



**Special Report: The Prevalence of Tetralogy of Fallot and
Ebstein's Anomaly in Europe**

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Funded by the Public Health Programme 2008-2013 of the Executive Agency for
Health and Consumers, European Commission

WHO Collaborating Centre for the Surveillance of Congenital Anomalies

The Prevalence of Tetralogy of Fallot and Ebstein's anomaly in Europe

Background

This short EUROCAT report reviewing the prevalence of Tetralogy of Fallot (TOF) and Ebstein's anomaly (EA) in Europe was prepared in response to an observation that the prevalence of TOF had risen over the past decade. This increase was statistically significant for years 2002-2011 with an average yearly increase of 2.25% (95%CI 0.53-3.99)¹. Anthony Wemakor, while working with Helen Dolk at Central Registry on the association between Selective Serotonin Reuptake Inhibitors (SSRIs) and congenital heart disease, has confirmed signals for specific associations between maternal use of SSRIs in the first trimester of pregnancy and both TOF and EA².

Method

The trends over time for prevalence and for pregnancy outcome were examined in 16 countries using data from 22 registries who replied to a request for data on the use of medicines in early pregnancy for a more detailed analysis which will be carried out early in 2014 (Table 1). Only seventeen of these registries will be able to take part in that analysis as they do not all collect data on medication and on maternal illness.

Results

Tetralogy of Fallot: Prevalence increased significantly between the first and second decade examined (Figure 1) and has continued to increase to 3.32 (95%CI 3.17-3.48) per 10,000 births: (Table 1). During 1992-2011 there was some variation between countries ranging from 1.93 (95%CI 1.29-2.88) per 10,000 births in Croatia to 3.78 (95% CI 3.26-4.60) per 10,000 births in Belgium (Figure 2). The proportions of livebirths (LB), stillbirths and fetal deaths after 20 weeks gestation (SB), termination of pregnancy for fetal anomaly (TOPFA) and early neonatal deaths have not changed over time (Figure 3), but there is variation between countries (Figure 4). The proportion of cases prenatally diagnosed has increased over time (Figure 5) but there is still wide variation between countries (Figure 6). The majority (67%) of TOF cases are isolated cardiac anomalies with 15% associated with either a chromosomal or a genetic syndrome (Figure 7)

Ebstein's anomaly: Prevalence increased significantly between the first and second decades studied (Figure 8) and decreased slightly, and non-significantly, in the third decade to 0.45 (95%CI 0.40-0.51) per 10,000 births (Table 3). In the period from 1992 to 2011 prevalence ranged from 0.16 (95%CI 0.04-0.64) per 10,000 births in Croatia to 1.08 (95%CI 0.56-2.08) per 10,000 births in Malta; (Figure 9). Overall there has been an increase in the proportion of cases which were TOPFA (Figure 10) and the proportions for each birth outcome vary widely between countries (figure 11). Prenatal diagnosis rates have not changed over the past two decades (Figure 12) but again, they vary between countries (Figure 13). EA is almost exclusively an isolated cardiac anomaly (88%), with very few cases having chromosomal anomalies and none diagnosed with a genetic syndrome (Figure 14).

Conclusion

Both these congenital cardiac anomalies have increased in prevalence over the past three decades although EA seems to be stabilizing. These increases cannot be fully explained through better diagnosis, prenatal diagnosis or increased TOPFA rates. As there are suggestions of

environmental causes for both types of congenital heart disease they require further investigation. In 2014 maternal illness and medication exposures will be examined as part of the EUROmediCAT project³.

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Table 1: Study population (countries and years), Prevalence of Tetralogy of Fallot and Ebstein's anomaly in Europe

Country	Years included	1982-1991	1992-2001	2002-2011	Total study years 1982-2011
Denmark (Odense)	1982-2011	49,475	5,7936	52,184	159,595
France (Paris)	1982-1011	365,807	361,464	267,343	994,614
Netherlands(Northern)	1982-2011	124,583	196,761	184,777	506,121
Switzerland (Vaud)	1989-2011	23,120	76,232	74,810	174,162
Croatia (Zagreb)	1983-2010	52,852	61,949	62,552	177,353
Malta	1986-2010	32,491	47,238	35,984	115,713
Belgium (Antwerp)	1990-2011	8,428	135,969	197,176	341,573
Germany (Saxony)	1987-2011	72,877	106,958	173,009	352,844
Austria (Styria)	1985-2011	80,223	119,413	82,950	282,586
Norway	1999-2011		177,352	597,649	775,001
Ukraine	2005-2011			208,772	208,772
Hungary	1998-2010		388,732	871,912	1,260,644
Ireland*	1996-2011		74,817	157,571	232,388
Italy*	1982-2011	315,353	507,186	674,268	1,496,807
UK*	1992-2011	5,878	470,412	158,6886	2,063,176
Spain*	1990-2010	32,729	163,572	399,121	595,422
Total	1982-2011	1,163,816	2,945,991	5,626,964	9,736,771

*Ireland = Cork and Kerry 1996-2010 & SE Ireland 1997-2010

Italy = Tuscany & Emilia Romagna 1982-2011

UK = Wales 1998-2011, Thames Valley 1991-2011, EMSYCAR 1998-2011 & Northern England 1990-2011

Spain = Basque Country 1990-2010 & Valencia 2007-2010

Tetralogy of Fallot

Table 2: Tetralogy of Fallot; Prevalence per 10,000 total births over time and by country 1982-2011

Country	n	1982-1991	n	1992-2001	n	2002-2011	n	1982-2011
Denmark	24	4.85 (3.25-7.24)	13	2.24 (1.30-3.86)	19	3.64 (2.32-5.71)	56	3.51 (2.70-4.56)
France	67	1.83 (1.44-2.33)	139	3.85 (3.26-4.54)	91	3.40 (2.77-4.18)	297	2.99 (2.67-3.35)
Netherlands	46	3.69 (2.77-4.93)	65	3.30 (2.59-4.21)	67	3.63 (2.85-4.61)	178	3.52 (3.04-4.07)
Switzerland	9	3.89 (2.03-7.48)	23	3.02 (2.00-4.54)	24	3.21 (2.15-4.79)	56	3.22 (2.47-4.18)
Croatia	7	1.32 (0.63-2.78)	11	1.78 (0.98-3.21)	13	2.08 (1.21-3.58)	31	1.75 (1.23-2.49)
Malta	4	1.23 (0.46-3.28)	19	4.02 (2.57-6.31)	12	3.33 (1.89-5.87)	35	3.02 (2.17-4.21)
Belgium	2	2.37 (0.59-9.49)	48	3.53 (2.66-4.68)	81	4.11 (3.3-5.11)	131	3.84 (3.23-4.55)
Germany	5	0.69 (0.29-1.65)	25	2.34 (1.58-3.46)	56	3.24 (2.49-4.21)	86	2.44 (1.97-3.01)
Austria	46	5.73 (4.29-7.66)	45	3.77 (2.81-5.05)	32	3.86 (2.73-5.46)	123	4.35 (3.65-5.19)
Norway	-	-	43	2.42 (1.80-3.27)	166	2.78 (2.39-3.23)	209	2.70 (2.35-3.09)
Ukraine	-	-	-	-	66	3.16 (2.48-4.02)	66	3.16 (2.48-4.02)
Hungary	-	-	103	2.65 (2.18-3.21)	243	2.79 (2.46-3.16)	346	2.74 (2.47-3.05)
Ireland			24	3.21 (2.15-4.79)	52	3.30 (2.51-4.33)	76	3.27 (2.61-4.09)
Italy	59	1.87 (1.45-2.41)	140	2.76 (2.34-3.26)	217	3.22 (2.82-3.68)	416	2.78 (2.52-3.06)
UK	0	0	161	3.42 (2.93-3.99)	621	3.91 (3.62-4.23)	782	3.79 (3.53-4.07)
Spain	7	2.14 (1.02-4.49)	51	3.12 (2.37-4.10)	109	2.73 (2.26-3.29)	167	2.80 (2.41-3.26)
Total	276	2.37 (2.11-2.67)	910	3.09 (2.89-3.30)	1,869	3.32 (3.17 - 3.48)	3,055	3.12 (3.02-3.24)

Figure 1: Tetralogy of Fallot; Prevalence by time with 95% confidence intervals, 1982-2011

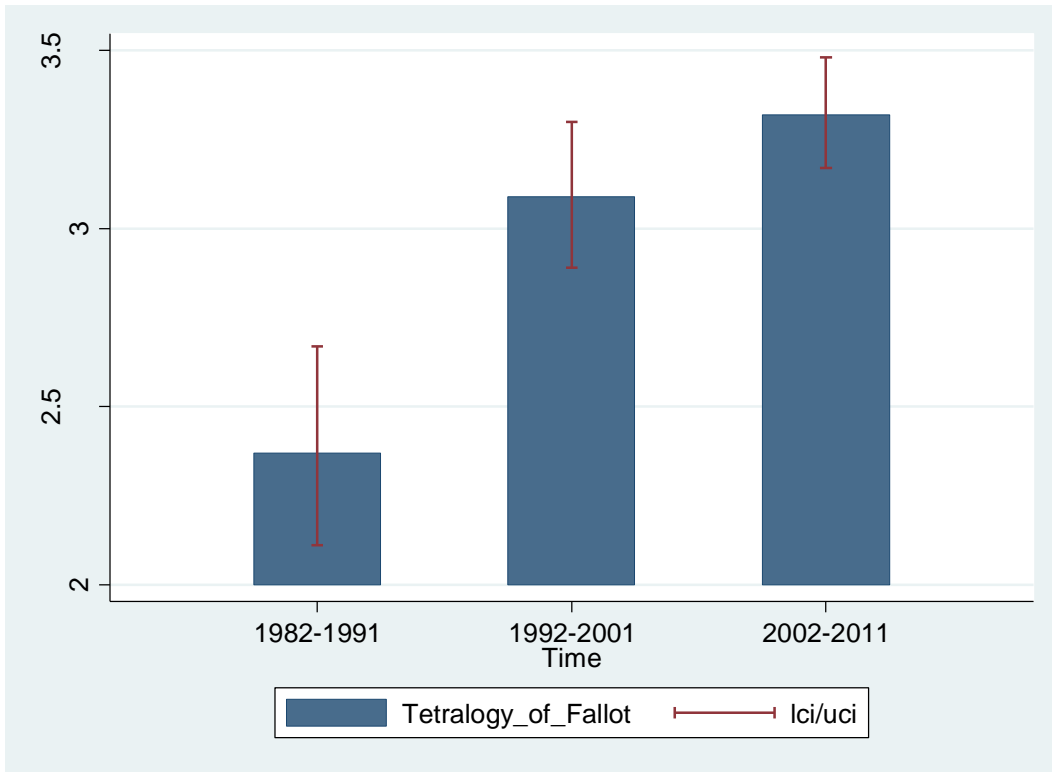


Figure 2: Tetralogy of Fallot; Prevalence by centre with 95% confidence intervals, 1992-2011

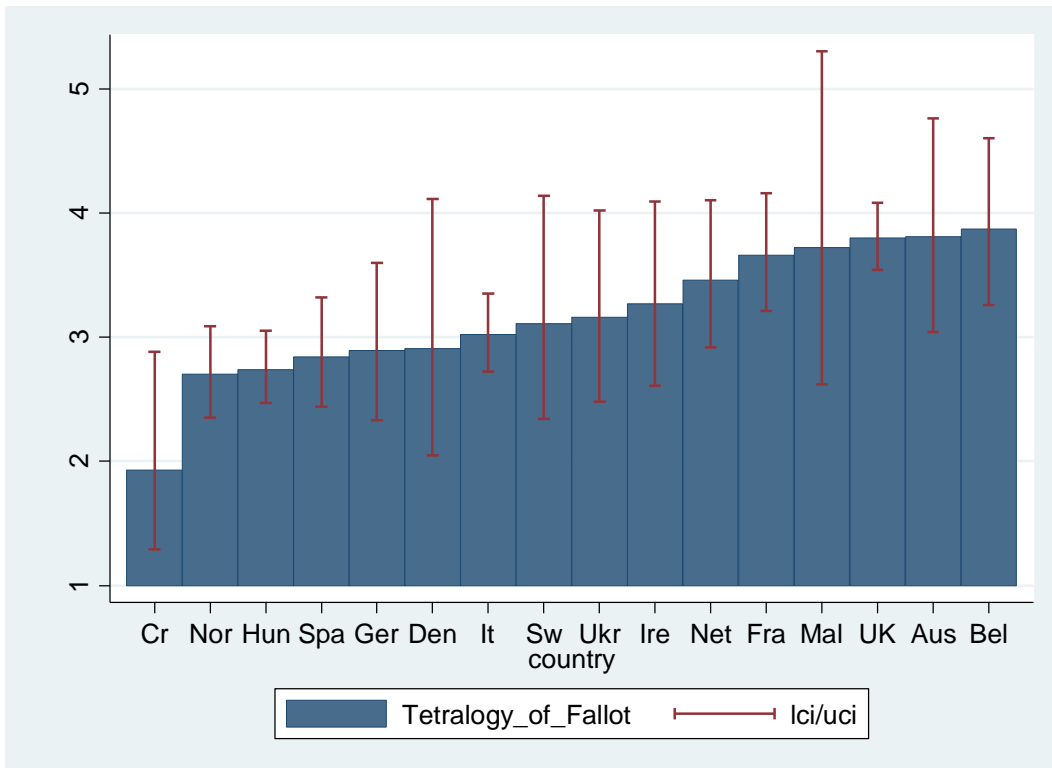
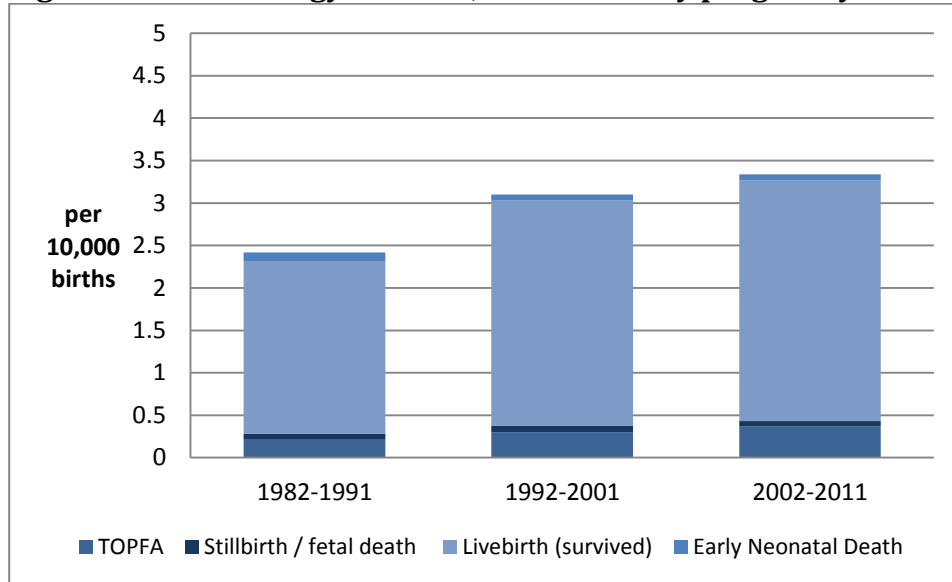
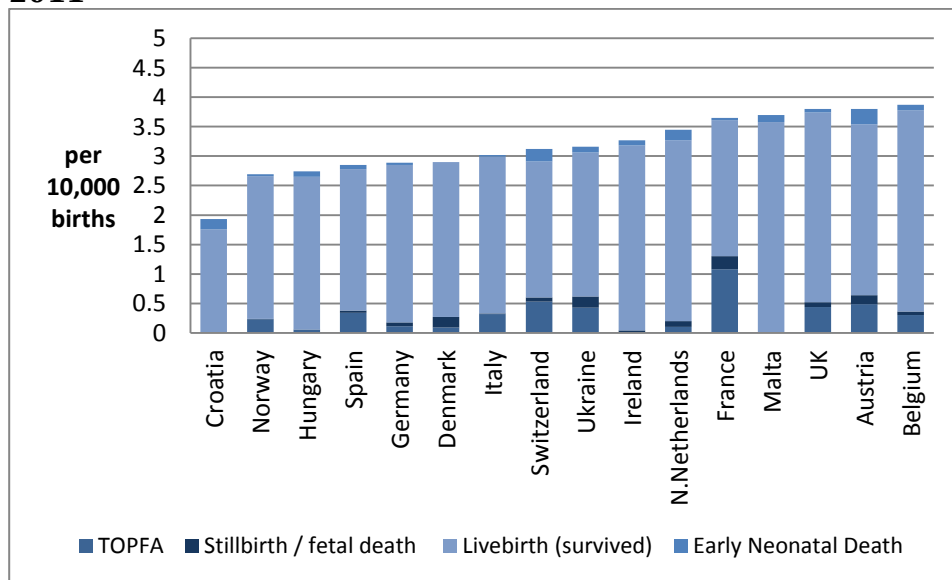


Figure 3: Tetralogy of Fallot; Prevalence by pregnancy outcomes over time, 1982-2011



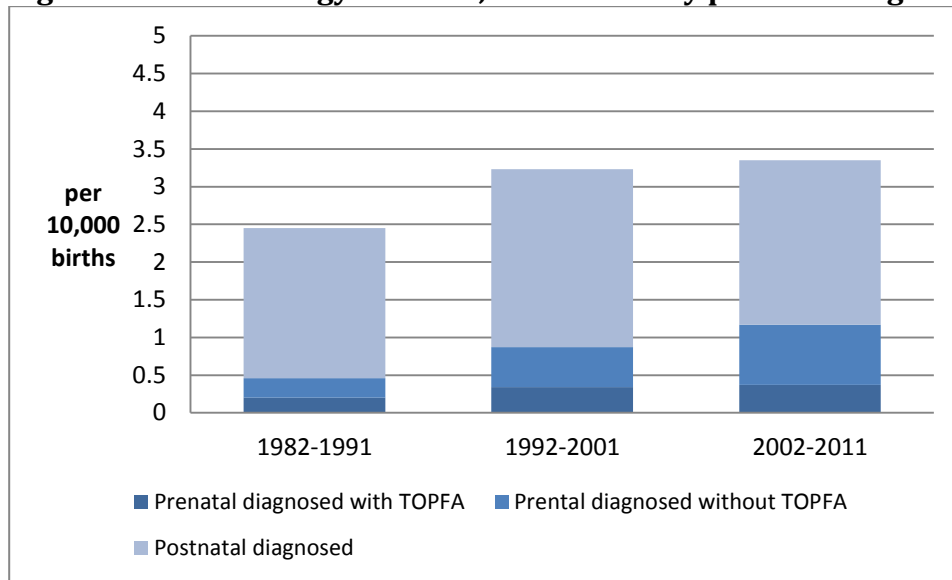
Termination of pregnancy for fetal anomaly (TOPFA)

Figure 4: Tetralogy of Fallot; Prevalence by country and pregnancy outcomes 1992-2011



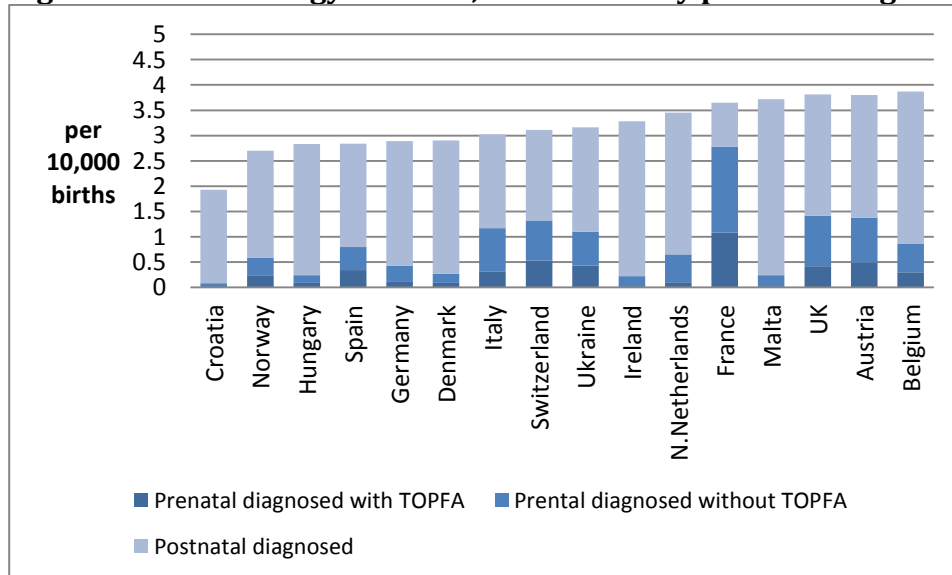
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Figure 5: Tetralogy of Fallot; Prevalence by prenatal diagnosis and time, 1982-2011



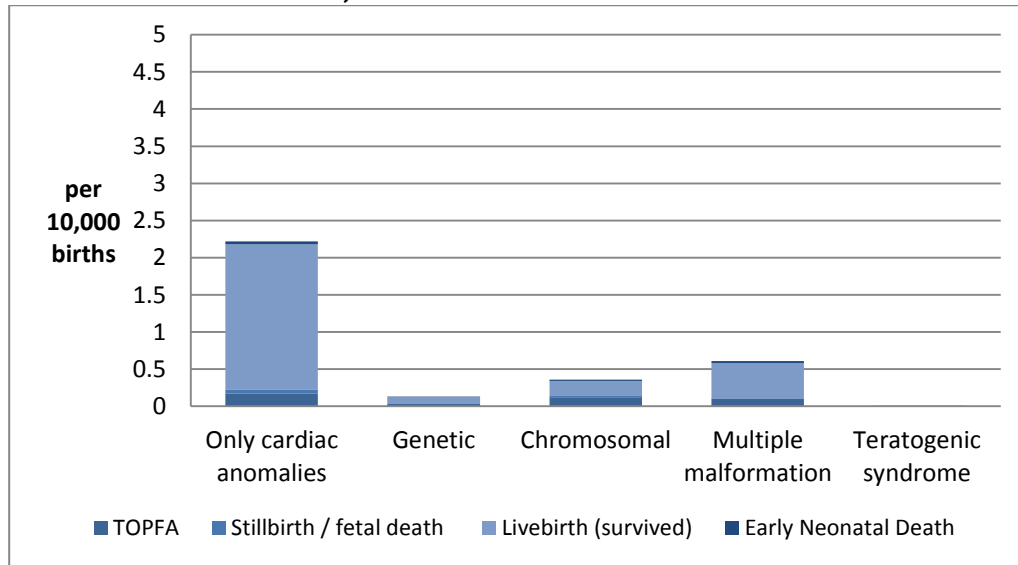
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Figure 6: Tetralogy of Fallot; Prevalence by prenatal diagnosis and country, 1992-2011



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Figure 7: Tetralogy of Fallot; Prevalence by malformation type and pregnancy outcomes, 2002-2011



Termination of pregnancy for fetal anomaly (TOPFA)

Ebstein's anomaly

Table 3: Ebstein's anomaly; Prevalence per 10,000 total births over time and by country 1982-2011

Country	n	1982-1991	n	1992-2001	n	2002-2011	n	1982-2011
Denmark	4	0.81 (0.30-2.15)	5	0.86 (0.36-2.07)	1	0.19 (0.03-1.36)	10	0.63 (0.34-1.16)
France	9	0.25 (0.13-0.47)	24	0.66 (0.45-0.99)	28	1.05 (0.72-1.52)	61	0.61 (0.48-0.79)
Netherlands	6	0.48 (0.22-1.07)	9	0.46 (0.24-0.88)	11	0.60 (0.33-1.07)	26	0.51 (0.35-0.75)
Switzerland	3	1.30 (0.42-4.02)	6	0.79 (0.35-1.75)	4	0.53 (0.20-1.42)	13	0.75 (0.43-1.29)
Croatia	0	0	1	0.16 (0.02-1.15)	1	0.16 (0.02-1.13)	2	0.11 (0.03-0.45)
Malta	2	0.62 (0.15-2.46)	4	0.85 (0.32-2.26)	5	1.39 (0.58-3.34)	11	0.95 (0.53-1.72)
Belgium	1	1.19 (0.17-8.42)	5	0.37 (0.15-0.88)	6	0.30 (0.14-0.68)	12	0.35 (0.20-0.62)
Germany	0	0	3	0.28 (0.09-0.87)	9	0.52 (0.27-1.00)	12	0.34 (0.19-0.60)
Austria	2	0.25 (0.06-1.00)	8	0.67 (0.34-1.34)	6	0.72 (0.32-1.61)	16	0.57 (0.35-0.92)
Norway		-	3	0.17 (0.05-0.52)	36	0.60 (0.43-0.84)	39	0.50 (0.37-0.69)
Ukraine		-		-	13	0.62 (0.36-1.07)	13	0.62 (0.36-1.07)
Hungary		-	4	0.10 (0.04-0.27)	24	0.28 (0.18-0.41)	28	0.22 (0.15-0.32)
Ireland		-	4	0.53 (0.20-1.42)	7	0.44 (0.21-0.93)	11	0.47 (0.26-0.85)
Italy	3	0.10 (0.03-0.29)	22	0.43 (0.29-0.66)	15	0.22 (0.13-0.37)	40	0.27 (0.20-0.36)
UK	0	0	29	0.62 (0.43-0.89)	75	0.47 (0.38-0.59)	104	0.50 (0.42-0.61)
Spain	1	0.31 (0.04-2.17)	10	0.61 (0.33-1.14)	12	0.30 (0.17-0.53)	23	0.39 (0.26-0.58)
Total	31	0.27 (0.19-0.38)	137	0.47 (0.39-0.55)	253	0.45 (0.40-0.51)	412	0.43 (0.39-0.48)

Figure 8: Ebstein's anomaly; Prevalence by time with 95% confidence intervals, 1982-2011

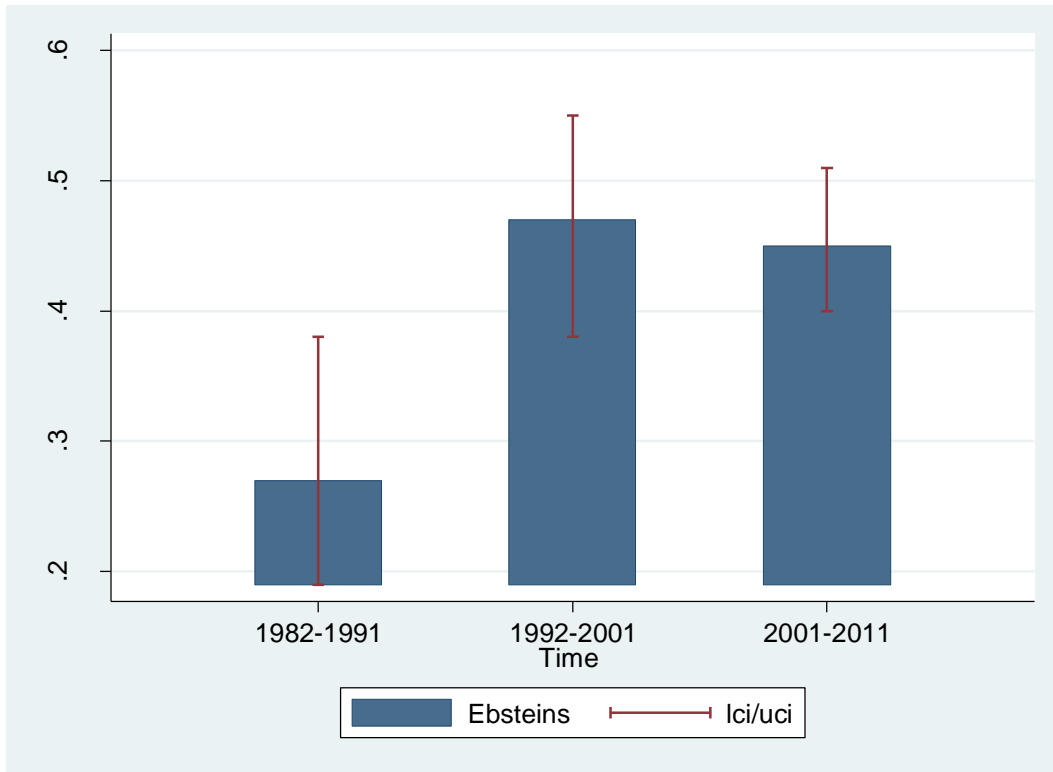


Figure 9: Ebstein's anomaly; Prevalence by centre with 95% confidence intervals, 1992-2011

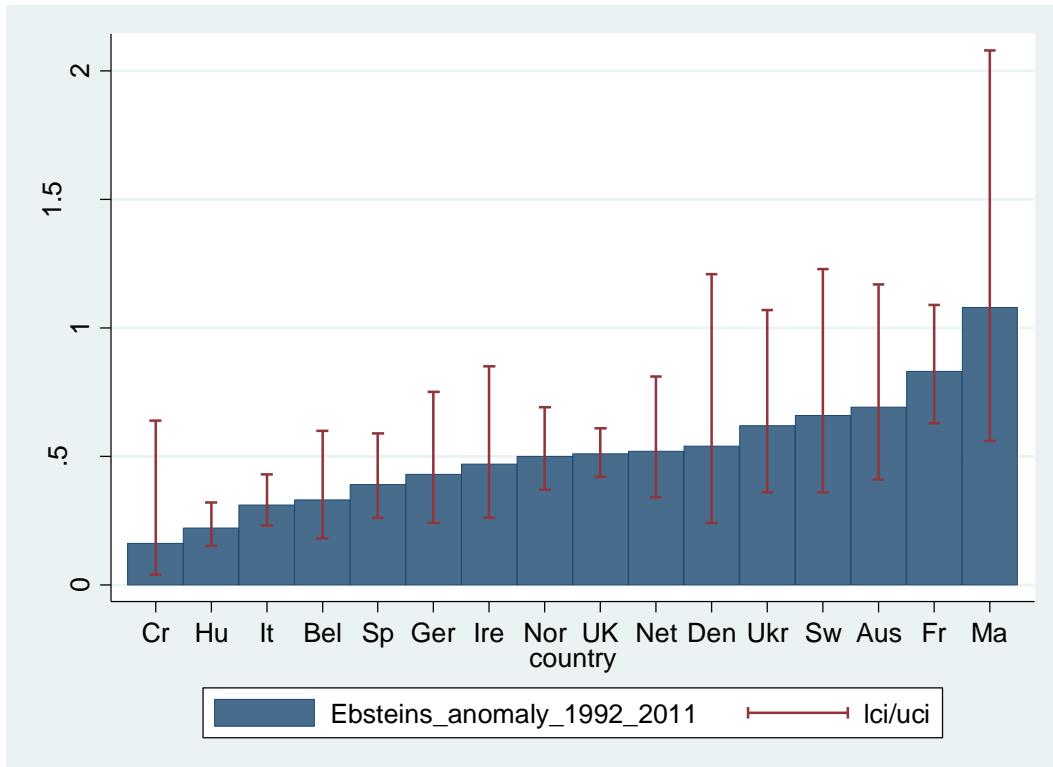
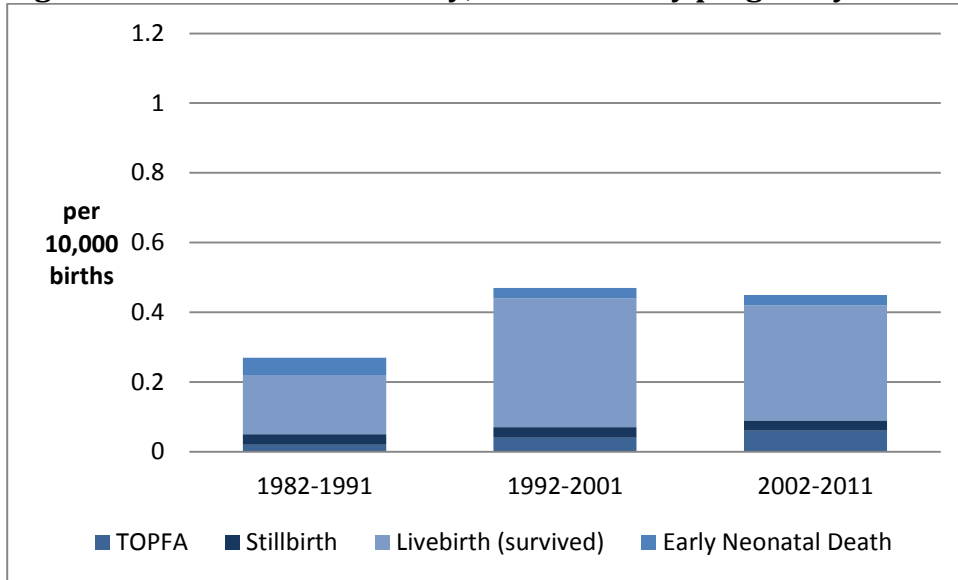
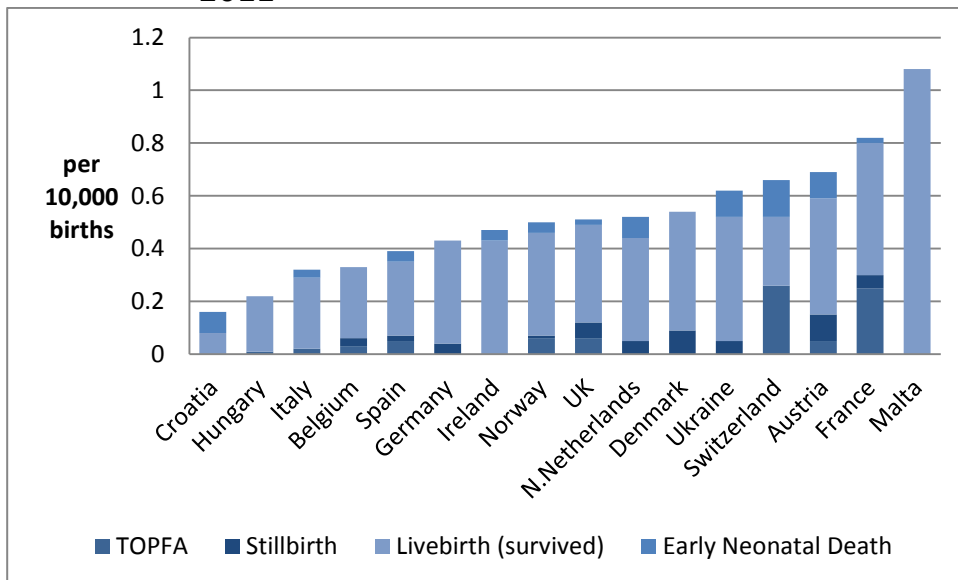


Figure 10: Ebstein's anomaly; Prevalence by pregnancy outcomes over time, 1982-2011



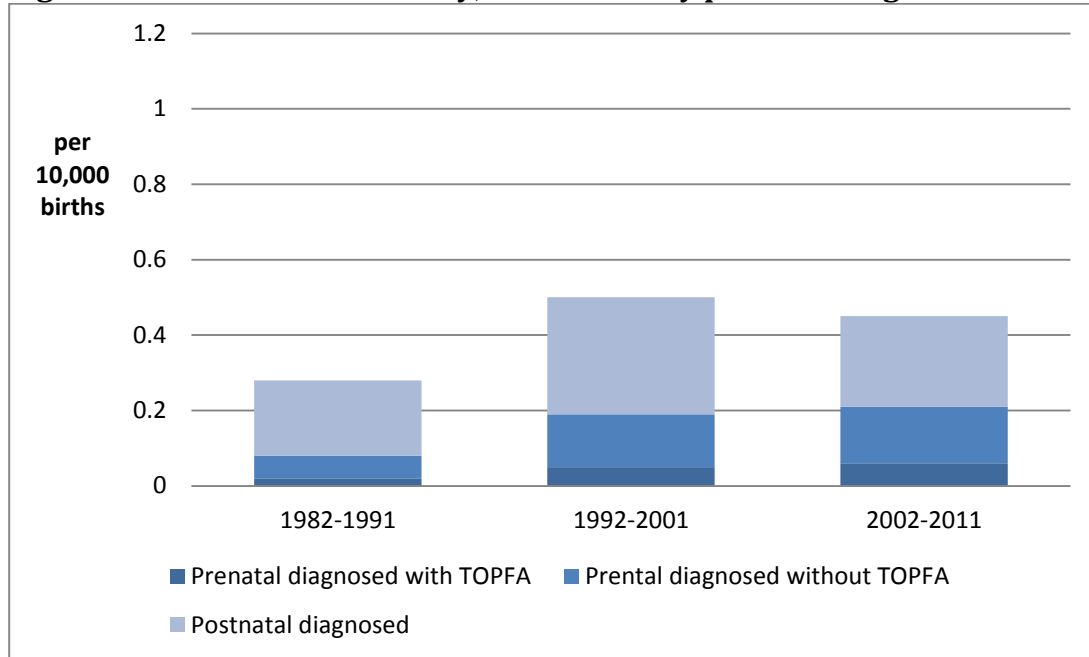
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Figure 11: Ebstein's anomaly; Prevalence by country and pregnancy outcomes 1992-2011



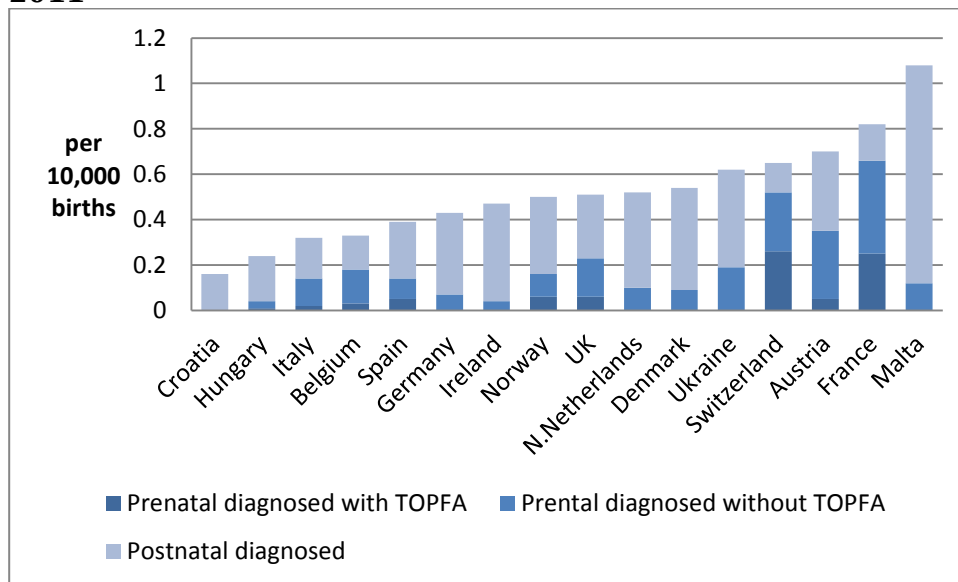
Termination of pregnancy for fetal anomaly (TOPFA)

Figure 12: Ebstein's anomaly; Prevalence by prenatal diagnosis and time, 1982-2011



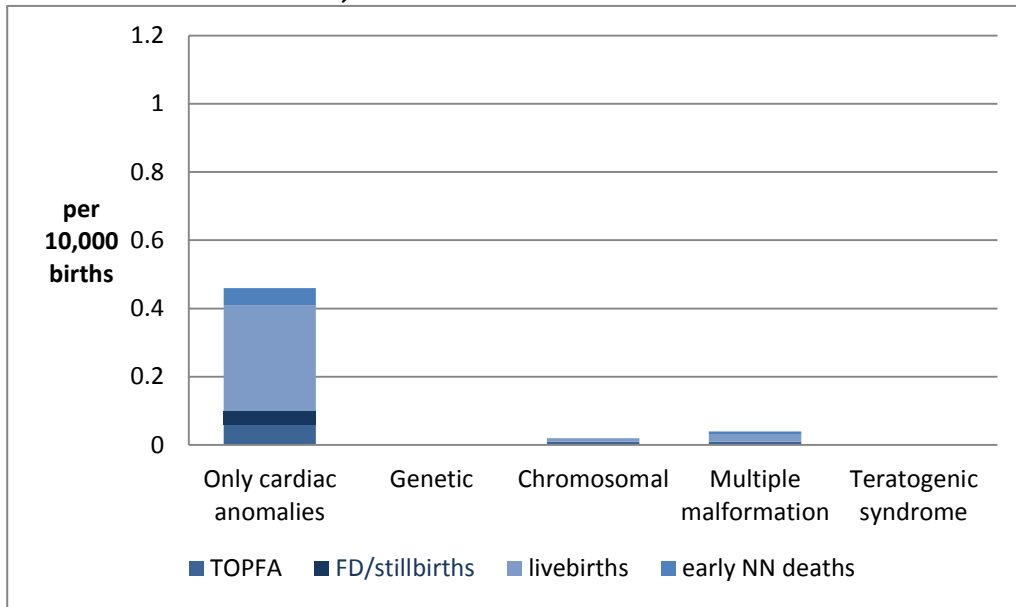
Termination of pregnancy for fetal anomaly (TOPFA)

Figure 13: Ebstein's anomaly; Prevalence by prenatal diagnosis and country, 1992-2011



Termination of pregnancy for fetal anomaly (TOPFA)

Figure 14: Ebstein’s anomaly; Prevalence by malformation type and pregnancy outcomes, 2002-2011



Termination of pregnancy for fetal anomaly (TOPFA)

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