

Supplementary Online Content

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

eTable 1. The Danish Infertility Cohort (DIC), comprising virtually all women in Denmark requiring fertility assistance in the period 1963-2012, based on information obtained from several Danish nationwide population-based registries and local databases

	Data Sources			
	Local databases	National Prescription Register^a	National Patient Registry^b	IVF Register^c
Established		1994	1976	1994
Complete from		1995	1977	1994
Data period included in the DIC	1963-1989	1995-2012	1977-2012	1994-2012
Examples of data included	PIN of women referred to public gynecological hospital departments or private fertility clinics for fertility problems identified through local electronic databases	Redeemed prescriptions for fertility drugs	Discharge diagnoses, and dates of diagnoses	Assisted reproduction technology treatments, treatment dates, fertility drugs used
PIN^d included	Yes	Yes	Yes	Yes
Criteria for women included in the DIC 1963-2012	All women identified	Women who redeemed prescriptions for fertility drugs ^e	Women with a diagnosis of infertility ^f	All women recorded in the registry
^a Reimbursement-driven, with automated bar-code-based data entry provides data of high quality ¹				
^b Contains information on all contacts with Danish hospitals since 1977 and outpatient contacts since 1995. Before 1995, all diagnoses were reported in this registry according to the International classification of diseases, revision 8 (ICD-8), whereas, after 1994, they were reported according to International classification of diseases, revision 10 (ICD-10). A comparison of various primary diagnoses showed correct categorization for up to 83% of all cases. ²				
^c It is obligatory for all IVF clinics to report each treatment cycle to the register using treatment report forms that contain clinical as well as laboratory data. ³				
^d PIN = personal identification number given to all Danish residents.				
^e Anatomical Therapeutical Chemical (ATC) codes: G03CA*, G03DA04, G03GA*, G03GB02, G03DA02, H01CA*, H01CC*, L02AE*, L02AB02 and N04BC01.				
^f ICD-8 code 628 and ICD-10 code N97.				

eTable 2. Baseline characteristics of children conceived after assisted reproduction technology

	Type of assisted reproduction technology								<i>p</i> ^a
	In vitro fertilization		Intracytoplasmic sperm injection		Frozen embryo replacement		Other/unknown		
	N	(%)	N	(%)	N	(%)	N	(%)	
Total	19,448	(100.0)	13,417	(100.0)	3,356	(100.0)	935	(100.0)	
Year of birth									<0.001
1996 -1999	5,622	(28.9)	2,086	(15.5)	539	(16.1)	124	(13.3)	
2000-2003	5,119	(26.3)	3,360	(25.0)	536	(16.0)	79	(8.4)	
2004-2007	4,648	(23.9)	3,856	(28.7)	945	(28.2)	234	(25.0)	
2008-2012	4,059	(20.9)	4,115	(30.7)	1,336	(39.8)	498	(53.3)	
<i>Median [IQR] years</i>	<i>2004 [2000-2008]</i>		<i>2006 [2002-2009]</i>		<i>2007 [2003-2010]</i>		<i>2009 [2006-2010]</i>		
Sex									<0.001
Female	9,275	(47.7)	6,900	(51.4)	1,683	(50.1)	461	(49.3)	
Male	10,173	(52.3)	6,517	(48.6)	1,673	(49.9)	474	(50.7)	
Birth weight (g)									<0.001
< 2500	3,622	(18.6)	2,357	(17.6)	410	(12.2)	191	(20.4)	
2500-4500	14,339	(73.7)	10,589	(78.9)	2,753	(82.0)	700	(74.9)	
> 4500	292	(1.5)	231	(1.7)	109	(3.2)	12	(1.3)	
Missing	1,195	(6.1)	240	(1.8)	84	(2.5)	32	(3.4)	
<i>Median [IQR] g</i>	<i>3,150 [2,625-3,600]</i>		<i>3,200 [2,695-3,640]</i>		<i>3,400 [2,870-3,839]</i>		<i>3,160 [2,622-3,615]</i>		
Multiplicity									<0.001
No	12,626	(64.9)	9,001	(67.1)	2,479	(73.9)	635	(67.9)	
Yes	6,822	(35.1)	4,416	(32.9)	877	(26.1)	300	(32.1)	
Gestational age (weeks)									<0.001
< 37	4,248	(21.8)	2,536	(18.9)	524	(15.6)	195	(20.9)	
37-42	14,815	(76.2)	10,615	(79.1)	2,738	(81.6)	715	(76.5)	
> 42	385	(2.0)	266	(2.0)	94	(2.8)	25	(2.7)	
<i>Median [IQR] weeks</i>	<i>38.7 [37.1-40.3]</i>		<i>39.0 [37.4-40.4]</i>		<i>39.3 [37.9-40.7]</i>		<i>38.7 [37.1-40.4]</i>		

	Type of assisted reproduction technology								<i>p</i> ^a
	In vitro fertilization		Intracytoplasmic sperm injection		Frozen embryo replacement		Other/unknown		
	N	(%)	N	(%)	N	(%)	N	(%)	
Birth order									<0.001
1	13,639	(70.1)	9,486	(70.7)	1,826	(54.4)	612	(65.5)	
> 2	5,809	(29.9)	3,931	(29.3)	1,530	(45.6)	323	(34.5)	
Maternal smoking^b									<0.001
No	15,383	(79.1)	11,650	(86.8)	2,905	(86.6)	784	(83.9)	
Yes	2,268	(11.7)	1,199	(8.9)	287	(8.6)	88	(9.4)	
Missing	1,797	(9.2)	568	(4.2)	164	(4.9)	63	(6.7)	
Paternal age at birth (years)									<0.001
<30	1,992	(10.2)	1,518	(11.3)	302	(9.0)	<60	-	
30 -34	7,067	(36.3)	4,845	(36.1)	1,183	(35.3)	219	(23.4)	
>34	10,086	(51.9)	7,022	(52.3)	1,839	(54.8)	653	(69.8)	
Missing	303	(1.6)	32	(0.2)	32	(1.0)	<5	-	
<i>Median [IQR] years</i>	<i>35.3 [32.3-38.9]</i>		<i>35.3 [32.2-39.0]</i>		<i>35.6 [32.6-39.4]</i>		<i>38.9 [34.1-43.7]</i>		
Maternal age at birth (years)									<0.001
<30	3,454	(17.8)	3,235	(24.1)	564	(16.8)	142	(15.2)	
30 -34	8,433	(43.4)	6,005	(44.8)	1,531	(45.6)	326	(34.9)	
>34	7,561	(38.9)	4,177	(31.1)	1,261	(37.6)	467	(49.9)	
<i>Median [IQR] years</i>	<i>33.7 [30.9-36.7]</i>		<i>32.8 [30.1-35.8]</i>		<i>33.8 [31.1-36.5]</i>		<i>35.0 [31.4-38.8]</i>		
Paternal educational level									<0.001
Basic	3,910	(20.1)	2,617	(19.5)	668	(19.9)	197	(21.1)	
Vocational	9,144	(47.0)	6,614	(49.3)	1,505	(44.8)	468	(50.1)	
Higher	5,713	(29.4)	3,929	(29.3)	1,097	(32.7)	252	(27.0)	
Missing	681	(3.5)	257	(1.9)	86	(2.6)	18	(1.9)	

	Type of assisted reproduction technology								<i>p</i> ^a
	In vitro fertilization		Intracytoplasmic sperm injection		Frozen embryo replacement		Other/unknown		
	N	(%)	N	(%)	N	(%)	N	(%)	
Maternal educational level									<0.001
Basic	3,943	(20.3)	2,316	(17.3)	589	(17.6)	167	(17.9)	
Vocational	7,572	(38.9)	5,311	(39.6)	1,173	(35.0)	344	(36.8)	
Higher	7,733	(39.8)	5,632	(42.0)	1,544	(46.0)	402	(43.0)	
Missing	200	(1.0)	158	(1.2)	50	(1.5)	22	(2.4)	
^a The <i>p</i> -values reflect a comparison of the three groups for each variable. The Chi2 test was used for the categorical variables and the Kruskal-Wallis test for the continuous variables.									
^b Measured during first trimester of pregnancy.									
IQR = Interquartile range.									

eTable 3. Hazard ratios (HRs), incidence rates (IRs) and incidence rate differences (IRDs) for hematological cancers according to maternal infertility and treatment

			Leukamias						Lymphomas					
	Person-years	No. of children	No. of events	HR ^{a,b}	95% CI	IR ^{a,c}	IRD ^{a,c}	95% CI	No. of events	HR ^{a,b}	95% CI	IR ^{a,c}	IRD ^{a,c}	95% CI
Maternal infertility^d														
No	10,385,749	910,291	538	1	(Ref.)	4.3	0	(Ref.)	211	1	(Ref.)	2.4	0	(Ref.)
Yes ^e	1,824,545	174,881	110	1.11	(0.90-1.37)	4.9	0.6	(-0.6-1.8)	31	0.86	(0.59-1.26)	1.9	-0.5	(-1.1-0.1)
Maternal fertility treatment^f	943,199	89,981	55	1.08	(0.82-1.43)	4.8	0.5	(-1.0-2.1)	15	0.80	(0.47-1.34)	1.8	-0.6	(-1.4-0.2)
Hormonal treatment	934,946	89,334	54	1.07	(0.81-1.41)	4.8	0.5	(-1.1-2.1)	15	0.80	(0.48-1.36)	1.8	-0.6	(-1.4-0.2)
Clomiphene	372,402	33,835	21	1.06	(0.69-1.64)	4.9	0.6	(-1.9-3.0)	<5	0.40	(0.13-1.26)	-	-	-
Gonadotropins	572,515	57,136	39	1.23	(0.89-1.71)	5.6	1.3	(-0.8-3.5)	7	0.62	(0.29-1.33)	1.5	-0.9	(-1.7-0.0)
Human chorionic gonadotropin	682,288	68,181	41	1.09	(0.79-1.50)	4.8	0.5	(-1.4-2.4)	12	0.89	(0.50-1.59)	1.9	-0.5	(-1.4-0.4)
Gonadotropin-releasing hormone analogues	393,199	38,653	26	1.21	(0.81-1.79)	5.5	1.2	(-1.4-3.8)	7	0.91	(0.43-1.92)	2.0	-0.3	(-1.6-0.9)
Progesterone	429,787	41,628	28	1.20	(0.82-1.76)	5.3	1.0	(-1.4-3.4)	9	1.05	(0.54-2.04)	2.5	0.1	(-1.3-1.4)
Estrogene	123,958	16,948	8	1.00	(0.50-2.03)	3.8	-0.5	(-4.7-3.7)	<5	1.16	(0.37-3.66)	-	-	-
Other/unknown	73,129	8,867	<5	0.89	(0.33-2.39)	-	-	-	<5	1.30	(0.32-5.26)	-	-	-
Assisted reproduction technologies	388,681	37,156	<30	1.28	(0.87-1.88)	5.8	1.5	(-1.1-4.1)	8	1.04	(0.52-2.12)	2.4	0.0	(-1.4-1.4)
In vitro fertilization	220,159	19,448	11	0.95	(0.52-1.73)	4.1	-0.2	(-3.1-2.8)	<5	0.68	(0.22-2.14)	-	-	-
Intracytoplasmic sperm injection	130,726	13,417	10	1.36	(0.73-2.54)	6.6	2.3	(-2.5-7.1)	<5	1.20	(0.38-3.77)	-	-	-
Frozen embryo replacement	30,260	3,356	5	2.87	(1.19-6.93)	14.4	10.1	(-4.0-24.2)	<5	3.24	(0.81-13.10)	-	-	-
Other/unknown	7,536	935	<5	2.19	(0.31-15.59)	-	-	-	0	-	-	-	-	-
^a Adjusted for year of birth of the child.														
^b Each HR is generated from a separate analysis comparing the children with each individual exposure to the first row (i.e. children born to fertile women).														
^c Per 100,000 person-years.														
^d Anytime before birth of the child.														
^e Children born to women requiring fertility assistance on index or prior pregnancy.														

^f In index pregnancy.												
CI = confidence interval.												

eTable 4. Hazard ratios (HRs), incidence rates (IRs) and incidence rate differences (IRDs) for neural cancers according to maternal infertility and treatment

	Person-years	No. of children	Central nervous system neoplasms						Sympathetic nervous system tumors					
			No. of events	HR ^{a,b}	95% CI	IR ^{a,c}	IRD ^{a,c}	95% CI	No. of events	HR ^{a,b}	95% CI	IR ^{a,c}	IRD ^{a,c}	95% CI
Maternal infertility^d														
No	10,385,749	910,291	459	1	(Ref.)	4.3	0	(Ref.)	113	1	(Ref.)	0.9	0	(Ref.)
Yes ^e	1,824,545	174,881	82	1.01	(0.80-1.28)	4.3	0.0	(-1.0-1.1)	17	0.81	(0.49-1.35)	0.7	-0.2	(-0.6-0.3)
Maternal fertility treatment^f	943,199	89,981	48	1.15	(0.85-1.54)	4.9	0.6	(-0.8-2.1)	9	0.83	(0.42-1.64)	0.7	-0.1	(-0.8-0.5)
<i>Hormonal treatment</i>	934,946	89,334	47	1.13	(0.84-1.53)	4.9	0.6	(-0.9-2.1)	8	0.74	(0.36-1.53)	0.6	-0.2	(-0.8-0.3)
Clomiphene	372,402	33,835	21	1.27	(0.82-1.97)	5.5	1.2	(-1.2-3.7)	<5	0.73	(0.23-2.29)	-	-	-
Gonadotropins	572,515	57,136	31	1.22	(0.85-1.75)	5.2	1.0	(-1.0-2.9)	<5	0.59	(0.22-1.60)	-	-	-
Human chorionic gonadotropin	682,288	68,181	33	1.09	(0.76-1.55)	4.7	0.4	(-1.3-2.1)	8	0.99	(0.48-2.03)	0.9	0.0	(-0.8-0.8)
Gonadotropin-releasing hormone analogues	393,199	38,653	20	1.14	(0.73-1.79)	5.0	0.7	(-1.6-2.9)	<5	0.43	(0.11-1.76)	-	-	-
Progesterone	429,787	41,628	18	0.94	(0.59-1.51)	4.0	-0.3	(-2.2-1.7)	<5	0.40	(0.10-1.62)	-	-	-
Estrogen	123,958	16,948	5	0.88	(0.36-2.14)	-	-	-	<5	0.55	(0.08-3.98)	-	-	-
Other/unknown	73,129	8,867	5	1.52	(0.63-3.68)	6.7	2.4	(-3.7-8.4)	0	-	-	-	-	-
<i>Assisted reproduction technologies</i>	388,681	37,156	<25	1.22	(0.79-1.89)	5.3	1.0	(-1.4-3.3)	<5	0.89	(0.33-2.42)	-	-	-
In vitro fertilization	220,159	19,448	9	0.93	(0.48-1.79)	4.0	-0.3	(-3.0-2.4)	<5	0.42	(0.06-2.97)	-	-	-
Intracytoplasmic sperm injection	130,726	13,417	10	1.72	(0.92-3.22)	7.5	3.2	(-1.6-8.0)	0	-	-	-	-	-
Frozen embryo replacement	30,260	3,356	<5	1.47	(0.37-5.91)	-	-	-	<5	7.82	(2.47-24.70)	-	-	-
Other/unknown	7,536	935	0	-	-	-	-	-	0	-	-	-	-	-

eTable 5. Hazard ratios, incidence rates and incidence rate differences for other cancers according to maternal infertility and treatment

	Person-years	Number of children	Number of events	Hazard ratio ^{a,b}	95% confidence interval	Incidence rate ^a per 100,000 person-years	Incidence rate difference ^a per 100,000 person-years	95% confidence interval
Maternal infertility^c								
No	10,385,749	910,291	559	1	(Reference)	5.7	0	(Reference)
Yes ^d	1,824,545	174,881	102	1.05	(0.85-1.30)	5.8	0.1	(-1.1-1.2)
Maternal fertility treatment^e	943,199	89,981	52	1.03	(0.77-1.37)	5.7	0.0	(-1.6-1.5)
<i>Hormonal treatment</i>	934,946	89,334	50	1.00	(0.75-1.33)	5.3	-0.2	(-1.7-1.3)
Clomiphene	372,402	33,835	17	0.86	(0.53-1.39)	4.7	-1.0	(-3.1-1.1)
Gonadotropins	572,515	57,136	32	1.05	(0.74-1.51)	5.9	0.2	(-1.8-2.1)
Human chorionic gonadotropin	682,288	68,181	35	0.96	(0.68-1.35)	5.6	-0.1	(-1.9-1.6)
Gonadotropin-releasing hormone analogues	393,199	38,653	26	1.24	(0.84-1.84)	7.0	1.3	(-1.3-3.9)
Progesterone	429,787	41,628	28	1.21	(0.83-1.77)	6.7	1.0	(-1.4-3.4)
Estrogen	123,958	16,948	6	0.84	(0.37-1.88)	4.8	-0.8	(-4.7-3.0)
Other/unknown	73,129	8,867	<5	0.97	(0.36-2.61)	-	-	-
<i>Assisted reproduction technologies</i>	388,681	37,156	<30	1.22	(0.81-1.82)	6.8	1.2	(-1.4-3.7)
In vitro fertilization	220,159	19,448	14	1.20	(0.71-2.04)	6.8	1.1	(-2.3-4.4)
Intracytoplasmic sperm injection	130,726	13,417	9	1.32	(0.68-2.55)	7.3	1.6	(-2.9-6.1)
Frozen embryo replacement	30,260	3,356	<5	1.20	(0.30-4.81)	-	-	-
Other/unknown	7,536	935	0	-	-	-	-	-
^a Adjusted for year of birth of the child.								
^b Each hazard ratio is generated from a separate analysis comparing the children with each individual exposure to the first row (i.e. children born to fertile women).								
^c Anytime before birth of the child.								
^d Children born to women requiring fertility assistance on index or prior pregnancy.								
^e In index pregnancy. Includes only the items listed below.								
"-" indicates that it was not possible to estimate the number in the model.								

eTable 6. Hazard ratios adjusted for sex and perinatal factors for any childhood cancer according to maternal infertility and treatment

	Person-years	Number of children	Number of events	Complete case hazard ratio ^{a,b}	(95% confidence interval)	Adjusted hazard ratio ^{a,b,c}	(95% confidence interval)
Maternal infertility^d							
No	9,222,935	846,489	16663	1	(Reference)	1	(Reference)
Yes ^e	1,696,691	167,742	319	1.03	(0.91-1.16)	1.03	(0.91-1.17)
Maternal fertility treatment^f	862,363	85,486	164	1.04	(0.88-1.22)	1.05	(0.89-1.24)
<i>Hormonal treatment</i>	854,794	84,876	159	1.01	(0.86-1.19)	1.02	(0.86-1.21)
Clomiphene	337,329	31,929	57	0.93	(0.72-1.22)	0.94	(0.74-1.22)
Gonadotropins	536,531	55,071	105	1.06	(0.87-1.30)	1.08	(0.88-1.33)
Human chorionic gonadotropin	634,231	65,469	120	1.02	(0.85-1.23)	1.04	(0.85-1.26)
Gonadotropin-releasing hormone analogues	366,370	37,122	75	1.11	(0.88-1.41)	1.14	(0.89-1.45)
Progesterone	394,545	39,632	80	1.10	(0.88-1.38)	1.12	(0.89-1.42)
Estrogen	121,951	16,783	23	0.93	(0.61-1.40)	0.94	(0.62-1.43)
Other/unknown	69,016	8,629	15	1.10	(0.66-1.83)	1.11	(0.67-1.86)
<i>Assisted reproduction technology</i>	361,025	35,605	<90	1.21	(0.97-1.52)	1.25	(0.99-1.58)
In vitro fertilization	198,532	18,253	34	0.95	(0.68-1.34)	0.96	(0.68-1.36)
Intracytoplasmic sperm injection	126,742	13,177	31	1.33	(0.93-1.90)	1.36	(0.95-1.96)
Frozen embryo replacement	28,769	3,272	14	2.55	(1.51-4.32)	2.58	(1.52-4.38)
Other/unknown	6,981	903	<5	0.71	(0.10-5.05)	0.72	(0.10-5.10)
^a Adjusted for year of birth of the child.							
^b Each hazard ratio is generated from a separate analysis comparing the children with each individual exposure to the first row (i.e. children born to fertile women).							
^c Adjusted for sex and perinatal factors (birthweight [<2500, 2500-4500, >4500g], gestational length [<37, 37-43, >43 weeks] and multiplicity [yes, no]) .							
^d Anytime before birth of the child.							
^e Children born to women requiring fertility assistance on index or prior pregnancy.							
^f In index pregnancy. Includes only the items listed below.							

eTable 7. Hazard ratios, incidence rates and incidence rate differences for any childhood cancer according to maternal fertility treatment, using children born to women requiring fertility assistance (without treatment in index pregnancy) as reference

	Person-years	Number of children	Number of events	Hazard ratio ^{a,b}	(95% confidence interval)	Incidence rate ^a per 100,000 person-years	Incidence rate difference ^a per 100,000 person-years	(95% confidence interval)
Maternal fertility treatment^c								
No	881,346	84,900	163	1	(Reference)	17.4	0	(Reference)
Yes	943,199	89,981	178	1.02	(0.82-1.26)	17.8	0.4	(-3.5-4.4)
Hormonal treatment	934,946	89,334	173	0.99	(0.80-1.23)	17.4	0.0	(-3.9-3.9)
Clomiphene	372,402	33,835	64	0.93	(0.70-1.25)	16.7	-0.7	(-5.8-4.4)
Gonadotropins	572,515	57,136	112	1.05	(0.82-1.33)	18.6	1.2	(-3.4-5.7)
Human chorionic gonadotropin	682,288	68,181	129	1.01	(0.80-1.27)	17.7	0.3	(-3.9-4.6)
Gonadotropin-releasing hormone analogues	393,199	38,653	81	1.11	(0.85-1.44)	19.7	2.3	(-2.9-7.6)
Progesterone	429,787	41,628	85	1.06	(0.82-1.38)	18.6	1.2	(-3.8-6.2)
Estrogen	123,958	16,948	23	0.90	(0.58-1.40)	16.1	-1.3	(-9.4-6.7)
Other/unknown	73,129	8,867	15	1.03	(0.61-1.75)	17.2	-0.2	(-10.5-10.2)
Assisted reproduction technologies	388,681	37,156	<90	1.18	(0.91-1.53)	21.0	3.6	(-1.8-9.0)
In vitro fertilization	220,159	19,448	38	0.95	(0.66-1.35)	17.1	-0.3	(-6.5-5.9)
Intracytoplasmic sperm injection	130,726	13,417	32	1.31	(0.90-1.92)	23.1	5.7	(-3.1-14.5)
Frozen embryo replacement	30,260	3,356	14	2.39	(1.39-4.13)	44.4	27.0	(2.7-51.3)
Other/unknown	7,536	935	<5	0.65	(0.09-4.66)	-	-	-
^a Adjusted for year of birth of the child.								
^b Each hazard ratio is generated from a separate analysis comparing the children with each individual exposure to the first row (i.e. children born to women requiring fertility assistance without treatment in index pregnancy).								
^c Children born to women requiring fertility assistance on index or prior pregnancy. Includes only the items listed below.								
“-“ indicates that it was not possible to estimate the number in the model.								

eTable 8. Hazard ratios (HRs), incidence rates (IRs) and incidence rate differences (IRDs) for hematological cancers according to maternal fertility treatment, using children born to women requiring fertility assistance (without treatment in index pregnancy) as reference

	Leukemias								Lymphomas					
	Person-years	No. of children	No. of events	HR ^{a,b}	(95% CI)	IR ^{a,c}	IRD ^{a,c}	(95% CI)	No. of events	HR ^{a,b}	(95% CI)	IR ^{a,c}	IRD ^{a,c}	(95% CI)
Maternal fertility treatment^d														
No	881,346	84,900	55	1	(Ref.)	5.0	0	(Ref.)	16	1	(Ref.)	2.2	0	(Ref.)
Yes	943,199	89,981	55	0.94	(0.65-1.37)	4.8	-0.1	(-2.4-2.1)	15	0.86	(0.42-1.73)	1.8	-0.2	(-1.2-0.9)
Hormonal treatment	934,946	89,334	54	0.93	(0.64-1.36)	4.8	-0.2	(-2.4-2.0)	15	0.806	(0.43-1.75)	1.8	-0.2	(-1.2-0.9)
Clomiphene	372,402	33,835	21	0.93	(0.56-1.53)	4.9	-0.1	(-3.0-2.8)	<5	0.43	(0.13-1.49)	-	-	-
Gonadotropins	572,515	57,136	39	1.07	(0.71-1.62)	5.6	0.6	(-2.0-3.3)	7	0.67	(0.28-1.63)	1.5	-0.4	(-1.6-0.7)
Human chorionic gonadotropin	682,288	68,181	41	0.95	(0.63-1.42)	4.8	-0.2	(-2.6-2.3)	12	0.96	(0.45-2.02)	1.9	-0.1	(-1.3-1.1)
Gonadotropin-releasing hormone analogues	393,199	38,653	26	1.05	(0.66-1.68)	5.5	0.5	(-2.5-3.5)	7	0.97	(0.40-2.37)	2.0	-0.2	(-1.2-0.9)
Progesterone	429,787	41,628	28	1.05	(0.67-1.65)	5.3	0.3	(-2.5-3.2)	9	1.13	(0.50-2.55)	2.5	0.5	(-1.1-2.1)
Estrogen	123,958	16,948	8	0.88	(0.42-1.85)	3.8	-1.2	(-5.6-3.3)	<5	1.25	(0.36-4.31)	-	-	-
Other/unknown	73,129	8,867	<5	0.78	(0.28-2.15)	-	-	-	<5	1.40	(0.32-6.10)	-	-	-
Assisted reproduction technologies.	388,681	37,156	<30	1.12	(0.70-1.77)	5.8	0.8	(-2.2-3.8)	8	1.12	(0.48-2.62)	2.4	0.4	(-1.2-2.0)
In vitro fertilization	220,159	19,448	11	0.83	(0.44-1.59)	4.1	-0.9	(-4.2-2.5)	<5	0.74	(0.21-2.53)	-	-	-
Intracytoplasmic sperm injection	130,726	13,417	10	1.18	(0.60-2.32)	6.6	1.6	(-3.4-6.7)	<5	1.29	(0.38-4.44)	-	-	-
Frozen embryo replacement	30,260	3,356	5	2.50	(1.10-6.26)	14.4	9.4	(-4.8-23.6)	<5	3.49	(0.80-15.21)	-	-	-
Other/unknown	7,536	935	<5	1.91	(0.26-13.81)	-	-	-	0	-	-	-	-	-
^a Adjusted for year of birth of the child.														
^b Each hazard ratio is generated from a separate analysis comparing the children with each individual exposure to the first row (i.e. children born to women requiring fertility assistance without treatment in index pregnancy).														
^c Per 100,000 person-years														
^d Children born to women requiring fertility assistance on index or prior pregnancy. Includes only the items listed below.														
“-” indicates that it was not possible to estimate the number in the model. CI= confidence interval.														

eTable 9. Hazard ratios (HRs), incidence rates (IRs) and incidence rate differences (IRDs) for neural cancers according to maternal fertility treatment, using children born to women requiring fertility assistance (without treatment in index pregnancy) as reference

	Central nervous system neoplasms								Sympathetic nervous system tumors					
	Person-years	No. of children	No. of events	HR ^{a,b}	(95% CI)	IR ^{a,c}	IRD ^{a,c}	(95% CI)	No. of events	HR ^{a,b}	(95% CI)	IR ^{a,c}	IRD ^{a,c}	(95% CI)
Maternal fertility treatment^d														
No	881,346	84,900	34	1	(Ref.)	3.6	0	(Ref.)	8	1	(Ref.)	0.7	0	(Ref.)
Yes	943,199	89,981	48	1.32	(0.85-2.04)	4.9	1.4	(-0.6-3.3)	9	1.06	(0.41-2.74)	0.7	0.0	(-0.8-0.9)
Hormonal treatment	934,946	89,334	47	1.30	(0.84-2.02)	4.9	1.3	(-0.6-3.2)	8	0.95	(0.35-2.52)	0.6	-0.1	(-0.9-0.8)
Clomiphene	372,402	33,835	21	1.46	(0.85-2.52)	5.5	2.0	(-0.8-4.7)	<5	0.93	(0.25-3.49)	-	-	-
Gonadotropins	572,515	57,136	31	1.40	(0.86-2.28)	5.2	1.6	(-0.6-3.9)	<5	0.75	(0.23-2.50)	-	-	-
Human chorionic gonadotropin	682,288	68,181	33	1.25	(0.77-2.01)	4.7	1.1	(-1.0-3.2)	8	1.26	(0.47-3.35)	0.9	0.2	(-0.8-1.2)
Gonadotropin-releasing hormone analogues	393,199	38,653	20	1.32	(0.76-2.28)	4.9	1.4	(-1.2-3.9)	<5	0.55	(0.12-2.60)	-	-	-
Progesterone	429,787	41,628	18	1.08	(0.61-1.92)	4.0	0.4	(-1.9-2.7)	<5	0.51	(0.11-2.39)	-	-	-
Estrogen	123,958	16,948	5	1.01	(0.39-2.60)	-	-	-	<5	0.70	(0.09-5.63)	-	-	-
Other/unknown	73,129	8,867	5	1.74	(0.68-4.47)	6.6	3.1	(-3.1-9.2)	0	-	-	-	-	-
Assisted reproduction technologies	388,681	37,156	<25	1.40	(0.81-2.41)	5.2	1.7	(-1.0-4.3)	<5	1.14	(0.34-3.77)	-	-	-
In vitro fertilization	220,159	19,448	9	1.06	(0.51-2.22)	4.0	0.4	(-2.6-3.4)	<5	0.53	(0.07-4.22)	-	-	-
Intracytoplasmic sperm injection	130,726	13,417	10	1.98	(0.98-4.00)	7.4	3.9	(-1.0-8.8)	0	-	-	-	-	-
Frozen embryo replacement	30,260	3,356	<5	1.69	(0.41-7.03)	-	-	-	<5	9.94	(2.63-37.54)	-	-	-
Other/unknown	7,536	935	0	-	-	-	-	-	0	-	-	-	-	-
^a Adjusted for year of birth of the child.														
^b Each hazard ratio is generated from a separate analysis comparing the children with each individual exposure to the first row (i.e. children born to women requiring fertility assistance without treatment in index pregnancy).														
^c Per 100,000 person-years														

^dChildren born to women requiring fertility assistance on index or prior pregnancy. Includes only the items listed below.

“-“ indicates that it was not possible to estimate the number in the model. CI= confidence interval.

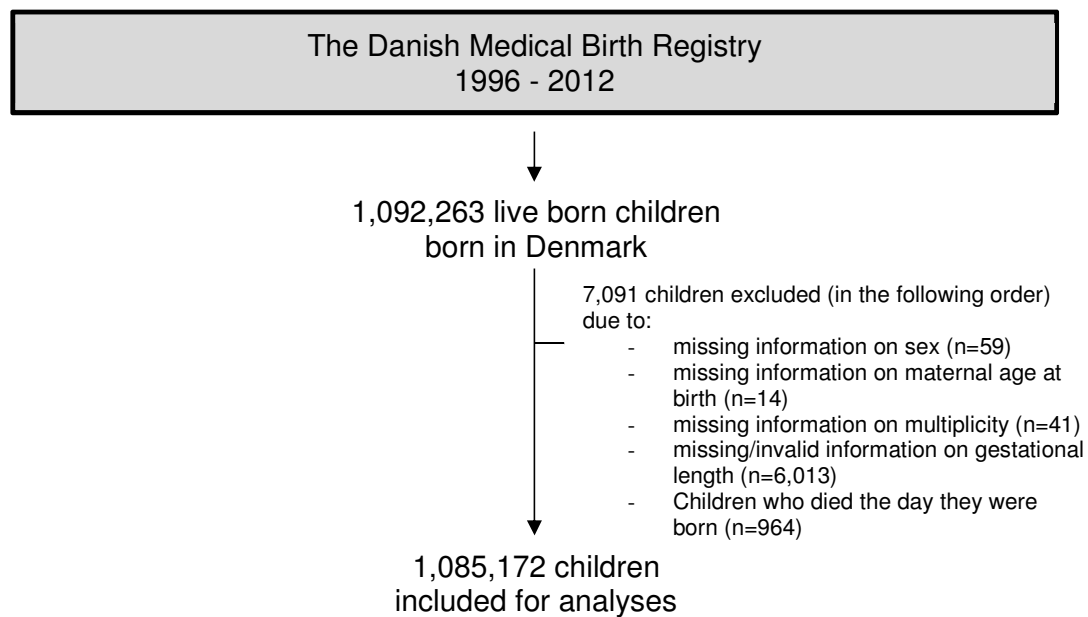
eTable 10. Hazard ratios, incidence rates and incidence rate differences for other cancers according to maternal fertility treatment, using children born to women requiring fertility assistance (without treatment in index pregnancy) as reference

	Person-years	Number of children	Number of events	Hazard ratio ^{a,b}	(95% confidence interval)	Incidence rate ^a per 100,000 person-years	Incidence rate difference ^a per 100,000 person-years	(95% confidence interval)
Maternal fertility treatment^c								
No	881,347	84,900	50	1	(Reference)	5.9	0	(Reference)
Yes	943,201	89,981	52	0.96	(0.90-1.37)	5.7	-0.3	(-2.4-1.8)
Hormonal treatment	934,946	89,334	50	0.93	(0.63-1.37)	5.5	-0.4	(-2.5-1.7)
Clomiphene	372,402	33,835	17	0.80	(0.46-1.38)	4.7	-1.2	(-3.8-1.4)
Gonadotropins	572,515	57,136	32	0.98	(0.63-1.53)	5.9	0.0	(-2.5-2.4)
Human chorionic gonadotropin	682,288	68,181	35	0.89	(0.58-1.37)	5.6	-0.3	(-2.6-1.9)
Gonadotropin-releasing hormone analogues	393,199	38,653	26	1.16	(0.72-1.86)	7.0	1.1	(-1.9-4.0)
Progesterone	429,787	41,628	28	1.13	(0.71-1.79)	6.7	-0.2	(-2.8-2.4)
Estrogen	123,958	16,948	6	0.78	(0.33-1.82)	4.8	-1.1	(-5.2-3.1)
Other/unknown	73,129	8,867	<5	0.90	(0.33-2.50)	-	-	-
Assisted reproduction technologies	388,681	37,156	<30	1.13	(0.70-1.82)	6.9	0.9	(-2.0-3.9)
In vitro fertilization	220,159	19,448	14	1.12	(0.62-2.02)	6.8	0.8	(-2.8-4.5)
Intracytoplasmic sperm injection	130,726	13,417	9	1.23	(0.60-2.49)	7.3	1.4	(-3.3-6.1)
Frozen embryo replacement	30,260	3,356	<5	1.11	(0.27-4.58)	-	-	-
Other/unknown	7,536	935	0	-	-	-	-	-
^a Adjusted for year of birth of the child.								
^b Each hazard ratio is generated from a separate analysis comparing the children with each individual exposure to the first row (i.e. children born to women requiring fertility assistance without treatment in index pregnancy).								
^c Children born to women requiring fertility assistance on index or prior pregnancy. Includes only the items listed below.								
“-“ indicates that it was not possible to estimate the number in the model.								

eTable 11. Hazard ratios taking into account sibling clustering for any childhood cancer according to maternal infertility and treatment

	Person-years	Number of children	Number of events	hazard ratio^{a,b}	(95% confidence interval)
Maternal infertility^c					
No	10,385,749	910,291	1876	1	(Reference)
Yes ^d	1,824,545	174,881	341	1.02	(0.91-1.15)
Maternal fertility treatment^e	943,199	89,981	178	1.03	(0.88-1.20)
<i>Hormonal treatment</i>	934,946	89,334	173	1.01	(0.86-1.18)
<i>Assisted reproduction technology</i>	388,681	37,156	<90	1.20	(0.96-1.49)
In vitro fertilization	220,159	19,448	38	0.96	(0.70-1.32)
Intracytoplasmic sperm injection	130,726	13,417	32	1.33	(0.94-1.89)
Frozen embryo replacement	30,260	3,356	14	2.43	(1.44-4.11)
Other/unknown	7,536	935	<5	0.66	(0.09-4.71)
^a Adjusted for year of birth of the child and taking into account the effect of sibling clustering using robust standard errors to account for correlation between siblings.					
^b Each hazard ratio is generated from a separate analysis comparing the children with each individual exposure to the first row (i.e. children born to fertile women).					
^c Anytime before birth of the child.					
^d Children born to women requiring fertility assistance on index or prior pregnancy.					
^e In index pregnancy. Includes only the items listed below.					

eFigure. Identification of the study cohort



eReferences

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