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European Monitoring of Congenital Anomalies

JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2007 - 2016)

Monica Lanzoni, Joan Morris, Ester Garne,
Maria Loane, Agnieszka Kinsner-Ovaskainen

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European Monitoring of Congenital Anomalies

JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2007 - 2016)

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The report was reviewed and approved by the JRC-EUROCAT Management Committee (Ester Garne, Maria Loane, Simona Martin, Joan Morris, Amanda Neville, Ciarán Nicholl, Judith Rankin, Anke Rissmann, Florence Rouget and David Tucker) and by the registry leaders.

Background

Worldwide, congenital anomalies are a leading cause of fetal death, infant mortality and morbidity in childhood. According to the EUROCAT estimates, of the 5.1 million births in the European Union (EU) each year [1] approximately 127,000 (2.5%) have a congenital anomaly.

EUROCAT is a European network of population-based registries whose objectives are to provide essential epidemiologic information on congenital anomalies in Europe, to facilitate the early warning of new teratogenic exposures and to evaluate the effectiveness of primary prevention.

Each year, EUROCAT performs statistical monitoring for both trends and clusters in time on 84 anomaly subgroups. The results of the statistical monitoring are the basis for instigating possible further investigations at the local registry level.

The present report shows the results of the monitoring performed on data for the birth years 2007-2016 by the JRC-EUROCAT Central Registry. Cases of congenital anomaly among livebirths, fetal deaths from 20 weeks gestational age and terminations of pregnancy for fetal anomaly (TOPFA) following prenatal diagnosis at any gestational age were included. We report both the statistical results and, where available, the outcome of the preliminary investigations conducted by registries.

1 Key findings

Pan-European Trends in Congenital Anomalies (excluding genetic conditions)

- **Tricuspid atresia/stenosis and Hypoplastic right heart**: Tricuspid atresia and stenosis is a severe congenital heart defect (CHD). It is usually associated with the underdevelopment of the right ventricle. Between 2007 and 2016 the prevalence of this anomaly is estimated to have increased each year by 4.7%. Hypoplastic right heart is one of the univentricular cardiac anomalies with underdevelopment of the right ventricle. Its prevalence increased each year by 9.8% over the same time period. Most cases also have tricuspid atresia or pulmonary atresia with intact ventricular septum. Both Tricuspid atresia and stenosis and Hypoplastic right heart are so rare that only the pan-European trend is informative. The analysis showed that there is some overlap of the cases in the two subgroups, but the pan-European prevalence of both subgroups is increasing, it is important to monitor these trends in the coming years and to follow-up on correct coding of cases.
- **Bilateral renal agenesis (including Potter syndrome):** Bilateral renal agenesis is usually associated with oligohydramnios and is lethal shortly after birth because of lung hypoplasia and no function of the kidneys. Potter syndrome is the clinical phenotype of a newborn baby without kidneys or with very limited renal function in fetal life. Between 2007 and 2016, the prevalence of bilateral renal agenesis (including Potter syndrome) is estimated to have increased each year by 4.2% on the pan-European level. The review of all cases included in the trend analysis showed that the large majority of cases were very severe as the TOPFA rate was high and there were few survivors after one week. In conclusion, the pan-European trend needs to be monitored.
- **Multicystic renal dysplasia:** Bilateral multicystic renal dysplasia (16% of cases) is usually lethal shortly after birth, while unilateral is much more common (84% of cases), and is asymptomatic. Multicystic renal dysplasia is usually diagnosed prenatally. The analysis of data from 2007-2016 confirmed the previously reported increasing trend in prevalence (+1.7% each year). There was no overlap in cases with bilateral renal agenesis. This trend will be followed but is most probably due to an increasing use of prenatal screening in Europe.
- **Congenital hydronephrosis:** Congenital hydronephrosis is mainly diagnosed prenatally, but cases have to be followed-up as some intrauterine diagnoses are not confirmed after birth. The prevalence of congenital hydronephrosis is increasing (each year by 4.3%) confirming the results from the previous report. As in the case of multicystic renal dysplasia, the increasing pan-European trend reflects changes in prenatal ultrasound screening over the last 10 years.
- **Clubfoot:** The prevalence increased dramatically (+76.5%) for Northern England, due to significant changes in ascertainment from the start of the 10 year period. The registry did not collect this condition at the start of the monitoring period, which resulted in the increase in prevalence noted. Performing the trend analysis

excluding the Northern England registry, the pan-European trend remains significantly increasing with an annual increase of 2.3% (95% CI: 1.2%; 3.4%).

- **Laterality anomalies:** This subgroup of laterality anomalies includes atrial isomerisms, dextrocardia, bronchopulmonary isomerism, situs inversus and anomalies of spleen. Another name for these anomalies is heterotaxy anomalies. Between 2007 and 2016, the prevalence of laterality anomalies is estimated to have increased by 3.7% each year on the pan-European level, confirming the results found for the first time in the previous report. This increasing trend will be monitored closely by EUROCAT and a study to investigate in detail the anomalies included in this subgroup is planned.
- **Severe microcephaly:** Severe congenital microcephaly is present if the head circumference (occipito-frontal) is less than -3 SD for sex and gestational age (GA). As in the previous report the prevalence of severe microcephaly is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by 3.8% each year on the pan-European level. The observed decreasing trend is probably due to improved coding according to the revised criteria for reporting microcephaly on the basis of head circumference measurements.
- **Cleft lip:** The prevalence of cleft lip is estimated to have decreased by 1.5% each year on the pan-European level between 2007 and 2016. Many registries show decreasing trends although they are not statistically significant, so the observed pan-European trend might reflect a true decrease in prevalence of cleft lip and will continue to be monitored.
- **Gastroschisis:** Gastroschisis is an abdominal wall defect known to be more common in teenage mothers and more common in the UK. The observed pan-European trend of gastroschisis is decreasing, which seems to be explained by less teenage pregnancies in the UK.

Clusters

Seventeen clusters were identified in the 11 registries included in the analysis. Three clusters will be followed (Encephalocele (Brittany), Ano-rectal atresia and stenosis (Paris) and Severe CHD (Vaud)). The remaining clusters were not of concern.

Limb reduction anomalies

Due to the concerns in France on geographical small-area clusters of upper limb reduction defects, an additional analysis was conducted specifically focusing on these anomalies, to provide an overview of the situation in Europe based on EUROCAT data. There was no Pan-European trend detected (only one registry had a significantly increasing trend and one registry had a significantly decreasing trend). No clusters in

time were identified in the 11 registries included in the analysis. There were no changes in the type of anomalies in the upper limb reduction defects.

2 Introduction

EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies which was established in 1979. Since 2015 the EUROCAT Central Registry is operated by the European Commission's Joint Research Centre (Ispra, Italy), as part of the European Platform on Rare Diseases Registration [2, 3].

EUROCAT surveys more than 1.4 million of births per year, which is more than one quarter of the European birth population. Registries from 20 European countries transmit yearly to the JRC-EUROCAT Central Registry individual case data (full member registries) or aggregate data (associate members) on congenital anomalies in their region.

The EUROCAT annual statistical monitoring report includes the analysis of trends and clusters in time performed in order to detect signals of new or increasing teratogenic exposures and to monitor progress in the prevention of congenital anomalies.

The analysis is done by the JRC-EUROCAT Central Registry on the data collected from EUROCAT registries, updated and validated annually [4].

Total prevalence rates of 84 subgroups of congenital anomalies, including all cases of livebirths, stillbirths/late fetal deaths from 20 weeks gestational age, and terminations of pregnancy for fetal anomaly (TOPFA) at any gestational age are monitored and reported. A full protocol is published online, providing details of the rationale and the methodology of the statistical monitoring, including changes to methodology and software [5].

A pan-European trend analysis enables the monitoring of rare congenital anomalies that have too few cases to be monitored at individual registry level, as well as presenting an overview of the situation in Europe. Preliminary investigations of trends and clusters have been performed at local and central registry level, and summaries of these investigations are reported. The last statistical monitoring report was published on the data from birth years 2006-2015 [6]. The statistical monitoring is based on a methodology for the surveillance of congenital anomalies and is also a tool for the harmonisation of data collected by the EUROCAT registries. The number of variables collected and the way these variables are coded are in continuous development in order to adapt to and represent correctly the evolving knowledge on the topic. In fact, identifying trends and clusters can be spurious due to different methods of ascertainment, the introduction of new diagnostic methods that increase the number of cases detected, and other reasons not related to a real increase/decrease of a given pathology. Hence the involvement of all the registries in the investigation into the results found at the local level by the Central Registry facilitates data harmonisation and interpretation.

We report here the results of the statistical monitoring performed on births over the ten year period (2007-2016) using data from 20 EUROCAT registries to describe trends and from 11 EUROCAT registries to detect recent clusters in time.

3 Population and Monitoring Process

3.1 Registries included in the 2007-2016 trend analysis

At the time of statistical monitoring in spring 2018, there were 33 full member registries in EUROCAT (see Appendix A). Twenty full member registries met the inclusion criteria for the individual 10-year trend analysis (see Box 1).

The registries included in the analysis were: Antwerp (Belgium), Hainaut (Belgium), Zagreb (Croatia), Paris (France), Ile de la Reunion (France), Saxony-Anhalt (Germany), Cork& Kerry (Ireland), Emilia Romagna (Italy), Tuscany (Italy), Malta, Northern Netherlands, South Portugal, Valencia Region (Spain), Vaud (Switzerland), Ukraine, Northern England (UK), South West England (UK), Thames Valley (UK), Wales (UK), Wessex (UK).

Box 1. Registry inclusion criteria for trend analysis

— *Pan-European and Individual Registry trends*: Registries that signed the JRC-EUROCAT collaboration agreement

— *Pan-European*: Registries no more than 1 year late with data transmission

— *Pan-European*: Registries that submitted data continuously for at least 9 calendar years starting from 2007, i.e. for 2007-2015 or 2007-2016

— *Pan-European*: Registries for which the number of submitted cases in the latest year was at least 80% of those submitted in previous calendar years

— *Individual registry trends*: registries no more than 1 year late with data transmission that submitted data continuously for at least 8 calendar years counting back from 2015 i.e. for 2007-2016, 2008-2015 or 2009-2016.

The registries excluded from the analysis were:

- Odense (Denmark) and Hungary were not in a position to sign the JRC-EUROCAT collaboration agreement and therefore they did not send data to the Central Registry for the years 2013 – 2016;
- Auvergne (France), Dublin (Ireland), Mainz (Germany), South East Ireland and the Basque Country (Spain) were more than one year behind in data transmission;
- East Midlands & South Yorkshire (UK) - cases were submitted for 2016 but not for the years 2013-2015;
- Styria (Austria), Wielkopolska (Poland) as well as the French West Indies (France) submitted substantially fewer cases than previously;
- Norway was not included because it sent 4 years of data after major changes in the data collection process and the completeness of the data with respect to the previous data collection is under evaluation;

- Brittany (France) was excluded from the trend analyses because it started collecting data in 2011 and hence has less than eight years of data in the Central Database.

3.2 Registries included in the 2016 cluster analysis

EUROCAT defines clusters as: 'An aggregation of cases of congenital anomaly in time and/or space which appears to be unusual'; the annual statistical monitoring performed at the central level concerns the detection of the time clusters only because the data collected does not permit geographical evaluations. Registries classified as "early responders", i.e. registries that meet the EUROCAT data transmission deadline of the 15th February, and with data for the most recent five years (2012-2016) were included in the monitoring of clusters (see Box 2). A five-year period is considered optimal for cluster monitoring because the inclusion of more than five years data may detect trends rather than clusters, while less than five years may fail to detect clusters if the most recent years are unusual compared to preceding years [7].

Box 2. Registry inclusion criteria for cluster analysis

— Registries must submit individual case data, i.e. must be full members

— Registries must have signed the collaboration agreement

— Registries must have transmitted data for all five years, i.e. for 2012-2016

— Registries for which the number of submitted cases was at least 80% of those submitted in previous calendar years

— Registries must have transmitted information on the date of birth for all cases

— Registries must have a stable birth population (annual birth population changes must be less than +/- 10% between any two years within the five year period)

A total of 16 full member registries transmitted information for calendar year 2016 to the EUROCAT Central Registry in February 2018 (see Appendix A). 11 registries were included in the cluster analysis, while the five registries from England were excluded because the date of birth transmitted by Public Health England to the Central Registry is not the exact date (for privacy reasons). The analysis done by the Central Registry cannot detect clusters unless an accurate date of birth is provided. Hence, in this situation only the cluster analysis performed by the local registry can be considered appropriate. Registries are encouraged to use the statistical monitoring function in the EUROCAT Data Management Programme (EDMP) to check for clusters or trends for their registry for time periods not covered by the annual statistical monitoring.

3.3 What was monitored?

For the purpose of monitoring, cases cover livebirths, stillbirths or late fetal deaths from 20 weeks of gestational age onwards, as well as TOPFA at any gestational age.

As the aim is to detect changes over time within individual registries, as well as across all registries (pan-European trends), 81 congenital anomaly subgroups, i.e. non-genetic ones defined by EUROCAT, plus three trisomy subgroups adjusted for maternal age and fetal survival to 20 weeks were included in both, the pan-European and individual registry trend analyses (see Appendix B).

Trend tests were performed for the most recent 10 years of data, or eight years if 10 years were unavailable, for every individual registry (cf. Box 1), and for 10 calendar years to establish the pan-European trends.

In order to detect clusters or deficits occurring during the last two years (2015-2016), and which lasted for less than 18 months, the EDMP software was used (see Appendix C) and run on 75 EUROCAT subgroups of congenital anomalies (see Appendix B).

In summary, the analyses covered:

- 20 registries with 4.57 million births (2007-2016) for the pan-European trends
- 11 registries with 0.26 million births (2015-2016) for the detection of clusters

3.4 Investigation process

The results of the statistical monitoring reported by the Central Registry were reviewed by the JRC-EUROCAT Management Committee (MC) in May 2018. The MC selected congenital anomalies with increasing or decreasing trends for preliminary investigation using a predefined prioritisation protocol (see Fig. 1).

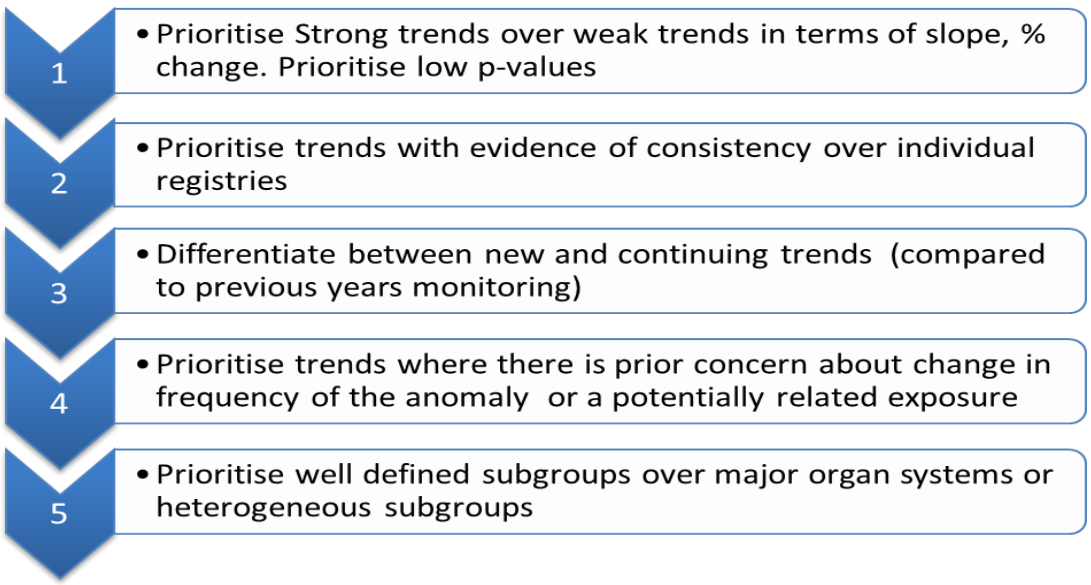

Fig. 1: Prioritisation criteria for the investigation of ten-year trends [5]

Then the Central Registry sent the results of the trends' and clusters' review to the individual registries in order to allow them to conduct preliminary investigations into the results for their registry.

These preliminary investigations were carried out according to a standardised protocol (see Appendix D). The increasing and decreasing trends selected for registry investigation are listed in Appendix E. In addition to these, registries were supplied also information on increasing or decreasing trends detected for their registry level only for which reporting was optional.

Once the preliminary investigations were carried out by the individual registries, they reported their findings to the JRC-EUROCAT Central Registry using standard reporting templates [7]. In these reports, they were asked to provide specific details, including the investigation methods, the results of the preliminary investigation and the public health authorities that were notified. Thereafter, the preliminary reports of the trend and cluster investigations were reviewed by the JRC-EUROCAT MC.

In the present annual report, trends not prioritised for investigation are not discussed but will be monitored further.

Finally, due to the concerns in France on geographical small-area clusters of upper limb reduction defects, a chapter focusing on these anomalies is included in this year's report to give an overview of the situation in Europe based on EUROCAT data.

3.5 Statistical software updates from the previous report

No changes were made to the software used to identify clusters and trends within each registry for this year’s statistical monitoring. Updates were made in the investigation of the pan-European trends using Poisson regression. For a full description of the methodology please refer to the EUROCAT Statistical Monitoring Protocol available on the EUROCAT website [7].

4 Pan-European Trends

4.1 Overview

The pan-European trend analysis was carried out for the time period 2007-2016. The analysis included data from 20 full member registries (Box 1 above and Appendix A).

The trend analysis included 81 subgroups, and the three trisomy subgroups adjusted for maternal age and fetal survival to 20 weeks. Figure 2 plots the estimated percentage change in yearly prevalence for each congenital anomaly subgroup. This enables congenital anomaly groups with statistically significant increasing or decreasing trends to be identified for further analysis. There were significant increasing trends for 11 congenital anomaly subgroups and decreasing trends for 15 subgroups (Figure 2 and Appendix E).

On the pan-European level, new **increasing trends**, i.e. increasing trends that were not mentioned as increasing in last year's report, were identified for the following subgroups: *Double outlet right ventricle, Bilateral renal agenesis (including Potter syndrome)* and *Polydactyly*. Pan-European trends that were already seen to increase in last year's report, i.e. during the period 2006-2015, and are also increasing during the period covered by the present report, are: *Ventricular Septal Defect (VSD); Atrial Septal Defect (ASD); Tricuspid atresia and stenosis; Hypoplastic right heart; Multicystic renal dysplasia; Congenital hydronephrosis; Clubfoot – talipes equinovarus* and *Laterality Anomalies*.

A new **decreasing trend** on the pan-European level is observed for *Teratogenic syndromes with malformations*. Pan-European decreasing trends identified for the period covered by the present report that were also identified as decreasing in last year's report are the following: *Hydrocephaly; Severe microcephaly; Anophthalmos/microphthalmos; Pulmonary valve stenosis; Patent ductus arteriosus (PDA); Cleft lip with or without palate; Cleft palate; Gastroschisis; Syndactyly; Vascular disruption anomalies; Valproate syndrome; Genetic syndromes + microdeletions; Klinefelter syndrome; Down syndrome (age adjusted)*.

The following subgroups were not considered further in this report. The subgroup of '*Teratogenic syndromes with malformations*' is very heterogeneous and the data collected from EUROCAT registries are not homogenously reported and many are underreported. Therefore, the results of the trends analysis could be misleading. The data on 'Genetic syndromes and microdeletions' for the last birth year collected are incomplete at the time of analysis, because of late reporting from the registries. 'Klinefelter syndrome' is underreported to EUROCAT due to many diagnoses occurring at the time of puberty rather than near the time of birth. Finally, 'Valproate syndrome' is monitored, but only very few cases were reported in the recent years [8].

The following sections provide further analysis on the significant increasing and decreasing pan-European trends, the preliminary investigations into them and their interpretation (Appendix E).

Three figures are examined for each congenital anomaly subgroup. Firstly, the pan-European prevalence of the congenital anomaly in each year with its 95% confidence intervals (CIs) is plotted against the year of birth and the estimated annual linear change is shown in red. This enables any sudden changes in prevalence to be identified, which

may be due to coding issues rather than an underlying change in prevalence. It also enables the potential under-reporting that may occur in the latest year of data available to be evaluated.

Secondly, the annual change in prevalence and 95% CIs in each registry is plotted together with the summary pan-European estimate. This enables the identification of any registries with inconsistently high or low changes in prevalence to be identified. The prevalence within each registry is also given to aid interpretation of the observed trends. For example, a registry with a very low prevalence that experiences a greater increase than the other registries could be interpreted as an improvement in data collection in that registry rather than as a cause for concern. Registries in which the change in prevalence is considered non-linear are indicated by a diamond and those with too few cases by a cross (see [7] for details of how these are derived).

Thirdly, the prevalence of the congenital anomaly subgroup in each registry over the whole time period is plotted. This is to illustrate the heterogeneity of reporting of the congenital anomaly between registries and to identify those registries potentially under or over-reporting. Such information is of use when interpreting any trends. If an anomaly is consistently reported across registries, the underlying trend will more likely reflect a true increase or decrease in prevalence. However, if there is great heterogeneity in the prevalence of an anomaly in registries, more caution should be taken in interpreting an observed trend as reflecting a true increase or decrease in prevalence.

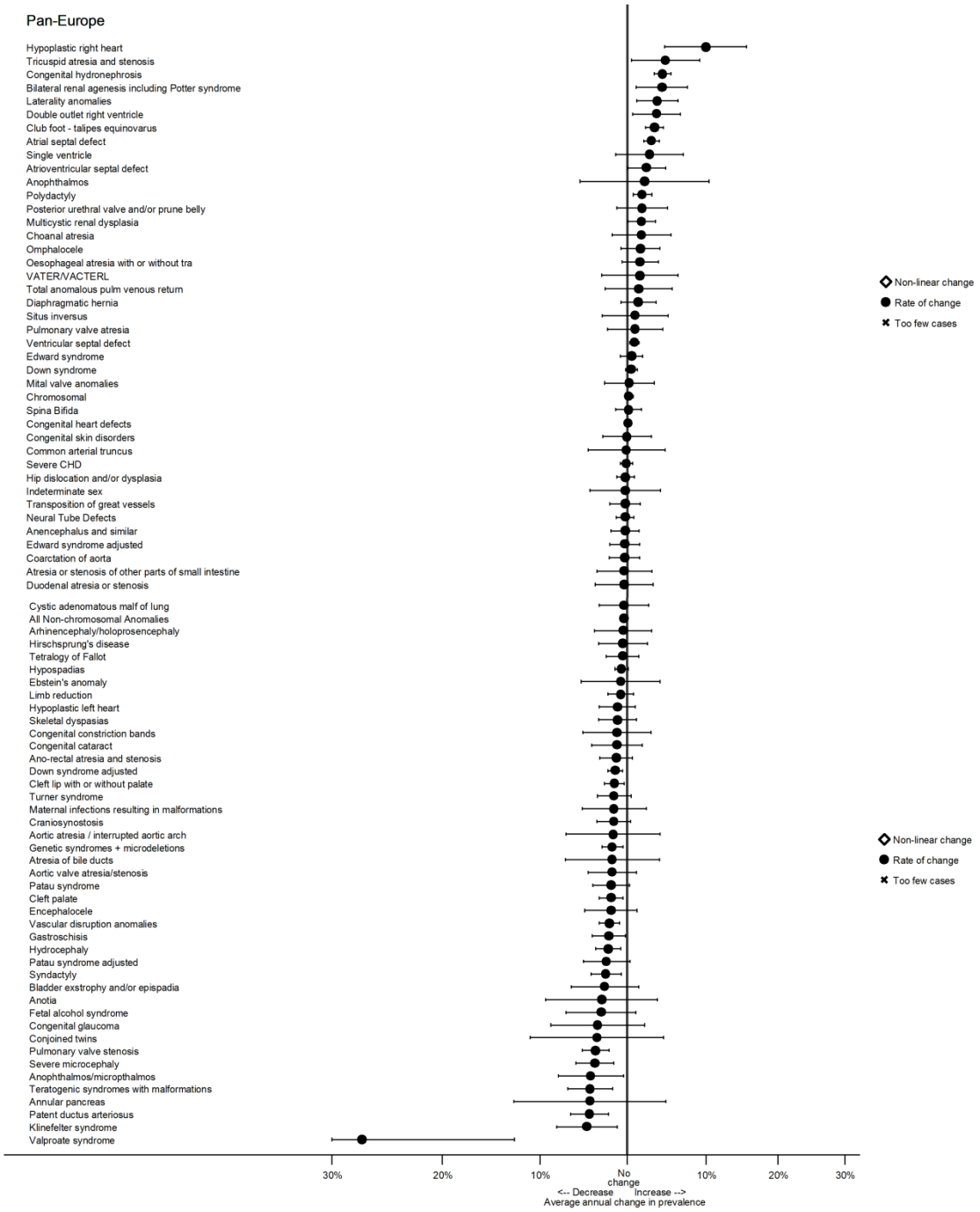

Fig. 2: Estimated annual percentage change in the prevalence and 95% CIs for the 84 congenital anomalies subgroups (pan-Europe analysis 2007-2016). For Valproate syndrome the lower limit of the CI is truncated at -30% (actual value = -39.6%).

4.2 Increasing trends identified at the pan-European level

Double outlet right ventricle

Double outlet right ventricle is a severe cardiac anomaly where both the aorta and the pulmonary artery originate from the right ventricle of the heart. The new born baby may be asymptomatic, but symptoms usually appear within the first weeks after birth. Corrective surgery is performed in infancy.

When taking into account the information from all European registries between 2007-2016, the prevalence of a double outlet right ventricle is estimated to have increased each year by 3.5% (95% CIs: 0.6%; 6.5%) on the pan-European level (Fig. 3a).

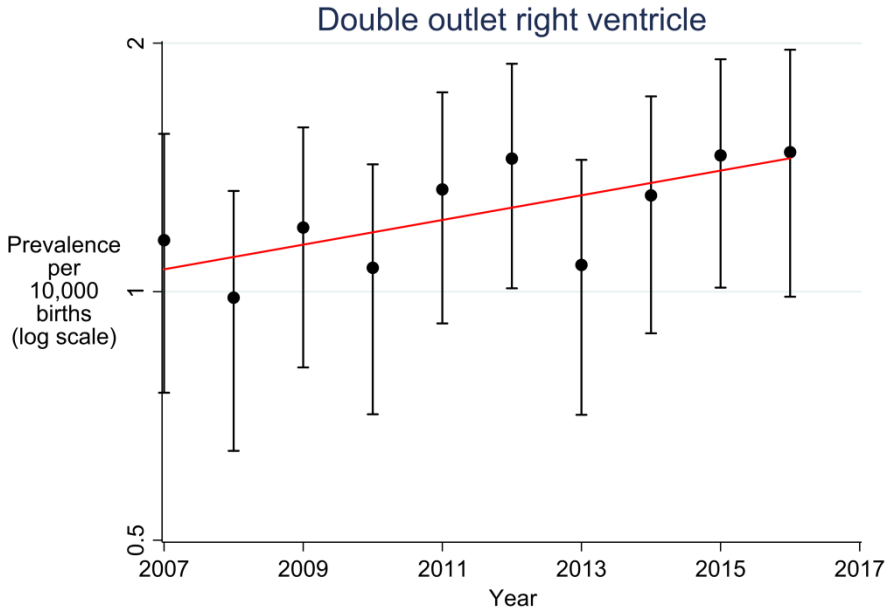

Fig. 3a Double outlet right ventricle - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

This congenital anomaly subgroup shows an increasing trend for the first time at the pan-European level. The only significant increasing trends are for the two English registries - South West England and Thames Valley (Fig. 3b).

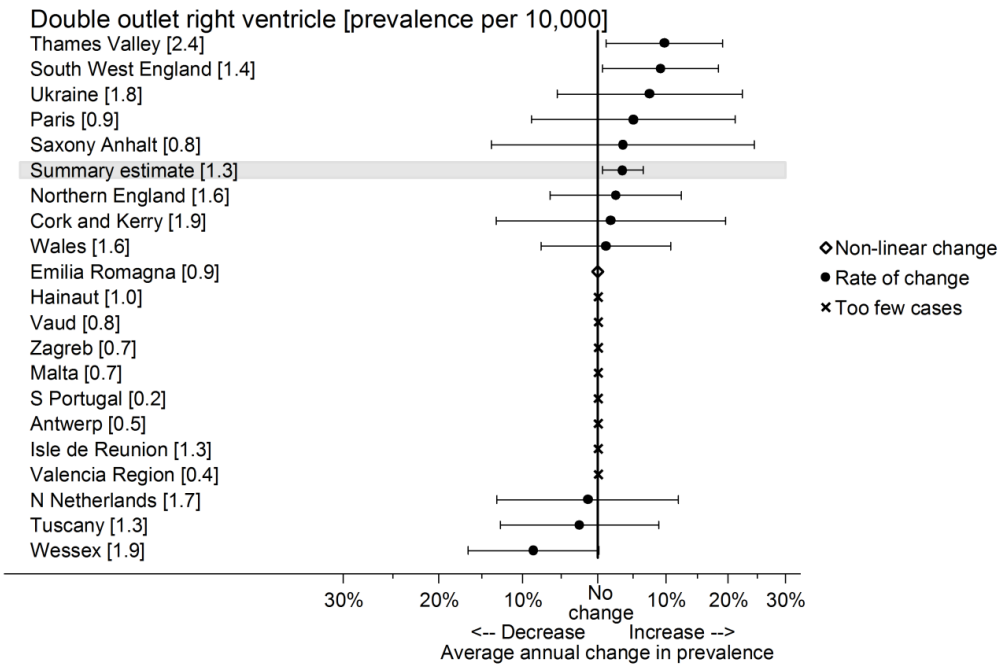

Fig. 3b: Double outlet right ventricle - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

There is considerable heterogeneity of the prevalence over the 10-year period in the registries with a minimum value in S. Portugal (0.2 per 10,000 births) and a maximum in Thames Valley (2.4 per 10,000) (Fig. 3c). Both English registries with significant increasing trends suggested that the changes in case ascertainment would explain the increasing trends.

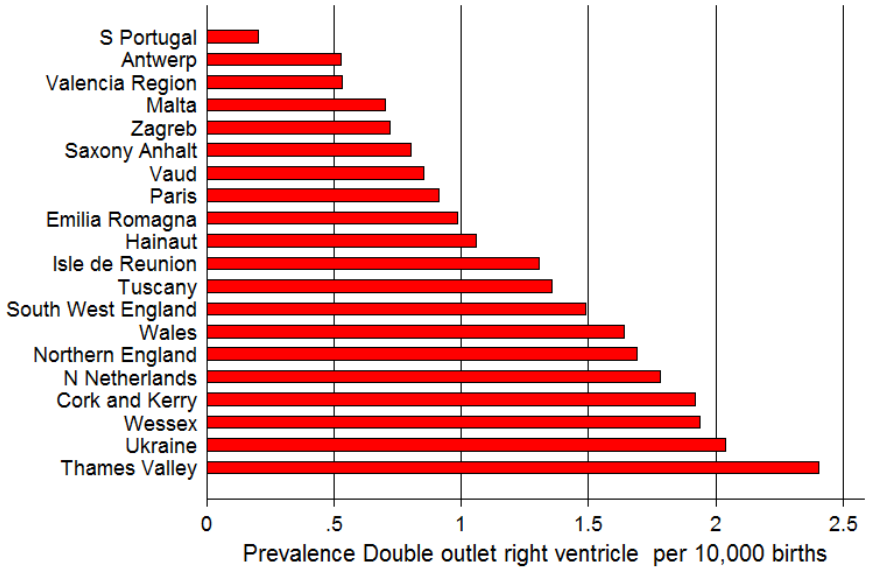

Fig. 3c: Double outlet right ventricle - Estimated 10 years prevalence for the registries included in the pan-European trend analysis (2007-2016).

In conclusion, the trend will be monitored but there are no major concerns.

Ventricular septal defect (VSD)

Ventricular septal defect (VSD) is the most common cardiac defect. A murmur is usually the first sign and the indication for referral for an echocardiography. There are several types of VSDs (perimembraneous, muscular, inlet), but they are all coded by the same ICD10 codes. Most muscular VSDs are small with a high rate of spontaneous closure within the first years after birth. Perimembraneous VSDs are more likely to become symptomatic 1-2 months after birth and surgery may be needed. Rate of spontaneous closure within the first years is lower than for muscular VSDs. The prevalence of VSD in a region is very dependent on the diagnostic level (routinely cardiac auscultation in all newborns, easy access to echocardiography).

Many complex cardiac defects also include a VSD, but these only account for a smaller proportion of all cases with a VSD.

As in the previous report on the period 2006-2015, the prevalence of a ventricular septal defect is increasing. Between 2007 and 2016, its prevalence is estimated to have increased each year by 0.8% (95% CI: 0.2%; 1.4%) on the pan-European level (Fig. 4a).

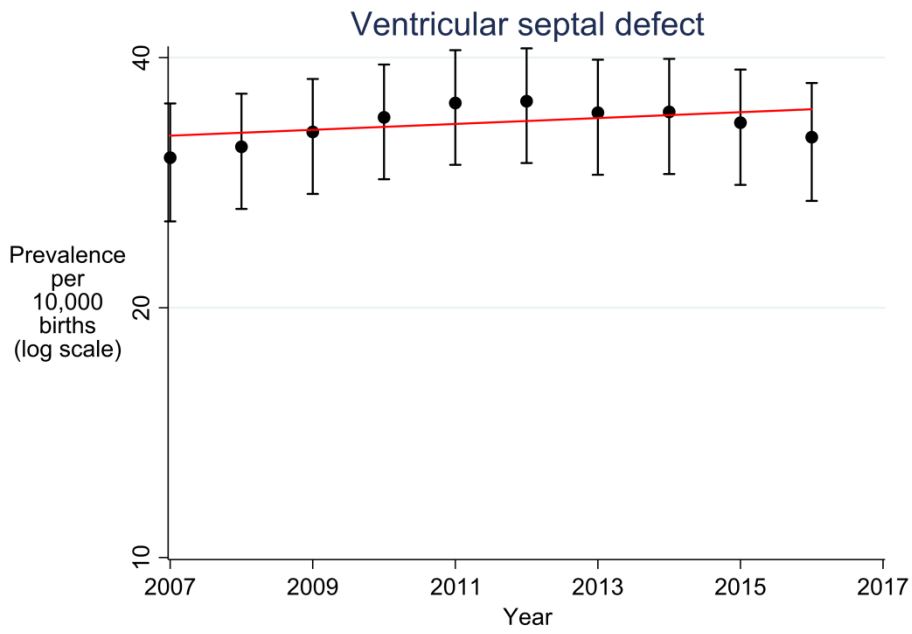

Fig. 4a Ventricular septal defect - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In addition, the prevalence increased significantly during the same period in seven individual registries: Antwerp, Emilia Romagna, Isle de Reunion, Tuscany, Valencia Region, Wessex, and Zagreb (Fig 4b).

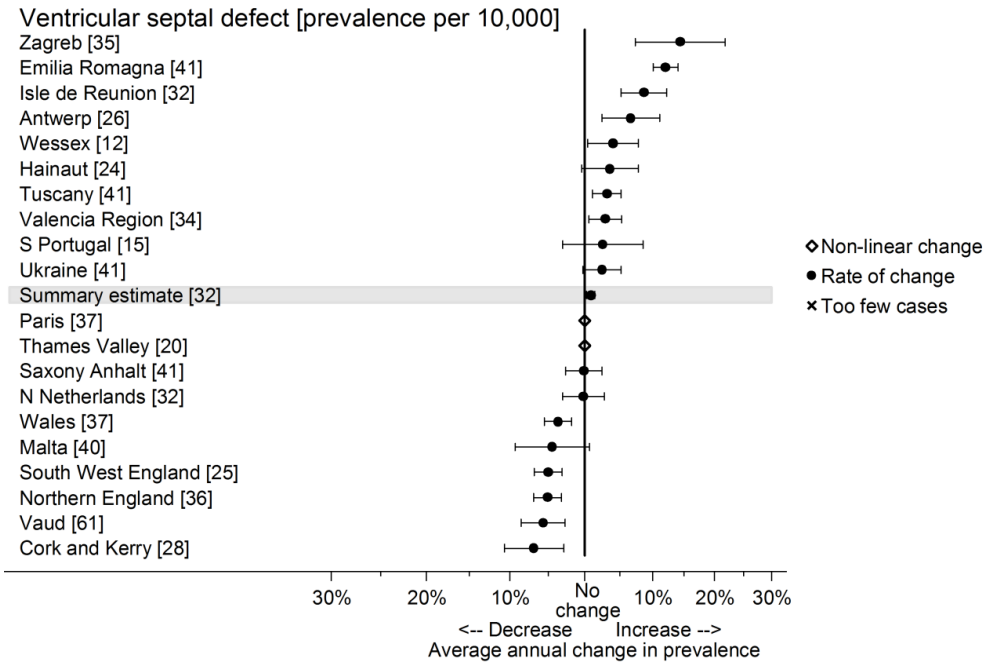

Fig. 4b: Ventricular septal defect - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

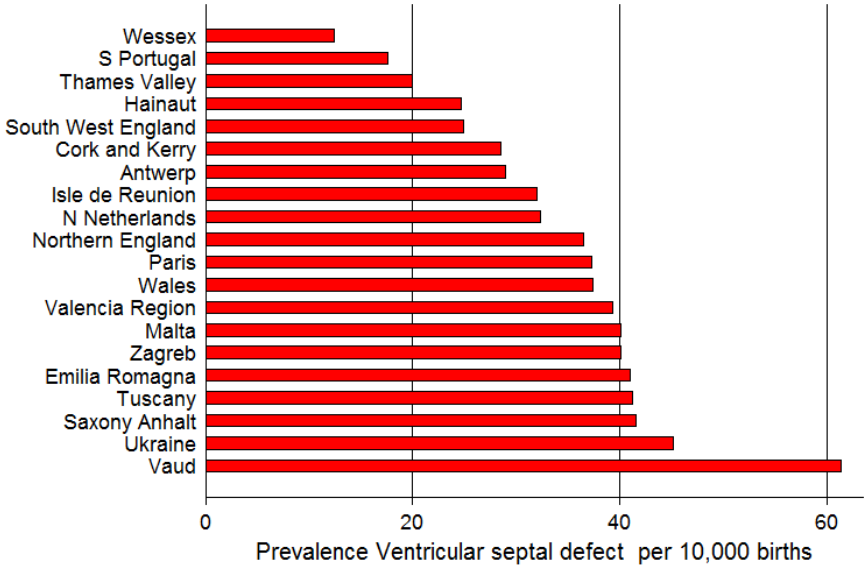

Fig. 4c: Ventricular septal defect - Estimated prevalence for the registries included in the pan-European trend analysis (2007-2016).

In order to find out if the increasing trend of VSD was explained by an increase of isolated VSD or VSD as part of a severe/complex CHD, an additional trend analysis was performed after exclusion of all cases classified as 'severe CHD'. The analysis included 85.7% of all cases reported with VSD (13,033 non severe cases vs 15,210 all cases). There was no significantly increasing pan-European trend of VSD excluding cases with severe CHD (Fig. 4d); the prevalence is estimated to have increased each year by 0.4%

(95% CI: -0.2%; 1.1%). The increasing trends in Emilia-Romagna, Isle de Reunion, Tuscany, Valencia Region and Zagreb were still significant.

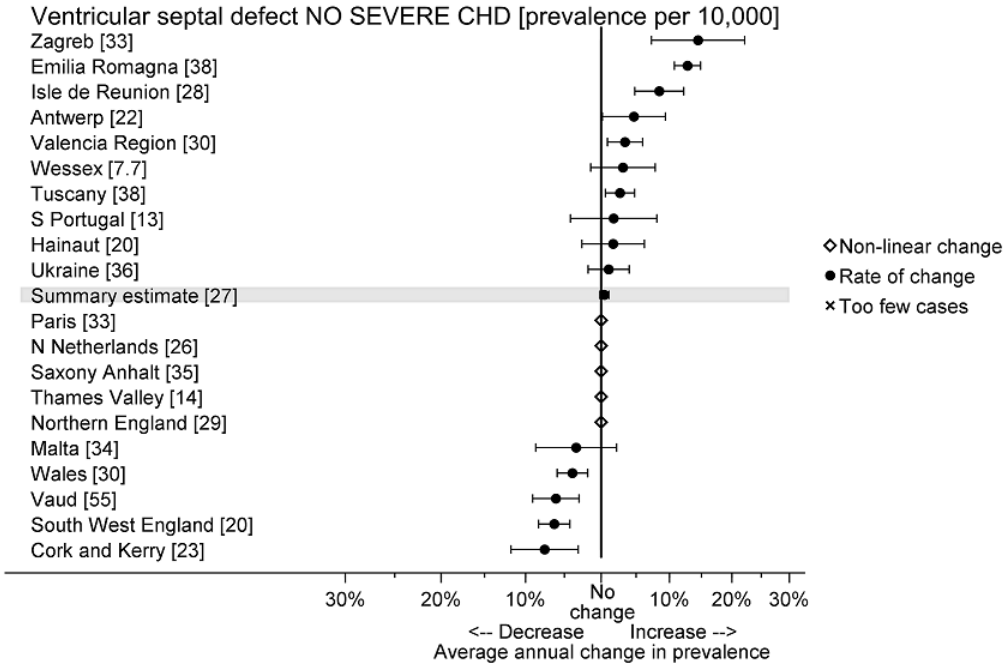

Fig. 4d: Ventricular septal defect - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis excluding cases classified as 'severe CHD'.

In conclusion, the pan-European trend of VSD reduced from an increase of 0.8% per annum down to an increase of 0.4% per annum which was no longer statistically significant when severe heart defects were excluded. This indicates the increase of VSD may be associated with an increase in reporting VSD for severe CHD cases. Improved data sources and improved diagnostics explained the increasing trends of VSD found in two registries.

Atrial septal defect (ASD)

Atrial septal defect (ASD) is one of the most common cardiac defects and is classified as a less severe cardiac defect by EUROCAT. ASD may not produce noticeable signs or symptoms in infancy or childhood and may therefore be diagnosed late, especially if the defect is small.

In fetal life, there is a natural flow of blood from the right to the left atrium. After birth this defect will close, but sometimes remains open for weeks or months as a persistent foramen ovale. EUROCAT recommends reporting only defects in the atrial septum if still open six months after birth.

As in the previous report for the period 2006-2015, the prevalence of an ASD is increasing. Between 2007 and 2016, the prevalence of this congenital anomaly is estimated to have increased each year by 2.9% (95% CI: 1.9%; 3.9%) on the pan-European level (Fig. 5a).

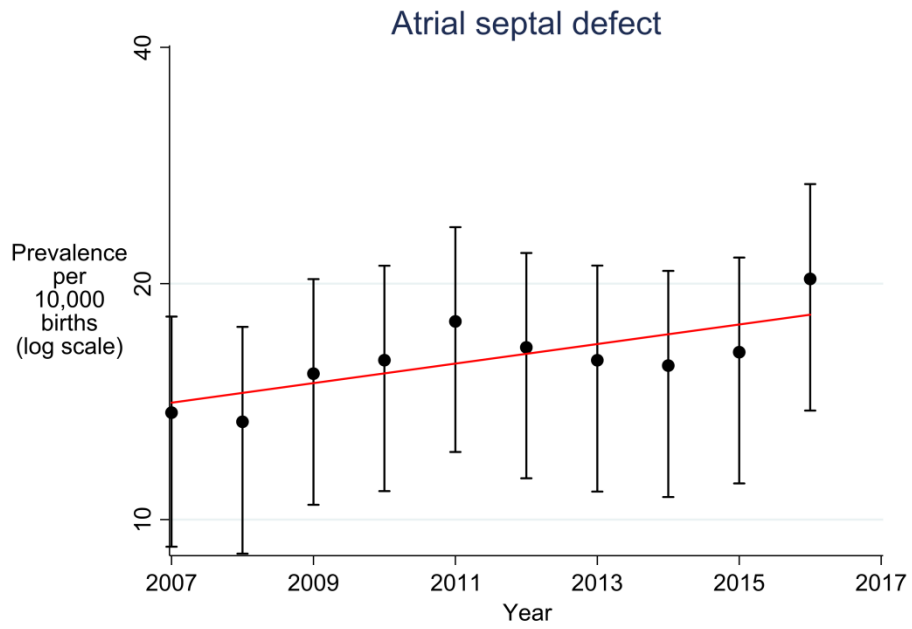

Fig. 5a Atrial septal defect - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In addition, the prevalence increased significantly during the same period in three individual registries (Saxony-Anhalt, Tuscany and Zagreb, Fig 5b). These trends may be due to changes in case ascertainment by paediatric cardiologists.

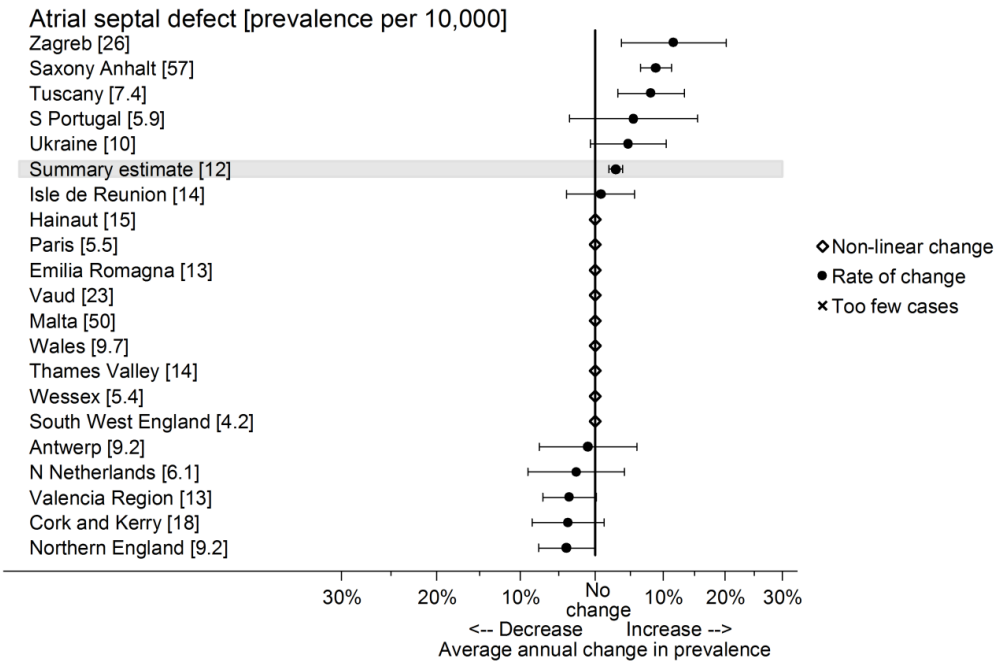

Fig. 5b: Atrial septal defect - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

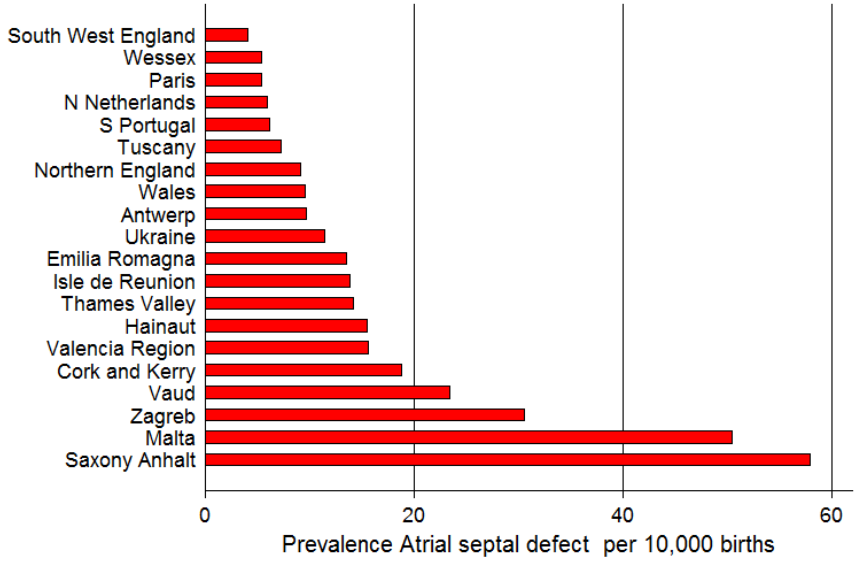

Fig. 5c: Atrial septal defect - Estimated prevalence for the registries included in the pan-European trend analysis (2007-2016).

In order to find out if the increasing trend of ASD was explained by an increase of isolated ASD or ASD as part of a severe/complex CHD, an additional trend analysis was performed after exclusion of all cases classified as severe CHD. The analysis included 85.6% of all cases reported with ASD (4,951 non severe cases *vs* 5,786 all cases). Excluding the severe cases, the increasing trend remained unaltered (3.0% (95% CI: 1.9%; 4.1%)).

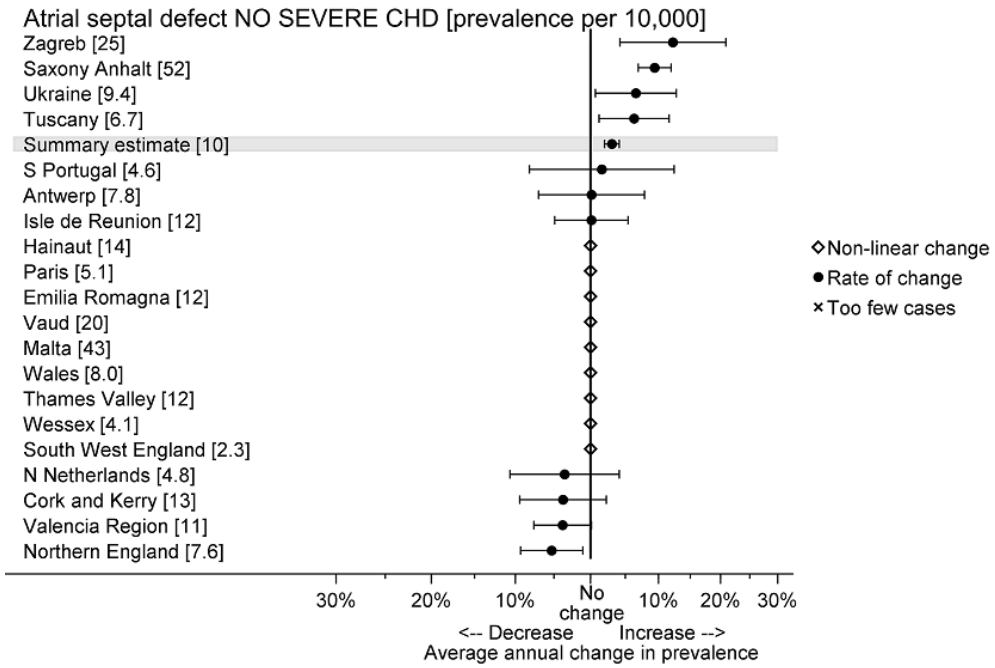

Fig. 5d: Atrial septal defect - Estimated prevalence for the registries included in the pan-European trend analysis excluding cases classified also in 'severe CHD' subgroup.

An additional analysis was performed excluding data from Saxony-Anhalt, which has a very high prevalence and increasing trend explained by over-reporting of the condition due to active screening in the first week of life. Also in this case the pan-European trend remains statistically significant with estimated increase each year by 1.5% (95% CI: 0.4%; 2.6%).

In conclusion, the pan-European increasing trend of ASD seems to be explained by an increase in reporting of ASD not associated with a severe CHD. Registries using patient discharge diagnosis from the neonatal period as a data source without validating the medical records 6 months after birth may have some over-reporting of ASD.

Tricuspid atresia and stenosis

Tricuspid atresia and stenosis is a severe congenital heart defect. It is usually associated with the underdevelopment of the right ventricle (see Appendix F). The anomaly is so rare that only the pan-Europe trend is informative.

As in the previous report on the period 2006-2015, the prevalence of tricuspid atresia and stenosis is increasing. Between 2007 and 2016, its prevalence is estimated to have increased each year by 4.7% (95% CI: 0.4%; 9.1%) on the pan-European level (Fig. 6a).

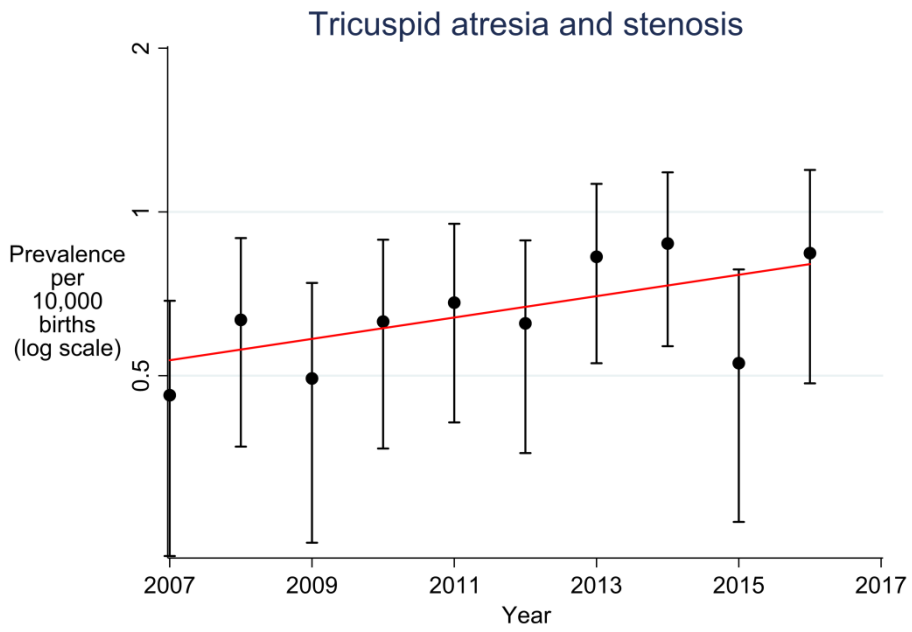

Fig. 6a Tricuspid atresia and stenosis - Prevalence and 95% CIs for the years included in the pan-European trend analysis (2007-2016).

No evidence of an increasing prevalence was found in any of the individual registries during the same period (Fig 6b).

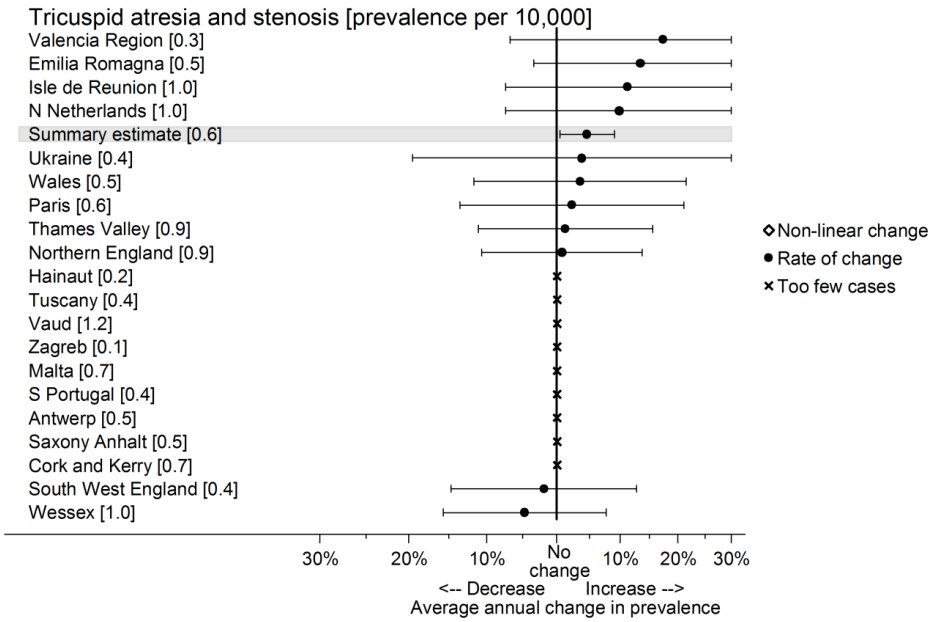

Fig. 6b: Tricuspid atresia and stenosis - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

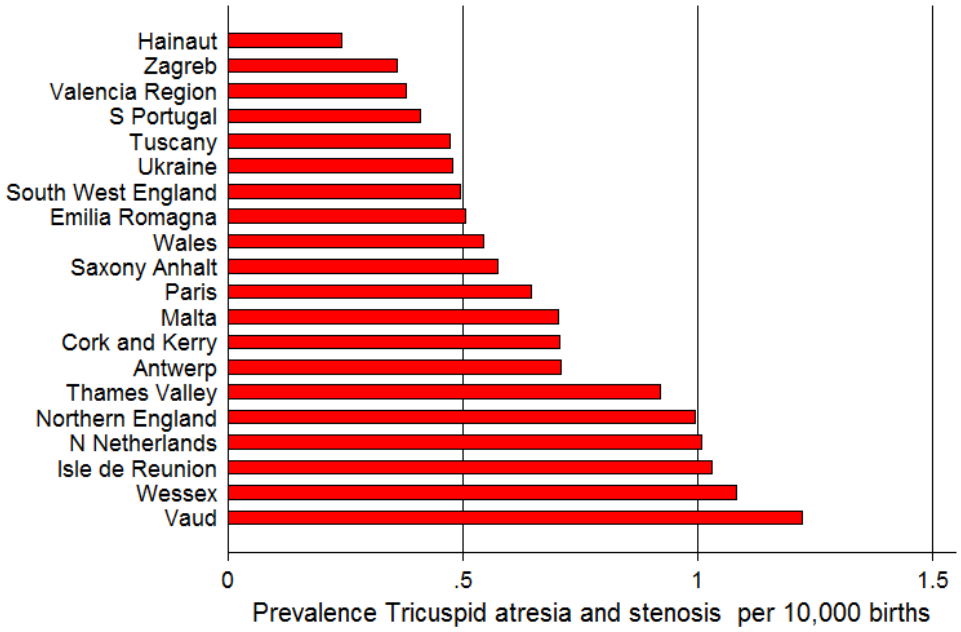

Fig. 6c: Tricuspid atresia and stenosis - Estimated prevalence for the registries included in the pan-European trend analysis (2007-2016).

In conclusion, as this subgroup shows an increasing pan-European trend, it is important to monitor it in the coming years and to follow-up on correct coding of cases.

Hypoplastic right heart

Hypoplastic right heart is one of the univentricular cardiac anomalies with underdevelopment of the right ventricle. Most cases also have tricuspid atresia or pulmonary atresia with intact ventricular septum (see Appendix F). Prenatal detection rate is usually high and in many countries there is a high rate of TOPFA due to the severity. The anomaly is so rare that only the pan-Europe trend can be informative.

As in the previous report for the period 2006-2015, the prevalence of hypoplastic right heart is increasing. Between 2007 and 2016, its prevalence is estimated to have increased each year by 9.8% (95% CI: 4.6%; 15.3%) on the pan-European level (Fig. 7a).

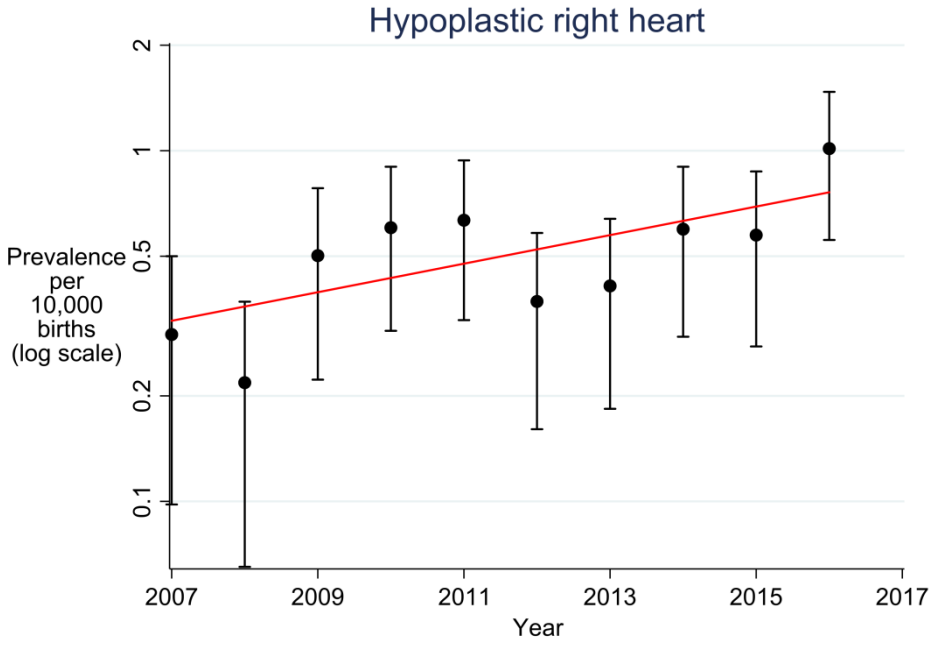

Fig. 7a Hypoplastic right heart - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

No evidence of an increasing prevalence was found in any of the individual registries during the same period (Fig 7b).

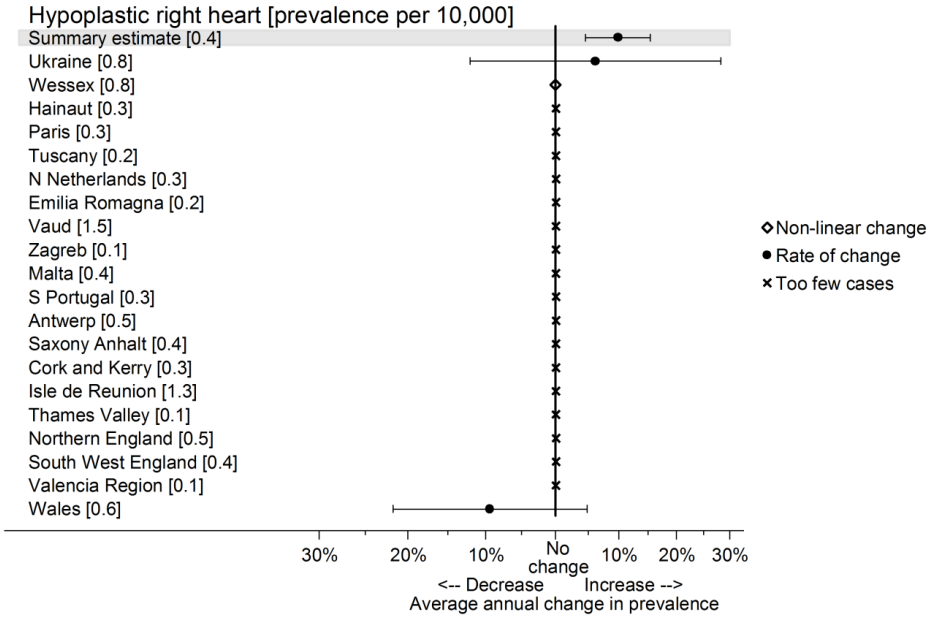

Fig. 7b: Hypoplastic right heart - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

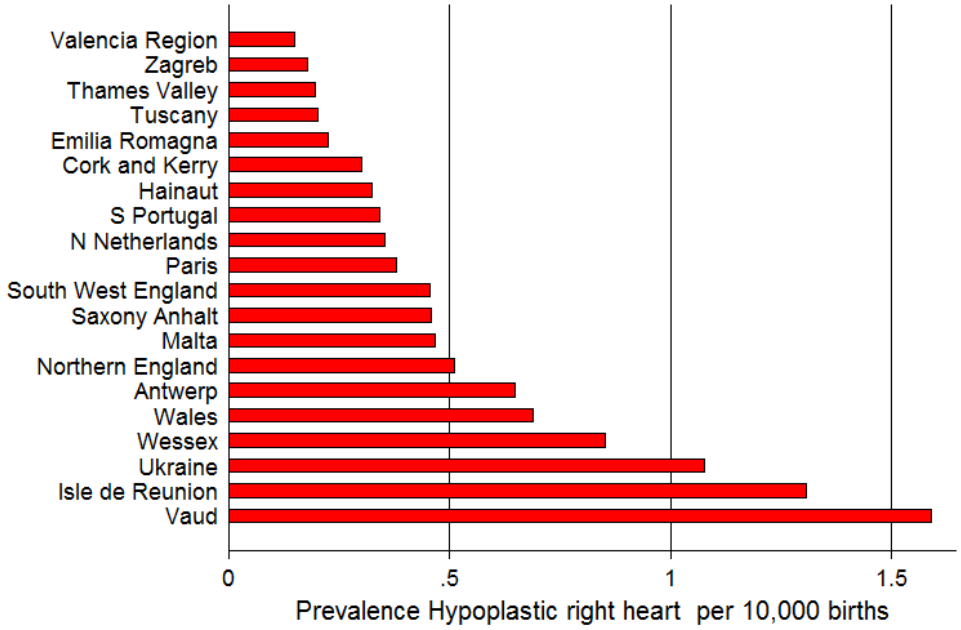

Fig. 7c: Hypoplastic right heart - Estimated prevalence for the registries included in the pan-European trend analysis (2007-2016).

An additional analysis was performed considering jointly the subgroups Tricuspid atresia and stenosis and Hypoplastic right heart. For almost all cases the written text for the ICD10 code for the subgroups is correct (Q224 – tricuspid atresia or stenosis, and Q226 – hypoplastic right heart), but additional coding is missing for approximately 10% of the

cases in each group. There is some overlap of the cases in the two subgroups, but also cases that are not the same (tricuspid valve stenosis and pulmonary valve atresia).

The cases classified in both the subgroups were 69, 232 had only Tricuspid atresia and 157 only Hypoplastic right heart. A significant increasing trend was found also when the two subgroups were combined (Fig. 7d).

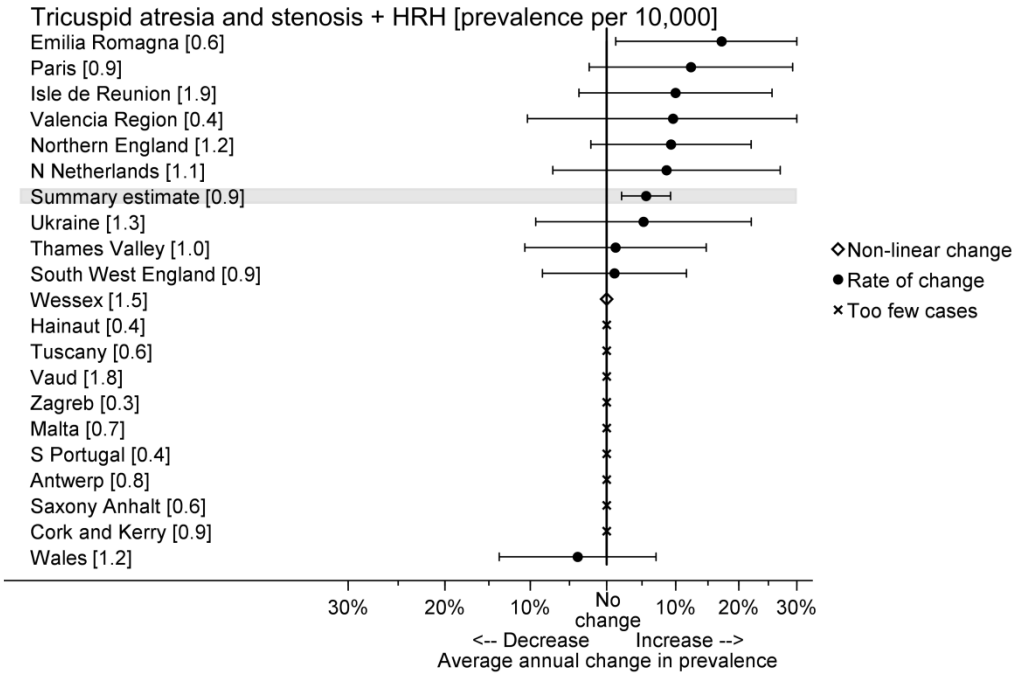

Fig. 7d: Joint evaluation of the two anomaly subgroups (Tricuspid atresia and stenosis and Hypoplastic right heart) - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

In conclusion, the increasing trends of hypoplastic right heart and tricuspid atresia will be monitored closely in the following years. It is important to find out if the trends are explained by changes in coding or if there is a true increase in these very severe cardiac defects.

Bilateral renal agenesis (including Potter syndrome)

Bilateral renal agenesis is usually associated with oligohydramnios and is lethal shortly after birth because of lung hypoplasia and no function of the kidneys. Potter syndrome is the clinical phenotype of a newborn baby without kidneys or with very limited renal function in fetal life. Prenatal detection rate is high and most pregnancies result in a TOPFA (see Appendix G).

Between 2007 and 2016, the prevalence of a bilateral renal agenesis (including Potter syndrome) is estimated to have increased each year by 4.2% (95% CI: 1.0%; 7.5%) on the pan-European level (Fig. 8a).

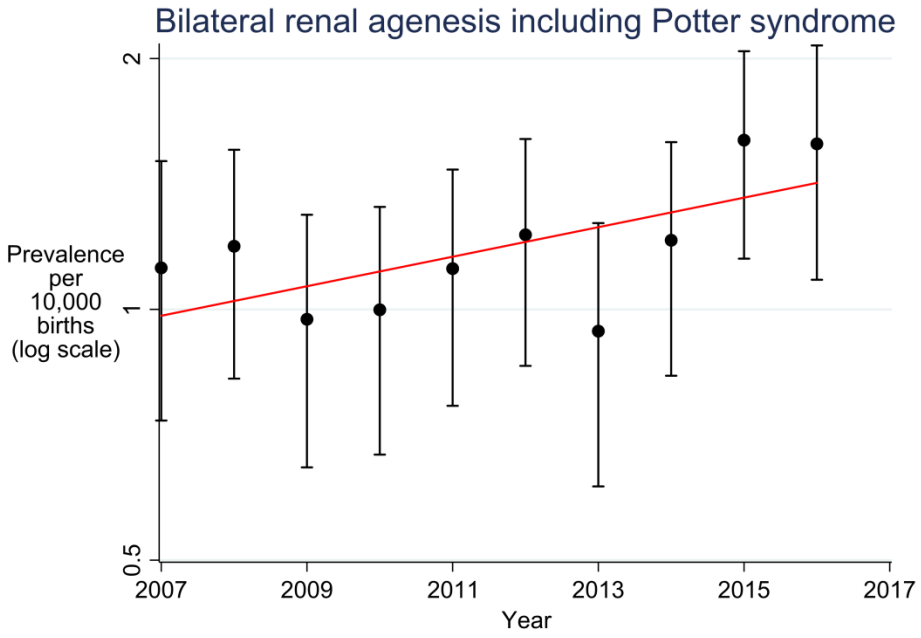

Fig. 8a Bilateral renal agenesis (including Potter syndrome) - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In addition, the prevalence increased significantly during the same period in two individual registries (Saxony-Anhalt and Valencia Region, Fig 8b).

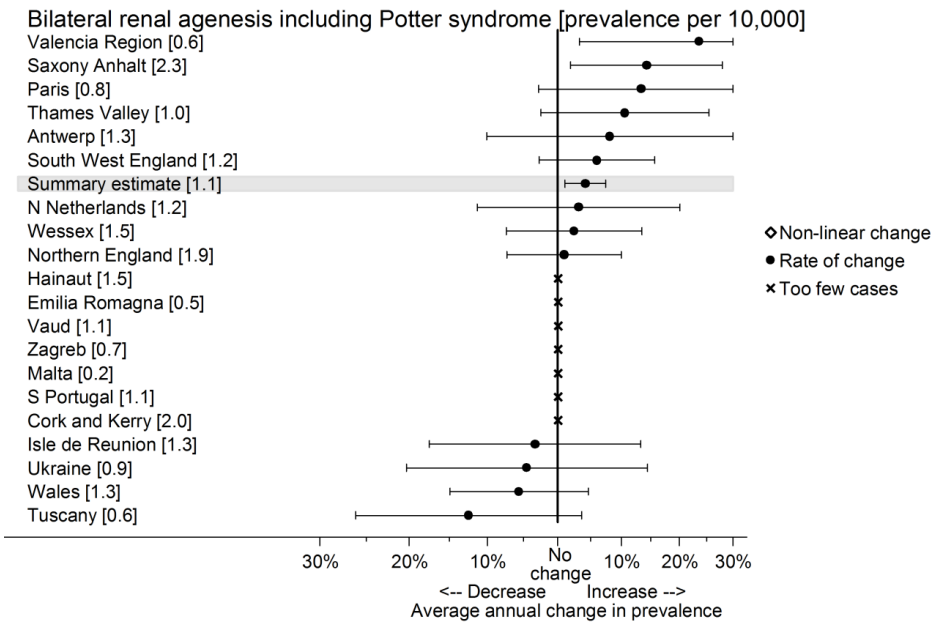

Fig. 8b: Bilateral renal agenesis (including Potter syndrome) - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

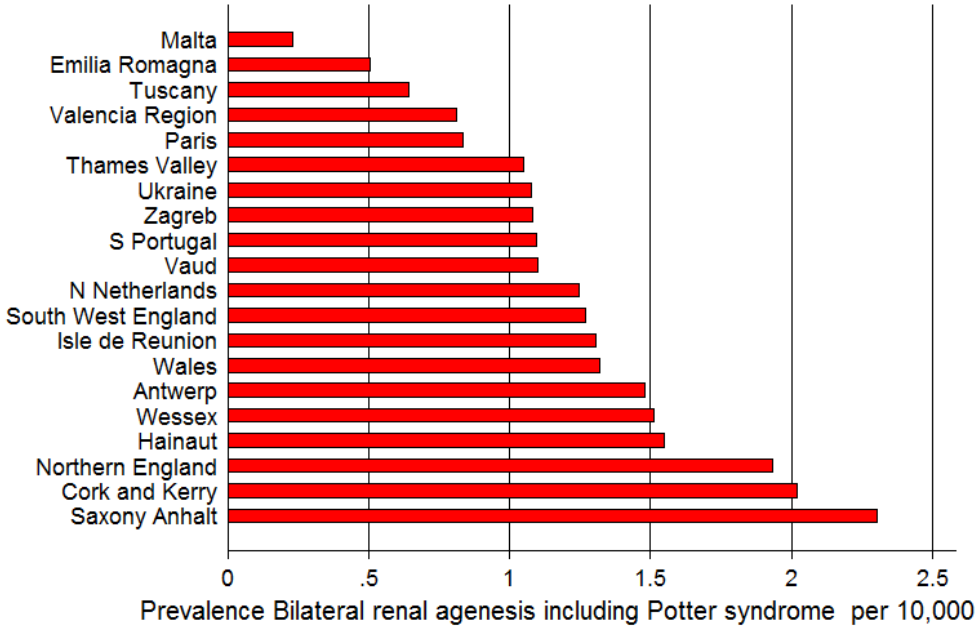

Fig. 8c: Bilateral renal agenesis (including Potter syndrome) - Estimated prevalence for the registries included in the pan-European trend analysis (2007-2016).

All cases included in the trend analysis were reviewed. The review showed that the large majority of cases were very severe as the TOPFA rate was high and there were few survivors after one week. Therefore, the coding of the diagnosis seems to be correct and valid (see Appendix G).

In conclusion, the pan-European trend is most likely correct and needs to be monitored.

Multicystic renal dysplasia

Bilateral multicystic renal dysplasia is usually lethal shortly after birth. Unilateral multicystic renal dysplasia is much more common, is asymptomatic and usually diagnosed prenatally. Kidneys with multicystic renal dysplasia usually undergo atrophy within the first year after birth. If diagnosed later in life, the diagnosis will be renal agenesis.

As in the previous report on the period 2006-2015, the prevalence of multicystic renal dysplasia is increasing. Between 2007 and 2016, its prevalence is estimated to have increased each year by 1.7% (95% CI: 0.0%; 3.4%) on the pan-European level (Fig. 9a). In total, 1,859 cases were included in the trend analysis, of which 1,699 (91%) were diagnosed prenatally. 84% were cases of unilateral multicystic renal dysplasia and 16% were bilateral.

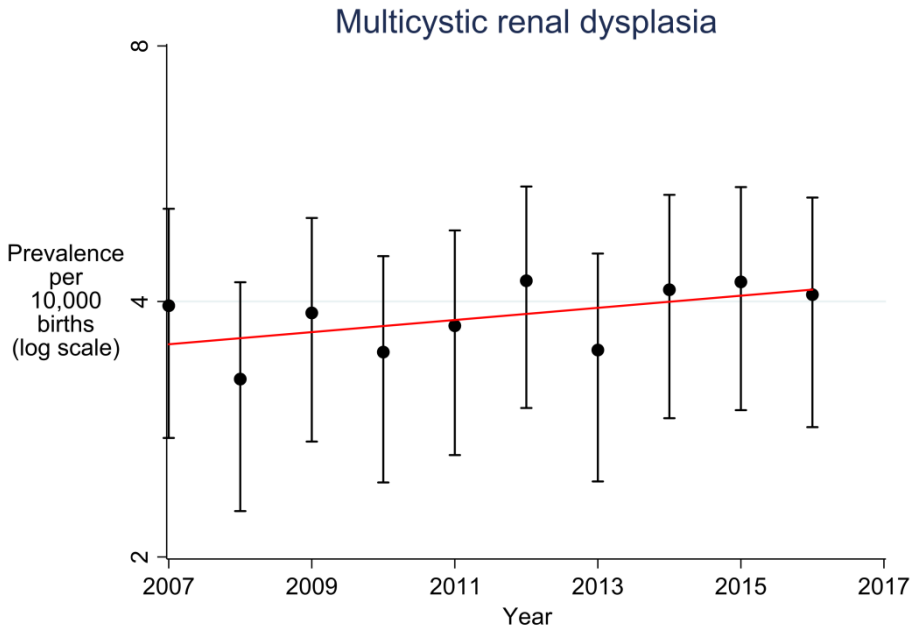

Fig. 9a Multicystic renal dysplasia - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

The prevalence increased significantly during the same period in three individual registries (Northern Netherlands, South West England and Thames Valley, Fig 9b).

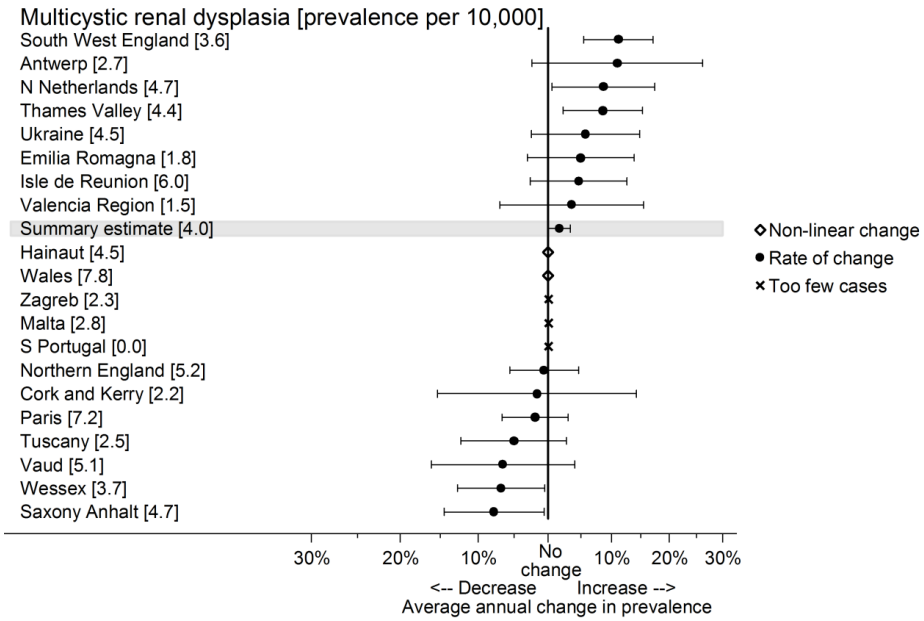

Fig. 9b: Multicystic renal dysplasia - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

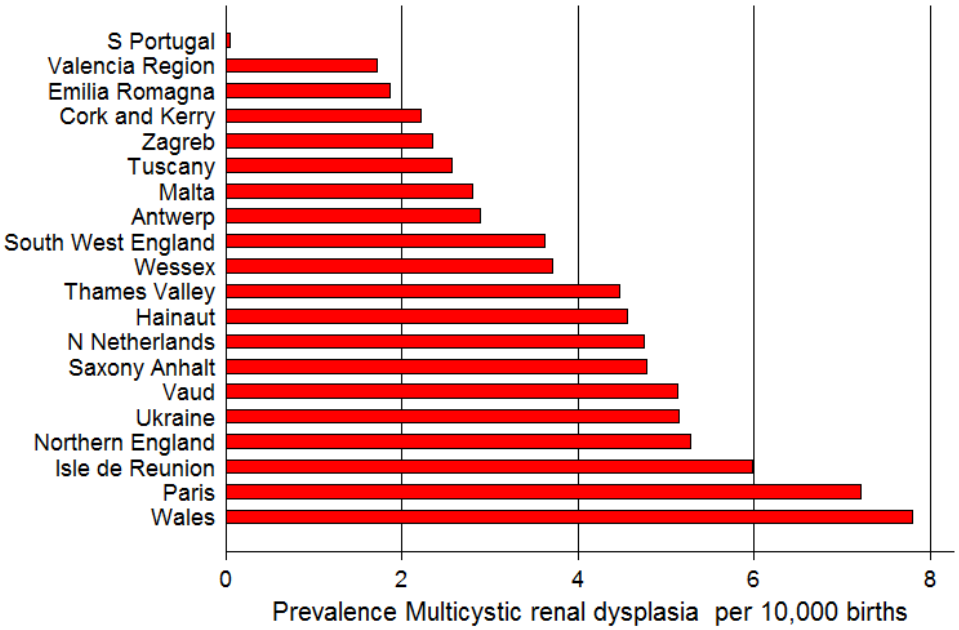

Fig. 9c: Multicystic renal dysplasia - Estimated prevalence for the registries included in the pan-European trend analysis (2007-2016).

In conclusion, this trend is mainly based on unilateral multicystic renal dysplasia diagnosed because of increasing use of prenatal screening in Europe. This trend does not include cases of bilateral renal agenesis.

Congenital hydronephrosis

Congenital hydronephrosis is mainly diagnosed prenatally. Cases have to be followed up as some intrauterine diagnoses are not confirmed after birth. Only cases where renal pelvis is ≥ 10 mm after birth should be reported to EUROCAT. Hydronephrosis caused by vesico-ureteral reflux should not be reported to EUROCAT.

As in the previous report on the period 2006-2015, the prevalence of congenital hydronephrosis is increasing. Between 2007 and 2016, its prevalence is estimated to have increased each year by 4.3% (95% CI: 3.3%; 5.3%) on the pan-European level (Fig. 10a).

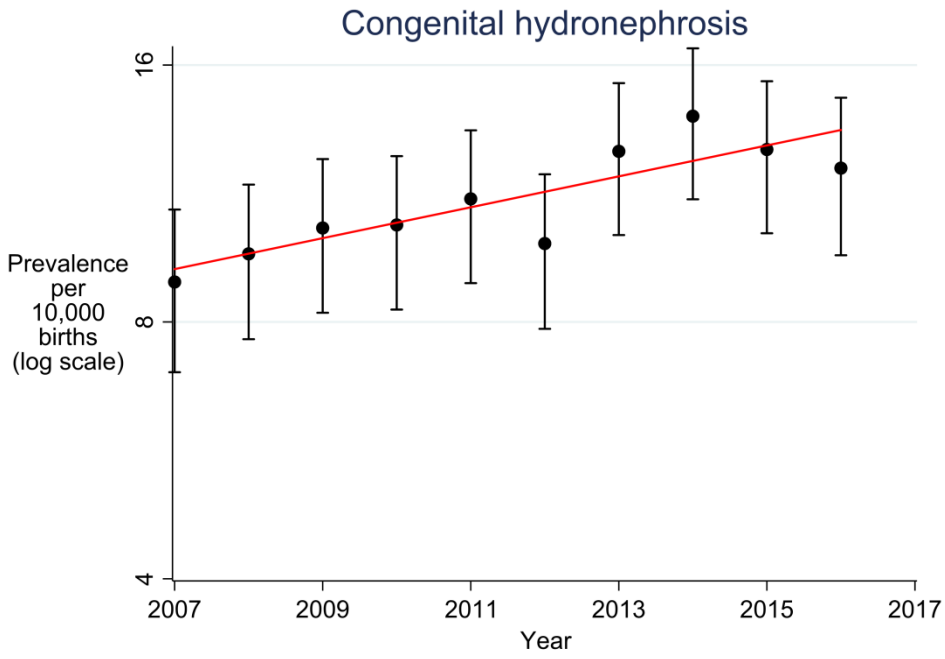

Fig. 10a Congenital hydronephrosis - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

The prevalence increased significantly during the same period in four individual registries (Antwerp, Emilia Romagna, Paris and Valencia Region, Fig 10b).

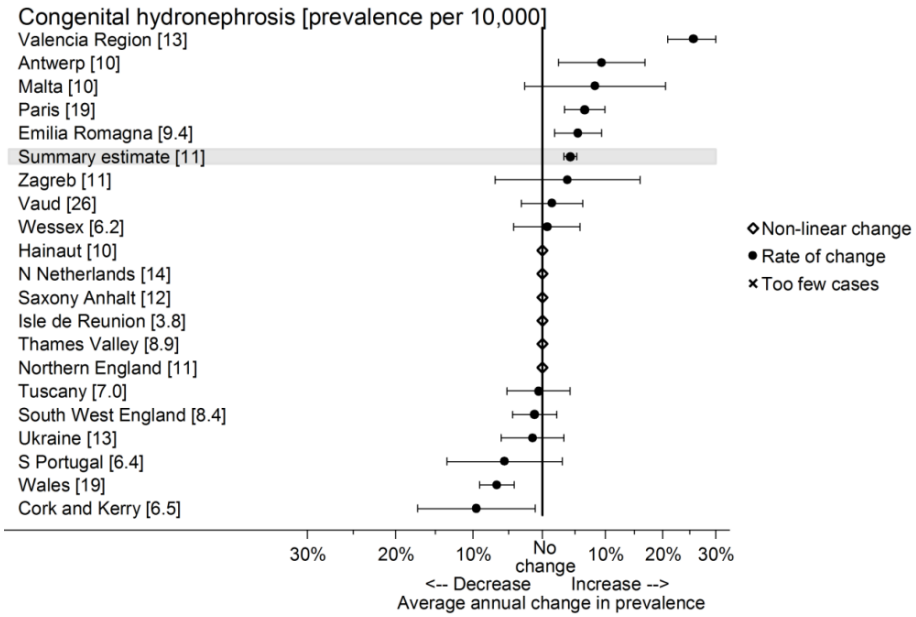

Fig. 10b: Congenital hydronephrosis - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

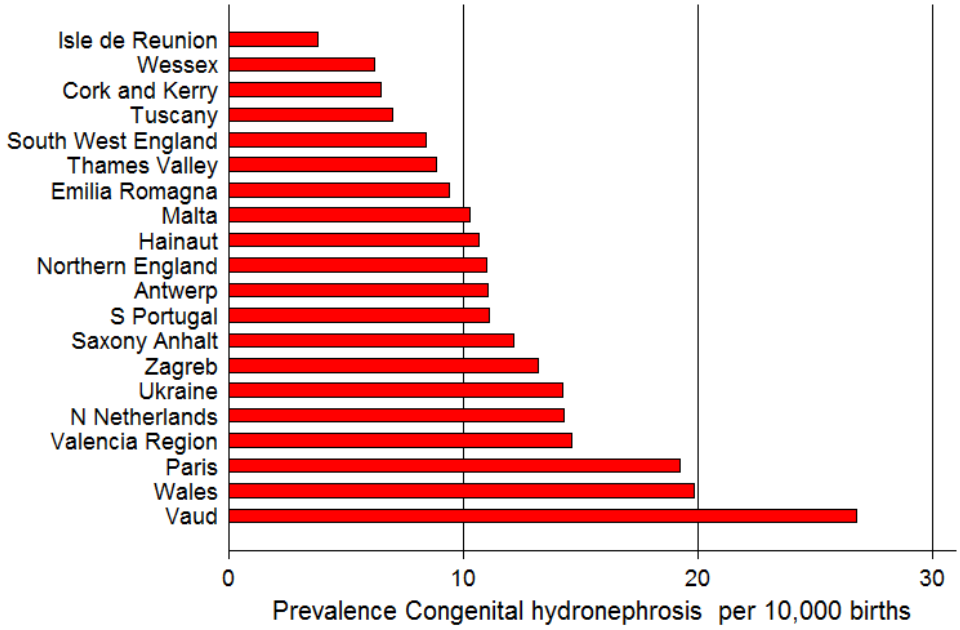

Fig. 10c: Congenital hydronephrosis - Estimated prevalence for the registries included in the pan-European trend analysis.

In conclusion, the increasing pan-European trend is likely to reflect changes in diagnostic methods over the last 10 years.

Clubfoot – talipes equinovarus

Clubfoot can be unilateral or bilateral and has a familial pattern of inheritance. Clubfoot cases requiring surgery or Ponseti treatment should be reported to EUROCAT as a major congenital anomaly. If the clubfoot is of postural origin and not receiving treatment as mentioned, the anomaly should be classified as a minor anomaly.

A recently published study on data from 18 EUROCAT registries found a decrease in prevalence of clubfoot in the years 1995-2011 [10], mainly after 2002 due to new coding recommendations.

The prevalence of clubfoot is now increasing, as documented in the previous report on the period 2006-2015 [6]. Between 2007 and 2016, its prevalence is estimated to have increased each year by 3.3% (95% CI: 2.2%; 4.4%) on the pan-European level (Fig. 11a).

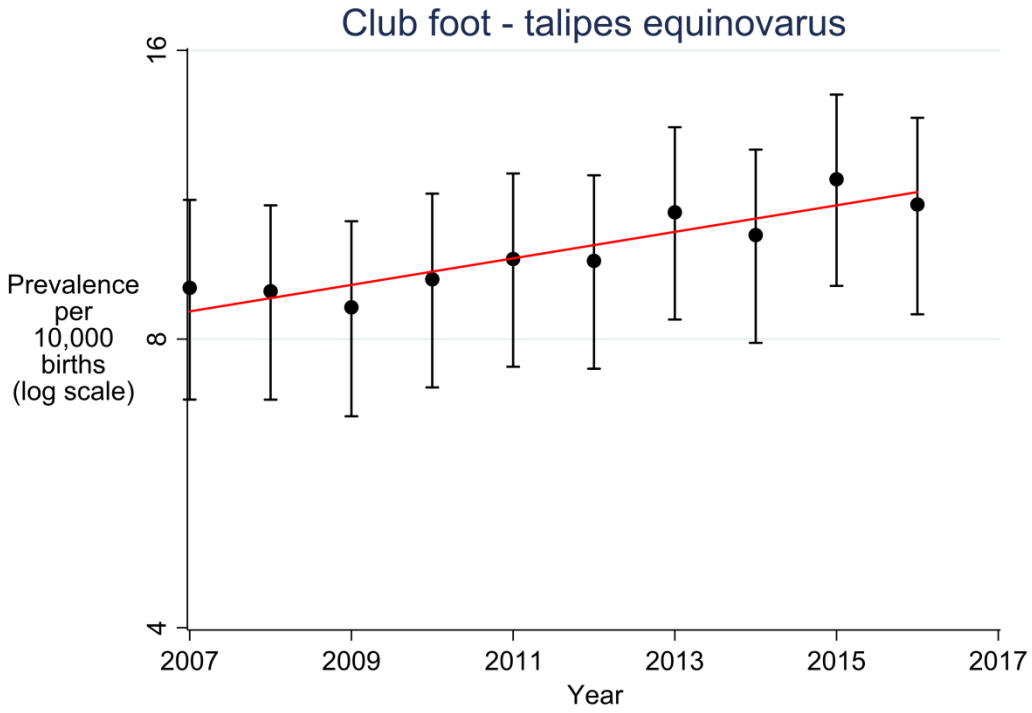

Fig. 11a Clubfoot - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

The prevalence increased dramatically (+76.5%) for Northern England, due to significant changes in ascertainment from the start of the 10 year period when there was under-reporting (Fig. 11c). In the same period, the trend increased significantly also in other three registries (Malta, Ukraine and Valencia Region, Fig 11b).

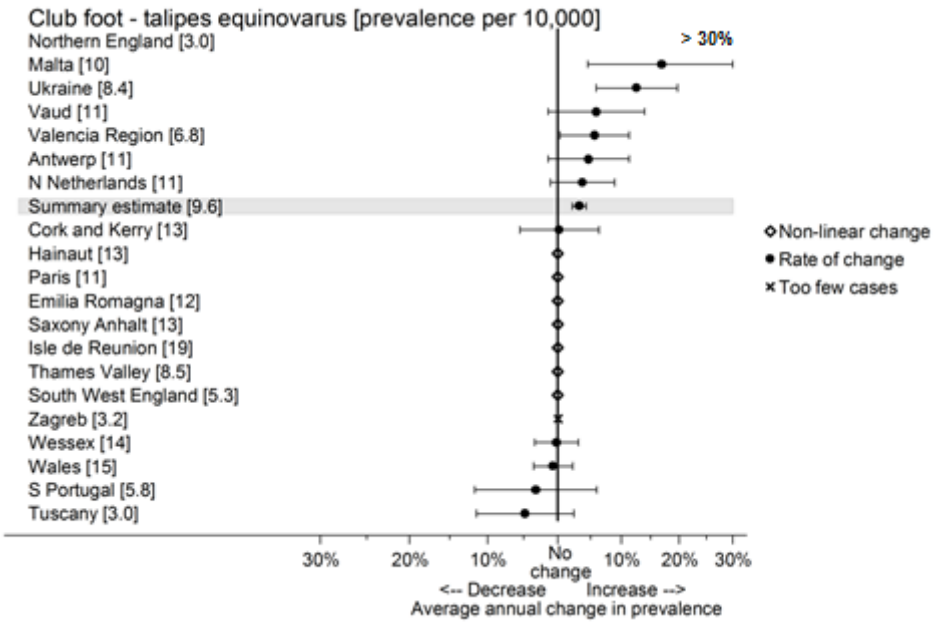

Fig. 11b: Clubfoot - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

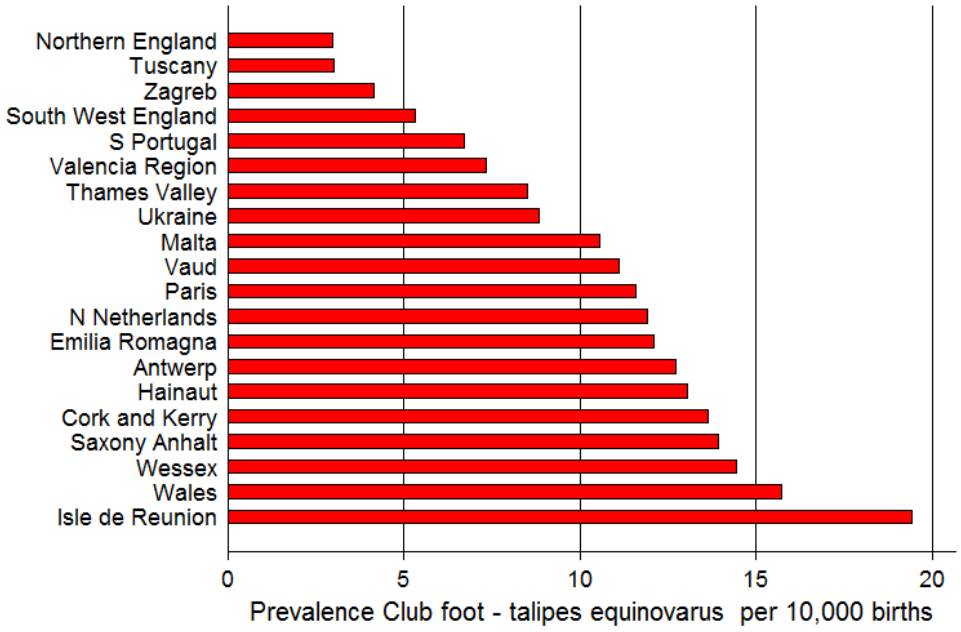

Fig. 11c: Clubfoot - Estimated prevalence for the registries included in the pan-European trend analysis.

Performing the trend analysis excluding the Northern England registry the pan-European trend remains significantly increasing with an annual increase of 2.3% (95% CI: 1.2%; 3.4%).

Maternal diabetes and smoking are a risk factor for clubfoot [11, 12]. The proportion of pregnant women in Europe with diabetes and of pregnant women with obesity is increasing. Therefore, the observed increasing trend might be of concern and there is an ongoing EUROCAT study investigating this in depth.

Polydactyly

Polydactyly is an extra finger or an extra toe. Minor cases are not reported to EUROCAT. Bilateral polydactyly is often associated with chromosomal or genetic syndromes. There are ethnic differences in the prevalence of simple polydactyly [13].

Between 2007 and 2016, the prevalence of polydactyly is estimated to have increased by 1.8% (95% CI: 0.7%; 3.0%) each year on the pan-European level (Fig. 12a).

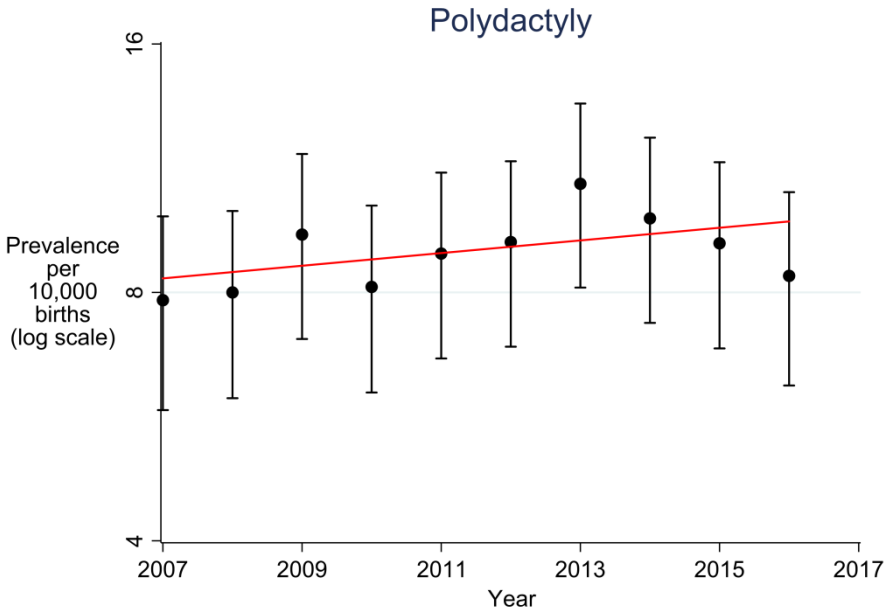

Fig. 12a Polydactyly - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In the Emilia Romagna registry, the prevalence increased significantly during the same period (Fig. 12b).

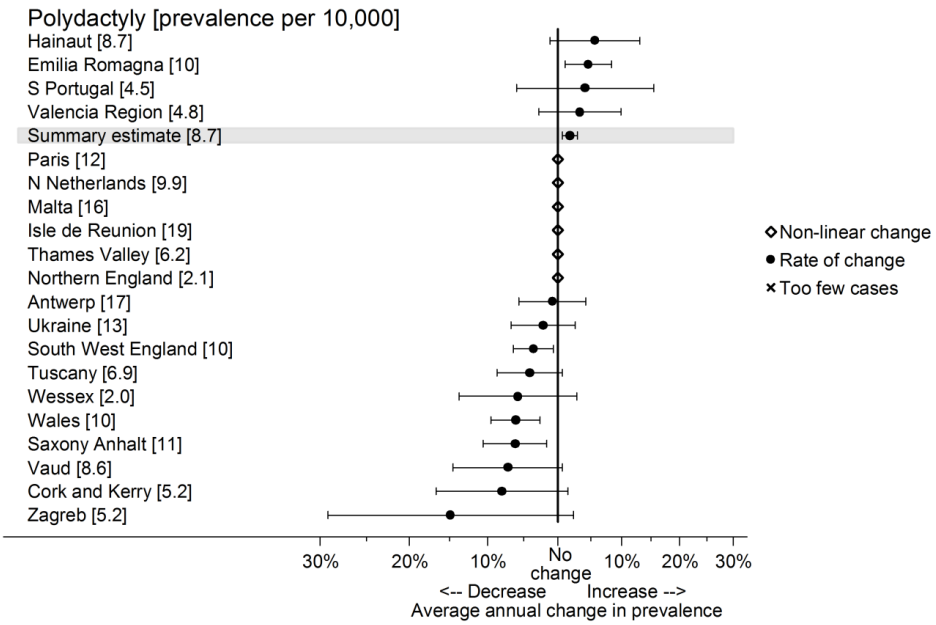

Fig. 12b: Polydactyly - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

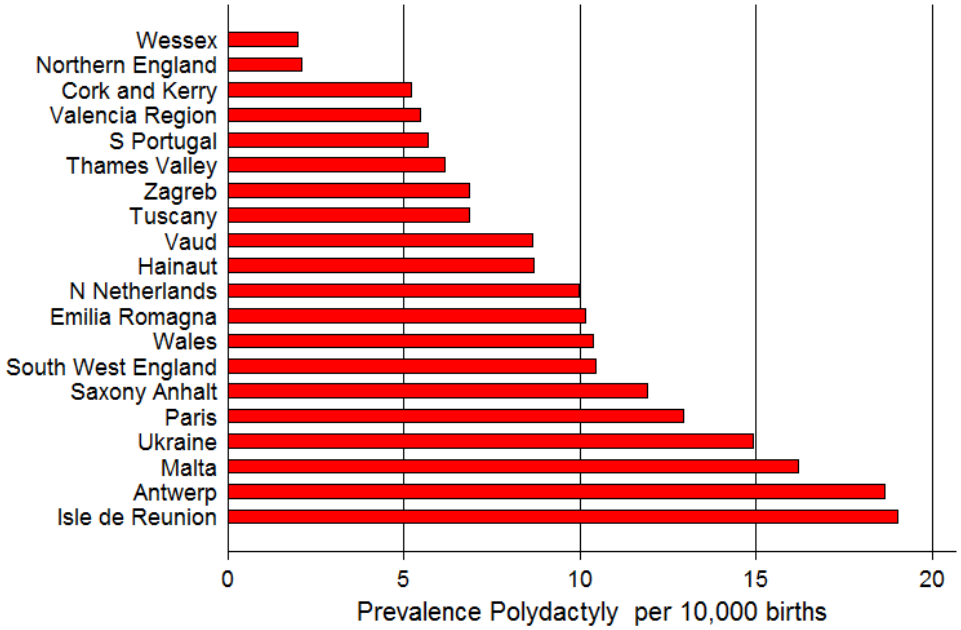

Fig. 12c: Polydactyly - Estimated prevalence for the registries included in the pan-European trend analysis.

In conclusion, although there is an increasing pan-European trend, it is not of concern as this anomaly may be associated with undiagnosed genetic syndromes.

Laterality Anomalies

This subgroup of laterality anomalies includes atrial isomerism, dextrocardia, bronchopulmonary isomerism, situs inversus and anomalies of spleen. Another name for these anomalies is heterotaxy anomalies.

As in the previous report on the period 2006-2015 the prevalence of laterality anomalies is increasing. Between 2007 and 2016, its prevalence is estimated to have increased by 3.7% (95% CI: 1.1%; 6.3%) each year on the pan-European level (Fig. 13a). The majority of the cases included in the trend (679/820 = 83%) had one of the anomalies in the subgroup and no other anomalies, with situs inversus (223/697=32.8%), dextrocardia (216/679=31.8%) and anomalies of spleen (118/679=17.4%) being most frequent.

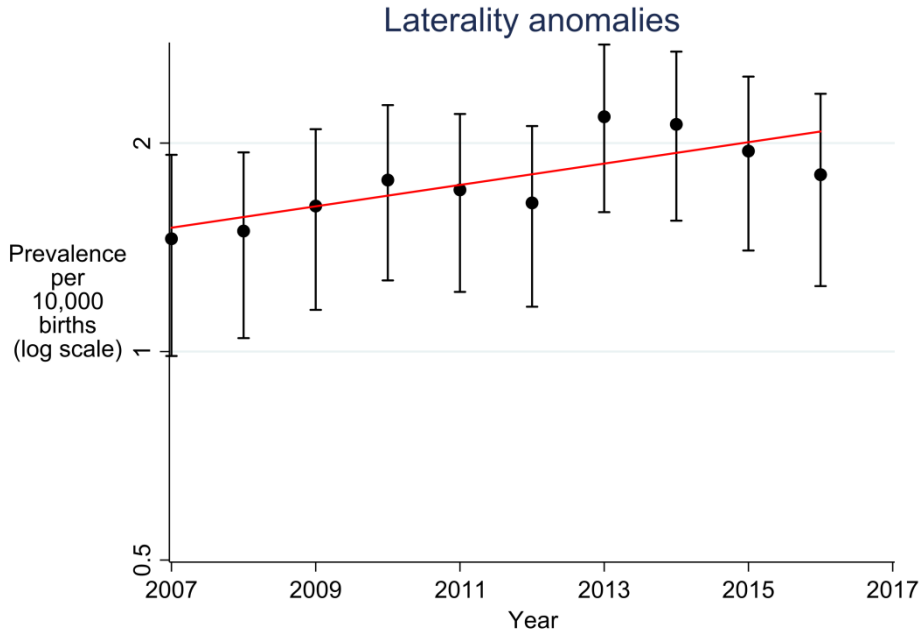

Fig. 13a Laterality anomalies - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

No evidence of an increasing trend in prevalence was found in any of the individual registries during the same period (Fig 13b).

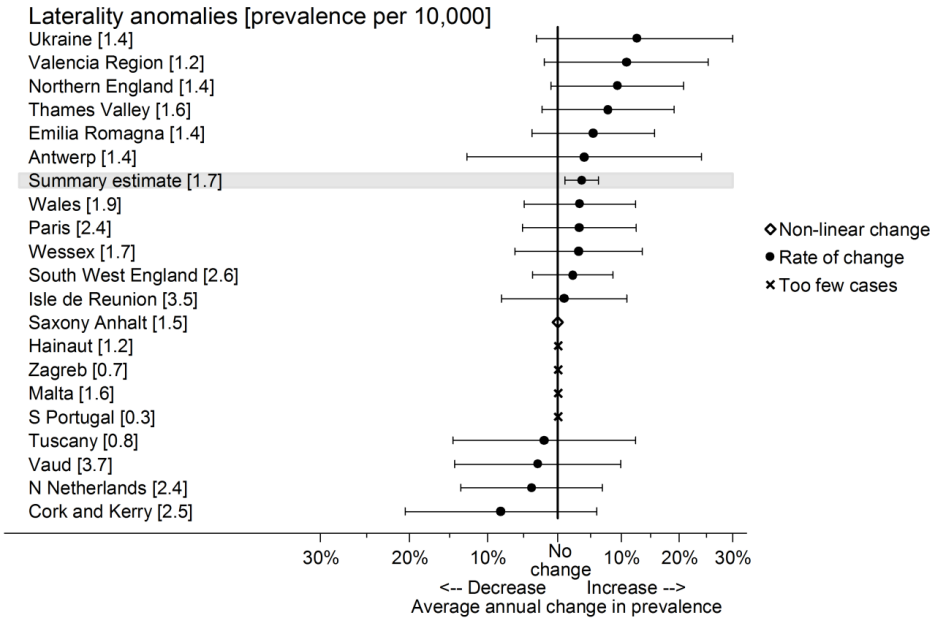

Fig. 13b: Laterality anomalies - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

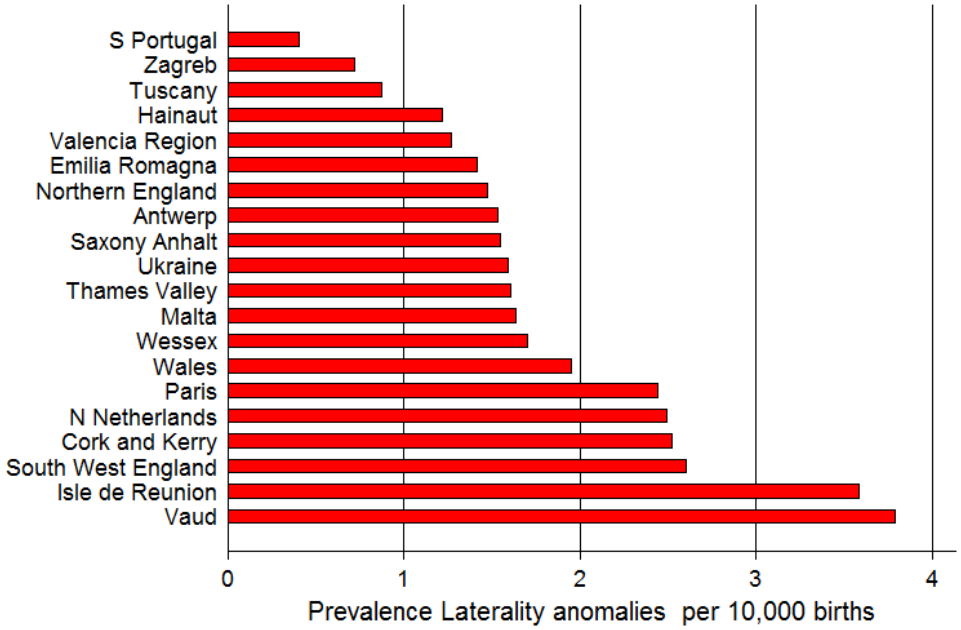

Fig. 13c: Laterality anomalies - Estimated prevalence for the registries included in the pan-European trend analysis.

In conclusion, the laterality subgroup was defined by the Coding Committee in 2013 and analysed for the first time last year. The increasing pan-European trend is continuing. Maternal diabetes is a risk factor for laterality anomalies [14]. The proportion of pregnant women in Europe with diabetes and of pregnant women with obesity is increasing. Therefore, the increasing trend of laterality anomalies will be monitored closely by EUROCAT.

4.3 Decreasing trends identified at the pan-Europe level

Hydrocephaly

The definition of hydrocephaly is dilatation of the ventricular system with impaired circulation and absorption of the cerebrospinal fluid. The dilatation should not be due to primary atrophy of the brain, with or without enlargement of the skull.

As in the previous report on the period 2006-2015, the prevalence of hydrocephaly is decreasing. Between 2007 and 2016, its prevalence is estimated to decrease by -2.3% (95% CI: -3.7%; -0.8%) each year on the pan-European level (Fig. 14a).

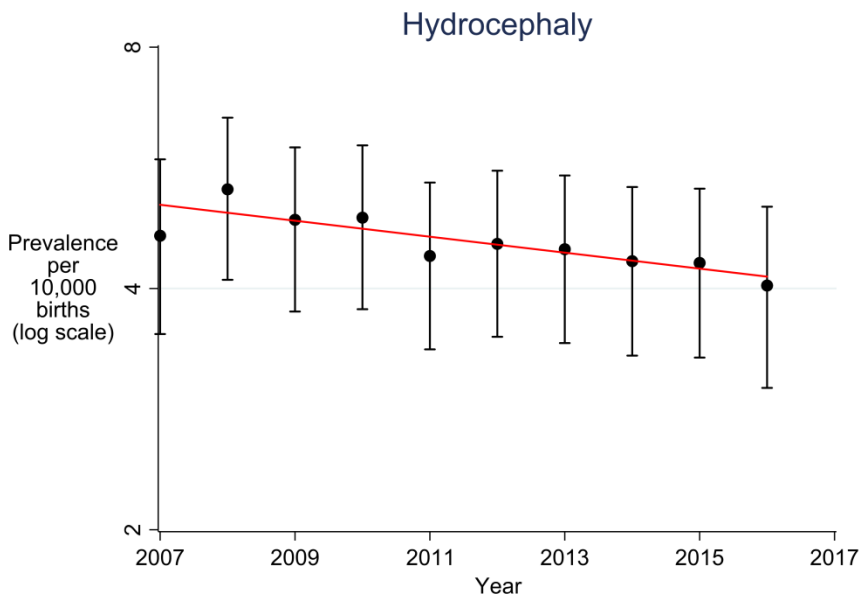

Fig. 14a Hydrocephaly - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In two individual registries, the prevalence decreased significantly during the same period (Paris and Wales, Fig 14b).

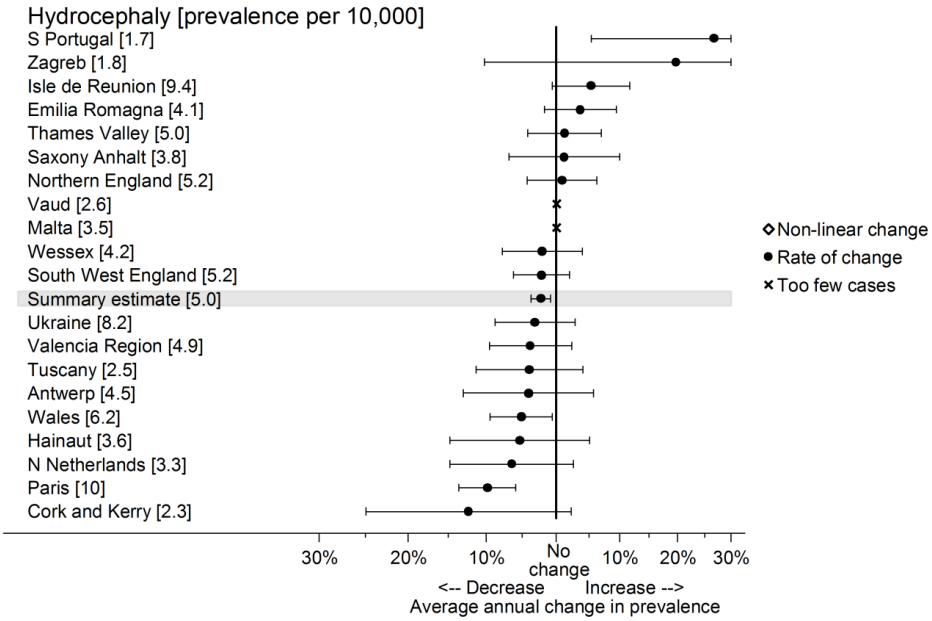

Fig. 14b: Hydrocephaly - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

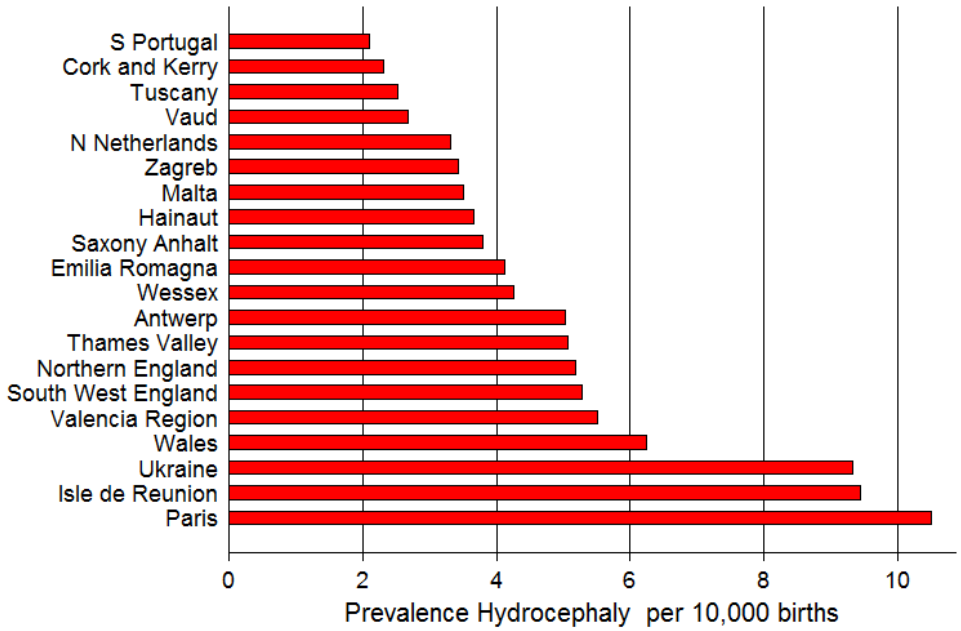

Fig. 14c: Hydrocephaly - Estimated prevalence for the registries included in the pan-European trend analysis.

In conclusion, hydrocephaly is decreasing in general in Europe. It may be due to improved maternal health and less infections during pregnancy [15].

Severe microcephaly

Severe microcephaly should be reported if the head circumference (occipito-frontal) is less than -3 SD for sex and GA. This anomaly will be followed closely due to the recent Zika virus outbreaks that started in 2015 in South America. The first births in Europe after possible exposure to Zika virus occurred in 2016.

As in the previous report on the period 2006-2015, the prevalence of *severe* microcephaly is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -3.8% (95% CI: -6.0%; -1.7%) each year on the pan-European level (Fig. 15a).

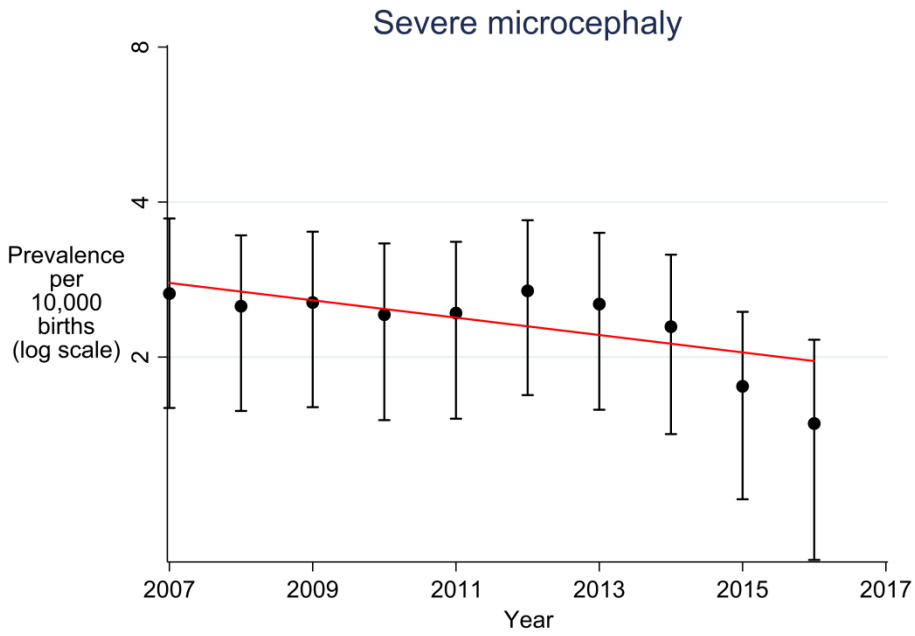

Fig. 15a Severe microcephaly - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In three individual registries, the prevalence decreased significantly during the same period (Saxony-Anhalt, South-West England and Wales, Fig 15b).

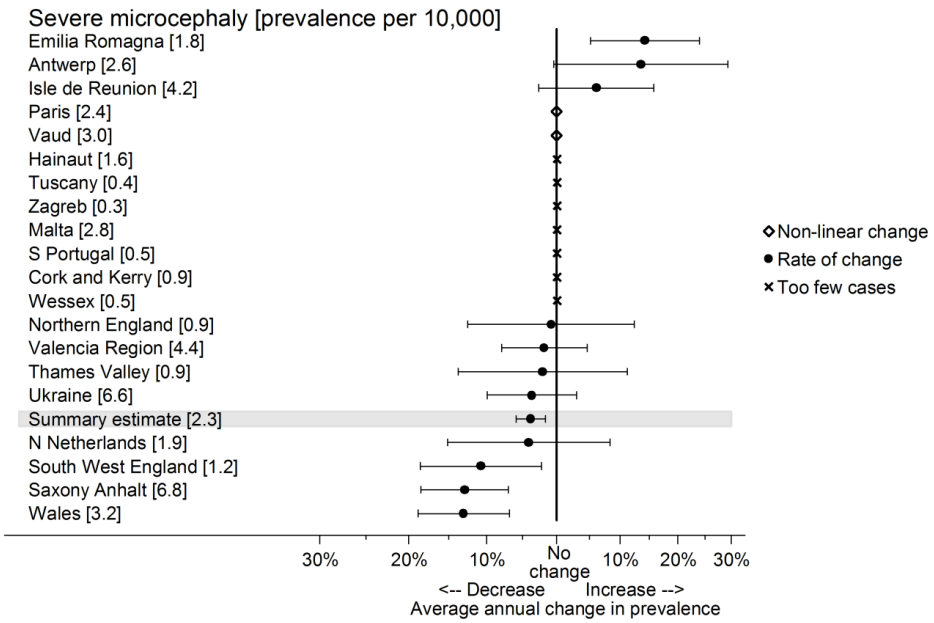

Fig. 15b: Severe microcephaly - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

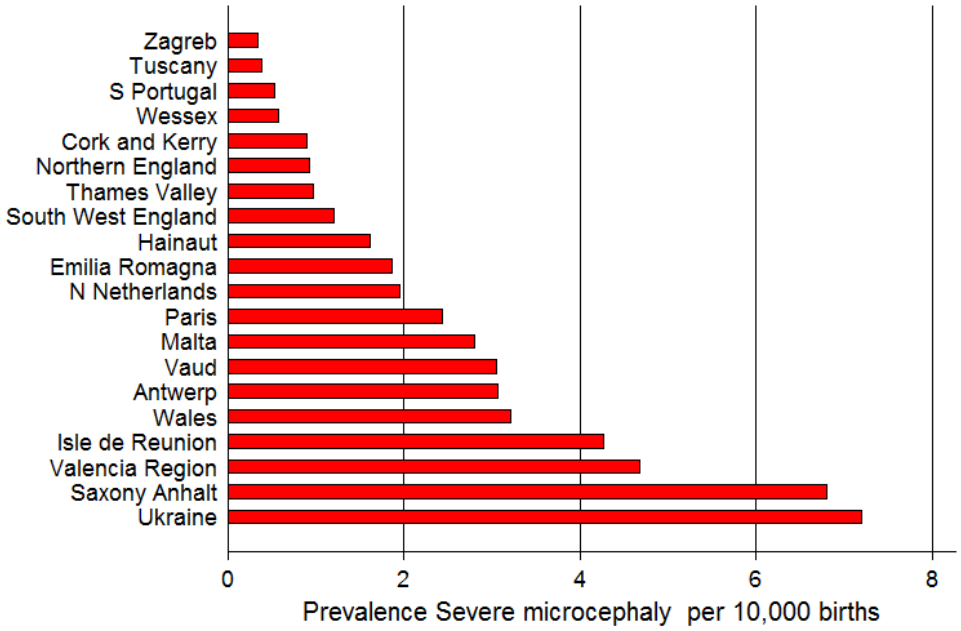

Fig. 15c: Severe microcephaly - Estimated prevalence for the registries included in the pan-European trend analysis.

In June 2016, the EUROCAT Coding and Classification Committee published a new coding tip on microcephaly to "report microcephaly if head circumference (occipito-frontal) is less than -3 SD for sex and GA. Add in written text the measurements and age at measurements. In case of maternal zika virus infection, use the code P358 for congenital viral infection in one of the malformation variables. Use local growth chart to confirm the diagnosis. Exclude secondary microcephaly (neonatal meningitis, birth asphyxia, extreme preterm birth)" [16].

In conclusion, the observed decreasing trend is probably due to the fact that some registries changed their inclusion criteria from -2 SD to -3 SD and thus fewer cases are reported to EUROCAT.

Anophthalmos / microphthalmos

Anophthalmos is a unilateral or bilateral absence of the eye tissue. Microphthalmos is defined as small eye/eyes with smaller than normal axial length.

As in the previous report on the period 2006-2015, the prevalence of anophthalmos / microphthalmos is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -4.3% (95% CI: -8.0%; -0.4%) each year on the pan-European level (Fig. 16a).

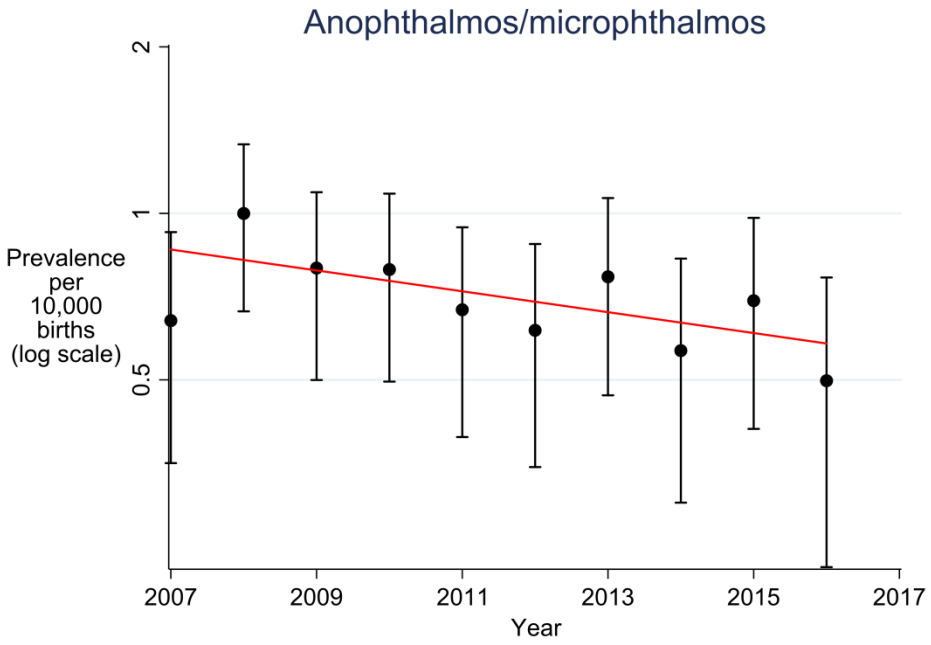

Fig. 16a Anophthalmos / microphthalmos - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

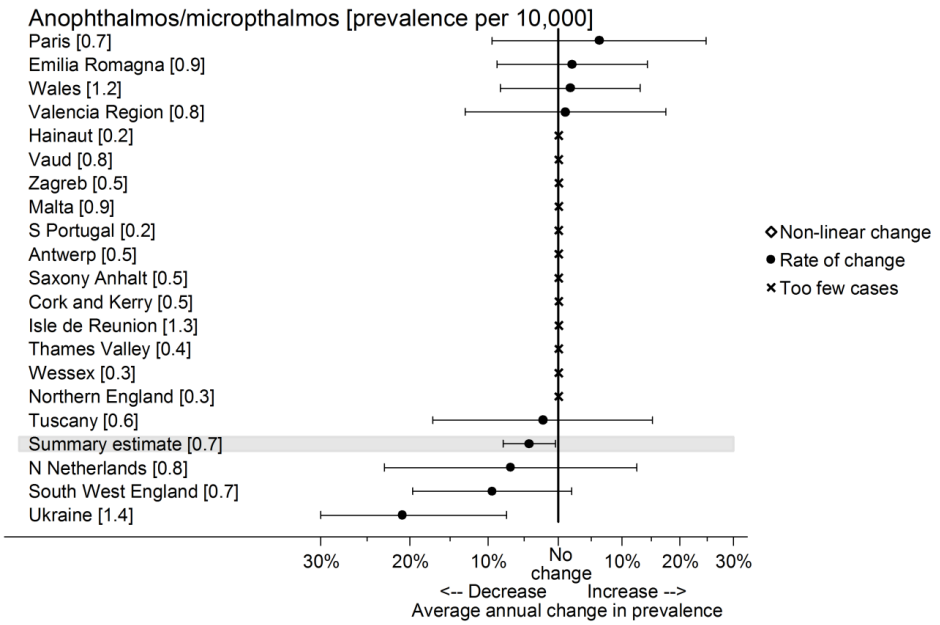

Fig. 16b: Anophthalmos / microphthalmos - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

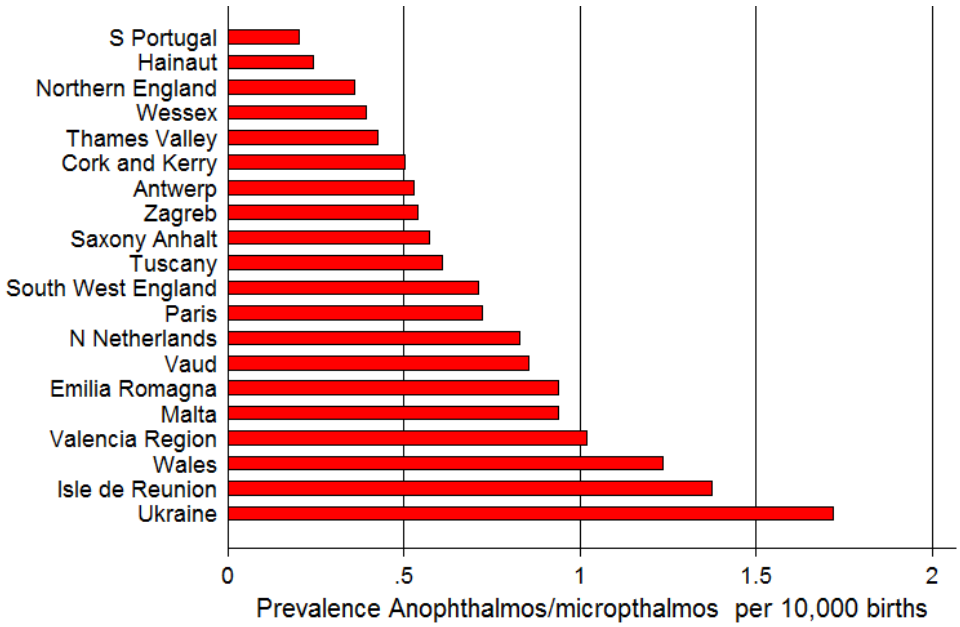

Fig. 16c: Anophthalmos / microphthalmos - Estimated prevalence for the registries included in the pan-European trend analysis.

To find out if the pan-European decreasing trend of anophthalmos/microphthalmos was explained by a significant decrease in prevalence in the registry with the highest prevalence of this anomaly, an additional analysis was performed excluding this registry (Ukraine). The result showed the decreasing pan-European trend disappeared (Fig. 16d; -3.1% (95% CI: -6.8%; +1.1%) each year).

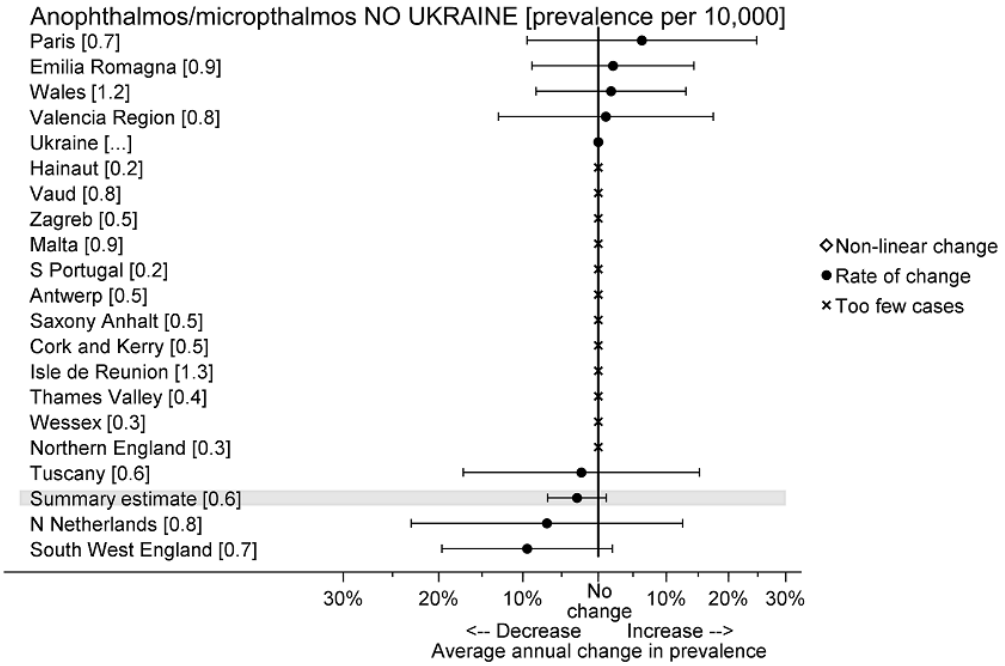

Fig. 16d: Anophthalmos / micropthalmos - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis excluding Ukraine registry.

In conclusion, the pan-European trend of anophthalmos/microphthalmos is likely to be explained by the decreasing trend in the Ukraine.

Pulmonary valve stenosis

Pulmonary valve stenosis is defined as obstruction or narrowing of the pulmonary valves, which may impair blood flow through the valves. The anomaly covers all spectra of severity - from small stenosis to critical pulmonary valve stenosis in severely ill neonates.

As in the previous report on the period 2006-2015, the prevalence of pulmonary valve stenosis is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -3.8% (95% CI: -5.3%; -2.2%) each year on the pan-European level (Fig. 17a).

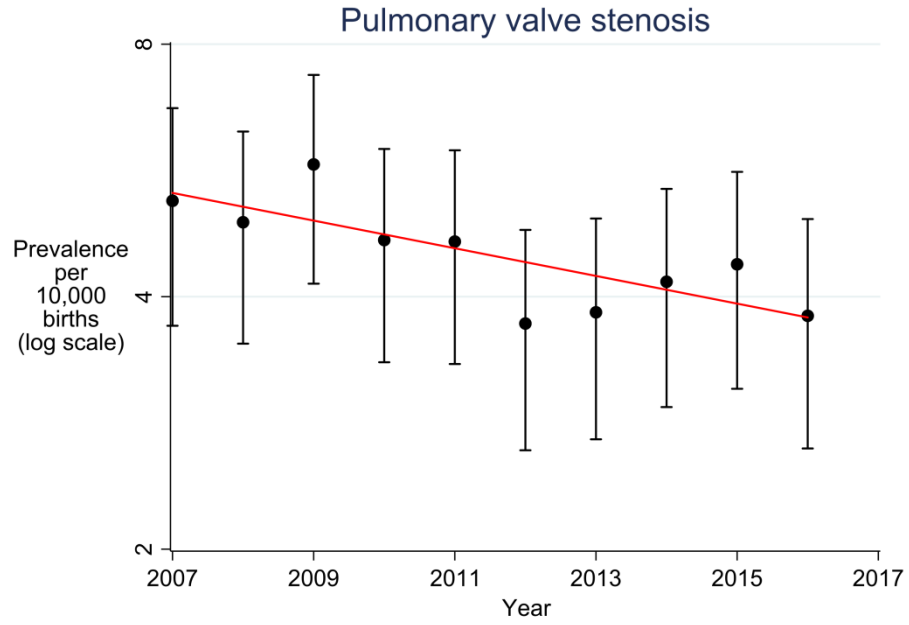

Fig. 17a: Pulmonary valve stenosis - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In five individual registries, the prevalence decreased significantly during the same period (Northern England, Paris, South Portugal, Wales and Wessex, Fig 17b).

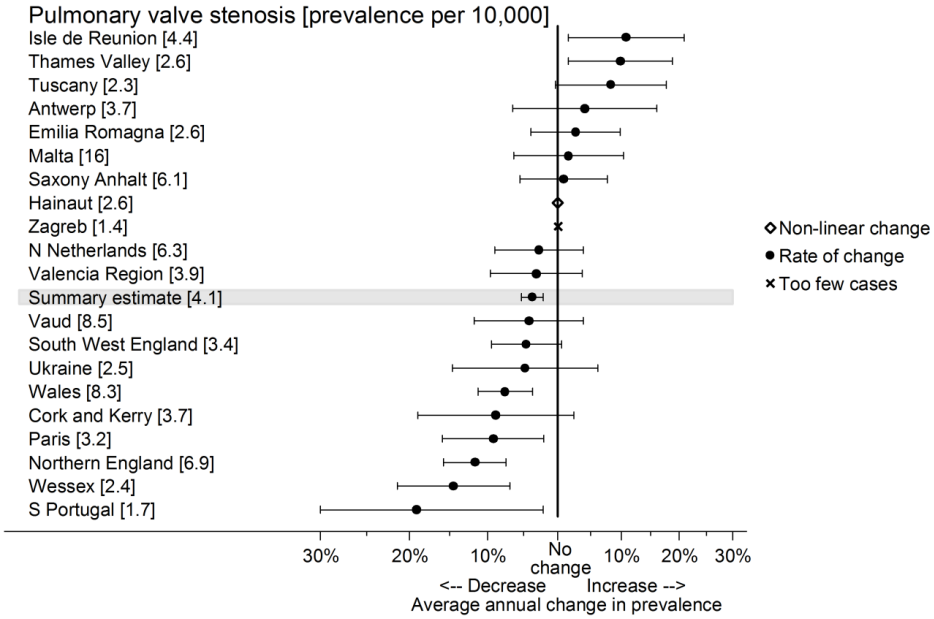

Fig. 17b: Pulmonary valve stenosis - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

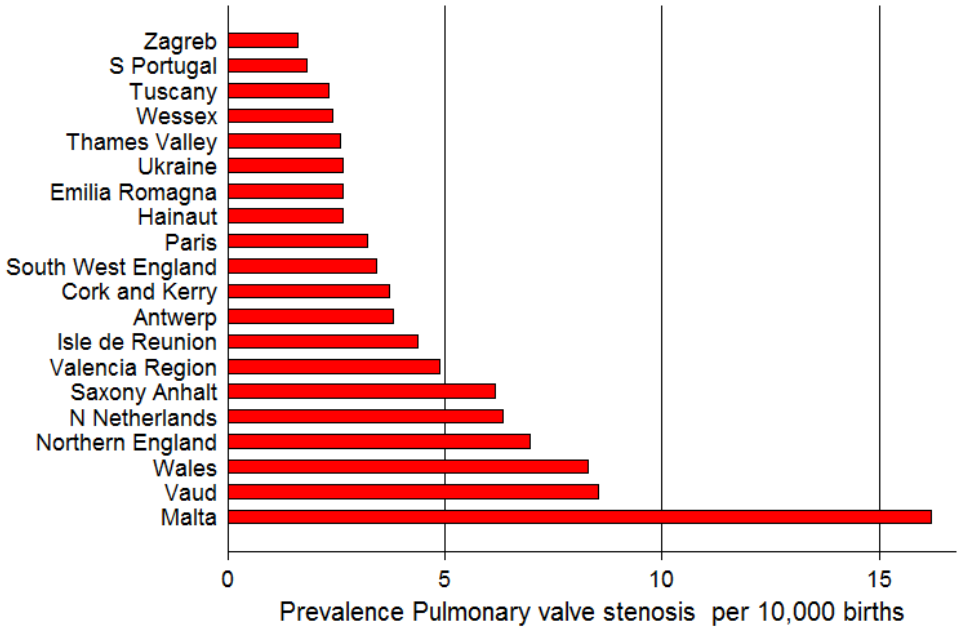

Fig. 17c: Pulmonary valve stenosis - Estimated prevalence for the registries included in the pan-European trend analysis.

There is considerable heterogeneity in the changes in prevalence with two registries with significantly increasing trends and five with significantly decreasing trends. In conclusion, the decreasing trend should be interpreted with caution.

Patent ductus arteriosus

Patent ductus arteriosus (PDA) is considered a major anomaly only if it occurs in term born babies (GA ≥ 37 weeks). Cases should be reported only if the PDA is still present six months after birth or if surgery/catheter closure is required. Many critically ill neonates have an open PDA for days or weeks with spontaneous closure. These babies should not be reported to EUROCAT.

As in the previous report on the period 2006-2015, the prevalence of patent ductus arteriosus is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -4.5% (95% CI: -6.6%; -2.3%) each year on the pan-European level (Fig. 18a).

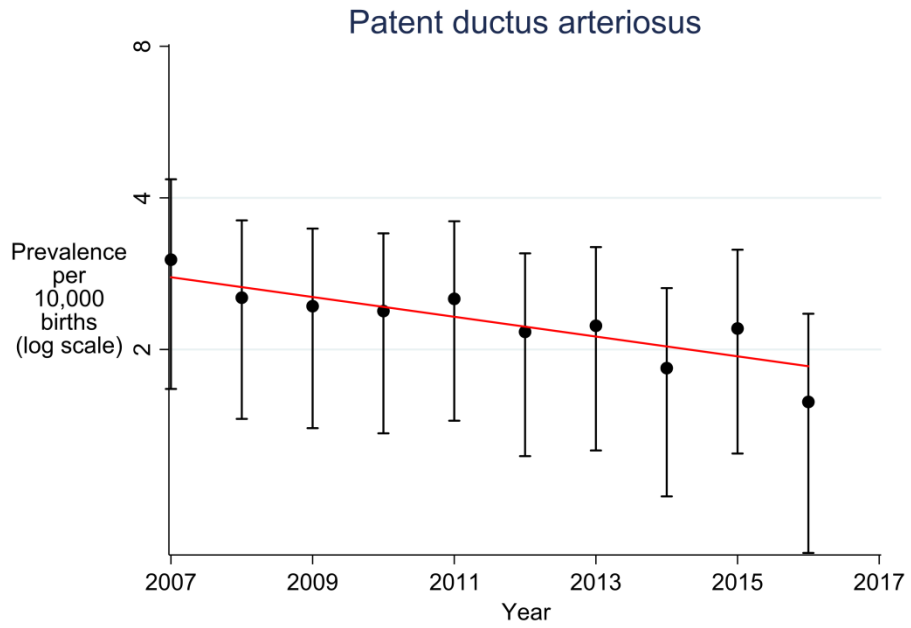

Fig. 18a: Patent ductus arteriosus - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In four individual registries, the prevalence also decreased significantly during the same period (Cork & Kerry, Northern England, Ukraine and Wales Fig 18b).

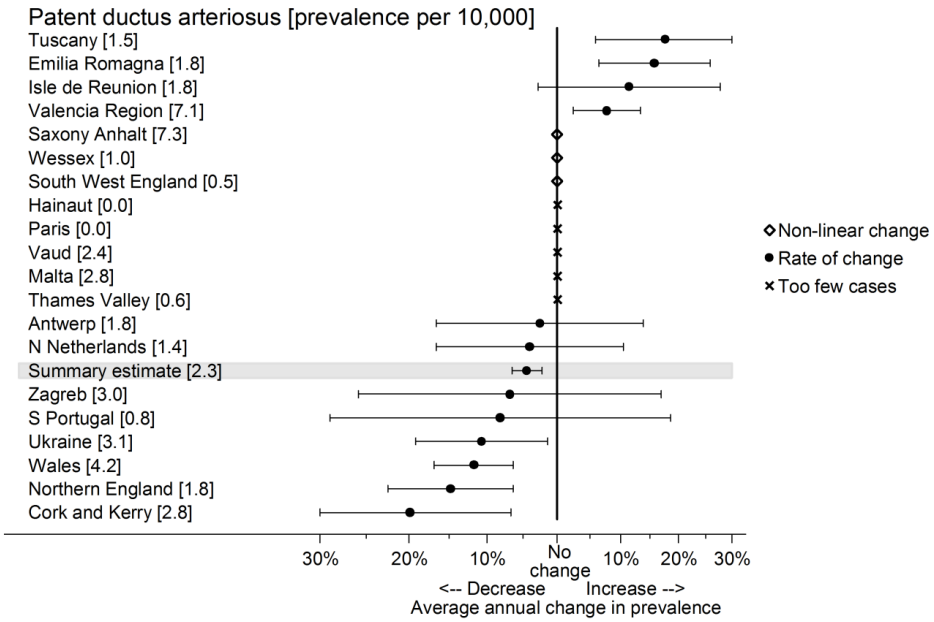

Fig. 18b: Patent ductus arteriosus - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

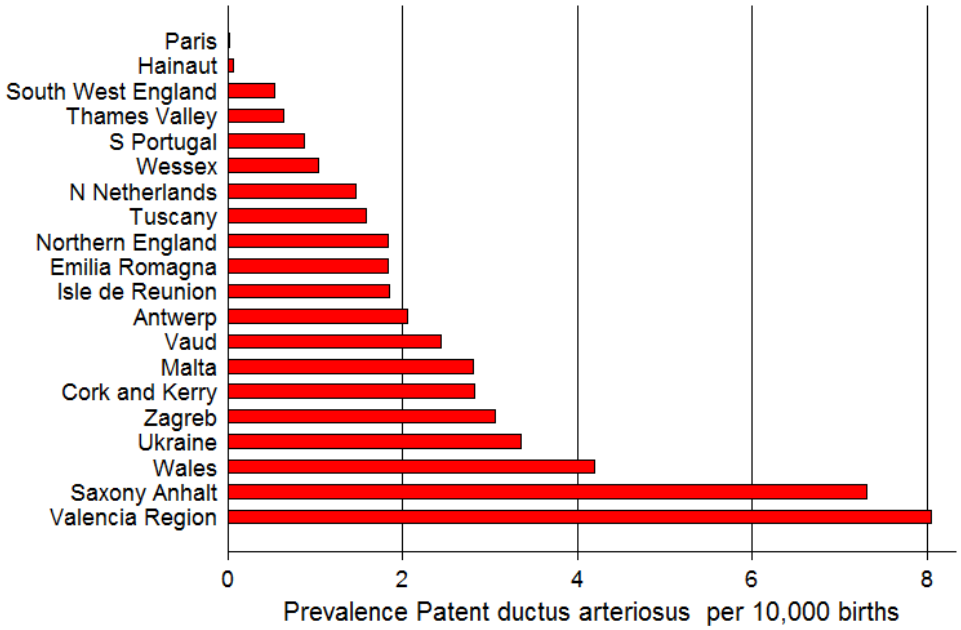

Fig. 18c: Patent ductus arteriosus - Estimated prevalence for the registries included in the pan-European trend analysis.

In 2016, the EUROCAT Coding and Classification Committee issued a coding tip for this anomaly: "Infants with patent ductus will be included as a major anomaly for term born babies only (GA ≥ 37 weeks). To be reported only if the PDA is still present six months after birth or if surgery/catheter closure is required. Many critically ill neonates have an open PDA for days or weeks with spontaneous closure. These babies should not be reported to EUROCAT. Do not code the PDA if part of a ductus dependent CHD such as transposition of great arteries (Q203), hypoplastic left heart (Q234) and coarctation of aorta (Q2510)" [16].

The large amount of heterogeneity in the prevalence in the different registries and in the changes in prevalence over the ten year period indicates that there are clear issues with reporting this anomaly. The coding tip will hopefully result in more homogeneous reporting. Until then any observed trends are most probably due to corrections in reporting and should not be interpreted as indicating underlying real changes in prevalence.

Cleft lip with or without palate

This is an anomaly where clefting of the upper lip occurs with or without clefting of the maxillary alveolar process and hard and soft palate. This anomaly is visible at birth and should have a high ascertainment rate. There is a known geographical difference in prevalence throughout Europe.

As in the previous report on the period 2006-2015, the prevalence of *cleft lip with or without palate* is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -1.5% (95% CI: -2.7%; -0.4%) each year on the pan-European level (Fig. 19a).

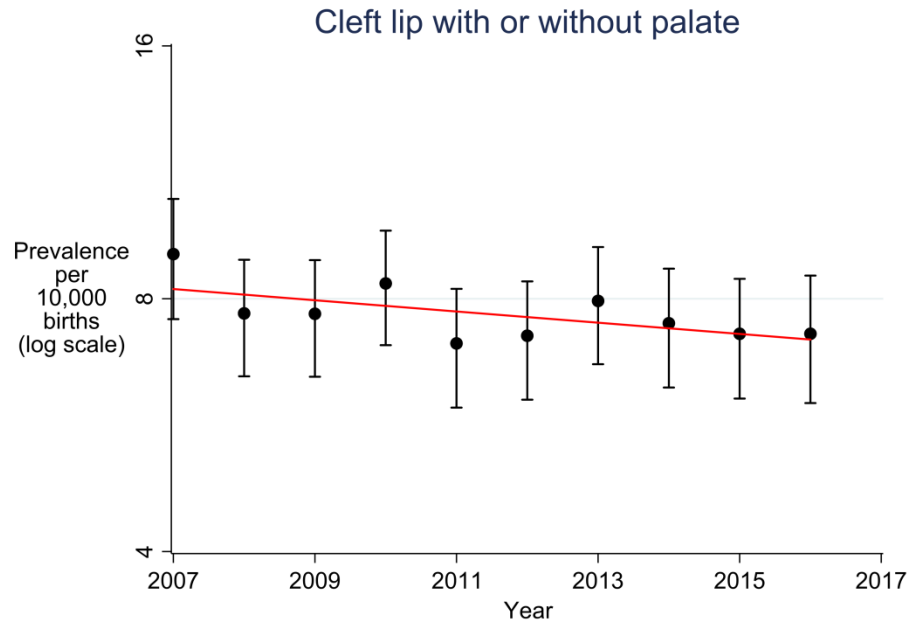

Fig. 19a: Cleft lip with or without palate - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

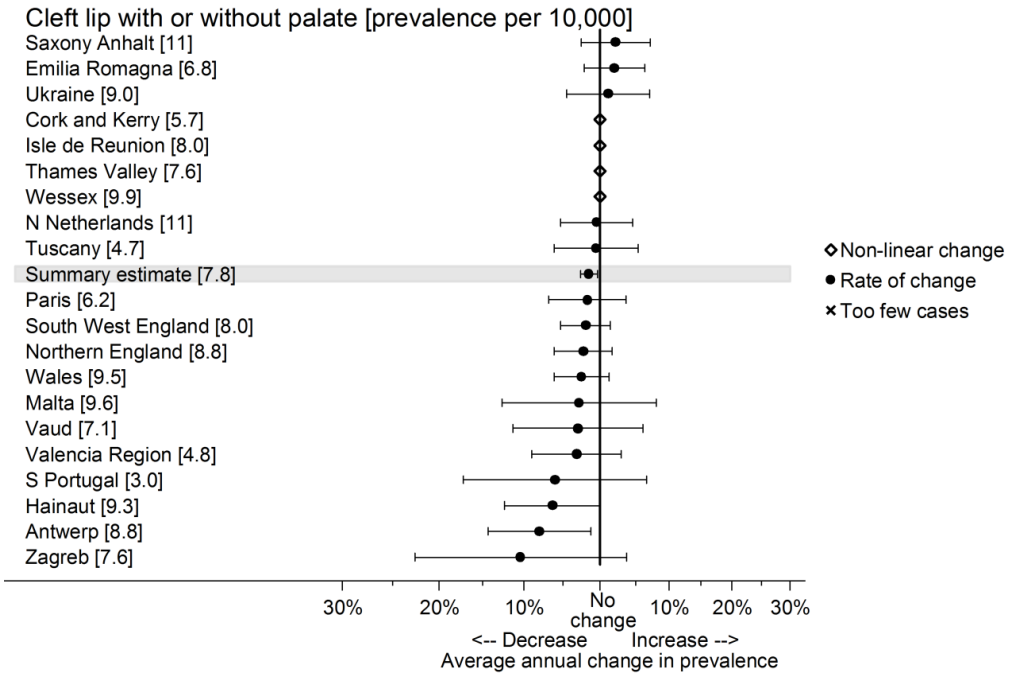

Fig. 19b: Cleft lip with or without palate - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

In the registry of Antwerp, the prevalence decreased significantly during the same period (Fig 19b). When asked to comment on the decrease, the registry of Antwerp confirmed the trend and stated the investigation is on-going. Except from the registry in Antwerp, no single registry shows a significant rate of change despite the high number of cases.

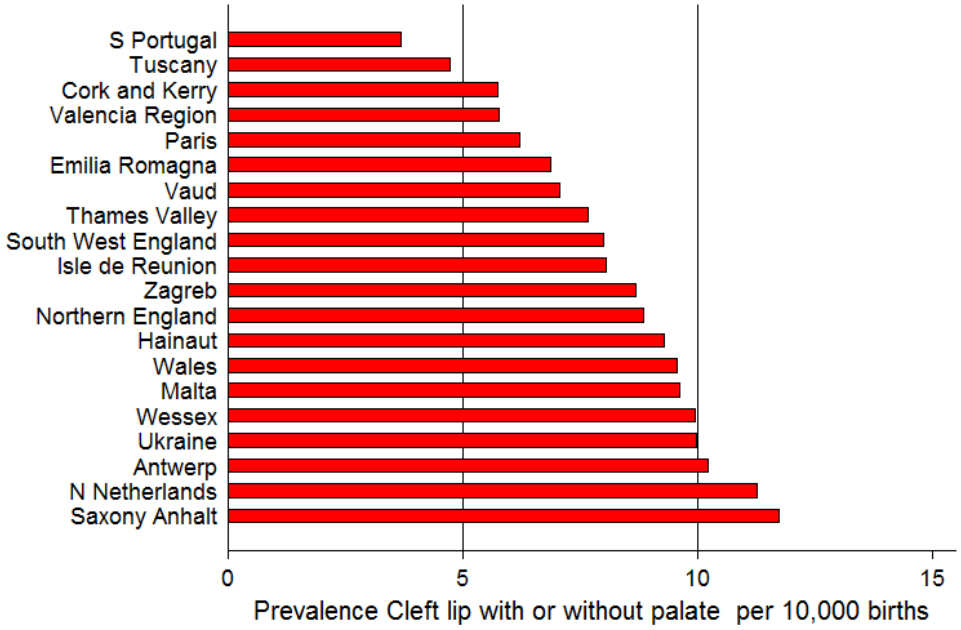

Fig. 19c: Cleft lip with or without palate - Estimated prevalence for the registries included in the pan-European trend analysis.

In conclusion, many registries show a decrease in prevalence although these individual trends were not statistically significant. The observed overall trend is likely to reflect a true decrease in prevalence of cleft lip and it will continue to be monitored.

Cleft palate

The subgroup "Cleft palate" is defined as fissure defect of the soft and/or hard palate(s) or submucous cleft and without having a cleft lip. The anomaly may be diagnosed days or weeks after birth. It is often associated with other severe anomalies that may have a high termination rate, in which case this specific anomaly might not be reported.

As in the previous report on the period 2006-2015, the prevalence of cleft palate is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -2.0% (95% CI: -3.4%; -0.5%) each year on the pan-European level (Fig. 20a).

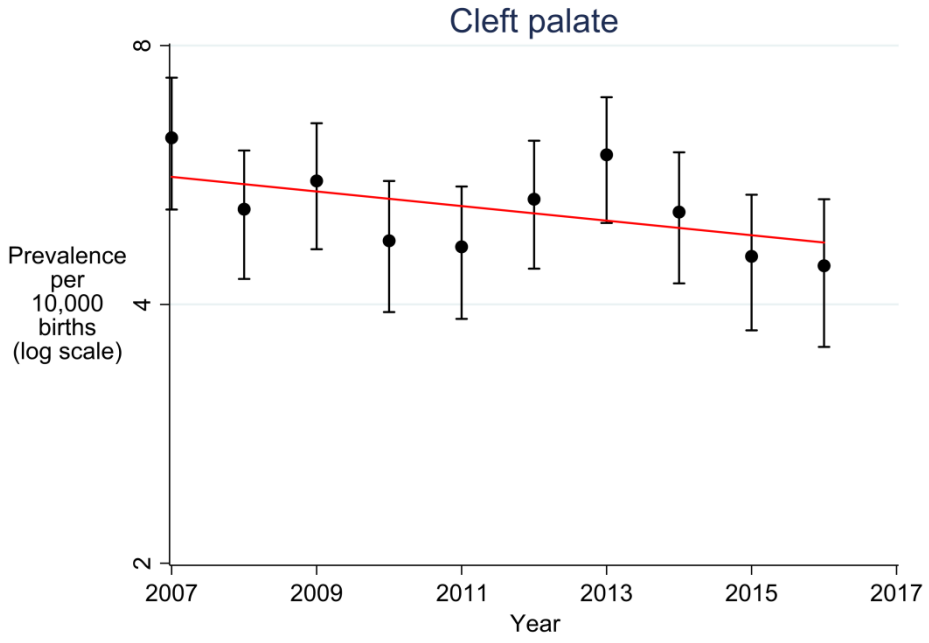

Fig. 20a: Cleft palate - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In two individual registries, the prevalence decreased significantly during the same period (Northern Netherlands and Zagreb, Fig 20b).

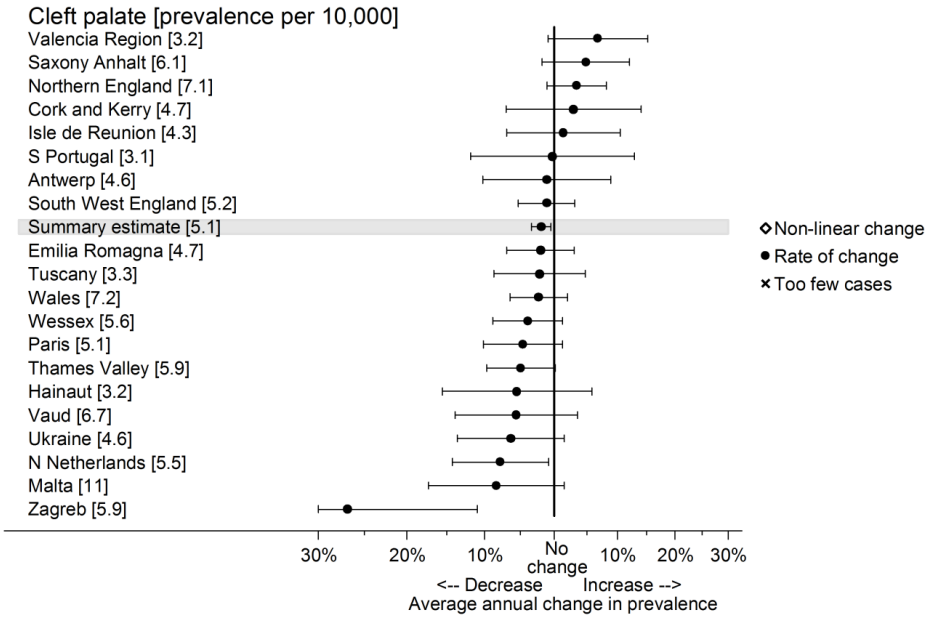

Fig. 20b: Cleft palate - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

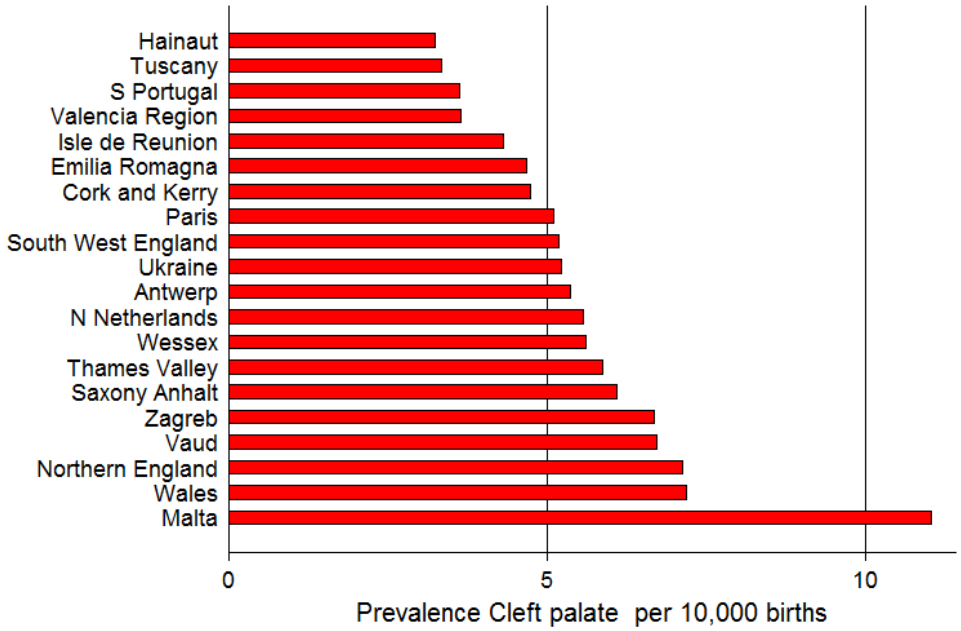

Fig. 20c: Cleft palate - Estimated prevalence for the registries included in the pan-European trend analysis.

The result may be a true decrease in prevalence of cleft palate in Europe, but the decrease may also be explained by late reporting of cases in the most recent years due

to late diagnosis of less severe cleft palate. It could also be due to a higher number of early TOPFA for other severe anomalies, when the associated cleft palate is not recognised.

In conclusion, due to the heterogeneity of the changes in prevalence in the different registries this decreasing trend should be interpreted with caution.

Gastroschisis

Gastroschisis is defined as a protrusion of the abdominal contents not covered by a membrane, through an abdominal wall defect lateral to an intact umbilical cord and. It is associated with low maternal age. From the 1990s for 20 years increases in prevalence have been observed in the UK and other areas outside Europe [17, 18, 19]. However, between 2007 and 2016 the prevalence of gastroschisis is now decreasing (as reported in the previous EUROCAT report on the period 2006-2015 [6]). Prevalence is estimated to have decreased by -2.2% (95% CI: -4.1%; -0.2%) each year on the pan-European level (Fig. 21a).

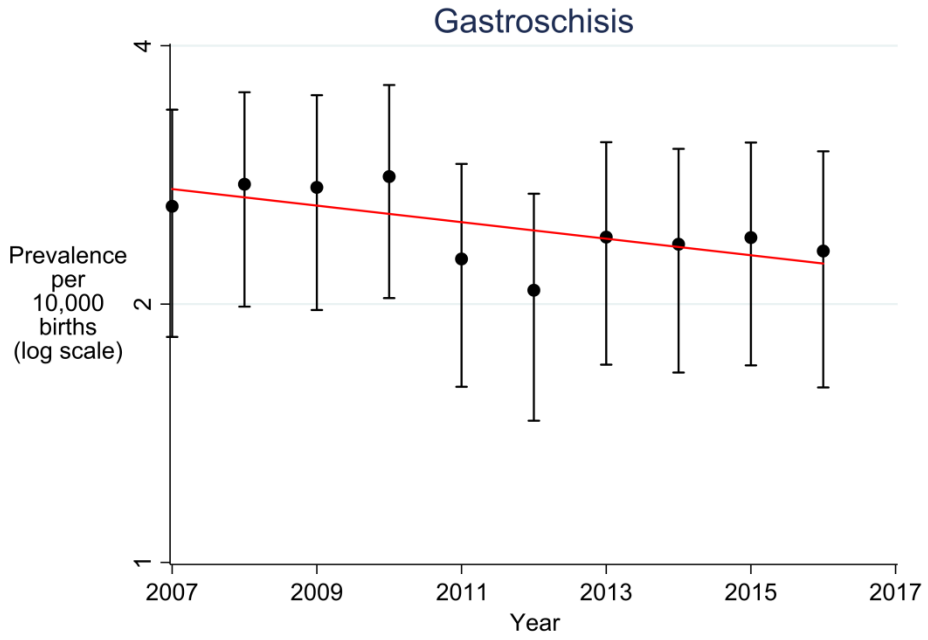

Fig. 21a: Gastroschisis - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In two individual registries, the prevalence also decreased significantly during the same period (Northern England and Wales, Fig 21b).

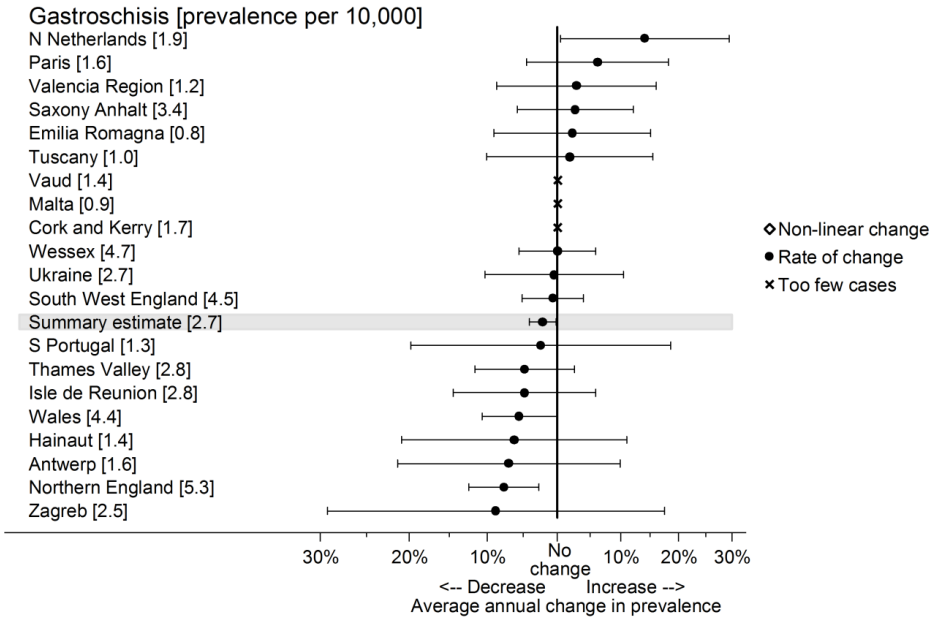

Fig. 21b: Gastroschisis - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

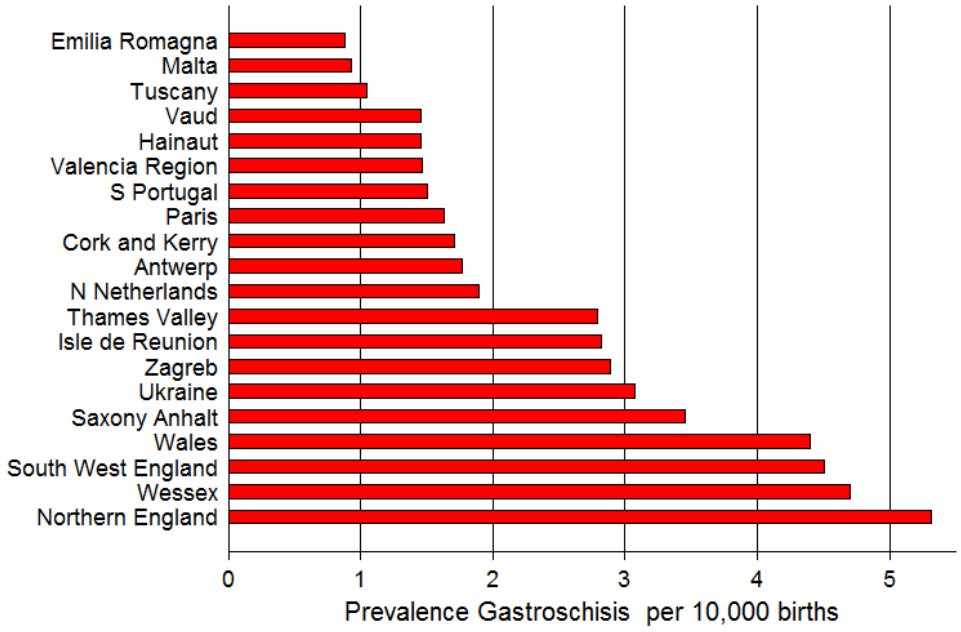

Fig. 21c: Gastroschisis - Estimated prevalence for the registries included in the pan-European trend analysis.

The analysis of maternal age showed that in every registry the odds of gastroschisis in mothers less than 20 years old are higher than in the 20-25 year age group (Table 1). This confirms published data [19], which found that low maternal age is a risk factor for this anomaly.

Table 1: Odds Ratio of mothers having a newborn with Gastroschisis by age group (reference age group '25-29' years). Registries included are those for which age distribution of the mothers in the population is available.

Centre Name	< 20	20-24	25-29	30-34	35-39	40+
Antwerp (BE)	13.7	4.8	1.0	1.4	0.5	0.0
Hainaut (BE)	3.4	1.0	1.0	0.3	0.0	2.5
Saxony Anhalt (DE)	4.5	3.0	1.0	0.4	0.2	0.0
Valencia Region (ES)	14.9	6.6	1.0	0.8	0.2	0.5
Isle de Reunion (FR)	2.5	2.0	1.0	0.2	0.3	0.0
Paris (FR)	12.5	3.1	1.0	0.6	0.2	0.2
Zagreb (HR)	6.9	1.9	1.0	0.9	0.7	3.4
Cork and Kerry (IE)	5.3	6.3	1.0	0.0	0.0	0.0
Emilia Romagna (IT)	1.8	3.4	1.0	0.4	0.5	0.3
Tuscany (IT)	12.0	3.4	1.0	0.3	0.3	0.7
Malta (MT)	0.0	2.3	1.0	1.8	0.0	0.0
N Netherlands (NL)	5.7	4.3	1.0	0.8	0.5	0.0
S Portugal (PT)	3.3	2.9	1.0	0.6	0.5	0.0
N England (UK)	4.2	2.8	1.0	0.6	0.3	0.0
South West England (UK)	7.7	3.2	1.0	0.4	0.2	0.1
Thames Valley (UK)	7.0	4.3	1.0	0.6	0.3	0.3
Wales (UK)	3.6	2.6	1.0	0.3	0.3	0.3
Wessex (UK)	8.3	3.3	1.0	0.5	0.3	0.0
Vaud (CH)	0.0	1.5	1.0	0.5	0.7	0.0
Ukraine (UA)	6.2	2.4	1.0	0.6	0.6	0.0
Overall	6.7	3.3	1.0	0.5	0.3	0.2
Non- UK registries	6.4	3.2	1.0	0.5	0.3	0.3
UK registries	12.8	6.8	2.2	1.0	0.6	0.3

Comparing the UK registries with all the other registries, we found that the odds were twice as high in the UK registries as in continental Europe for each maternal age group (Table 2).

Table 2: Odds Ratio of mothers having a newborn with Gastroschisis by age group for UK and non UK registries (reference age group '25-29' years in non UK registries). Registries included are those for which age distribution of the mothers in the population is available.

	< 20	20-24	25-29	30-34	35-39	40+
Non- UK registries	6.4	3.2	1.0	0.5	0.3	0.3
UK registries	12.8	6.8	2.2	1.0	0.6	0.3

The proportion of mothers having children before 20 years of age has decreased in the UK and other European countries from 2007 to 2016. The decrease in gastroschisis observed in the UK registries (Fig.21d) may be attributed to the decline in the proportion of pregnancies in this maternal age group (<20 years old).

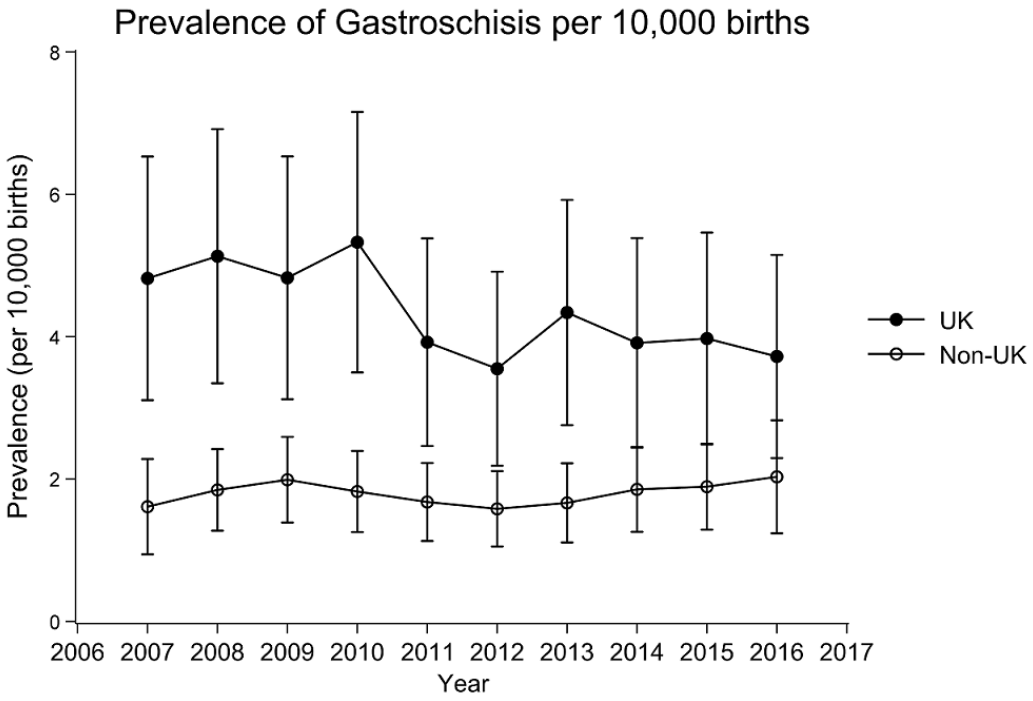

Fig. 21d: Gastroschisis - Prevalence and 95% CIs for the years included in the pan-European trend analysis grouped in UK and Non-UK registries.

In conclusion, the decreasing pan-European trend seems to be explained by less teenage pregnancies in the UK and not by a decrease in the age specific prevalence of gastroschisis.

Syndactyly

Syndactyly is defined as partial or total webbing between two or more digits, with the exclusion of syndactyly between 2nd and 3rd toes.

As in the previous report on the period 2006-2015, the prevalence of syndactyly is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -2.5% (95% CI: -4.3%; -0.8%) each year on the pan-European level (Fig. 22a).

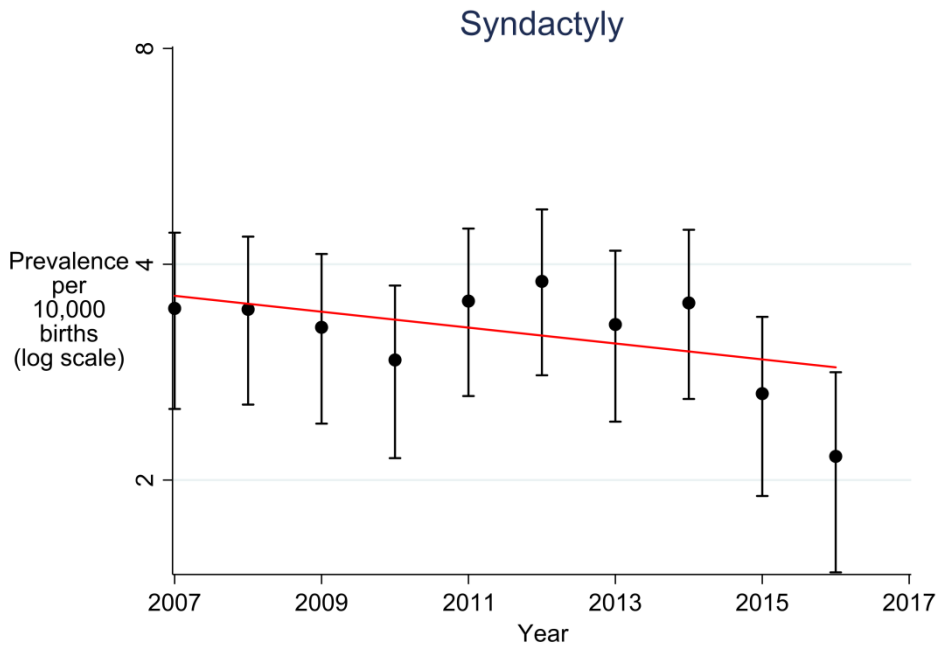

Fig. 22a: Syndactyly - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In two individual registries, the prevalence also decreased significantly during the same period (Hainaut and Wales, Fig 22b).

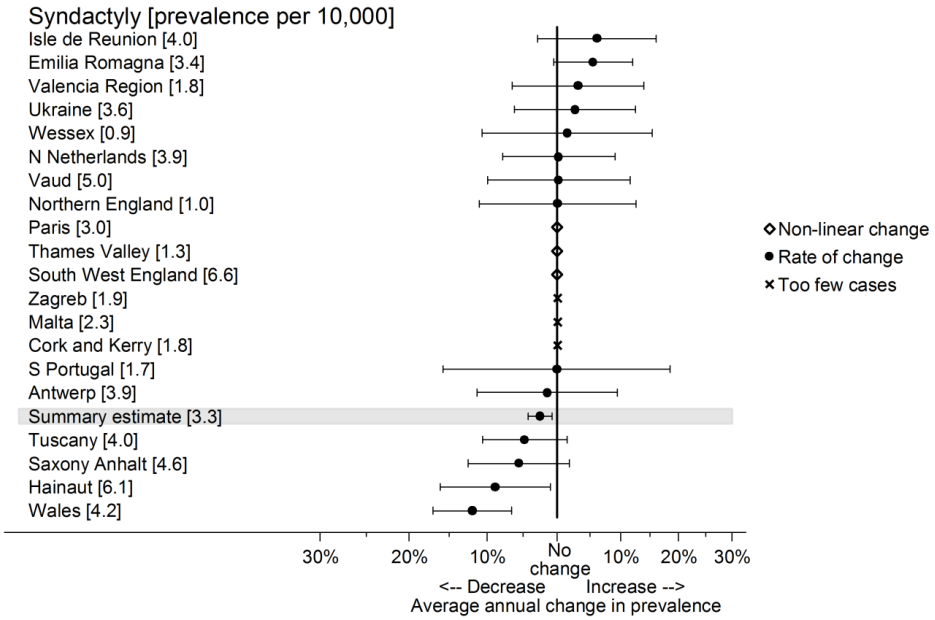

Fig. 22b: Syndactyly - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

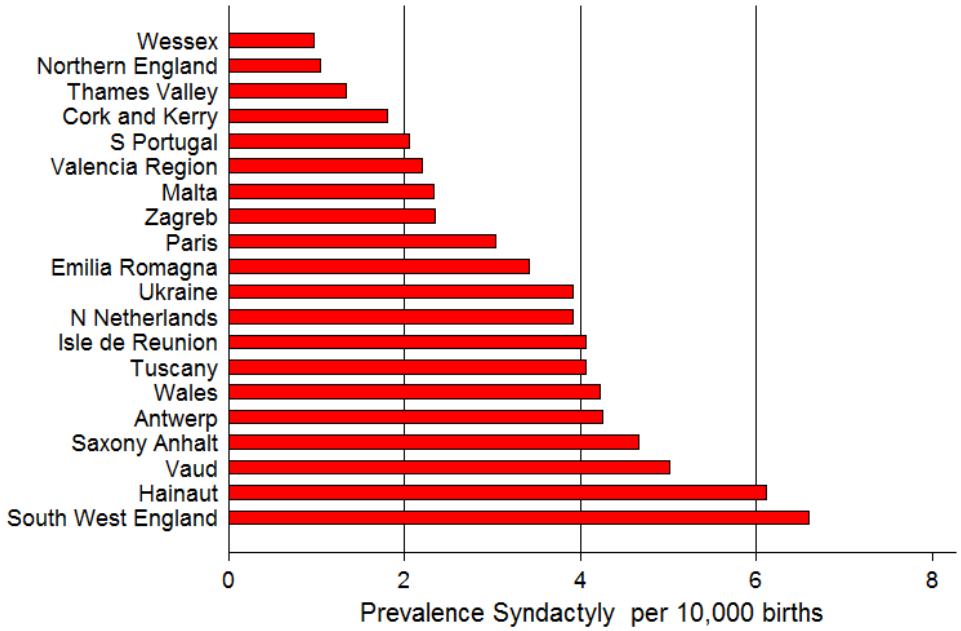

Fig. 22c: Syndactyly - Estimated prevalence for the registries included in the pan-European trend analysis.

In conclusion, the decreasing trend is probably due to reduced over-reporting of minor anomaly cases in two registries with previously high prevalence (Wales and Hainaut).

Vascular disruption anomalies

This subgroup includes all anomalies where the aetiology is thought to be vascular disruption. Anomalies included are small intestinal atresia, gastroschisis, limb reduction defects, amniotic bands, hydranencephaly and Moebius syndrome.

As in the previous report on the period 2006-2015 [6], the prevalence of vascular disruption anomalies is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -2.2% (95% CI: -3.4%; -0.9%) each year on the pan-European level (Fig. 23a).

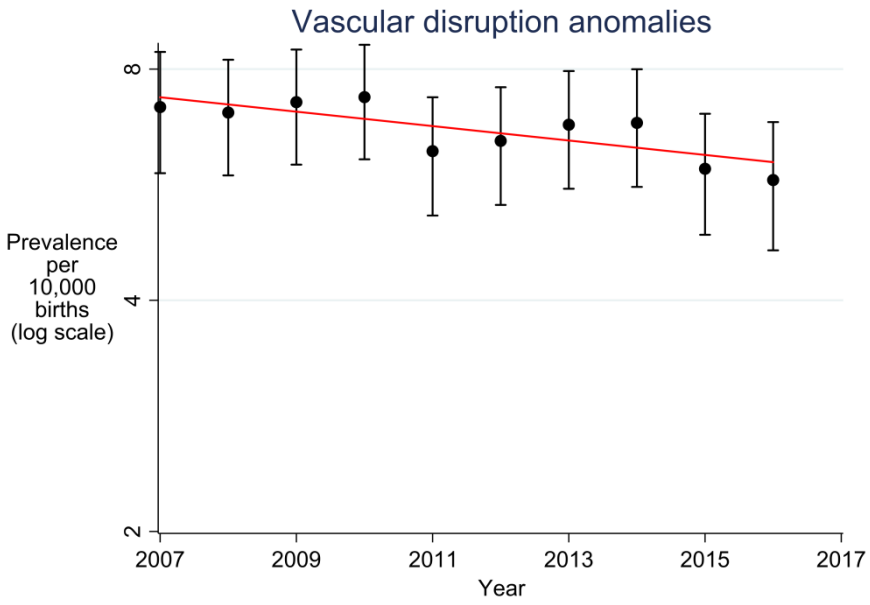

Fig. 23a: Vascular disruption anomalies - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In three individual registries, the prevalence also decreased significantly during the same period (Northern England, Thames Valley and Vaud, Fig 23b).

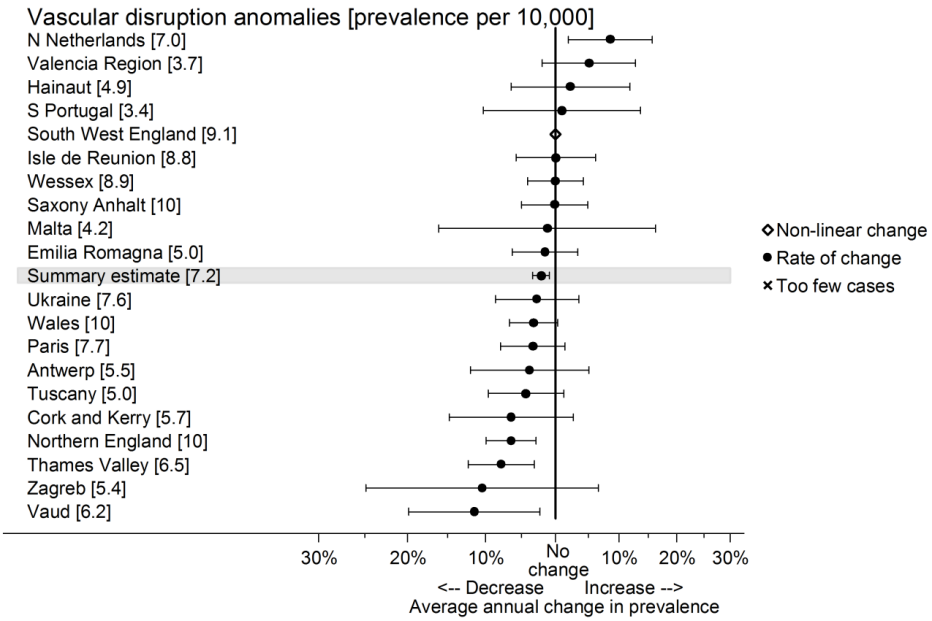

Fig. 23b: Vascular disruption anomalies - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

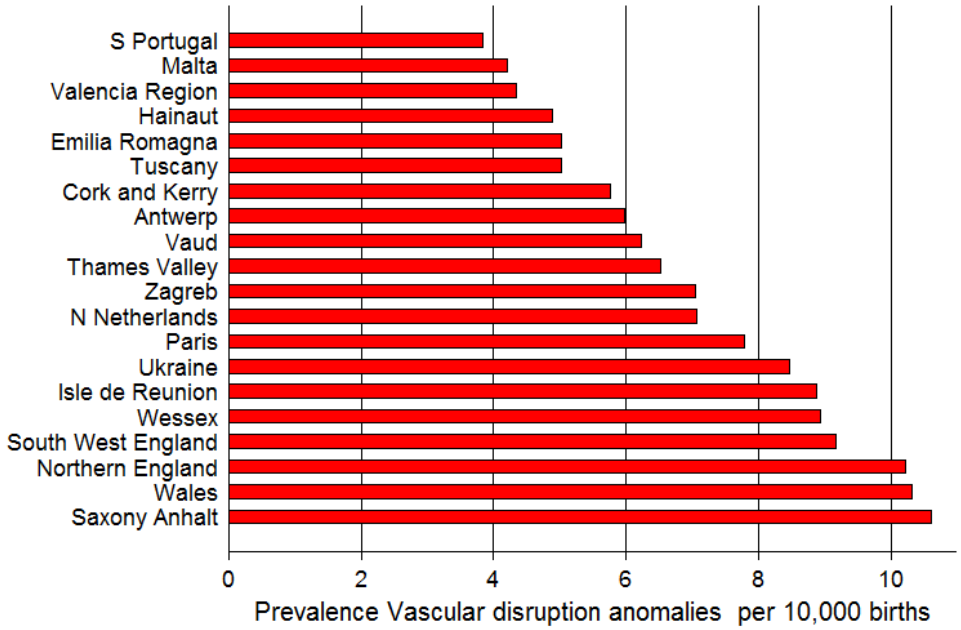

Fig. 23c: Vascular disruption anomalies - Estimated prevalence for the registries included in the pan-European trend analysis.

In conclusion, the decreasing trend in gastroschisis described above might contribute to the observed decrease in prevalence of the vascular disruption anomalies subgroup. A study is planned to investigate risk factors and trends.

Down syndrome (age adjusted)

Down syndrome is due to an additional chromosome 21. The risk of a Down syndrome pregnancy is highly associated with increasing maternal age. Therefore, any increasing or decreasing trends should be investigated only once maternal age is adjusted for.

As in the previous report on the period 2006-2015 [6], the prevalence of the Down syndrome is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -1.5% (95% CI: -2.3%; -0.6%) each year on the pan-European level (Fig. 27a). The analysis was performed for the registries that submitted ten years of data and denominators for maternal age groups.

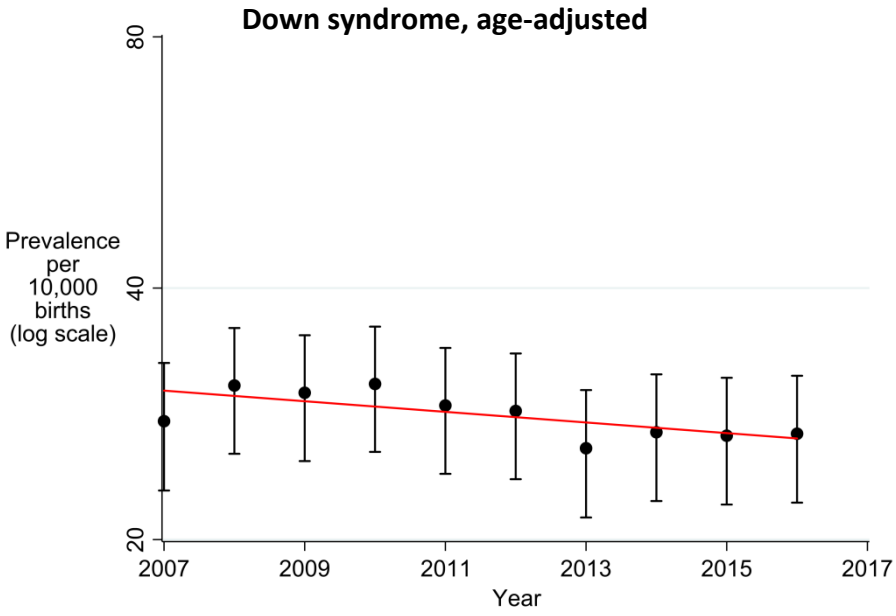

Fig. 27a: Down syndrome – age-adjusted. Prevalence and 95% CIs for the years included in the pan-European trend analysis.

In two individual registries, the prevalence also decreased significantly during the same period (Paris and Vaud, Fig 27b).

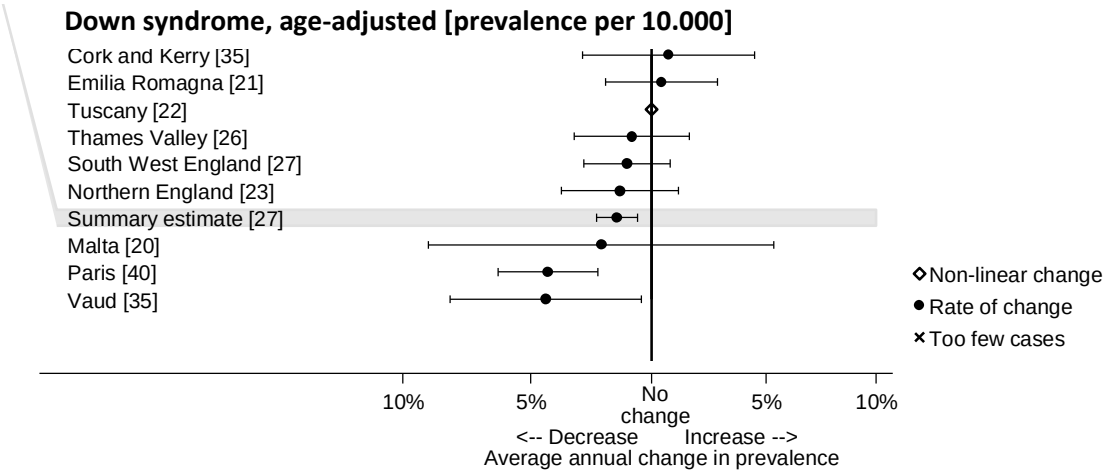

Fig. 27b: Down syndrome - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

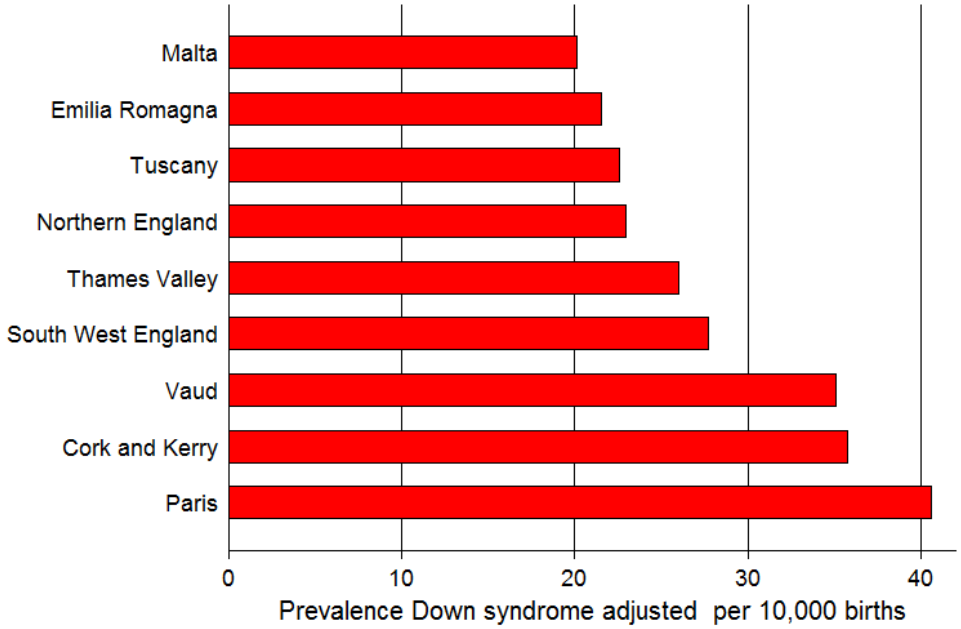

Fig. 27c: Down syndrome - Estimated prevalence adjusted for maternal age for the registries included in the pan-European trend analysis.

There is evidence that the risk of a Down syndrome pregnancy is predicted by a mother's age and that the age-specific risks are the same in all populations [20]. Differences in the uptake and timing of prenatal screening and diagnosis may cause apparent differences in the prevalence of Down syndrome in different populations.

In conclusion, the decreasing trend does not indicate a real decrease in the prevalence of age-adjusted Down syndrome.

5 Clusters

5.1 Overview

EUROCAT defines a cluster as an aggregation of cases of congenital anomaly in time and/or space which appears to be unusual. This definition includes space as defined by a common activity such as a place of work/ education/ recreation etc. and not just space as defined by residence. Currently, the statistical monitoring at the Central Registry detects temporal clusters within each registry area while the space investigation is conducted by the registry at a local level.

Currently, the JRC-EUROCAT Central Registry performs annual cluster analysis using the most recent five years of data.

Cluster detection is based on a moving window test. It detects whether the given number of cases has occurred in a shorter time than would be expected by chance. A minimum of seven cases over the study period of interest is needed to run the analysis. Each registry and anomaly subgroup is tested independently.

Since the exposure during early pregnancy, i.e. when organogenesis occurs, is pertinent, it is preferable to use the estimated date of conception rather than the date of birth. Cluster detection uses date of conception where gestational age is recorded for more than 90% of cases (for any one anomaly subgroup and registry) allowing its estimation.

Where gestational age is missing, it is estimated on the basis of the average gestational age in the registry, by year, anomaly subgroup, and outcome of pregnancy. Gestational age is not estimated if it is missing for more than 10% of cases for the registry and anomaly subgroup, in which case cluster detection is based on date of birth.

Central Registry produces a report of all clusters occurring in each registry. Every registry then receives a report with its clusters for investigation. In the report, the clusters are visually identified over the time period. If the investigation of clusters identifies data errors (e.g. incorrect diagnoses, incorrect dates of birth) these errors should be corrected and updated data included in the next data transmission to the Central Registry.

5.2 Cluster analysis 2012-2016

Eleven registries satisfied the criteria to be included in the cluster analysis reported here (see Appendix A). A total of 17 clusters were identified in eight registries (see Table 3 on page 74). The English registries were not considered, as explained in Section 3.2 of this report.

Reports on the investigation into the clusters were received from all registries. The registries carried out investigations into 17 clusters identified by the monitoring method described above. The conclusions from clusters investigation are detailed in the following section and summarised in Table 3.

For the following three clusters the local registries explained that a further period of surveillance would be needed to assess the cluster's significance: Encephalocele (Brittany), Ano-rectal atresia and stenosis (Paris) and Severe CHD (Vaud).

5.3 Investigations into specific clusters by the registries

Encephalocele

The cluster was detected in Brittany. The five cases are not clustered near each other within the region. They come from five different hospitals, located in four remote cities in four different departments. Among the five cases, no common factor was identified from the registry database and no local context can explain the cluster. Hence, it requires a further period of surveillance as it is not a continuing cluster so far.

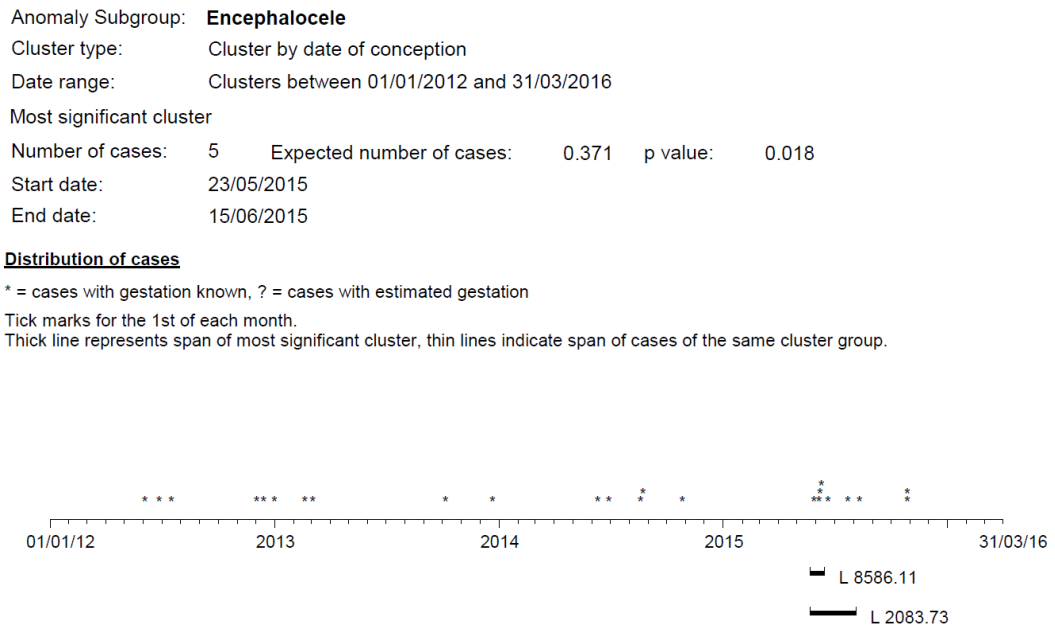

Fig. 28: Cluster of Encephalocele detected in Brittany.

Microcephaly

The cluster was detected in Emilia Romagna, Italy. The investigation showed that the cluster could be explained by incorrect definition of microcephaly used to report the cases.

Anomaly Subgroup: **Microcephaly**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 8 Expected number of cases: 0.799 p value: <0.001
Start date: 11/06/2014
End date: 11/07/2014

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation

Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

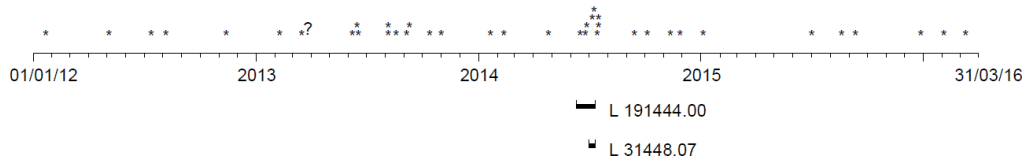

Fig. 29: Cluster of Microcephaly detected in Emilia Romagna.

Severe CHD

The cluster was detected in the registry of Vaud, Switzerland. The registry confirmed the cases but there is no clear explanation of the cluster and it requires a further period of surveillance. There is not significant change in prevalence in the 5-year and 10-years trend but the two most recent years before the cluster had a lower number of cases.

Anomaly Subgroup: **Severe CHD §**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 18 Expected number of cases: 5.960 p value: 0.049
Start date: 05/06/2015
End date: 07/10/2015

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation

Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

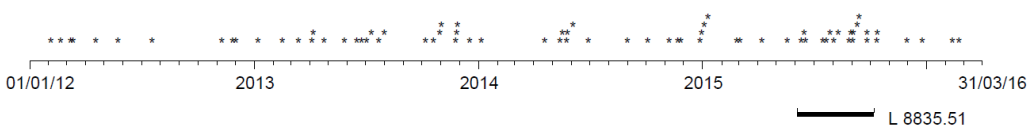

Fig. 30: Cluster of Severe CHD detected in Vaud.

Ventricular septal defect

The cluster was detected in Emilia Romagna and Tuscany, Italy. As regards the cluster observed for the register of Emilia-Romagna, it occurred on solely one conception day (see figure below). However, the date of conception is calculated based on completed weeks of gestation and is not accurate to one day, so this is not considered a cluster.

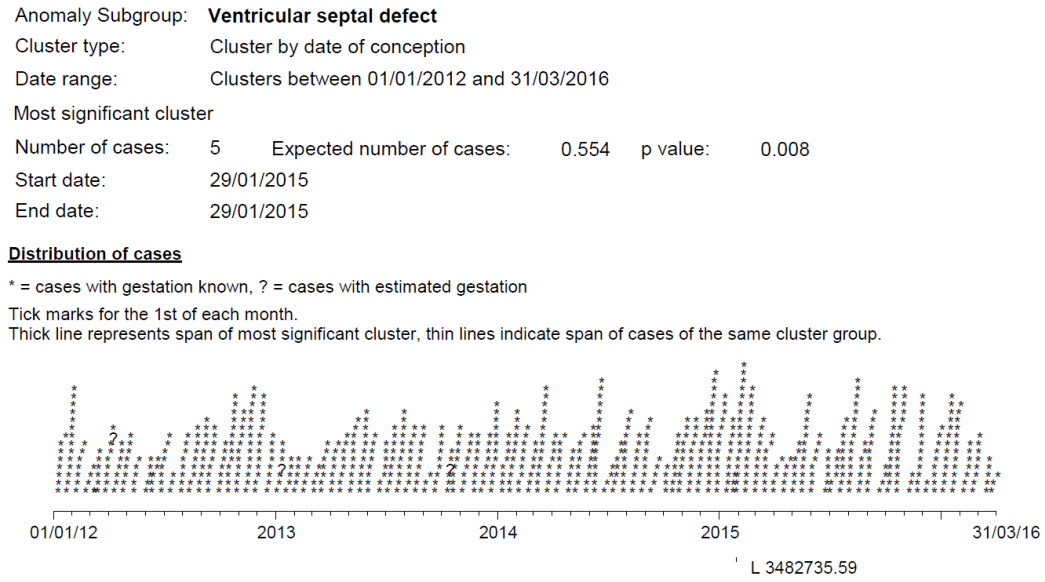

Fig. 31: Cluster of VSD detected in Emilia Romagna.

Similarly, in the cluster observed in Tuscany all cases occurred on one conception day. Hence, these five cases are not considered a cluster (see figure below).

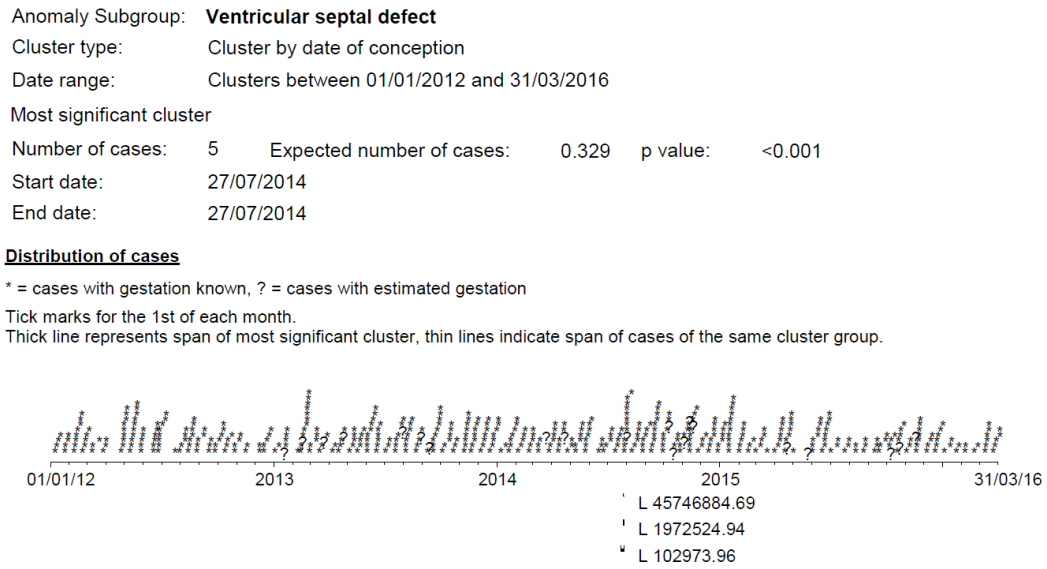

Fig. 32: Cluster of VSD detected in Tuscany.

Tricuspid atresia and stenosis

The cluster was detected in Emilia Romagna, Italy. The registry confirmed the cases, but it considers that these five cases of a very rare anomaly are not of public health concern (see Fig. 33).

Anomaly Subgroup: **Tricuspid atresia and stenosis**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 5 Expected number of cases: 0.805 p value: 0.050
Start date: 22/06/2015
End date: 24/10/2015

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

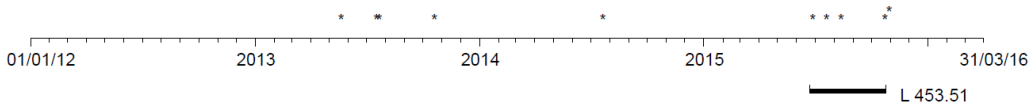

Fig. 33: Cluster of Tricuspid atresia and stenosis detected in Emilia Romagna.

Atresia or stenosis of other parts of small intestine

The cluster was detected in Wales, United Kingdom. The registry observes that among the six cases in the cluster, two were secondary to gastroschisis, so there were only four primary cases of atresia or stenosis of parts of small intestine, and thus do not meet the criteria for a cluster.

Anomaly Subgroup: **Atresia or stenosis of other parts of small intestine**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 6 Expected number of cases: 0.907 p value: 0.042
Start date: 09/12/2015
End date: 05/03/2016

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

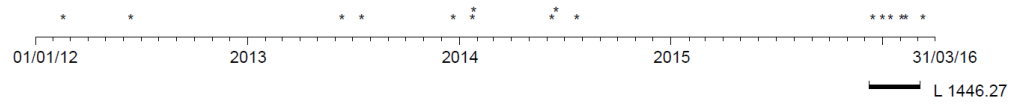

Fig. 34: Cluster of Atresia or stenosis of other parts of small intestine detected in Wales.

Ano-rectal atresia and stenosis

The cluster was detected in the registry of Paris, France. The registry indicates that it cannot explain the cluster and suggests that the cluster might be part of an increasing trend in anorectal atresia/stenosis observed in 2015 and which disappeared in 2016. Hence, the registry will continue to monitor this anomaly.

Anomaly Subgroup: **Ano-rectal atresia and stenosis**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 10 Expected number of cases: 2.018 p value: 0.015
Start date: 16/10/2014
End date: 08/02/2015

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

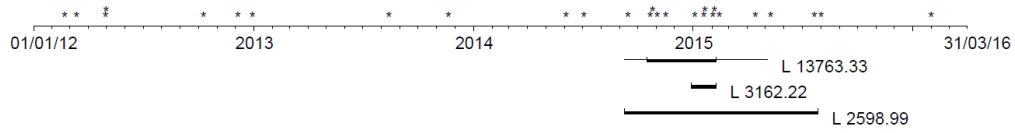

Fig. 35: Cluster of Ano-rectal atresia and stenosis detected in Paris.

Diaphragmatic hernia

The cluster was detected in Cork and Kerry, Ireland. The registry confirmed the six cases and explained the cluster by the low number of cases per annum resulting in large annual fluctuations and apparent clustering.

Anomaly Subgroup: **Diaphragmatic hernia**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 6 Expected number of cases: 1.009 p value: 0.013
Start date: 11/12/2013
End date: 02/06/2014

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

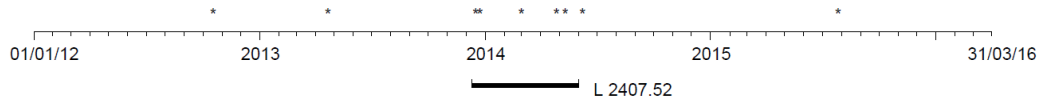

Fig. 36: Cluster of Diaphragmatic hernia detected in Cork and Kerry

Gastroschisis

The cluster was detected in Tuscany, Italy. After investigation the registry was reassured that there are no local concerns about environmental exposures, the prevalence of the anomaly observed in Tuscany is lower than the EUROCAT average and it is the first time that a cluster has been detected, indicates that no immediate action was necessary.

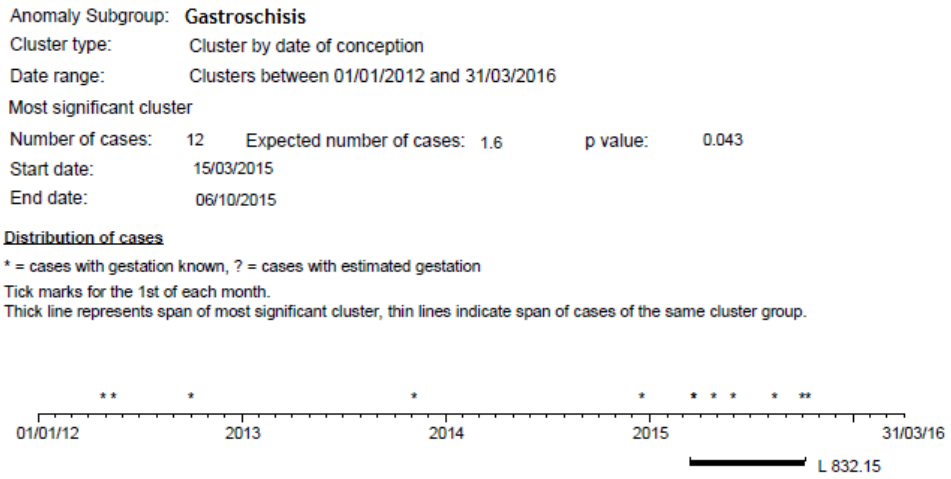

Fig. 37: Cluster of Gastroschisis detected in Tuscany

Omphalocele

The cluster was detected in Brittany, France. After investigation, one of the cases happened to be a confirmed genetic syndrome. Therefore, this case was excluded from the statistical monitoring and the cluster was no longer significant.

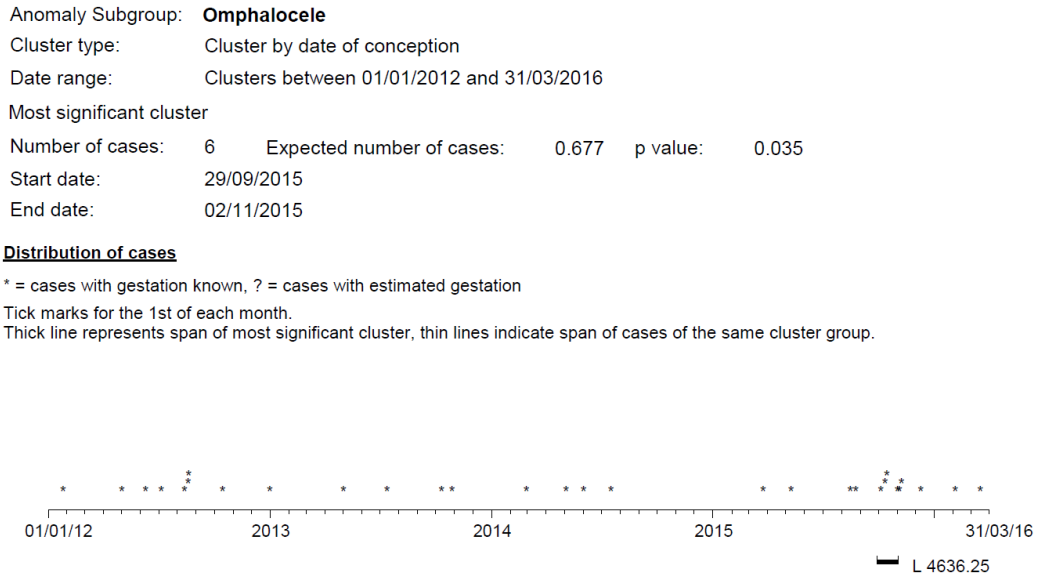

Fig. 38: Cluster of Omphalocele detected in Brittany.

Bladder exstrophy and/or epispadia

The cluster was detected in Wales, UK. According to the registry this cluster of five cases can be explained: When this cluster is broken down, there is one complex case, two cases of isolated bladder exstrophy and two cases of epispadia. The register notes that there is no spatial relationship and that bladder exstrophy is a very different anomaly to epispadias. Therefore, the registry plans no further action.

Anomaly Subgroup: **Bladder exstrophy and/or epispadia**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 5 Expected number of cases: 0.329 p value: 0.008
Start date: 25/12/2015
End date: 23/01/2016

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

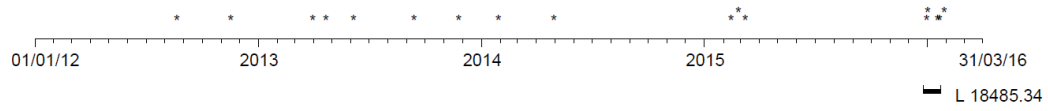

Fig. 39: Cluster of Bladder exstrophy and/or epispadia detected in Wales.

Posterior urethral valve and/or prune belly

The cluster was detected in the registry of Tuscany, Italy. The registry confirmed the cases. The local cluster investigation gave no explanation for the cluster. The prevalence of this anomaly was very low in the years before and the year after the cluster. All cases reported in the 5-year period in this subgroup had isolated posterior urethral valve anomaly and no non-renal anomalies. No immediate action seems necessary.

Anomaly Subgroup: **Posterior urethral valve and/or prune belly**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 5 Expected number of cases: 0.767 p value: 0.011
Start date: 25/11/2013
End date: 13/05/2014

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

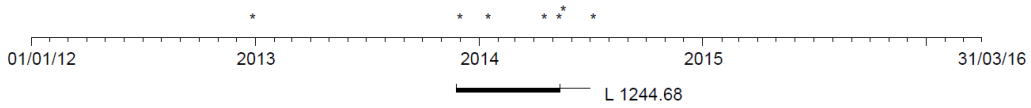

Fig. 40: Cluster of Posterior urethral valve and/or prune belly detected in Tuscany.

Hypospadias

The cluster was detected in the registry of Tuscany, Italy. The registry confirmed the cases. The cluster occurred on solely four conception days (Fig. 41). However, the date of conception is calculated based on completed weeks of gestation and is not accurate to one day, so this is not considered a cluster. No immediate action seems necessary.

Anomaly Subgroup: **Hypospadias**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 6 Expected number of cases: 0.466 p value: 0.019
Start date: 26/11/2014
End date: 29/11/2014

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

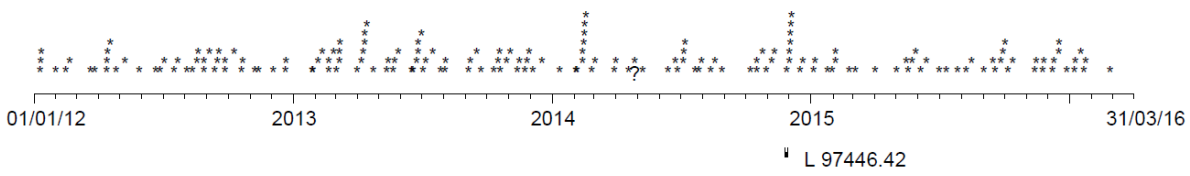

Fig. 41: Cluster of Hypospadias detected in Tuscany.

Hip dislocation and/or dysplasia

The cluster was detected in Cork and Kerry, Ireland. The registry explained that changes in ascertainment occurred over time due to the appointment of new staff and more active case finding. In addition, the most recent year is not yet fully reported to the Central Registry.

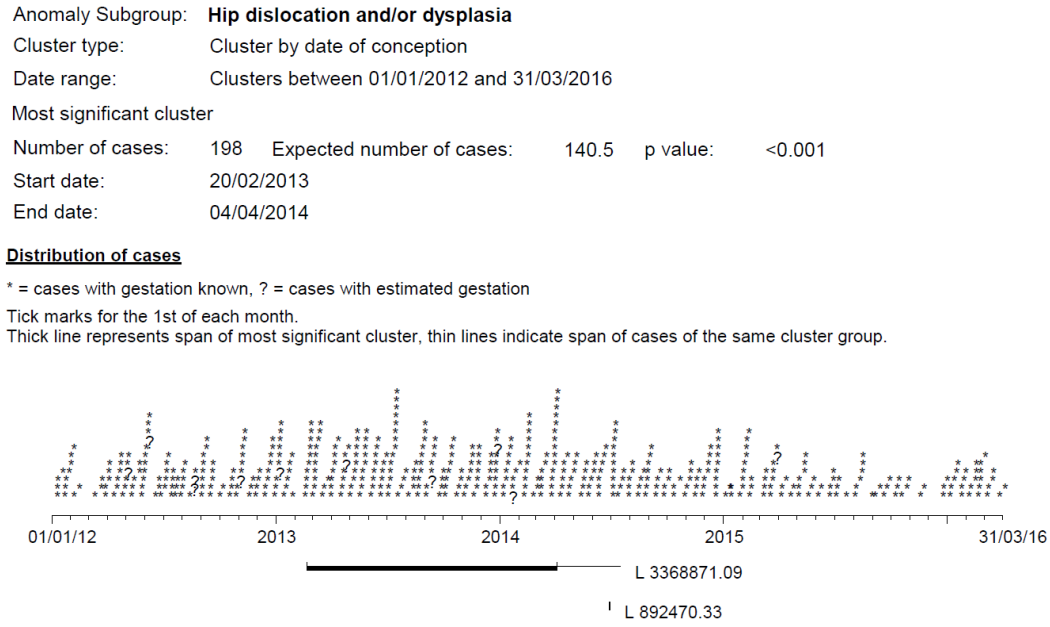

Fig. 42: Cluster of Hip dislocation and/or dysplasia detected in Cork and Kerry.

Turner syndrome

The cluster was detected in the registry of Northern Netherlands, Netherlands. The increase in cases with Turner syndrome could be due to increased prenatal diagnosis of Turner syndrome in more recent years. The registry indicates that no investigation of exposure was carried out as the aetiology of Turner is known (chromosomal). No action is necessary.

Anomaly Subgroup: **Turner syndrome**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 14 Expected number of cases: 5.864 p value: 0.047
Start date: 22/10/2013
End date: 12/02/2015

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation

Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

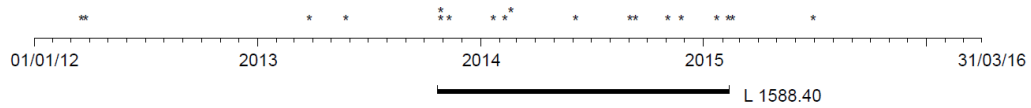

Fig. 43: Cluster of Turner syndrome detected in Northern Netherlands.

5.4 Clusters not considered for local investigation

Anophthalmos / microphthalmos

The cluster was detected in Wales, UK. The EUROCAT Management Committee decided not to request a report from the registry, since the cluster was investigated last year and did not continue. No action required.

Anomaly Subgroup: **Anophthalmos/micropthalmos**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2012 and 31/03/2016
Most significant cluster
Number of cases: 5 Expected number of cases: 0.465 p value: 0.029
Start date: 19/01/2015
End date: 25/02/2015

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation

Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

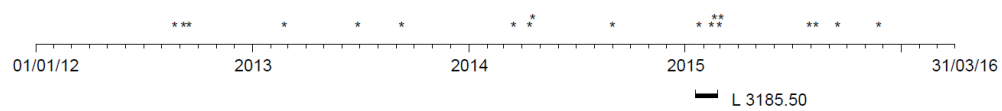

Fig. 44: Cluster of Anophthalmos / microphthalmos detected in Wales.

Table 3: Details of the 17 clusters detected in the 2012-2016 monitoring and outcomes of local registry preliminary investigations.

Anomaly	Registry	Classification of Explanations	No of cases in cluster	Expected cases	Valid cases	Length of cluster (days)	p-value
Encephalocele	Brittany (FR)	Excess of cases confirmed, further surveillance needed	5	0.37	24	23	0.018
Microcephaly	Emilia Romagna (IT)	Data reporting found to explain cluster	8	0.8	40	30	<0.001
Anophthalmos/micropthalmos	Wales (GB)	Cluster detected and discussed in last year's report: the cluster is too small to warrant further investigation.	5	0.47	19	37	0.029
Severe CHD	Vaud (CH)	Excess of cases confirmed and explained by better ascertainment	18	5.96	74	124	0.049
Ventricular septal defect	Emilia Romagna (IT)	Not considered to be a cluster	5	0.55	860	0	0.008
	Tuscany (IT)	Excess of cases confirmed but no immediate action needed	5	0.33	511	0	<0.001
Tricuspid atresia and stenosis	Emilia Romagna (IT)	Excess of cases confirmed but considered a random cluster	5	0.81	10	124	0.05
Atresia or stenosis of other parts of small intestine	Wales (GB)	Not considered to be a cluster	6	0.91	16	87	0.042
Ano-rectal atresia and stenosis	Paris (FR)	Excess of cases confirmed, further surveillance time needed	10	2.02	27	115	0.015
Diaphragmatic hernia	Cork and Kerry (IE)	Not considered to be a cluster	6	1.01	9	173	0.013
Gastroschisis	Tuscany (IT)	Excess of cases confirmed, further surveillance needed	7	1.6	12	206	0.043
Omphalocele	Brittany (FR)	Excess of cases and cluster not confirmed	6	0.68	30	34	0.035
Bladder exstrophy and/or epispadia	Wales (GB)	Excess of cases confirmed but considered a random cluster	5	0.33	17	29	0.008
Posterior urethral valve and/or prune belly	Tuscany (IT)	Excess of cases confirmed but considered a random cluster	5	0.77	7	169	0.011
Hypospadias	Tuscany (IT)	Excess of cases confirmed but considered a random cluster	6	0.47	181	3	0.019
Hip dislocation and/or dysplasia	Cork and Kerry (IE)	Excess of cases confirmed, cluster explained by changes in ascertainment over time	198	140.46	533	408	<0.001
Turner syndrome	N Netherlands (NL)	Not investigated	14	5.86	19	478	0.047

6 Limb reduction defects in Europe

Due to the concerns in France on geographical small-area clusters of upper limb reduction defects, a chapter focusing on these anomalies is included in this year's report.

In the analysis performed at the central level, no clusters in time over the period 2007-2016 were detected. There were no significant increasing or decreasing pan-European trends in the prevalence of limb reduction defects over the last 10 years. (Fig. 45)

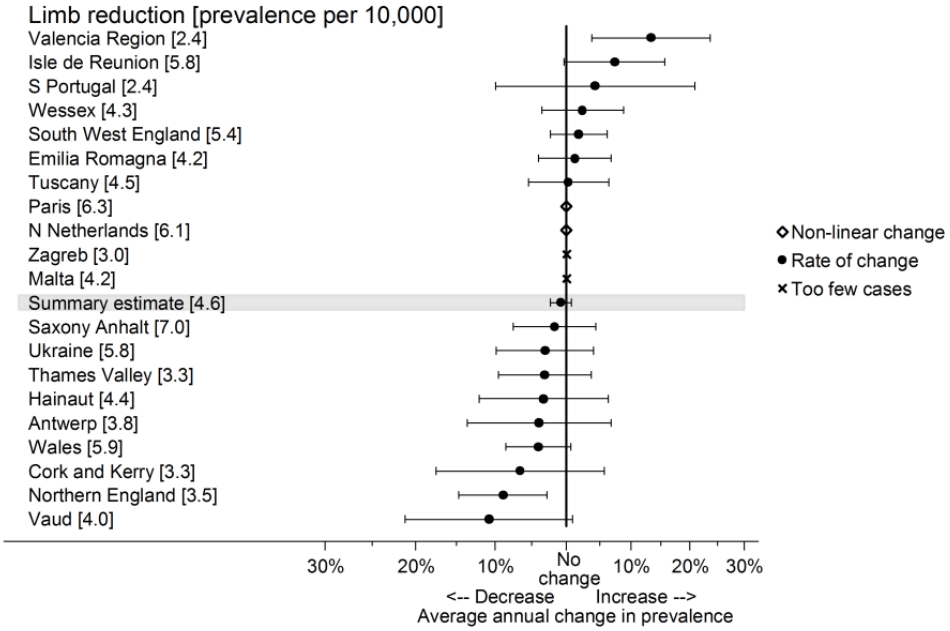

Fig. 45: Limb reduction defects – Estimated annual percentage change in the prevalence and 95% Cis for the registries included in the pan-European trend analysis.

There is only one increasing trend in the 20 registries analysed but the total prevalence in this registry (2.4 per 10,000 births) was half of the summary pan-European estimate (4.6 per 10,000 births) and very low if compared with the prevalence generally reported from the other registries, so this increase is not of concern and is probably due to improved ascertainment/better reporting of cases locally.

Table 4 provides the distribution of the type of limb reduction defect reported per year for the 2,107 cases included in the analysis.

Table 4: Distribution of the 2.107 cases included in the 10-year pan-European trend analysis, by type of limb reduction defect and by year.

All registries	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	All years
Total no. of cases	**188**	**224**	**210**	**234**	**203**	**251**	**244**	**233**	**182**	**138**	**2107**
% of cases with only upper limb reduction defect	64%	58%	57%	54%	58%	53%	55%	56%	53%	54%	56%
% of cases with only lower limb reduction defect	22%	26%	29%	30%	30%	30%	29%	33%	33%	32%	29%
% of cases with both upper and lower limb reduction defect	11%	14%	12%	12%	11%	13%	11%	8%	12%	12%	12%
% of cases with limb reduction defect (location unknown)	3%	2%	2%	3%	1%	4%	5%	3%	2%	3%	3%
Total prevalence (per 10.000 births)	5.26	4.46	4.22	4.64	4.11	5.13	5.24	5.03	3.93	4.04	4.60

Focusing on the upper limb defects only, Table 5 reports the number of cases for every type of limb reduction defect in the whole 10-years period and in two 5-year periods. The distribution of cases in the two 5-years periods was tested using the Chi-square test with 8 degrees of freedom (Q719 class not included) and is not statistically significant at a 0.05% level (Chi-square = 11.1, p=0.197). This indicates that there is no evidence of a change in the type of limb reduction defect reported in the two time periods.

Table 5: Number of cases reported by the EUROCAT registries* for every ICD10 code related to upper limb reduction defects reported for the 10-years period (2007-2016), and percentage distribution of the cases in 5-year periods (2007-2011 and 2012-2016).

ICD10 code in Chapter Q71: Reduction defects of upper limb	No. of cases 2007-2016	% of total Q71* cases	% of total Q71* cases 2007-2011	% of total Q71* cases 2012 -2016
Q710: Congenital complete absence of upper limb(s)	32	1.9%	2.4%	1.3%
Q711: Congenital absence of upper arm and forearm with hand present	23	1.3%	1.4%	1.3%
Q712: Congenital absence of both forearm and hand	108	6.3%	6.1%	6.6%
Q713: Congenital absence of hand and finger(s)	723	42.3%	43.2%	41.4%
Q714: Longitudinal reduction defect of radius	244	14.3%	14.0%	14.6%
Q715: Longitudinal reduction defect of ulna	89	5.2%	5.5%	4.9%
Q716: Lobster-claw hand	89	5.2%	4.6%	5.8%
Q718: Other reduction defects of upper limb(s)	344	20.1%	20.6%	19.7%
Q719: Reduction defect of upper limb, unspecified	57	3.3%	2.3%	4.5%

Note: one case may have more than one Q-code.

* Antwerp, Hainaut-Namur (BE), Isle de Reunion, Paris (FR), Emilia Romagna, Tuscany (IT), Northern Netherlands (NL), Vaud (CH), Zagreb (HR), Malta (MT), South Portugal (PT), Saxony Anhalt (DE), Cork & Kerry (IRL), Northern England, South West England, Thames Valley, Wales, Wessex (UK), Ukraine (UA), Valencia Region (ES).

In conclusion, there were no clusters in the 11 registries included in the analysis, no pan-European trends in the 10 year period 2007-2016 and no changes in the type of anomalies in the upper limb reduction defects during these 10 years.

Appendix A: EUROCAT full member registries inclusion list

	Pan-Europe trends		Cluster monitoring	
	Included in analysis	**Investigation report**	**Included in analysis**	**Investigation report**
Austria, Styria	No, substantial decrease in number of cases >1 year			
Belgium, Antwerp	✓	✓	No data for 2016	
Belgium, Hainaut	✓	X	✓	—
Croatia, Zagreb	✓	X	No data for 2016	
Denmark, Odense	No, as collaboration agreement not signed			
France, Auvergne	No, as data transmission >1 year late			
France, Brittany	No, as data for 6 years only		✓	✓
France, French West Indies	No, substantial decrease in number of cases >1 year			
France, Paris	✓	✓	✓	✓
France, Reunion	✓	✓	✓	—
Germany, Mainz	No, as data transmission >1 year late			
Germany, Saxony Anhalt	✓	✓	✓	—
Hungary	No, as collaboration agreement not signed			
Ireland, Cork & Kerry	✓	X	✓	✓
Ireland, Dublin	No, as data transmission >1 year late			
Ireland, South East	No, as data transmission >1 year late			
Italy, Emilia Romagna	✓	✓	✓	✓
Italy, Tuscany	✓	—	✓	✓
Malta	✓	✓	✓	—
Netherlands, Northern	✓	✓	✓	✓
Norway	No, major changes in the data collection process. Data under evaluation			
Poland, Wielkopolska	No, substantial decrease in number of cases >1 year			
Portugal, South	✓	X	No data for 2016	
Spain, Basque Country	No, as data transmission >1 year late			
Spain, Valencia Region	✓	X	No data for 2016	
Switzerland, Vaud	✓	✓	✓	✓
Ukraine	✓	✓	No data for 2016	
UK, E Midlands & S Yorkshire	No, data missing for >1 year			
UK, Northern England	✓	✓	Analysis not done (see chapter 3.2)	
UK, South West England	✓	✓	Analysis not done (see chapter 3.2)	
UK, Thames Valley	✓	✓	Analysis not done (see chapter 3.2)	
UK, Wales	✓	✓	Analysis not done (see chapter 3.2)	
UK, Wessex	✓	✓	Analysis not done (see chapter 3.2)	

✓ Investigation report received

X No Investigation report received

— Investigation report not required as no pan-Europe trends or clusters detected in registry

Appendix B: Congenital anomaly subgroup inclusion list

The EUROCAT congenital anomaly subgroups are defined in EUROCAT Guide 1.4, Chapter 3.3 (21), and are analysed in the following ways:

- Prevalence by outcome of pregnancy, by registry and year. *All cases* and *All cases excluding genetic conditions*[1] are included in the analysis and the results are published in the prevalence tables available on the EUROCAT website (http://www.eurocat-network.eu/accessprevalencedata/prevalencetables). It is possible to perform dynamic prevalence calculations for combined registries/years on the website.
- Analysis of trends, all outcomes of pregnancy are jointly considered. Genetic conditions are excluded from the statistical monitoring of all other subgroups.

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
All anomalies	✓	**NO**	**NO**
All anomalies excluding genetic conditions	✓	✓	**NO**
Nervous system	✓	**NO**	**NO**
Neural Tube Defects	✓	✓	✓
Anencephalus and similar	✓	✓	✓
Encephalocele	✓	✓	✓
Spina Bifida	✓	✓	✓
Hydrocephalus	✓	✓	✓
Severe microcephaly	✓	✓	✓
Arhinencephaly / holoprosencephaly	✓	✓	✓
Eye	✓	**NO**	**NO**
Anophthalmos / microphthalmos	✓	✓	✓
Anophthalmos	✓	✓	✓
Congenital cataract	✓	✓	✓
Congenital glaucoma	✓	✓	✓
Ear, face and neck	✓	**NO**	**NO**
Anotia	✓	✓	✓
Congenital heart defects (CHD)	✓	✓	**NO**
Severe CHD	✓	✓	✓
Common arterial truncus	✓	✓	✓

[1] Genetic syndromes/ microdeletions, skeletal dysplasias chromosomal anomalies

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
Double outlet right ventricle	✓	✓	✓
Transposition of great vessels	✓	✓	✓
Single ventricle	✓	✓	✓
VSD	✓	✓	✓
ASD	✓	✓	✓
AVSD	✓	✓	✓
Tetralogy of Fallot	✓	✓	✓
Tricuspid atresia and stenosis	✓	✓	✓
Ebstein's anomaly	✓	✓	✓
Pulmonary valve stenosis	✓	✓	✓
Pulmonary valve atresia	✓	✓	✓
Aortic valve atresia/stenosis	✓	✓	✓
Mitral valve anomalies	✓	✓	✓
Hypoplastic left heart	✓	✓	✓
Hypoplastic right heart	✓	✓	✓
Coarctation of aorta	✓	✓	✓
Aortic atresia/interrupted aortic arch	✓	✓	✓
Total anomalous pulm venous return	✓	✓	✓
PDA as only CHD in term infants (GA 37+ weeks)	✓	✓	✓
Respiratory	✓	**NO**	**NO**
Choanal atresia	✓	✓	✓
Cystic adenomatous malf of lung	✓	✓	✓
Oro-facial clefts	✓	**NO**	**NO**
Cleft lip with or without cleft palate	✓	✓	✓
Cleft palate	✓	✓	✓
Digestive system	✓	**NO**	**NO**
Oesophageal atresia with or without tracheo-oesophageal fistula	✓	✓	✓
Duodenal atresia or stenosis	✓	✓	✓
Atresia or stenosis of other parts of small intestine	✓	✓	✓
Ano-rectal atresia and stenosis	✓	✓	✓
Hirschsprung's disease	✓	✓	✓
Atresia of bile ducts	✓	✓	✓
Annular pancreas	✓	✓	✓

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
Diaphragmatic hernia	✓	✓	✓
Abdominal wall defects	✓	**NO**	**NO**
Gastroschisis	✓	✓	✓
Omphalocele	✓	✓	✓
Urinary	✓	**NO**	**NO**
Bilateral renal agenesis including Potter syndrome	✓	✓	✓
Multicystic renal dysplasia	✓	✓	✓
Congenital hydronephrosis	✓	✓	✓
Bladder exstrophy and/or epispadia	✓	✓	✓
Posterior urethral valve and/or prune belly	✓	✓	✓
Genital	✓	**NO**	**NO**
Hypospadias	✓	✓	✓
Indeterminate sex	✓	✓	✓
Limb	✓	**NO**	**NO**
Limb reduction	✓	✓	✓
Clubfoot - talipes equinovarus	✓	✓	✓
Hip dislocation and/or dysplasia	✓	✓	✓
Polydactyly	✓	✓	✓
Syndactyly	✓	✓	✓
Other anomalies/ syndromes	**NO**	**NO**	**NO**
Skeletal dysplasias	✓	✓	✓
Craniosynostosis	✓	✓	✓
Congenital constriction bands/amniotic band	✓	✓	✓
Situs inversus	✓	✓	✓
Conjoined twins	✓	✓	✓
Congenital skin disorders	✓	✓	✓
VATER/VACTERL	✓	✓	✓
Vascular disruption anomalies	✓	✓	✓
Laterality anomalies	✓	✓	✓
Teratogenic syndromes with malformations	✓	✓	**NO**
Fetal alcohol syndrome	✓	✓	✓
Valproate syndrome	✓	✓	✓
Maternal infections resulting in malformations	✓	✓	✓

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
Genetic syndromes + microdeletions	✓	✓	**NO**
Chromosomal	✓	✓	**NO**
Down syndrome	✓	✓	✓
Patau syndrome/trisomy 13	✓	✓	✓
Edward syndrome/trisomy 18	✓	✓	✓
Turner syndrome	✓	✓	✓
Klinefelter syndrome	✓	✓	✓
Down syndrome Adjusted	**NO**	✓	**NO**
Patau syndrome Adjusted	**NO**	✓	**NO**
Edward syndrome Adjusted	**NO**	✓	**NO**

Appendix C: Statistical methods used by EUROCAT

Part of the current monitoring strategy is the annual statistical monitoring for trends and clusters at central level, 15 months after last date of birth, e.g. year 2016 births included in monitoring in March 2018. More details on the statistical methods for monitoring given here can be found in the EUROCAT Statistical Monitoring Protocol [9].

Statistical methods for the detection of trends in every registry

Trend tests are performed for 81 anomaly subgroups (see Appendix B) for each registry, and for an additional 3 subgroups adjusting for maternal age and in utero survival for registries with maternal age denominators.

Currently, Central Registry performs a trend test for the most recent five years of data, as well as a trend test for the most recent 10 years (or 8 years if 10 years are not available). The analysis is based on the number of cases per year of birth and the number of births per year. Data is presented by individual year or grouped by two year intervals if there are too few cases to meet the criterion for testing by single year. A trend test is not performed if the expected number of cases per year (or 2 year interval) is less than 5 and if the observed number of cases in any one year (or 2 year interval) is less than 2.

Change over time is tested with a chi square test for heterogeneity, divided into the trend component ("chi square test for trend") and the non-linear component ("chi square test for non-linear change"). The average annual percentage change in prevalence per year is calculated from a logistic regression. The Chi square test for trend identifies evidence of an increasing or decreasing trend in prevalence. The Chi square test for non-linear change identifies evidence of significant change over time (i.e. the prevalence changes from year to year).

Monotonicity of the prevalence in five two yearly intervals is recorded. Monotonicity exists if for each point in turn the prevalence is greater than the previous point OR each point in turn the prevalence is less than the previous point. The significance level (p-value) for both chi squared tests, direction (upward or downward) and average annual percentage change in prevalence per year (with 95% confidence intervals) are given in the output

- Where $p<0.05$ for trend component and $p>0.01$ for non-linear component, the results are identified as an "increasing or decreasing trend". Since overall directional trend is of most concern for investigation, a chi square for trend p-value less than 0.05 is interpreted as a trend even where the p-value for non-linear change is weakly significant also (between 0.05 and 0.01).
- Where $p<0.05$ for trend component, $p<0.01$ for non-linear component and the prevalence trend is monotonic, the results are also identified as 'increasing or decreasing trend'.
- Where $p<0.05$ for trend component, $p<0.01$ for non-linear component and the prevalence trend is not monotonic, the results are identified as "non-linear change".
- Where $p>0.05$ for trend component and $p<0.05$ for non-linear component, the results are identified as "non-linear change".
- Where $p>0.05$ for trend component and $p>0.05$ for non-linear component, the results are interpreted as showing no significant change over time.

Since the Chi squared test is based on conventional probabilistic statistics, at a significance level of $p<0.05$, 5% of the test results will be statistically significant by chance. This should be kept in mind in interpretation (see protocol for investigation).

"Pan-Europe" trend detection.

The "Pan-Europe" analysis repeats the procedures above to present data from individual registries. In order to calculate the overall trend across Europe and include data across all eligible registries, Poisson random effects regression models with the registries as strata are fitted. These models can include data from registries with too few cases for the chi-squared analyses and they also allow for heterogeneity between registries. To be consistent with the registry analyses the Poisson model only includes 8 years of data for those registries in whom 10 years were not available. Tests for pan-European monotonicity are not performed.

Clusters

A 'scan' moving window method is used to detect clusters (see chapter 2.4 of *Monitoring Protocol 2012*), based on the cases who occurred in the period 2012-2016. The analysis for detecting clusters is run on 75 EUROCAT subgroups of congenital anomalies (see Appendix B). Excluded from the analysis are 17 major heterogeneous subgroups listed in Appendix B (e.g. nervous system, eye, congenital heart defects).

1. To run the scan analysis for cluster detection, a minimum of seven cases over the surveillance period (2012-2016) is needed.
2. Clusters are reported when they are within or overlapping the last two years (2015-2016) and are of less than 18 months in length.
3. The default scan analysis uses estimated dates of conception. If date of conception is missing for > 10% of cases, then the analysis is based on the date of birth.
4. When date of conception is used as a basis for cluster detection, the period of surveillance ends with dates of conception on 31 March in the last year under surveillance, i.e. 2016.

   If date of birth/delivery is used to detect clusters, the last full year (1 January – 31 December) is included in the surveillance.

Appendix D: Summary of a registry's preliminary investigation protocol for identified ten-year trends and clusters

Investigation protocols and templates, provided to make the reporting process consistent between registries, are described in full in the EUROCAT Statistical Monitoring Protocol [7]. Using the templates, registries were asked to include the following in their investigation report:

Ten-year trends:

1. Are there changes in diagnosis, in reporting, in coding, or in population definition that explain the trend?
2. Are there any known reasons why this might be a "real" trend in frequency of the anomaly?
3. Will the investigation continue (if so, how? if not, why not?)?
4. Which public health authority will the result be reported to?

Investigations into significant increasing trends are classified as follows:

A: Changes in case ascertainment (data quality)

B: Changes in local or central registry methods e.g. definitions and inclusion criteria

C: Changes in diagnostic methods

D: Trend confirmed, due to known demographic changes

E: Trend confirmed, investigation on-going

F: Trend confirmed, further surveillance proposed before more detailed investigation

G: Not real trend when additional years added, or heterogeneous subgroup

H: No report or clear interpretation of preliminary investigations sent

Some trends can be explained by a combination of the classification categories e.g. A/B. The first classification category is considered the principal one, so trends classified as A/B are counted in the A category.

Clusters:

1. The methods and results of investigations as to whether changes in diagnostic methods, training, personnel or reporting practice contributed to the cluster.
2. The methods and results of any investigation into aetiological factors, including which aetiological factors were investigated and which source of information was used (registry database, further access to medical records or parents etc.).
3. Any local concerns about exposures and how they came to your attention.
4. Whether anyone in your region (e.g. local community or health professional) had previously been aware of the cluster.

5. The basis for your decisions to conduct the investigation in the way you did, and whether you will continue to investigate (if so, how? if not, why not?).
6. Which public health authorities have been or will be notified about the cluster?
7. Registries are asked to conclude from their preliminary investigations if this is a 'true cluster of concern or not'

Cluster investigations can be classified as follows:

- Apparent cluster with cause for concern, further investigation on-going
- Cluster associated with etiologic heterogeneity, changes in inclusion criteria, diagnosis, familial or twin recurrence
- Excess of cases confirmed, but no further investigation proposed other than further surveillance
- Increase in cases, due to increasing use of invasive prenatal diagnostic procedures or improvements in prenatal ultrasound detection rates
- Data quality issues found to explain cluster
- No report of preliminary investigations sent to Central Registry

Appendix E: Summary of increasing and decreasing ten-year trends detected in the pan-European analysis

			95% CI limits	
Group of anomalies	**Trend's direction**	**Annual change**	**lower**	**upper**
Double outlet right ventricle	increasing	3.5%	0.6%	6.5%
Ventricular septal defect	increasing	0.8%	0.2%	1.4%
Atrial septal defect	increasing	2.9%	1.9%	3.9%
Tricuspid atresia and stenosis	increasing	4.7%	0.4%	9.1%
Hypoplastic right heart	increasing	9.8%	4.6%	15.3%
Bilateral renal agenesis including Potter syndrome	increasing	4.2%	1.0%	7.5%
Multicystic renal dysplasia	increasing	1.7%	0.0%	3.4%
Congenital hydronephrosis	increasing	4.3%	3.3%	5.3%
Clubfoot - talipes equinovarus	increasing	3.3%	2.2%	4.4%
Polydactyly	increasing	1.8%	0.7%	3.0%
Laterality anomalies	increasing	3.7%	1.1%	6.3%
Hydrocephaly	decreasing	-2.3%	-3.7%	-0.8%
Severe microcephaly	decreasing	-3.8%	-6.0%	-1.7%
Anophthalmos / microphthalmos	decreasing	-4.3%	-8.0%	-0.4%
Pulmonary valve stenosis	decreasing	-3.8%	-5.3%	-2.2%
Patent ductus arteriosus	decreasing	-4.5%	-6.6%	-2.3%
Cleft lip with or without palate	decreasing	-1.5%	-2.7%	-0.4%
Cleft palate	decreasing	-2.0%	-3.4%	-0.5%
Gastroschisis	decreasing	-2.2%	-4.1%	-0.2%
Syndactyly	decreasing	-2.5%	-4.3%	-0.8%
Vascular disruption anomalies	decreasing	-2.2%	-3.4%	-0.9%
Teratogenic syndromes with malformations	decreasing	-4.4%	-6.9%	-1.8%
Valproate syndrome	decreasing	-27.4%	-39.6%	-12.7%
Genetic syndromes and microdeletions	decreasing	-1.8%	-3.0%	-0.5%
Klinefelter syndrome	decreasing	-4.8%	-8.2%	-1.2%
Down syndrome (age adjusted)	decreasing	-1.5%	-2.3%	-0.6%

Appendix F: Revision of cases included in the Pan-European increasing trends on tricuspid atresia subgroup and hypoplastic right heart subgroup

The pan-European increasing trends included 458 cases in the tricuspid atresia subgroup and hypoplastic right heart subgroup. Although the multiple malformation classification was not available, there were no cases in chromosomal, genetic, skeletal dysplasia and congenital skin disorder subgroups.

There were 157 cases with hypoplastic right heart subgroup (Q226), 233 cases with tricuspid stenosis/tricuspid atresia subgroup (Q224) and 7 cases in both subgroups. Cases from the registries of Paris and Northern England could not be reviewed, as there was no text description (Paris) or only standard written text for most cases (Northern England).

Q226: Hypoplastic right heart, N = 157

The word 'tricuspid atresia' occurred 15 times in the malformation variables. For 14 cases, the text was written under the code for hypoplastic right heart. For one case, the text was written under the code for pulmonary valve atresia and seems to be a coding error. The 15 cases are from 3 registries. Feedback has been sent to the three registry leaders to update the coding of their cases before the surveillance for next year starts. The case list included 22 cases coded with Q220 (pulmonary valve atresia) as another reason for developing hypoplastic right heart.

Q224: Tricuspid stenosis/tricuspid atresia, N = 233

There were 24 cases with additional text description of hypoplasia of the right ventricle, but without the correct code (Q226). The cases were from 6 registries with 11 cases from one registry. All registries have been asked to update their cases before the surveillance for next year starts. For 20 cases the written text said 'tricuspid valve stenosis' and three of them were described with severe tricuspid stenosis. The seven cases in both subgroups all had written text for atresia of tricuspid valves.

Conclusion

For almost all cases the written text for the ICD10 code for the subgroup is correct (Q224 and Q226), but additional coding is missing for approximately 10% of the cases in each group. There is some overlap of the cases in the two subgroups, but there are also cases that are not the same (tricuspid valve stenosis and pulmonary valve atresia).

As both subgroups show an increasing pan-European trend, it is important to follow these trends in the coming years and to follow-up on correct coding of cases. It may be of value to perform a pan-European trend analysis on the subgroups together or to calculate the pan-European trend of all cases that may have hypoplasia of the right ventricle (Q224, Q226 and also Q220 pulmonary valve atresia cases without codes for VSD or Tetralogy of Fallot).

Appendix G: Revision of cases included in the Pan-European increasing trend on bilateral renal agenesis (including Potter syndrome)

In the JRC-EUROCAT Central database, there were 592 cases in the bilateral renal agenesis (incl. Potter syndrome) for the years 2007-2016 from 20 registries. The number of cases per registry ranged from 1 in Malta to 73 in South West England.

Cases excluded from the pan-European trend analysis: 29 syndrome cases, 18 chromosomal cases.

Cases excluded in the pan-European trend analysis: 545 cases with 109 livebirths, 27 fetal deaths and 409 TOPFA.

Classification	Livebirths	Fetal deaths	TOPFA
Isolated renal	67	17	236
Isolated other[1]			19
Potential multiple	38	10	151
Teratogenic	4		3
Total	109	27	409

[1]The 19 cases classified as 'isolated other' had sirenomelia or caudal regression sequence, mainly reported by English registries and Wales. The cases were equally distributed over the 10 years.

<u>One week survival</u>

Only 8 cases (1.5% of total) from 6 different registries were reported to be alive one week after birth. They were equally distributed over the 10 years.

Two cases had the written text of unilateral renal agenesis and should be recoded to the code Q600 (Wessex, Isle de Reunion).

One case had codes and text for Potter syndrome and ASD, but no specification of the renal anomaly (Hainaut).

One case had the additional code P964 termination of pregnancy affecting fetus (Thames Valley) and thus may be a coding error for survival.

Two cases had the code for Potter syndrome (Q606) and additional text for tubulary renal dysplasia and multicystic renal dysplasia. Both cases were classified as being linked to the use of a teratogen (Q8684 for anomaly due to ACE inhibitor) (Saxony Anhalt).

Two cases had correct text for bilateral renal agenesis and one had additional lung hypoplasia (Ukraine, Isle de Reunion).

Potter syndrome and multicystic renal dysplasia

20 cases had the code Q606 for Potter syndrome and an additional code for multicystic renal dysplasia. Most cases had bilateral multicystic renal dysplasia, but a few had unilateral dysplasia and unilateral renal agenesis. Half of the registries had at least one case, 7 were from South West England. Cases were equally distributed over the 10 years.

Potter syndrome and posterior urethral valves

There were 4 cases with posterior urethral valves and the code Q606 for Potter syndrome without mentioning renal agenesis (in 4 registries and years 2007, 2010, 2012, 2015).

Teratogenic syndrome

Seven cases were classified as teratogenic syndrome:

- three cases were reported as related to the use of ACE inhibitor (Saxony in the years 2009, 2010 and 2013),
- one case was reported as due to the use of misoprostol (Isle de Reunion),
- one case was unspecified external exposure (Northern England),
- one case had a reported CMV infection (South West England)
- one case was a coding error for dysmorphic face (Q868 instead of Q189).

Conclusions

The review showed that the large majority of cases were very severe as the TOPFA rate was high and there were very few survivors after one week. Therefore, the coding of the diagnosis seems to be correct and valid. There are a few coding issues with the inclusion of sirenomelia cases and multicystic renal dysplasia cases, but there are no time trends in this. The pan-European trend is most likely correct and needs to be followed. The issue of increased exposure to ACE inhibitors/sartans cannot be confirmed using this data.

References

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