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Reefhuis, J.; Zandwijken, G. R.J.; De Walle, H. E.K.; Cornel, M. C.

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Birth Defect and Risk Factor Surveillance in the Northern and Southwestern Netherlands

J. Reefhuis[a] G.R.J. Zandwijken[b] H.E.K. de Walle[a] M.C. Cornel[a]

[a]EUROCAT Northern Netherlands, Department of Medical Genetics, University of Groningen, Groningen,
[b]EUROCAT Southwestern Netherlands, Municipal Health Service Rotterdam, Rotterdam, The Netherlands

Key Words
Monitoring · Birth defects · Registries · Risk factor · Surveillance · Drugs · Pregnancy

Abstract
Objective: To survey the associations between several risk factors and birth defects, in order to detect potential new teratogens. ***Methods:*** Data of the two Dutch European Registration of Congenital Anomalies (EUROCAT) registries collected before January 1, 1998 were used to perform χ^2 tests for a large number of risk factors and birth defects. Defects caused by chromosomal or monogenic disorders were analyzed separately. ***Results:*** Cross-tabulations of 80 groups of birth defects with 303 risk factors were studied. Of these, 126 combinations had a p value under 0.05, and 34 had a p value under 0.001. Of these 34 associations, some are known in the literature, some were found before in the same databases and some were new associations. ***Conclusions:*** This is a good method for generating new hypotheses for associations between risk factors and birth defects. It can be a start for new, more in-depth studies of potential teratogens.

Introduction

One of the goals of birth defect registries is the detection of potential new teratogens. For this purpose, Ten Kate et al. [1] and Cornel et al. [2] published, in 1992 and 1996, respectively, the data from the European Registration of Congenital Anomalies (EUROCAT) for the northern Netherlands (NNL) on the development of an analysis of combinations of specific birth defects and risk factors. However, since 1996, many more cases have been registered, and therefore the method was repeated, also including data from the EUROCAT registry in the southwestern Netherlands (SWNL). Birth defect and risk factor monitoring can be seen as a hypothesis-generating method, not as a clear indication of actual increased risks. Therefore, the associations found should be used as a springboard for further research.

Materials and Methods

Data

There are two EUROCAT registries in the Netherlands. In 1981, the first was established in the north of the Netherlands. After two expansions, the yearly number of births in the region is approximately 20,000. In September 1990, the second registry started in the municipality of Rotterdam in the SWNL. After three expansions, the region now consists of the whole southwestern part of the Netherlands, with a total number of births of 32,000 per year. Both registries

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J. Reefhuis
EUROCAT NNL, Department of Medical Genetics
University of Groningen, Antonius Deusinglaan 4
NL–9713 AW Groningen (The Netherlands)
Tel. +31 50 363 2952, Fax +31 50 318 7268, E-Mail j.reefhuis@med.rug.nl

Table 1. List of congenital anomalies that were included in the birth defect and risk factor surveillance

ICD code	Anomaly	ICD code	Anomaly
740	anencephaly	7513	Hirschsprung's disease
741	spina bifida	75140	malrotation of cecum and colon
75610	spina bifida occulta	75260	hypospadias
7420	encephalocele	752611	epispadias
740–7420	neural tube defects	7527	indeterminate sex
7421	microcephaly	753503	exstrophy of bladder sequence
74226	arhinencephaly/holoprosencephaly	7535	exstrophy of bladder/cloaca
7423	hydrocephaly	753501	exstrophy of bladder
7430	anophthalmia	75351	exstrophy of cloaca
7431	microphthalmia	75300	bilateral renal agenesis
74320	congenital glaucoma	75301	unilateral renal agenesis
7430–7431	anophtalmia or microphtalmia	7530	renal agenesis (unilateral or bilateral)
74332	cataract	7531	cystic kidney
74343	coloboma of iris	75320	cong. hydronephrosis
74360	congenital ptosis	75332	horseshoe kidney
74400 or	microtia: absent auditory canal	7543	dysplasia of hip
74421	microtia	7545–7547	deformities of foot
7450	persistent truncus arteriosus	7550	polydactyly
7451	transposition of great vessels	755001–755004	polydactyly, postaxial hand
7452	tetralogy of Fallot	755011–755014	polydactyly, preaxial hand
7454	VSD	755015	triphalangeal thumb
7455–74560	ASD	755021–755024	polydactyly, postaxial foot
7460	anomalies of pulmonary valve	755025–755028	polydactyly, preaxial foot
7461	tricuspid atresia/stenosis	7551	syndactyly
7463	stenosis of aortic valve	7552	reduction defects, upper limb
7467	hypoplastic left heart	7553	reduction defects, lower limb
7471	coarctation of aorta	7552–7553	all limb reduction defects
745–747	cardiovascular defects	75661	diaphragmatic hernia
	multiple heart defects	756701	omphalocele
7480	choanal atresia	756711	gastroschisis
74800, 75805	bilateral choanal atresia/stenosis	756721	prune belly syndrome
74801, 75806	unilateral choanal atresia/stenosis	7780	idiopathic hydrops fetalis
7490	cleft palate	757384	cong. cystic hygroma
7491	cleft lip	7580	Down syndrome
7492	cleft lip with cleft palate	7581	Patau syndrome
7491–7492	cleft lip with or without cleft palate	7582	Edwards syndrome
7503	tracheoesophageal fistula; esophageal atresia/stenosis	75886	triploidy
7511	atresia/stenosis of small intestine	758	chromosomal anomalies
7512	atresia/stenosis of large intestine, rectum, anal canal		monogenic disorders
75121–75124	anorectal atresia		autosomal recessive disorders
7505	hypertrophic pyloric stenosis		autosomal dominant disorders

VSD = Ventricular septal defect; ASD = atrial septal defect.

receive their notifications on a voluntary basis from the health professionals in the region. Information on risk factors such as drugs or chronic diseases are requested from either the notifier or the general practitioner. Since July 1997 in the NNL, parents of children reported to the registry also receive a questionnaire, with more detailed questions on the pregnancy and the period around conception.

In the Netherlands, women generally have only one pharmacist. This makes it possible to ask the pharmacist of the mother to provide a list of drugs delivered to the mother from 3 months prior to the pregnancy until its end. Consequently, the mother was asked in a telephone interview whether she had actually taken these drugs. More information on data collection in the NNL has been published elsewhere [3, 4]. From birth years 1981 to 1996, 5,601 children had been registered in the NNL on the reference date of January 1, 1998.

In the SWNL, a parental questionnaire was used from the start of the registry in 1990 along with the notification form used by the health professional reporting the infant. The SWNL registry also

obtains information from pharmacies on prescribed drugs. In approximately 90% of the cases, the pharmacist provided information on prescribed drugs. An evaluation of the procedure was published by Rengelink-van der Lee et al. [5] in 1996. In the SWNL region, 2,158 children born between September 1990 and December 1998 were reported to the registry. The overall prevalence is lower in the SWNL due to underascertainment. However, the quality of the data that has been collected is very good. Thus, the data can be used for this study, since it does not compare prevalences.

Analysis

The data from both registries were merged and cross-tabulations were performed. A number of different exposures are studied here. All drugs that the mother used during the month before and/or the first trimester of the pregnancy were studied. A number of other potential risk factors were also included in the analyses: some chronic diseases, maternal age and consanguinity, since these are well-known risk factors for a number of birth defects. Since the number of assisted conceptions has increased in recent years and because of suspicion of increased risk for specific anomalies, we also included in vitro fertilization (IVF) and artificial insemination with donor sperm (AID) as risk factors. Finally, smoking and alcohol use during pregnancy were included as potential risk factors.

The birth defects included in these analyses are listed in table 1. Defects caused by chromosomal or monogenic disorders were excluded; these cases were only included as chromosomal or monogenic disorders. Anomalies that were part of multiple congenital anomalies without an overall diagnosis are analyzed as separate anomalies; e.g. a case with a cleft lip and a clubfoot is included in both categories. The birth defects are sorted and grouped according to the British Paediatric Association/International Classification of Diseases (ICD), 9th revision [6]. Also, an extra extension of these codes was used, which was provided by the central EUROCAT registry in Brussels [7]. These classifications do not code according to the stage of embryonic development. It is possible that if a classification had been performed according to embryonic development, more and different associations would be found. However, the ICD classification is the one most widely used by birth defect registries.

Dichotomous variables were created for the birth defect categories listed in table 1. Dichotomous variables were also created for asthma, diabetes, epilepsy, high maternal age ($\geqslant 40$), low maternal age ($\leqslant 20$), any smoking during pregnancy, any alcohol use during pregnancy, consanguinity, IVF and AID. The drugs in both registries are coded using the Anatomical Therapeutic Chemical (ATC) codes, which have several levels (3, 5 and 7 characters, respectively). For instance, G03 indicates all sex hormones and modulators of the genital system, G03GB are the synthetic ovulation stimulants and G03GB02 is the specific drug, clomifene. All drugs are grouped into these 3 levels. When there were at least 3 cases in which a particular drug was taken during the first trimester or 1 month before, this group of drugs or specific drug was included in the birth defect and risk factor surveillance. If the exact same cases are repeated, the most specific combination is studied. Two-by-two tables were created for every combination of exposure and birth defect, and only those were further considered that had at least 3 cases exposed; this number is relatively low, but it enables us to look for rare exposure/birth defect combinations. Odds ratios (ORs), confidence intervals (CIs) and p values were calculated using the statistical package SPSS, version 7.0. The attributable fraction (AF) was calculated using the following formula: $AF = f_c\,(OR - 1)/OR$, where f_c is the fraction of cases exposed [8].

Combinations of exposure and birth defect with a p value lower than 0.001 were submitted to one extra check. The reason for this was the possibility that a mother with a long exposure history to a certain drug has several infants with a similar defect. Therefore, these cases with a similar defect and exposure were checked to see whether the presence of sib pairs could explain the association.

Results

We studied the cross-tabulations of 80 groups of birth defects with 293 drugs used 1 month before or during the first trimester and 10 other risk factors, resulting in 24,240 two-by-two tables. First, all the tables with at least 3 exposed cases were selected. Then tables with a p value lower than 0.05 were further investigated. All combinations that had the exact same number of exposed cases but measured a cruder relationship were excluded from further analysis. For instance, there was a significant relationship between antiepileptics and spina bifida, but this was a cruder version (with the exact same number of exposed cases) of the relationship between valproic acid and spina bifida and was therefore not listed in table 2. However, there is still some overlap in the tables, as extra cases with a slightly less specific diagnosis or exposure have been included for completeness. This resulted in 125 combinations of exposures and birth defects with a p value under 0.05. In table 2, these combinations are listed according to p value and OR.

In table 3, the combinations are sorted by anomaly. From this table, it can be seen that it is not possible to control for confounding by indication; for example, all mothers with epilepsy that have an infant with spina bifida also took antiepileptics. This is also the case for diabetic mothers, who used insulin, with children that have a coarctation of the aorta. Table 4 shows the same results sorted by risk factor. Here, it is clear that one drug can have an association with different groups of anomalies. For instance, glucocorticoids (H02AB) show a significant relationship with transposition of the great vessels, hypospadias and neural tube defects.

The associations with small numbers of exposed cases and a p value under 0.001 were checked to see whether there were sib pairs among these cases. The 3 cases that were exposed in utero to gonadotropins (G03GA) and had a cystic kidney were triplets; therefore it is not clear whether it is a maternal risk or whether it is the gonadotropins which is associated with the cystic kidney. The only other sib pair occurred in the association between valproic acid and spina bifida.

Table 2. Significant associations from birth defect and risk factor surveillance sorted by p value and OR

Exposure	ATC code	Anomaly	Exp.	Non-exp.	OR	95% CI	p	AF %
Xylometazoline	R01AA07	reduction defects, lower limb	3	63	21.501	6.417–75.210	0.00000	4.33
Low maternal age (⩽20) [16, 17]		gastroschisis	5	13	13.252	4.681–37.522	0.00000	25.68
Clomifene	G03GB02	coloboma of the iris	3	20	12.602	3.680–43.155	0.00000	12.01
Insulins	A10AA09	coarctation of aorta	4	138	10.484	3.552–30.948	0.00000	2.55
Glucocorticoids	H02AB	transposition of great vessels	4	170	9.892	3.312–29.539	0.00000	2.07
Consanguinity		autosomal recessive disorders	29	216	7.936	5.183–12.152	0.00000	10.35
High maternal age (⩾40) [12, 13]		trisomy 18	9	53	7.173	3.484–14.767	0.00000	12.49
High maternal age (⩾40) [12, 13]		trisomy 21	39	382	4.960	3.435–7.163	0.00000	7.40
Homeopathic products	Z	cleft lip with cleft palate	9	286	4.666	2.273–9.581	0.00000	2.40
High maternal age (⩾40) [12, 13]		chromosomal anomalies	56	638	4.610	3.338–6.367	0.00000	6.32
Consanguinity		monogenic disorders	44	644	4.324	3.020–6.190	0.00000	4.92
Antianemic preparations	B03	dysplasia of hip	13	757	4.122	2.133–7.962	0.00000	1.28
Alcohol		dysplasia of hip	36	734	0.340	0.242–0.479	0.00000	−9.08
Antibiotics and chemotherapeutics for dermatological use	D06	spina bifida	3	200	10.289	2.848–37.164	0.00001	1.33
Valproic acid [14, 15]	N03AX04	spina bifida	3	200	9.430	2.641–33.677	0.00002	1.32
Antibiotics and chemotherapeutics for dermatological use	D06	neural tube defects	4	348	8.502	2.653–27.244	0.00002	1.00
Clomifene	G03GB02	ASD	11	314	3.103	1.638–5.878	0.00003	2.29
Oxazepam	N05BA04	cleft lip	3	207	9.103	2.550–32.500	0.00004	1.27
Other antiepileptics [16]	N03AX	spina bifida	4	199	6.884	2.350–20.161	0.00004	1.68
Sex hormones and modulators of the genital system	G03	coloboma of iris	4	19	6.840	2.309–20.265	0.00006	14.85
Folic acid	B03BB01	dysplasia of hip	11	759	3.737	1.846–7.564	0.0001	1.05
Antiepileptics	N03	microcephaly	3	84	7.175	2.172–23.700	0.0002	2.97
Smoking		deformities of foot	98	322	1.671	1.321–2.113	0.0002	9.37
Tetracyclines	J01AA	reduction defects, upper limb	3	132	8.641	2.537–29.434	0.0003	1.97
Imidazole derivatives	D01AC	all limb reduction defects	3	180	6.998	2.043–23.970	0.0003	1.41
Salicylic acid and derivatives	N02BA	coarctation of aorta	3	139	6.828	2.032–22.942	0.0003	1.80
Human menopausal gonadotropin	G03GA02	cystic kidney	3	93	6.648	2.014–21.947	0.0003	2.65
Diabetes [19, 20]		cardiovascular defects	23	1,737	2.635	1.526–4.547	0.0003	0.81
Sex hormones and modulators of the genital system	G03	dysplasia of hip	7	763	0.272	0.128–0.579	0.0003	−2.43
Low maternal age (⩽20)		chromosomal anomalies	5	686	0.227	0.093–0.553	0.0003	−2.46
Imidazole derivatives	D01AC	cleft palate	3	201	6.250	1.826–21.387	0.0008	1.24
Salbutamol	R03AC02	hypospadias	5	289	4.436	1.705–11.544	0.0008	1.32
Gynecological anti-infectives and antiseptics	G01	hypospadias	8	286	3.286	1.560–6.923	0.0009	1.89
Corticosteroids, moderately potent (group ii)	D07AB	multiple heart defects	3	365	6.742	1.817–25.007	0.001	0.69
Chorionic gonadotropin	G03GA01	cystic kidney	3	93	5.853	1.782–19.221	0.001	2.59
Drugs used in diabetes	A10	cardiovascular defects	18	1,742	2.685	1.446–4.986	0.001	0.64
Meclozine	R06AE05	cardiovascular defects	5	1,755	8.543	1.656–44.069	0.002	0.25
Throat preparations	R02	monogenic disorders	3	685	7.738	1.728–34.643	0.002	0.38
Antidiarrheals, intestinal anti-inflammatory/ anti-infective agents	A07	cleft lip	3	207	5.744	1.686–19.561	0.002	1.18
Diabetes		tetralogy of Fallot	3	85	5.380	1.646–17.586	0.002	2.78
Consanguinity		cataract	4	44	4.582	1.626–12.916	0.002	6.51
Benzodiazepine derivatives	N05BA	cleft lip	4	206	4.561	1.598–13.016	0.002	1.49
Diabetes		coarctation of aorta	4	138	4.477	1.593–12.578	0.002	2.19
Piperazine derivatives	R06AE	multiple heart defects	5	363	4.058	1.545–10.663	0.002	1.02
Antihistamines for systemic use	R06	cleft lip	5	205	3.978	1.564–10.116	0.002	1.78
Imidazole derivatives	G01AF	syndactyly	5	180	3.942	1.557–9.978	0.002	2.02
Psycholeptics	N05	cleft lip	5	205	3.811	1.502–9.674	0.002	1.76
Insulins	A10AA09	cardiovascular defects	12	1,748	3.161	1.440–6.940	0.002	0.47
Piperazine derivatives	R06AE	cardiovascular defects	14	1,746	2.998	1.461–6.155	0.002	0.53
Insulins	A10AA	cardiovascular defects	17	1,743	2.650	1.404–5.001	0.002	0.60
Salicylic acid and derivatives	N02BA	syndactyly	3	182	5.185	1.548–17.375	0.003	1.31
Epilepsy		polydactyly	5	202	3.790	1.494–9.613	0.003	1.78
Clomifene	G03GB02	anencephaly	5	116	3.656	1.458–9.167	0.003	3.00
Meclozine	R06AE05	VSD	3	787	6.638	1.483–29.711	0.004	0.32
Piperazine derivatives	R06AE	transposition of great vessels	3	171	4.911	1.476–16.344	0.004	1.37
Nasal preparations	R01	all limb reduction defects	4	179	4.107	1.455–11.588	0.004	1.65
Paracetamol, combinations excl. psycholeptics	N02BE51	cleft lip	3	207	4.742	1.413–15.919	0.005	1.13
Antiepileptics	N03	hypospadias	5	289	3.570	1.391–9.165	0.005	1.22
Homeopathic products	Z	spina bifida	5	198	3.508	1.388–8.865	0.005	1.76
IVF		anomalies of pulmonary valve	6	216	3.144	1.349–7.332	0.005	1.84
Urologicals	G04	cleft palate	3	201	4.683	1.399–15.680	0.006	1.16
Low maternal age (⩽20)		cystic hygroma	3	22	4.647	1.380–15.649	0.006	9.42
Anesthetics	N01	deformities of foot	4	416	4.141	1.387–12.363	0.006	0.72
Homeopathic products	Z	cleft lip	5	204	3.402	1.347–8.595	0.006	1.69
Amoxicillin	J01CA04	cleft lip with or without cleft palate	12	493	2.330	1.258–4.315	0.006	1.36
Clotrimazole	G01AF02	autosomal dominant disorders	4	319	3.873	1.336–11.227	0.007	0.92

Table 2 (continued)

Exposure	ATC code	Anomaly	Exp.	Non-exp.	OR	95% CI	p	AF %
Clomifene	G03GB02	reduction defects, upper limb	5	130	3.256	1.301–8.149	0.008	2.57
Antihistamines for systemic use	R06	cleft lip with or without cleft palate	8	497	2.699	1.262–5.773	0.008	1.00
Alcohol		polydactyly, postaxial hand	13	43	2.274	1.218–4.245	0.008	13.01
Imidazole derivatives	G01AF	hypospadias	6	288	2.970	1.265–6.971	0.009	1.35
Anilides	N02BE	renal agenesis (unilateral or bilateral)	6	128	2.859	1.237–6.608	0.010	2.91
Nasal preparations	R01	renal agenesis (unilateral or bilateral)	3	131	4.135	1.265–13.509	0.011	1.70
Consanguinity		microcephaly	5	82	3.079	1.230–7.704	0.011	3.88
Psycholeptics	N05	cleft lip with or without cleft palate	8	497	2.579	1.209–5.500	0.011	0.97
Ovulation stimulants, synthetic	G03GB	cardiovascular defects	25	1,735	1.865	1.142–3.044	0.011	0.66
Low maternal age (⩽20)		monogenic disorders	30	644	1.665	1.1122–2.472	0.011	1.78
Triamcinolone	D07AB09	cardiovascular defects	3	1,757	10.241	1.065–98.517	0.012	0.15
Antithrombotic agents	B01	deformities of foot	3	417	4.393	1.235–15.626	0.012	0.55
Piperazine derivatives	R06AE	ASD	4	321	3.550	1.232–10.233	0.012	0.88
Consanguinity		dysplasia of hip	6	764	0.363	0.160–0.824	0.012	−1.37
Diabetes		all limb reduction defects	4	179	3.433	1.226–9.614	0.013	1.55
Antiasthmatics, inhalants	R03	hypospadias	6	288	2.807	1.199–6.573	0.013	1.31
Piperazine derivatives	R06AE	cleft lip	3	207	4.038	1.215–13.415	0.014	1.07
Glucocorticoids	H02AB	hypospadias	3	291	4.040	1.189–13.730	0.015	0.77
Antifungals for dermatological use	D01	autosomal dominant disorders	4	319	3.441	1.197–9.892	0.015	0.88
Low maternal age (⩽20)		autosomal recessive disorders	13	226	2.000	1.124–3.561	0.016	2.72
Sex hormones and modulators of the genital system	G03	encephalocele	3	25	3.879	1.163–12.938	0.017	7.95
Anilides	N02BE	cleft lip with or without cleft palate	15	490	1.917	1.111–3.310	0.017	1.42
High maternal age (⩾40)		dysplasia of hip	9	761	0.450	0.229–0.883	0.017	−1.43
Anilides	N02BE	tracheoesophageal fistula; esophageal atresia/stenosis	4	75	3.223	1.161–8.950	0.018	3.49
Antiepileptics	N03	neural tube defects	5	347	2.950	1.151–7.565	0.018	0.94
Antihistamines for systemic use	R06	multiple heart defects	6	362	2.706	1.147–6.383	0.018	1.03
Sex hormones and modulators of the genital system	G03	ASD	17	308	1.827	1.101–3.032	0.018	2.37
Triazole derivatives	J02AC	chromosomal anomalies	3	691	4.378	1.129–16.966	0.020	0.33
Anesthetics	N01	cleft lip with or without cleft palate	4	501	3.399	1.139–10.139	0.020	0.56
Chorionic gonadotropin	G03GA01	ASD	5	320	2.888	1.132–7.367	0.020	1.01
Epilepsy		neural tube defects	6	346	2.659	1.130–6.255	0.020	1.06
Low maternal age (⩽20)		VSD	29	645	1.598	1.071–2.385	0.021	1.61
Smoking		VSD	103	687	0.778	0.626–0.966	0.023	−3.72
Sex hormones and modulators of the genital system	G03	hypoplastic left heart	5	59	2.751	1.094–6.918	0.025	4.97
Sex hormones and modulators of the genital system	G03	diaphragmatic hernia	5	59	2.751	1.094–6.918	0.025	4.97
AID		dysplasia of hip	6	764	2.737	1.096–6.835	0.025	0.49
Anilides	N02BE	atresia/stenosis of large intestine, rectum, anal canal	5	111	2.731	1.096–6.809	0.025	2.73
Progestogens and estrogens, fixed combinations	G03AA	cardiovascular defects	15	1,745	2.054	1.081–3.905	0.025	0.44
Psychoanaleptics	N06	trisomy 21	3	419	3.745	1.072–13.083	0.026	0.52
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	A07	cleft lip with or without cleft palate	4	501	3.210	1.082–9.519	0.026	0.55
Epilepsy		spina bifida	4	199	3.017	1.079–8.436	0.027	1.32
Consanguinity		chromosomal anomalies	6	688	0.408	0.180–0.925	0.027	−1.25
Asthma		stenosis of aortic valve	4	74	2.955	1.065–8.194	0.029	3.39
Estren derivatives	G03DC	monogenic disorders	5	683	2.868	1.062–7.750	0.030	0.47
Sex hormones and modulators of the genital system	G03	cataract	4	44	2.944	1.049–8.261	0.031	5.50
Clomifene	G03GB02	tracheoesophageal fistula; esophageal atresia/stenosis	3	76	3.292	1.020–10.629	0.035	2.64
Sex hormones and modulators of the genital system	G03	anomalies of pulmonary valve	12	210	1.874	1.039–3.404	0.036	2.52
Homeopathic products	Z	neural tube defects	6	346	2.406	1.027–5.636	0.037	1.00
Imidazole derivatives	D01AC	multiple heart defects	3	365	3.367	0.987–11.481	0.039	0.57
Analgesics	N02	trisomy 21	3	419	0.319	0.101–1.004	0.039	−1.52
Glucocorticoids	H02AB	neural tube defects	3	349	3.342	0.984–11.349	0.040	0.60
High maternal age (⩾40)		multiple heart defects	3	365	0.320	0.102–1.007	0.040	−1.73
Amoxicillin	J01CA04	trisomy 21	9	413	2.028	1.010–4.072	0.042	1.08
Paracetamol	N02BE01	atresia/stenosis of large intestine, rectum, anal canal	4	112	2.722	0.984–7.523	0.044	2.18
Imidazole derivatives	G01AF	reduction defects upper limb	3	132	3.128	0.966–10.125	0.045	1.51
Sex hormones and modulators of the genital system	G03	cardiovascular defects	66	1,694	1.344	1.006–1.795	0.045	0.96
IVF		multiple heart defects	7	361	2.185	0.995–4.800	0.046	1.03
High maternal age (⩾40)		monogenic disorders	9	679	0.510	0.260–1.002	0.046	−1.26

Exp. = Exposed cases; Nonexp. = nonexposed cases; OR = odds ratio; AF = attributable fraction; ASD = atrial septal defect; VSD = ventricular septal defect.

Table 3. Significant associations from birth defect and risk factor surveillance sorted by ICD code of the anomaly

Anomaly	Exposure	ATC code	Exp.	Non-exp.	OR	95% CI	p	AF %
Anencephaly	clomifene	G03GB02	5	116	3.656	1.458–9.167	0.003	3.00
Spina bifida	antibiotics and chemotherapeutics for dermatological use	D06	3	200	10.289	2.848–37.164	0.00001	1.33
Spina bifida [14, 15]	valproic acid	N03AX04	3	200	9.430	2.641–33.677	0.00002	1.32
Spina bifida [18]	other antiepileptics	N03AX	4	199	6.884	2.350–20.161	0.00004	1.68
Spina bifida	homeopathic products	Z	5	198	3.508	1.388–8.865	0.005	1.76
Spina bifida	epilepsy		4	199	3.017	1.079–8.436	0.027	1.32
Encephalocele	sex hormones and modulators of the genital system	G03	3	25	3.879	1.163–12.938	0.017	7.95
Neural tube defects	antibiotics and chemotherapeutics for dermatological use	D06	4	348	8.502	2.653–27.244	0.00002	1.00
Neural tube defects	antiepileptics	N03	5	347	2.950	1.151–7.565	0.018	0.94
Neural tube defects	epilepsy		6	346	2.659	1.130–6.255	0.020	1.06
Neural tube defects	homeopathic products	Z	6	346	2.406	1.027–5.636	0.037	1.00
Neural tube defects	glucocorticoids	H02AB	3	349	3.342	0.984–11.349	0.040	0.60
Microcephaly	antiepileptics	N03	3	84	7.175	2.172–23.700	0.0002	2.97
Microcephaly	consanguinity		5	82	3.079	1.230–7, 704	0.011	3.88
Cataract	consanguinity		4	44	4.582	1.626–12.916	0.002	6.51
Cataract	sex hormones and modulators of the genital system	G03	4	44	2.944	1.049–8.261	0.031	5.50
Coloboma of iris	clomifene	G03GB02	3	20	12.602	3.680–43.155	0.00000	12.01
Coloboma of iris	sex hormones and modulators of the genital system	G03	4	19	6.840	2.309–20.265	0.00006	14.85
Transposition of great vessels	glucocorticoids	H02AB	4	170	9.892	3.312–29.539	0.00000	2.07
Transposition of great vessels	piperazine derivatives	R06AE	3	171	4.911	1.476–16.344	0.004	1.37
Tetralogy of Fallot	diabetes		3	85	5.380	1.646–17.586	0.002	2.78
Hypoplastic left heart	sex hormones and modulators of the genital system	G03	5	59	2.751	1.094–6.918	0.025	4.97
ASD	clomifene	G03GB02	11	314	3.103	1.638–5.878	0.00003	2.29
ASD	piperazine derivatives	R06AE	4	321	3.550	1.232–10.233	0.012	0.88
ASD	sex hormones and modulators of the genital system	G03	17	308	1.827	1.101–3.032	0.018	2.37
ASD	chorionic gonadotropin	G03GA01	5	320	2.888	1.132–7.367	0.020	1.01
VSD	meclozine	R06AE05	3	787	6.638	1.483–29.711	0.004	0.32
VSD	low maternal age ($\leqslant$20)		29	645	1.598	1.071–2.385	0.021	1.61
VSD	smoking		103	687	0.778	0.626–0.966	0.023	–3.72
Anomalies of pulmonary valve	IVF		6	216	3.144	1.349–7.332	0.005	1.84
Anomalies of pulmonary valve	sex hormones and modulators of the genital system	G03	12	210	1.874	1.039 –3.404	0.036	2.52
Stenosis of aortic valve	asthma		4	74	2.955	1.065–8.194	0.029	3.39
Coarctation of aorta	insulins	A10AA09	4	138	10.484	3.552–30.948	0.00000	2.55
Coarctation of aorta	salicylic acid and derivatives	N02BA	3	139	6.828	2.032–22.942	0.0003	1.80
Coarctation of aorta	diabetes		4	138	4.477	1.593–12.578	0.002	2.19
Multiple heart defects	corticosteroids, moderately potent (group ii)	D07AB	3	365	6.742	1.817–25.007	0.001	0.69
Multiple heart defects	piperazine derivatives	R06AE	5	363	4.058	1.545–10.663	0.002	1.02
Multiple heart defects	antihistamines for systemic use	R06	6	362	2.706	1.147–6.383	0.018	1.03
Multiple heart defects	imidazole derivatives	D01AC	3	365	3.367	0.987–11.481	0.039	0.57
Multiple heart defects	high maternal age ($\geqslant$40)		3	365	0.320	0.102–1.007	0.040	–1.73
Multiple heart defects	IVF		7	361	2.185	0.995–4.800	0.046	1.03
Cardiovascular defects [19, 20]	diabetes		23	1,737	2.635	1.526–4.547	0.0003	0.81
Cardiovascular defects	drugs used in diabetes	A10	18	1,742	2.685	1.446–4.986	0.001	0.64
Cardiovascular defects	meclozine	R06AE05	5	1,755	8.543	1.656–44.069	0.002	0.25
Cardiovascular defects	insulins	A10AA09	12	1,748	3.161	1.440–6.940	0.002	0.47
Cardiovascular defects	piperazine derivatives	R06AE	14	1,746	2.998	1.461–6.155	0.002	0.53
Cardiovascular defects	insulins	A10AA	17	1,743	2.650	1.404–5.001	0.002	0.60
Cardiovascular defects	ovulation stimulants, synthetic	G03GB	25	1,735	1.865	1.142–3.044	0.011	0.66
Cardiovascular defects	triamcinolone	D07AB09	3	1,757	10.241	1.065–98.517	0.012	0.15
Cardiovascular defects	progestogens and estrogens, fixed combinations	G03AA	15	1,745	2.054	1.081–3.905	0.025	0.44
Cardiovascular defects	sex hormones and modulators of the genital system	G03	66	1,694	1.344	1.006–1.795	0.045	0.96
Cleft palate	imidazole derivatives	D01AC	3	201	6.250	1.826–21.387	0.0008	1.24
Cleft palate	urologicals	G04	3	201	4.683	1.399–15.680	0.006	1.16
Cleft lip	oxazepam	N05BA04	3	207	9.103	2.550–32.500	0.00004	1.27
Cleft lip	antidiarrheals, intestinal anti-inflammatory/anti-infective agents	A07	3	207	5.744	1.686–19.561	0.002	1.18
Cleft lip	benzodiazepine derivatives	N05BA	4	206	4.561	1.598–13.016	0.002	1.49
Cleft lip	antihistamines for systemic use	R06	5	205	3.978	1.564–10.116	0.002	1.78
Cleft lip	psycholeptics	N05	5	205	3.811	1.502–9.674	0.002	1.76
Cleft lip	paracetamol, combinations excl. psycholeptics	N02BE51	3	207	4.742	1.413–15.919	0.005	1.13
Cleft lip	homeopathic products	Z	5	204	3.402	1.347–8.595	0.006	1.69
Cleft lip	piperazine derivatives	R06AE	3	207	4.038	1.215–13.415	0.014	1.07
Cleft lip with cleft palate	homeopathic products	Z	9	286	4.666	2.273–9.581	0.00000	2.40
Cleft lip with or without cleft palate	amoxicillin	J01CA04	12	493	2.330	1.258–4.315	0.006	1.36
Cleft lip with or without cleft palate	antihistamines for systemic use	R06	8	497	2.699	1.262–5.773	0.008	1.00
Cleft lip with or without cleft palate	psycholeptics	N05	8	497	2.579	1.209–5.500	0.011	0.97

Table 3 (continued)

Anomaly	Exposure	ATC code	Exp.	Non-exp.	OR	95% CI	p	AF %
Cleft lip with or without cleft palate	anilides	N02BE	15	490	1.917	1.111–3.310	0.017	1.42
Cleft lip with or without cleft palate	anesthetics	N01	4	501	3.399	1.139–10.139	0.020	0.56
Cleft lip with or without cleft palate	antidiarrheals, intestinal anti-inflammatory/anti-infective agents	A07	4	501	3.210	1.082–9.519	0.026	0.55
Tracheoesophageal fistula; esophageal atresia/stenosis	anilides	N02BE	4	75	3.223	1.161–8.950	0.018	3.49
Tracheoesophageal fistula; esophageal atresia/stenosis	clomifene	G03GB02	3	76	3.292	1.020–10.629	0.035	2.64
Atresia/stenosis of large intestine, rectum, anal canal	anilides	N02BE	5	111	2.731	1.096–6.809	0.025	2.73
Atresia/stenosis of large intestine, rectum, anal canal	paracetamol	N02BE01	4	112	2.722	0.984–7.523	0.044	2.18
Hypospadias	salbutamol	R03AC02	5	289	4.436	1.705–11.544	0.0008	1.32
Hypospadias	gynecological anti-infectives and antiseptics	G01	8	286	3.286	1.560–6.923	0.0009	1.89
Hypospadias	antiepileptics	N03	5	289	3.570	1.391–9.165	0.005	1.22
Hypospadias	imidazole derivatives	G01AF	6	288	2.970	1.265–6.971	0.009	1.35
Hypospadias	antiasthmatics, inhalants	R03	6	288	2.807	1.199–6.573	0.013	1.31
Hypospadias	glucocorticoids	H02AB	3	291	4.040	1.189–13.730	0.015	0.77
Renal agenesis (unilateral or bilateral)	anilides	N02BE	6	128	2.859	1.237–6.608	0.010	2.91
Renal agenesis (unilateral or bilateral)	nasal preparations	R01	3	131	4.135	1.265–13.509	0.011	1.70
Cystic kidney	human menopausal gonadotropin	G03GA02	3	93	6.648	2.014–21.947	0.0003	2.65
Cystic kidney	chorionic gonadotropin	G03GA01	3	93	5.853	1.782–19.221	0.001	2.59
Dysplasia of hip	antianemic preparations	B03	13	757	4.122	2.133–7.962	0.00000	1.28
Dysplasia of hip	alcohol		36	734	0.340	0.242–0.479	0.00000	−9.08
Dysplasia of hip	folic acid	B03BB01	11	759	3.737	1.846–7.564	0.0001	1.05
Dysplasia of hip	sex hormones and modulators of the genital system	G03	7	763	0.272	0.128–0.579	0.0003	−2.43
Dysplasia of hip	consanguinity		6	764	0.363	0.160–0.824	0.012	−1.37
Dysplasia of hip	high maternal age (⩾40)		9	761	0.450	0.229–0.883	0.017	−1.43
Dysplasia of hip	AID		6	764	2.737	1.096–6.835	0.025	0.49
Deformities of foot	smoking		98	322	1.671	1.321–2.113	0.0002	9.37
Deformities of foot	anesthetics	N01	4	416	4.141	1.387–12.363	0.006	0.72
Deformities of foot	antithrombotic agents	B01	3	417	4.393	1.235–15.626	0.012	0.55
Polydactyly	epilepsy		5	202	3.790	1.494–9.613	0.003	1.78
Syndactyly	imidazole derivatives	G01AF	5	180	3.942	1.557–9.978	0.002	2.02
Syndactyly	salicylic acid and derivatives	N02BA	3	182	5.185	1.548–17.375	0.003	1.31
Polydactyly, postaxial hand	alcohol		13	43	2.274	1.218–4.245	0.008	13.01
Reduction defects, upper limb	tetracyclines	J01AA	3	132	8.641	2.537–29.434	0.0003	1.97
Reduction defects, upper limb	clomifene	G03GB02	5	130	3.256	1.301–8.149	0.008	2.57
Reduction defects, upper limb	imidazole derivatives	G01AF	3	132	3.128	0.966–10.125	0.045	1.51
Reduction defects, lower limb	xylometazoline	R01AA07	3	63	21.501	6.417–75.210	0.00000	4.33
All limb reduction defects	imidazole derivatives	D01AC	3	180	6.998	2.043–23.970	0.0003	1.41
All limb reduction defects	nasal preparations	R01	4	179	4.107	1.455–11.588	0.004	1.65
All limb reduction defects	diabetes		4	179	3.433	1.226–9.614	0.013	1.55
Diaphragmatic hernia	sex hormones and modulators of the genital system	G03	5	59	2.751	1.094–6.918	0.025	4.97
Gastroschisis [16, 17]	low maternal age (⩽20)		5	13	13.252	4.681–37.522	0.00000	25.68
Cystic hygroma	low maternal age (⩽20)		3	22	4.647	1.380–15.649	0.006	9.42
Trisomy 21 [12, 13]	high maternal age (⩾40)		39	382	4.960	3.435–7.163	0.00000	7.40
Trisomy 21	psychoanaleptics	N06	3	419	3.745	1.072–13.083	0.026	0.52
Trisomy 21	analgesics	N02	3	419	0.319	0.101–1.004	0.039	−1.52
Trisomy 21	amoxicillin	J01CA04	9	413	2.028	1.010–4.072	0.042	1.08
Chromosomal anomalies [12, 13]	high maternal age (⩾40)		56	638	4.610	3.338–6.367	0.00000	6.32
Chromosomal anomalies	low maternal age (⩽20)		5	686	0.227	0.093–0.553	0.0003	−2.46
Chromosomal anomalies	triazole derivatives	J02AC	3	691	4.378	1.129–16.966	0.020	0.33
Chromosomal anomalies	consanguinity		6	688	0.408	0.180–0.925	0.027	−1.25
Trisomy 18 [10, 11]	high maternal age (⩾40)		9	53	7.173	3.484–14.767	0.00000	12.49
Monogenic disorders	consanguinity		44	644	4.324	3.020–6.190	0.00000	4.92
Monogenic disorders	throat preparations	R02	3	685	7.738	1.728–34.643	0.002	0.38
Monogenic disorders	low maternal age (⩽20)		30	644	1.665	1.1122–2.472	0.011	1.78
Monogenic disorders	estren derivatives	G03DC	5	683	2.868	1.062–7.750	0.030	0.47
Monogenic disorders	high maternal age (⩾40)		9	679	0.510	0.260–1.002	0.046	−1.26
Autosomal recessive disorders	consanguinity		29	216	7.936	5.183–12.152	0.00000	10.35
Autosomal recessive disorders	low maternal age (⩽20)		13	226	2.000	1.124–3.561	0.016	2.72
Autosomal dominant disorders	clotrimazole	G01AF02	4	319	3.873	1.336–11.227	0.007	0.92
Autosomal dominant disorders	antifungals for dermatological use	D01	4	319	3.441	1.197–9.892	0.015	0.88

Exp. = Exposed cases; Nonexp. = nonexposed cases; OR = odds ratio; AF = attributable fraction; ASD = atrial septal defect; VSD = ventricular septal defect.

Table 4. Significant associations from birth defect and risk factor surveillance sorted by risk factor and ATC code

Exposure	ATC code	Anomaly	Exp.	Non-exp.	OR	95% CI	p	AF %
AID		dysplasia of hip	6	764	2.737	1.096–6.835	0.025	0.49
Alcohol		polydactyly, postaxial hand	13	43	2.274	1.218–4.245	0.008	13.01
Alcohol		dysplasia of hip	36	734	0.340	0.242–0.479	0.00000	–9.08
Asthma		stenosis of aortic valve	4	74	2.955	1.065–8.194	0.029	3.39
Consanguinity		autosomal recessive disorders	29	216	7.936	5.183–12.152	0.00000	10.35
Consanguinity		cataract	4	44	4.582	1.626–12.916	0.002	6.51
Consanguinity		monogenic disorders	44	644	4.324	3.020–6.190	0.00000	4.92
Consanguinity		microcephaly	5	82	3.079	1.230–7, 704	0.011	3.88
Consanguinity		dysplasia of hip	6	764	0.363	0.160–0.824	0.012	–1.37
Consanguinity		chromosomal anomalies	6	688	0.408	0.180–0.925	0.027	–1.25
Diabetes		tetralogy of Fallot	3	85	5.380	1.646–17.586	0.002	2.78
Diabetes		coarctation of aorta	4	138	4.477	1.593–12.578	0.002	2.19
Diabetes		all limb reduction defects	4	179	3.433	1.226–9.614	0.013	1.55
Diabetes [19, 20]		cardiovascular defects	23	1,737	2.635	1.526–4.547	0.0003	0.81
Epilepsy		polydactyly	5	202	3.790	1.494–9.613	0.003	1.78
Epilepsy		spina bifida	4	199	3.017	1.079–8.436	0.027	1.32
Epilepsy		neural tube defects	6	346	2.659	1.130–6.255	0.020	1.06
High maternal age (⩾40) [12, 13]		trisomy 18	9	53	7.173	3.484–14.767	0.00000	12.49
High maternal age (⩾40) [12, 13]		trisomy 21	39	382	4.960	3.435–7.163	0.00000	7.40
High maternal age (⩾40) [12, 13]		chromosomal anomalies	56	638	4.610	3.338–6.367	0.00000	6.32
High maternal age (⩾40)		monogenic disorders	9	679	0.510	0.260–1.002	0.046	–1.26
High maternal age (⩾40)		dysplasia of hip	9	761	0.450	0.229–0.883	0.017	–1.43
High maternal age (⩾40)		multiple heart defects	3	365	0.320	0.102–1.007	0.040	–1.73
IVF		anomalies of pulmonary valve	6	216	3.144	1.349–7.332	0.005	1.84
IVF		multipleheart defects	7	361	2.185	0.995–4.800	0.046	1.03
Low maternal age (⩽20) [16, 17]		gastroschisis	5	13	13.252	4.681–37.522	0.00000	25.68
Low maternal age (⩽20)		cystic hygroma	3	22	4.647	1.380–15.649	0.006	9.42
Low maternal age (⩽20)		autosomal recessive disorders	13	226	2.000	1.124–3.561	0.016	2.72
Low maternal age (⩽20)		monogenic disorders	30	644	1.665	1.1122–2.472	0.011	1.78
Low maternal age (⩽20)		VSD	29	645	1.598	1.071–2.385	0.021	1.61
Low maternal age (⩽20)		chromosomal anomalies	5	686	0.227	0.093–0.553	0.0003	–2.46
Smoking		deformities of foot	98	322	1.671	1.321–2.113	0.0002	9.37
Smoking		VSD	103	687	0.778	0.626–0.966	0.023	–3.72
Antidiarrheals, intestinal anti-inflammatory/ anti-infective agents	A07	cleft lip	3	207	5.744	1.686–19.561	0.002	1.18
Antidiarrheals, intestinal anti-inflammatory/ anti-infective agents	A07	cleft lip with or without cleft palate	4	501	3.210	1.082–9.519	0.026	0.55
Drugs used in diabetes	A10	cardiovascular defects	18	1,742	2.685	1.446–4.986	0.001	0.64
Insulins	A10AA	cardiovascular defects	17	1,743	2.650	1.404–5.001	0.002	0.60
Insulins	A10AA09	coarctation of aorta	4	138	10.484	3.552–30.948	0.00000	2.55
Insulins	A10AA09	cardiovascular defects	12	1,748	3.161	1.440–6.940	0.002	0.47
Antithrombotic agents	B01	deformities of foot	3	417	4.393	1.235–15.626	0.012	0.55
Antianemic preparations	B03	dysplasia of hip	13	757	4.122	2.133–7.962	0.00000	1.28
Folic acid	B03BB01	dysplasia of hip	11	759	3.737	1.846–7.564	0.0001	1.05
Antifungals for dermatological use	D01	autosomal dominant disorders	4	319	3.441	1.197–9.892	0.015	0.88
Imidazole derivatives	D01AC	all limb reduction defects	3	180	6.998	2.043–23.970	0.0003	1.41
Imidazole derivatives	D01AC	cleft palate	3	201	6.250	1.826–21.387	0.0008	1.24
Imidazole derivatives	D01AC	multiple heart defects	3	365	3.367	0.987–11.481	0.039	0.57
Antibiotics and chemotherapeutics for dermatological use	D06	spina bifida	3	200	10.289	2.848–37.164	0.00001	1.33
Antibiotics and chemotherapeutics for dermatological use	D06	neural tube defects	4	348	8.502	2.653–27.244	0.00002	1.00
Corticosteroids, moderately potent (group ii)	D07AB	multiple heart defects	3	365	6.742	1.817–25.007	0.001	0.69
Triamcinolone	D07AB09	cardiovascular defects	3	1,757	10.241	1.065–98.517	0.012	0.15
Gynecological anti-infectives and antiseptics	G01	hypospadias	8	286	3.286	1.560–6.923	0.0009	1.89
Imidazole derivatives	G01AF	syndactyly	5	180	3.942	1.557–9.978	0.002	2.02
Imidazole derivatives	G01AF	reduction defects, upper limb	3	132	3.128	0.966–10.125	0.045	1.51
Imidazole derivatives	G01AF	hypospadias	6	288	2.970	1.265–6.971	0.009	1.35
Clotrimazole	G01AF02	autosomal dominant disorders	4	319	3.873	1.336–11.227	0.007	0.92
Sex hormones and modulators of the genital system	G03	encephalocele	3	25	3.879	1.163–12.938	0.017	7.95
Sex hormones and modulators of the genital system	G03	cataract	4	44	2.944	1.049–8.261	0.031	5.50
Sex hormones and modulators of the genital system	G03	coloboma of iris	4	19	6.840	2.309–20.265	0.00006	14.85
Sex hormones and modulators of the genital system	G03	hypoplastic left heart	5	59	2.751	1.094–6.918	0.025	4.97
Sex hormones and modulators of the genital system	G03	diaphragmatic hernia	5	59	2.751	1.094–6.918	0.025	4.97
Sex hormones and modulators of the genital system	G03	ASD	17	308	1.827	1.101–3.032	0.018	2.37

Table 4 (continued)

Exposure	ATC code	Anomaly	Exp.	Non-exp.	OR	95% CI	p	AF %
Sex hormones and modulators of the genital system	G03	anomalies of pulmonary valve	12	210	1.874	1.039–3.404	0.036	2.52
Sex hormones and modulators of the genital system	G03	cardiovascular defects	66	1,694	1.344	1.006–1.795	0.045	0.96
Sex hormones and modulators of the genital system	G03	dysplasia of hip	7	763	0.272	0.128–0.579	0.0003	–2.43
Progestogens and estrogens, fixed combinations	G03AA	cardiovascular defects	15	1,745	2.054	1.081–3.905	0.025	0.44
Estren derivatives	G03DC	monogenic disorders	5	683	2.868	1.062–7.750	0.030	0.47
Chorionic gonadotropin	G03GA01	ASD	5	320	2.888	1.132–7.367	0.020	1.01
Chorionic gonadotropin	G03GA01	cystic kidney	3	93	5.853	1.782–19.221	0.001	2.59
Human menopausal gonadotropin	G03GA02	cystic kidney	3	93	6.648	2.014–21.947	0.0003	2.65
Ovulation stimulants, synthetic	G03GB	cardiovascular defects	25	1,735	1.865	1.142–3.044	0.011	0.66
Clomifene	G03GB02	anencephaly	5	116	3.656	1.458–9.167	0.003	3.00
Clomifene	G03GB02	coloboma of iris	3	20	12.602	3.680–43.155	0.00000	12.01
Clomifene	G03GB02	tracheoesophageal fistula; esophageal atresia/stenosis	3	76	3.292	1.020–10.629	0.035	2.64
Clomifene	G03GB02	reduction defects, upper limb	5	130	3.256	1.301–8.149	0.008	2.57
Clomifene	G03GB02	ASD	11	314	3.103	1.638–5.878	0.00003	2.29
Urologicals	G04	cleft palate	3	201	4.683	1.399–15.680	0.006	1.16
Glucocorticoids	H02AB	transposition of great vessels	4	170	9.892	3.312–29.539	0.00000	2.07
Glucocorticoids	H02AB	hypospadias	3	291	4.040	1.189–13.730	0.015	0.77
Glucocorticoids	H02AB	neural tube defects	3	349	3.342	0.984–11.349	0.040	0.60
Tetracyclines	J01AA	reduction defects, upper limb	3	132	8.641	2.537–29.434	0.0003	1.97
Amoxicillin	J01CA04	cleft lip with or without cleft palate	12	493	2.330	1.258–4.315	0.006	1.36
Amoxicillin	J01CA04	trisomy 21	9	413	2.028	1.010–4.072	0.042	1.08
Triazole derivatives	J02AC	chromosomal anomalies	3	691	4.378	1.129–16.966	0.020	0.33
Anesthetics	N01	deformities of foot	4	416	4.141	1.387–12.363	0.006	0.72
Anesthetics	N01	cleft lip with or without cleft palate	4	501	3.399	1.139–10.139	0.020	0.56
Analgesics	N02	trisomy 21	3	419	0.319	0.101–1.004	0.039	–1.52
Salicylic acid and derivatives	N02BA	coarctation of aorta	3	139	6.828	2.032–22.942	0.0003	1.80
Salicylic acid and derivatives	N02BA	syndactyly	3	182	5.185	1.548–17.375	0.003	1.31
Anilides	N02BE	tracheoesophageal fistula; esophageal atresia/stenosis	4	75	3.223	1.161–8.950	0.018	3.49
Anilides	N02BE	renal agenesis (unilateral or bilateral)	6	128	2.859	1.237–6.608	0.010	2.91
Anilides	N02BE	atresia/stenosis of large intestine, rectum, anal canal	5	111	2.731	1.096–6.809	0.025	2.73
Anilides	N02BE	cleft lip with or without cleft palate	15	490	1.917	1.111–3.310	0.017	1.42
Paracetamol	N02BE01	atresia/stenosis of large intestine, rectum, anal canal	4	112	2.722	0.984–7.523	0.044	2.18
Paracetamol, combinations excl. psycholeptics	N02BE51	cleft lip	3	207	4.742	1.413–15.919	0.005	1.13
Antiepileptics	N03	microcephaly	3	84	7.175	2.172–23.700	0.0002	2.97
Antiepileptics	N03	hypospadias	5	289	3.570	1.391–9.165	0.005	1.22
Antiepileptics	N03	neural tube defects	5	347	2.950	1.151–7.565	0.018	0.94
Other antiepileptics [18]	N03AX	spina bifida	4	199	6.884	2.350–20.161	0.00004	1.68
Valproic acid [14, 15]	N03AX04	spina bifida	3	200	9.430	2.641–33.677	0.00002	1.32
Psycholeptics	N05	cleft lip	5	205	3.811	1.502–9.674	0.002	1.76
Psycholeptics	N05	cleft lip with or without cleft palate	8	497	2.579	1.209–5.500	0.011	0.97
Benzodiazepine derivatives	N05BA	cleft lip	4	206	4.561	1.598–13.016	0.002	1.49
Oxazepam	N05BA04	cleft lip	3	207	9.103	2.550–32.500	0.00004	1.27
Psychoanaleptics	N06	trisomy 21	3	419	3.745	1.072–13.083	0.026	0.52
Nasal preparations	R01	renal agenesis (unilateral or bilateral)	3	131	4.135	1.265–13.509	0.011	1.70
Nasal preparations	R01	all limb reduction defects	4	179	4.107	1.455–11.588	0.004	1.65
Xylometazoline	R01AA07	reduction defects, lower limb	3	63	21.501	6.417–75.210	0.00000	4.33
Throat preparations	R02	monogenic disorders	3	685	7.738	1.728–34.643	0.002	0.38
Antiasthmatics, inhalants	R03	hypospadias	6	288	2.807	1.199–6.573	0.013	1.31
Salbutamol	R03AC02	hypospadias	5	289	4.436	1.705–11.544	0.0008	1.32
Antihistamines for systemic use	R06	cleft lip	5	205	3.978	1.564–10.116	0.002	1.78
Antihistamines for systemic use	R06	multiple heart defects	6	362	2.706	1.147–6.383	0.018	1.03
Antihistamines for systemic use	R06	cleft lip with or without cleft palate	8	497	2.699	1.262–5.773	0.008	1.00
Piperazine derivatives	R06AE	transposition of great vessels	3	171	4.911	1.476–16.344	0.004	1.37
Piperazine derivatives	R06AE	multiple heart defects	5	363	4.058	1.545–10.663	0.002	1.02
Piperazine derivatives	R06AE	cleft lip	3	207	4.038	1.215–13.415	0.014	1.07
Piperazine derivatives	R06AE	ASD	4	321	3.550	1.232–10.233	0.012	0.88
Piperazine derivatives	R06AE	cardiovascular defects	14	1,746	2.998	1.461–6.155	0.002	0.53
Meclozine	R06AE05	cardiovascular defects	5	1,755	8.543	1.656–44.069	0.002	0.25
Meclozine	R06AE05	VSD	3	787	6.638	1.483–29.711	0.004	0.32
Homeopathic products	Z	cleft lip with cleft palate	9	286	4.666	2.273–9.581	0.00000	2.40
Homeopathic products	Z	spina bifida	5	198	3.508	1.388–8.865	0.005	1.76
Homeopathic products	Z	cleft lip	5	204	3.402	1.347–8.595	0.006	1.69
Homeopathic products	Z	neural tube defects	6	346	2.406	1.027–5.636	0.037	1.00

Exp. = Exposed cases; Nonexp. = nonexposed cases; OR = odds ratio; AF = attributable fraction; VSD = ventricular septal defect; ASD = atrial septal defect.

Table 5. Associations found in EUROCAT NNL study in 1996 with p values under 0.01[1]

Anomaly	Exposure	ATC code	1995			1998		
			exp.	nonexp.	OR	exp.	nonexp.	OR
Spina bifida	other antiepileptics	N03AX	4	125	7.28	4	199	6.88
Spina bifida	valproic acid	N03AX04	3	126	10.25	3	200	9.43
Cardiovascular defects	diabetes		17	1,014	2.76	23	1,737	2.64
Trisomy 21	high maternal age (⩾40)		16	196	7.68	39	382	4.96
Chromosomal anomalies	high maternal age (⩾40)		25	327	8.95	56	638	4.61
Coloboma of iris	sex hormones and modulators of the genital system[2]	G03	3	10	20.76	3	20	12.60
Cleft lip with or without cleft palate	psycholeptics	N05	6	271	5.89	8	497	2.58
Cleft lip with or without cleft palate	homeopathic drugs[2]	Z	5	272	4.56	9	286	4.67
Renal agenesis	analgesics[3]	N02	4	64	5.42	6[3]	128	2.86
Deformities of foot	smoking		65	194	1.73	98	322	1.67

The data for these associations from 1998 is also listed. Exp. = Exposed cases; nonexp. = nonexposed cases; OR = odds ratio.
[1] In that study, the cutoff point was set at 0.01 [2].
[2] These associations were further specified in the present study.
[3] Specified to anilides in association with renal agenesis.

A number of associations were studied further. First the association between xylometazoline and reduction defects of the lower limbs. All these cases were registered at the EUROCAT SWNL registry within a period of 3 years. There has been a report including two of the three cases as part of a cluster [9]. In this report, no conclusion was drawn about the relationship between xylometazoline and reduction defects of the lower limb. It was mentioned, however, that since xylometazoline is a vasoconstrictive drug, there is a potential biological pathway. The association between folic acid and congenital dysplasia of the hip was also further studied. The explanation is probably that the campaign to promote folic acid use [10] coincided with a meeting with well-baby clinicians and orthopedic surgeons to clarify that hip dysplasia is a birth defect that is eligible for registration. Therefore, we saw an increase in both folic acid use and registered congenital hip dysplasia in the NNL.

The 10 associations that were found using the EUROCAT NNL data from 1981 to 1995 with a p value under 0.01 are listed in table 5 [2]. For all these associations, additional cases were identified in the present study, and these results are also shown in table 5. Three could be further refined. Firstly, the association between analgesics (N02) and renal agenesis. In the current study, we were able to refine this to an association between analides (N02BE) and renal agenesis. The second is the association between homeopathic products (Z) and cleft lip with or without cleft palate. In this study, associations were found between the separate diagnostic groups, isolated cleft lip, and cleft lip and palate, and homeopathic products. The association between sex hormones/modulators of the genital system (G03) and coloboma of the iris was also specified. Three out of 23 pregnancies resulting in an infant with coloboma of the iris were conceived by using clomifene as an ovulation stimulator. The results from the previous study concerning smoking and clubfoot resulted in another study using a larger European population, in which the relationship was confirmed [11].

Discussion

Among the new risk factors that were found in this study, no new thalidomides were found, meaning that there are no teratogens with an OR higher than 30. However, the method clearly works, since a number of known associations were confirmed. Examples of these associations are high maternal age with chromosomal anomalies [12, 13], and valproic acid with spina bifida [14, 15].

When many significance tests are performed, it can be expected that some associations are found by chance (type 1 error). For instance, the association between clotrimazole and autosomal dominant disorders is a clear example of a false positive result, since autosomal dominant disorders are hereditary. A way to correct for a type 1 error is to set a more restrictive cutoff level for the p value. When 24,240 tests are done and the cutoff level for the p value is set to 0.001, a total of 24 associations are expected to occur.

In this study, 33 associations were found, with 9 associations which are known in the current literature. These

associations are consanguinity with monogenic disorders, high maternal age with chromosomal anomalies [12, 13], low maternal age with gastroschisis [16, 17], antiepileptics (valproic acid) with neural tube defects [14, 15, 18] and diabetes with cardiovascular defects [19, 20].

Several levels of specificity are used in both exposure and defects; therefore, there are a number of associations that are almost duplicates. For instance, there are 5 cases with a cleft lip where the mother used systemic antihistamines (R06). Of these 5 cases, there are 3 mothers who used piperazine derivatives (R06AE) during the first trimester or just before pregnancy. It is not clear which association is most important, therefore both were included.

The exposure parameters are dichotomous variables. For drugs and chronic diseases, this means that if there is no record, it is assumed that the disease was not present and no drugs were taken. In order to be consistent, the same methodology was used for smoking and alcohol. Therefore, women are considered smokers if it was known they smoked, but all the women with missing data on smoking are considered to be nonsmokers, hence there could be some misclassification resulting in a bias to the null.

Homeopathic drugs are relatively nonspecific drugs. They are included because this study was intended to generate new hypotheses and it is possible that some homeopathic drugs have a teratogenic effect.

This study was intended to generate hypotheses. Therefore, we used a relatively crude measure for the exposure (dichotomous) and did not look at combinations of exposures or birth defects. The relatively small number of exposed cases is due to this fact. When doing further research into the discovered associations, more specific analyses would need to be done and corrections performed for time of exposure, dose and variety in outcome.

Using this methodology, it is hard to find protective effects. There is one protective effect detected with this method; that is, low maternal age with chromosomal anomalies. The power to find protective effects is low, since at least 3 exposed cases are needed. Also, not all known associations are found in this study. This can be explained by the fact that the combination of the exposure and birth defect occurred less than 3 times in our data.

In the literature, most studies that look at associations between drugs and birth defects are only able to look at either all birth defects as one group, or some larger groups of defects such as oral clefts. The ideal setting for this type of research are birth defect registries, since the numbers are large and information on drug use and chronic diseases is gathered using standard methodology. However, there could be ascertainment bias in birth defect registries, especially concerning exposure, but this would most likely result in false negatives. A good example of the use of the data of several birth defect registries is the MADRE (Malformation Drug Exposure Surveillance) project [21].

Monitoring of birth defects can be done in several ways. The purpose of monitoring is the detection of new risk factors for birth defects in space or time. In order to be able to do this, the EUROCAT NNL registry produces a report that includes the distribution of prevalences over the years and within the region that it covers. This paper can also be seen as a monitoring technique to detect new risk factors for birth defects. If new teratogenic risks are identified as soon as possible, potential future harm may be prevented at a much earlier stage.

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