

## Supplementary Content

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Table A. Classification of cancer. In Finland and Norway, we used ICD-O-3 codes for the whole period, in Denmark we used ICD-10 codes for the whole period, except for leukaemia and lymphoma which we classified according to ICD-O-3 morphology codes. In Sweden we used ICD-7 codes for the whole period.

ICD-10 group	ICD-O-3 rev. 1		Swedish ICD-7
	Topography	Morphology Site	
From Cancer in Norway 2017*	Converting from ICD-O-3 to ICD-10 group, based on International classification of diseases for oncology (ICD-O) – 3rd edition, 1st revision.		Swedish ICD-7 with minor adjustments.
1 'Lip (C00)'	C00	Lip	140.0, 140.1, 140.9
2 'Tongue (C01–02)'	C01 C02	Base of Tongue Other and unspecified parts of tongue	141.0, 141.7, 141.9
3 'Mouth, other (C03–06)'	C03 C04 C05 C06	Gum Floor of mouth Palate Other and unspecified parts of mouth	143, 144, 141.8
4 'Salivary glands (C07–08)'	C07 C08	Parotid gland Other and unspecified major salivary glands	142
5 'Pharynx (C09–14)'	C09 C10 C11 C12 C13 C14	Tonsil Oropharynx Nasopharynx Pyramidal sinus Hypopharynx Other and ill-defined sites in lip, oral cavity and pharynx	145.0, 145.7, 145.8, 145.9, 146, 147, 148
6 'Oesophagus (C15)'	C15	Oesophagus	150
7 'Stomach (C16)'	C16	Stomach	151
8 'Small intestine (C17)'	C17	Small intestine	152
9 'Colon (C18)'	C18	Colon	153
10 'Rectum, rectosigmoid (C19–20)'	C19 C20	Rectosigmoid junction Rectum	154.0
11 'Anus (C21)'	C21	Anus and anal canal	153.9, 154.1, 154.8
12 'Liver (C22)'	C22	Liver and intrahepatic bile ducts	155.0, 156
13 'Gallbladder, bile ducts (C23–24)'	C23 C24	Gallbladder Other and unspecified parts of biliary tract	152.0, 155.1, 155.2, 155.3, 155.8, 155.9
14 'Pancreas (C25)'	C25	Pancreas	157, 195.5
15 'Other digestive organs (C26)'	C26	Other and ill-defined digestive organs	
16 'Nose, sinuses (C30–31)'	C30 C31	Nasal cavity and middle ear Accessory sinuses	160
17 'Larynx, epiglottis (C32)'	C32	Larynx	161
18 'Lung, trachea (C33–34)'	C33 C34	Trachea Bronchus and lung	162.0, 162.1
19 'Heart, mediastinum and pleura (C38)'	C38	Heart, mediastinum, and pleura	162.2, 164, 197.5, (except if pad equals 776)

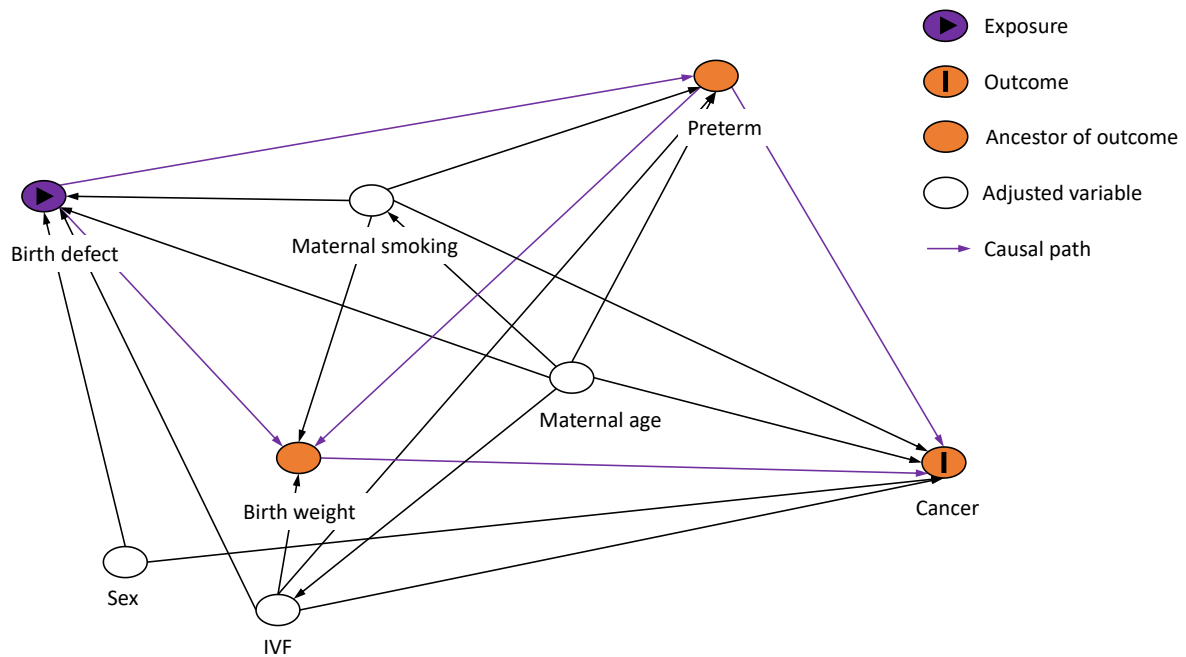
ICD-10 group	ICD-O-3 rev. 1		Swedish ICD-7
	Topography	Morphology Site	
20 'Bone (C40-41)'	C40 C41	Bones, joints and articular cartilage Bones, joints and articular cartilage of other and unspecified sites	196
21 'Melanoma of the skin (C43)'	C44	872-879	190
22 'Skin, non-melanoma (C44)'	C44	Skin (excludes skin of vulva C51, skin of penis C60.9, skin of scrotum C63.2)	191
23 'Mesothelioma (C45)'	C _ _ _	905	162.2, 197.5, 158 or 179.7, AND pad 776
24 'Peripheral nerves and autonomic nervous system (C47)'	C47	Peripheral nerves and autonomic nervous system (include autonomic nervous system, ganglia, nerve, parasympathetic nervous system, peripheral nerve, spinal nerve, sympathetic nervous system)	193.3, 193.8, 193.9
25 'Soft tissues (C48-49)'	C48 C49	Retroperitoneum and peritoneum Connective, subcutaneous and other soft tissues	158 (except if pad equals 776), 197.0-197.4, 197.7-197.9
26 'Breast (C50)'	C50	Breast (excludes skin of breast C44.5)	170
27 'Other female genital (C51-52, C57.7-9)'	C51 C52 C57.7 C57.8 C57.9	Vulva Vagina Other specified parts of female genital organs Overlapping lesion of female genital organs Female genital tract, NOS	176
28 'Cervix uteri (C53)'	C53	Cervix uteri	171
29 'Corpus uteri (C54)'	C54	Corpus uteri	172
30 'Uterus, other (C55)'	C55	Uterus, NOS	174
31 'Ovary etc. (C56, C57.0-4)'	C56 C57.0 C57.1 C57.2 C57.3 C57.4	Ovary Fallopian tube Broad ligament Round ligament Parametrium Uterine adnexa	175
32 'Placenta (C58)'	C58	Placenta	173
33 'Prostate (C61)'	C61	Prostate gland	177
34 'Testis (C62)'	C62	Testis	178
35 'Other male genital (C60, C63)'	C60 C63	Penis Other and unspecified male genital organs	179 (except 179.7 if pad equals 776)
36 'Kidney (excl. renal pelvis) (C64)'	C64	Kidney	180.0, 180.9
37 'Urinary tract (C65-68)'	C65 C66 C67	Renal pelvis Ureter Bladder	180.1, 181

ICD-10 group	ICD-O-3 rev. 1			Swedish ICD-7
	Topography	Morphology	Site	
	C68		Other and unspecified urinary organs	
38 'Eye (C69)'	C69		Eye and adnexa	192
39 'Central nervous system (C70–72, D32–33, D42–43)	C70 C71 C72		Meninges Brain Spinal cord, cranial nerves and other parts of central nervous system (excludes peripheral nerves, sympathetic and parasympathetic nerves and ganglia C47)	193.0, 193.1,193.8,193.9
40 Thyroid gland (C73)	C73		Thyroid gland	194
41 'Other endocrine glands (C37, C74-75, D35.2–35.4, D44.3–44.5)	C37 C74 C75		Thymus Adrenal gland Other endocrine glands and related structures	195, 164
42 Other or unspecified (C39, C76, C80)	C39  C76 C80		Other and ill-defined sites within respiratory system and intrathoracic organs Other and ill-defined sites Unknown primary site	199, 163
43 Hodgkin lymphoma (C81)	C_ _ _	959-999**	Lymphoid and hematopoietic diseases	201
44 Non-Hodgkin lymphoma (C82–86)				200.0, 200.1, 202.1, 202.2
45 Immunoproliferative disease (C88)				200.2, 200.3
46 Multiple myeloma (C90)				203
47 Acute lymphatic leukaemia (C91.0)				204.0
48 Chronic lymphatic leukaemia (C91.1)				204.1
49 Other and unspecified lymphatic leukaemia (C91.2-9)				202.4, 204.9
50 Acute myeloid leukaemia (C92.0+C93.0+C94.0+C94.2+C94.4-5)				205.0, 206.0
51 Chronic myeloid leukaemia (C92.1+C93.1+C94.1)				205.1
52 Other and unspecified myeloid leukaemia (C92.2-9+C93.2-9+C94.3+C94.7)				205.9
53 Leukaemia, cell unspecified (C95)				206.1, 206.9, 207.0, 207.2, 207.3, 209
54 Other hematopoietic diseases (C94.6, D45-47)				208, 207.9

\*Grouped according to *Cancer Registry of Norway. Cancer in Norway 2017 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway (2018)* except for leukaemia (C91–95, D45-47) which is grouped according to classification table from NORDCAN with minor adjustments.

\*\*Classified by morphology according to conversion table from IARC. In addition, from ICD-O-3 rev.1: Morphology 9751/3 - Use this code for all types of Langerhans cell histiocytosis, including the former 9751/1 through 9754/3 terms.

Figure A. Directed acyclic graph (DAG) illustrating confounder selection.



Potential confounders evaluated were sex, *in vitro* fertilization (IVF), maternal age, and maternal smoking. Since IVF and maternal smoking were only available in a subset of the study sample, adjustments for these were made in sensitivity analyses. We chose to perform the main analysis with minimal adjustment, including the matching variables (country and birth year) and sex only, since additional adjustment for maternal age did not change the effect estimates substantially. We did not adjust for intermediate factors (birth weight and being preterm) in order to estimate the total effect of birth defects on cancer risk.

Table B. Risk of any cancer in individuals with any, or specific, birth defects, stratified by age at diagnosis.

Birth defect*	0-14 years				15-19 years			20+ years		
	Controls n (%) N=724 542	Cases n (%) N=19 881	OR	99 % CI	Cases n (%) N=6 346	OR	99 % CI	Cases n (%) N=36 068	OR	99 % CI
All anomalies	15,826 (2.18)	1,164 (5.85)	2.52	2.32 to 2.74	225 (3.55)	1.64	1.37 to 1.95	771 (2.14)	1.22	1.11 to 1.35
All anomalies excl. chromosomal anomalies	15,067 (2.08)	887 (4.52)	2.03	1.85 to 2.23	206 (3.26)	1.58	1.31 to 1.90	725 (2.01)	1.21	1.09 to 1.33
Nervous system	593 (0.08)	170 (0.9)	9.72	7.66 to 12.3	12 (0.2)	2.30	1.09 to 4.89	43 (0.12)	1.76	1.16 to 2.65
<i>NTD</i>	216 (0.03)	62 (0.33)	10.1	6.84 to 15.0	7 (0.11)	3.93	1.46 to 10.6	21 (0.06)	2.08	1.14 to 3.79
Eye	373 (0.05)	42 (0.22)	3.54	2.29 to 5.46	6 (0.1)	1.68	0.58 to 4.85	12 (0.03)	0.88	0.41 to 1.88
Ear, face and neck	92 (0.01)	4 (0.02)	1.26	0.33 to 4.78	0 (0)			4 (0.01)	1.52	0.40 to 5.74
CHD	3 512 (0.49)	189 (1)	1.53	1.26 to 1.86	47 (0.76)	1.49	1.02 to 2.18	145 (0.41)	1.28	1.02 to 1.59
Respiratory system	239 (0.03)	16 (0.09)	2.06	1.04 to 4.06	2 (0.03)	0.93	0.15 to 5.81	6 (0.02)	0.75	0.26 to 2.19
Oro-facial clefts	1 242 (0.17)	48 (0.26)	1.35	0.92 to 1.98	12 (0.2)	1.08	0.51 to 2.29	56 (0.16)	0.98	0.69 to 1.40
<i>CPO</i>	397 (0.06)	14 (0.07)	1.05	0.52 to 2.14	4 (0.07)	1.08	0.30 to 3.96	14 (0.04)	0.90	0.44 to 1.83
<i>CL</i>	846 (0.12)	34 (0.18)	1.51	0.95 to 2.38	8 (0.13)	1.08	0.43 to 2.69	42 (0.12)	1.01	0.67 to 1.53
Digestive system	764 (0.11)	73 (0.39)	2.93	2.11 to 4.06	8 (0.13)	1.17	0.47 to 2.92	30 (0.08)	1.03	0.63 to 1.67
Abdominal wall defects	119 (0.02)	10 (0.05)	2.04	0.85 to 4.87	1 (0.02)	0.81	0.06 to 10.8	5 (0.01)	1.04	0.32 to 3.45
Urinary system	782 (0.11)	62 (0.33)	2.00	1.41 to 2.83	19 (0.31)	2.51	1.38 to 4.57	23 (0.07)	1.03	0.59 to 1.78
Genital organs	2 538 (0.36)	74 (0.39)	1.25	0.92 to 1.70	21 (0.34)	1.04	0.59 to 1.83	147 (0.41)	1.43	1.14 to 1.78
Limb	2 803 (0.39)	115 (0.61)	1.48	1.15 to 1.90	39 (0.63)	1.60	1.05 to 2.43	138 (0.39)	1.12	0.89 to 1.40
Skeletal dysplasia	114 (0.02)	15 (0.08)	3.59	1.74 to 7.42	4 (0.07)	3.38	0.91 to 12.6	11 (0.03)	3.54	1.54 to 8.15
Genetic syndromes and microdeletions	125 (0.02)	44 (0.23)	6.47	4.05 to 10.3	7 (0.11)	4.64	1.70 to 12.7	3 (0.01)	1.34	0.29 to 6.15
Chromosomal	759 (0.11)	277 (1.46)	11.3	9.35 to 13.8	19 (0.31)	2.75	1.51 to 5.00	46 (0.13)	1.50	1.01 to 2.24
Down syndrome	604 (0.09)	247 (1.3)	13.3	10.8 to 16.4	16 (0.26)	3.01	1.57 to 5.79	38 (0.11)	1.42	0.92 to 2.21
Other anomalies/ syndromes	2 790 (0.39)	211 (1.11)	3.11	2.57 to 3.76	60 (0.97)	2.64	1.88 to 3.71	153 (0.43)	1.24	1.00 to 1.54

ORs are adjusted for matching variables (birth year and country) and sex. In all analyses for specific sites, other than for chromosomal anomalies, individuals with chromosomal anomalies were excluded. In all analyses, the unexposed group was individuals without major birth defects. Abbreviations: OR odds ratio; CI confidence interval; *NTD* Neural Tube Defects; *CHD* Congenital Heart Defects; *CPO* Cleft palate only; *CL* Cleft lip with/ without cleft palate. \*Birth defects classified according to EUROCAT.

Table C. Risk of overall cancer in individuals with any, or specific, major birth defects, adjusted for country, birth year, sex and maternal age, among 62 295 cases and 724 542 controls.

<b>Birth defect*</b>	<b>OR</b>	<b>99% CI</b>
All anomalies	1.73	1.63 to 1.84
All anomalies excl. chromosomal anomalies	1.54	1.44 to 1.64
<i>Specific sites</i>		
Nervous system	4.76	3.89 to 5.83
<i>NTD</i>	4.99	3.61 to 6.91
Eye	2.07	1.44 to 2.96
Ear, face and neck	1.13	0.44 to 2.93
CHD	1.42	1.24 to 1.63
Respiratory system	1.24	0.71 to 2.15
Oro-facial clefts	1.12	0.87 to 1.44
<i>CPO</i>	0.97	0.60 to 1.56
<i>CL</i>	1.18	0.88 to 1.59
Digestive system	1.85	1.43 to 2.41
Abdominal wall defects	1.52	0.76 to 3.02
Urinary system	1.76	1.34 to 2.30
Genital organs	1.30	1.09 to 1.55
Limb	1.27	1.09 to 1.49
Skeletal dysplasia	3.34	1.97 to 5.67
Genetic syndromes and microdeletions	5.42	3.56 to 8.25
Chromosomal	5.46	4.61 to 6.46
<i>Down syndrome</i>	5.99	4.99 to 7.20
Other anomalies/ syndromes	1.95	1.70 to 2.23

In all analyses for specific sites, other than for chromosomal anomalies, individuals with chromosomal anomalies were excluded. In all analyses, the unexposed group was composed of individuals without major birth defects. Abbreviations: OR, odds ratio; CI, confidence interval; NTD, Neural Tube Defects; CHD, Congenital Heart Defects; CPO, Cleft palate only; CL, Cleft lip with/ without cleft palate. \*Categorized according to EUROCAT.



Table D. Risk of overall cancer in individuals with any, or specific, major birth defects, adjusted for country, birth year, sex, maternal age and smoking in the time period when smoking information was collected (1991-2013 in Denmark, 1987-2013 in Finland, 1998-2013 in Norway, and 1982-2014 in Sweden), among 18 614 cases and 255 346 controls.

Birth defect*	Adjusted <sup>†</sup> for maternal age		Adjusted <sup>†</sup> for maternal age and smoking <sup>‡</sup>	
	OR	99% CI	OR	99% CI
All anomalies	2.29	2.12 to 2.49	2.36	2.17 to 2.56
All anomalies excl. chromosomal anomalies	1.95	1.79 to 2.13	2.00	1.82 to 2.19
<i>Specific sites</i>				
Nervous system	6.06	4.60 to 8.00	5.97	4.46 to 7.99
<i>NTD</i>	5.59	3.34 to 9.35	4.84	2.73 to 8.56
Eye	2.78	1.78 to 4.34	2.99	1.90 to 4.70
Ear, face and neck	1.67	0.63 to 4.39	1.52	0.54 to 4.27
CHD	1.52	1.28 to 1.81	1.56	1.30 to 1.87
Respiratory system	1.68	0.85 to 3.32	1.54	0.74 to 3.18
Oro-facial clefts	1.13	0.76 to 1.70	1.22	0.81 to 1.85
<i>CPO</i>	1.00	0.51 to 1.95	1.00	0.50 to 1.99
<i>CL</i>	1.22	0.73 to 2.04	1.38	0.83 to 2.31
Digestive system	2.48	1.79 to 3.44	2.39	1.68 to 3.40
Abdominal wall defects	1.12	0.37 to 3.35	0.84	0.22 to 3.18
Urinary system	1.77	1.27 to 2.45	1.70	1.21 to 2.40
Genital organs	1.33	1.01 to 1.77	1.40	1.04 to 1.87
Limb	1.60	1.27 to 2.01	1.70	1.35 to 2.15
Skeletal dysplasia	3.92	2.17 to 7.07	3.91	2.11 to 7.23
Genetic syndromes and microdeletions	5.23	3.36 to 8.13	4.83	3.05 to 7.66
Chromosomal	7.86	6.37 to 9.71	8.21	6.59 to 10.2
<i>Down syndrome</i>	9.37	7.39 to 11.9	9.82	7.66 to 12.6
Other anomalies/ syndromes	3.46	2.90 to 4.12	3.52	2.93 to 4.22

In all analyses for specific sites, other than for chromosomal anomalies, individuals with chromosomal anomalies were excluded. In all analyses, the unexposed group was composed of individuals without major birth defects. Abbreviations: OR, odds ratio; CI, confidence interval; NTD, Neural Tube Defects; CHD, Congenital Heart Defects; CPO, Cleft palate only; CL, Cleft lip with/ without cleft palate. \*Categorized according to EUROCAT. <sup>†</sup>Also adjusted for country, birth year and sex.

<sup>‡</sup>Smoking information was missing for 8.4% of cases and 8.7% of controls.

Table E. OR (99% CI) of overall cancer in individuals with any major birth defects, adjusted for country, birth year, sex, maternal age and IVF in the time period when IVF information was reported (1990-2013 in Finland, 1984-2013 in Norway, and 1995-2014 in Sweden). In total, 1 424 out of 140 639 children were conceived through IVF.

<b>Birth defect</b>	<b>Adjusted for country, birth year, and sex</b>	<b>Adjusted for country, birth year, sex, and IVF</b>	<b>Adjusted for country, birth year, sex, IVF and maternal age</b>
All anomalies excl. chromosomal anomalies	2.22 (1.98 to 2.50)	2.22 (1.98 to 2.50)	2.21 (1.96 to 2.48)
Chromosomal anomalies	10.3 (7.87 to 13.6)	10.3 (7.86 to 13.6)	9.50 (7.22 to 12.5)

Abbreviations: OR, odds ratio; CI, confidence interval; IVF in vitro fertilization.