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Maternal use of hormonal contraception and risk of childhood leukemia: A Scandinavian population-based cohort study

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ABSTRACT

Background: Maternal hormonal contraception use has been associated with childhood leukemia risk. However, studies are few and often based on self-reported information.
Methods: Using registry data from Denmark, Norway, and Sweden, we identified 3,183,316 children (born 1996–2018) and followed them from birth until leukemia diagnosis, censoring (death, emigration, other cancer, 20th birthday) or study closure (December 31st, 2017, 2018 or 2020). We estimated hazard ratios (HRs) and 95 % confidence intervals (CIs) for childhood leukemia (any, lymphoid and non-lymphoid) associated with maternal recent use (≤ 3 months before or during pregnancy) or previous use (before recent use) of hormonal contraception overall and by type, compared to no use.
Results: During 29,455,528 person-years, 1701 children developed leukemia (no use: 518, previous use: 974, recent use: 209). Maternal recent use of hormonal contraception was associated with an increased leukemia risk in children (HR 1.22, 95 % CI 1.04–1.44; incidence rate per 1,000,000 person-years [IR] 65), compared to no use (IR 53). The association was strongest for non-lymphoid leukemia (HR 1.69, 95 % CI 1.20–2.37) and mainly driven by the oral combined products, both for any leukemia (HR 1.29, 95 % CI 1.05–1.59) and non-lymphoid leukemia (HR 1.75, 95 % CI 1.17–2.62). Additionally, non-lymphoid leukemia was associated with recent use of the non-oral progestin-only products (HR 2.10, 95 % CI 1.28–3.44).
Conclusions: Although the absolute risk was low, maternal hormonal contraception use up to or during pregnancy was associated with an increased childhood leukemia risk, particularly non-lymphoid leukemia, and mainly driven by oral combined and non-oral progestin-only products.

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1. Introduction

Childhood cancer is a major cause of death in children [1]. The incidence in Scandinavia is among the highest worldwide [1], with leukemia being the most common type [2]. Childhood leukemia is thought to be caused by both genetic and environmental risk factors [3]. However, ionizing radiation is the only well-established environmental risk factor [3].

Hormonal contraception is classified as carcinogenic to humans [4,5], and diethylstilbestrol and 17-α hydroxyprogesterone caproate (synthetic estrogen and progesterone) used to prevent miscarriage and preterm birth, have been associated with increased cancer risk in children exposed *in utero* [6,7]. In 2013, approximately 33–40 % of all Scandinavian women aged 15–49 years used hormonal contraception [8], with ~12 % using it right up to or during pregnancy, making it likely that *in utero* exposure occurs [9].

Maternal hormonal contraception use has been linked with childhood leukemia risk in five case-controls studies [10–14], whereas four reported no association [15–18]. All studies had methodological constraints, most importantly small sample sizes, and potential recall bias, as they were based on self-reported information. Only one cohort study, based on prospectively collected Danish registry data, found an increased leukemia risk after maternal hormonal contraception use, but included only few exposed cases [9]. The present cohort study is based on prospectively collected nationwide registry data from three Scandinavian countries which enable follow-up of more than three million liveborn children. The aim of this large population-based cohort study was to examine the association between maternal hormonal contraception use and childhood leukemia.

2. Materials and methods

The present study is based on information from several population-based nationwide Scandinavian registries, pooled and stored at Statistics Denmark (Supplementary eTable 1). All Scandinavian residents are assigned a unique personal identification number (PIN), enabling individual-level information linkage between registries [19].

From the medical birth registries, which include mandatory and virtually complete information on births, we identified all liveborn children and their mothers, in Denmark (1995–2018), Norway (2007–2013) and Sweden (2007–2018) (Fig. 1) [20]. Children with missing gestational age, PIN, date of birth, maternal PIN, or maternal age were excluded (1.0 %). To attain minimum 1 year of exposure information for all children, Danish children born in 1995 were excluded, leaving a final cohort of 3,183,316 children.

2.1. Hormonal contraception

In Scandinavia, hormonal contraceptives are only available by prescription, except for rare cases. Information on redeemed prescriptions of hormonal contraception (eTable 2) was obtained by linking maternal PIN with the prescription registries. These registries include barcode automatically registered information on all prescriptions filled at pharmacies since 1995 (Denmark), 2004 (Norway), and July 1, 2005 (Sweden) [21]. The data completeness and validity are considered high [21].

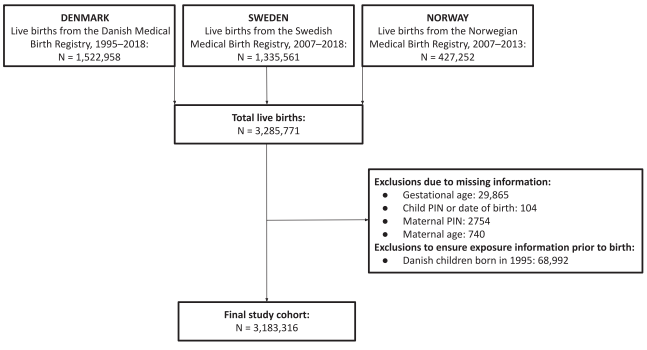

Fig. 1. Identification of the study cohort. Abbreviations: PIN: Personal identification number.

Hormonal contraception use was categorized according to pregnancy start (date of birth–gestational age at birth). Gestational age is primarily determined by ultrasound examination with a high registration completeness and validity (90–98 %) [22]. Most hormonal contraceptives are prescribed for three months. Hence, exposure was categorized as "previous use" (> 3 months before pregnancy start), "recent use" (≤ 3 months before start of or during pregnancy), and "no use" (reference group), excluding redeemed prescriptions in the third trimester (gestational age > 196 days). As some non-oral progestin-only products have different prescription patterns, the categorization was altered accordingly (eTable 3). Exposure was further grouped according to hormonal content (estrogen-progestin combined/progestin-only), and administration route (oral/non-oral).

2.2. Leukemia

Children diagnosed with leukemia (ages 0–19 years) were identified in the cancer registries, established in 1942–1958 with nationwide coverage [23,24]. These registries include information on diagnosis date and cancer type, registered using the International Classification of Diseases for Oncology third edition (ICD-O-3) codes. The information has a high completeness and validity (94–98 % are microscopically verified) [24]. The primary outcome was any leukemia, classified according to the International Classification of Childhood Cancer, third edition (ICCC-3: I) [25]. Secondary outcomes included lymphoid leukemia (Ia) and non-lymphoid leukemia (Ib–Ie).

2.3. Analyses

Cox Proportional Hazards models were used to estimate hazard ratios (HRs) with 95 % confidence intervals (CIs) for any leukemia, lymphoid leukemia, and non-lymphoid leukemia, separately. All children were followed from birth until leukemia diagnosis or censoring (death, emigration, other cancer, 20th birthday, or end of follow-up: December 31, 2017 [Norway], 2018 [Denmark], 2020 [Sweden]).

Leukemia risk was examined according to timing of use (previous/recent), as any maternal hormonal contraception use, and according to regimen (estrogen-progestin combined/progestin-only) and administration route (oral/non-oral), compared with no use. When recent use included ≥ 5 cases, we further examined use "0–3 months before pregnancy start" and "during pregnancy," separately. All analyses were adjusted for year of birth, maternal age, and country a priori. Using complete case analysis and a criteria of > 10 % change in estimate [26,27], birth order and maternal diabetes were tested as possible confounders in the model of any hormonal contraception use and risk of any leukemia. As they did not change the HR > 10 %, they were not included in further analyses. Year of birth and maternal age were included as continuous variables. All analyses accounted for within-cluster correlations between siblings, using a robust variance estimate [28].

Several sensitivity analyses defined a priori were performed. Firstly, to explore differences between countries, associations between any hormonal contraception and any leukemia were analyzed separately for each country. Secondly, to examine whether results differed for subtypes of non-lymphoid leukemia, analyses were conducted for "acute myeloid leukemia" and "other and unspecified types of leukemia", separately. Thirdly, to further explore potential bias, in complete case analyses, we adjusted for confounders not available for the full cohort (maternal infertility, smoking, origin, body mass index, paternal age, parental cancer, and education) and further applied "previous use" as reference

group instead of "no use". Fifth, as there was no emigration information in Swedish data, we explored whether excluding censoring for emigration in Danish and Norwegian data affected associations. Post hoc, for the association between recent use of any hormonal contraception and non-lymphoid leukemia, we calculated numbers needed to harm and the E-value [29]. Post hoc analyses were also carried out for specific types of non-oral progestin-only contraception and with "previous use" divided into different time-intervals. Lastly, post hoc age-stratified analyses (< 1, 1–5, 6–10, and 11–19 years) for any hormonal contraceptive use and lymphoid and non-lymphoid leukemia were carried out.

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) (eTable 4). STATA 16.1 was used for all analyses.

3. Results

The cohort included 3,183,316 Scandinavian live-born children (44.8 % Danish, 13.3 % Norwegian, and 42.0 % Swedish), followed from birth (median: 8.6 years); resulting in 29,455,528 person-years. During follow-up, 1701 children were diagnosed with leukemia; 1330 with lymphoid leukemia, and 371 with non-lymphoid leukemia. Over half (59.0 %) of the cohort were children of mothers who previously used hormonal contraception, 11.7 % used it recently, and 29.2 % had not used it before birth (Table 1).

The HR for any childhood leukemia was 1.22 for recent use (95 % CI 1.04–1.44) and 1.09 for previous use of any hormonal contraception (95 % CI 0.97–1.22), compared with no use (Table 2). The association with recent use was mainly observed for non-lymphoid leukemia with a HR of 1.69 (95 % CI 1.20–2.37; E-value = 2.77), corresponding to one additional child diagnosed per 142,857 exposed person-years (numbers needed to harm). The HR increased further for exposure during pregnancy (HR 2.22, 95 % CI 1.03–4.80). For lymphoid leukemia, no statistically significant associations were found.

For any leukemia, maternal recent use of oral combined products was associated with an increased HR of 1.29 (95 % CI 1.05–1.59), compared with no use (Table 3). The increased risk for the combined oral products was mainly observed for non-lymphoid leukemia, where the HR for recent use was 1.75 (95 % CI 1.17–2.62) which increased to 2.53 (95 % CI 1.11–5.78; < 10 cases) for use during pregnancy. Also, non-lymphoid leukemia was associated with previous use of oral progestin-only products (HR 1.43, 95% CI 1.03–2.01). However, when previous use was further subdivided into > 3–6, > 6–12, and > 12 months before pregnancy start, only use close to pregnancy start (> 3–6 months before pregnancy start) was associated with an increased non-lymphoid leukemia risk (HR 1.93, 95 % CI 1.00–3.74), compared to no use (eTable 5). Also, recent use of non-oral progestin-only products was associated with non-lymphoid leukemia (HR 2.10, 95 % CI 1.28–3.44), compared to no use (Table 3). This association was mainly driven by implants (HR 2.78, 95 % CI 1.20–6.46) and intrauterine devices (HR 2.03, 95 % CI 1.14–3.60) (Table 4).

For the association between recent use of any hormonal contraception and leukemia, country-specific estimates were only increased for Denmark and Sweden (eFigure 1). However, the confidence intervals overlapped with the Norwegian estimate, which was based on the lowest number of children. Separate estimates for "acute myeloid leukemia" and "other and unspecified types of leukemia" were similar to that of non-lymphoid leukemia (eTable 6), and results remained virtually unchanged when adjusted for additional potential confounders or leaving out censoring at emigration (eTables 7–14). Using "previous use" instead of "no use" as reference group did not substantially alter the main findings; however, estimates were attenuated and only the association between recent use and non-lymphoid leukemia remained statistically significant (eTable 15). Age-stratified analyses showed no consistent pattern with overlapping confidence intervals due to few number of exposed cases (eTable 16).

Table 1
Characteristics of the study cohort by maternal hormonal contraception use.

	Hormonal contraception use		
	No use	Previous use	Recent use
Total — no. (%)	930,934 (29.2)	1,879,345 (59.0)	373,037 (11.7)
Characteristics			
Birth country — 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. (%)[a]			
Yes	6069/930,934 (0.7)	12,027/1,879,345 (0.6)	2425/373,037 (0.7)

"No use" refers to no maternal use of hormonal contraception before birth. "Previous use" refers to use more than 3 months before the start of pregnancy. "Recent use" refers to use 0–3 months before or during pregnancy. Except for few products with a different prescription pattern. Prescriptions redeemed in the third trimester were excluded.
Abbreviations: no.: Number of children, IQR: Inter-quartile range, yr: Year(s).
[a] 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*.

4. Discussion

In this large Scandinavian registry-based study of ~3.2 million children, maternal hormonal contraception use up to or during pregnancy was associated with an increased childhood leukemia risk—mainly non-lymphoid leukemia—and strongest for use during pregnancy. The association was largely driven by the commonly used oral combined products but was also observed for oral and non-oral progestin-only products.

In accordance with our findings, six other studies also found an increased leukemia risk in children of women using hormonal contraception before birth [9–14], in contrast to four studies reporting no association [15–18]. The observed association in our study was primarily seen for non-lymphoid leukemia. Only four studies have investigated non-lymphoid leukemia specifically [9,10,16,18]. The largest was a Danish registry-based cohort study—somewhat overlapping with our data—finding a similarly increased non-lymphoid leukemia risk [9]. In contrast, three smaller case-control studies with self-reported exposure information reported no statistically significant associations between maternal hormonal contraceptive use and non-lymphoid leukemia [10,

Table 2
HRs (95% CIs) for childhood leukemia, according to maternal use of any hormonal contraception.

Hormonal contraception use	Any leukemia			Lymphoid leukemia		Non-lymphoid leukemia	
	Person-years	Cases (IR)[b]	HR (95% CI)[c]	Cases (IR)[b]	HR (95% CI)[c]	Cases (IR)[b]	HR (95% CI)[c]
No use	9,773,540	518 (53)	1 (Reference)	416 (43)	1 (Reference)	102 (10)	1 (Reference)
Previous use	16,476,050	974 (59)	1.09 (0.97–1.22)	760 (46)	1.05 (0.93–1.20)	214 (13)	1.24 (0.97–1.60)
Recent use	3,205,940	209 (65)	1.22 (1.04–1.44)	154 (48)	1.11 (0.92–1.35)	55 (17)	1.69 (1.20–2.37)
Before pregnancy start	2,883,330	189 (66)	1.22 (1.03–1.45)	141 (49)	1.12 (0.92–1.37)	48 (17)	1.63 (1.14–2.33)
During pregnancy	322,610	20 (62)	1.23 (0.79–1.93)	13 (40)	0.99 (0.57–1.73)	7 (22)	2.22 (1.03–4.80)

"No use" refers to no maternal use of hormonal contraception before birth. "Previous use" refers to use more than 3 months before the start of pregnancy. "Recent use" refers to use 0–3 months before or during pregnancy. Except for few products with a different prescription pattern. Prescriptions redeemed in the third trimester were excluded.
Lymphoid leukemia: International Classification of Childhood Cancer third edition (ICCC-3) code Ia. Non-lymphoid leukemia: ICCC-3 codes Ib–Ie.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[b] IR: Crude incidence rates per 1,000,000.
[c] Adjusted for year of birth, maternal age, and country.

Table 3
HRs (95% CIs) for childhood leukemia, according to maternal use of specific types of hormonal contraception.

Product type	Any leukemia			Lymphoid leukemia		Non-lymphoid leukemia	
	Person-years	Cases (IR)[d]	HR (95% CI)[e]	Cases (IR)[d]	HR (95% CI)[e]	Cases (IR)[d]	HR (95% CI)[e]
Any hormonal contraception							
No use	9,773,540	518 (53)	1 (Reference)	416 (43)	1 (Reference)	102 (10)	1 (Reference)
Combined products							
Oral							
Previous use	15,175,460	900 (59)	1.11 (0.99–1.25)	701 (46)	1.08 (0.94–1.23)	199 (13)	1.24 (0.96–1.61)
Recent use	1,944,760	122 (63)	1.29 (1.05–1.59)	< 90	1.18 (0.93–1.50)	< 35	1.75 (1.17–2.62)
0–3 months before pregnancy start	1,701,800	< 110	1.31 (1.05–1.62)	< 85	1.22 (0.95–1.57)	< 30	1.64 (1.06–2.54)
During pregnancy	242,960	< 15	1.20 (0.70–2.05)	< 10	0.86 (0.43–1.74)	< 10	2.53 (1.11–5.78)
Non-oral							
Previous use	1,187,040	85 (72)	1.15 (0.90–1.45)	68 (57)	1.11 (0.85–1.44)	17 (14)	1.31 (0.77–2.23)
Recent use	108,390	< 10	0.97 (0.43–2.16)	< 10	1.16 (0.52–2.60)	0	.
0–3 months before pregnancy start	92,570	< 10	0.94 (0.39–2.27)	< 10	1.13 (0.47–2.73)	.	.
During pregnancy	15,820	< 5	1.13 (0.16–8.03)	< 5	1.35 (0.19–9.65)	.	.
Progestin-only products							
Oral							
Previous use	4,114,430	253 (61)	1.00 (0.86–1.17)	191 (46)	0.91 (0.76–1.09)	62 (15)	1.43 (1.03–2.01)
Recent use	342,070	19 (56)	0.97 (0.61–1.54)	< 20	1.05 (0.64–1.71)	< 5	0.59 (0.15–2.40)
0–3 months before pregnancy start	287,900	< 20	0.91 (0.54–1.52)	< 15	1.02 (0.60–1.75)	.	.
During pregnancy	54,170	< 5	1.31 (0.49–3.50)	< 5	1.18 (0.38–3.69)	.	.
Non-oral							
Previous use	659,620	42 (64)	1.00 (0.72–1.37)	37 (56)	1.05 (0.75–1.49)	5 (8)	0.70 (0.28–1.73)
Recent use	885,310	< 70	1.21 (0.93–1.57)	< 50	1.02 (0.75–1.39)	< 25	2.10 (1.28–3.44)
Before pregnancy start	874,740	< 70	1.21 (0.93–1.57)	< 50	1.01 (0.74–1.38)	< 25	2.13 (1.30–3.48)
During pregnancy	10,570	< 5	1.65 (0.23–11.71)	< 5	1.99 (0.28–14.17)	0	.

"No use" refers to no maternal use of hormonal contraception before birth. "Previous use" refers to use more than 3 months before the start of pregnancy. "Recent use" refers to use 0–3 months before or during pregnancy. Except for few non-oral progestin-only products with a different prescription pattern (previous use of injections > 1 year, implants > 3–5 years and intrauterine devices > 3–6 years before pregnancy start and recent use of injections ≤ 1 year, implants ≤ 3–5 years and intrauterine devices ≤ 3–6 years before or during pregnancy). If recent use contained ≥ 5 cases, it was further divided into use "before pregnancy start" and "during pregnancy", separately. Prescriptions redeemed in the third trimester were excluded.
When the number of children with leukemia was less than 5, the count is presented as '< 5′ to maintain patient confidentiality according to the Danish Data Protection Law. Other numbers may be reported as '< n′ to prevent the disclosure of any number less than 5. Likewise, no IRs are presented for masked number of cases.
Lymphoid leukemia: International Classification of Childhood Cancer third edition (ICCC-3) code Ia. Non-lymphoid leukemia: ICCC-3 codes Ib–Ie.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[d] IR: Crude incidence rates per 1,000,000.
[e] Adjusted for year of birth, maternal age, and country.

16,18]. We found that the increased risk was mainly driven by recent use of the most commonly used oral combined contraceptives and contemporary non-oral progestin-only products. Five studies (exposed cases n = 36–562) likewise, observed an association between maternal oral contraception use and leukemia risk [9–11,13,14], whereas four other smaller studies (exposed cases n = 12–114) found no association [15–18]. Only two studies have examined maternal use of non-oral progestin-only products, finding no association with childhood leukemia [9,16]. The studies were, however, limited by few exposed cases (n < 9), and only one [9] included hormonal intrauterine devices, besides implants and injections.

The varying exposure categorizations (e.g., oral contraceptives versus any hormonal contraceptives) and time frames (e.g., ever use before pregnancy versus use during pregnancy only) make comparisons between studies difficult. Also, as childhood cancer is rare, studies were generally limited by few exposed cases, potentially leading to null findings. Additionally, all studies, except one [9], were based on self-reported exposure data, prone to recall bias.

Combined hormonal contraceptives are classified as "carcinogenic to humans" and progestogens as "possibly carcinogenic to humans," based on animal studies [4]. As opposed to exposure in adulthood, where sex hormones are considered mainly promoters of cancer [30], *in utero* exposure to diethylstilbestrol initiates a rare cancer in girls and young women [6]. Similarly, *in utero* exposure to synthetic progestogen used to

Table 4
HRs (95% CIs) for childhood non-lymphoid leukemia, according to maternal use of non-oral progestin-only contraceptives.

Hormonal contraception	Non-lymphoid leukemia		
	Person-years	Cases (IR)[f]	HR (95% CI)[g]
No use of any type	9,773,540	102 (10)	1 (Reference)
Recent use of:			
Injections	40,920	0	.
Implants	236,080	< 10	2.78 (1.20–6.46)
Intrauterine devices	608,310	14 (23)	2.03 (1.14–3.60)

"No use" refers to no maternal use of hormonal contraception before birth. "Recent use" refers to use of non-oral progestin-only contraceptives before and during pregnancy (injections ≤ 1 year, implants ≤ 3–5 years and intrauterine devices ≤ 3–6 years). Prescriptions redeemed in the third trimester were excluded.
When the number of children with leukemia was less than 5, the count is presented as '< 5′ to maintain patient confidentiality according to the Danish Data Protection Law. Other numbers may be reported as '< n′ to prevent the disclosure of any number less than 5. Likewise, no IRs are presented for masked number of cases.
Non-lymphoid leukemia: International Classification of Childhood Cancer third edition codes Ib–Ie.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[f] IR: Crude incidence rates per 1,000,000.
[g] Adjusted for year of birth, maternal age, and country.

prevent preterm birth has also been linked with childhood cancer [7]. However, the underlying mechanisms remain unclear. We found that hormonal contraception use up to and especially during pregnancy was associated with leukemia risk, indicating that timing of use is important. Around conception, the human genome undergoes extensive epigenetic changes including global DNA demethylation and remethylation [31], a process possibly modified by hormones, as they affect enzymes part of epigenetic marking [32]. That epigenetic changes may explain the found associations, are further supported by findings of epigenetic alterations caused by *in utero* exposure to ethinyl estradiol (synthetic estrogen) being associated with cancer in animals [33], and that epigenetic changes are linked with leukemia in humans [3,34]. However, topoisomerase II inhibitors, including estrogen substances, have also been proposed as a possible mechanism between maternal hormonal contraceptive use and childhood leukemia risk [35]. Nevertheless, even if the found associations are causal, the absolute risk increase remains low, as childhood leukemia is rare.

4.1. Strengths and limitations

The study is the largest to date including ~3.2 million children with virtually complete follow-up. The population-based nationwide registries provided continuously updated, independently, and prospectively collected information for the entire cohort, minimizing misclassification, selection, and recall bias. The exposure and outcome completeness and validity are considered high, as all filled hormonal contraceptive prescriptions are electronically registered in the prescription registries [21], and cancer registration is mandatory by law with microscopic verification of virtually all cases [24]. The large number of cases and long follow-up increased statistical precision and generalizability of the results, and enabled us to study rare exposure-outcome combinations and conduct country-specific analyses. Also, compared with a previous study on Danish data exclusively [9], we included a larger cohort of Danish children (birth year: 1996–2014 versus 1996–2018) with longer follow-up (follow-up end: 2014 versus 2018).

Our study also has limitations. First, we had no information on hormonal contraception non-adherence. Hence, redeemed prescriptions may have been unused or used at a different time. Also, due to lack of exposure information before the prescription registries were established, some children might have been categorized in "no use" instead of "previous use". Both factors could lead to non-differential exposure misclassification, potentially leading to results towards the null. Second, as hormonal contraception is commonly used in Scandinavia [8], maternal "no use" may constitute a selected group of children with different characteristics, compared to those using hormonal contraception. Should these characteristics also be related to leukemia risk, this may have affected our results. However, when using the reference group "previous use" instead of "no use", estimates were slightly attenuated but remained statistically significantly increased for the association between recent hormonal contraception use and non-lymphoid leukemia, indicating that this finding cannot be explained with confounding by reference group alone. Third, despite the ability to adjust for several potential confounders, including year of birth, country, birth order, parental cancer, education, and age as well as maternal infertility, smoking, origin, and body mass index we cannot rule out residual or unknown confounding. Hormonal contraception use during pregnancy is likely related to an unplanned pregnancy, which may differ from other pregnancies in risk-related behavior, including maternal smoking and alcohol consumption. However, except for ionizing radiation, no maternal behaviors related to unplanned pregnancy are known risk factors for childhood leukemia, and adjusting for smoking (a proxy for alcohol use) did not change the results. For ionizing radiation in an unplanned pregnancy to explain the found association, we would expect to see an increased risk for both lymphoid and non-lymphoid leukemia, which was not the case. Furthermore, any unknown confounder/set of confounders would have to be associated with both recent hormonal contraception use and non-lymphoid leukemia by a HR ≥ 2.77 to explain this association. Factors of this magnitude in this field are improbable [29]. Fourth, although this is the largest study to date, results for some hormonal contraceptives were based on few exposed cases and should be interpreted with caution.

5. Conclusion

This Scandinavian cohort study found an association between maternal hormonal contraception use up to or during pregnancy and childhood leukemia, particularly non-lymphoid leukemia. The association was mainly linked to oral combined and non-oral progestin-only products, though the absolute risk remains low.

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CRediT authorship contribution statement

Caroline H. Hemmingsen: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Susanne K. Kjaer**: Writing – review & editing, Supervision, Resources, Methodology, Conceptualization. **Sarah Hjorth**: Writing – review & editing, Software, Data curation. **Ulrika Nörby**: Writing – review & editing, Resources. **Anne Broe**: Writing – review & editing. **Anton Pottegård**: Writing – review & editing. **Justine Bénévent**: Writing – review & editing. **Kjeld Schmiegelow**: Writing – review & editing. **Charlotte Wessel Skovlund**: Writing – review & editing, Software, Data curation. **Maarit K. Leinonen**: Writing – review & editing, Software, Data curation. **Hedvig Nordeng**: Writing – review & editing, Resources, Funding acquisition. **Lina S. Mørch**: Writing – review & editing,

Supervision, Methodology, Conceptualization. **Marie Hargreave**: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115168.

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