RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Major Congenital Anomalies in Babies Born With Down Syndrome: A EUROCAT Population-Based Registry Study

Joan K. Morris,[1]* Ester Garne,[2] Diana Wellesley,[3] Marie-Claude Addor,[4] Larraitz Arriola,[5] Ingeborg Barisic,[6] Judit Beres,[7] Fabrizio Bianchi,[8] Judith Budd,[9] Carlos Matias Dias,[10] Miriam Gatt,[11] Kari Klungsoyr,[12] Babak Khoshnood,[13] Anna Latos-Bielenska,[14] Carmel Mullaney,[15] Vera Nelen,[16] Amanda J. Neville,[17] Mary O'Mahony,[18] Annette Queisser-Luft,[19] Hanitra Randrianaivo,[20] Judith Rankin,[21] Anke Rissmann,[22] Cath Rounding,[23] Antonin Sipek,[24] Sylvia Stoianova,[25] David Tucker,[26] Hermien de Walle,[27] Lyubov Yevtushok,[28] Maria Loane,[29] and Helen Dolk[29]

[1]Queen Mary University of London, London, United Kingdom

[2]Paediatric Department, Hospital Lillebaelt, Kolding, Denmark

[3]Faculty of Medicine, University of Southampton and Wessex Clinical Genetics Service, Southampton, United Kingdom

[4]Division of Medical Genetics, Lausanne, Switzerland

[5]Subdirección de Salud Pública, San Sebastian, Spain

[6]Children's Hospital Zagreb, Clinical Hospital Centre Sisters of Charity, Medical School University of Zagreb, Zagreb, Croatia

[7]Department of Hungarian Congenital Abnormality Registry and Surveillance, National Institute for Health Development, Budapest, Nagyvárad tér 2, Hungary

[8]CNR Institute of Clinical Physiology, Pisa, Italy

[9]University of Leicester, Leicester, United Kingdom

[10]Registo Nacional de Anomalias Congénitas, Escola Nacional de Saúde Pública, Lisbon, Portugal

[11]Department of Health Information and Research, Guardamangia, Malta Martin Haeusler, Medical University of Graz, Guardamangia, Australia

[12]Medical Birth Registry of Norway, Norwegian Institute of Public Health, Bergen Norway and Department of Global Public Health and primary Care, University of Bergen, Bergen, Norway

[13]INSERM U953, Paris, France

[14]Polish Registry of Congenital Malformations, Department of Medical Genetics, Poznan University of Medical Sciences, Poznan, Poland

[15]Health Service Executive, Kilkenny, Ireland

[16]Provincial Institute for Hygiene, Antwerp, Belgium

[17]Registro IMER, Universitaria di Ferrara, Ferrara, Italy

[18]Health Service Executive, Cork, Ireland

[19]University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[20]Chu Ia Reunion, Ile de Ia Reunion, St Pierre, Reunion

[21]Institute of Health & Society Newcastle University, Newcastle upon Tyne, United Kingdom

[22]Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty Otto-von-Guericke University Magdeburg, Magdeburg, Germany

[23]National Perinatal Epidemiology Unit, University of Oxford, Oxford, United Kingdom

[24]Thomayer University Hospital, Prague, Czech Republic

[25]St Michaels Hospital, Bristol, United Kingdom

[26]Public Health Wales, Swansea, United Kingdom

Conflict of interest: none.

*Correspondence to:
Joan K. Morris, Centre for Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, United Kingdom.
E-mail: j.k.morris@qmul.ac.uk

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 00 Month 2014
DOI 10.1002/ajmg.a.36780

[27]Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[28]OMNI-Net for Children, Rivne, Ukraine
[29]Institute of Nursing Research, University of Ulster, Newtonabbey, Co Antrim, Northern Ireland, United Kingdom

Manuscript Received: 22 May 2014; Manuscript Accepted: 24 August 2014

Previous studies have shown that over 40% of babies with Down syndrome have a major cardiac anomaly and are more likely to have other major congenital anomalies. Since 2000, many countries in Europe have introduced national antenatal screening programs for Down syndrome. This study aimed to determine if the introduction of these screening programs and the subsequent termination of prenatally detected pregnancies were associated with any decline in the prevalence of additional anomalies in babies born with Down syndrome. The study sample consisted of 7,044 live births and fetal deaths with Down syndrome registered in 28 European population-based congenital anomaly registries covering seven million births during 2000–2010. Overall, 43.6% (95% CI: 42.4–44.7%) of births with Down syndrome had a cardiac anomaly and 15.0% (14.2–15.8%) had a non-cardiac anomaly. Female babies with Down syndrome were significantly more likely to have a cardiac anomaly compared to male babies (47.6% compared with 40.4%, $P < 0.001$) and significantly less likely to have a non-cardiac anomaly (12.9% compared with 16.7%, $P < 0.001$). The prevalence of cardiac and non-cardiac congenital anomalies in babies with Down syndrome has remained constant, suggesting that population screening for Down syndrome and subsequent terminations has not influenced the prevalence of specific congenital anomalies in these babies. © 2014 Wiley Periodicals, Inc.

Key words: Down syndrome; cardiac anomalies; prenatal diagnosis

How to Cite this Article:
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 AJ, O'Mahony M, Queisser-Luft A, Randrianaivo H, Rankin J, Rissmann A, Rounding C, Sipek A, Stoianova S, Tucker D, 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 9999:1–8.

INTRODUCTION

Population-based studies based on data from 1976 to 2004 have shown that over 40% of babies with Down syndrome have a major cardiac anomaly, the most common being atrioventricular septal defects (AVSD) [Kallen et al., 1996; Freeman et al., 1998, 2008; Stoll et al., 1998; Torfs and Christianson, 1998; Bell et al., 2003; Rankin et al., 2012]. Other major congenital anomalies, particularly digestive system anomalies, were also more frequent than in babies without Down syndrome [Kallen et al., 1996; Bell et al., 2003; Freeman et al., 2009; Rankin et al., 2012]. In 1999 measuring the nuchal translucency (NT) of the fetus with ultrasound, in combination with several serum markers, was found to be an adequate method of screening for Down syndrome in the first trimester of pregnancy [Spencer et al., 1999; Wald et al., 2003]. Measuring the NT of the fetus is also considered as a potential antenatal screening test for cardiac anomalies [Hyett et al., 1999; Bruns et al., 2006; Müller et al., 2007; Mogra et al., 2011]. Many cardiac and other congenital anomalies are detectable during fetal anomaly ultrasound scans performed at 18–22 weeks gestation. Hence it might be expected that fetuses with Down syndrome and cardiac or other structural congenital anomalies may be more likely to be detected than those without. By 2010, 12 of 14 countries providing data to EUROCAT (a European network of population-based registries for the epidemiologic surveillance of congenital anomalies) had widespread availability of antenatal screening for Down syndrome including NT measurements and ultrasound scans performed at 18–22 weeks [EUROCAT, 2005a, 2010; Boyd et al., 2008]. As the presence of major congenital anomalies has implications for subsequent morbidity and mortality and provision of services, it is important to know the prevalence of cardiac and other congenital anomalies in babies with Down syndrome [Rankin et al., 2012].

This study aimed to quantify the prevalence of cardiac and other anomalies in babies born with Down syndrome from 2000 to 2010 and to determine if the widespread availability of antenatal screening for Down syndrome was associated with any decline in the prevalence of specific anomalies in these babies over this time period.

METHODS

Data for this study were extracted from the European Surveillance of Congenital Anomalies (EUROCAT) Central Register. In 2011 EUROCAT had 41 population based member registries in 20 countries covering 31% of all births in Europe [Boyd et al., 2011]. Information on member registries and their methods of case ascertainment are available [Greenlees et al., 2011]. Each registry sends an anonymized uniformly coded dataset to EUROCAT Central Registry containing information on cases of major congenital anomaly registered in the local population. Cases include live births, fetal deaths at or after 20 weeks of gestation, and terminations of pregnancy for fetal anomaly

(TOPFA) at any gestation. Up to nine anomalies for each case are coded according to the International Classification of Diseases with British Paediatric Association extension code (ICD9/BPA or ICD10/BPA).

In a previous EUROCAT study, cardiac anomalies were classified into three subgroups [Dolk et al., 2011], based on the perinatal mortality rate for each of these subgroups among non-chromosomal cases from I (high perinatal mortality) to III (low perinatal mortality): (see Box 1). Six percent of all cardiac anomalies were not classified to a severity group because the ICD code was for a poorly specified cardiac anomaly of unknown severity. These cases were included in counts relating to all cardiac anomalies but not in a severity category.

SEVERITY OF CARDIAC ANOMALIES

Severity I (SI): single ventricle, hypoplastic left heart, hypoplastic right heart, Ebstein anomaly, and tricuspid atresia (univentricular cardiac anomalies).
Severity II (SII): pulmonary valve atresia, common arterial truncus, AVSD, aortic valve atresia/stenosis, transposition of great vessels, tetralogy of Fallot, total anomalous pulmonary venous return, and coarctation of aorta, without additional cardiac anomalies classified as SI.
Severity III (SIII): ventricular septal defect (VSD), atrial septal defect (ASD), pulmonary valve stenosis, without additional cardiac anomalies classified as SI or SII. Isolated Patent ductus arteriosus (PDA) in term infants.

All anomalies were coded using the EUROCAT guide 1.3 [EUROCAT, 2005b]

For this study, the criteria for including registries were that: maternal age was recorded for ≥80% of all births in the registry population; and ≥75% ascertainment of Down syndrome according to an adapted version of the Down Syndrome Data Quality Indicator (DQI) [Loane et al., 2011] for 2005–2009. This Down syndrome DQI calculates the ratio of the number of observed to number of expected cases of Down syndrome for each registry based on the maternal age profile, external standard maternal age-specific rates and fetal survival correction factors to 20 weeks of gestation (see appendix Loane et al., 2013). The final study population consisted of 27 registries in 18 countries covering seven million births during 2000–2010. Cases of Down syndrome (ICD10 codes: Q90, ICD9 code: 7580) were extracted from the central database in June 2012. The study years were chosen because from 2000 standard prenatal care in many European countries included having a fetal echogram and therefore cardiac anomalies were likely to be detected antenatally [EUROCAT, 2005a; Boyd et al., 2008]. This study did not distinguish between Down syndrome arising as a trisomy, translocation or mosaic. Although most of the registries indicated that they consult or receive direct notification of all Down syndrome cases from cytogenetic laboratories in their region, some registries identified potential problems beyond their control; hence some cases may be missed. Saxony-Anhalt (Germany) and East Midlands & South Yorkshire (UK) have notifications from some but not all of the cytogenetic labs in their region. Wielkopolska (Poland) has complete information on live birth cases, but TOPFA cases are missed as the registry does not register TOPFAs; however, these are likely to be few as TOPFA is only allowed in Poland for "severe, irreversible damage of the fetus." Norway receives cases through the medical birth notification form from delivery units and neonatal intensive care units and misses about 20% of Down syndrome cases [EUROCAT, 2010]. In Cork and Kerry (Ireland) and South East Ireland case finding was mainly via obstetric or pediatric records. Four registries do not provide any information on whether a postmortem examination was performed or not and several other registries have a high proportion of missing information on whether a postmortem examination was performed or not. The proportion of TOPFA with gestations of at least 15 weeks that had a postmortem reported varies considerably from 79% in South Portugal down to only 12% in East Midlands and South Yorkshire.

STATISTICAL METHODS

Trends in the prevalence of cardiac anomalies and non-cardiac congenital anomalies were analyzed using multilevel logistic models to take account of differences among the registers. Ninety five percent confidence intervals for proportions were calculated using the binomial distribution. Sensitivity analyses were performed excluding Malta and Ireland (where TOPFA is not legal) and Poland (where TOPFA is only available for "severe, irreversible damage of the fetus") to ensure that these three countries were not influencing the overall results. Statistical analyses were performed using STATA version 10 (Statacorp LP, College Station, TX).

RESULTS

There were 14,109 cases with Down syndrome of whom 6,738 were live births, 306 fetal deaths, and 7,065 TOPFAs. Table I shows the proportions of births (live births and fetal deaths) and TOPFAs with Down syndrome with a cardiac anomaly diagnosed according to the severity of the anomaly. Table I also shows the proportion of TOPFAs that had a postmortem examination reported. Overall, 43.6% (42.4–44.7%) of births with Down syndrome had a cardiac anomaly, while only 8.1% (7.7.4–8.7%) of TOPFAs had a diagnosed cardiac anomaly. This increased to 18.1% (16.0–20.4%) when only those TOPFAs with a postmortem examination reported were included. As expected the more severe the diagnosis, the more likely that it was recorded for the TOPFAs. The proportion with a cardiac anomaly with high perinatal mortality was similar in both births and TOPFAs with a postmortem examination reported (0.3% (0.2–0.5%) and 0.5% (0.2–1.1%), respectively).

Table I shows a similar pattern with non-cardiac congenital anomalies. Overall, 15.0% (14.2–15.8%) of births with Down syndrome had a non-cardiac congenital anomaly, while only 7.3% (6.7–7.9%) of TOPFAs had a diagnosed non-cardiac congenital anomaly. However, this increased to 16.8% (14.8–19.1%) when only those TOPFAs with a postmortem examination reported were included, which was significantly higher than in live births and fetal deaths. The most common non-cardiac congenital anomalies

TABLE I. Associated Congenital Anomalies Present in Cases With Down Syndrome

	Live births and fetal deaths from 20 weeks of gestation with Down syndrome (n = 7,044)		TOPFAs[a] with Down syndrome (n = 7,065)		TOPFAs[a] with Down syndrome who have had a Postmortem examination (n = 1,217)	
Type of congenital anomaly	Number	Proportion of births (%) (95% CI)	Number	Proportion of TOPFAs (%) (95% CI)	Number	Proportion of TOPFAs (%) (95% CI)
Any cardiac anomaly[b]	3,068	43.6 (42.4–44.7)	570	8.1 (7.4–8.7)	220	18.1 (16.0–20.4)
Severity of cardiac anomaly						
High perinatal mortality[c]	21	0.3 (0.2–0.5)	14	0.2 (0.1–0.3)	6	0.5 (0.2–1.1)
Medium perinatal mortality[c]	1,111	15.8 (14.9–16.6)	332	4.7 (4.2–5.2)	115	9.4 (7.9–11.2)
Low perinatal mortality[c]	1,661	23.6 (22.6–24.6)	153	2.42 (1.8–2.5)	84	6.9 (5.5–8.5)
Any non-cardiac anomaly[b]	1,056	15.0 (14.2–15.8)	517	7.3 (6.7–7.9)	205	16.8 (14.8–19.1)
No associated anomaly	3,503	49.7 (48.6–50.9)	6,113	86.5 (85.7–87.3)	875	71.9 (69.3–74.4)

[a]TOPFA: termination of pregnancy for fetal anomaly.
[b]Cases with both a cardiac anomaly and a non-cardiac anomaly will be present in both rows of the table.
[c]High perinatal mortality includes single ventricle, hypoplastic left heart, hypoplastic right heart, Ebstein anomaly, and tricuspid atresia (univentricular cardiac anomalies). Medium perinatal mortality includes pulmonary valve atresia, common arterial truncus, atrioventricular septal defects, aortic valve atresia/stenosis, transposition of great vessels, tetralogy of Fallot, total anomalous pulmonary venous return, and coarctation of aorta, without additional cardiac anomalies classified as high perinatal mortality. Low perinatal mortality includes ventricular septal defect, atrial septal defect, pulmonary valve stenosis, without additional cardiac anomalies classified as medium or high perinatal mortality. Isolated Patent ductus arteriosus in term infants.

recorded in cases with postmortem examinations included limb anomalies and digestive system anomalies (both over 5%).

Table I demonstrates that there was under-reporting of medium and low mortality cardiac anomalies in TOPFAs, even when a postmortem examination had been performed. When examined according to gestation, TOPFAs occurring at earlier gestations (particularly before 20 weeks) had significantly fewer cardiac anomalies reported. Figure 1 shows that the proportion of all cases with Down syndrome that were TOPFAs occurring prior to 15 weeks gestation increased significantly since 2000 from 6% to 25% in 2010, with the median gestational age decreasing from 18 to 15 weeks. The proportion of all Down syndrome cases that were TOPFAs occurring after 15 weeks gestation decreased from 41% down to 36%.

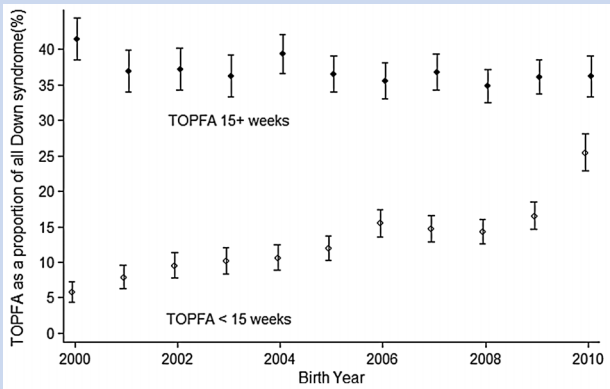

FIG. 1. Terminations of pregnancy for a fetal anomaly as a proportion of all diagnoses of Down syndrome (live births, fetal deaths from 20 weeks of gestation, and TOPFA at any gestation) according to gestation, 2000–2010.

Trends over time were examined using multi-level models to allow for differences between registers. There was no evidence of a trend in the proportions of births with Down syndrome with any associated cardiac anomaly, severe cardiac anomaly (severity 1 and 2) or non-cardiac congenital anomaly since 2000. This is illustrated in Figure 2, which shows the unadjusted proportions of births with Down syndrome with any associated cardiac

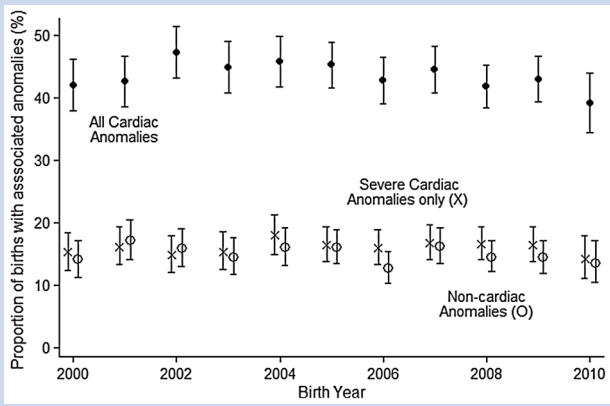

FIG. 2. The proportion of live births and fetal deaths from 20 weeks of gestation with Down syndrome with associated congenital anomalies according to severity of the cardiac anomaly[†] and year of birth, 2000–2010. [†]Severe cardiac anomalies include single ventricle, hypoplastic left heart, hypoplastic right heart, Ebstein anomaly, tricuspid atresia, pulmonary valve atresia, common arterial truncus, atrioventricular septal defects, aortic valve atresia/stenosis, transposition of great vessels, tetralogy of Fallot, total anomalous pulmonary venous return, and coarctation of aorta.

TABLE II. Associated Congenital Anomalies Present in Live Births and Fetal Deaths from 20 Weeks of Gestation With Down Syndrome According to Sex, 2000–2010

	Males with Down syndrome (n = 3,905)		Females with Down syndrome (n = 3,120)		
Type of congenital anomaly[a]	Number	Proportion of births (%) (95% CI)	Number	Proportion of births (%) (95% CI)	Odds male versus female (95% CI)
Nervous system	38	0.97 (0.69–1.33)	27	0.87 (0.57–1.26)	1.13 (0.69–1.84)
Neural tube defects	3	0.08 (0.02–0.22)	0	0 (0–0.12)	—
Hydrocephalus	11	0.28 (0.14–0.50)	9	0.29 (0.13–0.55)	0.98 (0.41–2.3)
Microcephaly	11	0.28 (0.14–0.50)	3	0.10 (0.02–0.28)	2.94 (0.88–9.78)
Eye	63	1.61 (1.24–2.06)	52	1.67 (1.25–2.18)	0.97 (0.67–1.4)
Anophthalmos/micropthalmos	3	0.08 (0.02–0.22)	0	0 (0–0.12)	—
Congenital cataract	11	0.28 (0.14–0.50)	17	0.54 (0.32–0.87)	0.52 (0.25–1.08)
Congenital glaucoma	1	0.03 (0.01–0.14)	2	0.06 (0.01–0.23)	0.40 (0.01–3.05)
Ear, face, and neck	45	1.15 (0.84–1.54)	36	1.15 (0.81–1.59)	1.00 (0.64–1.55)
Cardiac anomalies	1,579	40.40 (38.9–42.0)	1,485	47.60 (45.83–49.37)	0.75 (0.68–0.82)[b]
Severe cardiac anomalies	557	14.26 (13.2–15.4)	574	18.40 (17.05–19.8)	0.74 (0.65–0.84)[b]
Common arterial truncus	5	0.13 (0.04–0.30)	1	0.03 (0–0.18)	4.00 (0.55–29.1)
Transposition of great arteries	5	0.13 (0.04–0.30)	4	0.13 (0.03–0.33)	1.00 (0.29–3.44)
Single ventricle	1	0.03 (0.00–0.14)	2	0.06 (0.01–0.23)	0.40 (0.01–3.05)
Ventricular septal defect	518	13.27 (12.2–14.4)	500	16.03 (14.75–17.36)	0.80 (0.70–0.92)[b]
Atrial septal defect	665	17.03 (15.9–18.2)	580	18.59 (17.24–20.0)	0.90 (0.79–1.02)
Atrioventricular septal defect	471	12.06 (11.1–13.1)	506	16.22 (14.94–17.56)	0.71 (0.62–0.81)
Tetralogy of fallot	68	1.74 (1.35–2.20)	47	1.51 (1.11–2.00)	1.16 (0.80–1.68)
Tricuspid atresia and stenosis	5	0.13 (0.04–0.30)	4	0.13 (0.03–0.33)	1.00 (0.29–3.44)
Ebstein anomaly	5	0.13 (0.04–0.30)	3	0.10 (0.02–0.28)	1.33 (0.35–5.04)
Pulmonary valve stenosis	20	0.51 (0.31–0.79)	22	0.71 (0.44–1.07)	0.72 (0.40–1.32)
Pulmonary valve atresia	5	0.13 (0.04–0.30)	3	0.10 (0.02–0.28)	1.33 (0.35–5.04)
Aortic valve atresia/stenosis	2	0.05 (0.01–0.18)	1	0.03 (0.00–0.18)	1.60 (0.15–17.3)
Hypoplastic right heart	0	0 (0.00–0.09)	3	0.10 (0.02–0.28)	0.00 (0.00–1.02)
Coarctation of aorta	35	0.9 (0.63–1.24)	33	1.06 (0.73–1.48)	0.85 (0.53–1.36)
Patent ductus arteriosus as only cardiac anomaly in term infants (>=37 weeks)	74	1.90 (1.49–2.37)	63	2.02 (1.56–2.58)	0.94 (0.67–1.31)
Respiratory	47	1.20 (0.89–1.60)	39	1.25 (0.89–1.70)	0.96 (0.63–1.47)
Choanal atresia	7	0.18 (0.07–0.37)	8	0.26 (0.11–0.50)	0.70 (0.26–1.85)
Oro facial clefts	19	0.49 (0.29–0.76)	12	0.38 (0.20–0.67)	1.27 (0.62–2.57)
Cleft lip with or without palate	9	0.23 (0.11–0.44)	4	0.13 (0.03–0.33)	1.80 (0.59–5.51)
Cleft palate	10	0.26 (0.12–0.47)	8	0.26 (0.11–0.50)	1.00 (0.41–2.46)
Digestive system	302	7.73 (6.91–8.62)	187	5.99 (5.19–6.88)	1.31 (1.09–1.59)[b]
Esophageal atresia with or without tracheo-esophageal fistula	17	0.44 (0.25–0.70)	14	0.45 (0.25–0.75)	0.97 (0.48–1.94)
Duodenal atresia or stenosis	117	3.00 (2.48–3.58)	90	2.88 (2.33–3.53)	1.04 (0.79–1.37)
Atresia or stenosis of other parts of small intestine	6	0.15 (0.06–0.33)	0	0 (0.00–0.12)	—
Ano rectal atresia and stenosis	34	0.87 (0.60–1.21)	21	0.67 (0.42–1.03)	1.30 (0.76–2.22)
Hirschsprung disease	57	1.46 (1.11–1.89)	10	0.32 (0.15–0.59)	4.61 (2.38–8.93)[b]
Annular pancreas	17	0.44 (0.25–0.70)	10	0.32 (0.15–0.59)	1.36 (0.63–2.92)
Diaphragmatic hernia	9	0.23 (0.11–0.44)	6	0.19 (0.07–0.42)	1.20 (0.44–3.24)
Abdominal wall defects	14	0.36 (0.20–0.60)	4	0.13 (0.03–0.33)	2.80 (0.97–8.11)
Omphalocele	10	0.26 (0.12–0.47)	2	0.06 (0.01–0.23)	4.00 (1.00–16.3)[b]
Urinary	90	2.30 (1.86–2.83)	45	1.44 (1.05–1.93)	1.61 (1.13–2.31)[b]
Bilateral renal agenesis including Potter syndrome	2	0.05 (0.01–0.18)	2	0.06 (0.01–0.23)	0.80 (0.14–4.52)
Renal dysplasia	10	0.26 (0.12–0.47)	1	0.03 (0.00–0.18)	8.00 (1.42–45.1)[b]
Congenital hydronephrosis	45	1.15 (0.84–1.54)	21	0.67 (0.42–1.03)	1.72 (1.03–2.88)[b]
Bladder exstrophy and/or epispadia	2	0.05 (0.01–0.18)	1	0.03 (0.00–0.18)	1.60 (0.15–17.3)
Posterior urethral valve and/or prune belly	4	0.10 (0.03–0.26)	0	0 (0.00–0.12)	—

(*Continued*)

TABLE II. (*Continued*)

Type of congenital anomaly[a]	Males with Down syndrome (n = 3,905) Number	Proportion of births (%) (95% CI)	Females with Down syndrome (n = 3,120) Number	Proportion of births (%) (95% CI)	Odds male versus female (95% CI)
Genital	30	0.77 (0.52–1.09)	6	0.19 (0.07–0.42)	4.02 (1.71–9.42)[b]
Hypospadias	24	0.61 (0.39–0.91)	0	0.00 (0.00–0.12)	—
Limb	147	3.76 (3.19–4.41)	81	2.60 (2.07–3.22)	1.47 (1.12–1.93)[b]
Limb reduction	9	0.23 (0.11–0.44)	13	0.42 (0.22–0.71)	0.55 (0.24–1.26)
Upper limb reduction	7	0.18 (0.07–0.37)	9	0.29 (0.13–0.55)	0.62 (0.24–1.61)
Lower limb reduction	1	0.03 (0.00–0.14)	5	0.16 (0.05–0.37)	0.16 (0.01–1.03)
Talipesequinovarus	31	0.79 (0.54–1.12)	11	0.35 (0.18–0.63)	2.26 (1.15–4.45)[b]
Polydactyly	18	0.46 (0.27–0.73)	5	0.16 (0.05–0.37)	2.89 (1.11–7.50)[b]
Syndactyly	40	1.02 (0.73–1.39)	10	0.32 (0.15–0.59)	3.22 (1.63–6.36)[b]
Craniosynostosis	22	0.56 (0.35–0.85)	16	0.51 (0.29–0.83)	1.10 (0.58–2.07)
Congenital skin disorders	31	0.79 (0.54–1.12)	17	0.54 (0.32–0.87)	1.46 (0.81–2.62)

[a]Anomalies with less than three cases are excluded from the table.
[b]$P < 0.05$ difference between male and female

anomaly, severe cardiac anomaly (severity 1 and 2) or non-cardiac congenital anomaly. The same lack of trend was evident when Malta, Ireland and Poland were excluded from the analysis. There was no observed change in prevalence of ASD and VSD among births with Down syndrome over the 10 years. However, before 2005 the EUROCAT definition of ASD included a minor form whereas after 2005 these cases were excluded. Therefore there may have been a slight increase in ASD that was not detected due to the coding change.

Table II demonstrates the high prevalence of other major congenital anomalies in babies with Down syndrome and also highlights the prevalence differences according to sex. The most common cardiac anomalies were ASD, VSD, AVSD, patent ductus arteriosus, and tetralogy of Fallot with one of these present in over 99% of births with cardiac anomalies. Female babies with Down syndrome were significantly more likely to have a cardiac anomaly compared with male babies (47.6% compared with 40.4%, $P < 0.001$) and significantly less likely to have a non-cardiac anomaly (12.9% compared with 16.7%, $P < 0.001$). Digestive system anomalies were more common in males than females. In particular, Hirschsprung disease was almost five times more common in males than females (OR = 4.61; 95% CI: 2.38–8.93) and atresia or stenosis of parts of the small intestine excluding the duodenum occurred in six males and no females ($P < 0.029$). Urinary anomalies were more common in males with in particular renal dysplasia being nine times more likely in males than females (OR = 8.00; 95% CI: 1.42–45.1). Limb anomalies were more common in males, in particular talipes, polydactyly, and syndactyly.

DISCUSSION

The prevalence of all cardiac anomalies, severe cardiac anomalies and non-cardiac congenital anomalies has remained constant in babies born with Down syndrome from 2000 to 2010. Also the observed prevalence of ASD and VSD remained constant over the study period, indicating that the constant prevalence of cardiac anomalies was not due to increases in less severe cardiac anomalies offsetting decreases in more severe cardiac anomalies.

The recorded prevalence of all associated congenital anomalies is lower in pregnancies with Down syndrome that resulted in a TOPFA and significantly lower in TOPFAs occurring prior to 15 weeks gestation compared with later TOPFAs (data not shown). One explanation is that many congenital anomalies can be diagnosed during the routine fetal anomaly ultrasound scan, which generally occurs at around 18–22 weeks gestation 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 postmortem examination will be carried out. The proportion of TOPFAs occurring prior to 15 weeks gestation has increased continually from 2000 (see Fig. 2), reflecting the increased use of first trimester screening tests in Europe. For women who have received a fetal anomaly ultrasound scan before they have a TOPFA, the more severe forms of cardiac and non-cardiac congenital anomalies are searched for and reported, while the less severe congenital anomalies are not detectable by ultrasound and are only investigated after the birth of the infant with Down syndrome.

The most common screening tests for Down syndrome in the first trimester involve measuring the NT of the fetus between 11 and 13 weeks gestation. A large NT value has also been shown to be predictive of a cardiac anomaly [Hyett et al., 1999; Bruns et al., 2006; Müller et al., 2007]. Fetuses detected through this screening method might be expected to have a higher prevalence of cardiac anomalies than other fetuses with Down syndrome. However, Mogra et al. [2011] reported that among fetuses with Down syndrome, the presence of structural cardiac anomalies was not associated with an increased NT. Also the detection rates of screening tests including an NT measurement are over 85% for the commonly used 3% false positive rate [Spencer et al., 1999; Wald et al., 2003] and therefore

almost all fetuses with Down syndrome are being detected and not just the 44% with a cardiac anomaly. This confirms our results that increases in prenatal detection have not altered the prevalence of associated congenital anomalies in births with Down syndrome.

Population screening in Europe has not reduced the live birth prevalence of Down syndrome [Loane et al., 2013] and therefore the contribution of Down syndrome with cardiac anomalies to the total pediatric cardiac anomaly caseload will have remained constant in Europe. Dolk et al. [2011] estimated this contribution to vary from 3% to 4% (Italy, France, and Switzerland) to 15–19% (Ireland and Malta) from 2000 to 2005, consistent with the 6.4% reported by Dadvand et al. [2008] in Northern England.

The birth prevalence of specific cardiac anomalies among babies with Down syndrome in this study is in agreement with the prevalence observed in other studies [Kallen et al., 1996; Freeman et al., 1998, 2008; Stoll et al., 1998; Torfs and Christianson, 1998; Bell et al., 2003; Mogra et al., 2011; Rankin et al., 2012]. In particular, the proportion of cardiac anomalies that are severe was similar to that observed by Kallen et al. [1996] in data from 1976 to 1991.

In a meta-analysis from the results of five population-based studies of all births (not just those with Down syndrome). Tennant et al. [2011] showed that VSDs, ASDs, and AVSDs were more common in females and the other cardiac anomalies were more common in males. Our findings in births with Down syndrome are consistent with these results. Due to the large proportion of VSDs, ASDs, and AVSDs, overall cardiac anomalies are more common in females than males with Down syndrome in this study, as has been observed in other studies [Kallen et al., 1996; Freeman et al., 1998]. Similarly the observations in this study that digestive system anomalies (particularly Hirschsprung disease and atresia or stenosis of parts of the small intestine excluding the duodenum), urinary anomalies (in particular renal dysplasias) and limb anomalies were all more common in males 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] and for all live births [Tennant et al., 2011]. Potential mechanisms for these sex-specific differences have been proposed [Lary and Paulozzi, 2001].

The strengths of this study are that it uses recent population-based data across Europe covering a time period with a generally high prenatal detection rate and a high number of TOPFAs in countries where TOPFA is legal. All the members of EUROCAT use similar inclusion criteria and have a consistent approach to data collection, coding, and recording.

The weaknesses of this study are that for babies with a cardiac anomaly and a prenatal diagnosis, we do not know if the prenatal diagnosis refers to Down syndrome or to the cardiac anomaly. The information on which anomalies were diagnosed prenatally and which were only diagnosed after birth will not be available until 2015. In addition, many registries provided EUROCAT central registry with incomplete information on whether a postmortem examination had been performed or not. This means that there were more TOPFAs with postmortem examinations than reported in Table I. However, the prevalence of the anomalies in the TOPFAs with postmortem examinations in Table I is unlikely to be a biased sample of all TOPFAs with postmortem examinations. A further weakness is that not all registers send the precise karyotype to central registry and therefore this study could not distinguish between Down syndrome arising as a trisomy, translocation, or mosaic.

The birth prevalence of associated cardiac anomalies and non-cardiac congenital anomalies among babies with Down syndrome remained unchanged from 2000 to 2010 and was similar to that observed in much earlier studies before the occurrence of high levels of TOPFA. Although both first trimester screening tests and second trimester fetal anomaly ultrasound scans are likely to detect cardiac and other congenital anomalies, this has not altered the prevalence of associated congenital anomalies in births with Down syndrome.

REFERENCES

Badner JA, Sieber WK, Garver KL, Chakravarti A. 1990. A genetic study of Hirschsprung disease. Am J Hum Genet 46:568–580.

Bell R, Rankin J, Donaldson LJ. 2003. Down's syndrome: Occurrence and outcome in the north of England, 1985–99. Paediatr Perinat Epidemiol 17:33–39.

Boyd PA, de Vigan C, Khoshnood B, Loane M, Garne E, Dolk H. the EUROCAT Working Group. 2008. Survey of prenatal screening policies in Europe for structure malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. Br J Obstet Gynaecol 115:689–696.

Boyd PA, Haeusler M, Barisic I, Loane M, Garne E, Dolk H. 2011. The EUROCAT Network: Organisation and processes. Birth Defects Res A Clin Mol Teratol 91:S2–S15.

Bruns RF, Moron AF, Murta CGV, Goncalves LFA, Zamith MM. 2006. The role of nuchal translucency in the screening of congenital heart defects. Arquivos Brasilieros de Cardiologia 87:272–279.

Dadvand P, Rankin J, Shirley M, Rushton S, Pless-Mulloli T. 2008. Descriptive epidemiology of congenital heart disease in Northern England. Paed Perinat Epidemiol 23:58–65.

Dolk H, Loane M, Garne E. a European Surveillance of Congenital Anomalies (EUROCAT) Working Group. 2011. Congenital heart defects in Europe prevalence and perinatal mortality, 2000 to 2005. Circulation 123:841–849.

EUROCAT. 2005a. EUROCAT Special Report: Prenatal Screening Policies in Europe 2010", EUROCAT Central Registry, University of Ulster.

EUROCAT. 2005b. "EUROCAT Guide 1.3: Instruction for the Registration of Congenital Anomalies", EUROCAT Central Registry, University of Ulster. (www.eurocat.ulster.ac.uk/pubdata/Guide%201.3.html).

EUROCAT. 2010. "Special Report: Prenatal Screening Policies in Europe 2010", EUROCAT Central Registry, University of Ulster.

EUROCAT. member registries http://www.eurocat-network.eu/ABOUTUS/MemberRegistries/MembersAndRegistryDescriptions/FullMembers.

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.

Freeman SB, Bean LH, Allen EG, Tinker SW, Locke AE, Druschel C, Hobbs CA, Romitti PA, Royle MH, Torfs CP, Dooley KJ, Sherman SL. 2008. Ethnicity, sex, and the incidence of congenital heart defects: A report from the National Down Syndrome Project. Genet in Med 10:r173–r180.

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.

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-Ranjatoélina H, Rankin J, Rissmann A, Ritvanen A, Salvador J, Sipek A, Tucker D, Verellen-Dumoulin C, Wellesley D, Wertelecki W. 2011. EUROCAT member registries: Organization and activities. Birth Defects Res A Clin Mol Teratol 91:S51–S100.

Hyett J, Perdu M, Sharland G, Snijders R, Nicolaides KH. 1999. Using fetal nuchal translucency to screen for major congenital cardiac defects at 10–14 weeks of gestations: Population based cohort study. Br Med J 318:81–85.

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.

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. a EUROCAT Working Group. 2011. EUROCAT data quality indicators for population-based registers of congenital anomalies. Birth Defects Res A Clin Mol Teratol 91:S23–S30.

Loane M, Morris J, Addor M-C, Arriola L, Budd J, Doray B, Garne E, Gatt M, Haeusler M, Khoshnood B, Klungsoyr Melve, Latos- K, Bielenska A, McDonnell R, 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 trends 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.

Mogra R, Zidere V, Allan LD. 2011. Prenatally detectable congenital heart defects in fetuses with Down syndrome. Ultrasound Obstet Gynecol 38:320–324.

Müller MA, Clur SA, Timmerman E, Bilardo CM. 2007. Nuchal translucency measurement and congenital heart defects: models association in low-risk pregnancies. Prenat Diagn 27:164–169 [8].

Rankin J, Tennant P, Bythell M, Pearce M. 2012. Predictors of survival in children born with Down syndrome: A registry-based study. Pediatrics 129:e1373.

Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH. 1999. A screening program for trisomy 21 at 10–14 weeks using fetal nuchal translucency, maternal serum free β-human chorionic gonadotropin and pregnancy associated plasma protein-A. Ultrasound Obstet Gynecol 13:231–237.

StataCorp 2007. Stata Statistical Software: Release 10, College Station, TX: Stata Corp LP.

Stoll C, Alembik Y, Dott B, Roth MP. 1998. Study of Down syndrome in 238,942 consecutive births. Ann Genet 41:44–51.

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.

Torfs CP, Christianson RE. 1998. Anomalies in Down syndrome individuals in a large population-based registry. Am J Med Genet 77:431–438.

Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. 2003. First and second trimester antenatal screening for Down's syndrome: the results of the serum, urine and ultrasound screening study (SURUSS). J Med Screen 10:56–104.