Epidemiology of congenital cerebral anomalies in Europe: a multicentre, population-based EUROCAT study

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ABSTRACT

Objectives To describe the epidemiology and geographical differences in prevalence of congenital cerebral anomalies in Europe.

Design and setting Congenital cerebral anomalies (International Classification of Diseases, 10th Revision code Q04) recorded in 29 population-based EUROCAT registries conducting surveillance of 1.7 million births per annum (29% of all European births).

Participants All birth outcomes (live births, fetal deaths from 20 weeks gestation and terminations of pregnancy after prenatal diagnosis of a fetal anomaly (TOPFA)) from 2005 to 2014.

Main outcome measures Prevalence, proportion of associated non-cerebral anomalies, prenatal detection rate.

Results 4927 cases with congenital cerebral anomalies were identified; a prevalence (adjusted for under-reporting) of 9.8 (95% CI: 8.5 to 11.2) per 10 000 births. There was a sixfold difference in prevalence across the registries. Registries with higher proportions of prenatal diagnoses had higher prevalence. Overall, 55% of all cases were liveborn, 3% were fetal deaths and 41% resulted in TOPFA. Forty-eight per cent of all cases were an isolated cerebral anomaly, 25% had associated non-cerebral anomalies and 27% were chromosomal or part of a syndrome (genetic or teratogenic). The prevalence excluding genetic or chromosomal conditions increased by 2.4% per annum (95% CI: 1.3% to 3.5%), with the increases occurring only for congenital malformations of the corpus callosum (3.0% per annum) and 'other reduction deformities of the brain' (2.8% per annum).

Conclusions Only half of the cases were isolated cerebral anomalies. Improved prenatal and postnatal diagnosis may account for the increase in prevalence of congenital cerebral anomalies from 2005 to 2014. However, major differences in prevalence remain between regions.

What is already known on this topic?

- Previous studies of structural cerebral anomalies have often been based on small series of cases rather than population-based case series.
- Prevalence of megalencephaly has not been reported.

What this study adds?

- Forty-eight per cent of cases with a structural cerebral anomaly were classified as an isolated cerebral anomaly, 25% had associated non-cerebral anomalies and 27% were classified as chromosomal or part of a syndrome (genetic or teratogenic).
- Reported prevalence of congenital cerebral anomalies in Europe increased from 2005 to 2014 with major differences in prevalence between regions and with a significant association between prevalence and prenatal detection rate; improved prenatal and postnatal diagnosis may account for this increase.
- The prevalence of megalencephaly was 0.08 (95% CI: 0.05 to 0.11) per 10 000 births.

INTRODUCTION

It is important to have background information about the epidemiology of congenital cerebral anomalies including associated anomalies and trends over time. This enables a knowledge-based evaluation of possible future changes in the prevalence and associated anomalies, which could be related to the occurrence of new teratogens. For example, maternal Zika virus infection is acknowledged to increase the risk of microcephaly occurring in the fetus.[1 2] However, there is more uncertainty as to the association of maternal Zika virus infections with other structural cerebral anomalies.[3]

EUROCAT is a European network of population-based registries for the epidemiological surveillance of congenital anomalies (http://www.

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eurocat-network.eu/).[4 5] There are many EUROCAT publications on neural tube defects,[6–8] microcephaly,[9] hydrocephaly[10] and septo-optic dysplasia.[11] Individual EUROCAT registries have published data on corpus callosum anomalies in Emilia Romagna,[12] schizencephaly[13] and holoprosencephaly[14] in the United Kingdom. However, the epidemiology of these and other cerebral anomalies from the Q04 chapter in International Classification of Diseases, 10th Revision (ICD-10) such as reduction defects of the brain, microgyria, megalencephaly, cerebral cysts and schizencephaly has never been analysed at a European level and most of these anomalies are quite rare with little published epidemiological data. A previous EUROCAT collaboration with the Surveillance of Cerebral Palsy in Europe network has shown that the majority of congenital anomalies in children with cerebral palsy are cerebral anomalies,[15 16] indicating the severity of the clinical outcome of these congenital anomalies.

Most cerebral anomalies are not recognised at birth, but may be diagnosed prenatally and postnatally by ultrasound scans and other imaging examinations including MRI. 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 the prevalence of cerebral anomalies are expected.

The aim of this study was to describe the epidemiology of specific congenital cerebral anomalies in Europe and the observed geographical differences in prevalence using EUROCAT data.

METHODS

The EUROCAT registries are population based; the geographically defined populations and the methodology of collecting individual case data for EUROCAT are described elsewhere.[4] The registries ascertain congenital anomaly cases from multiple sources, using active case finding and passive notification, such as hospital discharge diagnoses, birth and death certificates and postmortem examinations. Information about live births (LBs), fetal deaths (FDs) with a gestational age (GA) ≥20 weeks and terminations of pregnancy after prenatal diagnosis of a fetal anomaly (TOPFA) at any gestation is included. All major structural congenital anomalies, syndromes and chromosomal anomalies are included in the database. Minor anomalies are excluded based on a list of ICD-10 codes for exclusion (EUROCAT Guide 1.4).[17] The congenital anomalies have been coded according to ICD-10 with the British Paediatric Association extension since 2005.

All full member registries were invited to take part in the study, and data from 29 EUROCAT registries are included. Data were extracted from the EUROCAT database on 31 May 2017 (table 1). All birth outcomes (LB, FD and TOPFA) with an ICD-10 code within the subchapter Q04 'Other congenital malformations of brain' and born in the years 2005–2014 were included. The anomalies included in Q04 are congenital anomalies of corpus callosum (Q040), arhinencephaly (Q041), holoprosencephaly (Q042), other reduction deformities of brain (Q043), septo-optic dysplasia (Q044), megalencephaly (Q045), congenital cerebral cysts (Q046), other specified anomalies of brain (Q048) and unspecified congenital anomalies of brain (Q049). Some registries added the fourth digit code from British Associations extension of ICD-10 for Q043 for further specification (agyria/lissencephaly, microgyria/polygyria, hydranencephaly, reduction anomalies of cerebrum, reduction anomalies of cerebellum). A previous article has reported data from the cases with septo-optic dysplasia,[11] which for completeness are also included in this article. Not all registries contributed data for all 10 years. Data about each case included year of birth, type of birth, GA at birth or termination, infant sex, time of diagnosis, maternal age and associated congenital anomalies.

Classification of the congenital anomalies

Cases were classified as isolated cerebral anomalies, chromosomal cases, teratogenic or genetic syndromes or multiple congenital anomalies (anomalies from other organ systems plus a cerebral anomaly) according to the EUROCAT multiple congenital anomaly flow chart[18] 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. Combinations of cerebral anomalies within the Q04 chapter were classified hierarchically according to table 2 so that all cases were allocated to one main cerebral anomaly diagnosis—diagnoses on the left taking precedence over those on the right. The diagnoses of single cerebral cyst, arachnoid and choroid plexus cysts and anomalies of septum pellucidum are on the EUROCAT list of minor anomalies for exclusion and these cases were, therefore, excluded if described in the written text as the only cerebral anomaly. Cases with written text description of large cisterna magna, asymmetric ventricles or minor ventriculomegaly (<15 mm) were excluded if these were the only cerebral anomalies. Colpocephaly was classified as a secondary anomaly if associated with agenesis of corpus callosum. There are no specific ICD-10 codes for the most frequent cerebral syndromes (Joubert, Aicardi, Walker-Warburg and Miller-Dieker syndromes), and these are reported based on written text descriptions. There were no written text descriptions for cases from the registries in Paris and Norway, and Northern England (NorCAS) used standard written text. Trends over time are presented as pan-European trends excluding genetic cases (chromosomal anomaly or genetic syndrome).

Method to identify under-reporting

A previous study of septo-optic dysplasia[11] found evidence that some registries were under-reporting cases and developed a method to estimate the prevalence adjusting for this under-reporting. In brief, for each separate anomaly, the average prevalence among the 15 registries with the highest prevalence 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 among 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 with the mean prevalence of all 29 registries assuming the number of cases follows a Poisson distribution with an expected value equal to the observed median number of cases in the 15 registries. For example, if only two 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.

Statistical analysis

The prevalence of the anomalies and the trends over time were investigated by fitting Poisson regression multilevel models with registry as a random effect. Associations between prevalence and prenatal diagnosis rates and the length of follow-up a registry performs (that is up to what age they still collect diagnoses classified into within 1 week, within 1 year and over 1 year) were investigated

Table 1 Number of cases with a congenital cerebral anomaly (ICD-10 code Q04), prevalence and proportion prenatally diagnosed in 29 EUROCAT registries in the period 2005–2014

Registry, country	Years of data	Population births (1000)	Total cases	Prevalence per 10 000 births	Proportion prenatally diagnosed (%)
South Portugal	2006–2014	161	44	2.7	68
South East Ireland	2005–2014	75	27	3.6	59
Zagreb, Croatia	2005–2014	58	24	4.1	71
Wessex, UK	2005–2014	298	156	5.2	86
East Midlands and South Yorkshire, UK	2005–2012	587	311	5.3	83
Tuscany, Italy	2005–2014	300	167	5.6	81
Norway	2005–2012	487	273	5.6	61
Malta	2005–2014	41	25	6.1	36
Cork and Kerry, Ireland	2005–2014	99	60	6.1	48
Hainaut, Belgium	2005–2014	126	85	6.7	72
Emilia Romagna, Italy	2005–2014	400	276	6.9	70
Valencia Region, Spain	2005–2014	403	278	6.9	59
Northern England, UK	2005–2014	331	231	7.0	71
Mainz, Germany	2005–2014	32	23	7.2	78
Ukraine	2005–2014	304	219	7.2	60
Thames Valley, UK	2005–2014	300	221	7.4	77
Northern Netherlands	2005–2014	174	130	7.5	62
Odense, Denmark	2005–2013	41	34	8.4	65
Wales, UK	2005–2014	347	305	8.8	64
Saxony-Anhalt, Germany	2005–2014	172	153	8.9	50
Antwerp, Belgium	2005–2014	206	185	9.0	56
Styria, Austria	2005–2012	83	77	9.3	75
Basque Country, Spain	2007–2014	205	201	9.8	77
South West England, UK	2005–2014	496	491	9.9	51
Isle de Reunion, France	2005–2014	146	176	12.1	78
Brittany, France	2011–2014	145	182	12.5	89
Vaud, Switzerland	2005–2014	79	122	15.4	73
Paris, France	2005–2012	214	352	16.5	94
French West Indies, France	2009–2014	60	99	16.6	92
Total	2005–2014	6368	4927	9.78 (95% CI: 8.50 to 11.16)*	70

*Total prevalence is adjusted for potential under-reporting (see Methods section).
ICD-10, International Classification of Diseases, 10th Revision.

using Poisson regression with prenatal diagnosis and length of follow-up as covariates. All other exploratory analyses between anomalies were investigated using analysis of variance and χ^2 tests according to whether the variable of interest was categorical or not.

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; figure 1), with more than a sixfold 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 2), but significant heterogeneity between registers still remained. There was no association between length of follow-up performed by the registry and the prevalence (p=0.5).

Congenital malformations of the corpus callosum and 'other reduction deformities of the brain' were the most common cerebral anomalies, with an adjusted prevalence of 3.3 (95% CI 2.7 to 3.8) and 2.9 (95% CI 2.5 to 3.4), respectively. The adjusted prevalence of holoprosencephaly was 1.6 (95% CI: 1.4 to 1.8) per 10 000 births and of megalencephaly was 0.08 (95% CI: 0.05 to 0.11) per 10 000 births.

Overall, 3448 cases were diagnosed prenatally (70% of the total, ranging from 50% to 94% among registries) and of these 2043 resulted in a TOPFA (59% of the prenatally diagnosed cases). The prenatal diagnosis may have occurred due to a different anomaly, we cannot distinguish which anomaly was diagnosed first. Overall, 55% of cases were LBs, 3% FDs and 41% TOPFAs, with large variation between registries and cerebral anomaly. Pregnancies with septo-optic dysplasia were most likely to result in an LB (96%) and pregnancies with arhinencephaly least likely to result in an LB (4%). Overall, 28% of all LBs were born preterm (GA <37 weeks) which varied according to anomaly; babies with septo-optic dysplasia and megalencephaly were the least likely to be born preterm (19% and 17%, respectively) (table 2).

The average maternal age for all cases of cerebral anomalies was 29.9 years. The mean maternal age was significantly lower in cases of septo-optic dysplasia (23.4 years).

For all the cases, 48% were isolated cerebral anomalies, 25% were classified as multiple congenital anomalies, 18% had an associated chromosomal anomaly (6% had Patau syndrome)

Table 2 Epidemiology data for congenital cerebral anomaly cases in 29 EUROCAT registries from 2005 to 2014 with cerebral anomaly cases classified according to one main cerebral anomaly category with the diagnoses present on the left taking precedence over the ones on the right

ICD-10 code	Q04.2	Q04.1	Q04.4	Q04.5	Q04.3	Q04.0	Q04.8	Q04.6	Q04.9	Q04
Anomaly	Holoprosencephaly	Arhinencephaly	Septo-optic dysplasia	Megalencephaly	Other reduction deformities of brain	Congenital malformations of corpus callosum	Other specified congenital malformations of brain	Congenital cerebral cysts	Congenital malformation of brain, unspecified	All cases
No of cases	865	33	94	49	1409	1476	383	375	243	4927
No of diagnoses*	865	46	99	49	1464	1748	550	555	273	5649
Prevalence per 10 000 births (95% CI)†	1.55 (1.37 to 1.77)	0.04 (0.01 to 0.07)	0.19 (0.11 to 0.26)	0.08 (0.05 to 0.11)	2.92 (2.51 to 3.35)	3.25 (2.72 to 3.82)	0.75 (0.53 to 1.01)	0.69 (0.49 to 0.93)	0.39 (0.29 to 0.52)	9.78 (8.5 to 11.16)
Live births, n (%)	155 (18)	2 (6)	90 (96)	33 (67)	792 (56)	975 (66)	259 (68)	302 (81)	112 (46)	2720 (55)
Fetal deaths, n (%)	34 (4)	1 (3)	0 (0)	1 (2)	55 (4)	37 (3)	12 (3)	6 (2)	18 (7)	164 (3)
TOPFA, n (%)	676 (78)	30 (91)	4 (4)	15 (31)	562 (40)	464 (31)	112 (29)	67 (18)	113 (47)	2043 (41)
Non-genetic, n (%)	539 (62)	12 (36)	91 (97)	43 (88)	1119 (79)	1156 (78)	307 (80)	325 (87)	192 (79)	3784 (77)
Average maternal age (years)	30 (30–31)	32 (30–34)	23 (22–24)	30 (28–32)	30 (30–30)	30 (30–31)	30 (30–31)	29 (28–30)	29 (29–30)	30 (30–30)
Preterm birth (GA <37 weeks) live births, n (%)	62 (40)	1 (50)	17 (19)	5 (17)	229 (29)	208 (22)	79 (31)	113 (38)	34 (32)	748 (28)
Prenatal diagnosis, n (%)	811 (94)	32 (97)	32 (34)	27 (55)	962 (68)	1038 (70)	207 (54)	182 (49)	157 (65)	3448 (70)
Males, n (%)	316 (37)	14 (42)	52 (55)	29 (59)	684 (49)	749 (51)	198 (52)	196 (52)	114 (47)	2352 (48)

*Number of diagnoses will be greater than the number of cases as each case may have more than one different diagnoses of a cerebral anomaly.
†Adjusted for potential under-reporting (see Methods section).
ICD-10, International Classification of Diseases, 10th Revision; GA, gestational age; TOPFA, terminations of pregnancy after prenatal diagnosis of a fetal anomaly.

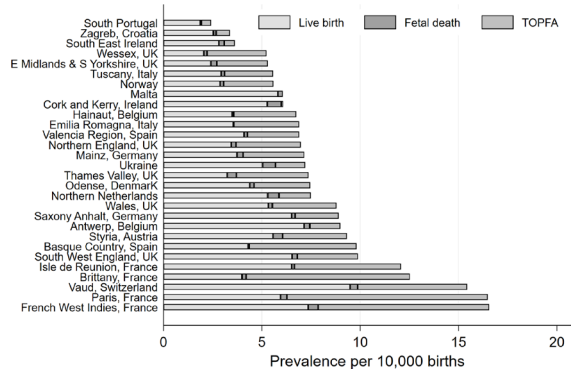

Figure 1 Cerebral anomalies (Q04) in EUROCAT registries according to outcome of pregnancy. TOPFA, terminations of pregnancy after prenatal diagnosis of a fetal anomaly.

and for 9% a teratogenic or genetic syndrome was diagnosed (table 3). The most common associated anomalies were congenital heart defects (CHDs, 9%) and septal defects (atrial septal defect and ventricular septal defect) were the most frequent CHDs. Cases with arhinencephaly or holoprosencephaly were more likely to have a chromosomal anomaly (46% and 36%, respectively), particularly Patau syndrome (33% and 24%, respectively). In contrast, cases with septo-optic dysplasia, megalencephaly or cerebral cysts were more likely to be isolated cerebral anomalies (72%, 71% and 67%, respectively). The most common genetic syndromes reported were Joubert syndrome (23 cases) and Aicardi syndrome (13 cases).

Figure 3A,D show that the pan-European prevalence of cases with cerebral anomalies not due to genetic or chromosomal conditions has increased from 2005 to 2014 by 2.4% per annum (94% CI: 1.3% to 3.5%), with the increases occurring for congenital malformations of the corpus callosum by 3.0% (0.8% to 5.3%) and 'other reduction deformities of the brain' by 2.8% (0.5% to 5.0%). These significant increases in prevalence remained after adjusting for increases in prenatal diagnoses and for the length of follow-up in the registries.

DISCUSSION

The overall prevalence (adjusted for under-reporting) of major congenital cerebral anomalies in Europe from 2005 to 2014 was 9.8 (95% CI: 8.5 to 11.2) per 10 000 births. The prevalence

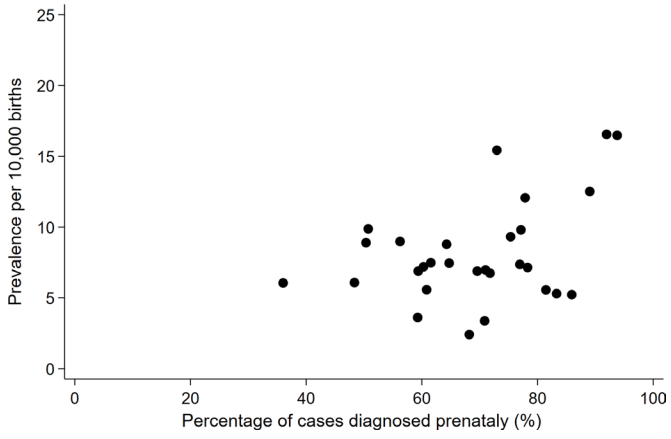

Figure 2 Association between the prevalence of cerebral anomalies (Q04) in EUROCAT registries and the percentage of cases diagnosed prenatally.

of non-genetic, non-chromosomal anomalies of corpus callosum and of other reduction defects of brain significantly increased, while the prevalences of the other cerebral anomalies were stable. The increases may be due to increased prenatal diagnosis as if cerebral anomalies are not diagnosed prenatally, they may not be diagnosed for several years of age until they emerge in relation to the diagnosis of developmental problems or cerebral palsy.[16]

Our adjusted prevalence for corpus callosum anomalies of 3.3 (95% CI: 2.72 to 3.82) per 10 000 births with 66% LBs was consistent with two other smaller studies of 38 and 630 cases which did not include fetal losses or TOPFAs.[19 20] The study from California from 1983 to 2003[20] showed a prevalence of corpus callosum anomalies 1.8 per 10 000 births and the study from Hungary from 1992 to 2006 showed a prevalence of 2.05 per 10 000 LBs.[19] The Californian study found 17% of cases had a chromosomal anomaly similar to the 16% in our study).[20] The increased risk of preterm birth was also observed in our study.[20]

The adjusted prevalence of holoprosencephaly was 1.6 (95% CI: 1.4 to 1.8) per 10 000 births. A literature review including 21 studies found that the prevalence of holoprosencephaly varied between 0.5 and 1.5 per 10 000 births.[21] The authors concluded that the differences in prevalence were mainly explained by the inclusion criteria (LBs or all pregnancy outcomes including early TOPFA). These studies also found a higher female rate and a high proportion of chromosomal cases as in our study (63% were female and 36% were chromosomal cases).

Our study showed an adjusted prevalence of megalencephaly of 0.08 (95% CI: 0.05 to 0.11) per 10 000 births. To our knowledge, there are no published prevalence figures for this anomaly. Most case series and reports describe megalencephaly as an isolated anomaly,[22] which is in line with our findings (71% isolated). A study from a tertiary centre in the USA described that almost half of their patients with unilateral megalencephaly had an additional syndrome diagnosis.[22] Tinkle *et al*[22] report a Japanese study that found 11 of 38 patients (29%) had a syndrome diagnosis (Sasaki *et al*, 2000—in Japanese so not referenced). In our study, we found a syndrome diagnosis in 16% of cases.

Our study showed an adjusted prevalence of arhinencephaly of 0.04 (95% CI: 0.01 to 0.07) per 10 000 births. The only study we identified reported a prevalence of arhinencephaly of 0.14 (95% CI: 0.06 to 0.25) per 10 000 births in Atlanta[23] and included only 10 cases, while our study included 46 cases.

The prevalence of our remaining three groups (cerebral cysts (Q046), other specified cerebral anomalies (Q048) and unspecified cerebral anomalies (Q049)) is more heterogeneous and therefore difficult to compare with other studies. Cases with congenital cerebral cysts were mainly liveborn (81%), mainly non-genetic (87%) and half of the cases were diagnosed prenatally. Some cases coded Q048 had the written text description 'ventriculomegaly'. The EUROCAT definition of hydrocephaly (ICD-10 codes in Q03) is a size of the lateral ventricles at 15 mm or more. Cases with an unspecified size of the lateral ventricles or a size at 10–14 mm may have been reported to EUROCAT with the code Q048 for other specified cerebral anomalies. Less than half of the cases reported with unspecified cerebral anomaly were liveborn, indicating the severity of the anomalies but lack of diagnostic details in the EUROCAT registries.

The association between prevalence and prenatal detection rate explains part of the European heterogeneity in the prevalence of cerebral anomalies. In addition, fetal MRI may be used more frequently in some areas and may increase the detection rate.[24] However, under-ascertainment of cases by the registry may also

Table 3 Classification of congenital cerebral anomaly cases according to associated anomalies and genetic diagnosis; 29 EUROCAT registries, 2005–2014

ICD-10 code	Q04.2	Q04.1	Q04.4	Q04.5	Q04.3	Q04.0	Q04.8	Q04.6	Q04.9	Q04
Associated anomalies and genetic diagnoses, n (%)	Holoprosencephaly	Arhinencephaly	Septo-optic dysplasia	Megalencephaly	Other reduction deformities of brain	Congenital malformations of corpus callosum	Other specified congenital malformations of brain	Congenital cerebral cysts	Congenital malformation of brain, unspecified	All cases
Isolated cerebral anomaly	305 (35)	2 (6)	68 (72)	35 (71)	663 (47)	764 (52)	180 (47)	251 (67)	112 (46)	2380 (48)
Chromosomal	309 (36)	21 (46)	1 (1)	0 (0)	203 (14)	280 (16)	68 (12)	43 (8)	39 (14)	876 (18)
Patau syndrome	206 (24)	11 (33)	0 (0)	0 (0)	31 (2)	24 (2)	2 (1)	0 (0)	11 (5)	285 (6)
Edward's syndrome	31 (4)	1 (3)	0 (0)	0 (0)	50 (4)	55 (4)	10 (3)	24 (6)	7 (3)	178 (4)
Down's syndrome	3 (0)	0 (0)	1 (1)	0 (0)	23 (2)	17 (1)	11 (3)	1 (0)	6 (2)	62 (1)
Genetic syndrome	13 (2)	4 (12)	1 (1)	8 (16)	152 (11)	92 (6)	31 (8)	15 (4)	13 (5)	329 (7)
Teratogenic syndromes including maternal infections*	0 (0)	0 (0)	1 (1)	0 (0)	34 (2)	17 (1)	15 (4)	9 (2)	13 (5)	89 (2)
Multiple congenital anomaly	238 (28)	10 (30)	23 (24)	6 (12)	372 (26)	364 (25)	109 (28)	63 (17)	68 (28)	1253 (25)
With congenital heart defects	68 (8)	3 (9)	8 (9)	1 (2)	133 (9)	143 (10)	40 (10)	22 (6)	30 (12)	448 (9)
With congenital limb anomalies	42 (5)	2 (6)	4 (4)	3 (6)	125 (9)	94 (6)	26 (7)	13 (3)	17 (7)	326 (7)
With congenital eye anomalies	46 (5)	2 (6)	9 (10)	0 (0)	21 (1)	43 (3)	6 (2)	8 (2)	5 (2)	140 (3)

*Under-reporting is likely to have occurred.
ICD-10, International Classification of Diseases, 10th Revision.

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 the cerebellum, often with the written text 'small cerebellum' was mainly reported by the English registries and there may be different diagnostic criteria for reporting this anomaly. For some cerebral anomalies, in particular reduction defects, the critical exposure period includes up to gestational week 18.[25] If ultrasound screening is performed at an earlier gestational age , cases may be missed.

There was a high rate of TOPFAs 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, the TOPFA rate was 31%, possibly due to more severe cerebral anomalies being present. Counselling and parental decision-making after prenatal diagnosis of anomalies of corpus callosum is difficult.[26] A study has shown that 25%–30% of fetuses with a prenatal diagnosis of isolated agenesis of corpus callosum have developmental delays.[27] However, a recent study on the use of MRI on fetuses with a suspected brain abnormality on ultrasound showed that fetal MRI changed the prognostic information in 20% of the cases.[24]

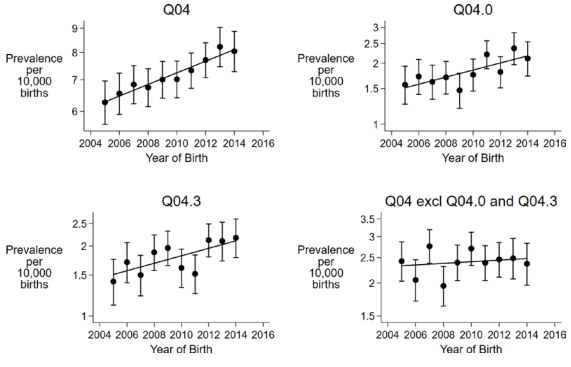

Figure 3 Pan-European trends of non-genetic congenital cerebral anomalies 2005–2014. Prevalence and 95% CIs. Q04, all cerebral anomalies; Q04.0, congenital malformations of corpus callosum; Q04.3, other reduction deformities of brain.

Strengths and limitations

The strength of our study is that it is the largest study covering 6.4 million births in Europe. All registries use the same inclusion criteria for major anomalies and the same coding and classification system for congenital anomalies. There may be under-reporting of cases in some registries, but this is adjusted for in the method for calculating the European prevalence of specific anomalies (which does assume that all populations are at equal risk of occurrence of the congenital anomalies of interest which may not be the case). There may also be some over-reporting of minor anomalies, reporting of diagnosis related to birth complications or misclassification of congenital hydrocephaly as ventriculomegaly.

CONCLUSIONS

Our study provides background prevalence information in the time period before the outbreak of the Zika virus. During this period, increasing prevalence was reported due to better prenatal detection. Heterogeneity in prevalence between regions of Europe may be explained by differences in the prenatal diagnoses and by under-reporting of major anomalies in some registries and reporting of minor anomalies as major in other registries.

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Correction notice This paper has been slightly amended since it was published Online First. Author Monica Lanzoni's affiliation has been changed and in the main article, figure 3 legend has been updated.

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Ethics approval Local procedures regarding ethics approval for the registries' activities and their collaborations with EUROCAT are available on the EUROCAT website (www.eurocat-network.eu/ABOUTUS/Member-Registries/MembersAndRegistryDescriptions/AllMembers).

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Data sharing statement The data used in this study belong to the individual registries. However, requests for case data can be made to the JRC-EUROCAT Central Registry (JRC-EUROCAT@ec.europa.eu) who will ask the individual registries permission to use the data. Aggregate data, updated biannually, are available from the EUROCAT website http://www.eurocat-network.eu/accessprevalencedata/prevalencetables. Data included in the paper was extracted from the EUROCAT database in April 2016.

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