



EUROCAT Statistical Monitoring Report – 2012

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Table of Contents

Acknowledgements	4
1 EUROCAT 2012 Statistical Monitoring of Congenital Anomalies: Executive Summary	5
2 Introduction	
2.1 Overview of Annual Statistical Monitoring	8
3 Population and Monitoring Process	
3.1 Registries included in the 2012 trend analysis	9
3.2 Registries included in the 2012 cluster analysis	9
3.3 What was monitored?	10
3.4 Investigation process	11
3.5 Statistical software updates from previous reports	13
4 Trends	
4.1 Overview	14
4.2 Increasing trends identified at pan-Europe level	14
4.2.1 New increasing trends identified at pan-Europe level	14
4.2.2 Continuing increasing trends identified at pan-Europe level	15
4.3 Decreasing trends identified at pan-Europe level	24
5 Clusters	
5.1 Overview	33
5.2 New clusters	33
5.2.1 Reports of preliminary investigations of specific clusters by registries	33
5.2.2 Continuing clusters	37
5.3 Country clusters	41
Use of the EDMP statistical monitoring function by registries to detect clusters or trends on recent data.	42
6	
7 Conclusions	42

List of Figures

Figure 1	Prioritisation criteria for the investigation of ten year trends	12
Figure 2	Prevalence of Oesophageal atresia with or without trachea-oesophageal fistula showing a significant increase in the pan-Europe analysis	15

Figure 3	Prevalence of Severe CHD showing a significant increase in the pan-Europe analysis	16
Figure 4	Prevalence of heart anomalies showing a significant increase in the pan-Europe analysis	17
Figure 5	Average annual change in prevalence in Tetralogy of Fallot by registry	18
Figure 6	Average annual change in prevalence of CCAM by registry	19
Figure 7	Prevalence of digestive system anomalies showing a significant increase in the pan-Europe analysis, 2003-2012	20
Figure 8	Average annual change in prevalence in Ano-rectal atresia and stenosis by registry	21
Figure 9	Clubfoot prevalence over time 2003-2012	22
Figure 10	Craniosynostosis by time of diagnosis, 2003-2012	24
Figure 11	Average annual change in prevalence in PDA by registry	25
Figure 12	Average annual change in prevalence in Microcephaly by registry	26
Figure 13	Average annual change in prevalence in Congenital skin disorders by registry	28
Figure 14	Average annual change in prevalence in Klinefelter syndrome by registry	29
Figure 15	Estimated average percentage change in prevalence and 95% confidence intervals (Pan-Europe analysis 2003-2012)	30

List of Tables

Table 1	Central Registry Statistical Monitoring Results: reported 8 or 10 year trends by individual registry, 2003-2012	32
Table 2	Outcomes of local registry preliminary investigations into 22 new clusters detected in 2012 monitoring	39

List of Boxes

Box 1	Registry inclusion criteria for trend analysis	9
Box 2	Registry inclusion criteria for cluster analysis	10

Appendices

Appendix A	EUROCAT full member registries inclusion list	43
Appendix B	Congenital anomaly subgroup inclusion list	44

Appendix C	Summary of statistical methods	47
Appendix D	Summary of local registry preliminary investigation protocols for identified ten year trends and clusters	49
Appendix E	Summary of significant ten year increasing and decreasing trends detected in the pan-Europe analysis 2012	51
Appendix F	Forest plots showing ten year increasing and decreasing trends detected in the pan-Europe analysis by anomaly subgroup	52
Appendix G	Forest plots showing ten year increasing and decreasing trends detected in the pan-Europe analysis by registry	93
Appendix H	Central Registry reports of selected pan-Europe trends	143
Appendix I	Outcomes of local registries preliminary investigations into pan-Europe and individual registry ten year trends	207
Appendix J	Trends by anomaly and registry– website details	210
Appendix K	Central Registry Statistical Monitoring Results: Summary table of detected clusters by registry and by anomaly 2011-2012	211
Appendix L	Details of clusters identified in the individual registry cluster analysis	218
Appendix M	Details of clusters identified in the country cluster analysis	223

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EUROCAT 2012 Statistical Monitoring of Congenital Anomalies: Executive Summary

Worldwide, congenital anomalies are a leading cause of fetal death, infant mortality and morbidity in childhood. Of the 5.2 million births in the EU each year, approximately 104,000 (2%) will be born with congenital anomalies. 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.

To meet these objectives, EUROCAT annually performs statistical monitoring for both trends and clusters in time in order to detect signals of new or increasing teratogenic exposures and monitor progress in the prevention of congenital anomalies. Total prevalence rates of 81 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 are monitored and reported. We report here on births over the ten year period 2003-2012, and include data from 25 EUROCAT registries to describe trends, and 18 EUROCAT registries to detect recent clusters in time. A pan-Europe trend and country cluster analyses enable 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 included.

Key findings

Congenital anomalies excluding genetic conditions¹

- **Neural tube defects (NTDs)**, which are largely preventable by raising periconceptional folate status, have not decreased in prevalence over the last 10 years. Prevalence was 9.47 per 10,000 births in 2003-2004 and 9.10 per 10,000 births in 2011-2012 indicating preventive measures should be reinforced.
- In this year's pan-Europe analysis, an *increasing* trend was again found for **Severe congenital heart defects (CHD)** which increased on average by 1.4% per year from 16.44 per 10,000 births in 2003-2004 to 17.92 per 10,000 births in 2011-2012. For the third consecutive year, increasing trends were found for **Single ventricle** and **Tetralogy of Fallot**. **Single ventricle** increased by 4.7% per year from 0.46 per

¹ Includes genetic syndromes / microdeletions, skeletal dysplasias, chromosomal anomalies

10,000 births in 2003-2004 to 0.65 per 10,000 births in 2011-2012, while **Tetralogy of Fallot** increased on average by 4.1% per year from 2.36 per 10,000 births in 2003-2004 to 3.21 per 10,000 births in 2011-2012. **Atrioventricular Septal Defect (AVSD)** increased by 3.5% per year from 1.57 per 10,000 births in 2003-2004 to 2.12 per 10,000 births in 2011-2012. Further monitoring and investigation of these trends is required as they are unlikely to be explained by diagnostic factors.

- *Increasing* trends were found for some gastrointestinal anomalies. A new increasing trend was found for **Oesophageal atresia with or without trachea-oesophageal fistula (OA)** which increased on average by 2.3% per year from 2.00 per 10,000 births in 2003-2004 to 2.24 per 10,000 births in 2011-2012. For the third consecutive year, an increasing trend was detected for **Duodenal atresia and stenosis** (N.B. pan-Europe trends exclude cases with chromosomal anomalies such as Down syndrome) which rose by 3.4% from 0.79 per 10,000 births in 2003-2004 to 1.02 per 10,000 births in 2011-2012. For the second consecutive year, an increasing trend was found for **Ano-rectal atresia and stenosis** which increased by 2.0% per year from 2.65 per 10,000 births in 2003-2004 to 2.80 per 10,000 births in 2011-2012.
- For the third consecutive year a significantly *increasing* trend was detected for the skeletal anomaly **Craniosynostosis**, which increased on average by 4.7% per year rising from 1.41 per 10,000 births in 2003-2004 to 2.09 per 10,000 births in 2011-2012.
- For the fourth consecutive year, an *increasing* pan-Europe trend was detected for **Cystic adenomatous malformation of the lung (CCAM)** which increased on average by 6.7% per year with prevalence rising from 0.62 per 10,000 births in 2003-2004 to 1.26 per 10,000 births in 2011-2012. Prevalence of CCAM is higher in the UK possibly due to better antenatal detection.
- A new *increasing* trend was found for **Maternal infections resulting in malformations** which includes Rubella, Cytomegalovirus (CMV) and Toxoplasmosis exposed cases. The pan-Europe analysis showed that the prevalence of Maternal infections increased on average by 3.9% per year from 0.51 per 10,000 births in 2003-2004 to 0.79 per 10,000 births in 2011-2012. The majority of cases in the pan-Europe monitoring had CMV which is associated with young maternal age. More neonatal screening and awareness of CMV infection in recent years may explain some of the increase.
- For the third consecutive year, *decreasing* trends were found for **Upper limb reduction defects**. Prevalence decreased by an average of 3.4% per year from 3.41 per 10,000 births in 2003-2004 to 2.57 per 10,000 births in 2011-2012.

Chromosomal anomalies

- *Increasing* trends were again detected in **Chromosomal anomalies**, due to the increasing trends in **Down syndrome and Edward syndrome**. These trends are due to rising maternal age across Europe.

Clusters

Thirteen new clusters in time were detected in individual registry populations which, following preliminary investigations, could not be explained by information held within the registries. The registries involved will continue to monitor these anomalies: **Arhinencephaly/holoprosencephaly** in Emilia Romagna (9 cases observed versus 2 expected); **Atrioventricular septal defect** in Antwerp (7 cases observed versus 1 expected); **Pulmonary valve stenosis** in Antwerp (17 cases observed versus 7 expected); **Pulmonary valve atresia** in Thames Valley (8 cases observed versus 2 expected); **Aortic valve atresia/stenosis** in Wales (8 cases observed versus 1 expected); **Coarctation of Aorta** in Emilia Romagna (5 cases observed versus 1 expected); **Cystic adenomatous malformation of lung** in Emilia Romagna (12 cases observed versus 4 expected); **Cleft lip with or without palate** in SE Ireland (5 cases observed versus 1 expected); **Bilateral renal agenesis including Potter syndrome** in Thames Valley (5 cases observed versus 1 expected); **Renal dysplasia** in Wessex (13 cases observed versus 3 expected); **Syndactyly** in Paris (15 cases observed versus 4 expected); **Congenital constriction bands/amniotic band** in N Netherlands (5 cases observed versus 1 expected); and **Turner syndrome** in Vaud (10 cases observed versus 3 expected).

At country level, no explanation was found for the **Duodenal atresia and stenosis** cluster detected in Belgium (5 cases observed versus 1 expected). The two Belgian registries will continue to monitor this anomaly.

Conclusion

The statistical monitoring of trends and clusters is fundamental to the primary prevention of congenital anomalies, providing timely information on the stability or changes in the prevalence of anomalies. Primary prevention of congenital anomalies continues to be a key objective of the EUROCAT network.

2. Introduction

2.1 Overview of Annual Statistical Monitoring

Each year, EUROCAT performs statistical monitoring for both trends and clusters in time. Statistical monitoring relates to two of EUROCAT's objectives:

- to provide essential epidemiologic information on congenital anomalies in Europe
- to co-ordinate the detection of, and response to, clusters and early warning of teratogenic exposures.

A full protocol is published annually online, providing details of the rationale and methodology of the statistical monitoring, including changes to methodology and software, (see EUROCAT Statistical Monitoring Protocol 2012 <http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2012>).

We report here the results up to birth year 2012. Cases of congenital anomaly among livebirths, fetal deaths from 20 weeks gestational age and terminations of pregnancy for fetal anomaly are included. Statistical monitoring also includes a small proportion of cases with unknown type of birth. We report both the statistical results and, where available, the outcome of preliminary investigations conducted by registries.

Registries can also use the statistical monitoring software EDMP (EUROCAT Data Management Program) to conduct monitoring locally using more recent data. Reports of these analyses conducted up to June 2014 are also included in this report. In addition, any trends or clusters detected outside of formal statistical monitoring (e.g. reported to the registry by local clinicians) are reported.

3. Population and Monitoring Process

3.1 Registries included in the 2012 trend analysis

At the time of statistical monitoring in Spring 2014, there were 31 full member registries in EUROCAT (see Appendix A). Twenty-six full member registries met the inclusion criteria for the individual 10-year trend analysis, and twenty-five met the inclusion criteria for the pan-Europe analysis (see Box 1, Appendix A).

Box 1 Registry inclusion/ exclusion criteria for trend analysis

- Registries >1 year late with data transmission excluded from analysis
- Pan-Europe: Registries with 9 or 10 years of continuous data starting from 2003 included (i.e. 2003-2011 or 2003-2012)
- Individual registry analysis: Registries with 8 or 10 years of continuous data included (i.e. 2004-2011 or 2005-2012 or 2003-2012)

Ukraine, French West Indies and Valencia Region were excluded from all trend analysis as they did not have 8 years of data in the monitoring time period. Styria and Wielkopolska were excluded as they were more than one year behind in data transmission. South West England was excluded from the Pan Europe analysis as the registry did not have 9 years of data in the monitoring time period (see Appendix A).

3.2 Registries included in the 2012 cluster analysis

EUROCAT defines clusters as 'An aggregation of cases of congenital anomaly in time and/or space which appears to be unusual'². Registries classified as “early response” i.e. registries that meet the EUROCAT data transmission deadline of February 15th, with data for the most recent 5 years (2008-2012) were included in cluster monitoring (see Box 2). Five years is considered an optimal period for cluster monitoring as the inclusion of more than five years data may detect trends rather than clusters, while less than five years may fail to detect if the most recent years are unusual compared to preceding years (see EUROCAT

² EUROCAT Working Group on the Management of Clusters and Environmental Exposure Incidents, 2003

Statistical Monitoring Protocol 2012 <http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2012>)

Box 2 Registry inclusion criteria for cluster analysis

- Registries must have transmitted data for all years 2008-2012
- Registries must have transmitted full date of birth information
- Registries must have individual case data (i.e. full member registries only)
- Registries must have a stable birth population (annual birth population changes must be less than +/- 10%)

A total of twenty-two full member registries transmitted year 2012 data to EUROCAT Central Registry by Feb 15th 2014 (see Appendix A). Four of the twenty-two registries were excluded from the cluster monitoring for the following reasons: Saxony-Anhalt and Norway did not have full date of birth information for the years 2008-2012; French West Indies had less than 5 years continuous data and Zagreb had population fluctuation >10% (see Appendix A).

Where registries do not meet the data transmission deadline, monitoring can be run locally to detect clusters and trends using software available in the EDMP. Pan-Europe monitoring can only be conducted centrally as it uses data from all the registries combined.

Registries are encouraged to use the EDMP statistical monitoring function in the periods between annual Statistical Monitoring to look for clusters or trends in more recent data. All full and associate member registries (n=37) were asked to report on their local use of the EDMP statistical monitoring function within the last year (see Chapter 6).

3.3 What was monitored?

Data from 24 full member registries were transmitted to Central Registry in February 2014. Cases included livebirths, stillbirths from 20 weeks gestational age and terminations of

pregnancy for fetal anomaly. In the period 2003-2012, 81.6% of cases were liveborn, 1.9% were stillborn and 16.5% were terminations of pregnancy for fetal anomaly. Type of birth was unrecorded for a small proportion of cases (0.05%) which are included in monitoring to avoid missing a potential cluster or trend.

Statistical monitoring is conducted to detect changes in time within individual registries, and also to detect trends across all registries (pan-Europe trends). Seventy-eight EUROCAT congenital anomaly subgroups plus the three trisomy subgroups adjusted for maternal age and fetal survival to 20 weeks were included in both the pan-Europe and individual registry trend analyses (see Appendix B for the anomaly subgroup inclusion list). Trend tests were performed for the most recent five and ten years of data (or eight years if ten years were unavailable).

Cluster analysis, which detects clusters or deficits occurring in the last 2 years (2011-2012) that are less than 18 months in length, was run on 72 EUROCAT subgroups of congenital anomalies (see Appendix B for the anomaly subgroup inclusion list and Appendix C for summary of statistical methods).

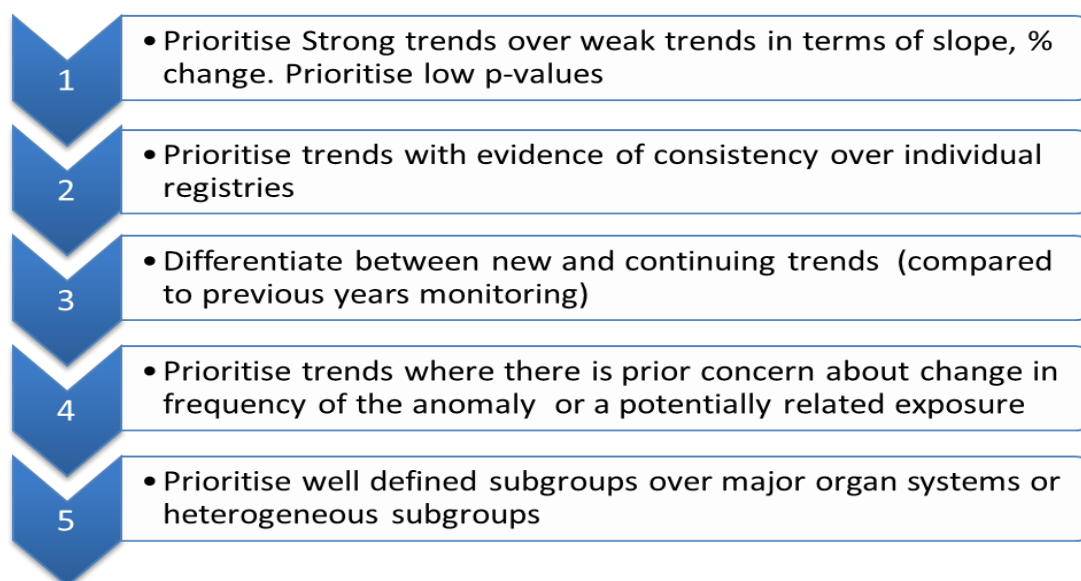
The following analyses were carried out:

- Analysis of individual registry trends for 26 registries covering 6.62 million births (2003-2012)
- Analysis of pan-European trends for 25 registries covering 6.23 million births (2003-2012)
- Cluster analysis to detect unusual aggregations of cases in 18 registries covering 0.96 million births (2011-2012)
- Country cluster analysis to detect unusual aggregations of cases in countries with more than one registry, 2011-2012 (Belgium, France, Ireland, Italy and UK).

3.4 Investigation process

The results of the statistical monitoring were reviewed by the Project Management Committee (PMC) in April 2014. Registries were asked to investigate all new and continuing clusters detected in the monitoring. The PMC selected congenital anomalies with significant increasing or decreasing trends for preliminary investigation using a predefined prioritisation protocol (see Figure 1). The anomalies were selected based on the pattern of the trend identified in the pan-Europe analysis.

Figure 1: Prioritisation criteria for the investigation of ten year trends³



The results of the trends and cluster analysis were communicated to the registries. Each registry was asked to conduct preliminary investigations using standardised guidelines (see EUROCAT Statistical Monitoring Protocol 2012, Appendix D). The significant increasing and decreasing trends selected for registry investigation are listed in Appendix E. Registries were also given the option to investigate and report on increasing and decreasing trends detected at local registry level only.

Registries reported their findings to Central Registry using standard reporting templates (see EUROCAT Statistical Monitoring Protocol 2012). 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 (see Appendix D).

A number of anomalies with significant increasing and decreasing trends were also investigated by Central Registry using the following standardised protocol:

- Conduct a literature review of risk factors for the anomaly
- Investigate if prevalence is affected by: type of birth; when discovered; multiple/ isolated malformations; gestational age; maternal age; year of birth; sex; registry; birthweight; karyotype; postmortem; single/ multiple births; survival to one week

³ Loane M, Dolk H, Kelly A, Teljeur, C, Greenlees, R, Densem, J and a EUROCAT Working Group, (2011). Paper 4: EUROCAT Statistical Monitoring: Identification and investigation of ten year trends of congenital anomalies in Europe. Birth Defects Research (Part A), 91. pp. S31-S43.

- Create graphs and forest plots to demonstrate differences in prevalence between individual and grouped registries compared to the EUROCAT average.

Trends not prioritised for investigation are not discussed in this report but will be subject to further monitoring.

Preliminary reports were received from 17 of the 22 registries asked to investigate significant trends detected in pan-Europe monitoring (see Appendix A). Central Registry trend investigation reports into 12 anomaly subgroups are also available (see Appendix H).

Preliminary reports of cluster investigations were received from 13 of the 14 registries with clusters detected in this year's monitoring (see Table 2 and Appendices K & L).

Five registries (Antwerp, N Netherlands, Paris, SE Ireland and Wales) stated that they would notify local public health authorities of their findings from the preliminary investigations into clusters and trends.

The preliminary reports of the trend and cluster investigations were reviewed and congenital anomalies thought to be of interest were selected for oral presentation at the Registry Leaders Meeting (RLM) held in Belfast, June 2014. A selection of the Central Registry trend investigation reports were also presented at the RLM (see Appendix H). The individual registry preliminary investigation reports into identified trends and clusters are available on the membership-only section of the EUROCAT website.

3.5 Statistical software updates from previous report

No changes were made to the software for this year's statistical monitoring. For a full description of statistical software updates in previous years, please see the annual Statistical Monitoring Protocol (<http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2012>).

4. Trends

4.1 Overview

Once again there was a decline in the prevalence of all non-chromosomal anomalies at pan-European level. The analysis identified increasing trends for 15 subgroups of anomalies and decreasing trends for 11 subgroups (see Figure 15 and Appendix E). Of the 26 trends detected, 23 were also detected in Statistical Monitoring 2011, thirteen of which were increasing trends and ten were decreasing.

For the 10-year trend analyses in individual registries a total of 1333 chi squared tests were performed with 19.2% being statistically significant compared with the 5% expected by chance. The analyses identified a total of 117 increasing trends and 139 decreasing trends (see Table 1). This section provides details of the results, investigations and interpretation of trends for specific anomaly subgroups that were prioritised for investigation (see Appendix E).

4.2 Increasing trends identified at pan-Europe level

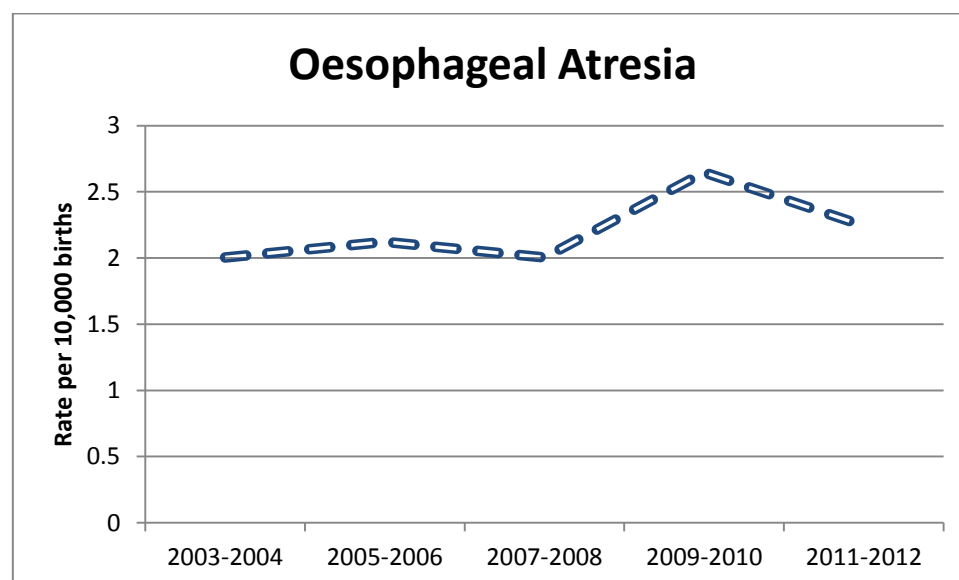
New increasing trends were identified in the pan-Europe analysis for the following anomaly subgroups: Oesophageal atresia with or without trachea-oesophageal fistula and Maternal infections resulting in malformations (see Figure 15). Trends previously reported in the 2011 Report were again found for the following anomaly subgroups: Severe CHD, Single ventricle; AVSD, Tetralogy of Fallot; Cystic adenomatous malformation of the lung; Duodenal atresia or stenosis; Ano-rectal atresia and stenosis, Renal dysplasia; Club foot – talipes equinovarus, Craniosynostosis; Chromosomal; Down syndrome/trisomy 21 and Edward syndrome/trisomy 18.

4.2.1 New increasing trends identified at pan-Europe level

Oesophageal atresia with or without trachea-oesophageal fistula (OA) is an anomaly of the oesophagus, and is characterised by a complete discontinuity of the oesophagus, with or without an abnormal fistula between the oesophagus and the trachea. The pan-Europe analysis showed that the prevalence of OA had increased on average by 2.3% per year from 2.00 per 10,000 births in 2003-2004 to 2.24 per 10,000 births in 2011-2012 (see Figures 2 and 15). The general pattern of the trend showed that it was increasing in 13 registries, but it was only significantly increasing in Hungary (see Appendix F). At the RLM, Hungary

commented that the introduction of electronic notification in 2009 may explain the slightly increasing trend. The Central Registry investigation report can be found in Appendix H.

Figure 2: Prevalence of Oesophageal atresia with or without trachea-oesophageal fistula showing a significant increase in the pan-Europe analysis, 2003-2012



Maternal infections resulting in malformations is a EUROCAT subgroup made up of Rubella, Cytomegalovirus (CMV) and Toxoplasmosis exposed cases where a case should have at least one major congenital anomaly present before being registered as a EUROCAT case. The pan-Europe analysis showed that the prevalence of Maternal infections increased on average by 3.9% per year from 0.51 per 10,000 births in 2003-2004 to 0.79 per 10,000 births in 2011-2012. Almost three quarters of the registries had too few cases to be included in the individual registry trend analysis. Only one registry, Basque Country, had a statistically significant increasing trend (see Appendix F). Preliminary investigations by this registry indicated that the increasing trend could be explained by under-reporting in previous years and changes in ascertainment. The registry suspects that changes in the diagnosis of CMV by more frequent use of Guthrie cards could also be a factor. The Central Registry investigation report can be found in Appendix H.

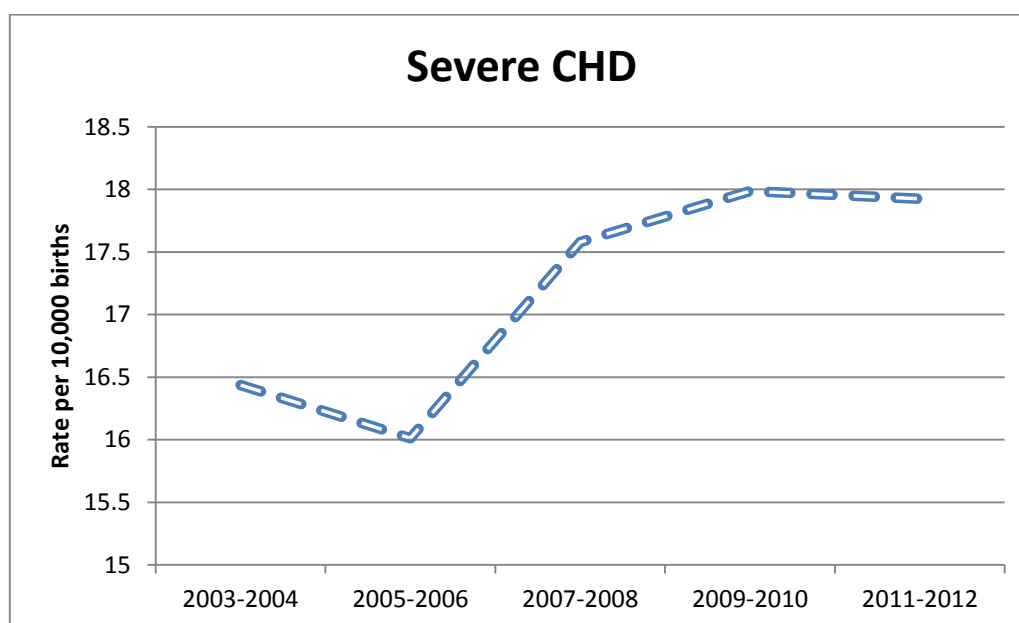
4.2.2 Continuing increasing trends identified at pan-Europe level

There were 13 continuing increasing trends. All of these trends (except Renal dysplasia, Chromosomal, Down syndrome and Edward syndrome) were investigated and reported on in last year's (2011) report. Expert consensus agreed that **Renal dysplasia** should not be

investigated further due to heterogeneity and changes in coding. The increasing trends detected in **Down syndrome and Edward syndrome** were not statistically significant after adjusting for maternal age. This section describes the remaining 9 continuing trends and outlines similarities and differences between the two monitoring periods.

Severe CHD is a EUROCAT derived subgroup that combines 13 subgroups of CHD based on mortality. Most of the severe CHD group needs surgery for survival. This year's pan-Europe analysis showed that the prevalence of severe CHD continued to increase on average by 1.4% per year from 16.44 per 10,000 births in 2003-2004 to 17.92 per 10,000 births in 2011-2012 (see Figures 3 and 15). The general pattern of the trend showed that severe CHD was increasing in 12 registries, although it was only significantly increasing in S Portugal, Vaud and E Midlands & S Yorkshire. Last year, the annual rate of change was 1.7%. Whilst the percentage annual change in prevalence has slowed, the trend continues. The Central Registry investigation report can be found in Appendix H

Figure 3: Prevalence of Severe CHD showing a significant increase in the pan-Europe analysis, 2003-2012



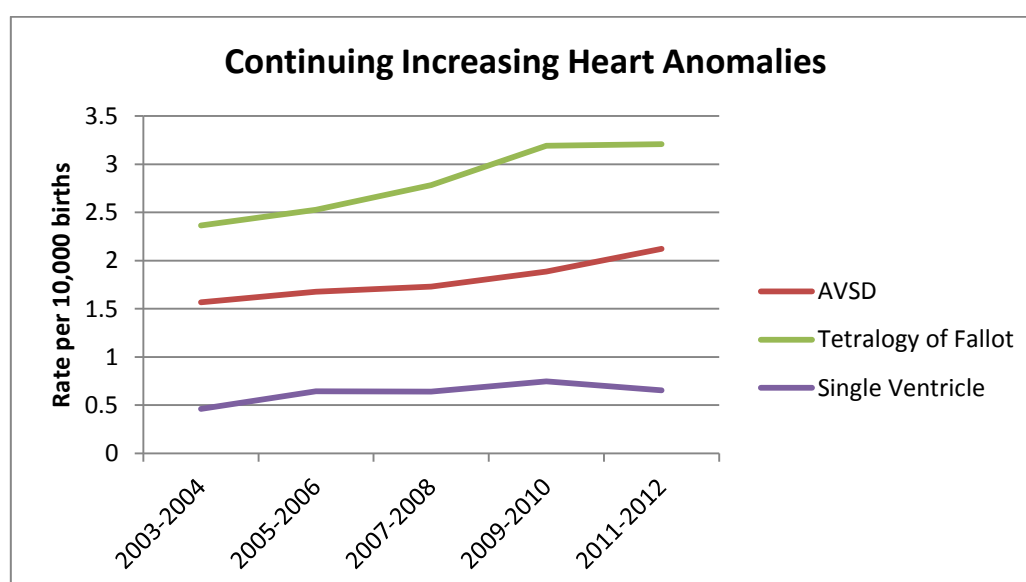
For the third consecutive year, an increasing trend was found in **Single ventricle**, a severe type of cyanotic CHD. This is a rare anomaly hence it was only monitored in 7 registries as the remaining 18 had too few cases to allow for individual registry analysis. Prevalence increased in three registries (Paris, Emilia Romagna and Norway), but not significantly. Last year's analysis showed that the prevalence of single ventricle had increased on average by

6.0% per year from 0.49 per 10,000 births in 2002-2003 to 0.65 per 10,000 births in 2010-2011. In this year's monitoring, prevalence rates increased on average by 4.7% per year from 0.46 per 10,000 births in 2003-2004 to 0.65 per 10,000 births in 2011-2012 (see Figures 4 and 15). A review of the trend over a longer time period by Central Registry showed that historically this trend has actually been decreasing over time (see Appendix H). The Coding & Classification Committee looked at the coding of this anomaly and produced the following Coding Tip in November 2013:

A single ventricle has absence or near total absence of the ventricular septum. If there is a hypoplastic ventricle, the anomaly should be coded as hypoplastic left heart (Q234) or hypoplastic right heart (Q226)

Central Registry undertook some data cleaning following last year's analysis, but the increasing trend in Single ventricle persists. However, it is recognised that the short turn-around time between the introduction of the coding tip and data transmission may mean that the new coding recommendation may not have filtered down to the person doing the coding at local registry level. In late 2014, a validation rule was added to the EDMP software in an effort to improve the coding of this anomaly.

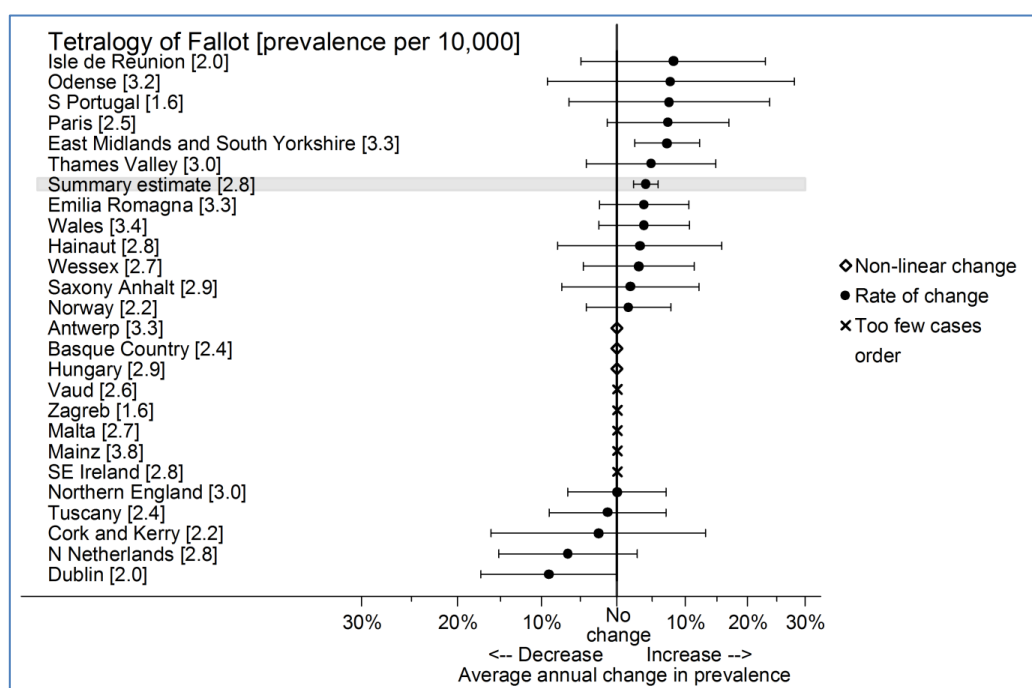
Figure 4: Prevalence of heart anomalies showing a significant increase in the pan-Europe analysis, 2003-2012



For the third consecutive year, a continuing increasing trend in **Tetralogy of Fallot** was found (see Figures 4, 5 and 15). Twelve registries had an increasing trend (see Figure 5), of

which six were above the summary estimate, but only E Midlands and S Yorkshire was statistically significant. A greater rate of annual change was found this year, with prevalence increasing by 4.1% from 2.36 per 10,000 births in 2003-2004 to 3.21 per 10,000 births in 2011-2012. Last year, the rate of change was slower at 2.2% per year; prevalence increased from 2.61 per 10,000 births in 2002-2003 to 3.02 per 10,000 births in 2010-2011. A study investigating the epidemiology of Tetralogy of Fallot in relation to time trends, geographical variation between registries and risk factors including medication exposure in the first trimester of pregnancy is currently being conducted by Central Registry.

Figure 5: Average annual change in prevalence in Tetralogy of Fallot by registry

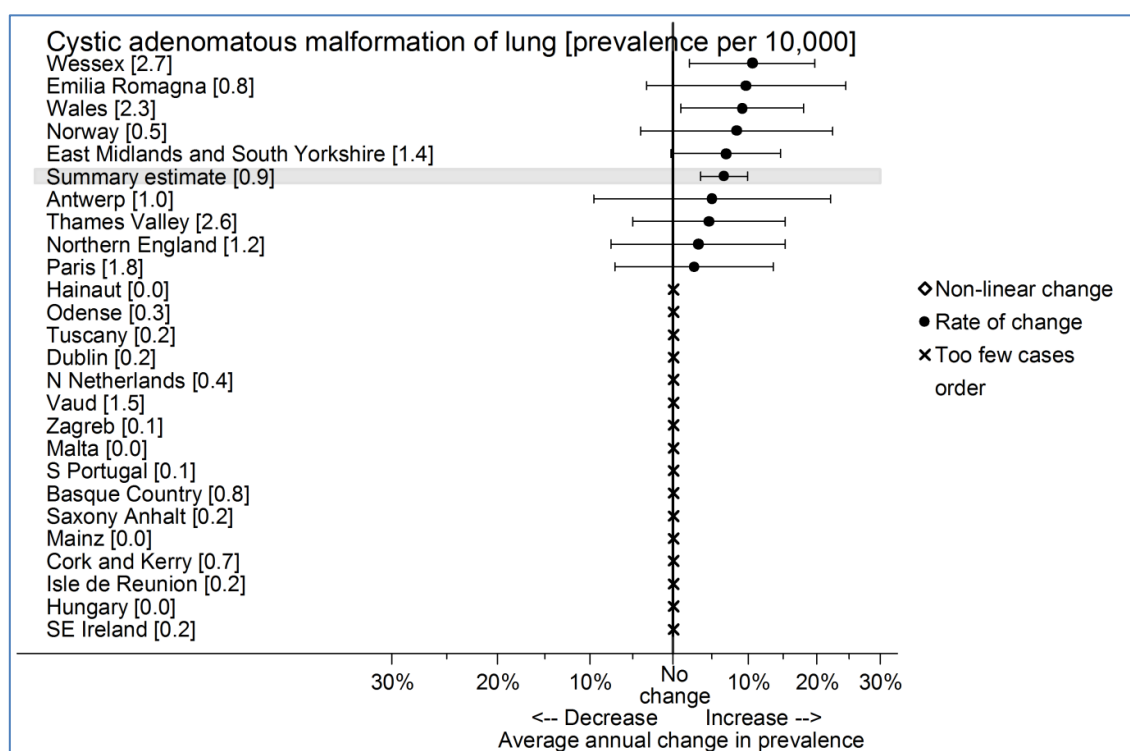


Atrioventricular Septal Defect (AVSD) is defined as a central defect of the cardiac septa and a common atrioventricular valve, and includes primum ASD defects. This condition requires surgery. The affected infants may develop cardiac symptoms within the first few months after birth and may have growth restriction. The pan-Europe analysis showed that the prevalence of AVSD continued to increase on average by 3.5% per year from 1.57 per 10,000 births in 2003-2004 to 2.12 per 10,000 births in 2011-2012 (see Figures 4 and 15). In last year's analysis, prevalence increased by 2.5% per year from 1.57 per 10,000 births in 2002-2003 to 2.02 per 10,000 births in 2010-2011. Ten registries had increasing trends, of which 8 were above the summary estimate. Only Hungary, Basque Country and Antwerp had statistically significant trends (see Appendix F). Antwerp reported that this is a real trend which is being investigated and that maternal obesity and diabetes are being

considered as contributing factors. Basque Country and Hungary did not send investigation reports. The Central Registry investigation report can be found in Appendix H.

For the fourth consecutive year, an increasing pan-Europe trend was detected for **Cystic adenomatous malformation of the lung (CCAM)** a rare condition in which a benign mass of abnormal lung tissue is present in a section of the lung. In this year's statistical monitoring, prevalence increased on average by 6.7% per year rising from 0.62 per 10,000 births in 2003-2004 to 1.26 per 10,000 births in 2011-2012. Last year, prevalence increased at a slightly higher rate of 7% per year, rising from 0.46 per 10,000 births in 2002-2003 to 1.06 per 10,000 births in 2010-2011. Whilst sixteen registries had too few cases to be included in the individual registry trend analysis, the prevalence of CCAM was increasing in the remaining 9 registries. It was only statistically significant in Wessex and Wales (see Figure 6).

Figure 6: Average annual change in prevalence of CCAM by registry

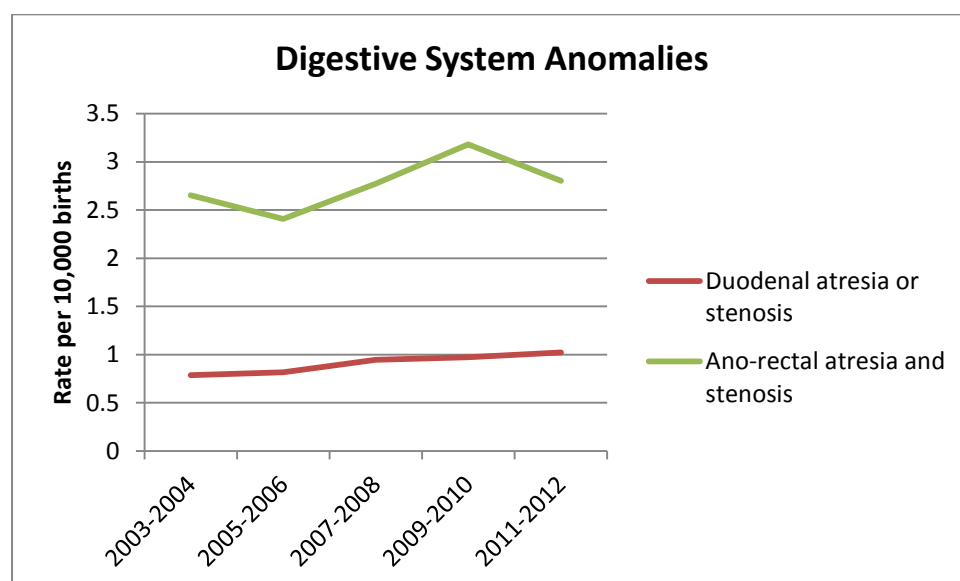


The causes of this condition are not well established. There is some indication that the increasing trend detected may be a consequence of diagnostic or coding issues. Indeed, Wales report that better antenatal detection is responsible for identifying more cases. A

study in Wessex concluded that the increase in CCAM seemed real rather than an artefactual increase due to increased antenatal recognition⁴.

For the third consecutive year, an increasing pan-European trend was detected in **Duodenal atresia or stenosis**, which is a digestive system anomaly (see Figures 7 & 15). In the 2012 monitoring, annual prevalence increased by an average of 3.4% from 0.79 per 10,000 births in 2003-2004 to 1.02 per 10,000 births in 2011-2012. Last year, the annual rate of change was slightly lower at 3.1%, with prevalence increasing from 0.75 per 10,000 births in 2002-2003 to 0.94 per 10,000 births in 2010-2011. Fourteen registries had too few cases for analysis. An increasing trend was found in four registries, although it was only significant in Hungary. No investigation report was provided. The Central Registry investigation report can be found in Appendix H.

Figure 7: Prevalence of digestive system anomalies showing a significant increase in the pan-Europe analysis, 2003-2012

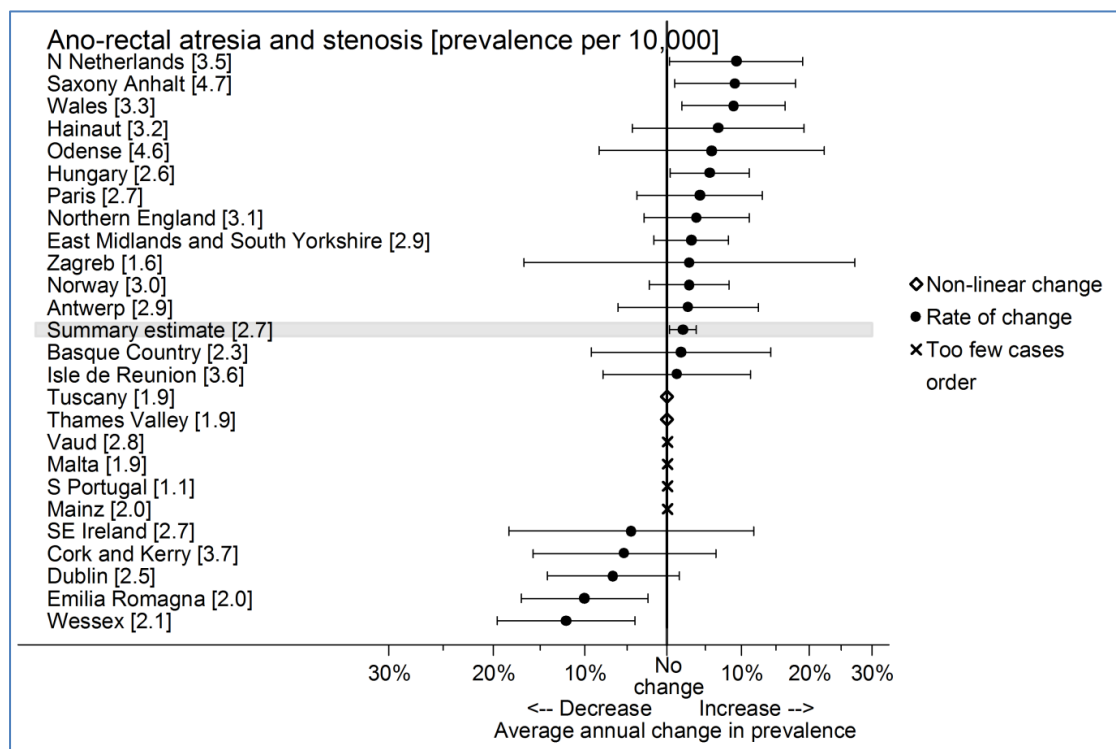


An increasing trend was found again in **Ano-rectal atresia and stenosis**. Anorectal malformations are a group of congenital anomalies which commonly affect the gastrointestinal tract and are characterised by a complete failure of the rectum to communicate with the anus or a narrowing of the ano-rectal canal. This anomaly requires surgery in the neonatal period. Prevalence increased by an estimated 2.0% per year from 2.65 per 10,000

⁴ Stocker L. J., Wellesley D. G., Stanton M. P., Parasuraman R., and Howe D. T. (2015) The increasing incidence of foetal echogenic congenital lung malformations: an observational study, Prenat Diagn, 35, 148–153, doi: [10.1002/pd.4507](https://doi.org/10.1002/pd.4507).

births in 2003-2004 to 2.80 per 10,000 births in 2011-2012. Last year, prevalence increased on average by 2.4% per year from 2.72 per 10,000 births in 2002-2003 to 3.13 per 10,000 births in 2010-2011.

Figure 8 Average annual change in prevalence in Ano-rectal atresia and stenosis by registry



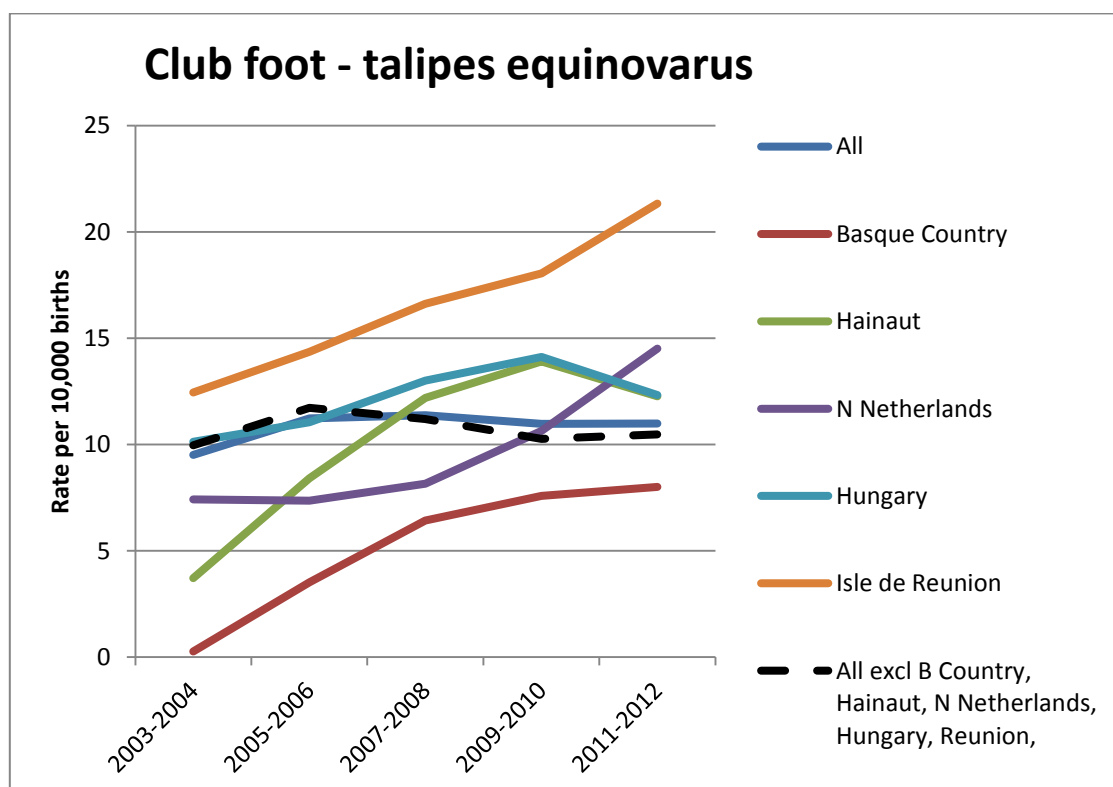
The general pattern of the trend showed that it was increasing in 14 registries, 12 of which had a higher prevalence compared to the EUROCAT average (see Figure 8). It was significantly increasing in 4 registries (N Netherlands, Saxony-Anhalt, Wales and Hungary). Wales reported that the increase in cases coincided with a new source of surgical inpatient data becoming available to the register. N Netherlands reported that the increase may be explained by changes in local registry methods i.e. since 2010, the registry includes the diagnosis of cases whose parents did not reply to the “opt-in” request to be included in the registry. Also the registry has actively been working on improving the coding of this group of anomalies using the Krickbeck criteria. Hungary did not provide a written report. Saxony Anhalt considers this to be a real trend and an investigation is on-going. The registry is collaborating with the German cure-net (network for anorectal malformations) and is working with university paediatric surgeons to conduct a retrospective case control study

A Central Registry investigation into the trend was conducted which concluded that the increase in prevalence in Ano-rectal atresia and stenosis could not be obviously explained

by changes in time of diagnosis, type of birth or the contribution of outlying registries (see Appendix H). As this anomaly is known to form part of the VACTERL (Vertebral, Ano-rectal, Cardiac Tracheo-Oesophageal, Renal, Limb) association, it was suggested that further investigations could consider the prevalence of the VACTERL association as a whole.

Clubfoot talipes equinovarus is a foot anomaly with equinus of the heel, varus of the hindfoot and adductus of the forefoot. The prevalence of this anomaly increased on average by 1.3% per year from 9.51 per 10,000 births in 2003-2004 to 10.99 per 10,000 births in 2011-2012. Last year, the rate of annual change was also 1.3%, rising from 10.09 per 10,000 births in 2002-2003 to 10.97 per 10,000 births in 2010-2011. The general pattern of the trend shows that it was increasing in 10 registries, but was only statistically significant in 5: Basque Country, Hainaut, N Netherlands, Hungary, Isle de Reunion (see Figure 9 & Appendix F). Isle de la Reunion has had a higher than average prevalence from 2003 and it continues to rise. The registry considers this to be a real trend and propose to keep it under surveillance. Basque Country had an extremely low prevalence at the start of the monitoring period. N Netherlands considers the increasing trend to be a consequence of changes in registry methods regarding informed consent. Hainaut and Hungary did not submit a report. The Central Registry investigation report is available in Appendix H.

Figure 9: Clubfoot prevalence over time 2003-2012

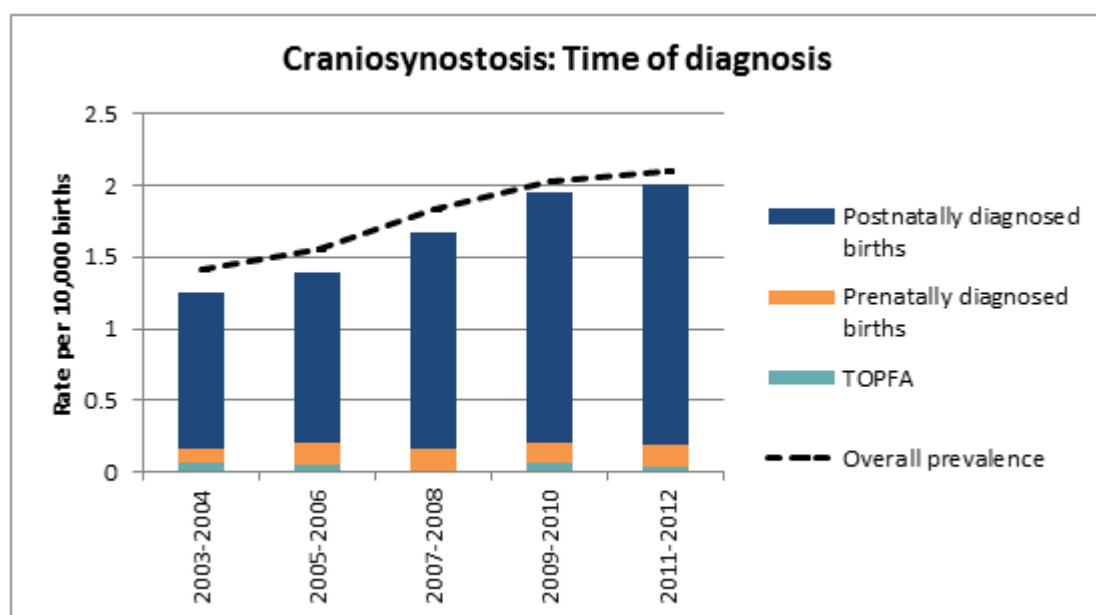


Craniosynostosis is a rare skeletal anomaly where the cranial sutures, which are open at birth to allow the newborn's head to mould as it passes through the birth canal and to facilitate growth, fuse prematurely. Surgery within the first year is the recommended treatment. If untreated, this anomaly can lead to problems with vision and hearing, raised intracranial pressure and intellectual impairment. Most cases are thought to be genetic; occurring either as part of a genetic syndrome or as an isolated anomaly. However, as the different types are not increasing at a uniform rate, environmental factors are also suspected, with evidence of an association with Valproic Acid.

This is the third consecutive year a significantly increasing trend was detected. The prevalence of craniosynostosis increased on average by 4.7% per year rising from 1.41 per 10,000 births in 2003-2004 to 2.09 per 10,000 births in 2011-2012. This rate of change is larger than reported in the 2 previous monitoring periods. Twelve registries had increasing trends but only Paris, Thames Valley, Emilia Romagna and Basque Country were significant. Thames Valley reported that, since 2007, they receive paediatric admission lists from a tertiary centre with a reputation for excellence in craniosynostosis leading to increased ascertainment of cases. Paris had no explanation for the trend and proposed a further period of surveillance as the trend appears to be real, and is collaborating with the 'Centre de reference des Dysostoses craniofaciales'. Emilia Romagna stated that case ascertainment methods have changed to include data from healthcare databases. The registry also suggests that, as craniosynostosis is reported to occur in >40% syndromic cases, an increase in isolated cases across Europe may infer that some regions are missing syndromic cases. Basque Country did not provide a report on this anomaly.

An investigation by Central Registry concluded that increasing ascertainment of late diagnosed cases across many of the registries may be contributing to the trend (see Figure 10). Nevertheless, EUROCAT will continue to monitor this congenital anomaly in case the trend is real. More details of the Central Registry investigation report can be found in Appendix H

Figure 10 Craniosynostosis by time of diagnosis, 2003-2012

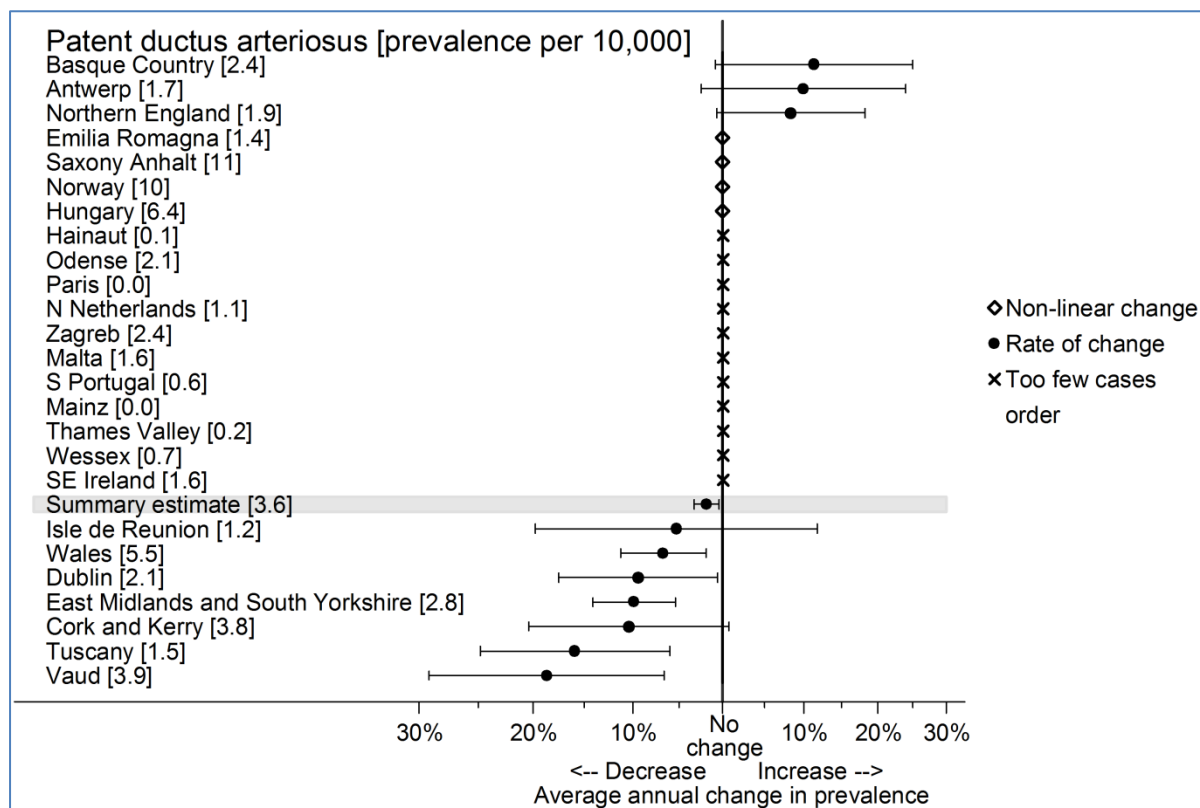


4.3 Decreasing trends identified at pan-Europe level

Eleven decreasing trends were identified in the 2012 pan-Europe statistical monitoring, of which 1 was new and 10 were continuing. A new decreasing trend was detected for **Patent ductus arteriosus** (see Figure 11). Continuing decreasing trends were detected for: All non-chromosomal anomalies; Microcephaly; Congenital hydronephrosis; Limb reduction; Upper limb reduction; Syndactyly; Congenital skin disorders; Genetic syndromes and microdeletions, Valproate syndrome and Klinefelter syndrome.

Patent ductus arteriosus (PDA) in term births is a cardiac disorder wherein the baby's ductus arteriosus fails to close after birth. Early symptoms are uncommon, but in the first year of life include increased work of breathing and poor weight gain. With age, the PDA may lead to congestive heart failure if left uncorrected. A new pan-Europe decreasing trend was detected for PDA with prevalence decreasing on average by 1.9% per year from 3.48 per 10,000 births in 2003-2004 to 3.22 per 10,000 births in 2011-2012. Prevalence decreased in 7 registries, but was significant in 5. Dublin, Wales and E Midlands & S Yorkshire suggest that data quality issues are responsible for the decrease. However both Vaud and Tuscany confirm the trend and propose further surveillance.

Figure 11 Average annual change in prevalence in PDA by registry

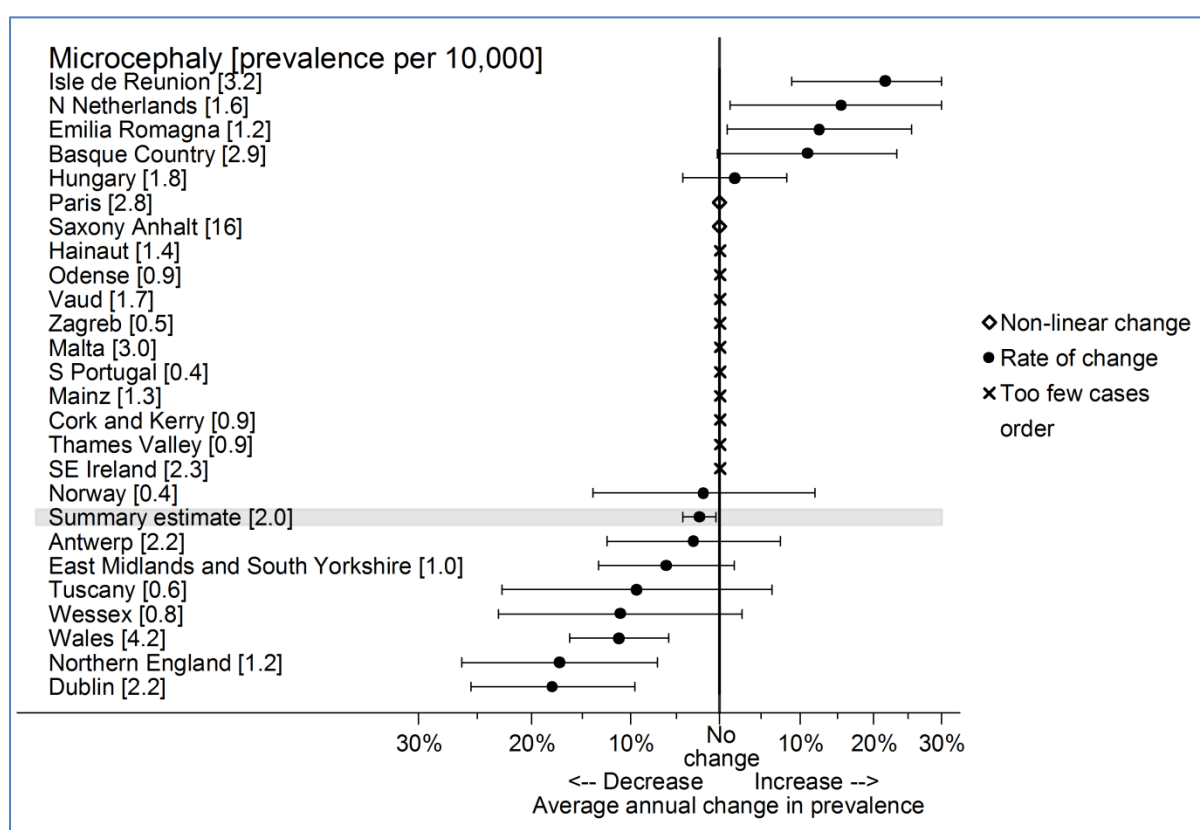


Valproate syndrome occurs as a result of prenatal exposure to valproic acid taken by women to control the symptoms of epilepsy. The fetus is at increased risk of developing dysmorphic features and intellectual deficits. Other anomalies strongly associated with preconceptional valproic acid exposure include Spina bifida, Cardiac anomalies, Cleft palate, Polydactyly and Craniosynostosis. This is the second year a decreasing trend was found in valproate syndrome with prevalence dropping on average by 10.0% per year from 0.05 per 10,000 births in 2003-2004 to 0.03 per 10,000 births in 2011-2012. In total, there were only 46 cases over this ten year period, hence there were too few cases to run the individual registry analysis. Eighteen cases were reported in the Ile de la Reunion registry.

All non chromosomal anomalies have decreased for the sixth consecutive year since pan-European monitoring was introduced in 2007. Prevalence decreased by 0.7% per year from 231.68 per 10,000 births in 2003-2004 to 203.68 per 10,000 births in 2011-2012. A EUROCAT investigation of long-term trends 1983-2012 is on-going and will be published separately.

A decreasing trend in the prevalence of **Microcephaly**, a defect of the nervous system, was detected for the third consecutive year. Prevalence decreased on average by 2.4% from 2.26 per 10,000 births in 2003-2004 to 1.77 per 10,000 births in 2011-2012. Eight registries showed a decreasing trend, but it was only significantly decreasing in Wales, N England and Dublin (Figure 12). The decreasing trend was explained by data quality issues. Wales state “This condition is hard to diagnose consistently. Some microcephaly is not truly congenital but secondary to haemorrhage or epilepsy. Access to neurology notes has not been possible for a few years and this change in ascertainment might explain the falling trend”. Dublin has strict data protection limitations which has been an issue for a number of years now. N England report staff changes may have caused cases to be missed which will be investigated when resources are available.

Figure 12 Average annual change in prevalence in Microcephaly by registry



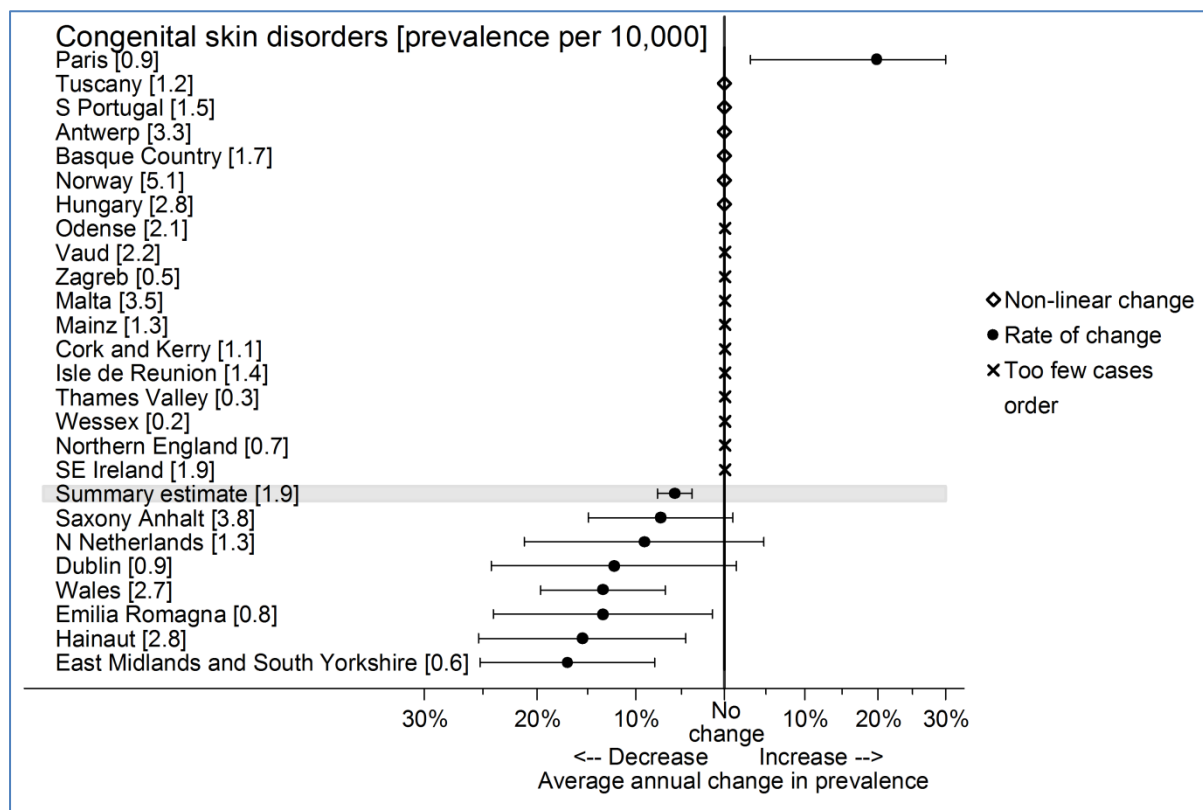
Congenital hydronephrosis has decreased for the sixth consecutive year since pan-European monitoring began. Prevalence decreased by an average of 1.4% per year from 10.13 per 10,000 births in 2003-2004 to 9.63 per 10,000 births in 2011-2012. This anomaly was not investigated further.

Continuing decreasing trends were detected for **Limb reduction** and **Upper limb reduction anomalies**. Upper limb reduction anomalies decreased for the third consecutive year, with prevalence dropping by an average of 3.4% per year from 3.41 per 10,000 births in 2003-2004 to 2.57 per 10,000 births in 2011-2012. Eleven registries showed a decreasing trend but it was only significant in N England, Wales, Emilia Romagna, Dublin and E Midlands & S Yorkshire. Dublin and N England report historically low ascertainment of cases. E Midlands & S Yorkshire and Emilia Romagna do not consider this to be a real trend. Wales state that reporting of this anomaly is excellent, and while it is thought to be a true decreasing trend, the registry will continue to monitor it.

Syndactyly is the most common type of hand deformity involving webbing of adjacent digits (fingers or toe) with the severity ranging from skin webbing to bone involvement. A decreasing pan-Europe trend was detected for the fourth consecutive year with prevalence decreasing on average by 2.8% per year from 5.48 per 10,000 births in 2003-2004 to 3.96 per 10,000 births in 2011-2012. Decreasing trends were found in 11 registries, but they were only significant in Tuscany, Saxony Anhalt, Wales, Dublin, Norway and E Midlands & S Yorkshire. Tuscany considered this to be a real trend and propose further surveillance. Wales and Saxony Anhalt suggest that the significant downward trend is due to the exclusion of minor forms of syndactyly by EUROCAT in 2005. E Midlands & S Yorkshire reported that the trend was due to data quality issues, notably the poor postnatal reporting of less severe anomalies, which is currently being addressed by the registry. Dublin was unable to investigate further due to data confidentiality restrictions and Norway does not consider this to be a real trend.

For the 6th consecutive year, a decreasing trend was detected for **Congenital skin disorders**. Prevalence decreased by 5.8% per year from 3.44 per 10,000 births in 2003-2004 to 1.75 per 10,000 births in 2011-2012. Eleven registries had too few cases for analysis. A decreasing trend was found in 7 registries, of which 4 were significant (Hainaut, Emilia Romagna, Wales and E Midlands & S Yorkshire). Hainaut did not send a report. The other 3 registries concluded that the decreasing trend may be explained by the exclusion of minor skin disorders. Paris was the only registry with a significant increasing trend (Figure 13).

Figure 13 Average annual change in prevalence in Congenital skin disorders by registry



Genetic syndromes and microdeletions decreased for the third consecutive year.

Prevalence dropped by 2.7% per year from 5.12 per 10,000 births in 2003-2004 to 4.44 per 10,000 births in 2011-2012. Only two registries had too few cases to run the analysis.

Prevalence was decreasing in 9 registries, but was only significantly decreasing in Dublin and Wales. Dublin was unable to access key data due to the local data protection legislation. Wales reported a specific problem in extracting syndromic diagnoses from a database in 2012. This problem has now been solved.

Klinefelter syndrome is caused by a sex chromosome trisomy (XXY) and is associated with increased maternal age. Pan-European monitoring found a decreasing trend in this anomaly for the third consecutive year. Prevalence decreased by approximately 5.1% per year from 0.97 per 10,000 births in 2003-2004 to 0.59 per 10,000 births in 2011-2012. Nine registries showed a decreasing trend, of which 6 (Basque Country, N England, Norway, East Midlands and South Yorkshire, Saxony-Anhalt and Wessex) had a higher prevalence compared to the EUROCAT average. The decreasing trend was only significant in Wessex (see Figure 14). Wessex did not provide a report.

Figure 14 Average annual change in prevalence in Klinefelter syndrome by registry

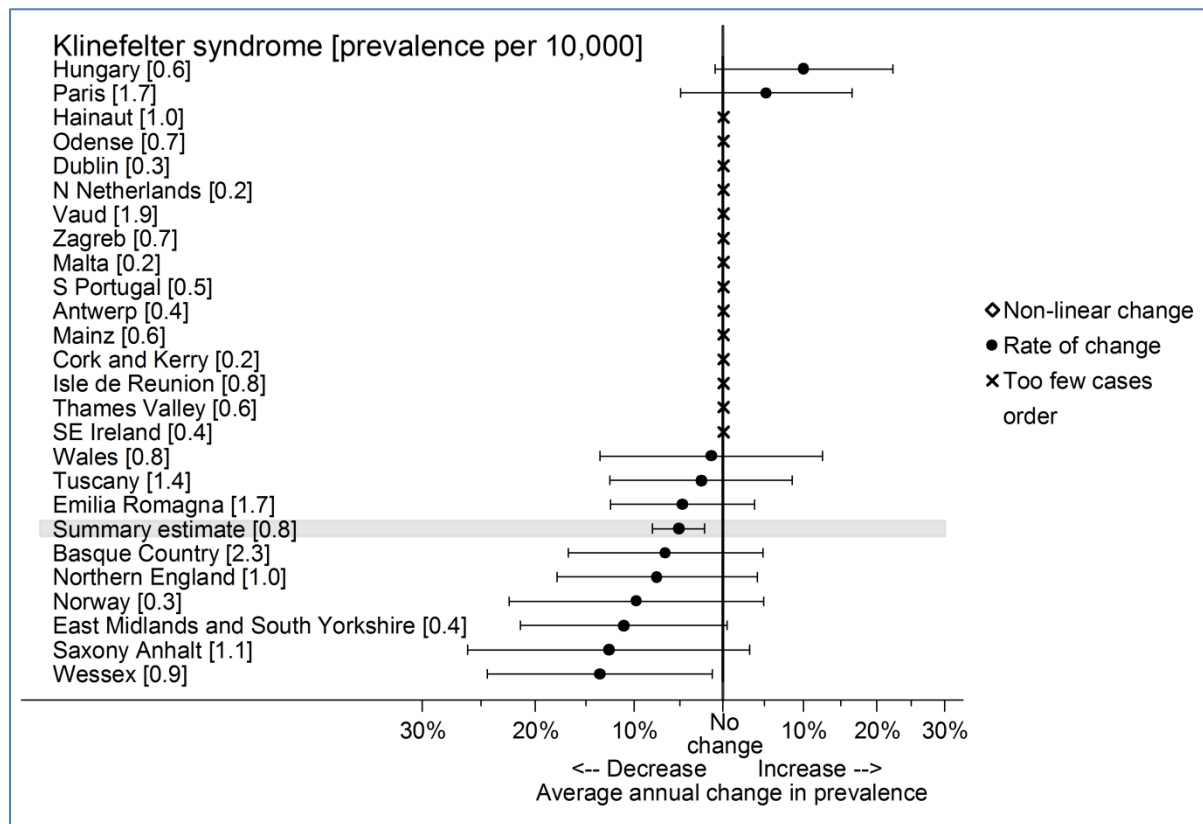
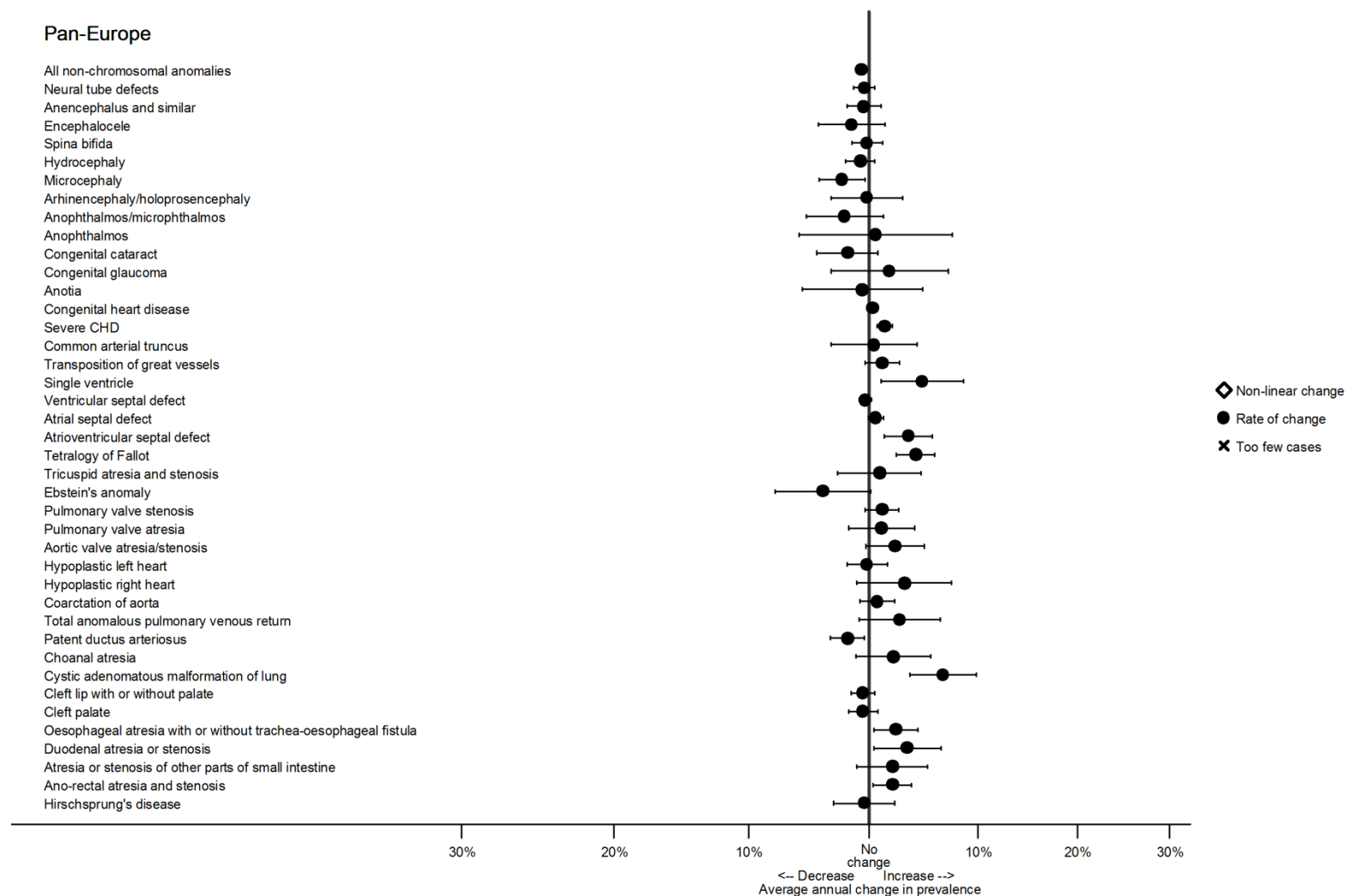


Figure 15: Estimated average percentage change in prevalence and 95% confidence intervals (Pan-Europe analysis 2003-2012)



Pan-Europe

Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb reduction
Upper limb reduction
Lower limb reduction
Complete absence of a limb
Club foot - talipes equinovarus
Hip dislocation and/or dysplasia
Polydactyly
Syndactyly
Skeletal dysplasias
Craniosynostosis
Congenital constriction bands/amniotic bands
Situs inversus
Conjoined twins
Congenital skin disorders
Teratogenic syndromes with malformations
Fetal alcohol syndrome
Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
Chromosomal
Down syndrome
Patau syndrome
Edwards syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted

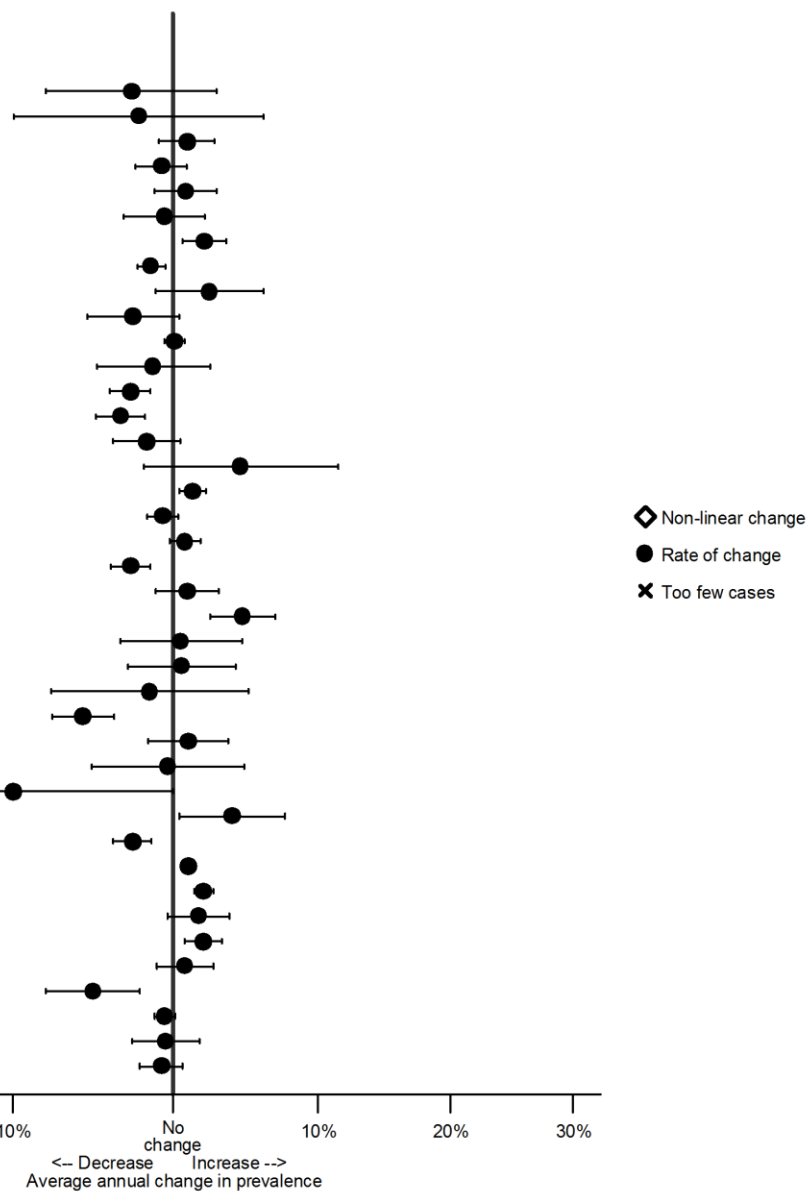


Table 1 Central Registry Statistical Monitoring Results: Reported 8 or 10 year trends by individual registry (2003-2012)

Registry				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Isle de Reunion (FR)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	S W England	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Years tested				2003-2012	2003-2012	2003-2012	2003-2012	2003-2012	2003-2012	2004-2011	2003-2012	2004-2011	2003-2012	2003-2012	2003-2012	2003-2012	2003-2012	2004-2011	2003-2012	2003-2012	2004-2011	2004-2011	2003-2012	2003-2012	2003-2012	2005-2012	2003-2012	2003-2012	2003-2012
Total / in registries	117			5	3	0	0	8	7	2	2	24	2	0	3	6	5	0	6	2	5	10	4	4	2	2	8	2	5
Total \ in registries		139		1	4	1	1	0	1	0	6	0	3	20	5	17	6	5	5	10	1	3	4	8	8	11	1	15	3
Total ~ in registries			173	9	4	6	4	4	11	2	8	25	2	8	1	15	10	2	6	9	8	3	2	12	2	3	7	7	3
Total any in registries	429			15	11	7	5	12	19	4	16	49	7	28	9	38	21	7	17	21	14	16	10	24	12	16	16	24	11

Key: / = significant upward trend \ = significant downward trend ~ = non-linear change over time

5. Clusters

5.1 Overview

For cluster analysis a total of 868 tests were performed with 3.3% being statistically significant, which is slightly higher than would be expected by chance (see Appendix K). A total of 29 clusters were identified: 22 were new, 3 were continuing (identified in the previous monitoring, and were growing in size) and 4 remained the same (and were reported last year <http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2011> (see Appendix L).

5.2 New clusters

Preliminary investigations by registries into the 22 new clusters detected in the monitoring indicated that 8 were not 'true' clusters as defined by EUROCAT, and were explained by data quality issues/ increases in case ascertainment. No preliminary report was available for one cluster (see Table 2, Appendix A). An excess of cases were confirmed for the following 13 congenital anomalies: **Arhinencephaly/holoprosencephaly** (Emilia Romagna); **Atrioventricular septal defect** (Antwerp); **Pulmonary valve stenosis** (Antwerp); **Pulmonary valve atresia** (Thames Valley); **Aortic valve atresia/stenosis** (Wales); **Coarctation of Aorta** (Emilia Romagna); **Cystic adenomatous malformation of lung** (Emilia Romagna); **Cleft lip with or without palate** (SE Ireland); **Bilateral renal agenesis including Potter syndrome** (Thames Valley); **Renal dysplasia** (Wessex); **Syndactyly** (Paris); **Congenital constriction bands/amniotic band** (N Netherlands); and **Turner syndrome** (Vaud).

5.2.1 Reports of preliminary investigations of specific clusters by registries

This section summarises the reports sent to Central Registry. Full investigation reports can be viewed on the members- only part of the EUROCAT website. A new cluster of **Arhinencephaly/holoprosencephaly** was detected in Emilia Romagna. Over a 9 month period, starting in October 2009 and finishing at the start of July 2010, 9 cases were found when an average of 1.98 would normally occur ($p < 0.001$). The preliminary investigation by the registry indicated that they had reviewed the cases and were unable to find an explanation. The registry was unable to explore the possible effect of anaesthesia during surgery due to restricted access to the hospital discharge database. The cluster did not

continue into 2011 and 2012. The registry plans to investigate this anomaly further in relation to asthma medication exposure.

In Antwerp two new cardiac clusters were detected - **Atrioventricular septal defect (AVSD)** and **Pulmonary valve stenosis (PVS)**. Over a 4 month period from late August 2011 to mid-December 2011, a total of 7 cases of AVSD were found when an average of 1.25 would normally occur ($p=0.036$). A significant increasing 10-year trend in AVSD was also detected in the Antwerp region during this period. The initial registry investigation confirmed that the cases were all correctly diagnosed with no duplicates recorded. Five of the 7 cases resided in the most densely populated area of the city. The registry reviewed the following aetiological factors: illness before and during pregnancy; medication use; assisted conception; occupation; consanguinity; familial anamnesis and maternal age. None of these factors explained the cluster and further follow-up is recommended.

The PVS cluster of 17 cases occurred from early February 2010 through to March 2011, when an average of 6.92 would be expected ($p=0.028$). The same aetiological factors as above were explored and again no explanation for the cluster was identified. The registry will continue to monitor this anomaly. Both cardiac clusters will be included in the next Antwerp EUROCAT report which is distributed to regional authorities.

A cluster of **Pulmonary valve atresia (PVA)** cases was detected in Thames Valley, starting in the middle of March 2010 and finishing mid December 2010. Over this 9 month period, a total of 8 cases were found when an average of 2.11 would normally occur ($p=0.034$). Preliminary registry investigation confirmed that all the cases were correctly recorded and that there were no unusual spatial or time dimensions. The registry suggested that access to 'Viewpoint' ultrasound scan information has provided more detailed information of cardiac anomalies, which has increased the antenatal ascertainment of PVA where it occurs alongside another cardiac anomaly. However, the registry regards this as only a partial explanation for the cluster and will continue to monitor this anomaly.

A new cluster of **Aortic valve atresia/stenosis** was detected in Wales. This cluster occurred in a 8 week period in May-June 2010, with 8 cases being found when an average of 1.36 would be expected ($p=0.046$). The registry carried out a preliminary investigation. The cases were verified and found to be spread across South Wales. Some aetiological factors examined were BMI, illness before and during pregnancy and medication. The registry state "An association between diabetes and congenital heart disease is well known and by extension to high BMI. This might be a possible causal explanation; but it would

better explain a long term trend rather than an apparent cluster. The other risk factors seem more disparate and less unifying as an explanation". The cluster will be reported to Public Health Wales.

Coarctation of aorta is a severe type of CHD that occurs due to constriction in the region of aorta where the ductus joins the aorta. A new cluster for this defect was observed in Emilia Romagna. This cluster occurred in April 2010 over a 5 day period, with 5 cases being found when an average of only 0.24 would be expected ($p=0.008$). The preliminary investigation noted that all cases were isolated. The registry reported that they had reviewed the following aetiological factors: socioeconomic status; smoking; alcohol intake; previous pregnancies; maternal age; citizenship and medications. A number of the mothers had taken asthma/allergy medication during pregnancy and the registry state that correlation between medication and Coarctation of aorta and CHD in general will be further examined, with feedback to the clinicians in the reporting centres.

In Emilia Romagna a new cluster of **Cystic adenomatous malformation of lung** occurred between mid April 2010 and the end of February 2011. The cluster contained 12 cases when 3.65 cases would be expected ($p=0.014$). The registry reported that they had reviewed the following aetiological factors: sex; marital status; maternal education; smoking; alcohol intake; previous pregnancies; family history; maternal age; citizenship; occupation and medications. No spatial concentration was observed. The registry concluded that there were no factors which merited further investigation of this cluster.

South East Ireland detected a new cluster of **Cleft lip with or without palate**. Five cases were observed in a 4 week period May-early June 2011 when an average of 0.42 cases would be expected ($p=0.029$). All cases were confirmed through examination of case records. The cases were not clustered near each other but dispersed across four counties in the region. The aetiological factors that the registry explored were: first trimester drugs exposure; fertility treatment; multiple pregnancy; mother's occupation; folic acid intake; genetic testing; assisted conception and family history. The registry conclude "This is a very small cluster, and there are no factors arising from the preliminary investigation that seem to warrant further investigation as yet, but further surveillance is warranted."

Bilateral renal agenesis including Potter syndrome is a urinary condition where there is bilateral absence, agenesis, dysplasia or hypoplasia of kidneys including Potter's syndrome. This is a fatal condition. A cluster was detected in Thames Valley over a 4 month period November 2011 to March 2012. Five cases were recorded when only 0.78 would have been

expected ($p=0.045$). The registry examined more recent data held locally and found further cases in 2013. As there have been no changes in reporting practice, this increase in cases cannot be explained. Further surveillance will be undertaken and BINOCAR will be informed with a view to action.

Renal dysplasia was a new cluster detected in Wessex over a 52 day period Jan-Apr 2010. It consisted of 13 cases when an average of 3.09 would normally occur ($p=0.022$). All cases were verified, 7 cases being unilateral, 4 bilateral, 1 with Meckel-Gruber syndrome and 1 with multiple anomalies. The registry investigation did not identify an explanation for the cluster. The registry will monitor this anomaly for another year.

In Paris a cluster of **Syndactyly** was detected. There were 15 cases over a 6 month period May-November 2011 when 4.14 would be expected ($p=0.008$). The registry examined the cases and found no duplicates or miscoding. Possible exposures were investigated including smoking; alcohol/drug use; medication; illness before and during pregnancy. The registry observes a continuing increase in prevalence in more recent data. However no obvious explanation for the cluster and increasing prevalence could be found. The registry will include this result in their annual report to the French Institute for Public Health Surveillance (InVS).

Congenital constriction bands/amniotic band (ABS) is a condition where bands in the amniotic fluid cause constriction of part of the brain, body or limbs, including limb-body-wall complex. It can range in severity with the more severe cases having decreased blood supply to limbs and amputation. If the bands become wrapped around the head or umbilical cord it can be life threatening for the fetus. Northern Netherlands had a new cluster, 5 cases over a 7 month period (late December 2009 through to early August 2010) when an average of 1.03 cases would be expected ($p=0.029$). After verification of cases, many aetiological factors were scrutinised but the most interesting was fertility. Three of the mothers were subfertile and became pregnant after some form of ART treatment. However there is nothing in the literature to support ART/subfertility as a risk factor for ABS. The registry report concluded "Looking at the heterogeneous nature of the malformations (isolated and multiple) and the low numbers per year, we consider this cluster has likely occurred by chance. Results will be presented at the meeting of the Ministry of Health, Welfare and Sports and the National Committee for registration of congenital anomalies." This anomaly will be followed up by the registry.

A cluster of **Turner syndrome** cases were detected in Vaud. Over a 14+ month period, starting towards the end of November 2009 and finishing in February 2011, 10 cases were found when an average of 3.48 would normally occur ($p=0.022$). The registry investigation found that the prevalence of Turner syndrome in 2008-2009, before the period of the cluster, was comparable to the rest of EUROCAT (Vaud 1.92, EUROCAT 2.3), but in the time period 2010-2011 Vaud's prevalence was much higher than the EUROCAT average (6.18 vs 2.27). They suggest that better and earlier detection by echography might explain the early TOPFA cases, which might otherwise have ended in spontaneous abortion. The registry plans further surveillance of this anomaly

5.2.2 Continuing clusters

This year we observed three clusters that were also detected in the 2011 Annual Statistical Monitoring and had continued to grow in size (increase in the number of cases) and occurred over a longer time period. The continuing clusters detected were: **Total anomalous pulmonary venous return (TAPVR)** in SW England; **Clubfoot** and **Polydactyly** in Paris. The SW England investigation into the TAPVR cluster concluded that this was not a true cluster but rather a statistical artefact caused by a deficit of cases in 2008-2009 which needs to be investigated rather than an excess of cases.

Club foot - talipes equinovarus is a foot anomaly with equinus of the heel, varus of the hindfoot and adductus of the forefoot. In this year's statistical monitoring (2012) there was a continuing cluster in the Paris registry, starting in late September 2009 and ending in February 2011. Over this period of 17 months a total of 72 cases were found when an average of 43.47 would normally occur ($p<0.001$). In statistical monitoring 2011, the cluster was much smaller and over a much shorter time period. Starting in early August 2010 over only a period of 6 days, 6 cases were found when an average of 0.56 would normally occur ($p=0.049$). The registry once again verified all cases in this increasing cluster and concluded that they were not able to explain the cluster but that it is part of an increasing trend in club foot in 2011. The registry report that the prevalence in 2012 is coming down. Plans are to continue to monitor and include in the annual report to the French Institute for Public Health Surveillance.

The **Polydactyly** cluster detected in the Paris registry (2012 Monitoring) started in April 2010 and finished at the start of October 2011. Over this 19 month period, a total of 70 cases were found when an average of 42.1 would normally occur ($p<0.001$). In 2011 there were a total of 60 cases in the 18 month period August 2009 to February 2011 when an average of

27.71 would normally occur ($p < 0.001$). A cluster of polydactyly cases was also detected in the 2010 monitoring report. However, it ended three months before the current cluster started, hence there was no overlap in time period. The cluster in the 2010 statistical monitoring was smaller and less significant. The registry conclude that “the cluster is likely to be due to under-registration of the isolated cases of polydactyly for the preceding years. The cluster is due to the fact that we have addressed and rectified the registration problem for cases of isolated polydactyly.”

Table 2: Outcomes of local registry preliminary investigations into 22 new clusters detected in 2012 monitoring

Anomaly	Registry	EUROCAT Classification of Explanation	No of cases in cluster	Length of cluster (days)	P value
Arhinencephaly/holoprosencephaly	Emilia Romagna (IT)	Excess of cases confirmed	9	278	<0.001
Atrial septal defect	Emilia Romagna (IT)	Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding	48	68	<0.001
Atrioventricular septal defect	Antwerp (BE)	Excess of cases confirmed	7	113	0.036
Tetralogy of Fallot	E Mid & S York (GB)	Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding	7	8	0.039
Pulmonary valve stenosis	Antwerp (BE)	Excess of cases confirmed	17	412	0.028
Pulmonary valve atresia	Thames Valley (GB)	Excess of cases confirmed	8	272	0.034
Aortic valve atresia/stenosis §	Wales (GB)	Excess of cases confirmed	8	56	0.046
Coarctation of aorta	Emilia Romagna (IT)	Excess of cases confirmed	5	4	0.008
Cystic adenomatous malformation of lung §	Emilia Romagna (IT)	Excess of cases confirmed	12	314	0.014
Cleft lip with or without palate	SE Ireland (IE)	Excess of cases confirmed	5	25	0.029

Anomaly	Registry	EUROCAT Classification of Explanation	No of cases in cluster	Length of cluster (days)	P
Ano-rectal atresia and stenosis	E Mid & S York (GB)	Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding	6	6	0.022
Bilateral renal agenesis including Potter syndrome	SW England (GB)	Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding i.e. 2 cases have suspected syndrome aetiology	5	22	0.023
Bilateral renal agenesis including Potter syndrome	Thames Valley (GB)	Excess of cases confirmed	5	120	0.045
Renal dysplasia	Wessex (GB)	Excess of cases confirmed	13	83	0.022
Indeterminate sex	Emilia Romagna (IT)	Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding	6	370	0.049
Hip dislocation and/or dysplasia	Cork and Kerry (IE)	No report received	58	189	<0.001
Hip dislocation and/or dysplasia	N Netherlands (NL)	Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding	144	532	<0.001
Polydactyly	N England (GB)	Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding	5	27	0.016
Syndactyly	Paris (FR)	Excess of cases confirmed	15	188	0.008
Syndactyly	Thames Valley GB)	Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding	18	505	0.037
Congenital constriction bands/amniotic band	N Netherlands (NL)	Excess of cases confirmed	5	227	0.029
Turner syndrome	Vaud (CH)	Excess of cases confirmed	10	449	0.022

For the second time, we conducted cluster monitoring at country level i.e. countries with more than one registry were monitored to detect clusters at a national as well as at a regional level. Five countries were included in this analysis:

- Belgium (Antwerp, Hainaut)
- France (Ile de la Reunion, Paris)
- Ireland (Cork & Kerry, Dublin, SE Ireland)
- Italy (Emilia Romagna, Tuscany)
- UK (E Midlands & S Yorkshire, N England, SW England, Thames Valley, Wales, Wessex)

Sixteen clusters were detected, of which 8 occurred in one of the component registries and were already identified in the individual registry monitoring. The remaining 8 country clusters were: **NTD** (UK); **Ventricular septal defect** (Italy); **Cleft lip with or without palate** (UK); **Duodenal atresia or stenosis** (Belgium); **Congenital hydronephrosis** (UK); **Craniosynostosis** (France); **Conjoined twins** (UK) and **Turner syndrome** (Belgium) (see Appendix M). The **Duodenal atresia or stenosis** cluster consisted of 5 cases occurring in a 6 week period April-May 2010 when an average of 0.33 would be expected ($p < 0.001$). A joint investigation is currently ongoing in the Belgian registries to see if a common cause can be found. The Belgian **Turner syndrome** cluster in April-June 2010 consisted of 8 cases when an average of 1.38 would be expected to occur ($p = 0.035$). Whilst there is general concern in some regions of Antwerp about the chemical industry and exposure to heavy metals, the preliminary investigation does not lead to a common cause or specific exposure that could be an explanation for this cluster. Antwerp advises follow-up and notification of the cluster to regional authorities.

Of the four clusters detected in the United Kingdom, **NTDs**, **cleft lip with or without palate** and **congenital hydronephrosis** were all clusters of one day duration. Investigation by the British Isles Network of Congenital Anomaly Registers (BINOCAR) network concluded: “these cases were considered a cluster as they all have the same date of conception. However, as date of conception was calculated using completed weeks of gestation, these cases may actually been conceived over one week. If this was the case the cluster would then not be statistically significant.” The **Conjoined twins** cluster which occurred late November 2011 to early March 2012 consisted of 10 cases when an average of 2.19 would be expected ($p = 0.036$). Preliminary investigation identified a duplicate case, which was

deleted. This correction to the data made the cluster disappear. No follow-up is proposed for these UK clusters.

6. Use of the EDMP statistical monitoring function by registries to detect clusters or trends on recent data.

We asked all full and associate member registries (n=37) to report if they had used the EDMP statistical monitoring function in the last year to look for clusters or trends using more recent data held locally. Responses were received from 22 full member and 6 associate member registries. Twelve registries reported that they had used the EDMP to look for clusters or trends in more recent data or to validate information on trends and clusters supplied by Central Registry. Isle de la Reunion provided details of their investigations into clusters of **Microcephaly** and **Congenital glaucoma** detected by local monitoring:

- The cluster in **Microcephaly** confirmed an excess of cases over a 14+ month period, 18 cases were detected when 5.77 were expected ($p=0.014$). The registry report states “In our island, we know that we have a public health problem about the foetal alcoholism syndrome and in this cluster this syndrome has a predominant place.”
- The cluster in **Congenital glaucoma** confirmed an excess of cases over a 6 month period, 6 cases were detected when 0.91 were expected ($p=0.049$). The registry proposes genetic counselling for parents to check genetic factors.

Sixteen registries reported that they did not use the EDMP. Reasons for not using the EDMP statistical monitoring function included: incompatibility with local coding systems; preference to use a common system that is in use in the registries own country/region, new staff as yet untrained on its use and poor resources.

7. Conclusion

The statistical monitoring of trends and clusters is fundamental to the primary prevention of congenital anomalies, providing timely information on the stability and change in rates. Whilst we observed a new decreasing trend in one of the heart anomalies (Patent ductus arteriosus) we are still experiencing continuing increasing trends in a number of severe cardiac defects (AVSD, Tetralogy of Fallot and Single ventricle). Primary prevention of congenital anomalies continues to be a key objective of the EUROCAT network.

Appendix A: EUROCAT full member registries inclusion list

	Pan-Europe trends		Cluster monitoring	
	Included in analysis	Investigation reports	Included in analysis	Investigation reports
Austria, Styria	No, as data transmission >1 year late			
Belgium, Antwerp	✓	✓	✓	✓
Belgium, Hainaut	✓	X	✓	-
Croatia, Zagreb	✓	-	No, as population fluctuation >10%	
Denmark, Odense	✓	-	✓	-
France, French West Indies	No, as data for 4 years only			
France, Paris	✓	✓	✓	✓
France, Reunion	✓	✓	✓	✓
Germany, Mainz	✓	-	No data for 2012	
Germany, Saxony Anhalt	✓	✓	No, as partial DOB information	
Hungary	✓	X	No data for 2012	
Ireland, Cork & Kerry	✓	X	✓	X
Ireland, Dublin	✓	✓	✓	-
Ireland, South East	✓	✓	✓	✓
Italy, Emilia Romagna	✓	✓	✓	✓
Italy, Tuscany	✓	✓	✓	-
Malta	✓	X	No data for 2012	
Netherlands, Northern	✓	✓	✓	✓
Norway	✓	✓	No, as partial DOB information	
Poland, Wielkopolska	No, as data transmission >1 year late			
Portugal, South	✓	✓	No data for 2012	
Spain, Basque Country	✓	✓	No data for 2012	
Spain, Valencia Region	No, as data for 5 years only		No data for 2012	
Switzerland, Vaud	✓	✓	✓	✓
Ukraine	No, as data for 7 years only		No data for 2012	
UK, E Midlands & S Yorkshire	✓	✓	✓	✓
UK, Northern England	✓	✓	✓	✓
UK, South West England	No, as data for 8 years only		✓	✓
UK, Thames Valley	✓	✓	✓	✓
UK, Wales	✓	✓	✓	✓
UK, Wessex	✓	X	✓	✓

✓ 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 1.3, Chapter 3.3 (<http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf>), and are analysed in the following ways:

1. Prevalence by outcome of pregnancy, by registry and year (or combined registries/years). All cases and All cases excluding genetic conditions⁵.
2. Analysis of trends, all outcomes of pregnancy combined. Genetic conditions are excluded from the statistical monitoring of all other subgroups.
3. Detection of clusters, all outcomes of pregnancy combined. Genetic conditions are excluded from the statistical monitoring of all other subgroups.

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Include in monitoring of trends	Include 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	✓	✓	✓
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	✓	✓	✓
Transposition of great vessels	✓	✓	✓
Single ventricle	✓	✓	✓
VSD	✓	✓	✓
ASD	✓	✓	✓
AVSD	✓	✓	✓

⁵ Genetic syndromes/ microdeletions, skeletal dysplasias chromosomal anomalies

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Include in monitoring of trends	Include in monitoring of clusters
Tetralogy of Fallot	✓	✓	✓
Tricuspid atresia and stenosis	✓	✓	✓
Ebstein's anomaly	✓	✓	✓
Pulmonary valve stenosis	✓	✓	✓
Pulmonary valve atresia	✓	✓	✓
Aortic valve atresia/stenosis	✓	✓	✓
Hypoplastic left heart	✓	✓	✓
Hypoplastic right heart	✓	✓	✓
Coarctation of aorta	✓	✓	✓
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	✓	✓	✓
Diaphragmatic hernia	✓	✓	✓
Abdominal wall defects	✓	NO	NO
Gastroschisis	✓	✓	✓
Omphalocele	✓	✓	✓
Urinary	✓	NO	NO
<i>Bilateral</i> renal agenesis including Potter syndrome	✓	✓	✓
Renal Dysplasia	✓	✓	✓
Congenital hydronephrosis	✓	✓	✓
Bladder exstrophy and/or epispadia	✓	✓	✓

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Include in monitoring of trends	Include in monitoring of clusters
Genital	✓	NO	NO
Posterior urethral valve and/or prune belly	✓	✓	✓
Hypospadias	✓	✓	✓
Indeterminate sex	✓	✓	✓
Limb	✓	NO	NO
Limb reduction	✓	✓	✓
Upper limb reduction	✓	✓	✓
Lower limb reduction	✓	✓	✓
Complete absence of a limb	✓	✓	✓
Club foot - talipes equinovarus	✓	✓	✓
Hip dislocation and/or dysplasia	✓	✓	✓
Polydactyly	✓	✓	✓
Syndactyly	✓	✓	✓
Other anomalies/ syndromes			
Skeletal dysplasias	✓	✓	NO
Craniosynostosis	✓	✓	✓
Congenital constriction bands/amniotic band	✓	✓	✓
Situs inversus	✓	✓	✓
Conjoined twins	✓	✓	✓
Congenital skin disorders	✓	✓	✓
Teratogenic syndromes with malformations	✓	✓	NO
Fetal alcohol syndrome	✓	✓	✓
Valproate syndrome	✓	✓	✓
Maternal infections resulting in malformations	✓	✓	✓
Genetic syndromes + microdeletions	✓	✓	NO
Sequences	✓	NO	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: Summary of statistical methods

Trends

The pan-Europe monitoring can only be conducted centrally as it uses data from all the registries combined. The methodology used for pan-Europe monitoring is the same as for the ten year trend monitoring (Box 1) with the exception that it is run using the last 10 years of data (2003-2012) or using 9 years of data within the 10 year period (2003-2012) and adjusts for the effect of registry by fitting a multi-level poisson regression model. Statistical methods:

1. A chi square test for trend and for non-linear change based on number of cases and number of births per year is performed.
2. Ten year trend tests are run using 8 or 10 years of data within the 10 year period (2003-2012).
3. Trend analysis is presented by individual year unless there are too few cases, when data is then grouped by two year intervals.
4. Trend analysis is always based on year of birth/delivery.
5. A trend test is performed if the average expected number of cases per 2 year interval is 5 or more, OR if the observed number of cases per 2 year interval is 2 or more
6. Significant increasing or decreasing monotonic (going in one direction) trends are reported.
 - Where $p < 0.05$ for trend component and $p > 0.01$ for non-linear component, the results are identified as 'increasing or decreasing trend'
 - Where $p < 0.05$ for trend component and $p < 0.01$ for non-linear component and the prevalence trend is monotonic, the results are identified as 'increasing or decreasing trend '
 - Where $p < 0.05$ for trend component and $p < 0.01$ 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.

The significance level (p-value) for both chi squared tests, direction (upward or downward) are given in the output.

7. Trend analysis is conducted on 78 EUROCAT congenital anomaly subgroups and the following computer generated subgroups adjusted for maternal age and in utero survival: Down syndrome, Patau syndrome and Edward syndrome.
8. Registries must have used ICD10 coding for the whole 10 year period tested to be included in surveillance of the following 7 subgroups:
 - Severe CHD
 - Aortic valve atresia/stenosis
 - Hypoplastic right heart
 - Cystic adenomatous malformation of lung
 - Skeletal dysplasia
 - Teratogenic syndromes with malformations
 - Valproate syndrome

Clusters

1. A 'scan' moving window method is used to detect clusters, (See EUROCAT Statistical Monitoring Protocol <http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2012.pdf>), scanning all recorded cases in the period 2008-2012.
2. Clusters or deficits occurring in the last 2 years (2011-2012) that are less than 18 months in length are reported.
3. A minimum of 7 cases over the surveillance period (2008-2012) is needed to run the scan analysis.
4. The default scan analysis uses estimated date of conception, if date of conception is cannot be estimated for > 10% of cases, then cluster analysis uses date of birth.
5. 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 (2012). If date of birth/delivery is used to detect clusters, the last full year (1 January – 31 December) is included in the surveillance.
6. The output of cluster analyses lists all significant clusters which may be over-lapping. All the output data should be examined to determine the full time period over which the excess number of cases is observed. This may be outside the start and end date of the most significant cluster. Cluster analysis is run on 72 EUROCAT subgroups of congenital anomalies (Appendix B). Seventeen major heterogeneous subgroups (e.g. nervous system, eye, congenital heart defects etc.) are excluded from analysis.
7. Cluster test results are presented alongside 5-year trend (chi square) results, to help assess whether the cluster could be described as a short term trend.

Appendix D: Summary of local registry preliminary investigation protocols 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 (<http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2012.pdf>). 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:

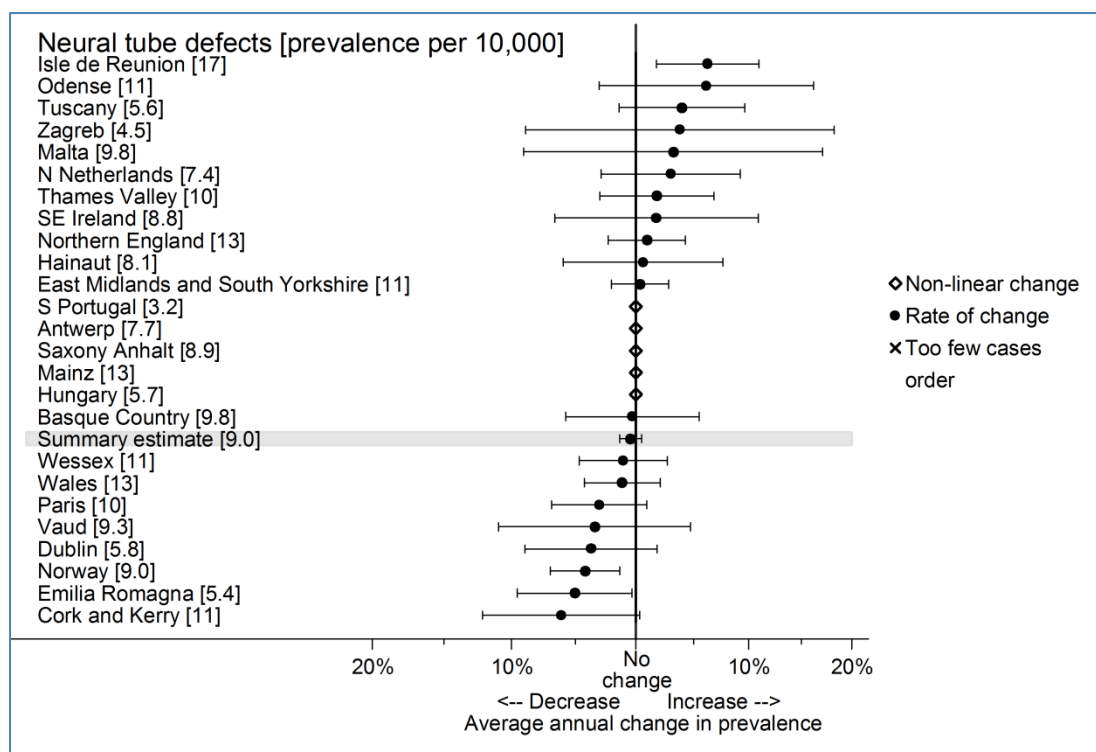
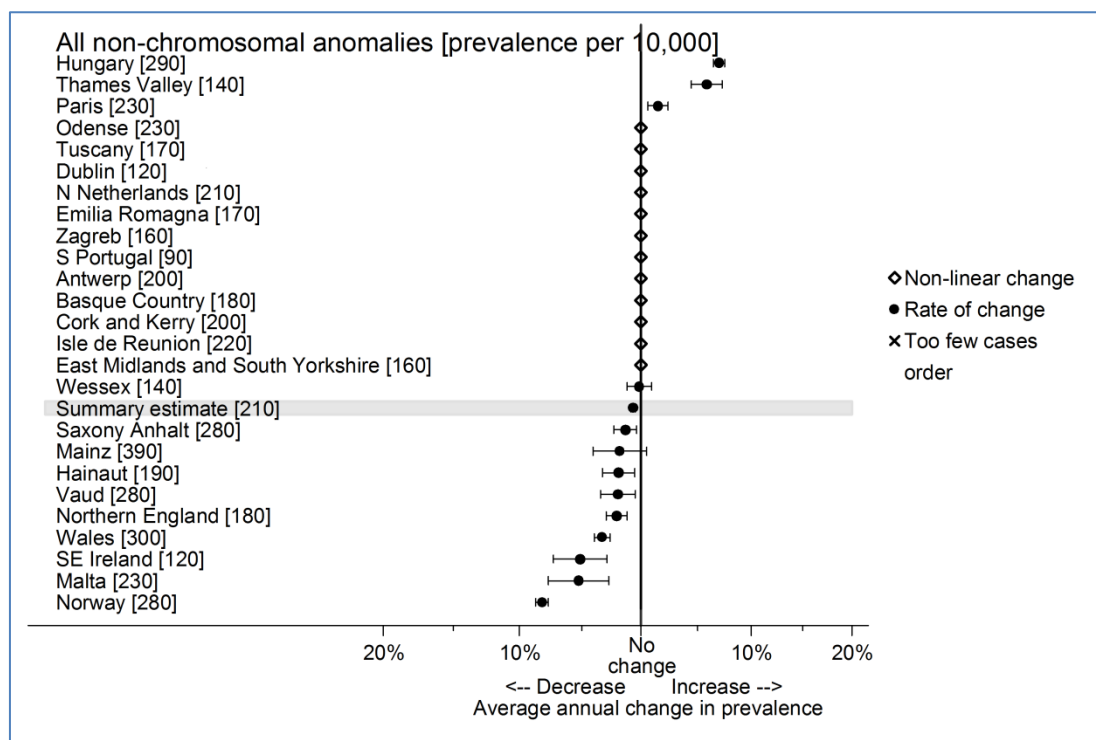
- Apparent cluster with cause for concern, further investigation on-going
- Cluster associated with aetiological heterogeneity, changes in inclusion criteria, diagnosis, familial or twin recurrence
- Excess of cases confirmed, but no further investigation proposed other than further surveillance
- Increase 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

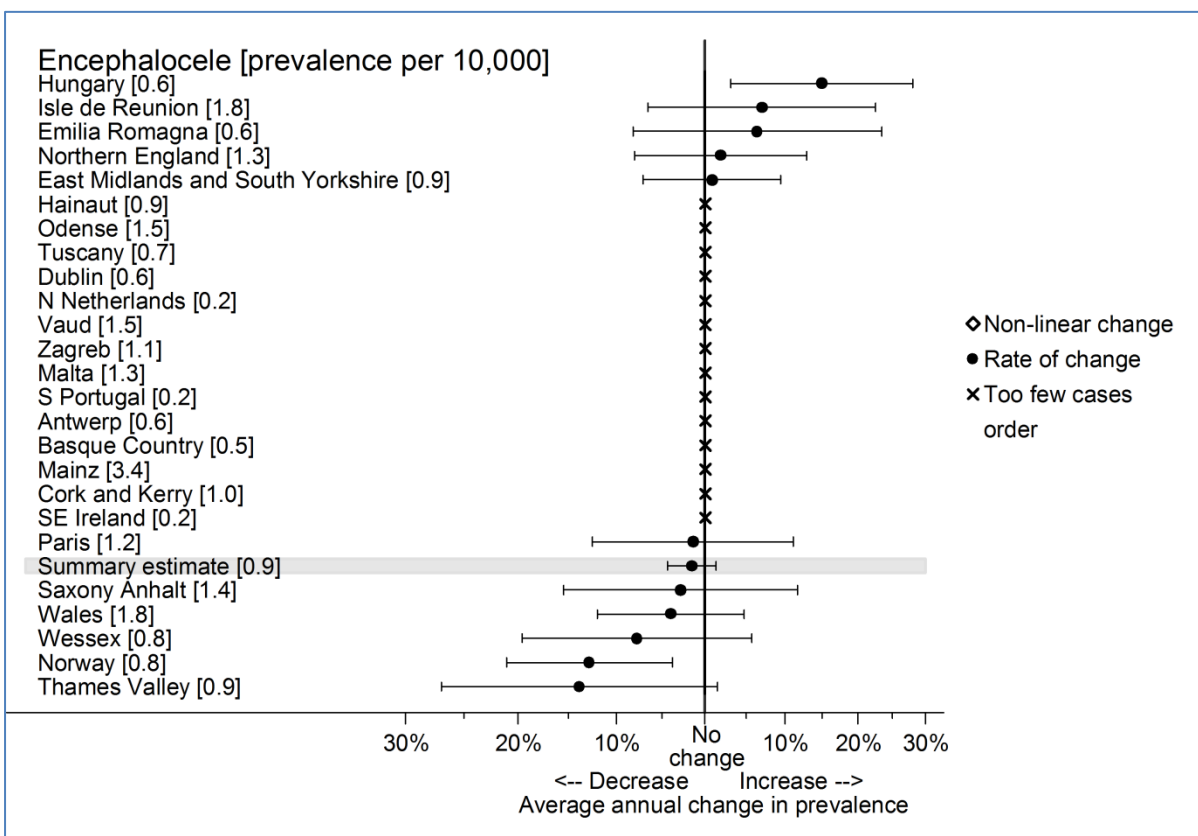
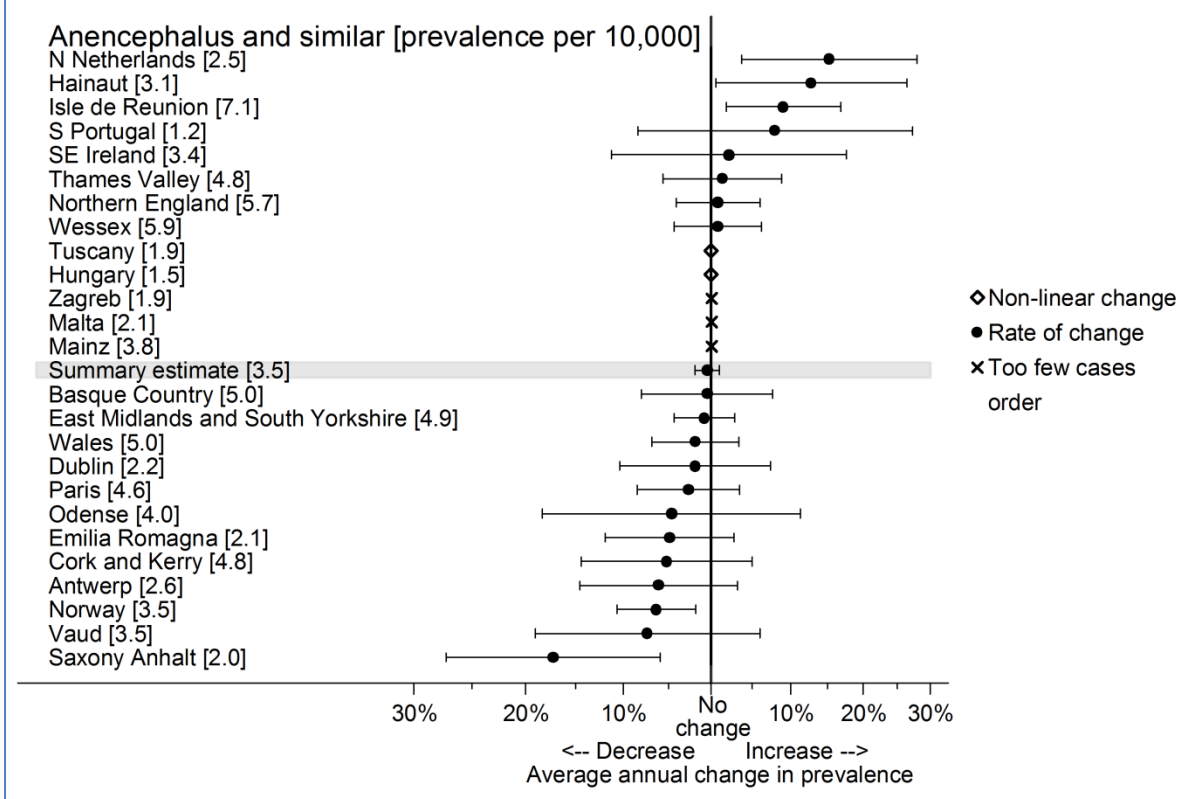
Appendix E: Summary of significant ten year increasing and decreasing trends detected in the pan-Europe analysis 2012*

Anomaly Subgroup	Direction	Signalled in 2011	Annual % Change			Trends prioritised for Investigation
			% change	Lower CI	Upper CI	
All non-chromosomal anomalies	Decreasing	Yes	-0.7	-0.9	-0.5	
Microcephaly	Decreasing	Yes	-2.4	-4.3	-0.4	
Severe CHD	Increasing	Yes	+1.4	+0.7	+2.1	✓
Single Ventricle	Increasing	Yes	+4.7	+1.1	+8.6	✓
AVSD	Increasing	Yes	+3.5	+1.3	+5.7	✓
Tetralogy of Fallot	Increasing	Yes	+4.1	+2.4	+5.9	✓
PDA as only	Decreasing	No	-1.9	-3.3	-0.4	
Cystic adenomatous malformation of lung	Increasing	Yes	+6.7	+3.6	+9.8	✓
Oesophageal atresia with or without trachea-oesophageal fistula	Increasing	No	+2.3	+0.4	+4.3	✓
Duodenal atresia or stenosis	Increasing	Yes	+3.4	+0.4	+6.5	✓
Ano-rectal atresia and stenosis	Increasing	Yes	+2.0	+0.3	+3.8	✓
Renal Dysplasia	Increasing	Yes	+2.1	+0.6	+3.5	✓
Congenital hydronephrosis	Decreasing	Yes	-1.4	-2.3	-0.6	
Limb reduction	Decreasing	Yes	-2.8	-4.1	-1.5	
Upper limb reduction	Decreasing	Yes	-3.4	-4.9	-1.8	
Club foot - talipes equinovarus	Increasing	Yes	+1.3	+0.4	+2.2	✓
Syndactyly	Decreasing	Yes	-2.8	-4.0	-1.5	
Craniosynostosis	Increasing	Yes	+4.7	+2.5	+6.9	✓
Congenital Skin Disorders	Decreasing	Yes	-5.8	-7.7	-3.8	
Valproate syndrome	Decreasing	Yes	-10.0	-18.9	0.0	
Maternal infections resulting in malformations	Increasing	No	+3.9	+0.4	+7.6	✓
Genetic syndromes and microdeletions	Decreasing	Yes	-2.7	-3.9	-1.5	
Chromosomal	Increasing	Yes	+1.0	+0.5	+1.4	✓
Down Syndrome unadjusted	Increasing	Yes	+2.0	+1.4	+2.6	✓
Edward Syndrome unadjusted	Increasing	Yes	+2.0	+0.7	+3.2	✓
Klinefelters	Decreasing	Yes	-5.1	-8.0	-2.2	

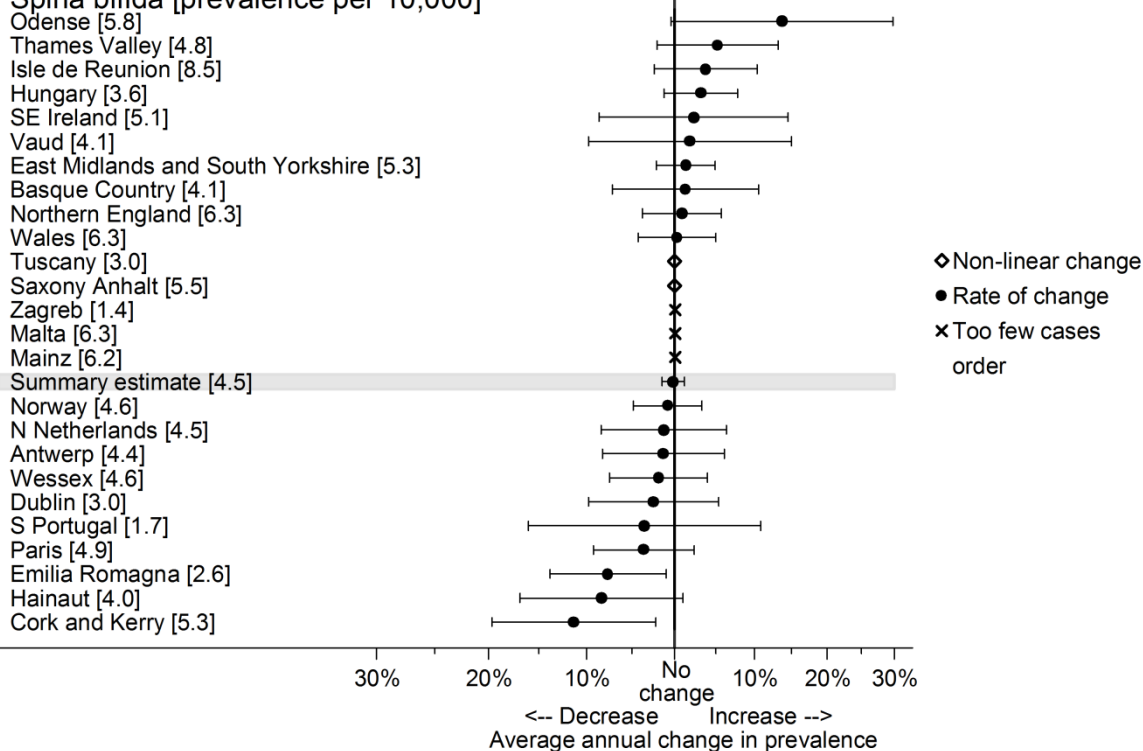
Note: *Significant non-linear change not included in this table

Appendix F: Forest plots showing ten year increasing and decreasing trends detected in the pan-Europe analysis by anomaly subgroup

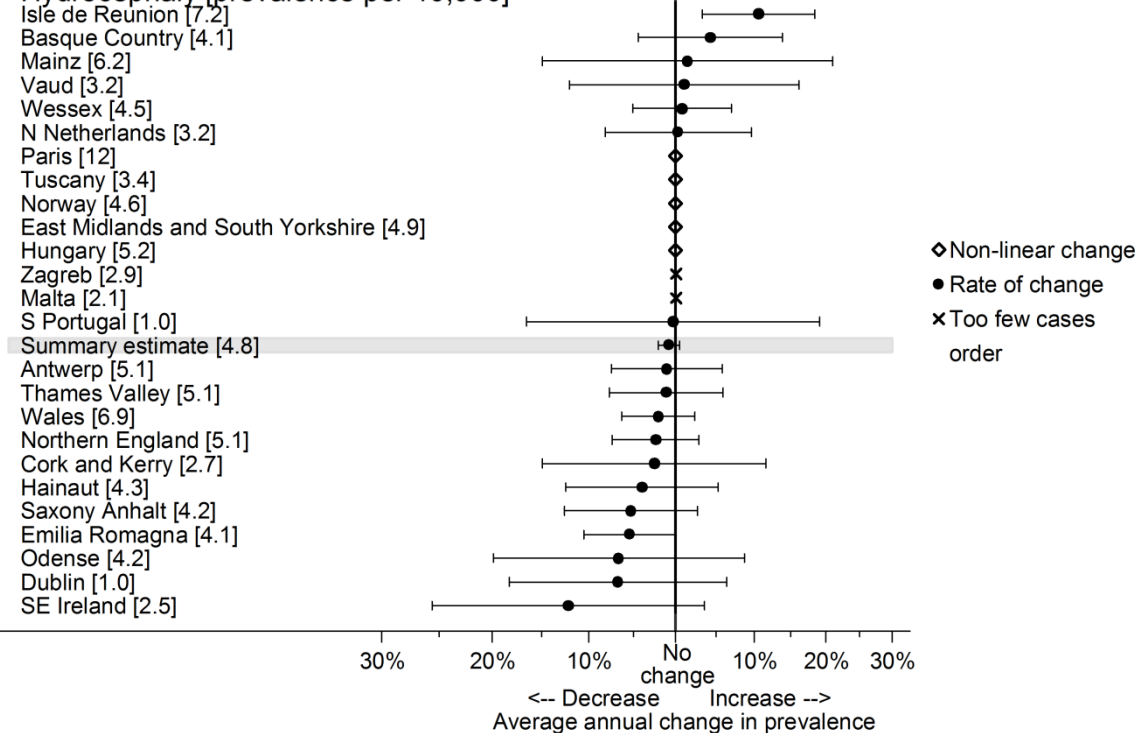


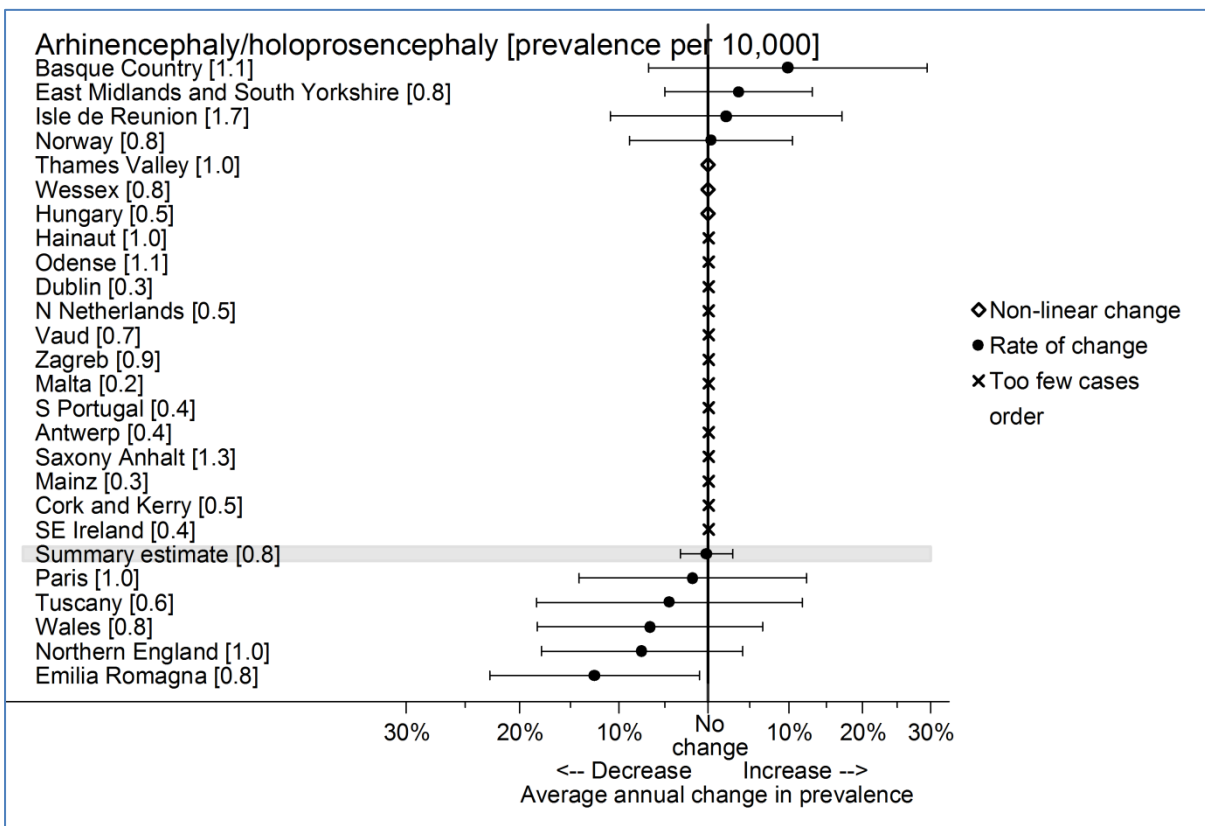
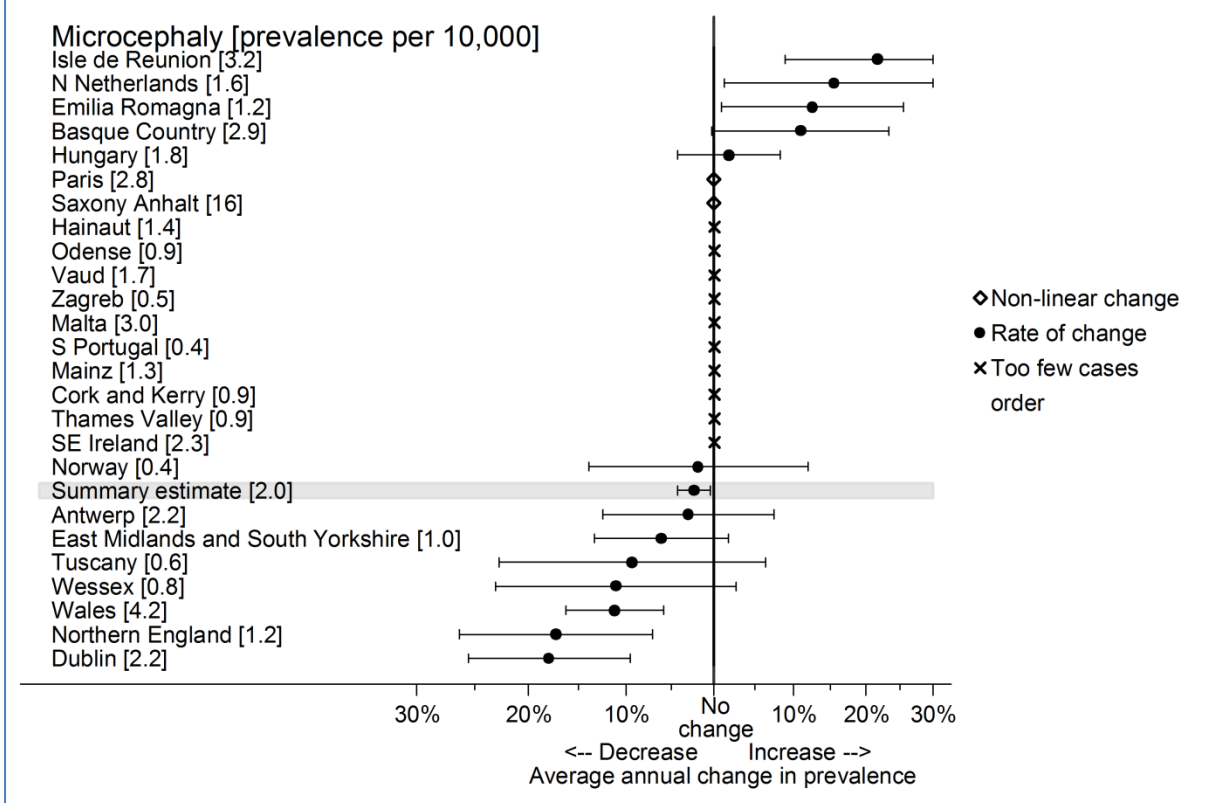


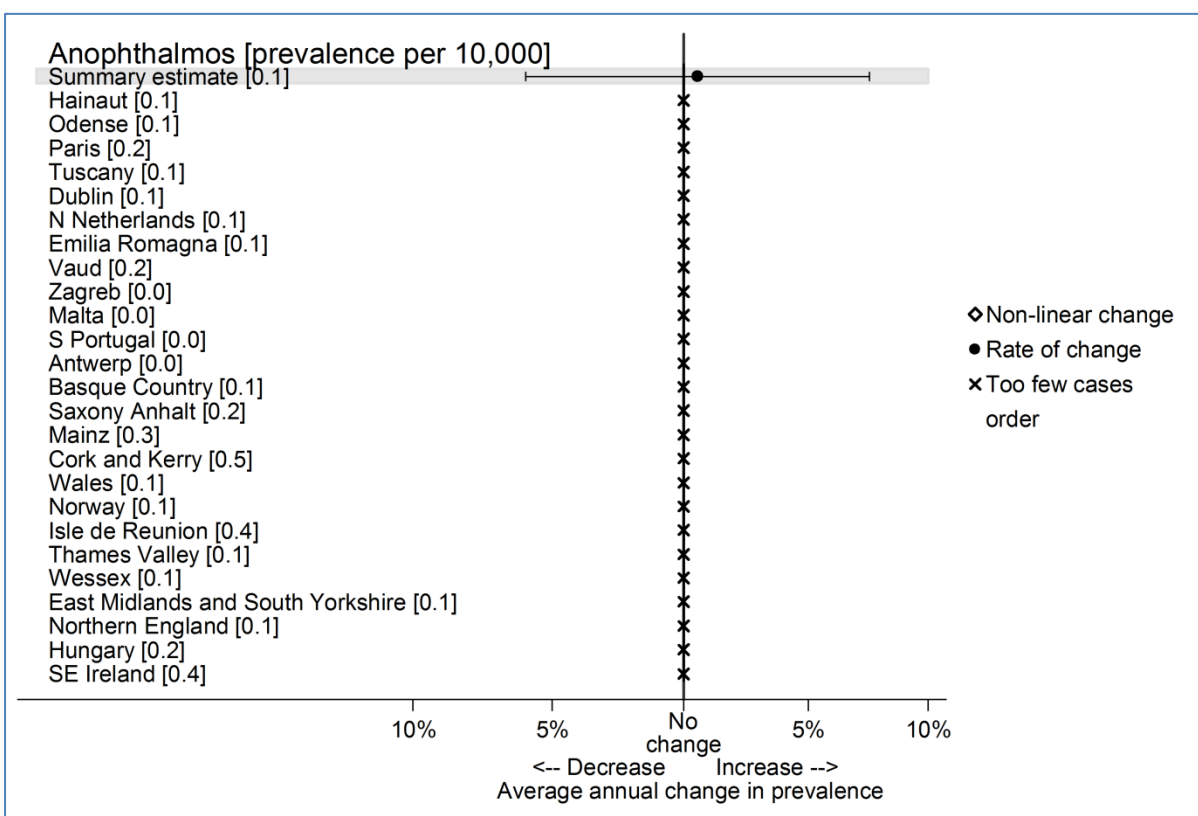
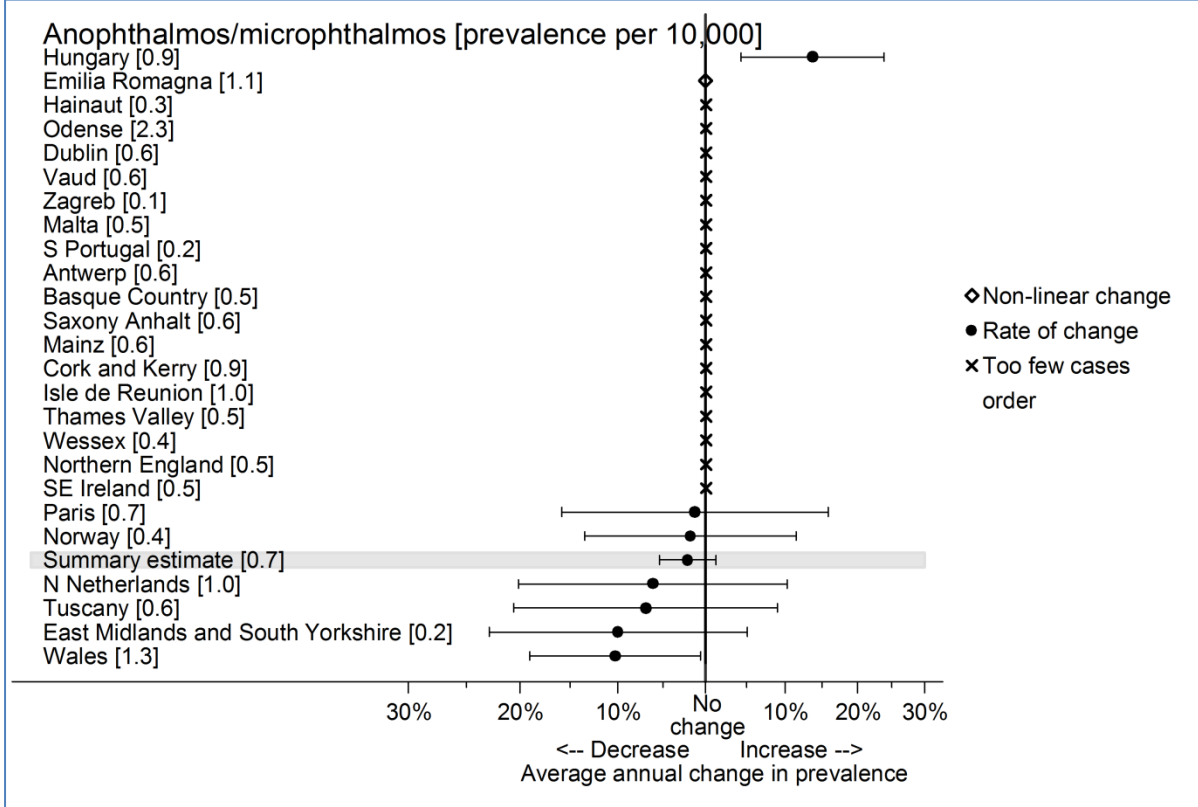
Spina bifida [prevalence per 10,000]



Hydrocephaly [prevalence per 10,000]







Congenital cataract [prevalence per 10,000]

Emilia Romagna [1.1]

Hungary [1.4]

Paris [0.9]

Basque Country [1.6]

Isle de Reunion [1.3]

Antwerp [1.0]

Hainaut [0.2]

Odense [1.5]

Vaud [0.2]

Zagreb [0.2]

Malta [0.5]

S Portugal [0.1]

Saxony Anhalt [0.4]

Mainz [0.6]

Cork and Kerry [1.0]

Thames Valley [0.3]

Wessex [0.5]

Northern England [0.6]

SE Ireland [1.0]

Summary estimate [1.1]

N Netherlands [2.4]

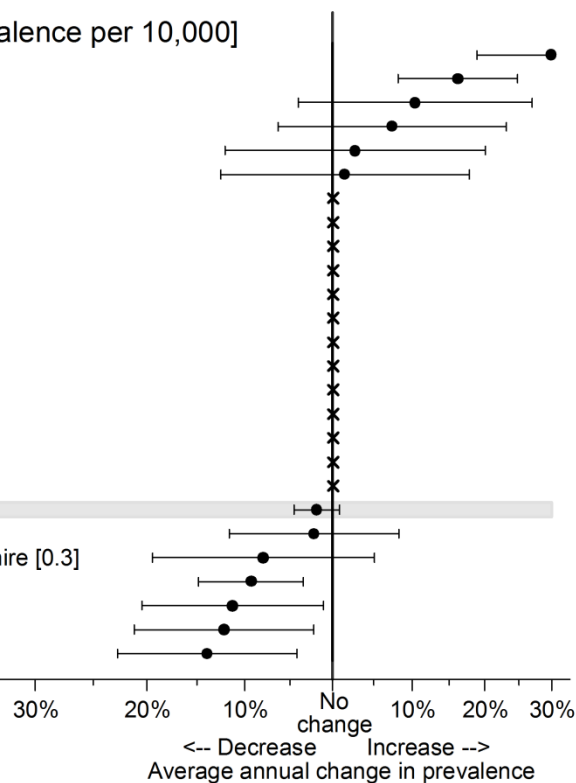
East Midlands and South Yorkshire [0.3]

Wales [3.6]

Tuscany [1.4]

Norway [0.7]

Dublin [1.7]



Congenital glaucoma [prevalence per 10,000]

Summary estimate [0.3]

Hungary [0.4]

Hainaut [0.2]

Odense [0.1]

Paris [0.1]

Tuscany [0.4]

Dublin [0.3]

N Netherlands [0.6]

Emilia Romagna [0.3]

Vaud [0.1]

Zagreb [0.4]

Malta [0.0]

S Portugal [0.0]

Antwerp [0.3]

Basque Country [0.6]

Saxony Anhalt [0.3]

Mainz [0.6]

Cork and Kerry [0.7]

Norway [0.1]

Isle de Reunion [0.8]

Thames Valley [0.1]

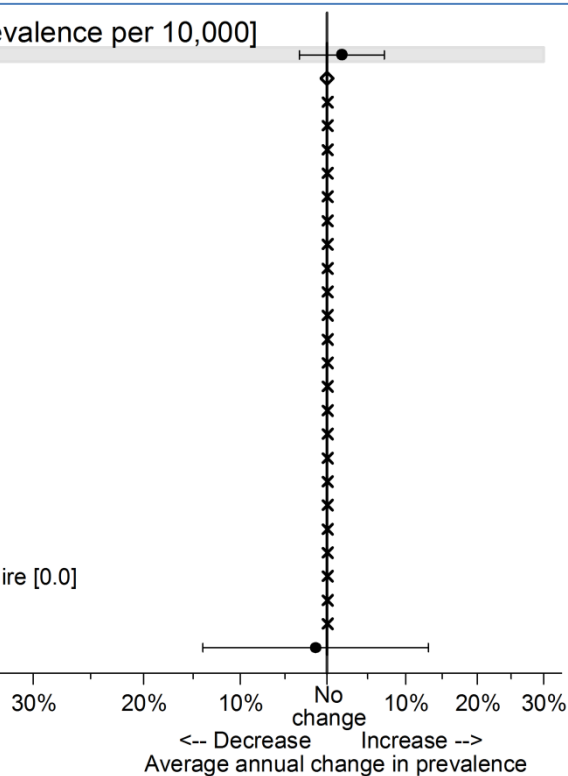
Wessex [0.0]

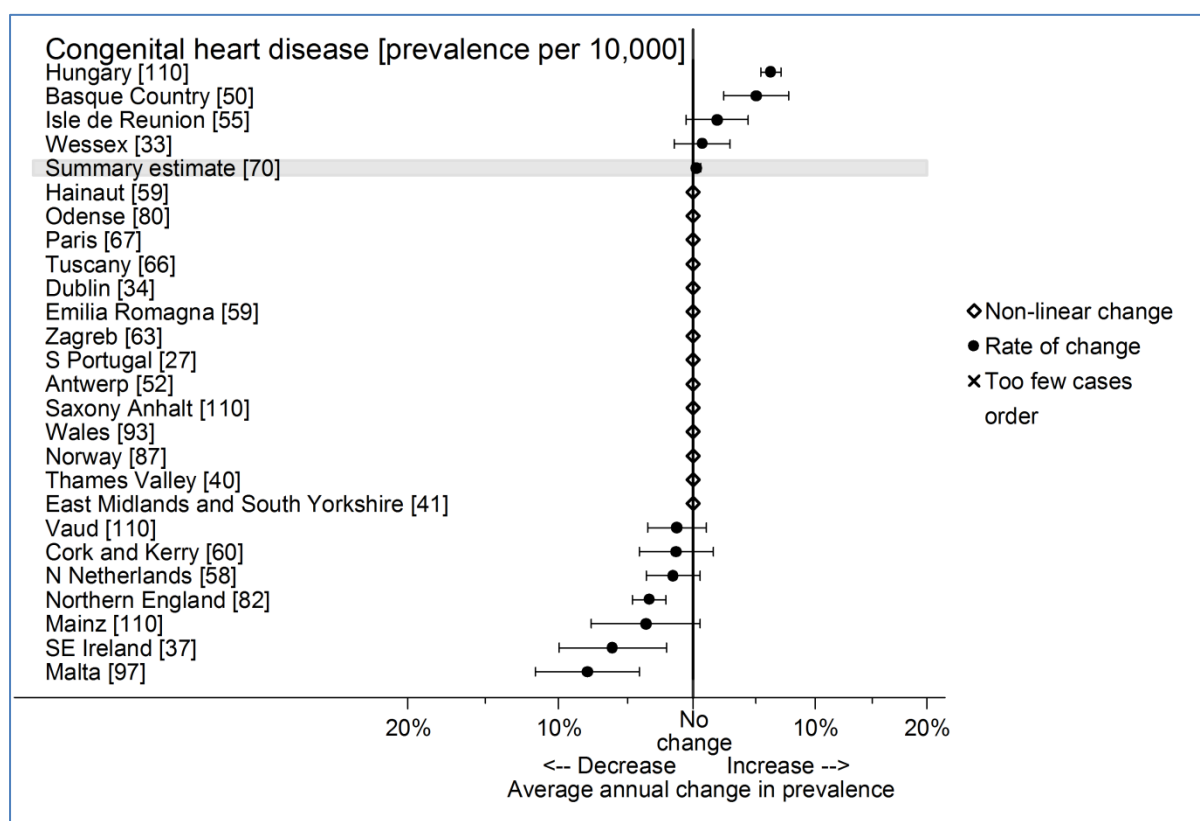
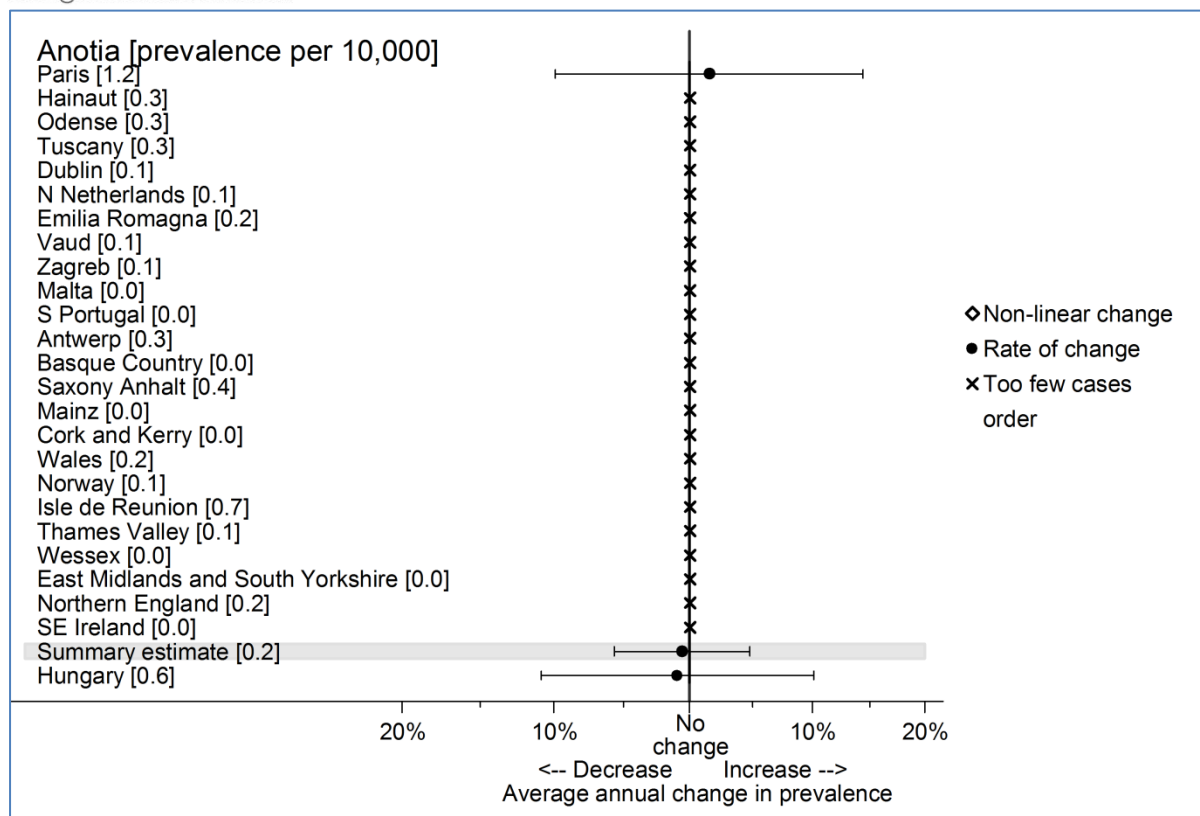
East Midlands and South Yorkshire [0.0]

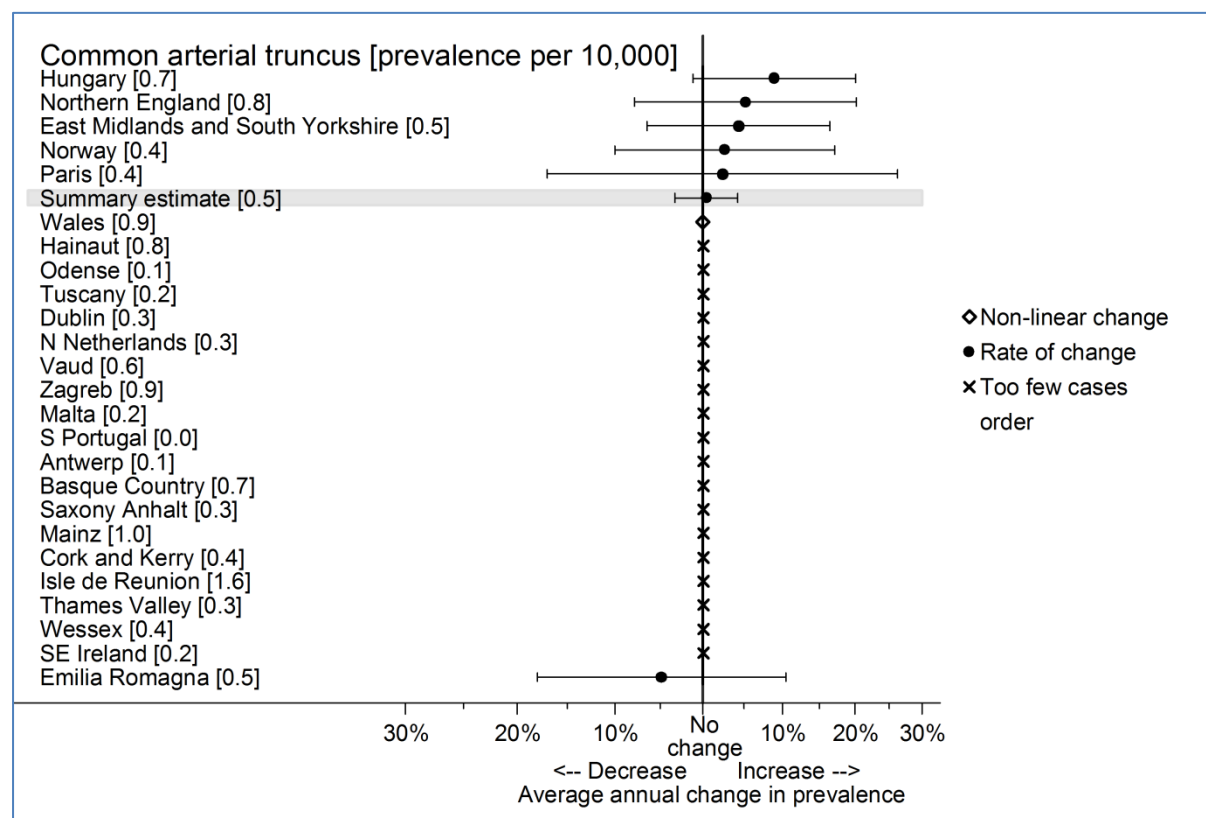
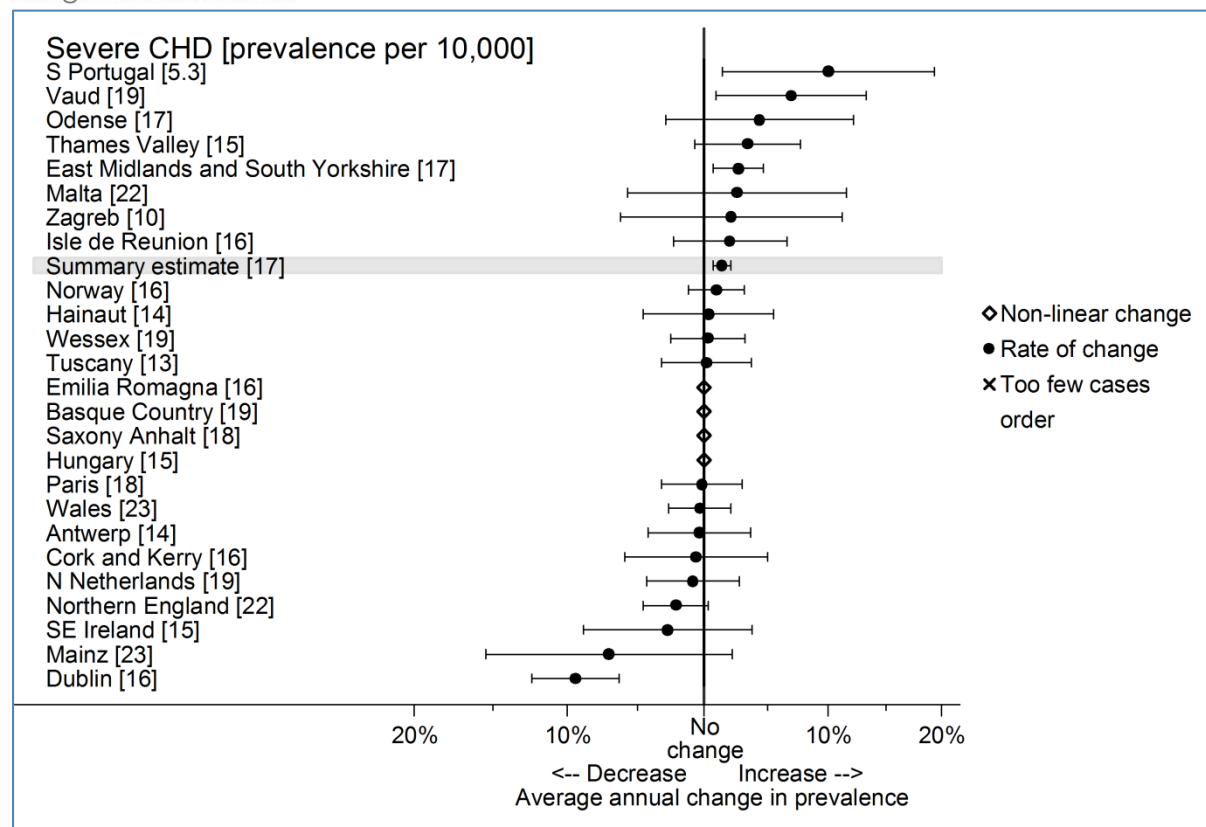
Northern England [0.0]

SE Ireland [0.1]

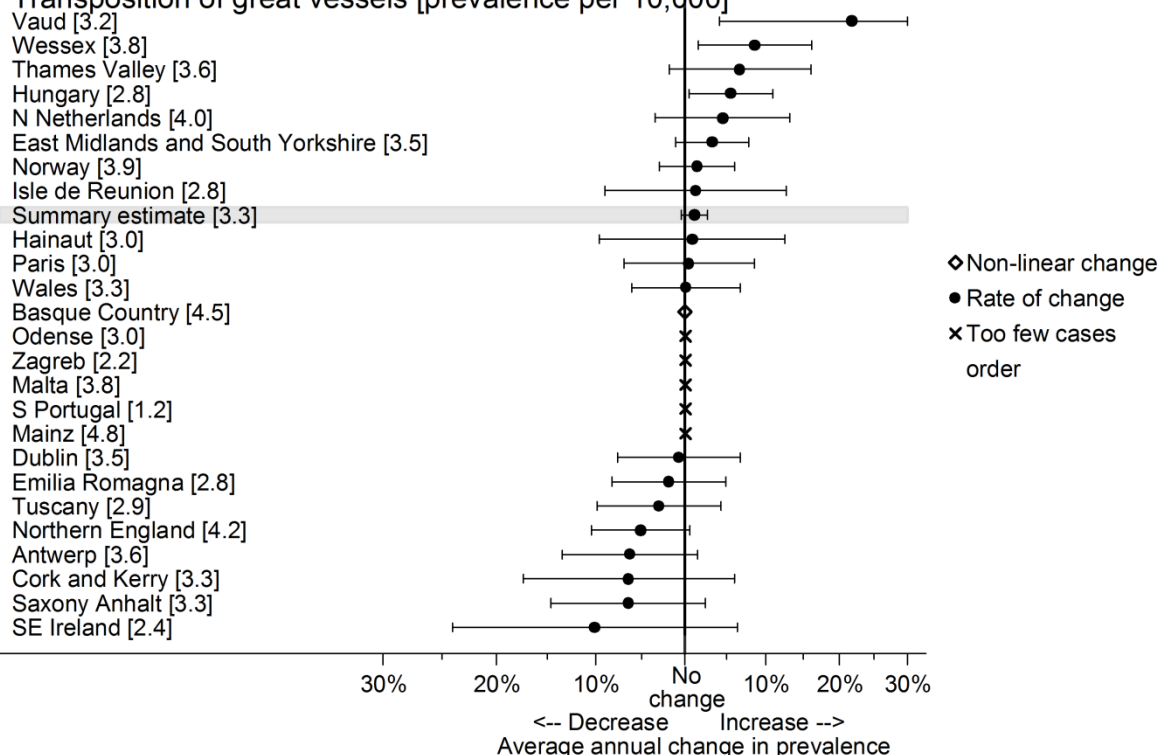
Wales [0.7]



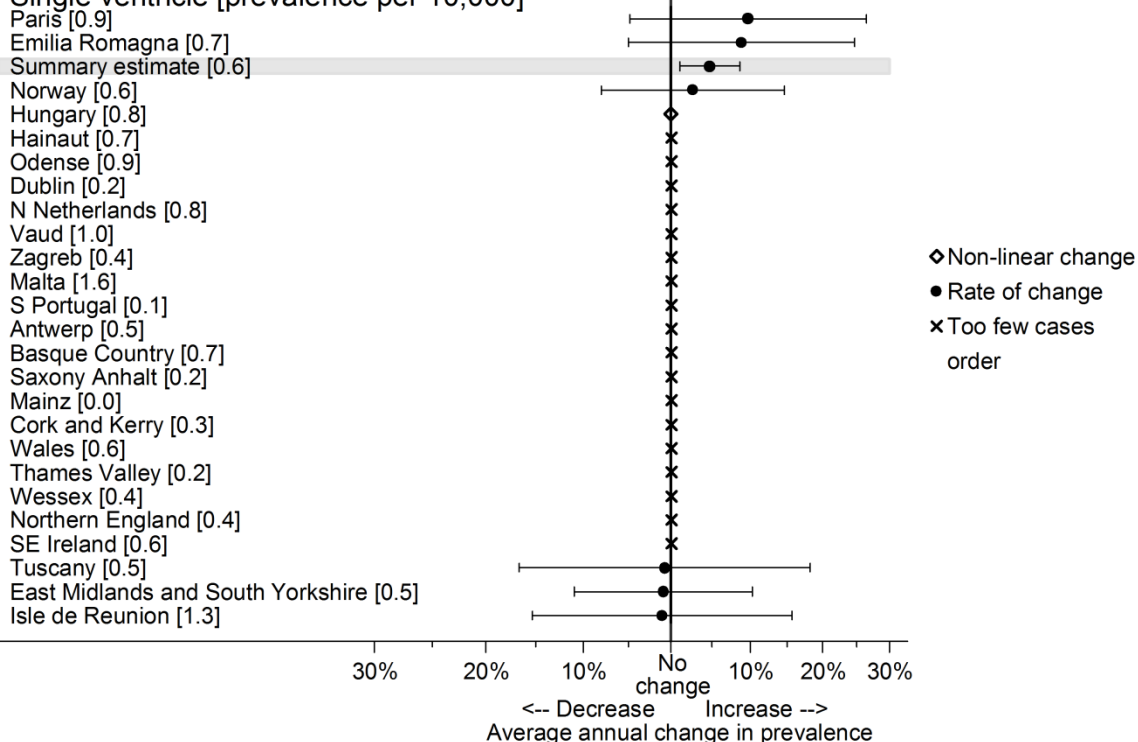


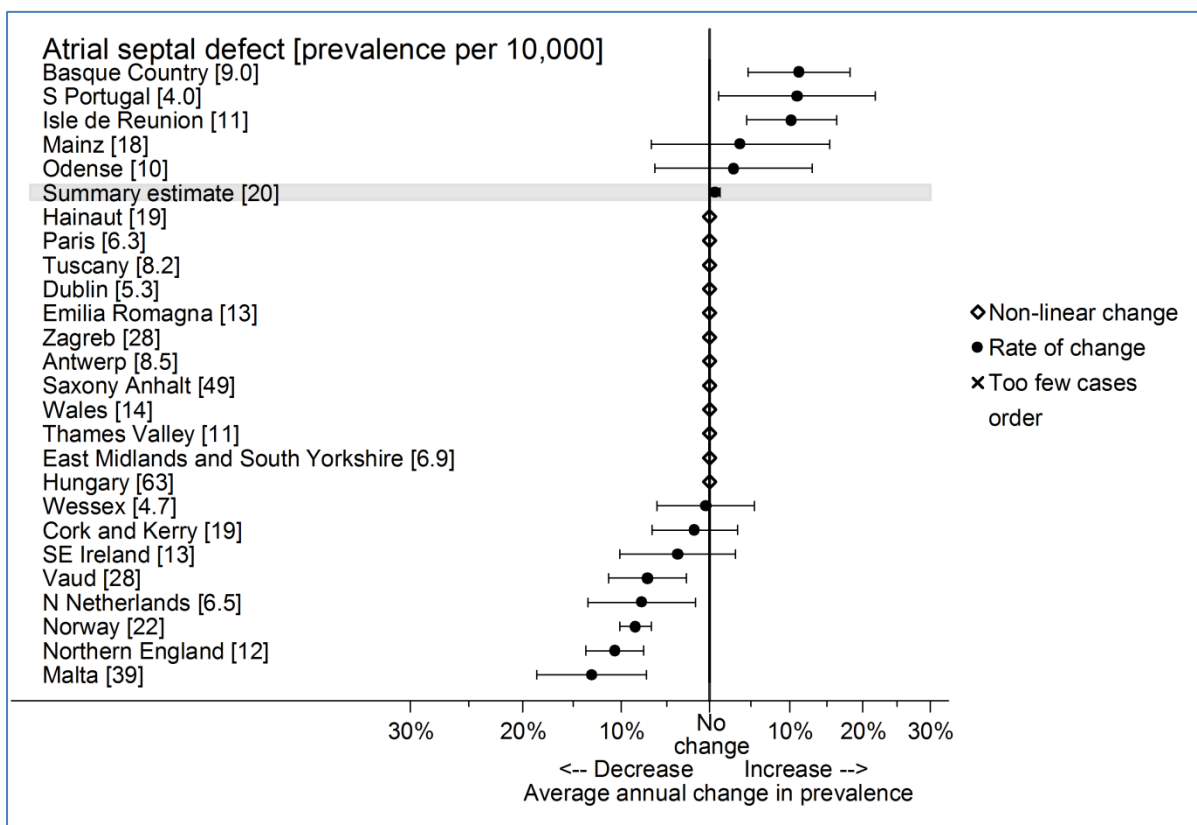
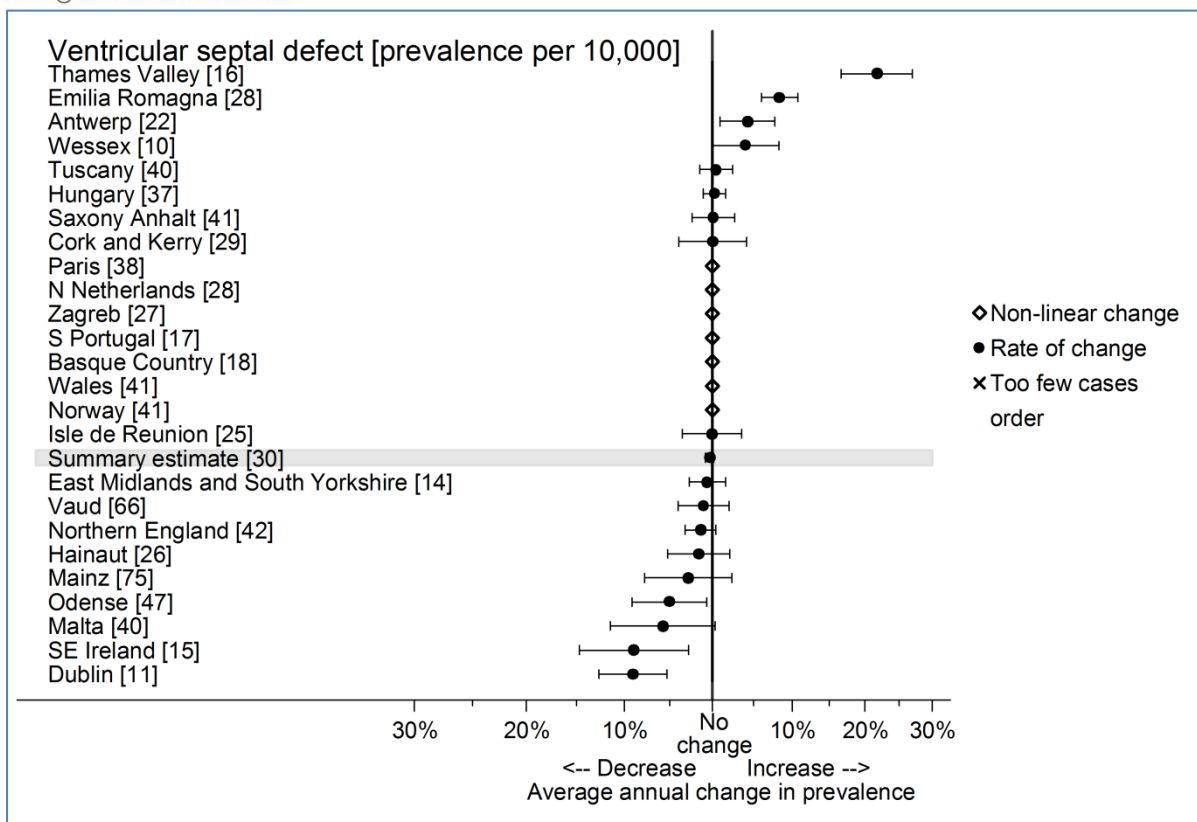


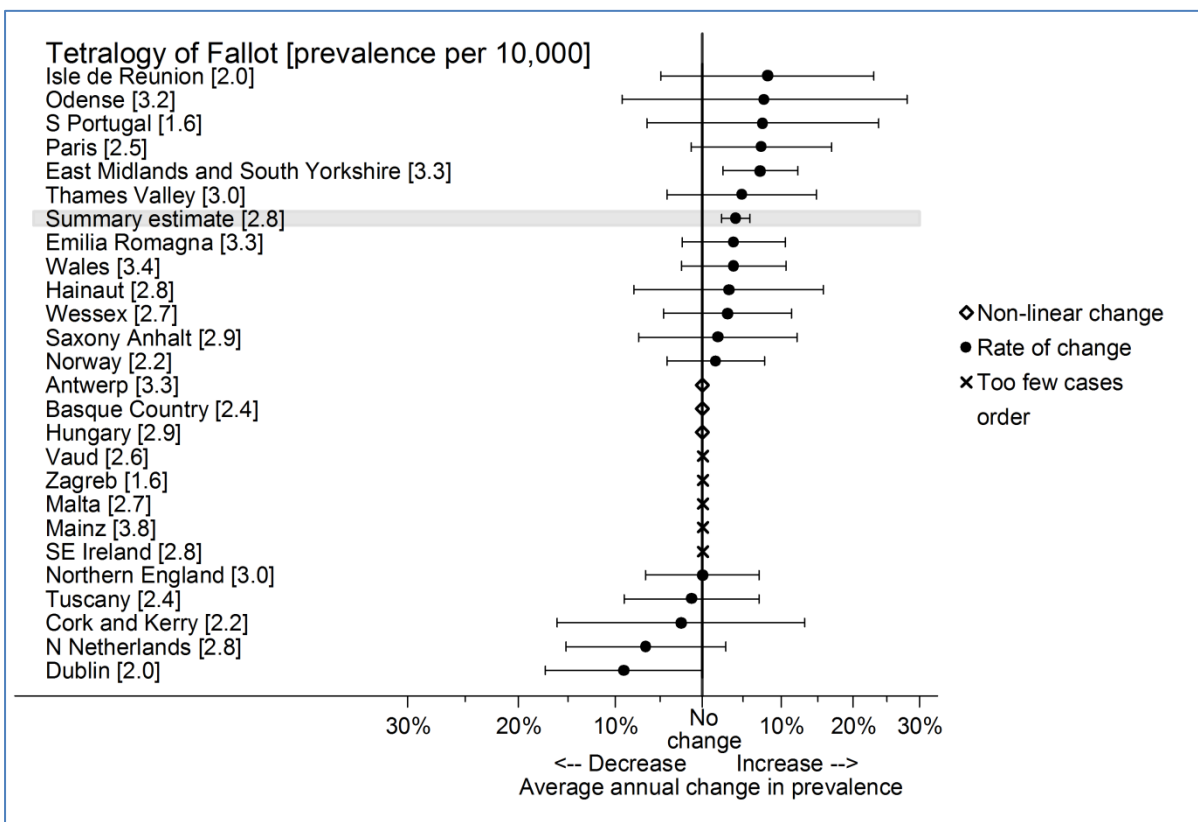
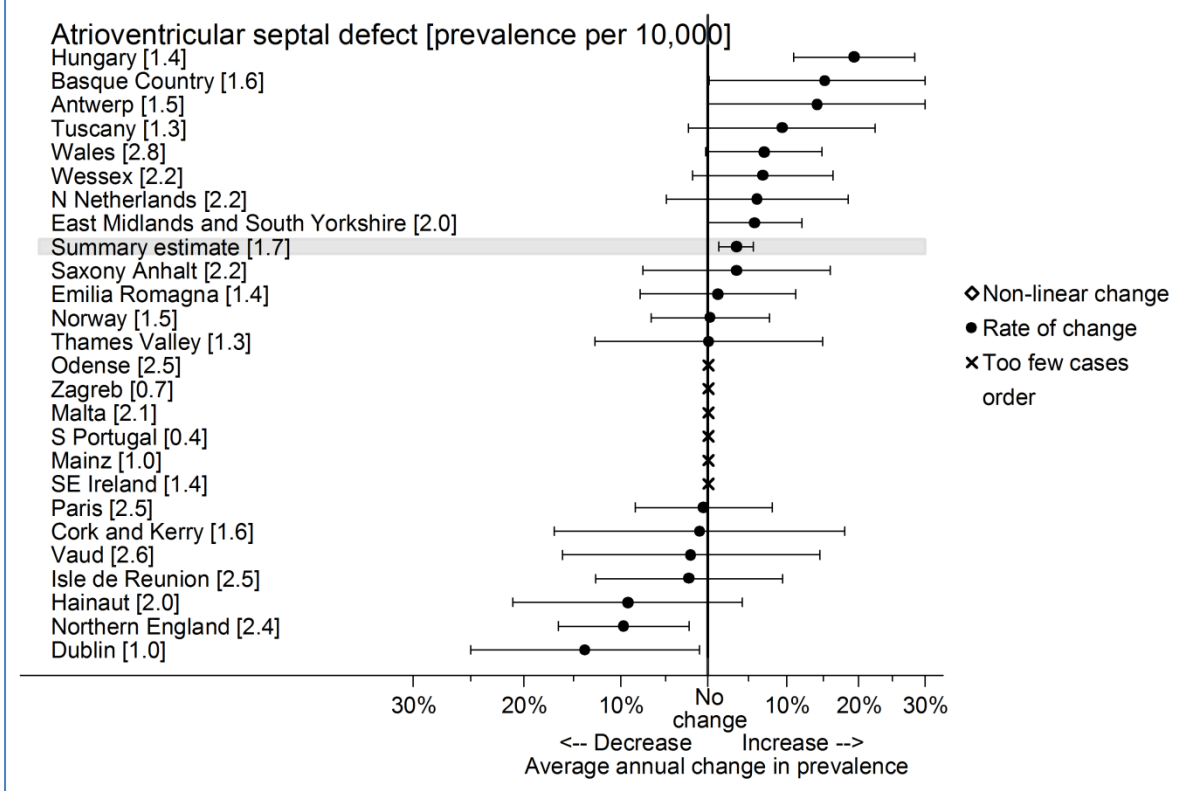
Transposition of great vessels [prevalence per 10,000]



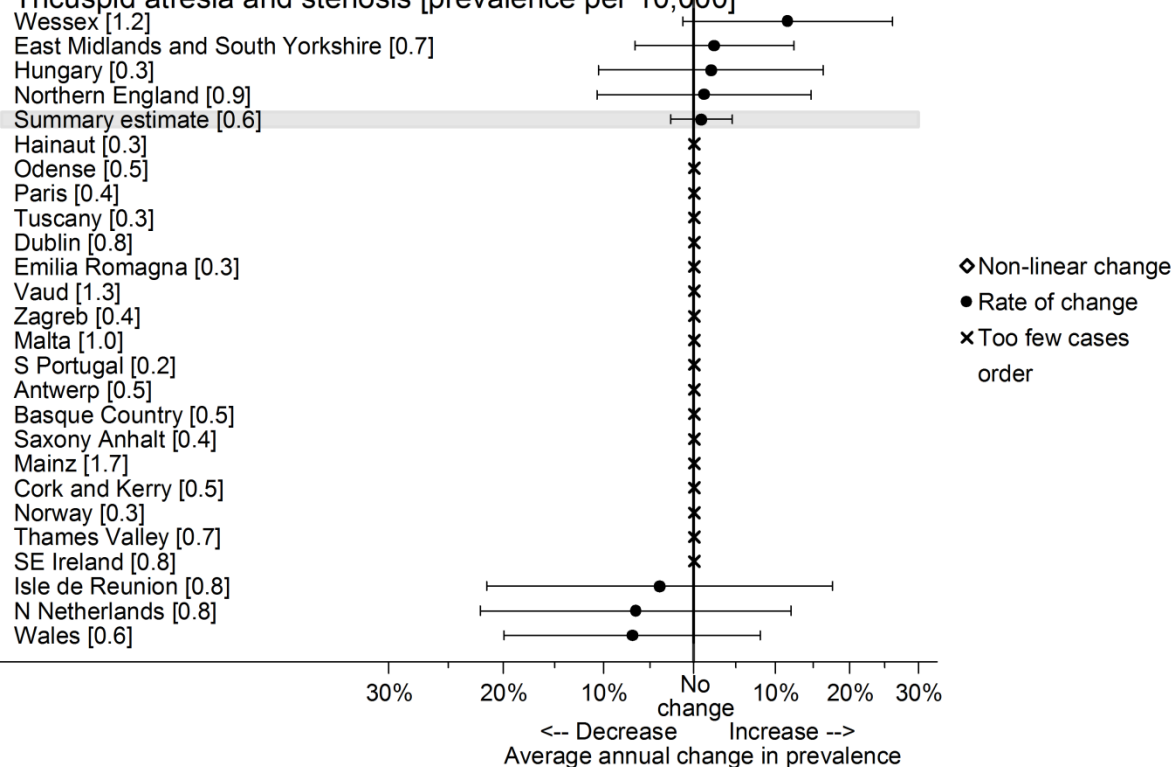
Single ventricle [prevalence per 10,000]



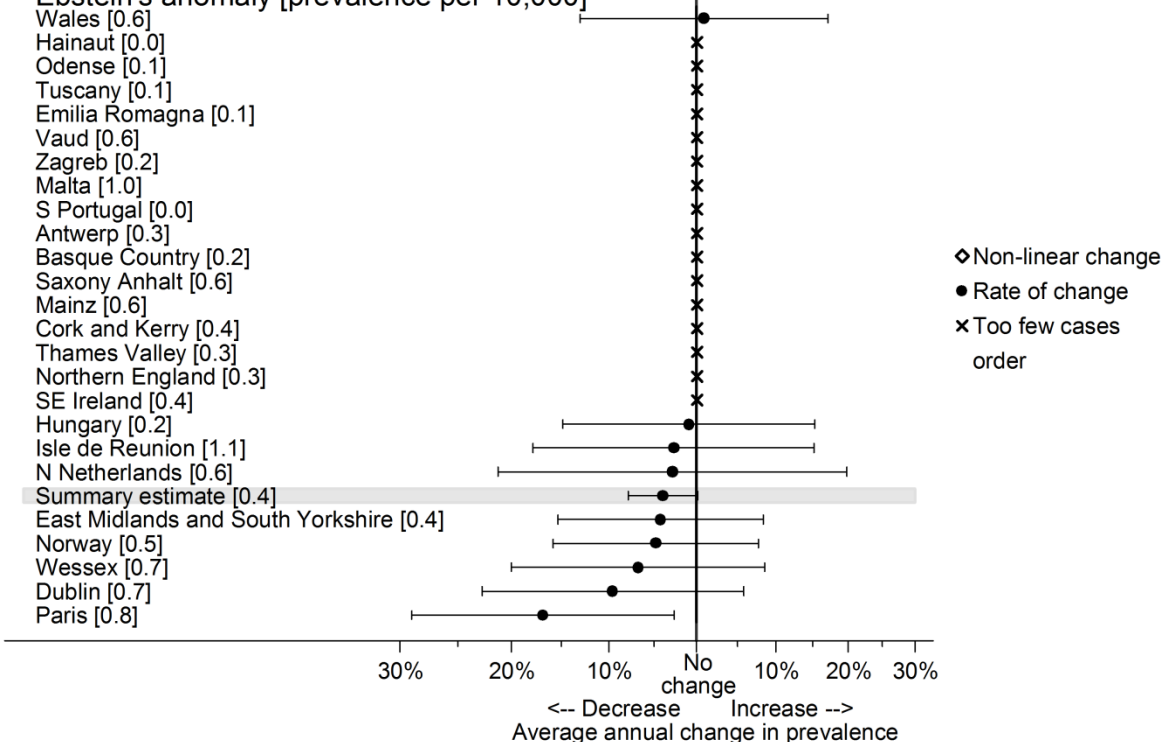




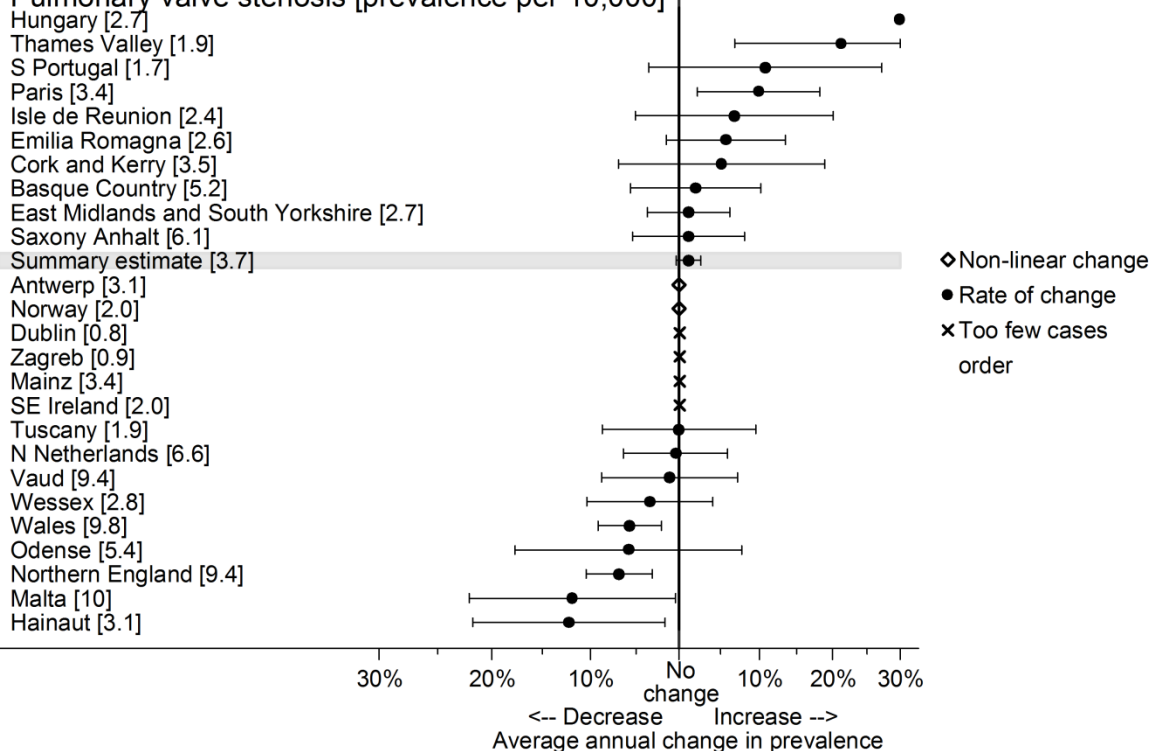
Tricuspid atresia and stenosis [prevalence per 10,000]



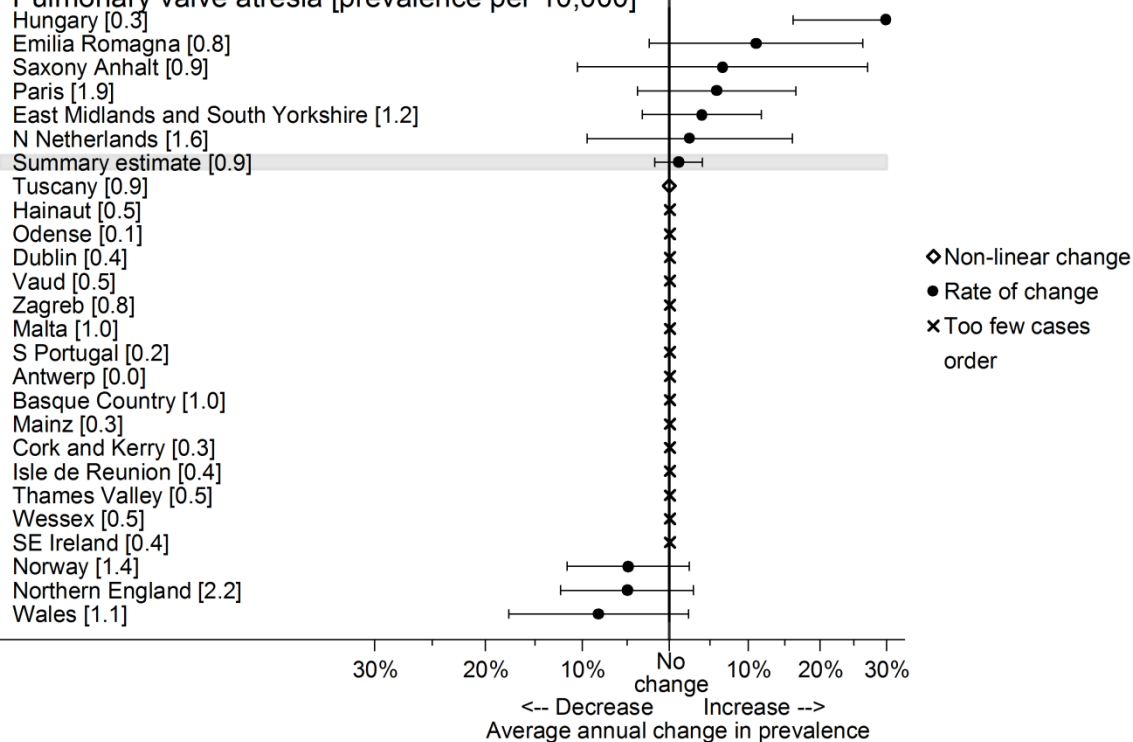
Ebstein's anomaly [prevalence per 10,000]



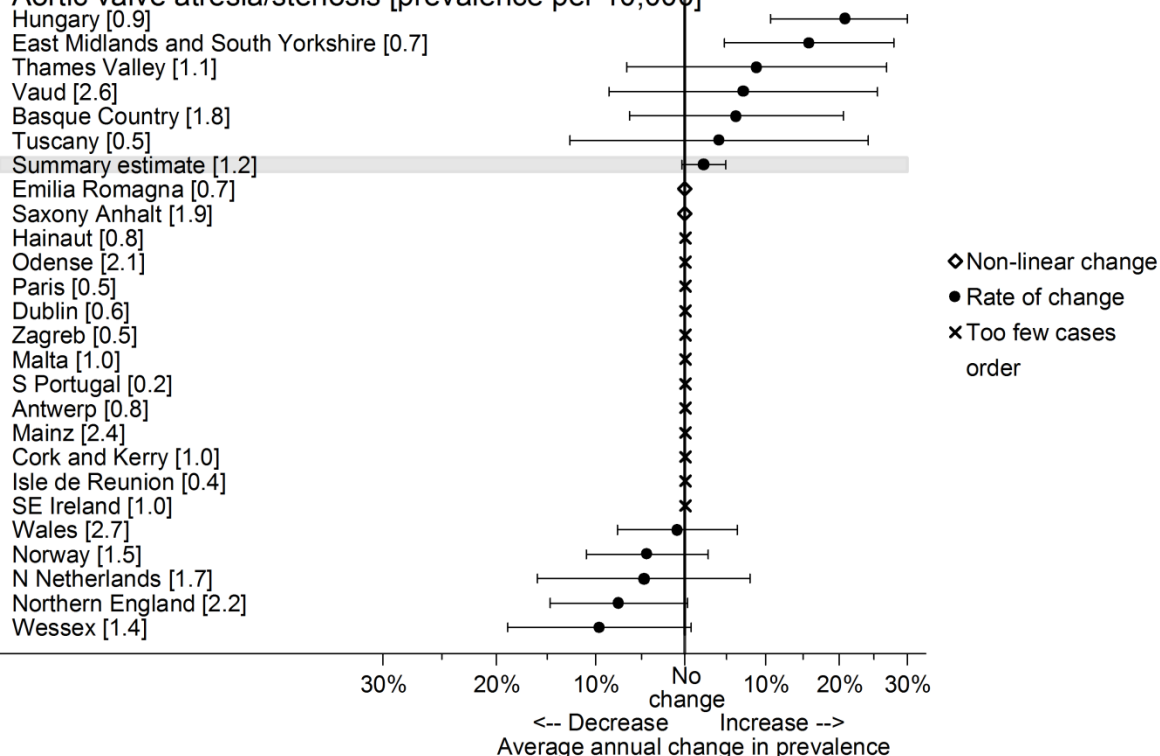
Pulmonary valve stenosis [prevalence per 10,000]



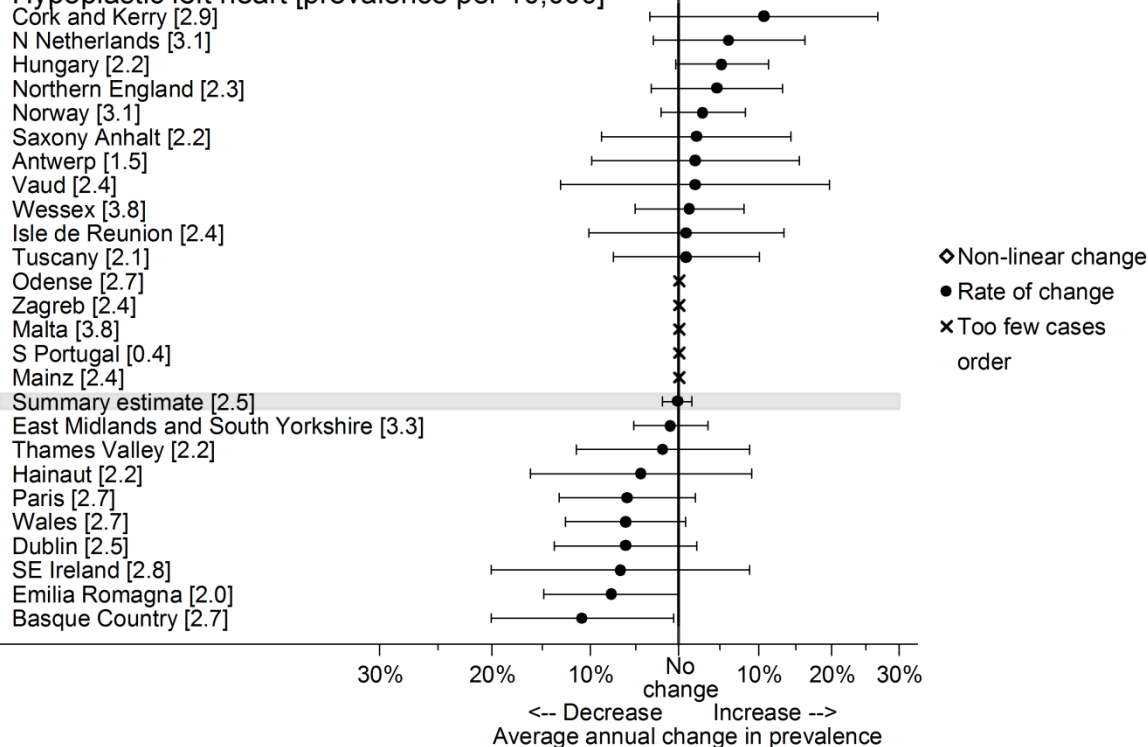
Pulmonary valve atresia [prevalence per 10,000]

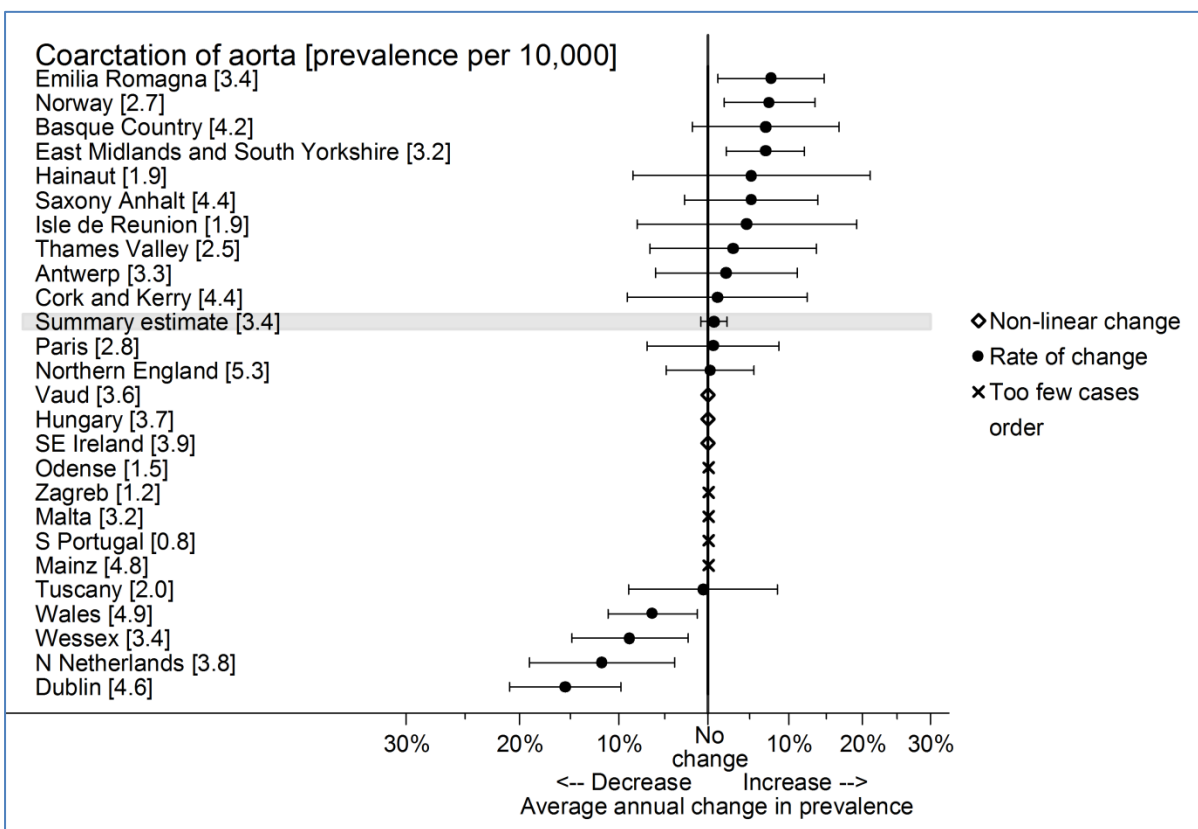
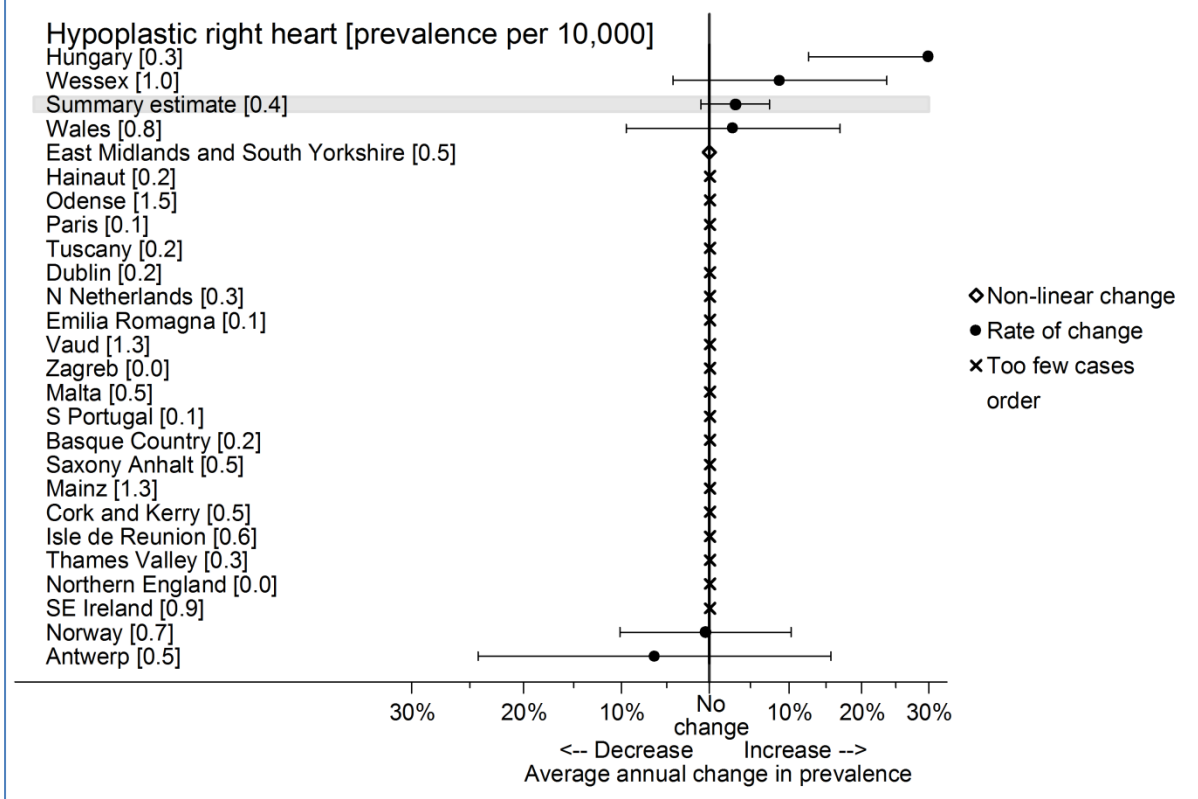


Aortic valve atresia/stenosis [prevalence per 10,000]

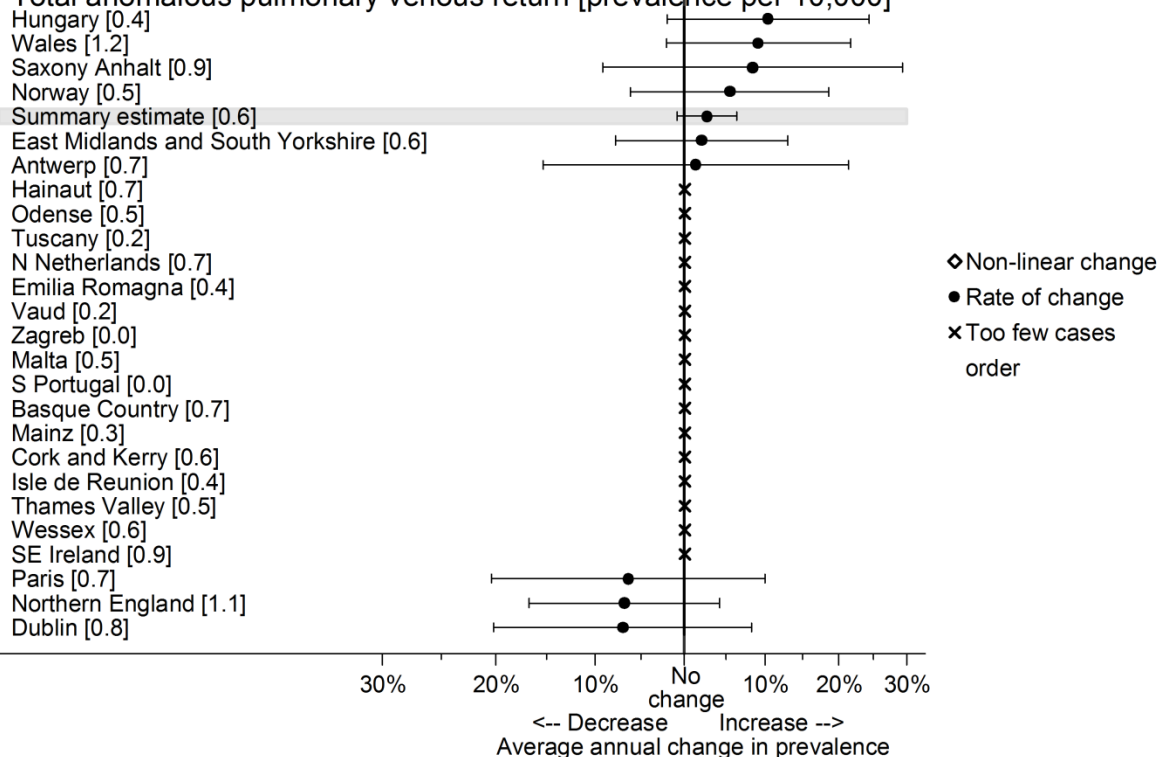


Hypoplastic left heart [prevalence per 10,000]

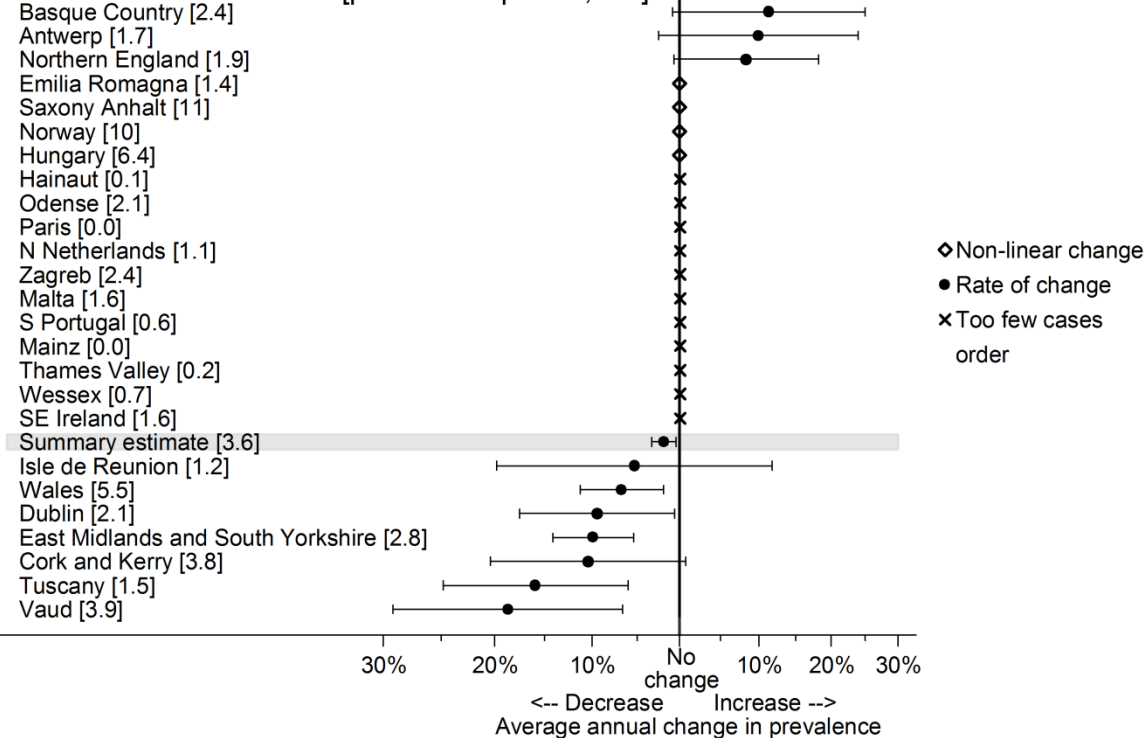


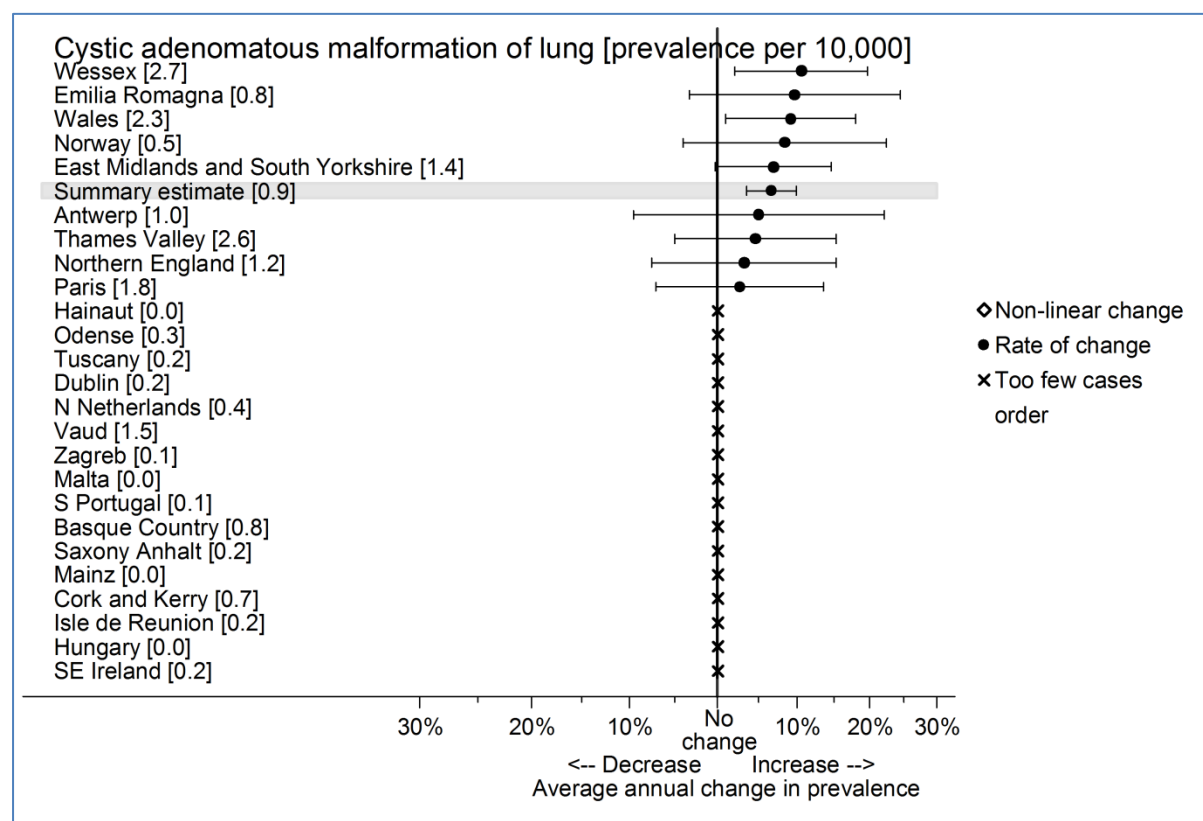
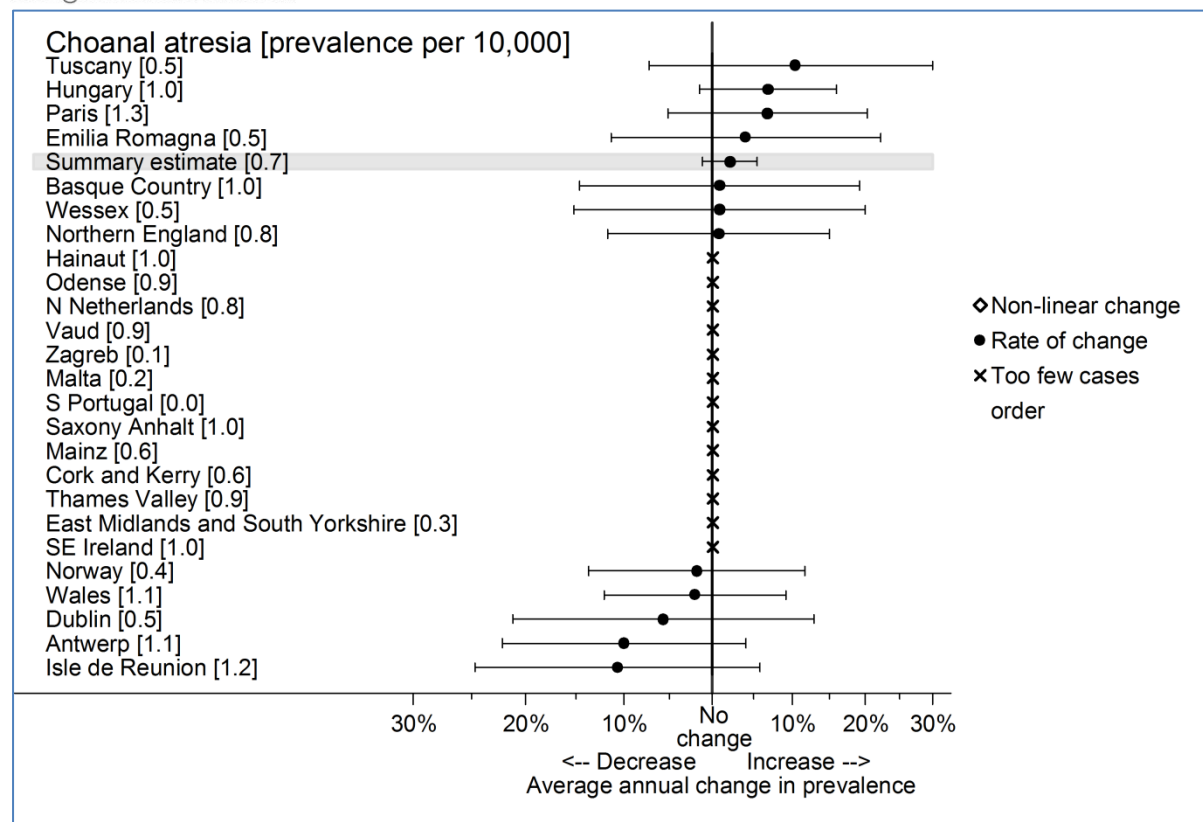


Total anomalous pulmonary venous return [prevalence per 10,000]

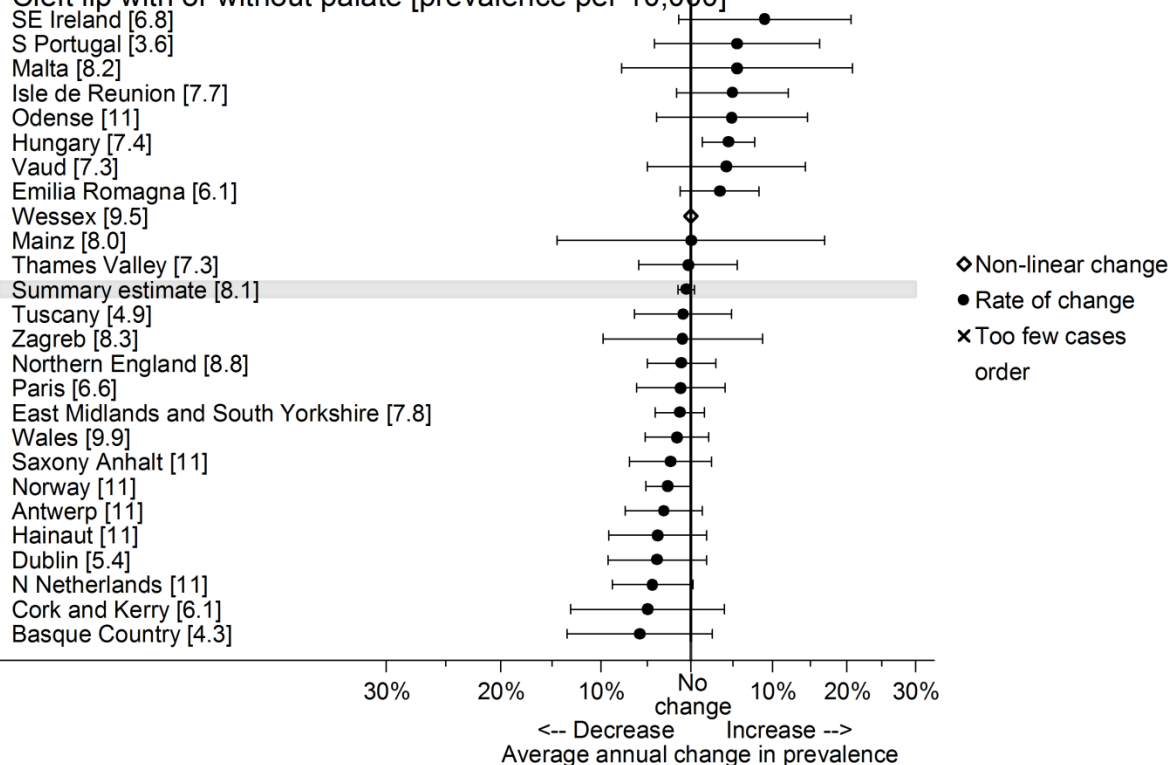


Patent ductus arteriosus [prevalence per 10,000]

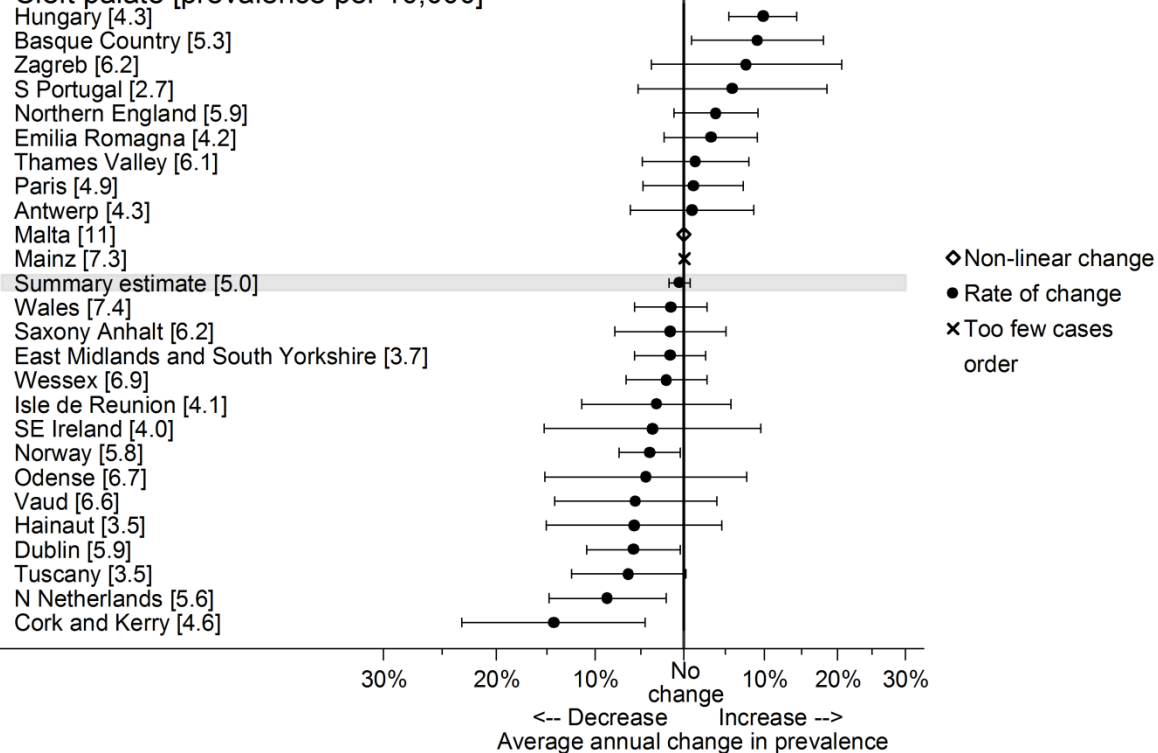


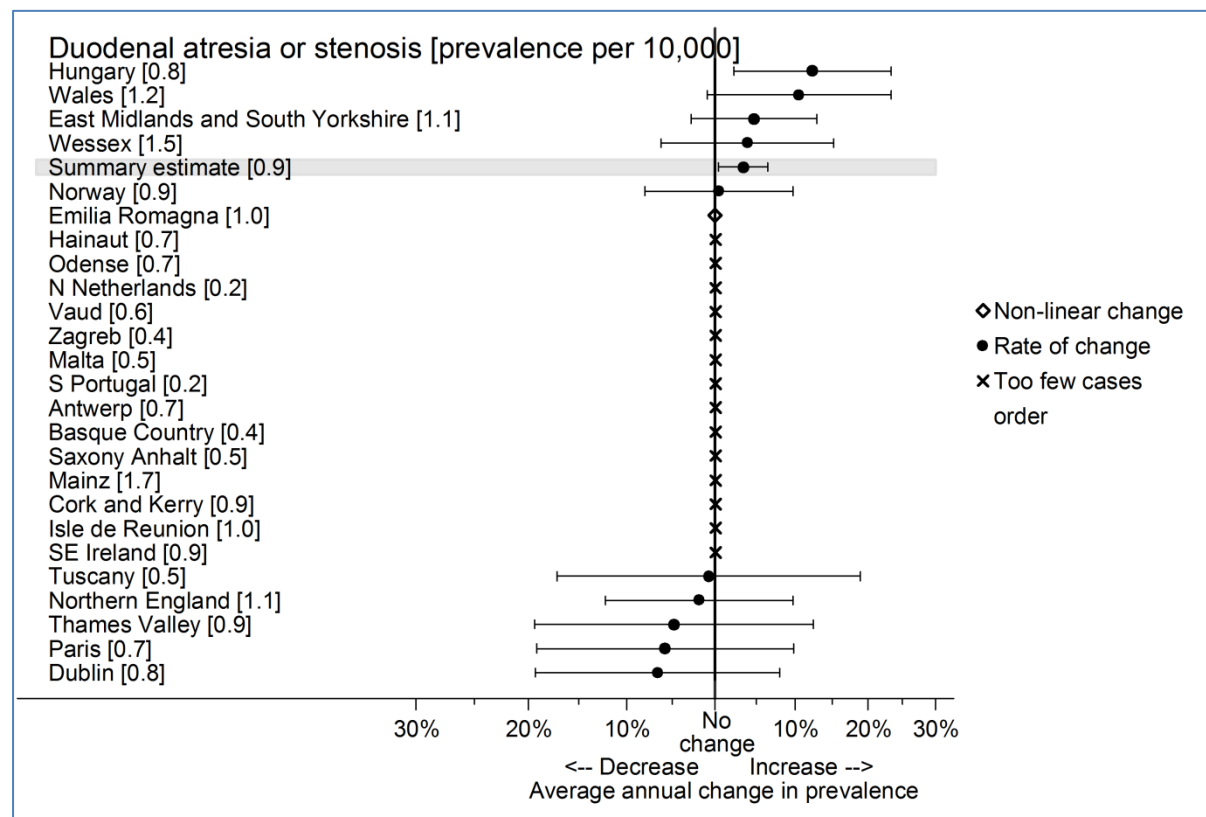
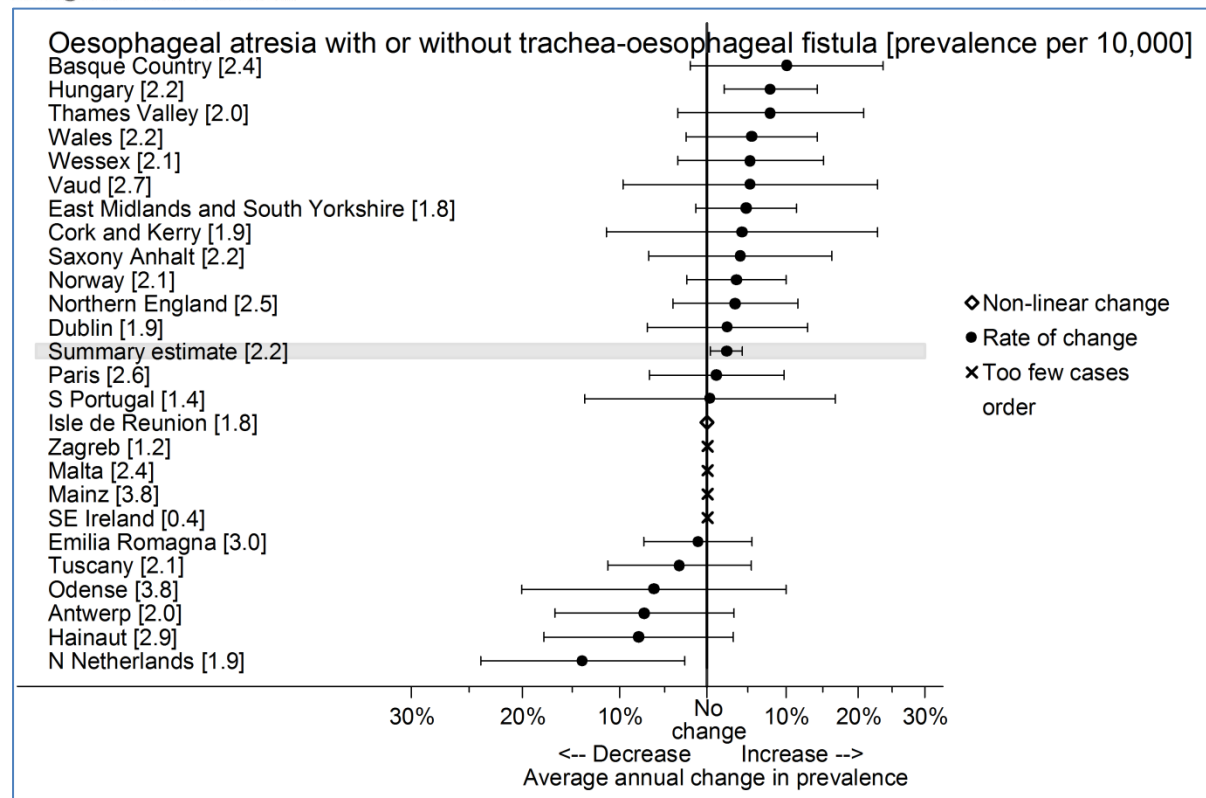


Cleft lip with or without palate [prevalence per 10,000]

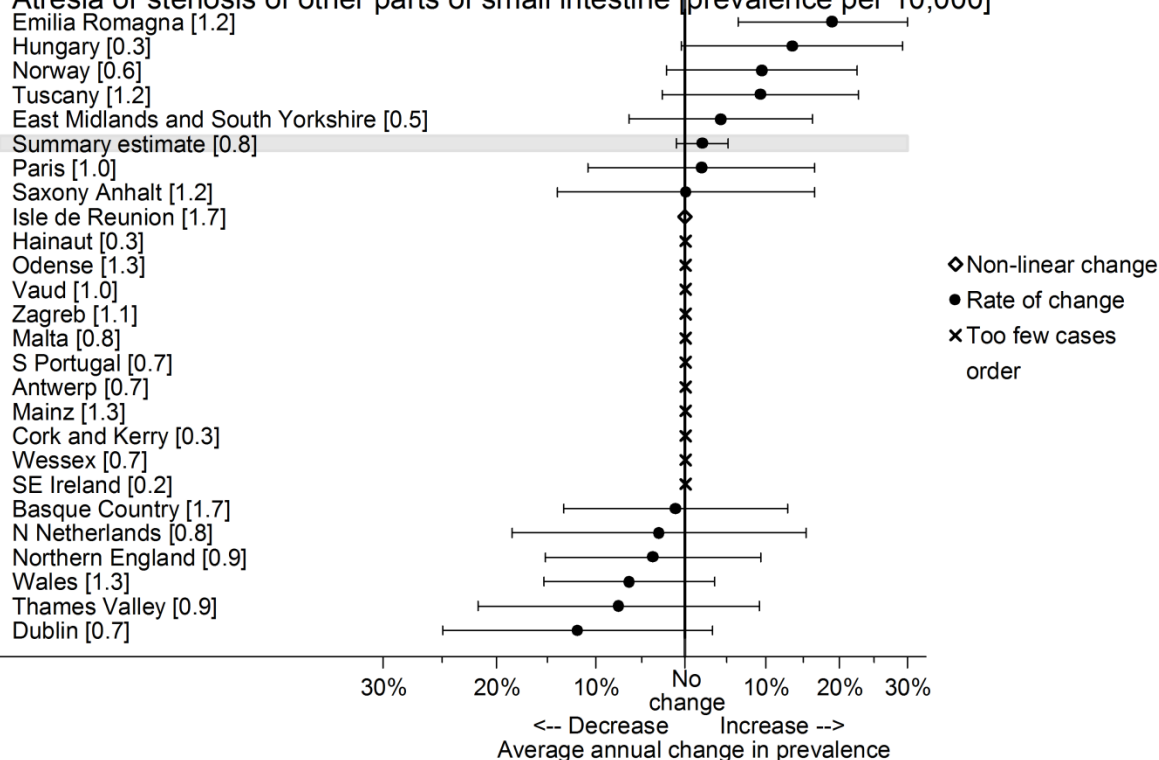


Cleft palate [prevalence per 10,000]

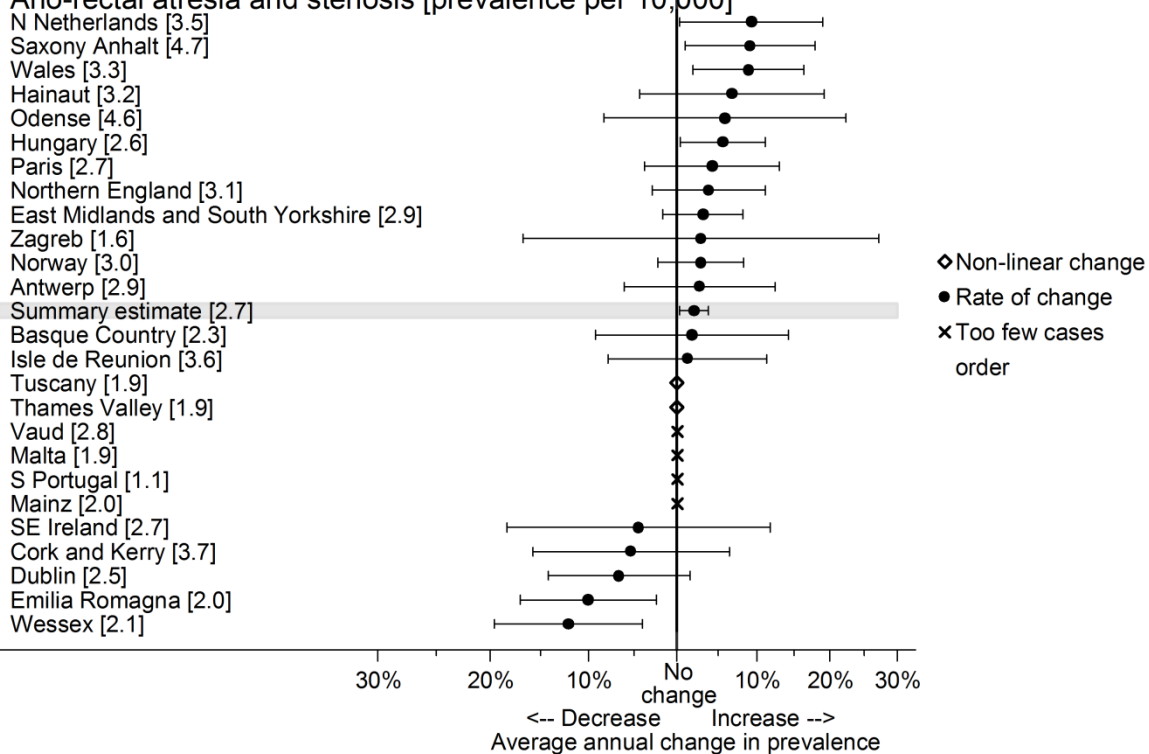


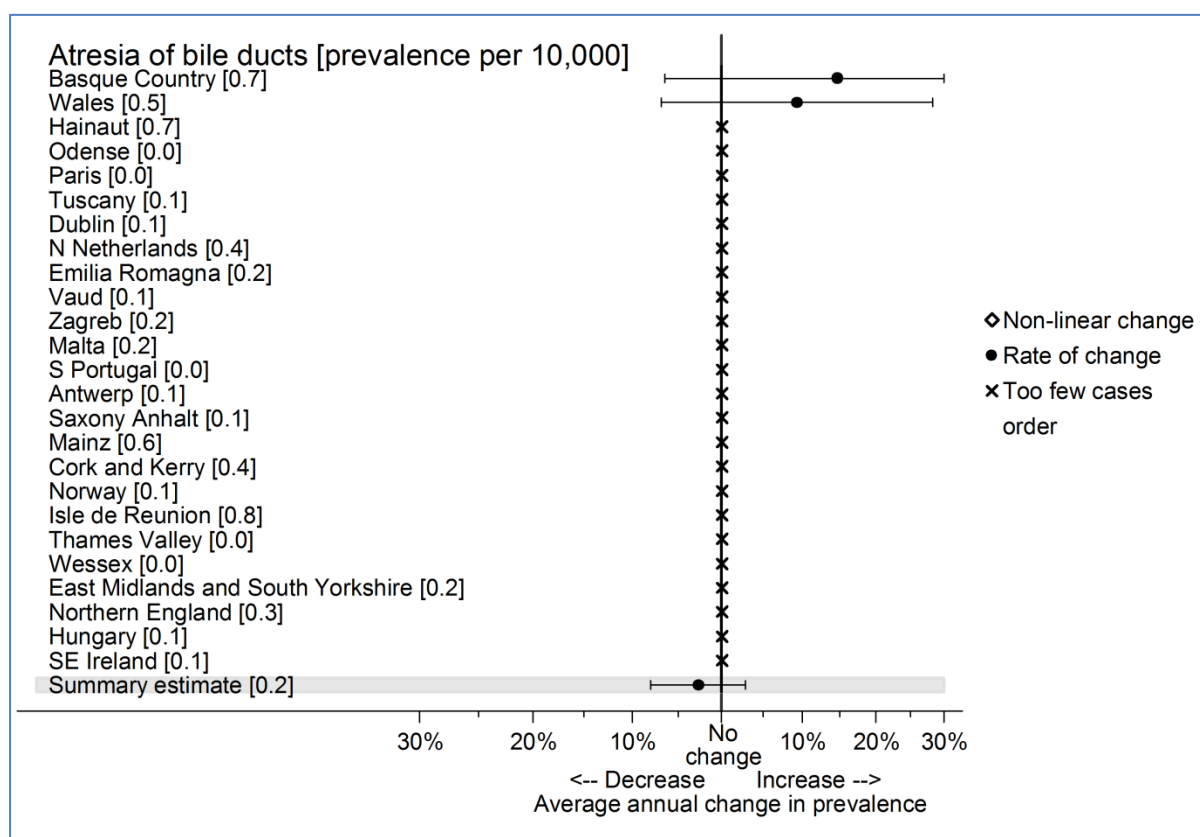
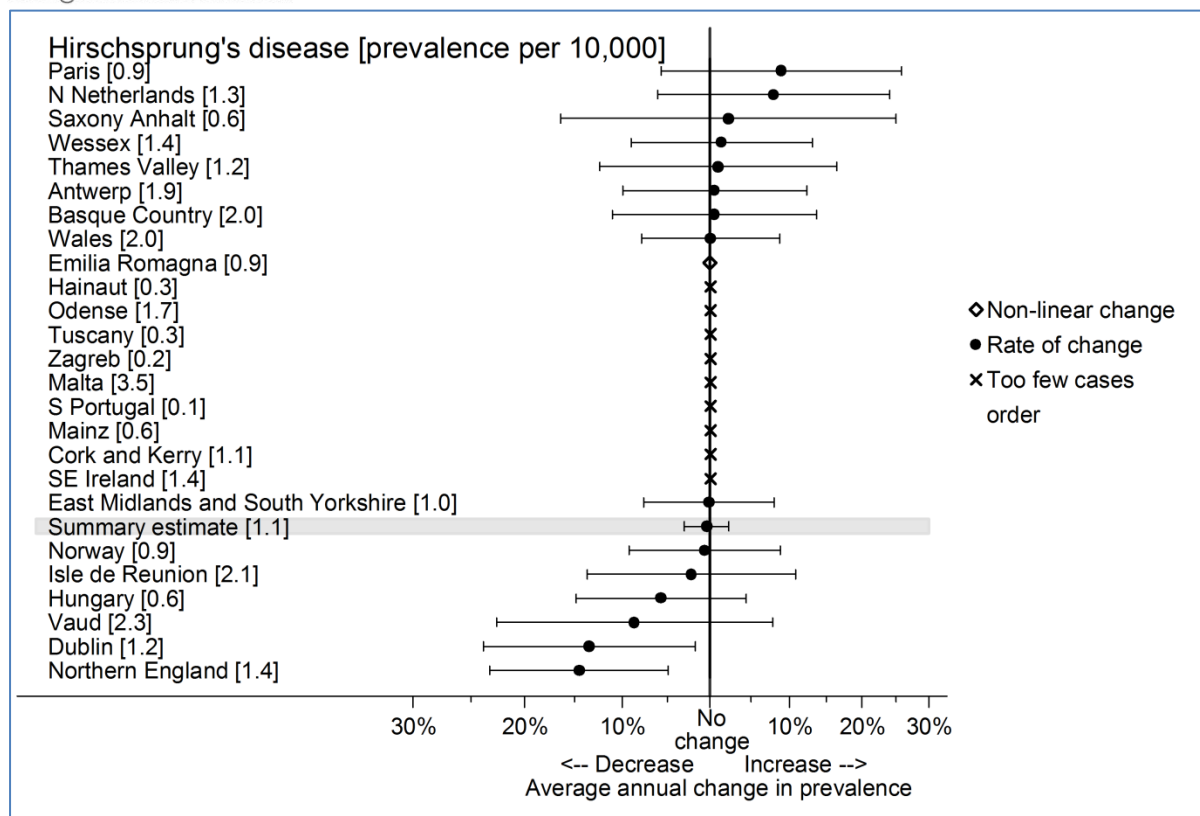


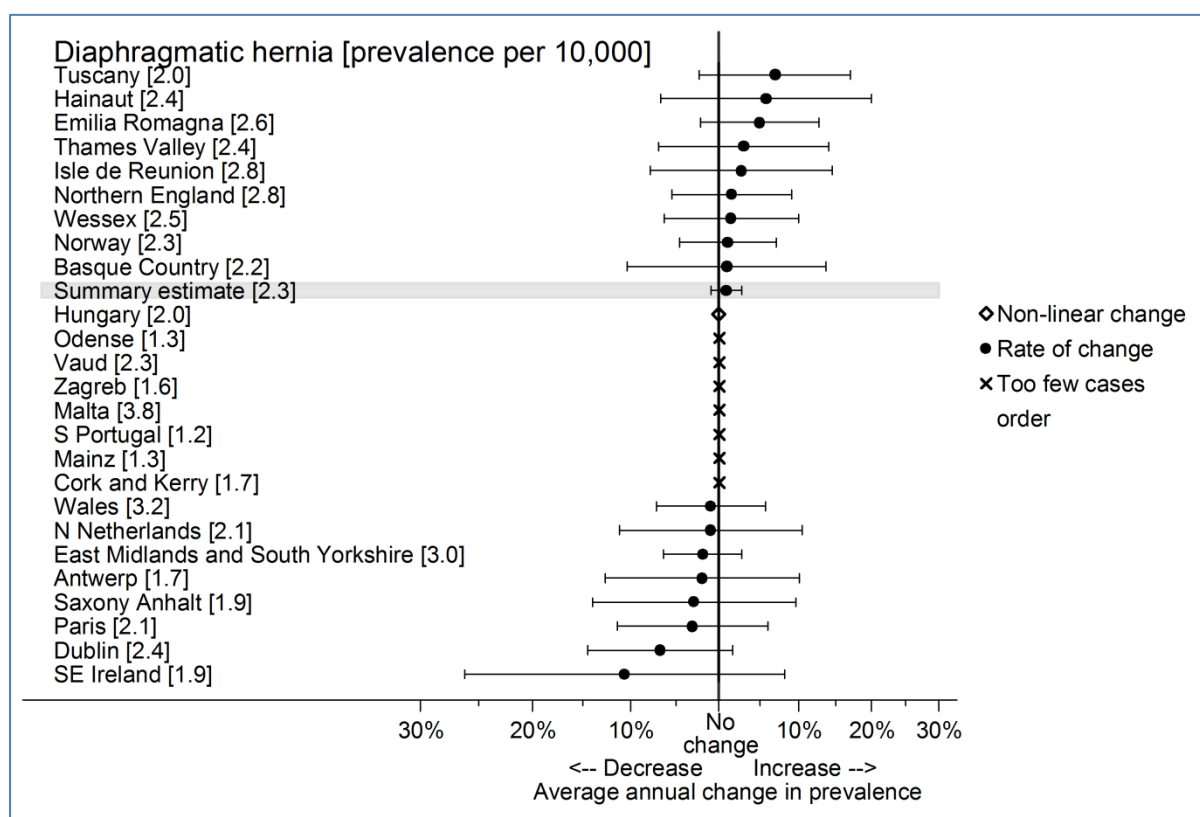
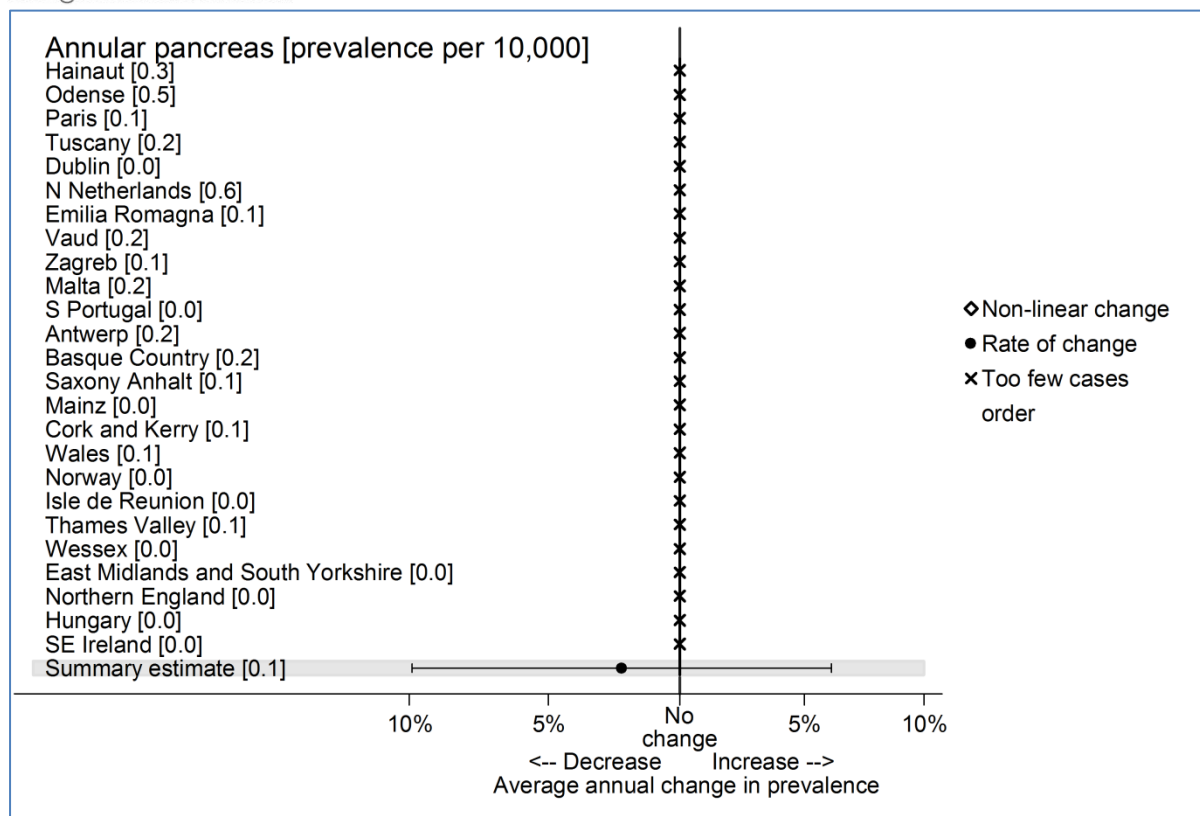
Atresia or stenosis of other parts of small intestine [prevalence per 10,000]

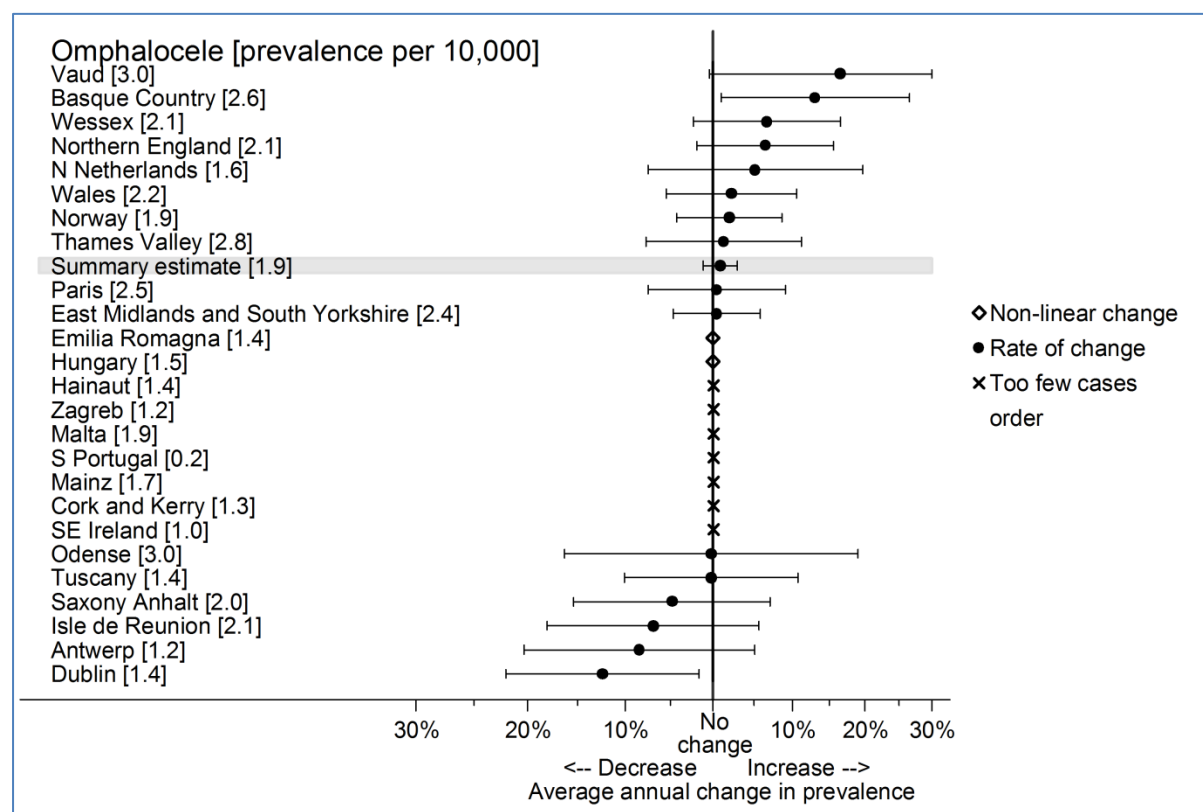
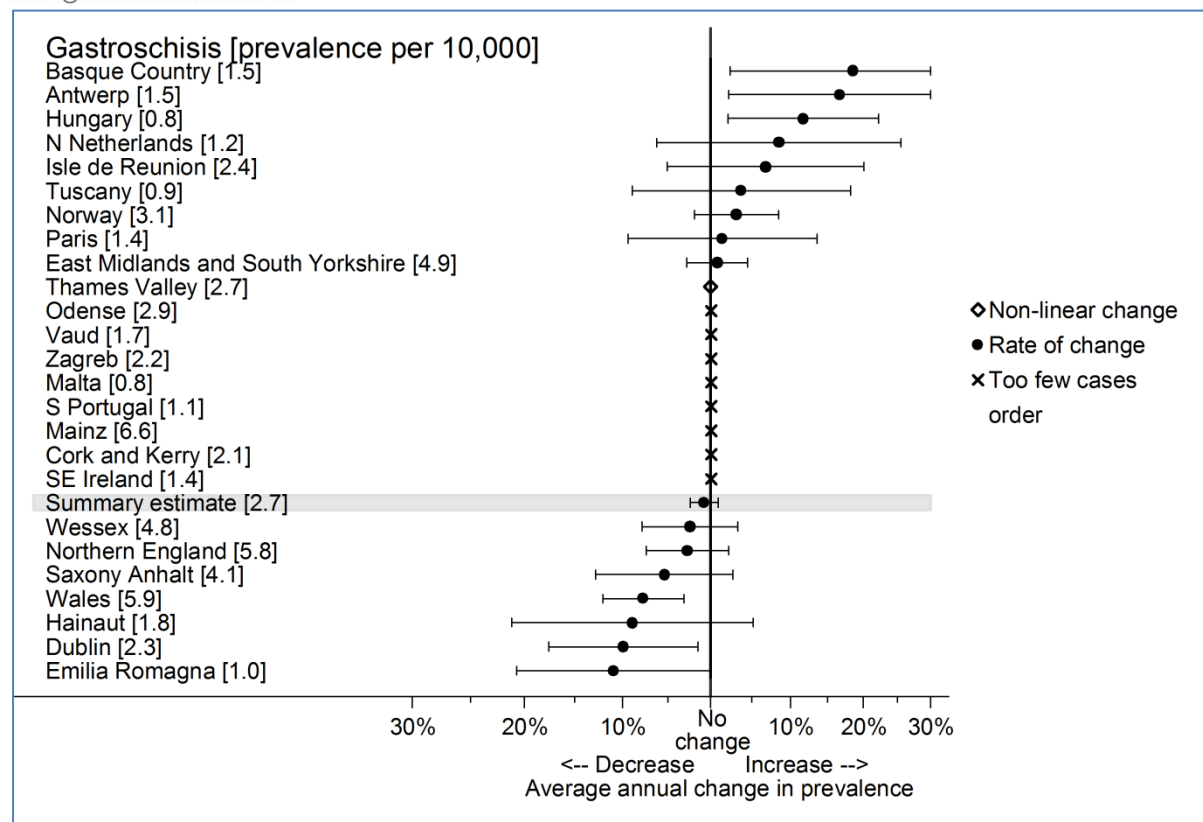


Ano-rectal atresia and stenosis [prevalence per 10,000]

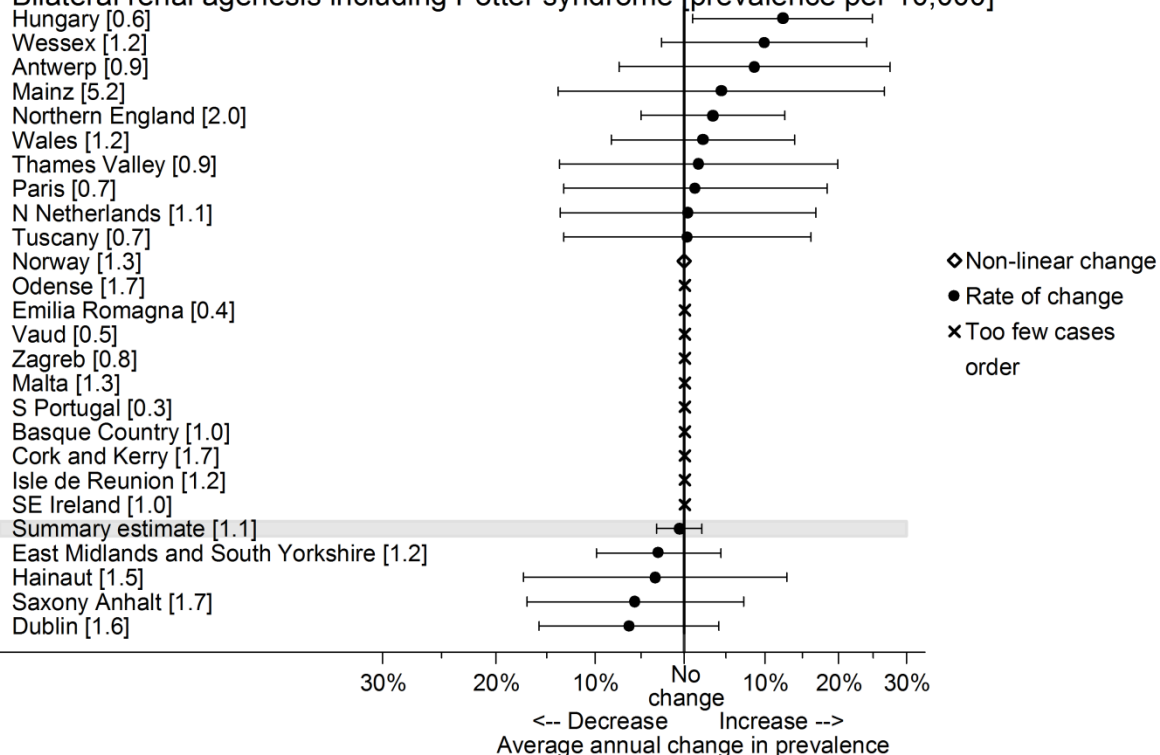




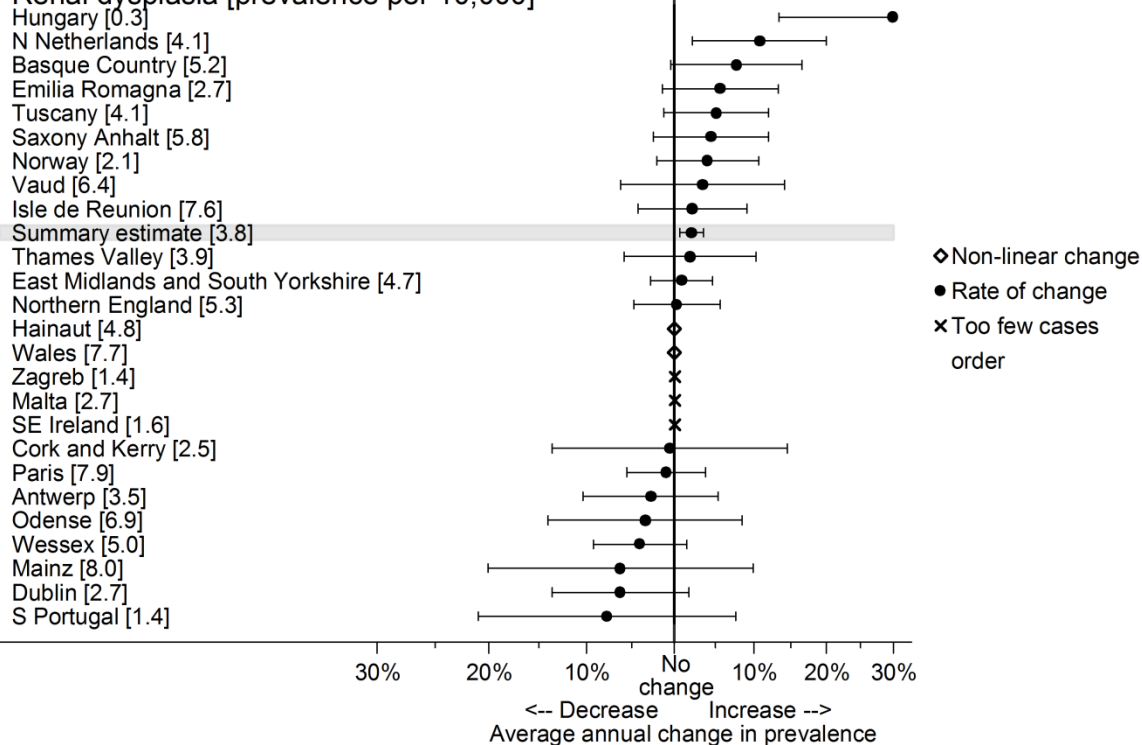




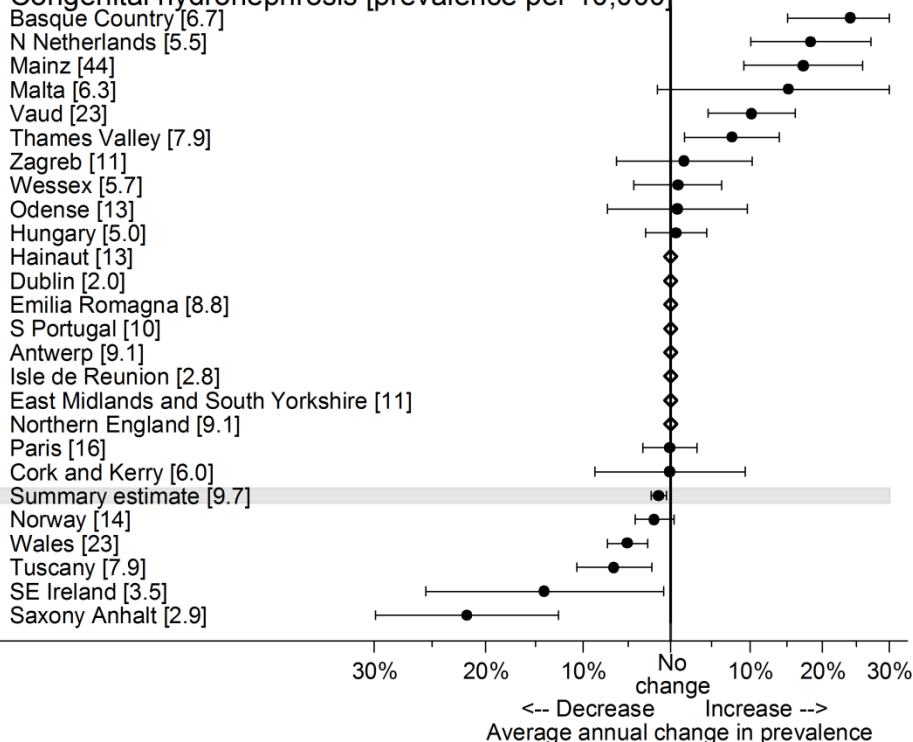
Bilateral renal agenesis including Potter syndrome [prevalence per 10,000]



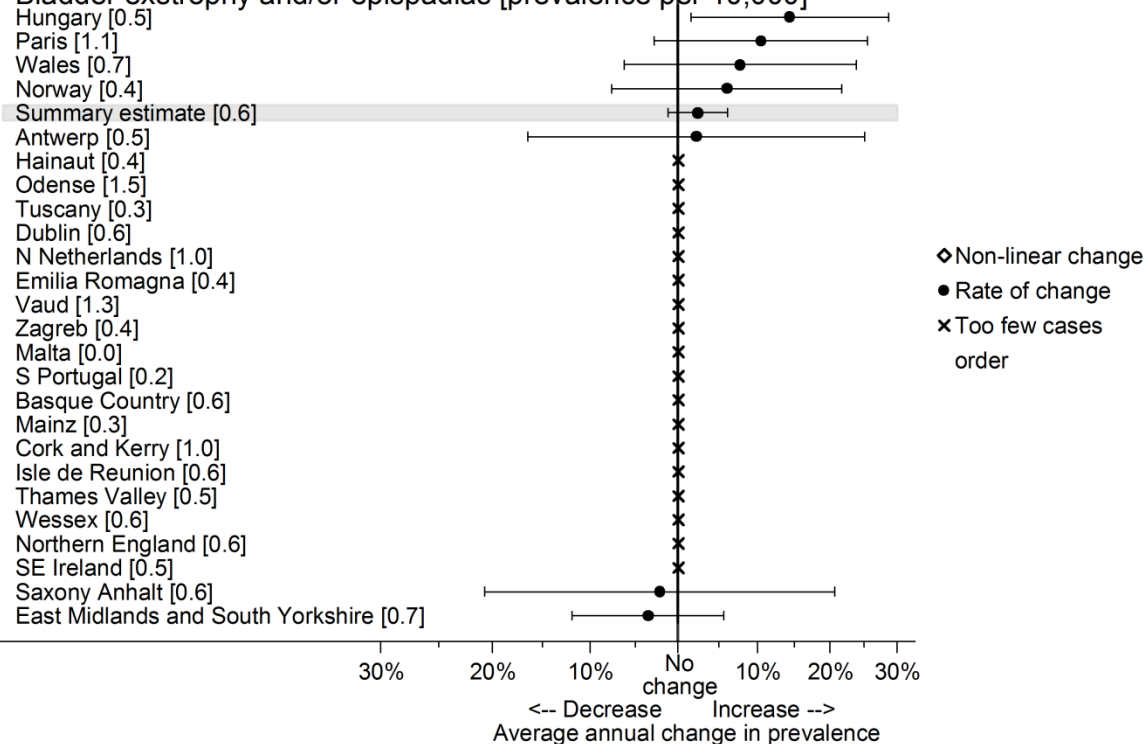
Renal dysplasia [prevalence per 10,000]



Congenital hydronephrosis [prevalence per 10,000]



Bladder exstrophy and/or epispadias [prevalence per 10,000]



Posterior urethral valve and/or prune belly [prevalence per 10,000]

East Midlands and South Yorkshire [0.5]

Emilia Romagna [0.5]

Antwerp [1.7]

Wessex [1.2]

Paris [1.4]

Wales [2.2]

Hainaut [0.7]

Odense [1.3]

Zagreb [0.0]

Malta [1.0]

S Portugal [0.2]

Saxony Anhalt [1.3]

Mainz [1.3]

Cork and Kerry [0.9]

Norway [0.1]

Northern England [0.7]

Hungary [0.1]

SE Ireland [0.8]

Tuscany [0.7]

Summary estimate [0.8]

Vaud [2.4]

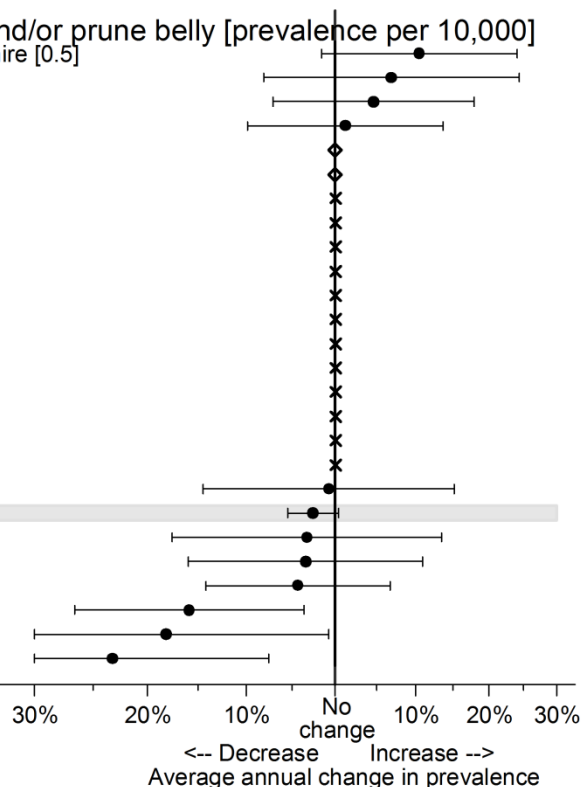
Thames Valley [1.2]

Isle de Reunion [2.7]

Basque Country [1.8]

Dublin [0.5]

N Netherlands [1.1]



Hypospadias [prevalence per 10,000]

Northern England [4.0]

Thames Valley [9.3]

Hainaut [13]

Isle de Reunion [15]

Emilia Romagna [14]

SE Ireland [10]

Summary estimate [17]

Paris [16]

N Netherlands [20]

Zagreb [24]

Malta [32]

S Portugal [6.1]

Basque Country [13]

Wessex [13]

East Midlands and South Yorkshire [13]

Hungary [25]

Wales [29]

Antwerp [17]

Norway [21]

Cork and Kerry [16]

Saxony Anhalt [18]

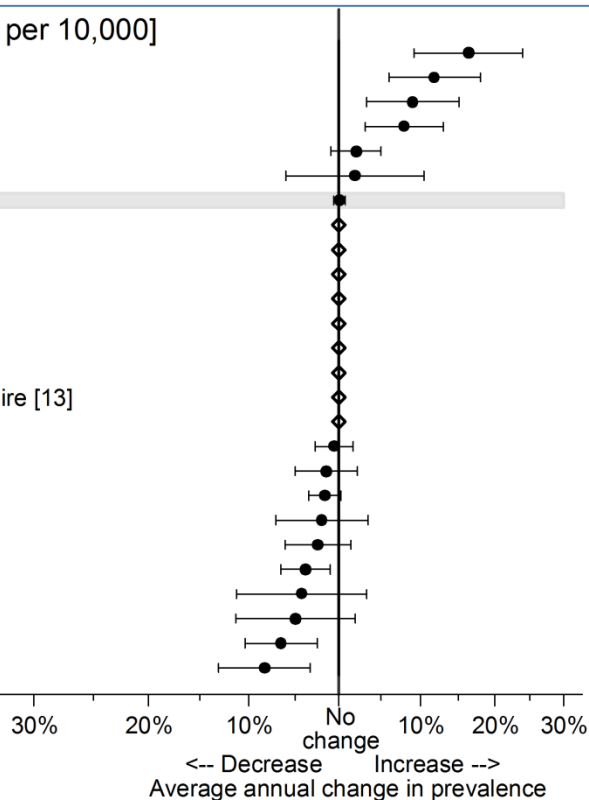
Tuscany [18]

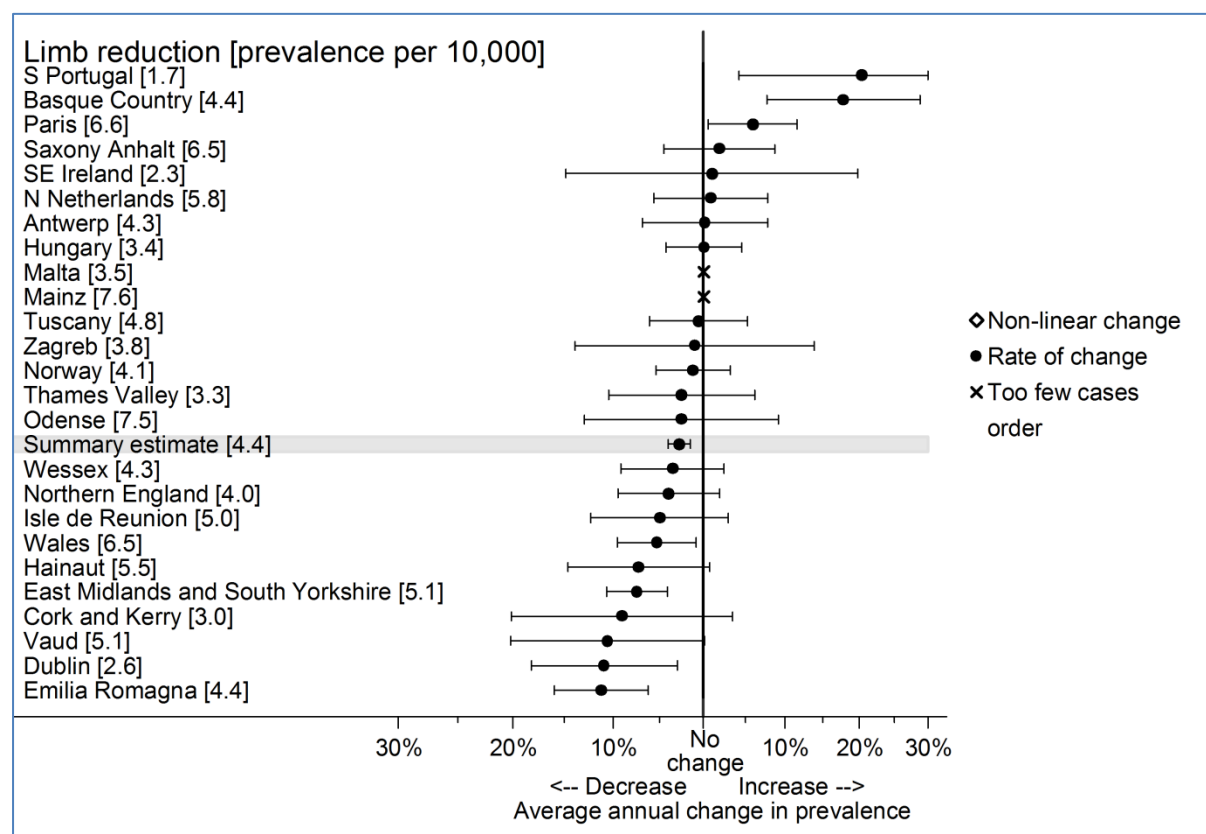
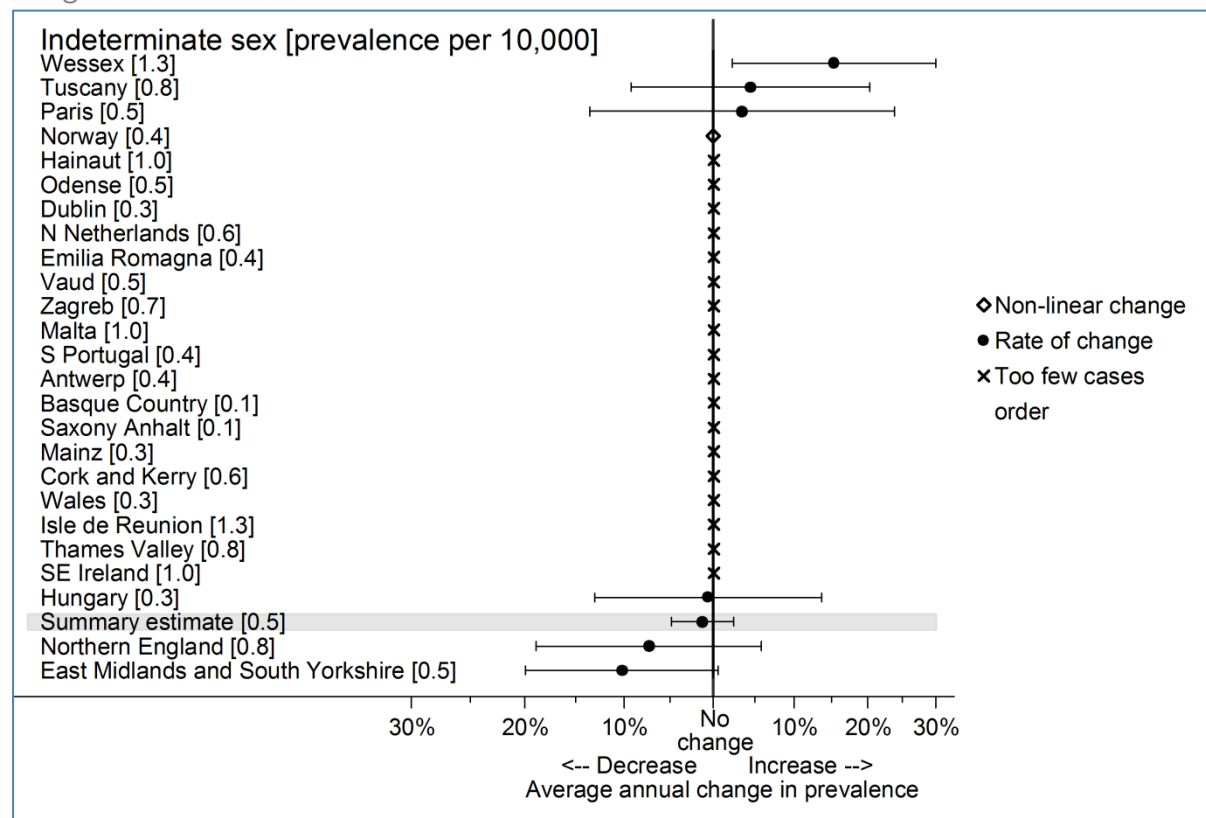
Mainz [35]

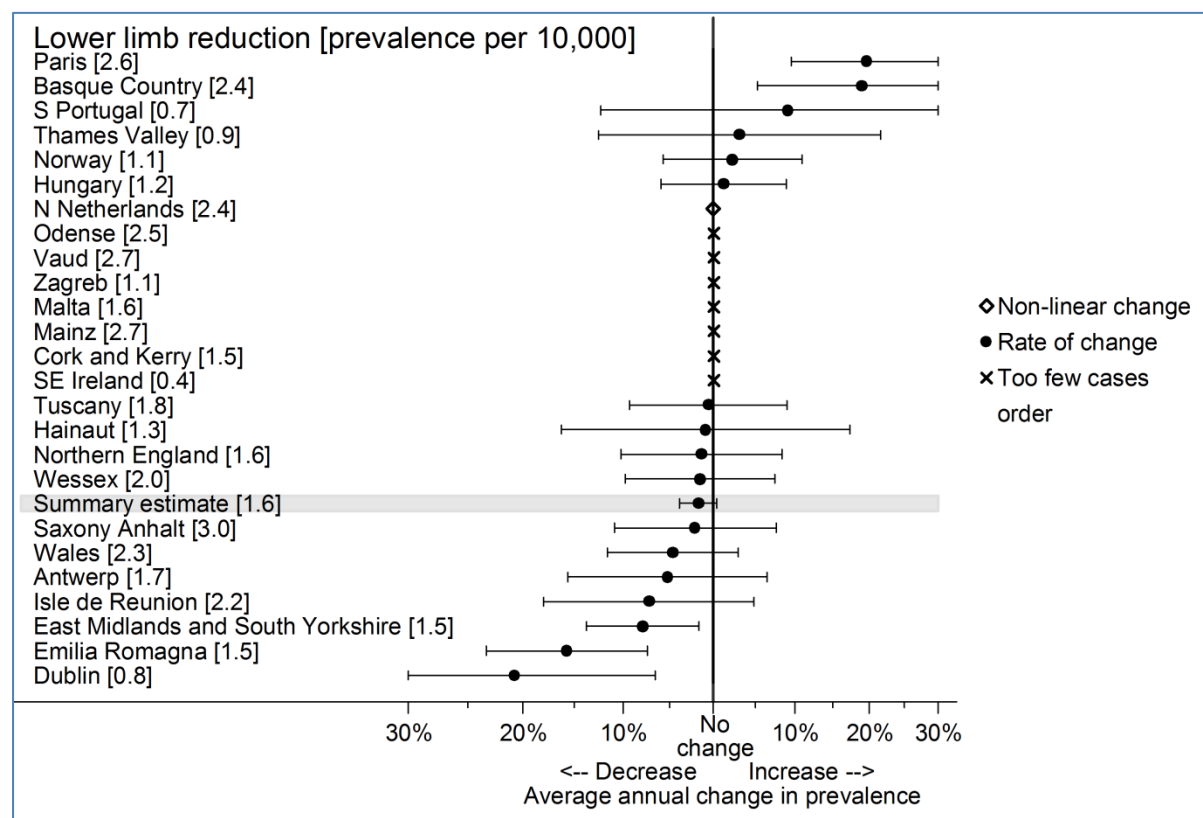
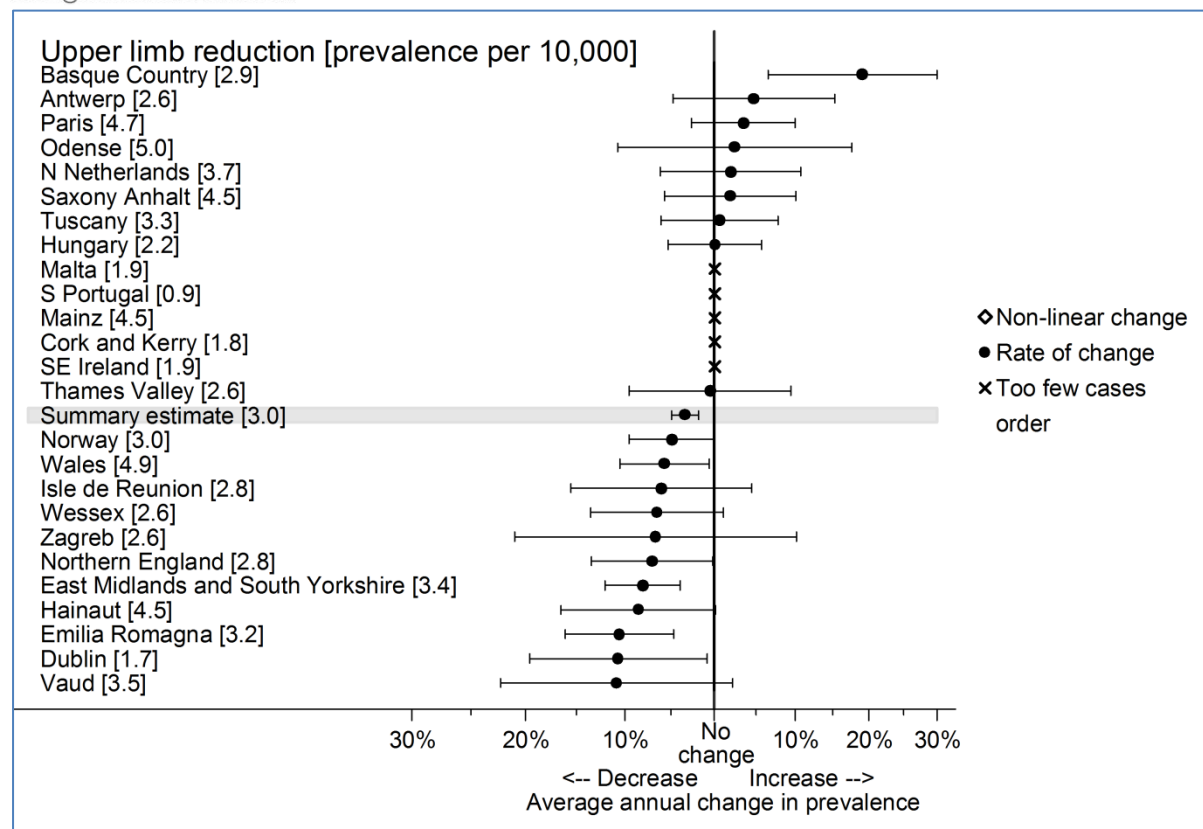
Odense [19]

Dublin [10]

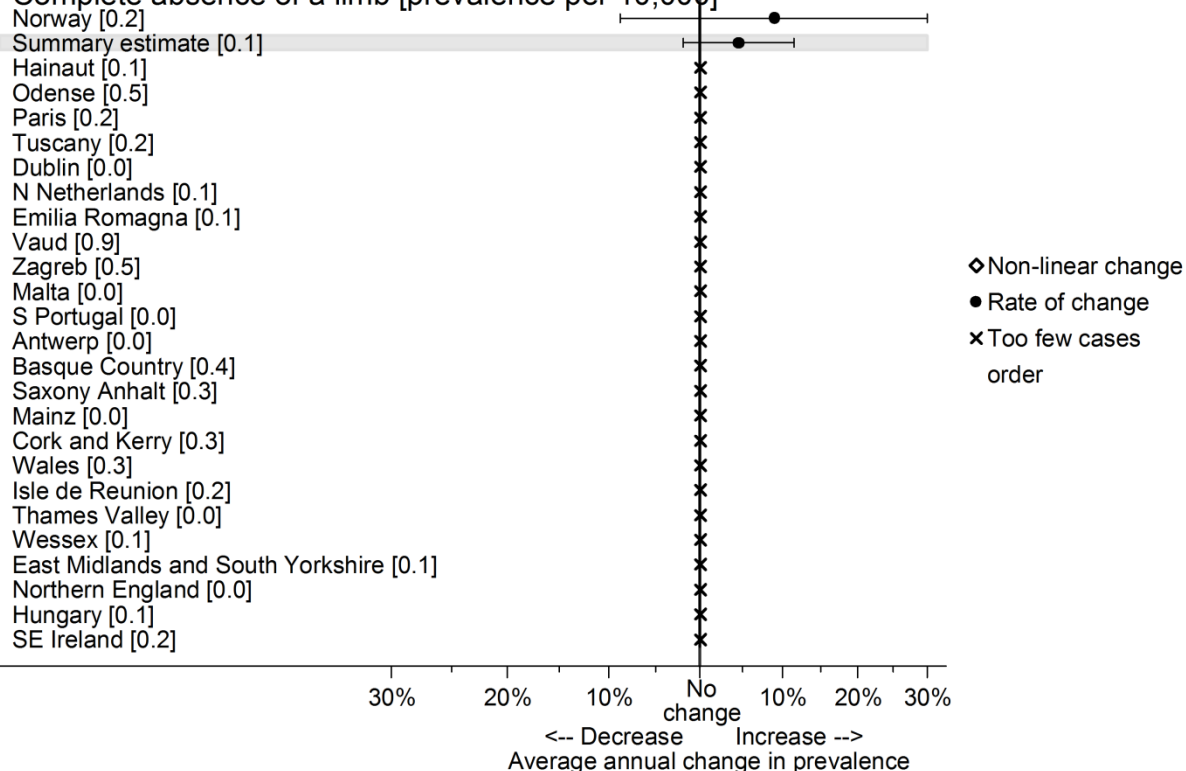
Vaud [21]



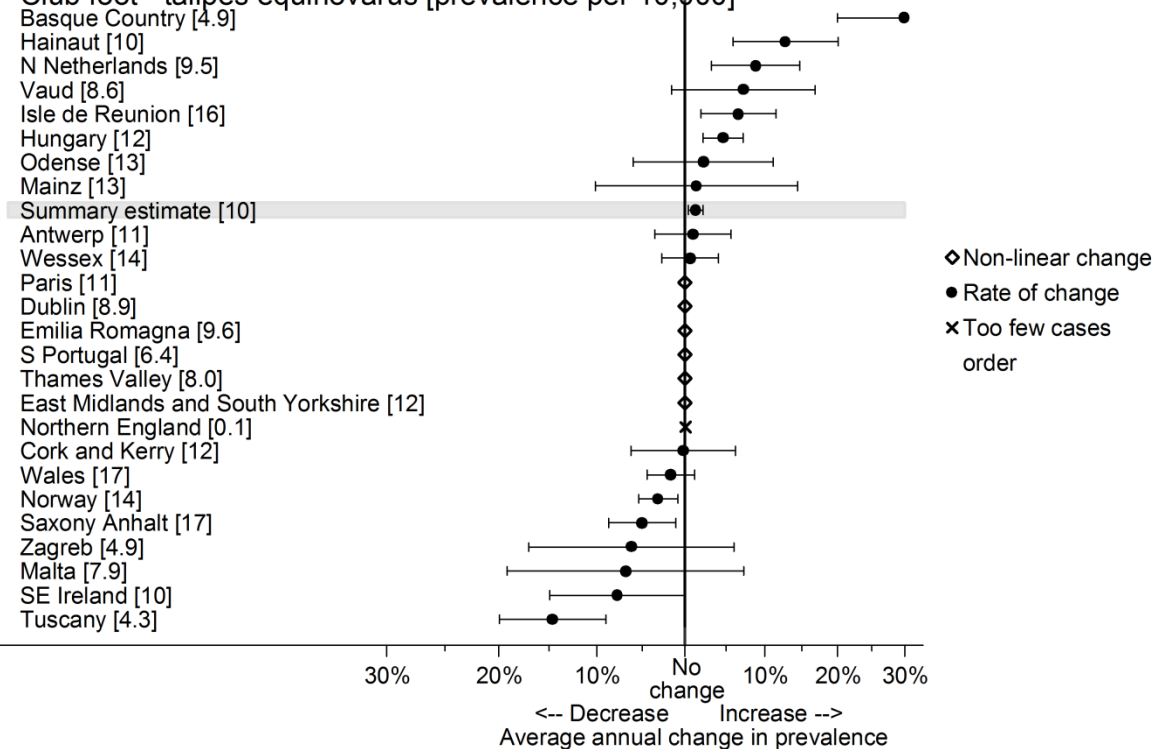




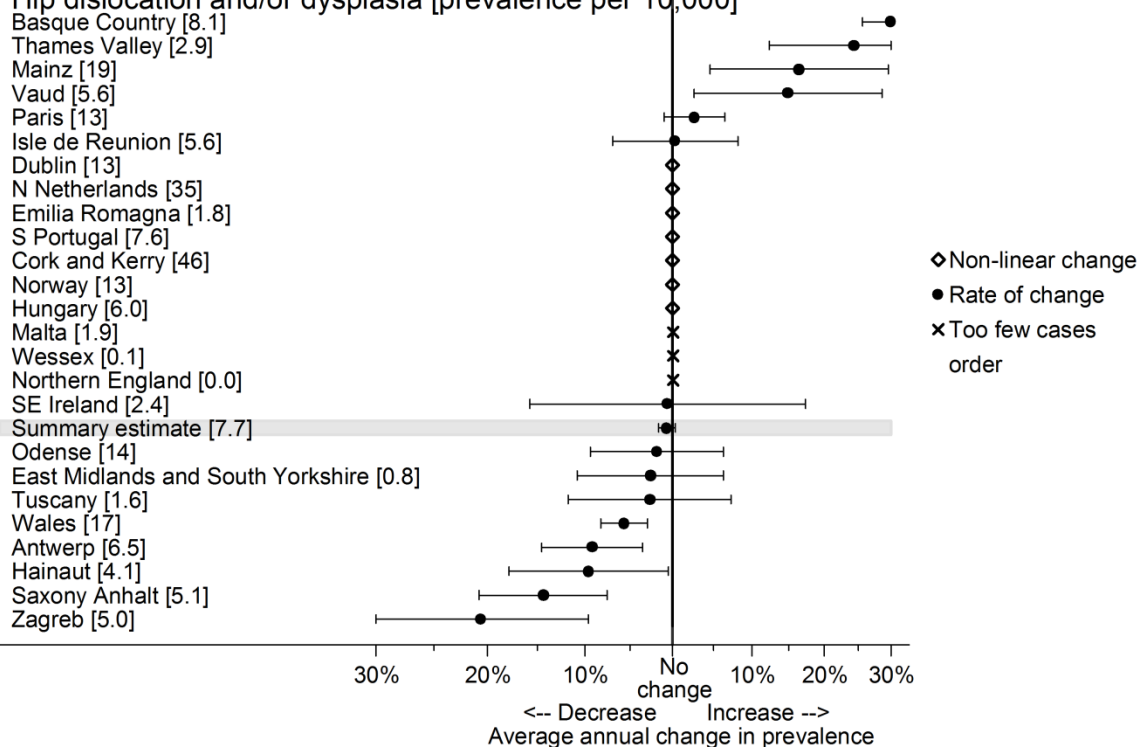
Complete absence of a limb [prevalence per 10,000]



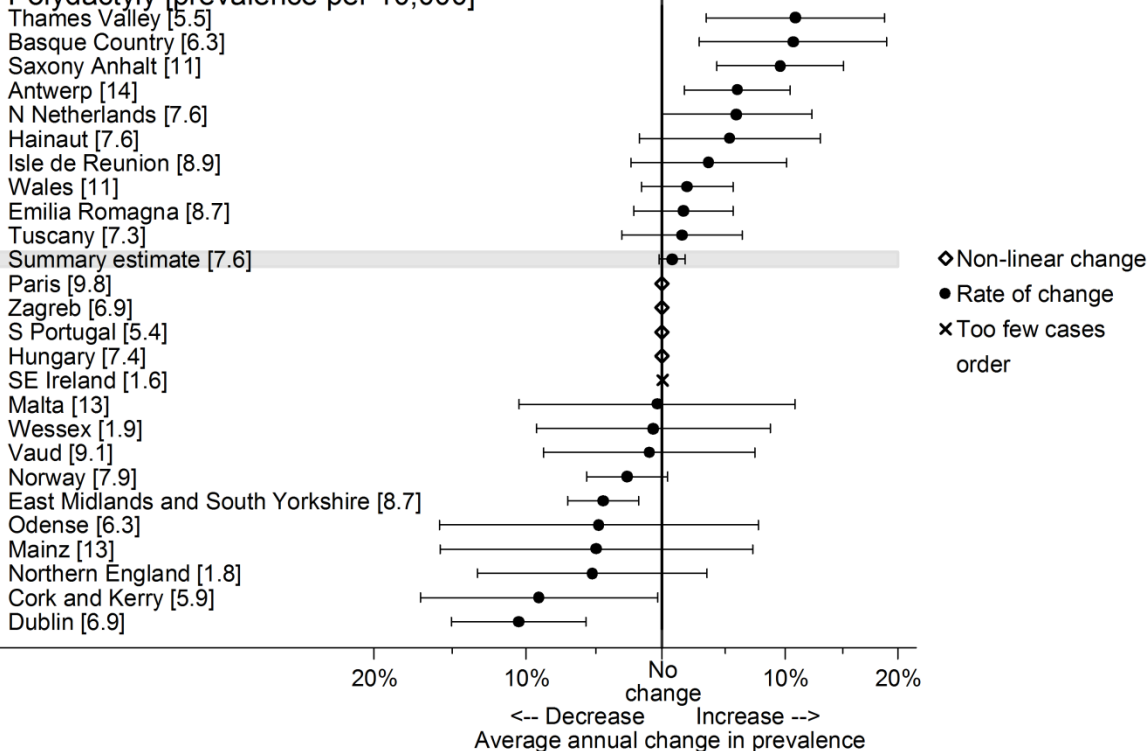
Club foot - talipes equinovarus [prevalence per 10,000]

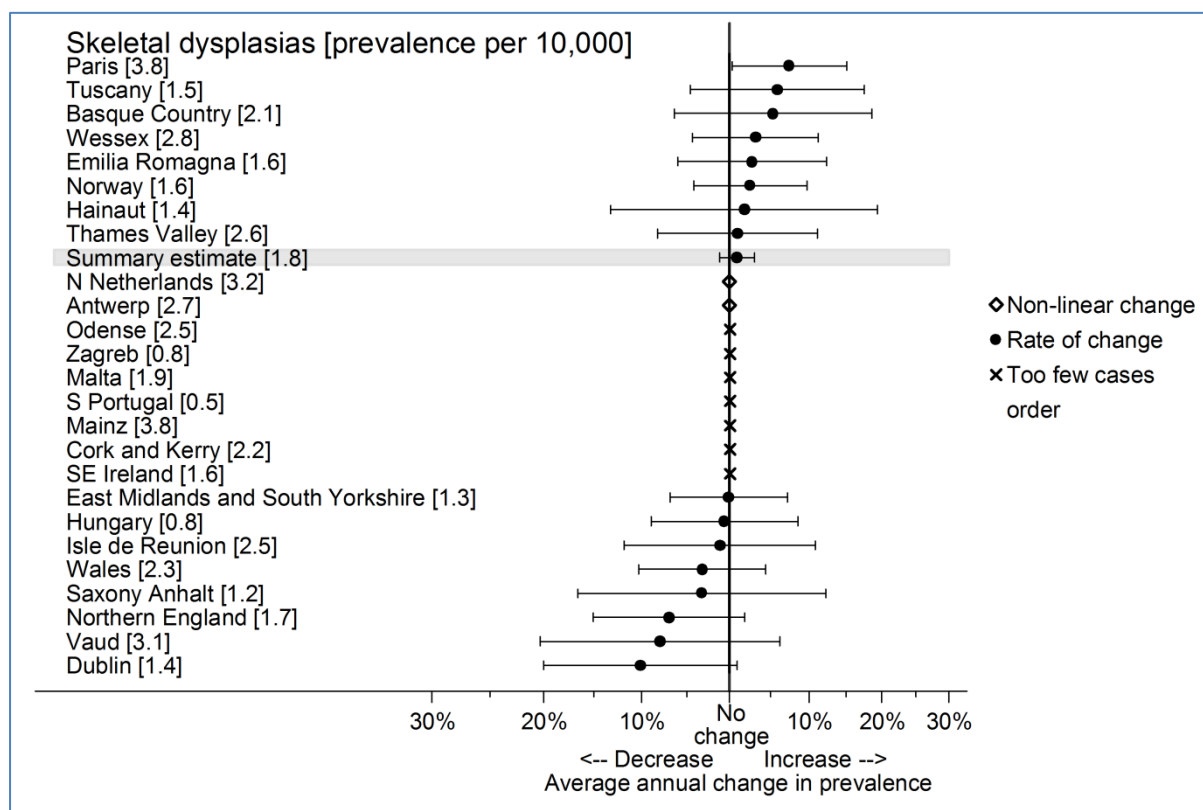
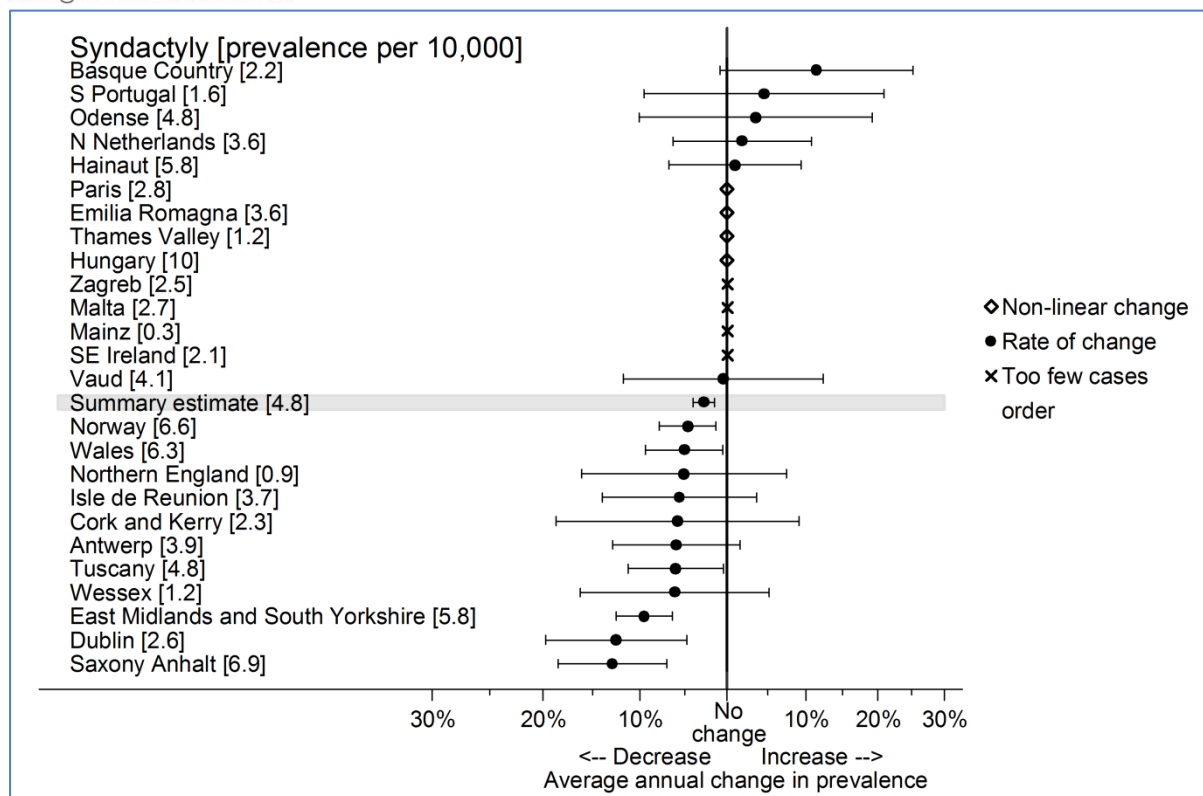


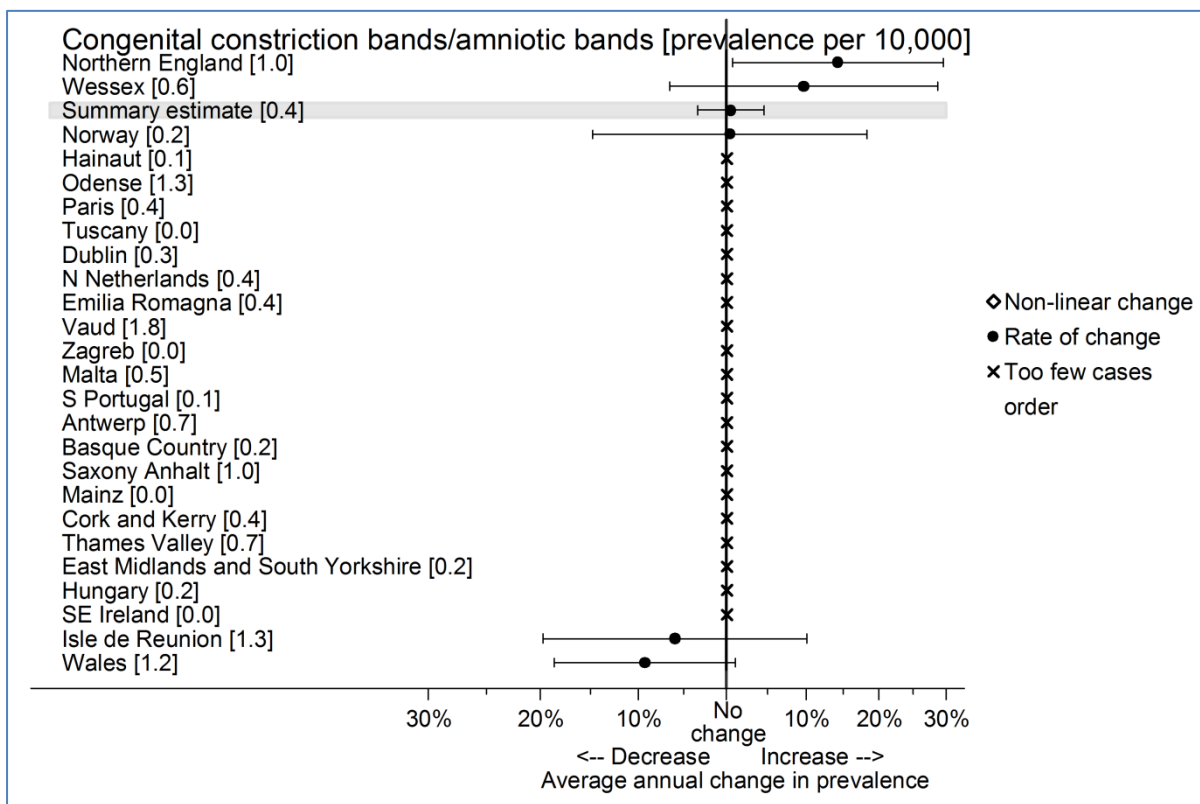
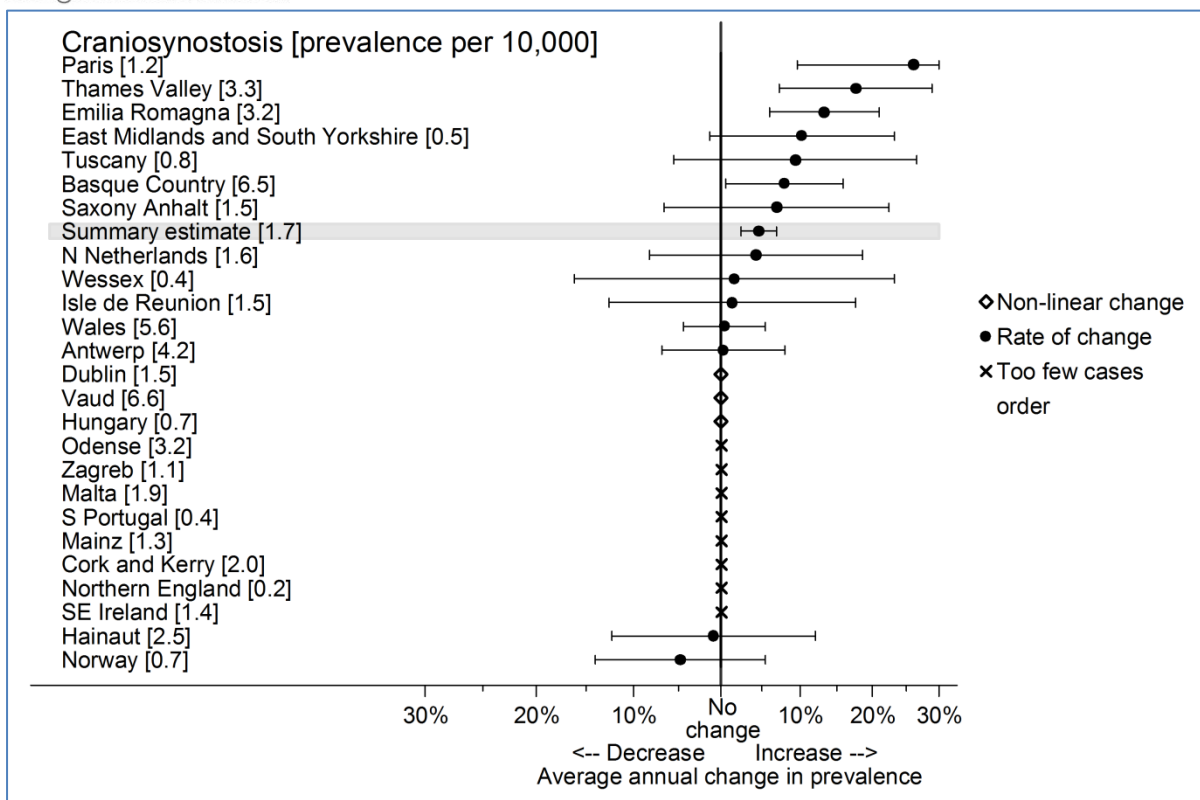
Hip dislocation and/or dysplasia [prevalence per 10,000]

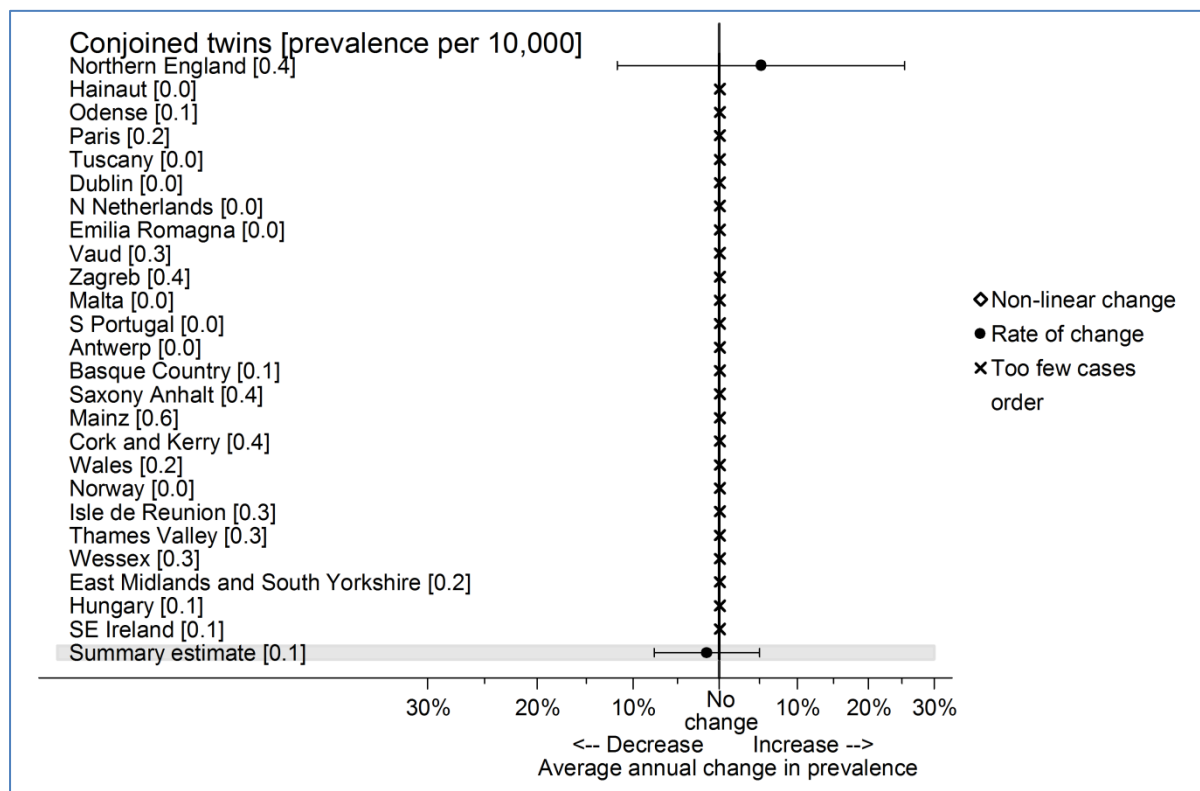
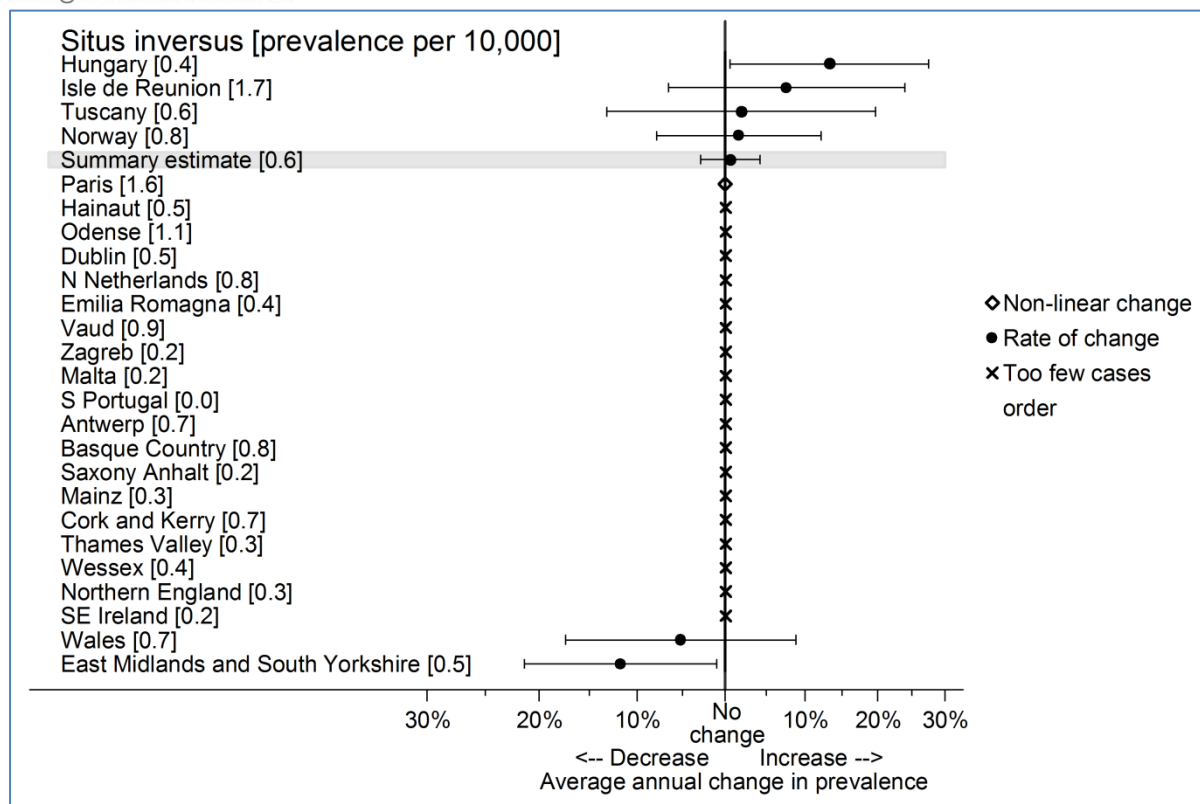


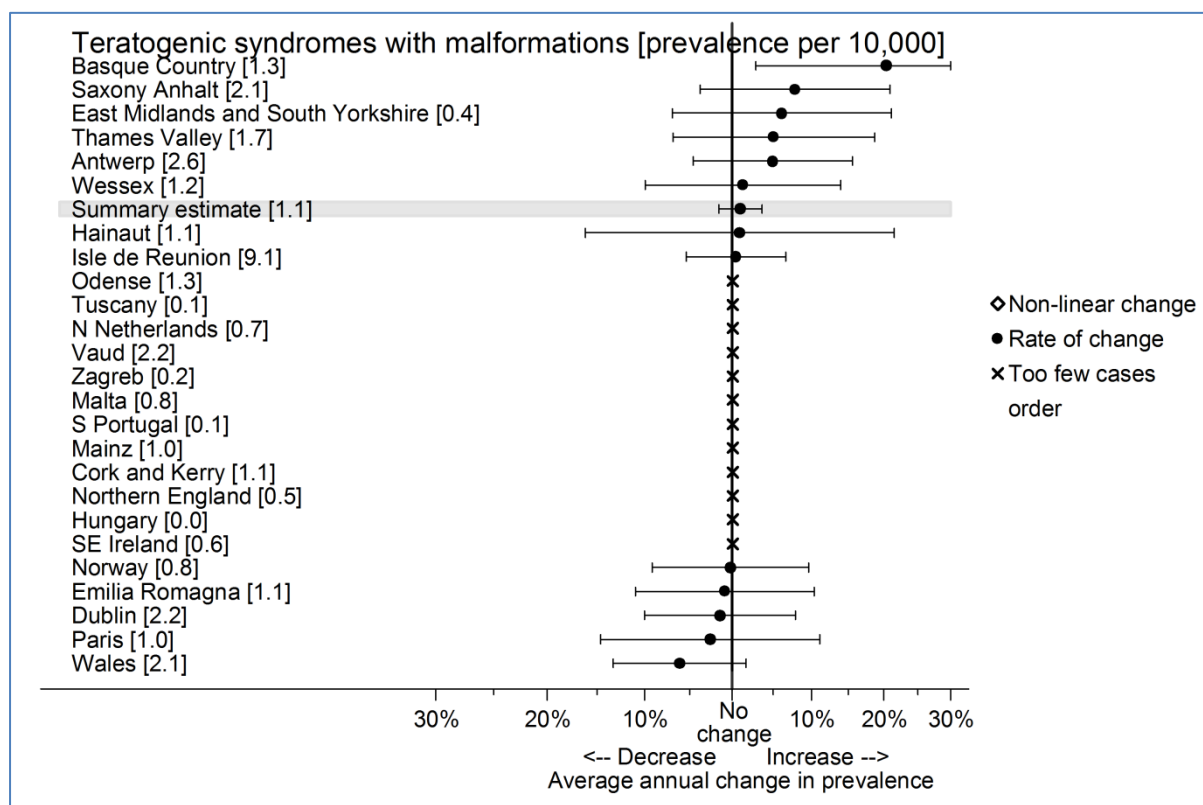
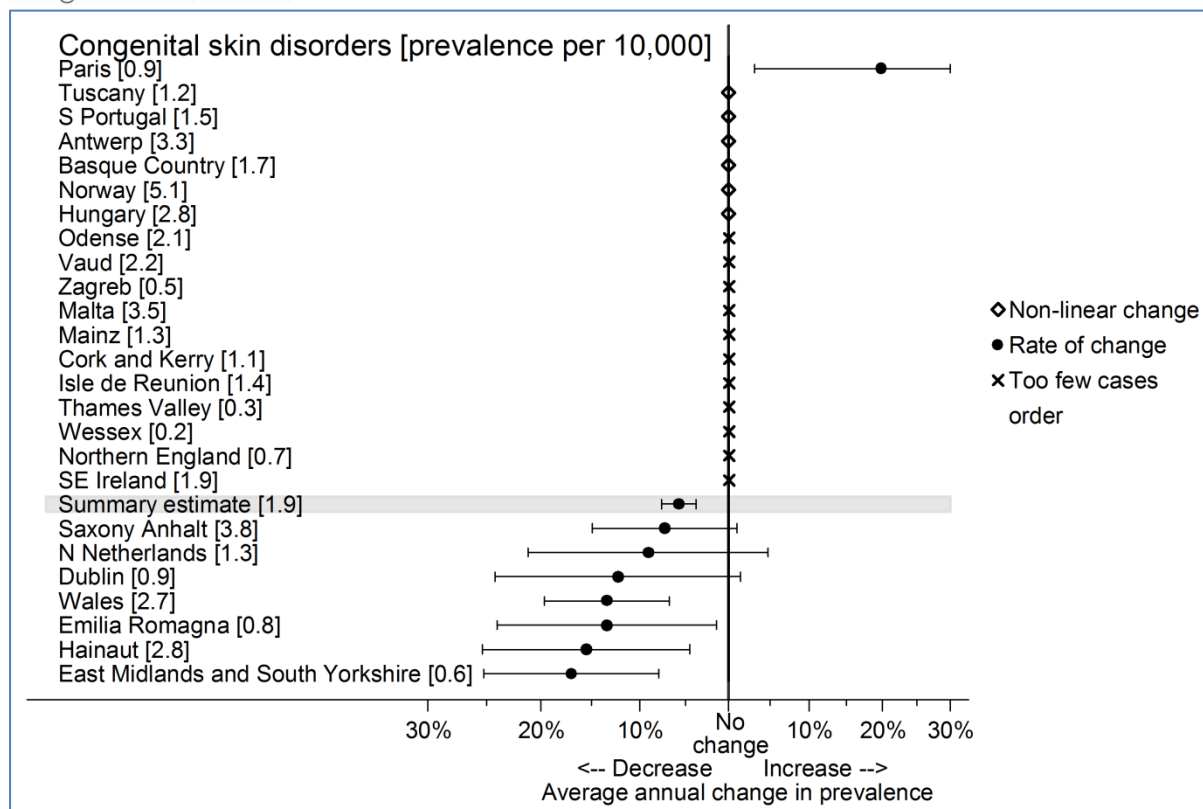
Polydactyly [prevalence per 10,000]

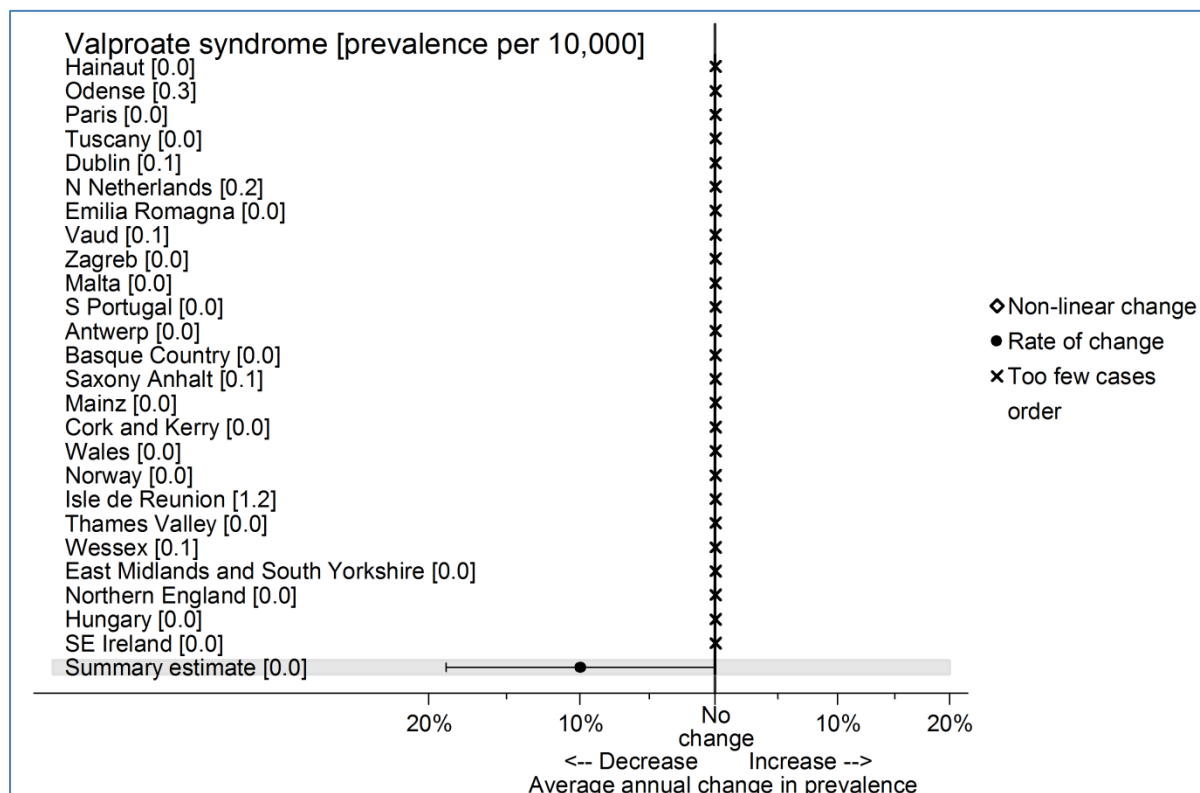
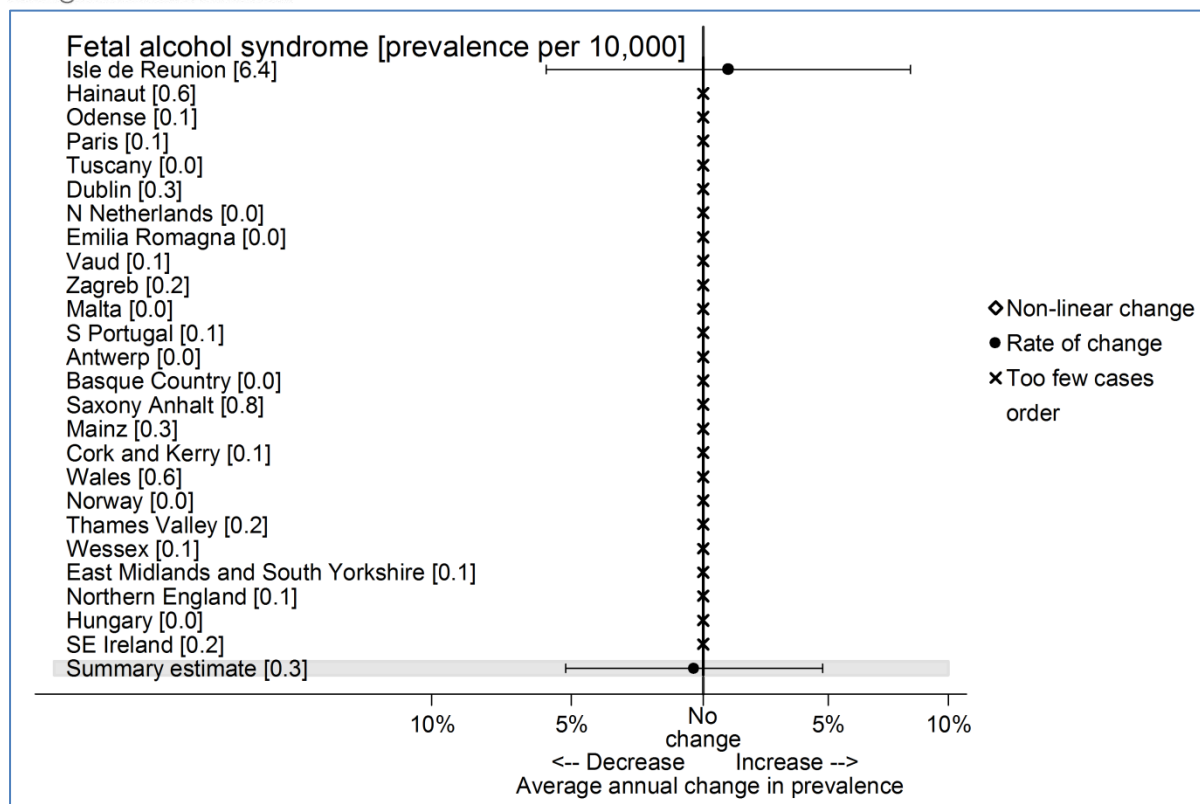




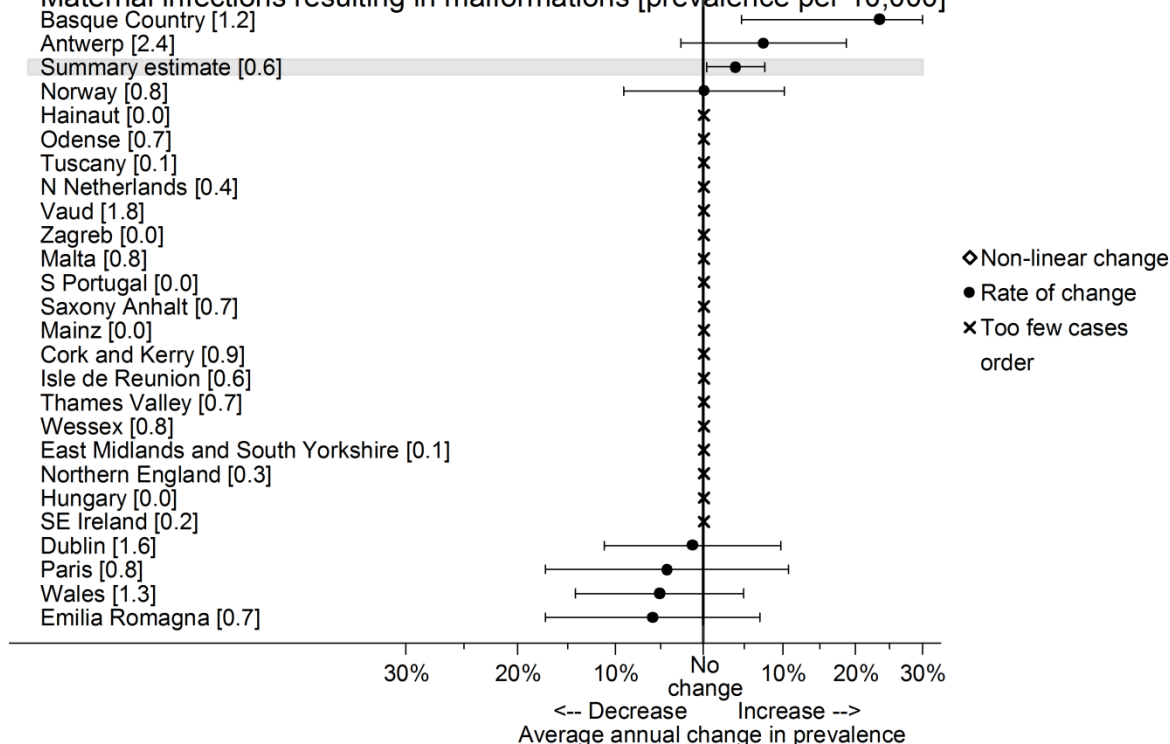




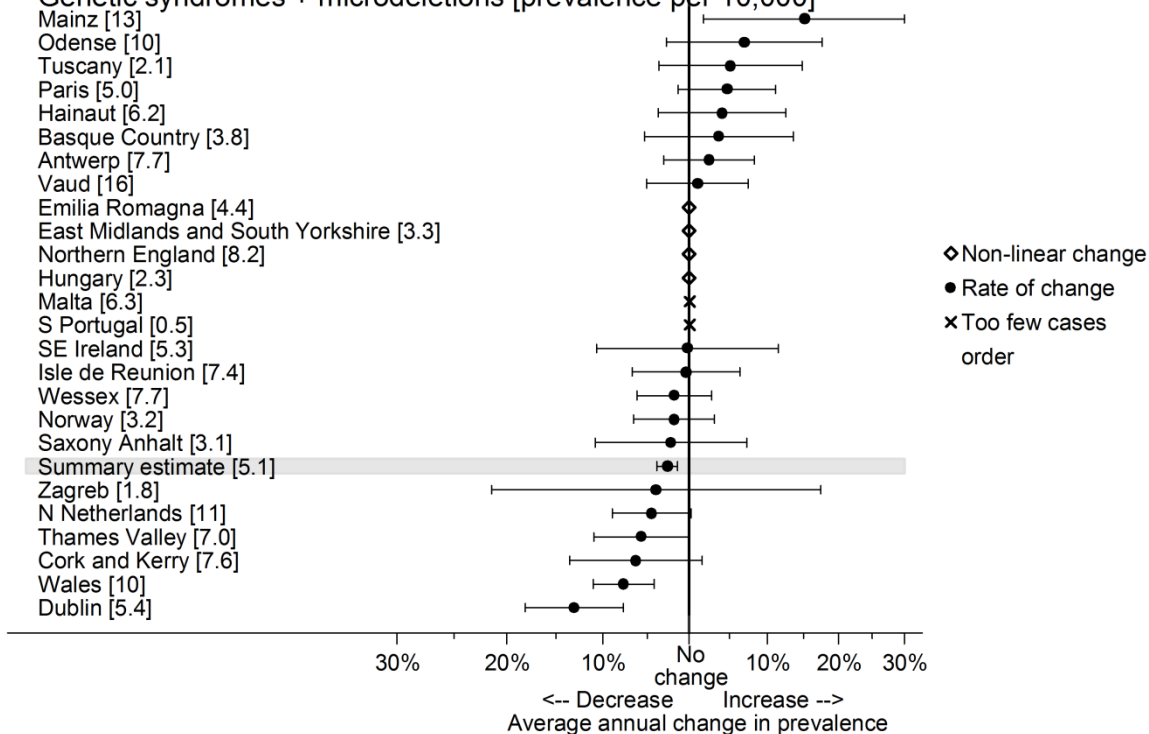


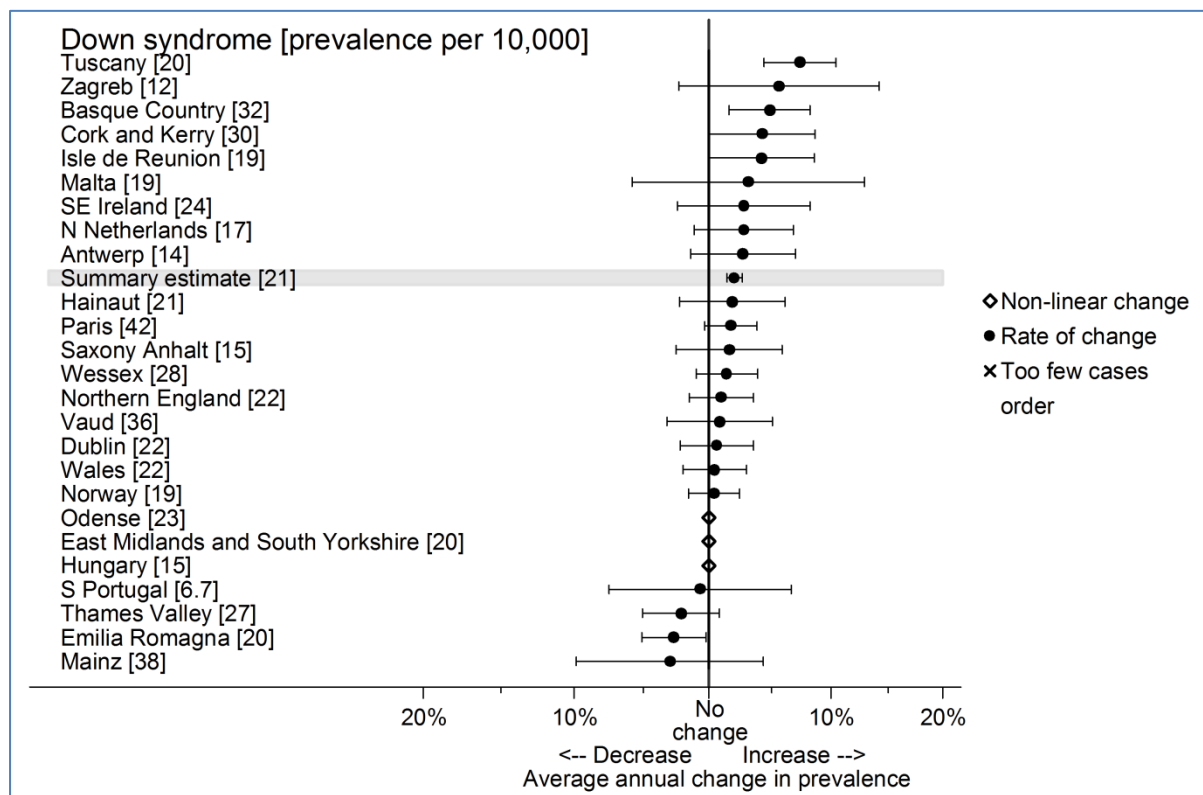
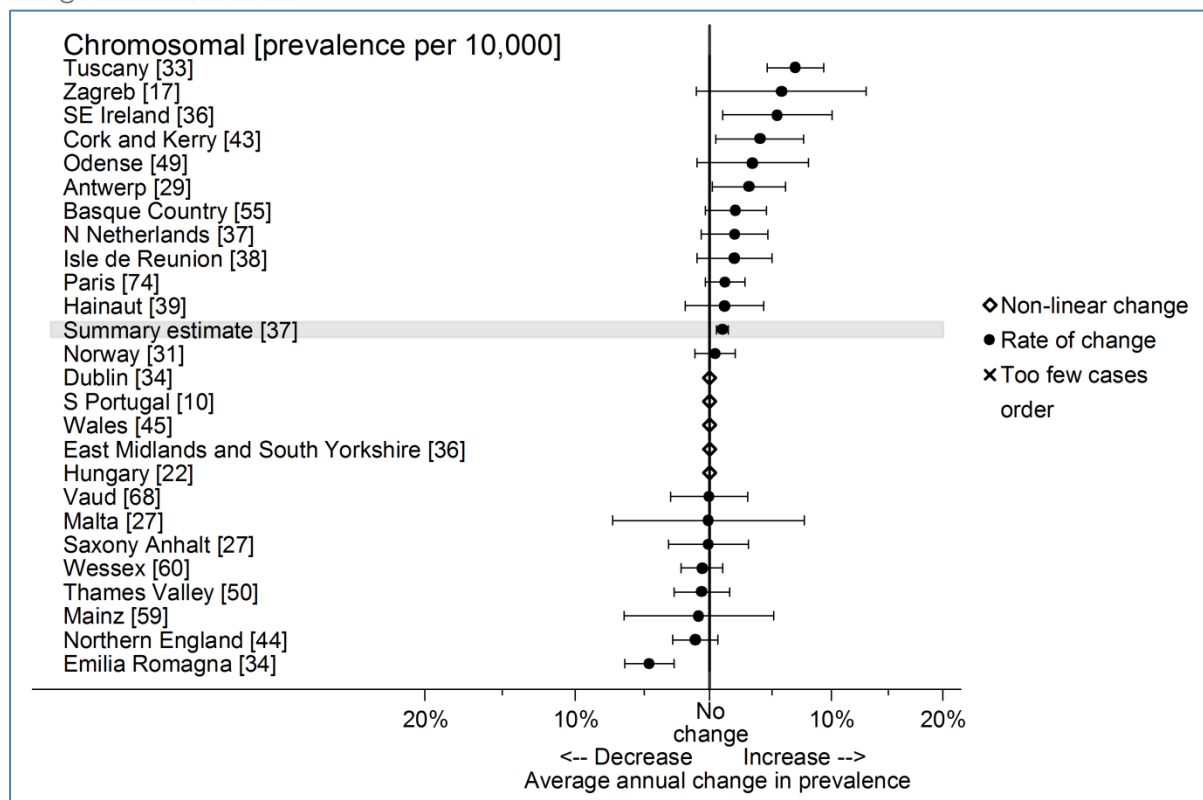


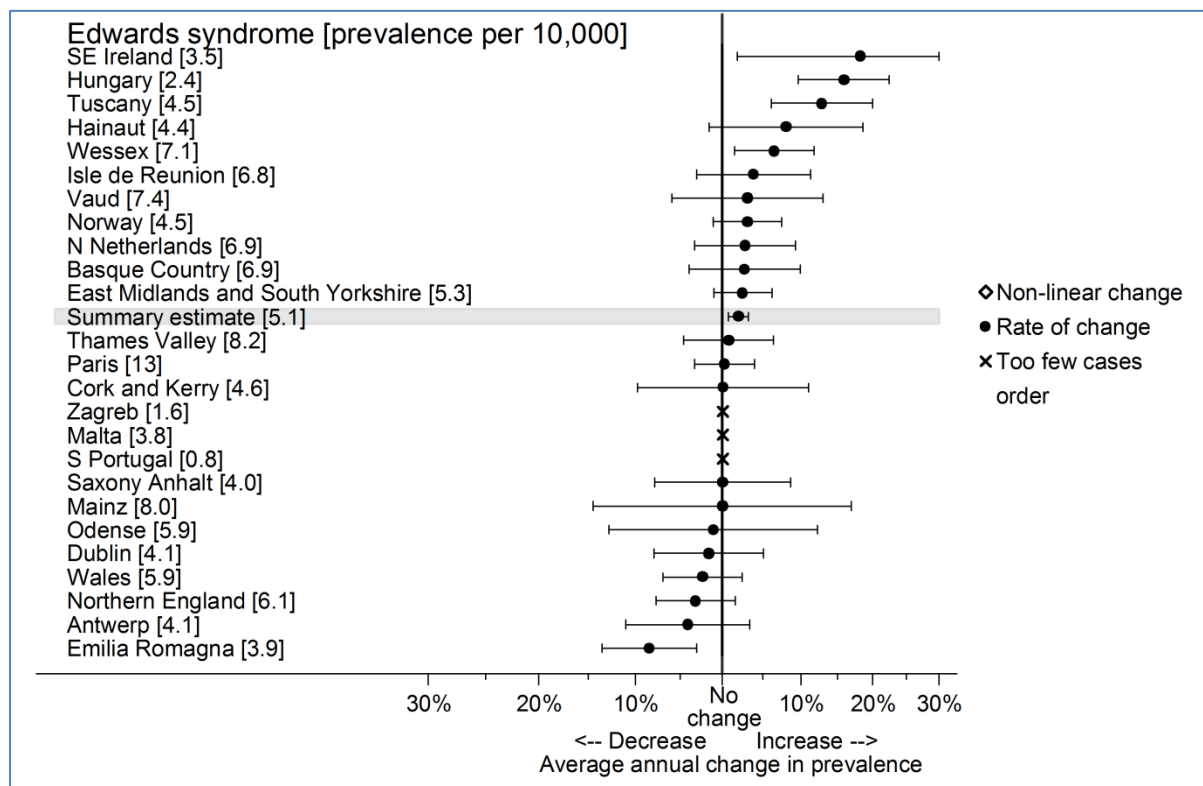
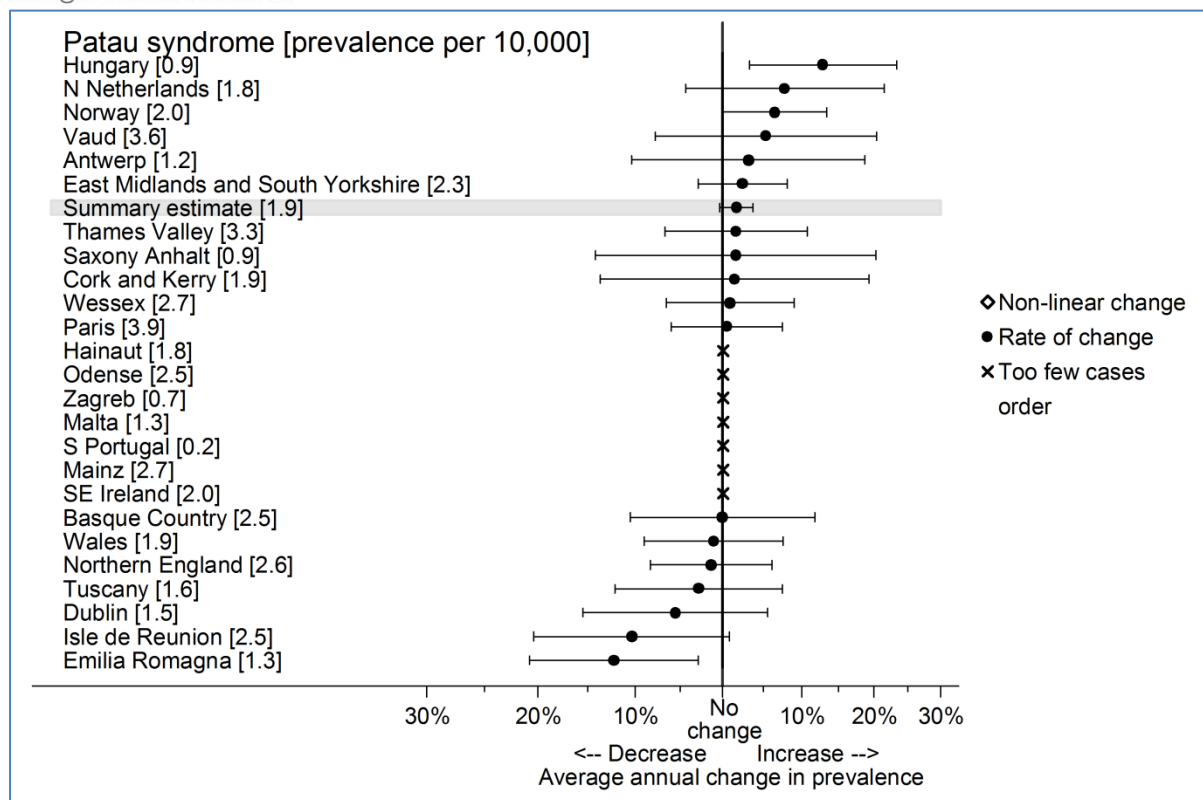
Maternal infections resulting in malformations [prevalence per 10,000]



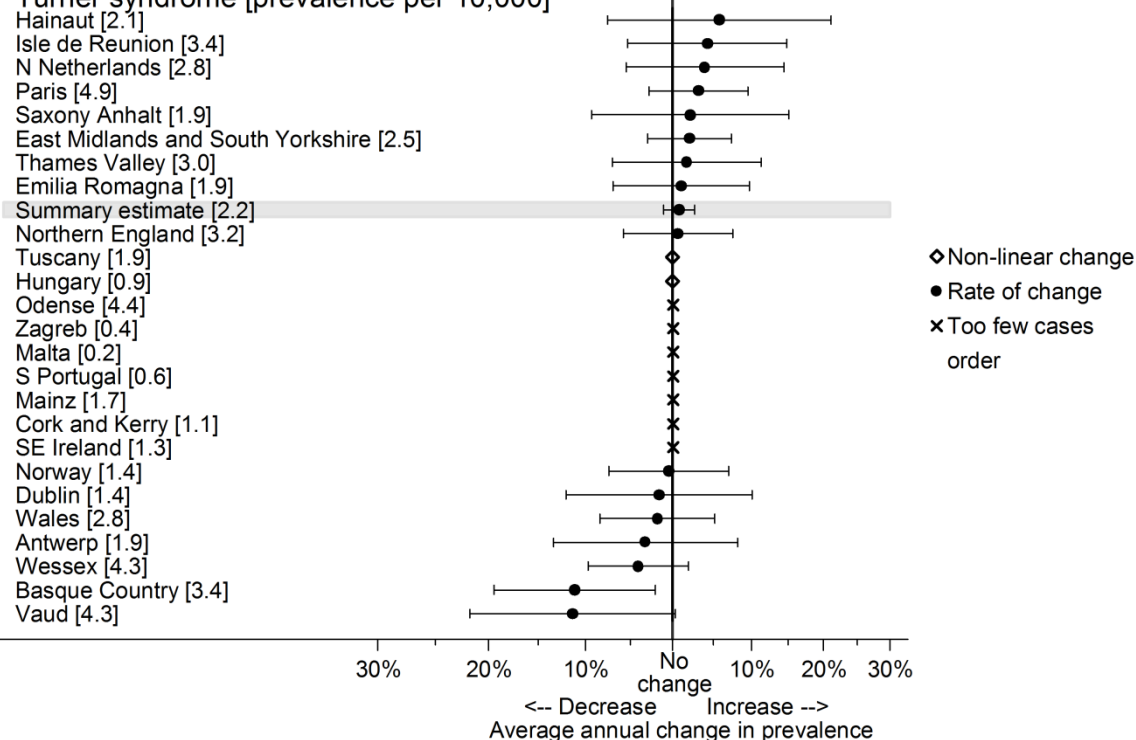
Genetic syndromes + microdeletions [prevalence per 10,000]



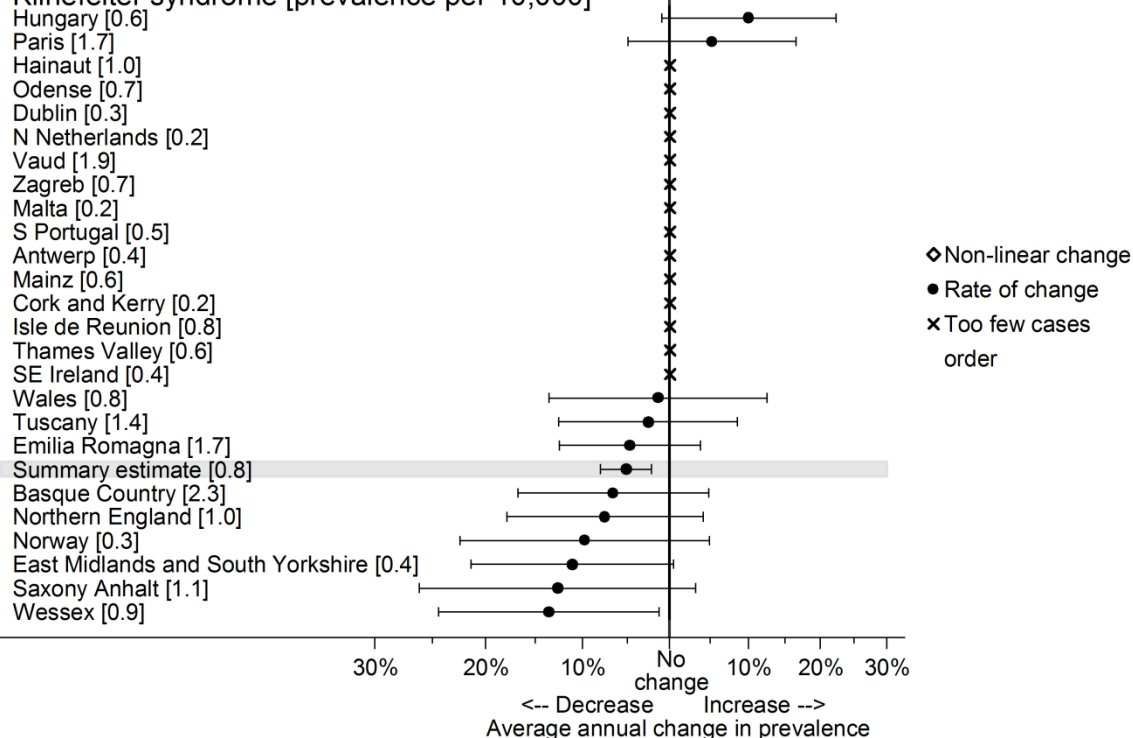


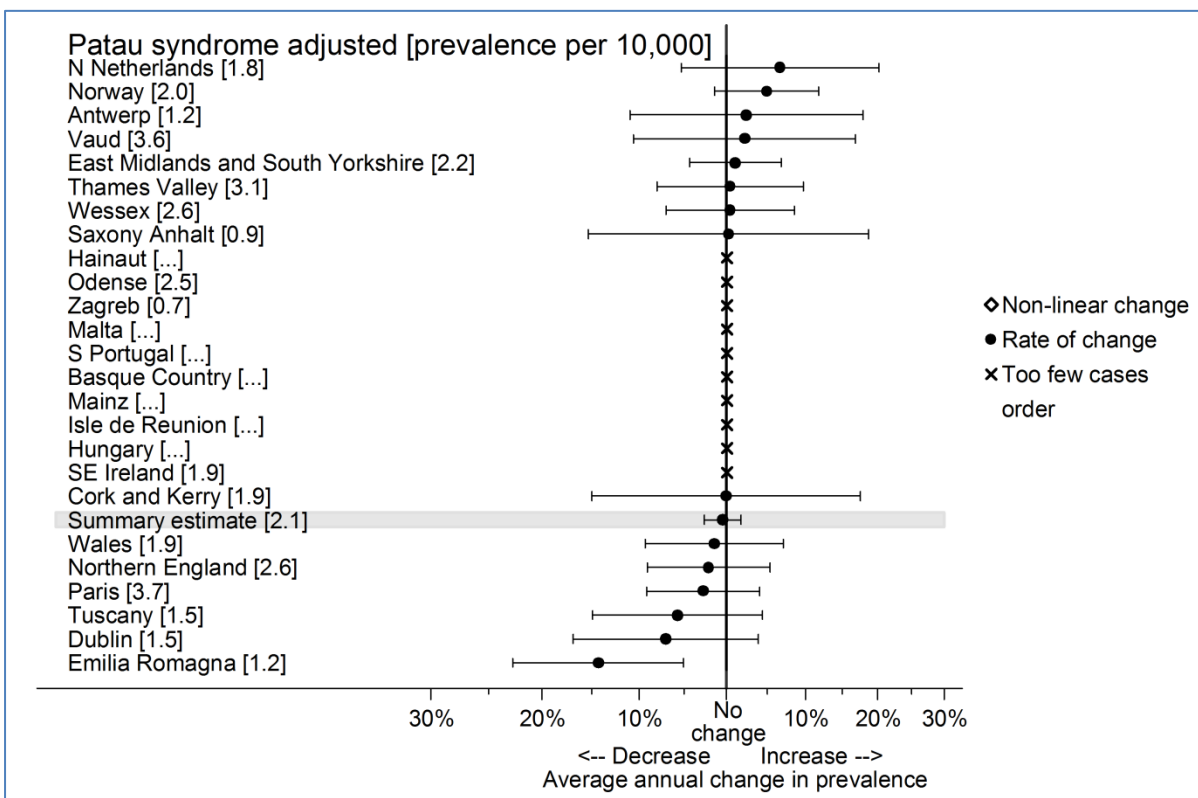
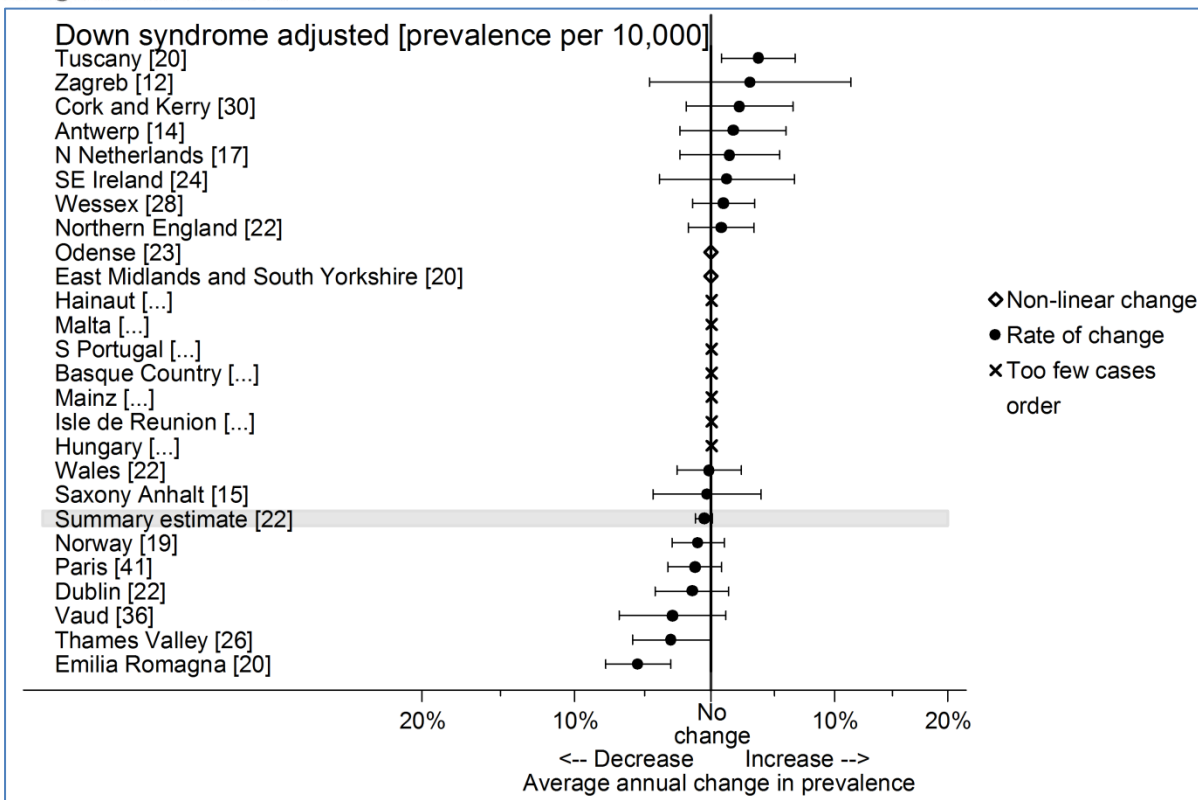


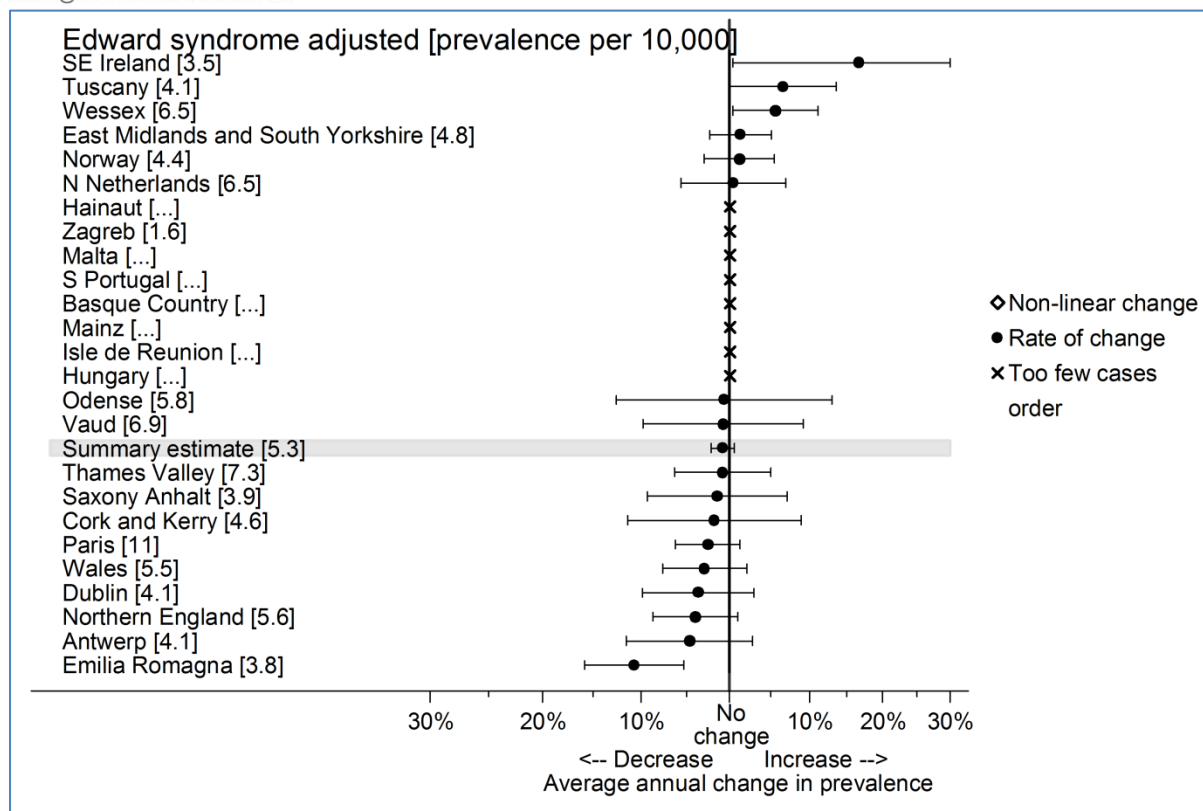
Turner syndrome [prevalence per 10,000]



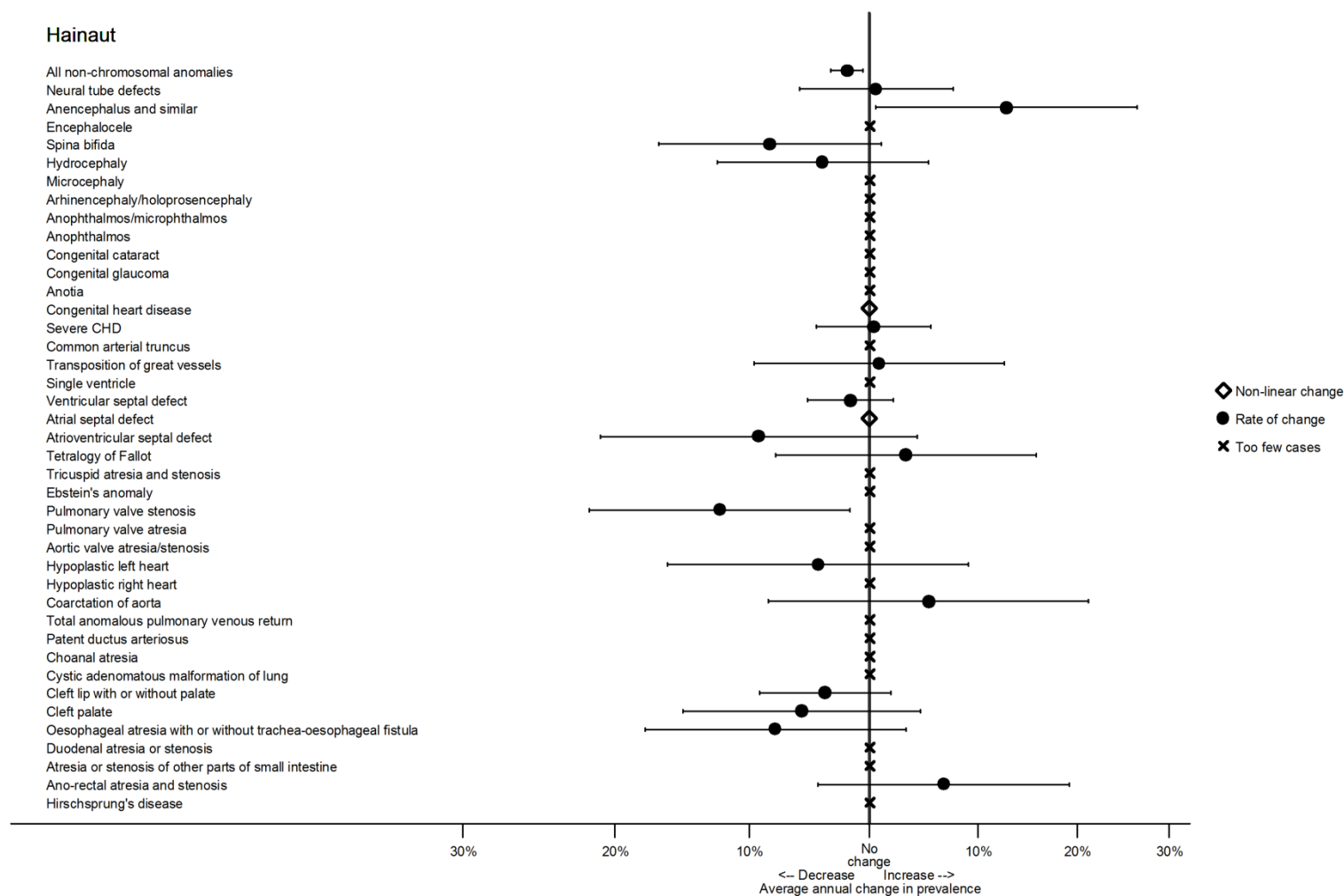
Klinefelter syndrome [prevalence per 10,000]





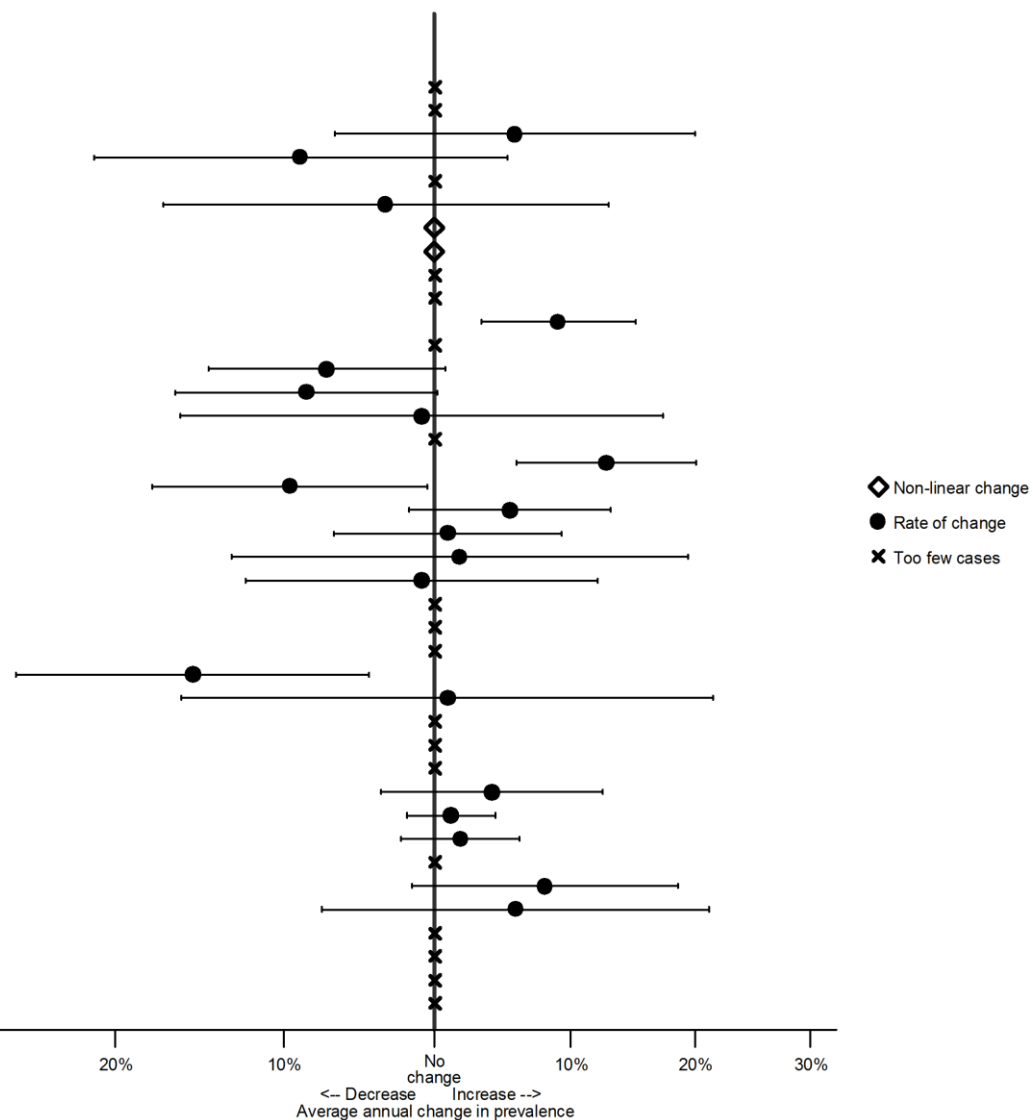


Appendix G: Forest plots showing ten year increasing and decreasing trends detected in the pan-Europe analysis by registry



Hainaut

Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb reduction
Upper limb reduction
Lower limb reduction
Complete absence of a limb
Club foot - talipes equinovarus
Hip dislocation and/or dysplasia
Polydactyly
Syndactyly
Skeletal dysplasias
Craniosynostosis
Congenital constriction bands/amniotic bands
Situs inversus
Conjoined twins
Congenital skin disorders
Teratogenic syndromes with malformations
Fetal alcohol syndrome
Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
Chromosomal
Down syndrome
Patau syndrome
Edwards syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted



Odense

All non-chromosomal anomalies

Neural tube defects

Anencephalus and similar

Encephalocele

Spina bifida

Hydrocephaly

Microcephaly

Arhinencephaly/holoprosencephaly

Anophthalmos/microphthalmos

Anophthalmos

Congenital cataract

Congenital glaucoma

Anotia

Congenital heart disease

Severe CHD

Common arterial truncus

Transposition of great vessels

Single ventricle

Ventricular septal defect

Atrial septal defect

Atrioventricular septal defect

Tetralogy of Fallot

Tricuspid atresia and stenosis

Ebstein's anomaly

Pulmonary valve stenosis

Pulmonary valve atresia

Aortic valve atresia/stenosis

Hypoplastic left heart

Hypoplastic right heart

Coarctation of aorta

Total anomalous pulmonary venous return

Patent ductus arteriosus

Choanal atresia

Cystic adenomatous malformation of lung

Cleft lip with or without palate

Cleft palate

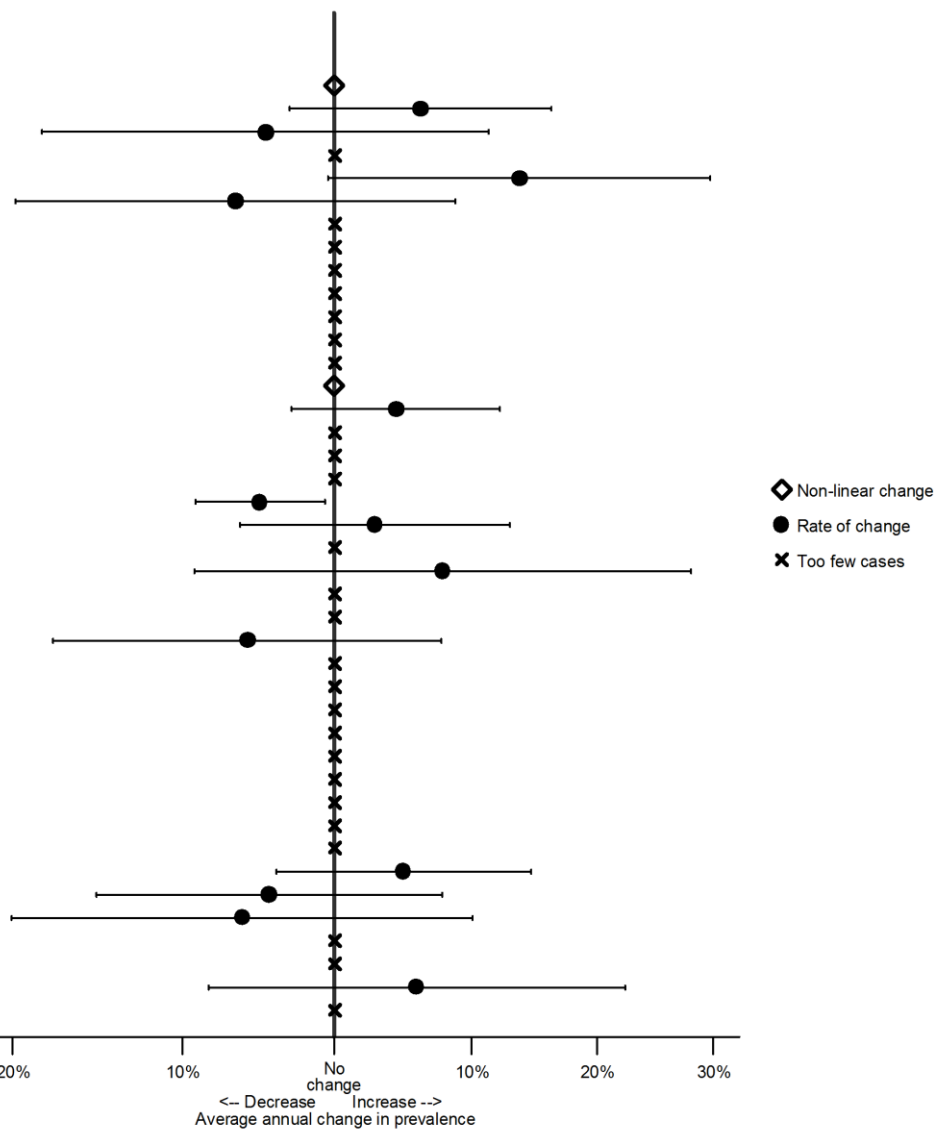
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

Atresia or stenosis of other parts of small intestine

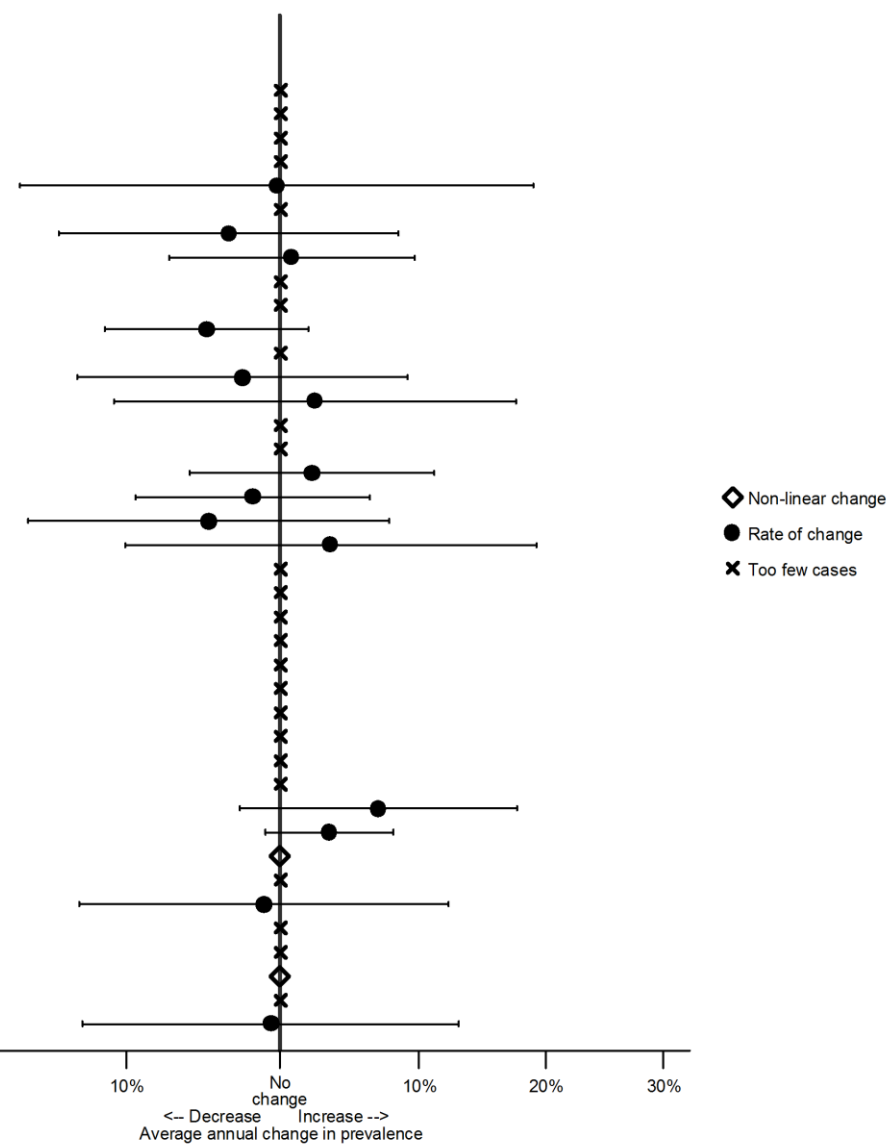
Ano-rectal atresia and stenosis

Hirschsprung's disease



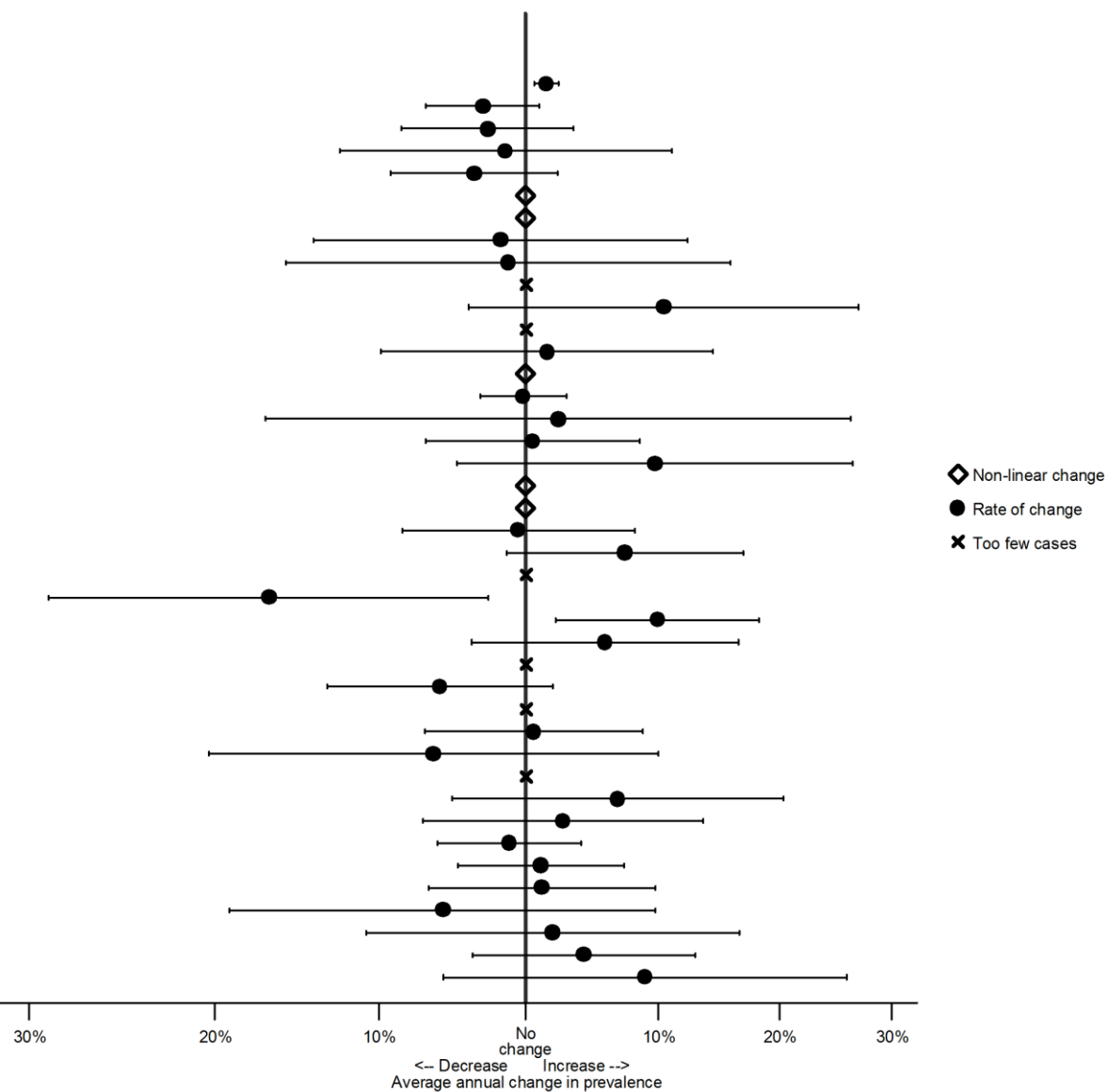
Odense

Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb reduction
Upper limb reduction
Lower limb reduction
Complete absence of a limb
Club foot - talipes equinovarus
Hip dislocation and/or dysplasia
Polydactyly
Syndactyly
Skeletal dysplasias
Craniosynostosis
Congenital constriction bands/amniotic bands
Situs inversus
Conjoined twins
Congenital skin disorders
Teratogenic syndromes with malformations
Fetal alcohol syndrome
Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
Chromosomal
Down syndrome
Patau syndrome
Edwards syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted



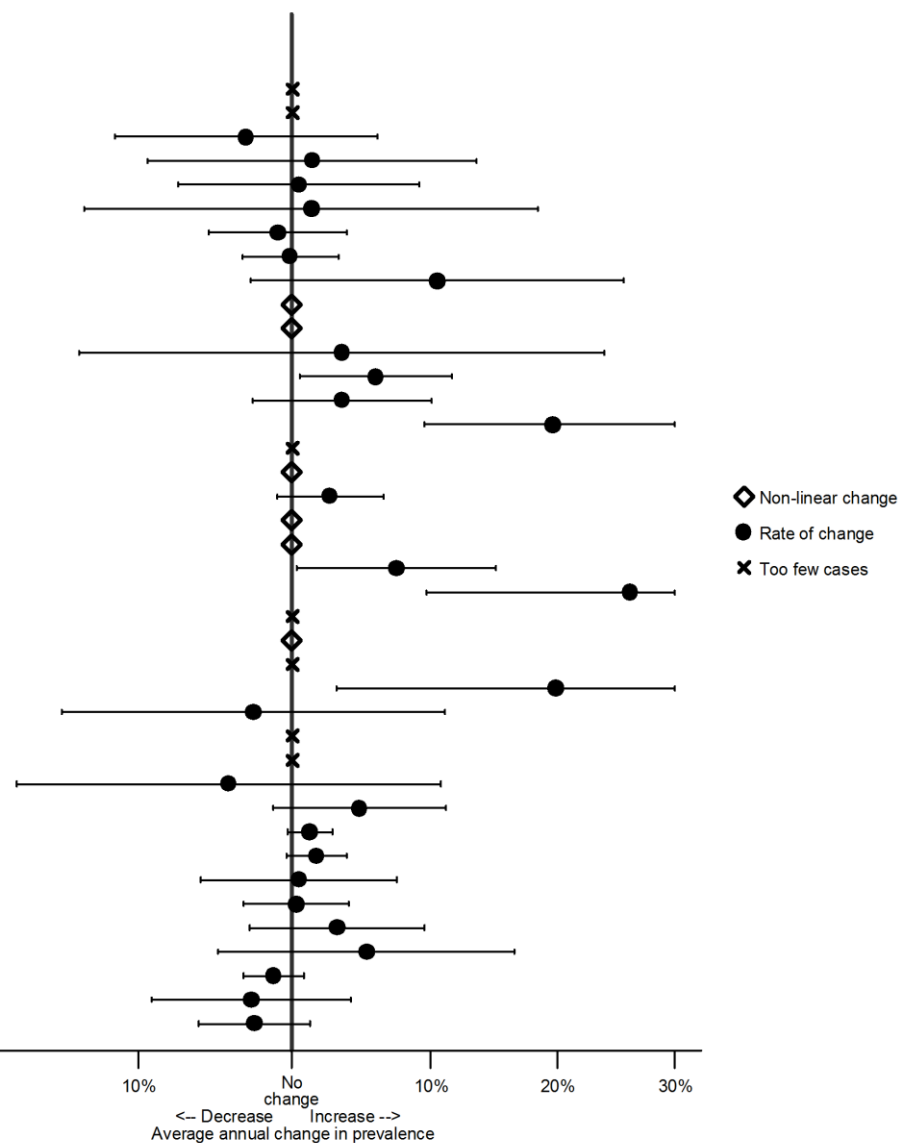
Paris

All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
Anophthalmos/microphthalmos
Anophthalmos
Congenital cataract
Congenital glaucoma
Anotia
Congenital heart disease
Severe CHD
Common arterial truncus
Transposition of great vessels
Single ventricle
Ventricular septal defect
Atrial septal defect
Atrioventricular septal defect
Tetralogy of Fallot
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Pulmonary valve stenosis
Pulmonary valve atresia
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Hypoplastic left heart
Hypoplastic right heart
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Total anomalous pulmonary venous return
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Cystic adenomatous malformation of lung
Cleft lip with or without palate
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Duodenal atresia or stenosis
Atresia or stenosis of other parts of small intestine
Ano-rectal atresia and stenosis
Hirschsprung's disease



Paris

Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb reduction
Upper limb reduction
Lower limb reduction
Complete absence of a limb
Club foot - talipes equinovarus
Hip dislocation and/or dysplasia
Polydactyly
Syndactyly
Skeletal dysplasias
Craniosynostosis
Congenital constriction bands/amniotic bands
Situs inversus
Conjoined twins
Congenital skin disorders
Teratogenic syndromes with malformations
Fetal alcohol syndrome
Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
Chromosomal
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Patau syndrome
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Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
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Tuscany

All non-chromosomal anomalies

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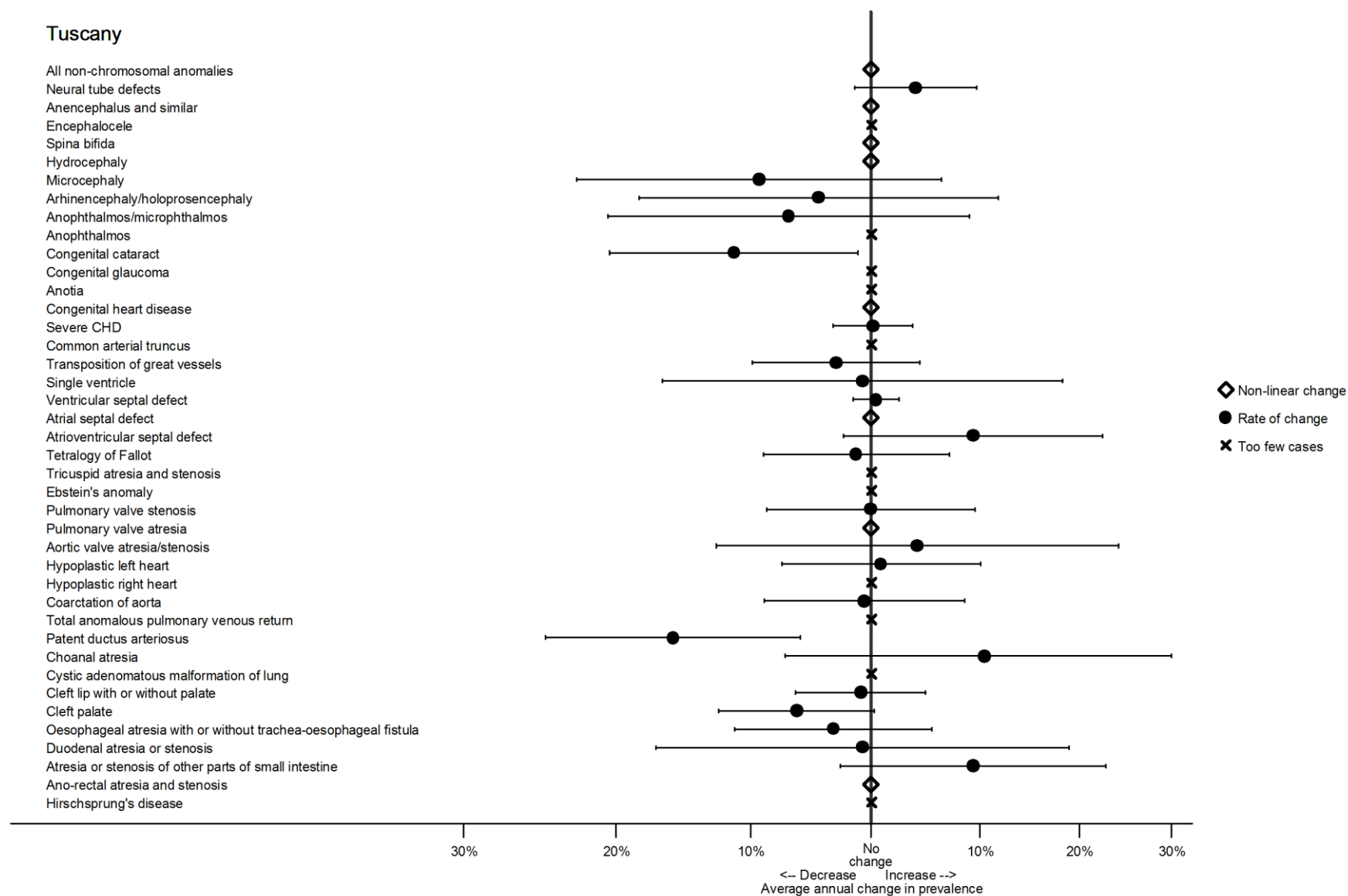
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

Atresia or stenosis of other parts of small intestine

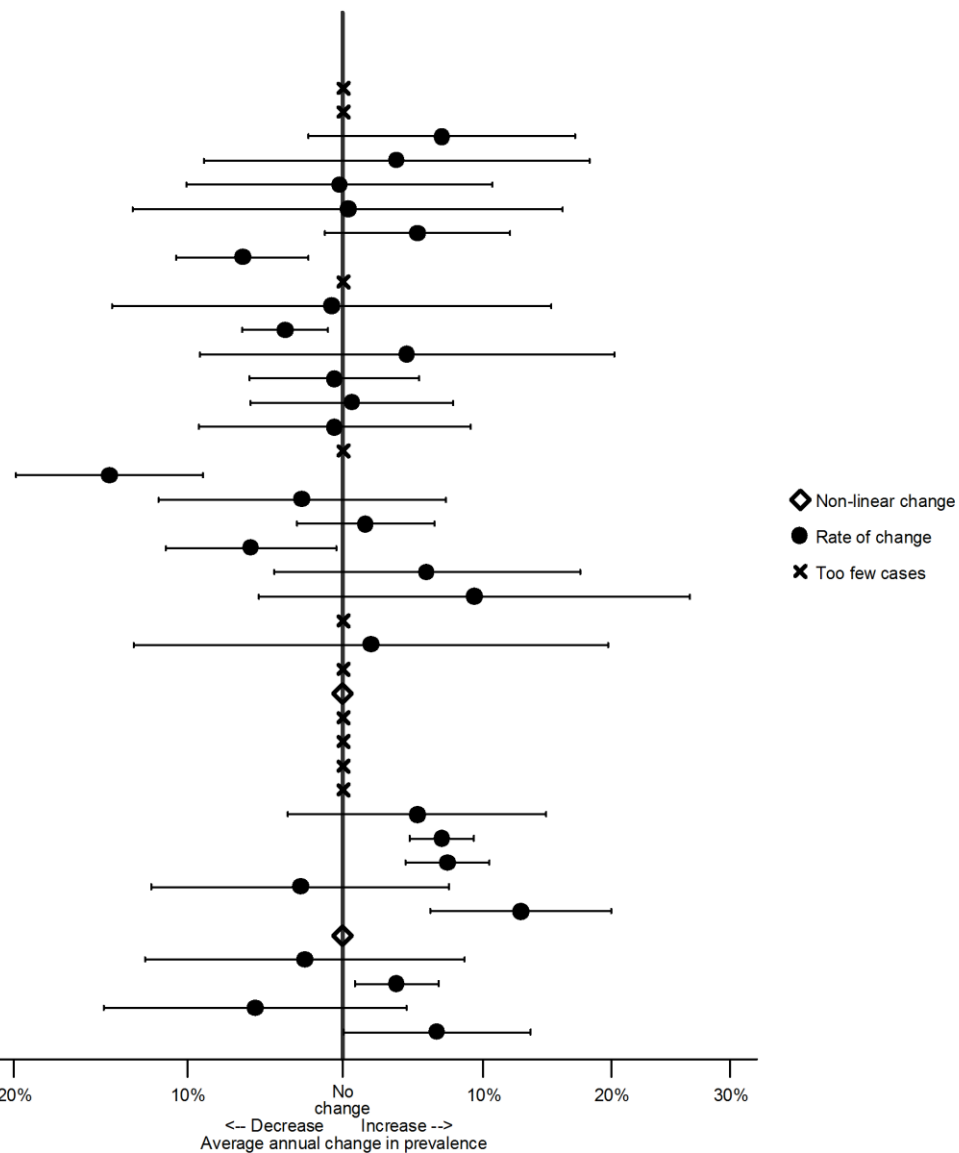
Ano-rectal atresia and stenosis

Hirschsprung's disease

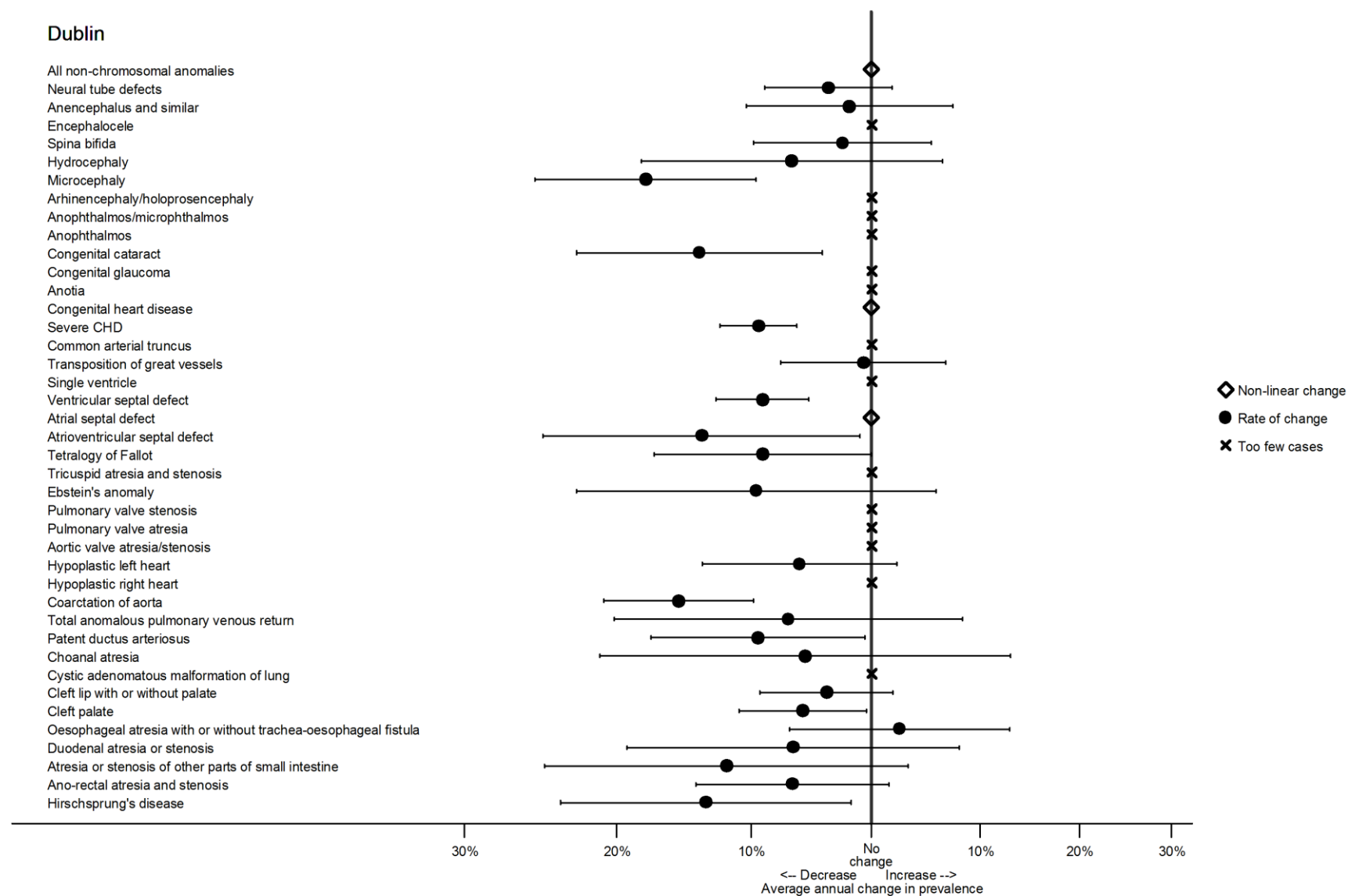


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Down syndrome adjusted
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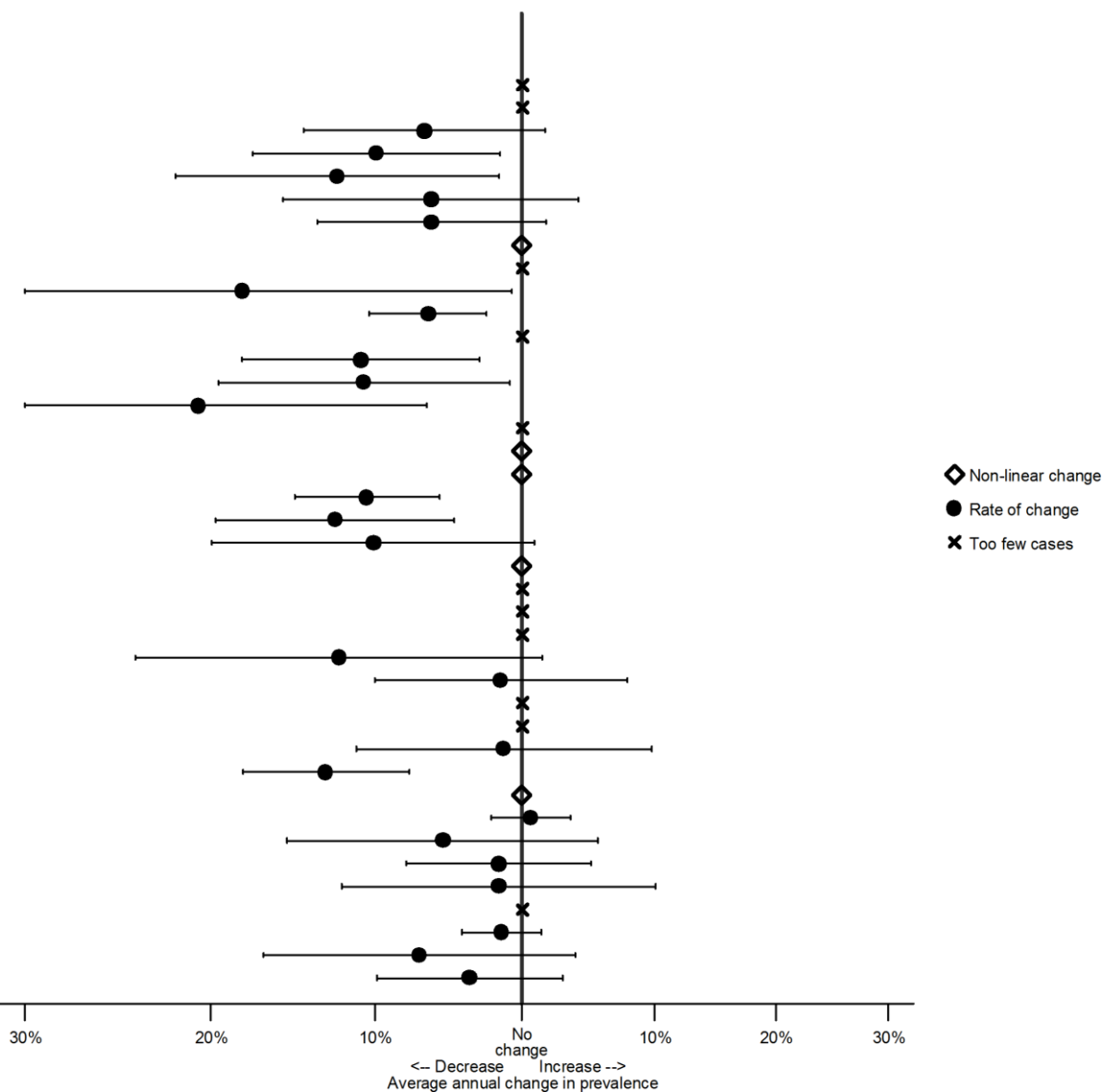


Dublin



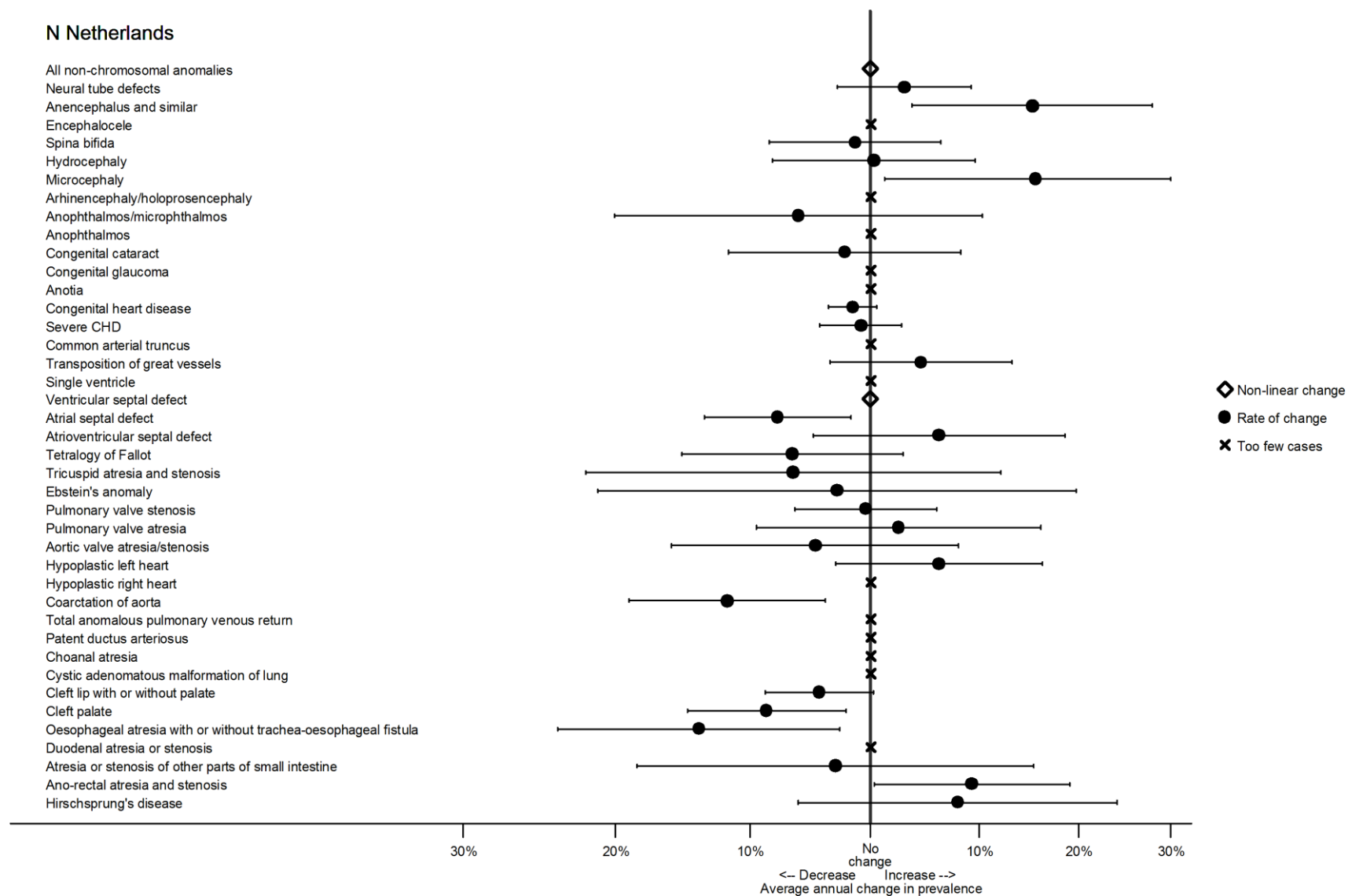
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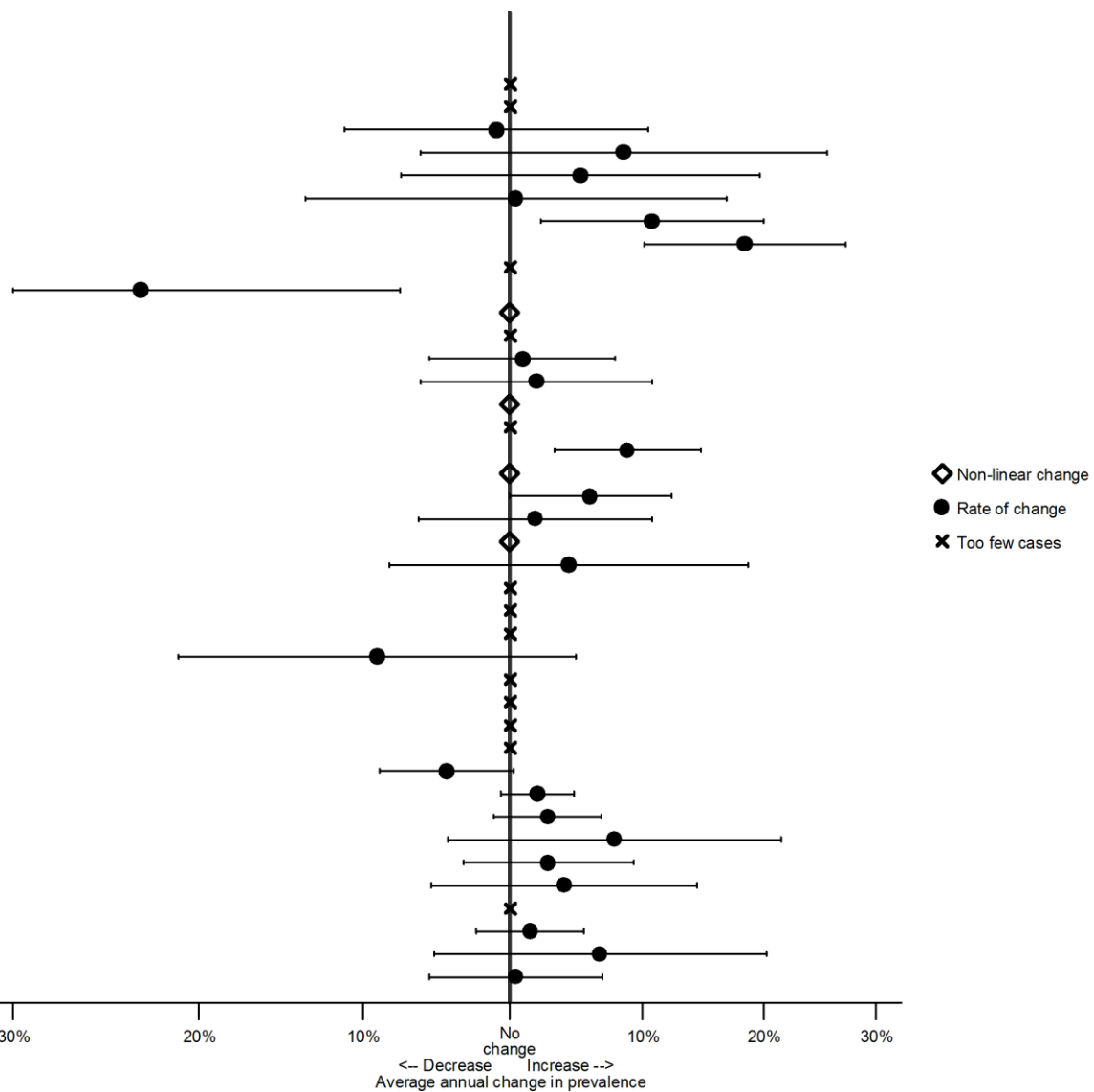
N Netherlands

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Emilia Romagna

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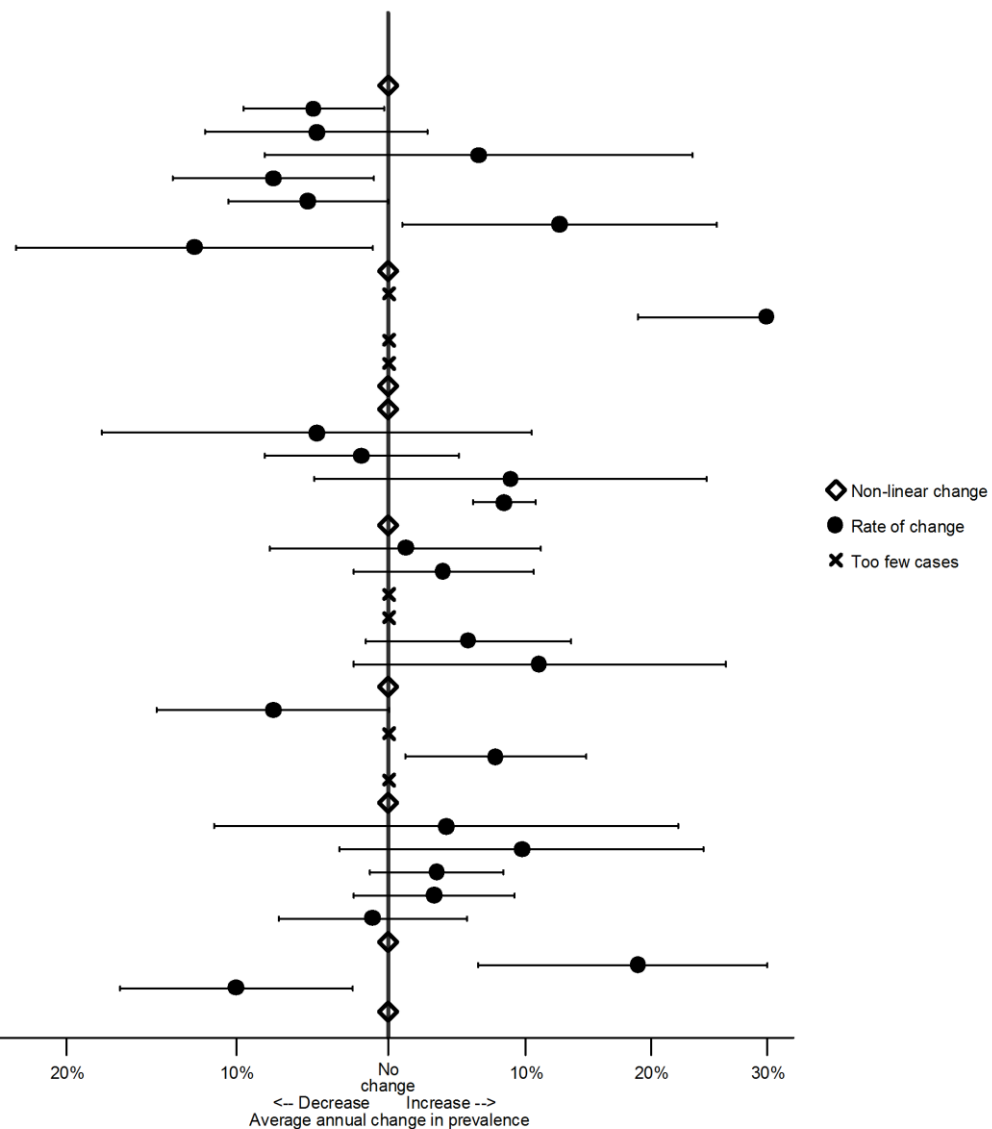
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

Atresia or stenosis of other parts of small intestine

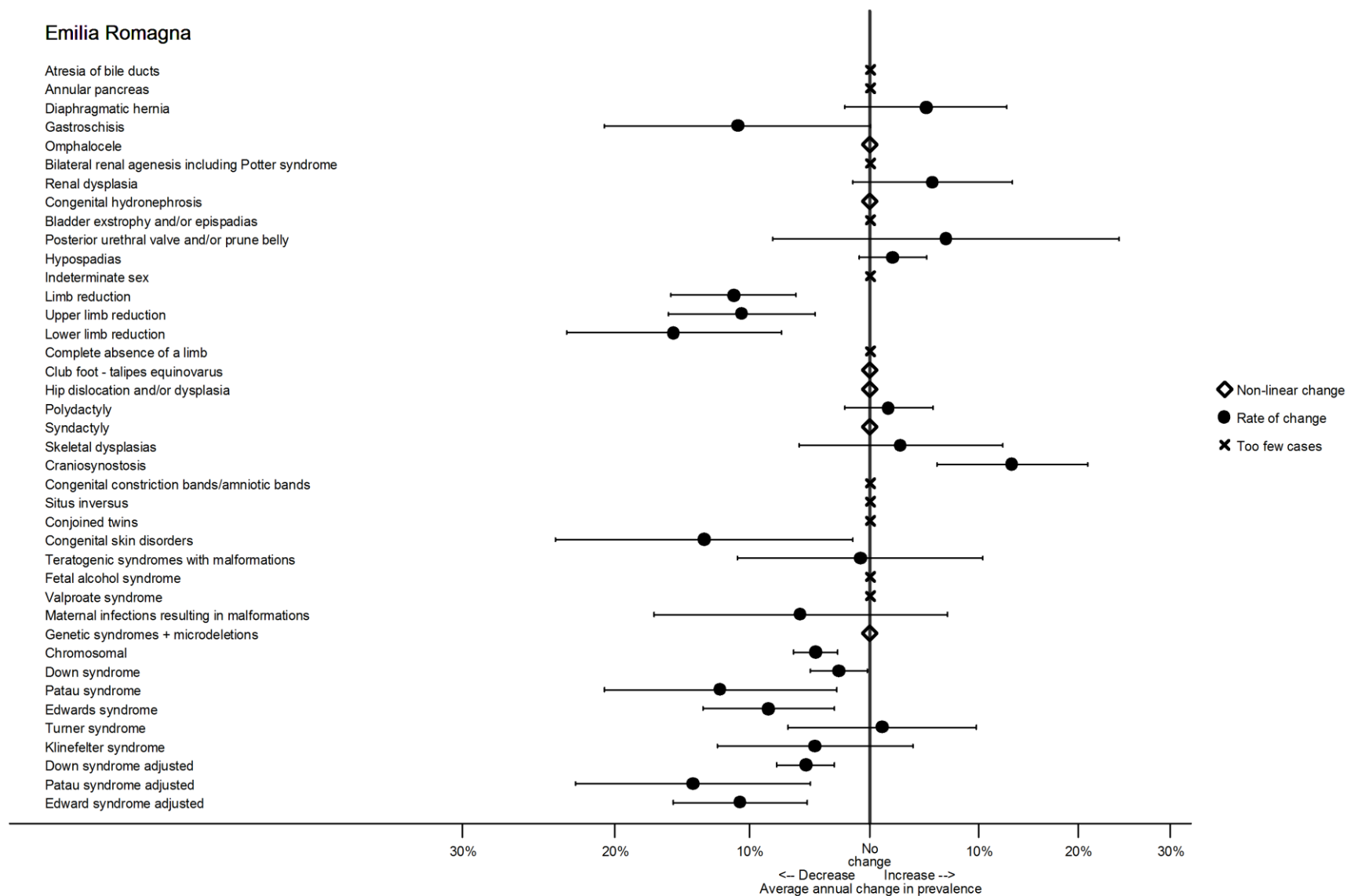
Ano-rectal atresia and stenosis

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Vaud

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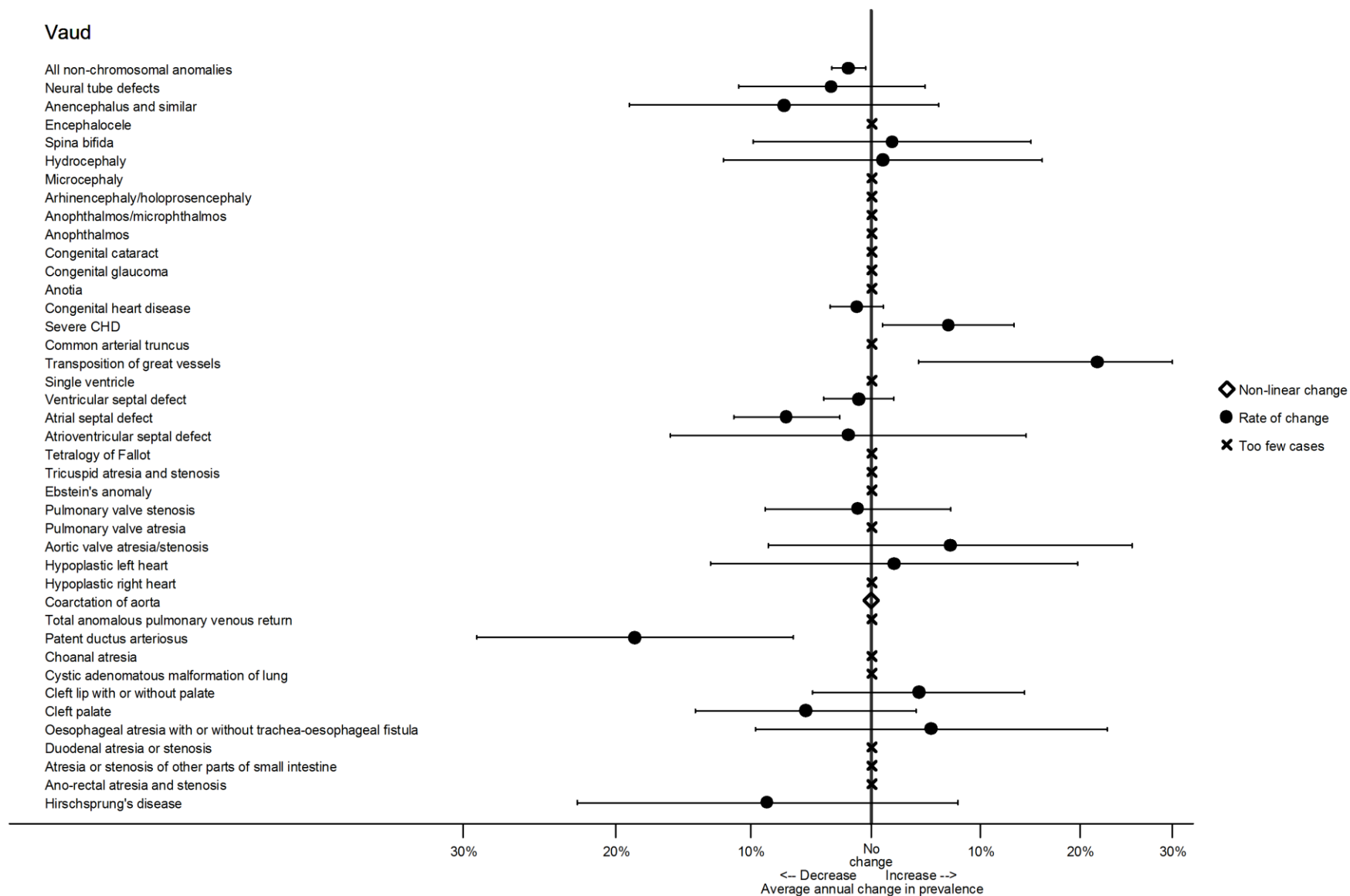
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

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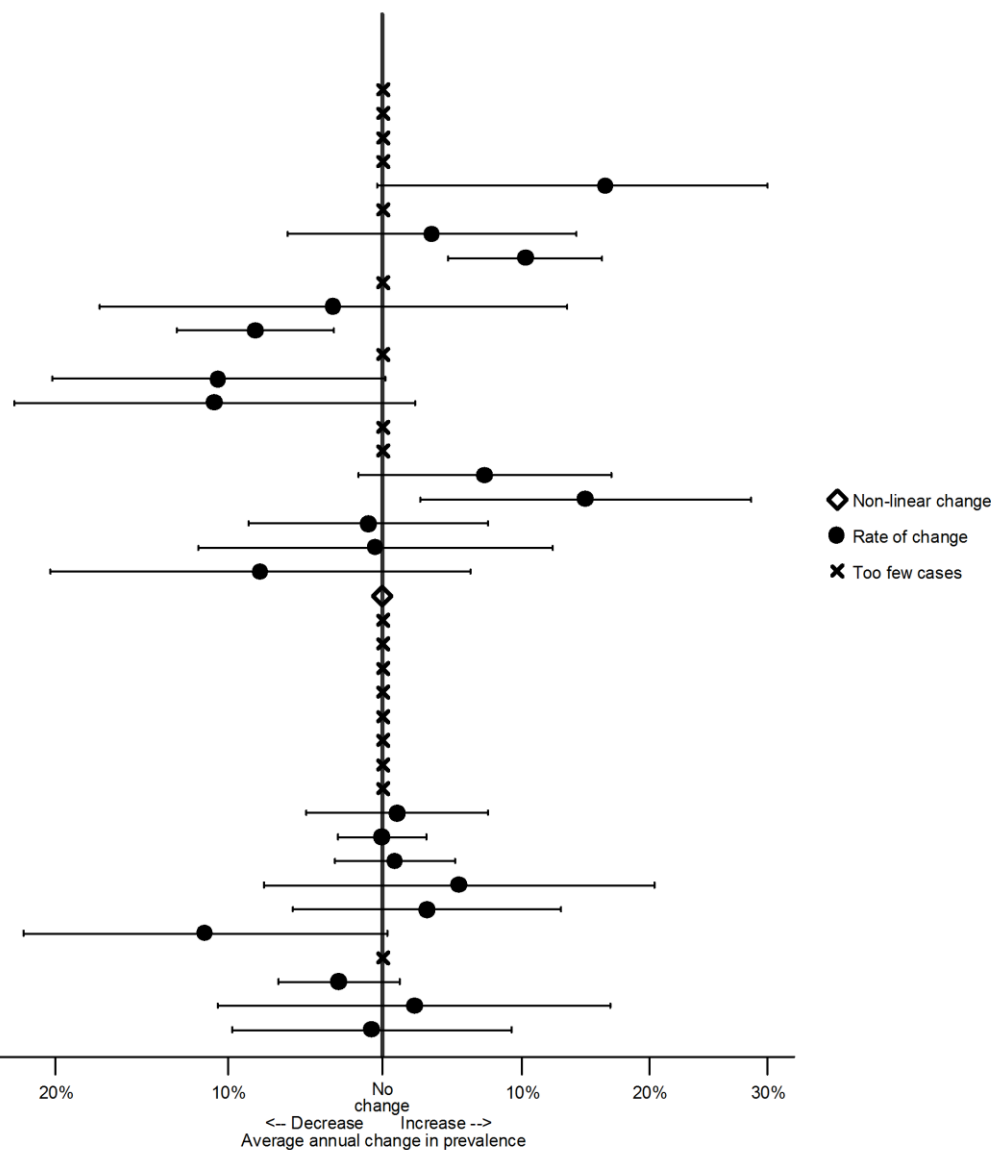
Ano-rectal atresia and stenosis

Hirschsprung's disease



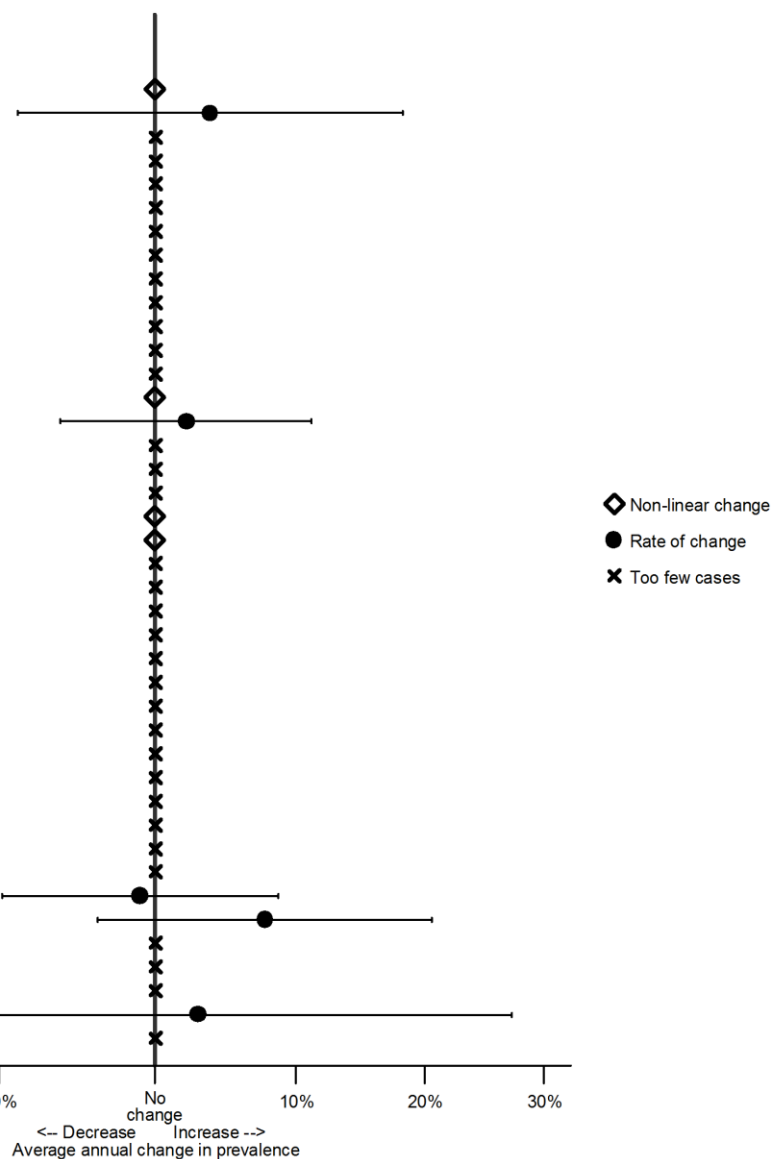
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 Genetic syndromes + microdeletions
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 Edwards syndrome
 Turner syndrome
 Klinefelter syndrome
 Down syndrome adjusted
 Patau syndrome adjusted
 Edward syndrome adjusted



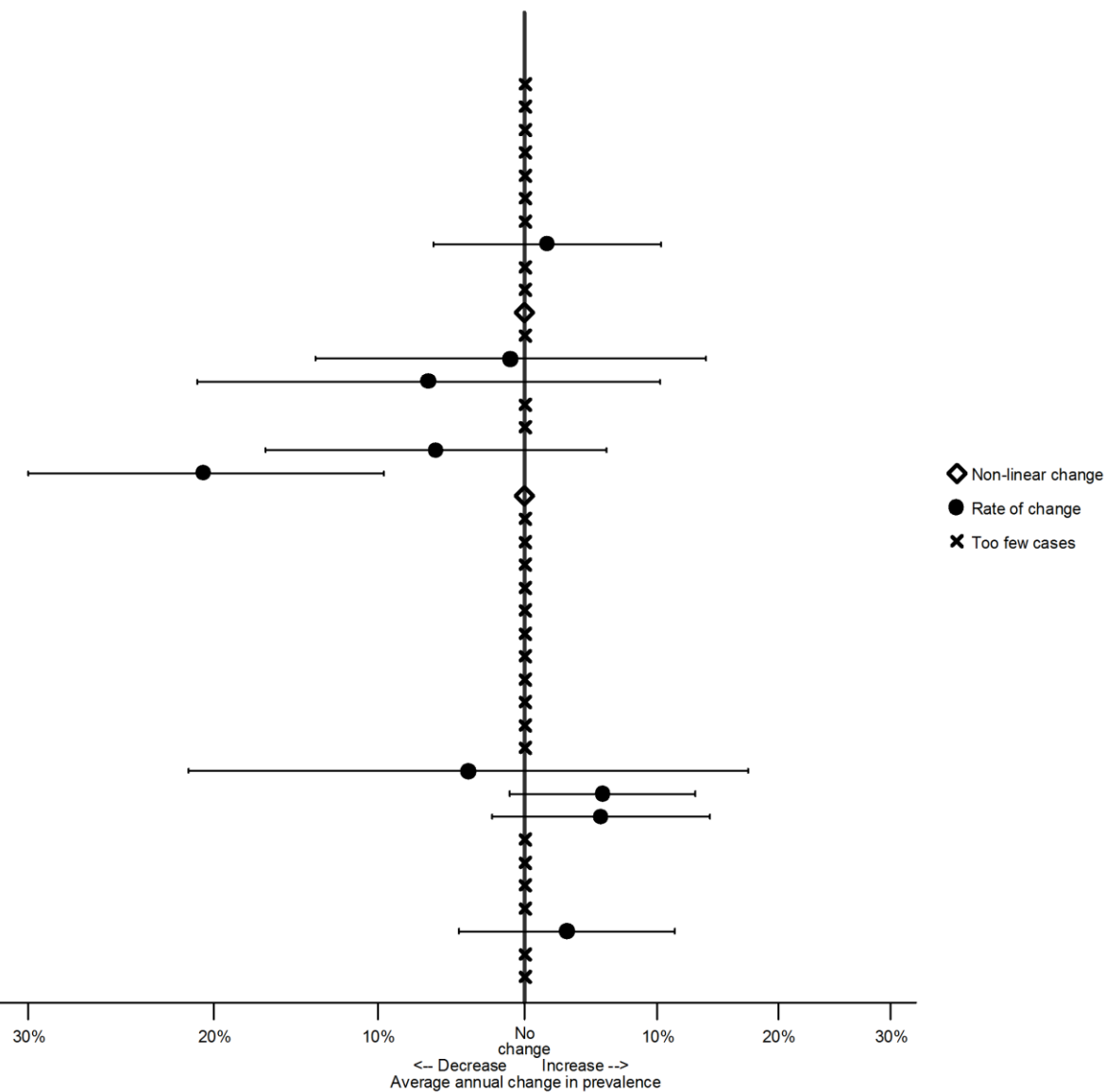
Zagreb

All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
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Malta

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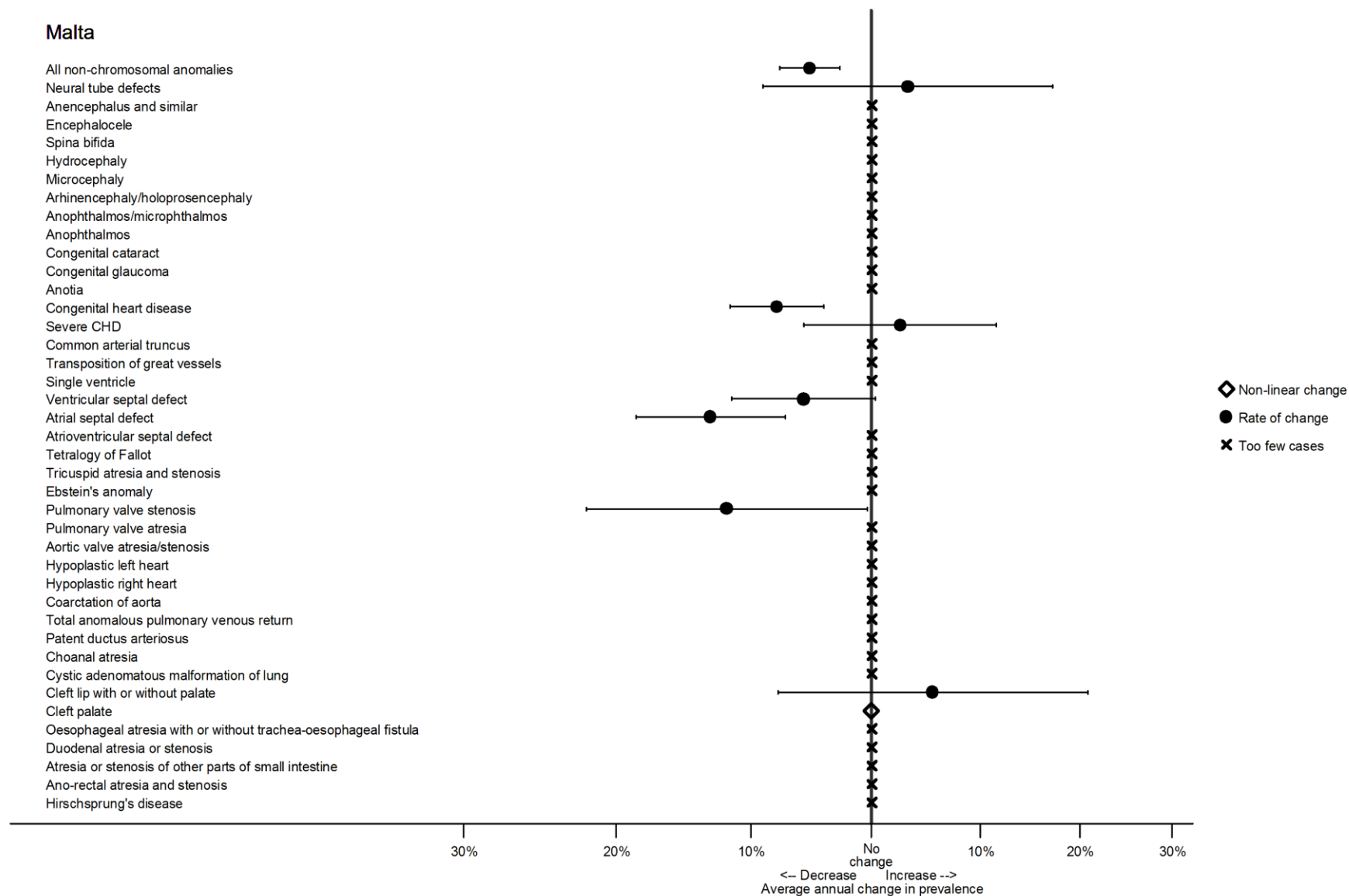
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

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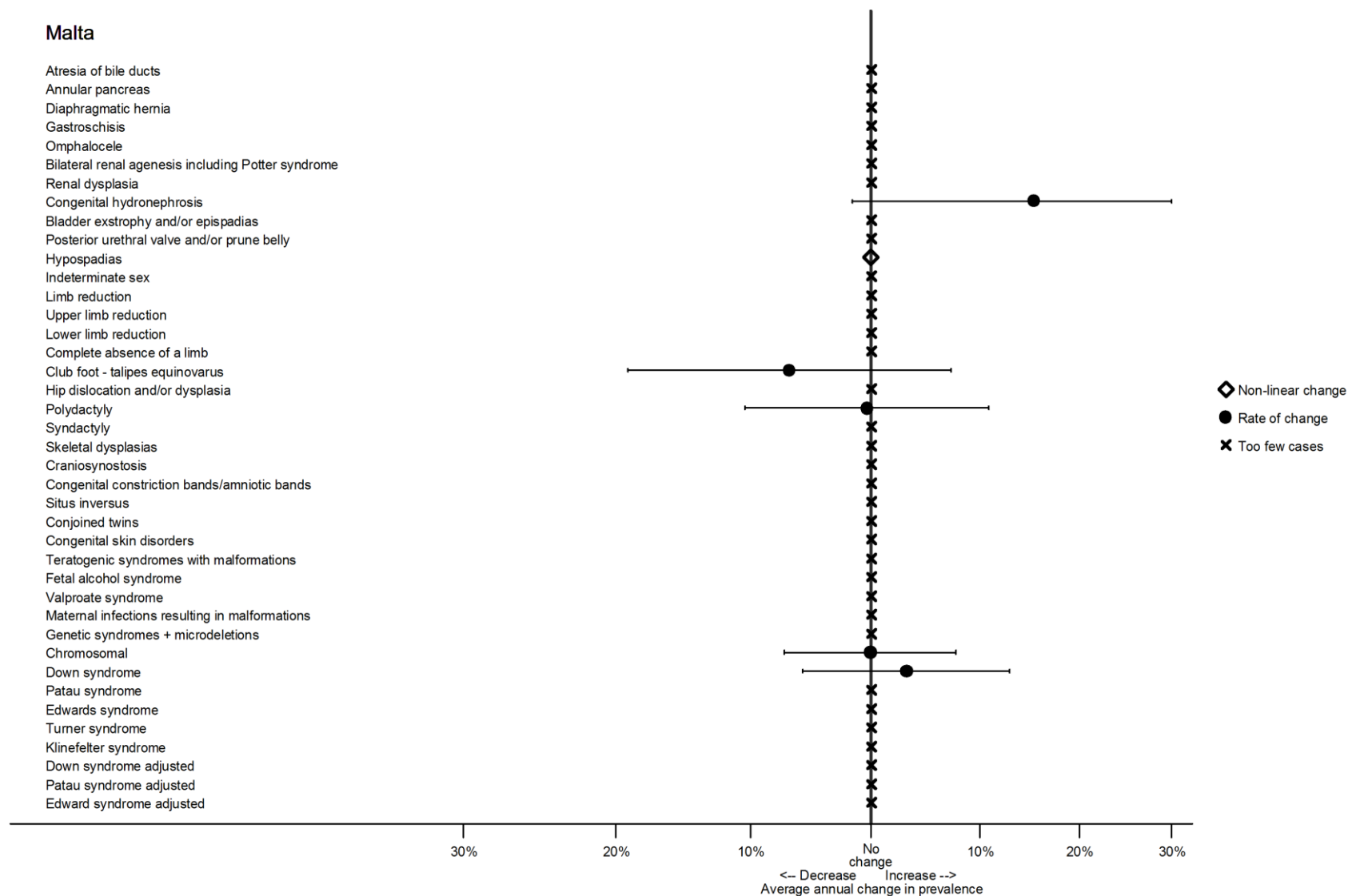
Ano-rectal atresia and stenosis

Hirschsprung's disease



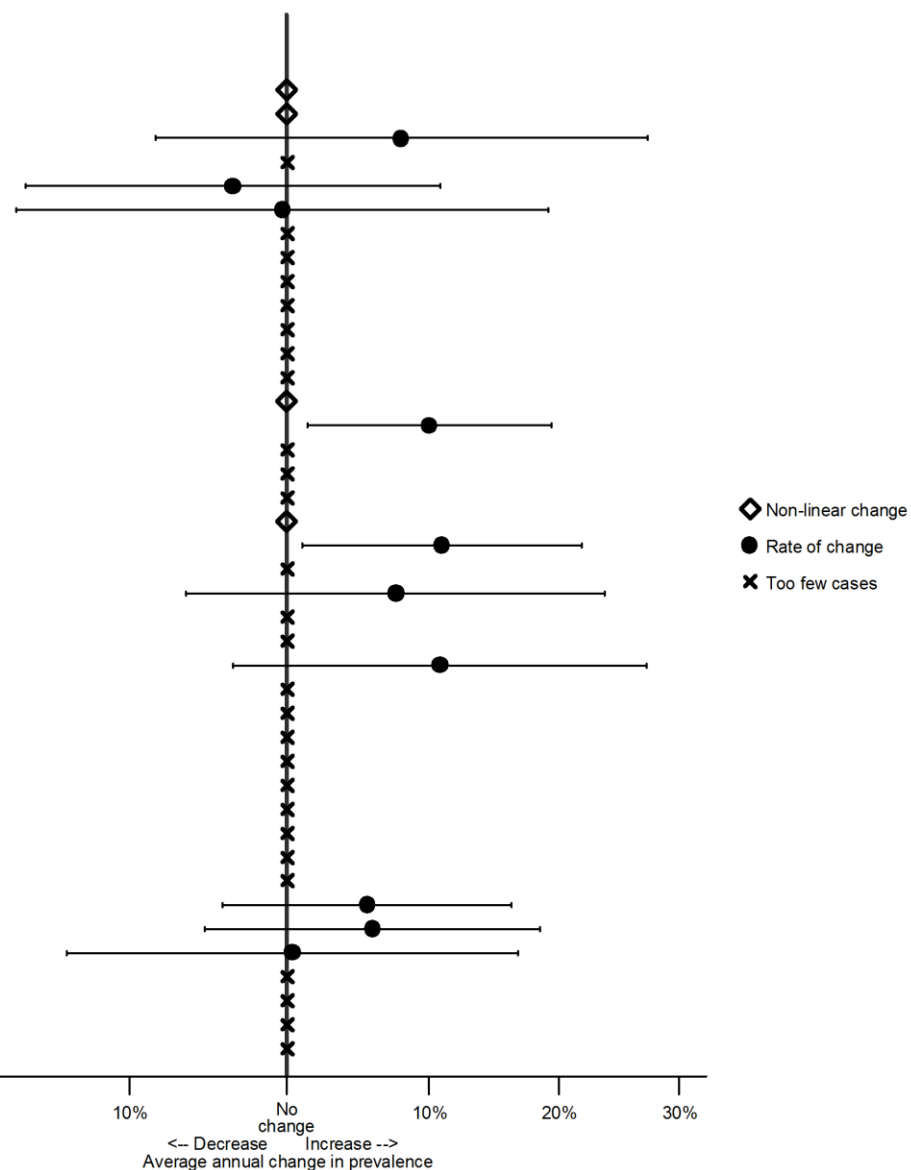
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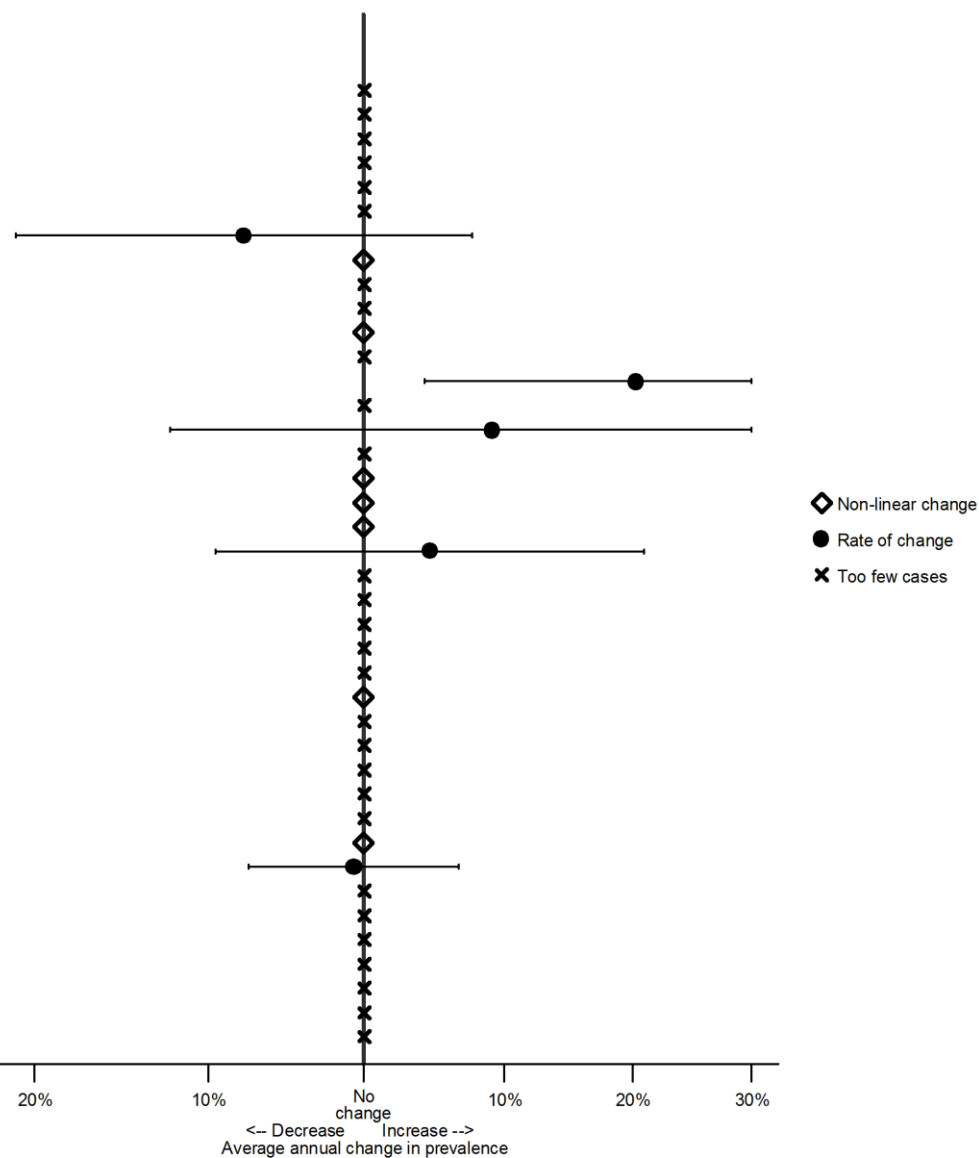
S Portugal

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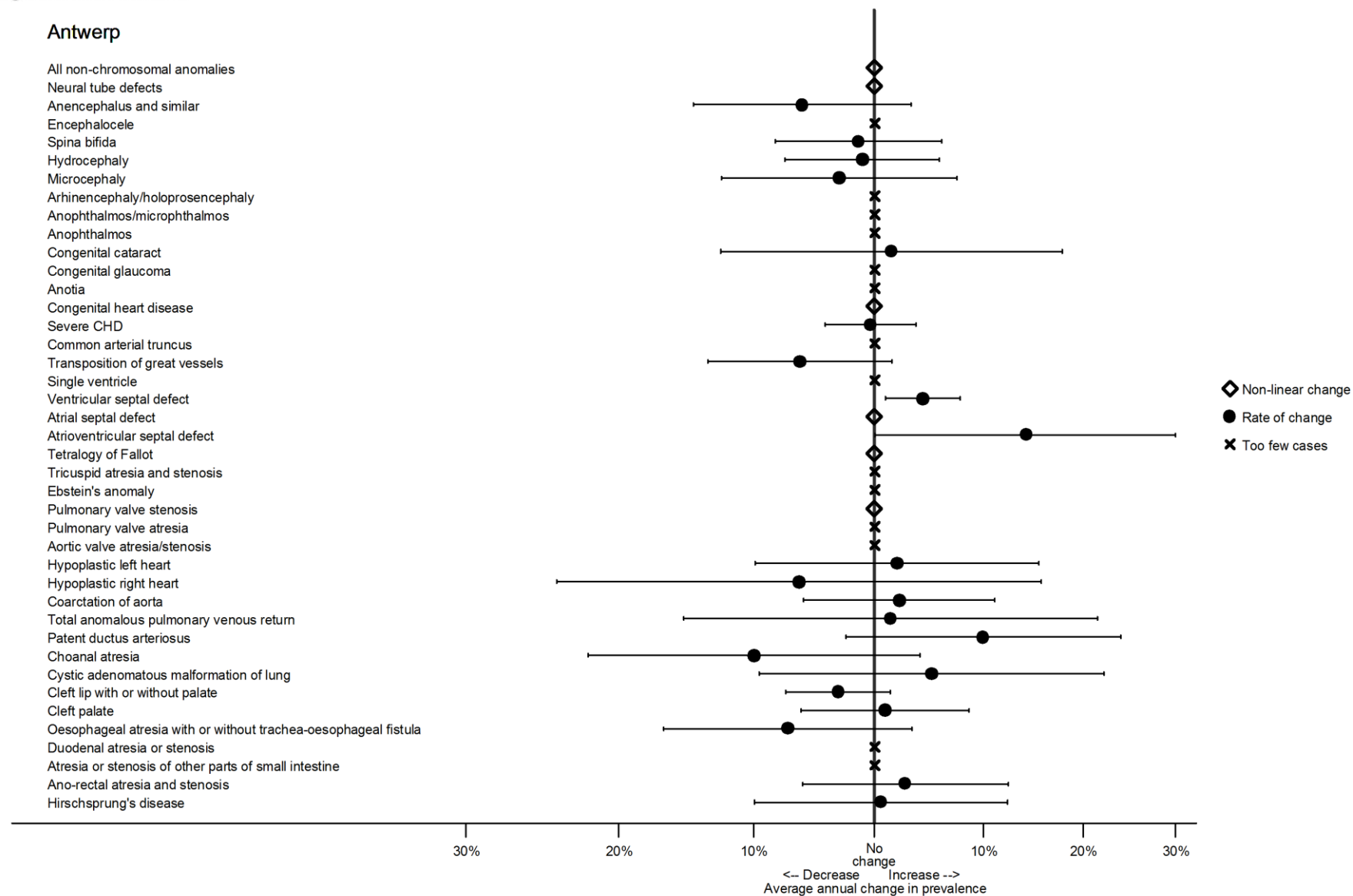
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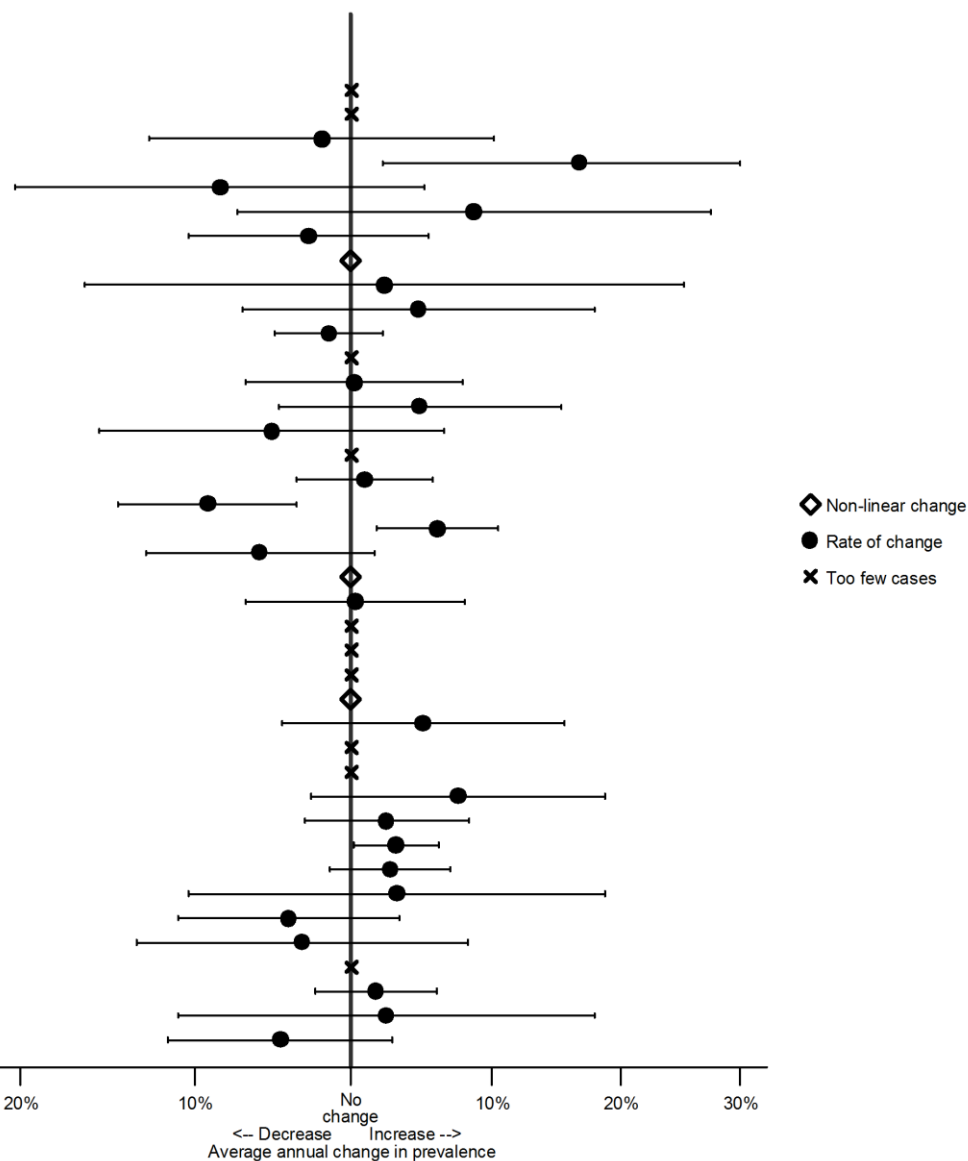
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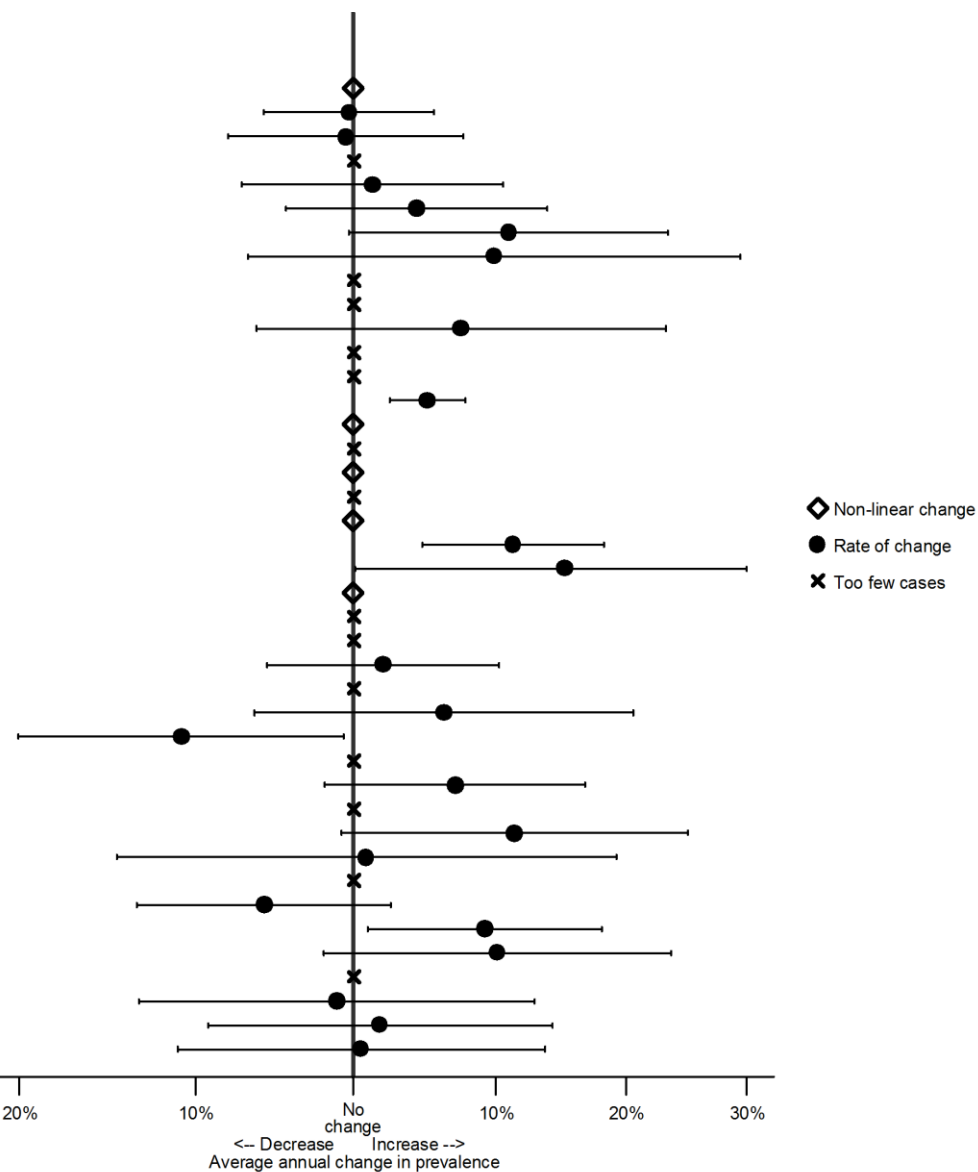
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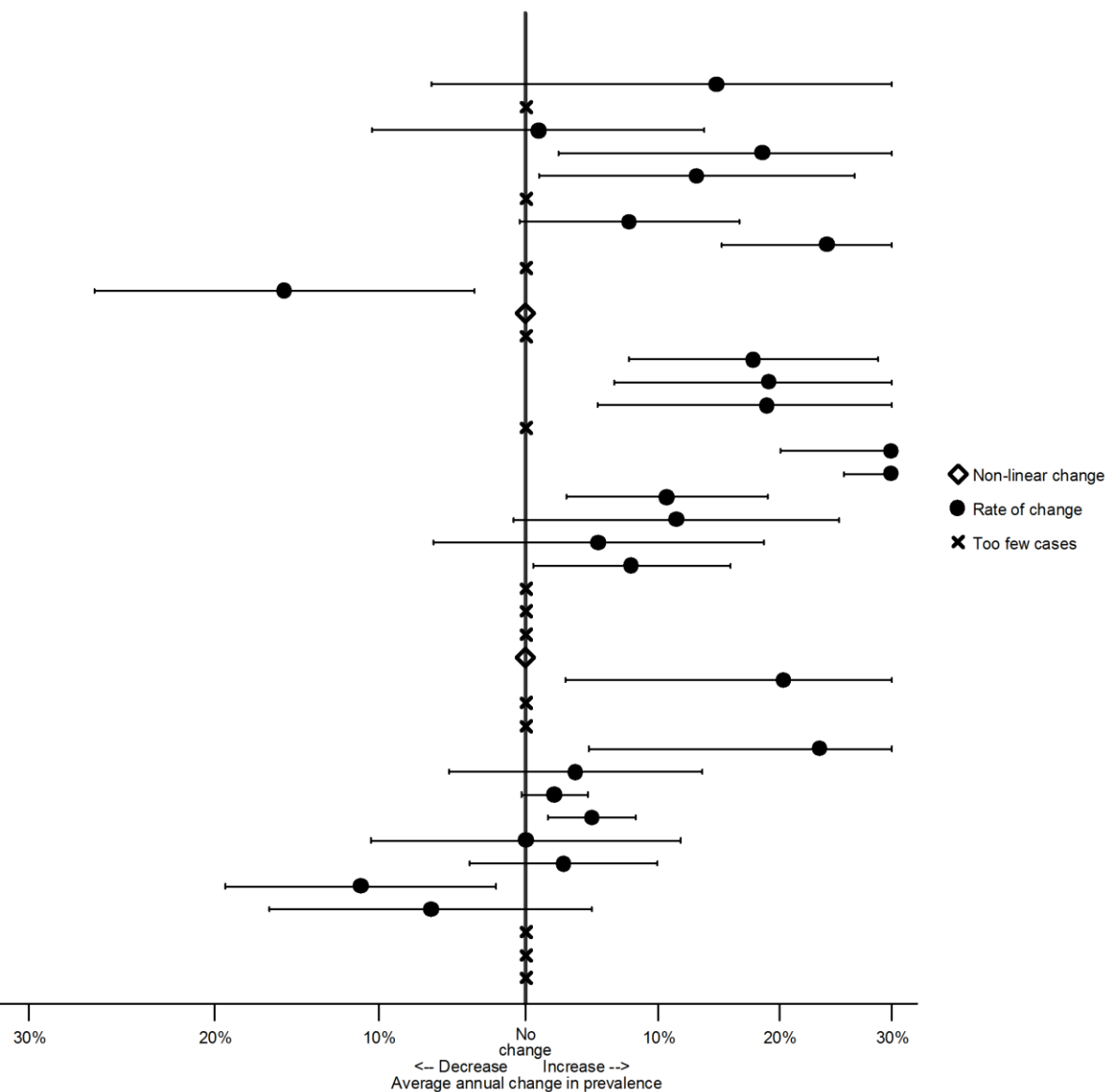
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Skeletal dysplasias
Craniosynostosis
Congenital constriction bands/amniotic bands
Situs inversus
Conjoined twins
Congenital skin disorders
Teratogenic syndromes with malformations
Fetal alcohol syndrome
Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
Chromosomal
Down syndrome
Patau syndrome
Edwards syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted



Saxony Anhalt

All non-chromosomal anomalies

Neural tube defects

Anencephalus and similar

Encephalocele

Spina bifida

Hydrocephaly

Microcephaly

Arhinencephaly/holoprosencephaly

Anophthalmos/microphthalmos

Anophthalmos

Congenital cataract

Congenital glaucoma

Anotia

Congenital heart disease

Severe CHD

Common arterial truncus

Transposition of great vessels

Single ventricle

Ventricular septal defect

Atrial septal defect

Atrioventricular septal defect

Tetralogy of Fallot

Tricuspid atresia and stenosis

Ebstein's anomaly

Pulmonary valve stenosis

Pulmonary valve atresia

Aortic valve atresia/stenosis

Hypoplastic left heart

Hypoplastic right heart

Coarctation of aorta

Total anomalous pulmonary venous return

Patent ductus arteriosus

Choanal atresia

Cystic adenomatous malformation of lung

Cleft lip with or without palate

Cleft palate

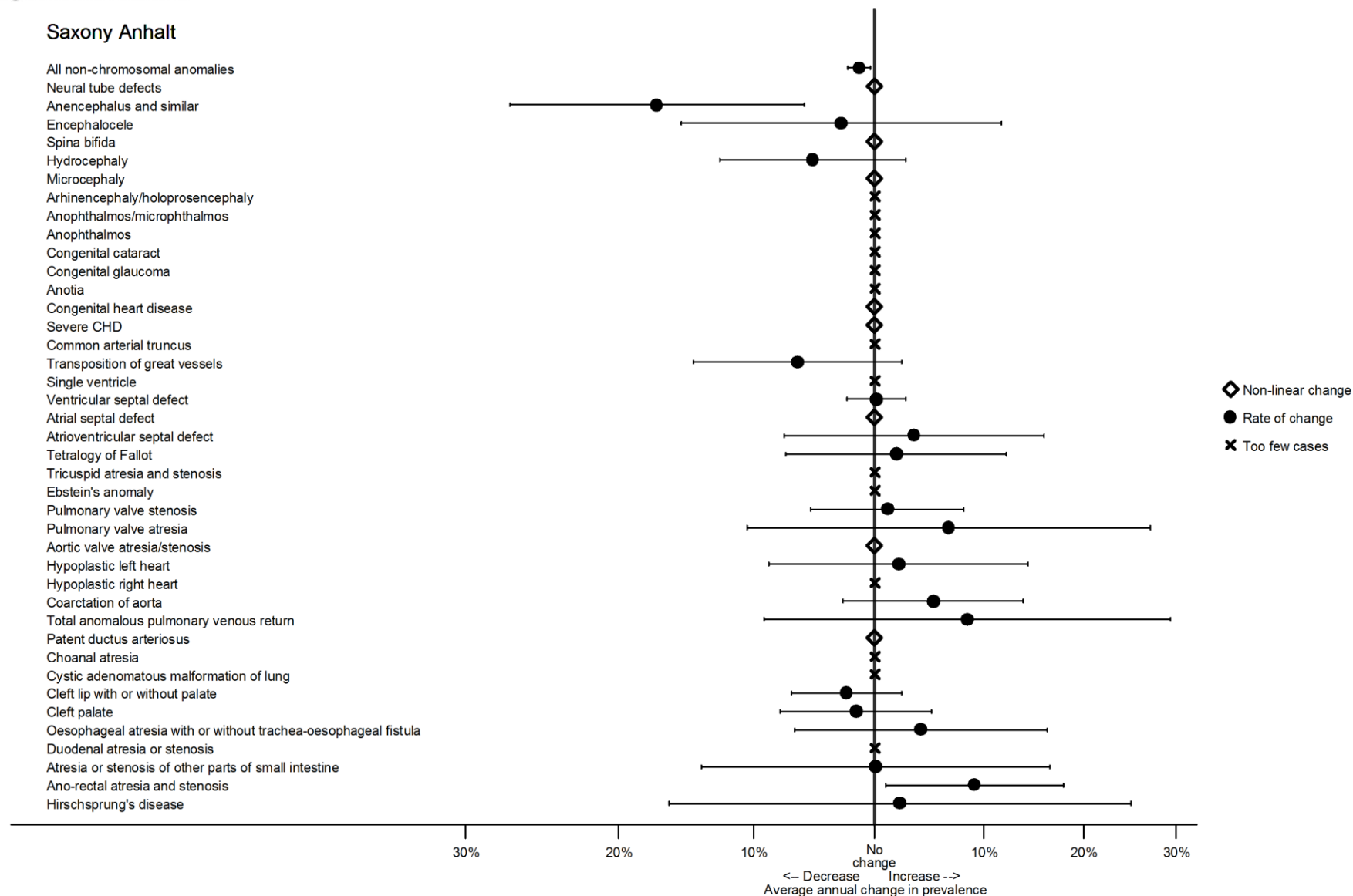
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

Atresia or stenosis of other parts of small intestine

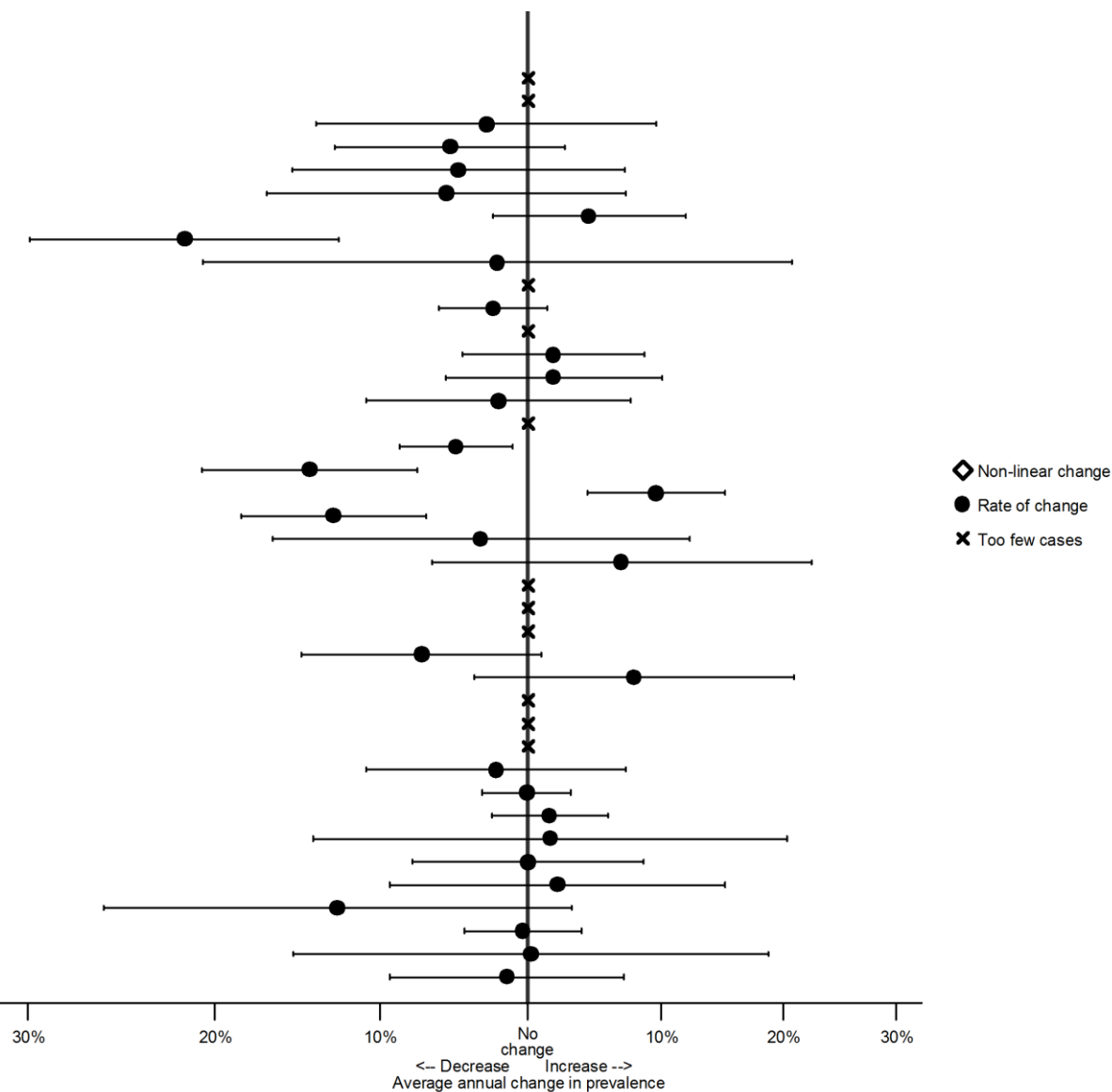
Ano-rectal atresia and stenosis

Hirschsprung's disease



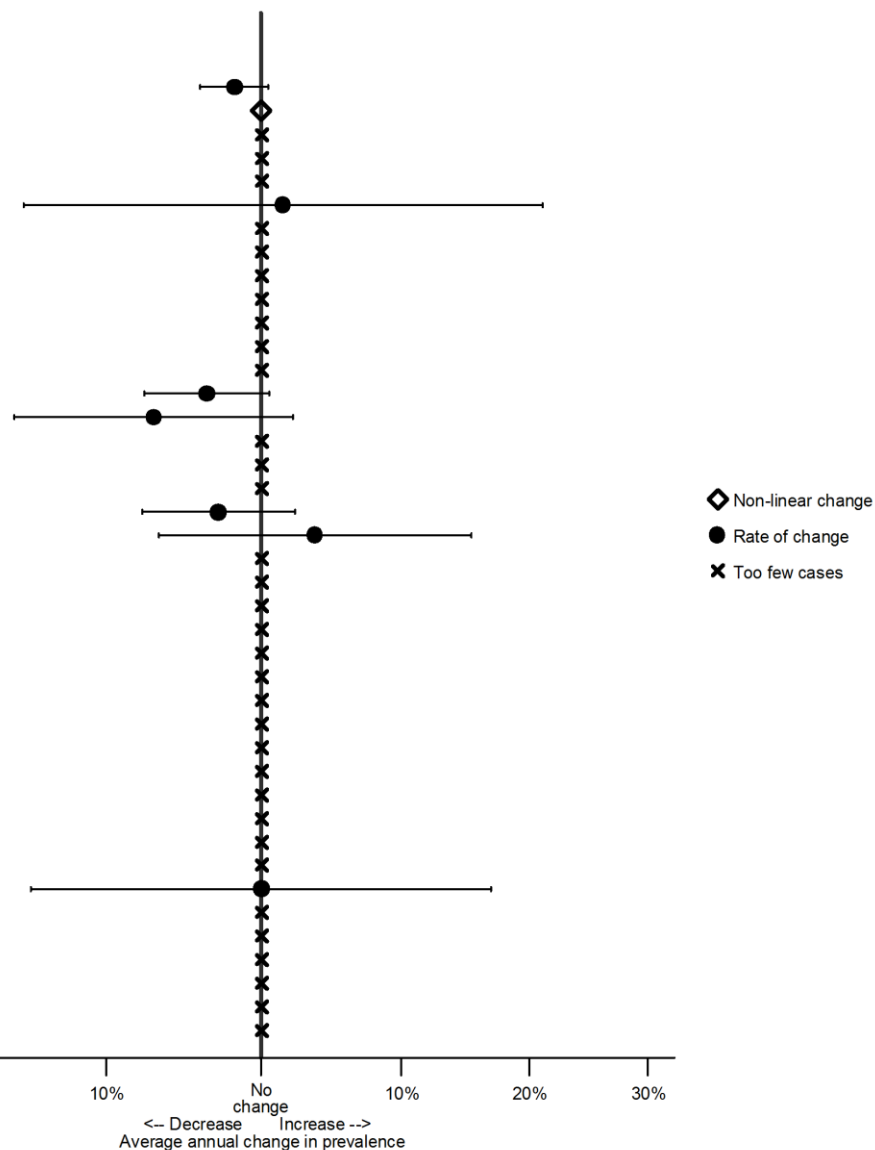
Saxony Anhalt

Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb reduction
Upper limb reduction
Lower limb reduction
Complete absence of a limb
Club foot - talipes equinovarus
Hip dislocation and/or dysplasia
Polydactyly
Syndactyly
Skeletal dysplasias
Craniosynostosis
Congenital constriction bands/amniotic bands
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Conjoined twins
Congenital skin disorders
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Fetal alcohol syndrome
Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
Chromosomal
Down syndrome
Patau syndrome
Edwards syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted



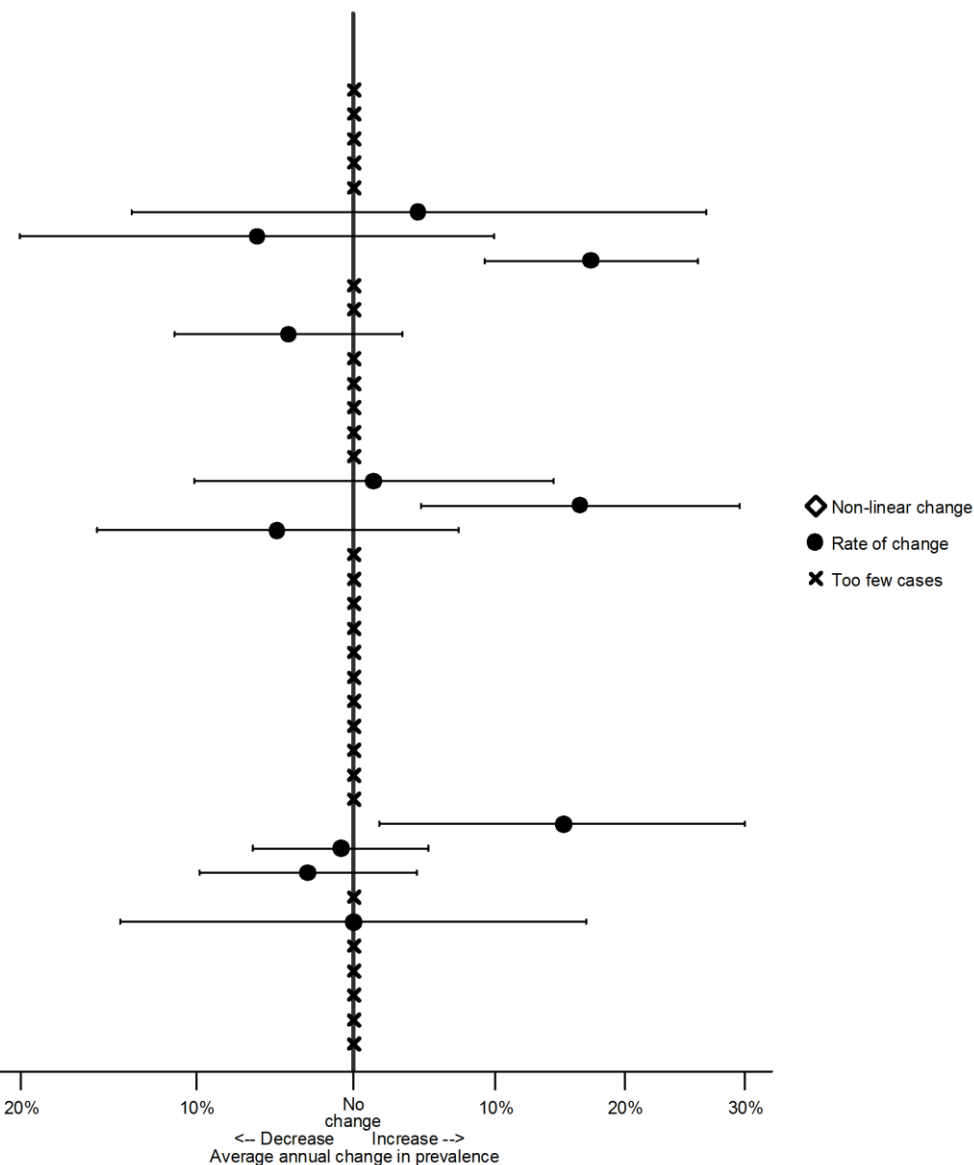
Mainz

All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
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Anophthalmos
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Congenital glaucoma
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Atrial septal defect
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Cleft palate
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Atresia or stenosis of other parts of small intestine
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Hirschsprung's disease



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Cork and Kerry

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Cleft lip with or without palate

Cleft palate

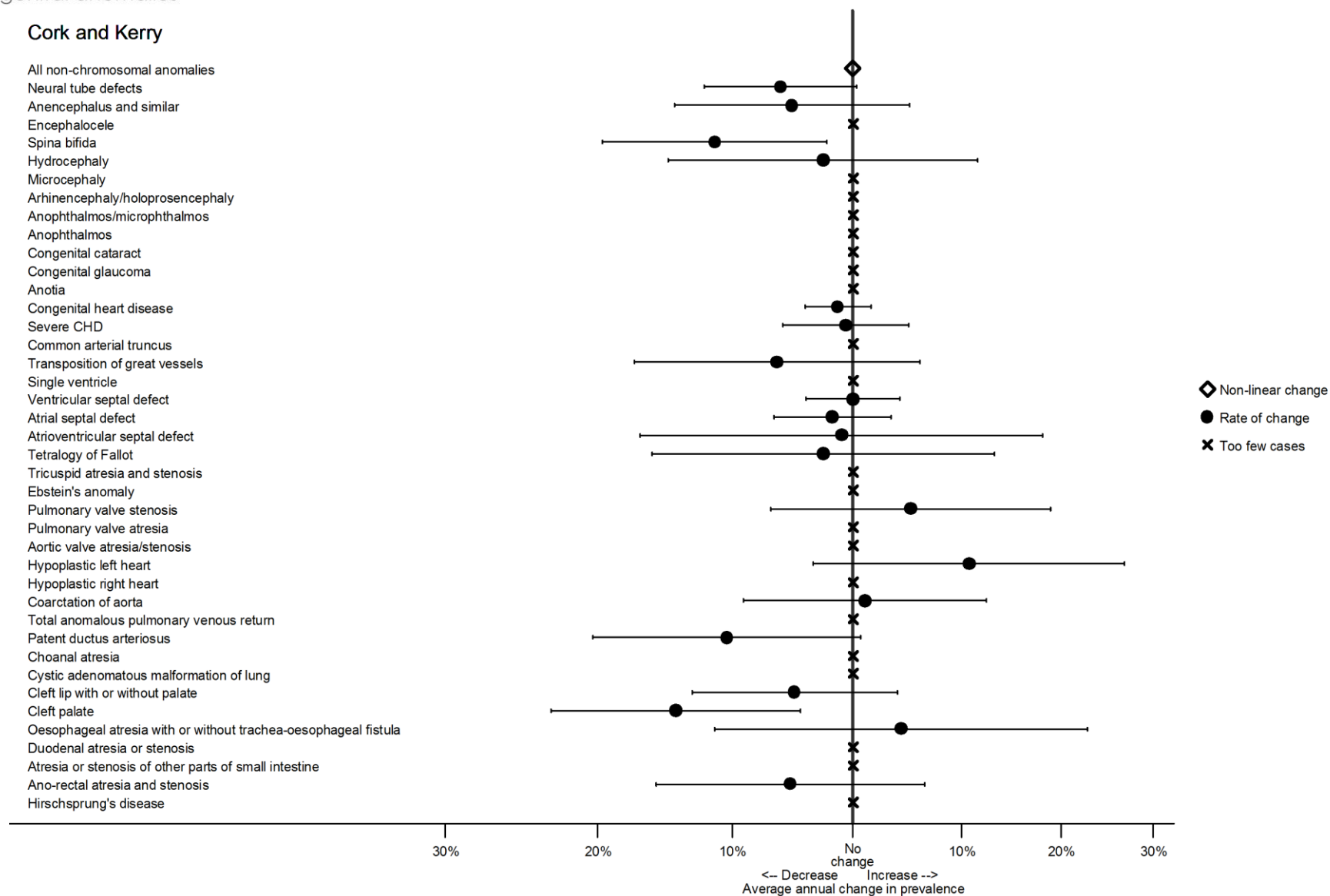
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

Atresia or stenosis of other parts of small intestine

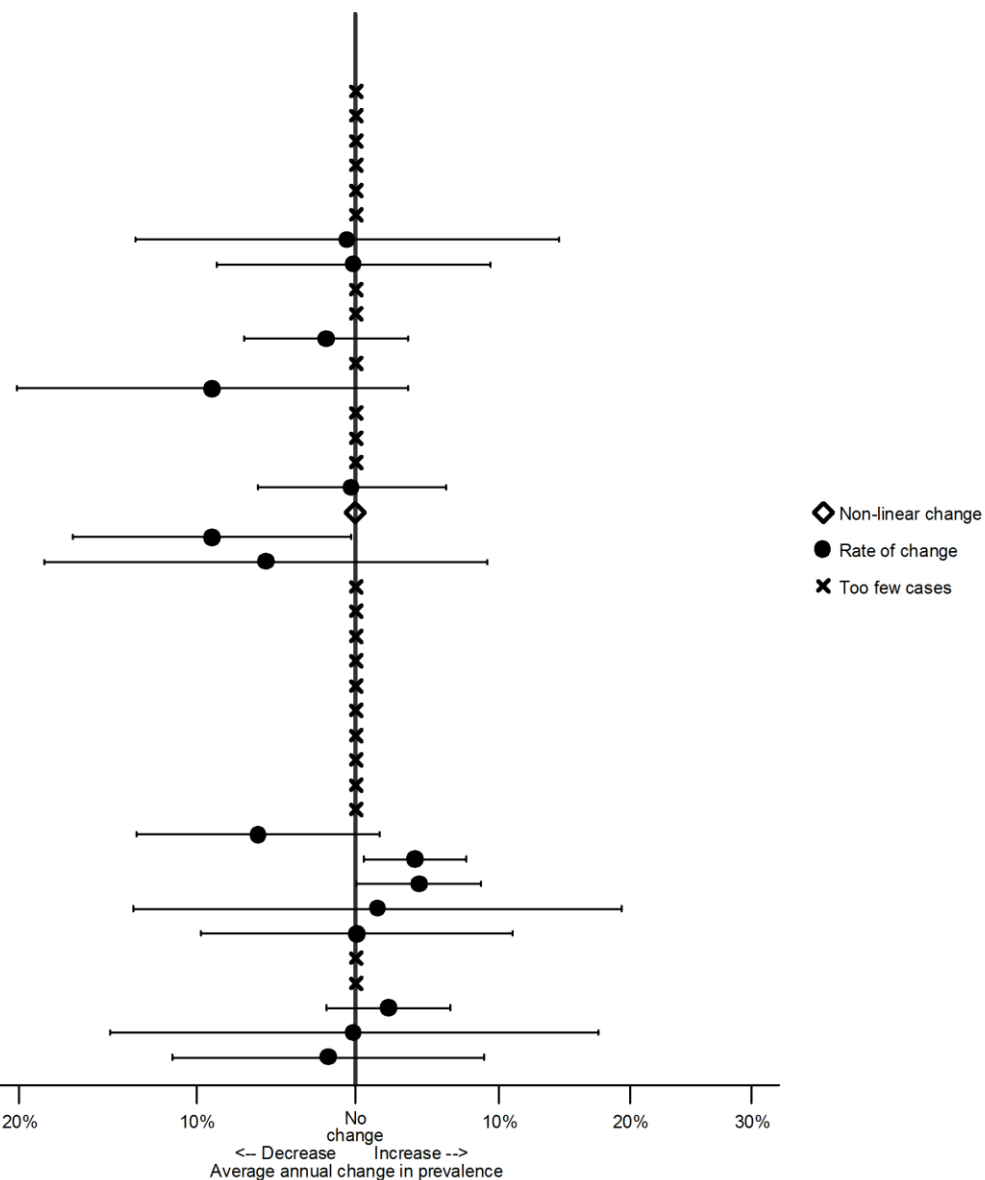
Ano-rectal atresia and stenosis

Hirschsprung's disease



Cork and Kerry

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Annular pancreas
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Klinefelter syndrome
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Patau syndrome adjusted
Edward syndrome adjusted



Wales

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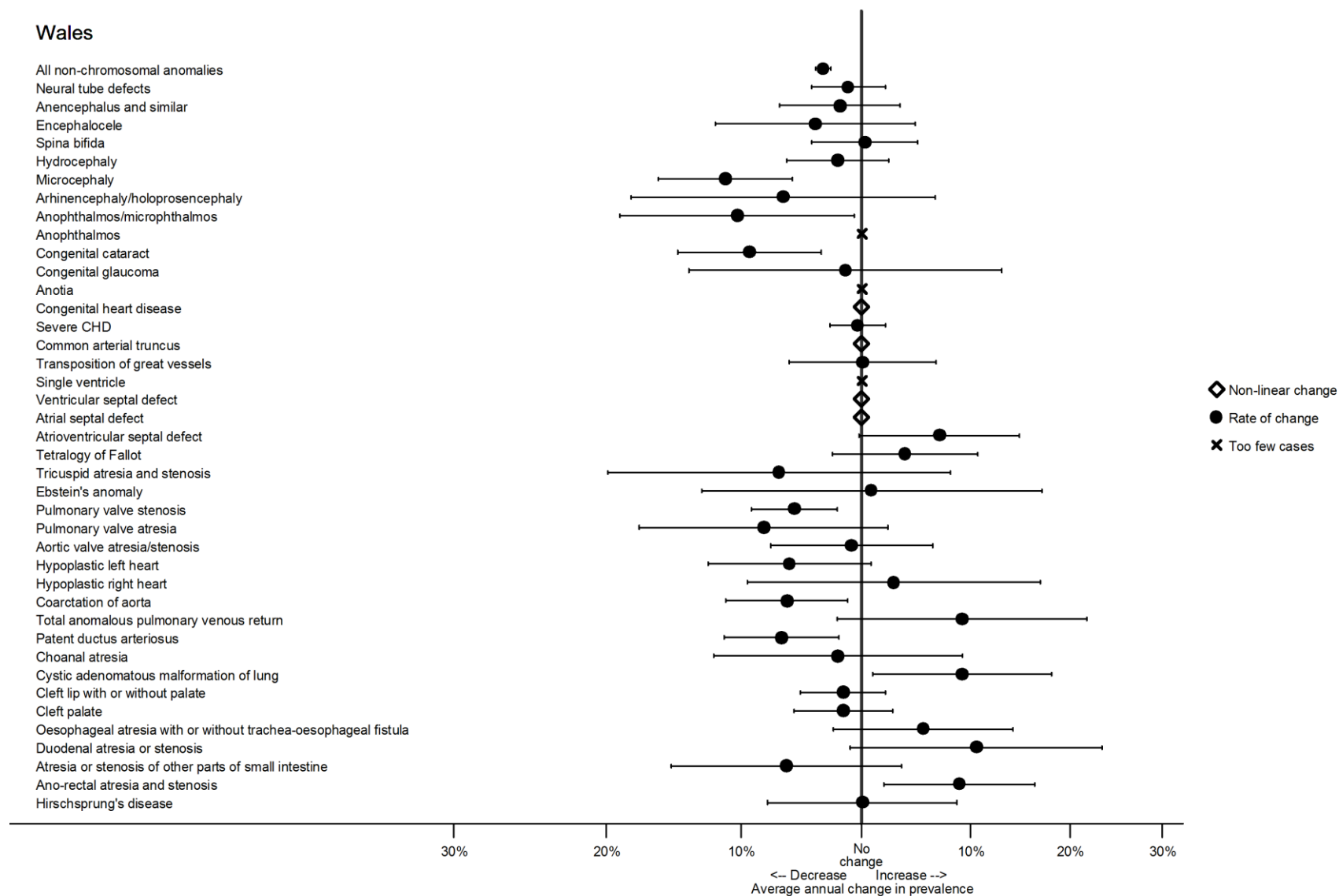
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

Atresia or stenosis of other parts of small intestine

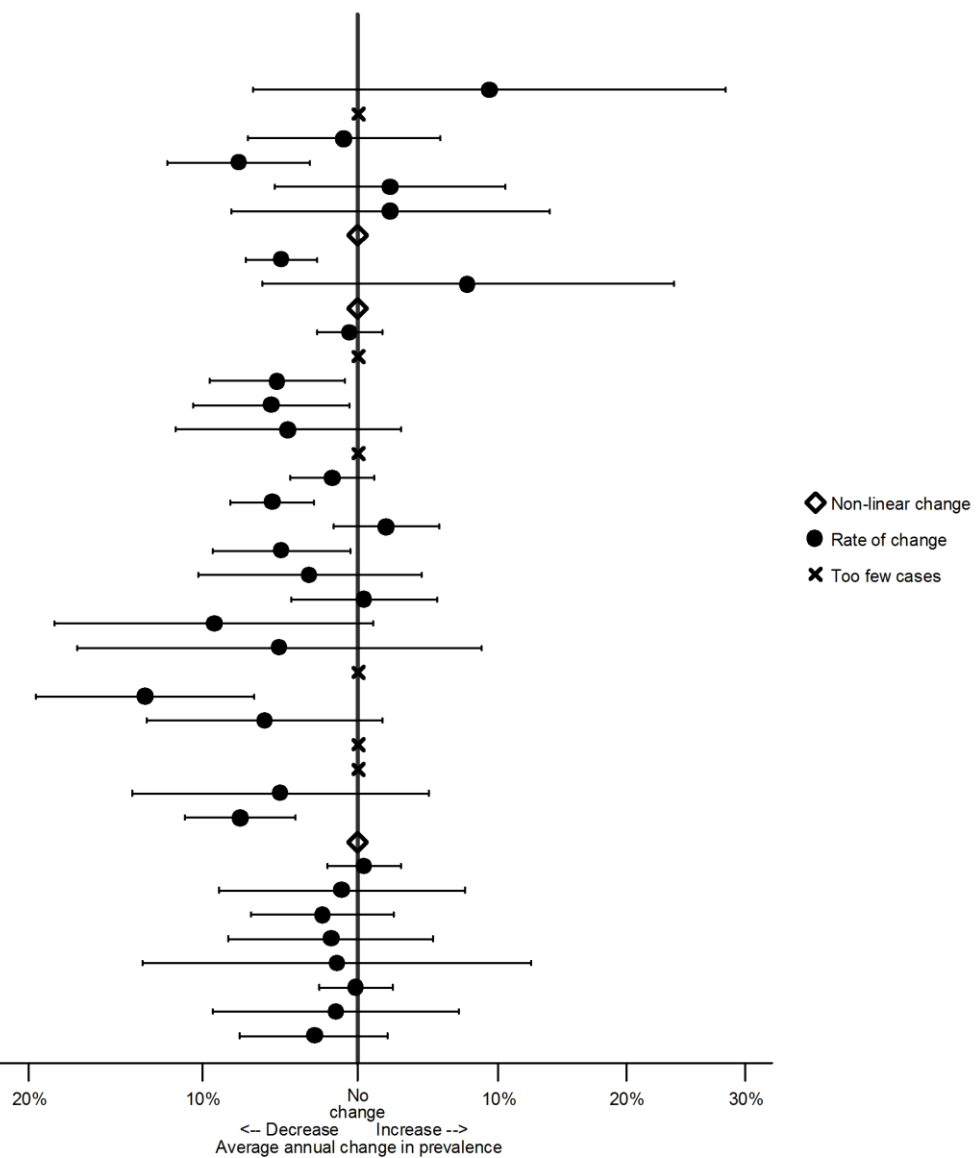
Ano-rectal atresia and stenosis

Hirschsprung's disease



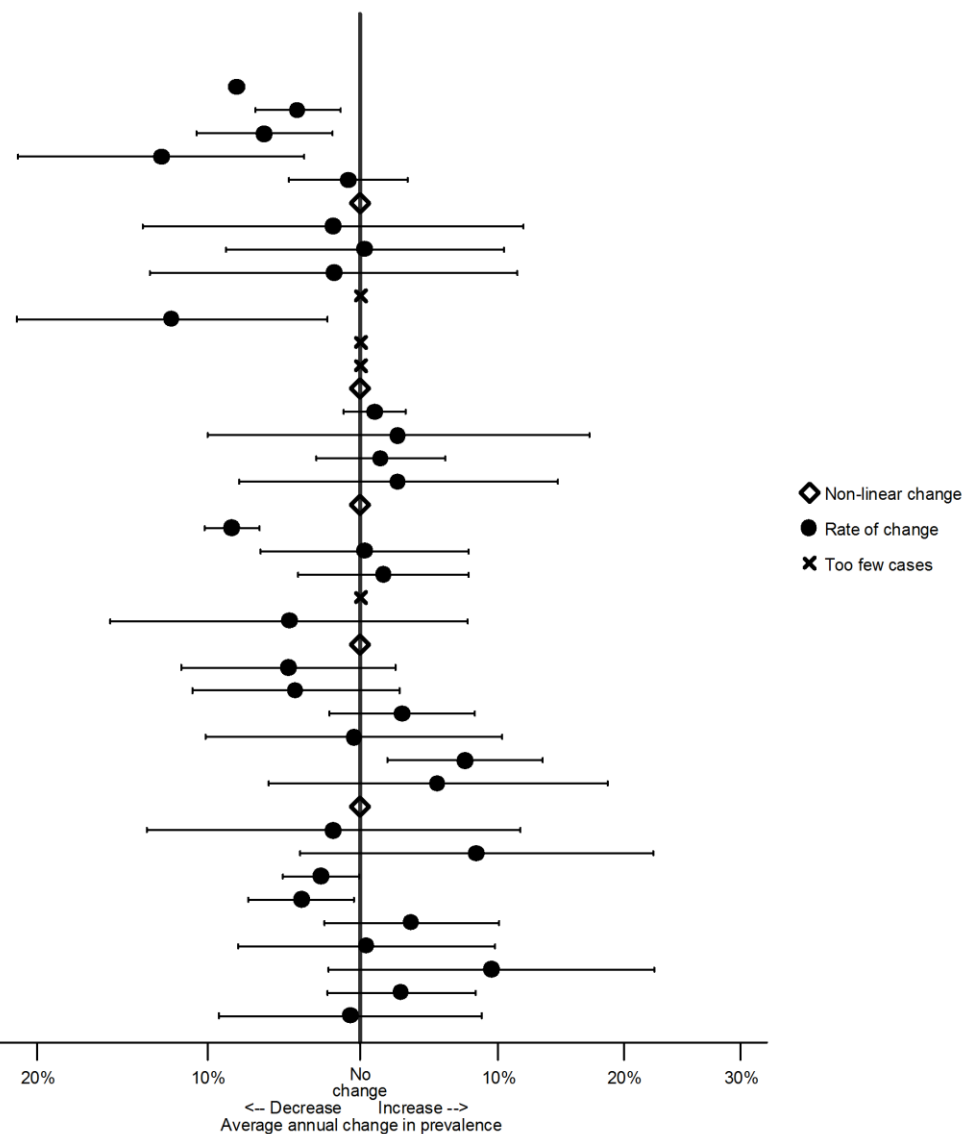
Wales

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Renal dysplasia
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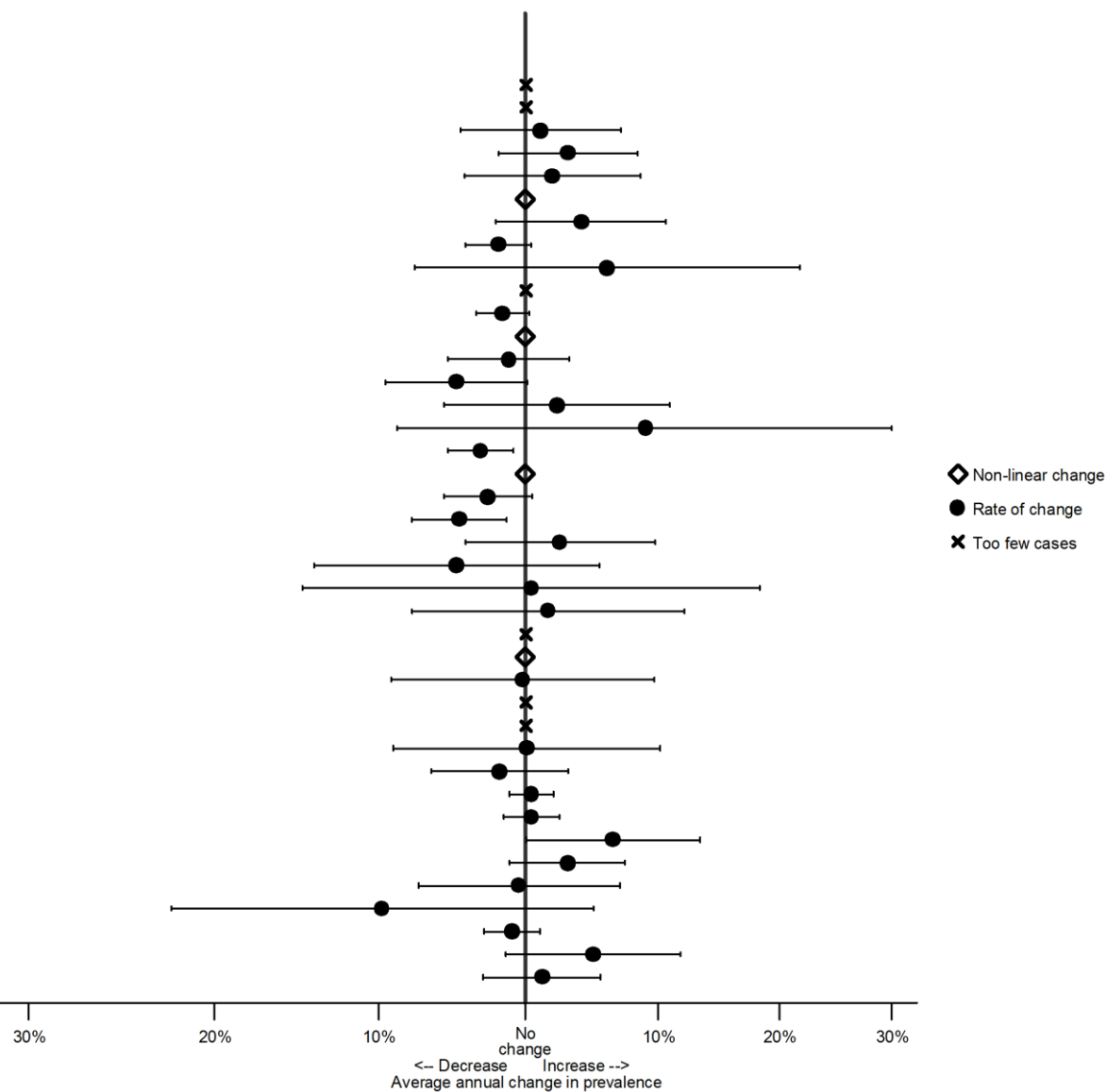
Norway

All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
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Anophthalmos
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Atrial septal defect
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Duodenal atresia or stenosis
Atresia or stenosis of other parts of small intestine
Ano-rectal atresia and stenosis
Hirschsprung's disease



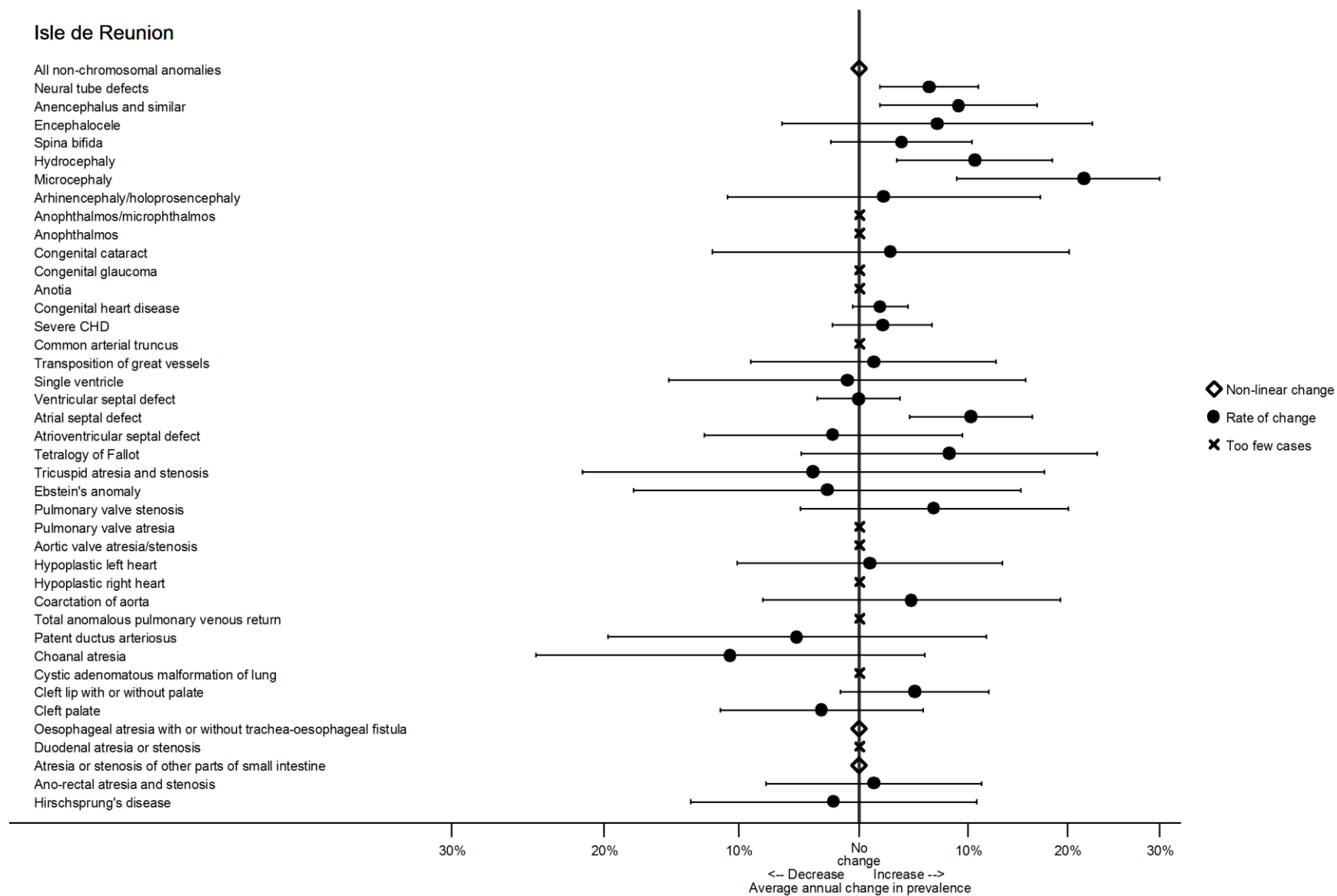
Norway

Atresia of bile ducts
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Edwards syndrome
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Patau syndrome adjusted
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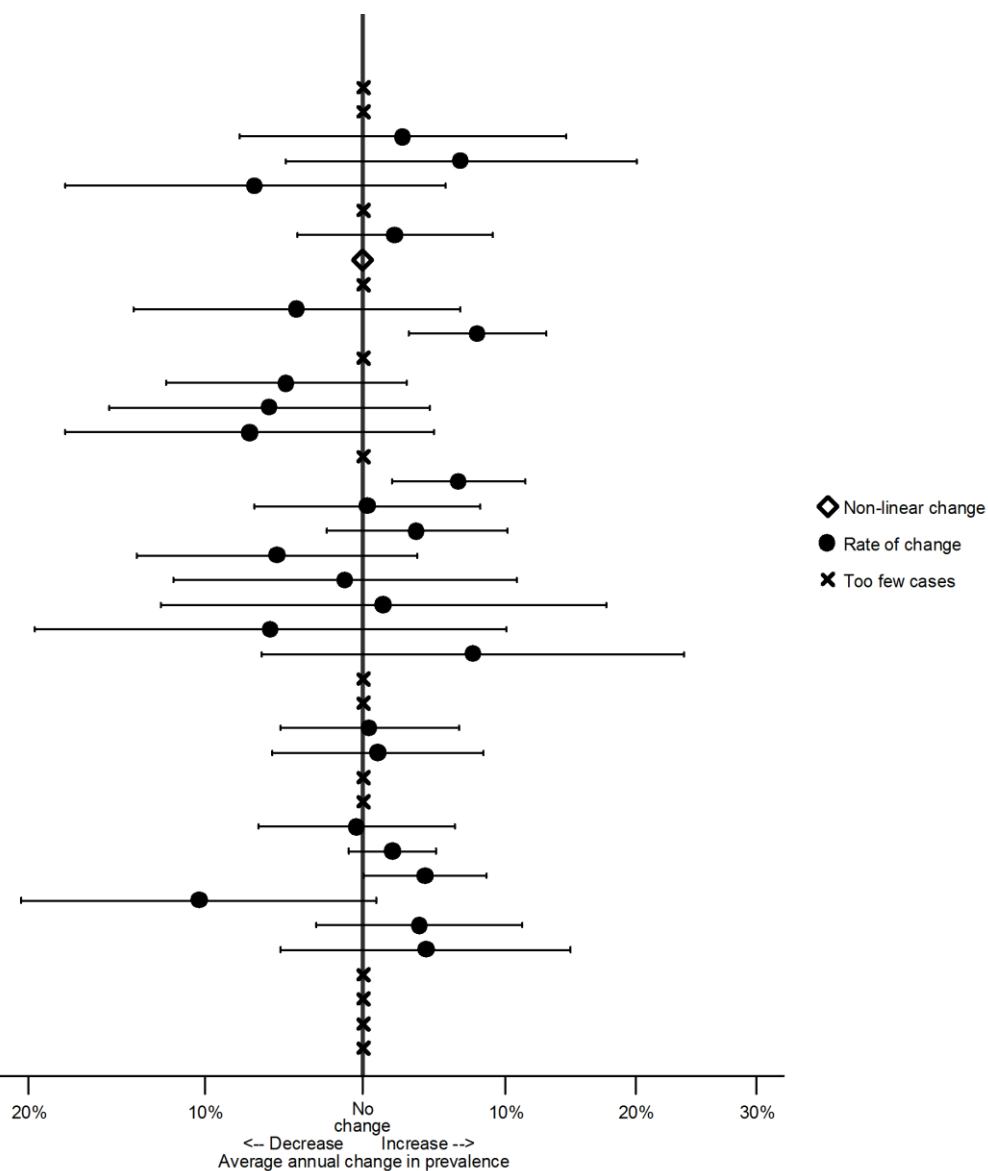
Isle de Reunion

All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
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Atresia or stenosis of other parts of small intestine
Ano-rectal atresia and stenosis
Hirschsprung's disease



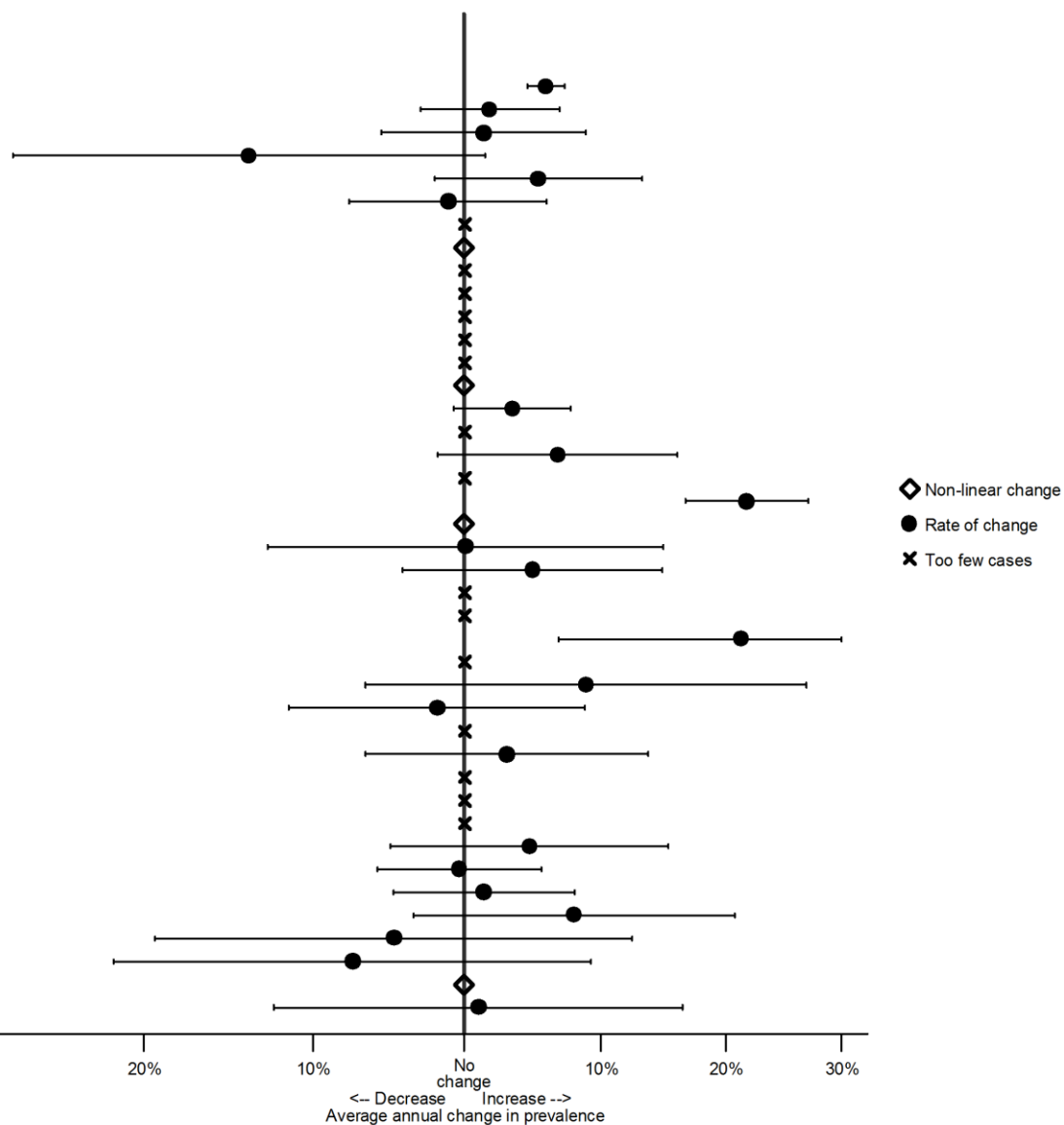
Isle de Reunion

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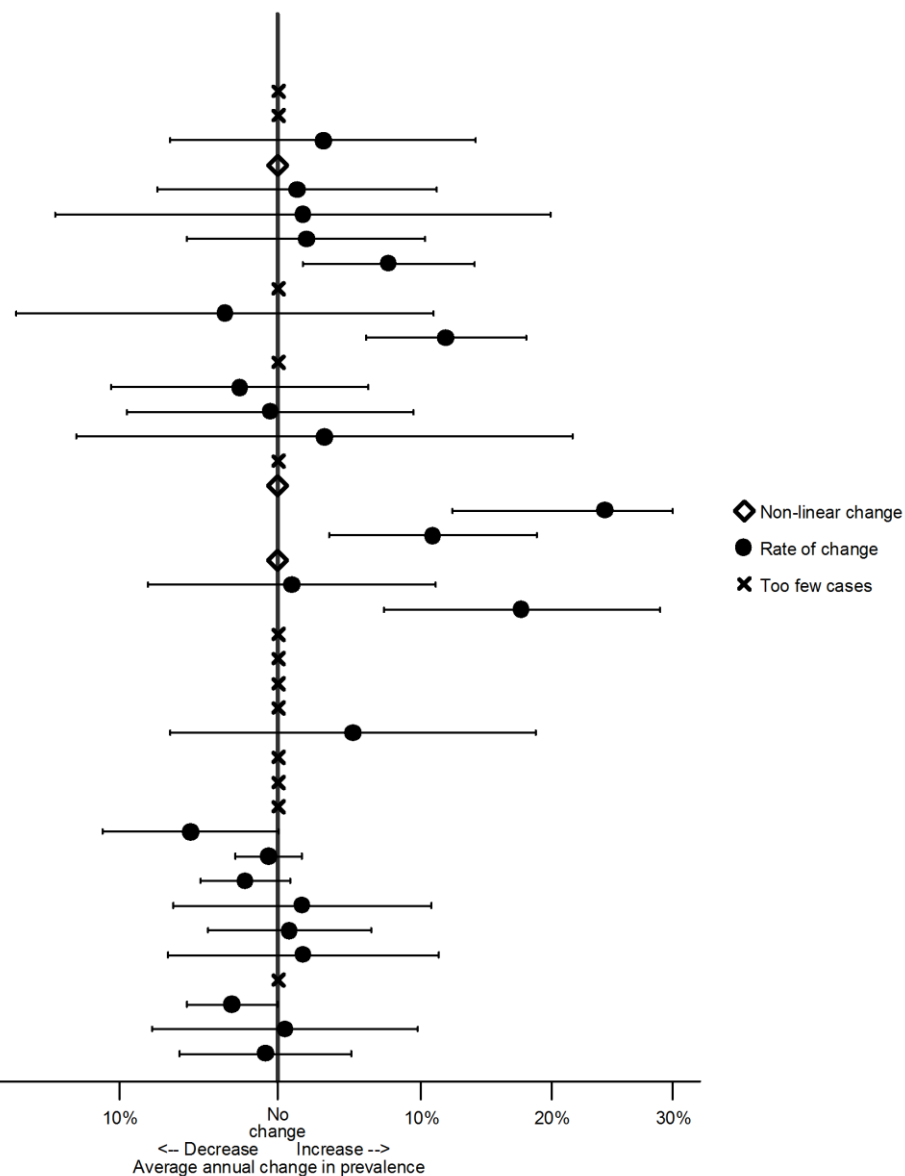
Thames Valley

All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
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Atresia or stenosis of other parts of small intestine
Ano-rectal atresia and stenosis
Hirschsprung's disease



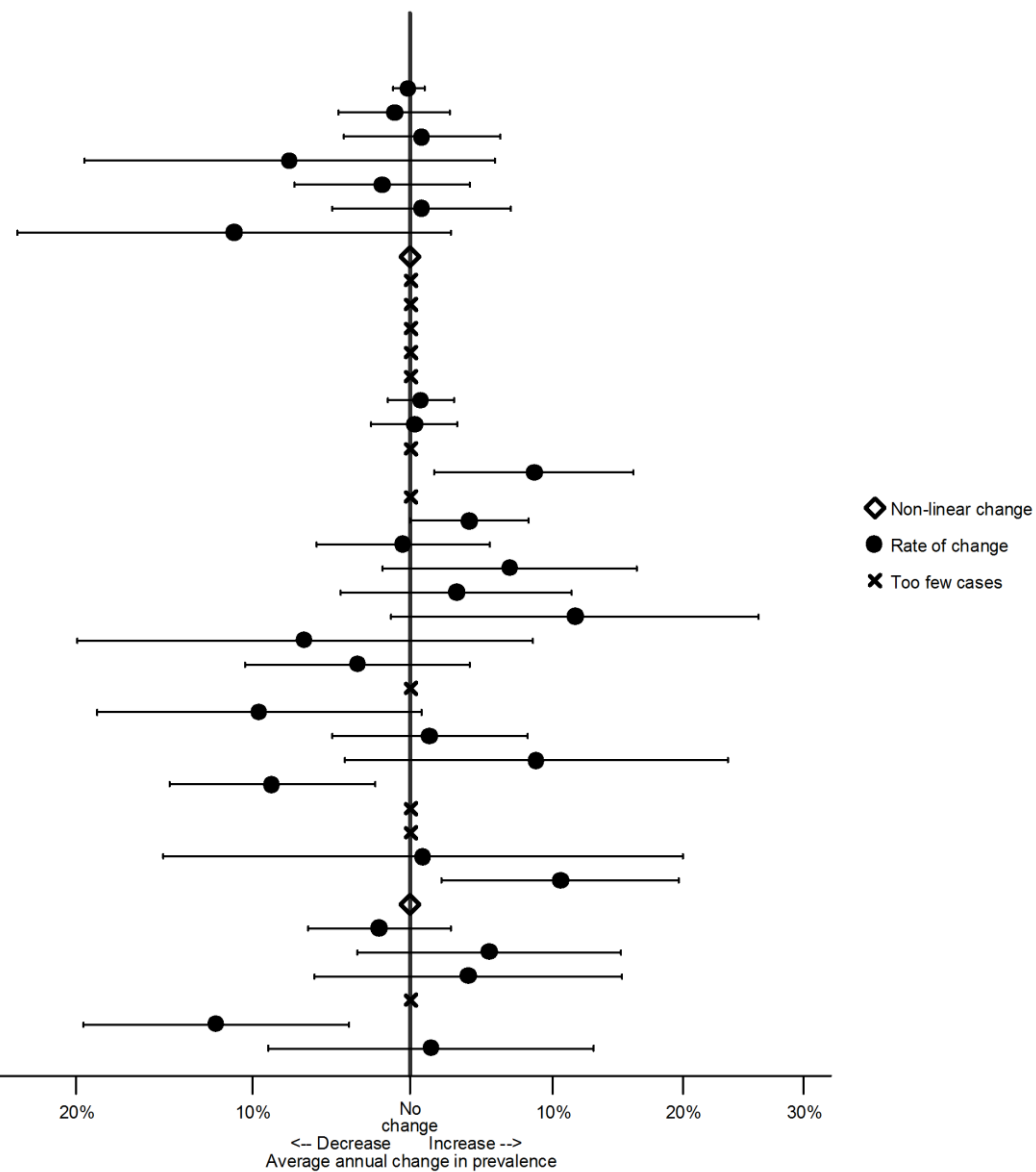
Thames Valley

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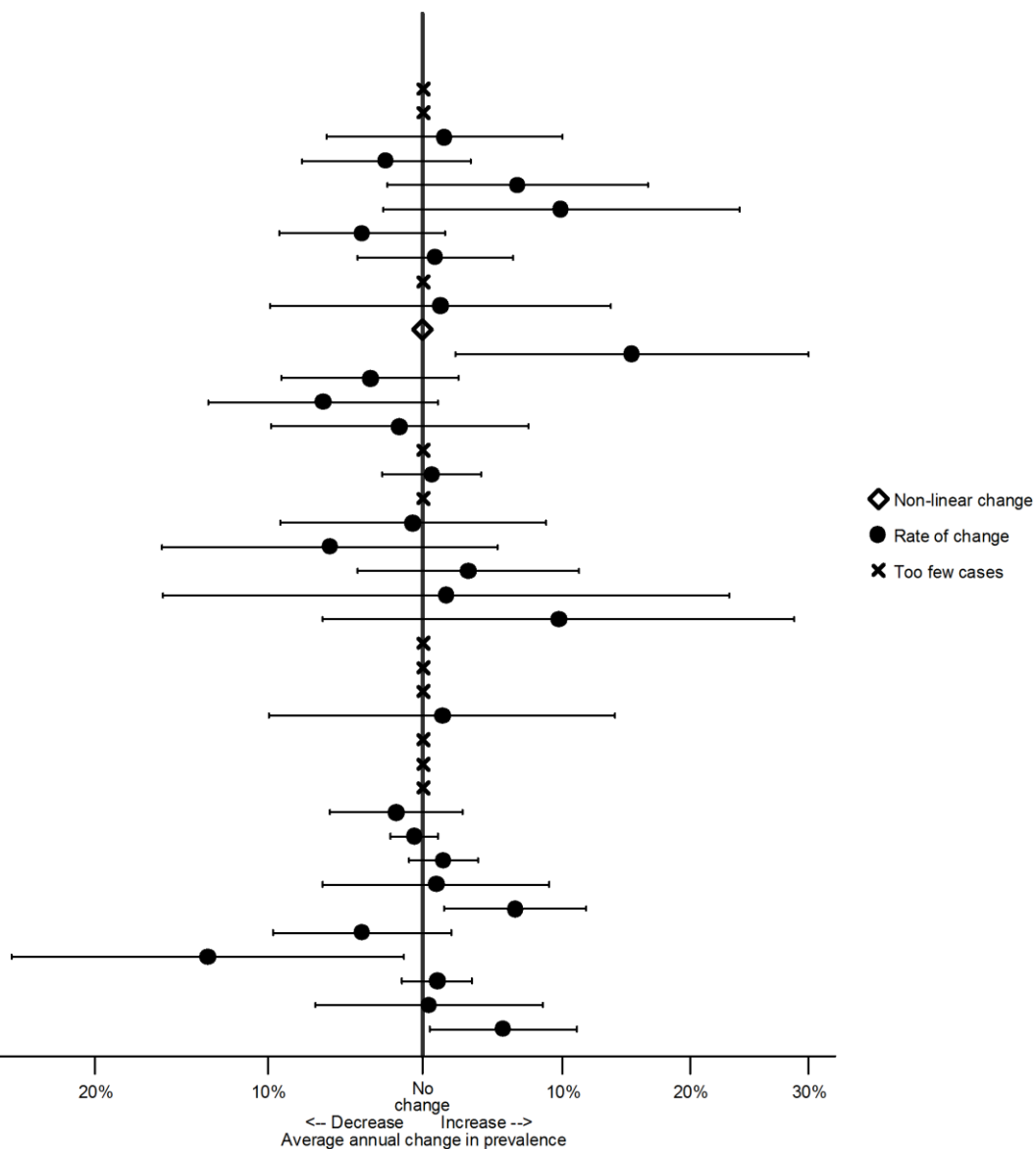
Wessex

All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
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Spina bifida
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East Midlands and South Yorkshire

All non-chromosomal anomalies

Neural tube defects

Anencephalus and similar

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Spina bifida

Hydrocephaly

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Choanal atresia

Cystic adenomatous malformation of lung

Cleft lip with or without palate

Cleft palate

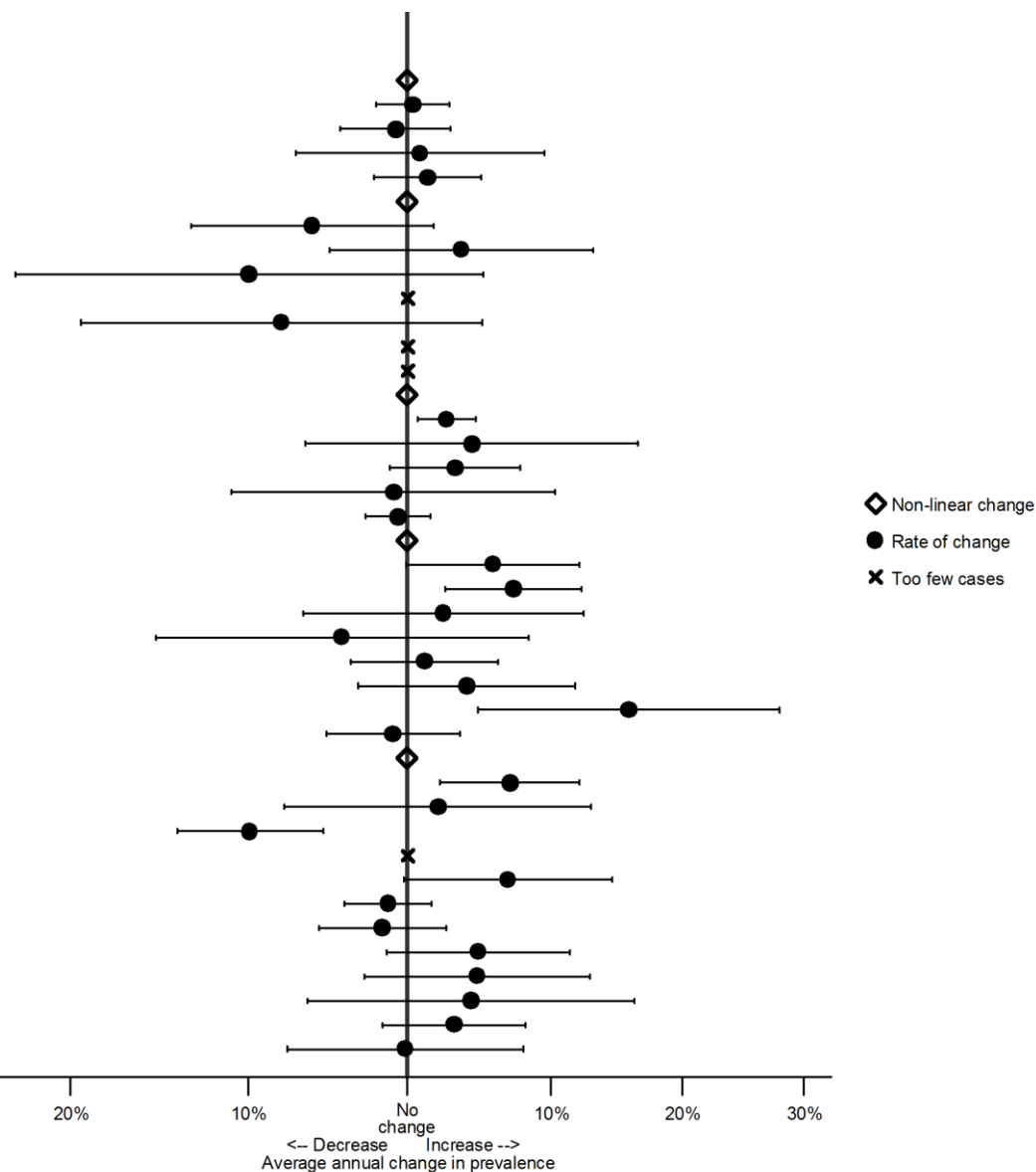
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

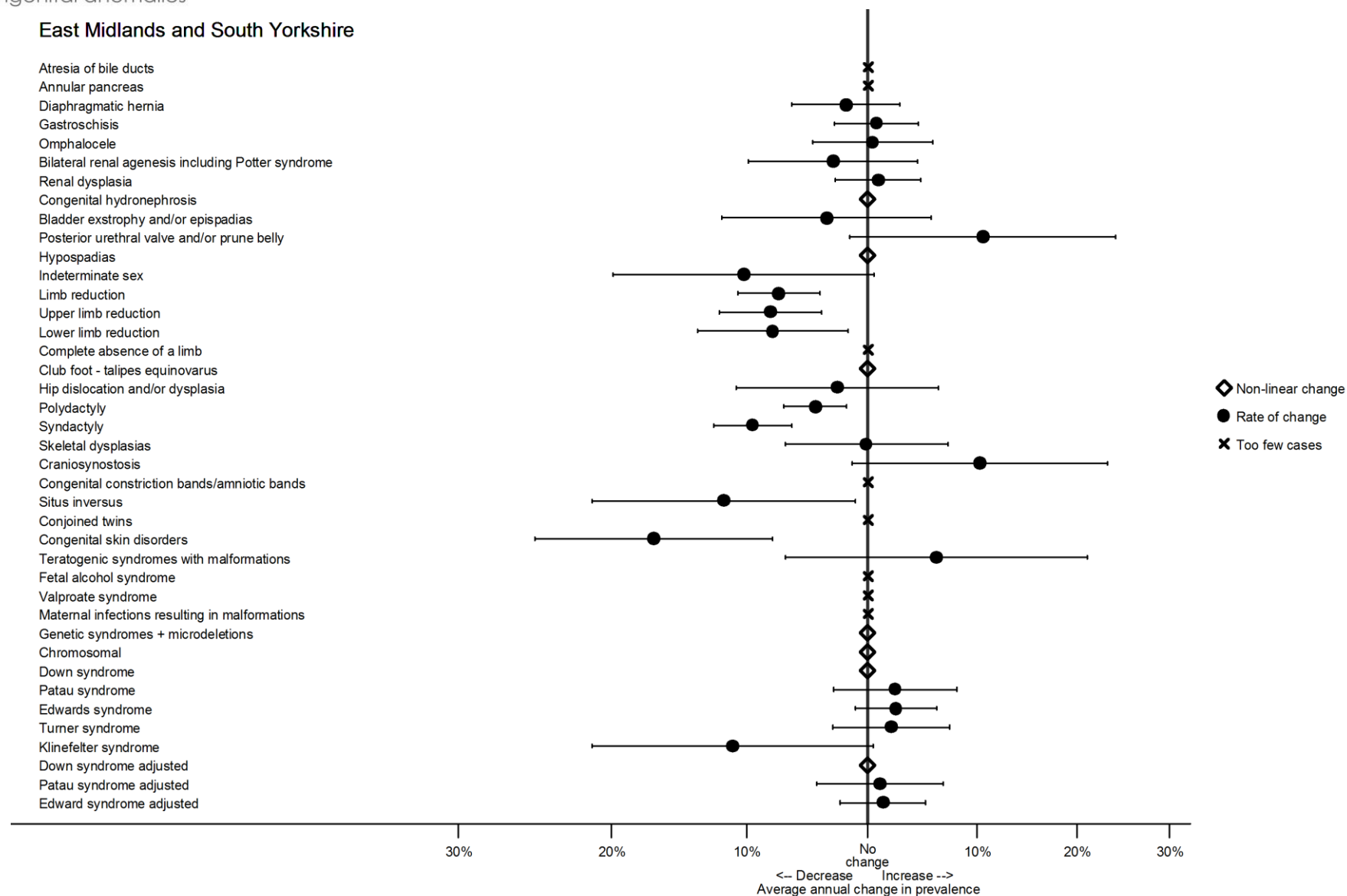
Atresia or stenosis of other parts of small intestine

Ano-rectal atresia and stenosis

Hirschsprung's disease



East Midlands and South Yorkshire



All non-chromosomal anomalies

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Chylothorax

Choanal atresia

Cystic adenomatous malformation of lung
Cleft lip with or without palate

Cleft lip with or without palate
Cleft palate

Cleft palate
Oesophagus

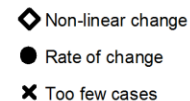
Duodenal atresia or stenosis

Atresia or stenosis of other part

Ano-rectal atresia and stenosis

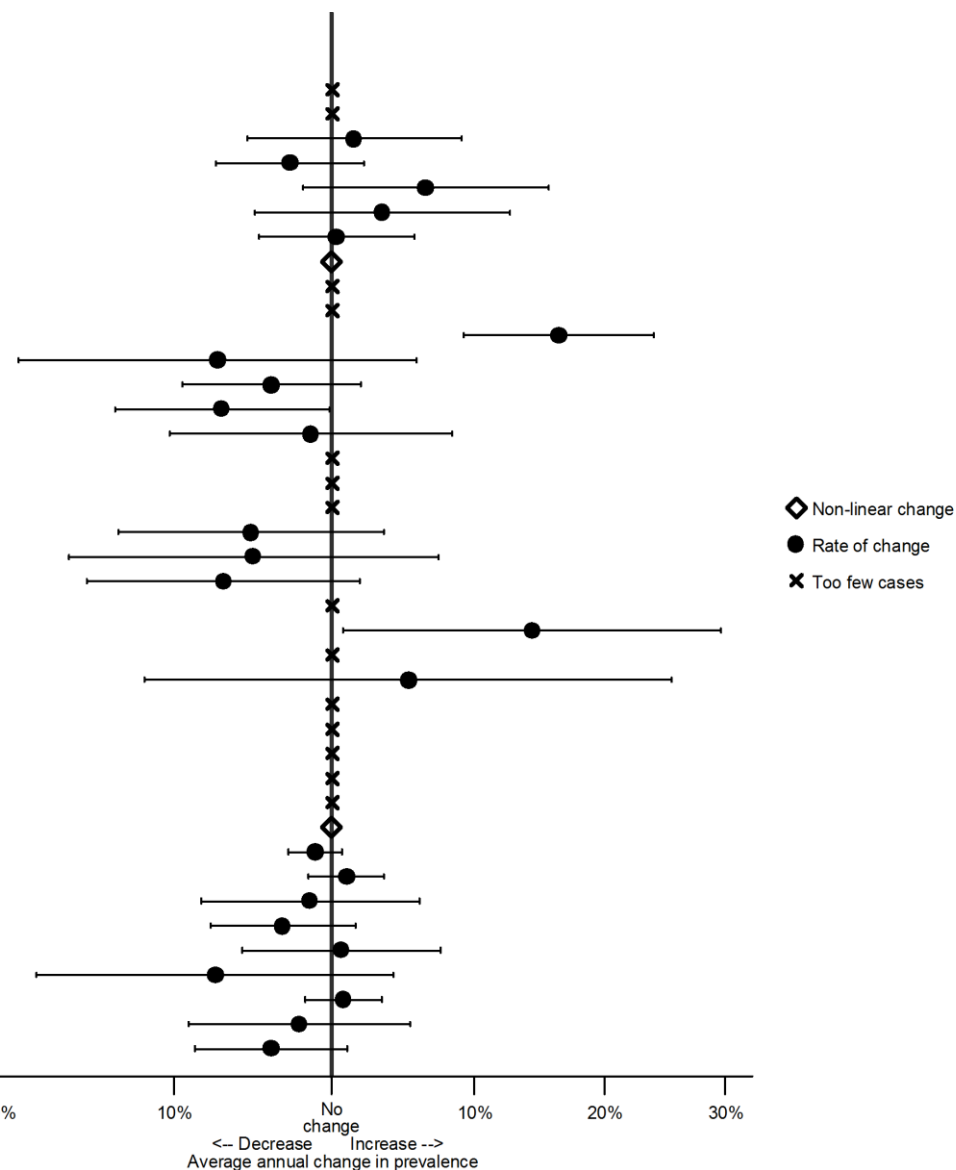
Hirschsprung's disease

Transcriptase's disease



Northern England

Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
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Hungary

All non-chromosomal anomalies

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Anencephalus and similar

Encephalocele

Spina bifida

Hydrocephaly

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Cystic adenomatous malformation of lung

Cleft lip with or without palate

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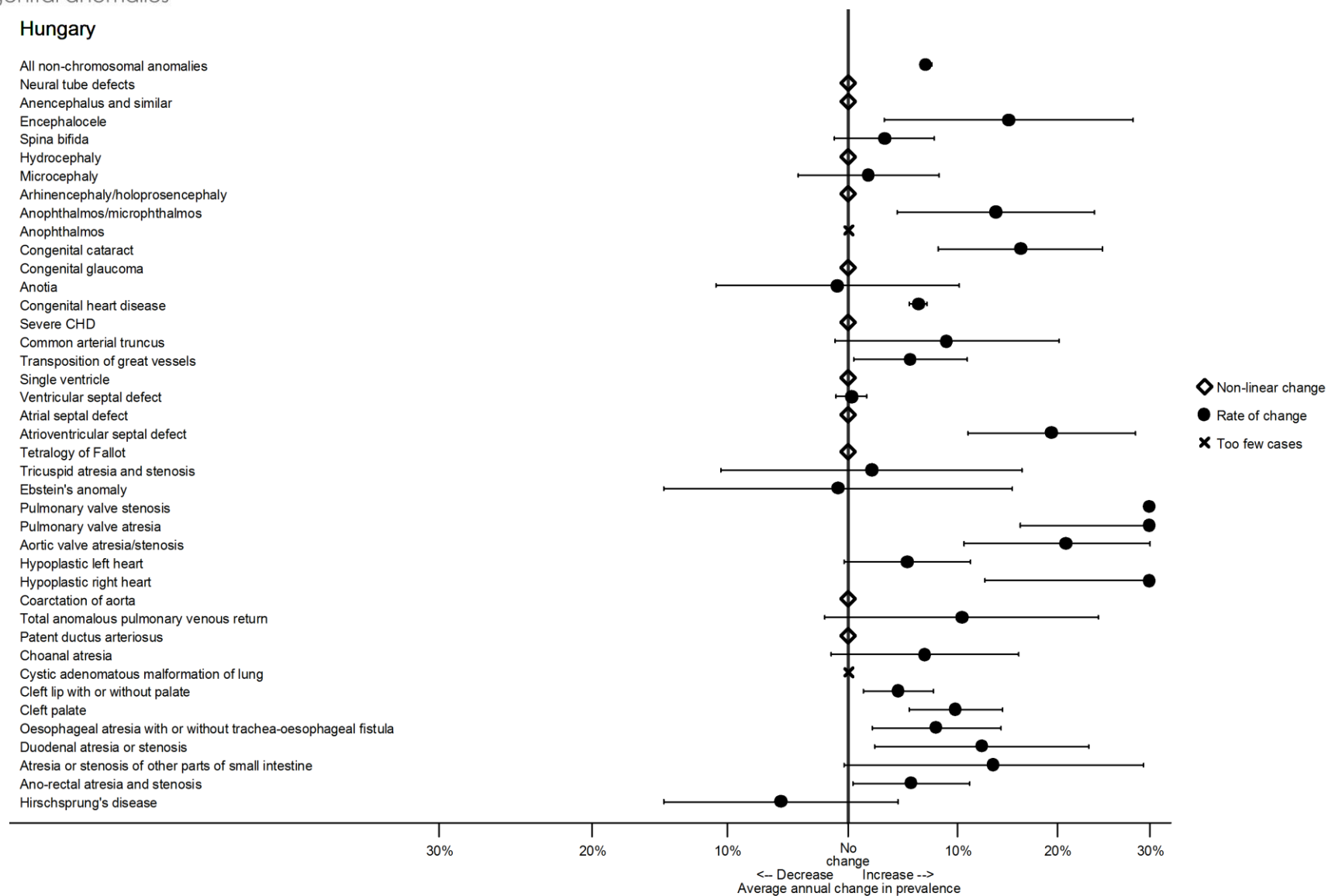
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

Atresia or stenosis of other parts of small intestine

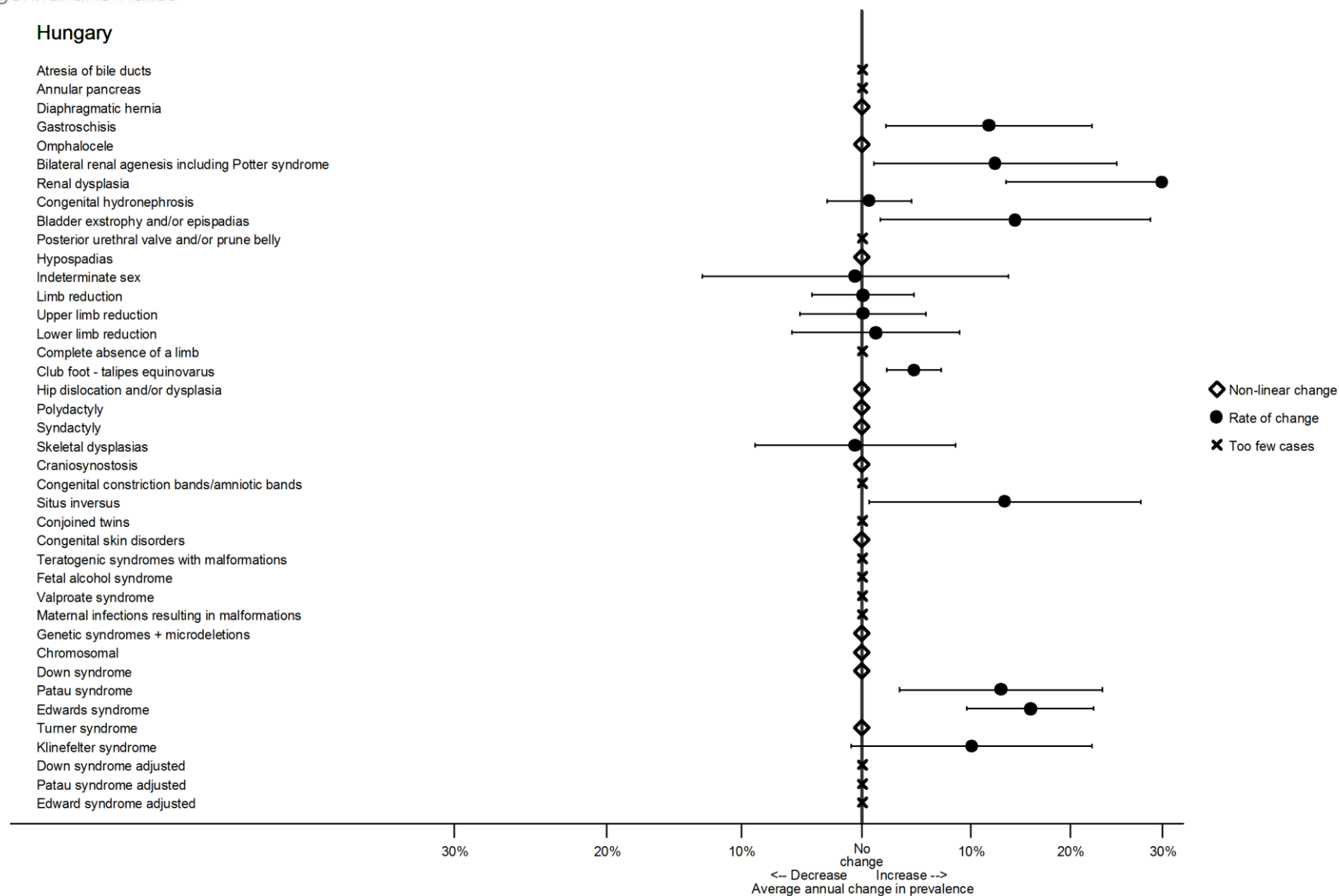
Ano-rectal atresia and stenosis

Hirschsprung's disease



Hungary

Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb reduction
Upper limb reduction
Lower limb reduction
Complete absence of a limb
Club foot - talipes equinovarus
Hip dislocation and/or dysplasia
Polydactyly
Syndactyly
Skeletal dysplasias
Craniosynostosis
Congenital constriction bands/amniotic bands
Situs inversus
Conjoined twins
Congenital skin disorders
Teratogenic syndromes with malformations
Fetal alcohol syndrome
Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
Chromosomal
Down syndrome
Patau syndrome
Edwards syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted



SE Ireland

All non-chromosomal anomalies

Neural tube defects

Anencephalus and similar

Encephalocele

Spina bifida

Hydrocephaly

Microcephaly

Arhinencephaly/holoprosencephaly

Anophthalmos/microphthalmos

Anophthalmos

Congenital cataract

Congenital glaucoma

Anotia

Congenital heart disease

Severe CHD

Common arterial truncus

Transposition of great vessels

Single ventricle

Ventricular septal defect

Atrial septal defect

Atrioventricular septal defect

Tetralogy of Fallot

Tricuspid atresia and stenosis

Ebstein's anomaly

Pulmonary valve stenosis

Pulmonary valve atresia

Aortic valve atresia/stenosis

Hypoplastic left heart

Hypoplastic right heart

Coarctation of aorta

Total anomalous pulmonary venous return

Patent ductus arteriosus

Choanal atresia

Cystic adenomatous malformation of lung

Cleft lip with or without palate

Cleft palate

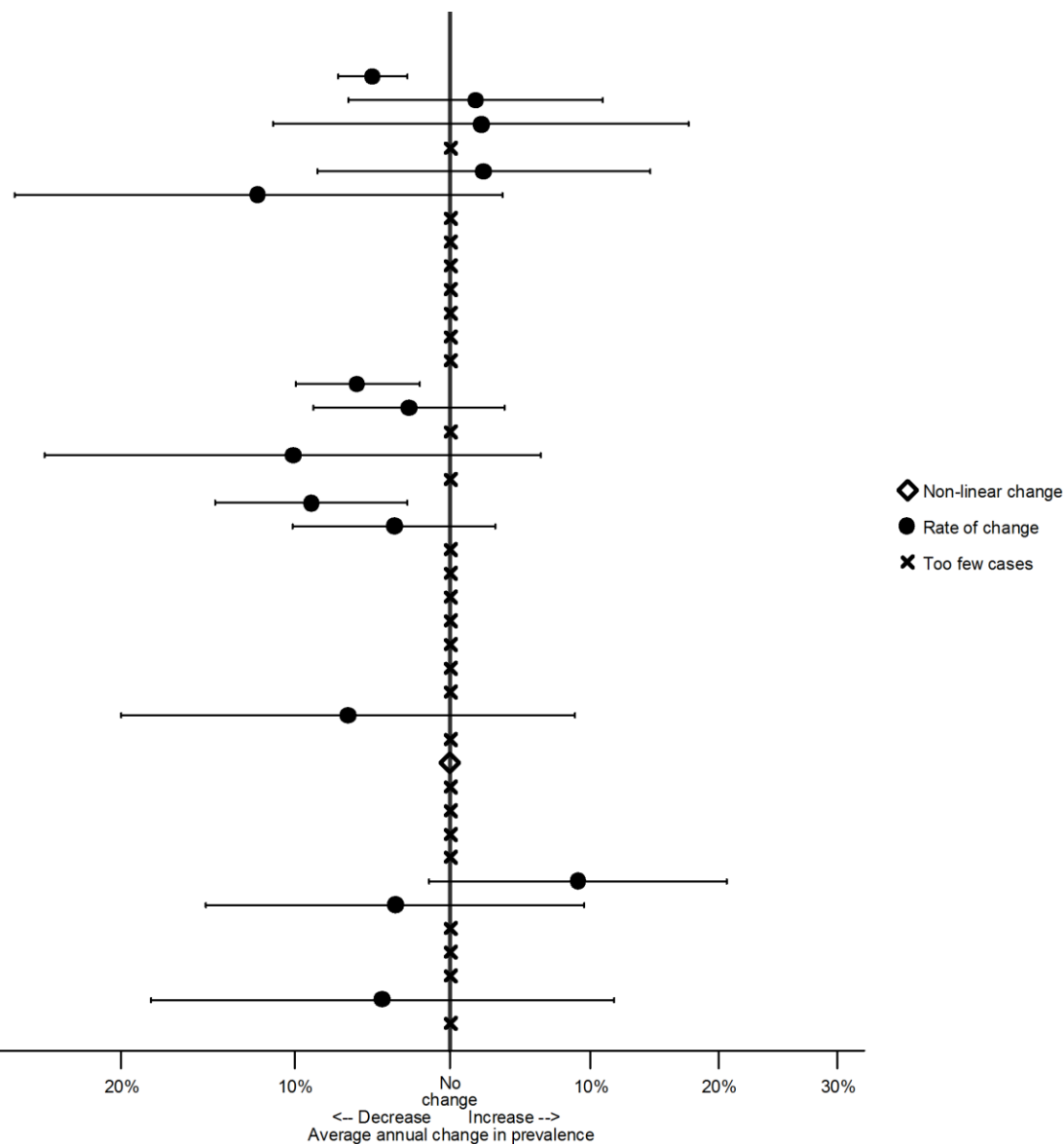
Oesophageal atresia with or without trachea-oesophageal fistula

Duodenal atresia or stenosis

Atresia or stenosis of other parts of small intestine

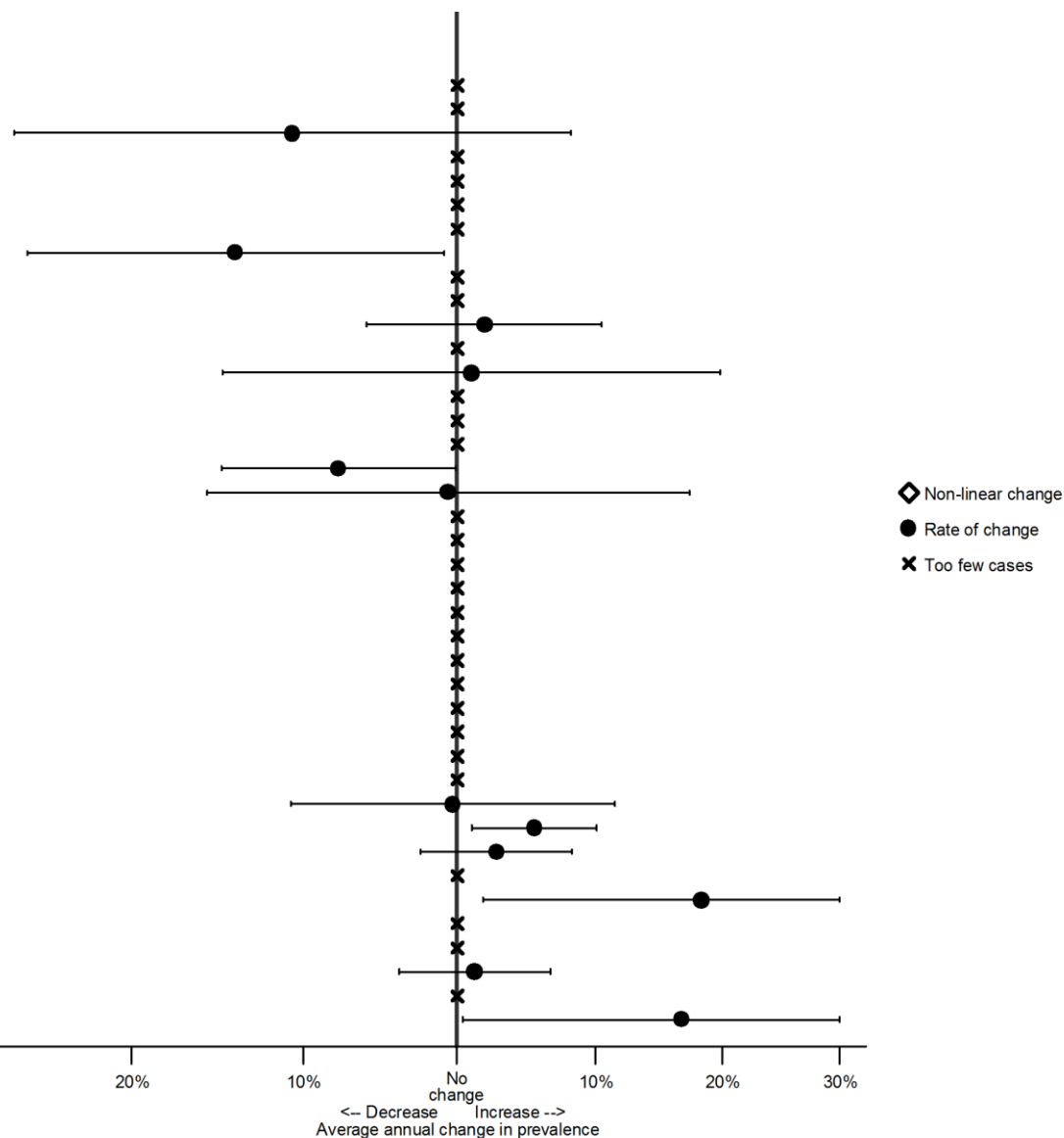
Ano-rectal atresia and stenosis

Hirschsprung's disease



SE Ireland

Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
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Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
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Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb reduction
Upper limb reduction
Lower limb reduction
Complete absence of a limb
Club foot - talipes equinovarus
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Skeletal dysplasias
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Situs inversus
Conjoined twins
Congenital skin disorders
Teratogenic syndromes with malformations
Fetal alcohol syndrome
Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
Chromosomal
Down syndrome
Patau syndrome
Edwards syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted



Appendix H: Central registry reports of pan-European trends

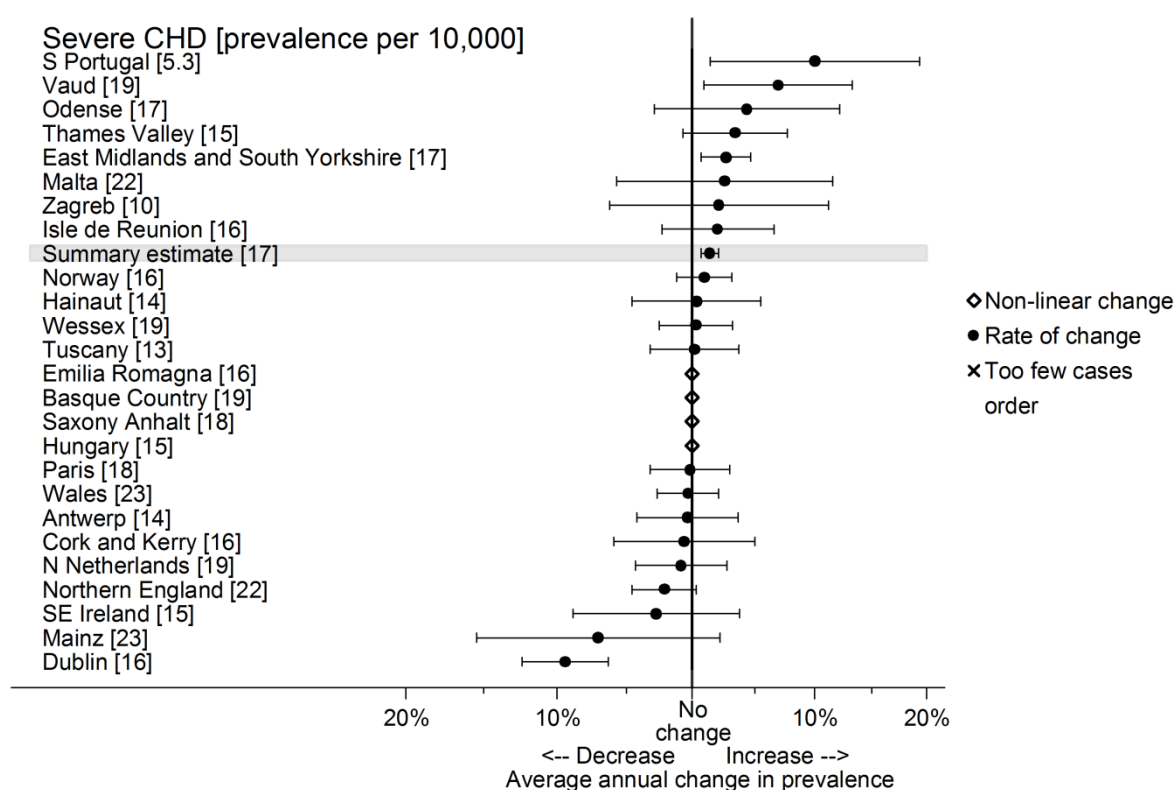
Trend Report

Severe CHD

This is a continuing increasing trend.

The registries which show a statistically significant trend moving in the same direction and which therefore may be contributing are: South Portugal, Vaud, E Midlands & S Yorkshire

Figure 1. The trend in prevalence¹ of severe CHD for the 10 years from 2003-2012, showing individual registries and the pan European trend



Consistency between registries

There were a total of 10,712 severe CHD cases included in the analysis over the ten year period. Prevalence ranged from 5.3 cases per 10,000 births in South Portugal to 23.8¹ cases per 10,000 births in Wales.

Figure 2. Prevalence of severe CHD by registry for 10 year period 2003 to 2012

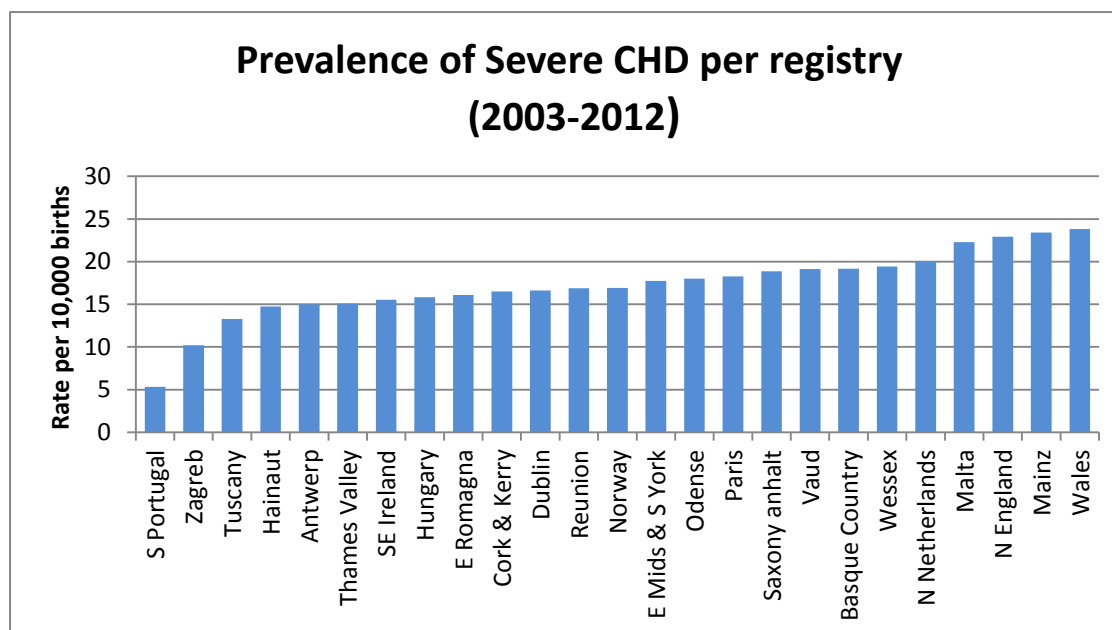


Figure 3: Severe CHD showing the increasing trend and that trend when the registries with a statistically significant rise in prevalence are excluded.

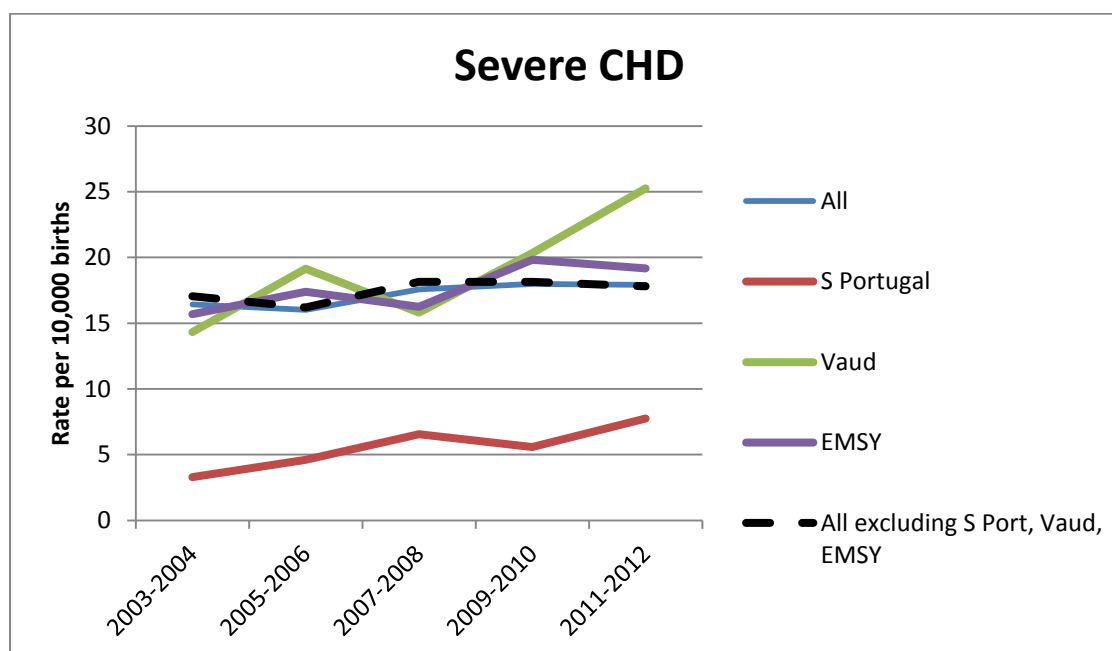


Figure 4: The prevalence of severe CHD over the past three decades

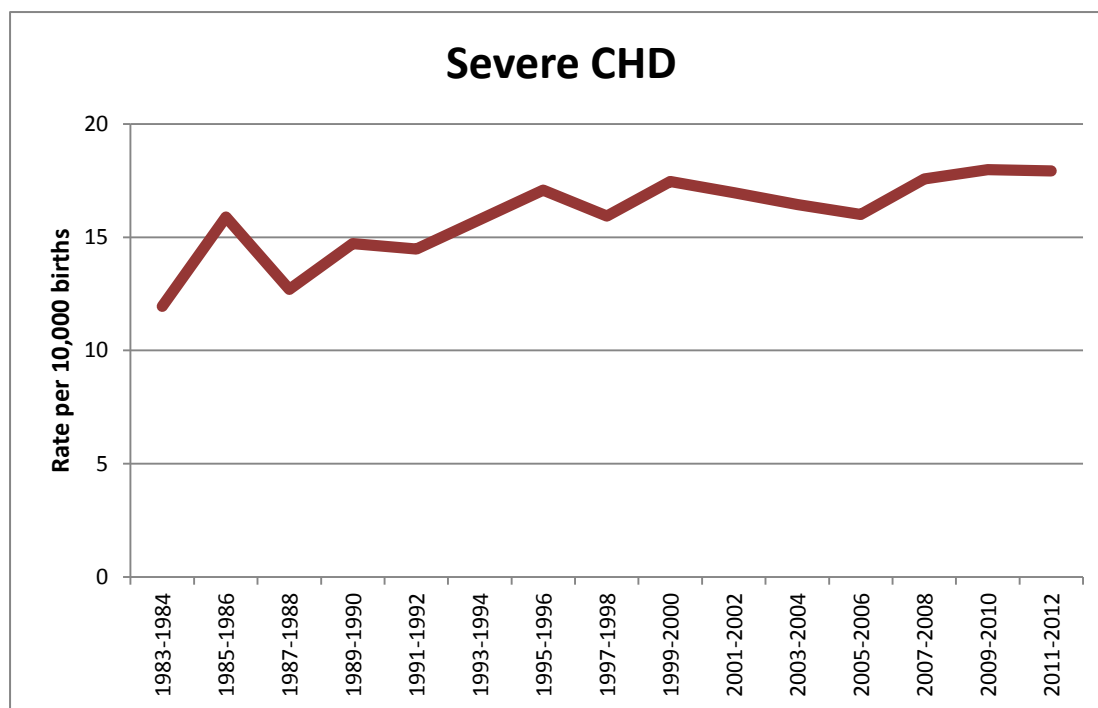


Figure 5: Prevalence of severe CHD as an isolated cardiac vs a potential multiple anomaly over time 2003-2012

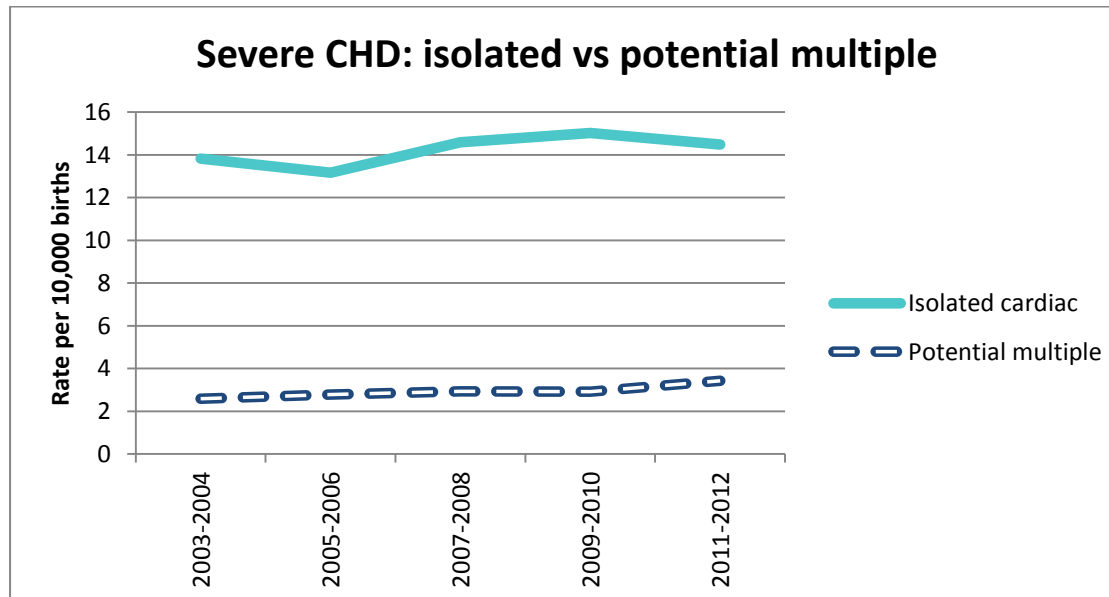


Table 1: Severe CHD: breakdown by multiple malformation algorithm 2003-2012

Isolated cardiac (A2)	Potential multiple (M2)	Teratogenic syndrome (T2)	Isolated other (I2)	Genetic syndrome, skeletal dysplasia and monogenic disorder (B2)
8863 (82.7%)	1820 (17.0%)	12 (0.1%)	8 (0.1%)	9 (0.1%)

Total number of severe CHD cases (2003-2012) = 10,712

Figure 6: Prevalence of severe CHD components over time 2003-2012

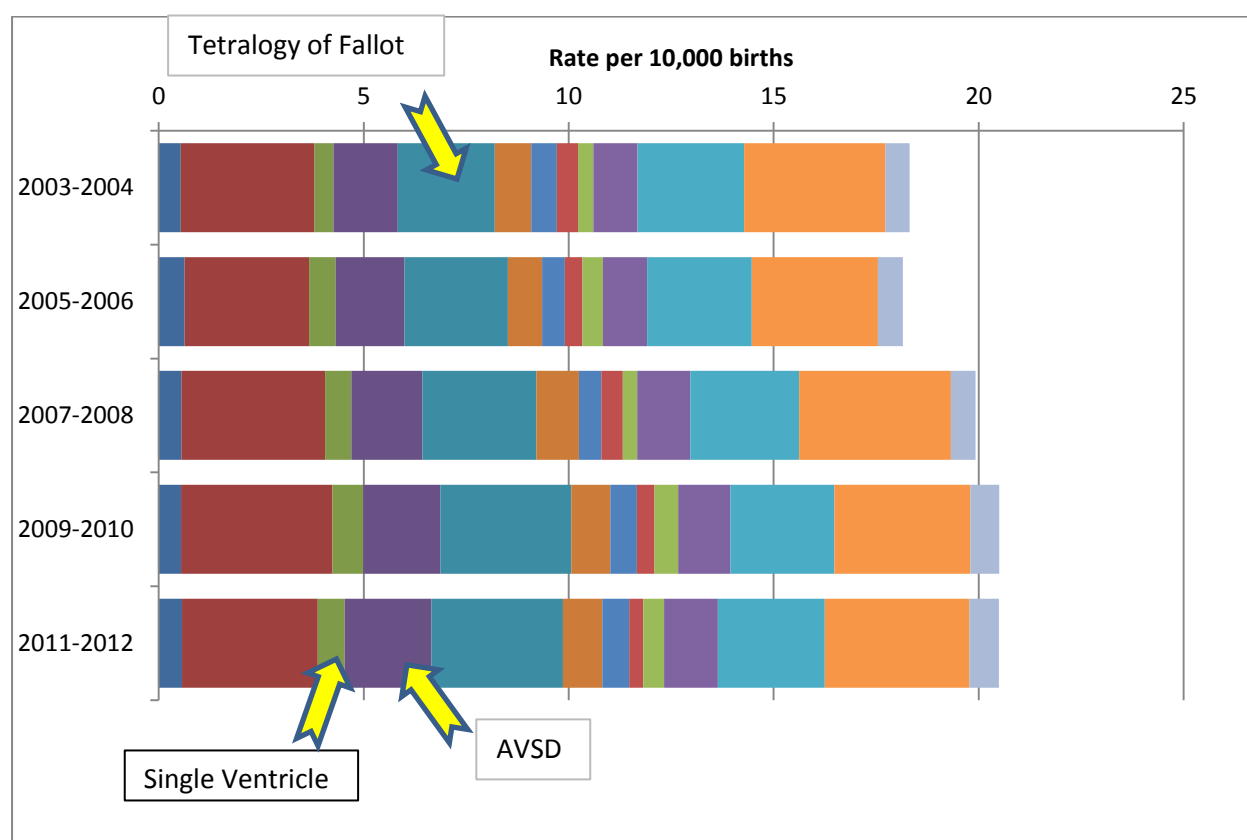


Figure 7: Severe CHD: Time of Diagnosis

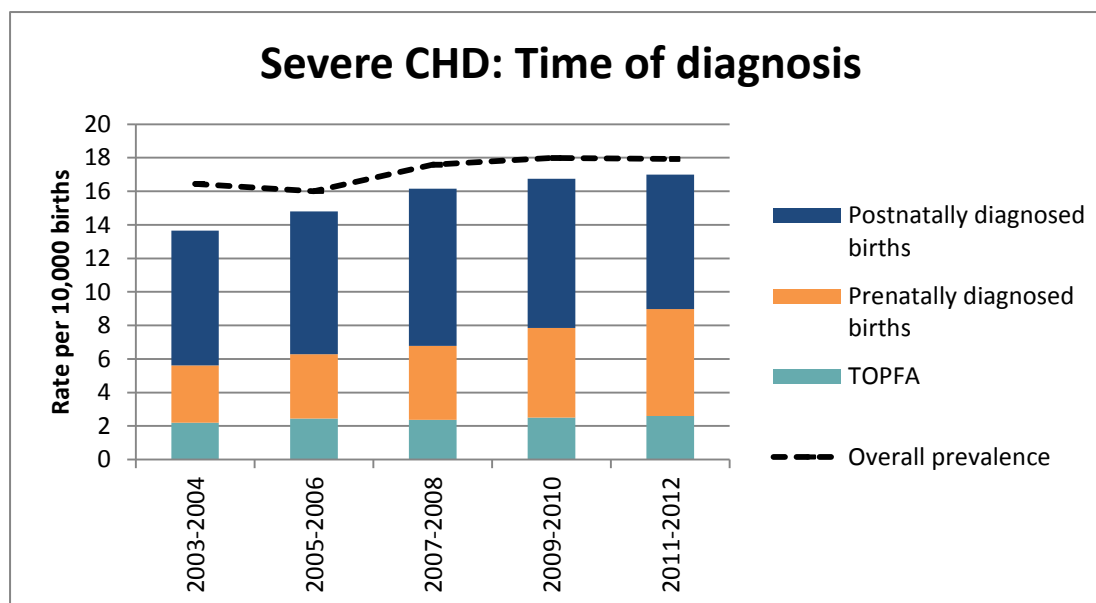


Table 2: Breakdown of postnatally diagnosed births

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	828 (88.2%)	844 (78.9%)	962 (78.2%)	932 (78.9%)	769 (82.5%)
>1 month	105 (11.2%)	86 (8.0%)	131 (10.7%)	106 (9.0%)	68 (7.3%)
postnatal, age n/k	6 (0.6%)	140 (13.1%)	137 (11.1%)	143 (12.1%)	95 (10.2%)

Conclusions:

- Whilst S Portugal have a significantly increasing trend, the prevalence rate is extremely low compared to the EUROCAT average. See figures 1, 2 & 3
- When the 3 significantly increasing registries are excluded, the prevalence rate remains unaffected. See figure 3. Vaud seems to have steady increase since 2008 and initial investigation by this registry suggests that this is a **real trend**, not an artefact of diagnosis or registration and further surveillance is proposed. In E Midlands & S Yorkshire registry it's considered more a data quality issue of increasing ascertainment combined with uncertainty about the population coverage for the older cases
- When looked at over a 30 year period 1983-2012, the trend is clearly upward
- There is huge disparity between isolated cardiac and potential multiple. But both on the increase. (Figure 5)

- The components of severe CHD which are contributing most to the increasing trend can be seen in figure 6. Tetralogy of Fallot, AVSD and single ventricle are 3 that also have continuing Pan European trends
- Whilst the rate of TOPFA with severe CHD has remained fairly constant over the 10 year period 2003-2012, the rate of prenatally liveborn cases has steadily increased (Figure 7)
- In time period 2011-2012 there were **more prenatally diagnosed cases than postnatally diagnosed cases for the first time**

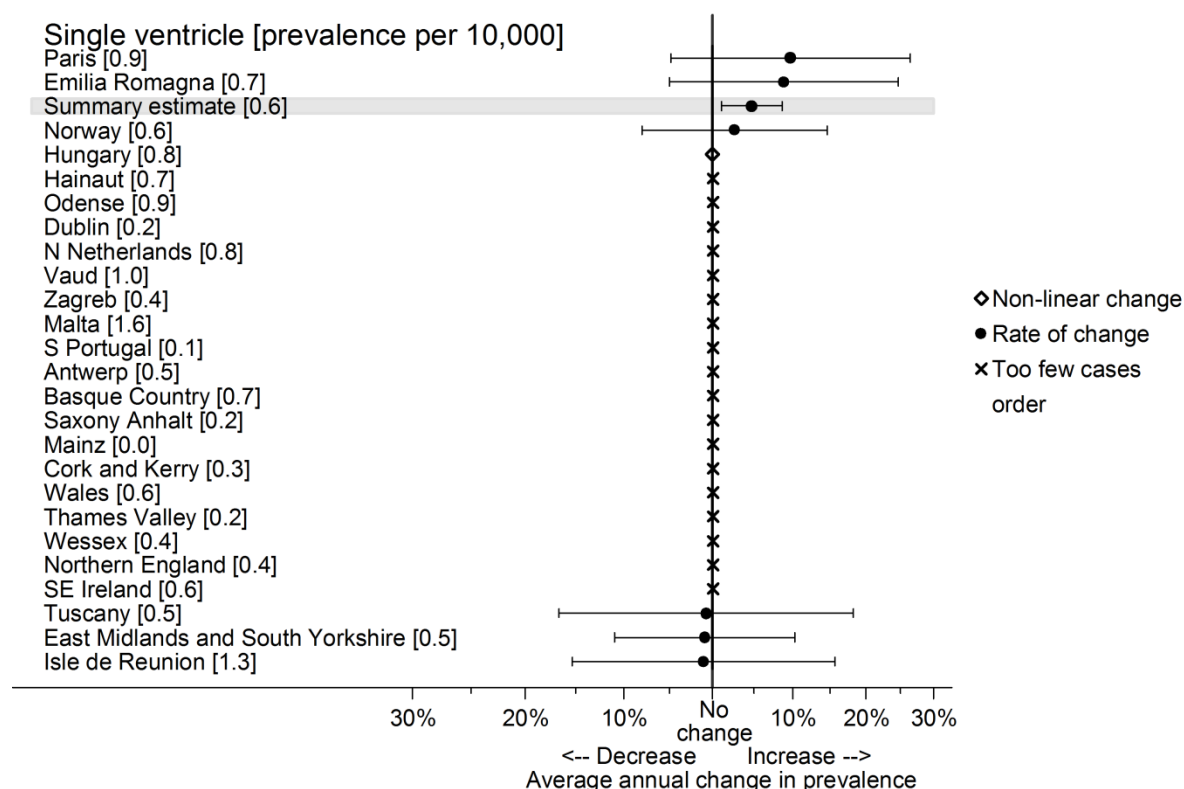
Trend Report

Single Ventricle

This is a continuing increasing trend.

There are no registries showing a statistically significant trend moving in the same direction. Only Paris and Emilia Romagna were above the EUROCAT average

Figure 1. The trend in prevalence¹ of Single Ventricle for the 10 year period 2003-2012, showing individual registries and the pan European trend



Literature review

Single ventricle is a severe congenital cardiac anomaly where the heart comprises only one complete ventricle with an inlet valve and an outlet portion even though the outlet valve is atretic. It is a serious, cyanotic, heart defect which requires surgery in the neonatal period and often throughout childhood. The surgery indicated is dependent on the complexity of the cardiac defect, but a structurally normal heart is not achievable, with many cases require a Fontan circulation.

Single ventricle has been associated with maternal phenylketonuria and with maternal diabetes, the latter also being associated with hypoplastic left heart (1). Pulmonary valve anomalies have been associated with maternal rubella, influenza and other febrile illnesses, with tricuspid atresia also associated with febrile general febrile illness (1). Hypoplastic left heart has also been associated with environmental pollutants, notably organic solvents (1).

Consistency between registries

There were a total of 394 single ventricle cases included in the analysis over the ten year period. Prevalence ranged from 0 cases per 10,000 births in Mainz to 1.6 cases per 10,000 births in Malta.

Figure 2. *Prevalence of Single ventricle by registry for 10 year period 2003 to 2012*

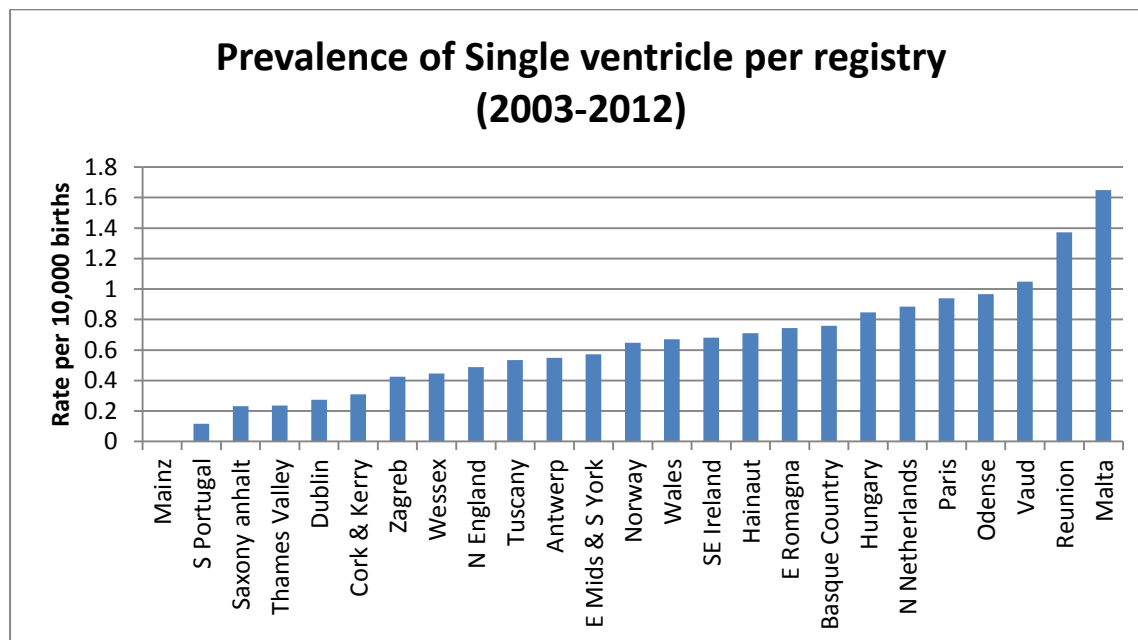


Figure 3: *The prevalence of single ventricle over the past three decades*

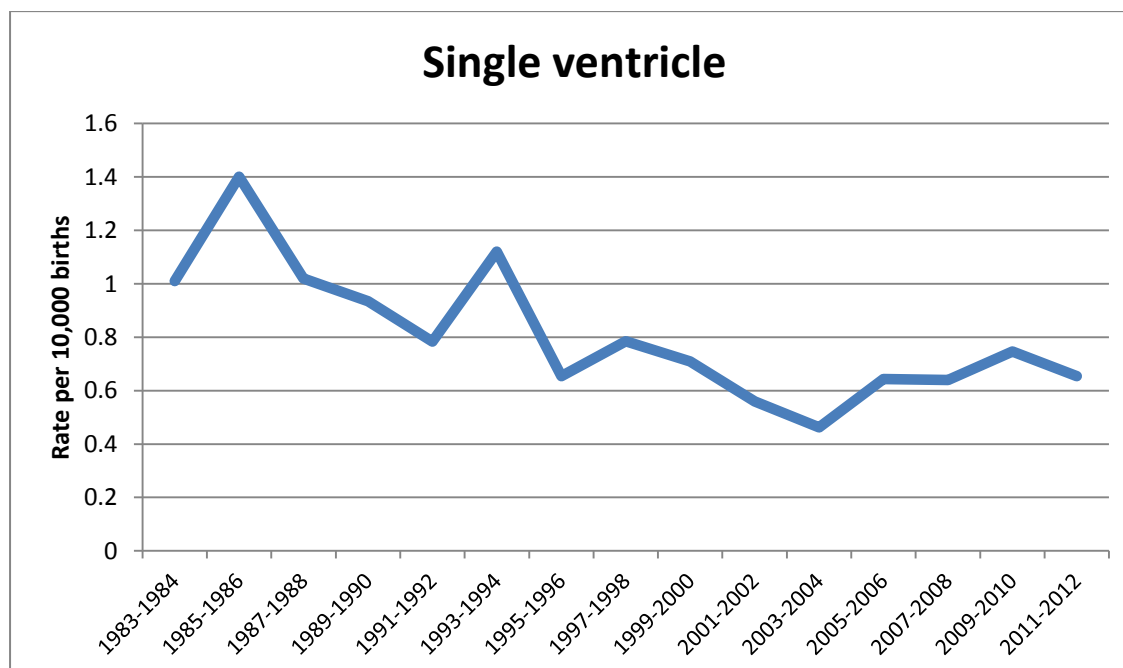


Figure 4: Prevalence of single ventricle as an isolated vs a potential multiple anomaly over time 2003-2012

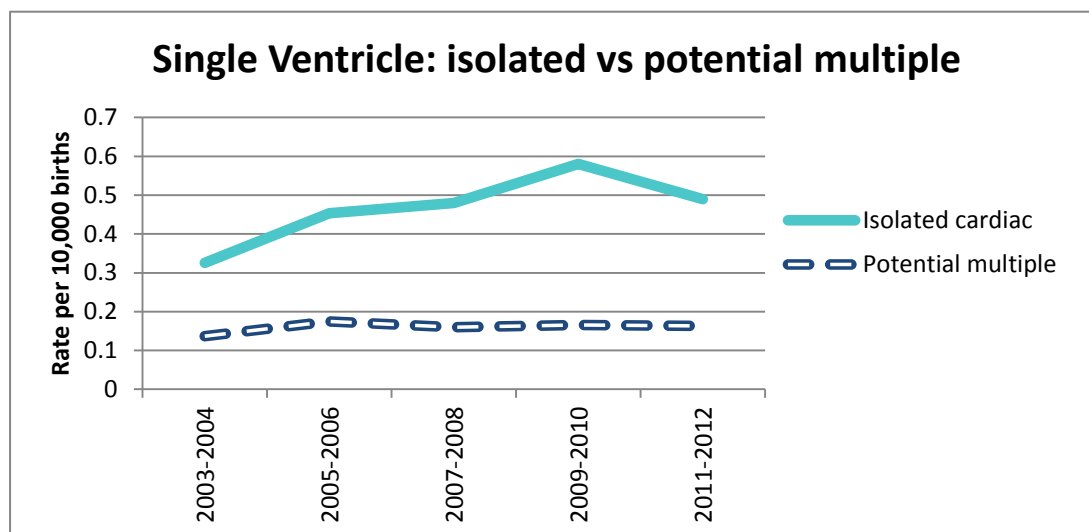


Figure 5: Time of diagnosis

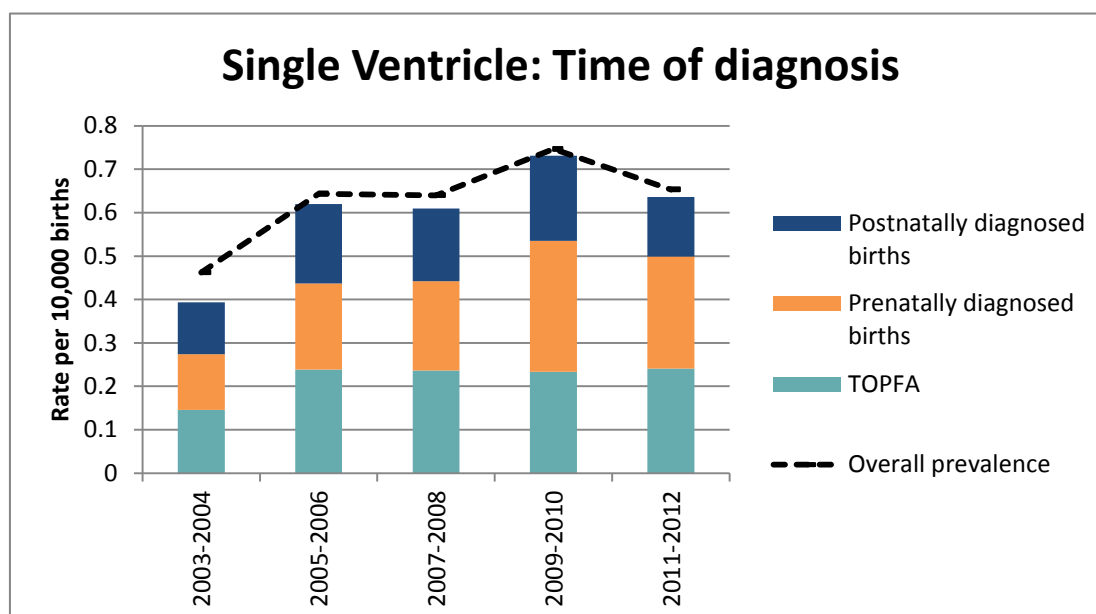


Table 1: Breakdown of postnatally diagnosed births

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	13 (92.9%)	19 (82.6%)	19 (86.4%)	24 (92.3%)	13 (81.3%)
>1 month	1 (7.1%)	4 (17.4%)	1 (4.5%)	1 (3.8%)	3 (18.8%)
postnatal, age n/k	0 (0.0%)	0 (0.0%)	2 (9.1%)	1 (3.8%)	0 (0.0%)

Conclusions:

- When examined over a 30 year period, we can see that the current prevalence, whilst still lower than in the 80's and 90's, is on the increase
- The data relating to single ventricle cases was scrutinised and cleaned following the 2011 monitoring. However the trend persists
- There are more cases diagnosed prenatally than postnatally. Approximately 50% of those prenatally diagnosed will be TOPFA

(1) Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* 2007 Jun 12;115(23):2995-3014.

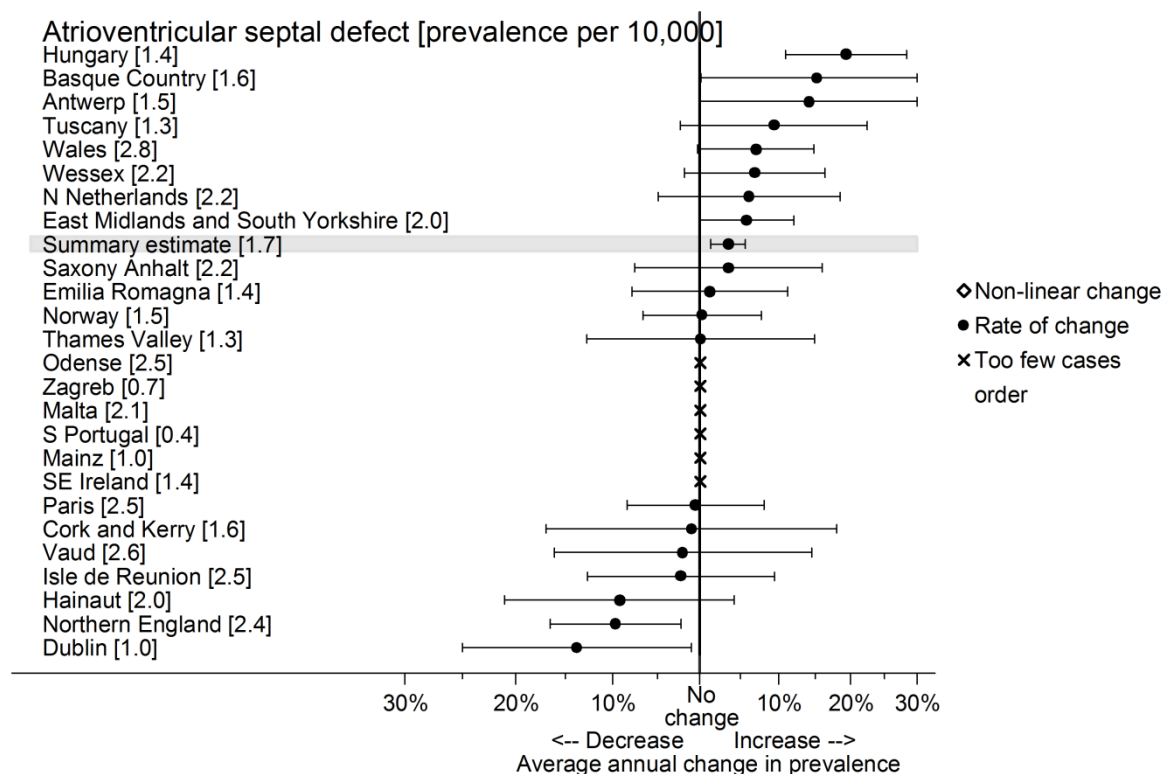
Trend Report

Atrioventricular Septal Defect (AVSD)

This is continuing increasing trend.

The registries which show a statistically significant trend moving in the same direction and which therefore may be contributing are: Hungary, Basque Country and Antwerp.

Figure 1. The trend in prevalence of AVSD for the 10 year period 2003-2012, showing individual registries and the pan European trend



Literature Review

AVSD is Central defect of the cardiac septa and a common atrioventricular valve, it includes primum ASD defects (1). It is strongly associated with chromosomal anomalies, but when seen in non-chromosomal cases it is often one of many non-chromosomal anomalies (2). It is associated with maternal diabetes, organic solvents, maternal use of ibuprofen and vitamin A (3). This congenital anomaly was the subject of a recent EUROCAT investigation (2).

Consistency between registries

There were a total of 1118 AVSD cases included in the analysis over the ten year period. Prevalence ranged from 0.4 cases per 10,000 births in South Portugal to 2.9¹ cases per 10,000 births in Wales.

Figure 2. Prevalence of AVSD by registry for 10 year period 2003 to 2012

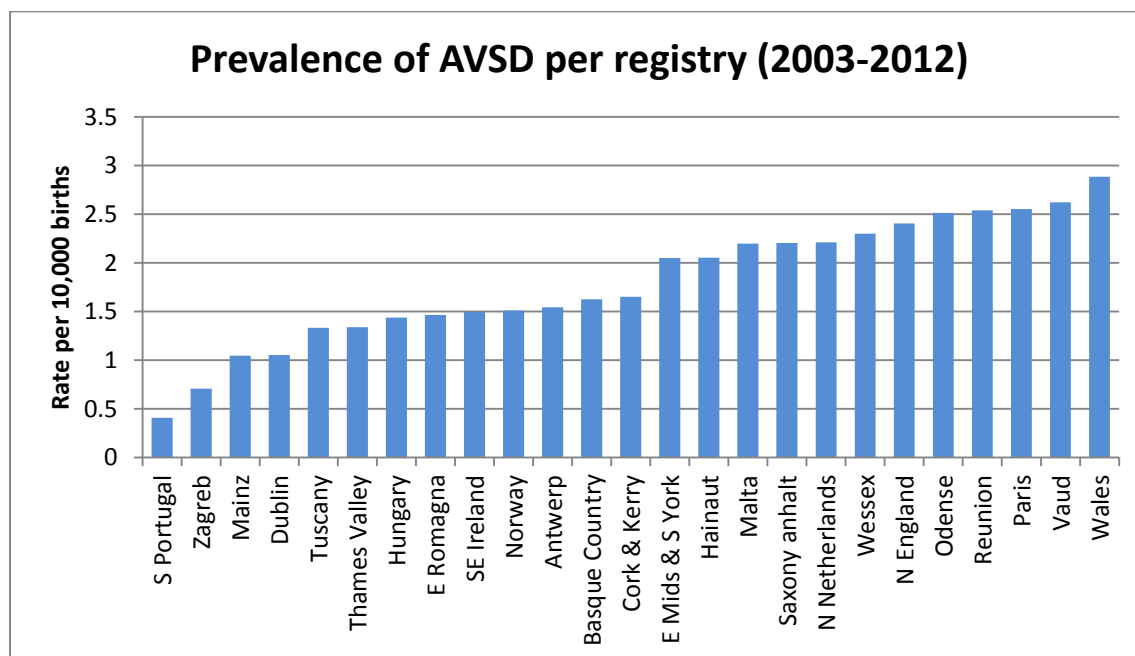


Figure 3: AVSD showing the increasing trend and that trend when the registries with a statistically significant rise in prevalence are excluded.

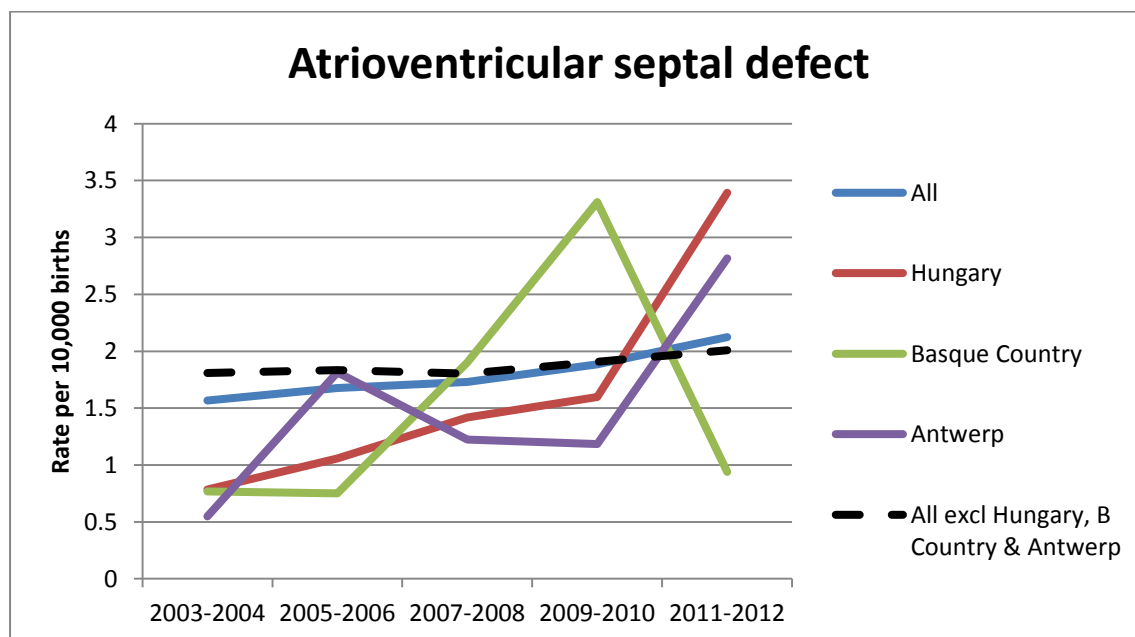


Figure 4: The prevalence of atrioventricular septal defect over the past three decades

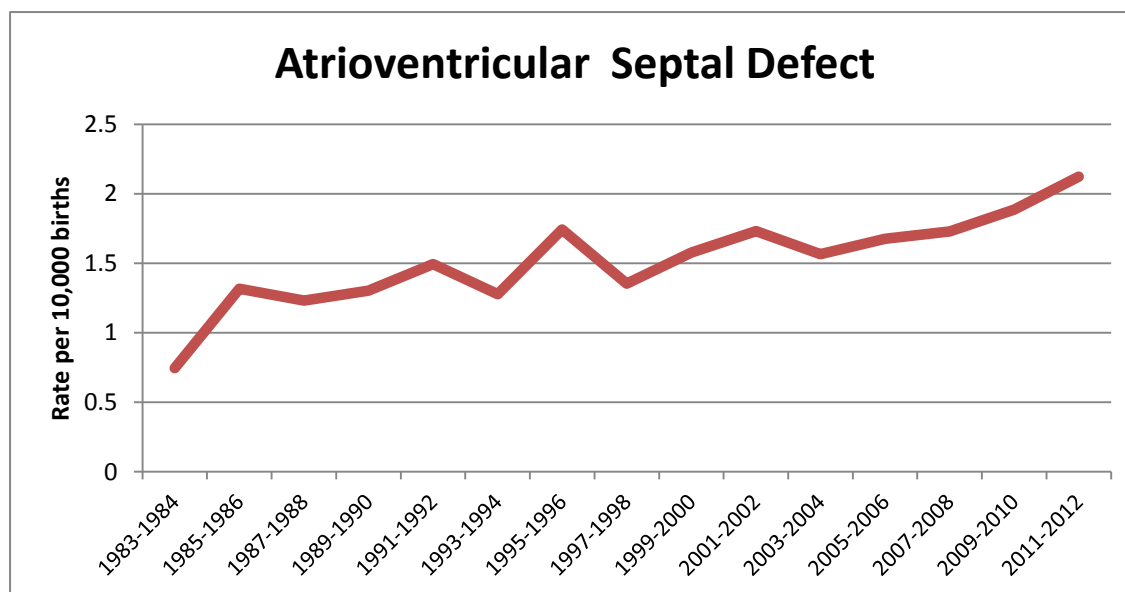


Figure 5: Prevalence of AVSD as an isolated cardiac and a potential multiple anomaly over time 2003-2012

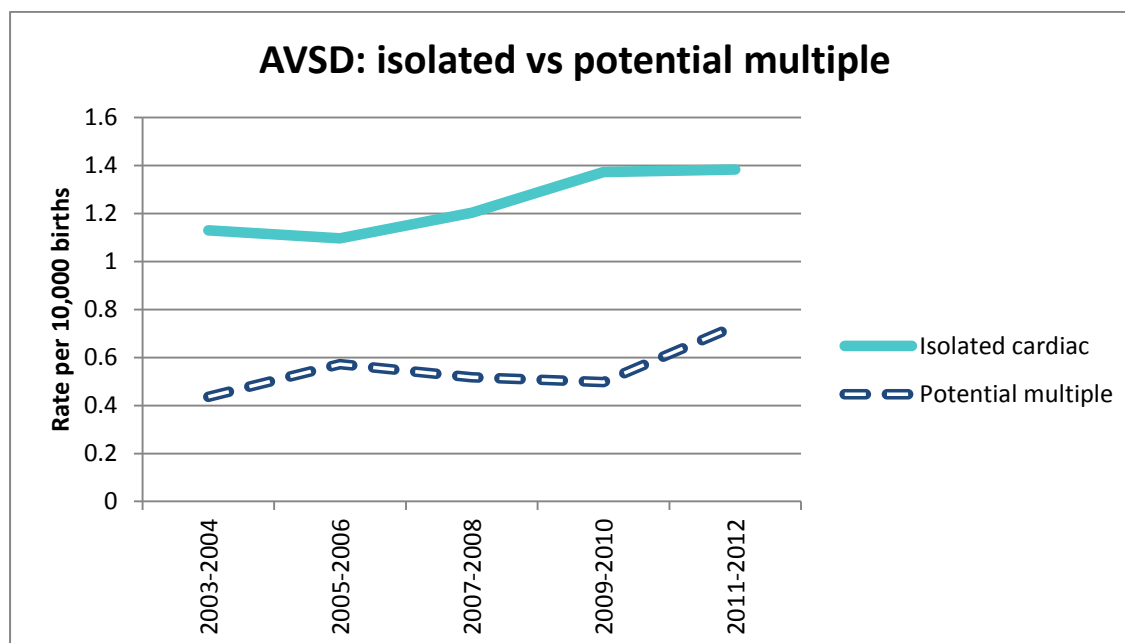


Figure 6: *Time of diagnosis*

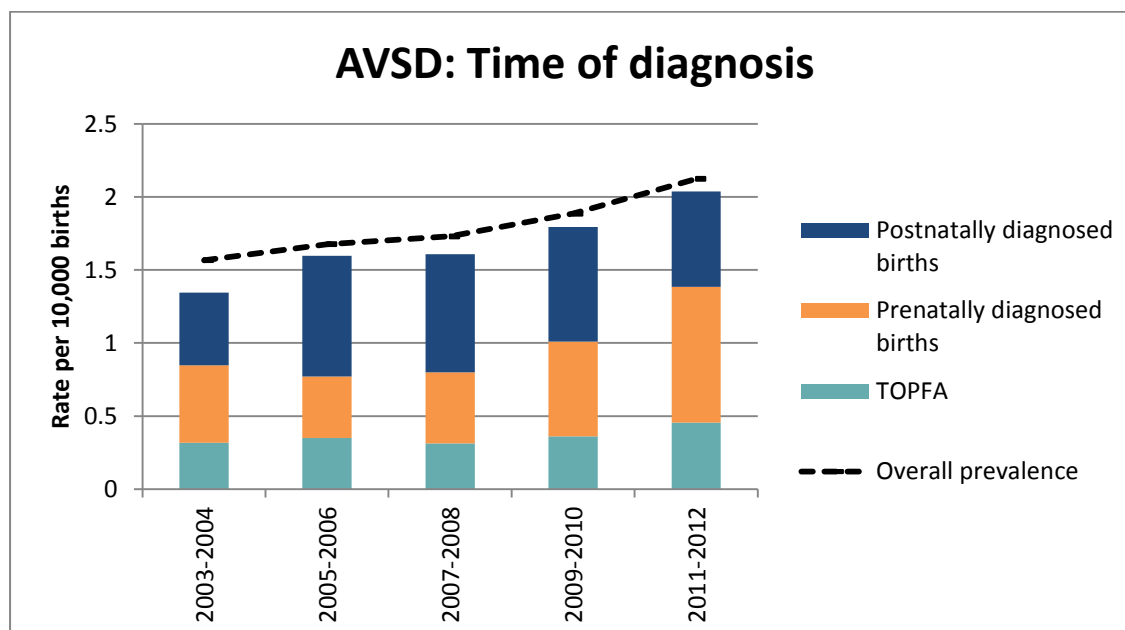


Table 1: *Breakdown of postnatally diagnosed births*

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	51 (87.9%)	80 (76.9%)	69 (65.1%)	76 (73.1%)	68 (89.5%)
>1 month	7 (12.1%)	11 (10.6%)	22 (20.8%)	21 (20.2%)	5 (6.6%)
postnatal, age n/k	0 (0.0%)	13 (12.5%)	15 (14.2%)	7 (6.7%)	3 (3.9%)

Conclusions

- Hungary, Basque Country and Antwerp have a significantly increasing trend. The prevalence rate in these 3 registries is comparable to the EUROCAT average (Figures 1 & 2) but when their prevalence is analysed over time period 2003-2012 we can see that all 3 registries started with a rate well below the EUROCAT average (Figure 3). When they are excluded the trend levels out a little.
Antwerp's initial investigation determines that this is a **real trend** and investigation is ongoing. Contributing factors may be maternal obesity and diabetes. Also more pregnancies in woman with a cardiac anomaly themselves.
- Examined over 30 years, there is a steadily increasing trend

- The prevalence of AVSD as an isolated cardiac anomaly is approximately double that of AVSD as a potential multiple anomaly
- The rate of TOPFA and the rate of prenatally diagnosed live births have both been increasing over the last decade, but the most rapid increase can be seen in the 2011-2012 time period

(1) EUROCAT. EUROCAT: Guide 1.3 and Reference Documents. 2013; Available at: <http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf>. Accessed 0704, 2014.

(2) Christensen N, Andersen H, Garne E, Wellesley D, Addor MC, Haeusler M, et al. Atrioventricular septal defects among infants in Europe: a population-based study of prevalence, associated anomalies, and survival. *Cardiol Young* 2013 Aug;23(4):560-567.

(3) Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* 2007 Jun 12;115(23):2995-3014.

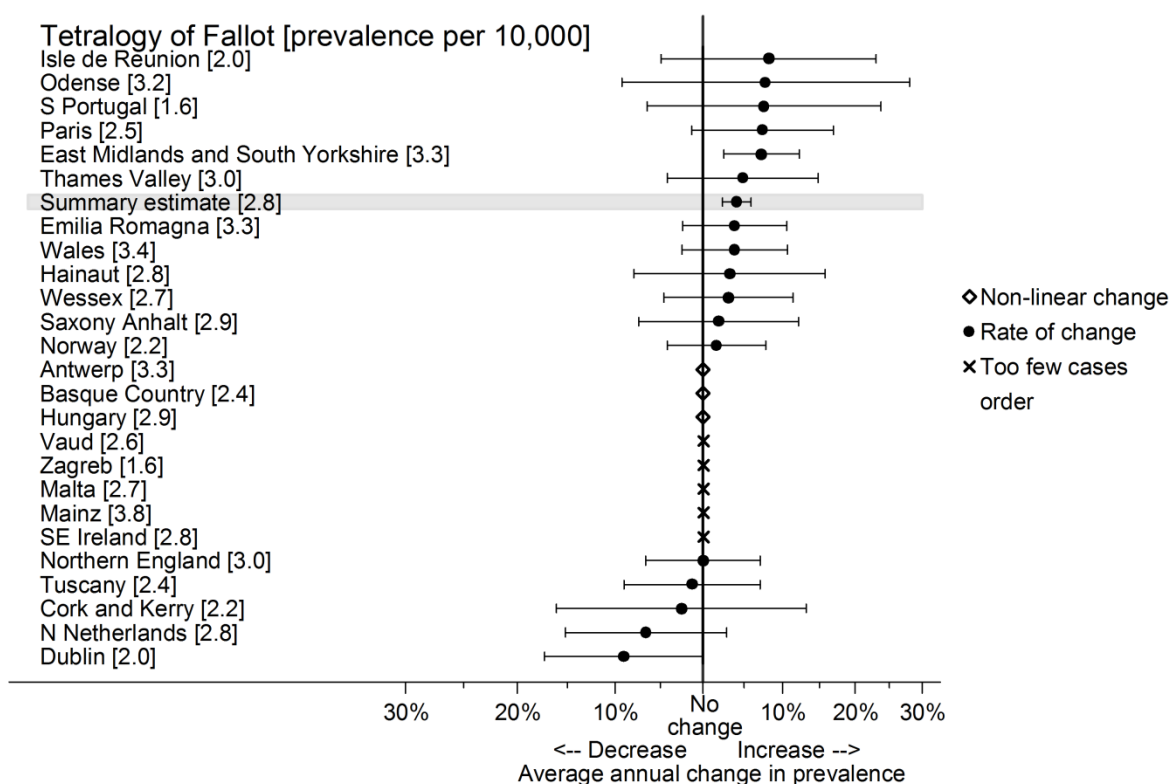
Trend Report

Tetralogy of Fallot (TOF)

This is a continuing increasing trend.

The registry which shows a statistically significant trend moving in the same direction and which therefore may be contributing is: East Midlands & South Yorkshire.

Figure 1. The trend in prevalence¹ of Tetralogy of Fallot for the 10 year period 2003-2012, showing individual registries and the pan European trend



Literature Review

TOF is a common cyanotic congenital heart defect often associated with extra cardiac malformations (1). It has been associated with both Genetic and chromosomal syndromes (2) and with maternal exposure to organic solvents in early pregnancy (3). It has also been associated with ART (4) and we are currently investigating signals of associations with SSRIs (5) and other medications

Consistency between registries

There were a total of 1755 tetralogy of Fallot cases included in the analysis over the ten year period. Prevalence ranged from 1.7¹ cases per 10,000 births in South Portugal to 3.8 cases per 10,000 births in Mainz.

Figure 2. Prevalence of Tetralogy of Fallot by registry for 10 year period 2003 to 2012

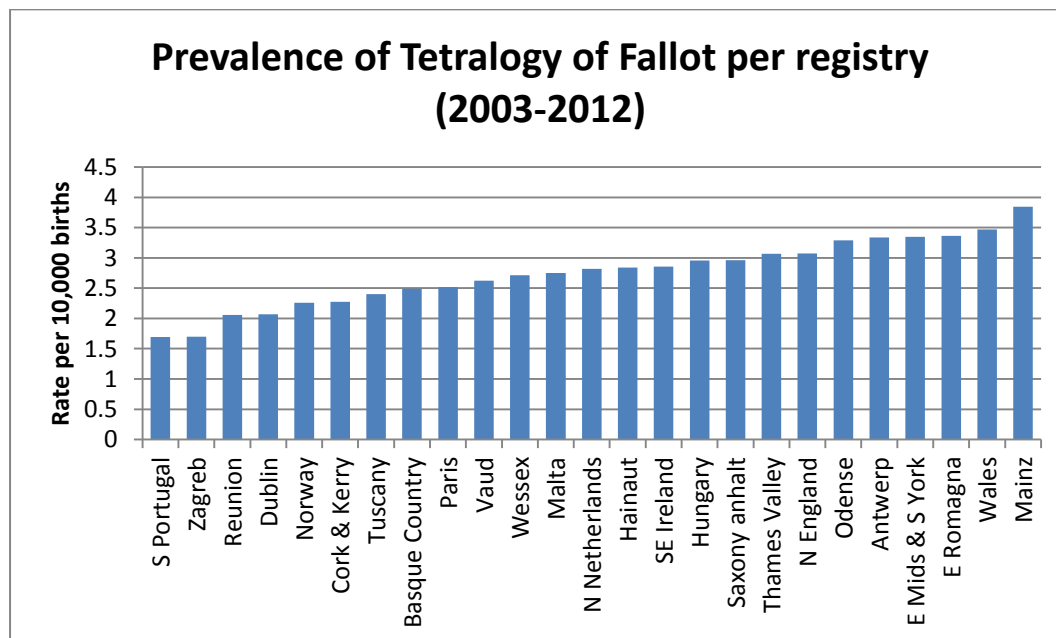


Figure 3: Tetralogy of Fallot showing the increasing trend and that trend when the registry with a statistically significant rise in prevalence is excluded.

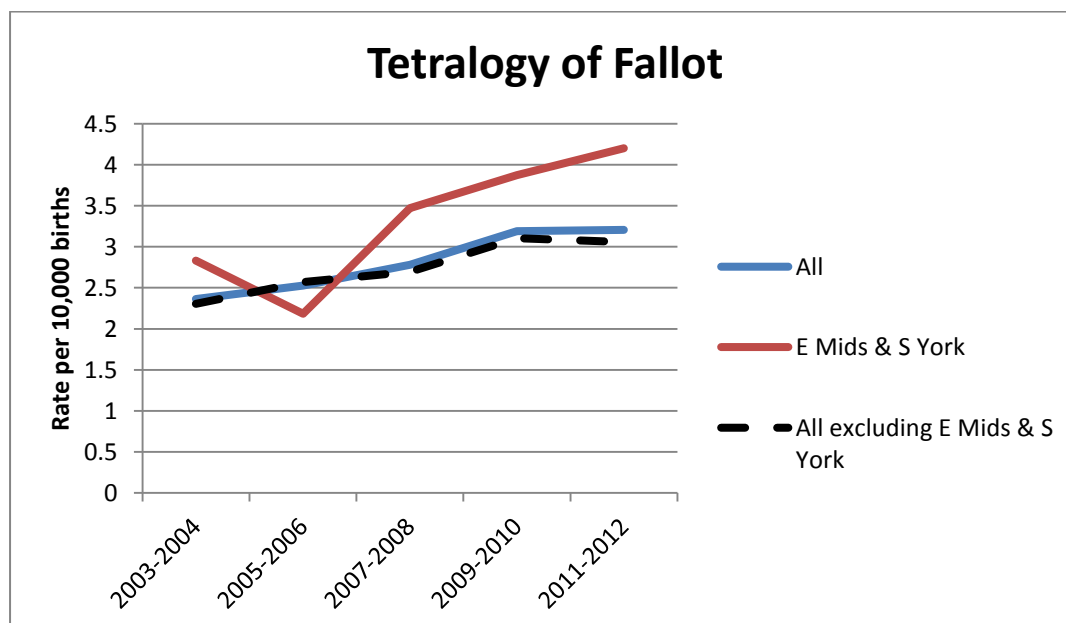


Figure 4: The prevalence of tetralogy of Fallot over the past three decades

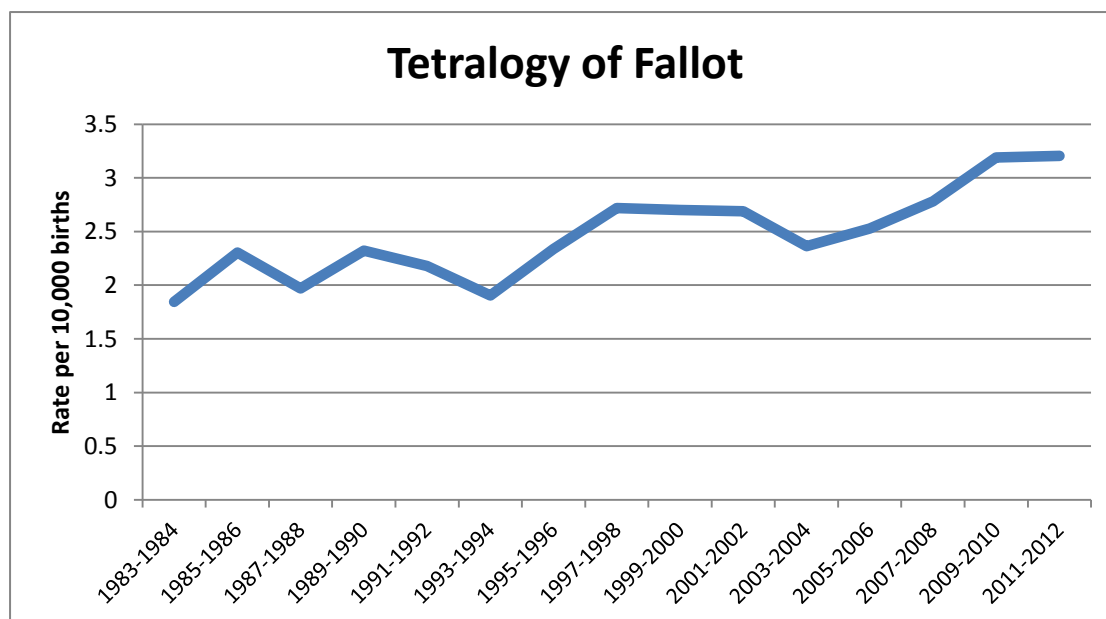


Figure 5: Prevalence of Tetralogy of Fallot as an isolated cardiac vs a potential multiple anomaly over time 2003-2012

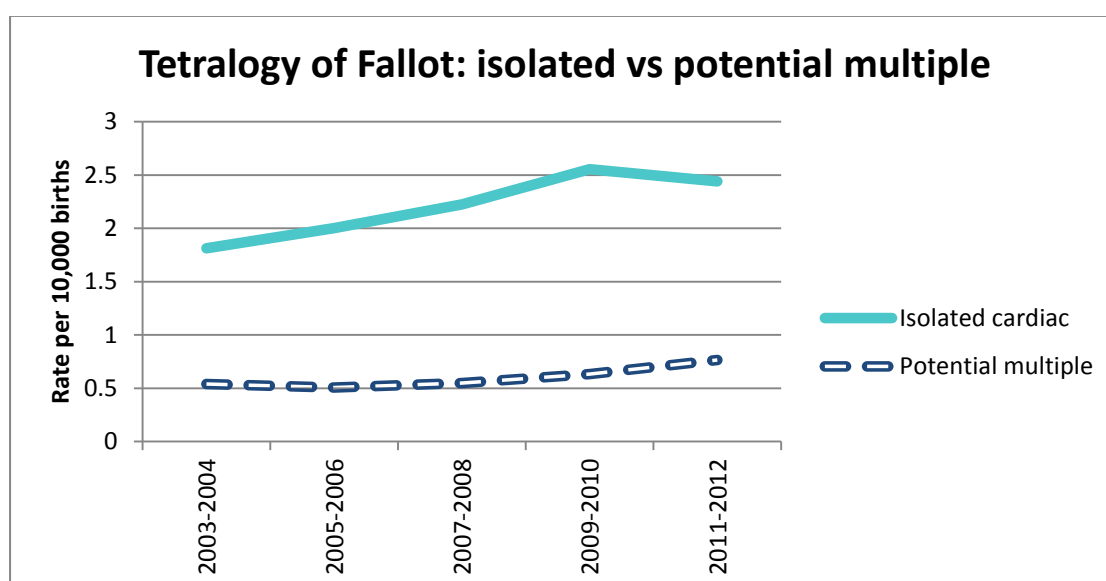


Figure 6: *Time of diagnosis*

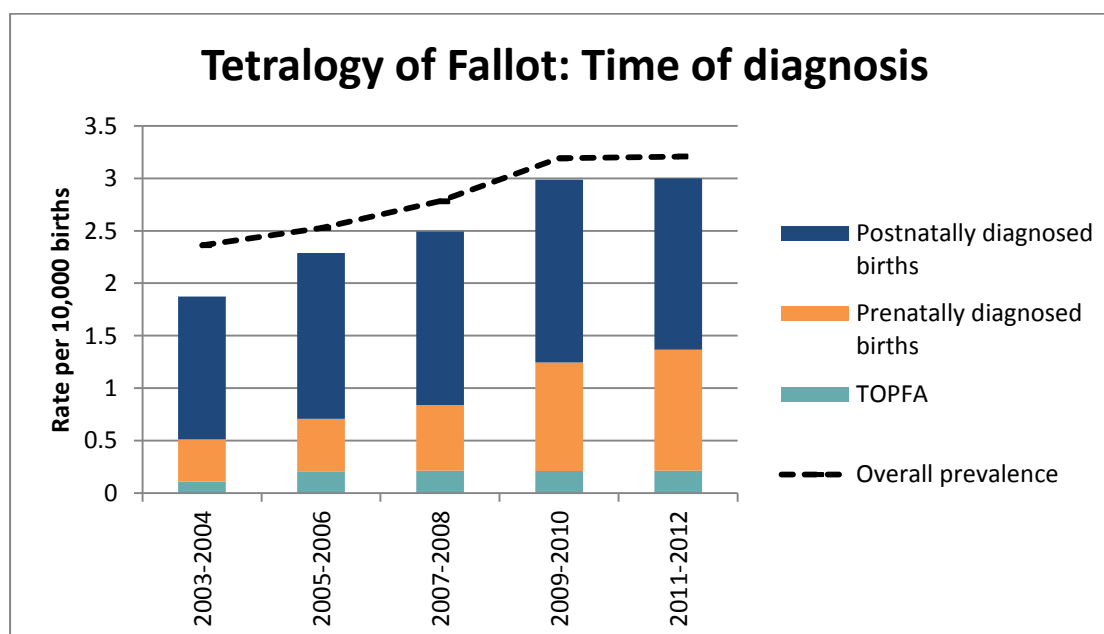


Table 1: *Breakdown of postnatally diagnosed births*

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	135 (84.9%)	165 (82.9%)	174 (80.2%)	179 (77.5%)	151 (79.5%)
>1 month	22 (13.8%)	10 (5.0%)	23 (10.6%)	25 (10.8%)	17 (8.9%)
postnatal, age n/k	2 (1.3%)	24 (12.1%)	20 (9.2%)	27 (11.7%)	22 (11.6%)

Conclusions

- Only E Midlands & S Yorkshire has a significantly increasing trend. When EMSY are excluded from the analysis, the prevalence is affected at the end of the time period
- When the figures are examined over a 30 year period, there is a definite increase from the mid 1990's onwards.
- There are more isolated cardiac cases compared to potential multiple cases. The isolated prevalence seems to be going down since 2009, whereas the multiple seems to be going up in the same period
- The rate of TOPFA has remained constant at approx. 0.2 per 10,000 births, whereas the prenatally diagnosed live births has increased from 0.4 to 1.52 per 10,000 and postnatal from 1.36 to 1.63

(1) Garne E, Nielsen G, Hansen OK, Emmertsen K. Tetralogy of Fallot. A population-based study of epidemiology, associated malformations and survival in western Denmark 1984-1992. Scandinavian Cardiovascular Journal 1999;33(1):45-48.

(2) Villafane J. Feinstein JA. Jenkins KJ. Vincent RN. Walsh EP. Dubin AM. Geva T. Towbin JA. Cohen MS. Fraser C. Dearani J. Rosenthal D. Kaufman B. Graham TP Jr. Adult Congenital and Pediatric Cardiology Section, American College of Cardiology. Hot topics in tetralogy of Fallot. J Am Coll Cardiol 2013 Dec 10;62(23):2155-2166.

(3) Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation 2007 Jun 12;115(23):2995-3014.

(4) Tararbit K, Lelong N, Thieulin AC, Houyel L, Bonnet D, Goffinet F, et al. The risk for four specific congenital heart defects associated with assisted reproductive techniques: a population-based evaluation. Human Reproduction 2013 Feb;28(2):367-374.

(5) A. Wemakor. Antidepressant Use in Pregnancy: Risks and Prevalence University of Ulster; 2013.

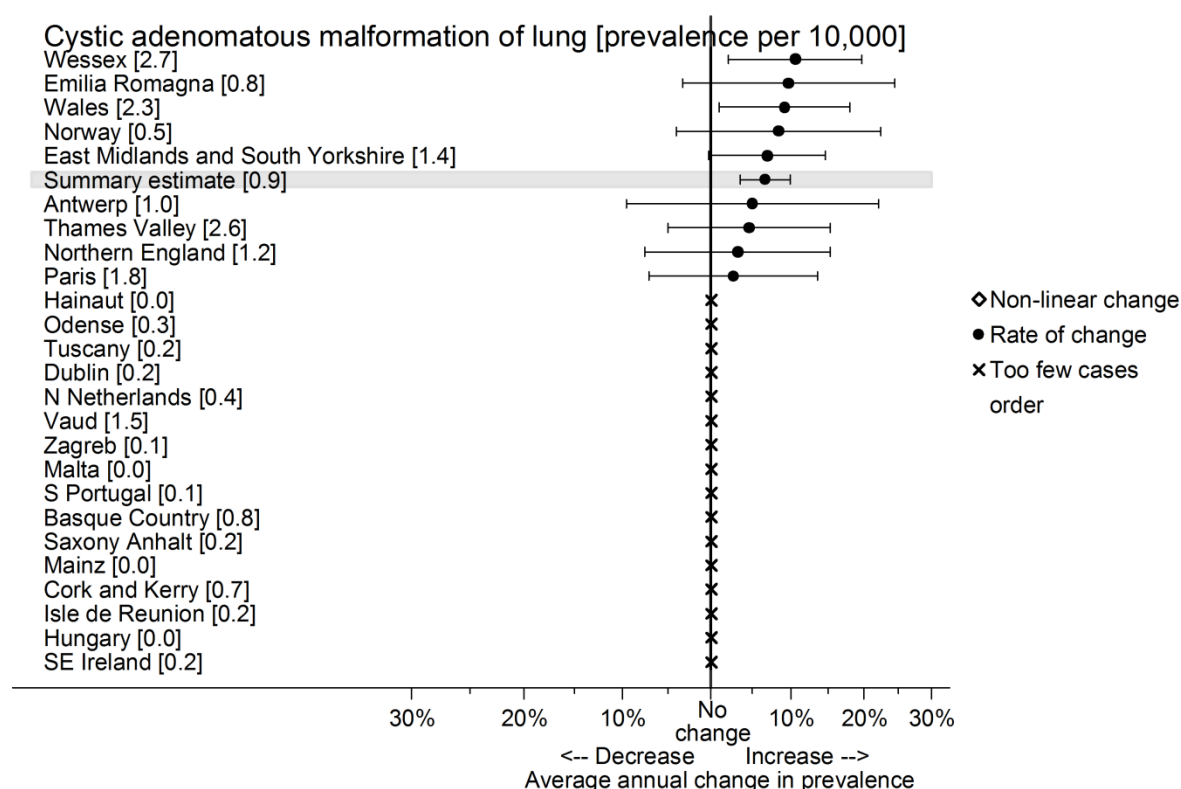
Trend Report

Cystic adenomatous malformation of lung

This is a continuing increasing trend.

The registries which show a statistically significant trend moving in the same direction and which therefore may be contributing are: Wessex and Wales.

Figure 1. The trend in prevalence¹ of cystic adenomatous malformation of lung for the 10 year period 2003-2012, showing individual registries and the pan European trend



Literature Review

There is a dearth of literature about this congenital anomaly

Consistency between registries

There were a total of 585 cystic adenomatous malformation of lung cases included in the analysis over the ten year period. Prevalence ranged from 0.0¹ cases per 10,000 births in Malta, Hungary and Mainz to 2.7 cases per 10,000 births in Wessex.

Figure 2. Prevalence of cystic adenomatous malformation of lung by registry for 10 year period 2003 to 2012

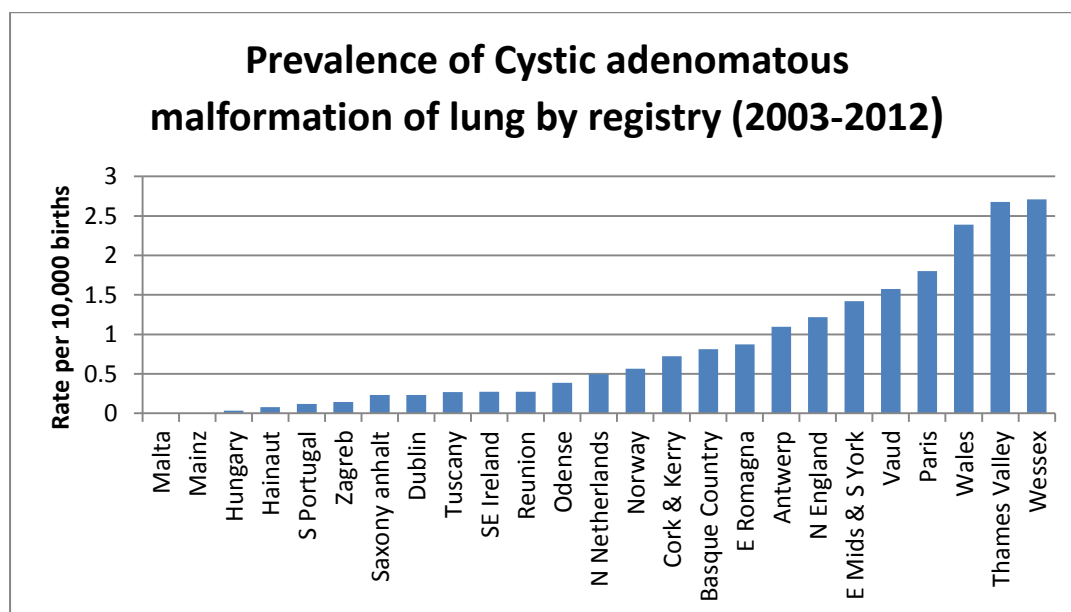


Figure 3: Cystic adenomatous malformation of lung showing the increasing trend and that trend when the registries with a statistically significant rise in prevalence are excluded.

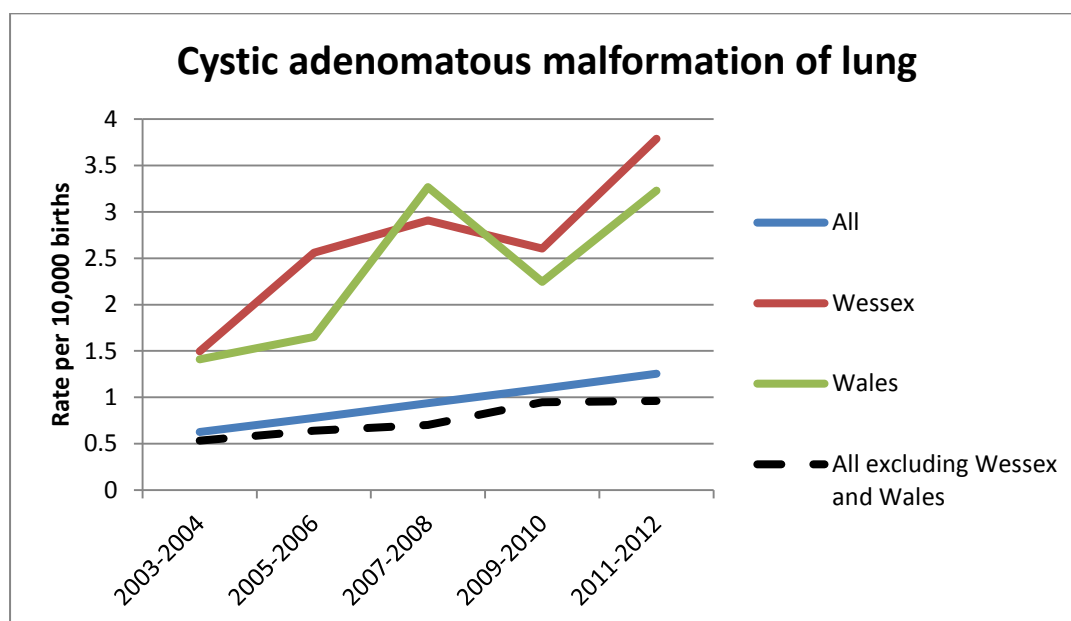


Figure 4: The prevalence of cystic adenomatous malformation of lung since the introduction of ICD10 coding for CCAM

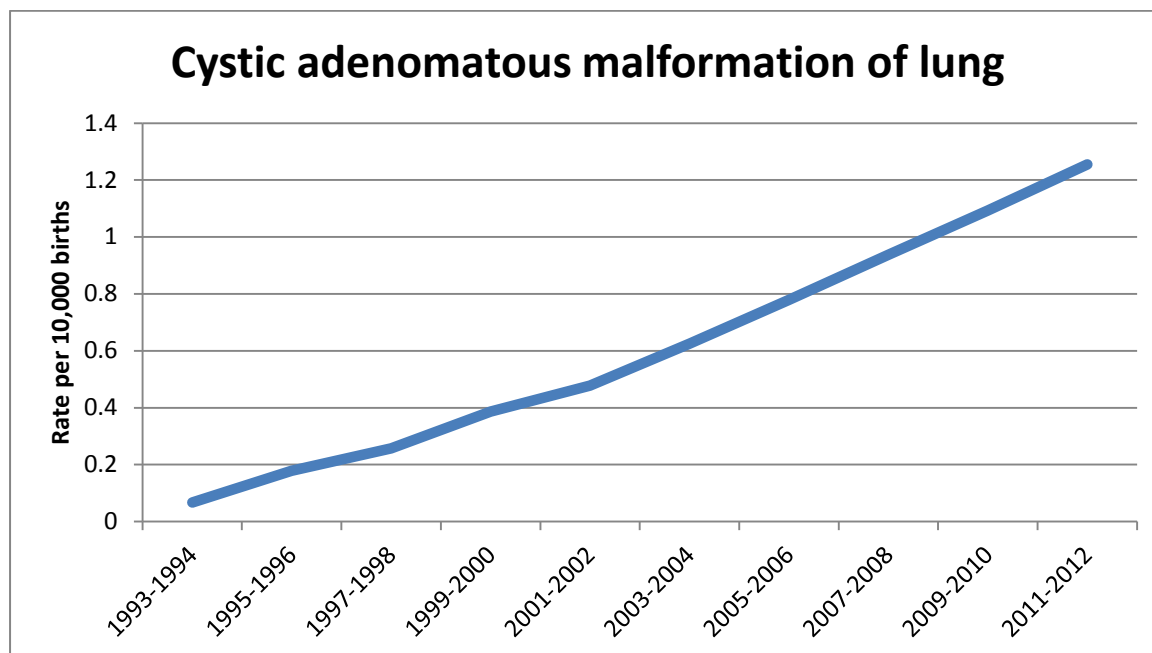


Figure 5: Prevalence of cystic adenomatous malformation as an isolated vs a potential multiple over time 2003-2012

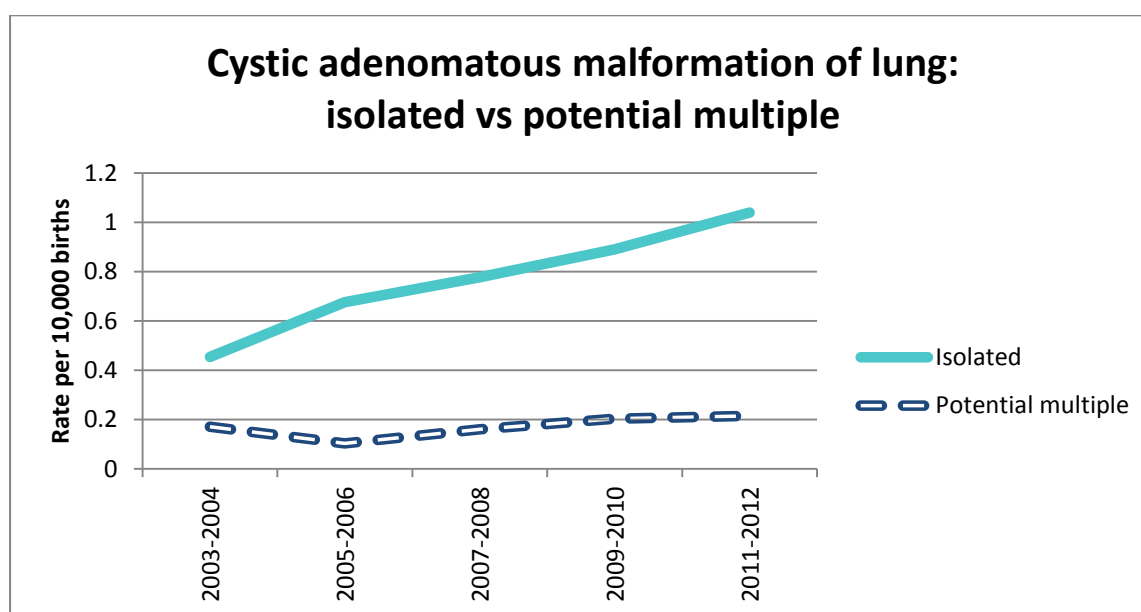


Figure 6: *Time of diagnosis*

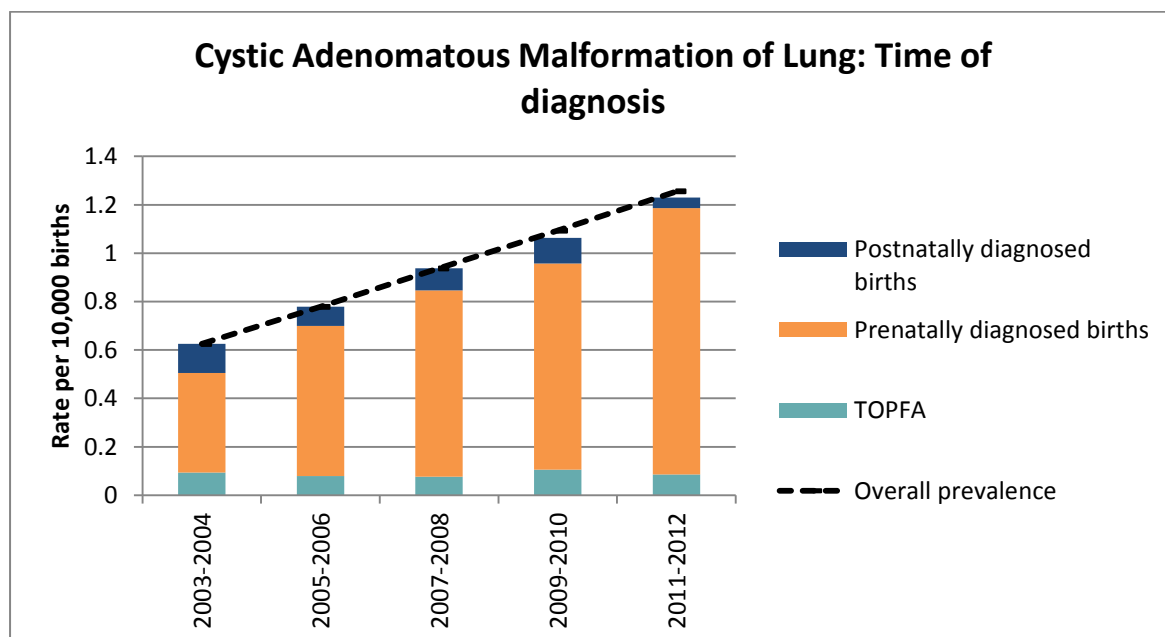


Table 1: *Breakdown of postnatally diagnosed births*

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	11 (78.6%)	4 (40.0%)	10 (83.3%)	12 (85.7%)	3 (60.0%)
>1 month	2 (14.3%)	4 (40.0%)	1 (8.3%)	1 (7.1%)	1 (20.0%)
postnatal, age n/k	1 (7.1%)	2 (20.0%)	1 (8.3%)	1 (7.1%)	1 (20.0%)

Conclusions

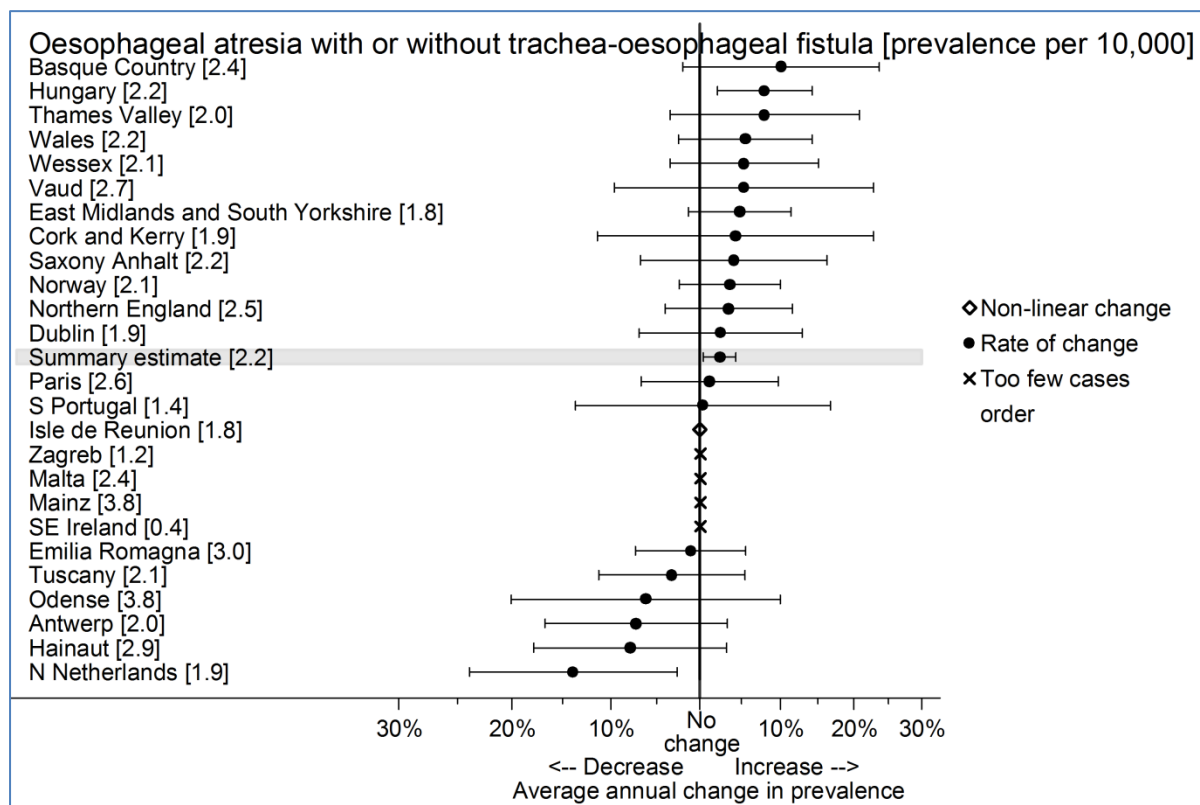
- When looked at over the 20 year period 1993-2012 (1993 being the introduction of ICD10 coding for CCAM), the trend is very clearly upward (Figure 4)
- The trend is more pronounced in isolated cases of CCAM (Figure 5)
- The rate of prenatal diagnosis has increased greatly over the past decade whilst the rate of TOPFA remains low, as Figure 6 demonstrates

Oesophageal atresia with or without trachea-oesophageal fistula (OA)

This is a **new** increasing trend

The registry which shows a statistically significant trend moving in the same direction and which may therefore be contributing is: **Hungary**

Figure 1. The trend in prevalence of OA for the 10 years from 2003-2012, showing individual registries and the pan European trend



Literature review

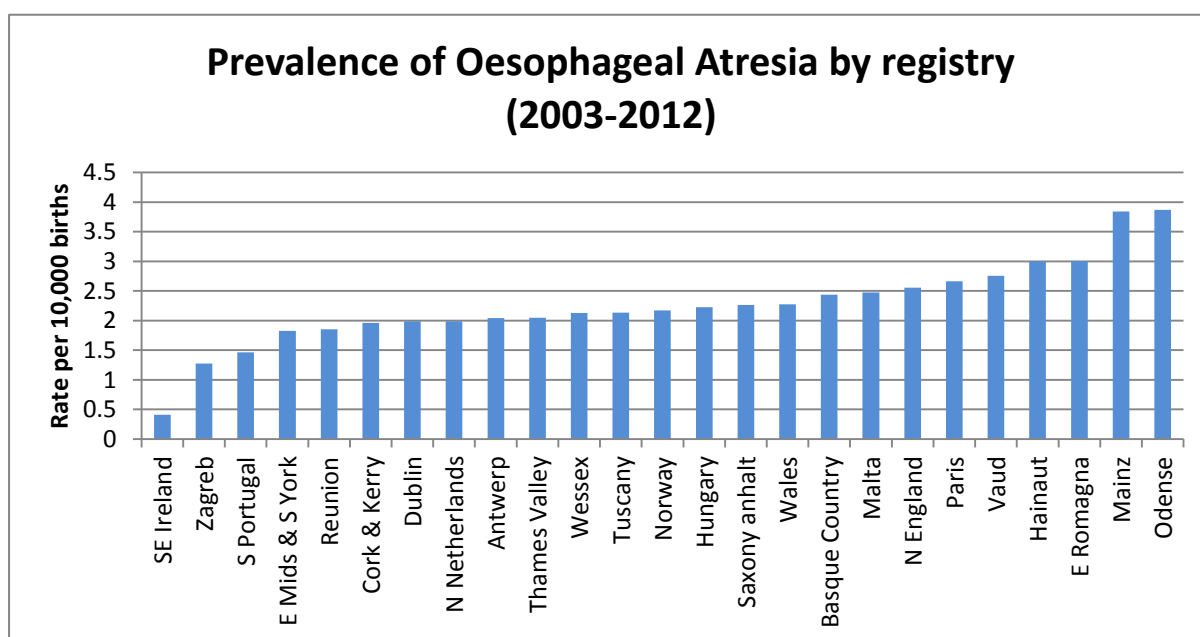
OA is the most common anomaly of the oesophagus, and is characterised by a complete discontinuity of the oesophagus, with or without an abnormal connection between the oesophagus and the trachea: Oesophageal stenosis is rare⁽¹⁾. This is a congenital anomaly which requires early intervention as the baby is unable to feed; and even if not offered a feed will have difficulty managing his or her saliva. There is a high risk of aspiration, even where there is no fistula to the trachea and surgery is required in the neonatal period. According to the literature more than 60% of OA cases have other congenital anomalies⁽¹⁾, usually forming a part of the VACTERL association⁽²⁾.

OA has been associated with twinning⁽³⁻⁵⁾ and has been associated with ART⁽⁶⁾

Consistency between registries

There were 1376 cases of OA registered over the 10 year period in the 25 registries included in the Pan-Europe trend monitoring. Prevalence ranged from 0.4 per 10,000 births in SE Ireland to 3.8¹ per 10,000 births in Odense.

Figure 2: Prevalence of Oesophageal Atresia by registry, 2003-2012



Trend over time

Figure 3: Oesophageal Atresia, showing the increasing trend for all registries and also the trend when the registry with a statistically significant rise in prevalence (Hungary) is excluded

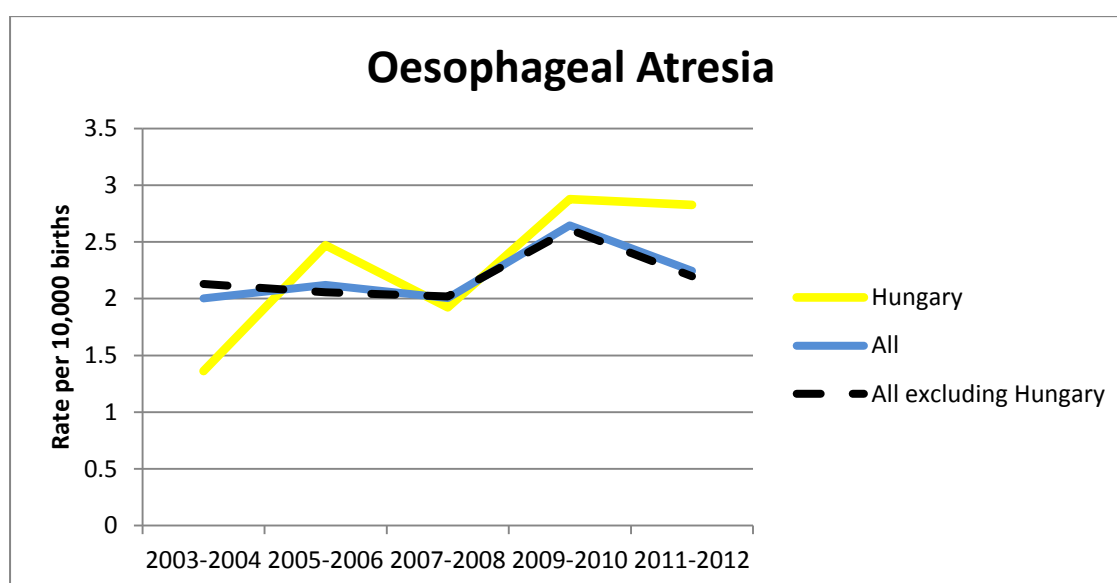


Figure 4: The prevalence of oesophageal atresia over the past three decades

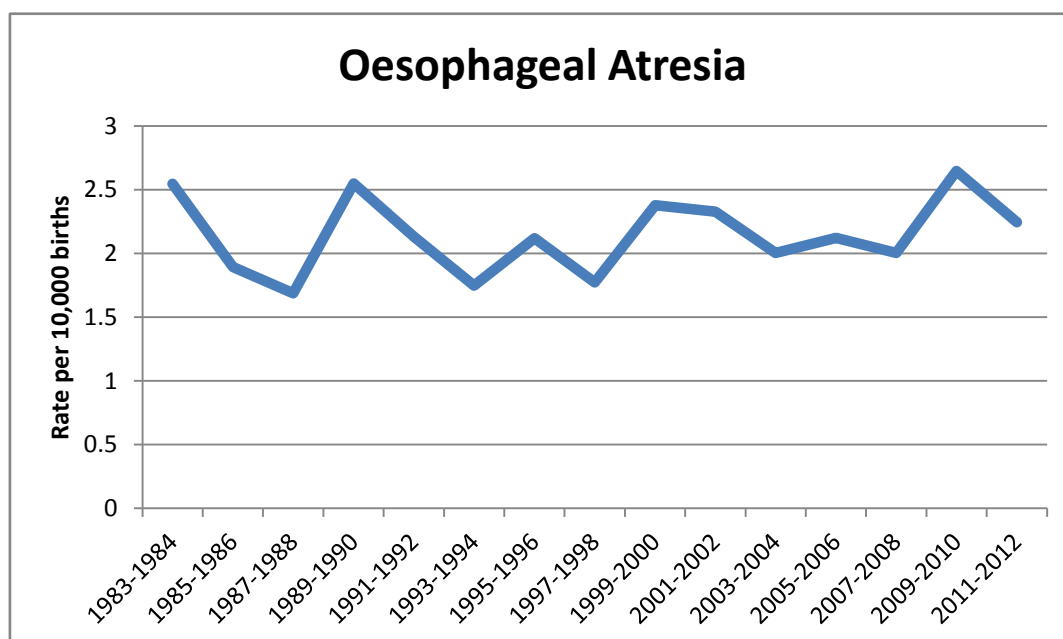


Figure 5: Prevalence of Oesophageal Atresia as an isolated and a non-isolated anomaly over time 2003-2012

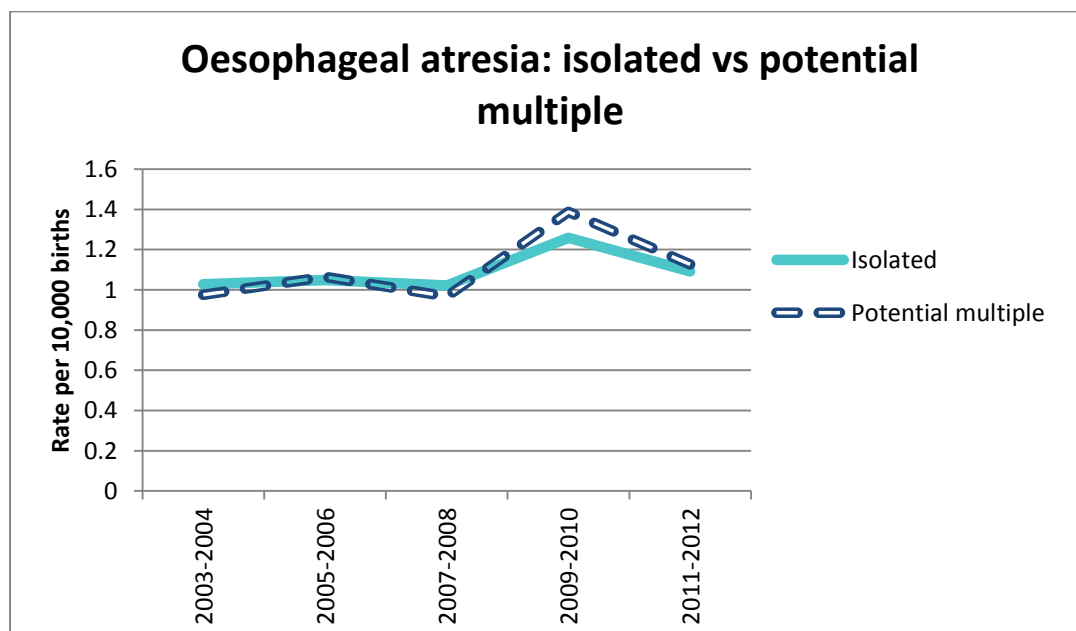


Figure 6: *Time of diagnosis*

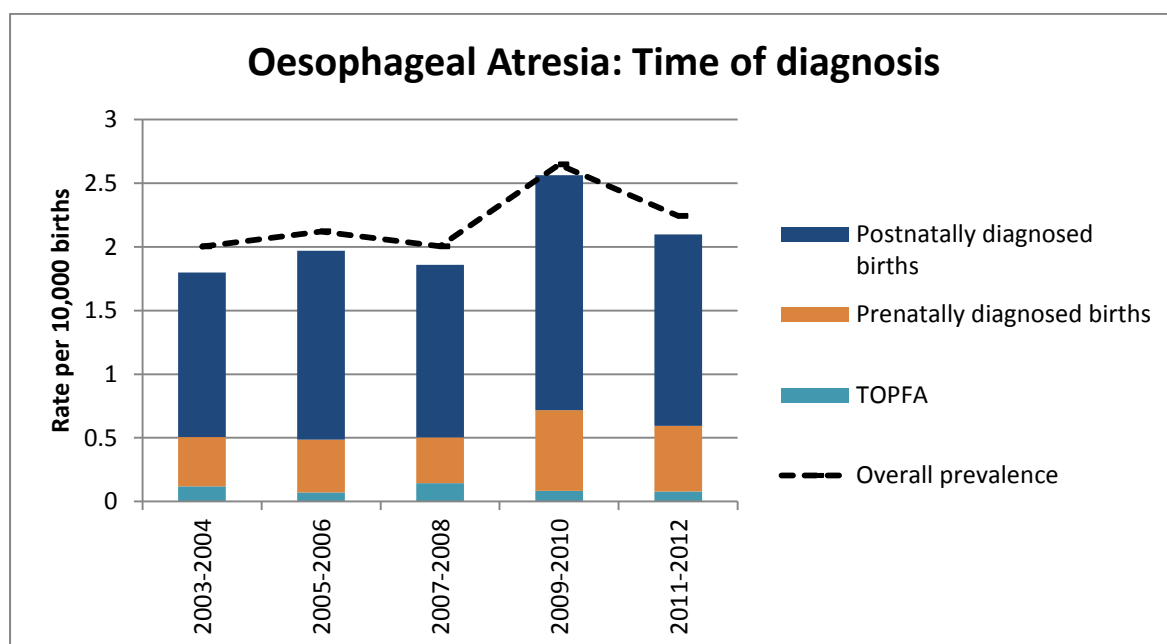


Table 1: *Breakdown of postnatally diagnosed births*

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	145 (96.0%)	168 (89.8%)	163 (91.6%)	230 (93.9%)	156 (89.1%)
>1 month	4 (2.6%)	6 (3.2%)	2 (1.1%)	2 (0.8%)	3 (1.7%)
postnatal, age n/k	2 (1.3%)	13 (7.0%)	13 (7.3%)	13 (5.3%)	16 (9.1%)

Figure 7: Prevalence amongst singleton and multiple births

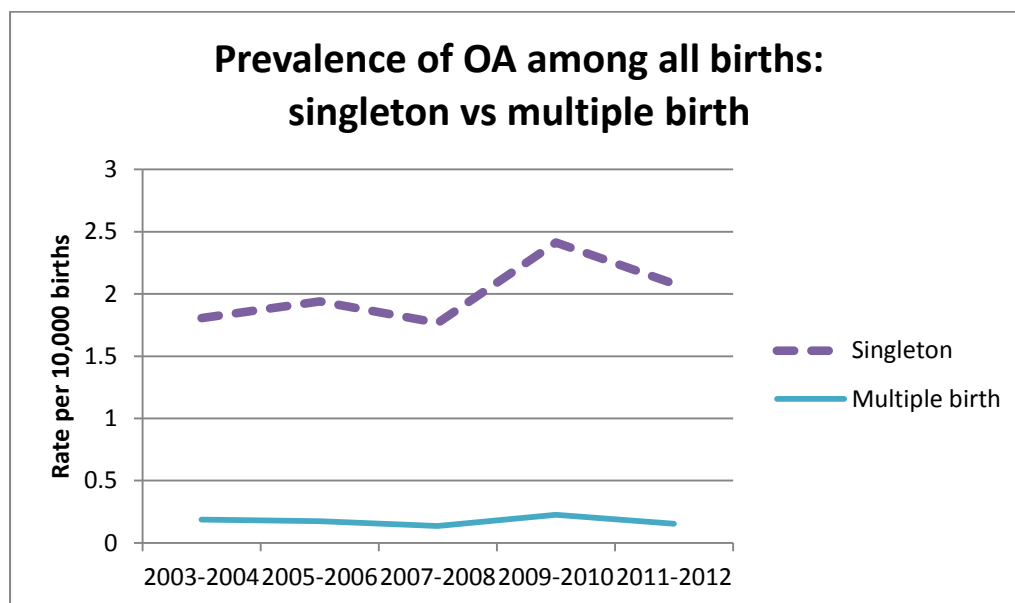
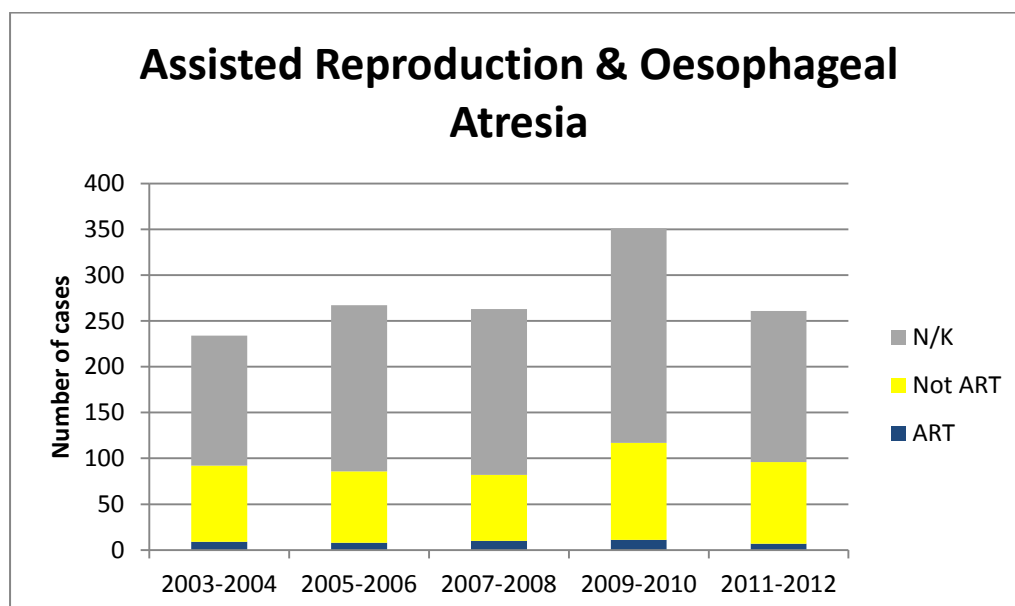


Figure 8: Number of cases with assisted reproduction



Conclusions:

- Hungary is the only registry with a *significantly* increasing trend, however prevalence in Hungary was lower than the EUROCAT average to begin with. There are 11 other registries above the summary estimate with trends moving in the same direction

- When Hungary is excluded from the analysis, the prevalence rate is not overly affected. Figure 3 shows that the prevalence is the same.
- There is an increase in both isolated and multiply malformed cases
- The majority of cases are diagnosed postnatally within the first month of life
- Rates for prenatally diagnosed and postnatally diagnosed are both going up
- The increase is in singletons and therefore not explained by the rise in multiple births in the background population
- The level of recording within EUROCAT for variable Assisted Reproduction (ART), is insufficient to draw any conclusions

(1) Nassar N, Leoncini E, Amar E, Arteaga-Vazquez J, Bakker MK, Bower C, et al. Prevalence of esophageal atresia among 18 international birth defects surveillance programs. Birth Defects Research 2012 Nov;94(11):893-899.

(2) Martinez-Frias ML, Frias JL. VACTERL as primary, polytopic developmental field defects. Am J Med Genet 1999 Mar 5;83(1):13-16.

(3) Doyle PE, Beral V, Botting B, Wale CJ. Congenital malformations in twins in England and Wales. Journal of Epidemiology & Community Health 1991 Mar;45(1):43-48.

(4) Mastroiacovo P, Castilla EE, Arpino C, Botting B, Cocchi G, Goujard J, et al. Congenital malformations in twins: an international study. Am J Med Genet 1999 Mar 12;83(2):117-124.

(5) Kallen B. Congenital malformations in twins: a population study. Acta Genet Med Gemellol 1986;35(3-4):167-178.

(6) Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Otterblad PO. Congenital malformations in infants born after in vitro fertilization in Sweden. Birth Defects Research 2010 Mar;88(3):137-143.

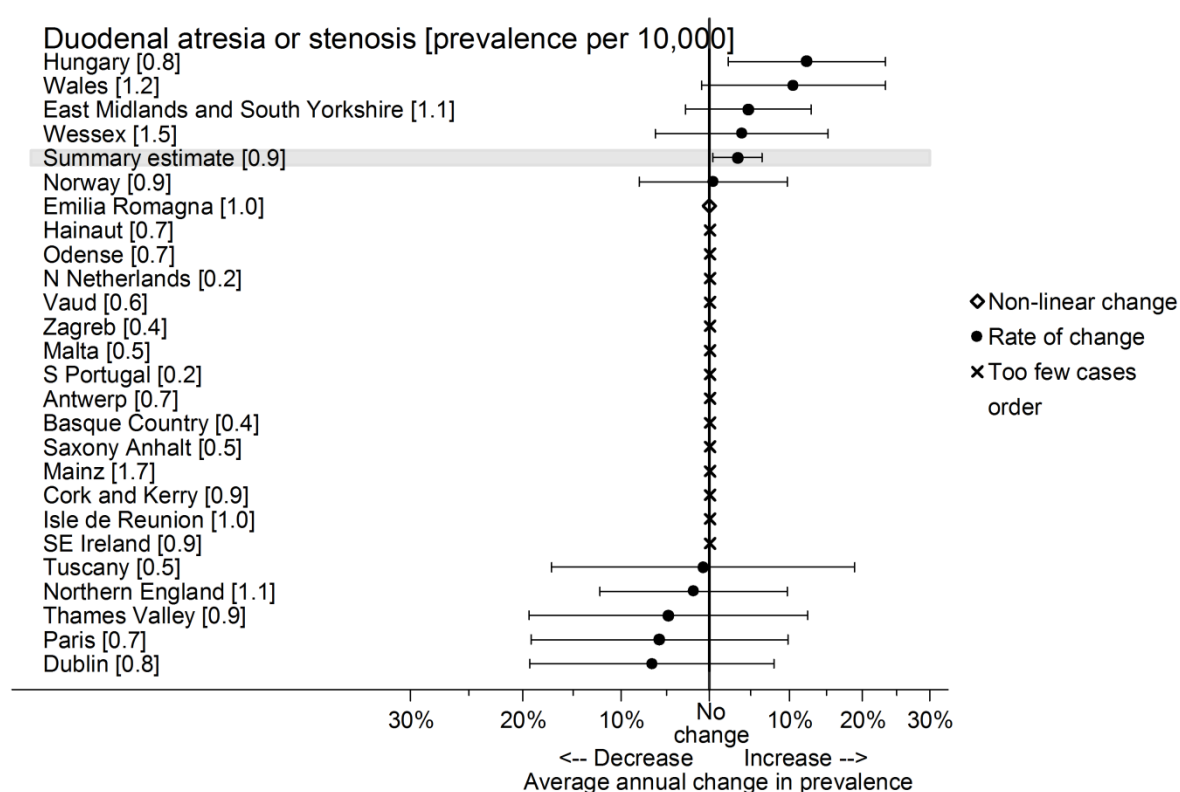
Trend Report

Duodenal Atresia or Stenosis

This is a continuing increasing trend.

The registry which shows a statistically significant trend moving in the same direction and which therefore may be contributing is Hungary.

Figure 1. The trend in prevalence¹ of duodenal atresia or stenosis for the 10 year period 2003-2012, showing individual registries and the pan European trend



Literature Review

Duodenal atresia is considered different aetiology than other atresias of the small bowel {{919 Barnard,C.N. 1957}}, but the anomalies are often studied together, with duodenal atresia in particular being very strongly associated with chromosomal anomalies {{918 Best,K.E. 2012}}. Duodenal atresia is not strongly associated with the VACTERL association {{197 Botto,L.D. 1997}}, but it is often associated with cardiac defects.

Consistency between registries

There were a total of 567 duodenal atresia or stenosis cases included in the analysis over the ten year period. Prevalence ranged from 0.3¹ cases per 10,000 births in Northern Netherlands to 1.7 cases per 10,000 births in Mainz.

Figure 2. Prevalence of duodenal atresia or stenosis by registry for 10 year period 2003 to 2012

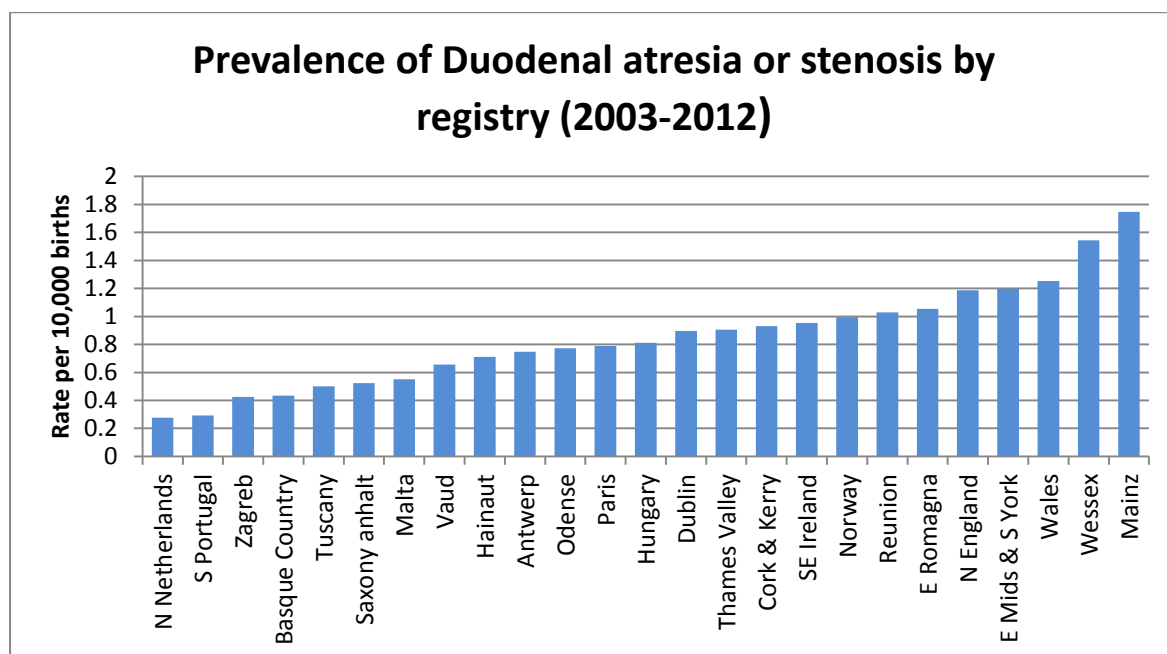


Figure 3: Duodenal atresia showing the increasing trend and that trend when the registry with a statistically significant rise in prevalence is excluded.

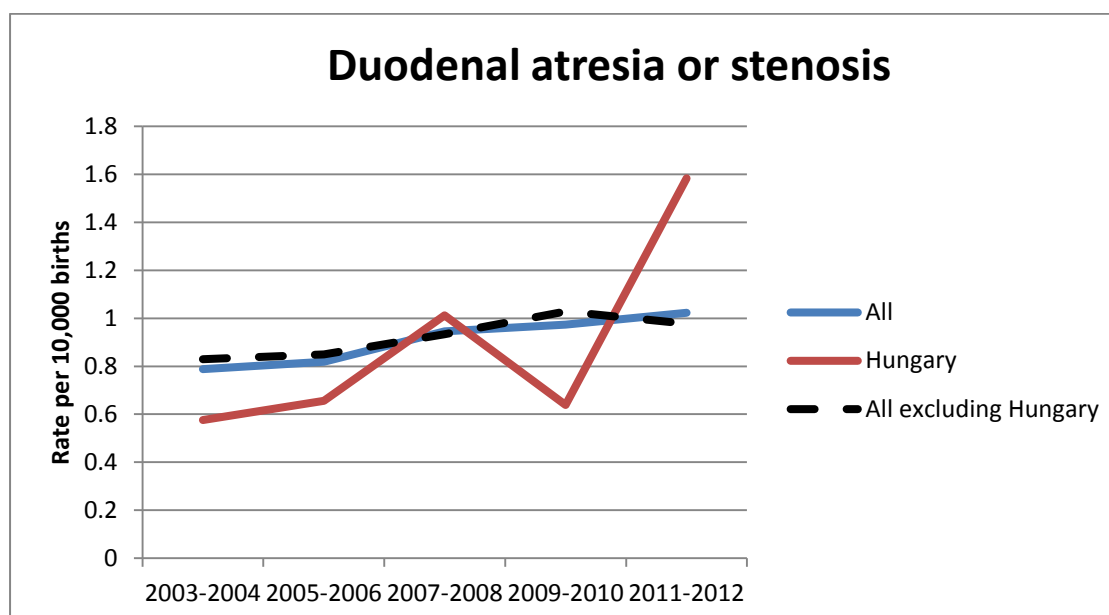


Figure 4: The prevalence of duodenal atresia or stenosis over the past three decades

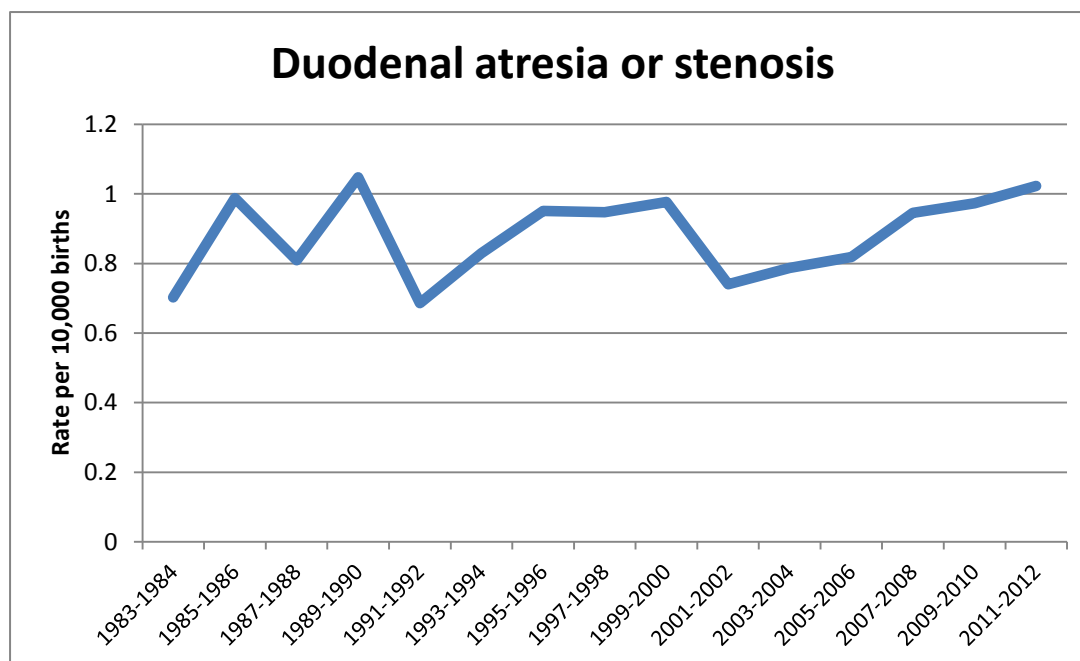


Figure 5: Prevalence of duodenal atresia or stenosis as an isolated vs a potential multiple anomaly over time 2003-2012

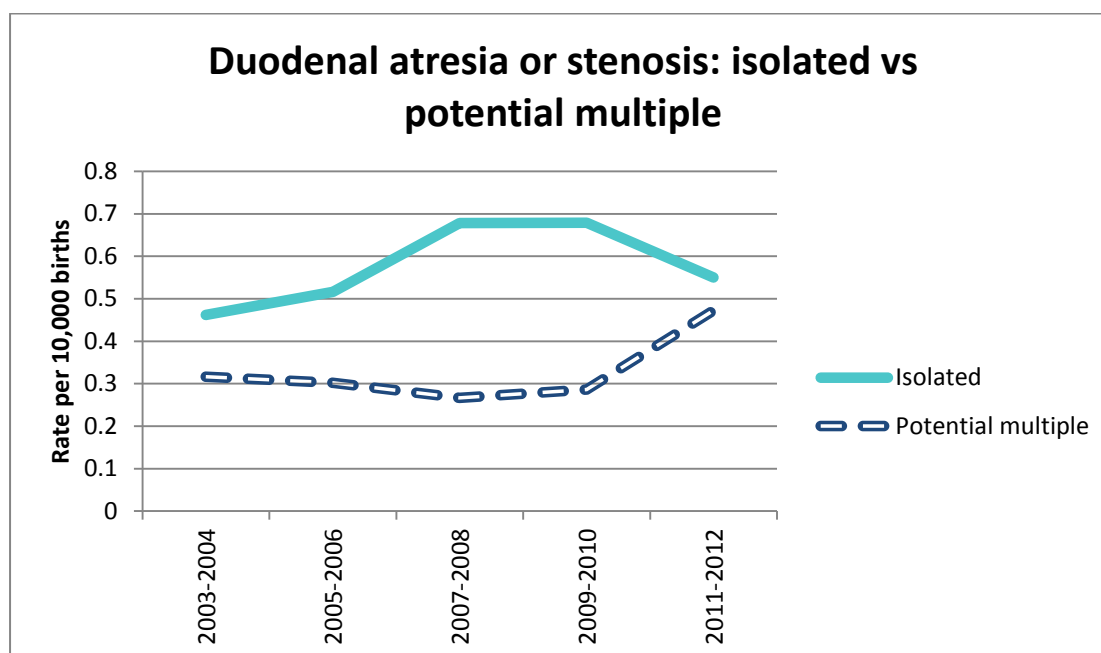


Figure 6: Time of diagnosis

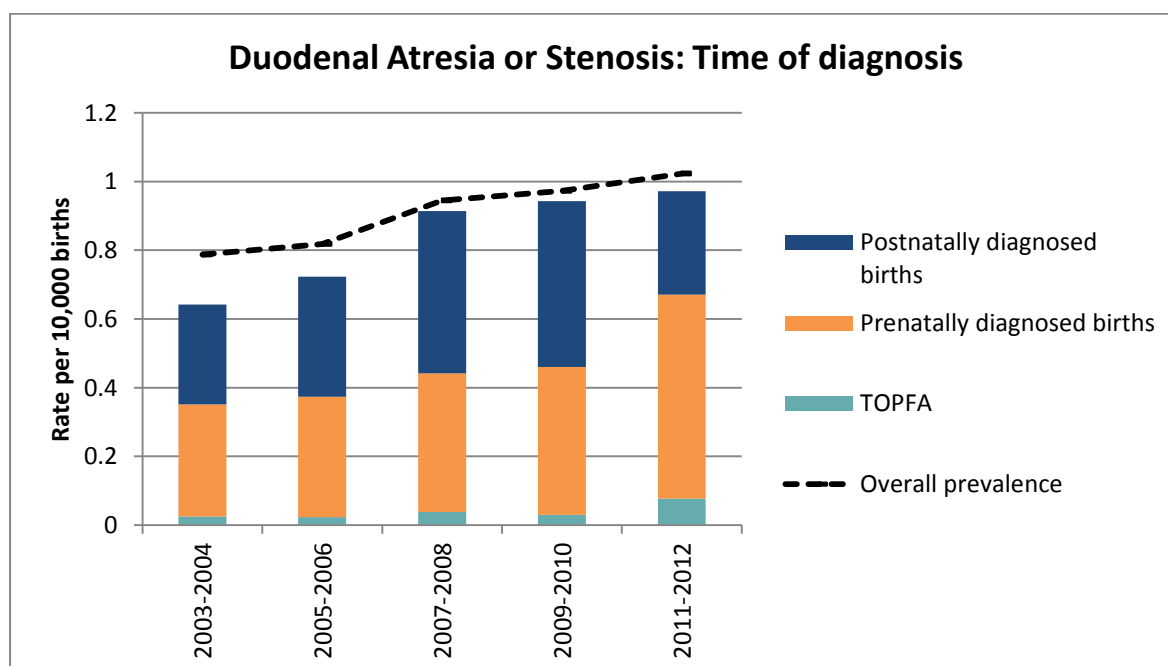


Table 1: Breakdown of postnatally diagnosed births

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	32 (94.1%)	41 (93.2%)	51 (82.3%)	59 (92.2%)	32 (91.4%)
>1 month	2 (5.9%)	1 (2.3%)	6 (9.7%)	3 (4.7%)	2 (5.7%)
postnatal, age n/k	0 (0.0%)	2 (4.5%)	5 (8.1%)	2 (3.1%)	1 (2.9%)

Conclusions

- The prevalence of duodenal atresia or stenosis is low. As figure 1 demonstrates 14 registries have too few cases to analyse
- When analysed over a longer period (30 years) the upward trend is less convincing
- In the more recent time period, 2009 onwards, whatever is causing the trend seems to be causing an increase of multiply malformed cases rather than isolated cases (Figure 5). Whereas in the 2003-2008 period the opposite appeared true.
- Generally the TOPFA rate has remained constant, whilst both prenatally diagnosed births and postnatally diagnosed births have been increasing. But in the 2011-2012 period, the TOPFA rate jumped as did the prenatally diagnosed births but the prevalence of postnatally diagnosed births fell.

(1) EUROCAT. EUROCAT: Guide 1.3 and Reference Documents. 2013; Available at: <http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf>. Accessed 0704, 2014.

(2) Christensen N, Andersen H, Garne E, Wellesley D, Addor MC, Haeusler M, et al. Atrioventricular septal defects among infants in Europe: a population-based study of prevalence, associated anomalies, and survival. Cardiol Young 2013 Aug;23(4):560-567.

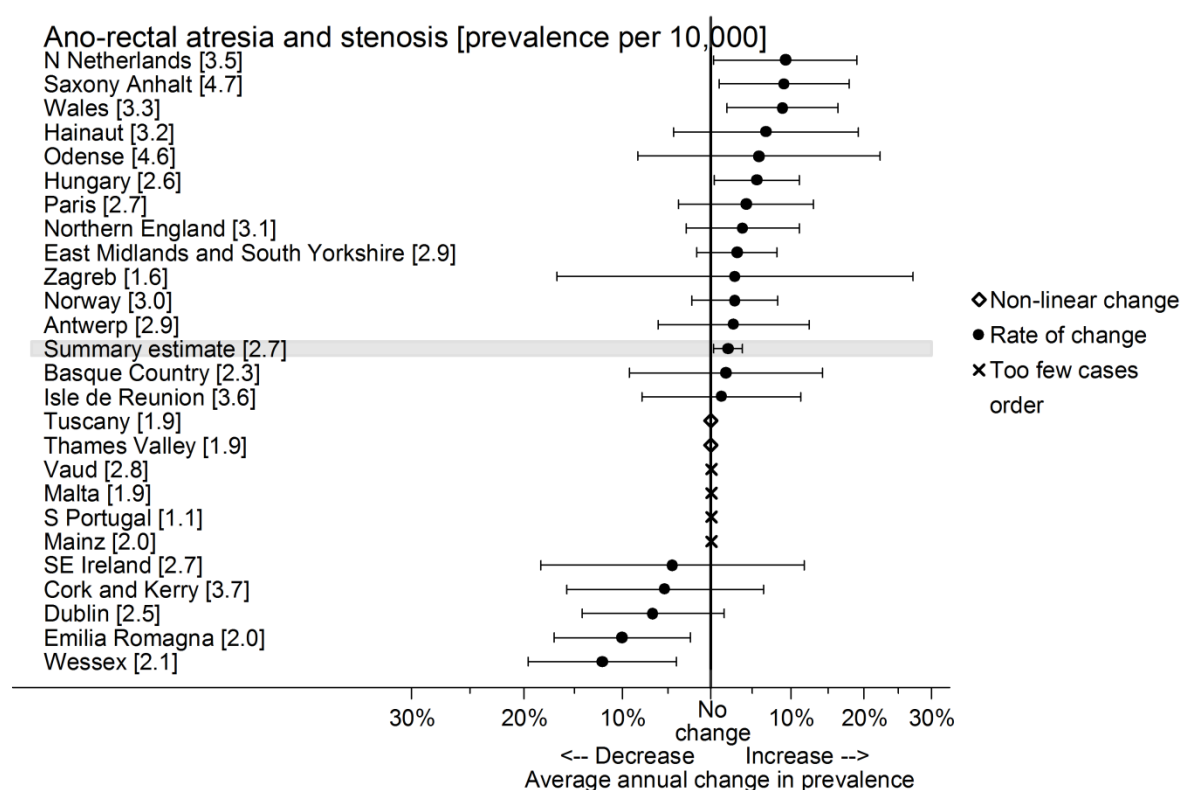
(3) Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation 2007 Jun 12;115(23):2995-3014.

Ano-rectal Atresia and Stenosis

This is a continuing increasing trend.

The registries which show a statistically significant trend moving in the same direction and which therefore may be contributing are: Hungary, Wales, Saxony Anhalt, and N Netherlands.

Figure 1. The trend in prevalence¹ of ano-rectal atresia and stenosis for the 10 year period 2003-2012, showing individual registries and the pan European trend



Literature review

Ano-rectal malformations (ARM) are the group of congenital anomalies which most commonly affect the gastro-intestinal tract (1). The anomalies are characterised by a complete failure of the rectum to communicate with the anus or a narrowing of the ano-rectal canal. The anomaly may be associated with a fistula which communicates with another organ or, in extreme cases, form part of a complete persistent cloaca. Most cases require surgery in the neonatal period.

ARM is known to form part of the VACTERL (Vertebral, Ano-rectal, Cardiac Tracheo-Oesophageal, Renal, Limb) association, and those cases which are associated with multiple congenital anomalies but do not fulfil the full VACTERL diagnosis often have at least one other congenital anomaly from that association (2). There is some evidence that more severe ARM is more likely to be associated with VACTERL and with multiple congenital anomalies in general (2). ARM has been theoretically linked with alterations in the Sonic hedgehog pathway (3) and this has been used to support a theory that ARM, and indeed the whole VACTERL phenotype, is a primary polytopic developmental field defect occurring in

the blastogenetic stage (4,5). ARM has been strongly associated with multiple birth (6-9) and with assisted reproductive technologies (1,10). There is also evidence that when an ARM case is from a multiple birth it is more likely to have multiple anomalies than a singleton case. Maternal health issues including lifestyle choices such as alcohol intake and smoking, obesity, maternal diabetes and the possibility of placental insufficiency have been implicated in the development of ARM and recently an association with maternal epilepsy has been highlighted (1).

Consistency between registries

There were a total of 1725 ano-rectal atresia and stenosis cases included in the analysis over the ten year period. Prevalence ranged from 1.1 cases per 10,000 births in South Portugal to 4.7 cases per 10,000 births in Saxony Anhalt.

Figure 2. Prevalence of ano-rectal atresia and stenosis by registry for 10 year period 2003 to 2012

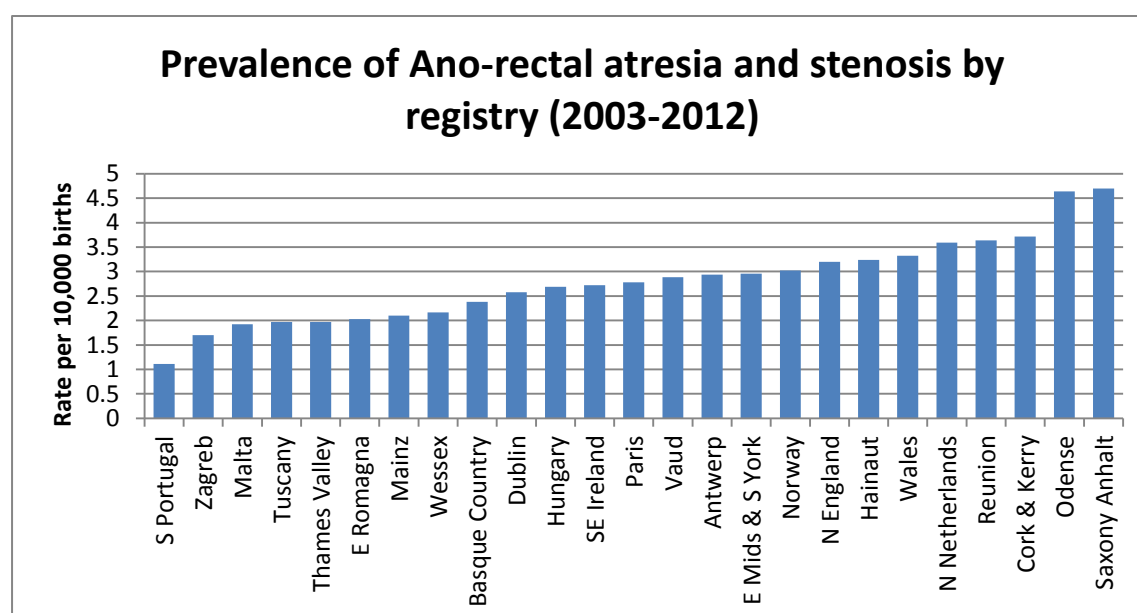


Figure 3: Ano-rectal atresia and stenosis showing the increasing trend and that trend when the registries with a statistically significant rise in prevalence (Hungary, Wales, Saxony Anhalt, N Netherlands) are excluded.

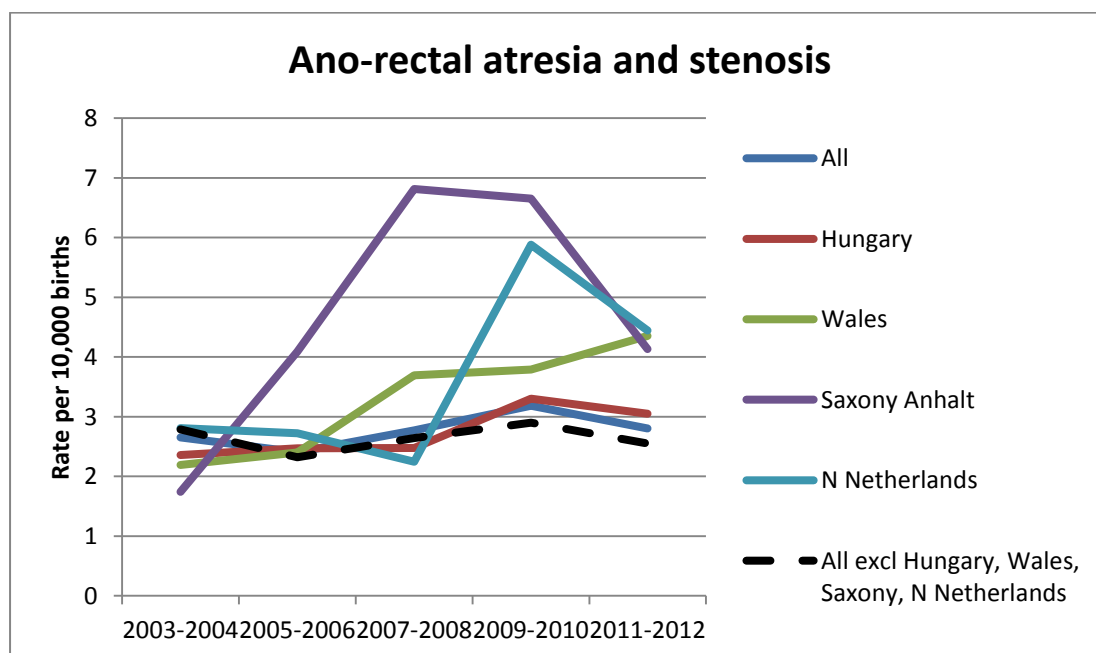


Figure 4: The prevalence of ano-rectal atresia and stenosis over the past three decades

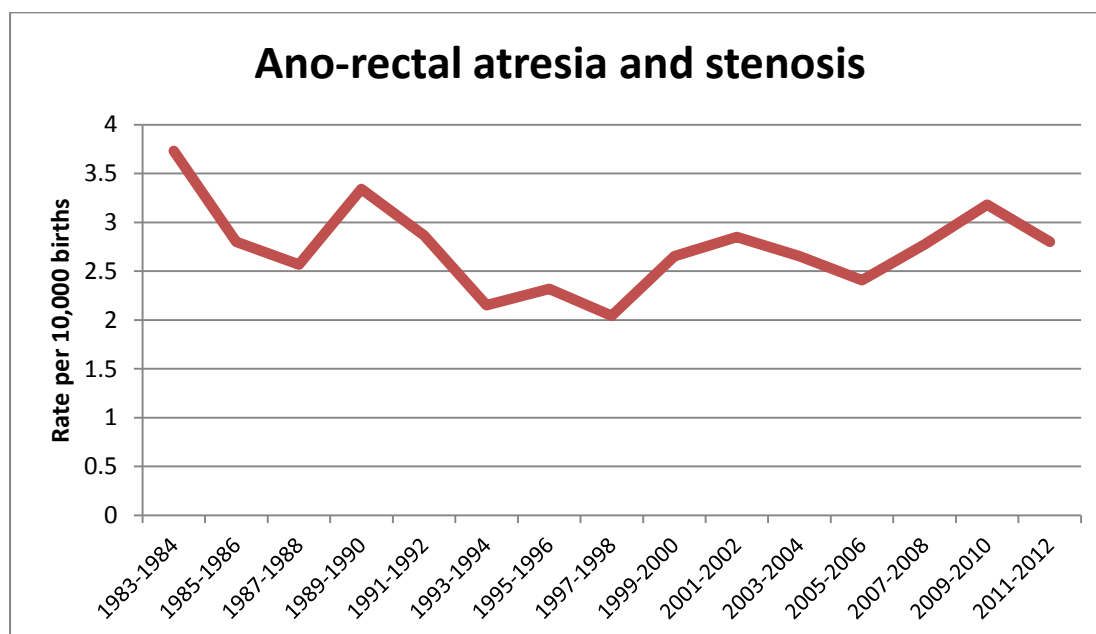


Figure 5: Prevalence of ano-rectal atresia and stenosis as an isolated vs a potential multiple anomaly over time 2003-2012

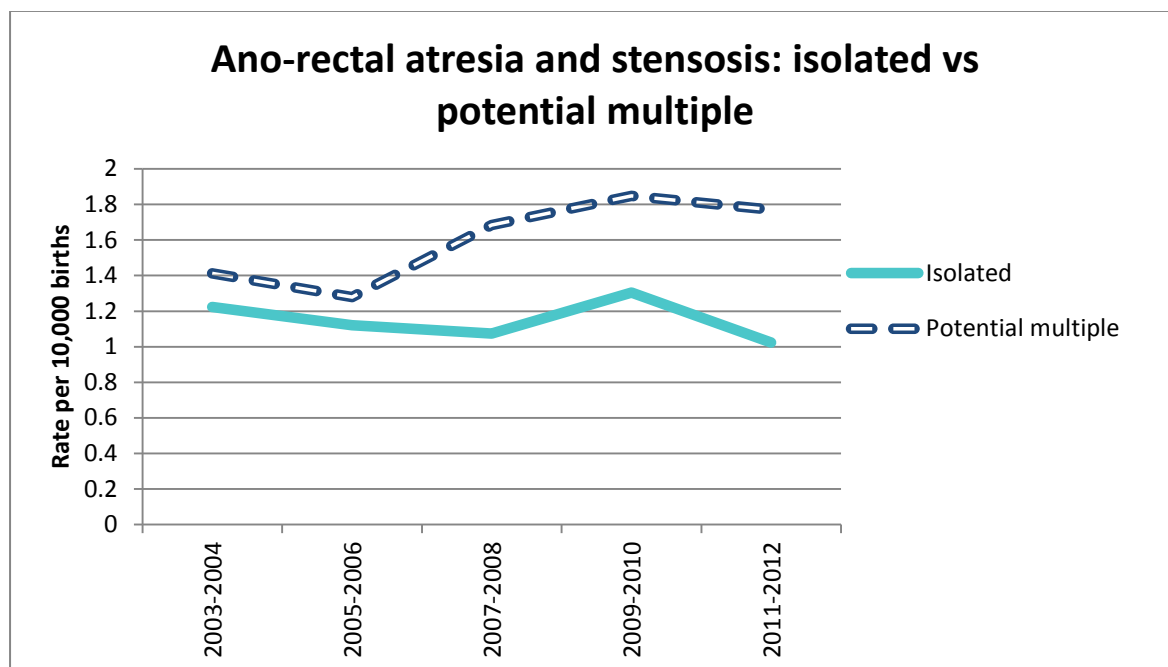


Figure 6: Time of diagnosis

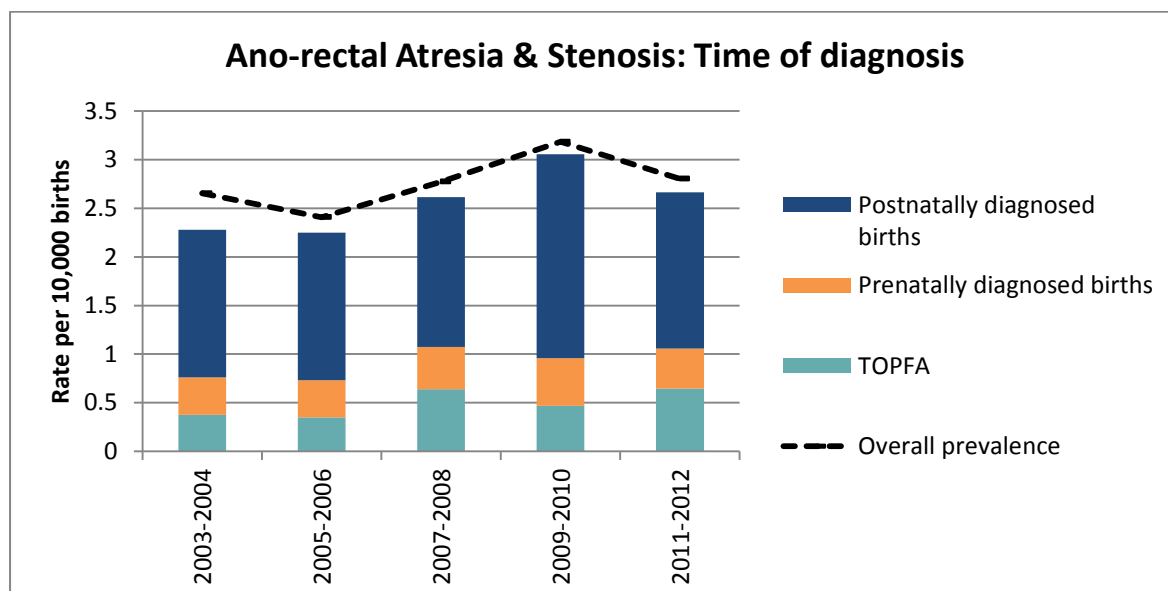


Table 1: Breakdown of postnatally diagnosed births

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	168 (94.9%)	165 (86.4%)	184 (91.1%)	259 (93.2%)	170 (90.9%)
>1 month	9 (5.1%)	14 (7.3%)	9 (4.5%)	8 (2.9%)	7 (3.7%)
postnatal, age n/k	0 (0.0%)	12 (6.3%)	9 (4.5%)	11 (4.0%)	10 (5.3%)

Conclusions

- The increase in prevalence in ARM is not fully explained by changes in time of diagnosis, type of birth or the contribution of outlying registries.
- Saxony-Anhalt have confirmed their increasing trend and there is an on-going investigation.
Inclusion of minor cases, especially before the present classification system was adopted, may contribute to the high prevalence of isolated cases in that registry, but does not fully explain the trend.
- Wales have stated that the trend in their registry is due to data quality issues
- N Netherlands have stated that the trend in their registry is due to changes in methods
- Overall there appears to be an increasing trend in the prevalence of ARM only when it is associated with other congenital anomalies and it may be worth considering the prevalence of the VACTERL association as a whole.

(1) Wijers CHW, van Rooij IALM, Bakker MK, Marcelis CLM, Addor MC, Barisic I, et al. Anorectal malformations and pregnancy-related disorders: a registry-based case-control study in 17 European regions. British Journal of obstetrics and gynaecology 2013;Online(DOI: 10.1111/1471-0528.12235).

(2) Cuschieri A, EUROCAT Working G. Anorectal anomalies associated with or as part of other anomalies. Am J Med Genet 2002 Jun 15;110(2):122-130.

(3) Mo R, Kim JH, Zhang J, Chiang C, Hui CC, Kim PC. Anorectal malformations caused by defects in sonic hedgehog signaling. Am J Pathol 2001 Aug;159(2):765-774.

(4) Martinez-Frias ML, Bermejo E, Frias JL. The VACTERL association: lessons from the Sonic hedgehog pathway. Clin Genet 2001 Nov;60(5):397-398.

(5) Martinez-Frias ML, Frias JL. VACTERL as primary, polytopic developmental field defects. Am J Med Genet 1999 Mar 5;83(1):13-16.

(6) Kallen B. Congenital malformations in twins: a population study. Acta Genet Med Gemellol 1986;35(3-4):167-178.

(7) Doyle PE, Beral V, Botting B, Wale CJ. Congenital malformations in twins in England and Wales. *Journal of Epidemiology & Community Health* 1991 Mar;45(1):43-48.

(8) Mastroiacovo P, Castilla EE, Arpino C, Botting B, Cocchi G, Goujard J, et al. Congenital malformations in twins: an international study. *Am J Med Genet* 1999 Mar 12;83(2):117-124.

(9) Li SJ, Ford N, Meister K, Bodurtha J. Increased risk of birth defects among children from multiple births. *Birth Defects Research* 2003 Oct;67(10):879-885.

(10) Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Otterblad PO. Congenital malformations in infants born after in vitro fertilization in Sweden. *Birth Defects Research* 2010 Mar;88(3):137-143.

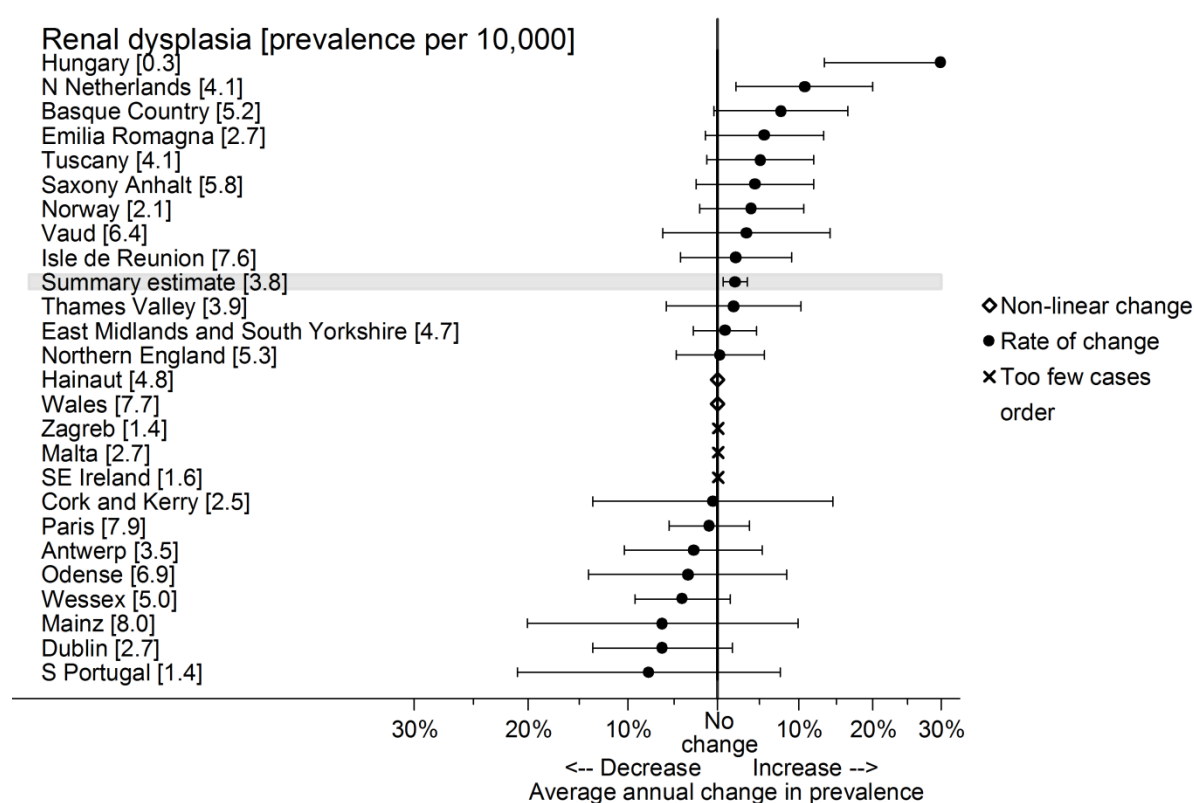
Trend Report

Renal Dysplasia

This is a continuing increasing trend.

The registries which show a statistically significant trend moving in the same direction and which therefore may be contributing are: Hungary and N Netherlands.

Figure 1. The trend in prevalence of renal dysplasia for the 10 year period 2003-2012, showing individual registries and the pan European trend



Literature Review

Renal dysplasias are a diverse group of congenital anomalies characterised as malformation of the kidney tissue, some of which are of limited clinical significance. Advances in prenatal ultrasound have led to greater diagnosis of renal anomalies in general (1).

Consistency between registries

There were a total of 2405 renal dysplasia cases included in the analysis over the ten year period. Prevalence ranged from 0.4¹ cases per 10,000 births in Hungary to 8.0 cases per 10,000 births in Mainz.

Figure 2. Prevalence of renal dysplasia by registry for 10 year period 2003 to 2012

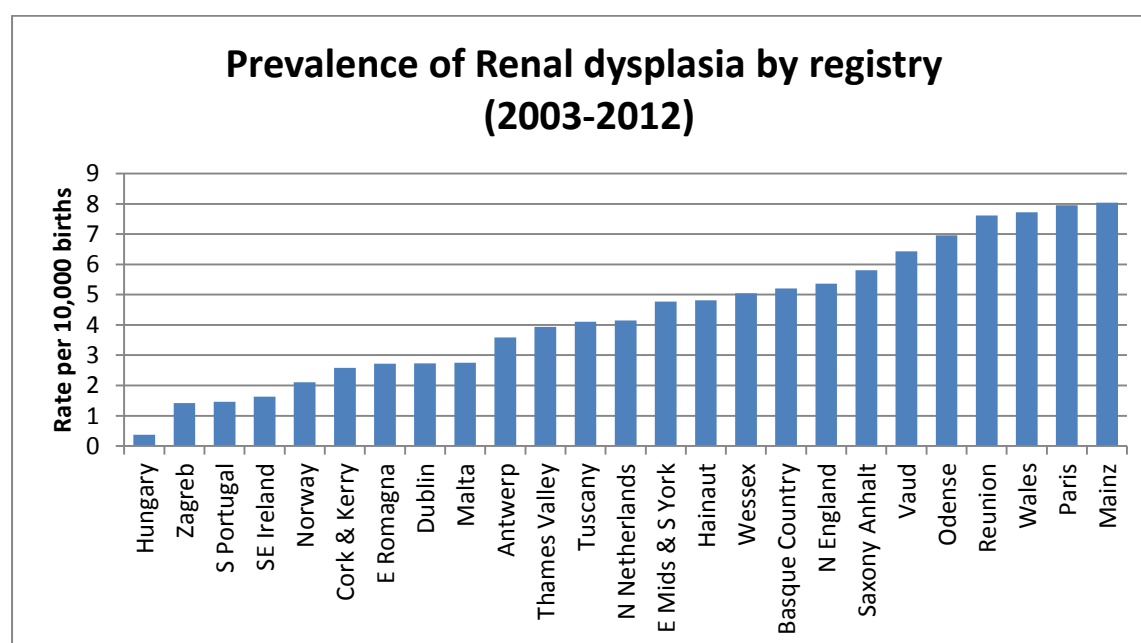


Figure 3: Renal dysplasia showing the increasing trend and that trend when the registries with a statistically significant rise in prevalence (Hungary, Northern Netherlands) are excluded.

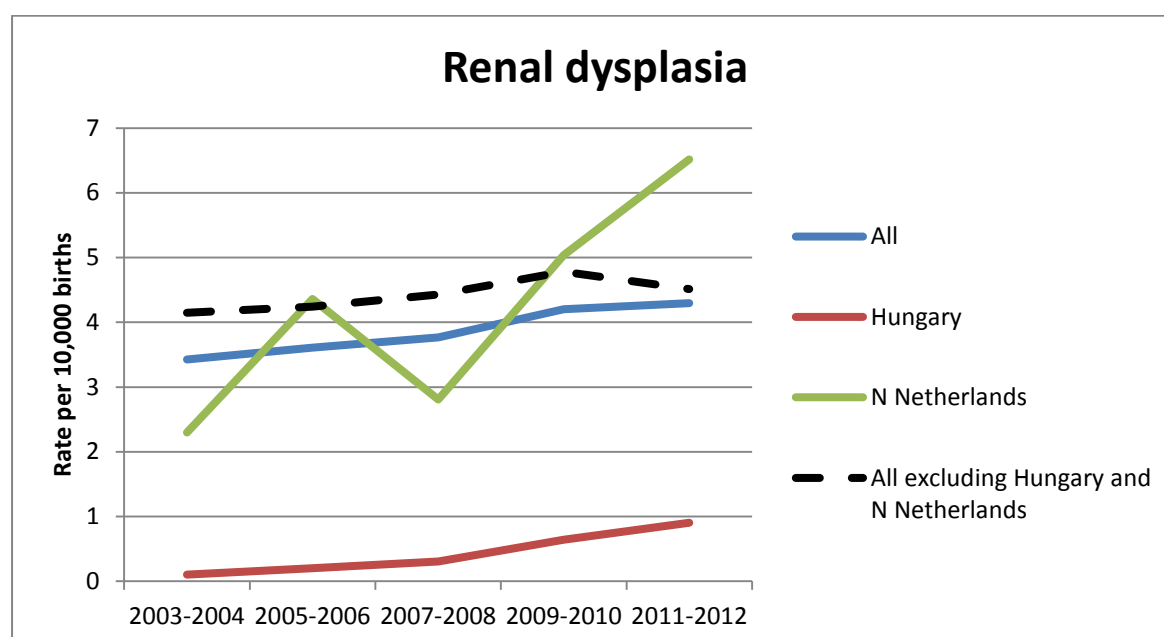


Figure 4: The prevalence of renal dysplasia over the past three decades

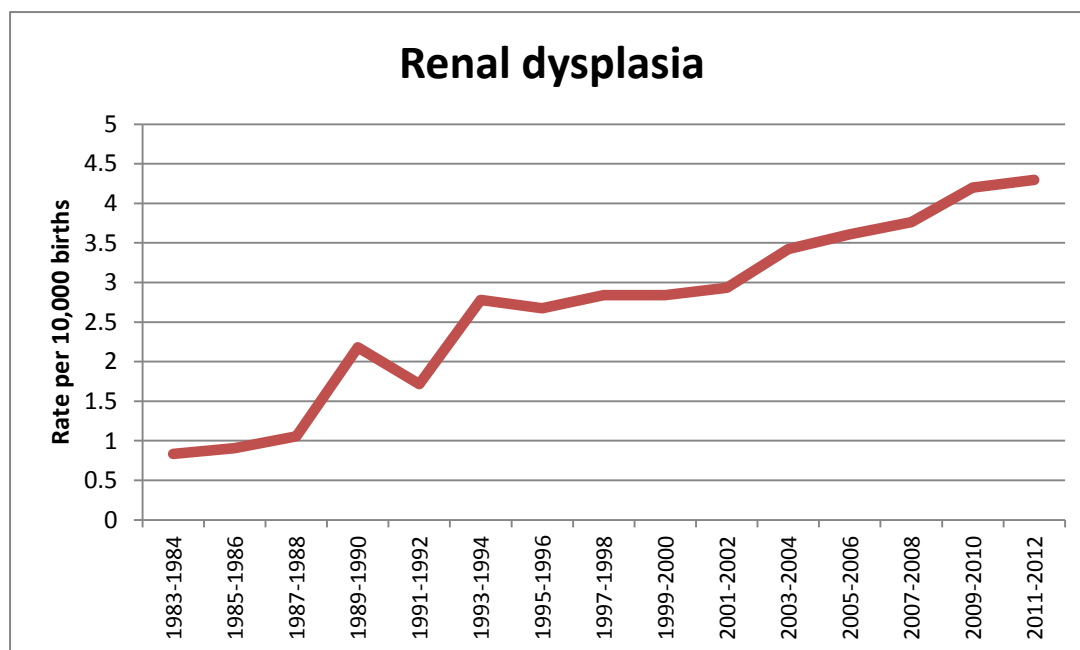
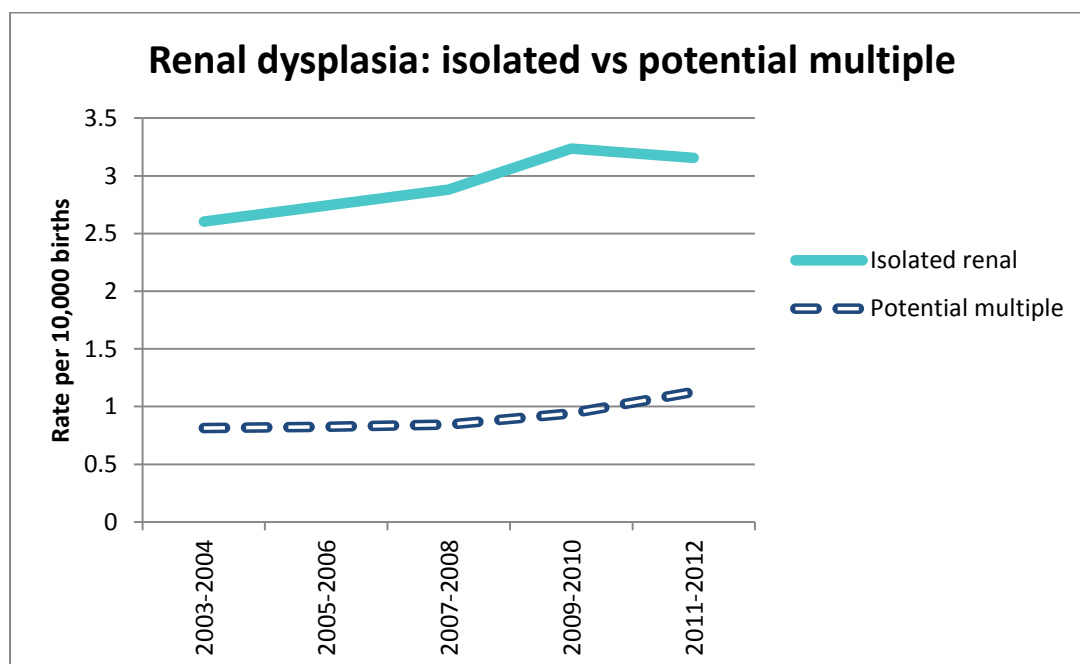


Figure 5: Prevalence of renal dysplasia as an isolated renal vs a potential multiple anomaly over time 2003-2012



Total number of renal dysplasia cases (2003-2012) = 2405

Isolated renal	Potential multiple	Teratogenic syndrome	Isolated other	Genetic syndrome, skeletal dysplasia and monogenic disorder
1823 (75.8%)	566 (23.5%)	5 (0.2%)	10 (0.4%)	1 (0.0%)

Figure 6: *Time of diagnosis*

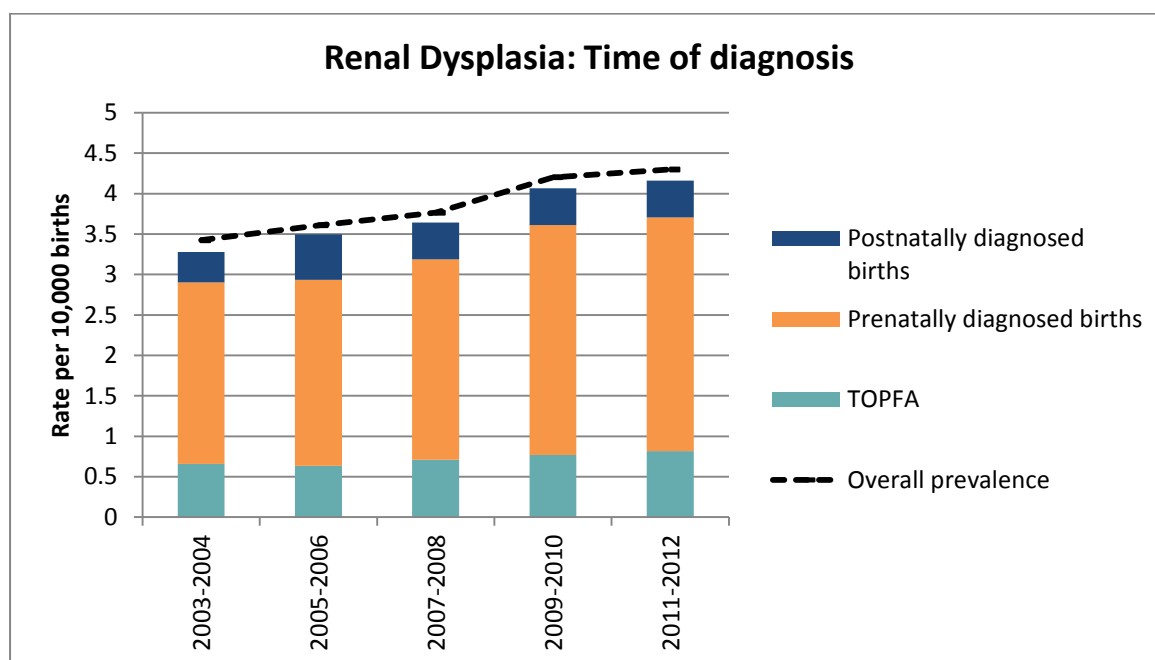


Table 1: *Breakdown of postnatally diagnosed births*

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	38 (86.4%)	59 (83.1%)	52 (86.7%)	48 (80.0%)	46 (86.8%)
>1 month	5 (11.4%)	10 (14.1%)	5 (8.3%)	7 (11.7%)	5 (9.4%)
postnatal, age n/k	1 (2.3%)	2 (2.8%)	3 (5.0%)	5 (8.3%)	2 (3.8%)

Conclusions

- Whilst Hungary have a significantly increasing trend, the prevalence rate is extremely low compared to the EUROCAT average. See figures 1, 2 & 3
- When the 2 significantly increasing registries are excluded, the trend evens out slightly. See figure 3. In Northern Netherlands the trend is considered to be due to

changes in diagnostic methods.

- When looked at over a 30 year period 1983-2012, the trend is very clearly upward

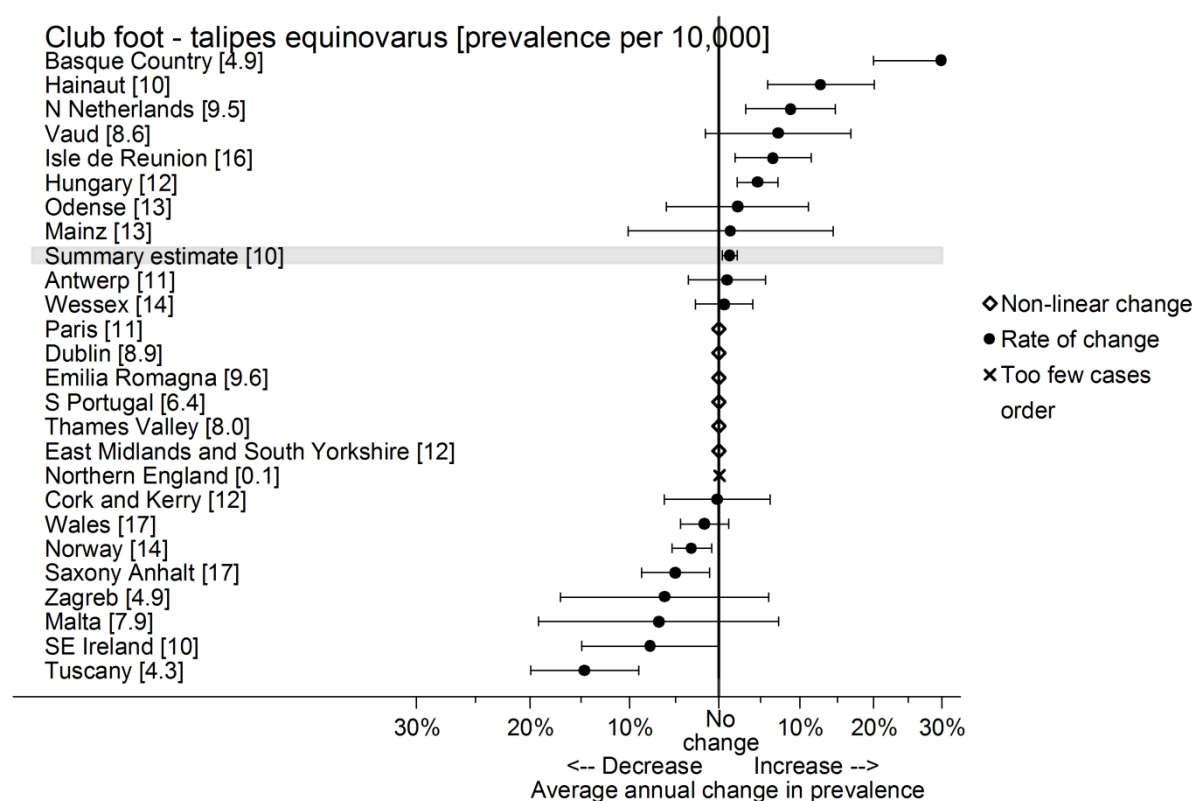
Trend Report

Club Foot

This is a continuing increasing trend

The registries which show a statistically significant trend moving in the same direction and which therefore may be contributing are: Basque Country, Hainaut, N Netherlands, Hungary, Isle de Reunion

Figure 1. The trend in prevalence¹ of Club foot – talipes equinovarus for the 10 year period 2003-2012, showing individual registries and the pan European trend



Literature Review

Club foot, sometimes seen as part of a sequence including spina bifida, is also seen as an isolated anomaly. It may have a teratogenic cause with an association with Valproic acid(1) and with SSRIs (2)

Consistency between registries

There were a total of 6749 clubfoot cases included in the analysis over the ten year period. Prevalence ranged from 0.2¹ cases per 10,000 births in N England to 17.0 cases per 10,000 births in Wales.

Figure 2. Prevalence of Club foot – *talipes equinovarus* by registry for 10 year period 2003 to 2012

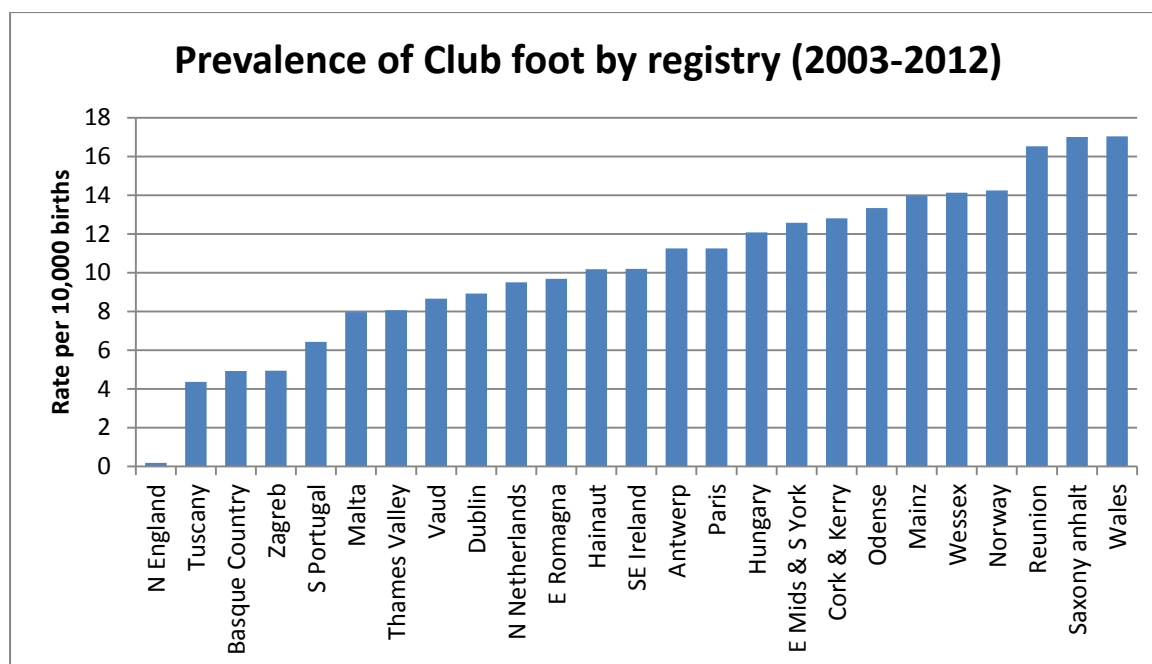


Figure 3: Club foot showing the increasing trend and that trend when the registries with a statistically significant rise in prevalence are excluded.

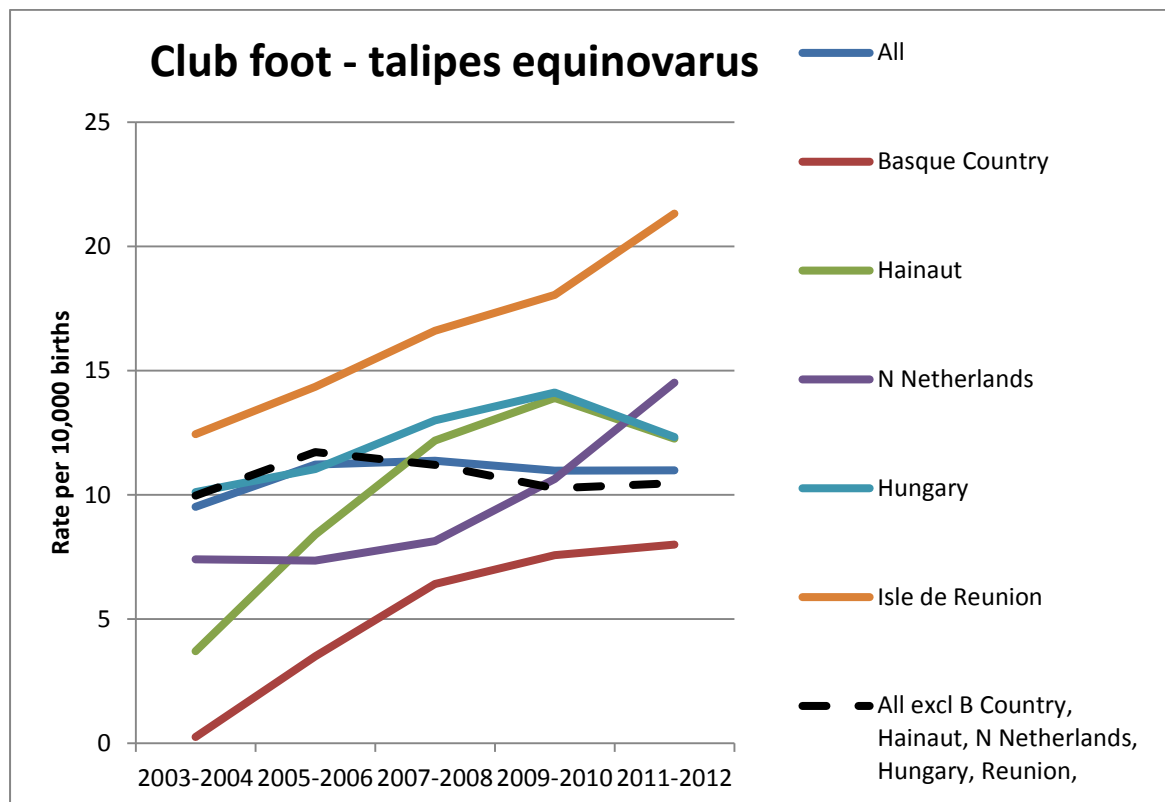


Figure 4: The prevalence of club foot – talipes equinovarus over the past three decades

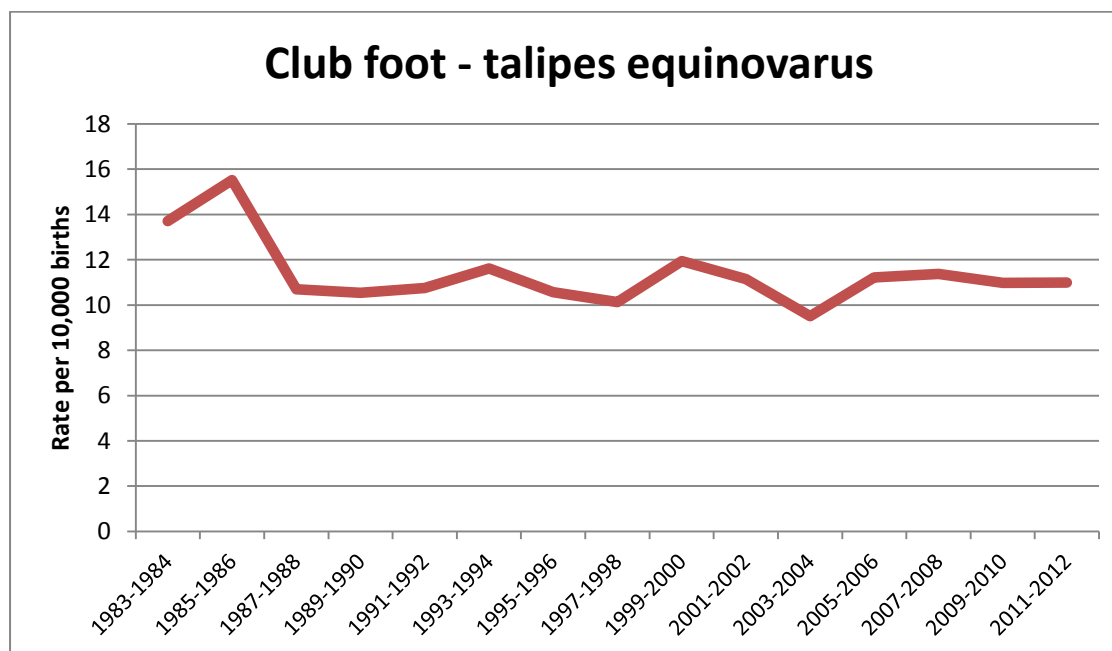


Figure 5: Prevalence of club foot as an isolated vs a potential multiple anomaly over time 2003-2012

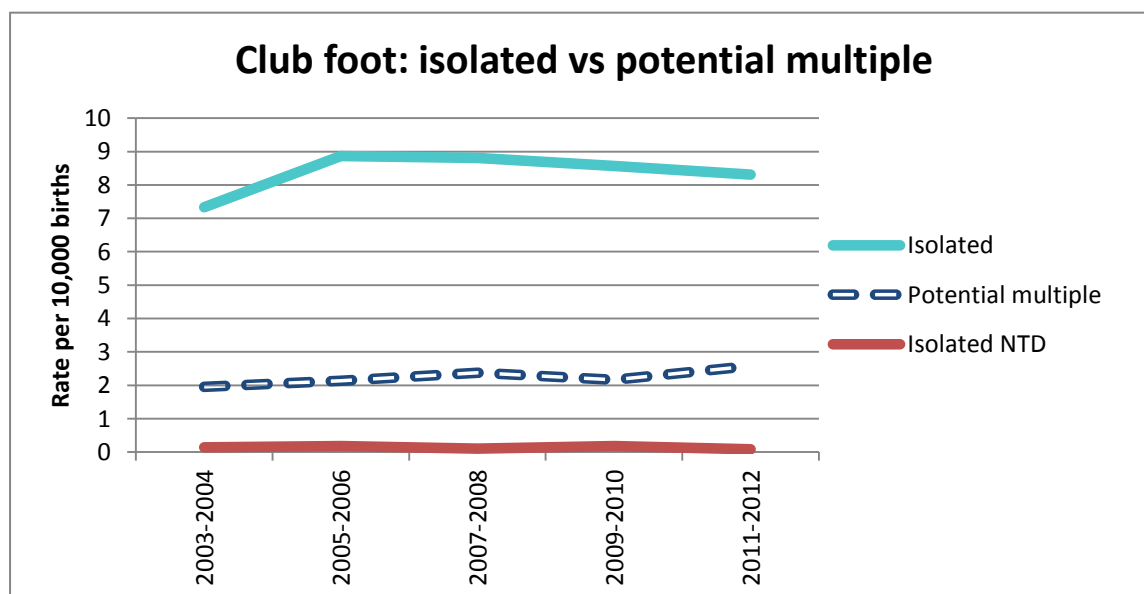


Table 1: Club foot: *breakdown by multiple malformation algorithm 2003-2012*

Isolated other (I2)	Potential multiple (M2)	Teratogenic syndrome (T2)	Isolated NTD (N2)	Isolated renal (R2)	Genetic syndrome, skeletal dysplasia and monogenic disorder (B2)
5232 (77.5%)	1396 (20.7%)	15 (0.2%)	85 (1.3%)	16 (0.2%)	5 (0.1%)

Total number of club foot cases (2003-2012) = **6,749**

Figure 6: *Time of diagnosis*

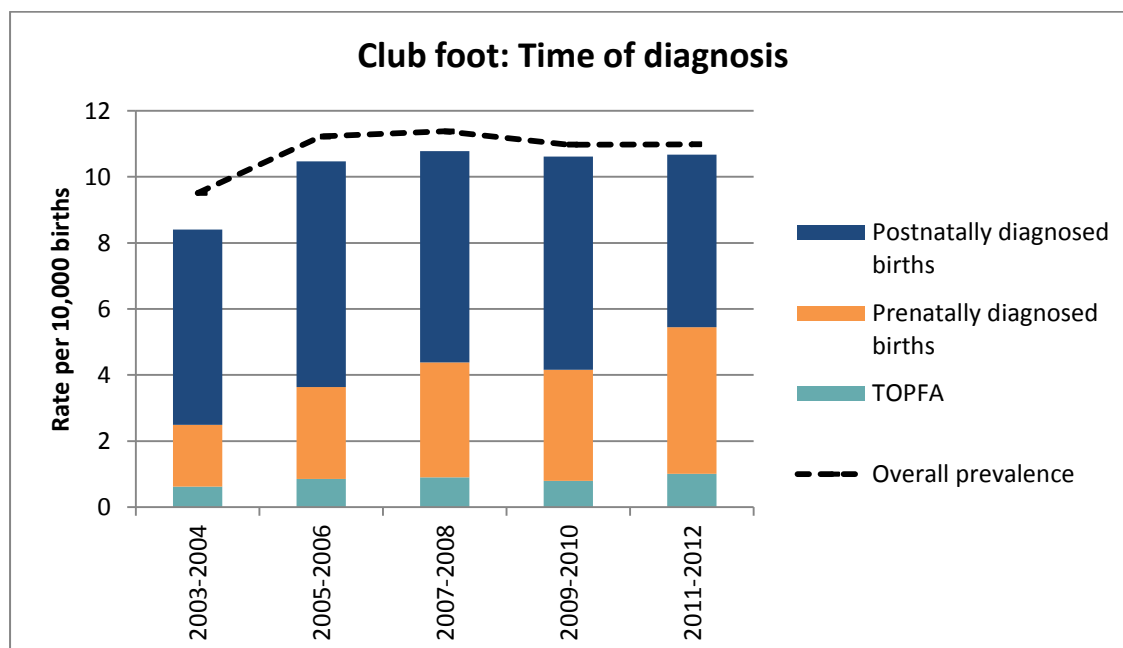


Table 2: *Breakdown of postnatally diagnosed births*

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	657 (95.1%)	811 (94.3%)	816 (97.1%)	835 (97.5%)	578 (95.2%)
>1 month	30 (4.3%)	44 (5.1%)	21 (2.5%)	20 (2.3%)	25 (4.1%)
postnatal, age n/k	4 (0.6%)	5 (0.6%)	3 (0.4%)	1 (0.1%)	4 (0.7%)

Conclusions

- There are 8 registries with an increasing trend above the EUROCAT summary estimate, 5 of which are significantly increasing
- Over the last decade, 2 of the registries contributing to the trend started at a low prevalence rate (Hainaut and Basque Country), with their prevalence then rising steeply until 2010 before slowing. Isle de la Reunion has had a higher than average prevalence from 2003 and continues to rise. Isle de la Reunion consider this a **real trend** and will keep under further surveillance. N Netherlands think their trend is more likely to be because of a change in registry recording methods to do with informed consent.
- Analysed over a longer time span of 30 years, clubfoot seemed to be highest in the 1980s before dropping to a prevalence of 10-12 per 10,000 births which has remained fairly constant.
- Club foot prevalence as a potential multiple anomaly is very much less than the prevalence of club foot as an isolated anomaly. It also occurs at a low prevalence as

an isolated NTD anomaly.

- Previously, clubfoot was diagnosed more often postnatally than prenatally, but in 2011-2012 we can see that the prevalence is approximately equal (Figure 6)

(1) Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med 2010 Jun 10;362(23):2185-2193.

(2) A. Wemakor. Antidepressant Use in Pregnancy: Risks and Prevalence University of Ulster; 2013.

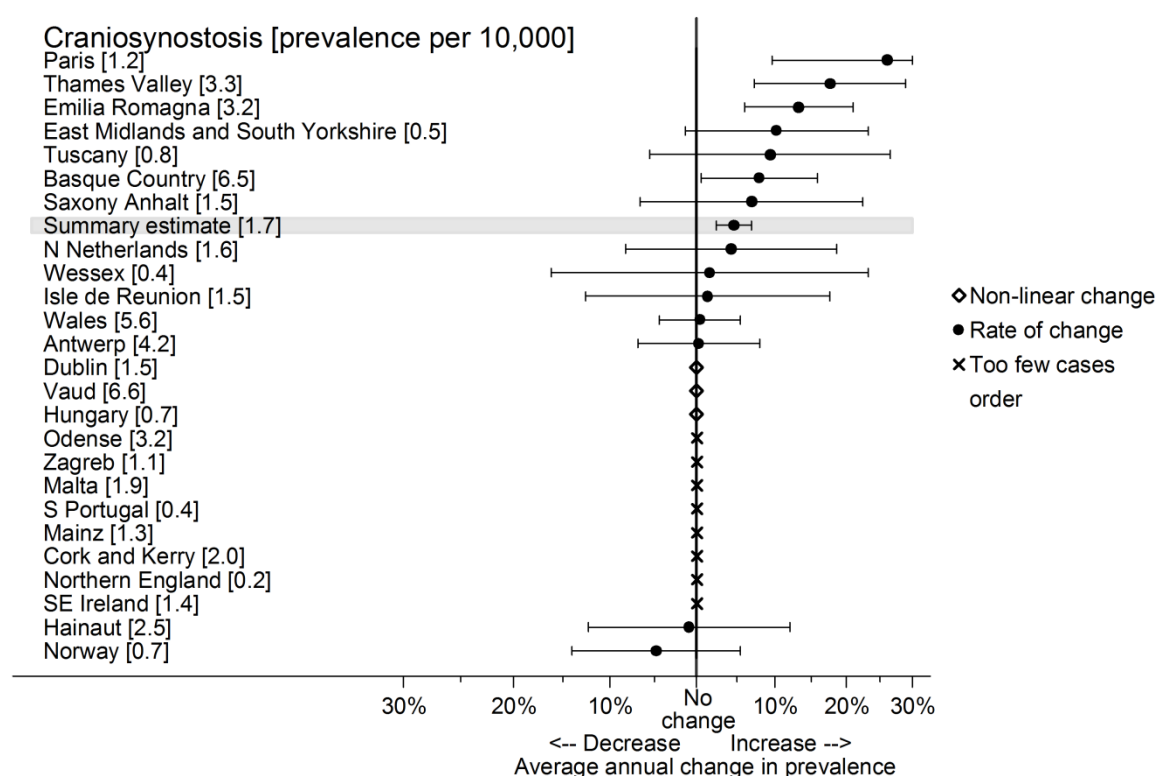
Trend Report

Craniosynostosis

This is a continuing increasing trend.

The registries which show a statistically significant trend moving in the same direction and which therefore may be contributing are: Paris, Thames Valley, Emilia Romagna and Basque Country

Figure 1. The trend in prevalence¹ of Craniosynostosis for the 10 year period 2003-2012, showing individual registries and the pan European trend



Literature Review

Craniosynostosis (CS) is a condition where the cranial sutures, which are open at birth to allow the newborn's head to mould as it passes through the birth canal and to facilitate rapid growth in infancy and childhood, fuse prematurely. Although the metopic suture typically closes at around eight months of age, the other three (sagittal, coronal and lambdoid) usually remain open into adulthood (1). The infant usually presents with an unusually shaped head which, if untreated, can lead to problems with vision and hearing and can lead to raised intracranial pressure and intellectual impairment. Surgery is typically performed during the first year of life (2). Most cases are thought to be genetic, occurring either as part of a genetic syndrome or as an isolated anomaly (1), but the condition has also been associated with teratogens, including valproic acid (3). It is believed that the main risk factors for craniosynostosis are genetic (1), but as the different types are not increasing at a uniform rate there may also be environmental factors involved (2). An association between CS and Valproic Acid has been demonstrated (3)

Consistency between registries

There were a total of 1113 Craniosynostosis cases included in the analysis over the ten year period. Prevalence ranged from 0.2 cases per 10,000 births in N England to 6.7¹ cases per 10,000 births in Vaud.

Figure 2. Prevalence of Craniosynostosis by registry for 10 year period 2003 to 2012

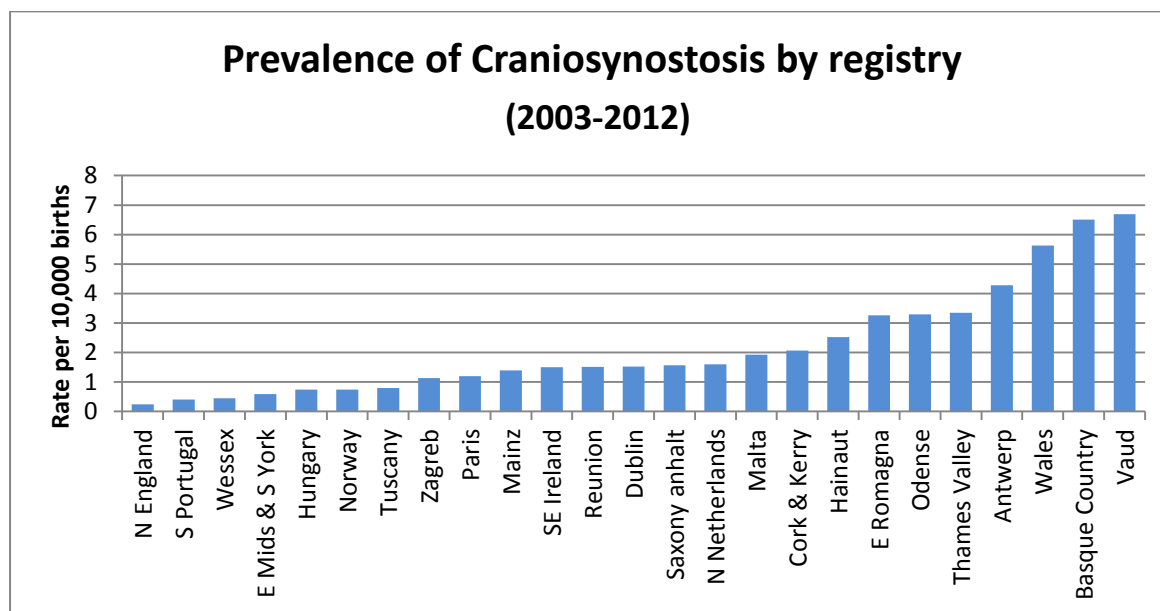


Figure 3: Craniosynostosis showing the increasing trend and that trend when the registries with a statistically significant rise in prevalence are excluded.

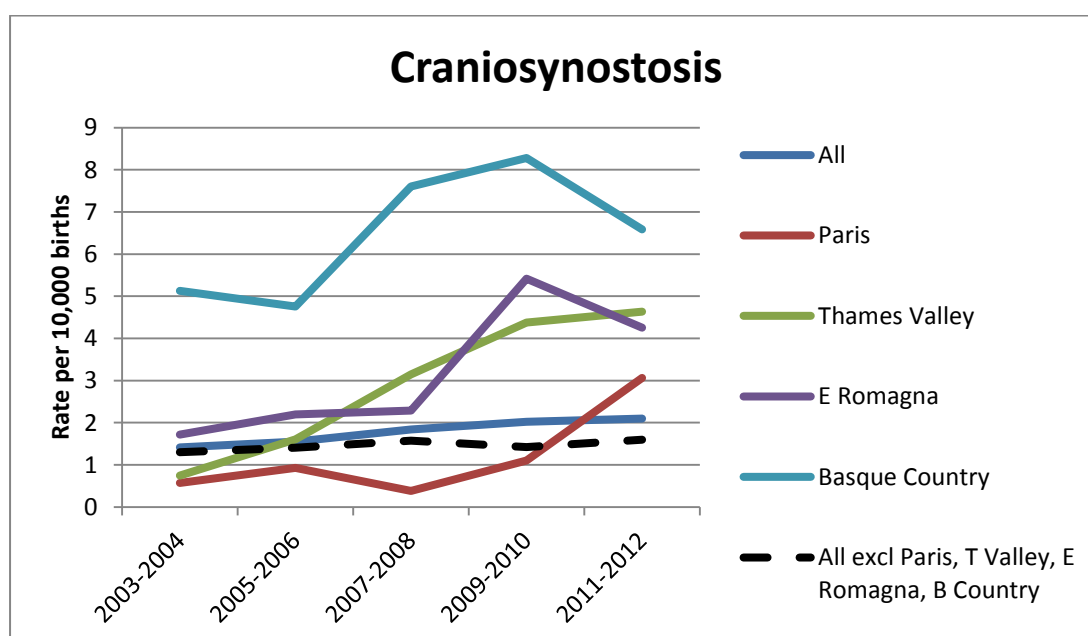


Figure 4: *The prevalence of craniosynostosis over the past three decades*

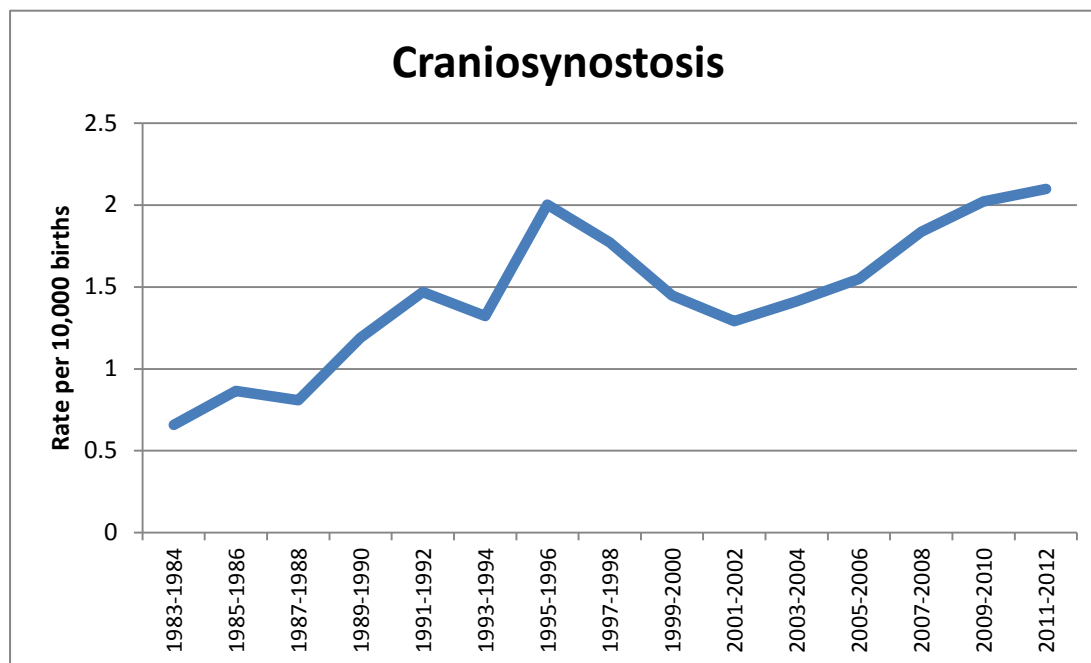


Figure 5: *Prevalence of Craniosynostosis as an isolated vs a potential multiple anomaly over time 2003-2012*

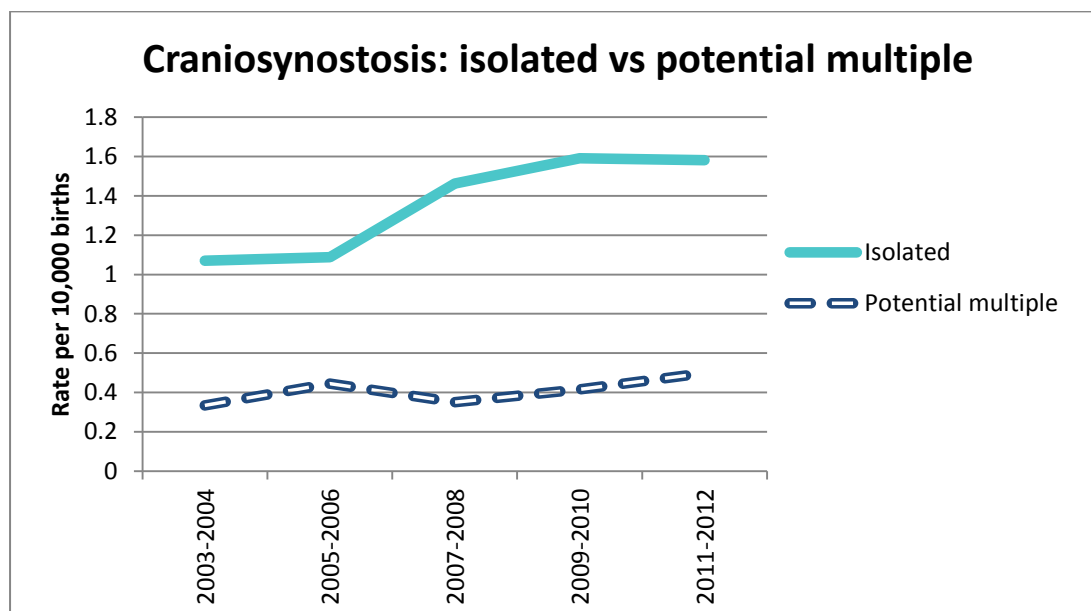


Figure 6: *Time of diagnosis*

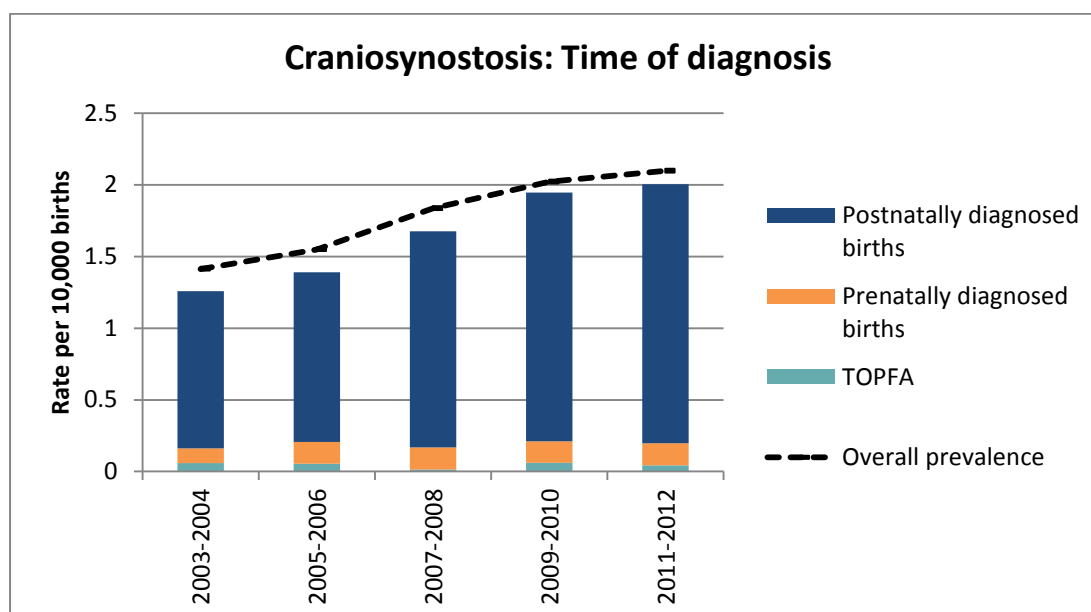


Table 1: *Breakdown of postnatally diagnosed births*

	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012
< 1 month	80 (62.5%)	103 (69.1%)	113 (57.1%)	118 (51.3%)	102 (48.6%)
>1 month	47 (36.7%)	39 (26.2%)	67 (33.8%)	102 (44.3%)	93 (44.3%)
postnatal, age n/k	1 (0.8%)	7 (4.7%)	18 (9.1%)	10 (4.3%)	15 (7.1%)

Conclusions

Based on the increasing ascertainment of late diagnosed cases it appears that this may not be a true trend but a demonstration of the registries increasing sufficiency in picking up late diagnosed cases.

We agreed to keep monitoring the situation as the prevalence continues to rise

(1) Rasmussen SA, Yazdy MM, Frias JL, Honein MA. Priorities for public health research on craniosynostosis: summary and recommendations from a Centers for Disease Control and Prevention-sponsored meeting. American Journal of Medical Genetics. Part A 2008;146A(2):149-158.

(2) Di Rocco F, Arnaud E, Meyer P, Sainte-Rose C, Renier D. Focus session on the changing "epidemiology" of craniosynostosis (comparing two quinquennia: 1985-1989 and 2003-2007) and its impact on the daily clinical practice: a review from Necker Enfants Malades. Childs Nervous System 2009 Jul;25(7):807-811.

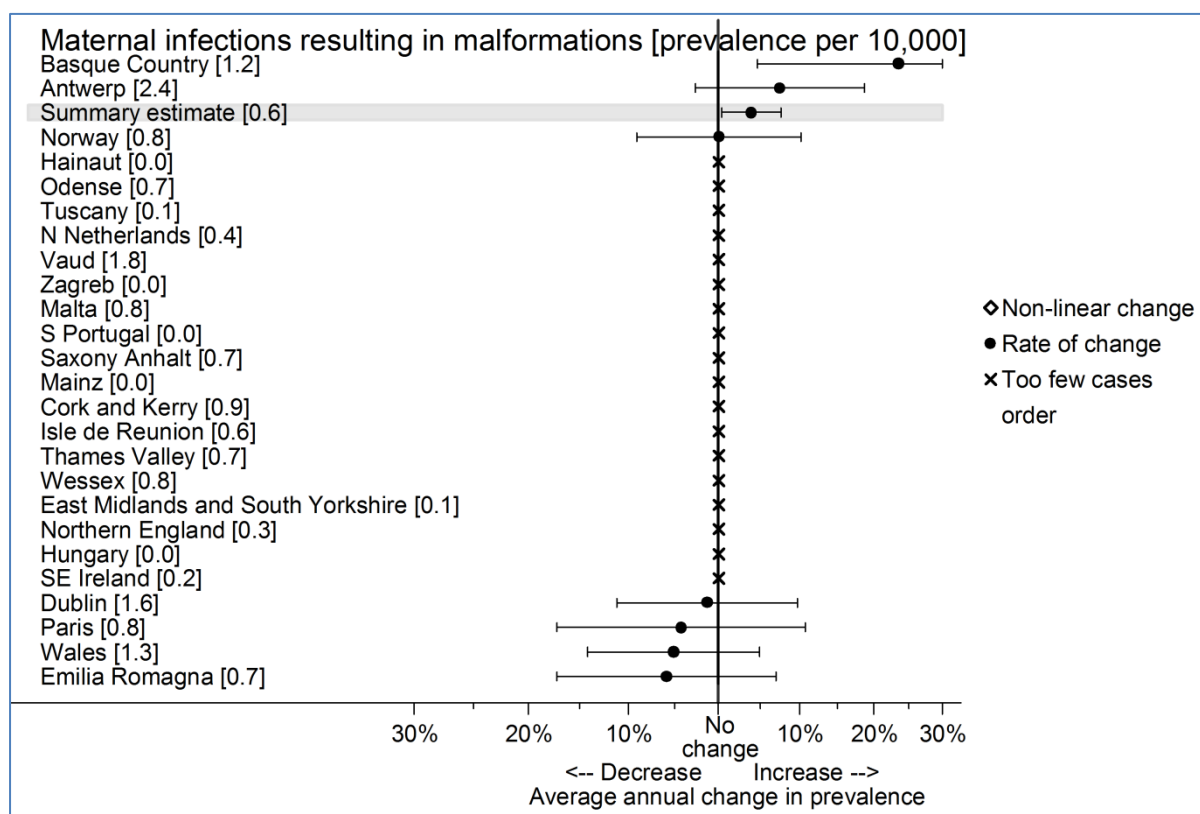
(3) Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med 2010 Jun 10;362(23):2185-2193.

Maternal Infections resulting in malformations

This is a new increasing trend.

The registry which shows a statistically significant trend moving in the same direction and which may therefore be contributing is: Basque Country

Figure 1 The trend in prevalence of Maternal infections for the 10 year period 2003-2012, showing individual registries and the pan European trend



Literature Review

Maternal infections, notably the TORCH Toxoplasmosis, Rubella, CMV and Herpes viruses are known to be associated with a collection of congenital anomalies including heart defects {{30 Jenkins,E.A. 2006}} and eye and ear anomalies {{905 Golalipour,M.J. 2009; 901 Horstmann,D.M. 1970}}. There is a EUROCAT subgroup “maternal illnesses” which is made up of Rubella, CMV and Toxoplasmosis exposed cases {{880 EUROCAT 2013}} where the exposed case should have other congenital anomalies recorded before they are registered.

Consistency between registries

There were a total of 403 maternal infection cases included in the analysis over the ten year period. Prevalence ranged from 0 cases per 10,000 births in Hungary, Zagreb, South Portugal and Mainz to 2.5¹ cases per 10,000 births in Antwerp.

Figure 2. Prevalence of Maternal infections by registry for 10 year period 2003 to 2012

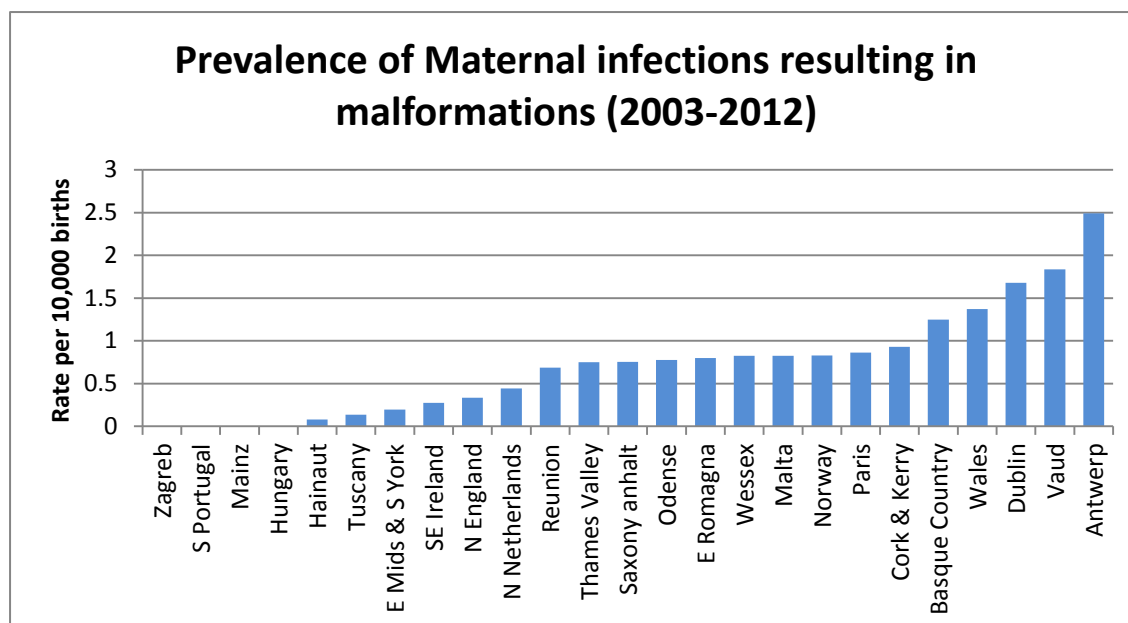


Figure 3: Maternal Infections showing the increasing trend and that trend when the registry with a statistically significant rise in prevalence is excluded.

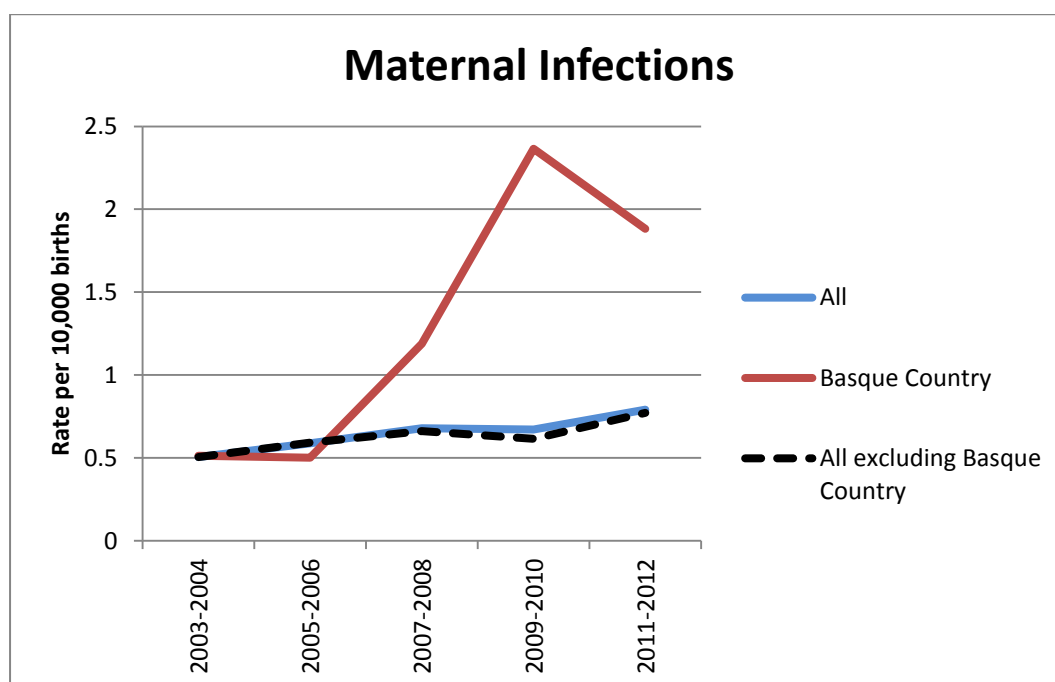


Figure 4: The prevalence of maternal infections over the past three decades

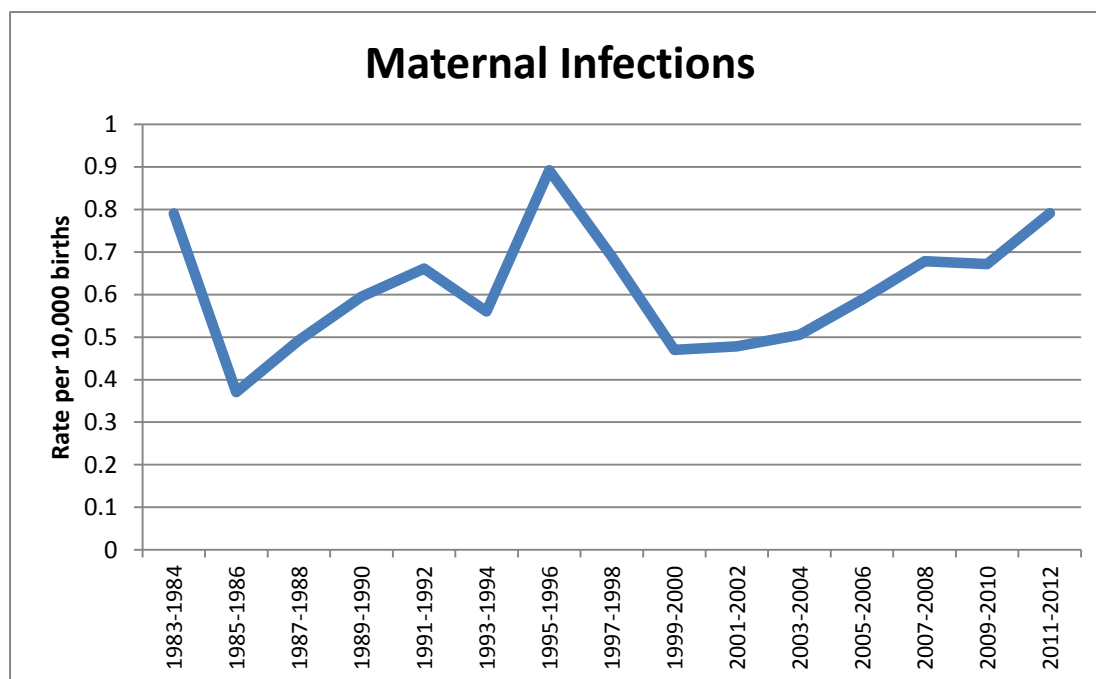


Figure 5: Maternal Infections (Congenital Rubella Syndrome; Congenital Cytomegalovirus; Toxoplasmosis) by type of birth, 2003-2012

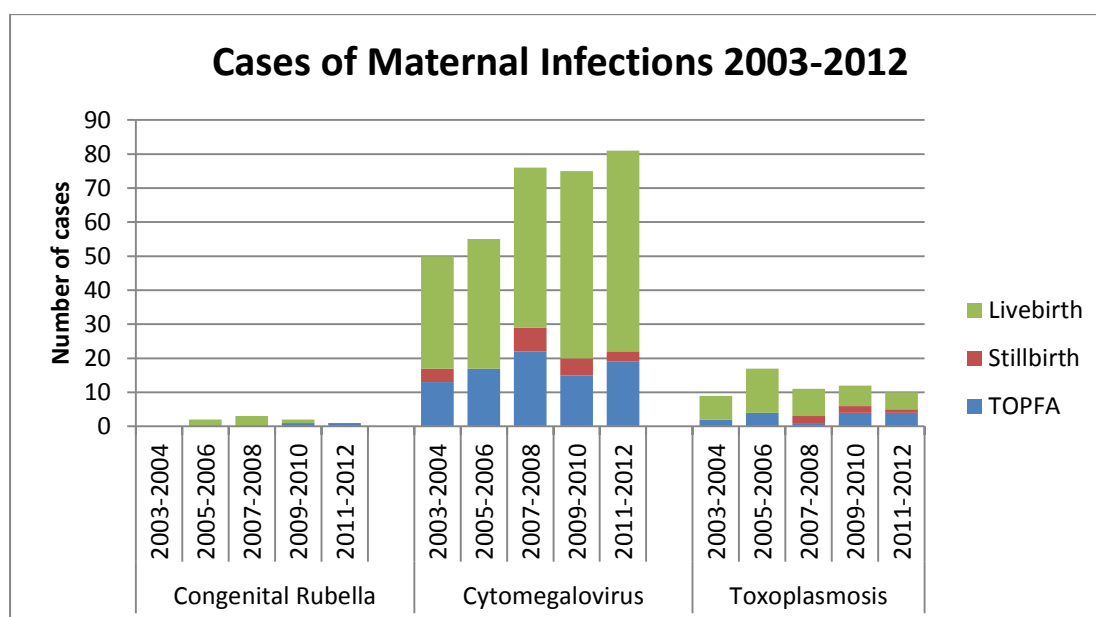


Table 1: Breakdown of Maternal Infection cases with or without other congenital anomaly

	Without other CA	With other CA
2003-2004	26 (44.1%)	33 (55.9%)
2005-2006	36 (48.6%)	38 (51.4%)
2007-2008	42 (46.7%)	48 (53.3%)
2009-2010	35 (39.3%)	54 (60.7%)
2011-2012	53 (57.6%)	39 (42.4%)
Overall	192 (47.5)	212 (52.5%)

Figure 6: Prevalence of Congenital CMV per registry, 2003-2012

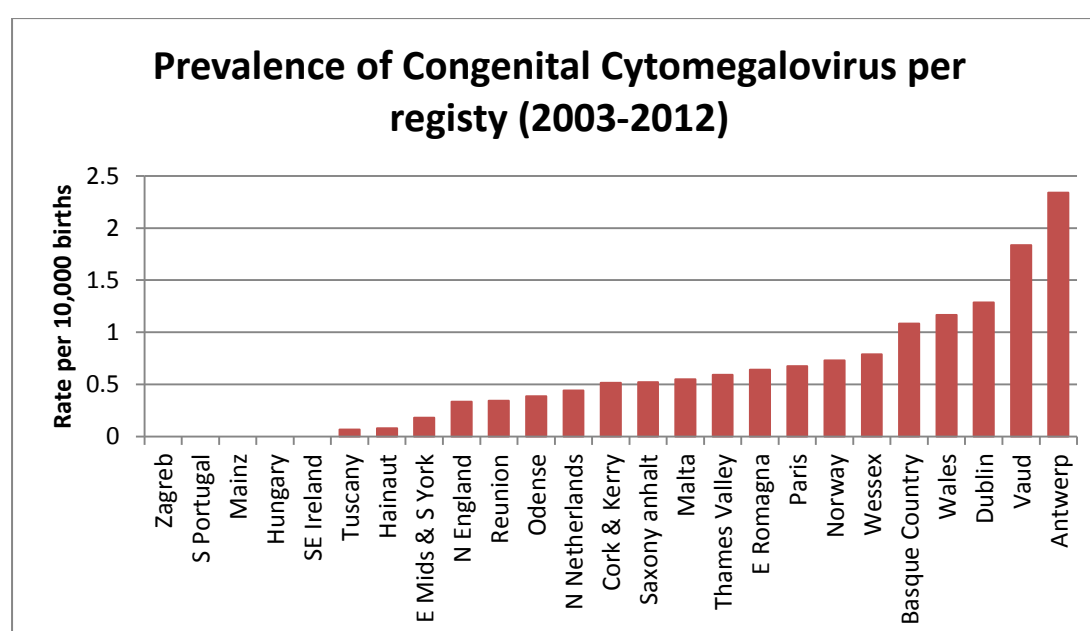


Figure 7: Number of Congenital CMV cases per registry, 2003-2012: With vs without other congenital anomaly

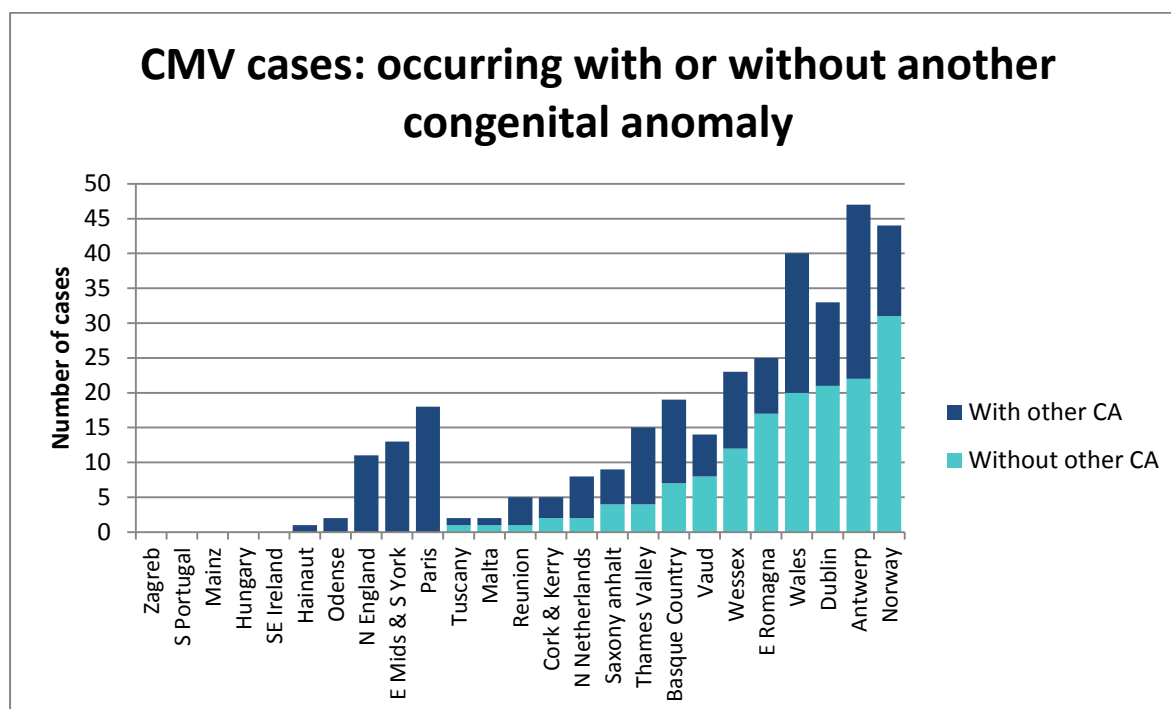
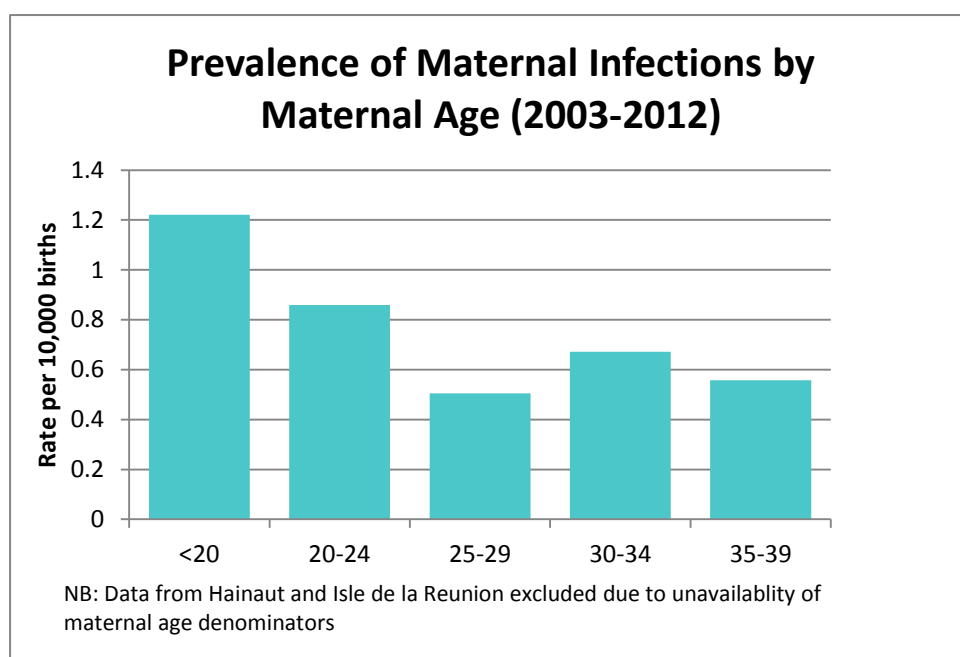


Table 2: Breakdown of CMV cases with other congenital anomaly

Other Anomaly	Number*
Nervous system	129
CHD	30
Respiratory	13
Limb	10
Digestive system	10
Urinary	9
Eye	7
Abdominal wall defect	4
Genital	3
Oro-facial clefts	1
Ear, face, neck	1

*each CMV case may have more than 1 other associated anomaly

Figure 8: Prevalence of Maternal Infections resulting in malformations by maternal age



Conclusions

- The Forest plot (Figure 1) demonstrates how infrequently maternal infections are coded in the EUROCAT database, with 18 registries having too few cases for analysis
- Antwerp has a considerably higher prevalence rate than other registries and Basque Country is the only significantly increasing registry (Figures 1 & 2)
- Over a 30 year period there seems to be no pattern to the prevalence rate
- The maternal infection most commonly recorded is Congenital CMV, rather than Congenital Rubella Syndrome or Toxoplasmosis
- Approximately half of all cases recorded between 2003 – 2012 have no other congenital anomaly.
- Where another congenital anomaly is recorded, the most frequent is an anomaly of the nervous system
- Prevalence is considerably higher in the <20 age group than any other (Figure 8)

(1) EUROCAT. EUROCAT: Guide 1.3 and Reference Documents. 2013; Available at: <http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf>. Accessed 0704, 2014.

(2) Christensen N, Andersen H, Garne E, Wellesley D, Addor MC, Haeusler M, et al. Atrioventricular septal defects among infants in Europe: a population-based study of prevalence, associated anomalies, and survival. *Cardiol Young* 2013 Aug;23(4):560-567.

(3) Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation 2007 Jun 12;115(23):2995-3014.

Appendix I Outcomes of local registries preliminary investigations into Pan-Europe and individual registry ten year trends

Table I1: Increasing trends

	Antwerp (BE)	Hainaut (BE)	Isle de la Reunion (FR)	Paris (FR)	Saxony Anhalt (DE)	Hungary (HU)	Cork & Kerry (IE)	S E Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Basque Country (ES)	S Portugal (PT)	Vaud (CH)	E Mids & S York (UK)	Thames Valley (UK)	Wales (UK)	Wessex(UK)
Severe CHD													C	F	A			
Atrioventricular septal defect	E					NR						NR						
Tetralogy of Fallot															A			
Cystic adenomatous malformation of lung																	C	NR
Oesophageal atresia with or without trachea-oesophageal fistula						NR												
Duodenal atresia or stenosis						NR												
Ano-rectal atresia and stenosis					E	NR					B						A	

Renal dysplasia						NR					C							
Club foot – talipes equinovarus		NR	F			NR					B	NR						
Craniosynostosis				F					?			NR				A		
Maternal infections resulting in malformations												A C						
Chromosomal	A C D						NR	A D		A								
Down syndrome			F				NR			A		NR						
Edward syndrome						NR		A D		A								NR

Key:

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

NI: Not investigated

NR: Report not returned

Appendix I Outcomes of local registries preliminary investigations into Pan-Europe and individual registry ten year trends

Table I2: Decreasing trends

	Hainaut (BE)	Saxony Anhalt (DE)	Dublin (IE)	S E Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	Norway (NO)	Vaud (CH)	E Mids & S York (UK)	N England (UK)	Wales (UK)	Wessex(UK)
All non-chromosomal anomalies	NR	G		A			NR	E A	NI		A	G	
Microcephaly			A								A	A	
Patent ductus arteriosus			A			F			F	A		A	
Congenital hydronephrosis		B		A		F						B	
Limb reduction			A		?					G		F	
Upper limb reduction			A		NR					G	A	F	
Syndactyly		B	A			F		G		A		B	
Congenital skin disorder	NR				?					B		B	
Genetic syndromes + microdeletions			A									A	
Klinefelter syndrome													NR

Appendix J: Trends by anomaly and registry– website details

Information on the number of cases in each anomaly subgroup, by registry and time period are available on the EUROCAT website: <http://www.eurocatnetwork.eu/ACCESSPREVALENCEDATA/PrevalenceTables>

To access this information, click on the link and you will be direct to our revised prevalence tables web page (see below)

Where am I? -> ACCESS PREVALENCE DATA -> [Prevalence Tables](#)
Direct Link for this page: <http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables>

Prevalence Tables
[Click here to select the Countries / Registries, Anomalies, Years and Data to create your own report](#)
[Click here to see preformatted tables for the last five years combined](#)
[Click here to access the old pre-formatted tables](#)

Example table - Cases and prevalence (per 10,000 births) for all full member registries from 2006 to 2010

Anomaly	LB N	FD N	TOPFA N	LB+FD+TOPFA N	LB+FD+TOPFA Rate (95% CI)	Excluding Chromosomal LB+FD+TOPFA N	Excluding Chromosomal LB+FD+TOPFA Rate (95% CI)
All Anomalies	101879	1957	17392	121219	209.17 (207.99 - 210.35)	104228	179.85 (178.76 - 180.85)
Nervous system	6673	429	4641	11943	20.61 (20.24 - 20.98)	10883	18.79 (18.43 - 19.14)
Neural Tube Defects	1681	172	2779	4632	7.99 (7.76 - 8.23)	4466	7.71 (7.48 - 7.94)
Anencephalus and similar	182	103	1226	1511	2.61 (2.48 - 2.74)	1478	2.55 (2.42 - 2.68)
Encephalocele	209	21	324	554	0.96 (0.88 - 1.04)	530	0.91 (0.84 - 1.00)
Spina Bifida	1290	48	1229	2567	4.43 (4.26 - 4.60)	2458	4.24 (4.08 - 4.41)
Hydrocephalus	1729	107	1005	2841	4.90 (4.72 - 5.09)	2579	4.45 (4.28 - 4.63)
Microcephaly	1044	42	85	1171	2.03 (1.91 - 2.15)	1068	1.85 (1.74 - 1.96)
Arhinencephaly/holoprosencephaly	202	37	416	655	1.13 (1.05 - 1.22)	455	0.79 (0.71 - 0.86)
Eye	2039	24	127	2190	3.78 (3.62 - 3.94)	1718	2.96 (2.83 - 3.11)
Anophthalmos/microphthalmos	459	12	71	542	0.94 (0.86 - 1.02)	440	0.76 (0.69 - 0.83)
Anophthalmos	105	5	23	133	0.23 (0.19 - 0.27)	119	0.21 (0.17 - 0.25)
Congenital cataract	508	1	7	516	0.89 (0.82 - 0.97)	481	0.83 (0.76 - 0.91)

Scroll down for more subgroups

LB = Live Births
FD = Fetal Deaths / Still Births from 20 weeks gestation
TOPFA = Termination of pregnancy for fetal anomaly following prenatal diagnosis

- = Data not available
§ = Incomplete or missing specification of ICD 9 codes

[Click here to view printable version of this table](#)
[Click here to view table details & technical notes](#)
[Click here to view prevalence rate calculations](#)
[Click here to view the interpreting prevalence rates guide](#)
[Click here to view coding of anomalies](#)

You can also access the old style formatted tables

Appendix K: Central Registry Statistical Monitoring Results: Summary table of detected clusters by registry and by anomaly 2011-2012

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Paris (FR)	Isle de Reunion (FR)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	E Mid & S York (GB)	N England (GB)	South West England	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Neural Tube Defects	0	0	0																		
Anencephalus and similar	0	0	0			*															
Encephalocele	0	0	0	*	*	*			*	*	*			*	*						
Spina Bifida	0	0	0																		
Hydrocephalus	0	0	0								*										
Microcephaly	0	0	0			*			*		*				*						
Arhinencephaly/holoprosencephaly	1	0	1	*	*	*			*	*	*	C		*	*						
Anophthalmos/microphthalmos	0	0	0	*	*	*			*	*	*		*		*		*				*
Anophthalmos	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	0	0	0		*	*			*		*				*		*		*		*
Congenital glaucoma	0	0	0	*	*	*	*		*	*	*		*	*	*	*	*		*		*

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Paris (FR)	Isle de Reunion (FR)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	E Mid & S York (GB)	N England (GB)	South West England	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Anotia	0	0	0	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Severe CHD §	1	0	1				C														
Common arterial truncus	0	0	0	*	*	*	*		*	*	*		*	*	*				*		*
Transposition of great vessels	0	0	0								*										
Single ventricle	0	0	0	*	*	*			*	*	*		*		*				*		*
Ventricular septal defect	0	0	0																		
Atrial septal defect	1	0	1									C									
Atrioventricular septal defect	1	0	1	C	*	*					*										
Tetralogy of Fallot	0	1	1													B					
Tricuspid atresia and stenosis	0	0	0	*	*	*	*	*	*		*		*	*	*						
Ebstein's anomaly	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*		
Pulmonary valve stenosis	1	0	1	C						*	*										

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Paris (FR)	Isle de Reunion (FR)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	E Mid & S York (GB)	N England (GB)	South West England	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Pulmonary valve atresia	1	0	1	*	*	*		*	*	*	*				*				C		*
Aortic valve atresia/stenosis §	1	0	1			*	*	*	*	*	*									C	
Hypoplastic left heart	0	0	0			*					*										
Hypoplastic right heart §	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*		*		*		
Coarctation of aorta	1	0	1			*						C									
Total anomalous pulm venous return	1	0	1	*	*	*		*	*	*	*		*	*	*			C			
PDA as only CHD in term infants (>=37 weeks)	0	0	0		*	*	*				*								*		
Choanal atresia	0	0	0		*	*		*	*	*	*				*						*
Cystic adenomatous malf of lung §	1	0	1		*	*		*	*	*	*	C	*	*	*						
Cleft lip with or without palate	1	0	1								C										
Cleft palate	0	0	0																		

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Paris (FR)	Isle de Reunion (FR)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	E Mid & S York (GB)	N England (GB)	South West England	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Oesophageal atresia with or without tracheo-oesophageal fistula	0	0	0			*					*										
Duodenal atresia or stenosis	0	0	0	*		*	*	*	*		*			*	*						
Atresia or stenosis of other parts of small intestine	0	0	0		*	*		*	*	*	*			*	*						
Ano-rectal atresia and stenosis	1	0	1								*					C					
Hirschsprung's disease	0	0	0		*	*			*		*				*						
Atresia of bile ducts	0	0	0	*	*	*	*	*	*	*	*		*	*	*		*		*		*
Annular pancreas	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	0	0			*					*				*						
Gastroschisis	0	0	0								*				*						
Omphalocele	0	0	0						*		*										
Bilateral renal agenesis including	2	0	2		*	*		*	*		*	*			*			C	C		

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Paris (FR)	Isle de Reunion (FR)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	E Mid & S York (GB)	N England (GB)	South West England	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Potter syndrome																					
Renal dysplasia	1	0	1																		C
Congenital hydronephrosis	0	0	0																		
Bladder exstrophy and/or epispadia	0	0	0	*	*			*	*	*	*		*		*				*		
Posterior urethral valve and/or prune belly	0	0	0		*	*			*	*	*			*							
Hypospadias	0	0	0																		
Indeterminate sex	0	1	1	*	*	*	*		*	*	*	B		*	*					*	
Limb reduction	0	0	0																		
Upper limb reduction	0	0	0												*						
Lower limb reduction	0	0	0			*				*	*				*						
Complete absence of a limb	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Paris (FR)	Isle de Reunion (FR)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	E Mid & S York (GB)	N England (GB)	South West England	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Club foot - talipes equinovarus	1	0	1				C										*				
Hip dislocation and/or dysplasia	1	1	2						C					B			*				*
Polydactyly	2	0	2				C				*						C				
Syndactyly	2	0	2				C				*								C		
Craniosynostosis	0	0	0			*				*	*						*				
Congenital constriction bands/amniotic band	1	0	1	*	*	*		*	*	*	*	*	*	C	*						
Situs inversus	0	0	0	*	*	*			*	*	*				*		*		*		*
Conjoined twins	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*			*	*	*	*
Congenital skin disorders	0	0	0			*			*		*				*				*		*
Fetal alcohol syndrome	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*		*
Valproate syndrome §	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Maternal infections resulting in	0	0	0		*	*			*		*		*	*			*	*			

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Paris (FR)	Isle de Reunion (FR)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	E Mid & S York (GB)	N England (GB)	South West England	Thames Valley (GB)	Wales (GB)	Wessex (GB)
malformations																					
Down Syndrome	1	0	1															C			
Patau syndrome/trisomy 13	1	0	1			*										C					
Edward syndrome/trisomy 18	0	0	0																		
Turner syndrome	2	0	2						*						C	C					
Klinefelter syndrome	0	0	0	*	*	*		*	*	*	*			*	*				*		
	26			2	0	0	4	0	1	0	1	4	0	1	1	3	1	3	3	1	1
		3		0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0
			29	2	0	0	4	0	1	0	1	5	0	2	1	4	1	3	3	1	1
	428			25	34	45	16	21	38	31	51	11	20	23	37	7	17	9	19	6	18

Key: GA: Gestational age; DOB: Date of Birth; * Too few cases to run the analysis; # Cluster detected by Date of birth

Appendix L: Details of clusters identified in the individual registry cluster analysis

Anomaly subgroup	Country	Registry	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA (invalid DOB)	Trend summary	Type of cluster
Arhinencephaly/holoprosencephaly	Italy	Emilia Romagna	9	01/10/2009	06/07/2010	1.98	<0.001	11	0	Not tested: Too few cases	New
Severe CHD §	France	Paris	5	28/04/2010	29/04/2010	0.26	0.006	198	0	No Significant change	Old
Atrial septal defect	Italy	Emilia Romagna	48	06/01/2012	14/03/2012	17.07	<0.001	384	1.8	Increasing trend	New
Atrioventricular septal defect	Belgium	Antwerp)	7	22/08/2011	13/12/2011	1.25	0.036	17	0	No Significant change	New
Tetralogy of Fallot	UK	E Mid & S York	7	09/03/2011	17/03/2011	0.74	0.039	151	0	No Significant change	New
Pulmonary valve stenosis	Belgium	Antwerp	17	03/02/2010	22/03/2011	6.92	0.028	26	7.7	Non-linear change	New

Anomaly subgroup	Country	Registry	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA (invalid DOB)	Trend summary	Type of cluster
Pulmonary valve atresia	UK	Thames Valley	8	16/03/2010	13/12/2010	2.11	0.034	12	0	Not tested: Too few cases	New
Aortic valve atresia/stenosis §	UK	Wales)	8	04/05/2010	29/06/2010	1.36	0.046	37	0	No Significant change	New
Coarctation of aorta	Italy	Emilia Romagna	5	27/04/2010	01/05/2010	0.24	0.008	74	4.1	Non-linear change	New
Total anomalous pulm venous return	UK	South West England	5	25/01/2011	20/05/2011	0.75	0.039	10	0	Not tested: Too few cases	Continuing
Cystic adenomatous malf of lung §	Italy	Emilia Romagna	12	15/04/2010	23/02/2011	3.65	0.014	18	0	Not tested: Too few cases	New
Cleft lip with or without palate	Ireland	SE Ireland	5	15/05/2011	09/06/2011	0.42	0.029	25	0	No Significant change	New

Anomaly subgroup	Country	Registry	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA (invalid DOB)	Trend summary	Type of cluster
Ano-rectal atresia and stenosis	UK	E Mid & S York	6	08/04/2011	14/04/2011	0.48	0.022	106	0.9	No Significant change	New
Bilateral renal agenesis including Potter syndrome	UK	South West England	5	13/01/2012	04/02/2012	0.39	0.023	26	0	No Significant change	New
Bilateral renal agenesis including Potter syndrome	UK	Thames Valley	5	17/11/2011	16/03/2012	0.78	0.045	10	0	Not tested: Too few cases	New
Renal dysplasia	UK	Wessex	13	20/01/2010	13/04/2010	3.09	0.022	57	0	No Significant change	New
Indeterminate sex	Italy	Emilia Romagna	6	30/01/2010	04/02/2011	1.62	0.049	8	0	Not tested: Too few cases	New
Club foot - talipes equinovarus	Paris	Paris	72	27/09/2009	23/02/2011	43.47	<0.001	131	0	Non-linear change	Continuing

Anomaly subgroup	Country	Registry	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA (invalid DOB)	Trend summary	Type of cluster
Hip dislocation and/or dysplasia	Ireland	Cork and Kerry	58	21/10/2010	28/04/2011	23.99	<0.001	196	2.6	Non-linear change	New
Hip dislocation and/or dysplasia	Netherlands	N Netherlands	144	10/08/2009	24/01/2011	98.31	<0.001	337	0	Non-linear change	New
Polydactyly	France	Paris	70	10/04/2010	01/10/2011	42.1	<0.001	121	0	Increasing trend	Continuing
Polydactyly	UK	N England	5	20/05/2011	16/06/2011	0.38	0.016	21	4.8	No Significant change	New
Syndactyly	France	Paris	15	19/05/2011	23/11/2011	4.14	0.008	34	0	Increasing trend	New
Syndactyly	UK	Thames Valley	18	28/06/2010	15/11/2011	8.15	0.037	25	4	Increasing trend	New
Congenital constriction bands/amniotic band	Netherlands	N Netherlands	5	25/12/2009	09/08/2010	1.03	0.029	7	0	Not tested: Too few cases	New

Anomaly subgroup	Country	Registry	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA (invalid DOB)	Trend summary	Type of cluster
Down Syndrome	UK	South West England	5	02/04/2010	02/04/2010	0.39	<0.001	604	8.4	No Significant change	Old
Patau syndrome/trisomy 13	UK	E Mid & S York	6	26/07/2010	03/08/2010	0.46	0.015	79	3.8	No Significant change	Old
Turner syndrome	Switzerland	Vaud	10	26/11/2009	18/02/2011	3.48	0.022	12	0	Not tested: Too few cases	New
Congenital constriction bands/amniotic band	UK	E Mid & S York	14	20/01/2011	24/02/2011	2.02	<0.001	87	3.4	No Significant change	Old

Key: GA: Gestational age; DOB: Date of Birth; * Too few cases to run the analysis; # Cluster detected by Date of birth

Anomaly subgroup	Country	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated gestation	Trend summary
Neural Tube Defects	UK	5	04/09/2011	04/09/2011	0.83	0.042	1286	0.8	
Arhinencephaly/holoprosencephaly	Italy	13	01/10/2009	26/08/2010	4.04	0.009	19	0	
Severe CHD	France	5	28/04/2010	29/04/2010	0.4	0.047	310	0.3	
Ventricular Septal Defect	Italy	5	14/12/2011	14/12/2011	0.74	0.029	1156	1.2	Significant upward trend
Atrial septal defect	Italy	58	13/04/2011	27/06/2011	24.14	<0.001	493	1.6	Significant upward trend
Atrioventricular Septal Defect	Belgium	10	02/06/2011	13/12/2011	2.64	0.041	21	4.8	Significant upward trend
Coarctation of Aorta	Italy	5	27/04/2010	01/05/2010	0.32	0.029	100	4	Significant non-linear change
Cleft lip with or without palate	UK	5	14/02/2012	14/02/2012	0.57	0.01	877	1.5	
Duodenal atresia or stenosis	Belgium	5	31/03/2010	12/05/2010	0.33	<0.001	12	0	
Congenital hydronephrosis	UK	7	13/04/2010	13/04/2010	0.72	0.002	1119	1.3	Significant non-linear change
Hip dislocation and or dysplasia	Ireland	72	09/10/2010	28/04/2011	36.57	<0.001	281	1.8	Significant non-linear change
Polydactyly	France	10	12/07/2010	24/07/2010	1.52	0.023	182	0	Significant upward trend
Syndactyly	France	13	19/05/2011	16/08/2011	3.13	0.023	54	0	Significant upward trend
Craniosynostosis	France	20	13/05/2010	02/09/2011	9.24	0.043	30	0	Significant upward trend
Conjoined twins	UK	10	21/11/2011	02/03/2012	2.19	0.036	33	0	
Turner syndrome	Belgium	8	12/04/2010	24/06/2010	1.38	0.035	29	3.4	