

Congenital Anomalies Associated with Trisomy 18 or Trisomy 13: A Registry-Based Study in 16 European Countries, 2000–2011

Anna Springett,¹ Diana Wellesley,² Ruth Greenlees,³ Maria Loane,³ Marie-Claude Addor,⁴ Larraitz Arriola,⁵ Jorieke Bergman,⁶ Clara Caverro-Carbonell,⁷ Melinda Csaky-Szunyogh,⁸ Elizabeth S. Draper,⁹ Ester Garne,¹⁰ Miriam Gatt,¹¹ Martin Haeusler,¹² Babak Khoshnood,¹³ Kari Klungsoyr,¹⁴ Catherine Lynch,¹⁵ Carlos Matias Dias,¹⁶ Robert McDonnell,¹⁷ Vera Nelen,¹⁸ Mary O'Mahony,¹⁹ Anna Pierini,²⁰ Annette Queisser-Luft,²¹ Judith Rankin,²² Anke Rissmann,²³ Catherine Rounding,²⁴ Sylvia Stoianova,²⁵ David Tuckerz,²⁶ Natalya Zymak-Zakutnia,²⁷ and Joan K. Morris^{1*}

¹Wolfson Institute, Queen Mary University of London, London, United Kingdom

²Faculty of Medicine, University of Southampton and Wessex Clinical Genetics Service, Southampton, United Kingdom

³Institute of Nursing Research, University of Ulster, Newtownabbey, United Kingdom

⁴Division of Medical Genetics, Lausanne, Switzerland

⁵Public Health Division of Gipuzkoa, Instituto BIO-Donostia, Basque Government, CIBER Epidemiologia y Salud Publica - CIBERESP, Spain

⁶Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

⁷Rare Diseases Research Area, FISABIO-Public Health, Valencia, Spain

⁸National Public Health and Medical Officer Service (NPHMOS), Budapest, Hungary

⁹Department of Health Sciences, University of Leicester, Leicester, United Kingdom

¹⁰Paediatric Department, Hospital Lillebaelt, Kolding, Denmark

¹¹Department of Health Information and Research, Guardamangia, Malta

¹²Medical University of Graz, Graz, Austria

¹³INSERM, Paris, France

¹⁴Department of Global Public Health and Primary Care, University of Bergen, Norway and Medical Birth Registry of Norway, Norwegian Institute of Public Health, Bergen, Norway

¹⁵Health Service Executive, Kilkenny, Ireland

¹⁶Centro de Estudos e registo de A C, Lisbon, Portugal

¹⁷Health Service Executive, Dublin, Ireland

¹⁸Provincial Institute for Hygiene, Antwerp, Belgium

¹⁹Health Service Executive, Cork, Ireland

²⁰CNR Institute of Clinical Physiology, Pisa, Italy

²¹University Medical Center of the Johannes Gutenberg University, Mainz, Germany

²²Institute of Health & Society, Newcastle University, Newcastle upon Tyne, United Kingdom

²³Medical Faculty Otto-von-Guericke University Magdeburg, Magdeburg, Germany

²⁴University of Oxford, Oxford, United Kingdom

Conflict of interest: None.

*Correspondence to:

Prof. Joan K. Morris, Wolfson Institute of Preventive Medicine, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ.

E-mail: j.k.morris@qmul.ac.uk

Article first published online in Wiley Online Library

(wileyonlinelibrary.com): 8 September 2015

DOI 10.1002/ajmg.a.37355

²⁵St Michael's Hospital, Bristol, United Kingdom

²⁶Public Health Wales, Swansea, United Kingdom

²⁷OMNI-Net Ukraine and Khmelnytsky Perinatal Center, Khmelnytsky, Ukraine

Manuscript Received: 11 March 2015; Manuscript Accepted: 8 August 2015

The aim of this study was to examine the prevalence of trisomies 18 and 13 in Europe and the prevalence of associated anomalies. Twenty-five population-based registries in 16 European countries provided data from 2000–2011. Cases included live births, fetal deaths (20+ weeks' gestation), and terminations of pregnancy for fetal anomaly (TOPFAs). The prevalence of associated anomalies was reported in live births. The prevalence of trisomy 18 and trisomy 13 were 4.8 (95%CI: 4.7–5.0) and 1.9 (95%CI: 1.8–2.0) per 10,000 total births. Seventy three percent of cases with trisomy 18 or trisomy 13 resulted in a TOPFA. Amongst 468 live born babies with trisomy 18, 80% (76–83%) had a cardiac anomaly, 21% (17–25%) had a nervous system anomaly, 8% (6–11%) had esophageal atresia and 10% (8–13%) had an orofacial cleft. Amongst 240 Live born babies with trisomy 13, 57% (51–64%) had a cardiac anomaly, 39% (33–46%) had a nervous system anomaly, 30% (24–36%) had an eye anomaly, 44% (37–50%) had polydactyly and 45% (39–52%) had an orofacial cleft. For babies with trisomy 18 boys were less likely to have a cardiac anomaly compared with girls (OR = 0.48 (0.30–0.77) and with trisomy 13 were less likely to have a nervous system anomaly [OR = 0.46 (0.27–0.77)]. Babies with trisomy 18 or trisomy 13 do have a high proportion of associated anomalies with the distribution of anomalies being different in boys and girls. © 2015 Wiley Periodicals, Inc.

Key words: trisomy 18; trisomy 13; Edwards syndrome; Patau syndrome; cardiac anomalies

INTRODUCTION

Trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) are, after trisomy 21 (Down syndrome), the second and third most common autosomal trisomies surviving to birth [Rasmussen et al., 2003]. The median survival time for live births with trisomy 18 is around 14 days and for live births with trisomy 13 around 10 days [Wu et al., 2013]. This is much shorter than for trisomy 21, which is around 58 years [Wu and Morris, 2013], as the anomalies associated with trisomies 18 and 13 are more severe.

The largest published study to date on associated anomalies, by Pont et al. [2006], consisted of 1,770 live born babies with trisomy 18 and 1,171 live born babies with trisomy 13 born between 1988 and 2002. They found that over 45% of babies with trisomy 18 had a major cardiac anomaly, 7% had trachea-esophageal fistula, 4% had cleft lip, 3% had diaphragmatic hernia, and 3% had spina bifida [Pont et al., 2006]. Over 34% of babies with trisomy 13 had a major cardiac anomaly, 25% had oro-facial clefts, 21% had abdominal wall defects, 16% had limb defects, and 11% had nervous system anomalies [Pont et al., 2006]. This study was based on hospital discharge

How to Cite this Article:

Springett A, Wellesley D, Greenlees R, Loane M, Addor M-C, Arriola L, Bergman J, Caverro-Carbonell C, Csaky-Szunyogh M, Draper ES, Garne E, Gatt M, Haeusler M, Khoshnood B, Klungsoyr K, Lynch C, Dias CM, McDonnell R, Nelen V, O'Mahony M, Pierini A, Queisser-Luft A, Rankin J, Rissmann A, Rounding C, Stoianova S, Tuckerz D, Zymak-Zakutnia N, Morris JK. 2015. Congenital anomalies associated with trisomy 18 or trisomy 13: A registry-based study in 16 European countries, 2000–2011. *Am J Med Genet Part A* 167A:3062–3069.

data on live births, and therefore excluded any conditions that may present after discharge from hospital and conditions in infants who may have died without further evaluation of the cause of death.

Since 1990, there has been an increase in prenatal screening and subsequent termination of fetuses with trisomies 18 or 13 in Europe [Loane et al., 2013]. This increased prenatal detection rate may influence the prevalence of associated anomalies in live births. Recent advances and greater availability of ultrasound screening of structural anomalies (e.g., cardiac anomaly) may result in a greater proportion of pregnancies with cardiac anomaly being diagnosed in more recent years.

Hence, the aim of this study was to examine the prevalence of trisomies 18 and 13 in Europe and the current prevalence of associated anomalies using data from high quality, population-based European congenital anomaly registries.

METHODS

The European Surveillance of Congenital Anomalies (EUROCAT) is a network of population-based registries of congenital anomaly in 21 countries of Europe. All the registries use multiple sources of case ascertainment to collect and validate their data. Sources, depending on the registry, include maternity, neonatal, and paediatric records; fetal medicine, cytogenetic, pathology, and medical genetics records; specialist services including paediatric cardiology; and hospital discharge and child health records. The EUROCAT database contains standardised data on congenital anomalies recorded by each registry using uniform definitions and coding, which are described elsewhere [Greenlees et al., 2011] (EUROCAT Members & Registry Descriptions and EUROCAT Guide 1.4: www.eurocat-network.eu).

The database includes live born congenital anomaly cases, fetal deaths after 20 weeks' gestation and prenatally diagnosed cases resulting in termination of pregnancy with fetal anomaly (TOPFA). Major malformations, syndromes, and chromosomal anomalies are coded according to the WHO International Classification of Diseases (ICD), ninth or tenth revision, and specified minor anomalies are excluded according to the EUROCAT classification (EUROCAT Guide 1.4: www.eurocat-network.eu).

For this study, the criteria for including registries were that: maternal age was recorded for $\geq 80\%$ of all births and TOPFAs in the registry population; and $\geq 75\%$ ascertainment of trisomy 21 according to an adapted version of the Trisomy 21 Data Quality Indicator (DQI) for 2005–2009 [Loane et al., 2011]. This Trisomy 21 DQI calculates the ratio of observed to expected trisomy 21 for each registry based on maternal age profile, external standard maternal age-specific rates, and fetal survival correction factors to 20 weeks of gestation. Twenty-five registries within 16 countries met these criteria and participated in the study.

For some affected cases only the karyotype was given and no associated anomalies were reported. These cases were excluded from the analysis. We only examined the prevalence of associated anomalies in live births and not TOPFAs or fetal deaths, as associated anomalies may not be diagnosed in pregnancies resulting in these outcomes. The reasons for this are that many structural congenital anomalies can only be diagnosed during the routine fetal anomaly ultrasound scan, which generally occurs within the 2nd trimester most often at around 18–22 weeks gestation (EUROCAT Special Report, Prenatal Screening Policies in Europe 2010: www.eurocat-network.eu), rather than earlier in gestation. If first trimester screening is done, followed quickly by a diagnostic test and subsequent TOPFA occurring prior to 15 weeks gestation, it is unlikely that these congenital anomalies will have been diagnosed and also less likely that a post mortem will be carried out. For women who have received a fetal anomaly ultrasound scan before they had a TOPFA, the more severe forms of cardiac and non-cardiac congenital anomalies are searched for and reported which may result in termination of pregnancy, whilst the less severe congenital anomalies are not detectable by ultrasound and are only investigated after the birth of the live infant. Similarly, in late fetal deaths (22+ weeks), some structural anomalies may have been identified by the ultrasound scan but further investigations may not have been carried out after the death to ascertain any other congenital anomalies. In addition, given the severity of a diagnosis of trisomy 13 or trisomy 18, it may be that the notifier does not see the necessity to record any structural anomalies.

Participating registries provided data for the 12-year study period on cases delivered between January 1, 2000 and December 31, 2011. Trends in the prevalence of these trisomies were analyzed using multilevel Poisson regression in order to adjust for differences between each registry. Formal comparisons of the prevalence of individual anomalies according to gestation were

performed using Fisher's exact test. The Poisson distribution was used to calculate 95% confidence intervals (CI) for prevalence, and the binomial distribution was used to calculate 95% CIs for proportions. Statistical analyses were carried out using STATA version 12.

RESULTS

Twenty-five registries in 16 countries provided information from 2000 to 2011 on 3,624 cases with trisomy 18 and 1,441 cases with trisomy 13 among 7,507,042 total births (live and still births). The mean age of the mother at delivery was 35 years (SD: 6 years) for trisomy 18 and 34 years (SD: 6 years) for trisomy 13.

Pregnancy Outcome

Eighteen percent (648/3,624) of cases with trisomy 18 and 21% (306/1,441) of cases with trisomy 13 were live births, and 73% of the pregnancies ended in a TOPFA for both trisomies (2,657/3,624 for trisomy 18 and 1,056/1,441 for trisomy 13, Table I). A slightly higher proportion of cases with trisomy 18 ended in a fetal death (20+ weeks' gestation) when compared with trisomy 13 [9% (315/3,624) vs. 5% (77/1,441)].

Prevalence

The total birth prevalence of trisomy 18 was 4.8 (95%CI: 4.7–5.0) and trisomy 13 was 1.9 (95%CI: 1.8–2.0) per 10,000 total births. The prevalence of trisomy 18 increased significantly by 4% per annum (95%CI: 2–5%) from 2000 to 2011 ($P < 0.001$). The prevalence of trisomy 13 also increased significantly by 2% per annum (95%CI: 0–4%) ($P = 0.006$).

The live birth prevalence of trisomy 18 was 0.87 (95%CI: 0.80–0.94) and trisomy 13 was 0.41 (95%CI: 0.37–0.46) per 10,000 live births. These have remained stable over the 12 years.

Amongst live births with trisomy 18, 35% (95%CI: 31–39%) were boys, and amongst live births with trisomy 13, 54% (95%CI: 48–60%) were boys.

Reporting of Associated Anomalies

The 50% of affected cases in whom a karyotype was reported but no associated anomalies were reported were excluded from the analy-

TABLE I. Pregnancy Outcome of Cases With Trisomies 18 or 13 in 25 EUROCAT Registries in 2000–2011

Pregnancy outcome	Trisomy 18		Trisomy 13	
	Number (n)	Proportion (%) [95%CI]	Number (n)	Proportion (%) [95%CI]
Live birth	648	18 [17–19]	306	21 [19–23]
Fetal death	315	9 [8–10]	77	5 [4–7]
Termination of pregnancy	2,657	73 [72–75]	1,056	73 [71–76]
Not known	4	0 [0–0]	2	0 [0–1]
Total	3,624	100	1,441	100

sis. For all those cases in which at least one major congenital anomaly was reported, a significantly higher percentage of live births with trisomy 18 had anomalies from at least two different organ systems compared to the percentage of fetal deaths and TOPFAs with trisomy 18 (58% vs. 53%). Similarly for trisomy 13 the percentages were 78% vs. 69%, respectively. These results indicate that there is, as expected, under-reporting of associated anomalies in fetal deaths and TOPFAs. Therefore the detailed investigation of specific anomalies associated with trisomies 18 and 13 has been restricted to 708 live births; 468 with trisomy 18 and 240 with trisomy 13.

Table II shows that 80% (95%CI:76–83) of babies with trisomy 18 had a cardiac anomaly; 20% with a severe cardiac anomaly (including common arterial truncus, transposition of great vessels, single ventricle, atrioventricular septal defect, tetralogy of Fallot, tricuspid atresia, and stenosis, Ebstein anomaly, pulmonary valve atresia, aortic valve atresia/stenosis, hypoplastic left heart, hypoplastic right heart, coarctation of aorta, total anomalous pulmonary venous return). It also shows that 57% (95%CI: 51–64) of babies with trisomy 13 had a cardiac anomaly; 17% with a severe cardiac anomaly.

Table III shows the odds of associated congenital anomalies present in live births in boys compared to girls with trisomy 18 or trisomy 13. These odds are also compared to those observed in Down syndrome births [from Morris et al., 2014]. The prevalence of cardiac anomalies in babies with trisomy 18 was significantly less in boys than girls [OR = 0.48 (95%CI: 0.30–0.77)], with an estimated prevalence of 71% in boys and 84% in girls). Similarly the prevalence of cardiac anomalies in babies with trisomy 13 was less in boys, but not statistically significantly due to the smaller numbers [OR = 0.64 (95%CI: 0.38–1.07)], with an estimated prevalence of 52% in boys and 63% in girls). This is similar to the lower prevalence of cardiac anomalies seen in boys with Down syndrome compared to girls.

Nervous system anomalies were present in 21% of babies with trisomy 18 and 39% of babies with trisomy 13, the most common anomalies being hydrocephalus (4%) and microcephaly (3%) in babies with trisomy 18, and arhinencephaly/holoprosencephaly (13%) and microcephaly (11%) in babies with trisomy 13.

Around 8% of babies with trisomy 18 had esophageal atresia, 10% had oro-facial clefts, 6% had omphalocele, 6% had diaphragmatic hernia, 7% had talipes equinovarus, and 5% had syndactyly. Over 44% of babies with trisomy 13 had polydactyly, 45% had oro-facial clefts, 22% had anophthalmos/microphthalmos, and 11% had omphalocele (Table II). Table III also shows that boys are more likely to have abdominal wall defects, limb anomalies and clefts compared to girls with trisomy 18 or 13, similar to the increased odds for boys with Down syndrome.

DISCUSSION

In agreement with other studies, we found that 35% of live births with trisomy 18 and 54% with trisomy 13 were male [Embleton et al., 1996; Rasmussen et al., 2003; Kosho et al., 2006; Pont et al., 2006; Boghossian et al., 2014]. Previous studies, often based on small samples, reported that between 32% and 100% of live born babies with trisomy 18 had a cardiac anomaly [Baty et al., 1994;

Rasmussen et al., 2003; Pont et al., 2006], and between 35% and 64% of live born babies with trisomy 13 had a cardiac anomaly [Baty et al., 1994; Embleton et al., 1996; Rasmussen et al., 2003; Pont et al., 2006]. In this study we found that 80% of live born babies with trisomy 18 had a cardiac anomaly and 57% of live born babies with trisomy 13 had a cardiac anomaly.

The only study reporting the associated anomalies in live births with trisomy 13 and 18 that has more than 1,000 births was the study by Pont et al. [2006]. Their study was carried out between 1988 and 2002 and included 11,433,660 hospitalizations of live births of which there were 1,770 live born infants with trisomy 18 and 1,171 with trisomy 13. Comparison with the study by Pont et al. indicated that the prevalence of cardiac anomalies in the trisomy 18 cases in our study was considerably higher (80% vs. 45%), partly due to VSDs being more commonly reported (55% vs. 31%). In addition, our study findings for trisomy 18 showed a significantly higher prevalence for the majority of the anomalies, in particular omphalocele (6% vs. 0.6% by Pont), and syndactyly (5% vs. 1.6%).

Likewise, the prevalence of cardiac anomalies in the trisomy 13 cases in our study was higher than in the Pont et al., [2006] study (57% vs. 35%), mainly due to VSDs (27% vs. 18%), and ASDs (18% vs. 10%). The prevalence was higher for the majority of other anomalies including anophthalmos/microphthalmos (22% vs. 8%), cleft lip (31% vs. 20%), omphalocele (11% vs. 1%), and polydactyly (44% vs. 16%).

The study by Pont et al. [2006] and our study are not completely comparable and this may explain some of the differences. Pont et al. [2006] only considered hospitalizations of babies after birth, so this would exclude any babies that go home with palliative care. It will also exclude any conditions that may present after discharge from hospital and conditions in infants who died without further evaluation of the cause of death. In contrast, the data from our study were derived from multiple sources attempting to ensure that information on all associated anomalies are collected for each case. Our study also only included a case if there was at least one associated anomaly reported.

Differences between studies may also be due to the time period studied. Recent advances and greater availability of prenatal ultrasound screening for structural anomalies (e.g., cardiac anomalies) may result in a greater proportion of cardiac anomalies being diagnosed in more recent data. The prevalence of specific cardiac anomalies is dependent on the proportion of infants with a particular trisomy that were evaluated for a cardiac anomaly (e.g., from autopsy or echocardiogram) regardless of clinical symptoms.

Other factors accounting for study differences may also include the accuracy of coding and the numbers of codes available. For the data in this study, efforts are made to ensure uniform coding in all registries with up to nine syndromes or anomalies for each case coded according to the WHO International Classification of Diseases with British Paediatric Association extension code (ICD9/BPA or ICD10/BPA) and minor anomalies are consistently excluded across the registries (EUROCAT Guide 1.4: www.eurocat-network.eu).

Many congenital anomalies can only be diagnosed during the routine fetal anomaly ultrasound scan which generally occurs at around 18–22 weeks gestation and some can only be diagnosed

TABLE II. Associated Congenital Anomalies Present in 468 Live Births With Trisomy 18 and in 240 Live Births With Trisomy 13 in 25 EUROCAT Registries in 2000–2011

	Trisomy 18		Trisomy 13	
	Number	Proportion per 100 live births (%) (95%CI)	Number	Proportion per 100 live births (%) (95%CI)
Nervous system	97	21 (17–25)	95	39 (33–46)
Neural tube defects	12	3 (1–4)	8	3 (1–6)
Anencephalus and similar	2	0 (0–2)	0	0 (0–2)
Encephalocele	2	0 (0–2)	2	1 (0–3)
Spina bifida	8	2 (1–3)	6	3 (1–5)
Hydrocephalus	18	4 (2–6)	5	2 (1–5)
Microcephaly	16	3 (2–6)	26	11 (7–15)
Arhinencephaly/holoprosencephaly	2	0 (0–2)	32	13 (9–18)
Eye	21	5 (3–7)	71	30 (24–36)
Anophthalmos/microphthalmos	10	2 (1–4)	54	22 (17–28)
Anophthalmos	0	0 (0–1)	11	5 (2–8)
Congenital cataract	1	0 (0–1)	6	3 (1–5)
Congenital glaucoma	2	0 (0–2)	1	0 (0–2)
Ear, face, and neck	37	8 (6–11)	14	6 (3–10)
Anotia	2	0 (0–2)	0	0 (0–2)
Cardiac anomalies	373	80 (76–83)	138	57 (51–64)
Severe cardiac anomaly ^a	93	20 (16–24)	42	17 (13–23)
Common arterial truncus	1	0 (0–1)	4	2 (1–4)
Transposition of great vessels	5	1 (0–3)	2	1 (0–3)
Single ventricle	2	0 (0–2)	2	1 (0–3)
Ventricular septal defect	258	55 (51–60)	66	27 (22–34)
Atrial septal defect	71	15 (12–19)	43	18 (13–23)
Atrioventricular septal defect	41	9 (6–12)	7	3 (1–6)
Tetralogy of Fallot	13	3 (2–5)	13	5 (3–9)
Tricuspid atresia and stenosis	2	0 (0–2)	0	0 (0–2)
Ebstein anomaly	0	0 (0–1)	0	0 (0–2)
Pulmonary valve stenosis	11	2 (1–4)	2	1 (0–3)
Pulmonary valve atresia	2	0 (0–2)	5	2 (1–5)
Aortic valve atresia/stenosis	2	0 (0–2)	0	0 (0–2)
Hypoplastic left heart	16	3 (2–6)	7	3 (1–6)
Hypoplastic right heart	0	0 (0–1)	0	0 (0–2)
Coarctation of aorta	17	4 (2–6)	5	2 (1–5)
Total anomalous pulmonary venous return	0	0 (0–1)	0	0 (0–2)
Patent ductus arteriosus (37+ weeks)	3	1 (0–2)	3	1 (0–4)
Respiratory	23	5 (3–7)	17	7 (4–11)
Choanal atresia	9	2 (1–4)	0	0 (0–2)
Cystic adenomatous malformation of lung	0	0 (0–1)	0	0 (0–2)
Oro-facial clefts	48	10 (8–13)	109	45 (39–52)
Cleft lip with or without cleft palate	33	7 (5–10)	75	31 (25–37)
Cleft palate	15	3 (2–5)	34	14 (10–19)
Digestive system	86	18 (15–22)	23	10 (6–14)
Esophageal atresia with or without trachea-esophageal fistula	37	8 (6–11)	1	0 (0–2)
Duodenal atresia or stenosis	0	0 (0–1)	0	0 (0–2)
Atresia or stenosis of other parts of small intestine	0	0 (0–1)	0	0 (0–2)
Ano-rectal atresia and stenosis	5	1 (0–3)	7	3 (1–6)
Hirschsprung's disease	0	0 (0–1)	0	0 (0–2)
Atresia of bile ducts	0	0 (0–1)	0	0 (0–2)
Annular pancreas	0	0 (0–1)	0	0 (0–2)
Diaphragmatic hernia	28	6 (4–9)	8	3 (1–6)
Abdominal wall defects	29	6 (4–9)	29	12 (8–17)
Gastroschisis	0	0 (0–1)	2	1 (0–3)
Omphalocele	29	6 (4–9)	26	11 (7–15)
Urinary	82	18 (14–21)	37	15 (11–21)
Bilateral renal agenesis including Potter syndrome	0	0 (0–1)	1	0 (0–2)

TABLE II. (Continued)

	Trisomy 18		Trisomy 13	
	Number	Proportion per 100 live births (%) (95%CI)	Number	Proportion per 100 live births (%) (95%CI)
Renal dysplasia	9	2 (1-4)	2	1 (0-3)
Congenital hydronephrosis	21	5 (3-7)	12	5 (3-9)
Bladder exstrophy and/or epispadias	0	0 (0-1)	1	0 (0-2)
Posterior urethral valve and/or prune belly	0	0 (0-1)	0	0 (0-2)
Genital	24	5 (3-8)	28	12 (8-16)
Hypospadias	11	2 (1-4)	5	2 (1-5)
Indeterminate sex	3	1 (0-2)	3	1 (0-4)
Limb	132	28 (24-33)	116	48 (42-55)
Limb reduction	21	5 (3-7)	5	2 (1-5)
Upper limb reduction	13	3 (2-5)	2	1 (0-3)
Lower limb reduction	4	1 (0-2)	3	1 (0-4)
Complete absence of a limb	0	0 (0-1)	0	0 (0-2)
Club foot - talipes equinovarus	33	7 (5-10)	10	4 (2-8)
Hip dislocation and/or dysplasia	7	2 (1-3)	1	0 (0-2)
Polydactyly	14	3 (2-5)	105	44 (37-50)
Syndactyly	25	5 (4-8)	4	2 (1-4)

*Severe cardiac anomaly includes the following heart defects: common arterial truncus, transposition of great vessels, single ventricle, atrioventricular septal defect, tetralogy of Fallot, tricuspid atresia and stenosis, Ebstein anomaly, pulmonary valve atresia, aortic valve atresia/stenosis, hypoplastic left heart, hypoplastic right heart, coarctation of aorta, total anomalous pulmonary venous return. Note: See the EUROCAT Guide 1.4 for more information about the inclusion and exclusion criteria for these congenital anomaly subgroups: www.eurocat-etwork.eu/anbouts/datacollection/guidelinesforregistration/guide1_4

TABLE III. The Odds of Associated Congenital Anomalies Present in Live Births in Boys Compared With Girls With Trisomy 18, Trisomy 13, or Down Syndrome. Anomalies With Less Than Three Cases Are Excluded From the Table

	Trisomy 18		Trisomy 13		Down syndrome ^a
	Number	OR (95%CI)	Number	OR (95%CI)	OR (95%CI)
Nervous system	97	1.26 (0.79-2.03)	95	0.46 (0.27-0.77)	1.13 (0.69-1.84)
Neural tube defects	12	0.74 (0.2-2.76)	8	5.79 (0.7-47.79)	-
Spina bifida	8	0.31 (0.04-2.57)	6	4.07 (0.47-35.38)	-
Hydrocephalus	18	1.44 (0.55-3.79)	5	0.52 (0.09-3.17)	0.98 (0.41-2.3)
Microcephaly	16	1.01 (0.35-2.97)	26	0.38 (0.16-0.88)	2.94 (0.88-9.78)
Arhinencephaly/holoprosencephaly			32	0.42 (0.2-0.91)	-
Eye	21	0.69 (0.25-1.91)	71	0.69 (0.39-1.2)	0.97 (0.67-1.4)
Anophthalmos/micropthalmos	10	0.55 (0.12-2.63)	54	0.67 (0.37-1.23)	
Anophthalmos			11	0.95 (0.28-3.19)	
Congenital cataract			6	0.79 (0.16-3.98)	0.52 (0.25-1.08)
Ear, face, and neck	37	0.59 (0.26-1.33)	14	0.57 (0.19-1.71)	1.00 (0.64-1.55)
Cardiac anomalies	373	0.48 (0.3-0.77)	138	0.64 (0.38-1.07)	0.75 (0.68-0.82)
Severe cardiac anomaly	93	0.63 (0.38-1.07)	42	1.14 (0.58-2.26)	0.74 (0.65-0.84)
Common arterial truncus			4	2.4 (0.25-23.45)	4.00 (0.55-29.1)
Transposition of great vessels	5	1.49 (0.25-9.03)			1.00 (0.29-3.44)
Ventricular septal defect	258	0.7 (0.47-1.03)	66	0.79 (0.45-1.39)	0.80 (0.70-0.92)
Atrial septal defect	71	0.55 (0.3-1.01)	43	0.89 (0.46-1.73)	0.90 (0.79-1.02)
Atrioventricular septal defect	41	0.36 (0.15-0.86)	7	0.58 (0.13-2.67)	0.71 (0.62-0.81)
Tetralogy of Fallot	13	0.66 (0.18-2.44)	13	0.78 (0.24-2.5)	1.16 (0.80-1.68)
Pulmonary valve stenosis	11	0 vs 11; P < 0.001			0.72 (0.40-1.32)
Pulmonary valve atresia			5	3.23 (0.36-29.34)	1.33 (0.35-5.04)
Hypoplastic left heart	16	1.01 (0.35-2.97)	7	2.02 (0.38-10.6)	-
Coarctation of aorta	17	0.93 (0.32-2.68)	5	1.19 (0.2-7.26)	0.85 (0.53-1.36)
Respiratory	23	0.45 (0.15-1.36)	17	0.68 (0.25-1.84)	0.96 (0.63-1.47)
Choanal atresia	9	0.27 (0.03-2.21)			0.70 (0.26-1.85)

(Continued)

TABLE III. (Continued)

	Trisomy 18		Trisomy 13		Down syndrome ^a
	Number	OR (95%CI)	Number	OR (95%CI)	OR (95%CI)
Oro-facial clefts	48	2.04 [1.12–3.74]	109	1.48 [0.88–2.48]	1.27 [0.62–2.57]
Cleft lip with or without cleft palate	33	1.71 [0.83–3.51]	75	1.77 [1.01–3.12]	1.80 [0.59–5.51]
Cleft palate	15	2.64 [0.94–7.41]	34	0.82 [0.39–1.71]	1.00 [0.41–2.46]
Digestive system	86	0.78 [0.46–1.31]	23	1.03 [0.43–2.45]	1.31 [1.09–1.59]
Esophageal atresia with or without trachea-esophageal fistula	37	0.94 [0.45–1.95]			0.97 [0.48–1.94]
Ano-rectal atresia and stenosis	5	3.39 [0.56–20.51]	7	2.02 [0.38–10.6]	1.30 [0.76–2.22]
Diaphragmatic hernia	28	0.73 [0.3–1.76]	8	0.78 [0.19–3.21]	1.20 [0.44–3.24]
Abdominal wall defects	29	2.19 [1.03–4.68]	29	2.78 [1.14–6.78]	2.80 [0.97–8.11]
Omphalocele	29	2.19 [1.03–4.68]	26	2.34 [0.94–5.79]	4.00 [1.00–16.3]
Urinary	82	1.36 [0.83–2.24]	37	2.42 [1.11–5.26]	1.61 [1.13–2.31]
Renal dysplasia	9	1.12 [0.28–4.53]			8.00 [1.42–45.1]
Congenital hydronephrosis	21	1.39 [0.56–3.44]	12	12 v 0 P < 0.001	1.72 [1.03–2.88]
Genital	24	2.79 [1.22–6.4]	28	7.49 [2.19–25.63]	4.02 [1.71–9.42]
Limb	132	1.78 [1.17–2.72]	116	1.29 [0.78–2.16]	1.47 [1.12–1.93]
Limb reduction	21	1.39 [0.56–3.44]	5	3.23 [0.36–29.34]	0.55 [0.24–1.26]
Club foot - talipes equinovarus	33	3.33 [1.62–6.84]	10	0.51 [0.14–1.87]	2.26 [1.15–4.45]
Hip dislocation and/or dysplasia	7	0 vs. 7; P = 0.10			
Polydactyly	14	1.25 [0.41–3.79]	105	1.51 [0.9–2.53]	2.89 [1.11–7.50]
Syndactyly	25	3.61 [1.58–8.25]	4	0.79 [0.11–5.69]	3.22 [1.63–6.36]

Values in bold are statistically significant at the 5% level of significance.

^aFrom Morris et al. [2014].

postnatally. This partly explains the observed under-detection of associated anomalies in TOPFAs, particularly in those occurring at very low gestations, and also in fetal deaths. Hence, in this study, only associated anomalies in live births were reported. It also means that the question of whether prenatal screening and subsequent termination in affected pregnancies is influenced by the prevalence of associated anomalies cannot be investigated.

The prevalence of cardiac anomalies in live births is also highly dependent on whether the baby receives a cardiac ultrasound, which may not be available for all babies. However, the observed greater prevalence of cardiac anomalies in girls than boys with trisomy 18 indicates that not all babies with trisomy 18 (in particular some boys) will have a cardiac anomaly, as there is no reason for girls to be more likely to receive an ultrasound than boys. It is likely therefore that although the prevalence of cardiac anomalies is an underestimate in our study (80% overall; 71% in boys; and 84% in girls), it is also unlikely that it is 100% particularly in boys. Similarly, the availability of cranial scans is likely to result in our estimates of brain abnormalities being too low. Sixty percent of the live births in this study were diagnosed postnatally. They may not have been detected prenatally due to their associated anomalies not being severe and hence this cohort may have fewer anomalies than would be expected if prenatal diagnosis were not available.

The statistically significant increases over time in prevalence seen in both trisomy 18 and 13 have also been noted by Loane et al. [2013] and Savva et al. [2010]. The increases in both trisomies

reflect the increases in maternal age in Europe [Embleton et al., 1996; Loane et al., 2013].

This study is the first study to have sufficient power to demonstrate that certain anomalies are more or less common in boys than girls with trisomy 18 or trisomy 13. Cardiac anomalies were more common in girls, which is in agreement with both population studies [Tennant et al., 2011] and in studies of babies with Down syndrome [Kallen et al., 1996; Freeman et al., 1998; Morris et al., 2014]. Also the observations in this study that digestive system anomalies, urinary anomalies (in particular renal dysplasias) and limb anomalies were all more common in boys has been reported in other studies for live births with Down syndrome [Badner et al., 1990; Kallen et al., 1996; Freeman et al., 2009; Ieiri et al., 2009; Morris et al., 2014] and for all live births [Tennant et al., 2011]. Potential mechanisms for these sex-specific differences have been proposed [Lary and Paulozzi, 2001].

CONCLUSION

This study provides up to date information on the major congenital anomalies associated with trisomies 18 and 13 live births in Europe based on data from 16 countries. The majority of fetuses with trisomies 18 or 13 are detected prenatally and result in a TOPFA. Those that survive to birth have a very high prevalence of associated anomalies, particularly cardiac anomalies. For trisomy 18 we confirm the frequent occurrence of esophageal atresia and ompha-

locele. For trisomy 13 we confirm the frequent occurrence of central nervous system anomalies, facial clefts and polydactyly. Babies with trisomy 18 or trisomy 13 do have a high proportion of associated anomalies with the distribution of anomalies being different in boys and girls.

REFERENCES

- Badner JA, Siebert WK, Garver KL, Chakravarti A. 1990. A genetic study of Hirschsprung disease. *Am J Hum Genet* 46:568–580.
- Baty BJ, Blackburn BL, Carey JC. 1994. Natural history of trisomy 18 and trisomy 13: I. Growth, physical assessment, medical histories, survival, and recurrence risk. *Am J Med Genet* 49:175–188.
- Boghossian NS, Hansen NI, Bell EF, Stoll BJ, Murray JC, Carey JC, Adams-Chapman I, Shankaran S, Walsh MC, Laptook AR, Faix RG, Newman NS, Hale EC, Das A, Wilson LD, Hensman AM, Grisby C, Collins MV, Vasil DM, Finkle J, Maffett D, Ball MB, Lacy CB, Bara R, Higgins RD. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network 2014. Mortality and morbidity of VLBW infants with trisomy 13 or trisomy 18. *Pediatrics* 133:226–235.
- Embleton ND, Wyllie JP, Wright MJ, Burn J, Hunter S. 1996. Natural history of trisomy 18. *Arch Dis Child Fetal Neonatal Ed* 75:F38.
- Freeman SB, Taft LF, Dooley KJ, Allran K, Sherman SL, Hassold TJ, Khoury MJ, Saker DM. 1998. Population-based study of congenital heart defects in Down syndrome. *Am J Med Genet* 80:213–217.
- Freeman SB, Torfs CP, Romitti PA, Royle MH, Druschel C, Hobbs CA, Sherman SL. 2009. Congenital gastrointestinal defects in Down syndrome: A report from the Atlanta and National Down Syndrome Projects. *Clin Genet* 75:180–184.
- Greenlees R, Neville A, Addor MC, Amar E, Arriola L, Bakker M, Barisic I, Boyd PA, Calzolari E, Doray B, Draper E, Vollset SE, Garne E, Gatt M, Haeusler M, Kallen K, Khoshnood B, Latos-Bielenska A, Martinez-Frias ML, Materna-Kiryluk A, Dias CM, McDonnell B, Mullaney C, Nelen V, O'Mahony M, Pierini A, Queisser-Luft A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Ritvanen A, Salvador J, Sipek A, Tucker D, Verellen-Dumoulin C, Wellesley D, Wertelecki W. 2011. Paper 6: EUROCAT member registries: Organization and activities. *Birth Defects Res A Clin Mol Teratol* 91:S51–S100.
- Ieiri S, Higashi M, Teshiba R, Saeki I, Esumi G, Akiyoshi J, Nakatsuji T, Taguchi T. 2009. Clinical features of Hirschsprung's disease associated with Down syndrome: A 30-year retrospective nationwide survey in Japan. *J Ped Surg* 44:2347–2351.
- Kallen B, Mastroiacovo P, Robert E. 1996. Major congenital malformations in Down syndrome. *Am J Med Genet* 65:160–166.
- Kosho T, Nakamura T, Kawame H, Baba A, Tamura M, Fukushima Y. 2006. Neonatal management of trisomy 18: Clinical details of 24 patients receiving intensive treatment. *Am J Med Genet A* 140:937–944.
- Lary JM, Paulozzi LJ. 2001. Sex differences in the prevalence of human birth defects: A population-based study. *Teratology* 64:237–251.
- Loane M, Dolk H, Garne E, Greenlees R. EUROCAT Working Group 2011. Paper 3: EUROCAT data quality indicators for population-based registries of congenital anomalies. *Birth Defects Res A Clin Mol Teratol* 91: S23–S30.
- Loane M, Morris JK, Addor MC, Arriola L, Budd J, Doray B, Garne E, Gatt M, Haeusler M, Khoshnood B, Klungsoyr Melve K, Latos-Bielenska A, McDonnell B, Mullaney C, O'Mahony M, Queisser-Wahrendorf A, Rankin J, Rissmann A, Rounding C, Salvador J, Tucker D, Wellesley D, Yevtushok L, Dolk H. 2013. Twenty-year trend in the prevalence of Down syndrome and other trisomies in Europe: Impact of maternal age and prenatal screening. *Eur J Hum Genet* 21:27–33.
- Morris JK, Garne E, Wellesley D, Addor M-C, Arriola L, Barisic I, Beres J, Bianchi F, Budd J, Dias CM, Gatt M, Klungsoyr K, Khoshnood B, Latos-Bielenska A, Mullaney C, Nelen V, Neville A, O'Mahony M, Queisser-Luft A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Rounding C, Sipek A, Tucker D, Stoianova S, de Walle H, Yevtushok L, Loane M, Dolk H. 2014. Major congenital anomalies in babies born with down syndrome: A EUROCAT population-based registry study. *Am J Med Genet Part A* 164:2979–2986.
- Pont SJ, Robbins JM, Bird TM, Gibson JB, Cleves MA, Tilford JM, Aitken ME. 2006. Congenital malformations among liveborn infants with trisomies 18 and 13. *Am J Med Genet Part A* 140:1749–1756.
- Rasmussen SA, Wong LC, Yang Q, May KM, Friedman JM. 2003. Population-based analyses of mortality in trisomy 13 and trisomy 18. *Pediatrics* 111:777–784.
- Savva GM, Walker K, Morris JK. 2010. The maternal age-specific live birth prevalence of trisomies 13 and 18 compared to trisomy 21 (Down syndrome). *Prenat Diagn* 30:57–64.
- Tennant P, Samarasekera SD, Pless-Mulloli T, Rankin J. 2011. Sex differences in the prevalence of congenital anomalies: A population based study. *Birth Defects Res A Clin Mol Teratol* 91A:894–901.
- Wu J, Springett A, Morris JK. 2013. Survival of trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) in England and Wales: 2004–2011. *Am J Med Genet A* 161:2512–2518.
- Wu J, Morris JK. 2013. The population prevalence of Down's syndrome in England and Wales in 2011. *Eur J Hum Genet* 21:1016–1019.