

Supplementary Materials: In Utero Exposure to Hormonal Contraception and Mortality in Offspring with and without Cancer: A Nationwide Cohort Study

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Table S1. Mortality in children who develop any type of cancer, leukemia or CNS tumor, according to maternal use of specific types of hormonal contraception.

	Children with any type of cancers				Children with leukemia				Children with CNS-tumors			
	Number of children	Number of deaths	HR (95% CI)*	Number of children	Number of deaths	HR (95% CI)*	Number of children	Number of deaths	Number of children	Number of deaths	HR (95% CI)*	Number of children
Any type												
Previous use	1 864	225	1 (reference)	548	52	1 (reference)	446	84	1 (reference)			
Combined contraceptives												
<i>Oral contraception</i>												
Recent use	251	36	1.17 (0.82-1.67)	76	11	1.34 (0.67-2.70)	63	8	0.65 (0.32-1.33)			
During pregnancy	35	6	1.36 (0.62-2.94)	10	<5 [‡]	2.78 (0.97-7.97)	8	<5 [‡]	0.76 (0.10-5.67)			
Progestin-only contraceptives												
<i>Oral contraception</i>												
During pregnancy	6	<5 [‡]	1.48 (0.23-9.54)	<5 [‡]	<5 [‡]	8.00 (1.44-44.39)						
<i>Non-oral contraceptives</i>												
Recent use	1864	7	1.51 (0.73-3.09)	8	<5 [‡]	1.66 (0.25-10.80)	15	<5 [‡]	1.52 (0.57-4.07)			

Exposure categories with zero number of deaths are not shown.

During refers to use during pregnancy.

Recent use refers to use 3 months or less before pregnancy start (except for non-oral progestin only products [for further specification, see the method section]).

Previous use refers to use more than 3 months before pregnancy start (except for non-oral progestin only products [for further specification, see the method section]).

*Stratified by year of birth (categories: 1996-1999, 2000-2004, 2005-2009, 2010-2014, 2015-2018) and maternal age at birth (categories: <28, 28-31, 32-35, >35).

‡Exact number <5 or equivalent is blinded according to the interpretation of General Data Protection Regulation by Statistics Denmark.

Of note, some HRs are not shown when estimation was not possible due to few observations.

HR = Hazard ratio.

Table S2. ATC-codes and classification of hormonal contraception.

Type of hormonal contraception	ATC-code(s)
Combined contraception	
<i>Oral</i>	G03AA01, G03AA03, G03AA05, G03AA07, G03AA09-12, G03AA14, G03AA16 G03AB03-06, G03AB8 G03HB01
<i>Non-oral</i>	G02BB01 G03AA13
Progestin-only contraception	
<i>Oral</i>	G03AC01-03 G03AC09
<i>Non-oral</i>	G02BA03, G03DA02* G03AC06, G03AC08
Emergency contraception	G03AD01, G03AD

ATC = anatomical therapeutic chemical.

*Only drugs with the trade name Depo-Provera.

Table S3. Perinatal characteristics of the study cohort.

Perinatal factors	No. (%)			
	During pregnancy	Recent use	Previous use	No use
Number of children	17 513 (1.2) ^a	154 381 (10.8) ^b	952 800 (66.8) ^c	301 698 (21.2)
<i>Cesarean delivery</i>	3 068 (17.5)	29 020 (18.8)	197 227 (20.7)	55 622 (18.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>Birth weight (g)</i>				
<2500	970 (5.5)	7 594 (4.9)	48 264 (5.1)	16 012 (5.3)
2500-4500	15 950 (91.1)	141 205 (91.5)	871 763 (91.5)	274 446 (91.0)
>4500	487 (2.8)	4 847 (3.1)	28 054 (2.9)	9 250 (3.1)
Missing	106 (0.6)	735 (0.5)	4 719 (0.5)	1 990 (0.7)
Median (IQR)	3490 (3110-3835)	3520 (3170-3870)	3510 (3156-3860)	3500 (3120-3850)
<i>Gestational length (wk)</i>				
<37	1 233 (7.0)	9 894 (6.4)	64 405 (6.8)	19 366 (6.4)
37-42	16 233 (92.7)	144 192 (93.4)	887 207 (93.1)	281 125 (93.2)
>42	47 (0.3)	295 (0.2)	1 188 (0.1)	1 207 (0.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Median (IQR)	40 (38-40)	40 (39-41)	40 (38-40)	40 (39-41)
<i>Multiplicity</i>	395 (2.3)	5 502 (3.6)	37 807 (4.0)	13 618 (4.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>Down syndrome^d</i>	14 (0.1)	85 (0.05)	596 (0.1)	338 (0.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>Neurofibromatosis^e</i>	11 (0.1)	71 (0.05)	390 (0.04)	141 (0.05)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>Other congenital disorders^f</i>	1 885 (10.8)	16 485 (10.7)	101 972 (10.7)	32 737 (10.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

^aDuring refers to use during pregnancy.^bRecent use refers to use 3 months or less before pregnancy start (except for non-oral progestin only products [for further specification, see the method section]).^cPrevious use refers to use more than 3 months before pregnancy start (except for non-oral progestin only products [for further specification, see the method section]).^dICD-10 code Q90*^eICD-10 code Q85*^fICD-10 code Q00-Q99* (excluding codes Q85* and Q90*).

Abbreviations: BMI = body mass index. wk = weeks. g = grams. No = number. IQR = interquartile range, ICD = International Classification of Diseases (ICD) codes version ICD-10.

Table S4. Characteristics of children who developed any type of cancer.

Characteristics	No. (%)			
	During pregnancy	Recent use	Previous use	No use
No. of children with any type of cancer	43 (1.4) ^a	304 (10.0) ^b	1 864 (61.6) ^c	816 (27.0)
Child characteristics				
<i>Year of birth</i>				
1996-1999	14 (32.6)	98 (32.2)	489 (26.2)	565 (69.2)
2000-2004	17 (40.5)	88 (29.0)	589 (31.6)	146 (17.9)
2005-2009	<10 (<15) [£]	70 (23.3)	451 (24.2)	76 (9.3)
2010-2014	6 (14.3)	37 (12.3)	269 (14.6)	24 (2.9)
2015-2018	<5 (<5) [£]	11 (3.7)	66 (3.6)	5 (0.6)
Median (IQR)	2002 (2000-2007)	2003 (1999-2009)	2004 (2000-2009)	1998 (1997-2002)
<i>Sex</i>				
Male	28 (65.1)	165 (54.3)	978 (52.5)	434 (53.2)
Female	15 (34.9)	139 (45.7)	879 (47.2)	381 (46.7)
Missing	0 (0.0)	0 (0.0)	7 (0.4)	<5 (<1) [£]
<i>Birth order</i>				
First	19 (44.2)	141 (46.4)	851 (46.7)	295 (36.2)
Second or higher	24 (55.8)	163 (53.6)	1 014 (54.4)	519 (63.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	<5 (<1) [£]
Parental characteristics				
<i>Origin (mother)</i>				
Danish or descendant of immigrant ^d	<40 (<95) [£]	290 (95.4)	1 746 (94.4)	620 (76.0)
Immigrant	<5 (<10) [£]	14 (4.6)	104 (5.6)	196 (24.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>BMI[£] (mother)</i>				
<25	8 (19.1)	80 (26.7)	612 (32.8)	79 (9.7)
25-30	<10 (<20) [£]	47 (15.7)	227 (12.2)	29 (3.6)
31-35	<5 (<5) [£]	9 (3.0)	93 (5.0)	13 (1.6)
>35	<5 (<5) [£]	5 (1.7)	52 (2.8)	6 (0.7)
Missing	25 (58.1)	159 (53)	880 (47.2)	689 (84.4)
<i>Maternal education^e</i>				
Basic	14 (32.6)	69 (22.7)	375 (20.1)	179 (21.9)
Vocational	22 (51.2)	136 (44.7)	796 (42.7)	360 (44.1)
Higher	7 (16.3)	96 (31.6)	667 (35.8)	200 (24.5)
Missing	0 (0.0)	<5 (<5) [£]	26 (1.4)	77 (9.4)
<i>Paternal education^e</i>				
Basic	10 (23.3)	60 (19.7)	377 (20.2)	171 (21.0)
Vocational	22 (51.2)	170 (55.9)	903 (48.4)	362 (44.4)
Higher	6 (14.0)	68 (22.4)	531 (28.5)	211 (25.9)
Missing	5 (11.6)	6 (2)	53 (2.8)	72 (8.8)
<i>Maternal age at birth (y)</i>				
<28	21 (48.8)	131 (43.1)	573 (30.7)	209 (25.6)

28-31	11 (25.6)	100 (32.9)	650 (34.9)	263 (32.2)
31-35	<10 (<20) [‡]	49 (16.1)	419 (22.5)	198 (24.3)
>35	<5 (<10) [‡]	24 (7.9)	222 (11.9)	146 (17.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Median (IQR)	28 (25-32)	28 (25-31)	30 (27-33)	31 (27-34)
<i>Paternal age at birth (y)</i>				
<28	10 (23.3)	84 (27.6)	351 (18.8)	112 (13.7)
28-31	14 (32.6)	103 (33.8)	573 (30.7)	189 (23.2)
31-35	10 (23.3)	59 (19.4)	491 (26.3)	231 (28.3)
>35	<10 (<15) [‡]	57 (18.8)	435 (23.3)	270 (33.1)
Missing	<5 (<10) [‡]	<5 (<5) [‡]	14 (0.8)	14 (1.7)
Median (IQR)	31 (27-33)	30 (27-34)	32 (28-35)	33 (30-37)
<i>Maternal smoking^f*</i>				
Missing	6 (14.0)	35 (11.5)	139 (7.5)	181 (22.2)
<i>Maternal infertility^g</i>				
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

^aDuring refers to use during pregnancy

^bRecent use refers to use 3 months or less before pregnancy start or during pregnancy (except for non-oral progestin only products (for further specification, see the method section)).

^cPrevious use refers to use more than 3 months before pregnancy start (except for non-oral progestin only products (for further specification, see the method section)).

^dDefined as having 2 parents without Danish citizenship and who were not born in Denmark.

^eHighest attained education before birth of the child. Basic indicates mandatory school grades 9-10; vocational, secondary school and vocational education; higher, short-, medium-, and long-term higher education.

^fMaternal smoking measured in the first trimester of pregnancy. *Information on maternal smoking was only available from 1998 onwards.

^gICD-8 code 628 and ICD-10 code N97.

^hInformation on BMI was only available from 2004 onwards.

ⁱExact number <5 or equivalent is blinded according the interpretation of General Data Protection Regulation by Statistics Denmark.

Abbreviations: BMI = body mass index. wk = weeks. No = number. IQR = interquartile range, ICD = International Classification of Diseases (ICD) codes version ICD-10.

Table S5. Characteristics of children who developed leukemia.

Characteristics	No. (%)			
	During pregnancy	Recent use	Previous use	No use
No. of children with leukemia	13 (1.6) ^a	86 (10.5) ^b	548 (66.6) ^c	176 (21.4)
Child characteristics				
<i>Year of birth</i>				
1996-1999	5 (38.5)	30 (34.9)	118 (21.5)	102 (58.0)
2000-2004	5 (38.5)	22 (25.6)	180 (32.9)	37 (21.0)
2005-2009	<5 (<5) [£]	22 (25.6)	141 (25.7)	31 (17.6)
2010-2014	<5 (<25) [£]	<15 (<15) [£]	89 (16.2)	6 (3.4)
2015-2018	0 (0.0)	<5 (<5) [£]	20 (3.7)	0 (0.0)
Median (IQR)	2001 (2000-2005)	2004 (1999-2008)	2005 (2001-2009)	2000 (1997-2004)
<i>Sex</i>				
Male	6 (46.2)	47 (54.7)	278 (50.7)	109 (61.9)
Female	7 (53.9)	39 (45.4)	268 (48.9)	67 (38.1)
Missing	0 (0.0)	0 (0.0)	<5 (<1) [£]	0 (0.0)
<i>Birth order</i>				
First	5 (38.5)	37 (43.0)	254 (46.4)	63 (35.8)
Second or higher	8 (61.5)	49 (57.0)	294 (53.7)	113 (64.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parental characteristics				
<i>Origin (mother)</i>				
Danish or descendant of immigrant ^d	<15 (<95) [£]	83 (96.5)	514 (93.8)	128 (72.7)
Immigrant ^d	<5 (<10) [£]	<5 (<5) [£]	34 (6.2)	48 (27.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>BMI[£] (mother)</i>				
<25	<5 (<25) [£]	25 (29.1)	202 (36.9)	25 (14.2)
25-30	<5 (<10) [£]	12 (14.0)	69 (12.6)	10 (5.7)
31-35	<5 (<10) [£]	<10 (<10) [£]	28 (5.1)	<10 (<5) [£]
>35	0 (0)	<5 (<5) [£]	14 (2.6)	<5 (<5) [£]
Missing	8 (61.5)	42 (48.8)	235 (42.9)	132 (75.0)
<i>Maternal education^e</i>				
Basic	<5 (<25) [£]	17 (19.8)	105 (19.2)	33 (18.8)
Vocational	<10 (<60) [£]	46 (53.5)	230 (43.0)	90 (51.1)
Higher	<5 (<25) [£]	22 (25.6)	206 (37.6)	39 (22.2)
Missing	0 (0.0)	<5 (<5) [£]	7 (1.3)	14 (8.0)
<i>Paternal education^e</i>				
Basic	<5 (<10) [£]	10 (11.6)	104 (19.0)	29 (16.5)
Vocational	8 (61.5)	53 (61.6)	274 (50.0)	91 (51.7)
Higher	<5 (<20) [£]	21 (24.4)	157 (28.7)	38 (21.6)
Missing	<5 (<20) [£]	<5 (<5) [£]	13 (2.4)	18 (10.2)
<i>Maternal age at birth (y)</i>				
<28	5 (38.5)	32 (37.2)	160 (29.2)	42 (23.9)

28-31	<5 (<25) [£]	29 (33.7)	179 (32.7)	47 (26.7)
31-35	<5 (<25) [£]	20 (23.3)	136 (24.8)	38 (21.6)
>35	<5 (<20) [£]	5 (5.8)	73 (13.3)	49 (27.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Median (IQR)	31 (27-32)	29 (25-32)	30 (27-33)	31 (28-36)
<i>Paternal age at birth (y)</i>				
<28	<5 (<20) [£]	23 (26.7)	94 (17.2)	16 (9.1)
28-31	<5 (<20) [£]	28 (32.6)	162 (29.6)	33 (18.8)
31-35	<5 (<35) [£]	16 (18.6)	143 (26.1)	51 (29.0)
>35	<5 (<35) [£]	19 (22.1)	145 (26.5)	73 (41.5)
Missing	<5 (<10) [£]	0 (0)	<5 (<1) [£]	<5 (<2) [£]
Median (IQR)	33 (30-37)	30 (27-34)	32 (29-36)	34 (31-39)
<i>Maternal smoking^{f*}</i>				
	<5 (<20) [£]	15 (17.4)	70 (12.8)	23 (13.1)
Missing	<5 (<25) [£]	8 (9.3)	31 (5.7)	29 (16.5)
<i>Maternal infertility^g</i>				
	0 (0.0)	<5 (<5) [£]	47 (8.6)	37 (21.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

^aDuring refers to use during pregnancy

^bRecent use refers to use 3 months or less before pregnancy start or during pregnancy (except for non-oral progestin only products (for further specification, see the method section)).

^cPrevious use refers to use more than 3 months before pregnancy start (except for non-oral progestin only products (for further specification, see the method section)).

^dDefined as having 2 parents without Danish citizenship and who were not born in Denmark.

^eHighest attained education before birth of the child. Basic indicates mandatory school grades 9-10; vocational, secondary school and vocational education; higher, short-, medium-, and long-term higher education.

^fMaternal smoking measured in the first trimester of pregnancy. ^{*}Information on maternal smoking was only available from 1998 onwards.

^gICD-8 code 628 and ICD-10 code N97.

^hInformation on BMI was only available from 2004 onwards.

[£]Exact number <5 or equivalent is blinded according the interpretation of General Data Protection Regulation by Statistics Denmark.

Abbreviations: BMI = body mass index. wk = weeks. No = number. IQR = interquartile range, ICD = International Classification of Diseases (ICD) codes version ICD-10.

Table S6. Characteristics of children who developed a CNS-tumor.

Characteristics	No. (%)			
	During pregnancy	Recent use	Previous use	No use
No. of children with CNS-tumors	9 (1.2) ^a	81 (10.7) ^b	446 (58.9) ^c	221 (29.2)
Child characteristics				
<i>Year of birth</i>				
1996-1999	<5 (<25) [£]	20 (24.7)	115 (25.8)	159 (72.0)
2000-2004	6 (66.7)	23 (28.4)	153 (34.3)	38 (17.2)
2005-2009	0 (0.0)	23 (28.4)	110 (24.7)	19 (8.6)
2010-2014	0 (0.0)	<15 (<15) [£]	51 (11.4)	5 (2.3)
2015-2018	<5 (<15) [£]	<5 (<5) [£]	17 (3.8)	0 (0.0)
Median (IQR)	2004 (2002-2005)	2005 (2001-2009)	2004 (2000-2009)	1998 (1997-2001)
<i>Sex</i>				
Male	<10 (<80)	39 (48.2)	216 (48.4)	97 (43.9)
Female	<5 (<25) [£]	42 (51.9)	229 (51.4)	124 (56.1)
Missing	0 (0.0)	0 (0.0)	<5 (<1) [£]	0 (0.0)
<i>Birth order</i>				
First	<5 (<45) [£]	33 (40.7)	193 (43.3)	77 (34.8)
Second or higher	<10 (<60) [£]	48 (59.3)	253 (56.7)	142 (64.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parental characteristics				
<i>Origin (mother)</i>				
Danish or descendant of immigrant ^d	<10 (<90) [£]	<80 (<100) [£]	417 (93.5)	181 (81.9)
Immigrant ^d	<5 (<15) [£]	<5 (<5) [£]	29 (6.5)	40 (18.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>BMI[§] (mother)</i>				
<25	<5 (<25) [£]	20 (24.7)	137 (30.8)	18 (8.1)
25-30	<5 (<25) [£]	16 (19.8)	49 (11.0)	5 (2.3)
31-35	0 (0.0)	<5 (<5) [£]	29 (6.5)	<5 (<5) [£]
>35	<5 (<15) [£]	<5 (<5) [£]	18 (4.0)	<5 (<5) [£]
Missing	<5 (<45) [£]	41 (50.6)	213 (47.8)	196 (88.7)
<i>Maternal education^e</i>				
Basic	<5 (<45) [£]	22 (27.2)	103 (23.1)	51 (23.1)
Vocational	<10 (<60) [£]	37 (45.7)	166 (37.2)	100 (45.3)
Higher	0 (0.0)	20 (24.7)	170 (38.1)	53 (24.0)
Missing	0 (0.0)	<5 (<5) [£]	7 (1.6)	17 (7.7)
<i>Paternal education^e</i>				
Basic	<5 (<35) [£]	18 (22.2)	84 (18.8)	55 (24.9)
Vocational	<10 (<60) [£]	49 (60.5)	225 (50.5)	95 (43.0)
Higher	0 (0.0)	12 (14.8)	121 (27.1)	50 (22.6)
Missing	<5 (<15) [£]	<5 (<5) [£]	16 (3.6)	21 (9.5)
<i>Maternal age at birth (y)</i>				
<28	<10 (<80) [£]	36 (44.4)	139 (31.2)	59 (26.7)

28-31	<5 (<15) [£]	28 (34.6)	163 (36.6)	75 (33.9)
31-35	0 (0.0)	12 (14.8)	91 (20.4)	51 (23.1)
>35	<5 (<15) [£]	5 (6.2)	53 (11.9)	36 (16.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Median (IQR)	25 (24-27)	28 (25-31)	30 (27-33)	30 (27-34)
<i>Paternal age at birth (y)</i>				
<28	<5 (<35) [£]	19 (23.5)	94 (21.1)	30 (13.6)
28-31	<5 (<45) [£]	31 (38.3)	143 (32.1)	64 (29.0)
31-35	0 (0.0)	14 (17.3)	115 (25.8)	55 (24.9)
>35	<5 (<15) [£]	17 (21.0)	91 (20.4)	66 (29.9)
Missing	<5 (11.1)	0 (0.0)	<5 (<5) [£]	6 (2.7)
Median (IQR)	29 (24-31)	30 (28-34)	31 (28-35)	32 (29-37)
<i>Maternal smoking^{f*}</i>				
Missing	<5 (<15) [£]	9 (11.1)	27 (6.0)	53 (24.0)
<i>Maternal infertility^g</i>				
Missing	0 (0.0)	<5 (<5) [£]	33 (7.4)	29 (13.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

^aDuring refers to use during pregnancy

^bRecent use refers to use 3 months or less before pregnancy start or during pregnancy (except for non-oral progestin only products (for further specification, see the method section)).

^cPrevious use refers to use more than 3 months before pregnancy start (except for non-oral progestin only products (for further specification, see the method section)).

^dDefined as having 2 parents without Danish citizenship and who were not born in Denmark.

^eHighest attained education before birth of the child. Basic indicates mandatory school grades 9-10; vocational, secondary school and vocational education; higher, short-, medium-, and long-term higher education.

^fMaternal smoking measured in the first trimester of pregnancy. ^{*}Information on maternal smoking was only available from 1998 onwards.

^gICD-8 code 628 and ICD-10 code N97.

^hInformation on BMI was only available from 2004 onwards.

[£]Exact number <5 or equivalent is blinded according the interpretation of General Data Protection Regulation by Statistics Denmark.

Abbreviations: BMI = body mass index. wk = weeks. No = number. IQR = interquartile range, ICD = International Classification of Diseases (ICD) codes version ICD-10.

Table S7. Type and dose of progestin in progestin-only products.

Hormonal contraception	ATC-code(s)	Product	DDD	U
Progestin-only contraception				
<i>Oral</i>				
	G03AC01	Norethisterone	0.35/300	mg/mcg
	G03AC02	Lynestrenol	0.5	mg
	G03AC03	Levonorgestrel	30	mcg
	G03AC09	Desogestrel	75	mcg
<i>Non-oral</i>				
	G02BA03	Levonorgestrel	13.5	mg
	G03DA02	Medroxyprogesterone (Depo-Provera)	5	mg
	G03AC06	Medroxyprogesterone (Depo-Provera)	5	mg
	G03AC08	Etonogestrel	68	mcg

Abbreviations: DDD = defined daily dose, U = unit, mg = milligram, mcg = microgram.

ATC = anatomical therapeutic chemical