










RESEARCH ARTICLE

Cancer Epidemiology

Maternal hormonal contraceptive use and childhood central nervous system tumor risk in a large Scandinavian cohort

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Abstract

An association between maternal hormonal contraception use and childhood central nervous system (CNS) tumors has been suggested, but findings are inconclusive. This population-based cohort study includes Scandinavian nationwide registry data on liveborn children (1996–2018). Children were followed from birth until CNS tumor (<20 years) or censoring (other cancer, emigration, death, 20th birthday, or end of follow-up in 2017–2020). Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between maternal hormonal contraception use (any type, type-specific) and CNS tumor risk (any, any malignant, type-specific). Maternal use was categorized as “recent use” (0–3 months before or during pregnancy, except for non-oral progestin-only types), “previous use” (before recent use), and “no use”. A total of 3,183,316 children were followed for 29,455,528 person-years, during which time 1384 children developed a CNS tumor (610 malignant). Compared with no use, maternal previous or recent use of any hormonal contraception (HR 0.93, 95% CI 0.82–1.05; HR 0.99, 95% CI 0.83–1.19), combined and progestin-only types (oral, non-oral), were not associated with childhood CNS tumor risk. However, maternal recent progestin-only injection use was associated with malignant childhood CNS tumors (HR 3.95, 95% CI 1.46–10.68), compared

with no use (number needed to harm: 1 per 14,577 person-years). In conclusion, no association was found between maternal use of common types of hormonal contraception and CNS tumors in children. The rarely used progestin-only injections (medroxyprogesterone acetate) were associated with malignant CNS tumor risk in children, though based on few children.

KEYWORDS

central nervous system tumor, childhood cancer, hormonal contraception, medroxyprogesterone acetate, Scandinavia

What's New?

Previous studies on maternal hormonal contraceptive use and risk of childhood tumors of the central nervous system (CNS) have yielded inconsistent results. In the present study, associations between maternal use of hormonal contraceptives and CNS tumor risk in offspring were investigated in a Scandinavian cohort consisting of more than 3 million children. Most maternal hormonal contraceptives showed no association with childhood CNS tumor risk. An exception was the injectable contraceptive medroxyprogesterone acetate, which was linked to a four-fold increase in risk of malignant CNS tumors in children. The findings warrant further research and evaluation of the safety of medroxyprogesterone acetate.

1 | INTRODUCTION

Despite advances in early detection and treatment, children with central nervous system (CNS) tumors face high mortality rates and potential severe late effects.¹ CNS tumors are the most common solid childhood cancer, accounting for ~25% of pediatric cancers.² The Scandinavian incidence rates (Denmark, Norway, Sweden) rank among the highest worldwide.^{2,3}

Ionizing radiation is currently the only well-established environmental risk factor.⁴ Hormonal contraception (natural/synthetic estrogen and/or progestin) is classified as carcinogenic to humans, and diethylstilbestrol (synthetic estrogen) is well-recognized to cause cancer in children exposed in utero.⁵ Natural or synthetic sex hormone use has been associated with several cancer types in women⁵ and recent studies have reported increased CNS tumor risk in women using progestin-only contraceptive injections and progestin-only menopausal therapy.^{6,7} Noteworthy, a recent study reported an almost 35-fold increased CNS tumor risk in children with in utero exposure to an injectable progestin used to prevent preterm birth which is structurally similar to the progestin used in hormonal contraception injections.⁸

Only six studies have examined the association between maternal hormonal contraception use and childhood CNS tumor risk.^{9–14} Four small case–control studies (≤ 17 exposed cases)^{11–14} found no association, whereas one case–control study¹⁰ reported an increased risk following maternal oral hormonal contraception use.¹⁰ The largest, a Danish cohort study, reported no association between hormonal contraceptive use and childhood CNS tumors, except for progestin-only injections (hazard ratio [HR] of 6.7, 95% confidence interval [CI] 2.1–21.1).⁹ All studies were limited by few exposed cases, and the five case–control studies included self-reported exposure information, potentially biasing the results.

In this large Scandinavian registry-based cohort of ~3.2 million children (born 1996–2018), we aim to investigate the association between maternal hormonal contraception use and CNS childhood tumor risk.

2 | MATERIALS AND METHODS

2.1 | Cohort

We conducted a registry-based cohort study by pooling high-quality data from Scandinavian nationwide registries. All Scandinavian residents are assigned a personal identification number (PIN), enabling precise data linkage in the registries.¹⁵ We identified all liveborn children (Denmark 1995–2018, Norway 2007–2013, Sweden 2007–2018) and their mothers in the medical birth registries, which contain information about all births.¹⁶ The cohort was linked with individual-level data from other nationwide registries (Table S1). Children with missing information on gestational age, PIN, date of birth, maternal PIN, or age were excluded. As the Danish Prescription Registry started in 1995,¹⁵ Danish children born in 1995 were excluded to ensure at least one year of exposure information (Figure S1).

2.2 | Hormonal contraception

Information on maternal filled prescriptions of hormonal contraception (before third trimester of index pregnancy) was included from the Scandinavian prescription registries. With few exceptions, all hormonal contraceptives require a prescription. Information from pharmacies on redeemed prescriptions has been electronically transferred to the prescription registries since 1995 (Denmark), 2004 (Norway),

and July 2005 (Sweden), ensuring high completeness and validity of information.¹⁷ Hormonal contraception was categorized according to administration (oral/non-oral), content (combined estrogen progestin/progestin-only) (Table S2), and timing of use according to index pregnancy. Since hormonal contraception is mainly redeemed for 3 months of use, exposure was categorized as follows: Recent use (≤ 0 –3 months before or during pregnancy [1–2. trimester]), previous use (any before recent use), and no use (reference group). Considering the extended contraceptive effect of injections,¹⁸ implants, and intrauterine devices (IUDs), recent use was modified accordingly: Injections ≤ 1 year, implants ≤ 3 –5 years, and intrauterine devices ≤ 3 –6 years before or during pregnancy (Figure S2).

2.3 | CNS tumors

The Scandinavian cancer registries receive compulsory information on all incident cancers since 1943–1958 and have a high degree of completeness and validity (94–98% of cases are microscopically verified).¹⁹ We identified childhood cancer (age 0–19 years) in the cancer registries by the relevant International Classification of Diseases for Oncology codes (third edition) and classified CNS tumors according to the International Classification of Childhood Cancer, third edition (ICCC-3)²⁰ into two main outcomes: (1) any CNS tumor (ICCC-3 = III) and (2) any malignant CNS tumor (ICCC-3 = III, behavior code = 3). We also examined five major CNS tumor types as secondary outcomes (ICCC-3 = IIIa–f).

2.4 | Statistical analyses

Children were followed from birth until CNS tumor, censoring (emigration, other cancer, 20th birthday, death), or end of follow-up on December 31 (2018 [Denmark], 2017 [Norway], 2020 [Sweden])—whichever occurred first. We used Cox proportional hazards models to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). CNS tumor risk was examined according to the timing of use (previous and recent use compared with no use) and hormonal contraception type (any, combined or progestin-only, administered orally or non-orally). When recent use included ≥ 5 cases, we further analyzed use during pregnancy separately and also examined recent use of injections, implants, and IUDs separately, since these non-oral progestin-only products include different progestins and are used for different time intervals. Age was used as the underlying time. A priori, all models were adjusted for country and year of birth. Assessed by complete case analysis, no other covariates—selected based on previous literature and availability—changed the results by $>10\%$ (birth order, maternal age, and diabetes) and were therefore not included in the final model.²¹ Correlation between siblings was accounted for by calculation of cluster-robust standard errors. Using Poisson regression, we estimated adjusted incidence rates (IRs) with 95% CIs.

Pre-planned sensitivity analyses were carried out. First, the results for any hormonal contraception and the two main outcomes

(any CNS tumor and any malignant CNS tumor) were adjusted for additional potential confounders that were not available for the entire cohort (maternal body mass index, smoking, infertility, ethnicity, paternal age, and parental education and cancer). Second, to investigate if missing emigration information in Sweden affected our results, we refrained from using emigration information in Denmark and Norway (used for censoring). Third, to investigate unmeasured confounding, the *E*-value was calculated for statistically significant results.²² Fourth, for statistically significant results we calculated numbers needed to harm ($1/|IR$ in exposed minus IR in unexposed]). Fifth, to examine if the choice of reference group (i.e., no use) affected the results, a reference group including no and previous use was applied. Sixth, as recent users of non-oral progestin-only products may cease treatment long before pregnancy, we examined use 0–3 months, 0–6 months, 0–1 year, and 0–1.5 years before pregnancy start, separately. Additionally, in two post hoc analyses, maternal recent injection use was compared with 1) previous injection use (>12 months before index pregnancy), and 2) injection use after index birth only. Post hoc, to further explore CNS tumor risk according to the timing of use, recent injection use was subdivided into use during pregnancy, 0–3 months, 0–6 months, and 0–1 year before pregnancy start. Finally, in a post hoc analysis, the cohort was restricted to children born in Denmark 1998–2018, Sweden 2009–2018, and Norway 2007–2013 to examine if longer exposure information in the prescription registries before study entry (minimum 3 years) affected the results.

Study approvals are reported in Table S3. Analyses were performed in STATA 16.1. All statistical tests were two-sided, and a *p*-value <0.05 was considered statistically significant.

3 | RESULTS

The cohort included 3,183,316 liveborn children, born 1996–2018. During 29,455,528 person-years of follow-up (median 8.6 years), 1384 children were diagnosed with a CNS tumor, of which 610 (44.1%) were malignant. Compared to children in the no use group ($n = 930,934$ [29.2%]), children of previous users ($n = 1,879,345$ [59.0%]) and recent users ($n = 373,037$ [11.7%]) were born in more recent years, more often as the firstborn, and by younger women (Table 1).

We found no association between maternal recent use of any hormonal contraception and any CNS tumor risk (HR 0.99, 95% CI 0.83 to 1.19) or any malignant CNS tumor risk (HR 0.80, 95% CI 0.59 to 1.07), compared with no use (Table 2). Also, no association was observed for recent use of any hormonal contraception and different CNS tumors including ependymomas and choroid plexus tumors (HR 0.98, 95% CI 0.52 to 1.87), astrocytomas (HR 0.71, 95% CI 0.49 to 1.03), intracranial and intraspinal embryonal tumors (HR 1.12, 95% CI 0.71 to 1.77), other gliomas (HR 0.93, 95% CI 0.35 to 2.49), and other specified and unspecified intracranial and intraspinal neoplasms (HR 1.15, 95% CI 0.88 to 1.49), compared with no use (Table S4). Similarly, no associations were observed for previous use or use during

TABLE 1 Characteristics of the study cohort.

Characteristics	Maternal hormonal contraception use					
	No use		Previous use		Recent use	
Total: no. (%)	930,934	(29.2)	1,879,345	(59.0)	373,037	(11.7)
Country of birth: no. (%)						
Denmark	310,924	(33.4)	945,073	(50.3)	170,395	(45.7)
Norway	146,455	(15.7)	219,248	(11.7)	55,936	(15.0)
Sweden	473,555	(50.9)	715,024	(38.1)	146,706	(39.3)
Sex: no./total no. (%)						
Male	478,596/930,027	(51.5)	962,654/1,877,672	(51.3)	192,447/372,756	(51.6)
Female	451,431/930,027	(48.5)	915,018/1,877,672	(48.7)	180,309/372,756	(48.4)
Year of birth: no. (%)						
1996–2000	155,328	(16.7)	138,891	(7.4)	29,747	(8.0)
2001–2005	64,166	(6.9)	219,832	(11.7)	35,011	(9.4)
2006–2010	357,264	(38.4)	526,225	(28.0)	106,928	(28.7)
2011–2015	244,601	(26.3)	650,445	(34.6)	127,167	(34.1)
2016–2018	109,575	(11.8)	343,952	(18.3)	74,184	(19.9)
Median year (IQR): yr	2009 (2007–2013)		2011 (2007–2014)		2011 (2007–2015)	
Birth order: no./total no. (%)						
First	355,418/930,658	(38.2)	876,344/1,879,163	(46.6)	154,118/373,000	(41.3)
Second or higher	575,240/930,658	(61.8)	1,002,819/1,879,163	(53.4)	218,882/373,000	(58.7)
Maternal age: no. (%)						
<28 yr	244,742	(26.3)	577,889	(30.8)	153,912	(41.3)
28–31 yr	239,703	(25.8)	614,155	(32.7)	104,886	(28.1)
>31 yr	446,489	(48.0)	687,301	(36.6)	114,239	(30.6)
Median age (IQR): yr	31 (27–35)		30 (27–33)		29 (25–32)	
Maternal diabetes: no./total no. (%)*						
Yes	6069/930,934	(0.7)	12,027/1,879,345	(0.6)	2425/373,037	(0.7)

Note: Maternal use of hormonal contraception is divided into three exposure groups: “No use” of hormonal contraception before birth, “previous use” more than 3 months before the start of pregnancy (injections >1 year, implants >3–5 years and intrauterine devices >3–6 years), and “recent use” 0–3 months before and during pregnancy (injections ≤1 year, implants ≤3–5 years and intrauterine devices ≤3–6 years). Prescriptions filled in the third trimester were excluded. *Maternal diabetes diagnosis included the following International Classification of Diseases, revision 8 and 9 (ICD-8 and ICD-9) codes: 249*, 250* and ICD-10 codes: O24.0*, O24.1*, E10*, E11*, E13*, E14*

Abbreviations: IQR, inter-quartile range; no., number of children; yr, Year(s).

pregnancy for any hormonal contraception and CNS tumor risk (Tables 2 and S4).

Maternal recent or previous use of oral combined, non-oral combined, oral progestin-only, and non-oral progestin-only products was also not associated with any CNS tumor risk or any malignant CNS tumor risk, compared with no use (Table 2). However, for use of non-oral progestin-only products 0–1 year before index pregnancy, a HR of 2.10 (95% CI 1.03 to 4.29) for malignant CNS tumors was observed, compared with no use (Table 2). This association was driven by recent injection use (HR 3.95, 95% CI 1.46 to 10.68; *E*-value = 7.36), corresponding to one extra child diagnosed with a malignant CNS tumor per 14,577 exposed person-years (number needed to harm) (Table 3). Specifically, injection use close to pregnancy was associated with the highest HR of 6.43 (95% CI 0.90 to

45.95) for use 0–6 months and HR 4.24 (95% CI 1.57 to 11.46) for use 0–12 months before pregnancy start (no cases for use “0–3 months before pregnancy” and “during pregnancy”). When using “previous injection use” or “injection use after index birth only” as reference group, instead of no use, the estimates were further increased (HR 8.03, 95% CI 1.80 to 35.86 and HR 11.53, 95% CI 2.88 to 46.25) (Table S5). The results for injections were based on <5 exposed cases. For recent use of progestin-only IUDs and implants, no statistically significant associations were found, compared with no use (Table 3).

Results were similar when (1) adjusting for additional potential confounders (Tables S6–S13), (2) excluding emigration information (Table S14), and (3) using previous and no use as the reference group, instead of no use only (Tables S15–S17). Finally, when

TABLE 2 Risk of any CNS tumor in Scandinavian children according to maternal use of hormonal contraception.

	Any CNS tumor			Malignant CNS tumor	
	Person-years	Cases (IR)*	HR (95% CI)*	Cases (IR)*	HR (95% CI)*
Hormonal contraception					
Any type					
No use	9,773,540	477 (4.94)	1 (reference)	222 (2.35)	1 (reference)
Previous use	16,476,050	751 (4.54)	0.93 (0.82 to 1.05)	331 (2.14)	0.92 (0.77 to 1.09)
Recent use	3,205,940	156 (4.86)	0.99 (0.83 to 1.19)	57 (1.87)	0.80 (0.59 to 1.07)
During pregnancy	322,610	13 (4.01)	0.82 (0.47 to 1.42)	<10 (1.67)	0.71 (0.29 to 1.74)
Combined products					
Oral					
Previous use	15,175,460	701 (4.59)	0.94 (0.83 to 1.06)	301 (2.16)	0.93 (0.77 to 1.11)
Recent use	1,944,760	92 (4.68)	0.96 (0.77 to 1.20)	30 (1.77)	0.76 (0.52 to 1.12)
During pregnancy	242,960	<10 (3.67)	0.75 (0.39 to 1.45)	<5 (1.40)	0.60 (0.19 to 1.87)
Non-oral					
Previous use	1,187,040	48 (4.07)	0.81 (0.60 to 1.10)	24 (1.86)	0.78 (0.51 to 1.20)
Recent use	108,390	<5 (3.71)	0.76 (0.28 to 2.03)	<5 (0.86)	0.37 (0.05 to 2.63)
Progestin-only products					
Oral					
Previous use	4,114,430	203 (5.03)	1.02 (0.86 to 1.21)	110 (2.50)	1.07 (0.84 to 1.35)
Recent use	342,070	12 (3.58)	0.73 (0.41 to 1.30)	5 (1.39)	0.59 (0.24 to 1.44)
During pregnancy	54,170	<15 (3.76)	0.77 (0.19 to 3.08)	<5 (1.76)	0.75 (0.11 to 5.36)
Non-oral					
Previous use	659,620	36 (5.58)	1.11 (0.79 to 1.56)	14 (1.91)	0.80 (0.47 to 1.39)
Recent use	885,310	<55 (5.87)	1.18 (0.88 to 1.59)	<25 (2.29)	0.97 (0.62 to 1.51)
0–1.5 years before pregnancy start	332,960	<25 (6.45)	1.38 (0.89 to 2.15)	<15 (2.88)	1.25 (0.65 to 2.38)
0–1 year before pregnancy start	158,660	<15 (7.74)	1.66 (0.93 to 2.96)	<10 (4.85)	2.10 (1.03 to 4.29)
0–6 months before pregnancy start	37,200	<5 (5.50)	1.18 (0.29 to 4.73)	<5 (5.21)	2.26 (0.56 to 9.09)
0–3 months before pregnancy start	12,030	<5 (8.41)	1.81 (0.26 to 12.83)	<5 (8.05)	3.50 (0.49 to 24.77)
During pregnancy	10,570	<5 (9.60)	1.96 (0.28 to 13.98)	<5 (8.87)	3.78 (0.53 to 27.03)

Note: Maternal use of hormonal contraception was divided into three exposure groups: “No use” of hormonal contraception before birth, “previous use” more than 3 months before the start of pregnancy (injections >1 year, implants >3–5 years and intrauterine devices >3–6 years), and “recent use” 0–3 months before and during pregnancy (injections ≤1 year, implants ≤3–5 years and intrauterine devices ≤3–6 years). When recent use included ≥5 cases, “use during pregnancy” was analyzed separately. For non-oral progestin only contraception, recent use before pregnancy start was divided in four subgroups: Use 0–3 months, 0–6 months, 0–1 year and 0–1.5 year before pregnancy start. Prescriptions filled in the third trimester are not included. When <5 children with a CNS tumor, the count of cases is reported as ‘<5’ in accordance with the Danish Data Protection Law, ensuring patient confidentiality. Similarly, other counts are presented as ‘<n’ to avoid revealing specific numbers below 5. Any CNS tumor (International Classification of Childhood Cancer, third edition [ICCC-3]: IIIa-f), and malignant CNS tumor (ICCC-3 codes: IIIa-f and International Classification of Diseases for Oncology third edition morphology behavior code: 3). *Adjusted for year of birth and country of birth.

Abbreviations: CI, Confidence interval; CNS, Central nervous system; HR, Hazard ratio; IR, Incidence rate (IR per 100,000 person-years).

ensuring a minimum of 3 years of exposure information in the prescription registries before study entry, the results were virtually unchanged (Table S18).

4 | DISCUSSION

In this large cohort including ~3.2 million children, we found no association between maternal use of most hormonal contraceptives and CNS tumor risk. The rarely used progestin-only injection was

associated with an increased malignant CNS tumor risk in children, if used ≤1 year before pregnancy start.

4.1 | Study comparison

Only six studies have examined associations between maternal hormonal contraception use and childhood CNS tumors, of which all, except one,⁹ included only oral contraceptives.^{10–14} Similar to our findings of no association between maternal oral contraceptive use

TABLE 3 Maternal use of non-oral progestin-only contraceptives and risk of CNS tumor in Scandinavian children according to product types and time before pregnancy start.

	Any CNS tumor			Malignant CNS tumor	
	Person-years	Cases (IR)*	HR (95% CI)*	Cases (IR)*	HR (95% CI)*
Hormonal contraception					
Any type					
No use	9,773,540	477 (4.94)	1 (reference)	222 (2.36)	1 (reference)
Injections					
≤1 year before or during pregnancy (recent use)	40,920	<5 (9.88)	2.03 (0.76 to 5.46)	<5 (9.22)	3.95 (1.46 to 10.68)
0–1 year before pregnancy start	38,150	<5 (10.60)	2.18 (0.81 to 5.86)	<5 (9.88)	4.24 (1.57 to 11.46)
0–6 months before pregnancy start	6390	<5 (15.75)	3.24 (0.46 to 23.07)	<5 (14.98)	6.43 (0.90 to 45.96)
0–3 months before pregnancy start	1900	0		0	
During pregnancy	2770	0		0	
Implants					
≤3–5 years before or during pregnancy (recent use)	236,080	<15 (4.34)	0.87 (0.47 to 1.64)	<10 (1.90)	0.80 (0.33 to 1.96)
Intrauterine devices					
≤3–6 years before or during pregnancy (recent use)	608,310	37 (6.15)	1.24 (0.88 to 1.74)	<15 (1.98)	0.84 (0.48 to 1.48)

Note: “No use” refers to no maternal use of hormonal contraception before birth. “Recent use” refers to use of progestin-only injections ≤1 year, implants ≤3–5 years, or intrauterine devices ≤3–6 years before or during pregnancy. Recent use of injections was further divided into “use during pregnancy”, “0–3 months”, “0–6 months”, and “0–1 year before pregnancy start”. Prescriptions filled in the third trimester were not included. When <5 children with a CNS tumor, the count of cases is reported as ‘<5’ in accordance with the Danish Data Protection Law, ensuring patient confidentiality. Similarly, other counts are presented as ‘<n’ to avoid revealing specific numbers below 5. Any CNS tumor (International Classification of Childhood Cancer, third edition (ICCC-3): IIIa-f), and malignant CNS tumor (ICCC-3 codes: IIIa-f and International Classification of Diseases for Oncology third edition morphology behavior code: 3). *Adjusted for year of birth and country of birth.

Abbreviations: CI, Confidence interval; CNS, Central nervous system; HR, Hazard ratio; IR, Incidence rate (IR per 100,000 person-years).

and childhood CNS tumor risk, five studies including 234–1,185,063 children (7–490 exposed cases) also found no association.^{9,11–14} Conversely, one Swedish case-control study¹⁰ (22 exposed cases) found maternal oral contraceptive use <3 months before conception associated with an increased childhood CNS tumor risk (odds ratio 1.6, 95% CI 1.0–2.8). However, the study was based on self-reported contraceptive information, prone to recall bias. Also, older, higher-dose oral contraceptives (types used before 1990) were included compared to the more contemporary types in our study, potentially explaining the different results.

Only one cohort study, based on Danish data (1,185,063 children born 1996–2014; follow-up: 15,335,990 person-years), has assessed the association between maternal non-oral progestin-only contraception use and childhood CNS tumors. This Danish study,⁹ with overlapping data, likewise found maternal progestin-only injection use ≤1 year before pregnancy start to be associated with an increased childhood CNS tumor risk (HR 6.7, 95% CI 2.1 to 21.1). In our study, the association observed for maternal use of progestin-only injections ≤1 year before pregnancy start partly reflects data from the previous Danish cohort study.⁹ However, the present study includes additional follow-up and incorporates data from Sweden and Norway, offering a more comprehensive assessment. The inclusion of multi-country data supports the robustness and generalizability of the findings.

Although no other study has examined the association with injections, the structurally similar progestin “17 α -hydroxyprogesterone caproate” (17-OHPC), injected in early pregnancy to prevent preterm birth, has recently been linked with a 35-fold increased brain cancer risk in children exposed in utero.⁸ Likewise, children born following fertility treatment, commonly involving nonoral administration of progesterone (a natural equivalent of progestin), have been reported to have an increased CNS tumor risk.^{23,24}

4.2 | Biological mechanisms

The International Agency for Research on Cancer classifies progestin-only contraceptives as “possibly carcinogenic to humans” based on animal studies, as studies in humans are limited.²⁵ Progesterone receptors are widely distributed in the brain,²⁶ and high-dose progestin (cyproterone acetate) indicated for hyperandrogenism,²⁷ progestin-only contraceptives²⁸ including progestin injections⁷ and progestin-only menopausal treatments⁶ have all been associated with an increased CNS tumor risk in women, indicating an effect of progestin exposure on CNS tumor development. Although epigenetic changes and an influence on the division, differentiation, and number of susceptible cells have been suggested as mechanisms,²⁹ it remains undetermined what may link maternal hormonal contraceptive use with

malignant childhood CNS tumors. Non-oral progestin-only contraceptives used up to pregnancy have been associated with childhood epilepsy,³⁰ autism,³¹ attention-deficit/hyperactivity disorder,³² and congenital malformations.³³ However, we found no association with the other types of non-oral progestin-only contraception (implants and IUDs). In-utero exposure to the progestins in implants and IUDs is likely more misclassified since these products are prescribed for 3–6 years but may have been removed long before pregnancy. This would lead to estimates towards the null. Contraceptive injections are administered every third month with a high dose (150 mg medroxyprogesterone acetate) and are detectable in the blood up to 200 days.³⁴ Hence, injections given ≤ 1 year before pregnancy potentially expose maturing ovarian follicles and the embryo. However, if the lack of association for other types of progestin is real (i.e., not due to misclassification) and the found association for injections is real, the observed effect may be related to either the higher dose of progestin in injections or the type of progestin (medroxyprogesterone acetate) administered. Medroxyprogesterone acetate in contraceptive injections (linked with CNS tumor risk in women⁷), high-dose cyproterone acetate (indicated for hyperandrogenism and linked with CNS tumor risk in women²⁷), chlormadinone acetate (indicated for contraception and hormone replacement therapy and linked with CNS tumor risk in women)³⁵ and 17-OHPC (used to prevent preterm birth and recently linked with CNS tumor risk in children)⁸ are all 17 α -hydroxyprogesterone derivatives and structurally similar. Recently, the European Medicines Agency (1) suspended the marketing authorizations of 17-OHPC due to inefficient preterm birth prevention and a potential cancer risk in people exposed in utero,³⁶ as well as (2) recommended reducing high-dose cyproterone acetate and chlormadinone acetate use due to meningioma risk in women.^{37,38} Hence, these recent developments and our findings highlight the pressing need for further studies on the effects of 17 α -hydroxyprogesterone derivatives on the health of users and their children, specifically focusing on neurodevelopment, cancer, and CNS tumors. While our findings on the most commonly used hormonal contraceptives are reassuring, the strong association we observed between medroxyprogesterone acetate and malignant CNS tumors in children suggests a need to reassess the safety of this progestin, with potential implications for current contraceptive practices and regulatory policies.

4.3 | Strengths

This study is the largest to date, including high-quality individual-level prospectively collected data of ~3.2 million children from three countries, ensuring temporality and increasing validity, statistical power, and generalizability of the results. Reliable linkage between nationwide registries facilitated long follow-up, with nearly no loss to follow-up and detailed information on all births, redeemed prescriptions of hormonal contraception, childhood cancer diagnoses, and potential confounders. Hormonal contraceptives sold at pharmacies are automatically and digitally registered in the prescription registries, ensuring detailed, complete, and valid exposure information.¹⁷

This enabled assessment of all types of contemporary hormonal contraceptives, in contrast to other studies mainly examining oral contraceptives. Likewise, registration of cancer diagnoses is mandatory by law in all three countries, ensuring high completeness, and 94%–98% of all cancers are microscopically verified.¹⁹

4.4 | Limitations

The study also has some limitations. First, missing information on hormonal contraceptive compliance or usage before the prescription registries started, may have introduced non-differential exposure misclassification, leading to estimates toward the null. Especially for recent use of implants and IUDs, which could have been removed several years before pregnancy. However, ensuring a minimum of 3 years of exposure information in the prescription registries before birth resulted in virtually unchanged findings, suggesting that lack of early exposure data before the start of prescription registries did not substantially impact the findings. Second, despite efforts to account for various potential confounders, unmeasured or residual confounding may still have affected the results. As women using hormonal contraceptives around conception may not expect a pregnancy, confounding from other harmful exposures, for example, ionizing radiation may have affected the results. However, any unmeasured confounding should be associated with both recent injection use and malignant childhood CNS tumors by a HR ≥ 7.36 to reduce the finding to null. Injections are rarely used in Scandinavia³⁹ and known to be used by disabled women,⁴⁰ making children of injection users a potentially selected group. However, to our knowledge, no studies have linked maternal disabilities with childhood CNS tumor risk and the association for recent injection use remained, when using “previous injection use” or “injection use after index birth only” as reference groups, instead of no use. Hence, the association seems unlikely to be explained by indication of contraceptive injection use alone. Third, despite the large cohort, some analyses were constrained by few exposed cases, emphasizing cautious interpretation.

In conclusion, maternal use of almost all hormonal contraceptives was not associated with CNS tumor risk in Scandinavian children. However, the rarely used progestin-only injection (medroxyprogesterone acetate) was associated with increased malignant CNS tumor risk.

AUTHOR CONTRIBUTIONS

Caroline H. Hemmingsen: Conceptualization; software; data curation; methodology; investigation; formal analysis; visualization; writing – original draft; writing – review and editing; project administration. **Susanne K. Kjaer:** Conceptualization; methodology; resources; writing – review and editing; supervision. **Sarah Hjorth:** Software; data curation; writing – review and editing. **Ulrika Nörby:** Resources; writing – review and editing. **Anton Pottegård:** Writing – review and editing. **René Mathiasen:** Writing – review and editing. **Charlotte Wessel Skovlund:** Software; data curation; writing – review and editing. **Maarit K. Leinonen:** Software; data curation; resources; writing – review and editing. **Hedvig Nordeng:** Funding acquisition;

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data is stored on a secure platform at Statistics Denmark and can be accessed after approval. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Ethical approval is not required for register-based research in Denmark, but ethical approvals were obtained in Norway (Regional Committee for Medical Research Ethics in South-Eastern Norway, 2018/142/REK Sør-Øst) and Sweden (Swedish Ethical Review Authority, 2019-00268, 2021-02627).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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