EUROCAT study: Epidemiology of congenital cerebral anomalies in Europe.

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Introduction

Maternal zika virus infection is now acknowledged to increase the risk of microcephaly occurring in the fetus[1, 2]. There are now indications that maternal zika virus infections also increases the risk of structural cerebral anomalies[3]. As more and more knowledge about the potential teratogenicity of zika virus is published, it is important to have background information about the epidemiology of congenital cerebral anomalies.

EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies (http://www.eurocat-network.eu/) [4]. EUROCAT has a long tradition for studies on neural tube defects [5] and recently EUROCAT papers on microcephaly [6],hydrocephaly (Garne 2010) [7] and septo-optic dysplasia [8] have been published. The epidemiology of other cerebral anomalies from the Q04 chapter in ICD10 such as corpus callosum anomalies, reduction defects of the brain, microgyria, megalencephaly, cerebral cysts and schizencephaly have never been analyzed in the EUROCAT database. Most of these anomalies are quite rare with little epidemiology data published in the literature.

Previous EUROCAT collaboration with the European cerebral palsy network (SCPE) has described that the majority of congenital anomalies in children with cerebral palsy are cerebral anomalies[9, 10], indicating the severity of these congenital anomalies.

Most cerebral anomalies are not visible at birth, but may be diagnosed pre and postnatally by ultrasound scans and other imaging examinations (MR, CT scans). As diagnostic methods prenatally and in the neonatal period are known to vary over time and between countries in Europe and because some registries include late diagnosed cases up to 5 years of age or more, major European differences in prevalence are expected.

The aim of this study was to use data from EUROCAT to study the prevalence of specific congenital cerebral anomalies in Europe and examine observed geographical differences in prevalence, which may reflect true differences in prevalence or may arise due to diagnostic differences. Associated anomalies will be identified and birth outcome and maternal characteristics described.

Methods

EUROCAT surveys over 1.7 million births (29% of European birth population) per year from 38 registries in 21 countries in Europe. The EUROCAT registries are population based and the geographically defined populations and the methodology of collecting individual case data for EUROCAT is described elsewhere [4]. The registries are based on multiple sources of information such as hospital discharge diagnosis, birth and death certificates and post mortem examinations, and include information about livebirths (LB), fetal deaths (FD) with gestational age (GA) $\geq$ 20 weeks and terminations of pregnancy (TOPFA) after prenatal diagnosis of congenital anomaly. All major structural congenital anomalies, syndromes and chromosomal anomalies are included in the database. Minor malformations are excluded based on a list of ICD10 codes for exclusion (Guide 1.4)[11]. The congenital anomalies are coded according to ICD10 with the BPA extension.

All full member registries were invited to take part in the study and data from 29 EUROCAT registries are included in the study (Table 1). All birth outcomes (LB, FD and TOPFA) with an ICD10 code within the subchapter Q04 and born in the years 2005-2014 were included. A previous paper has reported on the data from the cases with septo-optic dysplasia[8], but for completeness the information is included in this paper also. Not all registries contributed with data for all 10 years. Data on each case included year of birth, type of birth, sex, time of diagnosis, maternal age and associated congenital anomalies.

Cases were classified as isolated cerebral anomalies, chromosomal cases, teratogenic or genetic syndromes or multiple congenital anomalies according to the EUROCAT multiple flowchart [12] and manual review of the written text description of the anomalies. Cases with additional codes and/or written text description of microcephaly, ventriculomegaly and hydrocephaly were classified as isolated cerebral anomalies. The diagnosis single cerebral cyst, arachnoid and choroid plexus cysts and anomalies of septum pellucidum are on the EUROCAT list of minors for exclusion and cases were excluded, if described in written text as the only cerebral anomaly. Cases with written text description of large cisterna magna, asymmetric ventricles or minor ventriculomegaly were excluded if these were the only cerebral anomalies. Colpocephaly was classified as a secondary anomaly if associated with agenesis of corpus callosum. There were no written text description for cases from the registries in Paris and Norway and NORCAS used standard written text only. Trend over time is presented as a pan-European trend with data pooled for all 29 registries excluding genetic cases (chromosomal anomaly or genetic syndrome).

Method to Identify Under-reporting

A previous study on septo-optic dysplasia [8] found evidence that some registries were under-reporting cases of septo-optic dysplasia and developed a method to estimate the prevalence adjusting for this under-reporting. In brief for each separate anomaly, the average prevalence amongst the 15 registries with the highest prevalences is calculated using a random effects meta-analysis. The average prevalence of the whole population is then estimated by adjusting the prevalence observed in these 15 registries by factors to adjust for the fact that these registries have the highest prevalence estimate amongst 29 registries. These factors depend only on the average number of cases in the registries. The factors are obtained by simulation and calculation of the ratio of the mean prevalence of 15 out of 29 registries compared to the mean prevalence of all 29 registries assuming the number of cases is a Poisson distribution with an expected value of the median observed number of cases in the 15 registries. For example if only 2 cases are observed in each registry the correction factor is 1.7, whereas if 75 cases are observed the correction factor is only 1.09.

The prevalence of the anomalies and the trends over time were investigated by fitting poisson regression multi-level models with registry as a random effect. An association between prenatal diagnoses rates and prevalence was investigated at a registry level using poisson regression with prenatal diagnoses as a covariate All other exploratory analysis between anomalies were investigated using anova and chi-squared analyses according to the variable of interest.

Results

The study included 4927 cases with a congenital cerebral anomaly giving an overall prevalence (adjusted for under-reporting) of 9.8 (95% CI: 8.5 to 11.2) per 10,000 births in the 29 registries. There were major differences in prevalence by registry (Table 1), with over a six fold difference between the registry with the lowest prevalence (South Portugal; 2.7 per 10,000) and the registry with the highest prevalence (French West Indies; 16.6 per 10,000). The proportions of cases that were diagnosed prenatally varied considerably between registries. There was an association between prevalence and the proportion of prenatal diagnoses; registries with higher proportions of prenatal diagnoses had a higher prevalence (p=0.029; Figure 1).

Congenital malformations of the corpus callosum and “other reduction deformities of the brain” were the most common anomalies, with adjusted prevalences of 3.84 (3.22 - 4.51) and 2.98 (2.56 - 3.44) respectively. The adjusted prevalence of holoprosencephaly was 1.55 (95%CI: 1.37 - 1.77) per 10,000 births and of megalencephaly was 0.08 (95%CI: 0.05 - 0.11) per 10,000 births.

Overall 3448 cases were diagnosed prenatally (70% of the total) and of these 2043 resulted in a termination of pregnancy (59% of the prenatally diagnosed cases). Figure 2 and Table 2 shows the birth outcome for the cases with cerebral anomalies, overall with 55% resulting in a live birth, 3% were fetal deaths from GA 20 weeks and 41% were terminations of pregnancy after prenatal diagnosis. Again, there was considerable variation between registries. The proportions of live births varied according to anomaly, with infants with Septo-optic dysplasia being most likely to result in a live birth (96%) and lowest for arhinencephaly with 4% livebirths . Overall 31% of all fetal deaths and livebirths occurred before 37 weeks gestation and this varied considerably according to anomaly; babies with septo-optic dysplasia were the least likely to be born preterm (18% occurred before 37 weeks) (Table 2) .

The average maternal age was 29.9 years. The only anomaly that had a significantly different maternal age was Septo-optic dysplasia with much lower maternal ages (23.5 years). The proportion of fetus's that were male did not differ significantly according to the anomaly.

Classification of cases according to associated anomalies and genetic diagnosis is presented in Table 3. For all the cerebral anomaly cases in the study 48% had an isolated cerebral anomaly, 25% were classified as multiple congenital anomaly, 18% had an associated chromosomal anomaly (6% had Patau syndrome) and for 9% a syndrome was diagnosed (7% genetic and 2% teratogenic). For the multiple anomaly cases the most common associated anomaly was congenital heart defect. Cases with arhinencephaly or holoprosencephaly were more likely to have a chromosomal anomaly , particularly Patau syndrome. In contrast cases with septo-optic dysplasia, megalencephaly or cerebral cysts were more likely to have isolated cerebral anomalies. The most common genetic syndromes reported were Joubert syndrome (23 cases) and Aicardi syndrome (13 cases) with numbers based on written text descriptions from the registries.

Figure 3 shows that the pan-European prevalence of cases with Q04 not due to genetic conditions has increased from 2005 to 2014, with the increases occurring only for Congenital malformations of the corpus callosum and "other reduction deformities of the brain".

Discussion

The overall prevalence (adjusted for under-reporting) of major cerebral anomalies in Europe in the ten years before the occurrence of Zika virus was 9.8 (95%CI: 8.5 – 11.2) per 10,000 births. There was a significant increase in the prevalence of anomalies of corpus callosum and of other reduction defects of brain, while the prevalence of the other cerebral anomalies included were stable.

The increasing European trend of anomalies of corpus callosum and other reduction deformities of brain may be due to increased prenatal diagnosis as a high proportion of these two anomalies were diagnosed prenatally (72% and 69%). Most EUROCAT registries include cases diagnosed within the first year of life. If cerebral anomalies are not diagnosed prenatally, they may not be diagnosed before several years of age in relation to the diagnosis of developmental problems or cerebral palsy.

Our adjusted prevalence for corpus callosum anomalies of 3.84 (95%CI: 3.22 – 4.51) per 10,000 births was consistent with that reported by two other studies. A study from California 1983-2003 [13] showed a prevalence of corpus callosum anomalies diagnosed only in liveborn infants of 1.8 per 10,000 births and a study from Hungary from 1992-2006 showed a prevalence of 2.05 per 10,000 live births (95% CI: 1.4-2.7) [14]. The study by Glass also found an increased proportion of males (52%) compared with the 53% we observed and the proportions with a chromosomal anomaly 17% was similar to the 16% we observed. The increased risk of prematurity we observed was also noted by Glass.

The adjusted prevalence of holoprosencephaly was 1.55 (95%CI: 1.37 - 1.77) per 10,000 births and is comparable to other studies. A literature review including data from 21 studies found that the published prevalence of holoprosencephaly mainly varied between 0.5 to 1.5 per 10,000 births and with a much higher prevalence in Japan (Orioli et al 2010). The authors conclude that the differences in prevalence were mainly explained by the inclusion criteria (livebirths or all pregnancy outcomes). These studies also found a higher female rate and a high proportion of chromosomal cases [15]. In our study the proportion of males was 47% but this was not statistically significantly different from 50%.

Our study showed an adjusted prevalence of megalencephaly of 0.08 (95%CI: 0.05 - 0.11) per 10,000 births. To our knowledge there is no previous published prevalence of this congenital anomaly in the literature. Most case series and reports describe megalencephaly as an isolated anomaly [16], which is in line with our findings. A study from a tertiary center in US described that almost half of their patients had

an additional syndrome diagnosis [16].Tinkle et al {Tinkle, 2005 #1644} reports that a Japanese study that found that 11 of 38 patients (29%) had a syndrome diagnosis (Sasaki et al 2000 – in Japanese).

Our study showed an adjusted prevalence of arhinencephaly of 0.05 (95%CI: 0.02 – 0.11) per 10,000 births which is consistent with the only other study we identified reported the prevalence of arhinencephaly of 0.14 (95%CI : 0.06 – 0.25) per 10,000 births [17] and included only 10 cases. Our study included 46 cases.

The association between prevalence and prenatal detection rate explains part of the European heterogeneity in the prevalence of cerebral anomalies. However, under-ascertainment of cases by the registry may explain the very low prevalence in some registries. In other registries there may be over-reporting of minor anomalies seen on cerebral imaging or by reporting cerebral injuries after preterm birth or birth asphyxia using ICD codes from the congenital anomaly chapter. The diagnosis of reduction defect of cerebellum, often with the written text "small cerebellum" was heterogeneously reported by registries and there may be different diagnostic criteria for reporting this anomaly.

For some cerebral anomalies as reduction defects, the critical exposure period is extended up to gestational week 18[18]. This means that maternal viral infections may be teratogenic to the brain in a longer period of pregnancy. This has impact on the prenatal detection rate if the ultrasound screening is performed earlier than GA 20 weeks.

There was a high rate of terminations of pregnancy for the anomalies included in this study indicating the severity of cerebral anomalies. Overall 41% of all cases were TOPFA with the highest TOPFA rate found for arhinencephaly (91%) and holoprosencephaly (78%). For anomalies of corpus callosum TOPFA rate was 33%. Half of the cases with anomalies of corpus callosum were classified as isolated cerebral anomalies (Table 3), but there may be associated more severe cerebral anomalies present. Counselling and parental decision-making after prenatal diagnosis of anomalies of corpus callosum is difficult [19]. A study has shown that 25-30% of fetuses with a prenatal diagnosis of isolated agenesis of corpus callosum have developmental delays [20].

Conclusions.

This is the one of the largest population-based study to describe the prevalence of anomalies of the corpus callosum and other reduction deformities of the brain. Our study is consistent with others for the

prevalences of corpus callosum anomalies, holoprosencephaly and arhinencephaly, and to our knowledge we are the first to report the prevalence of megalencephaly. Our study provides the background information against which to compare the occurrence of cerebral anomalies in countries where the Zika virus is prevalent.

Table 1

Table 1: Number of cases with a congenital cerebral anomaly (ICD10 code Q04) in EUROCAT registries, prevalence and proportion prenatally diagnosed

Registry, Country	Total Cases	Prevalence per 10,000 births	Proportion prenatally diagnosed (%)
South Portugal	44	2.7	68
South East Ireland	27	3.6	59
Zagreb, Croatia	24	4.1	71
Wessex, UK	156	5.2	86
E Midlands & York, UK	311	5.3	83
Tuscany, Italy	167	5.6	81
Norway	273	5.6	61
Malta	25	6.1	36
Cork and Kerry, Ireland	60	6.1	48
Hainaut, Belgium	85	6.7	72
Emilia Romagna, Italy	276	6.9	70
Valencia Region, Italy	278	6.9	59
Northern England, UK	231	7.0	71
Mainz, Germany	23	7.2	78
Ukraine	219	7.2	60
Thames Valley, UK	221	7.4	77
North Netherlands	130	7.5	62
Odence, Denmark	34	8.4	65
Wales, UK	305	8.8	64
Saxony Anhalt, Germany	153	8.9	50
Antwerp, Belgium	185	9.0	56
Styria, Austria	77	9.3	75
Basque Country, Spain	201	9.8	77
South West England, UK	491	9.9	51
Isle de Reunion, France	176	12.1	78

Brittany, France	182	12.5	89
Vaud, Switzerland	122	15.4	73
Paris, France	352	16.5	94
French West Indies, France	99	16.6	92
Total	4927	9.78 (95%CI: 8.50 - 11.16)[1]	70

1 : Adjusted for potential under-reporting (see methods)

Table 2

ICD 10 Code	Q04.0	Q04.1	Q04.2	Q04.3	Q04.4	Q04.5	Q04.6	Q04.8	Q04.9	Q04
Anomaly	Congenital malformations of corpus callosum	Arhin-encephaly	Holopros-encephaly	Other reduction deformities of brain	Septo-optic dysplasia	Megal-encephaly	Congenital cerebral cysts	Other specified congenital malformations of brain	Congenital malformation of brain, unspecified	All Cases
Total No.	1748	46	865	1464	99	49	555	550	273	4927
Prevalence per 10,000 births (95%CI)[1]	3.84 (3.22 - 4.51)	0.05 (0.02 - 0.11)	1.55 (1.37 - 1.77)	2.98 (2.56 - 3.44)	0.19 (0.12 - 0.26)	0.08 (0.05 - 0.11)	1.11 (0.86 - 1.38)	1.13 (0.81 - 1.51)	0.46 (0.34 - 0.58)	9.78 (8.5 - 11.16)
Live births No. (%)	1131 (65)	2 (4)	155 (18)	815 (56)	96 (96)	33 (67)	428 (77)	369 (67)	130 (48)	2720 (55)
Fetal Deaths No. (%)	41 (2)	2 (4)	34 (4)	56 (4)	0 (0)	1 (2)	8 (1)	16 (3)	19 (7)	164 (3)
TOPFA No. (%)	576 (33)	42 (91)	676 (78)	593 (40)	4 (4)	15 (31)	119 (21)	165 (30)	124 (45)	2043 (41)
Non-genetic No.(%)	1367 (78)	21 (46)	539 (62)	1157 (79)	96 (96)	43 (88)	489 (88)	432 (79)	219 (80)	3784 (77)
Maternal age (years) (95% CI)	30.2 (29.9-30.5)	31.2 (29.5-32.9)	30.2 (29.8-30.6)	29.9 (29.6-30.3)	23.4 (22.3-24.6)	29.6 (27.7-31.6)	28.6 (28.0-29.1)	30.3 (29.9-30.9)	29.5 (28.8-30.3)	29.9 (29.8-30.1)
Gestation <37 weeks (%) (95% CI)	25 (22-27)	75 (19-99)	45 (38-53)	33 (30-36)	18 (11-28)	19 (7-37)	34 (30-39)	32 (27-37)	37 (29-46)	31 (29-33)
Prenatal Diagnosis (%) (95% CI)	72 (69-74)	96 (85-99)	94 (92-95)	69 (67-71)	34 (25-44)	55 (40-69)	54 (49-58)	59 (55-63)	65 (59-70)	70 (69-71)
Male (%) (95% CI)	53 (51-56)	41 (25-59)	47 (43-51)	53 (50-55)	55 (45-65)	63 (48-77)	55 (51-59)	56 (52-60)	55 (48-62)	53 (51-54)

1 : Adjusted for potential under-reporting (see methods)

Table 3. Classification of congenital cerebral anomaly cases according to associated anomalies and genetic diagnosis.

ICD 10 Code	**Q04.0**	**Q04.1**	**Q04.2**	**Q04.3**	**Q04.4**	**Q04.5**	**Q04.6**	**Q04.8**	**Q04.9**	Q04
Associated anomalies and genetic diagnoses No. (%)	Congenital malform-ations of corpus callosum	Arhin-encephaly	Holopros-encephaly	Other reduction deformities of brain	Septo-optic dysplasia	Megal-encephaly	Congenital cerebral cysts	Other specified congenital malform-ations of brain	Congenital malform-ation of brain, unspecified	All Cases
Isolated cerebral anomaly	895 (51)	3 (7)	305 (35)	682 (47)	73 (74)	35 (71)	356 (64)	248 (45)	128 (47)	2380 (48)
Chromosomal	280 (16)	21 (46)	309 (36)	203 (14)	1 (1)	0 (0)	43 (8)	68 (12)	39 (14)	876 (18)
Patau syndrome	39 (2)	13 (28)	206 (24)	42 (3)	0 (0)	0 (0)	0 (0)	5 (1)	11 (4)	285 (6)
Edwards syndrome	61 (3)	2 (4)	31 (4)	51 (3)	0 (0)	0 (0)	25 (5)	12 (2)	7 (3)	178 (4)
Downs syndrome	18 (1)	0 (0)	3 (0)	24 (2)	1 (1)	0 (0)	1 (0)	13 (2)	6 (2)	62 (1)
Genetic syndrome	113 (6)	4 (9)	13 (2)	155 (11)	1 (1)	8 (16)	26 (5)	56 (10)	15 (5)	329 (7)
Teratogenic syndromes including maternal infections	22 (1)	(0)	(0)	34 (2)	1 (1)	0 (0)	16 (3)	17 (3)	16 (6)	89 (2)
Multiple congenital anomaly	438 (25)	18 (39)	238 (28)	390 (27)	23 (23)	6 (12)	114 (21)	161 (29)	75 (27)	1253 (25)
with congenital heart defects	162 (9)	3 (7)	68 (8)	138 (9)	8 (8)	1 (2)	40 (7)	56 (10)	34 (12)	448 (9)
with congenital limb anomalies	120 (7)	4 (9)	42 (5)	133 (9)	4 (4)	3 (6)	30 (5)	43 (8)	21 (8)	326 (7)
with congenital eye anomalies	51 (3)	3 (7)	46 (5)	25 (2)	9 (9)	0 (0)	13 (2)	12 (2)	5 (2)	140 (3)
with renal anomalies	12 (1)	0 (0)	5 (1)	17 (1)	(0)	0 (0)	2 (0)	3 (1)	2 (1)	38 (1)

Figure 1 : Cerebral Anomalies (Q04) in EUROCAT registries according to Outcome of Pregnancy

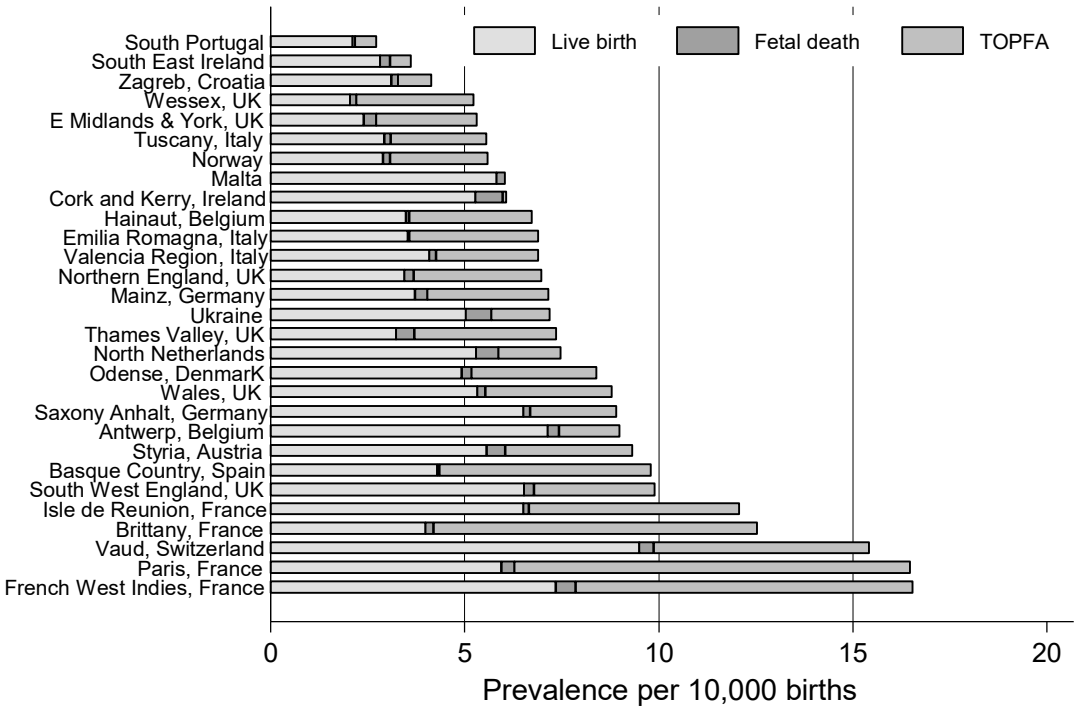


Figure 2 : Association between the prevalence of Cerebral Anomalies (Q04) in EUROCAT registries according to the percentage of cases diagnosed prenatally

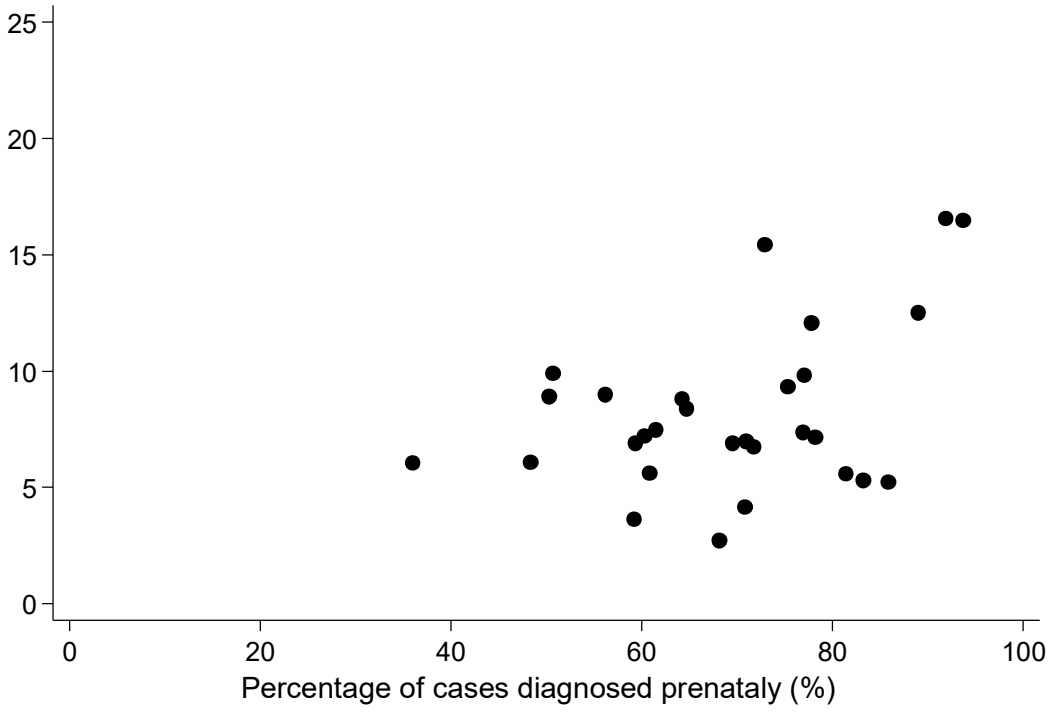
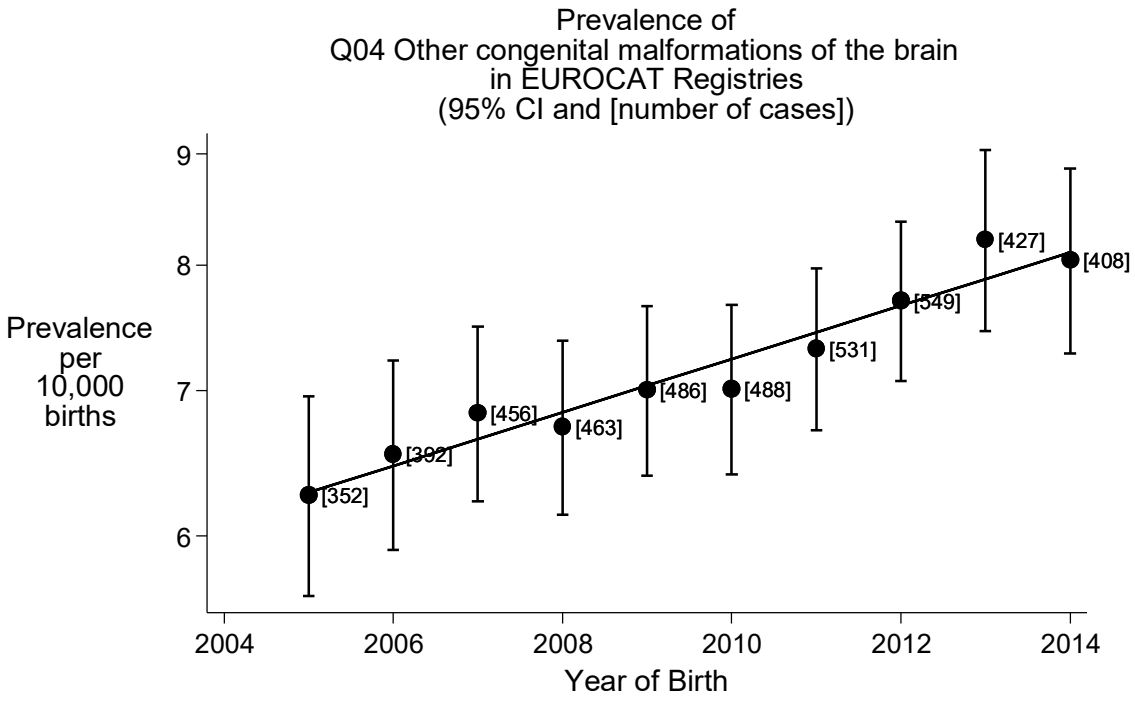
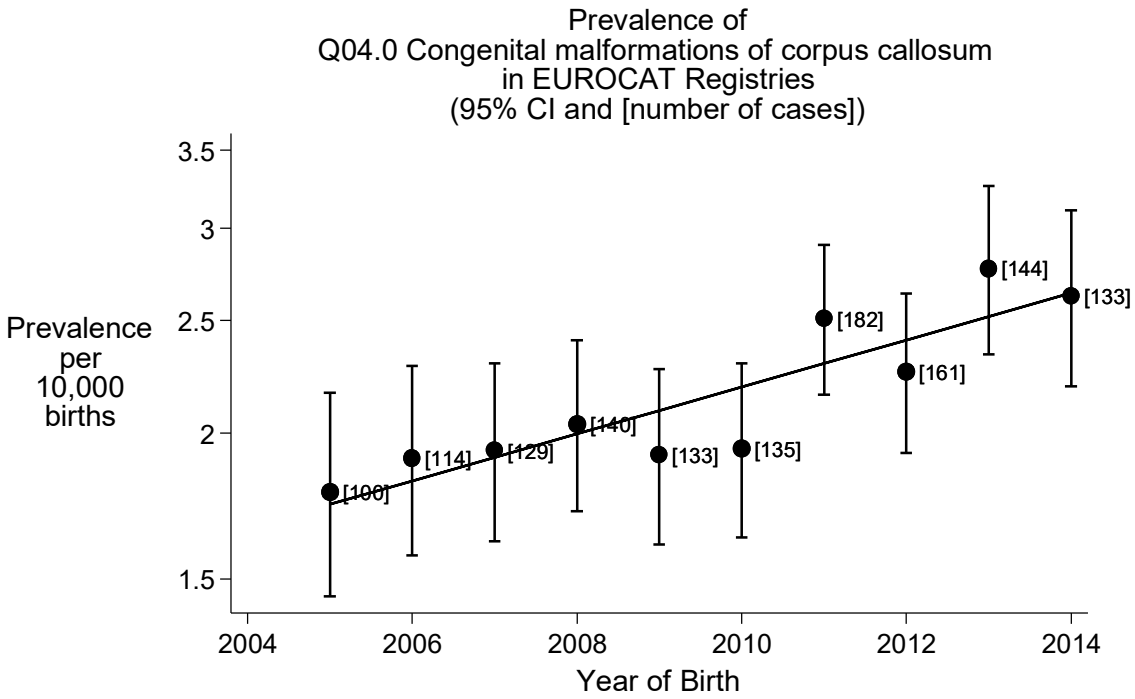
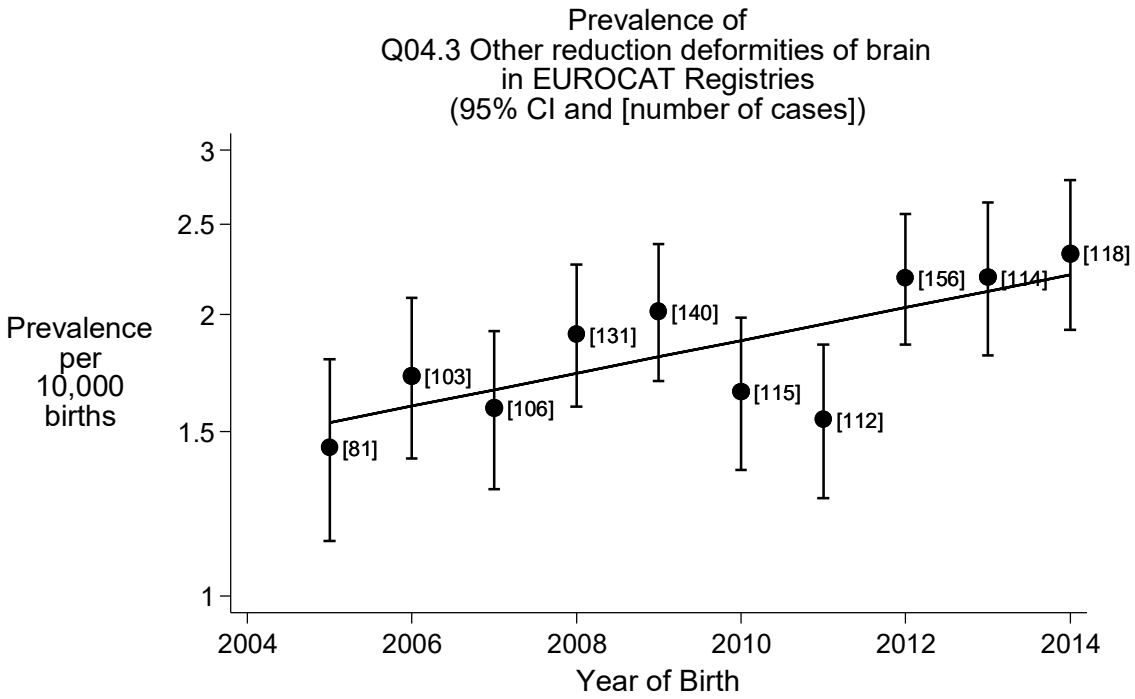
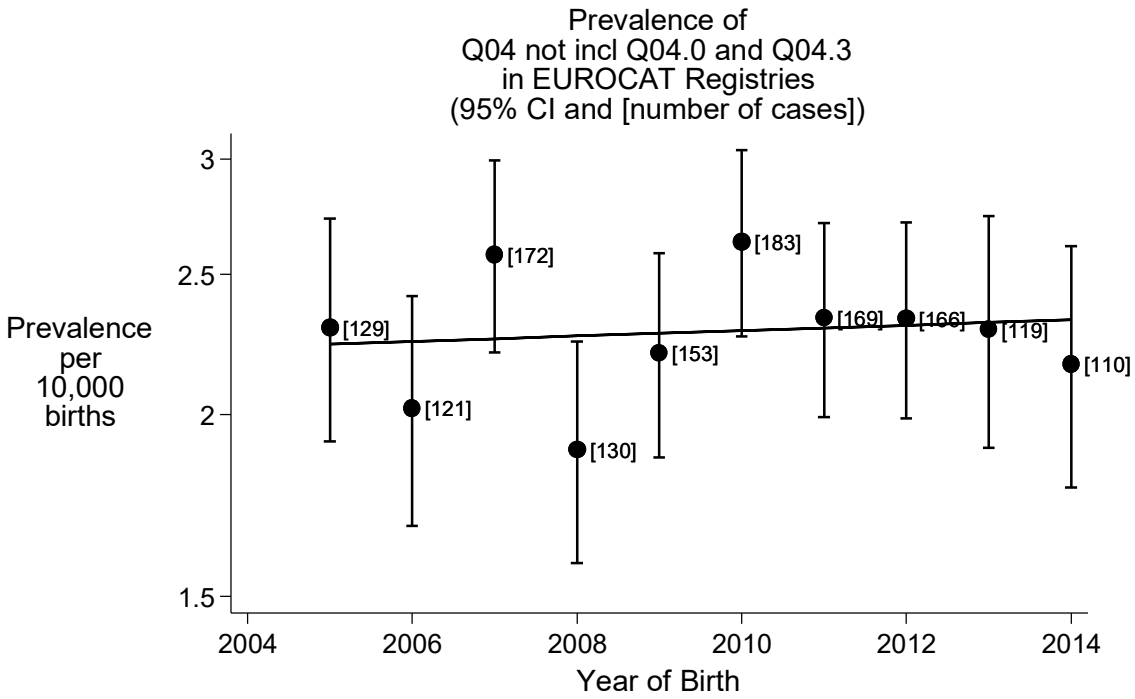


Figure 3a, 3b, 3c, 3d. Pan-European trends of non-genetic congenital cerebral anomalies 2005-2014.




Prevalence of
Q04.0 Congenital malformations of corpus callosum
in EUROCAT Registries
(95% CI and [number of cases])
Prevalence per 10,000 births
3.5
3
2.5
2
1.5
[106]
[114]
[129]
[140]
[133]
[135]
[182]
[161]
[144]
[133]
2004
2006
2008
2010
2012
2014
Year of Birth


Prevalence of
Q04.3 Other reduction deformities of brain
in EUROCAT Registries
(95% CI and [number of cases])
Prevalence per 10,000 births
3
2.5
2
1.5
1
[81]
[103]
[106]
[131]
[140]
[115]
[112]
[156]
[114]
[118]
2004
2006
2008
2010
2012
2014
Year of Birth


Prevalence of
Q04 not incl Q04.0 and Q04.3
in EUROCAT Registries
(95% CI and [number of cases])
Prevalence per 10,000 births
3
2.5
2
1.5
[129]
[121]
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2004
2006
2008
2010
2012
2014
Year of Birth

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