ALLO levels, but also in GABA(A) receptor subunit expression levels, which were induced by the LNG component of the COC steroids (Porcu et al. 2012). These effects have been coupled with induced anxiety-like behavior, reduction in social behavior, and decreased sexual motivation in rats (Follesa et al. 2002; Porcu et al. 2012; Santoru et al. 2014). Furthermore, a LNG dose-response difference in anxiolytic-like behavior has been observed in rodents: lower dosage was associated with anxiolytic-like effects, while higher dosage induced a larger reduction in serum estradiol levels (Simone et al. 2015). The authors speculated that this could be related to the paradoxical U-shaped effect of the downstream neurosteroid, ALLO (Andréen et al. 2009; T. Bäckström et al. 2011).

GABAergic signaling is likely to play an important underlying role in the neurobiology of stress-reactivity via feedback inhibition of the hypothalamic-pituitary-adrenal axis (Maguire 2019; Pisu et al. 2022). Changes in sensitivity to ALLO can result in altered stress sensitivity, which is seen to correlate across the menstrual cycle (Ossewaarde et al. 2010). Altered stress reactivity has been seen in women with PMDD (Liu et al. 2017), and women with PMDD show a blunted cortisol awakening response and cortisol reactivity to stressors (Beddig, Reinhard, and Kuehner 2019; Huang et al. 2015), which has been linked to a blunted ALLO stress response (Girdler et al. 2001). Similarly, a dysregulated stress reactivity in the form of a blunted cortisol awakening response and attenuated stress-induced ALLO, have been observed in women with PPD and in relation to HC administration (Pisu et al. 2022; Porcu, Serra, and Concas 2019). LNG-IUS use has also shown an altered stress-response axis, characterized by increased chronic cortisol levels as measured by hair cortisol and blunted cortisol response to adrenocorticotropic hormone stimulation. On the contrary, a potentiated response to stress stimuli was also observed (Aleknaviciute et al. 2017).

The understanding of how and if the studied hormonal transitions across Study I-III share a mechanistic link to depressive episodes remains to be further clarified. However, emerging evidence supports such serotonergic and GABAergic neurotransmission pathways to be involved (Kundakovic and Rocks 2022; Schweizer-Schubert et al. 2021). This may pave the way to better understanding the hormonal link to depressive episodes, as well as to better identify women susceptible to hormonal transitions and how this knowledge can be used to optimize prevention and treatment algorithms.

5.3 Methodological Considerations

5.3.1 Strengths

The studies included in this thesis have several strengths: 1) The leverage of healthcare data on nationwide populations, including all individuals within the target populations of Denmark where loss to follow-up only occurred in the event of death or emigration, which mitigates vulnerability to non-response and healthy survivor bias. 2) The use of comprehensive data on hospitalizations and filled drug prescriptions for a population with free access to healthcare, reflecting routine clinical care, and which was collected independently of the research questions reducing risks of certain types of bias, e.g., selection, recall, confirmation, and observer bias. 3) The populations were specifically selected to mitigate potential confounding, such as surveillance bias and bias related to health-seeking behavior and physicians' prescription trends. Study I only compared users of different LNG-IUS and not to a non-user population. Study II compared women who all had prior depression and had used HC before. Studies II and III only included first-time mothers, ensuring some level of homogeneity in terms of shared life circumstances between the comparison groups. 4) The longitudinal designs, with relatively short follow-up times, provide a perspective on the temporal relationship between exposure and outcome, while reducing the risk of exposure misclassification due to HC discontinuation and depletion of susceptible individuals, i.e., frailty, discussed further in section 5.3.2. These strengths enable the assessment of the research questions in Study I-III with the necessary precision to detect potential associations. In contrast, randomized settings would have faced challenges due to the required sample sizes and ethical considerations in maintaining blinding procedures in a placebo-controlled study.

5.3.2 Limitations

The use of register-based studies also entails limitations, some of which are specific to each of the study designs addressed in Appendix I-III, and some of which are shared across Study I-III considered in the following.

First and most importantly, the studies were designed to investigate and quantify associations, but not establish causal relationships. The distinction is important because one cannot rule out residual confounding in the observational study designs. At best, we have mitigated such by accounting for potentially important confounders in the models and by conducting several sensitivity analyses.

Second, there is a risk of misclassifying depression outcomes by relying on antidepressant prescriptions as they can be prescribed for other indications than depression. This will introduce a misclassification, assumably non-differential, biasing the estimate towards the null. Additionally, by only capturing medically treated or hospital-diagnosed cases, the studies are likely to miss less severe cases of depression, and hence the observations may not be generalizable to these. However, assuming a similar relationship between exposure and outcome in the less severe cases, it would mainly impact the absolute risk estimates.

Third, there is a risk of misclassification of the exposure, perhaps particularly in Study III, where the timing of HC prescription filling may not align with the actual start of usage as it may be delayed due to breastfeeding. A similar issue would exist due to early discontinuation. Furthermore, such a phenomenon may also challenge time-to-event analyses, assuming proportional hazards, as such misclassification may change over the follow-up time and by such can result in time-varying hazard ratios. This may explain the time-varying coefficients observed for the POP exposure in Study III. Frailty introduces a similar issue, e.g. in Study I. If susceptible women are depleted to a faster degree when exposed to high-dose LNG-IUs than when exposed to lower dosages, it can bias the estimates towards the null, particularly if there is a long follow-up time (Hernán 2010). Conversely, in situations where the exposure might have a protective effect, frailty can be resembled by early discontinuation (Aalen, Borgan, and Gjessing 2008), which could be an alternative explanation for the time-varying coefficient for POP exposure in Study III. Additionally, violation of the proportionality assumption can arise if the outcome depends on multiple time scales. For instance, in Study III, time since delivery is considered the underlying time-scale, but time since the start of HC exposure may also affect the hazard for the exposure. Employing more flexible models capable of handling multiple timescales (Iacobelli and Carstensen 2013), as planned for a follow-up analysis of Study III, may address these complexities.

6. Conclusions and Perspectives

The observations shown in this thesis support an association between exogenous hormone exposure and heightened depression risk. Specifically, there was evidence of a dose-dependent association between LNG and depression, as well as an association between postpartum HC exposure and depression, at least for HC types other than POP. Further, the results supported that depressive episodes across reproductive events are associated, indicating that a subgroup of women might be more susceptible to hormonal transitions and that HC-associated depression could serve as an indicator of PPD susceptibility.

The implications of these findings should be seen in light of the limitations alluded to in section 5.3.2. Most importantly, unmeasured confounding remains a challenge in observational studies, meaning that causal conclusions are not to be inferred in any of the studies in this thesis. Nonetheless, the results add to the body of evidence regarding the potential link between exogenous hormone exposure and depression risk. The evidence indicates, if any, that only a small proportion of women using HC may develop a depressive episode requiring medical attention. Importantly, the level of evidence and the magnitude of the potential risk provided by these studies are not in itself sufficient to support any general advice against HC use. Especially, also given its benefits in preventing unwanted pregnancies and treating medical conditions like menorrhagia and dysmenorrhea. Yet, it highlights that potential mood symptoms and depression should be considered and conveyed as potential side effects both at the general contraceptive counseling as well as at the postpartum contraceptive counseling. Follow-up consultation should include mood symptom evaluation shortly after HC initiation. Moreover, the findings provide evidence that depressive mood symptoms related to HC use may be used to identify women more susceptible to hormonal fluctuations. This aids healthcare professionals in PPD screenings and risk profiling, and may also be relevant in the context of other reproductive events such as the perimenopausal transition.

Considering the limitations outlined in section 5.3.2, future research should focus on several perspectives. Randomized placebo-controlled studies are crucial for establishing causal inference; however, they face significant challenges to be considered: 1) the requirement of very large sample sizes; 2) ideally comprised of HC-naïve women to mitigate healthy user bias; 3) addressing issues with high HC discontinuation rates leading to potential underestimation of potential effect, including proper intention-to-treat analysis strategies; 4) challenges obtaining proper contraceptive protection in the placebo group; 5) difficulties in maintaining blinding and consequently issues with confirmation and reporting bias. Conducting

a comparative study with the three different LNG-IUS dosages could alleviate some of these challenges, e.g., maintaining blinding and obtaining proper contraceptive protection. Conversely, recruiting HC-naïve women may be challenging given the prevalent use of especially COC as the initial HC method, although trends are shifting towards increased LNG-IUS use, even at a young age.

Given the mentioned challenges, another way forward is to explore potential underlying mechanisms that could explain the link between mood symptoms and exogenous hormone exposure, which may provide another form of support for such evidence. This includes preclinical and clinical studies investigating effects on brain biology and function, behavioral effects, and cognitive effects. With the present finding of a positive association between LNG dose and depression risk, it would be compelling to study such a dose-response effect on brain biology. We are currently pursuing prior observational findings of lower 5-HT4R levels in women using oral contraceptives compared to non-users in a randomized, placebo-controlled trial. We aim to assess how such potential biological effects may relate to mood and behavioral effects (Clinical trial identifier: NCT05212389).

The question raised about the possible presence of a vulnerable time window during hormonal transitions prompts further research to investigate the potential relevance of the timing of HC initiation postpartum. This consideration may also be relevant in other transitions, such as in adolescence.

Given the discovery of a possible connection between HC-associated depression and PPD, this suggests the existence of a subgroup of women who are more susceptible to hormonal fluctuations. This insight could inform clinical research, opening up new avenues for exploring underlying mechanisms and developing new prevention and treatment strategies for depression, particularly in the context of PPD. Further investigation into whether this susceptibility extends to hormonal fluctuations during other reproductive events, such as the perimenopausal transition, would be worthwhile and could provide valuable insights.

In summary, the research presented in this thesis underscores the need for further exploration of the relationship between HC exposure and the risk of depression. This entails the investigation into underlying mechanisms and how varying hormonal content and routes of administration may impact this relationship. Moreover, it prompts inquiry into whether these mechanisms are consistent across different reproductive events. Such insights could pave the way for future prevention and treatment strategies tailored to the subgroup of women more susceptible to hormonal fluctuations throughout their reproductive lives.

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Appendix

Study I

Association between intrauterine system hormone dose and depression risk

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Submitted November, 2023. Revised and resubmitted February, 2024

Study II

Depression associated with hormonal contraceptive use as a risk indicator for postpartum depression

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Published in JAMA Psychiatry, 2023, doi: 10.1001/jamapsychiatry.2023.0807.

Study III

Postpartum hormonal contraceptive use and risk of depression

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Manuscript in prep.

Study I

Association between intrauterine system hormone dose and depression risk

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Disclosures: VGF has received honorarium as a consultant for Sage Therapeutics and lectures for Lundbeck Pharma A/S, Janssen-Cilag A/S and Gedeon-Richter A/S. ØL has received lecture honorarium and his institution research funding from Exeltis. TMO reports having received a speaker fee from Lundbeck. The rest of the authors report no conflicts of interest.
Acknowledgements: The study was funded by The Independent Research Fund Denmark (grant identifier: 0134-00278B and 7025-00111B). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Status: Under review

Abstract

Objective: To compare the associated risk of incident depression between first-time users of low-, medium-, and high-dose levonorgestrel-releasing intrauterine systems (LNG-IUS).

Methods: This national cohort study is based on Danish register data on first-time users of low-, medium-, or high-dose LNG-IUS aged 15-44 years between 2000-2022. Cox regression and a G-formula estimator were used to report 1-year average absolute risks, risk differences and risk ratios (RRs) of incident depression defined as antidepressant initiation or receive of depression diagnose standardized for calendar year, age, educational level, parental history of mental disorders, endometriosis, menorrhagia, polycystic ovary syndrome, dysmenorrhea, leiomyoma, and postpartum initiation.

Results: In total, 149,200 women started using an LNG-IUS, of which 22,029 started a low-dose (mean [SD] age, 22.9 [4.5] years), 47,712 a medium-dose (mean [SD] age, 25.2 [6.2] years), and 79,459 a high-dose LNG-IUS (mean [SD] age, 30.2 [5.6] years). The associated subsequent 1-year adjusted absolute risks of incident depression were 1.21% (95% CI, 1.06-1.36), 1.46% (95% CI, 1.33-1.59), and 1.84% (95% CI, 1.72-1.96), respectively. For high-dose, the RRs were 1.52 (95% CI, 1.30-1.74) and 1.26 (95% CI, 1.10-1.41) compared to low- and medium-dose LNG-IUS. For the medium-dose, the RR was 1.21 (95% CI, 1.03-1.39) compared to low-dose LNG-IUS.

Conclusions: First-time use of LNG-IUS was positively associated with incident depression in an LNG-dose-dependent manner across low-, medium-, and high-dose LNG-IUS. The observational design does not permit causal inference, however, the dose-response relationship contributes to the body of evidence suggesting a relationship between levonorgestrel exposure and risk of depression.

Introduction

Levonorgestrel-releasing intrauterine system (LNG-IUS) use has been associated with an approximately 40% increased risk of developing depression and initiating antidepressant medication (1–3). This has also been reported, when LNG-IUS users were compared to users of non-hormonal IUS, i.e., the copper IUS (4). However, the literature on mood symptoms related to LNG-IUS use has also shown mixed results (5). Most of the current literature is limited by their observational nature and by its vulnerability to confounding, including a healthy user bias (6), which might explain the conflicting results in the existing literature. Therefore, more research is needed which addresses the potential relationship between exogenous hormone exposure from LNG-IUS and risk of developing depression.

LNG-IUS is available in over 120 countries worldwide and is used by about 14% of women in the reproductive age in Denmark equivalent to one out of three of the hormonal contraceptive users (7,8). Today, LNG-IUS exists in three formulations differentiated by the total LNG content and daily release dose; low-dose (13.5 mg; 14 µg/day initial release dose; 8 µg/day average over first year) (9), medium-dose (19.5 mg; 17.5 µg/day initial release dose, 12.6 µg/day average over first year) (10), and high-dose LNG-IUS (52 mg; 21 µg/day initial release dose, 20 µg/day average over first year) (11). All three types are used as birth control and in addition, the high-dose LNG-IUS is approved for treating heavy menstrual bleeding (menorrhagia) (11). The mechanism of action of LNG-IUS as a contraceptive method is exerted via local effects in the uterus by inducing endometrial thinning and increased cervical mucus, which inhibits sperm survival and prevents fertilization and implementation of the oocyte (12). However, only about 50-76.5%, 88%, and 97% of high-, medium-, and low-dose users have ovulation during the first year after insertion, increasing to about 80-100% the following year, which indicates some systemic effects of LNG-IUS particularly early after insertion (13–15). This is in line with a higher daily release dose of LNG during the early treatment phase which declines with the longer duration of use; the daily release doses decline to 6 µg/day, 10 µg/day, 19 µg/day for low-, medium- and high-dose LNG-IUS one year after insertion (9–11). LNG is able to inhibit ovulation as it is a potent progesterone receptor agonist, by which it can mimic endogenous progesterone effects and provide negative feedback on the hypothalamic-pituitary-gonadal axis (16). However, it also activates other receptors, including androgen, glucocorticoid, and mineralocorticoid receptors with the potential to affect brain biology (17).

A recent observational study compared the risk of antidepressant use within two years after LNG-IUS use between the medium vs. the high-dose LNG-IUS and found an increased risk in high-dose LNG-IUS users (18). So far, no study has investigated the existence of a dose-response relationship across all three dosages while considering a close temporal relationship between the start of the hormone exposure and the subsequent risk of developing depression. This could further elucidate the relationship between progestogen exposure and subsequent development of mood symptoms. Here, we aimed to compare the 1-year associated risk of incident depression between first-time users of low-, medium-, and high-dose LNG-IUS and we hypothesized that the associated risk would increase in a dose-dependent manner.

Methods

Study design

This is a population-based cohort study based on Danish registry data. The registers and variables used are listed in **ST1**. Data were provided by the Danish e-Health Authority, hosted by Statistics Denmark and linked via the unique personal identification number given to Danish residents at birth or immigration. The study period was from 1995 to 2022, in which the first five years were used to distinguish incident from prevalent LNG-IUS and antidepressant users.

Study population

All women living in Denmark born after 1978 (ensuring women maximum 15 years of age when entering in 1995) who started use of LNG-IUS for the first time at an age of 15-44 years between January 1, 2000 through 2022 were eligible for inclusion. Women were excluded if they 1) immigrated after turning 15 years 2) emigrated after turning 15 years 3) were known to have a mental disorder from a psychiatric in- or outpatient clinic (International Classification of Diseases version 8 codes 290-315, or version 10 codes F00-F99) or previously used a psychotropic drug (Anatomical Therapeutic Chemical (ATC) codes N05* and N06*).

Exposure

The exposure of interest was incident use of LNG-IUS with different initial hormone-release dose; low-dose (14 µg/day), medium-dose (17.5 µg/day), or high-dose (21 µg/day) levonorgestrel-release dose identified via the Danish Prescription Register (ATC code G02BA03) (19). Day of filling the first prescription was used as the index date.

Outcome

The outcome was incident depression within 12 months after initiating an LNG-IUS. Depression was defined as incident use of antidepressant medication (ATC codes N06A*) or incident diagnose of depression at an in- or outpatient psychiatric department (ICD-10 codes DF32-34 and DF38-39)).

Covariates

We considered the following potential confounders defined at the index date: Age (in 5-year periods), highest educational level (below high school, high school/vocational education, or bachelor degree or above), parental history of mental disorder, and postpartum LNG-IUS use defined as use within 6 months after delivery. In addition, we accounted for potential confounding by indication by including the following medical diagnoses, as high-dose LNG-IUS may be preferred in women diagnosed with

such conditions: Menorrhagia (20), leiomyoma (21) polycystic ovarian syndrome (22), dysmenorrhea, and endometriosis (23). Finally, we controlled for time trends by including calendar-year in 5-year periods.

Statistical analysis

Women were followed for 12 months from first-time use of an LNG-IUS or until incident depression, emigration, death, or end of study period, whichever came first. A single Cox regression model (since too few died during follow-up to be able to estimate the parameters of a cause-specific Cox model relative to death) was used to estimate cause-specific hazard rates between low-, medium- and high-dose LNG-IUS use adjusted for the listed covariates. Time-on-study was used as underlying time-scale. Estimated hazard rates were used as inputs in a G-formula estimator to determine the associated average absolute risks, risk differences, and risk ratios (RRs) after 12 months of use (24).

The following sensitivity analyses were conducted where; a) depression diagnosis and antidepressant use were separately used as outcome, and the latter also after excluding prescriptions specifically addressed for other indications unless depression was confirmed by diagnosis; b) the study period was restricted to 2017-2022 during which all three LNG-IUS were concurrently prescribed in Denmark; c) the population was restricted to nulliparous first-time users younger than 30 years as the frequency of prescribed high-dose LNG-IUS is particularly high in the population older than 30 years compared to low- and medium-dose LNG-IUS (8); d) potential confounding by indication was further handled by adjusting for menorrhagia as LNG-IUS prescription indication and number of previous HC types (specified in **ST1**) used. Missing prescription indications were handled by performing multiple imputations with the *MICE*-package in R where prescription indication was imputed using logistic regression and educational level using polytomous logistic regression based on the listed covariates and outcome with 10 iterations and 5 imputations (25); e) E-values were estimated as a quantitative summary of the strength of the association of an unmeasured confounder to the exposure and the outcome required to solely explain the observed associations (26); f) an alternative modelling approach for handling confounding was assessed using a propensity score weighted analysis where the covariate effects are not assumed to be time-constant and the additivity assumption of the covariate effects are made on the logit scale for the probability of treatment and not on the log hazard scale. This was performed on first-time users during 2017-2022 (to ensure overlap of the distribution of calendar periods across all three groups) using multinominal propensity scores based on the listed covariates by use of the *mnps*-function from the *twang*-package (27,28); g) the potential influence of prior mental comorbidity excluded in the main analysis was assessed by restricting the population to women with prior mental disorder but no potentially ongoing depression defined as having received a depression diagnosis or filled a prescription for antidepressant medication within two years prior to filling the LNG-IUS prescription.

The proportional hazard assumption was assessed for each dependent variable by evaluating the correlation between scaled Schoenfeld residuals against time with the *survival*-package in R (29).

In case of a violation of the proportional hazard assumption, a stratified Cox proportion hazard model was used. Outcome estimates were calculated with 95% confidence intervals and the null-hypothesis was rejected if this did not overlap with zero for the absolute risk difference and 1.00 for the RR. Analyses were performed using R statistical software (version (4.2.2)) (R foundation for Statistical Computing) and the *riskRegression*-package was used to compute average treatment effects (30).

Approval to access National health register data was granted through the Danish Data Protection Agency. According to Danish law, no ethical approval or informed consent are needed for Danish register studies. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (31).

Results

The study population included 149,200 LNG-IUS first-time users (**SF1**), of which 22,029 (14.8%) used low-dose, 47,712 (32.0%) medium-dose, and 79,459 (53.2%) high-dose LNG-IUS (**Table 1)**. First-time users of low-dose LNG-IUS were younger (mean [SD] age, 22.9 [4.5] years) than first-time users of medium-dose (mean [SD] age, 25.2 [6.2] years) and high-dose LNG-IUS (mean [SD] age, 30.2 [5.6] years). Correspondingly, they also had lower educational level and were more often nulliparous (89.7% vs. 69.8% vs. 17.9%). Compared to first-time users of low-dose LNG-IUS, high-dose LNG-IUS users were more often diagnosed with potential medical indications for LNG-IUS use, but this was not the case for medium-dose LNG-IUS, except for the diagnosis of polycystic ovary syndrome. Notably, 3.4% vs. 6.1% vs. 10.9% had menorrhagia as prescription indication in low-, medium-, and high-dose LNG-IUS users.

Within 12 months from initiating low-dose LNG-IUS use, 279 were registered with incident depression, compared to 633 among medium-dose users, and 1,346 among high-dose users. This corresponded to adjusted absolute risks of 1.21% (95% CI, 1.06-1.36), 1.46% (95% CI, 1.33-1.59), and 1.84% (95% CI, 1.72-1.96), respectively. The RRs of developing depression for high-dose LNG-IUS use were 1.52 (95% CI, 1.30-1-74) and 1.26 (95% CI, 1.10-1.41) compared to low-dose and medium-dose LNG-IUS use, respectively. The RR for medium-dose LNG-IUS use was 1.21 (95% CI,1.03-1.39) compared to low-dose LNG-IUS use (**Table 2, Figure 1A-B**). The estimated hazard ratios for the complete Cox proportion hazard model are shown in **SF2**. Similar trends were found when the outcome was analyzed as incident antidepressant use and depression diagnosis, separately (**ST2**). However, due to lower number of depression diagnoses, these risks were estimated with larger uncertainty. When excluding prescriptions for antidepressant with other indications than depression, the estimates supported the main finding (**ST3**).

When the population was restricted to first-time users between 2017-2022 (demographics, see **ST4**) the RRs were 1.37 (95% CI, 1.10-1.64) and 1.17 (95% CI, 1.01-1.34) between high- vs. low-dose and high- vs. medium-dose, respectively (**ST5**). When the population was restricted to nulliparous first-time users younger than 30 years, the groups were more comparable in terms of educational level and age with a mean [SD] age of 21.7 [3.3] years, 21.7 [3.2] years, and 22.3 [3.3]

years for low-, medium-, and high-dose LNG-IUS users, respectively (**ST6**). The results based on this population (**ST7**) were also in line with the main analysis with RRs of 1.42 (95% CI, 1.16-1.68) and 1.21 (95% CI, 0.98-1.44) between high- vs. low-dose and high- vs. medium-dose LNG-IUS use, respectively. When menorrhagia as prescription indication and previous HC use were adjusted for, the RRs were 1.50 (95% CI; 1.28-1.71) and 1.24 (95% CI; 1.08-1.40) between high- vs. low-dose and high- vs. medium-dose LNG-IUS users, respectively (**ST8**). The RRs of depression due to menorrhagia as diagnosis and prescription indication were 1.52 (95% CI, 1.20-1.85) and 1.19 (95% CI, 1.02-1.36), respectively. Based on the estimated RRs from the main analysis, E-values were estimated to 2.41 (with lower border of 1.92) and 1.71 (with lower border of 1.21) for the association of depression in high- and medium- compared to low-dose LNG-IUs users, respectively. The propensity score weighted analysis, which showed balanced standardized mean differences of covariates (**ST9**) and overlapping propensity score distributions (**SF3**), showed comparable risks as obtained with the G-formula; 1.16%, 1.47%, and 1,62% in absolute risk in low-, medium-, and high-dose LNG-IUS users and HRs of 1.40 (95% CI, 1.10-1.77) and 1.27 (95% CI, 1.02-1.59) for high- and medium- compared to low-dose LNG-IUS users. In the final sensitivity analysis on women with prior mental disorder (n=48,937), the absolute risks were 4.80%, 5.22% and 5.91% for low-, medium-, and high-dose LNG-IUS users with RRs of 1.23 (95% CI, 1.07-1.40) and 1.13 (95% CI, 1.01-1.25) in high- compared to low- and medium-dose LNG-IUS users (**ST10**).

Discussion

This population-based cohort study demonstrated a positive association between LNG-dose and risk of incident depression across an initial LNG-release dose of 14 µg/day, 17.5 µg/day, and 21 µg/day. Notably, the 1-year absolute risks of depression were relatively small with 1.21%, 1.46%, and 1.84% in first-time users of low-, medium-, and high-dose LNG-IUS, respectively.

This is supported by findings from a randomized, international multicenter study linking LNG exposure and risk of developing depressive symptoms. Here, a higher frequency of self-reported depressive symptoms in the initial treatment phase and higher rates of discontinuation reported as due to depression was observed in women allocated to LNG-IUS compared to women allocated to copper IUS (32). Further, the present study is consistent with results from a recent observational study, which showed a 13% higher risk of antidepressant use in high-dose vs. medium-dose LNG-IUS users (18).

A recent study compared the incidence of starting antidepressant medication associated with first-time use of the three different doses of LNG-IUS in a population restricted to nulliparous women, which similarly showed an association with increased 1-year risk among high- (34.8 per 1000 person-years) compared to medium- (18.6 per 1000 person-years) and low-dose (14.0 per 1000 person-years) LNG-IUS users (33). However, it found no statistically significant difference between the low- and medium-dose LNG-IUS, which was explained by a lack of difference in the LNG plasma levels in users of these two LNG-IUS. This explanation, however, is not supported by studies demonstrating that the hormone exposure increases with the increasing release dose (15,34). The present study

excluded all the women with prior mental disorder or who had ever used a psychotropic drug. Prior mental disorder appeared to attenuate the estimated relative risk, despite the presence of absolute differences, but these were not sufficiently large to follow the relative higher absolute risk in this population. This observation has also been reported in other studies (4,35). It does not necessarily contradict that prior mental disorder increases the likelihood of experiencing mood symptoms after initiation of hormonal contraception (36). However, the relatively lower risk associated with HC use or with the higher LNG-IUD dose in the high-risk population could be explained by a lower representation of the more hormone-susceptible population when different etiologies are likely to be highly represented. Alternatively, it could also be explained by a potential selection bias if more susceptibility women with prior mental disorder to a larger degree prefer lower hormone exposure due to the concern about the potential mood side effects.

Intriguingly, our study provides evidence of a dose-dependent association between LNG exposure and risk of subsequent depression across three dosages, which was consistent after considering potential confounders such as menstrual bleeding indications for high-dose LNG-IUS use. As addressed in a recent meta-analysis, the role of the of the hormonal contraceptive formulation on mood symptoms has been inconclusive (37), however, this adds new evidence to the potential role of the progestogen component of hormonal contraception in the development of mood disorders (38). The knowledge on how progestogen affects the brain and mood and whether the route of administration play a role is still limited (5). Some evidence points to a potential mechanism through modulating effects on the regulation of stress reactivity via the hypothalamic-pituitary-adrenal axis (39), and preclinical evidence points to a link between LNG-induced alterations in brain γ-amino-butyric acid receptor plasticity and anxiety-like behavior in rats (40).

Even though, the 21% and 52% higher relative risk associated with medium- and high- compared to low-dose LNG-IUS only counted an absolute difference of 0.27% and 0.66%, it highlights the clinical relevance of considering LNG-hormone exposure dose in contraceptive counselling, which may prove relevant together with information on prior reactions to hormonal contraceptives or postpartum depressive episodes (41). These risk differences should be weighed against beneficial medical aspects including better bleeding control when using high-dose LNG-IUS (20), but also possible negative outcomes including an increased risk of ectopic pregnancy with lower LNG dosage (42,43). Further, it highlights the importance of educating women to be aware of potential mental health side-effects and of clinical evaluation of mood symptoms at follow-up visits after LNG-IUS insertion.

The strength of the current study includes the use of national register data enabling the study of an unselected nationwide population of first-time users of the different LNG-IUS who never had used any form of psychotropic medicine or had a prior mental disorder. Furthermore, it is a strength that the study compares the risk between users of different LNG-IUS and not to a non-user population, which makes it less prone to a surveillance bias (44) or behavioral confounders related the point of starting contraception (45). It is as strength that the study used both prescriptions with information about prescription indication as well as depression diagnoses to best capture depressive

episodes. Last and importantly, the use of a relative short follow-up time increases the likelihood that the event of starting an LNG-IUS and the event of depression could be causally linked and it reduces the risk of healthy-survivor bias and the number of women who discontinued within the follow-up time. Discontinuation most often goes undetected in the registers, yet, even if it had been possible to censor at time of discontinuation, this could be due to mood symptoms and thus it would be a violation of discontinuation being independent of the outcome.

The study also has limitations: 1) First and foremost, per nature an observational study does not justify direct causal inference, although, the choice of a close temporal window between incidence use of LNG-IUS and registration of antidepressant initiation together with the demonstration of a dose-response relationship jointly adds indirect evidence supporting a causal relationship, 2) Prescription patterns of antidepressants and LNG-IUS changed during the study period which may introduce bias, however, the sensitivity analysis restricting the study period to 2017-2022 supported the main finding, 3) First-time users of the different LNG-IUS differed in age and parity, where higher age and recent delivery may induce confounding by indication as some chronic diseases and recent birth would make women choose a progesterone-only contraceptive. However, the sensitivity analysis restricted to nulliparous first-time users younger than 30 years, where the groups were more comparable in age, confirmed the main results, 4) Potential confounders such as undiagnosed medical conditions and unregistered off-label medical indications for the use of the high-dose LNG-IUS. However, women having an LNG-IUS inserted at the hospital for treating a medical condition or if bought directly in a specialist clinic are not included in the current study. Further, we did account for various diagnosed medical indications and menorrhagia as prescription indication, in which as many as 4.5%, 7.3%, and 12.4% were known with menorrhagia (diagnosed or via prescription indication) among first-time users of low-, medium-, and high-dose LNG-IUS. In comparison the prevalence of menorrhagia is estimated to be 9-14%, although self-reported estimates reach 27% (46,47). Nonetheless, this had little impact on the results, which may relate to the fact that high-dose LNG-IUS are effective in treating these medical disorders resulting in improvement of quality of life (48,49). Additionally, based on the E-values, an unmeasured confounder should be associated with the exposure and the outcome with a strength of 2.41 and 1.71 to explain the increased risk associated with high- and medium- compared to low-dose LNG-IUS, which is larger than the estimated RRs of menorrhagia as diagnose and as prescription indication. This indicates that the confounding would need to be strong for the observed association to hold under the null hypothesis, i.e., a false positive result.

As hypothesized, the current study provides evidence of a dose-dependent association between intrauterine levonorgestrel exposure and incident depression; i.e., high-dose LNG-IUS was associated with 26% higher relative risk than medium-dose LNG-IUS, which was associated with 21% higher relative risk than low-dose LNG-IUS. This remained after controlling for medical diagnoses and indications for prescribing high-dose LNG-IUS. The 1-year absolute risks were 1.21% vs. 1.46% vs. 1.84% emphasizing that increasing the dose were only associated with few women developing depression to a degree that resulted in medical attention. These findings should be interpreted in light

of the limitations of an observational study design with risk of residual confounding and the observed risk differences should be weighed against potential benefits as well as other side effects of LNG-IUS use when providing personalized contraceptive counseling.

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Tables

Table 1. Demographics and clinical profiles						
Profiles	**Exposure**					
	Low-dose LNG-IUS		**Medium-dose LNG-IUS**		**High-dose LNG-IUS**	
	No.	**(%)**	**No.**	**(%)**	**No.**	**(%)**
Total	22,029	(14.8)	47,712	(32.0)	79,459	(53.3)
Age						
15-19	6,362	(28.9)	10,498	(22.0)	3,839	(4.8)
20-24	9,707	(44.1)	17,175	(36.0)	10,799	(13.6)
25-29	4,173	(18.9)	9,282	(19.5)	21,675	(27.3)
30-34	1,403	(6.4)	6,429	(13.5)	27,681	(34.8)
35-39	357	(1.6)	3,348	(7.0)	12,847	(16.2)
40-44	27	(0.1)	980	(2.1)	2,618	(3.3)
Calendar period						
2000-2004	0	(0.0)	0	(0.0)	419	(0.5)
2005-2009	0	(0.0)	0	(0.0)	4799	(6.0)
2010-2014	2,009	(9.1)	0	(0.0)	22,858	(28.8)
2015-2019	14,296	(64.9)	14,603	(30.6)	34,727	(43.7)
2020-2022	5,724	(26.0)	33,109	(69.4)	16,656	(21.0)
Educational level[a]						
Below high school	6.374	(28.9)	10,484	(22.0)	9,358	(11.8)
High school/vocational education	10,274	(46.6)	21,506	(45.1)	30,783	(38.7)
Bachelor degree or above	5,368	(24.4)	15,706	(32.9)	39,252	(49.4)
Postpartum initiation	1,355	(6.2)	7,135	(15.0)	28,404	(35.7)
Nulliparous	19,765	(89.7)	33,311	(69.8)	14,216	(17.9)
Parental history of mental disorder	3,044	(13.8)	6,930	(14.5)	10,223	(12.9)
Endometriosis	68	(0.3)	186	(0.4)	1,273	(1.6)
Polycystic ovarian syndrome	104	(0.5)	372	(0.8)	1,268	(1.6)
Dysmenorrhea	162	(0.7)	314	(0.7)	747	(0.9)
Leiomyoma	12	(0.1)	54	(0.1)	242	(0.3)
Menorrhagia	327	(1.5)	694	(1.5)	2,442	(3.1)
Menorrhagia as prescription indication[b]	753	(3.4)	2,926	(6.1)	8.658	(10.9)
Previous HC use						
None	2,582	(11.7)	4,742	(9.9)	2,166	(2.7)
1 type	15,257	(69.3)	32,871	(68.9)	52,671	(66.3)
2 types	3,778	(17.2)	9,232	(19.3)	21,718	(27.3)
3 or more types	412	(1.9)	867	(1.8)	2,904	(3.7)

LNG-IUS, levonorgestrel-releasing intrauterine system.

[a]0.1%, 0.0%, 0.1% had missing information about education level among low-, medium-, and high-dose LNG-IUS users.

[b]11.5%, 4.7%, and 12.0% had missing prescription indication among low-, medium-, and high-dose LNG-IUS users.

Table 2. Average absolute risks, risk differences, and risk ratios of developing depression between different LNG-IUS

LNG-IUS	Low-dose		Medium-dose		High-dose	
	(%)	(95% CI)	(%)	(95% CI)	(%)	(95% CI)
Absolute risk[a]	1.19	(1.04-1.33)	1.43	(1.30-1.56)	1.88	(1.75-2.00)
Absolute risk[b]	1.21	(1.06-1.36)	1.46	(1.33-1.59)	1.84	(1.72-1.96)
Absolute risk difference[b]	Reference		0.26	(0.06-0.45)	0.63	(0.43-0.83)
RR[b]	Reference		1.21	(1.03-1.39)	1.52	(1.30-1.74)
Absolute risk difference[b]	-		Reference		0.37	(0.17-0.58)
RR[b]	-		Reference		1.26	(1.10-1.41)

LNG-IUS, levonorgestrel-releasing intrauterine system; RR, risk ratio.

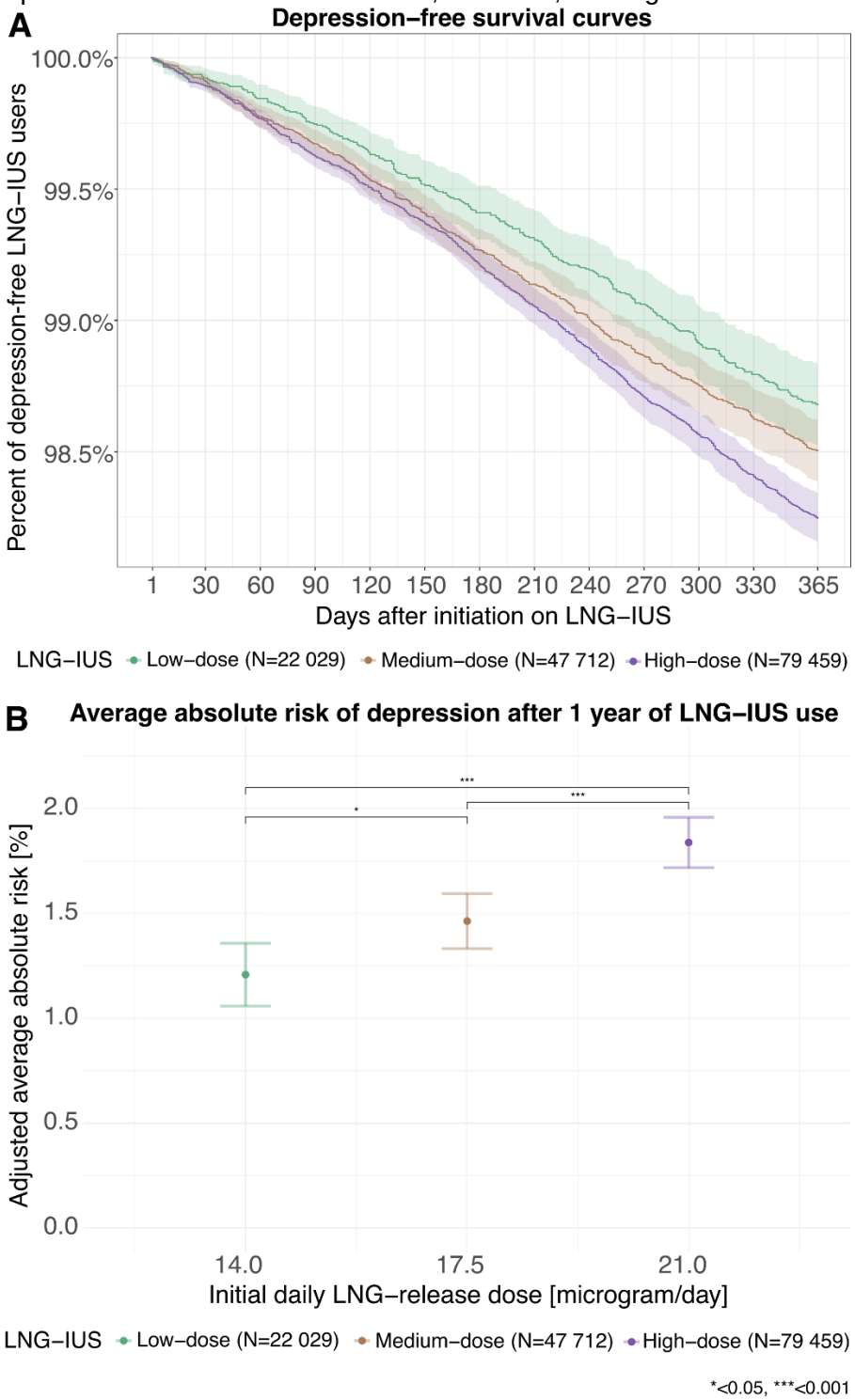
[a]Standardized over calendar period and age.

[b]Standardized over calendar period, age, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use.

0.1%, 0.0%, 0.1% had missing information about education level among low-, medium-, and high-dose LNG-IUS users. These were imputed to a separate group in the analyses.

Figure legends

Figure 1. Depression in first-time users of low-, medium-, and high-dose LNG-IUS



A) Depression-free survival curves with 95% confidence intervals for the different LNG-IUS doses within one year after initiation. **B**) The 1-year estimated depression risks for the different LNG-IUS doses standardized over calendar period, age, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, menorrhagia, leiomyoma, and postpartum incident LNG-IUS use. Error bars represent 95% confidence intervals.

LNG-IUS, levonorgestrel-releasing intrauterine system.

Supplementary Online Content

ST1. Overview of registers, variables, and codes

ST2. Average absolute risks, risk differences, and risk ratios for depression diagnosis and antidepressant prescription

ST3. Average absolute risks, risk differences, and risk ratios of starting antidepressant not specifically prescribed for other indications

ST4. Demographics and clinical profiles restricted to incident users between 2017-2022

ST5. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUS restricted to incident users between 2017-2022

ST6. Demographics and clinical profiles restricted to nulliparous incident LNG-IUS users younger than 30 years of age

ST7. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUS restricted to nulliparous incident LNG-IUS users younger than 30 years of age

ST8. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUS when adjusted for menorrhagia as prescription indication and previous hormonal contraceptive use

ST9. Standard means and standard mean differences of covariates between the groups before and after propensity score weighting

ST10. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUS in women with history of mental disorder

SF1. Flowchart of how study population was obtained from source population

SF2. Forest plot with hazard ratios of starting antidepressant medication for the complete output of the main analysis

SF3. Propensity scores distribution

ST1. Overview of registers, variables, and codes

Registers	Variables	Codes
Danish Civil Registration System (data since 1968)		
	Date of birth, immigration, emigration	
Demographic Registers of Statistics Denmark		
	Educational degree	
Danish Medical Birth Register (complete data since 1973)		
	Date of childbirth	
Danish National Patient Register (complete data since 1977)		
	Polycystic ovary syndrome	ICD-8: 256.9 ICD-10: E282
	Endometriosis	ICD-8: 625.3 ICD-10: N80
	Dysmenorrhea	ICD-8: 626.3 ICD-10: N943-946
	Leiomyoma	ICD-8: 218 ICD-10: D25
	Menorrhagia	ICD-8: 626.2 ICD-10: N92
The Psychiatric Central Register (complete data since 1969 on hospital admission and 1995 on outpatient contacts)		
	Mental disorders	ICD-8: 290-315 (except 302.0 and 302.3) ICD-10: F00-99
	Depression	ICD-8: 296.09, 296.29, 298.09, 300.49, 301.19 ICD-10: DF32-34, DF38, DF39
Danish Prescription Register (complete data since 1995)		
	LNG-IUS	ATC: G02BA03
	Other HC types	
	COC	ATC: G03AA* (except for G03AA13) and G03AB*
	Patch	ATC: G03AA13
	Vaginal ring	ATC: G02BB01
	POP	ATC: G03AC* (except for G03AC06 and G03AC08)
	Implant	ATC: G03AC06
	Depot injections	ATC: G03AC08
	Antidepressant medication	ATC: Codes starting with N06A
	Psychotropic drugs	ATC: Codes starting with N05 and N06

ATC, Anatomical Therapeutic Chemical Classification system; ICD-8, International Classification of Disease and Health Related Problems, 8th revision; COC, combined oral contraceptive; HC; hormonal contraception; ICD-10, 10th revision; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen

ST2. Average absolute risks, risk differences, and risk ratios for depression diagnosis and antidepressant prescription

Antidepressant medication (n=2110)

LNG-IUS	Low-dose		Medium-dose		High-dose	
	(%)	(95% CI)	(%)	(95% CI)	(%)	(95% CI)
Absolute risk[a]	1.06	(0.92-1.21)	1.33	(1.20-1.45)	1.77	(1.65-1.88)
Absolute risk[b]	1.08	(0.94-1.22)	1.35	(1.23-1.48)	1.73	(1.62-1.85)
Absolute risk difference[b]	Reference		0.27	(0.09-0.46)	0.65	(0.46-0.85)
RR[b]	Reference		1.25	(1.05-1.45)	1.61	(1.36-1.86)
Absolute risk difference[b]	-		Reference		0.38	(0.19-0.58)
RR[b]	-		Reference		1.28	(1.11-1.45)

Depression diagnosis[c] (n=366)

LNG-IUS	Low-dose		Medium-dose		High-dose	
	(%)	(95% CI)	(%)	(95% CI)	(%)	(95% CI)
Absolute risk[a]	0.20	(0.15-0.25)	0.25	(0.21-0.30)	0.32	(0.26-0.37)
Absolute risk[b]	0.21	(0.16-0.26)	0.26	(0.21-0.31)	0.30	(0.24-0.35)
Absolute risk difference[b]	Reference		0.05	(-0.02-0.12)	0.09	(0.01-0.16)
RR[b]	Reference		1.24	(0.86-1.62)	1.41	(0.95-1.86)
Absolute risk difference[b]	-		Reference		0.03	(-0.05-0.12)
RR[b]	-		Reference		1.13	(0.80-1.47)

LNG-IUS, levonorgestrel-releasing intrauterine system; RR, risk ratio.

[a]Standardized over calendar period and age.

[b]Standardized over calendar period, age, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use.

[c]Since no events were registered in the oldest age group and in women diagnosed with leiomyoma resulting in lack of convergence in the Cox regression, these categories were pooled with the second oldest age group and with menorrhagia, respectively.

0.1%, 0.0%, 0.1% had missing information about education level among low-, medium-, and high-dose LNG-IUS users. These were imputed to a separate group in the analyses.

ST3. Average absolute risks, risk differences, and risk ratios

Depression as prescription indication (n=1198)

LNG-IUS	Low-dose		Medium-dose		High-dose	
	(%)	(95% CI)	(%)	(95% CI)	(%)	(95% CI)
Absolute risk[a]	0.57	(0.47-0.67)	0.68	(0.59-0.76)	1.06	(0.96-1.15)
Absolute risk[b]	0.59	(0.49-0.69)	0.70	(0.61-0.79)	1.02	(0.94-1.11)
Absolute risk difference[b]	Reference		0.11	(-0.03-0.24)	0.43	(0.29-0.58)
RR[b]	Reference		1.18	(0.93-1.43)	1.73	(1.38-2.08)
Absolute risk difference[b]	-		Reference		0.33	(0.18-0.47)
RR[b]	-		Reference		1.47	(1.21-1.73)

Depression or missing prescription indication (n=1574)

LNG-IUS	Low-dose		Medium-dose		High-dose	
	(%)	(95% CI)	(%)	(95% CI)	(%)	(95% CI)
Absolute risk[a]	0.74	(0.62-0.85)	0.93	(0.82-1.04)	1.33	(1.23-1.43)
Absolute risk[b]	0.75	(0.63-0.87)	0.95	(0.83-1.06)	1.31	(1.21-1.41)
Absolute risk difference[b]	Reference		0.19	(0.03-0.36)	0.56	(0.40-0.71)
RR[b]	Reference		1.26	(1.02-1.50)	1.74	(1.43-2.05)
Absolute risk difference[b]	-		Reference		0.36	(0.19-0.53)
RR[b]	-		Reference		1.38	(1.16-1.60)

LNG-IUS, levonorgestrel-releasing intrauterine system; AR, absolute risk; RR, risk ratio.

[a]Standardized over age and calendar year.

[b]Standardized over age, calendar year, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use.

0.1%, 0.0%, 0.1% had missing information about education level among low-, medium-, and high-dose LNG-IUS users. These were imputed to a separate group in the analyses.

ST4. Demographics and clinical profiles restricted to incident users between 2017-2022

Profiles	Exposure		
	Low-dose LNG-IUS, no. (%)	Medium-dose LNG-IUS, no. (%)	High-dose LNG-IUS, no. (%)
Total	12,940 (13.3)	47,712 (48.9)	36,850 (37.8)
Age			
15-19	3,768 (29.1)	10,498 (22.0)	1,467 (4.0)
20-24	5,560 (43.0)	17,175 (36.0)	4,119 (11.2)
25-29	2,541 (19.6)	9,282 (19.5)	8,633 (23.4)
30-34	837 (6.5)	6,429 (13.5)	11,348 (30.8)
35-39	207 (1.6)	3,348 (7.0)	8,665 (23.5)
40-44	27 (0.2)	980 (2.1)	2,618 (7.1)
Calendar year			
2017	3,186 (24.6)	1,855 (3.9)	7,749 (21.0)
2018	2,272 (17.6)	5,312 (11.1)	6,557 (17.8)
2019	1,758 (13.6)	7,436 (15.6)	5,888 (16.0)
2020	2,102 (16.2)	10,200 (21.4)	5,596 (15.2)
2021	2,053 (15.9)	12,221 (25.6)	5,950 (16.1)
2022	1,569 (12.1)	10,688 (22.4)	5,110 (13.9)
Educational level[a]			
Below high school	3,620 (28.0)	10,484 (22.0)	3,209 (8.7)
High school/vocational education	6,016 (46.5)	21,506 (45.1)	13,818 (37.5)
Bachelor degree or above	3,300 (25.5)	15,706 (32.9)	19,809 (53.8)
Postpartum initiation	858 (6.6)	7,135 (15.0)	12.353 (33.5)
Nulliparous	11,558 (89.3)	33,311 (69.8)	6,286 (17.1)
Parental history of mental disorder	1,846 (14.3)	6,930 (14.5)	5,115 (13.9)
Endometriosis	37 (0.3)	186 (0.4)	725 (2.0)
Polycystic ovarian syndrome	53 (0.4)	372 (0.8)	787 (2.1)
Dysmenorrhea	98 (0.8)	314 (0.7)	444 (1.2)
Leiomyoma	7 (0.1)	54 (0.1)	146 (0.4)
Menorrhagia	162 (1.3)	694 (1.5)	1,315 (3.6)
Menorrhagia as prescription indication[b]	555 (4.3)	2,926 (6.1)	4,774 (13.0)
Previous HC use			
None	1,646 (12.7)	4,742 (9.9)	1,010 (2.7)
1 type	9,111 (70.4)	32,871 (68.9)	23,711 (64.3)
2 types	2,010 (15.5)	9,232 (19.3)	10,748 (29.2)
3 or more types	173 (1.3)	867 (1.8)	1,381 (3.7)

LNG-IUS, levonorgestrel-releasing intrauterine system.

[a]0.0%, 0.0%, 0.0% had missing information about education level among low-, medium-, and high-dose LNG-IUS users.

[b]5.3%, 4.7%, and 5.1% had missing prescription indication among low-, medium-, and high-dose LNG-IUS users.

ST5. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUS restricted to incident users between 2017-2022

LNG-IUS	Low-dose		Medium-dose		High-dose	
	(%)	(95% CI)	(%)	(95% CI)	(%)	(95% CI)
Absolute risk[a]	1.20	(1.01-1.40)	1.40	(1.29-1.52)	1.71	(1.53-1.88)
Absolute risk[b]	1.21	(1.02-1.41)	1.42	(1.30-1.53)	1.66	(1.49-1.83)
Absolute risk difference[b]	Reference		0.20	(-0.03-0.43)	0.45	(0.18-0.71)
RR[b]	Reference		1.17	(0.96-1.38)	1.37	(1.10-1.64)
Absolute risk difference[b]	-		Reference		0.24	(0.02-0.46)
RR[b]	-		Reference		1.17	(1.01-1.34)

LNG-IUS, levonorgestrel-releasing intrauterine system; AR, absolute risk; RR, risk ratio.

[a]Standardized over age and calendar year.

[b]Standardized over age, calendar year, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use.

0.0%, 0.0%, 0.0% had missing information about education level among low-, medium-, and high-dose LNG-IUS users. These were imputed to a separate group in the analyses.

ST6. Demographics and clinical profiles restricted to nulliparous incident LNG-IUS users younger than 30 years of age

Profiles	Exposure		
	Low-dose LNG-IUS, no. (%)	Medium-dose LNG-IUS, no. (%)	High-dose LNG-IUS, no. (%)
Total	19,042 (30.0)	31,949 (50.3)	12,576 (19.8)
Age			
15-19	6,352 (33.4)	10,461 (32.7)	3,474 (27.6)
20-24	9,457 (49.7)	16,453 (51.5)	6,414 (51.0)
25-29	3,233 (17.0)	5,035 (15.8)	2,688 (21.4)
Calendar period			
2000-2004	0 (0.0)	0 (0.0)	147 (1.2)
2005-2009	0 (0.0)	0 (0.0)	921 (7.3)
2010-2014	1,666 (8.7)	0 (0.0)	4,145 (33.0)
2015-2019	12,388 (65.1)	9,020 (28.2)	4,661 (37.1)
2020-2022	4,988 (26.2)	22,929 (71.8)	2,702 (21.5)
Educational level[a]			
Below high school	6,196 (32.5)	9,766 (30.6)	3,962 (31.5)
High school/vocational education	9,507 (49.9)	17,103 (53.5)	6,400 (50.9)
Bachelor degree or above	3,329 (17.5)	5,070 (15.9)	2,201 (17.5)
Parental history of mental disorder	2,622 (13.8)	4,618 (14.5)	1,695 (13.5)
Endometriosis	46 (0.2)	50 (0.2)	122 (1.0)
Polycystic ovarian syndrome	67 (0.4)	86 (0.3)	57 (0.5)
Dysmenorrhea	144 (0.8)	196 (0.6)	165 (1.3)
Leiomyoma	5 (0.0)	6 (0.0)	11 (0.1)
Menorrhagia	270 (1.4)	355 (1.1)	342 (2.7)
Menorrhagia as prescription indication[b]	668 (3.5)	2,273 (7.1)	1,545 (12.3)
Previous HC use			
None	2,525 (13.3)	4,432 (13.9)	1,176 (9.4)
1 type	13,286 (69.8)	23,155 (72.5)	8,819 (70.1)
2 types	2.949 (15.5)	4,096 (12.8)	2,272 (18.1)
3 or more types	282 (1.5)	266 (0.8)	309 (2.5)

LNG-IUS, levonorgestrel-releasing intrauterine system.

[a]0.1%, 0.0%, 0.1% had missing information about education level among low-, medium-, and high-dose LNG-IUS users.

[b]11.4%, 4.6%, and 18.3% had missing prescription indication among low-, medium-, and high-dose LNG-IUS users.

ST7. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUS restricted to nulliparous incident LNG-IUS users younger than 30 years of age

LNG-IUS	Low-dose		Medium-dose		High-dose	
	(%)	(95% CI)	(%)	(95% CI)	(%)	(95% CI)
Absolute risk[a]	1.45	(1.26-1.64)	1.71	(1.54-1.88)	2.14	(1.85-2.44)
Absolute risk[b]	1.47	(1.27-1.66)	1.72	(1.55-1.89)	2.08	(1.79-2.37)
Absolute risk difference[b]	Reference		0.26	(-0.01-0.52)	0.62	(0.28-0.95)
RR[b]	Reference		1.17	(0.97-1.38)	1.42	(1.16-1.68)
Absolute risk difference[b]	-		Reference		0.36	(0.00-0.73)
RR[b]	-		Reference		1.21	(0.98-1.44)

LNG-IUS, levonorgestrel-releasing intrauterine system; AR, absolute risk; RR, risk ratio.

[a]Standardized over calendar period and age.

[b]Standardized over calendar period, age, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use.

0.1%, 0.0%, 0.1% had missing information about education level among low-, medium-, and high-dose LNG-IUS users. These were imputed to a separate group in the analyses.

ST8. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUS when adjusted for menorrhagia as prescription indication and previous hormonal contraceptive use

LNG-IUS	Low-dose		Medium-dose		High-dose	
	(%)	(95% CI)	(%)	(95% CI)	(%)	(95% CI)
Absolute risk	1.22	(1.07-1.37)	1.47	(1.34-1.61)	1.83	(1.71-1.94)
Absolute risk difference	Reference		0.25	(0.06-0.45)	0.60	(0.40-0.81)
RR	Reference		1.21	(1.03-1.39)	1.50	(1.28-1.71)
Absolute risk difference	-		Reference		0.35	(0.15-0.56)
RR	-		Reference		1.24	(1.08-1.40)

LNG-IUS, levonorgestrel-releasing intrauterine system; AR, absolute risk; RR, risk ratio.

Estimates are standardized over calendar period, age, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, postpartum incident LNG-IUS use, number of hormonal contraceptive types used previously, and menorrhagia as prescription indication of LNG-IUS.

Prescription information was missing for 11.5%, 4.7%, and 12.0% and educational level for 0.1%, 0.0% and 0.1% among low-, medium-, and high-dose LING-IUS users. This was handled by performing multiple imputations with the MICE package in R where prescription indication was imputed using logistic regression and educational level using polytomous logistic regression based on the listed covariates and outcome with 10 iterations and 5 imputations

ST9. Standard means and standard mean differences of covariates between the groups before and after propensity score weighting

Covariates	Mean IUS-low	Mean IUS-med	Mean IUS-high	Pop.sd	Std.eff.sz high vs. low	Std.eff.sz high vs. med	Std.eff.sz med vs. low
	Unweighted						
Age							
15-19	0.29	0.22	0.04	0.37	**0.68**	**0.49**	**0.19**
20-24	0.43	0.36	0.11	0.45	**0.71**	**0.56**	**0.16**
25-29	0.20	0.19	0.23	0.41	**0.09**	**0.10**	**0.00**
30-34	0.06	0.13	0.31	0.39	**0.62**	**0.44**	**0.18**
35-39	0.02	0.07	0.24	0.33	**0.66**	**0.50**	**0.16**
40-44	0.00	0.02	0.07	0.19	**0.36**	**0.27**	**0.10**
Calendar year							
2017	0.25	0.04	0.21	0.34	**0.11**	**0.51**	**0.61**
2018	0.18	0.11	0.18	0.35	**0.01**	**0.19**	**0.18**
2019	0.14	0.16	0.16	0.36	**0.07**	**0.01**	**0.06**
2020	0.16	0.21	0.15	0.39	**0.03**	**0.16**	**0.13**
2021	0.16	0.26	0.16	0.41	**0.01**	**0.23**	**0.24**
2022	0.12	0.22	0.14	0.38	**0.05**	**0.22**	**0.27**
Educational level[a]							
Below high school	0.28	0.22	0.09	0.38	**0.50**	**0.35**	**0.16**
High school/vocational education	0.46	0.45	0.37	0.49	**0.18**	**0.15**	**0.03**
Bachelor degree or above	0.26	0.33	0.54	0.49	**0.58**	**0.43**	**0.15**
Unknown	0.00	0.00	0.00	0.02	**0.00**	**0.00**	**0.00**
Postpartum initiation	0.07	0.15	0.34	0.41	**0.66**	**0.46**	**0.20**
Parental history of mental disorder	0.14	0.15	0.14	0.35	**0.01**	**0.02**	**0.01**
Endometriosis	0.00	0.00	0.02	0.10	**0.17**	**0.16**	**0.01**
Polycystic ovarian syndrome	0.00	0.01	0.02	0.11	**0.16**	**0.12**	**0.03**
Dysmenorrhea	0.01	0.01	0.01	0.09	**0.05**	**0.06**	**0.01**
Leiomyoma	0.00	0.00	0.00	0.05	**0.07**	**0.06**	**0.01**
Menorrhagia	0.01	0.01	0.04	0.15	**0.16**	**0.14**	**0.01**
	Weighted						
Age							
15-19	0.16	0.16	0.16	0.37	**0.01**	**0.00**	**0.01**
20-24	0.28	0.28	0.28	0.45	**0.01**	**0.00**	**0.01**
25-29	0.21	0.21	0.21	0.41	**0.01**	**0.00**	**0.00**
30-34	0.19	0.19	0.19	0.39	**0.00**	**0.00**	**0.00**
35-39	0.12	0.12	0.13	0.33	**0.01**	**0.00**	**0.00**
40-44	0.03	0.04	0.04	0.19	**0.03**	**0.00**	**0.03**
Calendar year							
2017	0.14	0.13	0.13	0.34	**0.01**	**0.01**	**0.02**
2018	0.15	0.14	0.14	0.35	**0.01**	**0.00**	**0.01**
2019	0.16	0.16	0.16	0.36	**0.00**	**0.00**	**0.00**
2020	0.18	0.18	0.18	0.39	**0.01**	**0.00**	**0.01**
2021	0.20	0.21	0.21	0.41	**0.01**	**0.00**	**0.02**
2022	0.18	0.18	0.18	0.38	**0.00**	**0.00**	**0.00**
Educational level[a]							
Below high school	0.18	0.18	0.18	0.38	**0.01**	**0.00**	**0.01**
High school/vocational education	0.42	0.42	0.42	0.49	**0.01**	**0.00**	**0.01**
Bachelor degree or above	0.40	0.40	0.40	0.49	**0.00**	**0.00**	**0.00**
Unknown	0.00	0.00	0.00	0.02	**0.01**	**0.00**	**0.00**
Postpartum initiation	0.21	0.21	0.21	0.41	**0.00**	**0.00**	**0.00**
Parental history of mental disorder	0.15	0.14	0.14	0.35	**0.01**	**0.00**	**0.01**
Endometriosis	0.01	0.01	0.01	0.10	**0.04**	**0.00**	**0.03**
Polycystic ovarian syndrome	0.01	0.01	0.01	0.11	**0.02**	**0.00**	**0.02**
Dysmenorrhea	0.01	0.01	0.01	0.09	**0.02**	**0.00**	**0.02**
Leiomyoma	0.00	0.00	0.00	0.05	**0.01**	**0.01**	**0.01**
Menorrhagia	0.02	0.02	0.02	0.15	**0.02**	**0.01**	**0.02**

Standard mean and mean differences obtained before and after weighting on multinomial propensity scores obtained with gradient boosted logistic regression. The maximum number of iterations was set to 15000, and the measure of balance was summarized as the absolute standardized mean difference by setting the stop.method to “es.mean”. After weighting, the effective sample sizes were; 4,779,442 for low-, 32,680.0 for medium-, and 19,066.4 for high-dose LNG-IUS users. The effective sample size is the number of observations which would give the same estimates when the sampling variation is similar to the variation obtained after the weighting. IUS-low, low-dose levonorgestrel-releasing intrauterine system; IUS-med, medium-dose levonorgestrel-releasing intrauterine system; IUS-high, high-dose levonorgestrel-releasing intrauterine system; Pop.sd, pooled sample standard deviation, Std.eff.sz, standardized effect size.

ST10. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUS in women with history of mental disorder

LNG-IUS	Low-dose		Medium-dose		High-dose	
	(%)	(95% CI)	(%)	(95% CI)	(%)	(95% CI)
Absolute risk[a]	4.77	(4.20-5.34)	5.12	(4.69-5.55)	5.96	(5.65-6.27)
Absolute risk[b]	4.80	(4.22-5.37)	5.22	(4.78-5.66)	5.91	(5.60-6.22)
Absolute risk difference[b]	Reference		0.42	(-0.28-1.12)	1.11	(0.44-1.78)
RR[b]	Reference		1.09	(0.93-1.24)	1.23	(1.07-1.40)
Absolute risk difference[b]	-		Reference		0.69	(0.10-1.27)
RR[b]	-		Reference		1.13	(1.01-1.25)

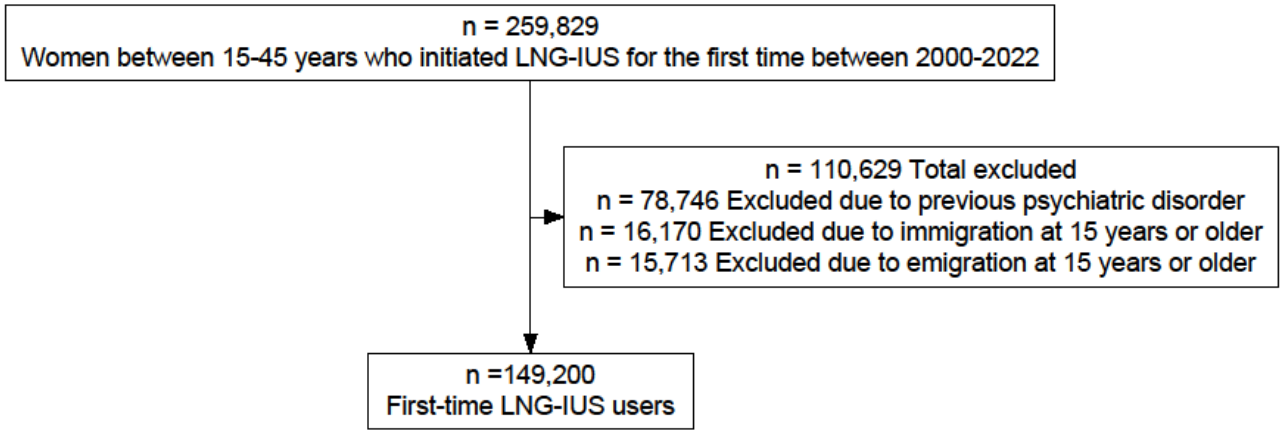
LNG-IUS, levonorgestrel-releasing intrauterine system; AR, absolute risk; RR, risk ratio.

[a]Standardized over calendar period and age.

[b]Standardized over calendar period, age, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use.

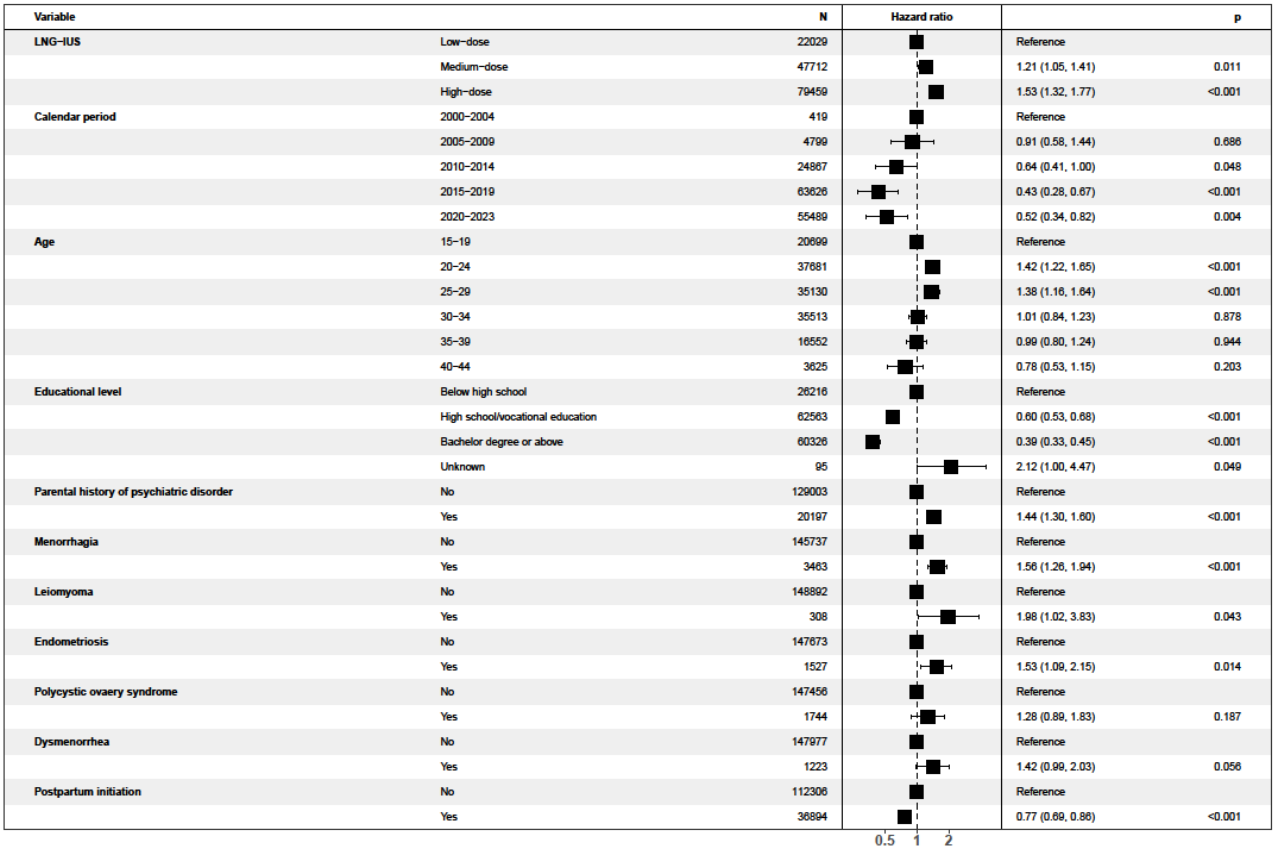
0.2%, 0.1%, 0.2% had missing information about education level among low-, medium-, and high-dose LNG-IUS users. These were imputed to a separate group in the analyses.

SF1. Flowchart of how study population was obtained from source population



LNG-IUS, levonorgestrel-releasing intrauterine system.

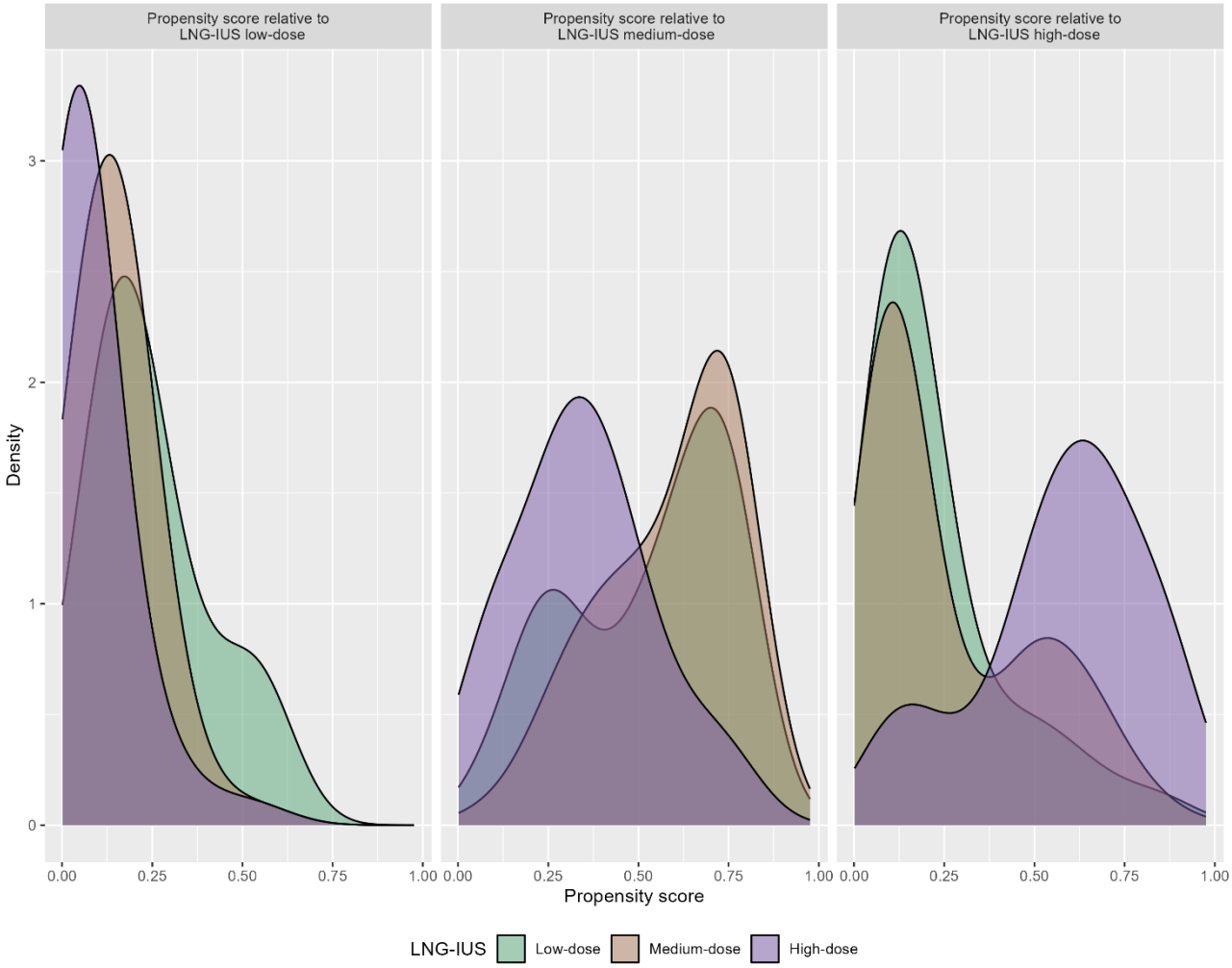
SF2. Forest plot with hazard ratios of starting antidepressant medication for the complete output of the main analysis



Variable		N	Hazard ratio	p
LNG-IUS	Low-dose	22029	Reference	
	Medium-dose	47712	1.21 (1.05, 1.41)	0.011
	High-dose	79459	1.53 (1.32, 1.77)	<0.001
Calendar period	2000-2004	419	Reference	
	2005-2009	4799	0.91 (0.58, 1.44)	0.686
	2010-2014	24867	0.64 (0.41, 1.00)	0.048
	2015-2019	63626	0.43 (0.28, 0.67)	<0.001
	2020-2023	55489	0.52 (0.34, 0.82)	0.004
Age	15-19	20699	Reference	
	20-24	37681	1.42 (1.22, 1.65)	<0.001
	25-29	35130	1.38 (1.16, 1.64)	<0.001
	30-34	35513	1.01 (0.84, 1.23)	0.878
	35-39	16552	0.99 (0.80, 1.24)	0.944
	40-44	3625	0.78 (0.53, 1.15)	0.203
Educational level	Below high school	26216	Reference	
	High school/vocational education	62563	0.60 (0.53, 0.68)	<0.001
	Bachelor degree or above	60326	0.39 (0.33, 0.45)	<0.001
	Unknown	95	2.12 (1.00, 4.47)	0.049
Parental history of psychiatric disorder	No	129003	Reference	
	Yes	20197	1.44 (1.30, 1.60)	<0.001
Menorrhagia	No	145737	Reference	
	Yes	3463	1.56 (1.26, 1.94)	<0.001
Leiomyoma	No	148892	Reference	
	Yes	308	1.98 (1.02, 3.83)	0.043
Endometriosis	No	147673	Reference	
	Yes	1527	1.53 (1.09, 2.15)	0.014
Polycystic ovaery syndrome	No	147456	Reference	
	Yes	1744	1.28 (0.89, 1.83)	0.187
Dysmenorrhea	No	147977	Reference	
	Yes	1223	1.42 (0.99, 2.03)	0.056
Postpartum initiation	No	112306	Reference	
	Yes	36894	0.77 (0.69, 0.86)	<0.001

LNG-IUS, levonorgestrel-releasing intrauterine system.

SF3. Propensity scores distribution



LNG-IUS, levonorgestrel-releasing intrauterine system.

Study II

JAMA Psychiatry | Original Investigation

Depression Associated With Hormonal Contraceptive Use as a Risk Indicator for Postpartum Depression

Søren Vinther Larsen, MD; Anders Pretzmann Mikkelsen, PhD; Øjvind Lidegaard, DMSc; Vibe Gedso Frokjaer, PhD

IMPORTANCE Hormonal sensitivity may contribute to the risk of depression in some women, as observed during the premenstrual, postpartum, and perimenopausal phases, and when initiating hormonal contraception (HC). However, little evidence exists to support that such depressive episodes are linked across the reproductive life span.

OBJECTIVE To determine whether prior depression associated with HC initiation is coupled with a higher risk of postpartum depression (PPD) than prior depression not associated with HC initiation.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used Danish health registry data collected from January 1, 1995, through December 31, 2017, and analyzed from March 1, 2021, through January 1, 2023. All women living in Denmark born after 1978 with their first delivery between January 1, 1996, and June 30, 2017, were eligible for inclusion; 269 354 met these criteria. Women were then excluded if they had never used HC or if they had a depressive episode before 1996 or within 12 months prior to delivery.

EXPOSURES Prior depression associated with vs not associated with HC initiation, ie, if developed within 6 months after start of an HC exposure or not. Depression was defined as a hospital diagnosis of depression or filling a prescription for antidepressant medication.

MAIN OUTCOMES AND MEASURES Crude and adjusted odds ratios (ORs) were calculated for the incidence of PPD defined as the development of depression within 6 months after first delivery.

RESULTS Of 188 648 first-time mothers, 5722 (3.0%) (mean [SD] age, 26.7 [3.9] years) had a history of depression associated with initiation of HC use, and 18 431 (9.8%) (mean [SD] age, 27.1 [3.8] years) had a history of depression not associated with the initiation of HC. Women with HC-associated depression had a higher risk of PPD than women with prior non–HC-associated depression (crude OR, 1.42 [95% CI, 1.24-1.64]; adjusted OR, 1.35 [95% CI, 1.17-1.56]).

CONCLUSIONS AND RELEVANCE These findings suggest that a history of HC-associated depression may be associated with a higher risk of PPD, supporting that HC-associated depression may indicate PPD susceptibility. This finding offers a novel strategy in clinical PPD risk stratification and points to the existence of a hormone-sensitive subgroup of women.

JAMA Psychiatry. 2023;80(7):682-689. doi:10.1001/jamapsychiatry.2023.0807
Published online April 26, 2023.

Supplemental content

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Women are approximately twice as likely to develop depressive episodes compared with men.[1] This gap between sexes starts during adolescence, which coincides with menarche in girls, and lasts until menopause.[2] Hence, a woman's reproductive life span is a time of heightened vulnerability for depression, aligning with an increased risk of depression associated with hormonal transitions across the menstrual cycle, when 3% to 8% of women experience premenstrual dysphoric disorder (PMDD)[3]; the peripartum period, when approximately 13% of women experience postpartum depression (PPD)[4]; and the perimenopausal period, when large estradiol fluctuations predict risk of perimenopausal depression.[5] Concerningly, initiating hormonal contraception (HC) also has been associated with an increased risk of developing a depressive episode.[6,7]

Women experiencing depressive episodes associated with hormonal transitions may comprise a certain hormone-sensitive subgroup of women within the broader diagnostic category of major depressive disorder. Since treatment of major depressive disorder is far from optimal, identification of relevant subgroups with distinct etiologic contributions to the disorder and responsiveness to certain triggers or treatments would help to build a much-needed rationale for precision medicine in psychiatry. However, little is known about whether the depressive

episodes across women's reproductive lives share similar etiology or whether they are linked.[8] Some evidence supports that women with PPD are more likely to have a history of PMDD and that women who experience depressive symptoms in perimenopause are more likely to have a history of PPD and PMDD.[9,10] However, the evidence is based on retrospective reports susceptible to recall and confirmation biases and lack the use of confirmed clinical diagnoses and, therefore, represent only limited evidence. The few studies that have investigated depressive symptoms associated with hormonal transitions and HC-associated mood deterioration are likely underpowered and have shown inconsistent results.[11-15] Therefore, large-scale observational studies spanning the reproductive age are needed to shed light on the complex associations between depressive episodes occurring throughout women's lives.

This study takes advantage of Danish national health registers to evaluate the existence of a subgroup of women who are prone to develop depressive episodes across hormonal transitions, including transitions induced by exogenous hormone exposure in terms of HC. We examined whether such depressive episodes are associated with one another across a woman's reproductive life span; specifically, we examined whether a history of a depressive episode associated with initiation of HC poses a higher risk for later PPD compared with a history of depression not associated with HC initiation.

Key Points

Question Is prior hormonal contraception (HC)–associated depression associated with a higher risk of postpartum depression compared with prior depression not associated with HC use?

Findings In this cohort study of 188 648 first-time mothers, prior depression after initiation of HC was associated with a higher risk of postpartum depression than prior depression not associated with HC initiation.

Meaning The study's findings suggest that depression associated with HC use can indicate postpartum depression susceptibility and may provide evidence for a link between depressive episodes with possible hormonal contributions and point to the existence of a subgroup of women sensitive to hormonal transitions across their reproductive life spans.

Methods

Study Design

This population-based cohort study is based on health care data from Danish national registers. The specific registers and variables used are listed in eTable 1 in Supplement 1. Data were provided by the Danish eHealth Authority hosted by Statistics Denmark and linked via the unique personal identification number given to Danish residents at birth or immigration. Approval of the study was achieved through the Danish Data Protection Agency (journal No. Pactius-2020-217). According to Danish law, no ethics approval or informed consent are needed for register-based studies. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[16]

Study Population

The study population included all women in Denmark born after 1978 (ie, women aged a maximum of 16 years in 1995) who delivered their first child between January 1, 1996, and June 30, 2017, according to the Danish Civil Registration System and the Medical Birth Registry.[17,18] Women were excluded if they (1) had never used HC (to minimize potential confounding associated with personality or behavior associated with HC use and depression susceptibility and to test for HC sensitivity before pregnancy); (2) immigrated at 16 years or older or emigrated for more than 6 consecutive months after turning 16; (3) had a depressive episode before 1996 or within 12 months prior to delivery, as this could indicate an ongoing depression while entering pregnancy; and (4) had a multiple birth or stillbirth.

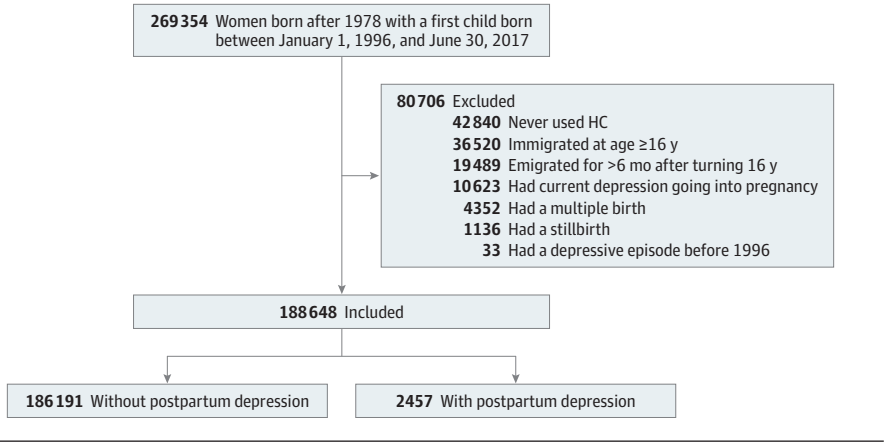
Exposures

The exposure of interest was prior depression associated with initiation of HC defined as a depressive episode that developed within 6 months after the start of HC exposure, as depression risk seems to peak within this period.[6] Start of HC exposure was defined as the start or restart of HC use or a change in type of HC used (ie, when a change in the Anatomical Therapeutic Chemical code was registered). To ensure that a depressive episode could only be linked to a new HC exposure, a restart was registered if a new prescription happened more than 6 months after the end of the duration of the last prescription (the duration of implants and hormonal intrauterine device prescriptions was set to 1000 days). A depressive episode was defined as filling a prescription of antidepressant medication or obtaining a depression discharge diagnosis from an inpatient or outpatient psychiatric clinic with the admission day as the index date identified in the Psychiatric Central Register.[19] To distinguish multiple depressive episodes, a new depressive episode was registered if 1 of the following criteria was met: (1) when a new prescription was filled later than the end of the duration of the last prescription plus a 30-day grace period[20] or a minimum of 6 months after a depression discharge diagnosis or (2) when a depression discharge diagnosis occurred a minimum of 6 months after the end of a treatment period or after a previous depression discharge diagnosis. The duration of a prescription was calculated by multiplying the number of packages dispensed by the number of defined daily doses per package. If more prescriptions were dispensed on the same day, the duration was calculated as the sum of the treatment days for each prescription. In cases of multiple depressive episodes, having 1 episode associated with initiation of HC exposure was used to define a history of HC-associated depression. Women not fulfilling this definition were considered to have a history of non–HC-associated depression or no history of depression.

Outcome and Covariates

The outcome was PPD, which was defined as filling a prescription for antidepressant medication or obtaining a hospital discharge diagnosis of depression within 6 months after first childbirth according to the National Prescription Register or National Patient Register, respectively.[21,22] To adjust for potential

Figure 1. Study Population



The study population was derived from the source population. The same individual could have met multiple exclusion criteria; thus, the sum of the numbers from all exclusion criteria does not equal the total number excluded. HC indicates hormonal contraception.

confounders, we obtained information on maternal age at delivery (younger than 20 years and 5-year bands thereafter); highest educational level at delivery (less than high school, high school or vocational education, or bachelor's degree or higher); family history of depression, defined as having a parent with a depression diagnosis; civil status (married or not); and potential obstetric risk factors, including preterm birth, instrument-assisted or cesarean delivery, preeclampsia or eclampsia, and pregestational or gestational diabetes. Furthermore, we acquired information on other potential confounding factors, such as other major psychiatric disorders, including organic mental disorders, mental and behavioral disorders due to substance use, schizophrenia, bipolar disorder, eating disorders, and mental disability; and medical indications for HC use, including polycystic ovary syndrome, endometriosis, premenstrual syndrome, dysmenorrhea, heavy menstrual bleeding, hirsutism, and acne. We also controlled for time trends in depression diagnostics and prescriptions of antidepressants by including calendar year in 5-year bands.

Statistical Analysis

Analyses were conducted between March 1, 2021, and January 1, 2023. We used logistic regression to calculate odds ratios (ORs) among the 3 exposure groups: (1) history of non-HC-associated depression, (2) history of HC-associated depression, and (3) no history of depression. The first group was used as the reference. We calculated crude ORs and ORs adjusted for the listed covariates. Estimates were interpreted as relative risks according to the rare disease assumption.[23]

Sensitivity Analyses

We conducted 5 sensitivity analyses. First, we removed obstetric risk factors from the adjustment set to minimize the risk of overadjusting the model. Second, we used perinatal depression as an outcome, ie, we included depressive episodes developed late in pregnancy (in the third trimester) and post partum to address that depressive episodes frequently emerge in late pregnancy.[24] Third, we excluded mothers who started using HC after delivery but before they developed PPD. Fourth, we increased the grace period from 30 days to 90 and 180 days to distinguish a new prescription of antidepressant medication. Fifth, exposure classification was restricted to the first depressive episode, which was repeated with the framework from the first and second sensitivity analyses. Odds ratios were calculated with 95% CIs, and the null-hypothesis was rejected if they did not overlap 1.00. All analyses were conducted using R, version 4.1.3 statistical software (R Foundation for Statistical Computing).

Results

The study population included 188 648 first-time mothers (**Figure 1**). Of all 269 354 eligible women, 84% had used HC before their first child was born. Of the study population, 2457 developed PPD, corresponding to an incidence rate of 1.3%. Furthermore, 5722 first-time mothers (3.0%; mean [SD] age, 26.7 [3.9] years) had a history of HC-associated depression, 18 431 (9.8%; mean age [SD], 27.1 [3.8] years) had a history of non-HC-associated depression, and 164 495 (87.2%; mean age [SD], 26.3 [3.9] years) had no history of depression. A summary of demographic characteristics and clinical profiles among the exposure groups is shown in **Table 1**. Notably, women with HC-associated depression had more depressive episodes than women with non-HC-associated depression, with 63.4% vs 38.6% having had more than 1 episode, respectively.

Women with a history of HC-associated depression had a higher risk of PPD than women with a history of non-HC-associated depression, with a crude OR of 1.42 (95% CI, 1.24-1.64) and an adjusted OR of 1.35 (95% CI, 1.17-1.56) (**Figure 2**A). The risk of PPD was lower for women with no previous depression vs women with non-HC-associated depression, with an adjusted OR of 0.25 (95% CI, 0.23-0.27). A complete summary of results is shown in **Table 2**. The results remained essentially unchanged in a sensitivity analysis not including obstetric risk factors in the adjustment set (eTable 2 in Supplement 1). When perinatal depression was used as the outcome (ie, including depressive episodes within the third trimester until 6 months post partum), the adjusted OR was 1.41 (95% CI, 1.23-1.60) (Figure 2B; eTable 3 in Supplement 1).

Table 1. Demographic Characteristics and Clinical Profiles

Profile	Exposure, No. (%)		
	Non-HC-associated depression	HC-associated depression	No depression
Total	18 431 (9.8)	5722 (3.0)	164 495 (87.2)
Maternal age at delivery, y			
<20	415 (2.3)	191 (3.3)	9880 (6.0)
20-24	5221 (28.3)	1830 (32.0)	49 885 (30.3)
25-29	8656 (47.0)	2527 (44.2)	77 738 (47.3)
30-34	3721 (20.2)	1059 (18.5)	25 171 (15.3)
35-39	418 (2.3)	115 (2.0)	1821 (1.1)
Educational level			
Less than high school	5571 (30.2)	2143 (37.5)	37 035 (22.5)
High school or vocational education	7735 (42.0)	2174 (38.0)	66 645 (40.5)
Bachelor's degree or higher	5125 (27.8)	1405 (24.6)	60 815 (37.0)
Married	8402 (45.6)	2344 (41.0)	87 862 (53.4)
Familial disposition for depression	2020 (11.0)	761 (13.3)	11 172 (6.8)
Other major psychiatric disorder	2224 (12.1)	934 (16.3)	2750 (1.7)
BMI[a]			
<18.5	955 (5.2)	353 (6.2)	6996 (4.3)
18.5-24.9	10 135 (55.0)	3184 (55.6)	94 627 (57.5)
25.0-29.9	3806 (20.6)	1143 (20.0)	30 527 (18.6)
≥30.0	2717 (14.7)	798 (13.9)	16 952 (10.3)
Smoker[b]	4352 (23.6)	1515 (26.5)	27 451 (16.7)
Pregestational or gestational diabetes	765 (4.2)	210 (3.7)	4080 (2.5)
Eclampsia or preeclampsia	927 (5.0)	265 (4.6)	7194 (4.4)
Preterm birth[c]	1189 (6.5)	389 (6.8)	10 148 (6.2)
Instrument-assisted delivery	2324 (12.6)	740 (12.9)	22 431 (13.6)
Cesarean delivery	4003 (21.7)	1238 (21.6)	29 470 (17.9)
Medical indication for HC	1413 (7.7)	552 (9.6)	7163 (4.4)
Age at first depression, mean (SD), y	21.5 (3.6)	20.3 (3.4)	NA
Age at exposure-defining episode, mean (SD), y	21.5 (3.6)	21.2 (3.6)	NA
No. of depressive episodes			
0	NA	NA	164 495 (100.0)
1	11 319 (61.4)	2101 (36.7)	NA
2	3832 (20.8)	1359 (23.8)	NA
3	1667 (9.0)	833 (14.6)	NA
≥4	1613 (8.8)	1429 (25.0)	NA

Abbreviations: BMI, body mass index as measured by weight in kilograms divided by height in meters squared; HC, hormonal contraception; NA, not applicable.

[a] Unknown for 818 (4.4%), 244 (4.3%), and 15 393 (9.4%), for each exposure group, respectively.

[b] Unknown for 424 (2.3%), 128 (2.2%), and 3981 (2.4%) for each exposure group, respectively.

[c] Unknown for 102 (0.6%), 34 (0.6%), and 960 (0.6%) for each exposure group, respectively.

To exclude a potential contribution of HC use post partum to PPD incidence, women who started using HC after delivery but before they developed PPD were excluded in a sensitivity analysis. The proportions of women starting an HC post partum were 40.8% vs 42.0% in those with a history of non-HC-associated vs HC-associated depression. The adjusted OR was 1.44 (95% CI, 1.23-1.69) (eTable 4 in Supplement 1).

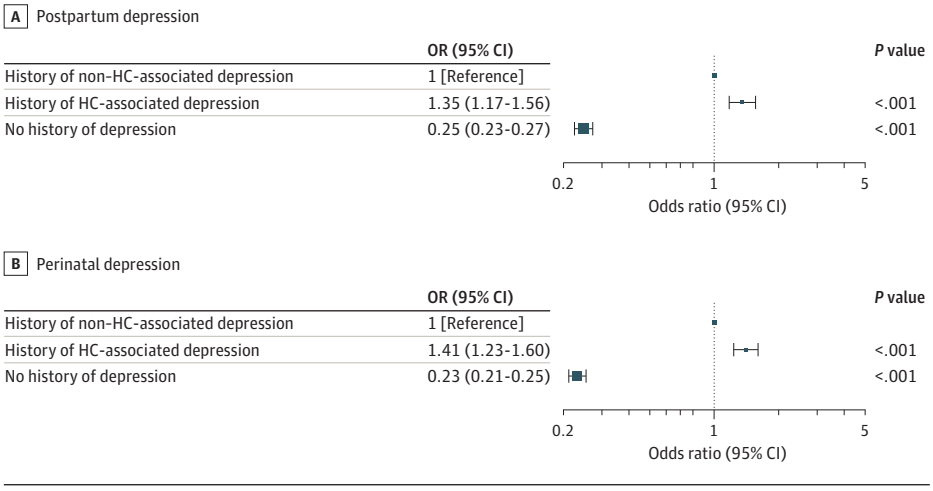
When the 90-day and 180-day treatment-free intervals were used to distinguish depressive episodes, the proportions of women with more than 1 depressive episode were 27.6% vs 49.7% and 22.1% vs 41.3% in those with prior non-HC-associated vs HC-associated depression, respectively. The adjusted ORs between PPD and HC-associated depression were 1.33 (95% CI, 1.14-1.53) and 1.32 (95% CI, 1.14-1.53) (eTable 5 in Supplement 1).

When exposure was classified based on women's first depressive episode, 3792 (2.0%) and 20 361 (10.8%) women were classified as having a history of HC-associated vs non-HC-associated depression. The proportions of women who had more than 1 depressive episode were similar between the groups (44.4% vs 44.6% of women with non-HC-associated vs HC-associated depression) (eTable 6 in Supplement 1). The adjusted OR for developing PPD was 1.19 (95% CI, 1.00-1.40) and for perinatal depression, 1.18 (95% CI, 1.01-1.38). After excluding women who started HC post partum but before PPD onset, the adjusted OR was 1.24 (95% CI, 1.02-1.49) (eTable 7 in Supplement 1).

Discussion

This population-based cohort study of 188 648 first-time mothers provides evidence for the existence of a subgroup of women who are sensitive to hormonal transitions across their repro-

Figure 2. Risk of Postpartum and Perinatal Depression Depending on Depression History



Odds ratios (ORs) were adjusted for year of delivery and maternal age, educational level, familial disposition for depression, other major psychiatric disorder, civil status, preterm birth, pregestational or gestational diabetes, eclampsia or preeclampsia, instrument-assisted or cesarean delivery, and medical indication for hormonal contraception (HC) use. HC-associated depression was defined as a depressive episode that developed within 6 months after the start of a new HC exposure. The 95% CIs are plotted on a log scale.

ductive lives by showing an association between 2 types of depressive episodes with plausible hormonal contributions. The findings show that women with a history of depression associated with HC initiation had a higher risk of developing a depressive episode during pregnancy and after childbirth compared with women with a history of depression not associated with HC initiation.

Our findings contribute new evidence for an association between depressive episodes across hormonal transitions in the reproductive life span, supporting the existence of a hormone-sensitive subgroup of women.[8] Our findings also align with previous findings suggesting an association between PPD and the retrospective reporting of experienced mood deterioration associated with HC use.[13,14] Furthermore, the finding of a similar association with perinatal depression, ie, when both late pregnancy and postpartum onset of depressive episodes were included, suggests that both the pregnancy (ie, during high hormone levels) and postnatal (ie, during abrupt hormone decline) states contribute to the mechanisms by which depression emerges in women who may be sensitive to HC exposure. This outcome is in line with findings from a study that compared women with and without a history of PPD who underwent pharmacologic sex hormone manipulation; women with a history of PPD developed depressive symptoms both during the withdrawal phase of a pharmacologic hormone manipulation and the subsequent hormone add back.[25]

The mechanistic understanding of how changes in the hormone milieu induce depressive symptoms in some women, but not in others, is far from well established. Some evidence points toward a genetic predisposition; for example, a large twin study of the psychiatric adverse effects of oral contraceptives found a distinct genetic basis for depressive symptoms associated vs not associated with HC use.[26] Furthermore, a specific pattern of gene expression during pregnancy shows a high level of accuracy in predicting the development of PPD, and many of these genes are suggested to be involved in estrogen receptor signaling.[27] Notably, this finding translates to a pharmacologic sex hormone manipulation study in healthy women where the pharmacologically induced change in a subset of these gene transcripts correlated with the emergence of depressive symptoms and changes in a marker of brain serotonin signaling.[28] This finding indicates that serotonin-related brain mechanisms may be involved in the pathophysiology of hormone-triggered depressive symptoms.[29] Furthermore, hormones, including HC, may affect the monoaminergic brain system, especially the serotonin system, which may play a key role in reproductive mood disorders.[2,30-33]

This work contributes evidence to guide clinical PPD risk stratification and potentially improve PPD prediction models.[34] Future work should evaluate risk models for PPD that include information on previous depressive episodes and subclinical depressive symptoms associated with HC use, which could potentially further inform a stratified approach to reproductive care. These risk models could be a useful tool in future precision medicine, as some women may benefit more from prophylactic strategies or treatments targeting the hormonal mechanisms of depression.[35,36] Furthermore, future work should investigate whether our findings can be generalized to depressive episodes associated with other hormonal transitions, such as depression in perimenopause.

Strengths and Limitations

The strengths of the study include the use of national registers to obtain health data on a large population over 23 years. The use of registry data enabled us to obtain extensive health information on all women living in Denmark from when they were maximally 16 years of age without the risk of recall bias.

The study also has some limitations. First, our study is based on the assumption that HC use is associated with an increased risk of depression at the population level. However, at the individual level we were not able to verify whether a depressive episode developed because of HC use. In addition, we were not able to detect women who developed depression while using HC but were not treated with antidepressants or diagnosed with depression at a psychiatric inpatient or outpatient clinic; hence, the magnitude of the associated PPD risk should be interpreted with caution. Furthermore, by using pre-

Table 2. Risk Factors Associated With Postpartum Depression (PPD)

	No. (%)		OR (95% CI)	
Risk factor	No PPD	PPD	Univariable	Multivariable
Exposure group				
Non-HC-associated depression	17 749 (96.3)	682 (3.7)	1 [Reference]	1 [Reference]
HC-associated depression	5425 (94.8)	297 (5.2)	1.42 (1.24-1.64)	1.35 (1.17-1.56)
No depression	163 017 (99.1)	1478 (0.9)	0.24 (0.22-0.26)	0.25 (0.23-0.27)
Year of delivery				
1996-2001	2598 (99.5)	13 (0.5)	1 [Reference]	1 [Reference]
2001-2006	18 927 (98.8)	226 (1.2)	2.39 (1.42-4.40)	3.03 (1.79-5.62)
2006-2011	58 091 (98.3)	1011 (1.7)	3.48 (2.10-6.35)	4.86 (2.90-8.93)
2011-2016	78 369 (98.8)	940 (1.2)	2.40 (1.45-4.38)	2.97 (1.77-5.48)
2016-June 30, 2017	28 206 (99.1)	267 (0.9)	1.89 (1.13-3.48)	2.34 (1.38-4.35)
Maternal age, y				
12-19	10 256 (97.8)	230 (2.2)	1 [Reference]	1 [Reference]
20-24	56 040 (98.4)	896 (1.6)	0.71 (0.62-0.83)	0.66 (0.56-0.77)
25-29	87 970 (98.9)	951 (1.1)	0.48 (0.42-0.56)	0.55 (0.46-0.65)
30-34	29 595 (98.8)	356 (1.2)	0.54 (0.45-0.63)	0.70 (0.57-0.86)
35-40	2330 (99.0)	24 (1.0)	0.46 (0.29-0.69)	0.57 (0.36-0.88)
Educational level				
Less than high school	43 776 (97.8)	973 (2.2)	1 [Reference]	1 [Reference]
High school or vocational education	75 614 (98.8)	940 (1.2)	0.56 (0.51-0.61)	0.73 (0.66-0.81)
Bachelor's degree or higher	66 801 (99.2)	544 (0.8)	0.37 (0.33-0.41)	0.57 (0.50-0.65)
Familial disposition for depression				
No	172 516 (98.8)	2179 (1.2)	1 [Reference]	1 [Reference]
Yes	13 675 (98.0)	278 (2.0)	1.61 (1.42-1.82)	1.28 (1.13-1.46)
Other major psychiatric disorder				
No	180 482 (98.8)	2258 (1.2)	1 [Reference]	1 [Reference]
Yes	5709 (96.6)	199 (3.4)	2.79 (2.40-3.22)	1.23 (1.05-1.43)
Married				
No	88 637 (98.4)	1403 (1.6)	1 [Reference]	1 [Reference]
Yes	97 554 (98.9)	1054 (1.1)	0.68 (0.63-0.74)	0.85 (0.78-0.93)
Preterm birth[a]				
No	173 540 (98.7)	2286 (1.3)	1 [Reference]	1 [Reference]
Yes	11 565 (98.6)	161 (1.4)	1.06 (0.90-1.24)	0.96 (0.81-1.13)
Unknown	1086 (99.1)	10 (0.9)	0.70 (0.35-1.23)	0.78 (0.39-1.38)
Pregestational or gestational diabetes				
No	181 233 (98.7)	2360 (1.3)	1 [Reference]	1 [Reference]
Yes	4958 (98.1)	97 (1.9)	1.50 (1.22-1.83)	1.32 (1.07-1.62)
Eclampsia or preeclampsia				
No	177 948 (98.7)	2314 (1.3)	1 [Reference]	1 [Reference]
Yes	8243 (98.3)	143 (1.7)	1.33 (1.12-1.58)	1.28 (1.07-1.51)
Instrument-assisted or cesarean delivery				
No	129 004 (98.8)	1611 (1.2)	1 [Reference]	1 [Reference]
Yes	57 187 (98.5)	846 (1.5)	1.18 (1.09-1.29)	1.16 (1.07-1.27)
Medical indication for HC use				
No	177 223 (98.7)	2297 (1.3)	1 [Reference]	1 [Reference]
Yes	8968 (98.2)	160 (1.8)	1.38 (1.17-1.61)	1.18 (1.00-1.39)

Abbreviations: HC, hormonal contraception; OR, odds ratio.

[a] Missing for 0.6% for each exposure group, which was handled by grouping women with missing data in a separate group.

scription of antidepressants or depression diagnosis to measure depressive episodes, we may have only captured the most severe cases. We acknowledge that our findings may not necessarily be generalizable to mild depressive episodes. Second, the use of antidepressant prescriptions as a proxy for depression can introduce misclassification bias, as antidepressants

are used for other indications, such as anxiety and obsessive-compulsive disorder. In Denmark, however, 60% to 80% of prescribed antidepressants are used for treating depression.[37,38] Third, using our defined time gap between treatments to define new onsets of depressive episodes might not always apply, as time gaps in treatment can be due to periods of noncompliance or a mismatch between the daily dose used and the defined daily dose. This potential misclassification of new-onset depressive episodes is reflected by the large reduction in the number of depressive episodes that was observed when a 90-day and a 180-day grace period were used instead of a 30-day grace period between treatments. However, the results from the sensitivity analyses with longer grace periods did not differ markedly from the main analysis. Fourth, women with HC-associated depression had more depressive episodes than women with non-HC-associated depression, perhaps because prior depression has been shown to be associated with a higher risk of subsequent recurrent depression triggered by HC use.[39] However, if due to other reasons, then the higher number of depressive episodes may increase the likelihood that an episode will coincide with a new HC exposure by chance. This coincidence may induce a bias, as we expect that a history of recurrent depressive episodes compared with a single episode is associated with a higher risk of PPD. Nonetheless, this does not explain the observed association between HC-related depression and PPD, because when the exposure groups were defined based on the first depressive episode, the groups showed similar numbers of depressive episodes and the risk of PPD was, though less pronounced, still higher in the women with HC-associated depression compared with those with non-HC-associated depression. Fifth, a potential influence of unmeasured confounders cannot be excluded, such as differences in prescription patterns; however, by only including ever-users of HC and by comparing groups of women with a history of depression, the risk of confounding was minimized. Furthermore, no diagnosis code exists for PMDD in the 8th and 10th revisions of the *International Classification of Diseases and Related Health Problems*, which could be a potential confounder. Such confounding would, however, still provide evidence for hormonal sensitivity being associated with an increased risk of depressive episodes across the reproductive life span in a subgroup of women.

Conclusions

This study provides evidence for the existence of a subgroup of women who are sensitive to hormonal transitions across the reproductive life span by showing that a history of depression coinciding with the initiation of HC may be associated with a higher risk of PPD beyond the risk of a history of depression not coinciding with HC initiation. Importantly, the findings do not imply that HC use leads to a higher risk of PPD but do indicate that a history of HC-associated depression may unmask PPD susceptibility, which may prove useful as a clinical tool in PPD risk stratification.

ARTICLE INFORMATION

Accepted for Publication: February 27, 2023.

Published Online: April 26, 2023. doi:10.1001/jamapsychiatry.2023.0807

Author Contributions: Drs Larsen and Mikkelsen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Larsen, Frokjaer.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Larsen, Mikkelsen.
Obtained funding: Frokjaer.
Administrative, technical, or material support: Mikkelsen.
Supervision: Lidegaard, Frokjaer.

Conflict of Interest Disclosures: Dr Lidegaard reported receiving an institutional grant from Exeltis for a phase 4 study on a new progesterone-only pill requested by the European Medicines Agency outside the submitted work. Dr Frokjaer reported receiving advisory board fees from Sage Therapeutics and lecture fees from Lundbeck A/S and Janssen-Cilag A/S outside the submitted work. No other disclosures were reported.

Funding/Support: The study was funded by grants 0134-00278B and 7025-00111B from the Independent Research Fund Denmark.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: This study was presented at the 35th European College of Neuropsychopharmacology Congress; October 16, 2022; Vienna, Austria.

Data Sharing Statement: See Supplement 2.

Additional Contributions: The authors thank Brice Ozenne, PhD, Section of Biostatistics, Department of Public Health, University of Copenhagen, and Neurobiology Research Unit, Copenhagen University Hospital–Rigshospitalet, for valuable statistical insights. He received no compensation for his role in the study.

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Supplemental Online Content

Larsen SV, Mikkelsen AP, Lidegaard O, Frokjaer VG. Depression associated with hormonal contraceptive use as a risk indicator for postpartum depression. *JAMA Psychiatr*. Published online April 26, 2023. doi:10.1001/jamapsychiatry.2023.0807

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Overview of Registers, Variables, and Codes

Registers	Variables	Codes
Danish Civil Registration System (data since 1968)		
	Date of birth, immigration, emigration, kinship, civil status	
Demographic Registers of Statistics Denmark		
	Educational degree	
Danish Medical Birth Register (complete data since 1973)		
	Twin birth, stillbirth, gestational age, BMI, smoking status	
Danish National Patient Register (complete data since 1977)		
	Postpartum/perinatal depression	ICD-8: 296.09, 296.29, 298.09, 300.49, 301.19 ICD-10: DF32-34, DF38, DF39, DF530
	Instrument-assisted and caesarean delivery	ICD-10: DO81, DO82 NCSP-D: KMAE, KMAF0-2, KMAG03, KMAG13, KMCA
	Preeclampsia/eclampsia	ICD-8: 637, ICD-10: DO11, DO14-15
	Pre-gestational/gestational diabetes	ICD-8: 249-250 ICD-10: DE10-14, DO24
Medical indications for HC use	Polycystic ovary syndrome	ICD-8: 256.9 ICD-10: DE282
	Endometriosis	ICD-8: 625.3 ICD-10: DN80
	Premenstrual syndrome	ICD-10: DN943
	Dysmenorrhea	ICD-8: 626.3 ICD-10: DN944-946
	Heavy menstrual bleeding	ICD-8: 626.2 ICD-10: DN92
	Hirsutism	ICD-10: DL680
	Acne	ICD-8: 706.1 ICD-10: DL70
The Psychiatric Central Register (complete data since 1969 on hospital admission and 1995 on outpatient contacts)		
	Depression diagnosis	ICD-8: 296.09, 296.29, 298.09, 300.49, 301.19 ICD-10: DF32-34, DF38, DF39
Other major psychiatric disorders	Organic, including symptomatic, mental disorders	ICD-8: 290.09-11, 290.18-9, 292-294 ICD-10: DF00-09
	Mental and behavioral disorders due to psychoactive substance use	ICD-8: 291, 303.09, 303.19-20, 303.28-9, 303.91, 303.99, 304 ICD-10: DF10-DF19, DF55
	Schizophrenia, Schizotypal and delusional disorders	ICD-8: 295, 297-9 ICD-10: DF20-DF29
	Mood disorders	ICD-8: 296.19, 296.39, 296.89, 296.99 ICD-10: DF30-31
	Eating Disorder	ICD-8: 306.5 ICD-10: DF50
	Mental retardation	ICD-8: 310-4 ICD-10: DF7
Danish Prescription Register (complete data since 1995)		
	Hormonal contraception	ATC: Codes starting with G03A (except G03AD), G02BA03, G02BB01, and G03HB01
	Antidepressant medication	ATC: Codes starting with N06A

ATC: Anatomical Therapeutic Chemical Classification system; ICD-8: International Classification of Disease and Health Related Problems, 8th revision; ICD-10: 10th revision, NCSP-D: Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures – Denmark.

eTable 2. Without Adjusting for Obstetric Risk Factors for Postpartum Depression

Risk factors		No PPD (%)	PPD (%)	OR (95% CI) (univariable)	OR (95% CI) (multivariable)
Exposure group	Non–HC-associated depression	17,749 (96.3)	682 (3.7)	Ref	Ref
	HC-associated depression	5,425 (94.8)	297 (5.2)	1.42 (1.24-1.64)	1.35 (1.17-1.55)
	No depression	163,017 (99.1)	1,478 (0.9)	0.24 (0.22-0.26)	0.25 (0.22-0.27)
Year of delivery	(1996, 2001]	2,598 (99.5)	13 (0.5)	Ref	Ref
	(2001, 2006]	18,927 (98.8)	226 (1.2)	2.39 (1.42-4.40)	3.05 (1.80-5.65)
	(2006, 2011]	58,091 (98.3)	1,011 (1.7)	3.48 (2.10-6.35)	4.91 (2.93-9.02)
	(2011, 2016]	78,369 (98.8)	940 (1.2)	2.40 (1.45-4.38)	3.01 (1.79-5.54)
	(2016, June 2017]	28,206 (99.1)	267 (0.9)	1.89 (1.13-3.48)	2.36 (1.39-4.39)
Maternal age	(12,20]	10,256 (97.8)	230 (2.2)	Ref	Ref
	(20,25]	56,040 (98.4)	896 (1.6)	0.71 (0.62-0.83)	0.67 (0.57-0.78)
	(25,30]	87,970 (98.9)	951 (1.1)	0.48 (0.42-0.56)	0.56 (0.47-0.67)
	(30,35]	29,595 (98.8)	356 (1.2)	0.54 (0.45-0.63)	0.73 (0.60-0.89)
	(35,40]	2,330 (99.0)	24 (1.0)	0.46 (0.29-0.69)	0.61 (0.38-0.94)
Educational level	<high school	43,776 (97.8)	973 (2.2)	Ref	Ref
	High school/vocational	75,614 (98.8)	940 (1.2)	0.56 (0.51-0.61)	0.73 (0.66-0.81)
	≥Bachelor degree	66,801 (99.2)	544 (0.8)	0.37 (0.33-0.41)	0.56 (0.49-0.64)
Familial disposition for depression	No	172,516 (98.8)	2,179 (1.2)	Ref	Ref
	Yes	13,675 (98.0)	278 (2.0)	1.61 (1.42-1.82)	1.28 (1.13-1.46)
Other major psychiatric disorder	No	180,482 (98.8)	2,258 (1.2)	Ref	Ref
	Yes	5,709 (96.6)	199 (3.4)	2.79 (2.40-3.22)	1.22 (1.04-1.42)
Married	No	88,637 (98.4)	1,403 (1.6)	Ref	Ref
	Yes	97,554 (98.9)	1,054 (1.1)	0.68 (0.63-0.74)	0.85 (0.78-0.93)
Medical indication for HC use	No	177,223 (98.7)	2,297 (1.3)	Ref	Ref
	Yes	8,968 (98.2)	160 (1.8)	1.38 (1.17-1.61)	1.20 (1.01-1.41)

PPD, postpartum depression. HC: hormonal contraceptive.

eTable 3. History of Hormonal Contraceptive-Associated Depression and Risk of Perinatal Depression

History of depression	No PPD (%)	PPD (%)	OR (95% CI) (univariable)	OR (95% CI) (multivariable)
Non–HC-associated depression	17,749 (95.8)	787 (4.2)	Ref	Ref
HC-associated depression	5,425 (93.8)	356 (6.2)	1.48 (1.30-1.68)	1.41 (1.23-1.60)
No depression	163,017 (99.0)	1,579 (1.0)	0.22 (0.20-0.24)	0.23 (0.21-0.25)

PPD, postpartum depression. HC: hormonal contraceptive.

eTable 4. Without Women With Postpartum Depression Potentially Triggered by Hormonal Contraceptive Use

History of depression	No PPD (%)	PPD (%)	OR (95% CI) (univariable)	OR (95% CI) (multivariable)
Non–HC-associated depression	17,749 (97.3)	493 (2.7)	Ref	Ref
HC-associated depression	5,425 (96.0)	228 (4.0)	1.51 (1.29-1.77)	1.44 (1.23-1.69)
No depression	163,017 (99.3)	1,073 (0.7)	0.24 (0.21-0.26)	0.25 (0.22-0.28)

PPD, postpartum depression. HC: hormonal contraceptive.

eTable 5. Depressive Episodes Are Distinguished by a Minimum of 90-day and 180-day Treatment-Free Intervals

90-days treatment free interval

	Exposure	
	Non–HC-associated depression	**HC-associated depression**
Number of depressive episodes, no. (%)		
1	13,826 (72.4)	2,546 (50.3)
2	3,628 (19.0)	1,396 (27.6)
3	1,118 (5.9)	642 (12.7)
≥4	516 (2.7)	481 (9.5)

History of depression	No PPD (%)	PPD (%)	OR (95% CI) (univariable)	OR (95% CI) (multivariable)
Non–HC-associated depression	18,372 (96.2)	716 (3.8)	Ref	Ref
HC-associated depression	4,802 (94.8)	263 (5.2)	1.41 (1.21-1.62)	1.33 (1.14-1.53)
No depression	163,017 (99.1)	1,478 (0.9)	0.23 (0.21-0.25)	0.24 (0.22-0.27)

180-days treatment free interval

	Exposure	
	Non–HC-associated depression	**HC-associated depression**
Number of depressive episodes, no. (%)		
1	15,102 (77.9)	2,794 (58.7)
2	3,313 (17.1)	1,306 (27.4)
3	756 (3.9)	450 (9.5)
≥4	221 (1.1)	211 (4.4)

History of depression	No PPD (%)	PPD (%)	OR (95% CI) (univariable)	OR (95% CI) (multivariable)
Non–HC-associated depression	18,661 (96.2)	731 (3.8)	Ref	Ref
HC-associated depression	4,513 (94.8)	248 (5.2)	1.40 (1.21-1.62)	1.32 (1.14-1.53)
No depression	163,017 (99.1)	1,478 (0.9)	0.23 (0.21-0.25)	0.24 (0.22-0.27)

PPD, postpartum depression. HC, hormonal contraceptive.

eTable 6. Demographic Characteristics and Clinical Profiles When Exposure Is Defined Based on First Depression

Profiles	Exposure, No. (%)		
	Non–HC-associated depression	HC-associated depression	No depression
Total	20,361 (10.8)	3,792 (2.0)	164,495 (87.2)
Maternal age at delivery, y			
<20	456 (2.2)	150 (4.0)	9,880 (6.0)
20-24	5,743 (28.2)	1,308 (34.5)	49,885 (30.3)
25-29	9,535 (46.8)	1,648 (43.5)	77,738 (47.3)
30-34	4,151 (20.4)	629 (16.6)	25,171 (15.3)
35-39	476 (2.3)	57 (1.5)	1,821 (1.1)
Educational level			
Less than high school	6,253 (30.7)	1,461 (38.5)	37,035 (22.5)
High school or vocational education	8,473 (41.6)	1,436 (37.9)	66,645 (40.5)
Bachelor's degree or higher	5,635 (27.7)	895 (23.6)	60,815 (37.0)
Married	9,185 (45.1)	1,561 (41.2)	87,862 (53.4)
Familial disposition for depression	2,300 (11.3)	481 (12.7)	11,172 (6.8)
Other major psychiatric disorder	2,637 (13.0)	521 (13.7)	2,750 (1.7)
BMI[a]			
<18.5	1,076 (5.3)	232 (6.1)	6,996 (4.3)
18.5 - 24.9	11,210 (55.1)	2,109 (55.6)	94,627 (57.5)
25.0-29.9	4,206 (20.7)	743 (19.6)	30,527 (18.6)
≥30.0	2,987 (14.7)	528 (13.9)	16,952 (10.3)
Smoker[b]	4,845 (23.8)	1,022 (27.0)	27,451 (16.7)
Pregestational or gestational diabetes	846 (4.2)	129 (3.4)	4,080 (2.5)
Eclampsia or preeclampsia	1,018 (5.0)	174 (4.6)	7,194 (4.4)
Preterm birth[c]	1,312 (6.4)	266 (7.0)	10,148 (6.2)
Instrument-assisted delivery	2,597 (12.8)	467 (12.3)	22,431 (13.6)
Cesarean delivery	4,437 (21.8)	804 (21.2)	29,470 (17.9)
Medical indication for HC	1,615 (7.9)	350 (9.2)	7,163 (4.4)
Age at first depression, mean (SD), y	21.3 (3.6)	20.6 (3.4)	-
No. of depressive episodes			
0	-	-	164,495 (100.0)
1	11,319 (55.6)	2,101 (55.4)	-
2	4,374 (21.5)	817 (21.5)	-
3	2,113 (10.4)	387 (10.2)	-
≥4	2,555 (12.5)	487 (12.8)	-

[a]882 (4.3%) of the first-time mothers with a history of non-HC-triggered depression, 180 (4.7%) of those with HC-triggered depression, and 15,393 (9.4%) of those with no history of depression had unknown BMI. [b]Correspondingly, 474 (2.3%), 78 (2.1%), and 3,981 (2.4%) had unknown smoking status, and [c]111 (0.5%), 25 (0.7%) and 960 (0.6%) had unknown gestational age from each exposure group, respectively.

BMI, Body Mass Index as measured by weight in kilograms divided by height in meters squared; HC, hormonal contraceptive.

eTable 7. Exposure Defined at First Depressive Episode

History of depression	No PPD (%)	PPD (%)	OR (95% CI) (univariable)	OR (95% CI) (multivariable)
Outcome: Postpartum depression				
Non–HC-associated	19,567 (96.1)	794 (3.9)	Ref	Ref
HC-associated	3,607 (95.1)	185 (4.9)	1.26 (1.07-1.49)	1.19 (1.00-1.40)
No depression	163,017 (99.1)	1,478 (0.9)	0.22 (0.20-0.24)	0.24 (0.22-0.26)
Outcome: Perinatal depression				
Non–HC-associated	19,567 (95.5)	928 (4.5)	Ref	Ref
HC-associated	3,607 (94.4)	215 (5.6)	1.26 (1.08-1.46)	1.18 (1.01-1.38)
No depression	163,017 (99.0)	1,579 (1.0)	0.20 (0.19-0.22)	0.22 (0.20-0.24)
Outcome: Postpartum depression not potentially triggered by hormonal contraceptive use				
Non–HC-associated	19,567 (97.1)	581 (2.9)	Ref	Ref
HC-associated	3,607 (96.3)	140 (3.7)	1.31 (1.08-1.57)	1.24 (1.02-1.49)
No depression	163,017 (99.3)	1,073 (0.7)	0.22 (0.20-0.25)	0.24 (0.21-0.26)

PPD, postpartum depression. HC, hormonal contraceptive.

Data Sharing Statement

Data
Data available: No

Additional Information
Explanation for why data not available: Danish national health register data cannot be distributed, but access to the data can be granted by the appropriate authorities.

Study III

Postpartum hormonal contraceptive use and risk of depression

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Key Points

Question: Is postpartum hormonal contraceptive (HC) exposure associated with an increased risk of depression within 12 months postpartum?

Findings: In this cohort study of 610,038 first-time mothers, HC initiation postpartum was associated with an 1.49 times higher instantaneous risk of depression compared to no HC use within 12 months. The increased risk was consistent across all age groups and HC types, except for progestogen-only pills, for which it was less conclusive.

Meaning: These findings support that HC initiation after delivery is associated with an increased risk of developing depression in the postpartum period.

Abstract

Importance: Hormonal contraceptive (HC) use has been associated with depression. It is not known whether this relationship also holds true in the postpartum period - a time of heightened depression risk and where marked hormonal changes take place.

Objective: To determine if HC initiation postpartum is associated with depression.

Design: A cohort study based on Danish register data analyzed from April 1, 2023, to January 31, 2024.

Setting: Nationwide population-based.

Participants: All women in Denmark who delivered for the first time from 1997 through 2022. Women were excluded if they had a depression within 24 months prior to delivery, had multiple birth or stillbirth, or had a diagnosis of breast cancer or liver tumor.

Exposure: HC initiation 0-12 months postpartum was treated as a time-varying exposure. HC types were categorized as combined oral contraceptives (COCs), combined non-oral contraceptives (CNOCs), progestogen-only pills (POPs), and progestogen-only non-oral contraceptives (PNOCs).

Main Outcome and Measure: Adjusted hazards ratios (HRs) and average absolute risks of depression within 12 months postpartum were estimated using cox regression models and G-formula estimator. Depression was defined as filling an antidepressant prescription or receiving a hospital depression diagnosis.

Results: Of 610,038 first-time mothers, 41% initiated HC within 12 months postpartum (mean [SD] age; 27.6 [4.3] years for HC users vs. 29.6 [4.8] years for non-users). HC initiation was associated with subsequent depression with a HR of 1.49 (95% CI, 1.42;1.56) compared to no use, which resulted in an increase in the 12-month absolute risk from 1.37% to 1.55%. The HR was for COC 1.72 (1.63;1.82); for CNOC 1.97 (1.65;2.37); for PNOC 1.40 (1.25;1.56). POP exposure was associated with an initial lower instantaneous risk, which increased above 1 in the late postpartum period.

Conclusions and Relevance: HC initiation postpartum was associated with 1.49 times increased instantaneous depression risk resulting in an increase from 1.37% to 1.55% in 12-month depression risk in the observed population. This was consistent across all HC types except POP, for which the evidence was less conclusive. This raises the question if depression incidence postpartum is inflated by routine postpartum HC initiation.

Introduction

Starting on hormonal contraception (HC) has been associated with an increased risk of developing depressive episodes, especially in in adolescents.[1–3] It is unclear whether this is also applies in the postpartum period,[4] where women are already at heightened risk of developing a depressive episode.[5] Only a few studies have previously addressed this and found conflicting results; however, they were limited by lack of generalizability, insufficient follow-up time, and insufficient accounting for potentially important confounders.[4]

The postpartum period is a critical time to avoid unintended pregnancies, as short interpregnancy intervals may lead to increased perinatal and maternal health risks.[6,7] Therefore, mothers are routinely advised by their general practitioners to consider contraceptive methods at the eight-week postpartum visit in Denmark,[8] and HC is initiated by as many as 40% within the first year after giving birth and within the last 20 years, mothers start earlier and earlier after giving birth.[(in press)]

The increased risk of depressive episodes in the postpartum period has been hypothesized to be, at least in some women, attributed to the large drop in estradiol levels after delivery followed by a period of almost undetectably low levels.[9] Such a drastic hormonal shift is incomparable to any other lifetime events; hence women who recently gave birth may be differently affected by exogenous hormone exposure, including the different types of exogenous hormones contained in the various HC types, than women at other lifetime periods. This raises the question of whether the routine practice of HC use inflates the already heightened risk of depression in the postpartum period and whether it depends on which HC type is initiated. Further, as the risk of depressive episodes may be more pronounced in adolescent than in adult HC users [1–3], this questions whether a potential risk of depression postpartum associated with HC use is age-dependent.

Here, we take advantage of the Danish national health registers to investigate this relationship in a large, unselected population with sufficient follow-up time while accounting for various potentially important confounders such as medical indications for hormonal contraceptive use, prior mental disorder, and pregnancy complications. Specifically, the objective is to determine if HC exposure in the postpartum period increases the risk of incident depression compared to no HC exposure and whether such an association is modified by age and HC type.

Methods

Study design

This population-based cohort study used healthcare data from the Danish registers listed in **eTable 1**. Data were linked via the unique personal identification number given to Danish residents at birth or immigration. The data were provided by the Danish e-Health Authority and approval was obtained from the Regional Data Health Board “Privacy”. No ethical approval or informed consent are required

for register-based studies in Denmark. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[10]

Study population

The source population included all women living in Denmark for at least 24 months before giving birth for the first time between January 1st 1997 through December 2022 (n=663,654), identified from the Danish Civil Registration System and the Medical Birth Registry.[11,12] We excluded 34,633 women who had received a depression diagnosis or filled a prescription for antidepressant medication in a period of 24 months before delivery to ensure only new cases of depression onset were included, 16,316 women who had a multiple birth or stillbirth as this may influence probability of starting HC and may be associated with depression risk,[13,14] and 2,667 women who had a contraindication for any HC type in the form of a history of diagnosis with breast cancer or a liver tumor.[15] A total of 610,038 first-time mothers were left in the analyses (**eFigure 2**).

Exposure

HC use postpartum was treated as a time-varying exposure such that all women contributed to non-exposed time until the day they filled a HC prescription after giving birth and hereafter contributed to the exposure time for the rest of the follow-up time. We differentiated the exposure dependent on the HC type into the following categories; combined oral contraceptives (COCs) (ATC: G03AA*, except for G03AA13, and G03AB*); combined non-oral contraceptives (CNOCs) (patch (ATC: G03AA13) and vaginal ring (ATC: G02BB01)); progestogen-only pills (POPs) (ATC: G03AC*, except for G03AC06 and G03AC08); and progestogen-only non-oral contraceptives (PNOCs) (implant (ATC: G03AC08), depot injection (ATC: G03AC06), and levonorgestrel-releasing intrauterine system (LNG-IUS) (ATC: G02BA03)).

Outcome

The outcome of interest was depression within 12 months after delivery. A depressive episode was defined as filling a prescription of antidepressant medication identified in the National Prescription Register (ATC: N06A*),[16] or a hospital discharge diagnosis of depression identified in the National Patient Register (ICD-8: 296.09, 296.29, 298.09, 300.49, 301.19, (ICD-10): F32-34, F38, F39, F530).[17]

Covariates

The following covariates measured at time of delivery were included in the analyses: Maternal age (below 20 years, 20-29 years, and 30 years and above); highest educational level (below high school, high school or vocational education, or bachelor degree or above); civil status (living with a partner or

not); history of any other mental disorder including previous use of psychoactive drugs; parental history of mental disorders; medical indications for HC use including polycystic ovary syndrome, endometriosis, premenstrual syndrome, dysmenorrhea, heavy menstrual bleeding, hirsutism, and acne; having received in vitro fertilization treatment; preterm birth; instrument-assisted- or cesarean delivery; pre-eclampsia/eclampsia; pre-gestational- or gestational diabetes; and finally, we controlled for period effects by including calendar-year in 5-year bands.

Statistical analysis

The mothers were followed from day of delivery until 12 months postpartum, the development of depression, emigration, death, or end of the study period, whichever came first. We used Cox proportional hazard models adjusted for the listed covariates to estimate hazard ratios (HRs) for developing depression in the postpartum period between HC exposed vs. non-exposed. To examine whether the association differed by HC type and age group, we further analyzed the association stratified on these.

To assess the proportionality assumption for the exposure, we considered a Cox model with time-varying coefficient for the exposure using the *cox.aalen* function of the *timereg* package.[18] The exposure showing violation of the proportion hazard assumption was modelled with a flexible parametric survival model via the *stpm2* function of the *rstpm2* package to display the hazard ratio as a function of time.[19] To assess the sensitivity of the estimates to the proportional hazard assumption on the covariates, we used test based on Schoenfeld residuals to identify possible violation of the proportional hazard assumption. The baseline hazard of the Cox regression model was stratified on the variables showing evidence for non-proportionality.

We report the average estimated risk of developing depression in the postpartum period as well as the average hypothetical risk had nobody started HC. The risk difference between these two scenarios is considered to be the average risk effect of HC on depression in the postpartum period in the investigated population. This was performed in a multistate model considering the three possible states (non-exposed, exposed, and depressive state) (for more details about the model, please see **eMethods 1** and **eFigure 1**) where transition hazards were estimated using Cox models[20], assuming that the hazard in the exposed state was not dependent on the entrance time to this state (Markov assumption).The average risk under current/observed HC use was obtained via the G-formula by evaluating the risk for each individual and averaging these risks (formula 12 in Cortese et al 2020).[21] The average hypothetical risk had nobody started HC was evaluated with the same formula setting the transition hazard to the exposed state to 0. When average risks were estimated for the different HC types, the multistate model was expanded to contain a state for each HC type for which a transition intensity was calculated (**eFigure 2a**). In another multistate Markov Cox model, the proportional hazard assumption was relaxed by using a different baseline hazard for the exposed and the non-exposed states instead of using regression coefficient for the exposure, so risks and risk curves could be estimated without relying on proportional hazards.

Sensitivity analyses

We conducted five sensitivity analyses to test the robustness of our results. First, we repeated the analyses while changing the covariate adjustment set; one model only containing age and calendar period and another model additionally adjusting for immigration status (immigrant or descendant of an immigrant), smoking status, and highest obtained educational level of the parents. Due to considerable missing information about the parents' educational level (7.8%) and smoking status (7.9%), we performed multiple imputations to impute missing values with the Multivariate Imputation by Chained Equations (mice) package in R where binary variables were imputed with logistic regression and categorical data with polytomous logistic regression.[22] Second, the PNOC group was re-defined to only include LNG-IUS to reduce the risk of confounding by indication related to the use of implants and depot injections. Third, we re-defined the starting time of the HC exposure to be 28 days after the first HC prescription was filled to accommodate that women may not start HC as they filled a prescription. Fourth, women were right-censored at the time a new pregnancy was registered if it happened within a one-year follow-up time. Last, we stratifying the association between HC exposure and the outcome on history of mental disorder as prior studies have shown this to moderate the association between HC use and depression risk [23,24].

HRs were calculated with 95% confidence intervals (CI), and the null-hypothesis was rejected if this did not overlap 1.00. All analyses were conducted using R version 4.2.2.[25] The analysis plan was pre-registered on www.aspredicted.org (#125589).

Results

Of 610,038 first-time mothers included in the study, 248,274 (40.7%) started using HC, of which 143,751 (23.6%) initiated COC, 5,465 (0.9%) CNOC, 66,612 (10.9%) POP, and 32,446 (5.3%) PNOC within the first year after delivery. 48 were lost to follow-up due to death and 3,287 due to emigration. Their characteristics and clinical profiles are shown in **Table 1**. The proportions of mothers with a history of mental disorder were 17.9% and 18.2% in mothers initiating and not initiating HC postpartum, respectively, and this number was between 23.3% and 24.4% in users of different non-oral contraceptives. The timing of initiation of the different types is illustrated by cumulative incidence curves in **eFigure 2A-B**. Notably, about 50% of those who initiated POP filled their first prescription between seven to ten weeks postpartum.

Within 12 months after delivery, 9251 (1.5%) of the first-time mothers developed a depressive episode. The crude incidence rate of depression was 21 per 1,000 person-years for the mothers exposed to HC and 14 per 1,000 person-years for non-exposed mothers. HC initiation was associated with an increased instantaneous risk of depression in the postpartum period with an adjusted HR of 1.49 (95% CI, 1.42;1.56) compared to no use (**Table 2**). When stratified on HC type, the adjusted HR was 1.72 (1.63;1.82) for COC, 1.97 (1.65;2.37) for CNOC, 1.40 (1.25;1.56) for PNOC, and specifically for LNG-IUS it was 1.27 (1.12;1.44) (**Table 2**). As POP exposure showed time-varying effects, the HR

for POP is represented as a function of time in **eFigure 4**, which shows a HR<1 early postpartum, which subsequently increased across the postpartum period to be significantly increased from about eight months postpartum. If proportional hazard assumption was assumed, the average HR was estimated to be 1.04 (0.95;1.13) over the whole follow-up time. Adjusting only on age and calendar period led to larger estimated HRs (up to +0.23), except for LNG-IUS that was estimated to be 1.22. Including immigration- and smoking status and highest obtained educational level of the parents to the adjustment set, led to very similar estimated HRs (maximum absolute difference of 0.04) (**Table 2**). For mothers younger than 20 years of age, HC initiation postpartum was associated with depression with an HR of 1.63 (1.37;1.94), which was 1.55 (1.46;1.64) for mothers aged 20-29 years and 1.35 (1.24;1.47) for mothers aged 30 years or older (**eTable 2**).

The observed average absolute risk of depression at 12 months postpartum for the study population was 1.55% (1.52;1.58) (**Table 3**). In comparison, in the hypothetical scenario had no one initiated HC, the estimated average risk was 1.37% (1.34;1.41) (**Figure 2A**), resulting in a risk difference of 0.18% (0.16;0.20) (**Figure 2B**). Had all those who initiated an HC started on COC, the estimated average risk would have been 1.63% (1.59;1.67), on CNOC 1.72% (1.59;1.67), on POP 1.38% (1.34;1.42), and on PNOC 1.51% (1.45;1.57) with a risk of 1.45 (1.39;1.51) specifically for LNG-IUS (**Table 3**, **Figure 2C-D**). The corresponding risks estimated with a multistate Markov Cox model with relaxed proportional hazard assumption are shown in **eTable3** and **eFigure 5A-C**. The estimated risks were similar to the ones under proportional hazard (largest risk difference of 0.01), but confidence intervals were typically wider.

The sensitivity analyses also showed similar results (**eTable 4**). When HC exposure started with 28 days delay, the HR was 1.45 (1.38;1.53); when follow-up time ended at new pregnancy, the HR was 1.49 (1.42;1.56); when stratifying the HC exposure effect on prior mental disorder, the HR was 1.63 (1.53;1.73) for women with no prior history (n=499,936) and 1.32 (1.23;1.41) for women with prior history (n=110,102), and the ratio between the two was 1.23 (1.13;1.35).

When the proportional hazard assumption was relaxed for covariates, for which there was evidence indicating violation of the proportional hazard, the estimates did not change remarkably (largest absolute difference was 0.11), except the estimated HRs for the mothers younger than 20 years that were considerably lower (1.33 instead of 1.63) (**eTable 5**).

Discussion

The findings from this population-based cohort study on 610,038 first-time mothers showed that HC initiation postpartum was associated with an increased instantaneous risk of depression across all age groups. This phenomenon was most pronounced for women with no prior mental disorder. An increased instantaneous risk was observed for COC, CNOC, and PNOC, but not for POP exposure.

Previous research on the association between postpartum HC use and depression has shown conflicting results.[4] An observational study found that postpartum HC users were more likely to spontaneously report postpartum depression as a side effect compared to users of other drugs postpartum.[26] Another large observational study based on military healthcare system data found a

reduced instantaneous risk of antidepressant drug use among POP users and increased among subdermal implant and vaginal ring users, but no association with COC or LNG-IUS use, although, the LNG-IUS use was associated with increased risk of depression diagnosis.[27] Similar to the present study, POP prescriptions were filled shortly after delivery with a mean time of initiation of 0.9 months, but as they only followed these for 4.3 months on average, they may have missed essential follow-up time. The present study showed a time-varying POP effect across the 12 months postpartum and likewise found a decreased instantaneous risk in the early postpartum phase, but it increased across the postpartum period and reached an increased instantaneous risk eight to 12 months postpartum. These findings may show that risk of depression risk associated with POP exposure depends on time since delivery or it might be explained by a delay in the actual time of initiation. About 50% of POP prescriptions were filled within a few weeks postpartum coinciding with the eight-week postpartum visit to the general practitioner. However, this does not necessarily reflect the actual timing of initiation since among mothers with an early postpartum POP prescription, only about half of them used POP three and six months postpartum.[28] Furthermore, the estimated risk can be attenuated by early discontinuation or even a lack of initiation among those who filled a prescription. In Denmark, as many as one out of four filled one POP prescription only.[(in press)] In addition, the lower risk in the early postpartum phase may be explained by selection bias. Progestogen-only contraceptives are recommended over combined hormonal contraceptives while breastfeeding due to a putative negative impact of combined hormonal contraceptives on lactation.[15] Hence, mothers who filled a POP prescription early postpartum might be overrepresented by breastfeeding mothers and hence reflect a population associated with a lower risk of developing depression.[29] Accordingly, 13% of those who initially used POP switched to COC within the postpartum period, which might be those choosing to switch after terminating breastfeeding.[(in press)]

Studies with more precise track of the time of initiation have supported a link between postpartum progestogen exposure and the development of depressive symptoms; a double-blind, randomized placebo-controlled study showed increased risk of depressive symptoms in women allocated to a single depot injection compared to placebo at six weeks, but not three months postpartum;[30] also a randomized study found more depressive symptoms reported at one and three months postpartum in women allocated to depot injections compared to women allocated to cobber IUS.[31] But in contrast, this was not supported by two retrospective observational studies, which found no increased level of depressive symptoms 6 weeks postpartum in women receiving depot injection compared to non-users.[32,33]

The higher depression risk associated with HC exposure in women without compared to women with prior mental disorder is supported by previous observational studies.[23,24] However, this is in contrast to a randomized study, where prior or ongoing mental disorder was shown to be a risk factor for HC-induced mood lability.[34] This discrepancy may be explained by a healthy user bias in the observational studies, i.e., women with prior mental disorder may be less likely to be prescribed HC due to reported mood-related side effect. Alternatively, it may reflect that the relative contribution from HC exposure in the development of clinical depression plays a less prominent role when the relative

contribution is higher of other risk factors or pathophysiological mechanisms. Therefore, we interpret the less pronounced risk associated with HC use in women with prior mental disorder, among whom depression was also more frequent, with caution. Importantly, it indicates that HC-associated depression is seen despite no prior mental disorder, which is also supported by a prospective study demonstrating postpartum mood symptoms associated with HC exposure irrespective of psychiatric symptoms during pregnancy.[35]

The present study found no conclusive pattern of higher risk associated with HC use among the younger relative to older women as observed outside the postpartum period,[1–3] despite a larger fraction of mothers of older age started POP[(in press)]. It has been hypothesized that a younger brain under development, i.e., in adolescence, may be more susceptible to exogenous hormones,[23] but such difference in susceptibility may diminish due to the structural and functional brain changes happening in relation to pregnancy and childbirth.[36]

The higher risk of depression in the postpartum period associated with HC initiation highlights the importance of considering the contribution of HC exposure to the already heightened risk of depression in women in the postpartum period. Especially, this should be considered at postpartum contraceptive counseling where a history of HC-associated mood deterioration, premenstrual dysphoric disorder, or postpartum depression adds to the risk profile.[37,38]

Strengths and limitations

The strength of the study is the use of national health registers, providing a nationwide, unselected study population with information on various potential confounders. Further, it provides new evidence on the association between HC exposure and depression from an alternative and likely more homogenous population of women, having in common that they all just delivered for the first time, compared to previous studies on this topic [1–3].

Our study also has several limitations. First and most importantly, the findings should be interpreted based on the observational nature of the study; hence, a causal link cannot be definitely inferred due to potential unmeasured confounding. Second, depression is not always the indication for antidepressant use which may lead to a misclassification bias; however, as many as 80% of antidepressants are prescribed for depression during pregnancy,[39] and as such a misclassification is expected to be non-differential, it would bias the results towards the null and thus not be an explanation of the observed association.[40] Third, the day a prescription was filled may not mirror the day of initiation nor who was actually using HC postpartum, potentially leading to a differential misclassification bias. If HC exposure is assumed to increase the risk of depression, this would tend to bias the results towards the null, but combined with a potential healthy user bias related to filling a prescription early postpartum, this would bias towards a lower risk, which may explain the time-varying POP effect, as discussed in detail earlier. Fourth, the findings may also be attenuated by a healthy user bias due to women not starting HC postpartum because of previous adverse experience.

Last, our findings may not extend to milder cases of depressive episodes, which go undetected or are just not treated medically or diagnosed at the hospital.

Conclusions

These findings show that HC use is associated with an increased risk of depression in the postpartum period. The increased risk was observed for COC, CNOC, PNOC, but was inconclusive for POP. In conclusion, these findings raise the question if the incidence of depressive episodes postpartum may be inflated by routine HC initiation, which is important information to be conveyed at postpartum contraceptive counseling.

Acknowledgements

Author Contributions

Concept and design: All authors

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Larsen.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Larsen, Ozenne.

Obtaining funding: Frokjaer.

Administrative, technical, or material support: Mikkelsen, Lidegaard.

Supervision: Ozenne, Mikkelsen, Liu, Bang-Madsen Lidegaard, Frokjaer.

Non-Author Contributions

Conflicts of interest: VGF has received honorarium as a speaker for Lundbeck Pharma A/S, Janssen-Cilag A/S and Gedeon-Richter A/S. Juliane Marie Center has received research funding from Exeltis. KBM has received speaker's fee from Medice Nordic. TMO has received a speaker honorarium from Lundbeck Pharma A/S. The rest of the authors report no conflicts of interest.

Financial support (and role of the funding source): The study was funded by The Independent Research Fund Denmark (grant identifier: 0134-00278B and 7025-00111B). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Dara Access, Responsibility, and Analysis: SV had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Paper presentation information: Abstract was presented at the 36th ECNP Congress, The European College of Neuropsychopharmacology, Barcelona, Spain, 7-10 October 2023.

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Tables

Table 1. Characteristics and clinical profiles of users of different types of hormonal contraception and of non-users.							
	Exposure, No. (%)						
Profile	**Non-users**	**HC users**	**COC users**	**CNOC users**	**POP users**	**PNOC users**	
						All users	**IUS users**
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Total	361,764 (59.3)	248,274 (40.7)	143,751 (23.6)	5465 (0.9)	66,612 (10.9)	32,446 (5.3)	29,864 (4.9)
Maternal age, y							
<20	6429 (1.8)	8426 (3.4)	6108 (4.2)	323 (5.9)	1039 (1.6)	956 (2.9)	480 (1.6)
20-29	194,036 (53.6)	171,993 (69.3)	104,171 (72.5)	3720 (68.1)	44,203 (66.4)	19,899 (61.3)	18,122 (60.7)
≥30	161,299 (44.6)	67,855 (27.3)	33,472 (23.3)	1422 (26.0)	21,370 (32.1)	11,591 (35.7)	11,262 (37.7)
Educational level[a]							
Below high school	47,370 (13.1)	42,448 (17.1)	29,817 (20.7)	1227 (22.5)	7395 (11.1)	4009 (12.4)	2554 (8.6)
High school/vocational education	123,022 (34.0)	103,969 (41.9)	67,357 (46.9)	2120 (38.8)	24,920 (37.4)	9572 (29.5)	8816 (29.5)
Bachelor degree or above	187,427 (51.8)	100,777 (40.6)	45,951 (32.0)	2075 (38.0)	34,007 (51.1)	18,744 (57.8)	18,412 (61.7)
Highest educational level of parents[b]							
Below high school	50,562 (14.0)	40,258 (16.2)	28,407 (19.8)	759 (13.9)	8059 (12.1)	3033 (9.3)	2361 (7.9)
High school/vocational education	145,299 (40.2)	120,518 (48.5)	73,409 (51.1)	2583 (47.3)	30,619 (46.0)	13,907 (42.9)	12,622 (42.3)
Bachelor degree or above	129,051 (35.7)	77,059 (31.0)	37,021 (25.8)	1814 (3æ3.2)	24,340 (36.5)	13,884 (42.8)	13,422 (44.9)
Familial disposition for mental disorder	36,852 (10.2)	27,869 (11.2)	14,254 (9.9)	759 (13.9)	8214 (12.3)	4642 (14.3)	4949 (13.5)
History of mental disorder	65,720 (18.2)	44,382 (17.9)	22,213 (15.5)	1275 (23.3)	12,980 (19.5)	7914 (24.4)	7015 (23.5)
Immigrant or descendant of immigrant	55,378 (15.3)	18,606 (7.5)	9055 (6.3)	514 (9.4)	6334 (9.5)	2703 (8.3)	2334 (7.8)
Civil status[c]	140,647 (38.9)	70,553 (28.4)	40,693 (28.3)	1433 (26.2)	19.549 (29.3)	8878 (27.4)	8467 (28.4)
Smoking status[d]	40,006 (11.1)	39,414 (15.9)	27,479 (19.1)	1024 (18.7)	7342 (11.0)	3569 (11.0)	2620 (8.8)
Medical indication for HC	19,062 (5.3)	10,161 (4.1)	5145 (3.6)	259 (4.7)	2944 (4.4)	1813 (5.6)	1689 (5.7)
IVF treatment	64,073 (17.7)	14,260 (5.7)	7587 (5.3)	292 (5.3)	4234 (6.4)	2147 (6.6)	2074 (6.9)
(Pre-)gestational diabetes	11,634 (3.2)	6677 (2.7)	3447 (2.4)	133 (2.4)	1895 (2.8)	1202 (3.7)	1467 (4.9)
Eclampsia/preeclampsia	15,895 (4.4)	11,376 (4.6)	6484 (4.5)	225 (4.1)	3058 (4.6)	1609 (5.0)	1467 (4.9)
Preterm birth[e]	21,206 (5.9)	15,608 (6.3)	9513 (6.6)	308 (5.6)	3984 (6.0)	1803 (5.6)	1605 (5.4)
Instrument-assisted delivery	121,217 (33.5)	83,346 (33.6)	49,471 (34.4)	1860 (34.0)	22,174 (33.3)	9841 (30.3)	9019 (30.2)

[a]0.4%, 0.4%, 0.8%, 0.4%, 0.4%, 0.3%, and 1.1% had missing information among mothers initiating HC, COC, CNOC, POP, PNOC, IUS, and not initiating HC postpartum, respectively.

[b]4.2%, 3.4%, 5.7%, 5.4%, 5.0%, 4.9%, and 10.2% had missing information among mothers initiating HC, COC, CNOC, POP, PNOC, IUS, and not initiating HC postpartum, respectively.

[c]0.1%, 0.2%, 0.1%, 0.1%, 0.1%, 0.1%, and 0.2% had missing information among mothers initiating HC, COC, CNOC, POP, PNOC, IUS, and not initiating HC postpartum, respectively.

[d]6.9%, 9.4%, 2.5%, 4.0%, 2.8%, 2.8%, and 8.6% had missing information among mothers initiating HC, COC, CNOC, POP, PNOC, IUS, and not initiating HC postpartum, respectively.

[e]0.7%, 1.0%, 0.5%, 0.4%, 0.3%, 0.3%, and 1.3% had missing information among mothers initiating HC, COC, CNOC, POP, PNOC, IUS, and not initiating HC postpartum, respectively.

Table 2. Hazard ratios for depression in the postpartum period for HC exposed compared to non-exposed mothers					
Exposure	**Person-years**	**No. of events**	**aHR$^{\alpha}$ (95% CI)**	**aHR$^{\beta}$ (95% CI)**	**aHR$^{\gamma}$ (95% CI)**
Non-exposed	434 620	5980	1 (reference)	1 (reference)	1 (reference)
HC exposed	156 928	3271	1.53 (1.46;1.61)	1.49 (1.42;1.56)	1.46 (1.40;1.53)
COC	83 246	2157	1.83 (1.73;1.93)	1.72 (1.63;1.82)	1.68 (1.59;1.77)
CNOC	3334	121	2.20 (1.84;2.64)	1.97 (1.65;2.37)	1.93 (1.61;2.31)
POP*	48 886	640	See e**Figure 4**		
PNOC	21 462	353	1.42 (1.27;1.58)	1.40 (1.25;1.56)	1.38 (1.23;1.54)
IUS	19 722	272	1.22 (1.08;1.38)	1.27 (1.12;1.44)	1.26 (1.11;1.43)

*HRs for POP violated the non-proportional hazard assumption, hence the time-varying HR is shown in **eFigure 4**.

$^{\alpha}$Adjusted for age and calendar year.

$^{\beta}$ Adjusted for age, calendar year, educational level, civil status, history of mental disorder, parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes. Missing values were handled as a separate group for educational level, civil status, and preterm delivery status.

$^{\gamma}$Adjusted for age, calendar year, educational level, civil status, history of mental disorder, parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes, immigration status, parental educational level, and smoking status. Missing values were handled by use of multiple imputations for parental education, smoking status, educational level, civil status, and preterm delivery status.

HC, hormonal contraceptive. aHR, adjusted hazard ratio. COC, combined oral contraceptive. CNOC, combined non-oral contraceptive. POP, progesterone-only pill. PNOC, progesterone-only non-oral contraceptive. IUS, intrauterine system.

Table 3. 12-month average absolute risk of depression in the postpartum period		
Scenario	**Absolute risk % (95% CI)**	**Absolute risk difference % (95% CI)**
No HC initiation[a]	1.37 (1.34;1.41)	Reference
Observed HC initiation	1.55 (1.52;1.58)	0.18 (0.16;0.20)
All initiating HC start on COC[b]	1.63 (1.59;1.67)	0.26 (0.23;0.29)
All initiating HC start on CNOC[b]	1.72 (1.59;1.85)	0.35 (0.22;0.48)
All initiating HC start on POP[b]	1.38 (1.34;1.42)	0.01 (-0.02;0.04)
All initiating HC start on PNOC[b]	1.51 (1.45;1.57)	0.14 (0.08;0.19)
All initiating HC start on IUS[b]	1.45 (1.39;1.51)	0.10 (0.04;0.15)

[a]A hypothetical scenario obtained by setting the transition hazard from non-exposed to HC exposed to 0.

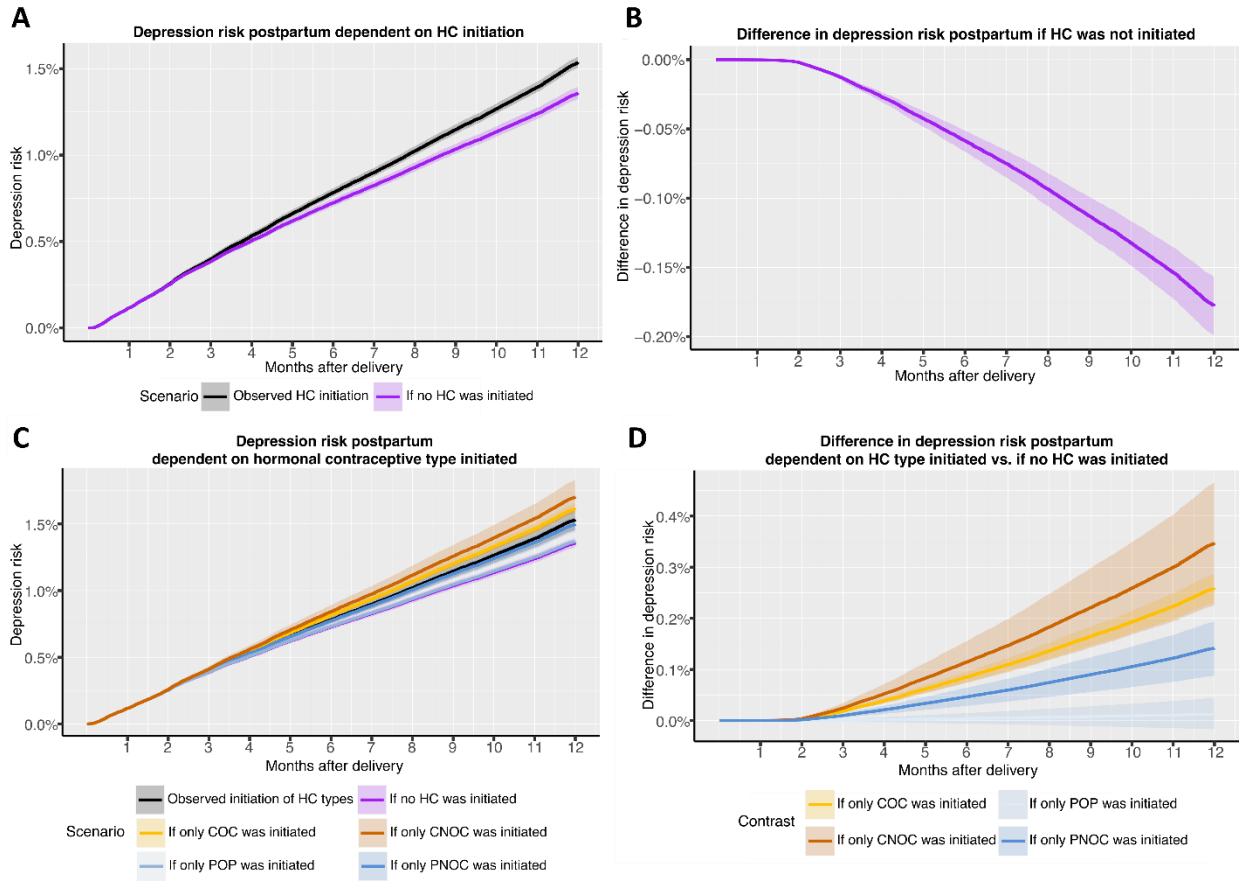
[b]A hypothetical scenario obtained by setting the transition hazard from non-exposed to COC/CNOC/POP/PNOC/IUS by adding the transition hazard for each type and by setting the transition hazard to 0 for the rest of the types.

Adjusted for age, calendar year, educational, cohabitation status, immigration status, history of mental disorder; parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes. Missing values were handled by imputing to separate groups for educational level, immigration status, cohabitant status, and preterm delivery status.

HC, hormonal contraceptive. aHR, adjusted hazard ratio. COC, combined oral contraceptive. CNOC, combined non-oral contraceptive. POP, progesterone-only pill. PNOC, progesterone-only non-oral contraceptive. IUS, intrauterine system.

Figures

Figure 1.



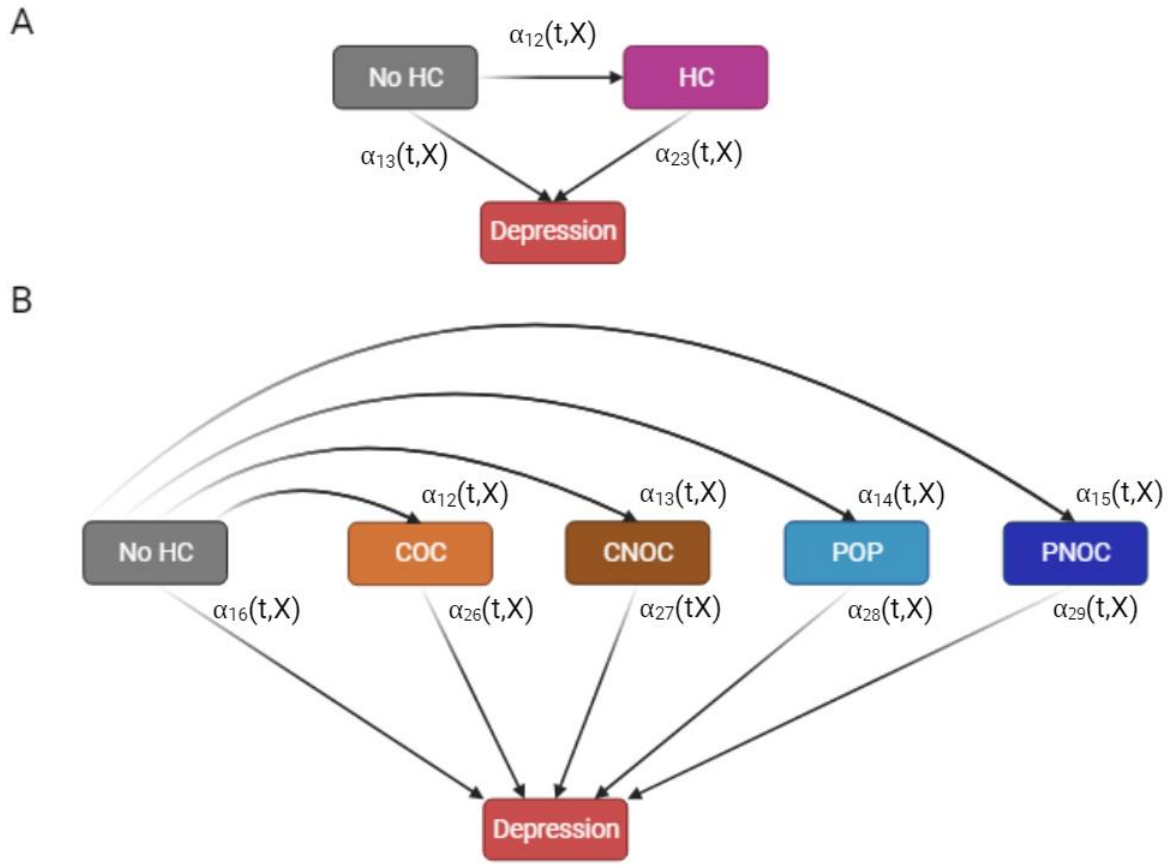
A) Average absolute risk with 95% confidence intervals of depression within 12 months from delivery under scenario 0; observed initiation of hormonal contraception (HC) postpartum vs. scenario 1; nobody had initiated HC. **B**) Average absolute risk difference with 95% confidence interval within 12 postpartum between these two scenarios. **C**) Average absolute risk with 95% confidence intervals of depression within 12 months from delivery for the scenarios where all mothers who are observed to initiate HC initiated either only combined oral contraception (COC, scenario 2), combined non-oral contraception (CNOC), progestogen-only pill (POP), or progestogen-only non-oral contraception (PNOC), with the observed transition intensity observed for each type vs. if nobody had initiated HC. **D**) Average absolute risk difference with 95% confidence interval within 12 postpartum contrasting scenarios 0 to scenario 2-5.

Supplementary Online Content

eMethods 1. The multistate Markov cox models

The multistate Markov cox models included two Cox regression models; one modelling the transition intensity from the non-exposed to the exposed state, and one modelling the transition intensities to the depressive state from the exposed and non-exposed states assuming proportional hazard between these. The follow-up time of the mothers who initiated HC was therefore split into two; time from delivery to start of HC exposure and time from HC initiation to depression or end of follow-up. Both models were adjusted for covariates listed in the main text, which were assumed to be time-invariant. The hypothetical risk had nobody initiated HC was obtained by setting the transition intensity from non-exposed to exposed to zero, which is only valid under the strong assumptions; 1) first-time mothers start HC for reasons unrelated to their risk of depression conditioned on the included covariates and 2) any prevention from HC initiation does not affect the direct transition from the non-exposed to the depressive state. In the main analysis we model the HC effect under the proportional hazard assumption, i.e. $\alpha_{23}(t, X) = \alpha_{13}(t, X)e^{\gamma}$ (**eFigure 1**) where X is the vector of covariates. In the sensitivity analysis to evaluate the risks without relying on the proportional assumption for the HC effect, a different baseline hazard was used for $\alpha_{13}(t, X)$ and $\alpha_{23}(t, X)$ while keeping common log hazard ratio coefficients for the covariates. The RiskIDM function was used for the multistate Markov Cox modelling (https://rdrr.io/github/bozenne/butils/src/R/riskIDM.R).

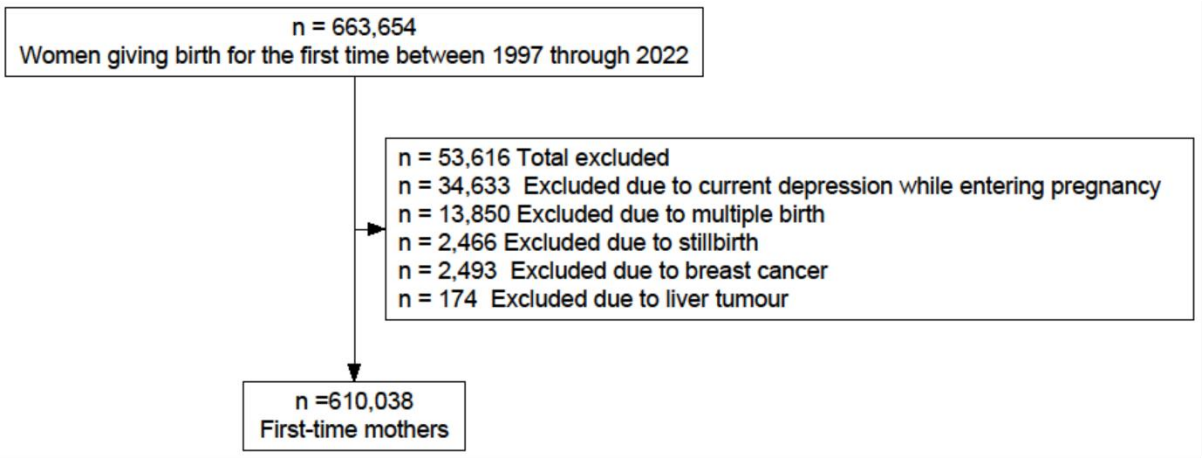
eFigure 1. Multistate models



A) Multistate model with three possible states: "No HC", "HC", "Depression". α_{12}, α_{13}, and α_{23} refers to the transition intensities between the states. All women started in the "No HC" state and either stayed in this state or switched to the other states during the postpartum period. Mothers switched from non-exposed to HC exposed once they filled a HC prescription and stayed exposed during the rest of the follow-up time. **B**) This multistate model includes a state for each HC type grouped as "COC", "CNOC", "POP", and "PNOC". Once mothers initiated an HC type, they stayed exposed to this specific type for the rest of the follow-up time regardless of whether they discontinued or switched to another type.

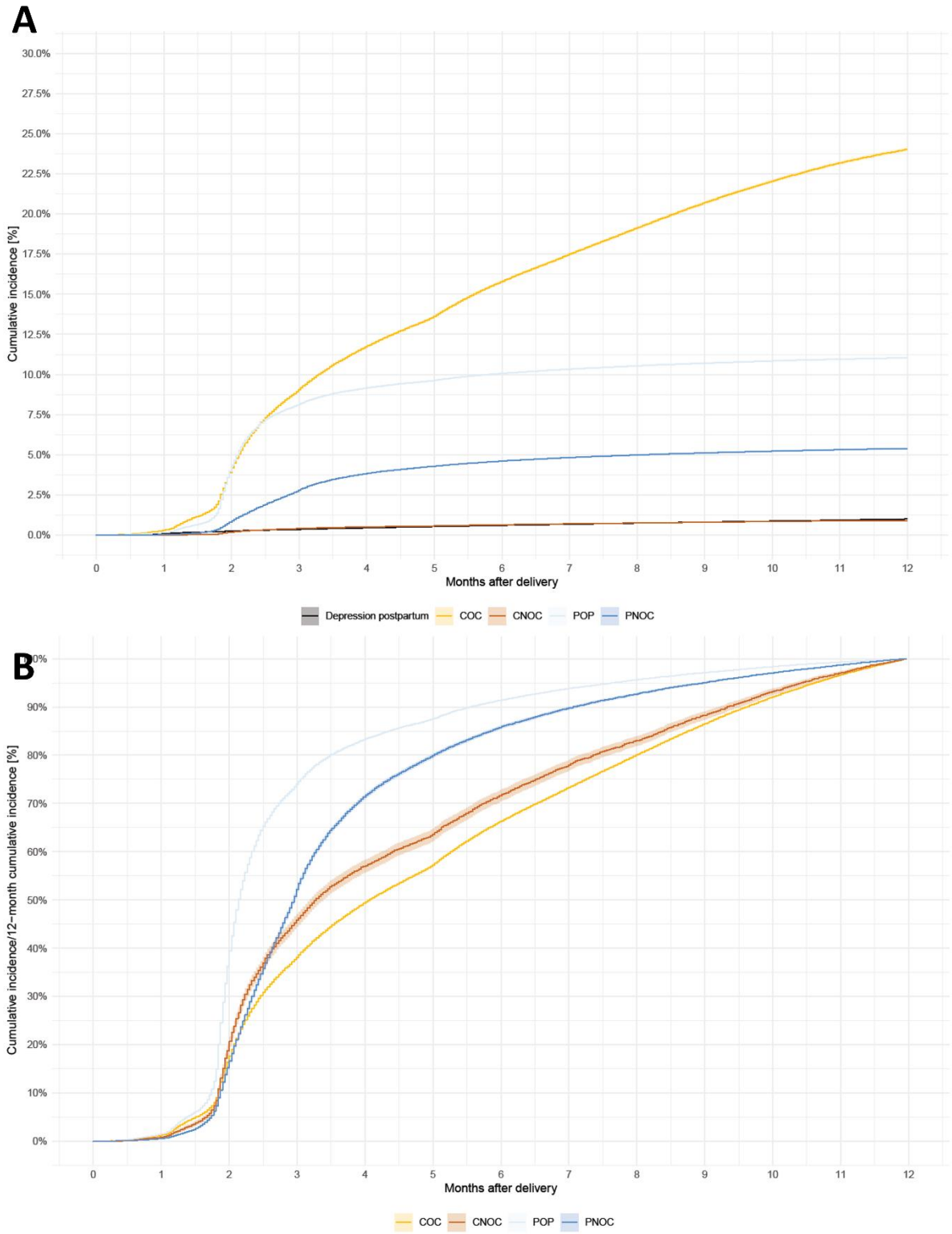
HC, hormonal contraceptive. COC, combined oral contraceptive. CNOC, combined non-oral contraceptive. POP, progesterone-only pill. PNOC, progesterone-only non-oral contraceptive.

eFigure 2. Study population



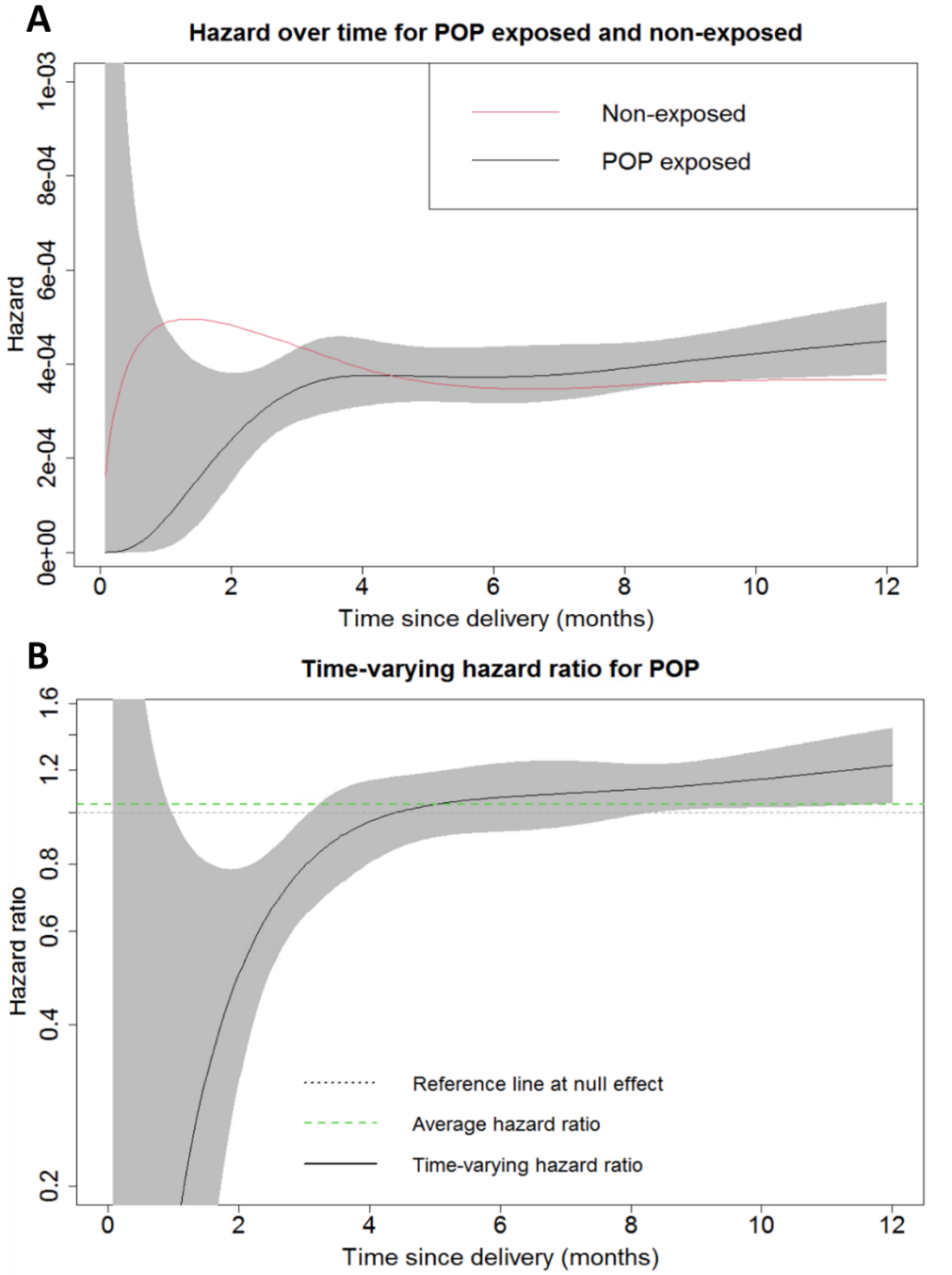
Flowchart illustrating the selection of the study population from the source population.

eFigure 3. (**A**) The cumulative incidence of initiating the different hormonal contraceptive types before depression postpartum, (**B**) and when divided by the 12 months cumulative incidence.



The terminology “cumulative incidence” was used as the probability of starting contraception with depression postpartum as competing risk.

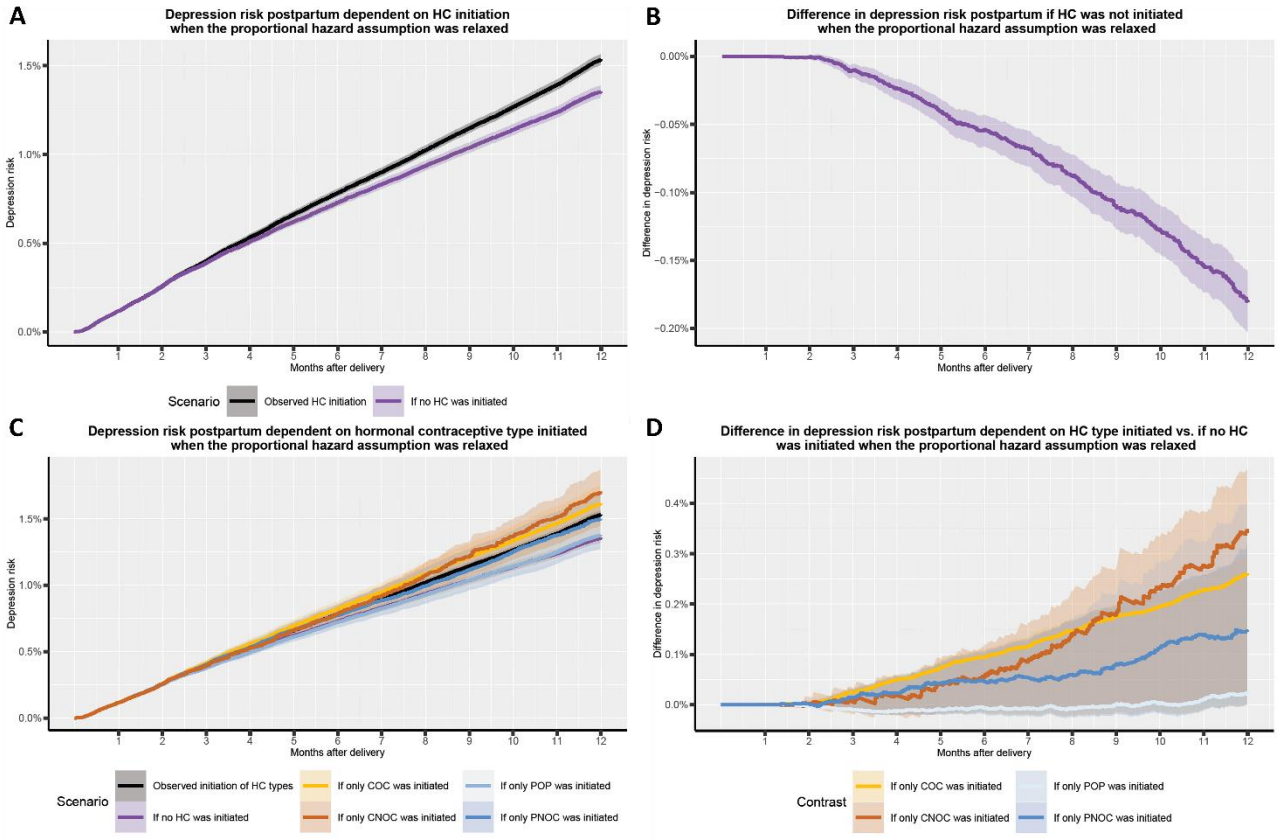
eFigure 4. Time-varying hazard and hazard ratio for POP exposure



A) Time-varying hazard for developing depression in the postpartum period for mothers exposed to progestogen-only pill (POP) (solid black line with 95% confidence interval) and non-exposed (solid red line) across the postpartum period. **B**) The time-varying hazard ratio (HR) (the solid line with 95% confidence interval) for developing depression in the postpartum period for women starting on progesterone-only pills (POP) compared to non-exposed adjusted for age, calendar year, educational level, civil status, history of mental disorder, parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes. Missing values were handled by imputing to separate groups for educational level, civil status, and preterm delivery status. The dotted gray line shows the HR=1 and the dotted green line shows the estimated HR under the proportional hazard assumption. The large reduction in the instantaneous risk in the early postpartum period is due to a relative high hazard for the non-exposed in combination with very few cases

among the few mothers who had already filled a POP prescription shortly after delivery, hence the early postpartum HR has a very large uncertainty illustrated by the wide confidence interval.

eFigure 5 Risk curves for depression postpartum when proportional hazard assumptions were relaxed for the transition intensity from the exposed and the non-exposed state to depression state in the multistate Markov Cox model.



A) Shows the average absolute risk with 95% confidence intervals of depression within 12 months from delivery for the observed population with the observed fraction of mothers initiating hormonal contraception (HC) postpartum with the observed transition intensity vs. if nobody had initiated HC. **B**) Shows the average absolute risk difference with 95% confidence interval within 12 postpartum between these two scenarios. **C**) Shows the average absolute risk with 95% confidence intervals of depression within 12 months from delivery for the scenarios had all mothers who initiated HC initiated either combined oral contraception (COC), combined non-oral contraception (CNOC), progestogen-only pill (POP), or progestogen-only non-oral contraception (PNOC), with the observed transition intensity observed for each type vs. if nobody had initiated HC. **D**) Shows the average absolute risk difference with 95% confidence interval within 12 postpartum between these scenarios.

eTable 1. Overview of registers, variables, and codes

Registers	Variables	Codes
Danish Civil Registration System (data since 1968)		
	Date of birth, immigration, emigration, kinship, civil status	
Demographic Registers of Statistics Denmark		
	Educational degree	
Danish Medical Birth Register (complete data since 1973)		
	Twin birth, stillbirth, gestational age, smoking status	
Danish National Patient Register (complete data since 1977)		
	Depression postpartum	ICD-8: 296.09, 296.29, 298.09, 300.49, 301.19 ICD-10: F32-34, F38, F39, F530
	Instrument-assisted and caesarean delivery	ICD-10: O81, O82 NCSP-D: KMAE, KMAF0-2, KMAG03, KMAG13, KMCA
	Preeclampsia/eclampsia	ICD-8: 637, ICD-10: O11, O14-15
	Pre-gestational/gestational diabetes	ICD-8: 249-250 ICD-10: E10-14, O24
	Breast cancer	ICD-8: 174, 233 ICD-10: C50
	Liver tumor	ICD.8: 155, 197.7-8,211.5, 230.5 ICD-10: C22, D015B, D134, D376A, C787
Medical indications for HC use	Polycystic ovary syndrome	ICD-8: 256.9 ICD-10: E282
	Endometriosis	ICD-8: 625.3 ICD-10: N80
	Premenstrual syndrome	ICD-10: N943
	Dysmenorrhea	ICD-8: 626.3 ICD-10: N944-946
	Heavy menstrual bleeding	ICD-8: 626.2 ICD-10: N92
	Hirsutism	ICD-10: L680
	Acne	ICD-8: 706.1 ICD-10: L70
The Psychiatric Central Register (complete data since 1969 on hospital admission and 1995 on outpatient contacts)		
	Mental disorders	ICD-8: 300.0-315.0 (except 302.0 and 302.3) ICD-10: F00-F99
Danish Prescription Register (complete data since 1995)		
Hormonal contraceptives	COC	ATC: G03AA* (except for G03AA13) and G03AB*
	CNOC	ATC: G03AA13 and G02BB01
	POP	ATC: G03AC* (except for G03AC06 and G03AC08)
	PNOC	ATC: G02BA03, G03AC06, and G03AC08
	Antidepressant medication	ATC: N06A*
	Psychotropic medicine	ATC: N05* and N06*
	IVF-treatment	ATC: G03G*, G03DA04, H01CC01, H01CC02, L02AE01

ATC: Anatomical Therapeutic Chemical Classification system; ICD-8: International Classification of Disease and Health Related Problems, 8th revision; ICD-10: 10th revision, NCSP-D: Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures – Denmark.

eTable 2. **Risk of depression postpartum stratified on age groups**					
Exposure	**Person-years**	**No. of events**	**aHR$^{\alpha}$ (95% CI)**	**aHR$^{\beta}$ (95% CI)**	**aHR$^{\gamma}$ (95% CI)**
<20 years					
Non-exposed	9025	263	1 (reference)	1 (reference)	1 (reference)
HC exposed	5487	252	1.65 (1.38;1.96)	1.63 (1.37;1.94)	1.59 (1.34;1.89)
20-29 years					
Non-exposed	247,364	3340	1 (reference)	1 (reference)	1 (reference)
HC exposed	108,414	2257	1.61 (1.52;1.70)	1.55 (1.46;1.64)	1.51 (1.43;1.60)
≥30 years					
Non-exposed	178,232	2377	1 (reference)	1 (reference)	1 (reference)
HC exposed	43,027	762	1.36 (1.26;1.48)	1.35 (1.24;1.47)	1.33 (1.22;1.44)

$^{\alpha}$Adjusted for age and calendar year.

$^{\beta}$ Adjusted for age, calendar year, educational level, civil status, history of mental disorder, parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes. Missing values were handled by imputing to separate groups for educational level, civil status, and preterm delivery status.

$^{\gamma}$Adjusted for age, calendar year, educational level, civil status, history of mental disorder, parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes, immigration status, parental educational level, and smoking status. Missing values were handled by use of multiple imputations for parental education, smoking status, educational level, civil status, and preterm delivery status.

HC, hormonal contraceptive. aHR, adjusted hazard ratio. COC, combined oral contraceptive. CNOC, combined non-oral contraceptive. POP, progesterone-only pill. PNOC, progesterone-only non-oral contraceptive. IUS, intrauterine system.

eTable 3. Average absolute risk of depression in the postpartum period with relaxed proportional hazard assumption		
Scenario	**Absolute risk % (95% CI)**	**Absolute risk difference % (95% CI)**
No HC initiation[a]	1.37 (1.33;1.40)	Reference
Observed HC initiation	1.55 (1.52;1.58)	0.18 (0.16;0.20)
All initiating HC start on COC[b]	1.63 (1.33;1.77)	0.26 (0.00;0.29)
All initiating HC start on CNOC[b]	1.51 (1.28;1.74)	0.35 (0.02;0.47)
All initiating HC start on POP[b]	1.39 (1.30;1.72)	0.02 (0.00;0.40)
All initiating HC start on PNOC[b]	1.72 (1.46;1.89)	0.14 (0.00;0.34)
All initiating HC start on IUS[b]	1.45 (1.25;1.73)	0.10 (0.00;0.38)

[a]A hypothetical scenario obtained by setting the transition hazard from non-exposed to HC exposed to 0

[b]A hypothetical scenario obtained by setting the transition hazard from non-exposed to COC/CNOC/POP/PNOC/IUS by adding the transition hazard for each type and by setting the transition hazard to 0 for the rest of the types.

Adjusted for age, calendar year, educational, cohabitation status, immigration status, history of mental disorder; parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes. Missing values were handled as a separate group for educational level, immigration status, cohabitant status, and preterm delivery status.

HC, hormonal contraceptive. aHR, adjusted hazard ratio. COC, combined oral contraceptive. CNOC, combined non-oral contraceptive. POP, progesterone-only pill. PNOC, progesterone-only non-oral contraceptive. IUS, intrauterine system.

eTable 4. Sensitivity analyses			
HC exposure started 28 days after filling HC prescription			
Exposure	**Person-years**	**No. of events**	**aHR (95% CI)**
Non-exposed	453,415	6378	1 (reference)
HC exposed	138,133	2873	1.48 (1.41;1.56)
Follow-up time ending at new pregnancy			
Exposure	**Person-years**	**No. of events**	**aHR (95% CI)**
Non-exposed	434.514	5980	1 (reference)
HC exposed	156,907	3271	1.49 (1.42;1.56)
First-time mothers stratified on history of mental disorder			
Exposure	**Person-years**	**No. of events**	**aHR (95% CI)**
Mothers with no history of mental disorder			
Non-exposed	358 648	3416	1 (reference)
HC exposed	128 280	1995	1.63 (1.53;1.73)
Mothers with history of mental disorder			
Non-exposed	75 972	2564	1 (reference)
HC exposed	28 638	1276	1.32 (1.23;1.41)

Hazard ratios are adjusted for age, calendar year, educational level, civil status, history of mental disorder, parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes. Missing values were handled by imputing to separate groups for educational level, civil status, and preterm delivery status.

eTable 5. When proportional hazard was relaxed for covariates showing potential time-varying effects			
Exposure	**Person-years**	**No. of events**	**aHR (95% CI)**
Non-exposed	434 620	5980	1 (reference)
HC exposed	156 928	3271	1.46 (1.39;1.53)
COC	83 246	2157	1.66 (1.57;1.75)
CNOC	3334	121	1.86 (1.55;2.24)
POP*	48 886	640	Non-PH
PNOC	21 462	353	1.42 (1.27;1.59)
IUS	19 722	272	1.31 (1.15;1.48)
Stratified on age groups			
<20 years			
Non-exposed	9025	263	1 (reference)
HC exposed	5487	252	1.33 (1.11;1.61)
20-29 years			
Non-exposed	247,364	3340	1 (reference)
HC exposed	108,414	2257	1.49 (1.40;1.58)
≥30 years			
Non-exposed	178,232	2377	1 (reference)
HC exposed	43,027	762	1.43 (1.31;1.56)
HC exposure started 28 days after filling HC prescription			
Non-exposed	453,415	6378	1 (reference)
HC exposed	138,133	2873	1.45 (1.38;1.53)
Follow-up time ending at new pregnancy			
Non-exposed	434.514	5980	1 (reference)
HC exposed	156,907	3271	1.46 (1.39;1.53)
First-time mothers stratified on history of mental disorder			
Mothers with no history of mental disorder			
Non-exposed	358 648	3416	1 (reference)
HC exposed	128 280	1995	1.59 (1.50;1.68)
Mothers with history of mental disorder			
Non-exposed	75 972	2564	1 (reference)
HC exposed	28 638	1276	1.30 (1.21;1.39)

*HRs for POP violated the non-proportional hazard (Non-PH) assumption, hence the time-varying HR is shown in e**Figure 4**.

The Cox regression models were adjusted for age group, calendar period, educational level, cohabitation status, history of mental disorder; parental disposition for mental disorders, medical indications for HC use, IVF-treatment, preterm birth, instrument-assisted- or caesarean delivery, pre-eclampsia/eclampsia, pre-gestational- or gestational diabetes, parental educational level, immigration status, and smoking status. The proportional hazard was relaxed for the following variables; age group, calendar period, educational level, civil status, and IVF-treatment. Missing values were handled by imputing to a separate group educational level (0.2% missing data), immigration status (0.1% missing data), cohabitant status (0.1% missing data), and preterm delivery status (0.1% missing data).