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european surveillance of congenital anomalies

EUROCAT Statistical Monitoring Report – 2011

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Acknowledgements

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EUROCAT 2011 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 95,000 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 and 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 2002-2011, and include data from 26 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 syndromes[1]

- In this year's pan-Europe analysis, *decreasing* trends were found for **Neural tube defects (NTDs)** which declined on average by 1.4% per year from 9.90 per 10,000 births in 2002-2003 to 8.96 per 10,000 births in 2010-2011. **Anencephalus** decreased on average by 2.3% per year from 4.08 per 10,000 births in 2002-2003 to 3.54 per 10,000 births in 2010-2011. Despite the decline in prevalence, the magnitude in annual average change for NTDs continues to be very small, indicating a need for reinforced public health actions to promote adequate periconceptional folic acid levels for pregnant women.

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

- Although there was an overall decreasing trend in **Congenital heart defects (CHD)** from 2002, there were *increasing* trends for specific subgroups of **Severe CHD**: **Atrioventricular septal defect (AVSD)** increased on average 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; and **Pulmonary valve atresia (PVA)** increased on average by 3.7% per year from 0.74 per 10,000 births in 2002-2003 to 1.07 per 10,000 births in 2010-2011**.** Increasing trends were once again detected for **Single ventricle** which increased by 6.0% per year from 0.49 per 10,000 births in 2002-2003 to 0.70 per 10,000 births in 2010-2011 and **Tetralogy of Fallot** which increased on average by 2.25% per year from 2.61 per 10,000 births in 2002-2003 to 3.02 per 10,000 births in 2010-2011**.** These increasing trends require monitoring and further investigation.

- *Increasing* trends were found for some gastrointestinal anomalies. A new trend was detected in **Ano-rectal atresia and stenosis** which 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. Increasing trends were detected once again for **Duodenal atresia and stenosis** (N.B. trends reported here exclude babies with chromosomal anomalies such as Down syndrome) which rose by 3.1% from 0.75 per 10,000 births in 2002-2003 to 0.94 per 10,000 births in 2010-2011, and **Atresia and Stenosis of other parts of the small intestine** which increased on average by 4.0% per year from 0.57 per 10,000 births in 2002-2003 to 0.88 per 10,000 births in 2010-2011. For the fourth consecutive year, a decreasing trend was reported for **Atresia of the bile ducts (biliary atresia),** with prevalence falling by an average of 5.8% per year from 0.32 per 10,000 births in 2002-2003 to 0.18 per 10,000 births in 2010-2011.

- An increasing trend was again detected for the skeletal anomaly **Craniosynostosis,** which increased on average by 2.8% per year rising from 1.41 per 10,000 births in 2002-2003 to 1.90 per 10,000 births in 2010-2011. Although it was suggested that increasing ascertainment of late diagnosed cases across many of the registries may partly explain the increase in this anomaly, a true increase in the birth prevalence of Craniosynostosis cannot be ruled out.

Chromosomal anomalies

- *Increasing* trends were again detected in **Chromosomal anomalies**, due to the increasing trends in **Down syndrome and Edwards syndrome**. **Down syndrome** increased on average by 1.4% per year from 18.71 per 10,000 births in 2002-2003 to

22.00 per 10,000 births in 2010-2011. **Edwards syndrome** increased by an average of 1.9% per year from 4.19 per 10,000 births in 2002-2003 to 5.14 per 10,000 births in 2010-2011. After adjusting for the effect of maternal age which has been rising across Europe, the increasing trend in **Edwards syndrome** disappeared, while a significant decreasing trend was detected for **Down syndrome** (the adjusted prevalence rate decreased from 21.74 per 10,000 births in 2002-2003 to 21.06 per 10,000 births in 2010-2011)**.** A decreasing trend was again detected for **Klinefelter syndrome** which decreased by approximately 4.4% per year from 0.83 per 10,000 births in 2002-2003 to 0.66 per 10,000 births in 2010-2011. There is some suggestion that this is a consequence of changes in prenatal screening due to implementation of first trimester screening tests and less use of invasive prenatal testing.

Clusters

Seven new clusters in time were detected in individual registry populations which following preliminary investigations could not be explained by information held within the registries: **Total anomalous venous return** (5 cases observed versus 1 expected)**; Coarctation of Aorta** (12 cases observed versus 5 expected); **Anorectal atresia and stenosis** (5 cases observed versus 1 expected)**; Hypospadias** (37 cases observed versus 16 expected)**; Club foot** (6 cases observed versus 1 expected)**; Patau syndrome** (5 cases observed versus <1 expected)**; Turner syndrome** (14 cases observed versus 2 expected)**;** and one continuing cluster **Arhinencephaly/ holoprosencephaly** (23 cases observed versus 11 expected). The registries reported that these clusters, identified in the period 2010-2011, would remain under surveillance. The country cluster analysis detected a cluster of **Situs inversus** (5 cases observed versus 1 expected), which is currently under investigation.

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 2011 http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2011.pdf).

We report here the results up to birth year 2011. 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 to conduct their own monitoring on more recent data, and reports of any such analyses that may have been conducted up to June 2013 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 2011 trend analysis

At the time of statistical monitoring in Spring 2013, there were 31 full member registries in EUROCAT. Twenty-six full member registries met the inclusion criteria for both the individual 10-year trend analysis (see Box 1), and the pan-Europe analysis.

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 2001 included (i.e. 2002-2011 or 2002-2010)
- Individual registry analysis: Registries with 8 or 10 years of continuous data included (i.e. 2002-2011 or 2003-2010)

Ukraine, South West England, French West Indies and Valencia Region were excluded from the trend analysis as they did not meet the inclusion criteria for the time period coverage. Styria was excluded due to being more than one year late with their data.

3.2 Registries included in the 2011 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 (2007-2011) 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 Statistical Monitoring Protocol 2011 http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2011.pdf).

[22] EUROCAT Working Group on the Management of Clusters and Environmental Exposure Incidents, 2003

Box 2 Registry inclusion criteria for cluster analysis

- Registries must have transmitted year 2007-2011 data
- 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 2011 data to EUROCAT Central Registry by Feb 15th 2013. Four of the twenty-two registries were excluded from the cluster monitoring for the following reasons: Mainz, Saxony-Anhalt and Norway did not have full date of birth information for the years 2007-2011; and French West Indies had less than 5 years continuous data.

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 (EUROCAT Data Management Program). 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 26 EUROCAT registries were transmitted to Central Registry in February 2013. Cases included livebirths, stillbirths from 20 weeks gestational age and terminations of pregnancy for fetal anomaly. In the period 2002-2011, 83.0% of cases were liveborn, 1.8% were stillborn and 15.2% were terminations of pregnancy for fetal anomaly. Type of birth was

unrecorded for a small proportion of cases (0.04%) 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 A for the anomaly subgroup inclusion list). Changes to the EUROCAT list of subgroups implemented in January 2012 means there are currently fewer subgroups of congenital anomalies compared to previous years which also explains the decrease in the number of congenital anomaly subgroups included in statistical monitoring (seehttp://www.eurocat-network.eu/content/EUROCAT-Guide-1.3-Chapter-3.3-Jan2012.pdf). 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 (2010-2011) that are less than 18 months in length, was run on 72 EUROCAT subgroups of congenital anomalies (see Appendix A for the anomaly subgroup inclusion list and Appendix B for summary of statistical methods).

The following analyses were carried out:

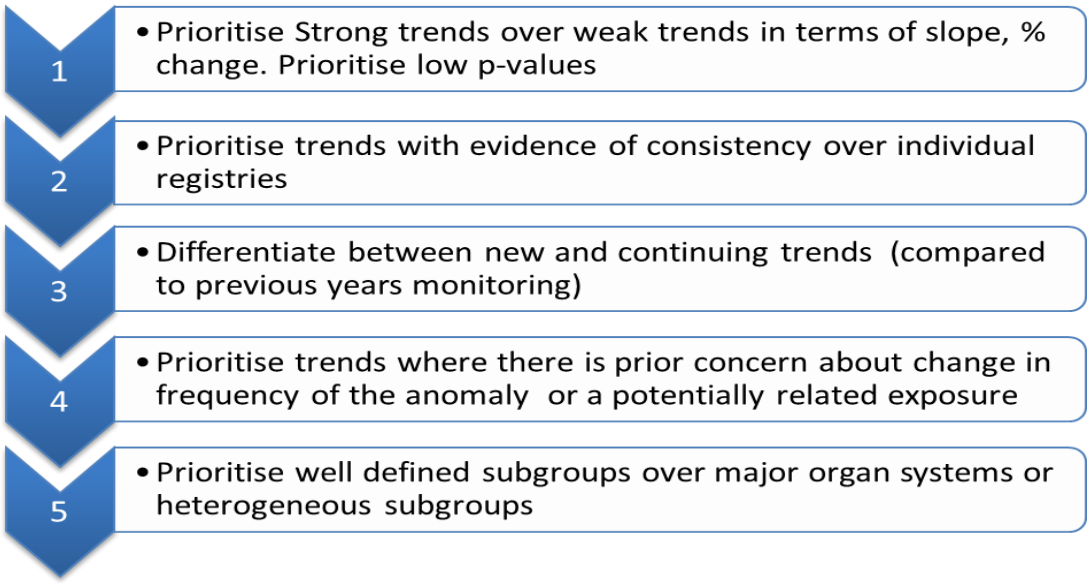
- Analysis of individual registry trends for 26 registries covering 6.28 million births (2002-2011)
- Analysis of pan-European trends for 26 registries covering 6.46 million births (2002-2011)
- Cluster analysis to detect unusual aggregations of cases in 18 registries covering 1.01 million births (2010-2011)
- Country cluster analysis to detect unusual aggregations of cases in countries with more than one registry, 2010-2011 (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 2013. 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 trends[3]



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). The significant increasing and decreasing trends selected for registry investigation are listed in Appendix D. Registries were also given the option to investigate and report on increasing and decreasing trends unique to their registry.

Registries reported their findings to Central Registry using standard reporting templates (see EUROCAT Statistical Monitoring Protocol 2011). 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 C for a summary).

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

[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.

- 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.

- Graphs and forest plots 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 25 of the 26 registries asked to investigate significant trends detected in pan-Europe monitoring (see Table 1). Central Registry trend investigation reports into 8 anomaly subgroups are also available (see Appendix G).

Preliminary reports of cluster investigations were received from 9 registries with newly detected clusters in this year's monitoring (see Table 2 and Appendices J & K).

14 registries stated that they would notify the results and the findings of their preliminary investigations into clusters and trends to public health authorities.

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 Zagreb, June 2013. The Central Registry trend investigation reports were also presented at the RLM (see Appendix G). 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

In addition to excluding chromosomal anomalies, cases with genetic syndromes and microdeletions or skeletal dysplasias are also now excluded from trend and cluster monitoring of non-chromosomal anomalies. The pan-Europe analysis adjusts for the effect of registry by fitting a multi-level poisson regression model. Forest plots now include individual registry prevalence rates per 10,000 births.

For a full description of statistical software updates, please see the annual Statistical Monitoring Protocol (http://www.eurocat-network.eu/content/Stat-Mon-Protocol-(May-2013)-2011.pdf). All changes identified in the protocol should be taken into consideration when comparing the results of this year's statistical monitoring with monitoring conducted in previous years.

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 17 subgroups (see Figure 17 and Appendix D). Of the 32 trends detected, 26 were also detected in Statistical Monitoring 2010, ten of which were increasing trends and sixteen were decreasing.

For ten year trends in individual registries a total of 1635 chi squared tests were performed with 16% being statistically significant compared with the 5% expected by chance. The analysis identified a total of 118 increasing trends and 146 decreasing trends (see Table 1). This section provides details of the results, investigations and interpretation of trends in specific anomaly subgroups that were prioritised for investigation (see Appendix D).

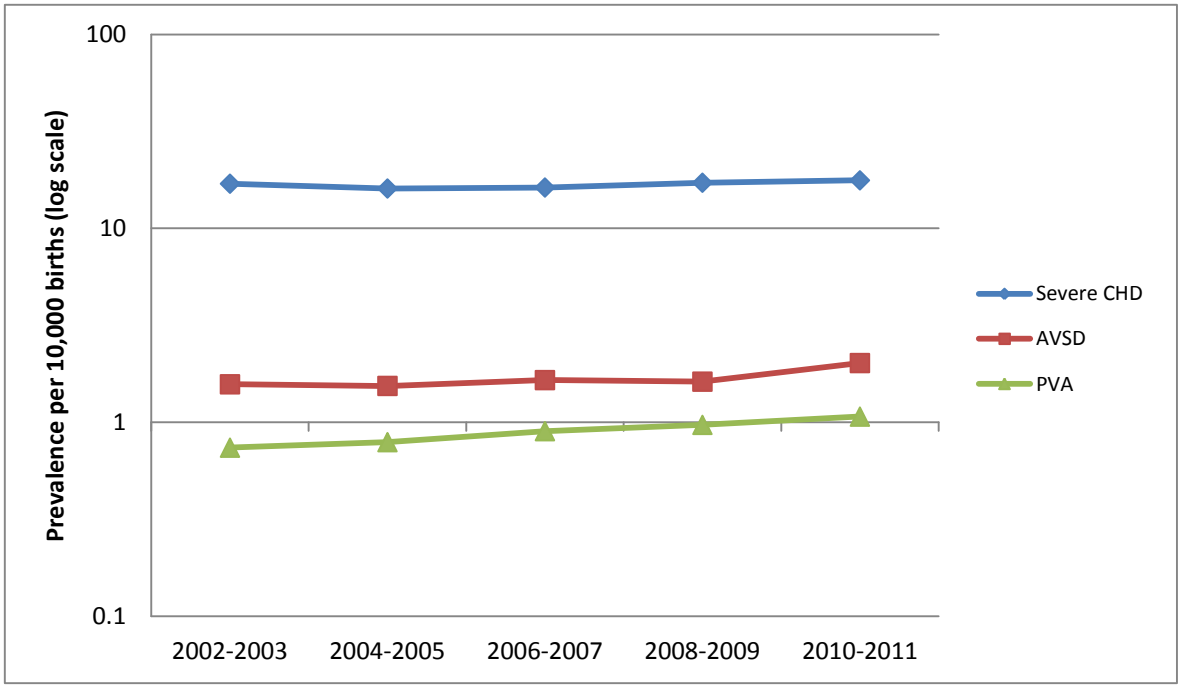
4.2 Increasing trends identified at pan-Europe level

New increasing trends were identified in the pan-Europe analysis for the following anomaly subgroups: Severe CHD; Atrioventricular septal defect (AVSD); Pulmonary valve atresia (PVA); Ano-rectal atresia and stenosis and Club foot. Trends previously reported in the 2010 Report were once again found for the following anomaly subgroups: Single ventricle; Tetralogy of Fallot; Cystic adenomatous malformation of the lung; Duodenal atresia; Atresia and stenosis of other parts of the small intestine; Renal dysplasia; Craniosynostosis; Chromosomal anomalies; Down syndrome/trisomy 21 and Edwards syndrome/trisomy 18.

4.2.1 New increasing trends identified at pan-Europe level

New increasing trends were found for three subgroups of cardiac anomalies: Severe CHD, AVSD and PVA (see Figure 17). **Severe CHD** is a EUROCAT derived subgroup that combines 13 subgroups of severe CHD, including AVSD and PVA. The pan-Europe analysis showed that the prevalence of severe CHD had increased on average by 1.74% per year from 16.19 per 10,000 births in 2002-2003 to 17.68 per 10,000 births in 2010-2011 (see Figures 2 and 17). The general pattern of the Severe CHD trend showed that it was increasing in almost half of the registries, but it was only significantly increasing in East Midlands and South Yorkshire, (see Appendix E). Preliminary investigations by this registry indicated that the increasing trend was explained by changes in case ascertainment due to the recent acquisition of data from a cardiac specialist centre.

Figure 2: Prevalence of severe cardiac anomalies showing a significant increase in the pan-Europe analysis



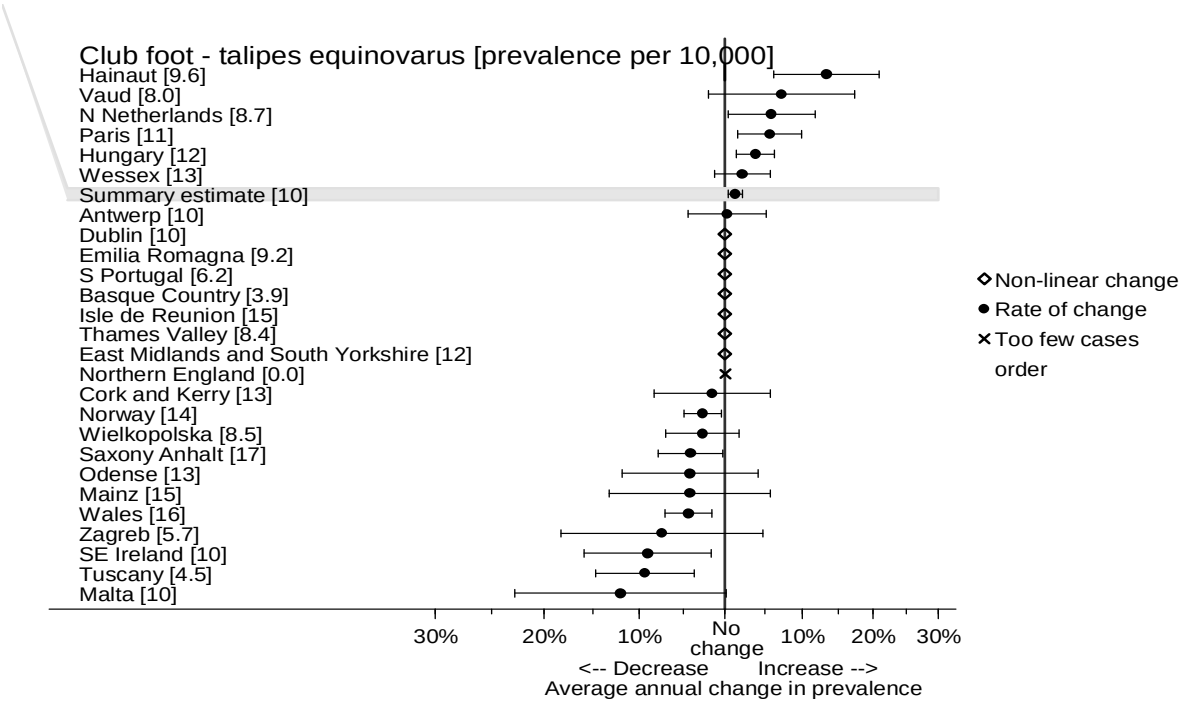
AVSD is defined as a central defect of the cardiac septa and a common atrioventricular valve, and includes primum ASD defects. This condition requires surgery. The affected infants may develop cardiac symptoms within the first few months after birth and may have growth restriction. The pan-Europe analysis showed that the prevalence of AVSD increased on average by 2.48% per year from 1.57 per 10,000 births in 2002-2003 to 2.02 per 10,000 births in 2010-2011. Almost a third of the registries had too few cases to be included in individual registry analysis. Only two registries, Hungary and Wales, had statistically significant increasing trends (see Appendix E). The Wales registry reported that they were currently investigating all cardiac data including AVSD. It was suggested that better antenatal diagnosis may be a contributing factor to increasing prevalence. Hungary did not send a report.

Pulmonary valve atresia (PVA), is defined as a lack of patency or failure of formation altogether of the pulmonary valve, resulting in obstruction of the blood flow from the right ventricle to the pulmonary artery. In the pan-Europe analysis the prevalence of PVA increased on average by 3.70 % per year from 0.74 per 10,000 births in 2002-2003 to 1.07 per 10,000 births in 2010-2011. Whilst almost two thirds of the registries had too few cases to allow individual registry analysis (see Appendix E), statistically significant increasing

trends were detected in the two Italian registries, Emilia Romagna and Tuscany, which are currently under investigation.

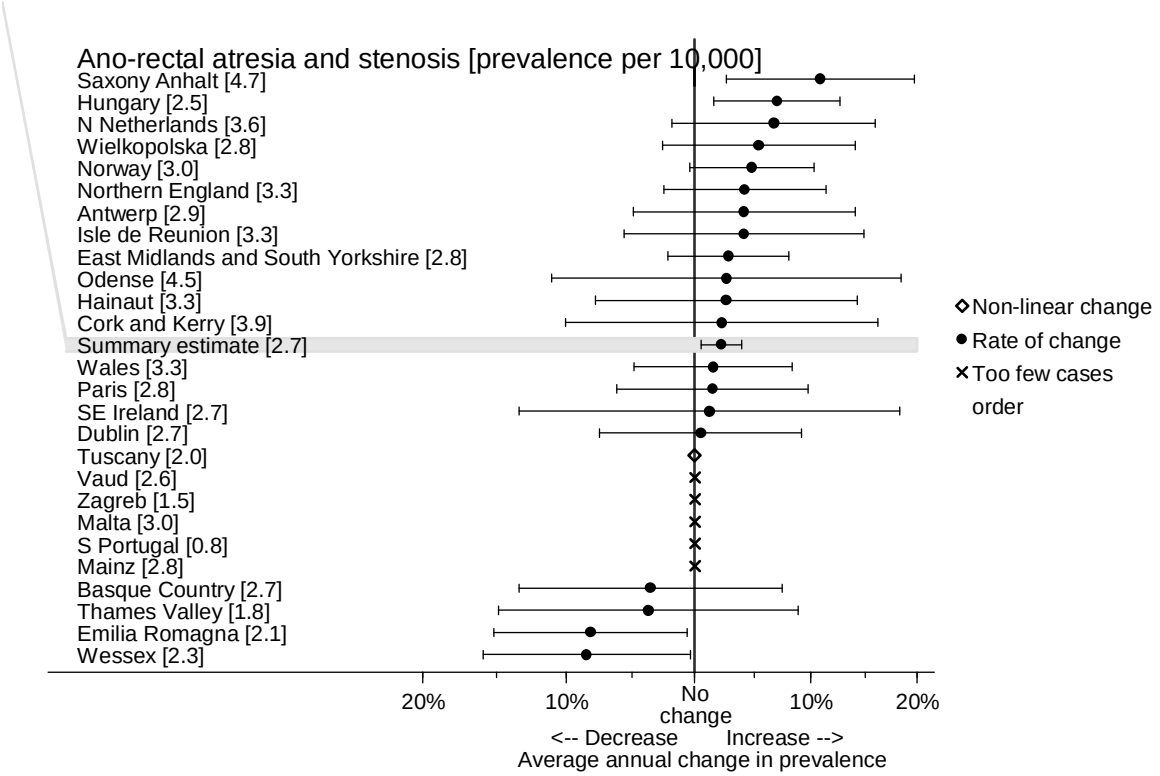
Clubfoot talipes is a foot anomaly with equinus of the heel, varus of the hindfoot and adductus of the forefoot**.** A new increasing trend for this anomaly was detected in this year's pan-Europe analysis. The prevalence of this anomaly increased on average by an estimated 1.27% per year from 10.09 per 10,000 births in 2002-2003 to 10.97 per 10,000 births in 2010-2011. Statistically significant increasing trends were detected in 4 registries: Hainaut, N Netherlands, Paris and Hungary (see Figure 3). Hainaut reported that the increasing trend was likely to be a consequence of local coding changes i.e. the registry now includes clubfoot cases associated with other malformations such as spina bifida whereas previously only isolated clubfoot cases were included. The registry investigation is ongoing. N Netherlands reported that the increasing trend was a consequence of changes in registry methods regarding informed consent and notification of anomalies i.e. since 2010 a case may be included in the registration when the parents do not respond to letters of the registration asking permission (called "non responders"). For these cases, key variables such as type of birth and type of congenital anomaly are notified in the registry. When the registry excluded non-responders, no increase in clubfoot was found. Paris confirmed the trend and proposed further surveillance as no obvious explanation was found. A cluster of clubfoot cases was also detected in Paris during the monitoring period. Hungary did not send a report.

Figure 3 Average annual change in prevalence in Clubfoot by registry



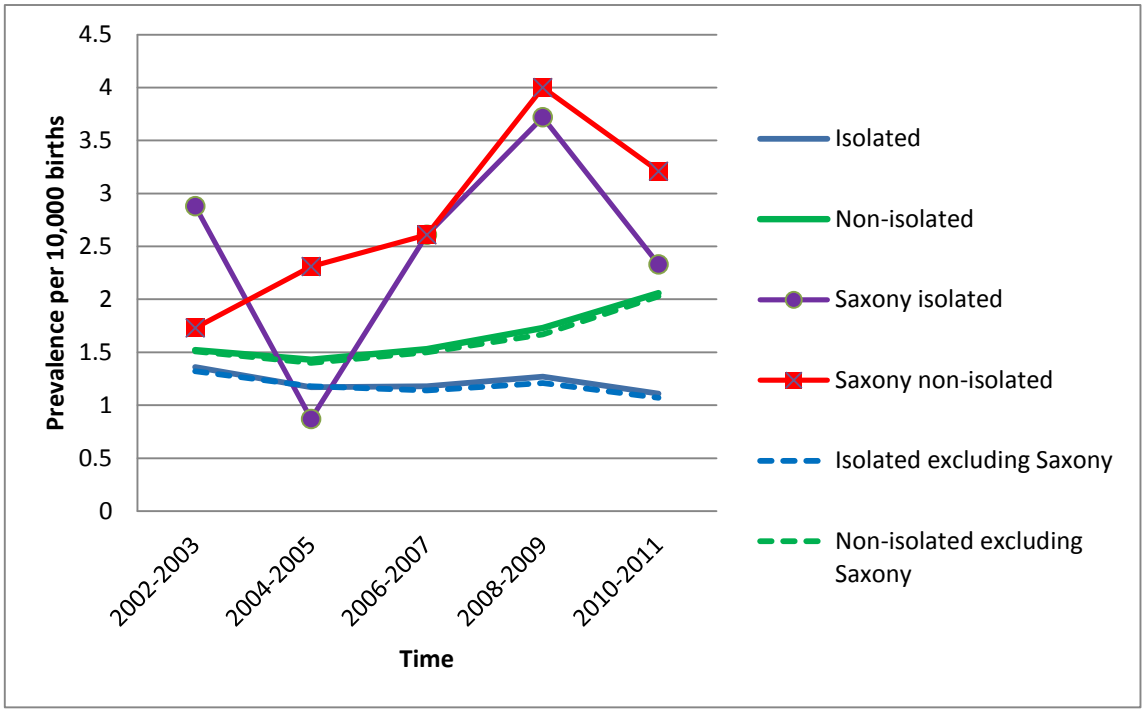
A new increasing pan-Europe trend was detected for **Ano-rectal atresia and stenosis.** Ano-rectal malformations, a group of congenital anomalies which commonly affect the gastro-intestinal tract and are characterised by a complete failure of the rectum to communicate with the anus or a narrowing of the ano-rectal canal. This anomaly requires surgery in the neonatal period. Suspected risk factors for this anomaly include maternal lifestyle choices such as smoking and alcohol intake, chronic health conditions such as maternal diabetes, diabetes and epilepsy. There is also evidence to suggest that Ano-rectal atresia and stenosis is more likely to occur in multiple births and with assistive reproductive technologies. Prevalence increased on average by an estimated 2.4 % per year from 2.72 per 10,000 births in 2002-2003 to 3.13 per 10,000 births in 2010-2011. The general trend pattern showed that it was increasing in 16 registries, 12 of which had annual average increasing prevalence higher than the EUROCAT average (see Figure 4). It was only significantly increasing in 2 registries, Saxony-Anhalt and Hungary.

Figure 4 Average annual change in prevalence in Ano-rectal atresia and stenosis by registry



A Central Registry investigation was conducted (see Appendix G for full report) 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. The increasing trend was only seen when ano-rectal atresia was associated with other anomalies (i.e. non-isolated) and this trend did not change when data from Saxony-Anhalt were excluded (see Figure 5). 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.

Figure 5: Prevalence of Anorectal atresia and stenosis, by isolated/ non-isolated anomaly, including/ excluding Saxony-Anhalt, 2002-2011



4.2.2 Continuing increasing trends identified at pan-Europe level

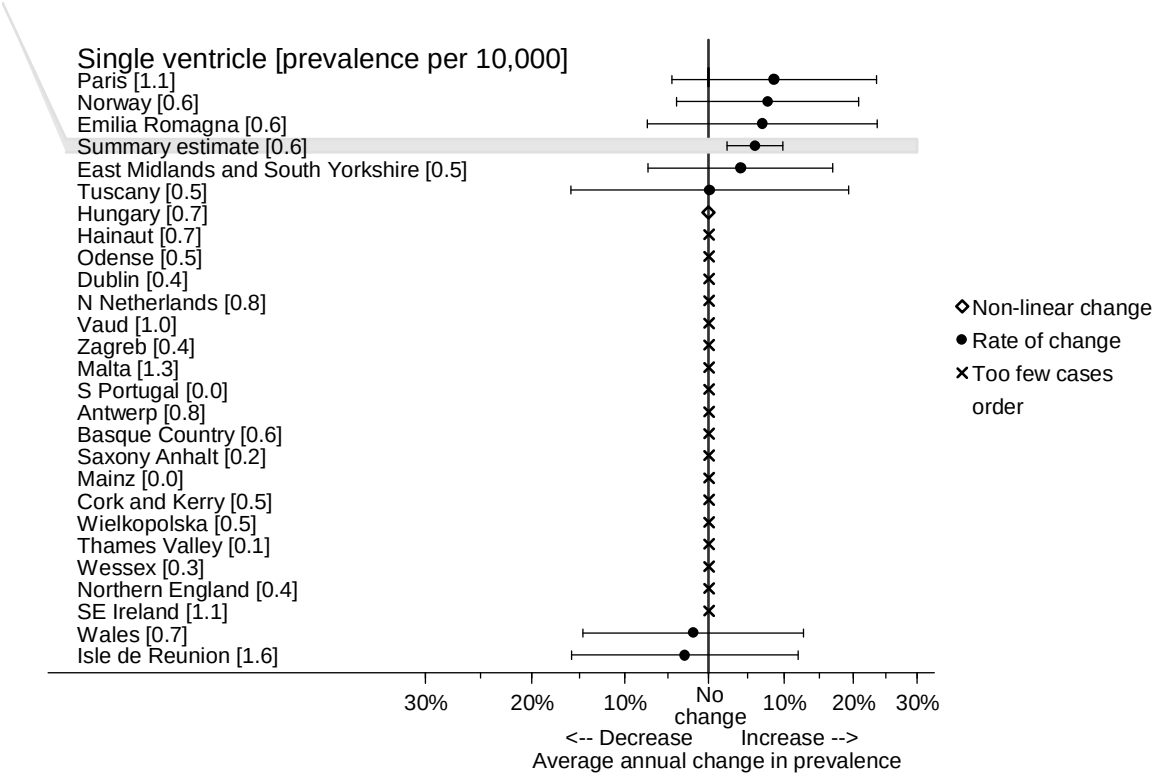
All ten of the continuing increasing trends detected in this year's monitoring were investigated and reported on in last year's (2010) report. This section will provide an overview of the trends and outline similarities and differences in the trends between each of the time periods.

The prevalence rates of Single ventricle and Tetralogy of Fallot, both of which are severe types of cyanotic CHD, increased again in this year's statistical monitoring. **Single ventricle** is a severe congenital cardiac anomaly. This year's Pan-Europe analysis showed that the prevalence of single ventricle had increased on average by 6.03% per year from 0.49 per

10,000 births in 2002-2003 to 0.65 per 10,000 births in 2010-2011 (see Figures 6 and 17). In the 2010 annual statistical monitoring this anomaly had increased on average by 5.9% per year from 0.53 per 10,000 births in 2001-2002 to 0.74 per 10,000 births in 2009-2010. A review of the trend over a longer time period by Central Registry showed that historically this trend has actually been decreasing over time. The prevalence per 10,000 births was 1.08 during the ten year period 1982-1991 and 0.76 per 10,000 births during the 10 year period

1992-2001. Compared to other types of CHD, single ventricle is rare. A total of eighteen registries had too few cases to allow for individual registry analysis. Statistically significant trends were not detected in 7 of the remaining registries (see Figure 6). The Central Registry investigation report can be found in Appendix G. The increasing trend detected for **Tetralogy of Fallot** which had increased on average by 2.25% per year from 2.61 per 10,000 births in 2002-2003 to 3.02 per 10,000 births in 2010-2011 was not prioritised for investigation.

Figure 6 Average annual change in prevalence in Single ventricle by registry



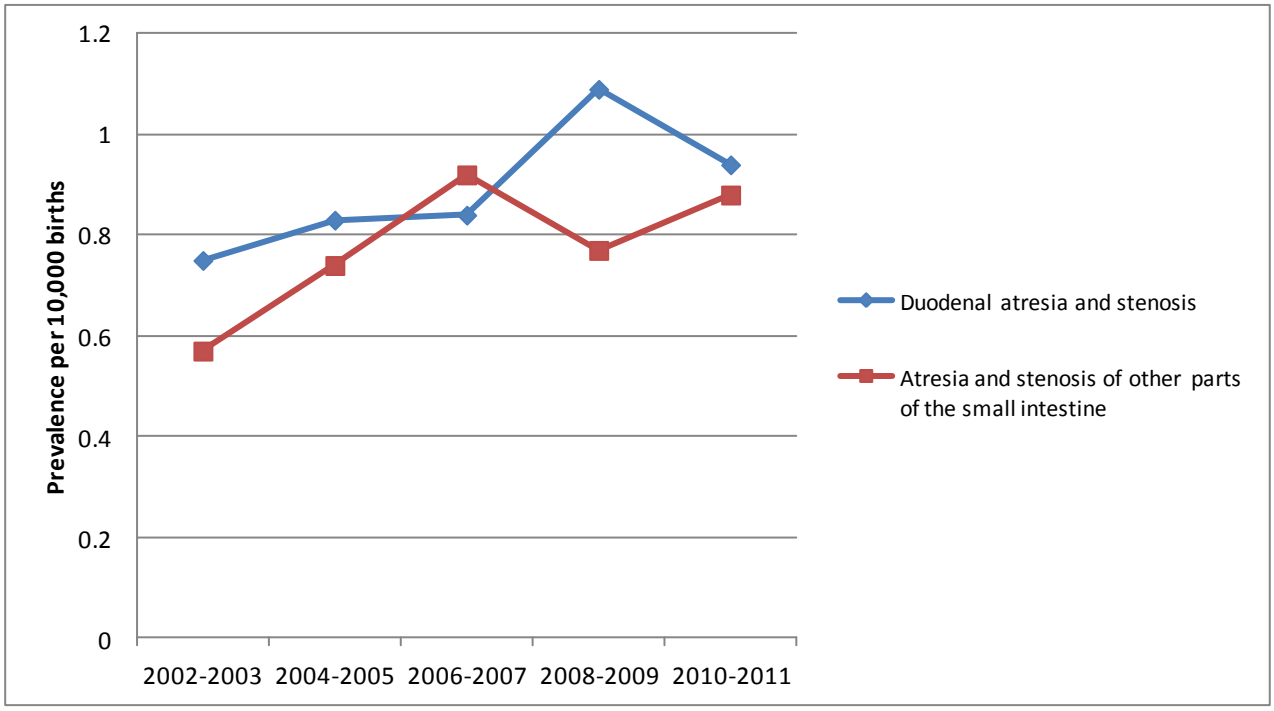
For the third consecutive year, an increasing pan-Europe trend was detected for **Cystic adenomatous malformation of the lung (CCAM)** a rare condition in which a benign mass of abnormal lung tissue is present in a section of the lung. During this year's statistical monitoring, the prevalence of this anomaly increased on average by 7% per year with the prevalence rising from 0.46 per 10,000 births in 2002-2003 to 1.06 per 10,000 births in 2010-2011 (see Figure 17). Individual increasing trends were observed in Wessex and Norway. A similar increasing, pattern was observed in the 2010 annual statistical monitoring, with the prevalence of CCAM increasing on average by 7.8% per year rising from 0.51 per 10,000 births in 2001-2002 to 1.11 per 10,000 births in 2009-2010. During this period statistically significant increasing trends were observed in two individual registries, Wales and East

Midlands and South Yorkshire. 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. This increasing trend is currently under investigation by EUROCAT.

Once again increasing pan-European trends were detected for two of the numerically smaller subgroups of digestive system anomalies, Duodenal atresia and stenosis and Atresia and stenosis of other parts of the small intestine (see Figures 7 &17). In this year's analysis, **Duodenal atresia and stenosis** increased on average each year by 3.13% from 0.75 per 10,000 births in 2002-2003 to 0.94 per 10,000 births in 2010-2011. In the 2010 annual statistical monitoring the magnitude of change was slightly stronger with the prevalence increasing on average by 4.4% per year from 0.73 per 10,000 births in 2001-2002 to 1.03 per 10,000 births in 2009-2010. Last year significant increasing trends were identified in two registries Wielkopolska and Wales. However, in this year's monitoring only Wales had a significant increasing trend. The registry confirmed the trend, but a lack of resources prevented them from looking at this anomaly more closely. It was also noted by Wales that despite the rise in trend the absolute number of cases remained quite small.

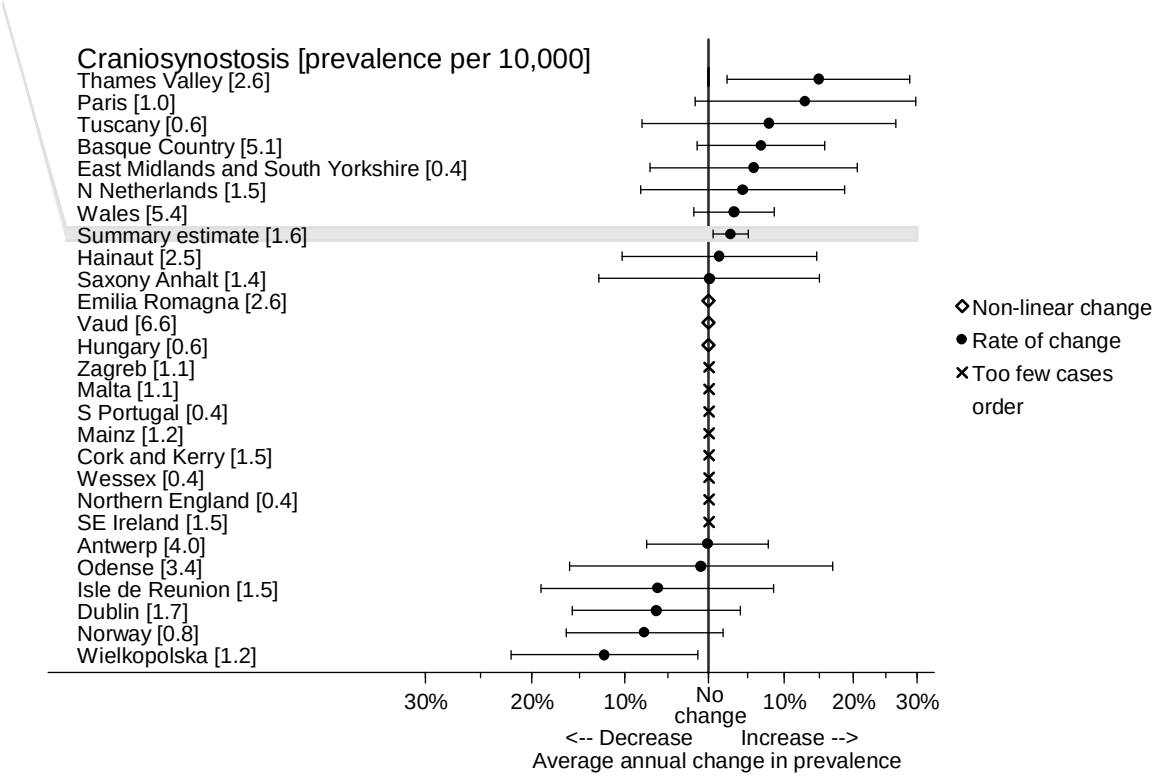
In this year's monitoring **Atresia and Stenosis of other parts of the small intestine** increased from 0.57 per 10,000 births in 2002-2003 to 0.88 per 10,000 births in 2010-2011, with an estimated annual average change of 3.96%. In last year's monitoring the estimated magnitude of average change was slightly stronger at 4.4%, with the prevalence increasing from 0.55 per 10,000 births in 2001-2002 to 0.96 per 10,000 births in 2009-2010. This year statistically significant increasing trends were detected in the Emilia Romagna and Hungary registries (last year no single registry had a significant individual increasing trend). Emilia-Romagna reported that they have a new system for ascertaining cases from their surgical units and that duodenal atresia and atresia and stenosis of other parts of the small intestine are being reported using the same code. The registry will attempt to rectify this problem.

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



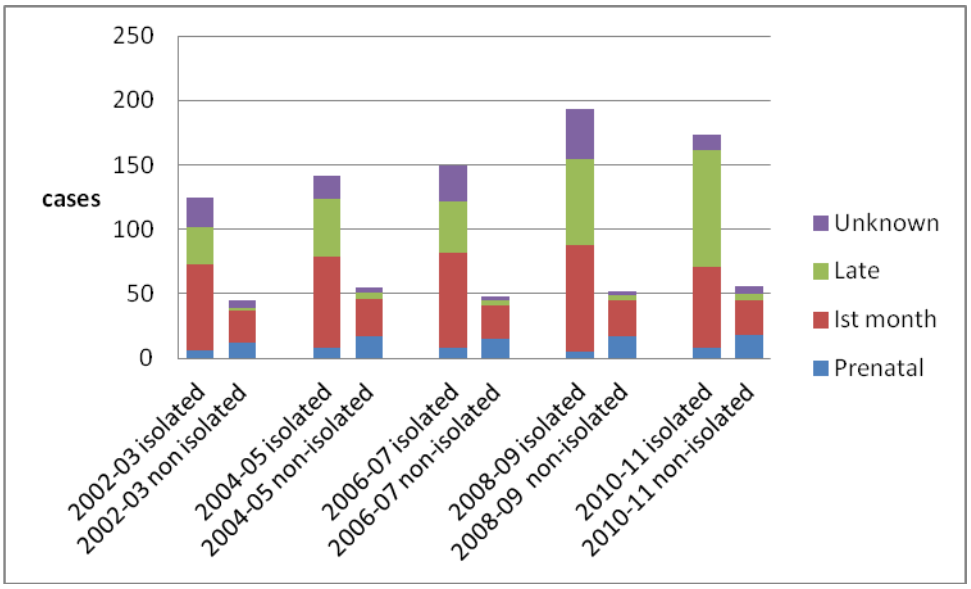
Craniosynostosis is a rare skeletal anomaly where the cranial sutures, which are open at birth to allow the newborn's head to mould as it passes through the birth canal and to facilitate rapid growth in infancy and childhood, fuse prematurely. Surgery is the recommended treatment within the first year of life. If untreated, this anomaly can lead to problems with vision and hearing and can lead to raised intracranial pressure and intellectual impairment. Most cases are thought to be genetic; occurring either as part of a genetic syndrome of as an isolated anomaly, but as the different types are not increasing at a uniform rate there may also be environmental factors involved, with evidence of an association with Valproic Acid. The prevalence of craniosynostosis increased on average by 2.79% per year rising from 1.41 per 10,000 births in 2002-2003 to 1.90 per 10,000 births in 2010-2011. In the 2010 annual statistical monitoring the magnitude to change was slightly stronger with the prevalence increasing on average by 3.6% per year rising from 1.37 per 10,000 births in 2001-2002 to 2.07 per 10,000 births in 2009-2010. This year statistically significant individual increasing trends were only detected in the Thames Valley registry (see Figure 8).

Figure 8 Average annual change in prevalence in Craniosynostosis by registry



Following preliminary investigation, Thames Valley reported that the increasing trend had occurred due to changes in case ascertainment, as the registry had access to paediatric admissions lists since 2006. Whilst non-significant increasing trends were observed in 8 registries, in general this is a rare defect as a further 8 registries had too few cases to be included in the monitoring of this anomaly. In the previous year's statistical monitoring Individual increasing trends were detected in four registries including Thames Valley. An investigation by Central Registry also concluded that increasing ascertainment of late diagnosed cases across many of the registries may be contributing to the trend (see Figure 9). Nevertheless, EUROCAT will continue to monitor this congenital anomaly in case the trend is real. More details of the Central Registry investigation into craniosynostosis can be found in Appendix G

Figure 9 Craniosynostosis by time of diagnosis and isolated/ non-isolated anomaly, 2002-2011



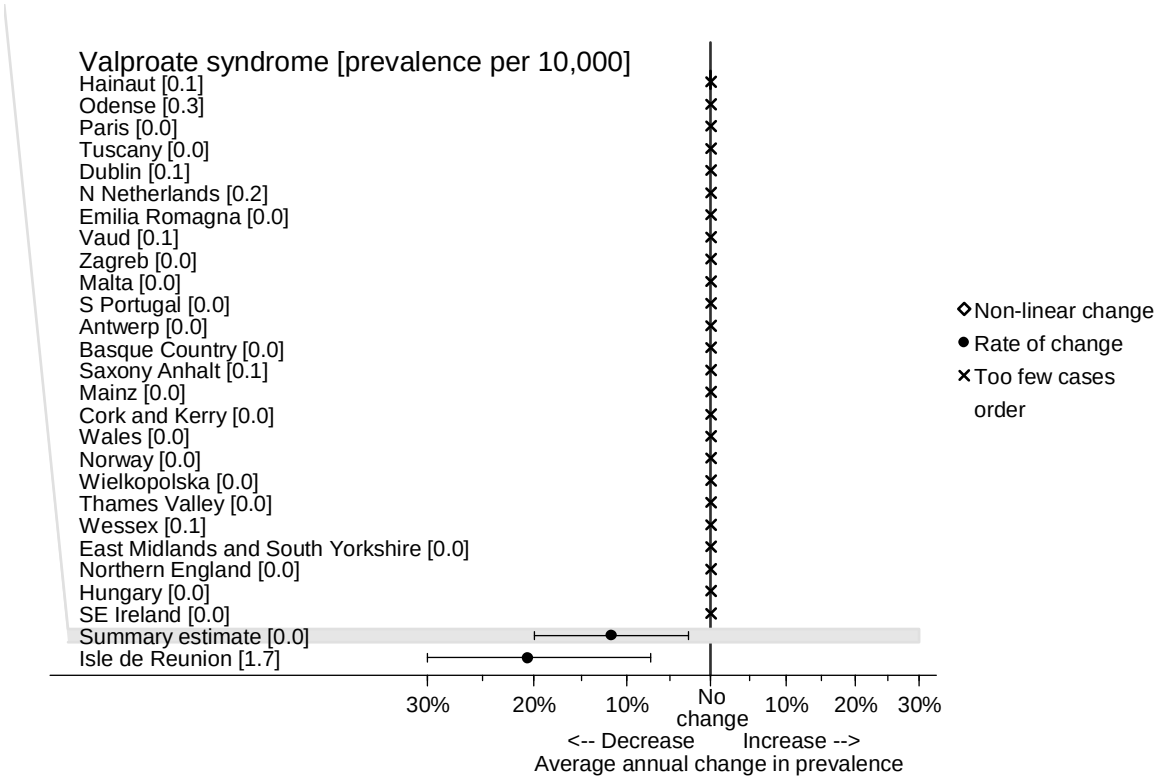
Other continuing increasing trends detected in this year's monitoring include Renal dysplasia, Chromosomal anomalies, Down syndrome and Edwards syndrome. Following expert consensus it was agreed that the increasing trend in **Renal dysplasia** should not be investigated further at this point due to heterogeneity and changes in coding. Furthermore, a EUROCAT paper on renal dysplasia is currently being published. The increasing trends detected in **Down syndrome and Edwards syndrome** were not statistically significant after adjusting for maternal age.

4.3 Decreasing trends identified at pan-Europe level

Decreasing trends were identified in the 2011 pan-Europe statistical monitoring for 17 anomaly subgroups, 16 of which were also identified in 2010 Annual Statistical Monitoring: All non-chromosomal anomalies; NTDs; Anencephalus and similar; Microcephaly; CHD; ASD; Atresia of bile ducts; Congenital hydronephrosis; Limb reduction; Upper limb reduction; Hip dislocation; Syndactyly; Congenital skin disorders; Genetic syndromes and microdeletions; Klinefelter syndrome and the adjusted Down syndrome/trisomy 21 subgroup. A new decreasing trend was detected for Valproate syndrome (see Figure 17). This section summarises the results, investigation and interpretation of specific anomaly subgroups considered to be either numerically large (in comparison to other subgroups), have clinical relevance to public health authorities, or have consistent evidence of a strong trend.

Valproate syndrome occurs as result of prenatal exposure to valproic acid, which is 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. A new pan-Europe decreasing trend was detected for valproate syndrome with prevalence decreasing on average by 11.78% per year from 0.12 per 10,000 births in 2002-2003 to 0.03 per 10,000 births in 2010-2011. Over this ten year period a total of 54 cases were ascertained, 26 of which were in the Ile de la Reunion registry (see Figure 10). The prevalence of Valproate syndrome in this registry decreased on average by 20.58% per year from 3.42 per 10,000 births in 2002-2003 to 0.0 per 10,000 births in 2010-2011. Ile de la Reunion confirmed this trend and a registry investigation is on-going.

Figure 10 Average annual change in prevalence in Valproate syndrome by registry

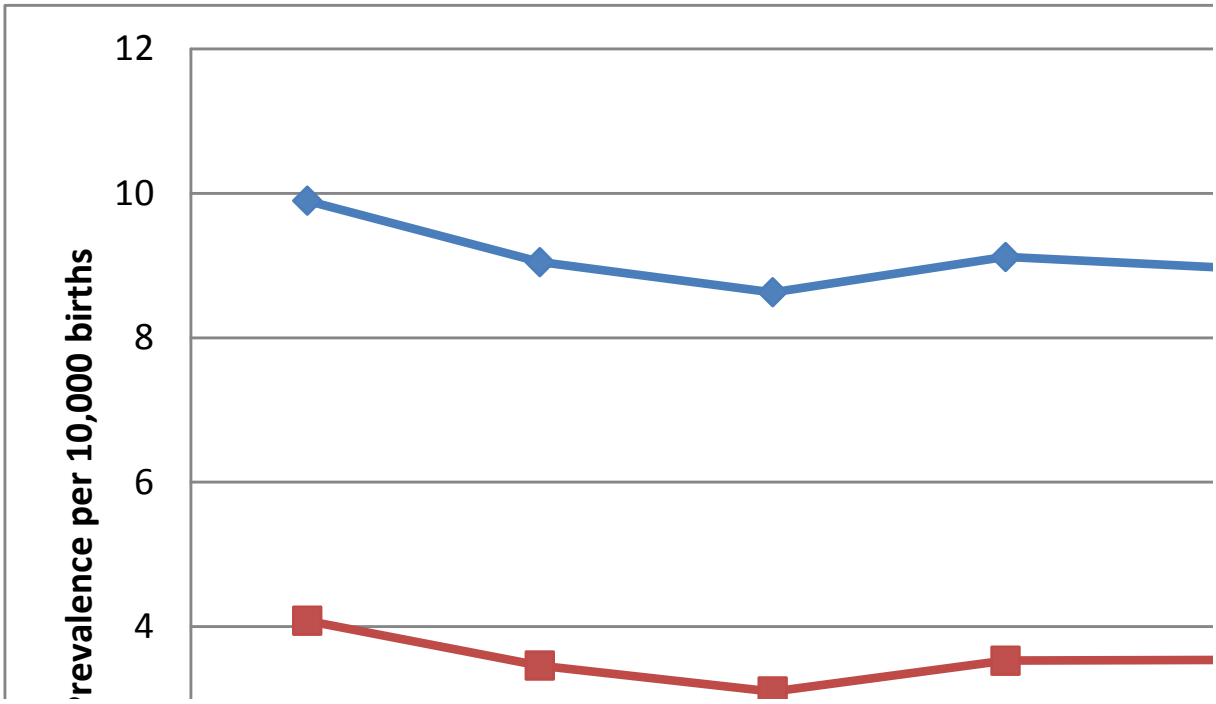


All non chromosomal anomalies decreased for the fifth consecutive year of statistical monitoring by 1.50% per year from 230.72 per 10,000 births in 2002-2003 to 198.44 per 10,000 births in 2010-2011.

The prevalence of **NTDs,** which includes anencephaly, decreased for the fifth consecutive year of statistical monitoring by 1.40% per year from 9.90 per 10,000 births in 2002-2003 to 8.96 per 10,000 births in 2010-2011 (see Figures 11 and 17). Statistically significant decreasing trends were observed in Norway, Emilia Romagna and Wielkopolska (see Appendix E).

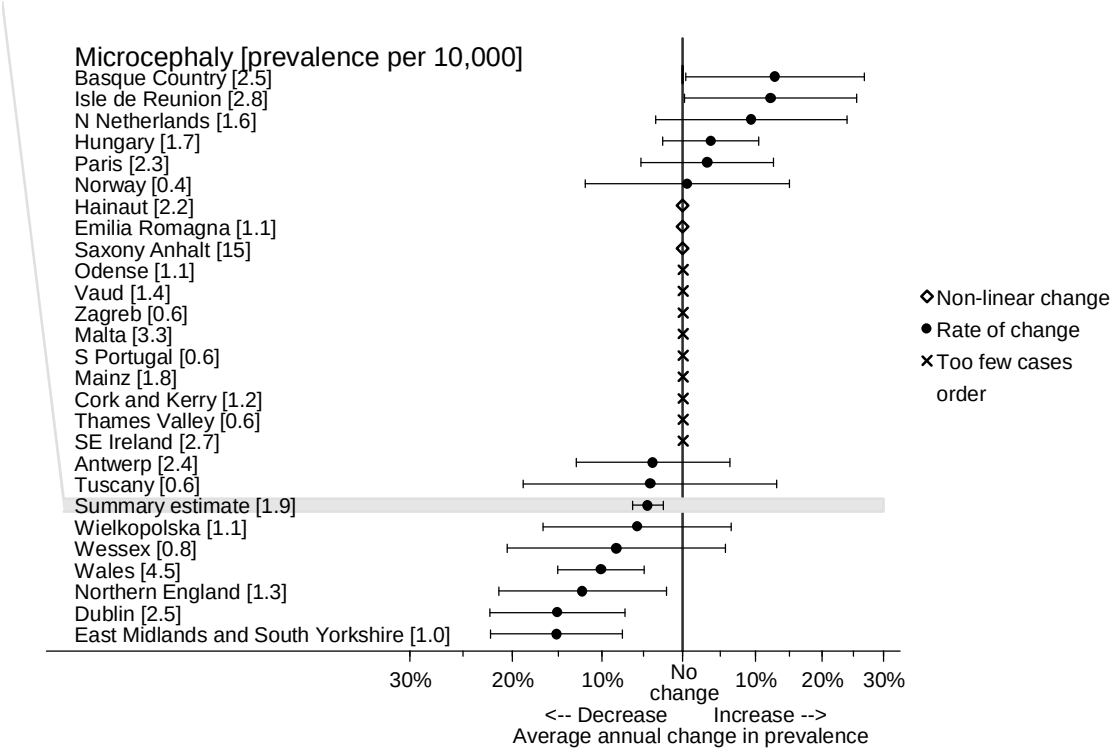
A decreasing trend was also detected in the subgroup **Anencephalus** which is characterised by the total or partial absence of brain tissue and the cranial vault. This is the second consecutive year that a decreasing trend has been detected for anencephalus, which decreased on average by 2.26% per year from 4.08 per 10,000 births in 2002-2003 to 3.54 per 10,000 births in 2010-2011. This decrease was larger in magnitude compared to the trend detected last year in which the prevalence declined on average each year by 1.9% from 3.82 per 10,000 births in 2001-2002 to 3.6 per 10,000 births in 2009-2010. This year statistically significant decreases were detected in Norway, Emilia Romagna, Saxony Anhalt and Wielkopolska. Norway confirmed that the decreasing trend in Anencephalus could be explained in part by an "increased use of folic acid, with registered preconceptional use increasing from 8% to 28% between 2001 and 2011, and registered use during pregnancy increasing from 26% to 71% in the same period." Saxony Anhalt reported that they did not consider this to be a real trend as the trend disappeared when the analysis covered a longer time period. Emilia Romagna and Wielkopolska did not send a report. Despite consistently decreasing in prevalence each year, the magnitude of change in NTDs in general continues to remain small (last year's annual average change for NTD's was 2.1% indicating a slowing down). Once again we suggest that renewed or more targeted campaigns may be required to accelerate the reduction in NTDs across Europe.

Figure 11: Prevalence of the Neural tube defects and Anencephalus anomalies in the pan-Europe analysis



A decreasing trend in the prevalence of **Microcephaly,** a defect of the nervous system, was detected again in this year's statistical monitoring. The prevalence rate decreased on average by 4.46% from 2.21 per 10,000 births in 2002-2003 to 1.53 per 10,000 births in 2010-2011, with significant decreasing trends detected in four registries Wales, Northern England, Dublin and East Midlands and South Yorkshire (see Figures 12 & 17). This is considered to be mostly a UK registry based decline that may be a consequence of population changes or changes in local guidelines. Preliminary reports by Dublin and Wales indicate that the decreasing trend could be explained by under ascertainment of cases, while East Midlands and South Yorkshire indicated that the trend in their registry was not real. Northern England confirmed a significant drop in reported cases and that this required further investigation.

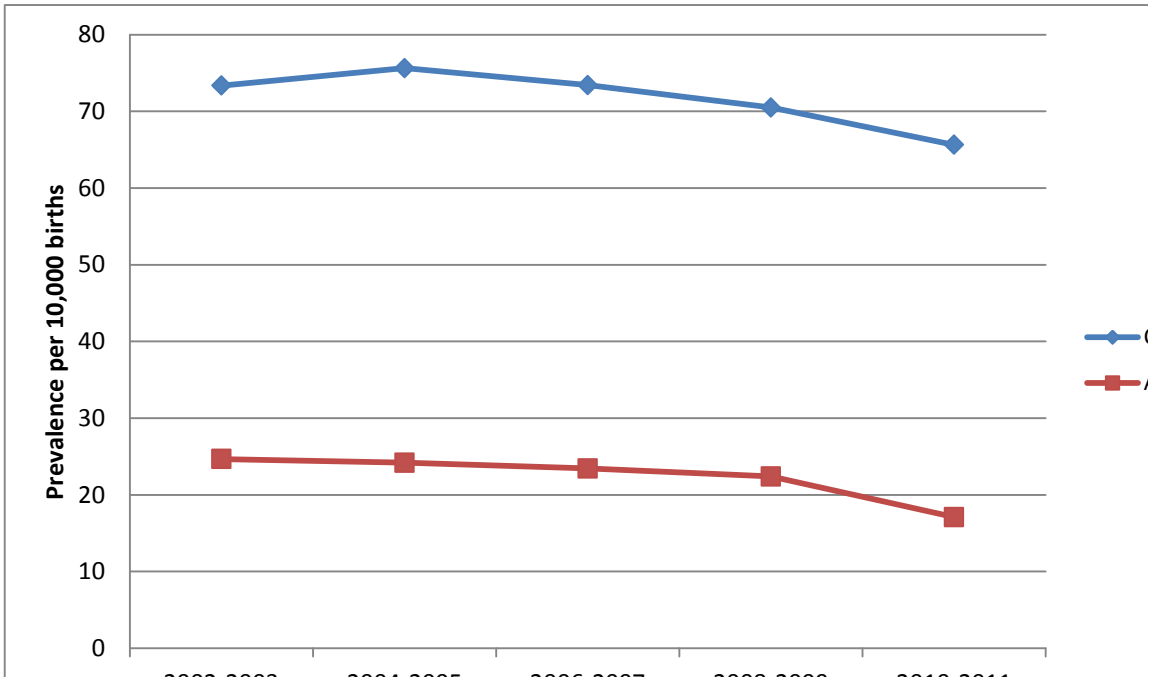
Figure 12 Average annual change in prevalence in Microcephaly by registry



Congenital heart defects (CHD) are the most common subgroup of congenital anomalies, with known risk factors including maternal chronic health conditions and maternal health risk behaviours. This year's pan-Europe analysis showed that CHD decreased on average by 0.59% per year from 73.13 per 10,000 births in 2002-2003 to 65.63 per 10,000 births in 2010-2011 (see Figures 13 & 17). This is similar in magnitude to the decreasing trend detected in the 2010 Report when CHD decreased on average by 0.6% per year from 74.17 per 10,000 births in 2001-2002 to 62.37 per 10,000 births in 2009-2010. Statistically significant decreasing trends were detected in 4 registries Malta, Wales, Northern England and SE Ireland. Following preliminary investigations the registries reported that this was not a real trend but that the decrease in prevalence was a consequence of changes in case ascertainment (n=1), changes in local or central registry methods (n=1) or not a real trend when additional years were added (n=2) (see Appendix H). ASD decreased on average by 1.7% per year from 24.63 per 10,000 births in 2002-2003 to 17.10 per 10,000 births in 2010-2011. Statistically significant decreasing trends were detected in five registries: North Netherlands, Vaud, Malta, Wales and Northern England, four of which reported that the decreasing trend was not real but a consequence of changes in local or central registry methods (n=3) or a consequence of changes in case ascertainment (n=1). One registry,

Vaud, reported that the trend was confirmed and that they planned further surveillance before undertaking a more detailed investigation.

Figure 13 Prevalence of CHD and ASD in the pan-Europe analysis



Atresia of the bile ducts (biliary atresia) declined on average by 5.77% each year from 0.32 per 10,000 births in 2002-2003 to 0.18 per 10,000 births in 2010-2011. This anomaly was not investigated further,

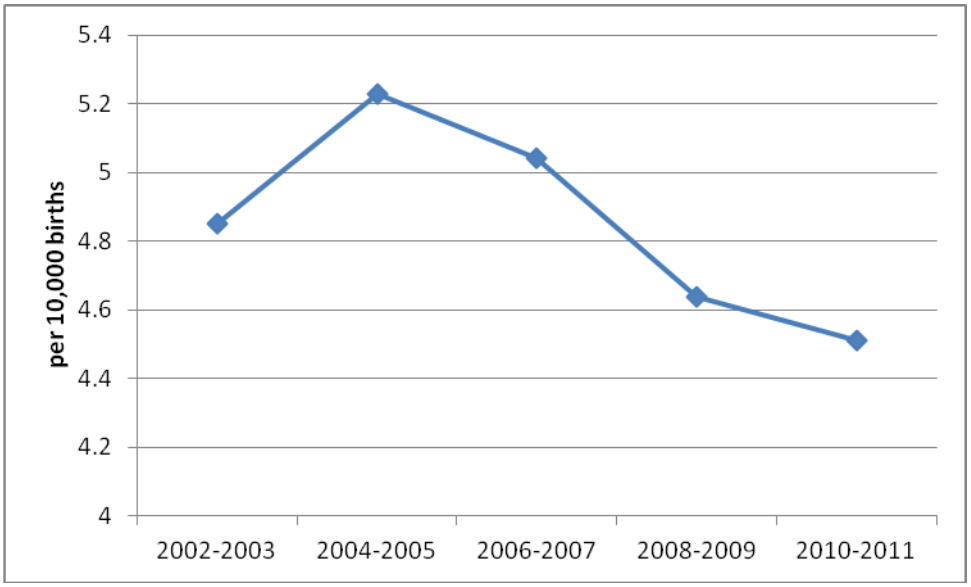
Hip dislocation and/or dysplasia declined on average by 1.98% each year from 8.60 per 10,000 births in 2002-2003 to 6.87 per 10,000 births in 2010-201. This anomaly was not investigated further,

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. Risk factors include maternal smoking and low socio-economic status which may include poor nutrition. A decreasing pan-Europe trend was detected with prevalence decreasing on average by 3.41% per year over the 10 year period from 5.95 per 10,000 births to 4.03 per 10,000 births (see figure 17). Decreasing trends were observed in over half the registries, seven of which were statistically significant. Only one registry Hungary had a statistically significant increasing trend over time. As the decrease in prevalence of syndactyly continued after 2005

changes in registering cases with minor syndactyly do not fully explain the overall decrease. A full Central registry report is available in Appendix G.

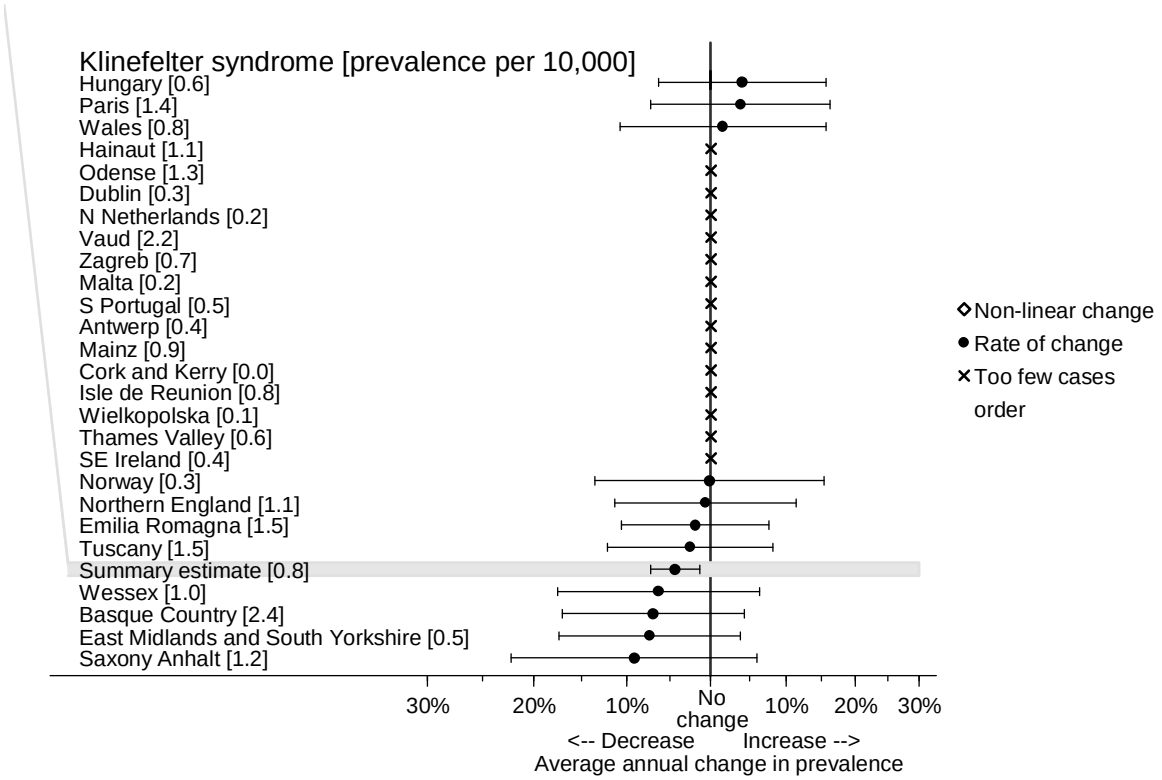
Genetic syndromes and microdeletions decreased by approximately 2.29% per year from 4.85 per 10,000 births in 2002-2003 to 4.51 per 10,000 births in 2010-2011. A Central Registry investigation report concluded that the decrease is likely due to ascertainment issues, rather than a true decrease in prevalence (see Appendix G).

Figure 14: Prevalence of Genetic syndromes & microdeletions in the pan-Europe analysis



Klinefelter syndrome is caused by a sex chromosome trisomy (XXY) and is associated with increased maternal age. The Pan-European analysis showed that the prevalence of Klinefelter syndrome decreased by approximately 4.37% per year from 0.83 per 10,000 births in 2002-2003 to 0.66 per 10,000 births in 2010-2011. No statistically significant changes were detected in individual registries. Four registries, Saxony-Anhalt, East Midlands and South Yorkshire, Basque Country and Wessex all showed larger annual average change in prevalence compared to the EUROCAT average (see Figure 15).

Figure 15 Average annual change in prevalence in Klinefelter syndrome by registry



Further investigation of this decreasing trend by Central Registry showed that Saxony Anhalt, Basque Country and Wessex all had higher than average prevalence rates at the beginning of the monitoring period. Excluding Saxony-Anhalt, East Midlands and South Yorkshire, Basque Country and Wessex from analysis, the overall decreasing trend was no longer observed (see Figure 16). It was concluded that the decreasing trend in prevalence for Klinefelter's syndrome could be attributed to the high rates of ascertainment in these registries, with the decrease due to changes in either their ascertainment or prenatal diagnostic methods with cases diagnosed postnatally, usually after the onset of puberty still to be notified (see Appendix G for full report)

Figure 16 Prevalence of Klinefelter syndrome by selected registries in the pan-Europe analysis

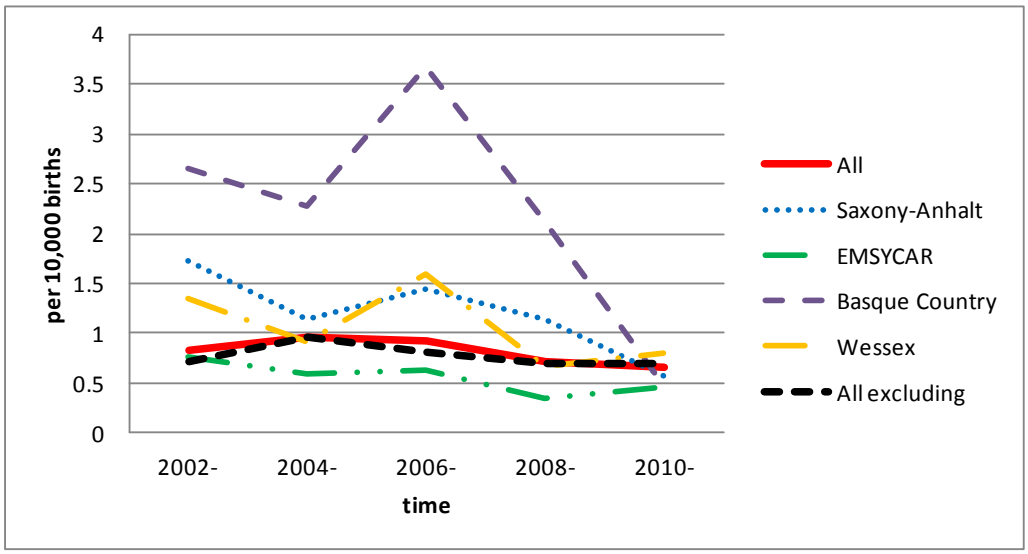
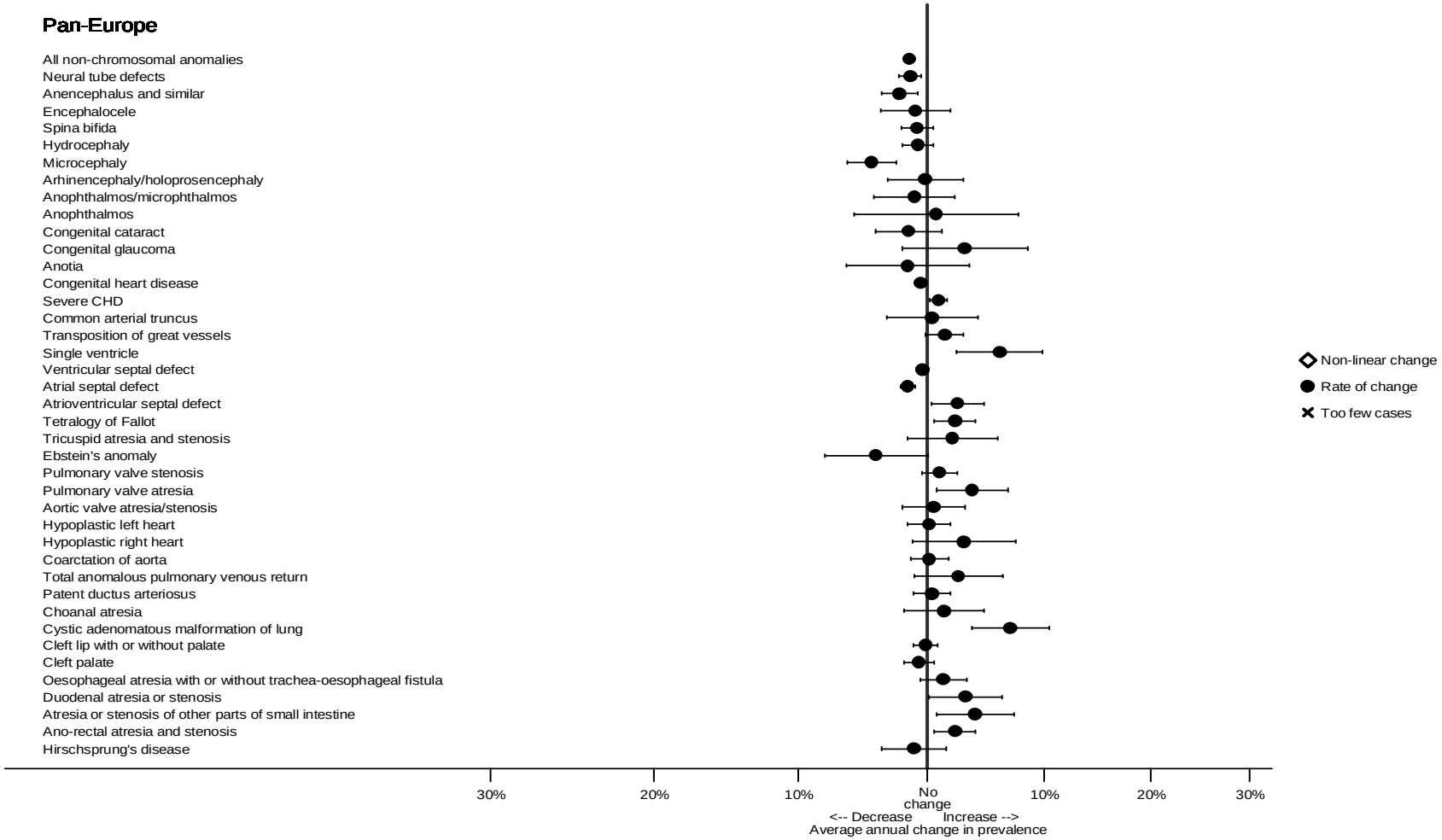


Figure 17: Estimated average percentage change in prevalence and 95% confidence intervals (Pan-Europe analysis 2002-2011)



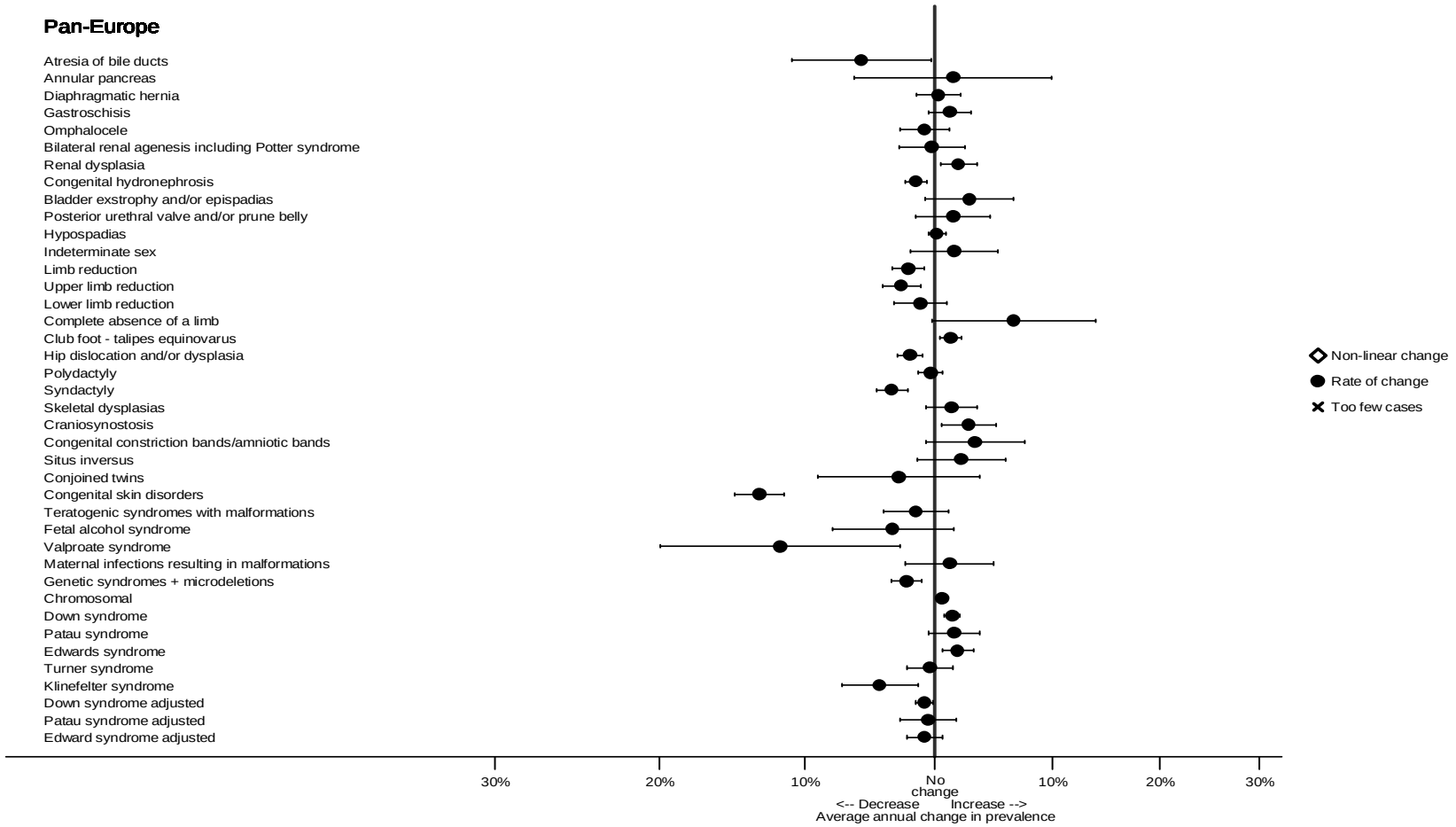

Pan-Europe
Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb 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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases

Table 1 Central Registry Statistical Monitoring Results: Reported 8 or 10 year trends by individual registry (2002-2011)

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)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Years tested				2002-2011	2002-2011	2003-2010	2002-2011	2002-2011	2002-2011	2002-2011	2002-2011	2003-2010	2003-2010	2002-2011	2002-2011	2002-2011	2002-2011	2003-2010	2002-2011	2002-2011	2003-2010	2003-2010	2003-2010	2002-2011	2002-2011	2002-2011	2002-2011	2002-2011	2002-2011
Total / in registries	118			2	2	0	1	14	3	2	3	26	2	0	4	8	5	0	5	8	2	2	10	1	6	2	4	3	3
Total \ in registries		146		4	7	1	0	1	1	0	7	0	0	15	5	12	6	4	3	5	21	0	3	4	15	11	5	15	1
Total ~ in registries			160	6	3	5	6	3	11	0	7	19	2	7	1	16	9	0	3	9	8	12	5	3	8	3	7	5	2
Total any in registries	424			12	12	6	7	18	15	2	17	45	4	22	10	36	20	4	11	22	31	14	18	8	29	16	16	23	6

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

5. Clusters

5.1 Overview

For cluster analysis a total of 901 tests were performed with 3.8% being statistically significant, which is slightly higher than would be expected by chance (see Appendix J). A total of thirty four clusters were identified: twenty were new, seven were continuing (identified in the previous monitoring, and were growing in size) and seven remained the same (and had been reported in the previous year's Statistical Monitoring Report http://www.eurocat-network.eu/content/Stat-Mon-Report-2010.pdf) (see Appendix K).

5.2 New clusters

Preliminary investigations by registries into the 20 new clusters detected in the analysis indicated that 13 were not 'true' clusters as defined by the EUROCAT definition. A total of 9 could be explained by data quality issues/ increases in case ascertainment, 1 was explained by methodological issues, and 3 were explained by heterogeneous anomaly (see Table 2). An excess of cases were confirmed for the following 7 congenital anomaly subgroups: **Total anomalous venous return** (Emilia Romagna); **Coarctation of Aorta** (SE Ireland); **Anorectal atresia and stenosis** (SE Ireland); **Hypospadias** (Tuscany); **Club foot** (Paris); **Patau syndrome** (E Midlands and S Yorkshire) and **Turner syndrome** (E Midlands and S Yorkshire).

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: http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2011/investigationreports-2011

Total anomalous pulmonary venous return (TAPVR) is a severe cardiac defect, in which all four pulmonary veins drain to the right atrium or one of the venous tributaries. A cluster of TAPVR was detected in Emilia Romagna. Over a 4 month period, starting towards the end of June 2010 and finishing towards the end of October 2010, 5 cases were found when an average of 0.78 would normally occur (p=0.045). The preliminary investigation by the registry indicated that they had reviewed the cases with an expert clinician and were unable to find an explanation. The registry plans to continue monitoring this anomaly.

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 the SE Ireland registry. This cluster started at the end of April 2008 and finished at the end of August 2009. Over a 16 month period, a total of 12 cases were found when an average of 4.78 would normally occur (p=0.036). The preliminary investigation by the registry verified all cases, and that there was no common association with location and time factors. It was noted that most of the cases had multiple malformations. The registry reported that the "overall EUROCAT rate of Coarctation of aorta for the period 2007 -11 according to the website prevalence tables was 2.93 per 10,000 births (95% CI 2.79 – 3.07) compared to the SE Ireland rate of 5.12 per 10,00 births (96%CI 3.13 - 7.91). The rate at the beginning of the period for the combined years 2002-2006 for SE Ireland was 3.59 per 10,000 births (95%CI 1.85 - 6.27)". The registry investigated and confirmed that changes in diagnostic and reporting practices had not contributed to the cluster. The registry reported that they had reviewed the following aetiological factors that were recorded in the registry: sex; syndromes; folic acid; maternal medications; fertility treatment; maternal occupation and migrant status. Based on the preliminary investigations the registry concluded that "there was a need to monitor the incidence to ascertain whether this cluster is continuing or if it is part of a trend. There is no factor evident from the preliminary investigation which suggests further investigation at this stage, but further surveillance is warranted".

A new cluster was also detected for the digestive anomaly **Anorectal atresia and stenosis** in the SE Ireland registry. This cluster started towards the end of November 2009 and finished mid-April 2010. Over a 4 to 5 month period a total of 5 cases were found when an average of 0.82 would normally occur (p=0.039). The preliminary investigation by the registry verified all cases, that there was no common association with diagnosis, location and time factors and that the rate of Anorectal atresia and stenosis in the registry before the cluster was similar to the overall rate in EUROCAT for the same time period. The registry reported that they had reviewed the following aetiological factors recorded in the registry: anti-epileptic drugs; fertility treatment; multiple pregnancy; maternal occupation and folic acid intake (some of which had missing data). Based on the preliminary investigation the registry concluded that this is a very small cluster, with no factors arising from the preliminary investigation that warrant further investigation. Further surveillance is necessary.

Hypospadias is a common male genital anomaly which occurs when the urethral meatus is abnormally located and is displaced proximally on the ventral surface of the penis. A cluster of Hypospadias was detected in the Tuscany registry, starting at the end of October 2009 and finishing mid-February 2010. Over a 3.5 month period, 37 cases were found when only

15.86 would normally occur (p=0.024). The preliminary investigation by the registry verified all cases, that there was no indication of association with diagnosis, location and time variables, nor had there been changes in diagnostic or reporting practices. The registry reported a higher prevalence of this anomaly (20.56 per 10,000 births) before the cluster (2000-2007 period) compared to most EUROCAT registries (total mean prevalence=16.60 per 10,000 births). The registry concluded that they did not consider the cluster to be explained by their preliminary investigation, and reported that "*the cluster will be communicated in October during the Tuscany Registry annual meeting for the paediatricians, obstetricians and neonatologists involved in the Tuscany network of congenital defects. The result of surveillance will also be included in the next annual report".*

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 a new cluster was detected in the Paris registry, starting in early August 2010. Over a period of 6 days a total of 6 cases were found when an average of 0.56 would normally occur (p=0.049). The preliminary investigation by the registry verified all cases, and that there was no indication of any common association with diagnosis, location and variables. The registry reported that they had examined the following aetiological factors: exposure to alcohol/drugs (rarely recorded); medication use; maternal illness before and during pregnancy. They observed that none of the mothers had been exposed to anti-epileptic medication. The registry concluded that they were not able to explain the cluster following preliminary investigation. They suggest that it is possible that the excess of cases may be part of the increasing trend detected for this anomaly in this year's pan-Europe analysis for which they also do not have an explanation. The registry plans to continue to monitor and investigate further changes in population exposure to explain the increase in the number of cases, and stated that the cluster would be included in the annual report to the French Institute for Public Health Surveillance.

Two new clusters of chromosomal anomalies were detected in the East Midlands and South Yorkshire Registry. The first cluster was for **Patau syndrome**, an anomaly that occurs due to the addition of an extra 13th chromosome. This cluster started towards the end of July 2010 and finished early August 2010. Over a 7 day period a total of 5 cases were found when an average of 0.35 would be expected (p=0.037). The second cluster was for **Turner syndrome**, which only affects females and occurs when all or part of the X chromosome is absent. Starting just after mid-January 2011 and finishing towards the end of February 2011,

a period of 36 days, a total of 14 cases were found when an average of 2.14 would normally occur ($p<0.001$). The preliminary investigation by the registry verified the cases in both clusters. Whilst there was no association with diagnosis, location and time variables for the Patau cluster, the registry reported that 7 of the 14 cases in the Turner syndrome cluster were concentrated in a relatively small area, with 3 cases liveborn in one hospital within 8 days of each other and the remaining 4 cases delivered in a second hospital (only one of which was liveborn, with the remaining 3 TOPFA). The registry also stated that intensive efforts had been made to elicit outcome information for antenatally suspected cases and cases with potentially relevant soft markers, particularly Cystic Hygromas and raised Nuchal thickness/Translucency measurements, and that they had reviewed the following broad based aetiological factors: maternal; locational diagnostic and reporting. The registry concluded that the Patau syndrome cluster could be explained by their preliminary investigation stating the following "***EMSYCAR covers an area in excess of 18,000 Km^2 and a population of over 6 million, with 76,000 births per annum. Rates for Trisomy 13 throughout this period (2.31 per 10,000 births (95% C.I. 1.85 - 2.85)) remained above EUROCAT mean (2.02 per 10,000 births (95% C.I. 1.88 - 2.16)), though slightly below the mean for the whole of the UK (2.59 per 10,000 births (95% C.I. 2.32 - 2.88)). There is no evidence that the unusual pattern identified has continued into 2011 or 2012, but the situation will be reviewed when the data collection for 2012 is complete"*** The registry reported that they do not plan to report the cluster to the public health authorities, but should there be any further cause for concern, they would be notified in the first instance.

For the Turner syndrome cluster, the registry concluded that the cluster could not be entirely explained by their preliminary investigation and that the "**possibly unusual spatial clustering of 7 of the 14 cases may require further monitoring before a decision is made regarding closer investigation. The registry also reported that they had observed that rates of 45X between 2007 and 2011 in the three County (rural) PCTs appeared to be higher than in the three City (urban) areas. And that since reporting bias cannot account for this difference, they planned to investigate this rather unusual, and unexpected, finding more closely.**" The registry reported that they did not plan to report the cluster to the public health authorities, but should there be any further cause for concern, they would be notified in the first instance.

5.2.2 Continuing clusters

This year we observed seven clusters that were first detected in either the 2010 or 2009 Annual Statistical Monitoring and had continued to grow in size (increase in the number of cases). The continuing clusters detected were: Arhinencephaly/ holoprosencephaly in Ukraine; ASD in Thames Valley and Emilia Romagna; PVA in Emilia Romagna, Congenital hydronephrosis in Ile de la Reunion and Northern England and Polydactyly in Paris.

The **Arhinencephaly/ holoprosencephaly** cluster detected in the Ukraine registry (2011 Monitoring) started in late March 2008 and ended in early July 2009. Over a 15.5 month period, a total of 23 cases were found when an average of 10.54 would normally occur (p=0.02). This registry was last included in the 2009 Statistical Monitoring for clusters when over a period of 35 days from late April 2008 to late May 2008 a total of 7 Arhinencephaly/ holoprosencephaly cases were found when an average of 0.77 was expected (p=0.015). At that time, the registry reported that the start of the cluster had coincided with the acquisition of new equipment for pre and post-natal diagnosis for a number of hospitals and training of personnel. However as the rates continue to remained elevated, the registry concluded that this could not explain the cluster and that further data collection was warranted.

The **Atrial Septal Defect (ASD)** cluster detected in the Thames Valley registry (2011 Monitoring) started at the end of July 2008 and ended towards the end of January 2010. Over this 18 month period, there were 97 cases of ASD when an average of 64.54 would normally occur (p=0.013). In the 2010 Statistical Monitoring for clusters, there were 68 ASD cases between mid May 2008 to early November 2009 when an average of 34.58 would normally o (p<0.001). Investigations by the registry concluded that this cluster was due to "**getting access to outpatient records from 2009. This has added more isolated cases diagnosed after the neonatal period. There was very little ascertainment of milder cardiac cases prior to having access to outpatient records and the registry believes the result is due to improved ascertainment. We will continue to monitor locally**"

The **ASD** cluster detected in Emilia Romagna (2011 Monitoring) started mid October 2009 and ended early December 2010. Over this 14 month period, a total of 95 cases were found when an average of 56.99 would normally occur (p<0.001). In the 2010 Statistical Monitoring for clusters, over a period of 17.5 months, from the end of August 2008 to early February 2010 a cluster of 85 ASD cases were found in the registry when an average of 53.38 was expected (p<0.001). In addition, a cluster of 10 **PVA (Pulmonary valve atresia)** cases was detected in Emilia Romagna between March and August 2009 (35 days), when 2.24 cases were expected (p=0.017), (2011 Monitoring). This cluster was also detected in 2010

monitoring when 9 cases were observed between March and August 2009 (34 days) when 1.71 was expected (p=0.008). Investigations by the registry concluded that these clusters were due to classification errors. They stated: "**In the past all complex cardiopathies were reviewed by a Pediatric Cardiologist whilst in the study period all anomalies were coded without any clinical interpretation. We now plan to reinstate the review of complex cardiologies**".

The **Congenital hydronephrosis** cluster detected in the Ile de la Reunion registry (2011 Monitoring) started mid July 2008 and ended at the beginning of January 2010. Over this 18 month period, a total of 29 cases were found when an average of 12.76 would normally occur (p<0.001). This registry was last included in the 2009 Statistical Monitoring for clusters when over a period of 35 days from mid April 2008 to late March 2009 a total of 21 cases were found when an average of 5.06 was expected (p<0.001). Investigations by the registry concluded that this cluster was due to data quality errors/late case ascertainment and coding issues in both periods of analysis.

The **Congenital hydronephrosis** cluster detected in the Northern England registry (2011 Monitoring) began towards the end of December 2009 and finished in early March 2011. Over this 15 month period, a total of 78 cases were found when an average of 49.81 would normally occur (p=0.043). This registry was included in the 2010 Statistical Monitoring for clusters when over an 18 month period from the beginning of October 2008 to the end of March 2010 a total of 75 cases were found when an average of 49.01 was expected (p<0.001). In their 2011 investigation report, the registry concluded that this cluster was due to coding issues, and also that a renal project in the local tertiary referral centre may have resulted in increased ascertainment of renal cases.

The **Polydactyl** cluster detected in the Paris registry (2011 Monitoring) started towards the middle of August 2009 and finished in early February 2011. Over this 18 month period, a total of 60 cases were found when an average of 27.71 would normally occur (p<0.001). This registry was included in the 2010 Statistical Monitoring for clusters when over 5.5 months, from the middle of August 2009 through to February 2010 a total of 19 cases were found when an average of 5.68 was expected (p=0.006). In their 2011 investigation report, the registry concluded that this cluster was explained by coding issues, due to under registration of cases in previous years.

Table 2: Outcomes of local registry preliminary investigations into 20 new clusters detected in 2011 monitoring

Anomaly	Registry	EUROCAT Classification of Explanation	No of cases in cluster	Length of cluster (days)	P
Microcephaly	Emilia Romagna	**Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding.**	14	494	0.028
Severe CHD	Paris	**Cluster associated with diagnostic criteria: aetiologic heterogeneity, changes in inclusion criteria or diagnosis, familial or twin occurrence.**	5	2	0.01
Atrial Septal Defect	Paris	**Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding.**	46	545	0.048
Coarctation of Aorta	SE Ireland	**Excess of cases confirmed**	12	494	0.036
Total Anomalous Pulmonary Venus return	SW England	**Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding.**	5	63	0.034
Total Anomalous Pulmonary Venus return	Emilia Romagna	**Excess of cases confirmed**	5	121	0.045
PDA as only CHD in term infants	SW England	**Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding.**	14	532	0.021
Cleft lip with or without palate	Tuscany	**Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding.**	38	530	0.014
Duodenal atresia or stenosis	Hainaut	**Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding.**	6	240	0.045
Atresia and other small parts of the intestine	East Mids & S Yorkshire	**Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding.**	14	529	0.02

Anomaly	Registry	EUROCAT Classification of Explanation	No of cases in cluster	Length of cluster (days)	P
Ano-rectal atresia and stenosis	SE Ireland	**Excess of cases confirmed**	5	141	0.039
Congenital hydronephrosis	Emilia Romagna	**Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding.**	9	14	0.042
Hypospadias	Tuscany	**Excess of cases confirmed**	37	106	0.024
Indeterminate sex	Wessex	**Cluster associated with diagnostic criteria: aetiologic heterogeneity, changes in inclusion criteria or diagnosis, familial or twin occurrence.**	5	39	0.04
Club foot	Paris	**Excess of cases confirmed**	6	6	0.049
Hip Dislocation	Isle de la Reunion	**Cluster associated with diagnostic criteria: aetiologic heterogeneity, changes in inclusion criteria or diagnosis, familial or twin occurrence.**	5	10	0.007
Congenital skin disorders	SW England	**Data Quality Issues found to explain cluster: changes in ascertainment methods; duplicate cases or miscoding.**	5	14	0.028
Down syndrome	SW England	**Methodological Issue found to explain cluster. EUROCAT estimates date of conception using date of birth and gestational age in weeks, whereas the registry can estimate date of conception more accurately using expected date of delivery (EDD). Using the EDD, only 2 cases had the same date of conception as opposed to the 5 found using EUROCAT methodology.**	5	1	<0.001
Patau syndrome	East Mids & S Yorkshire	**Excess of cases confirmed**	5	7	0.037
Turner syndrome	East Mids & S Yorkshire	**Excess of cases confirmed**	14	36	<0.001

5.3 Country clusters

For the first 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 (Dublin, SE Ireland)
- Italy (Emilia Romagna, Tuscany)
- UK (E Midlands & S Yorkshire, N England, SW England, Thames Valley, Wales, Wessex)

Fourteen clusters were detected, of which 7 occurred in one of the component registries and were already identified in the individual registry monitoring. The remaining 7 country clusters were: NTD, UK; Ventricular septal defect, Italy; Cleft palate, UK; Ano-rectal atresia and stenosis, Italy, UK; Club foot, UK; and Situs inversus in Belgium (see Appendix L). The **Situs inversus** cluster was considered to be especially interesting since the EUROCAT seasonality study conducted as part of the EUROCAT pandemic influenza surveillance response, detected strong seasonality in the prevalence of situs inversus, with conception peaks in the winter.[4] The Belgian situs inversus clusters' dates of conception coincide with the 2009 H1N1 pandemic influenza outbreak[5] and for this reason, the Belgian situs inversus cluster was selected for investigation in the context of the EUROCAT pandemic influenza surveillance response. Between September 2009 to June 2010, 5 cases of situs inversus were detected with a date of conception occurring during this 9 month period, when 1.18 cases were expected. An investigation is currently ongoing.

[4] Seasonality of congenital anomalies in Europe. Luteijn, Johannes Michiel; Dolk, Helen; Addor, Marie-Claude; Arriola, Larraitz; Barisic, Ingeborg; Bianchi, Fabrizio; Calzolari, Elisa; Draper, Elizabeth; Garne, Ester; Gatt, Miriam; Haeusler, Martin; Khoshnood, Babak; McDonnell, Robert; Nelen, Vera; O'Mahony, Mary; Mullaney, Carmel; Queisser-Luft, Annette; Rankin, Judith; Tucker, David; Verellun-Dumoulin, Christine; Walle, Hermien; Yevtushok, Lyubov. Birth Defects Research Part A: Clinical and Molecular Teratology 2014 – *in press*

[5] http://euroflu.org/site/tables.php

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

This year, 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 5 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. Two registries provided details of their investigations:

- The Valencia Region registry identified no clusters and some 5-year trends which were explained by improvements in case ascertainment.
- Norway reported 2 overlapping clusters in **Severe CHD** and **Coarctation of Aorta.** The registry confirmed an excess of severe CHD cases over a 2 day period, 8 cases were detected when 0.52 was expected. The registry has no plans to investigate this further. Over a 5 month period, 24 cases with Coarctation of aorta were found when 6.67 were expected. The registry will keep this anomaly under surveillance, as coding differences between hospitals need to be addressed. .

Fifteen registries reported that they did not use the EDMP. Reasons for not using the EDMP statistical monitoring function included: incompatibility with local coding systems/data protection requirements; preference to use a common system that is in use in the registries own country/region 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 decrease in the prevalence of CHD overall, this is contrasted by increasing trends in a number of severe types of cardiac defects. Primary prevention of congenital anomalies continues to be a key objective of the EUROCAT network.

Appendix A: 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). The following list shows which subgroups are to be 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 chromosomal cases.
2. Analysis of trends, all outcomes of pregnancy combined. Genetic syndromes, skeletal dysplasias and chromosomal cases are excluded from the statistical monitoring of all other subgroups.
3. Detection of clusters, all outcomes of pregnancy combined. Genetic syndromes, skeletal dysplasias and chromosomal cases 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**
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	✓	✓	✓
Tetralogy of Fallot	✓	✓	✓
Tricuspid atresia and stenosis	✓	✓	✓
Ebstein's anomaly	✓	✓	✓

. EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Include in monitoring of trends	Include in monitoring of clusters
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**
Bilateral renal agenesis including Potter syndrome	✓	✓	✓
Renal Dysplasia	✓	✓	✓
Congenital hydronephrosis	✓	✓	✓
Bladder exstrophy and/or epispadia	✓	✓	✓
Posterior urethral valve and/or prune belly	✓	✓	✓
Genital	✓	**NO**	**NO**
Hypospadias	✓	✓	✓

. EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Include in monitoring of trends	Include in monitoring of clusters
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 B: 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 (2002-2011) or using 9 years of data within the 10 year period (2002-2011) 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 (2002-2011).

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 all 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-2011.pdf), scanning all recorded cases in the period 2007-2011.

2. Clusters or deficits occurring in the last 2 years (2010-2011) that are less than 18 months in length are reported.

3. A minimum of 7 cases over the surveillance period (2007-2011) 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 (2011). 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 73 EUROCAT subgroups of congenital anomalies (Appendix A). Seventeen major heterogeneous subgroups (e.g. Nervous system, Eye, Congenital heart disease 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 C: 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-2011.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 decreasing 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:

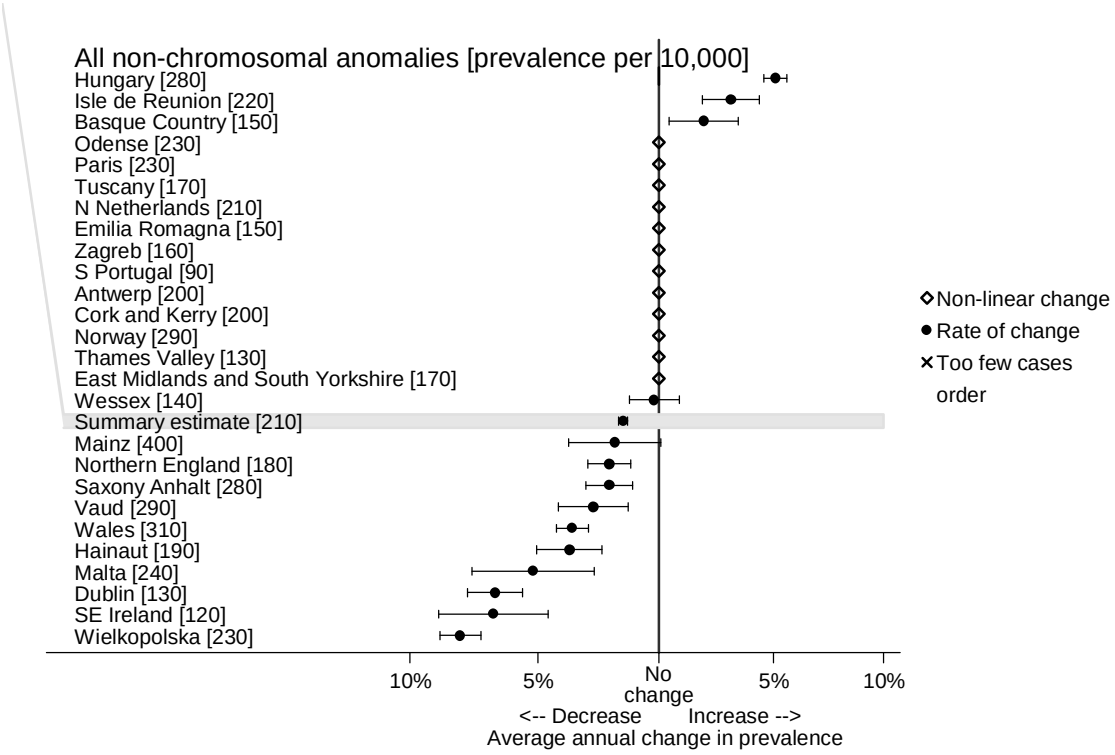
- Apparent cluster with cause for concern, further investigation on-going
- Cluster associated with aetiologic heterogeneity, changes in inclusion criteria, diagnosis, familial or twin recurrence
- Excess of cases confirmed, but no further investigation proposed other than further surveillance
- Increase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

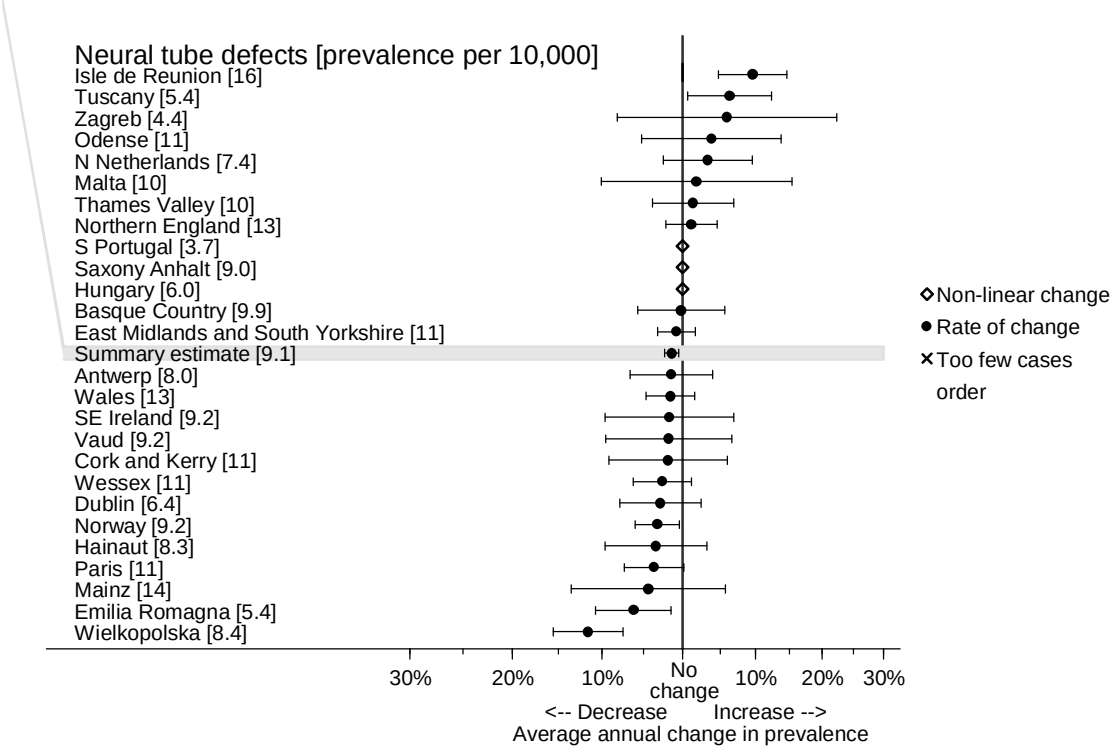
Appendix D: Summary of significant ten year increasing and decreasing trends detected in the pan-Europe analysis*

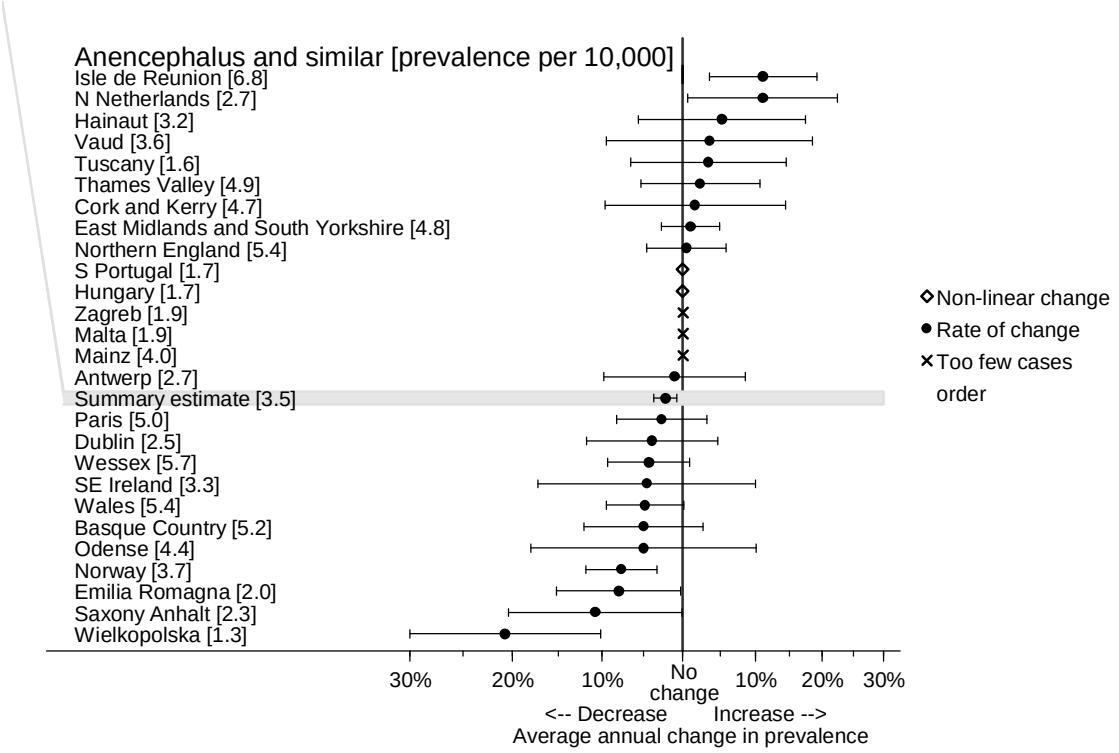
Anomaly Subgroup	Direction	Signalled in 2010	% Change	Lower CI	Upper CI	Trends prioritised for Investigation
All non-chromosomal anomalies	Decreasing	Yes	-1.5	-1.7	-1.3	
Neural tube defects	Decreasing	Yes	-1.4	-2.3	-0.	✓
Anencephalus and similar	Decreasing	Yes	-2.3	-3.7	-0.8	✓
Microcephaly	Decreasing	Yes	-4.5	-6.3	-2.5	✓
Congenital heart defects	Decreasing	Yes	-0.6	-0.9	-0.3	✓
Severe CHD	Increasing	No	+0.9	+0.2	+1.6	✓
Single ventricle	Increasing	Yes	+6.0	+2.4	+9.8	✓
Atrial septal defect	Decreasing	Yes	-1.6	-2.2	-1.0	✓
Atrioventricular septal defect	Increasing	No	+2.5	+0.3	+4.7	✓
Tetralogy of Fallot	Increasing	Yes	+2.2	+0.5	+4.0	✓
Pulmonary valve atresia	Increasing	No	+3.7	+0.7	+6.8	✓
Cystic adenomatous malformation of lung	Increasing	Yes	+7.0	+3.6	+10.5	✓
Duodenal atresia or stenosis	Increasing	Yes	+3.1	+0.1	+6.2	✓
Atresia or stenosis of other parts of small intestine	Increasing	Yes	+4.0	+0.7	+7.3	✓
Ano-rectal atresia and stenosis	Increasing	No	+2.2	+0.6	+4.0	✓
Atresia of bile ducts	Decreasing	Yes	-5.8	-10.9	-0.3	
Renal dysplasia	Increasing	Yes	+1.9	+0.5	+3.4	
Congenital hydronephrosis	Decreasing	Yes	-1.5	-2.4	-0.7	
Limb reduction	Decreasing	Yes	-2.2	-3.4	-0.9	
Upper limb reduction	Decreasing	Yes	-2.7	-4.2	-1.2	
Club foot- talipes equniovarus	Increasing	No	+1.3	+0.4	+2.1	✓
Hip dislocation and/or dysplasia	Decreasing	Yes	-2.0	-3.0	-1.0	
Syndactyly	Decreasing	Yes	-3.4	-4.6	-2.2	✓
Craniosynostosis	Increasing	Yes	+2.8	+0.5	+5.1	✓
Congenital skin disorders	Decreasing	Yes	-13.3	-15.0	-11.5	
Valproate syndrome	Decreasing	No	-11.8	-19.9	-2.8	✓
Genetic syndromes + microdeletions	Decreasing	Yes	-2.3	-3.5	-1.1	✓
Chromosomal	Increasing	Yes	+0.5	+0.1	+1.0	
Down syndrome (unadjusted)	Increasing	Yes	+1.4	+0.8	+2.0	
Edwards syndrome (unadjusted)	Increasing	Yes	+1.9	+0.6	+3.2	
Klinefelter syndrome	Decreasing	Yes	-4.4	-7.3	-1.4	✓
Down syndrome adjusted	Decreasing	Yes	-0.8	-1.5	-0.1	

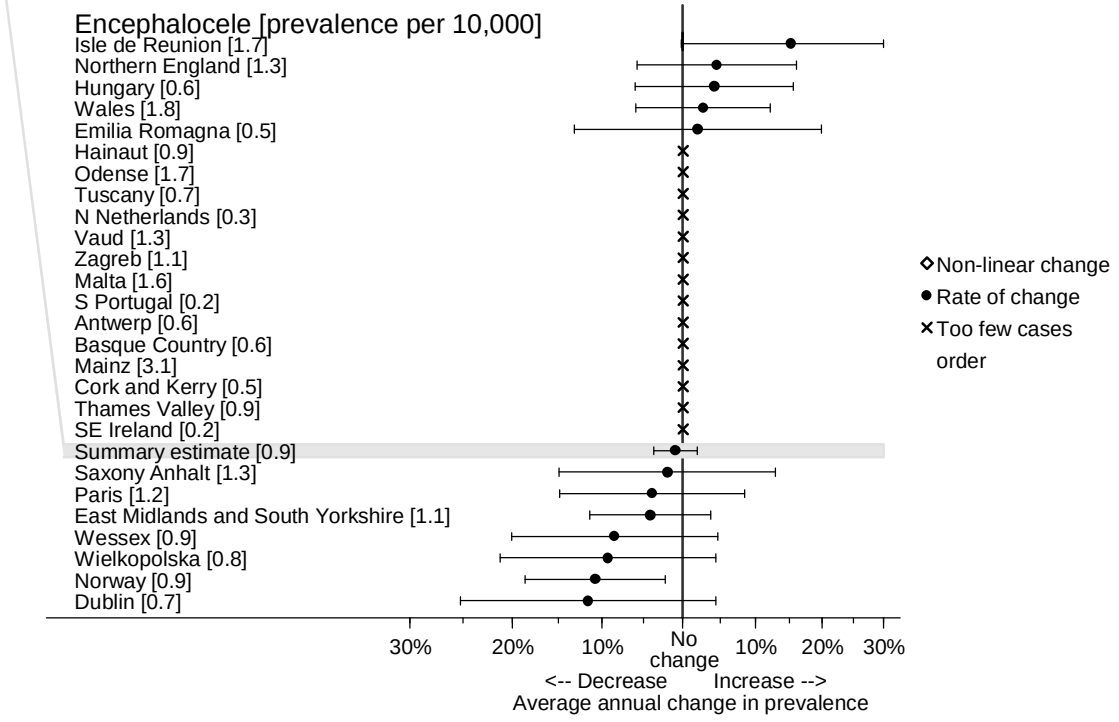
Note: *Significant non-linear change not included in this table

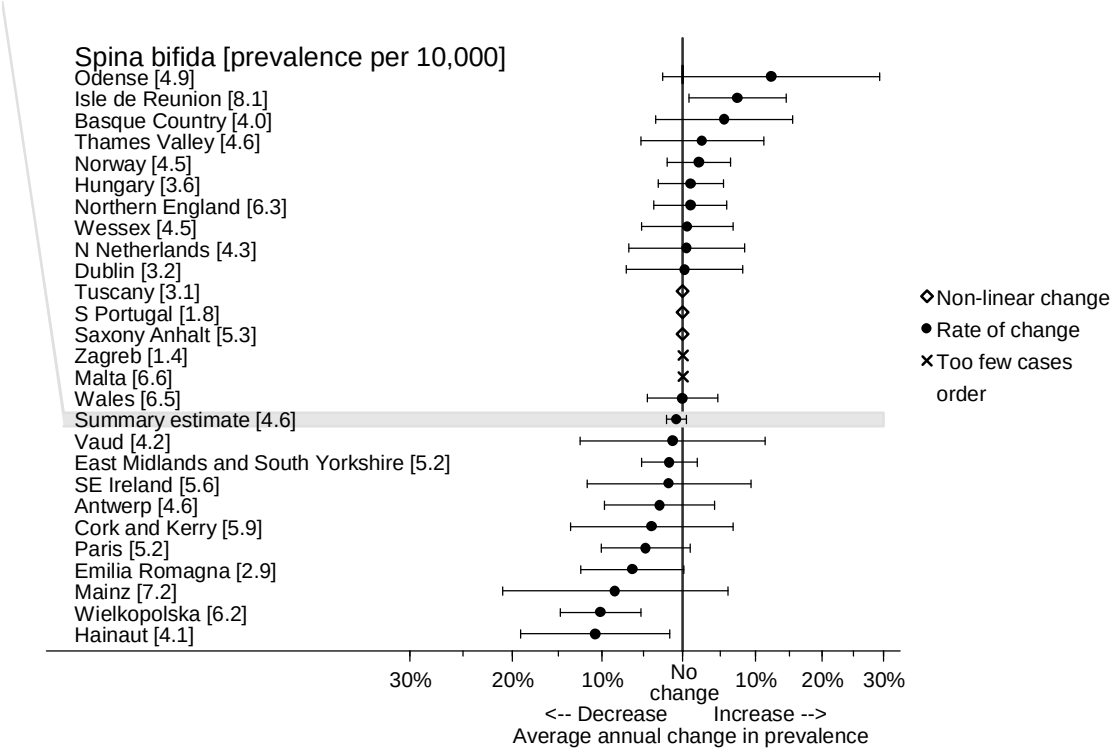
Appendix E: Forest plots showing ten year increasing and decreasing trends detected in the pan-Europe analysis by anomaly subgroup

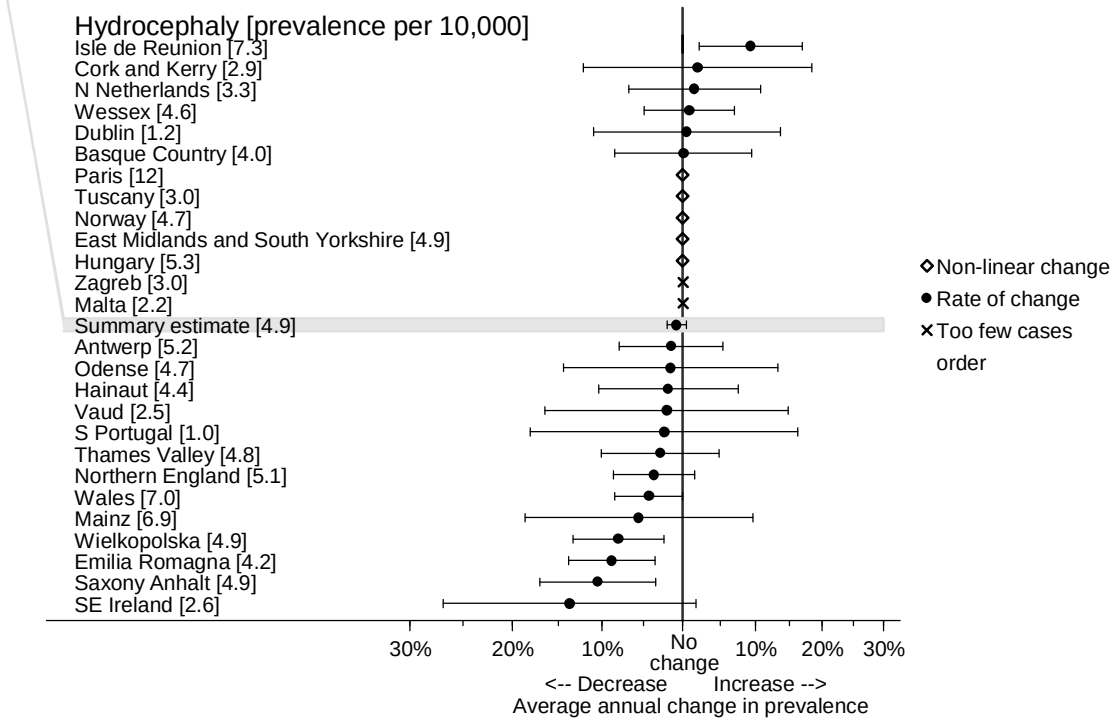


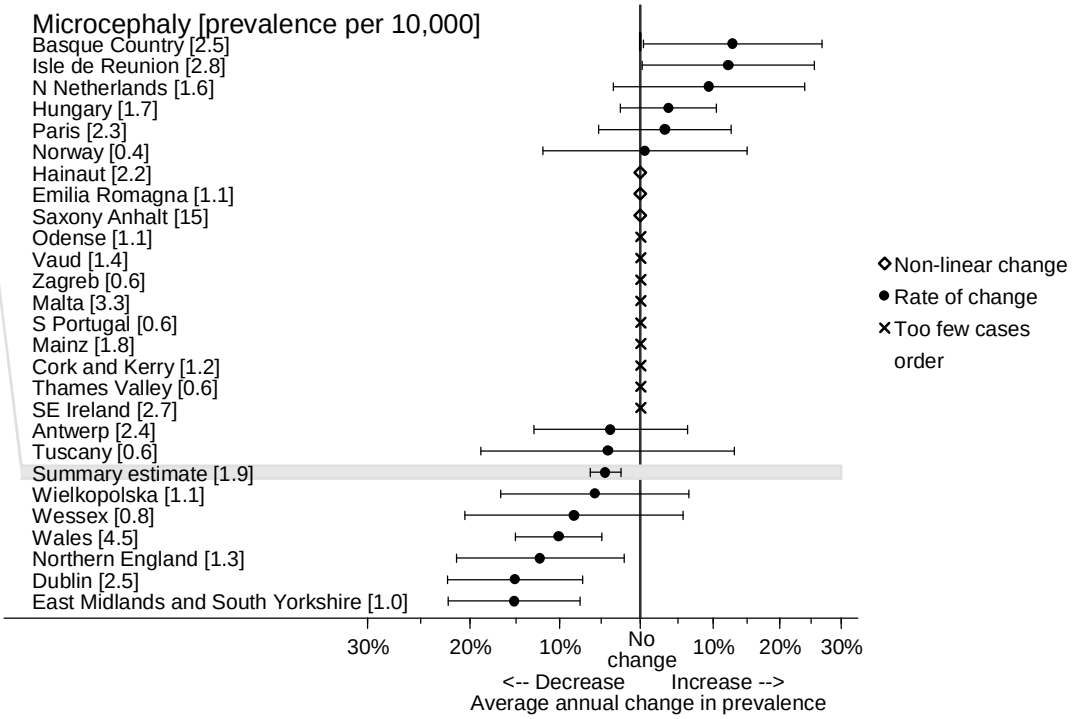


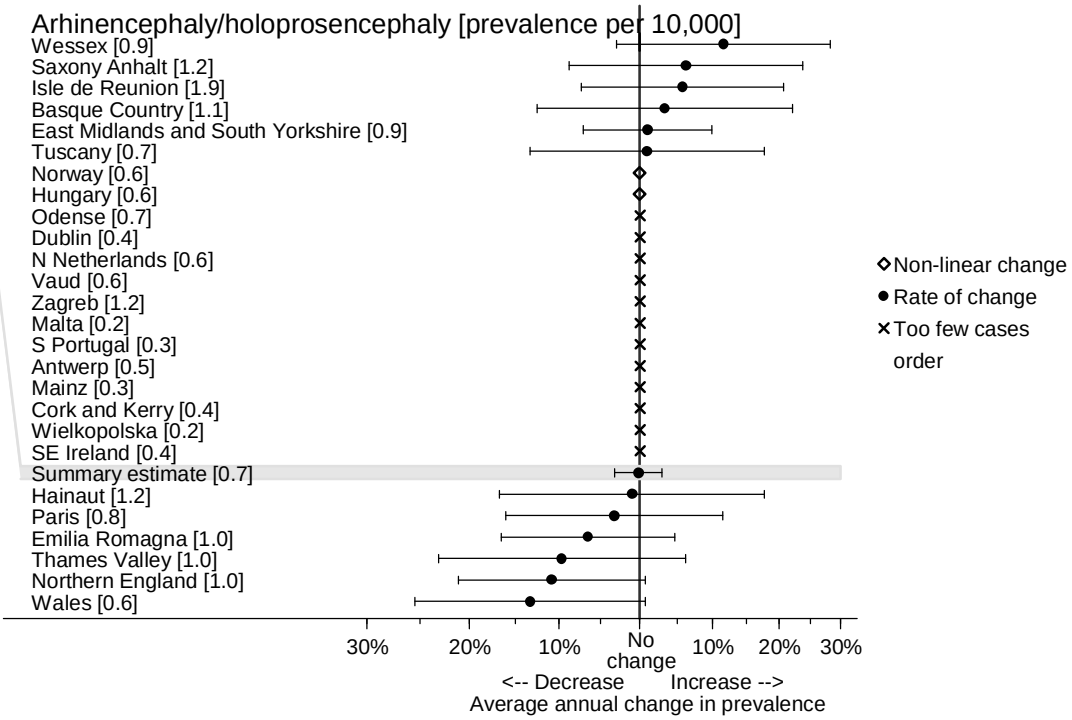

Anencephalus and similar [prevalence per 10,000]
Isle de Reunion [6.8]
N Netherlands [2.7]
Hainaut [3.2]
Vaud [3.6]
Tuscany [1.6]
Thames Valley [4.9]
Cork and Kerry [4.7]
East Midlands and South Yorkshire [4.8]
Northern England [5.4]
S Portugal [1.7]
Hungary [1.7]
Zagreb [1.9]
Malta [1.9]
Mainz [4.0]
Antwerp [2.7]
Summary estimate [3.5]
Paris [5.0]
Dublin [2.5]
Wessex [5.7]
SE Ireland [3.3]
Wales [5.4]
Basque Country [5.2]
Odense [4.4]
Norway [3.7]
Emilia Romagna [2.0]
Saxony Anhalt [2.3]
Wielkopolska [1.3]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

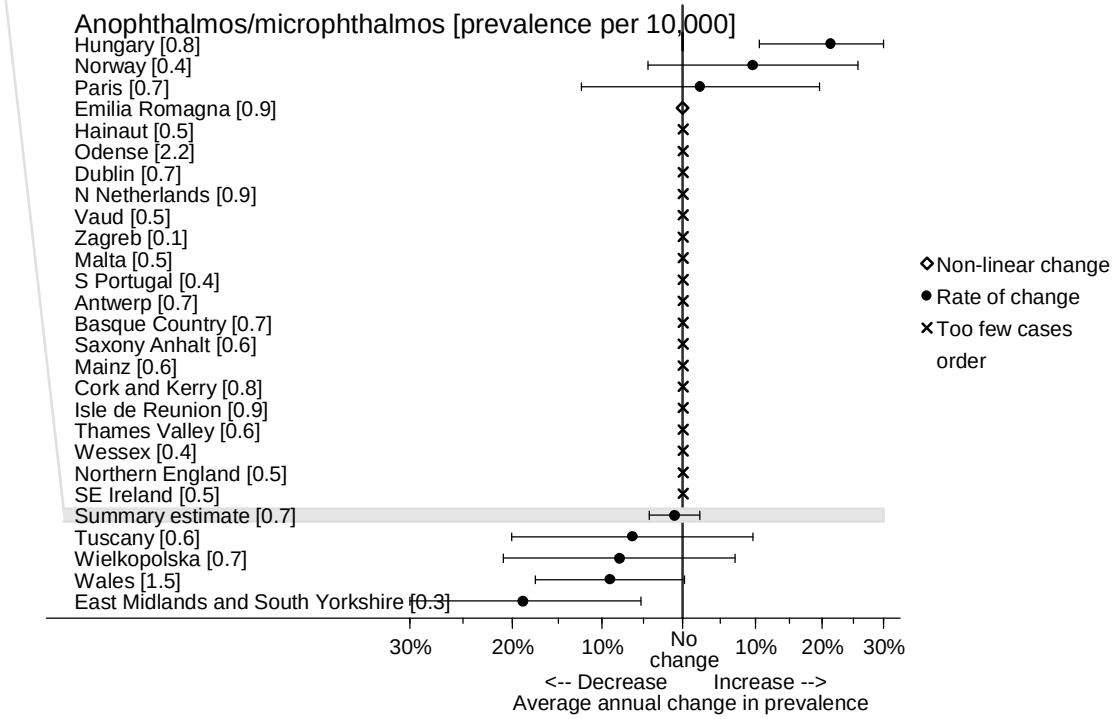

Encephalocele [prevalence per 10,000]
Isle de Reunion [1.7]
Northern England [1.3]
Hungary [0.6]
Wales [1.8]
Emilia Romagna [0.5]
Hainaut [0.9]
Odense [1.7]
Tuscany [0.7]
N Netherlands [0.3]
Vaud [1.3]
Zagreb [1.1]
Malta [1.6]
S Portugal [0.2]
Antwerp [0.6]
Basque Country [0.6]
Mainz [3.1]
Cork and Kerry [0.5]
Thames Valley [0.9]
SE Ireland [0.2]
Summary estimate [0.9]
Saxony Anhalt [1.3]
Paris [1.2]
East Midlands and South Yorkshire [1.1]
Wessex [0.9]
Wielkopolska [0.8]
Norway [0.9]
Dublin [0.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

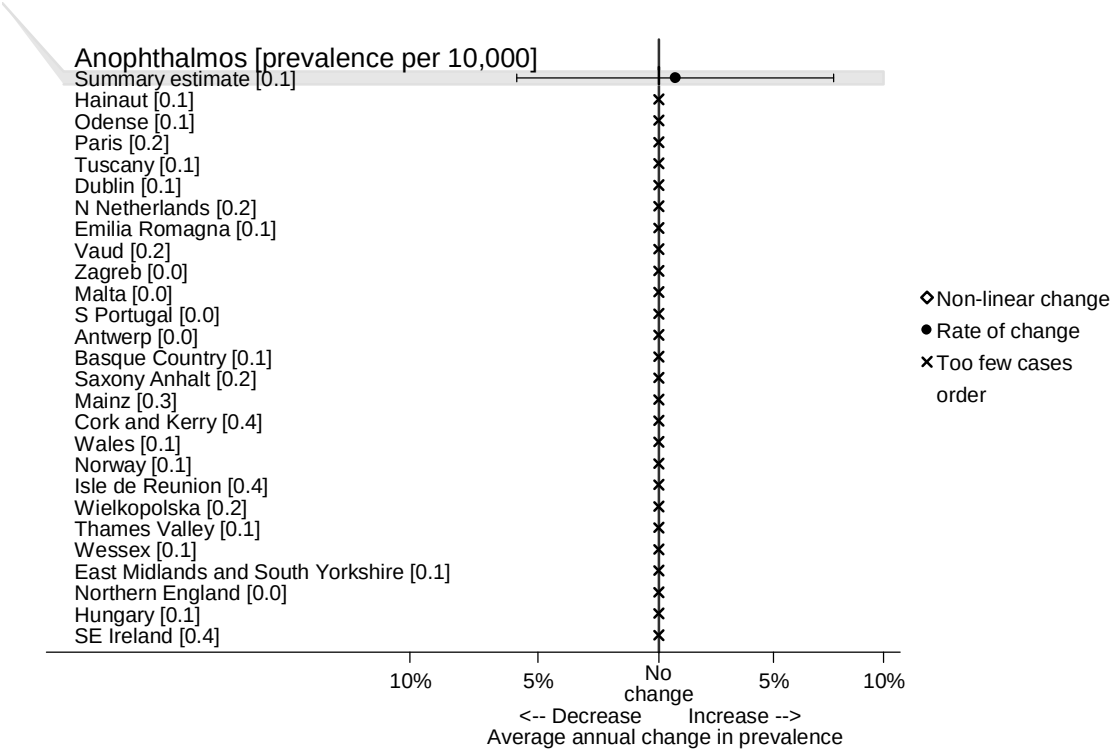

Spina bifida [prevalence per 10,000]
Odense [4.9]
Isle de Reunion [8.1]
Basque Country [4.0]
Thames Valley [4.6]
Norway [4.5]
Hungary [3.6]
Northern England [6.3]
Wessex [4.5]
N Netherlands [4.3]
Dublin [3.2]
Tuscany [3.1]
S Portugal [1.8]
Saxony Anhalt [5.3]
Zagreb [1.4]
Malta [6.6]
Wales [6.5]
Summary estimate [4.6]
Vaud [4.2]
East Midlands and South Yorkshire [5.2]
SE Ireland [5.6]
Antwerp [4.6]
Cork and Kerry [5.9]
Paris [5.2]
Emilia Romagna [2.9]
Mainz [7.2]
Wielkopolska [6.2]
Hainaut [4.1]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

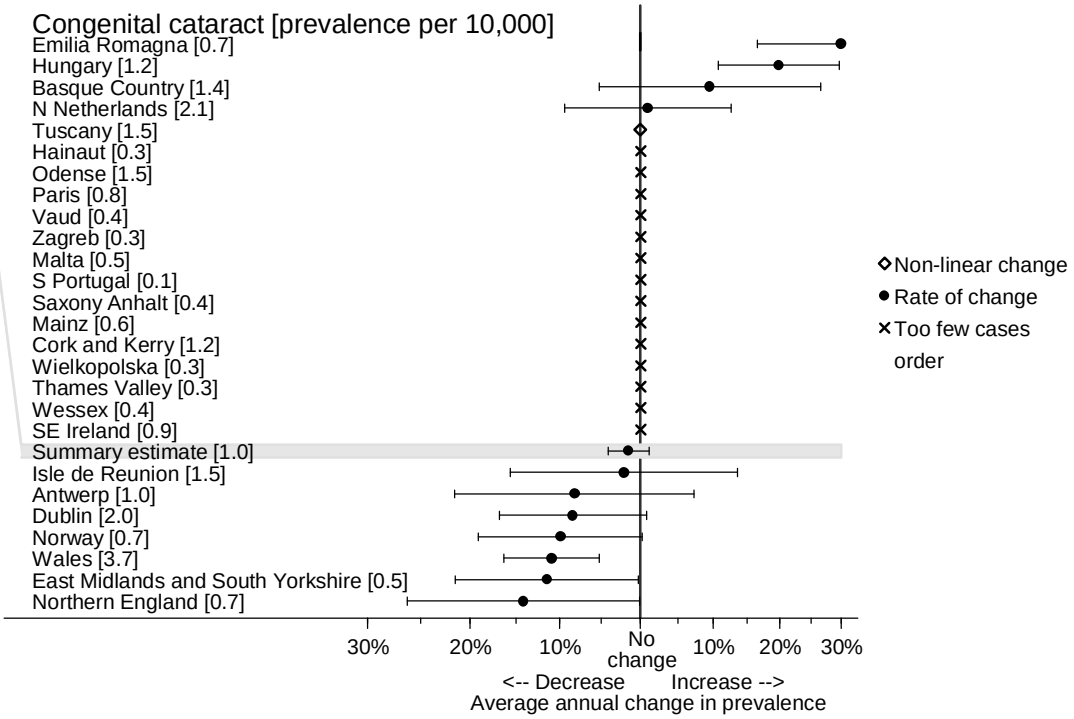

Hydrocephaly [prevalence per 10,000]
Isle de Reunion [7.3]
Cork and Kerry [2.9]
N Netherlands [3.3]
Wessex [4.6]
Dublin [1.2]
Basque Country [4.0]
Paris [12]
Tuscany [3.0]
Norway [4.7]
East Midlands and South Yorkshire [4.9]
Hungary [5.3]
Zagreb [3.0]
Malta [2.2]
Summary estimate [4.9]
Antwerp [5.2]
Odense [4.7]
Hainaut [4.4]
Vaud [2.5]
S Portugal [1.0]
Thames Valley [4.8]
Northern England [5.1]
Wales [7.0]
Mainz [6.9]
Wielkopolska [4.9]
Emilia Romagna [4.2]
Saxony Anhalt [4.9]
SE Ireland [2.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

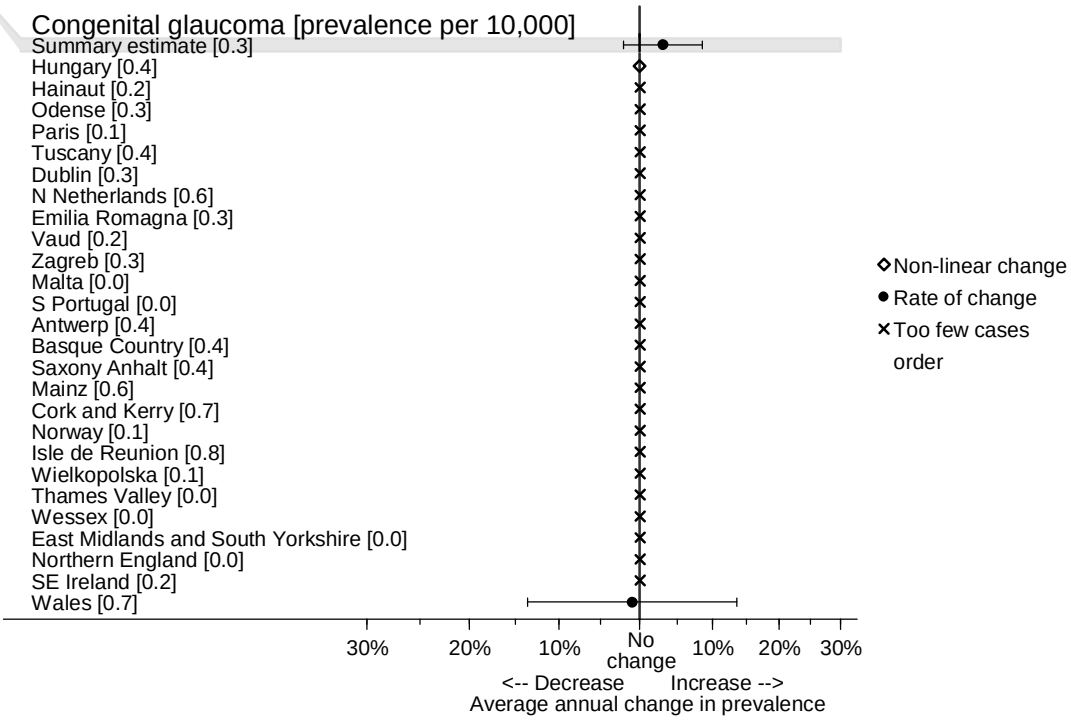

Microcephaly [prevalence per 10,000]
Basque Country [2.5]
Isle de Reunion [2.8]
N Netherlands [1.6]
Hungary [1.7]
Paris [2.3]
Norway [0.4]
Hainaut [2.2]
Emilia Romagna [1.1]
Saxony Anhalt [15]
Odense [1.1]
Vaud [1.4]
Zagreb [0.6]
Malta [3.3]
S Portugal [0.6]
Mainz [1.8]
Cork and Kerry [1.2]
Thames Valley [0.6]
SE Ireland [2.7]
Antwerp [2.4]
Tuscany [0.6]
Summary estimate [1.9]
Wielkopolska [1.1]
Wessex [0.8]
Wales [4.5]
Northern England [1.3]
Dublin [2.5]
East Midlands and South Yorkshire [1.0]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

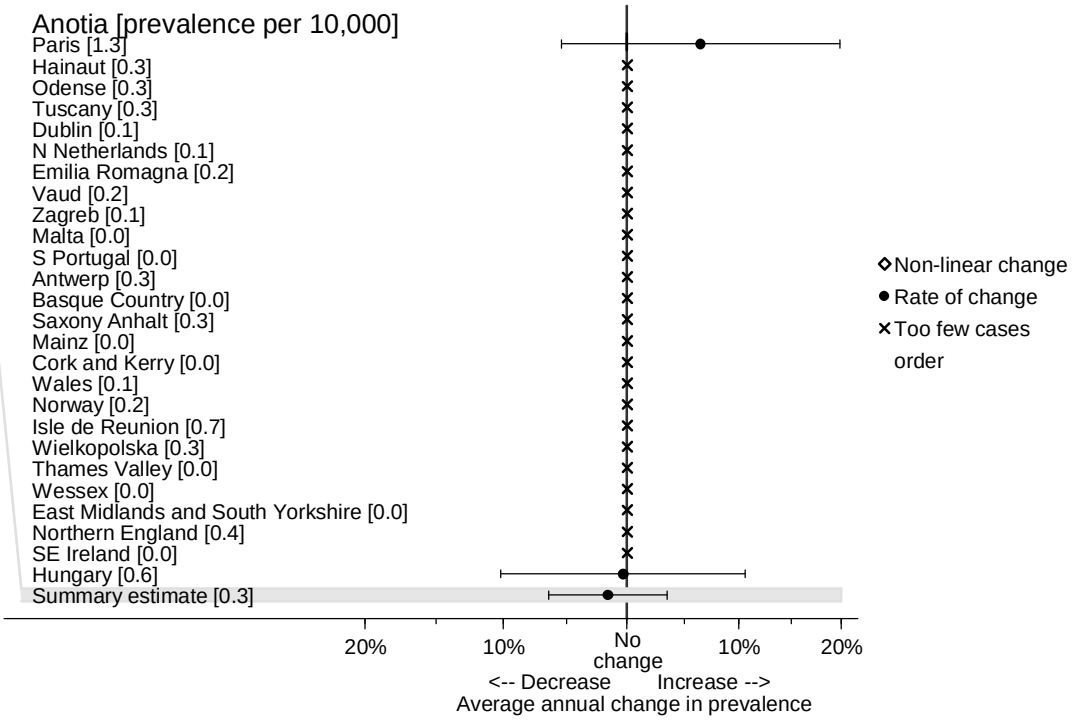

Arhinencephaly/holoprosencephaly [prevalence per 10,000]
Wessex [0.9]
Saxony Anhalt [1.2]
Isle de Reunion [1.9]
Basque Country [1.1]
East Midlands and South Yorkshire [0.9]
Tuscany [0.7]
Norway [0.6]
Hungary [0.6]
Odense [0.7]
Dublin [0.4]
N Netherlands [0.6]
Vaud [0.6]
Zagreb [1.2]
Malta [0.2]
S Portugal [0.3]
Antwerp [0.5]
Mainz [0.3]
Cork and Kerry [0.4]
Wielkopolska [0.2]
SE Ireland [0.4]
Summary estimate [0.7]
Hainaut [1.2]
Paris [0.8]
Emilia Romagna [1.0]
Thames Valley [1.0]
Northern England [1.0]
Wales [0.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

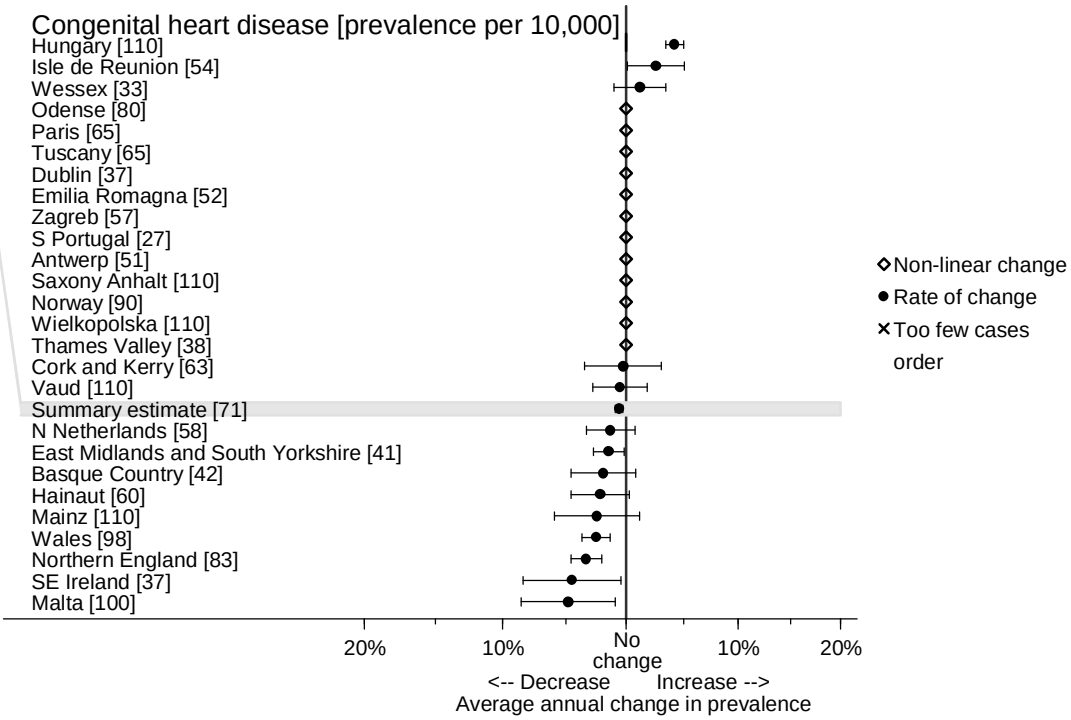

Anophthalmos/microphthalmos [prevalence per 10,000]
Hungary [0.8]
Norway [0.4]
Paris [0.7]
Emilia Romagna [0.9]
Hainaut [0.5]
Odense [2.2]
Dublin [0.7]
N Netherlands [0.9]
Vaud [0.5]
Zagreb [0.1]
Malta [0.5]
S Portugal [0.4]
Antwerp [0.7]
Basque Country [0.7]
Saxony Anhalt [0.6]
Mainz [0.6]
Cork and Kerry [0.8]
Isle de Reunion [0.9]
Thames Valley [0.6]
Wessex [0.4]
Northern England [0.5]
SE Ireland [0.5]
Summary estimate [0.7]
Tuscany [0.6]
Wielkopolska [0.7]
Wales [1.5]
East Midlands and South Yorkshire [0.3]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

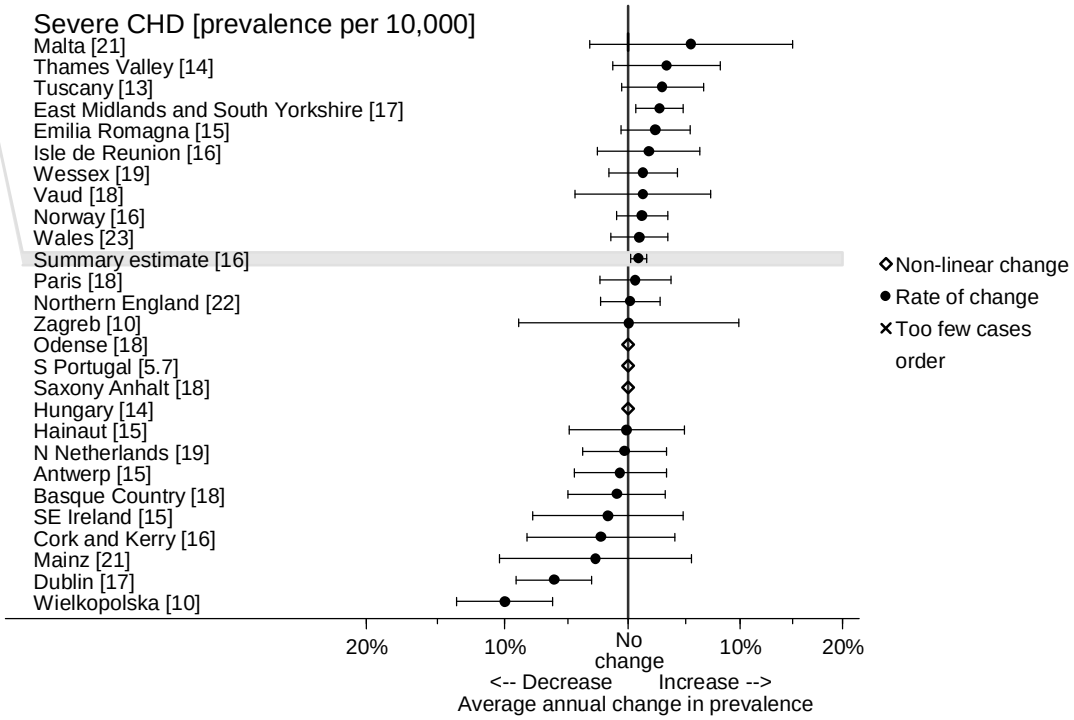

Anophthalmos [prevalence per 10,000]
Summary estimate [0.1]
Hainaut [0.1]
Odense [0.1]
Paris [0.2]
Tuscany [0.1]
Dublin [0.1]
N Netherlands [0.2]
Emilia Romagna [0.1]
Vaud [0.2]
Zagreb [0.0]
Malta [0.0]
S Portugal [0.0]
Antwerp [0.0]
Basque Country [0.1]
Saxony Anhalt [0.2]
Mainz [0.3]
Cork and Kerry [0.4]
Wales [0.1]
Norway [0.1]
Isle de Reunion [0.4]
Wielkopolska [0.2]
Thames Valley [0.1]
Wessex [0.1]
East Midlands and South Yorkshire [0.1]
Northern England [0.0]
Hungary [0.1]
SE Ireland [0.4]
10%
5%
No change
5%
10%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

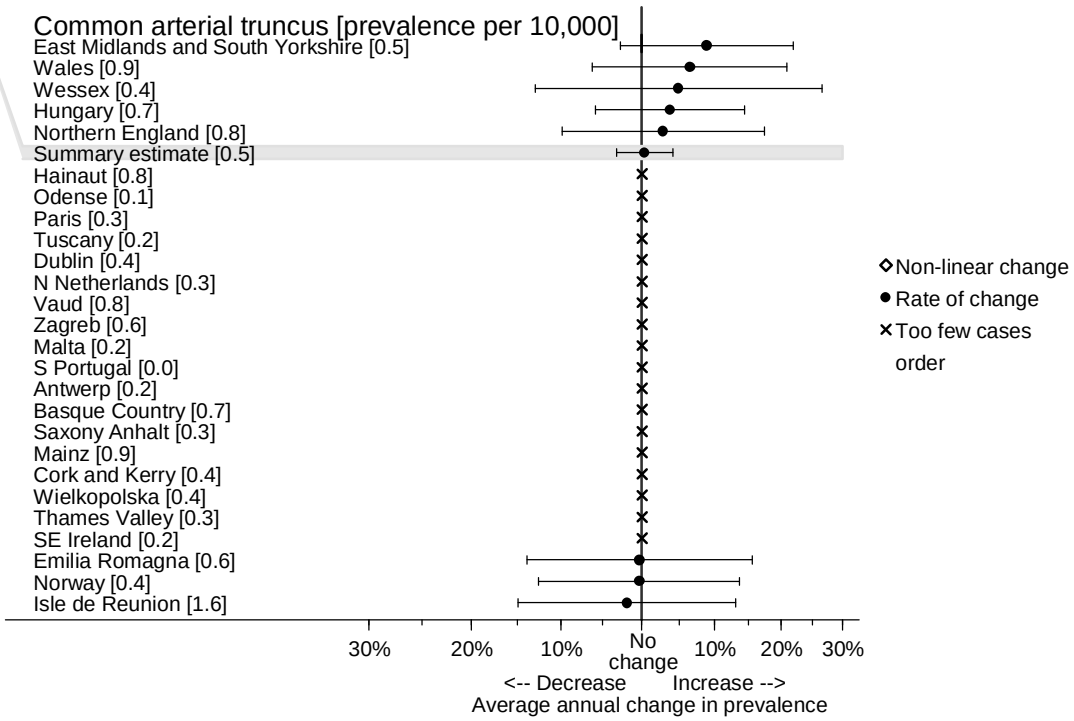

Congenital cataract [prevalence per 10,000]
Emilia Romagna [0.7]
Hungary [1.2]
Basque Country [1.4]
N Netherlands [2.1]
Tuscany [1.5]
Hainaut [0.3]
Odense [1.5]
Paris [0.8]
Vaud [0.4]
Zagreb [0.3]
Malta [0.5]
S Portugal [0.1]
Saxony Anhalt [0.4]
Mainz [0.6]
Cork and Kerry [1.2]
Wielkopolska [0.3]
Thames Valley [0.3]
Wessex [0.4]
SE Ireland [0.9]
Summary estimate [1.0]
Isle de Reunion [1.5]
Antwerp [1.0]
Dublin [2.0]
Norway [0.7]
Wales [3.7]
East Midlands and South Yorkshire [0.5]
Northern England [0.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

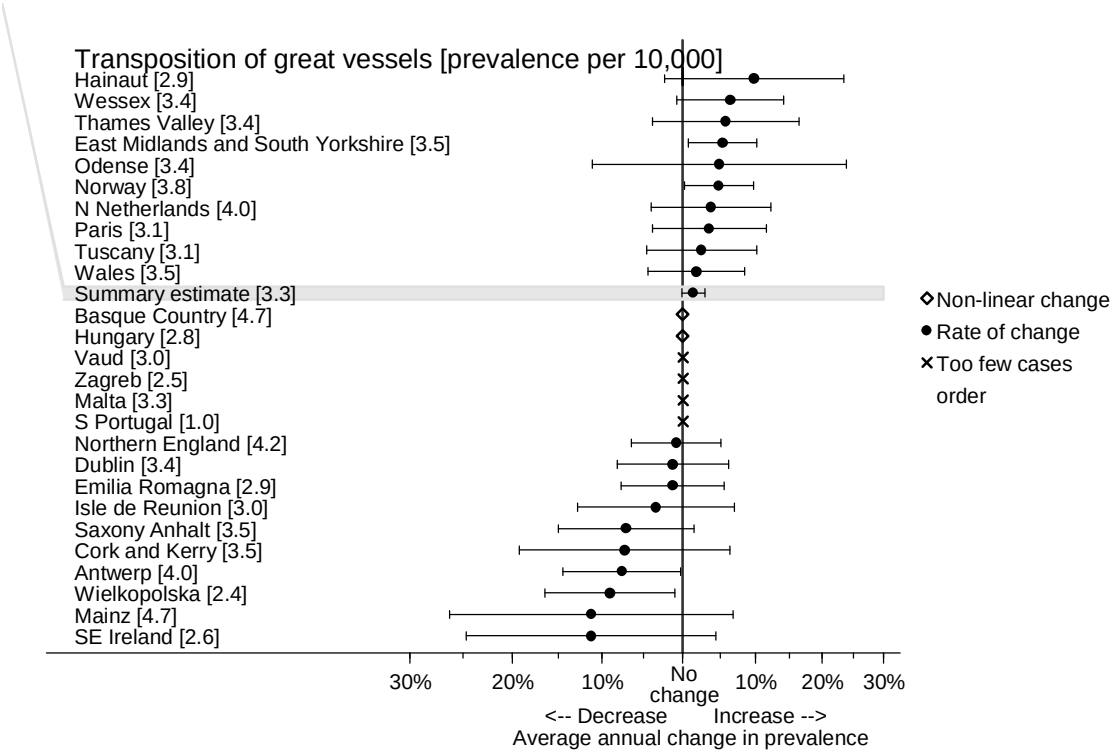

Congenital glaucoma [prevalence per 10,000]
Summary estimate [0.3]
Hungary [0.4]
Hainaut [0.2]
Odense [0.3]
Paris [0.1]
Tuscany [0.4]
Dublin [0.3]
N Netherlands [0.6]
Emilia Romagna [0.3]
Vaud [0.2]
Zagreb [0.3]
Malta [0.0]
S Portugal [0.0]
Antwerp [0.4]
Basque Country [0.4]
Saxony Anhalt [0.4]
Mainz [0.6]
Cork and Kerry [0.7]
Norway [0.1]
Isle de Reunion [0.8]
Wielkopolska [0.1]
Thames Valley [0.0]
Wessex [0.0]
East Midlands and South Yorkshire [0.0]
Northern England [0.0]
SE Ireland [0.2]
Wales [0.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

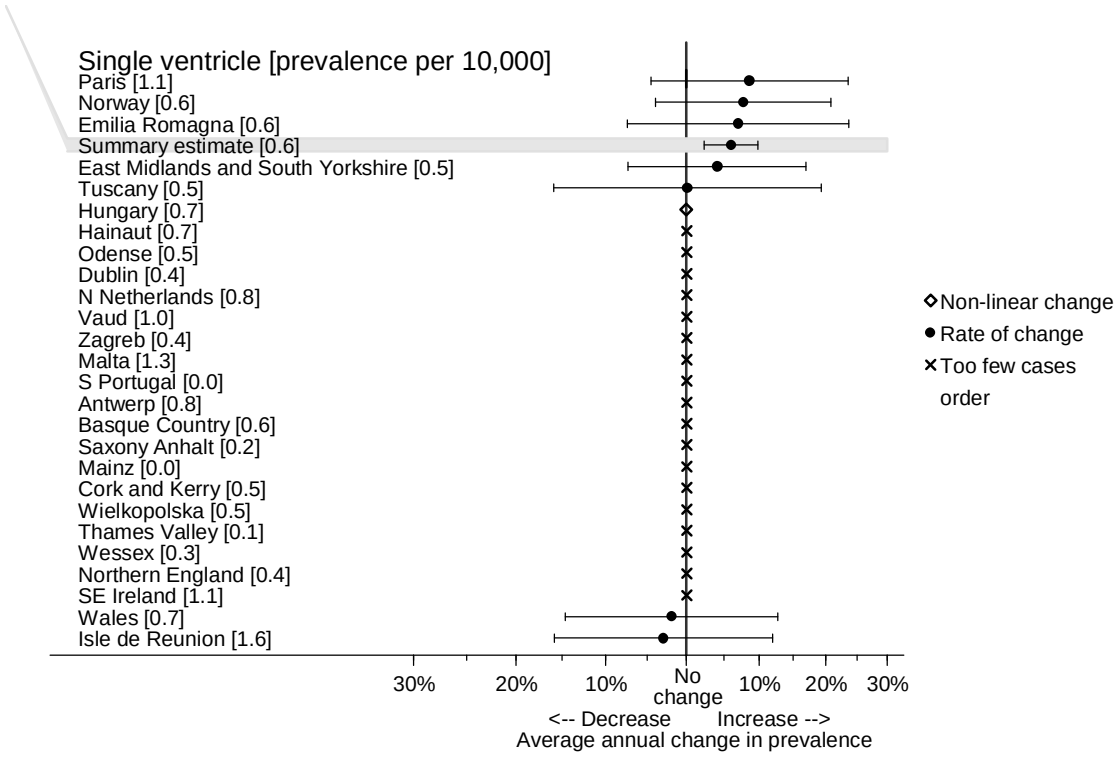

Anotia [prevalence per 10,000]
Paris [1.3]
Hainaut [0.3]
Odense [0.3]
Tuscany [0.3]
Dublin [0.1]
N Netherlands [0.1]
Emilia Romagna [0.2]
Vaud [0.2]
Zagreb [0.1]
Malta [0.0]
S Portugal [0.0]
Antwerp [0.3]
Basque Country [0.0]
Saxony Anhalt [0.3]
Mainz [0.0]
Cork and Kerry [0.0]
Wales [0.1]
Norway [0.2]
Isle de Reunion [0.7]
Wielkopolska [0.3]
Thames Valley [0.0]
Wessex [0.0]
East Midlands and South Yorkshire [0.0]
Northern England [0.4]
SE Ireland [0.0]
Hungary [0.6]
Summary estimate [0.3]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

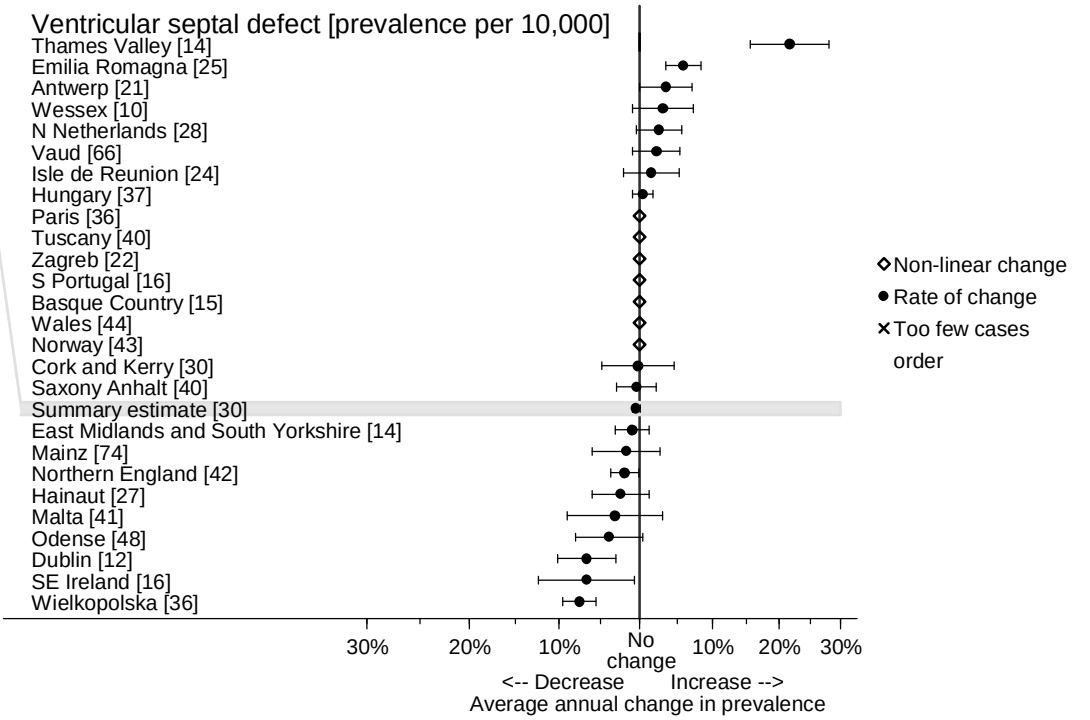

Congenital heart disease [prevalence per 10,000]
Hungary [110]
Isle de Reunion [54]
Wessex [33]
Odense [80]
Paris [65]
Tuscany [65]
Dublin [37]
Emilia Romagna [52]
Zagreb [57]
S Portugal [27]
Antwerp [51]
Saxony Anhalt [110]
Norway [90]
Wielkopolska [110]
Thames Valley [38]
Cork and Kerry [63]
Vaud [110]
Summary estimate [71]
N Netherlands [58]
East Midlands and South Yorkshire [41]
Basque Country [42]
Hainaut [60]
Mainz [110]
Wales [98]
Northern England [83]
SE Ireland [37]
Malta [100]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

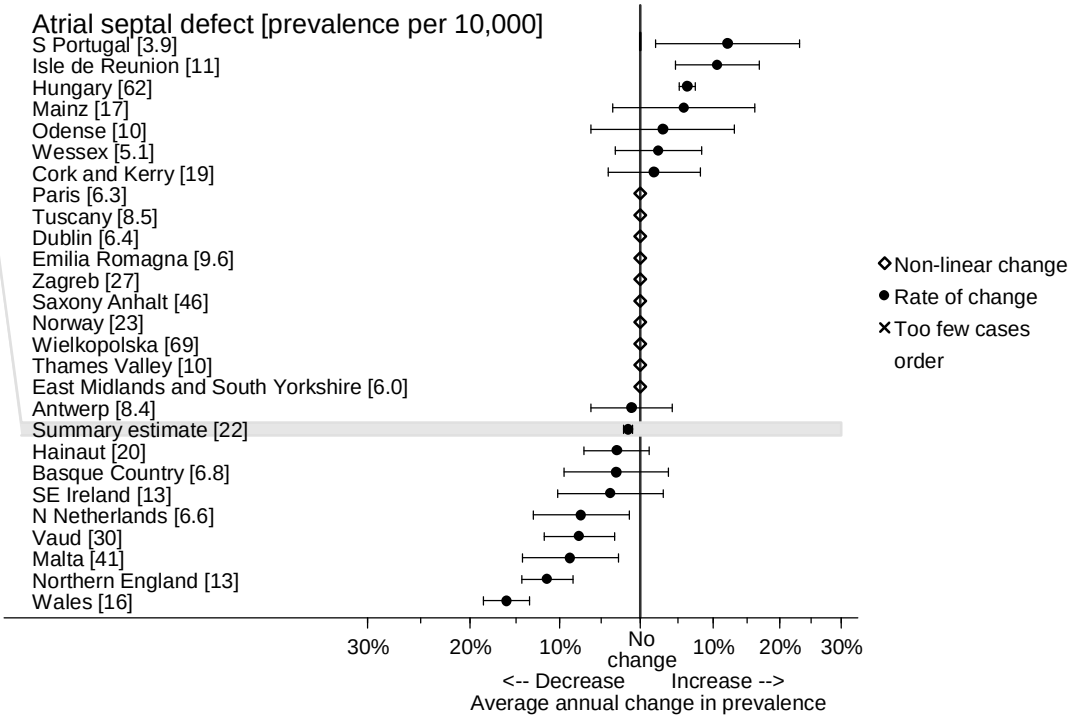

Severe CHD [prevalence per 10,000]
Malta [21]
Thames Valley [14]
Tuscany [13]
East Midlands and South Yorkshire [17]
Emilia Romagna [15]
Isle de Reunion [16]
Wessex [19]
Vaud [18]
Norway [16]
Wales [23]
Summary estimate [16]
Paris [18]
Northern England [22]
Zagreb [10]
Odense [18]
S Portugal [5.7]
Saxony Anhalt [18]
Hungary [14]
Hainaut [15]
N Netherlands [19]
Antwerp [15]
Basque Country [18]
SE Ireland [15]
Cork and Kerry [16]
Mainz [21]
Dublin [17]
Wielkopolska [10]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

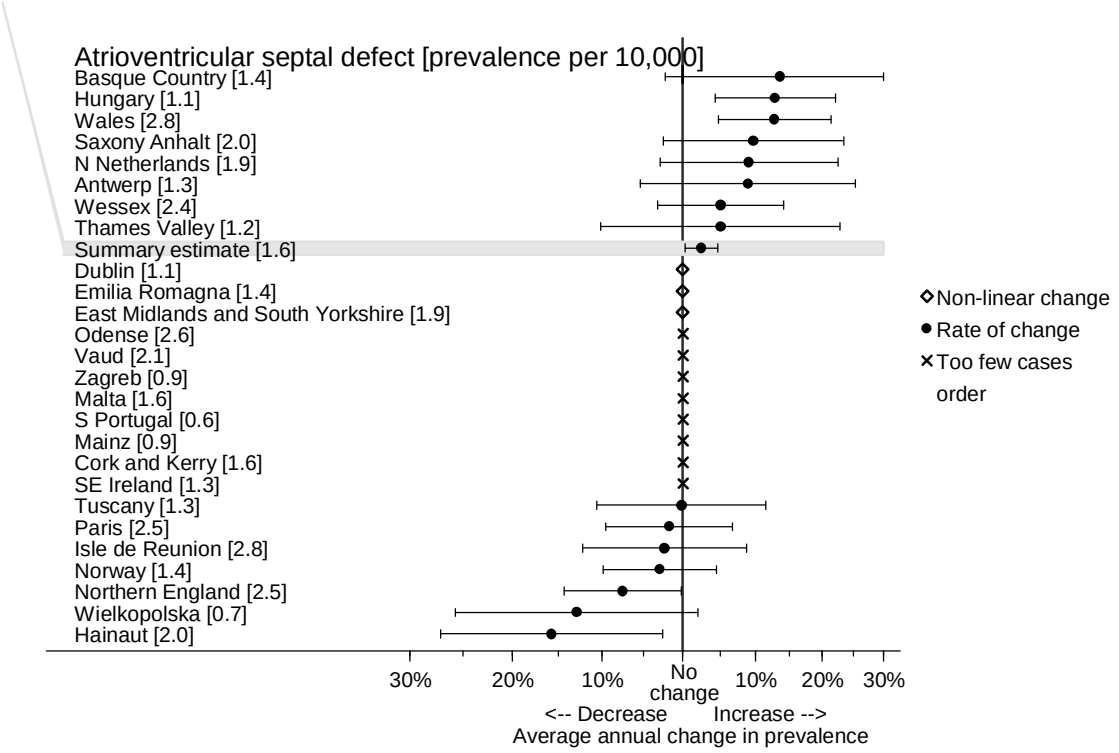

Common arterial truncus [prevalence per 10,000]
East Midlands and South Yorkshire [0.5]
Wales [0.9]
Wessex [0.4]
Hungary [0.7]
Northern England [0.8]
Summary estimate [0.5]
Hainaut [0.8]
Odense [0.1]
Paris [0.3]
Tuscany [0.2]
Dublin [0.4]
N Netherlands [0.3]
Vaud [0.8]
Zagreb [0.6]
Malta [0.2]
S Portugal [0.0]
Antwerp [0.2]
Basque Country [0.7]
Saxony Anhalt [0.3]
Mainz [0.9]
Cork and Kerry [0.4]
Wielkopolska [0.4]
Thames Valley [0.3]
SE Ireland [0.2]
Emilia Romagna [0.6]
Norway [0.4]
Isle de Reunion [1.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

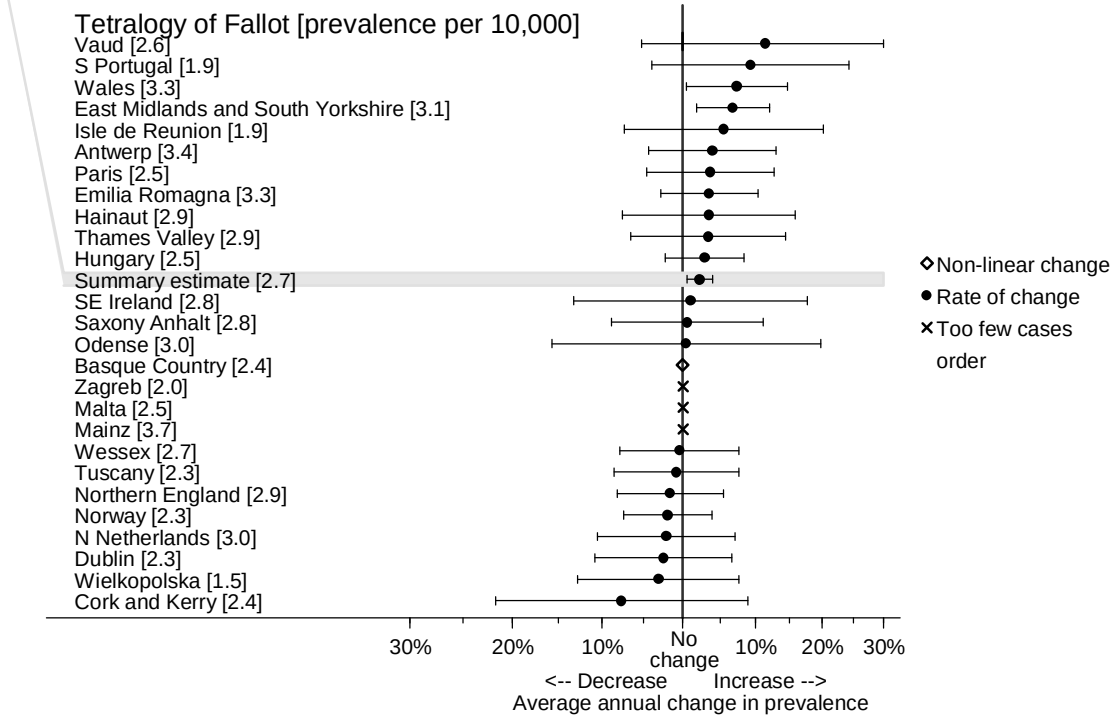

Transposition of great vessels [prevalence per 10,000]
Hainaut [2.9]
Wessex [3.4]
Thames Valley [3.4]
East Midlands and South Yorkshire [3.5]
Odense [3.4]
Norway [3.8]
N Netherlands [4.0]
Paris [3.1]
Tuscany [3.1]
Wales [3.5]
Summary estimate [3.3]
Basque Country [4.7]
Hungary [2.8]
Vaud [3.0]
Zagreb [2.5]
Malta [3.3]
S Portugal [1.0]
Northern England [4.2]
Dublin [3.4]
Emilia Romagna [2.9]
Isle de Reunion [3.0]
Saxony Anhalt [3.5]
Cork and Kerry [3.5]
Antwerp [4.0]
Wielkopolska [2.4]
Mainz [4.7]
SE Ireland [2.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

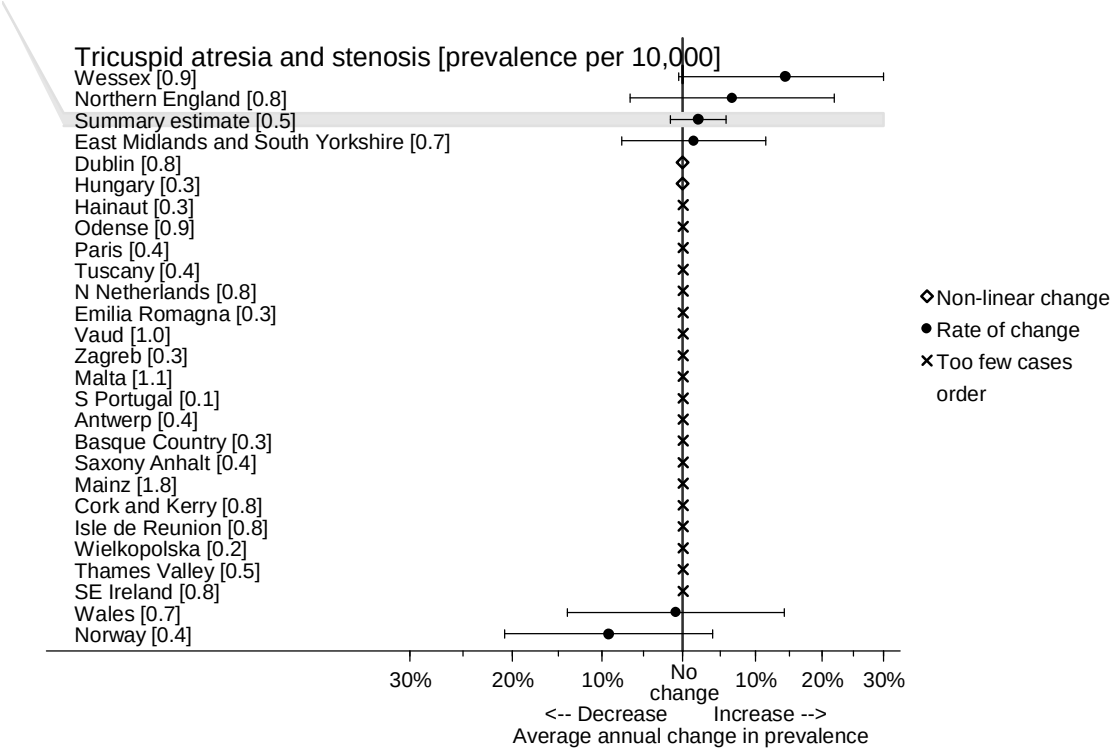

Single ventricle [prevalence per 10,000]
Paris [1.1]
Norway [0.6]
Emilia Romagna [0.6]
Summary estimate [0.6]
East Midlands and South Yorkshire [0.5]
Tuscany [0.5]
Hungary [0.7]
Hainaut [0.7]
Odense [0.5]
Dublin [0.4]
N Netherlands [0.8]
Vaud [1.0]
Zagreb [0.4]
Malta [1.3]
S Portugal [0.0]
Antwerp [0.8]
Basque Country [0.6]
Saxony Anhalt [0.2]
Mainz [0.0]
Cork and Kerry [0.5]
Wielkopolska [0.5]
Thames Valley [0.1]
Wessex [0.3]
Northern England [0.4]
SE Ireland [1.1]
Wales [0.7]
Isle de Reunion [1.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

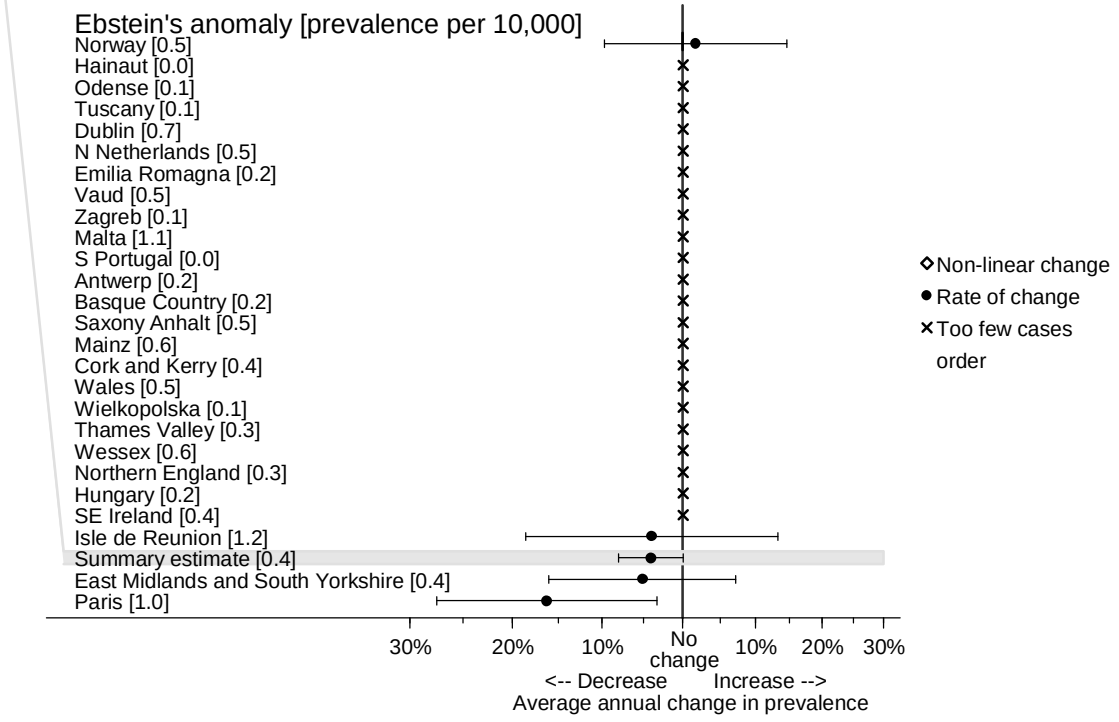

Ventricular septal defect [prevalence per 10,000]
Thames Valley [14]
Emilia Romagna [25]
Antwerp [21]
Wessex [10]
N Netherlands [28]
Vaud [66]
Isle de Reunion [24]
Hungary [37]
Paris [36]
Tuscany [40]
Zagreb [22]
S Portugal [16]
Basque Country [15]
Wales [44]
Norway [43]
Cork and Kerry [30]
Saxony Anhalt [40]
Summary estimate [30]
East Midlands and South Yorkshire [14]
Mainz [74]
Northern England [42]
Hainaut [27]
Malta [41]
Odense [48]
Dublin [12]
SE Ireland [16]
Wielkopolska [36]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

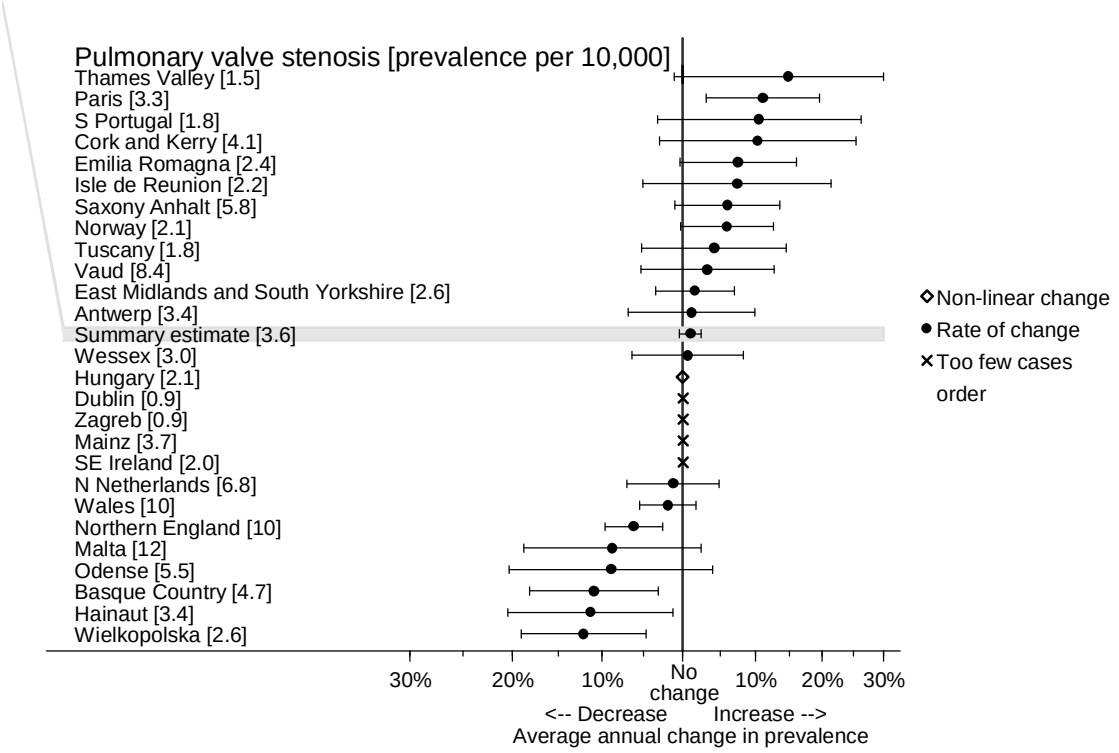

Atrial septal defect [prevalence per 10,000]
S Portugal [3.9]
Isle de Reunion [11]
Hungary [62]
Mainz [17]
Odense [10]
Wessex [5.1]
Cork and Kerry [19]
Paris [6.3]
Tuscany [8.5]
Dublin [6.4]
Emilia Romagna [9.6]
Zagreb [27]
Saxony Anhalt [46]
Norway [23]
Wielkopolska [69]
Thames Valley [10]
East Midlands and South Yorkshire [6.0]
Antwerp [8.4]
Summary estimate [22]
Hainaut [20]
Basque Country [6.8]
SE Ireland [13]
N Netherlands [6.6]
Vaud [30]
Malta [41]
Northern England [13]
Wales [16]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

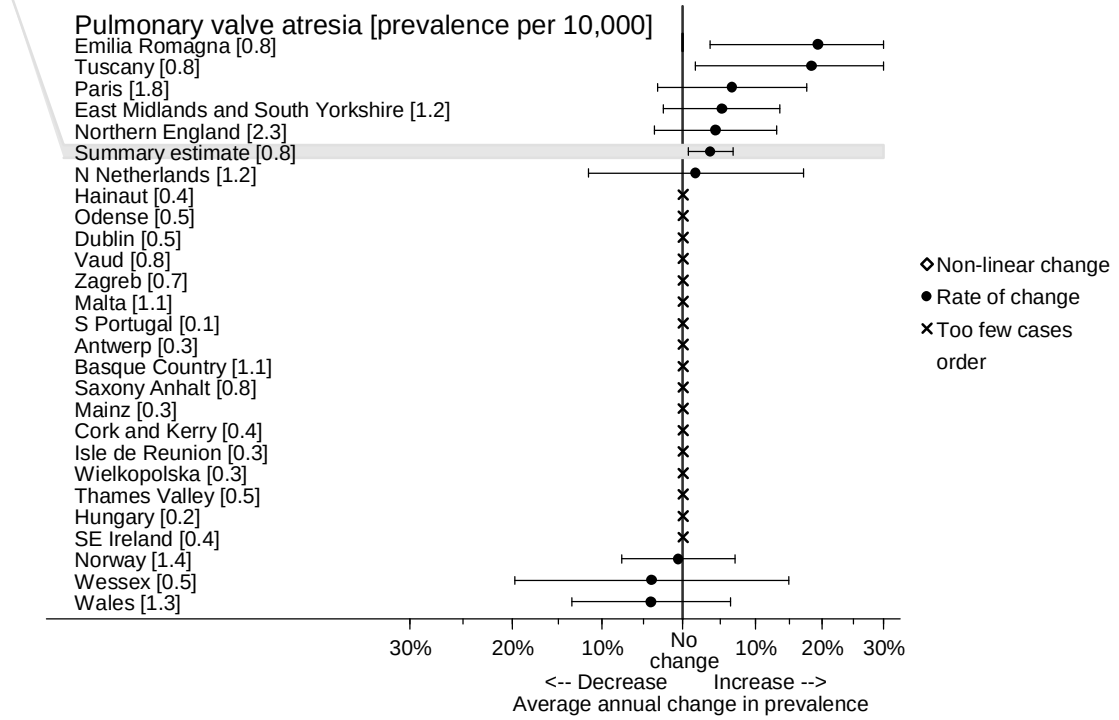

Atrioventricular septal defect [prevalence per 10,000]
Basque Country [1.4]
Hungary [1.1]
Wales [2.8]
Saxony Anhalt [2.0]
N Netherlands [1.9]
Antwerp [1.3]
Wessex [2.4]
Thames Valley [1.2]
Summary estimate [1.6]
Dublin [1.1]
Emilia Romagna [1.4]
East Midlands and South Yorkshire [1.9]
Odense [2.6]
Vaud [2.1]
Zagreb [0.9]
Malta [1.6]
S Portugal [0.6]
Mainz [0.9]
Cork and Kerry [1.6]
SE Ireland [1.3]
Tuscany [1.3]
Paris [2.5]
Isle de Reunion [2.8]
Norway [1.4]
Northern England [2.5]
Wielkopolska [0.7]
Hainaut [2.0]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

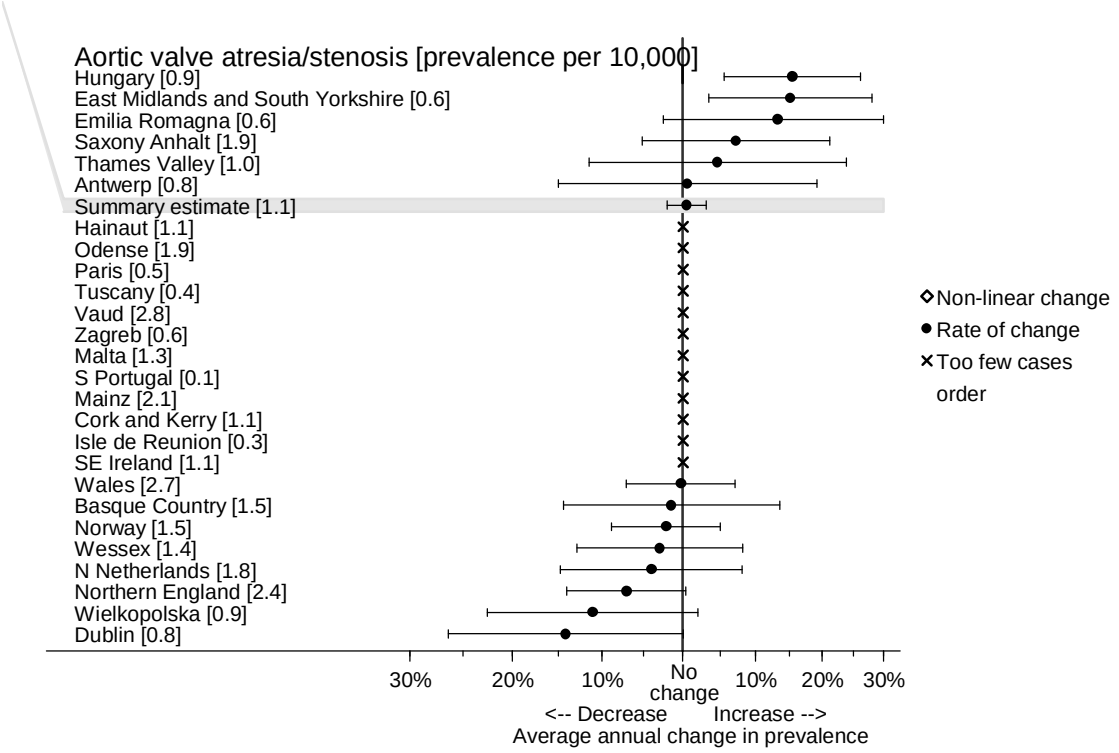

Tetralogy of Fallot [prevalence per 10,000]
Vaud [2.6]
S Portugal [1.9]
Wales [3.3]
East Midlands and South Yorkshire [3.1]
Isle de Reunion [1.9]
Antwerp [3.4]
Paris [2.5]
Emilia Romagna [3.3]
Hainaut [2.9]
Thames Valley [2.9]
Hungary [2.5]
Summary estimate [2.7]
SE Ireland [2.8]
Saxony Anhalt [2.8]
Odense [3.0]
Basque Country [2.4]
Zagreb [2.0]
Malta [2.5]
Mainz [3.7]
Wessex [2.7]
Tuscany [2.3]
Northern England [2.9]
Norway [2.3]
N Netherlands [3.0]
Dublin [2.3]
Wielkopolska [1.5]
Cork and Kerry [2.4]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

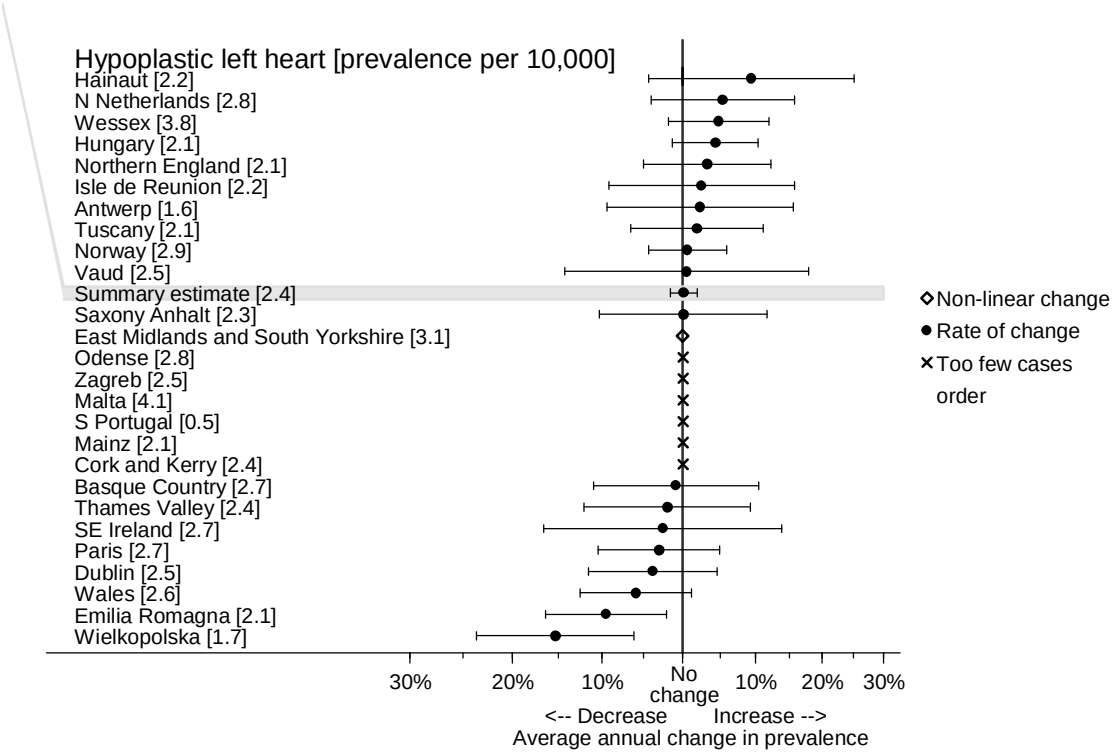

Tricuspid atresia and stenosis [prevalence per 10,000]
Wessex [0.9]
Northern England [0.8]
Summary estimate [0.5]
East Midlands and South Yorkshire [0.7]
Dublin [0.8]
Hungary [0.3]
Hainaut [0.3]
Odense [0.9]
Paris [0.4]
Tuscany [0.4]
N Netherlands [0.8]
Emilia Romagna [0.3]
Vaud [1.0]
Zagreb [0.3]
Malta [1.1]
S Portugal [0.1]
Antwerp [0.4]
Basque Country [0.3]
Saxony Anhalt [0.4]
Mainz [1.8]
Cork and Kerry [0.8]
Isle de Reunion [0.8]
Wielkopolska [0.2]
Thames Valley [0.5]
SE Ireland [0.8]
Wales [0.7]
Norway [0.4]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

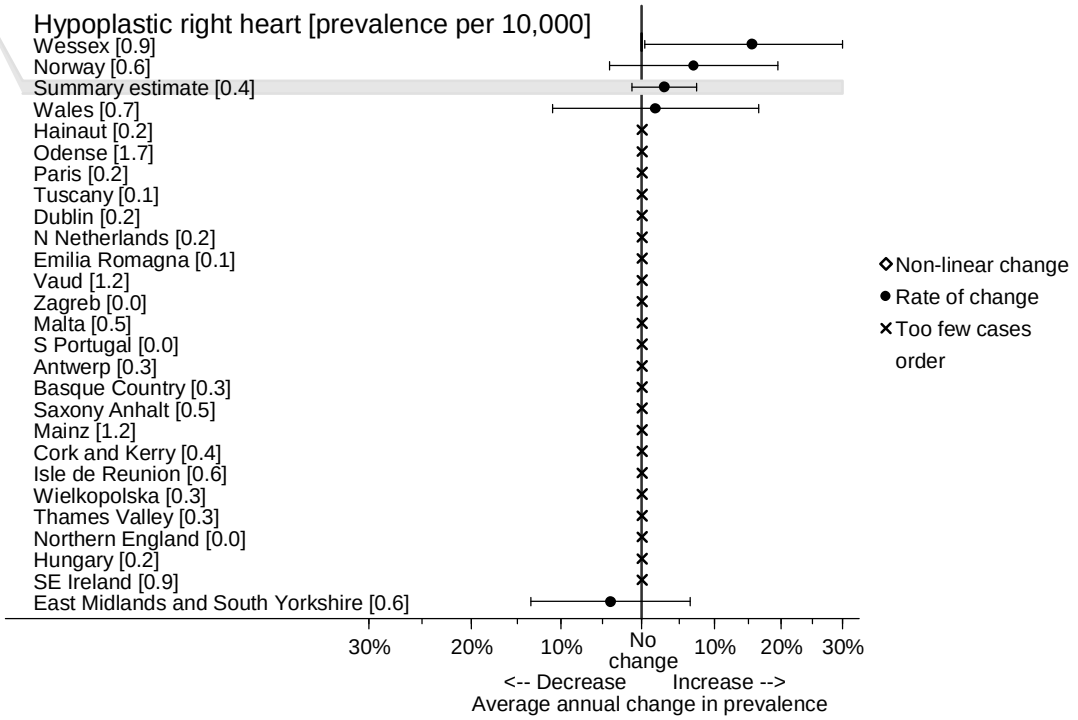

Ebstein's anomaly [prevalence per 10,000]
Norway [0.5]
Hainaut [0.0]
Odense [0.1]
Tuscany [0.1]
Dublin [0.7]
N Netherlands [0.5]
Emilia Romagna [0.2]
Vaud [0.5]
Zagreb [0.1]
Malta [1.1]
S Portugal [0.0]
Antwerp [0.2]
Basque Country [0.2]
Saxony Anhalt [0.5]
Mainz [0.6]
Cork and Kerry [0.4]
Wales [0.5]
Wielkopolska [0.1]
Thames Valley [0.3]
Wessex [0.6]
Northern England [0.3]
Hungary [0.2]
SE Ireland [0.4]
Isle de Reunion [1.2]
Summary estimate [0.4]
East Midlands and South Yorkshire [0.4]
Paris [1.0]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

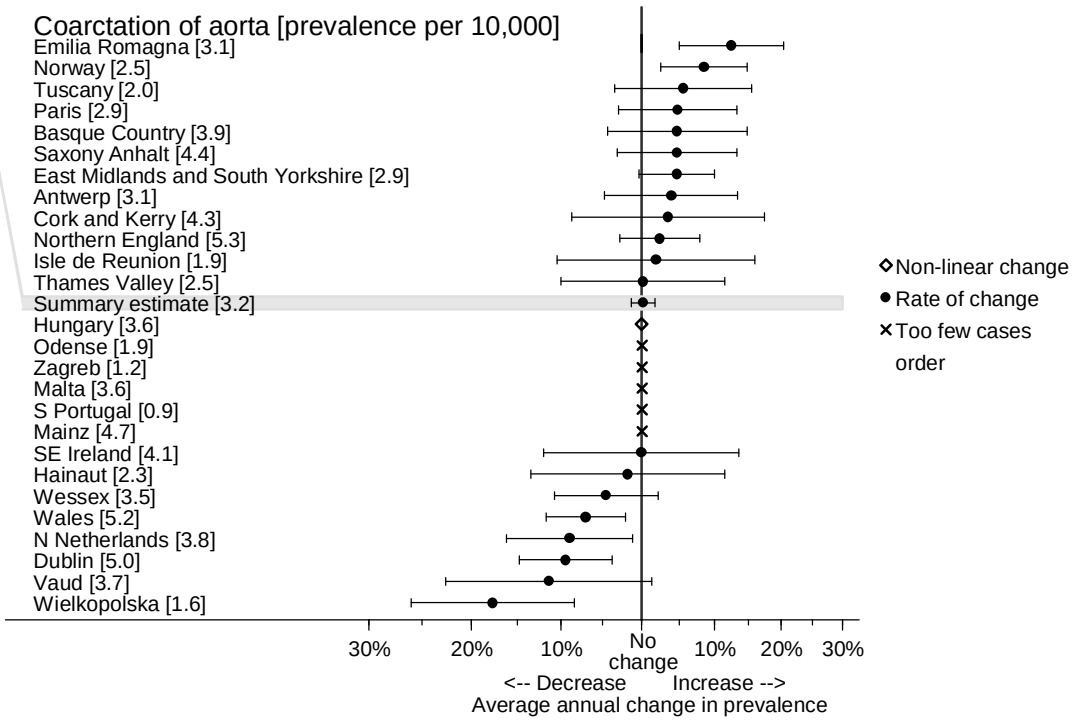

Pulmonary valve stenosis [prevalence per 10,000]
Thames Valley [1.5]
Paris [3.3]
S Portugal [1.8]
Cork and Kerry [4.1]
Emilia Romagna [2.4]
Isle de Reunion [2.2]
Saxony Anhalt [5.8]
Norway [2.1]
Tuscany [1.8]
Vaud [8.4]
East Midlands and South Yorkshire [2.6]
Antwerp [3.4]
Summary estimate [3.6]
Wessex [3.0]
Hungary [2.1]
Dublin [0.9]
Zagreb [0.9]
Mainz [3.7]
SE Ireland [2.0]
N Netherlands [6.8]
Wales [10]
Northern England [10]
Malta [12]
Odense [5.5]
Basque Country [4.7]
Hainaut [3.4]
Wielkopolska [2.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

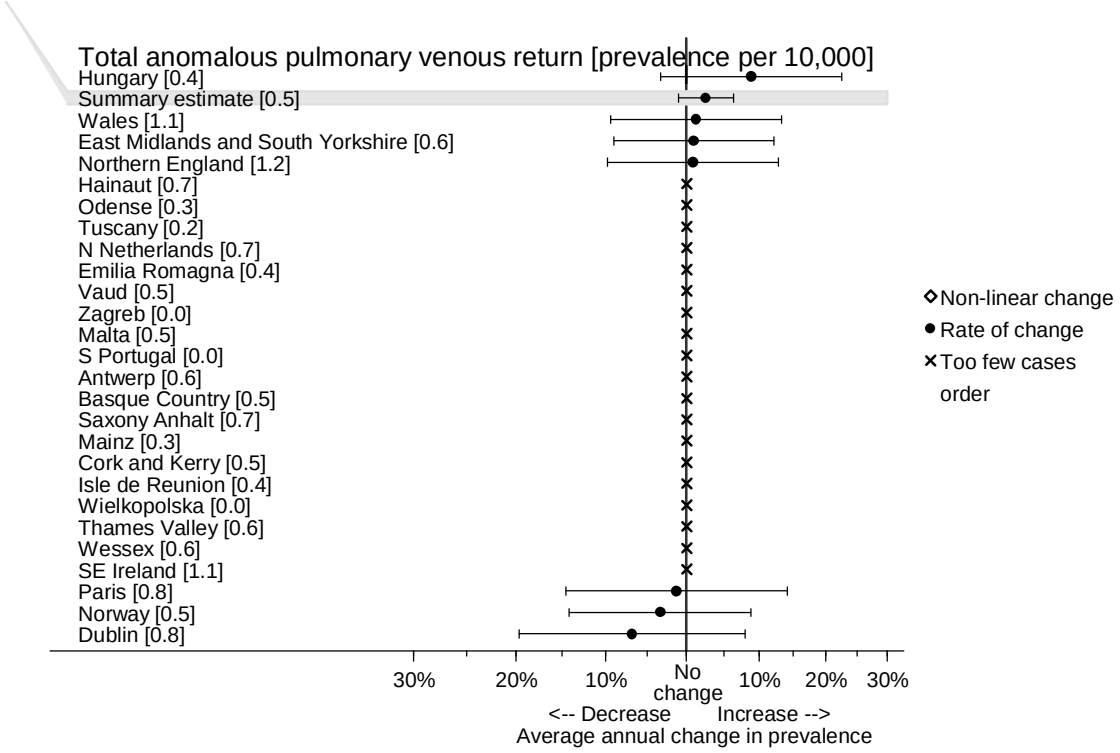

Pulmonary valve atresia [prevalence per 10,000]
Emilia Romagna [0.8]
Tuscany [0.8]
Paris [1.8]
East Midlands and South Yorkshire [1.2]
Northern England [2.3]
Summary estimate [0.8]
N Netherlands [1.2]
Hainaut [0.4]
Odense [0.5]
Dublin [0.5]
Vaud [0.8]
Zagreb [0.7]
Malta [1.1]
S Portugal [0.1]
Antwerp [0.3]
Basque Country [1.1]
Saxony Anhalt [0.8]
Mainz [0.3]
Cork and Kerry [0.4]
Isle de Reunion [0.3]
Wielkopolska [0.3]
Thames Valley [0.5]
Hungary [0.2]
SE Ireland [0.4]
Norway [1.4]
Wessex [0.5]
Wales [1.3]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

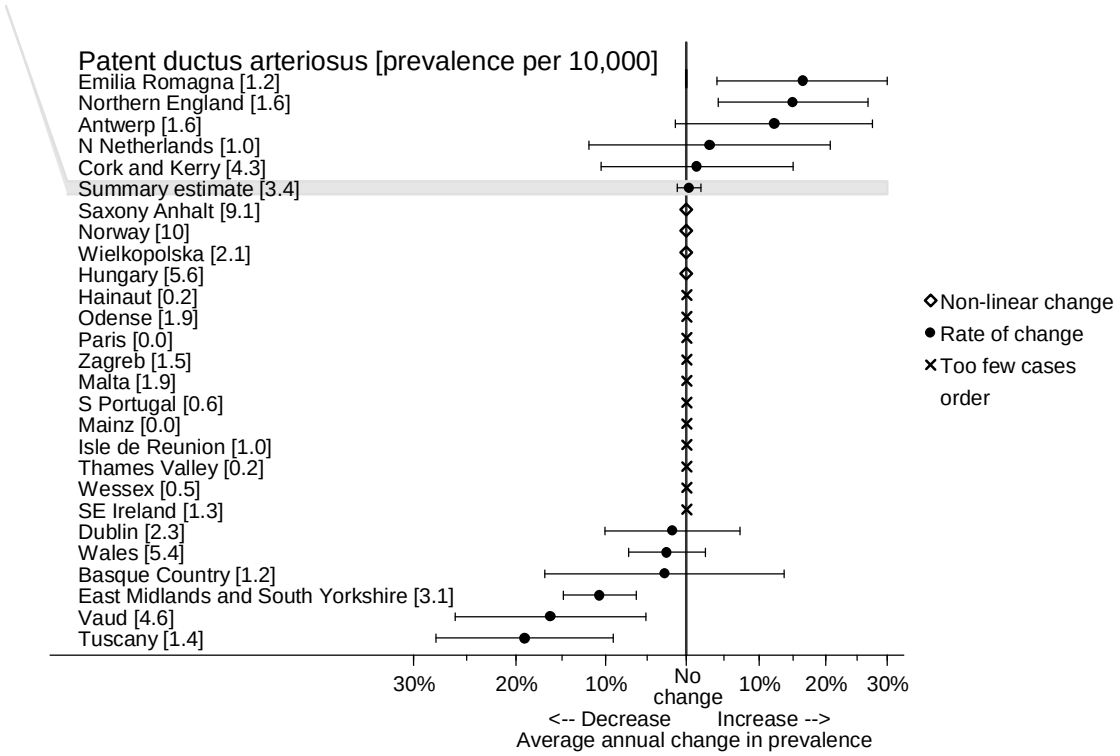

Aortic valve atresia/stenosis [prevalence per 10,000]
Hungary [0.9]
East Midlands and South Yorkshire [0.6]
Emilia Romagna [0.6]
Saxony Anhalt [1.9]
Thames Valley [1.0]
Antwerp [0.8]
Summary estimate [1.1]
Hainaut [1.1]
Odense [1.9]
Paris [0.5]
Tuscany [0.4]
Vaud [2.8]
Zagreb [0.6]
Malta [1.3]
S Portugal [0.1]
Mainz [2.1]
Cork and Kerry [1.1]
Isle de Reunion [0.3]
SE Ireland [1.1]
Wales [2.7]
Basque Country [1.5]
Norway [1.5]
Wessex [1.4]
N Netherlands [1.8]
Northern England [2.4]
Wielkopolska [0.9]
Dublin [0.8]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

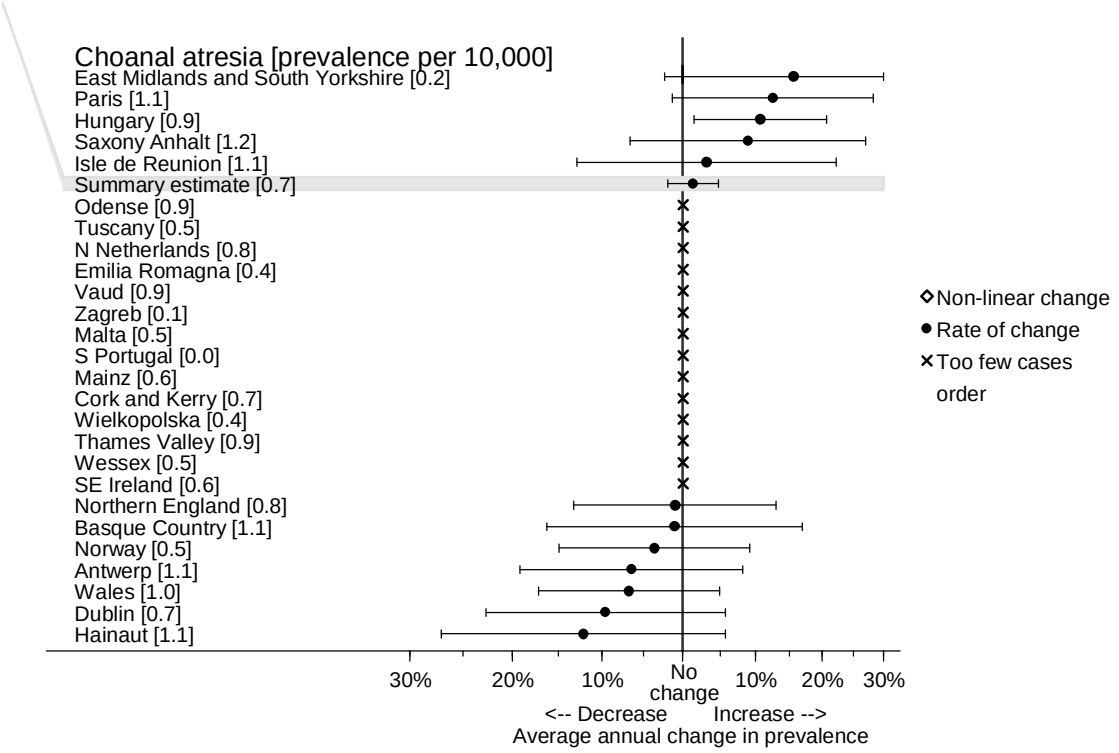

Hypoplastic left heart [prevalence per 10,000]
Hainaut [2.2]
N Netherlands [2.8]
Wessex [3.8]
Hungary [2.1]
Northern England [2.1]
Isle de Reunion [2.2]
Antwerp [1.6]
Tuscany [2.1]
Norway [2.9]
Vaud [2.5]
Summary estimate [2.4]
Saxony Anhalt [2.3]
East Midlands and South Yorkshire [3.1]
Odense [2.8]
Zagreb [2.5]
Malta [4.1]
S Portugal [0.5]
Mainz [2.1]
Cork and Kerry [2.4]
Basque Country [2.7]
Thames Valley [2.4]
SE Ireland [2.7]
Paris [2.7]
Dublin [2.5]
Wales [2.6]
Emilia Romagna [2.1]
Wielkopolska [1.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

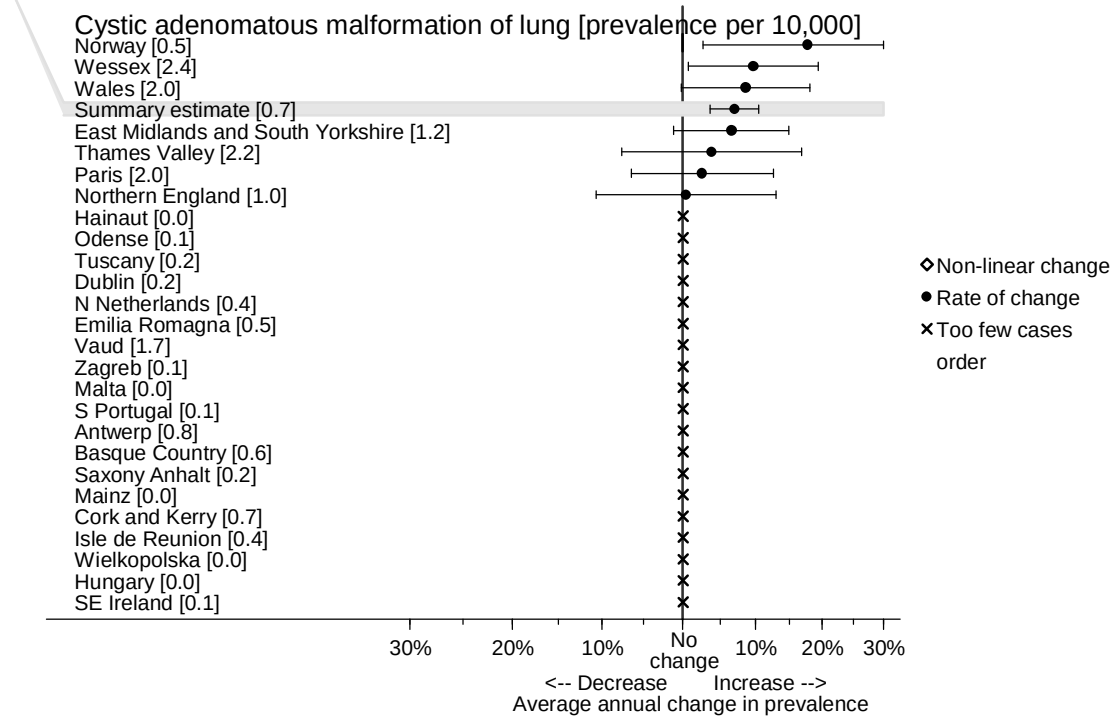

Hypoplastic right heart [prevalence per 10,000]
Wessex [0.9]
Norway [0.6]
Summary estimate [0.4]
Wales [0.7]
Hainaut [0.2]
Odense [1.7]
Paris [0.2]
Tuscany [0.1]
Dublin [0.2]
N Netherlands [0.2]
Emilia Romagna [0.1]
Vaud [1.2]
Zagreb [0.0]
Malta [0.5]
S Portugal [0.0]
Antwerp [0.3]
Basque Country [0.3]
Saxony Anhalt [0.5]
Mainz [1.2]
Cork and Kerry [0.4]
Isle de Reunion [0.6]
Wielkopolska [0.3]
Thames Valley [0.3]
Northern England [0.0]
Hungary [0.2]
SE Ireland [0.9]
East Midlands and South Yorkshire [0.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

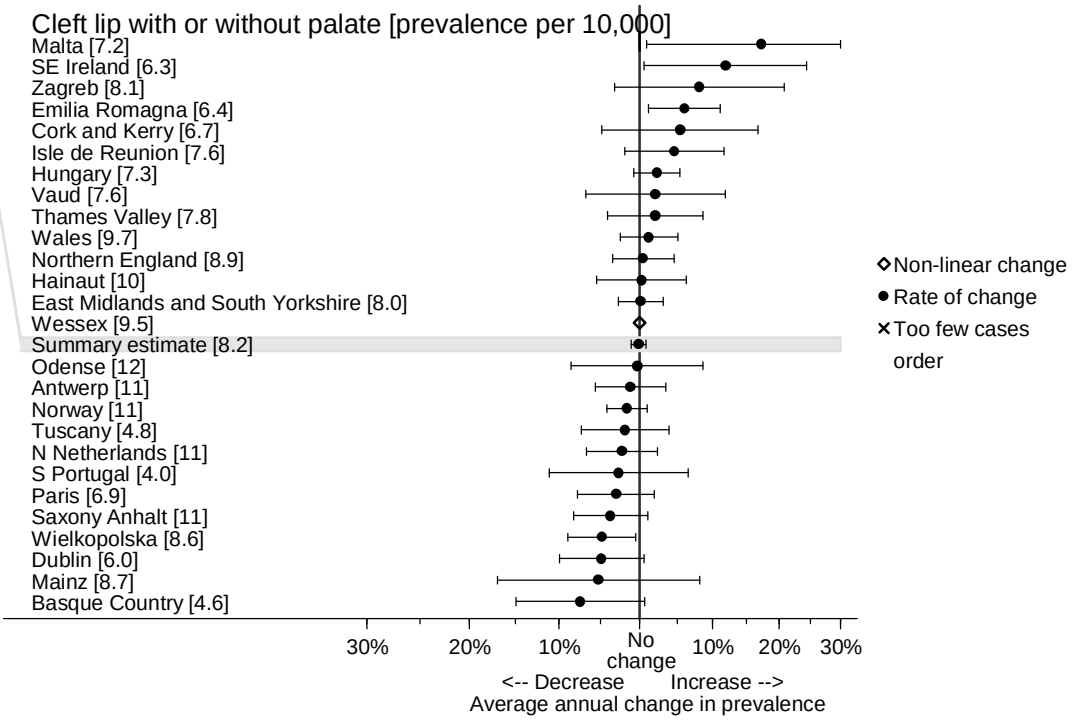

Coarctation of aorta [prevalence per 10,000]
Emilia Romagna [3.1]
Norway [2.5]
Tuscany [2.0]
Paris [2.9]
Basque Country [3.9]
Saxony Anhalt [4.4]
East Midlands and South Yorkshire [2.9]
Antwerp [3.1]
Cork and Kerry [4.3]
Northern England [5.3]
Isle de Reunion [1.9]
Thames Valley [2.5]
Summary estimate [3.2]
Hungary [3.6]
Odense [1.9]
Zagreb [1.2]
Malta [3.6]
S Portugal [0.9]
Mainz [4.7]
SE Ireland [4.1]
Hainaut [2.3]
Wessex [3.5]
Wales [5.2]
N Netherlands [3.8]
Dublin [5.0]
Vaud [3.7]
Wielkopolska [1.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

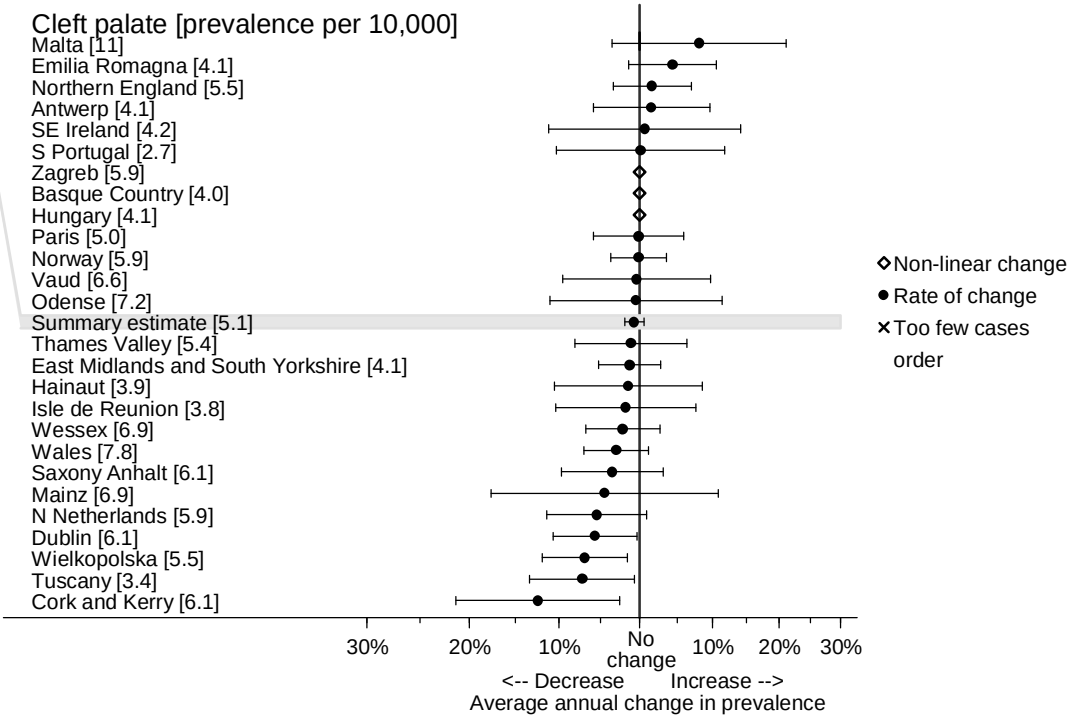

Total anomalous pulmonary venous return [prevalence per 10,000]
Hungary [0.4]
Summary estimate [0.5]
Wales [1.1]
East Midlands and South Yorkshire [0.6]
Northern England [1.2]
Hainaut [0.7]
Odense [0.3]
Tuscany [0.2]
N Netherlands [0.7]
Emilia Romagna [0.4]
Vaud [0.5]
Zagreb [0.0]
Malta [0.5]
S Portugal [0.0]
Antwerp [0.6]
Basque Country [0.5]
Saxony Anhalt [0.7]
Mainz [0.3]
Cork and Kerry [0.5]
Isle de Reunion [0.4]
Wielkopolska [0.0]
Thames Valley [0.6]
Wessex [0.6]
SE Ireland [1.1]
Paris [0.8]
Norway [0.5]
Dublin [0.8]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

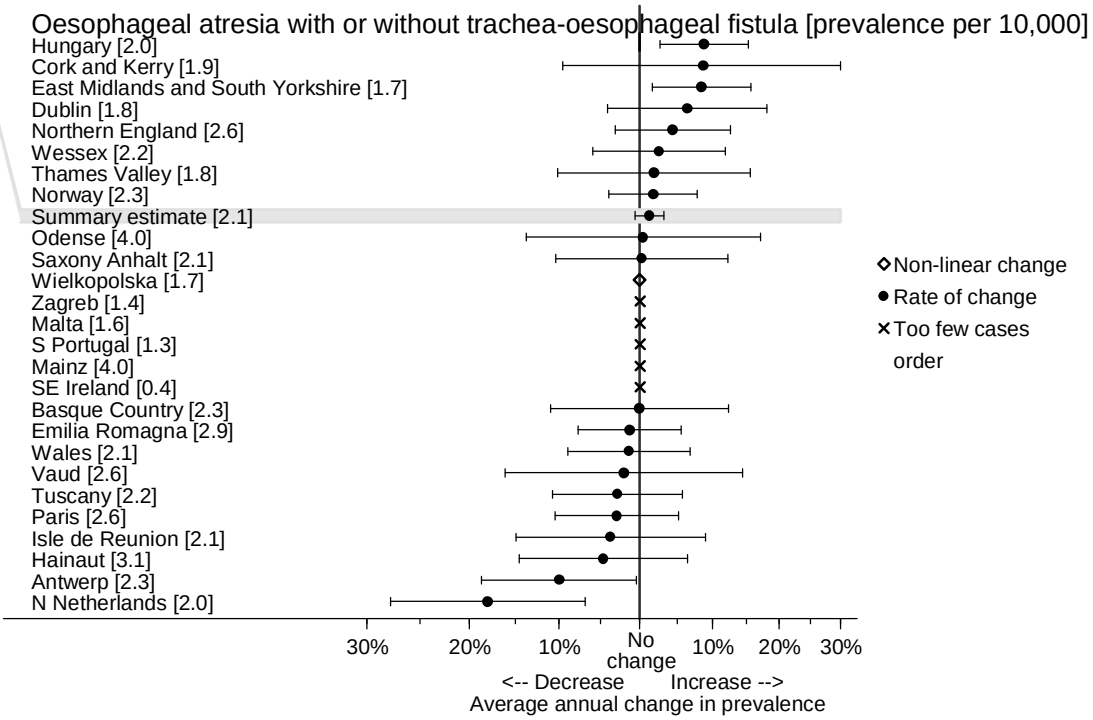

Patent ductus arteriosus [prevalence per 10,000]
Emilia Romagna [1.2]
Northern England [1.6]
Antwerp [1.6]
N Netherlands [1.0]
Cork and Kerry [4.3]
Summary estimate [3.4]
Saxony Anhalt [9.1]
Norway [10]
Wielkopolska [2.1]
Hungary [5.6]
Hainaut [0.2]
Odense [1.9]
Paris [0.0]
Zagreb [1.5]
Malta [1.9]
S Portugal [0.6]
Mainz [0.0]
Isle de Reunion [1.0]
Thames Valley [0.2]
Wessex [0.5]
SE Ireland [1.3]
Dublin [2.3]
Wales [5.4]
Basque Country [1.2]
East Midlands and South Yorkshire [3.1]
Vaud [4.6]
Tuscany [1.4]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

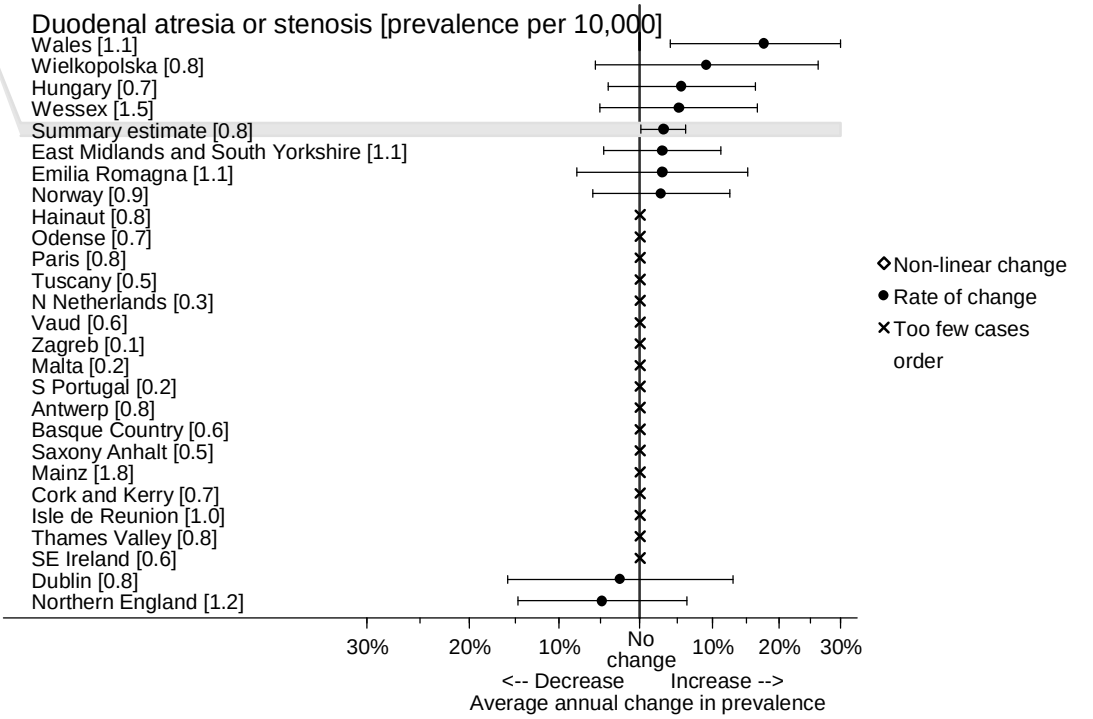

Choanal atresia [prevalence per 10,000]
East Midlands and South Yorkshire [0.2]
Paris [1.1]
Hungary [0.9]
Saxony Anhalt [1.2]
Isle de Reunion [1.1]
Summary estimate [0.7]
Odense [0.9]
Tuscany [0.5]
N Netherlands [0.8]
Emilia Romagna [0.4]
Vaud [0.9]
Zagreb [0.1]
Malta [0.5]
S Portugal [0.0]
Mainz [0.6]
Cork and Kerry [0.7]
Wielkopolska [0.4]
Thames Valley [0.9]
Wessex [0.5]
SE Ireland [0.6]
Northern England [0.8]
Basque Country [1.1]
Norway [0.5]
Antwerp [1.1]
Wales [1.0]
Dublin [0.7]
Hainaut [1.1]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

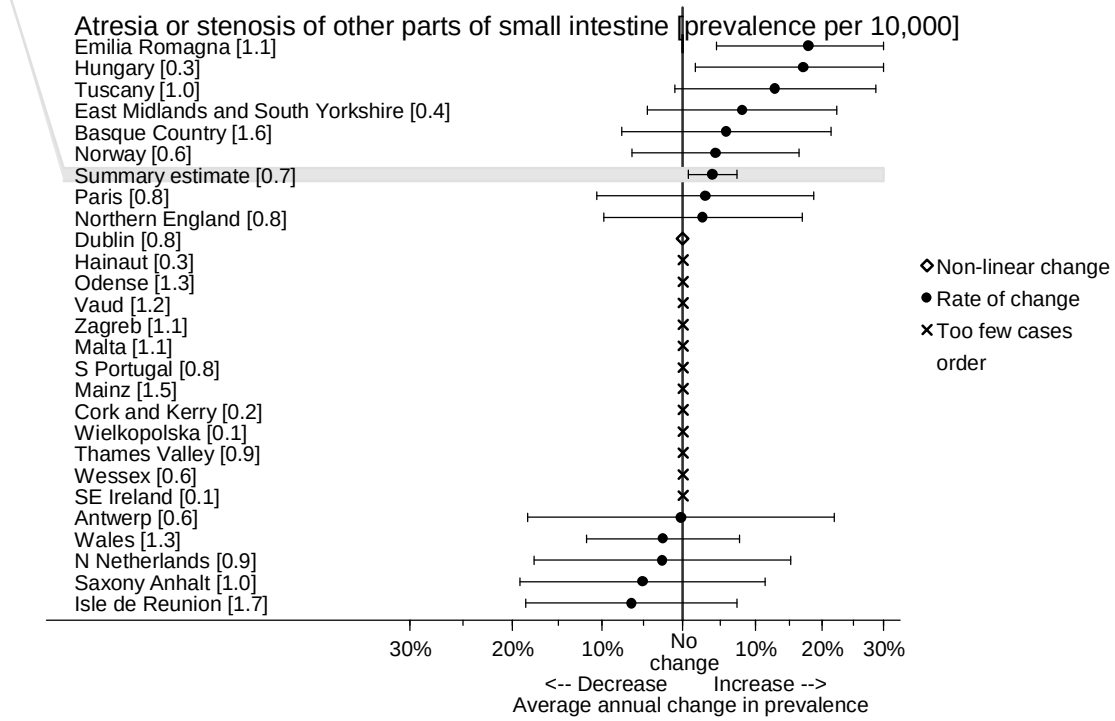

Cystic adenomatous malformation of lung [prevalence per 10,000]
Norway [0.5]
Wessex [2.4]
Wales [2.0]
Summary estimate [0.7]
East Midlands and South Yorkshire [1.2]
Thames Valley [2.2]
Paris [2.0]
Northern England [1.0]
Hainaut [0.0]
Odense [0.1]
Tuscany [0.2]
Dublin [0.2]
N Netherlands [0.4]
Emilia Romagna [0.5]
Vaud [1.7]
Zagreb [0.1]
Malta [0.0]
S Portugal [0.1]
Antwerp [0.8]
Basque Country [0.6]
Saxony Anhalt [0.2]
Mainz [0.0]
Cork and Kerry [0.7]
Isle de Reunion [0.4]
Wielkopolska [0.0]
Hungary [0.0]
SE Ireland [0.1]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

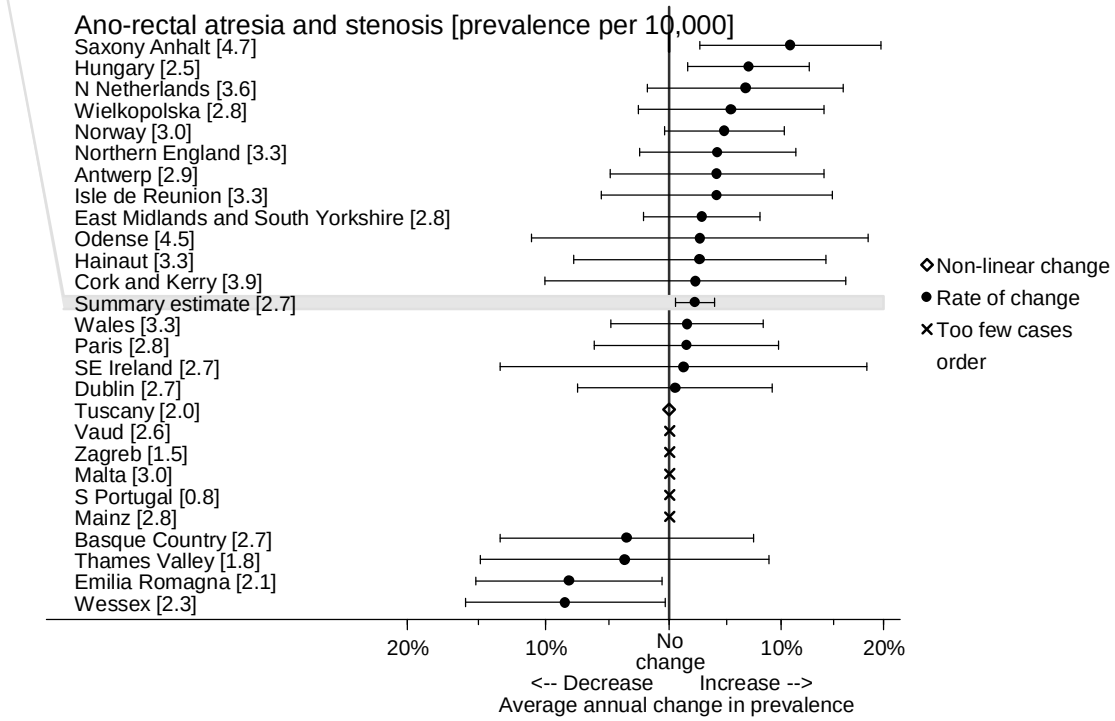

Cleft lip with or without palate [prevalence per 10,000]
Malta [7.2]
SE Ireland [6.3]
Zagreb [8.1]
Emilia Romagna [6.4]
Cork and Kerry [6.7]
Isle de Reunion [7.6]
Hungary [7.3]
Vaud [7.6]
Thames Valley [7.8]
Wales [9.7]
Northern England [8.9]
Hainaut [10]
East Midlands and South Yorkshire [8.0]
Wessex [9.5]
Summary estimate [8.2]
Odense [12]
Antwerp [11]
Norway [11]
Tuscany [4.8]
N Netherlands [11]
S Portugal [4.0]
Paris [6.9]
Saxony Anhalt [11]
Wielkopolska [8.6]
Dublin [6.0]
Mainz [8.7]
Basque Country [4.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

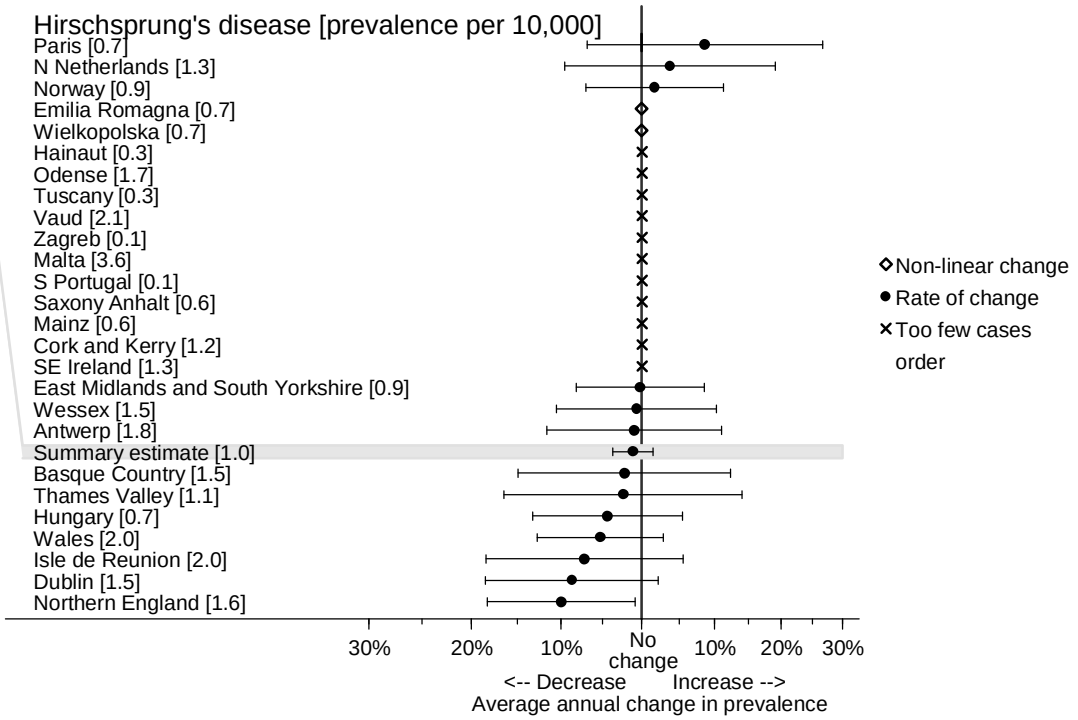

Cleft palate [prevalence per 10,000]
Malta [11]
Emilia Romagna [4.1]
Northern England [5.5]
Antwerp [4.1]
SE Ireland [4.2]
S Portugal [2.7]
Zagreb [5.9]
Basque Country [4.0]
Hungary [4.1]
Paris [5.0]
Norway [5.9]
Vaud [6.6]
Odense [7.2]
Summary estimate [5.1]
Thames Valley [5.4]
East Midlands and South Yorkshire [4.1]
Hainaut [3.9]
Isle de Reunion [3.8]
Wessex [6.9]
Wales [7.8]
Saxony Anhalt [6.1]
Mainz [6.9]
N Netherlands [5.9]
Dublin [6.1]
Wielkopolska [5.5]
Tuscany [3.4]
Cork and Kerry [6.1]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

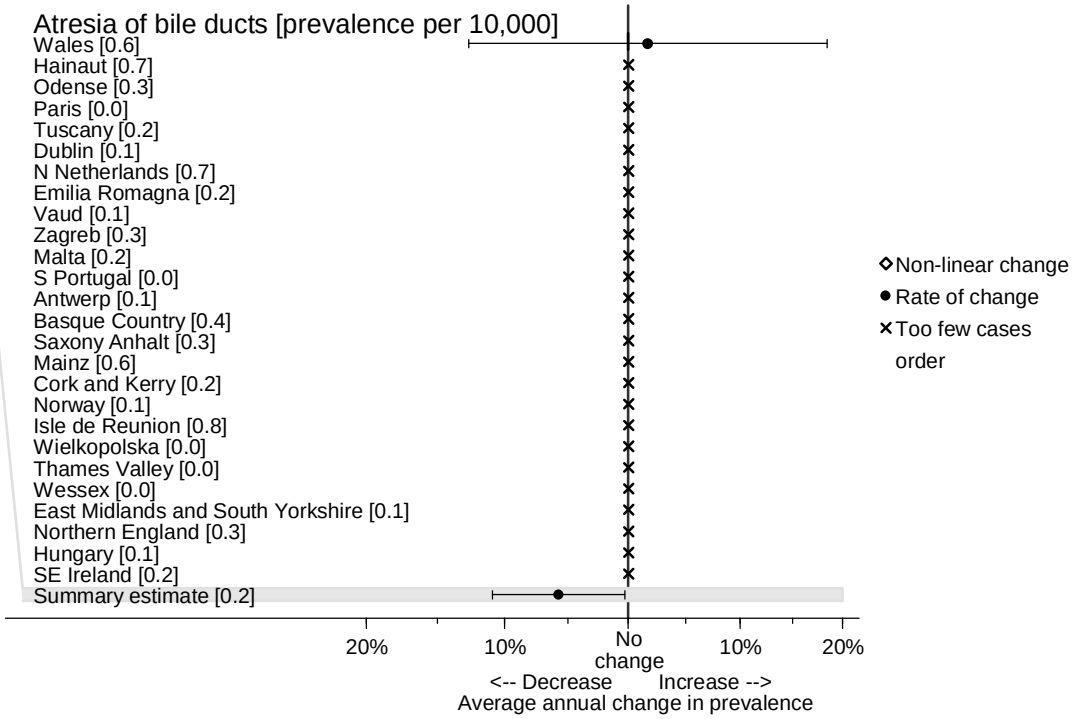

Oesophageal atresia with or without trachea-oesophageal fistula [prevalence per 10,000]
Hungary [2.0]
Cork and Kerry [1.9]
East Midlands and South Yorkshire [1.7]
Dublin [1.8]
Northern England [2.6]
Wessex [2.2]
Thames Valley [1.8]
Norway [2.3]
Summary estimate [2.1]
Odense [4.0]
Saxony Anhalt [2.1]
Wielkopolska [1.7]
Zagreb [1.4]
Malta [1.6]
S Portugal [1.3]
Mainz [4.0]
SE Ireland [0.4]
Basque Country [2.3]
Emilia Romagna [2.9]
Wales [2.1]
Vaud [2.6]
Tuscany [2.2]
Paris [2.6]
Isle de Reunion [2.1]
Hainaut [3.1]
Antwerp [2.3]
N Netherlands [2.0]
Non-linear change
Rate of change
Too few cases
order
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence

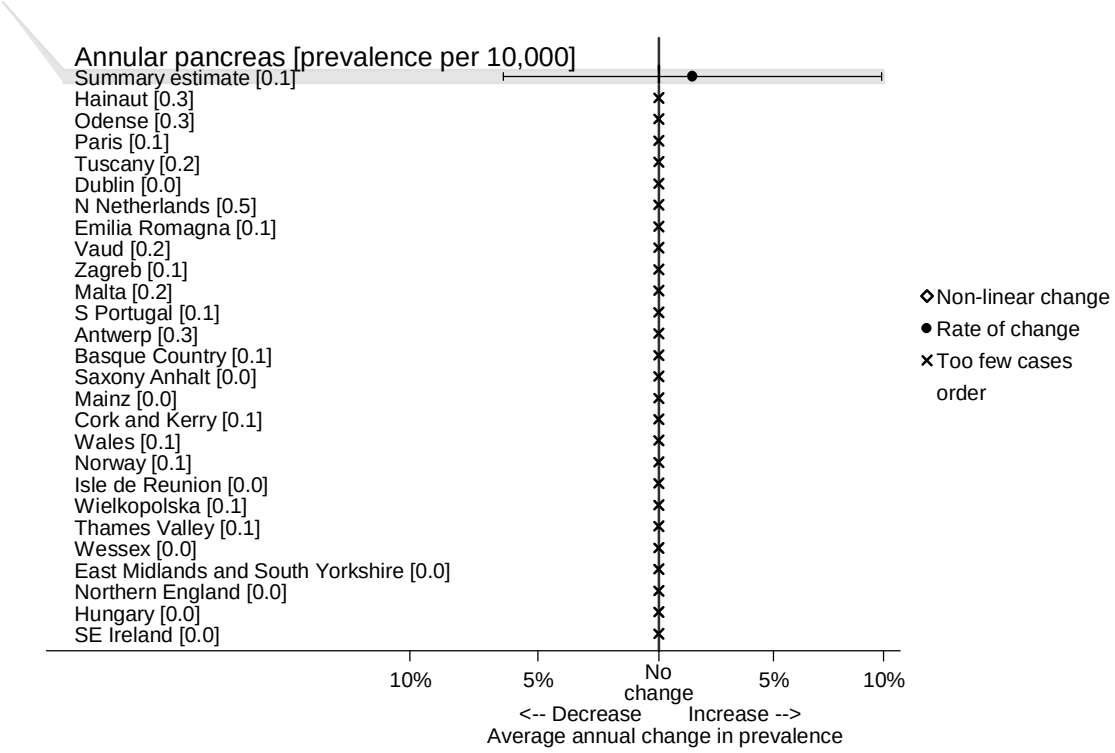

Duodenal atresia or stenosis [prevalence per 10,000]
Wales [1.1]
Wielkopolska [0.8]
Hungary [0.7]
Wessex [1.5]
Summary estimate [0.8]
East Midlands and South Yorkshire [1.1]
Emilia Romagna [1.1]
Norway [0.9]
Hainaut [0.8]
Odense [0.7]
Paris [0.8]
Tuscany [0.5]
N Netherlands [0.3]
Vaud [0.6]
Zagreb [0.1]
Malta [0.2]
S Portugal [0.2]
Antwerp [0.8]
Basque Country [0.6]
Saxony Anhalt [0.5]
Mainz [1.8]
Cork and Kerry [0.7]
Isle de Reunion [1.0]
Thames Valley [0.8]
SE Ireland [0.6]
Dublin [0.8]
Northern England [1.2]
Non-linear change
Rate of change
Too few cases
order
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence

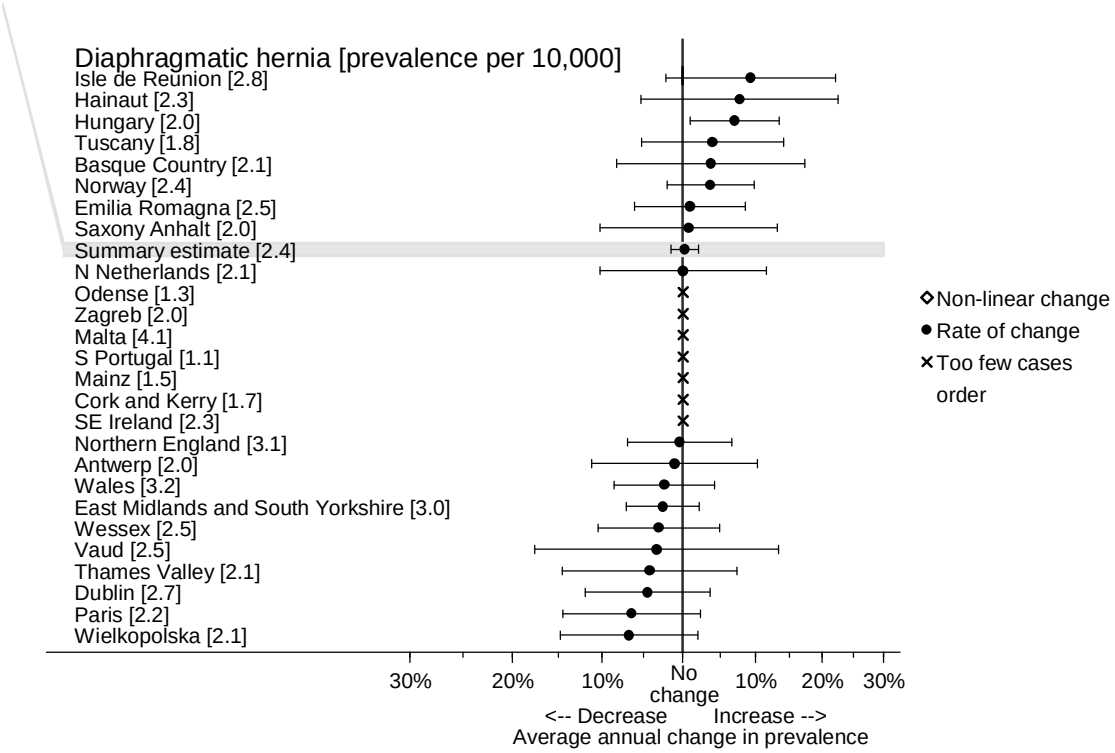

Atresia or stenosis of other parts of small intestine [prevalence per 10,000]
Emilia Romagna [1.1]
Hungary [0.3]
Tuscany [1.0]
East Midlands and South Yorkshire [0.4]
Basque Country [1.6]
Norway [0.6]
Summary estimate [0.7]
Paris [0.8]
Northern England [0.8]
Dublin [0.8]
Hainaut [0.3]
Odense [1.3]
Vaud [1.2]
Zagreb [1.1]
Malta [1.1]
S Portugal [0.8]
Mainz [1.5]
Cork and Kerry [0.2]
Wielkopolska [0.1]
Thames Valley [0.9]
Wessex [0.6]
SE Ireland [0.1]
Antwerp [0.6]
Wales [1.3]
N Netherlands [0.9]
Saxony Anhalt [1.0]
Isle de Reunion [1.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

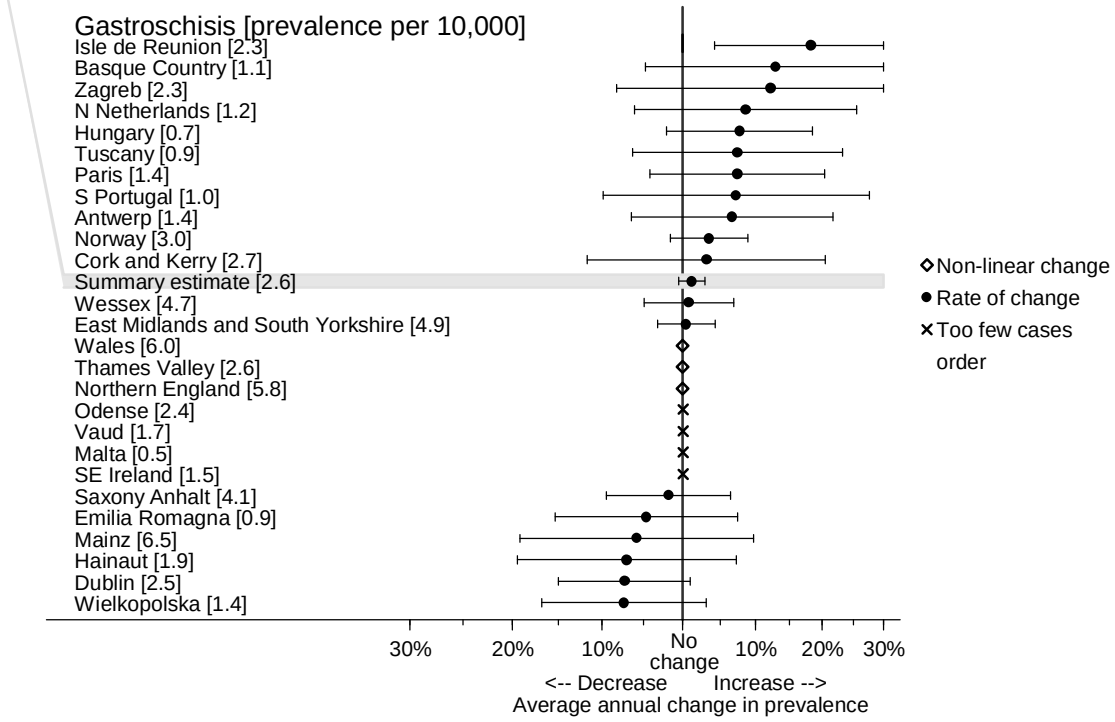

Ano-rectal atresia and stenosis [prevalence per 10,000]
Saxony Anhalt [4.7]
Hungary [2.5]
N Netherlands [3.6]
Wielkopolska [2.8]
Norway [3.0]
Northern England [3.3]
Antwerp [2.9]
Isle de Reunion [3.3]
East Midlands and South Yorkshire [2.8]
Odense [4.5]
Hainaut [3.3]
Cork and Kerry [3.9]
Summary estimate [2.7]
Wales [3.3]
Paris [2.8]
SE Ireland [2.7]
Dublin [2.7]
Tuscany [2.0]
Vaud [2.6]
Zagreb [1.5]
Malta [3.0]
S Portugal [0.8]
Mainz [2.8]
Basque Country [2.7]
Thames Valley [1.8]
Emilia Romagna [2.1]
Wessex [2.3]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

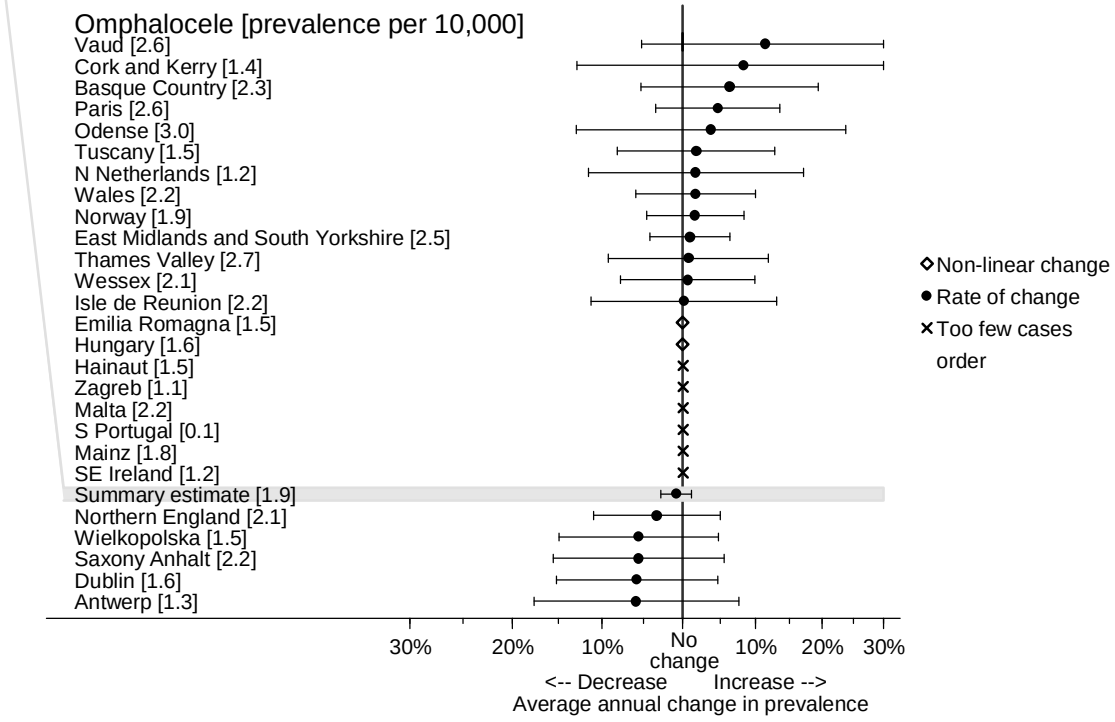

Hirschsprung's disease [prevalence per 10,000]
Paris [0.7]
N Netherlands [1.3]
Norway [0.9]
Emilia Romagna [0.7]
Wielkopolska [0.7]
Hainaut [0.3]
Odense [1.7]
Tuscany [0.3]
Vaud [2.1]
Zagreb [0.1]
Malta [3.6]
S Portugal [0.1]
Saxony Anhalt [0.6]
Mainz [0.6]
Cork and Kerry [1.2]
SE Ireland [1.3]
East Midlands and South Yorkshire [0.9]
Wessex [1.5]
Antwerp [1.8]
Summary estimate [1.0]
Basque Country [1.5]
Thames Valley [1.1]
Hungary [0.7]
Wales [2.0]
Isle de Reunion [2.0]
Dublin [1.5]
Northern England [1.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

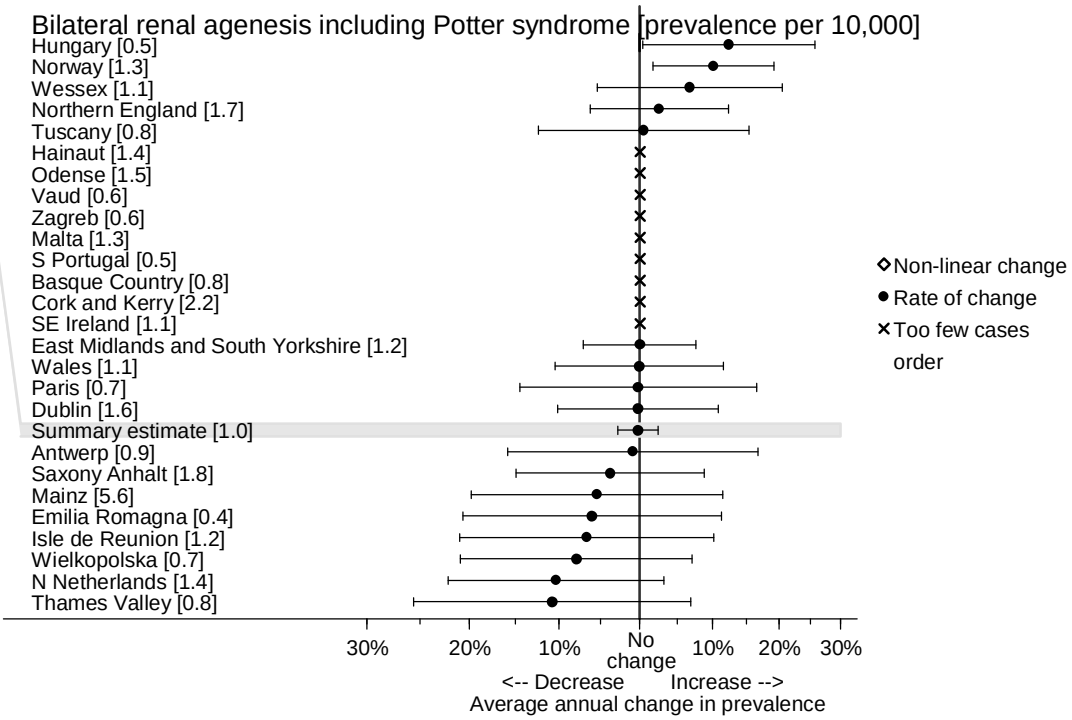

Atresia of bile ducts [prevalence per 10,000]
Wales [0.6]
Hainaut [0.7]
Odense [0.3]
Paris [0.0]
Tuscany [0.2]
Dublin [0.1]
N Netherlands [0.7]
Emilia Romagna [0.2]
Vaud [0.1]
Zagreb [0.3]
Malta [0.2]
S Portugal [0.0]
Antwerp [0.1]
Basque Country [0.4]
Saxony Anhalt [0.3]
Mainz [0.6]
Cork and Kerry [0.2]
Norway [0.1]
Isle de Reunion [0.8]
Wielkopolska [0.0]
Thames Valley [0.0]
Wessex [0.0]
East Midlands and South Yorkshire [0.1]
Northern England [0.3]
Hungary [0.1]
SE Ireland [0.2]
Summary estimate [0.2]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

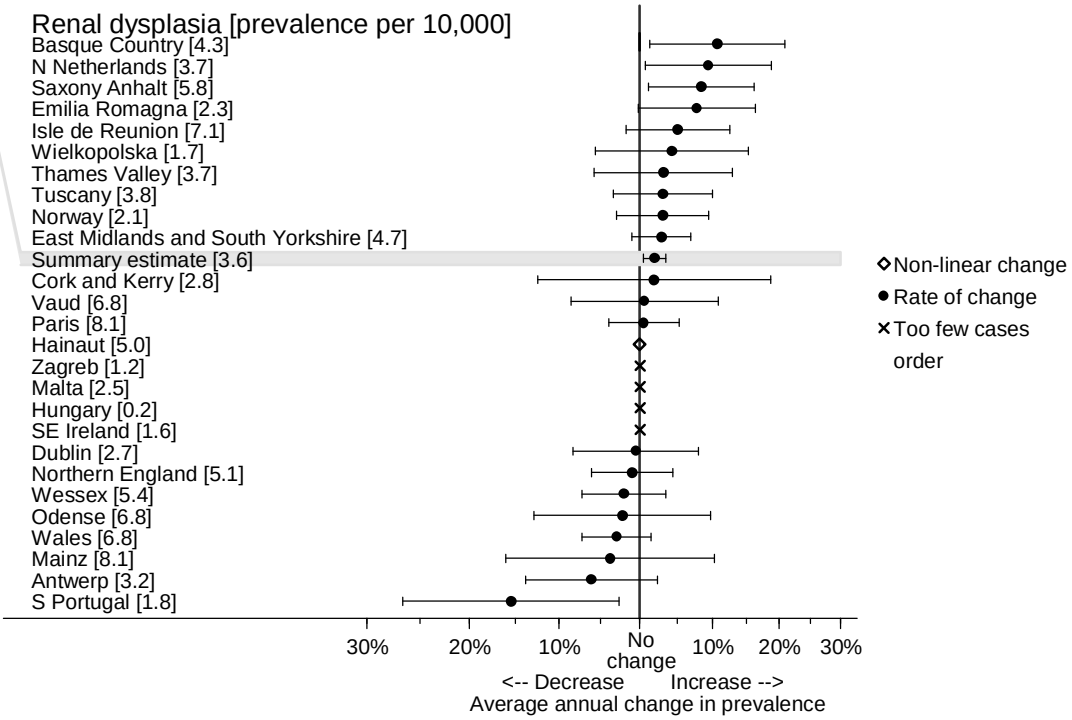

Annular pancreas [prevalence per 10,000]
Summary estimate [0.1]
Hainaut [0.3]
Odense [0.3]
Paris [0.1]
Tuscany [0.2]
Dublin [0.0]
N Netherlands [0.5]
Emilia Romagna [0.1]
Vaud [0.2]
Zagreb [0.1]
Malta [0.2]
S Portugal [0.1]
Antwerp [0.3]
Basque Country [0.1]
Saxony Anhalt [0.0]
Mainz [0.0]
Cork and Kerry [0.1]
Wales [0.1]
Norway [0.1]
Isle de Reunion [0.0]
Wielkopolska [0.1]
Thames Valley [0.1]
Wessex [0.0]
East Midlands and South Yorkshire [0.0]
Northern England [0.0]
Hungary [0.0]
SE Ireland [0.0]
10%
5%
No change
5%
10%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

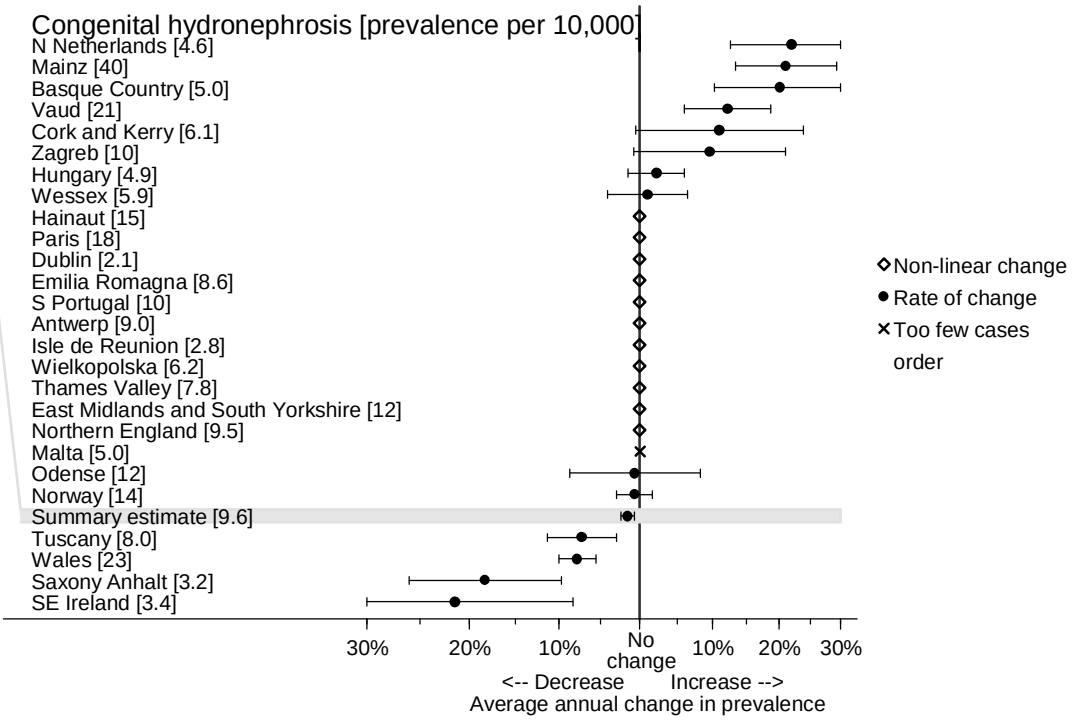

Diaphragmatic hernia [prevalence per 10,000]
Isle de Reunion [2.8]
Hainaut [2.3]
Hungary [2.0]
Tuscany [1.8]
Basque Country [2.1]
Norway [2.4]
Emilia Romagna [2.5]
Saxony Anhalt [2.0]
Summary estimate [2.4]
N Netherlands [2.1]
Odense [1.3]
Zagreb [2.0]
Malta [4.1]
S Portugal [1.1]
Mainz [1.5]
Cork and Kerry [1.7]
SE Ireland [2.3]
Northern England [3.1]
Antwerp [2.0]
Wales [3.2]
East Midlands and South Yorkshire [3.0]
Wessex [2.5]
Vaud [2.5]
Thames Valley [2.1]
Dublin [2.7]
Paris [2.2]
Wielkopolska [2.1]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

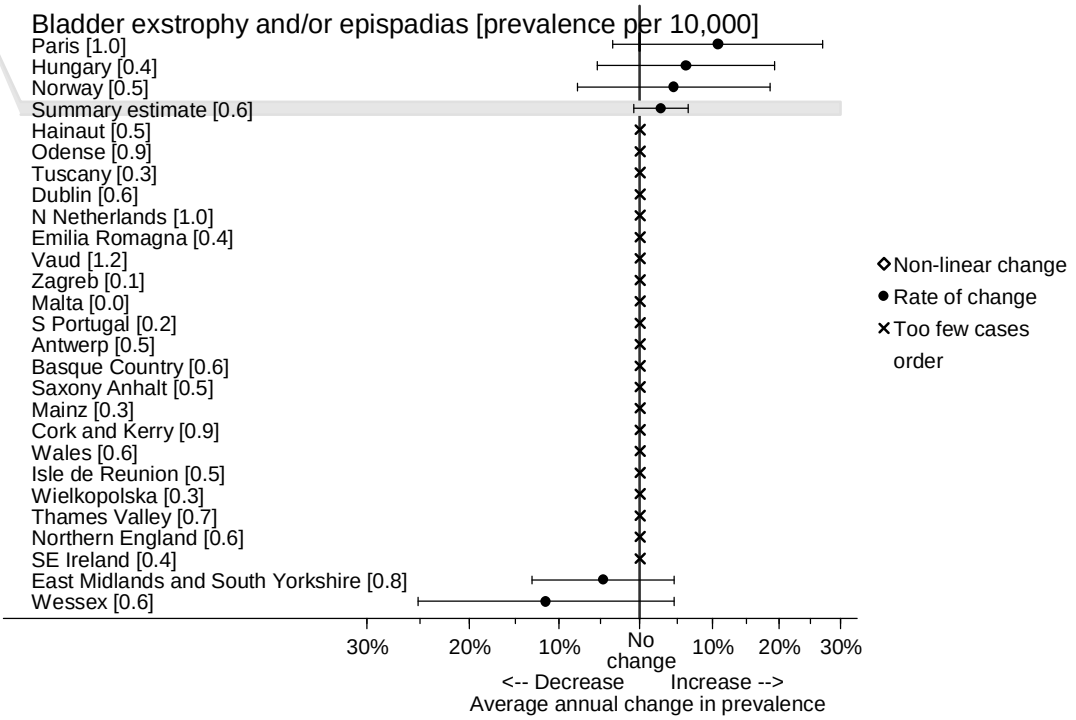

Gastroschisis [prevalence per 10,000]
Isle de Reunion [2.3]
Basque Country [1.1]
Zagreb [2.3]
N Netherlands [1.2]
Hungary [0.7]
Tuscany [0.9]
Paris [1.4]
S Portugal [1.0]
Antwerp [1.4]
Norway [3.0]
Cork and Kerry [2.7]
Summary estimate [2.6]
Wessex [4.7]
East Midlands and South Yorkshire [4.9]
Wales [6.0]
Thames Valley [2.6]
Northern England [5.8]
Odense [2.4]
Vaud [1.7]
Malta [0.5]
SE Ireland [1.5]
Saxony Anhalt [4.1]
Emilia Romagna [0.9]
Mainz [6.5]
Hainaut [1.9]
Dublin [2.5]
Wielkopolska [1.4]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

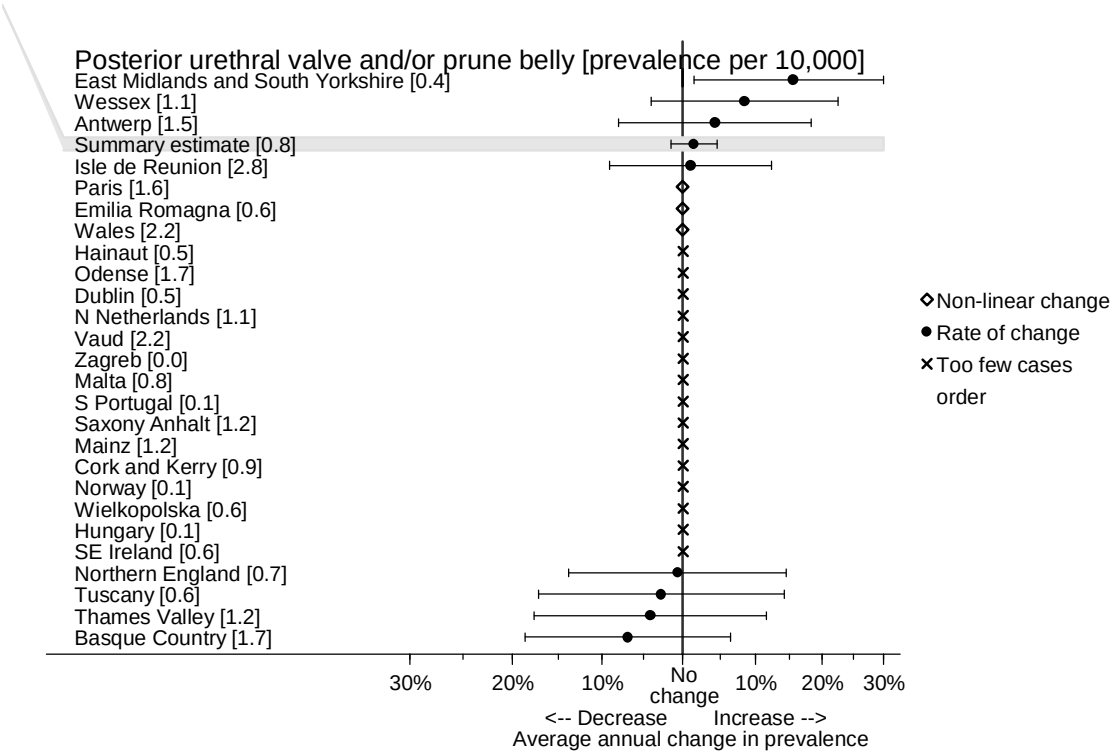

Omphalocele [prevalence per 10,000]
Vaud [2.6]
Cork and Kerry [1.4]
Basque Country [2.3]
Paris [2.6]
Odense [3.0]
Tuscany [1.5]
N Netherlands [1.2]
Wales [2.2]
Norway [1.9]
East Midlands and South Yorkshire [2.5]
Thames Valley [2.7]
Wessex [2.1]
Isle de Reunion [2.2]
Emilia Romagna [1.5]
Hungary [1.6]
Hainaut [1.5]
Zagreb [1.1]
Malta [2.2]
S Portugal [0.1]
Mainz [1.8]
SE Ireland [1.2]
Summary estimate [1.9]
Northern England [2.1]
Wielkopolska [1.5]
Saxony Anhalt [2.2]
Dublin [1.6]
Antwerp [1.3]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

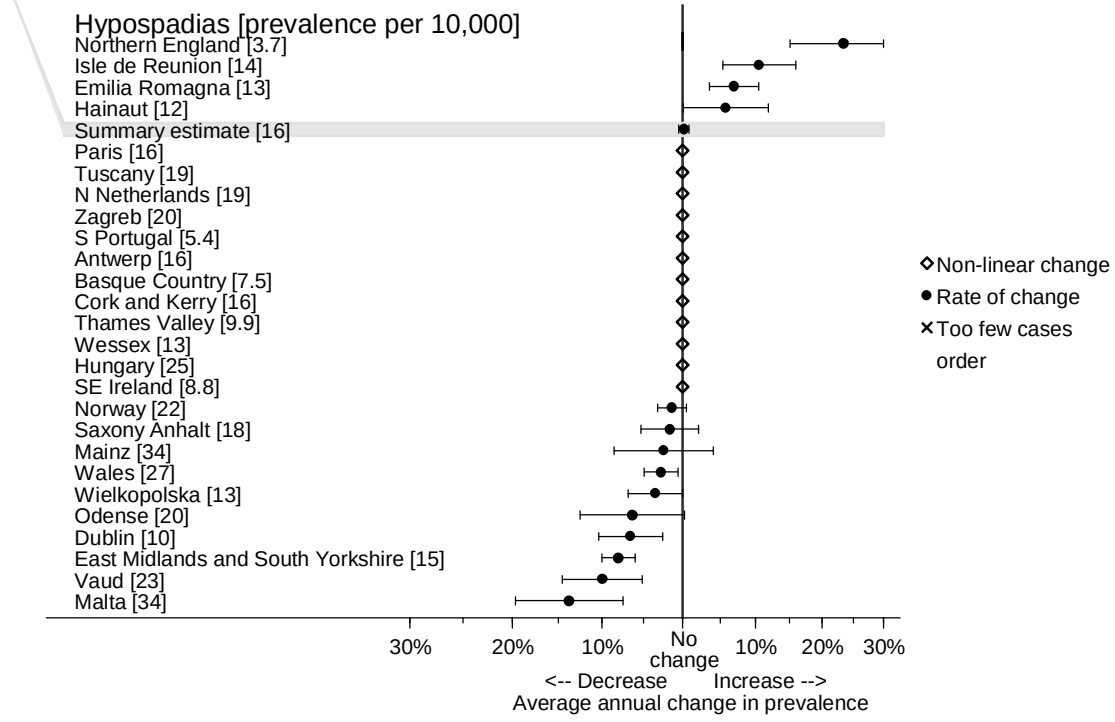

Bilateral renal agenesis including Potter syndrome [prevalence per 10,000]
Hungary [0.5]
Norway [1.3]
Wessex [1.1]
Northern England [1.7]
Tuscany [0.8]
Hainaut [1.4]
Odense [1.5]
Vaud [0.6]
Zagreb [0.6]
Malta [1.3]
S Portugal [0.5]
Basque Country [0.8]
Cork and Kerry [2.2]
SE Ireland [1.1]
East Midlands and South Yorkshire [1.2]
Wales [1.1]
Paris [0.7]
Dublin [1.6]
Summary estimate [1.0]
Antwerp [0.9]
Saxony Anhalt [1.8]
Mainz [5.6]
Emilia Romagna [0.4]
Isle de Reunion [1.2]
Wielkopolska [0.7]
N Netherlands [1.4]
Thames Valley [0.8]
Non-linear change
Rate of change
Too few cases
order
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence

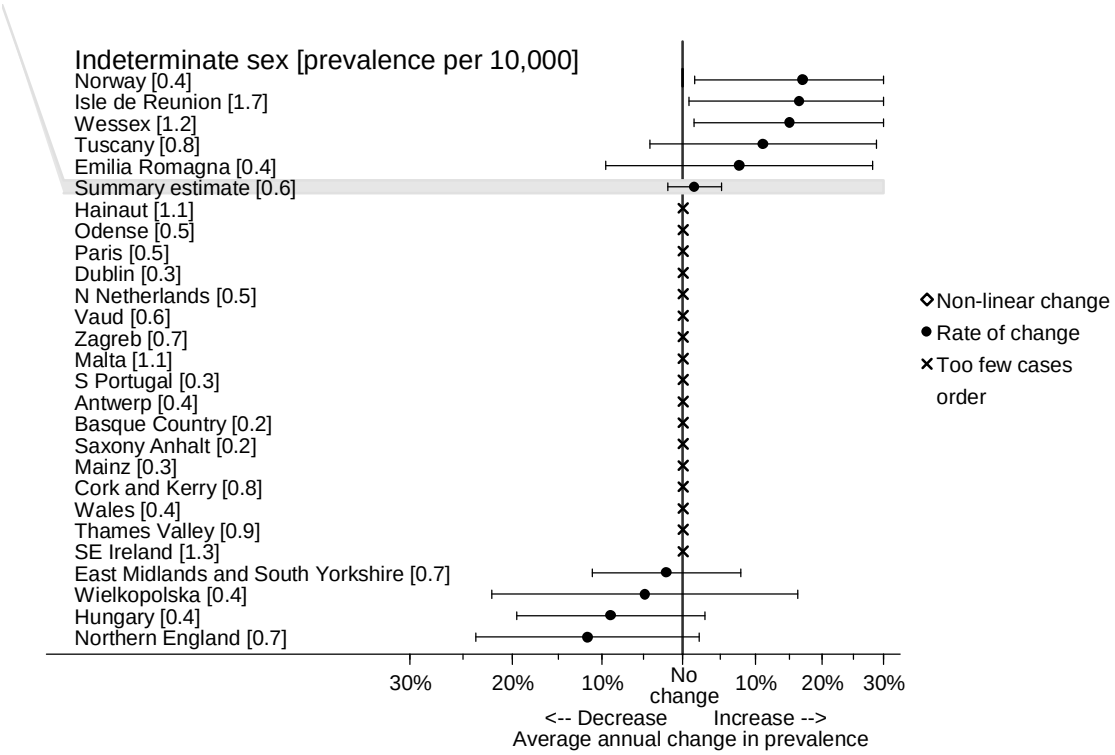

Renal dysplasia [prevalence per 10,000]
Basque Country [4.3]
N Netherlands [3.7]
Saxony Anhalt [5.8]
Emilia Romagna [2.3]
Isle de Reunion [7.1]
Wielkopolska [1.7]
Thames Valley [3.7]
Tuscany [3.8]
Norway [2.1]
East Midlands and South Yorkshire [4.7]
Summary estimate [3.6]
Cork and Kerry [2.8]
Vaud [6.8]
Paris [8.1]
Hainaut [5.0]
Zagreb [1.2]
Malta [2.5]
Hungary [0.2]
SE Ireland [1.6]
Dublin [2.7]
Northern England [5.1]
Wessex [5.4]
Odense [6.8]
Wales [6.8]
Mainz [8.1]
Antwerp [3.2]
S Portugal [1.8]
Non-linear change
Rate of change
Too few cases
order
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence

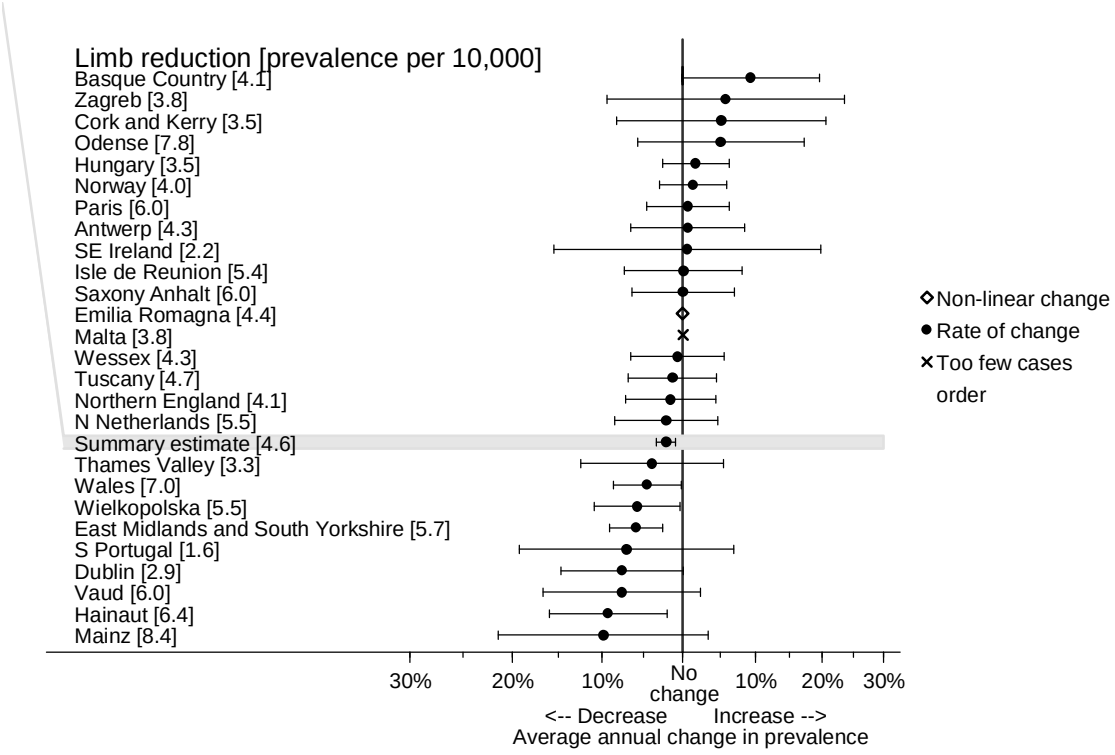

Congenital hydronephrosis [prevalence per 10,000]
N Netherlands [4.6]
Mainz [40]
Basque Country [5.0]
Vaud [21]
Cork and Kerry [6.1]
Zagreb [10]
Hungary [4.9]
Wessex [5.9]
Hainaut [15]
Paris [18]
Dublin [2.1]
Emilia Romagna [8.6]
S Portugal [10]
Antwerp [9.0]
Isle de Reunion [2.8]
Wielkopolska [6.2]
Thames Valley [7.8]
East Midlands and South Yorkshire [12]
Northern England [9.5]
Malta [5.0]
Odense [12]
Norway [14]
Summary estimate [9.6]
Tuscany [8.0]
Wales [23]
Saxony Anhalt [3.2]
SE Ireland [3.4]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

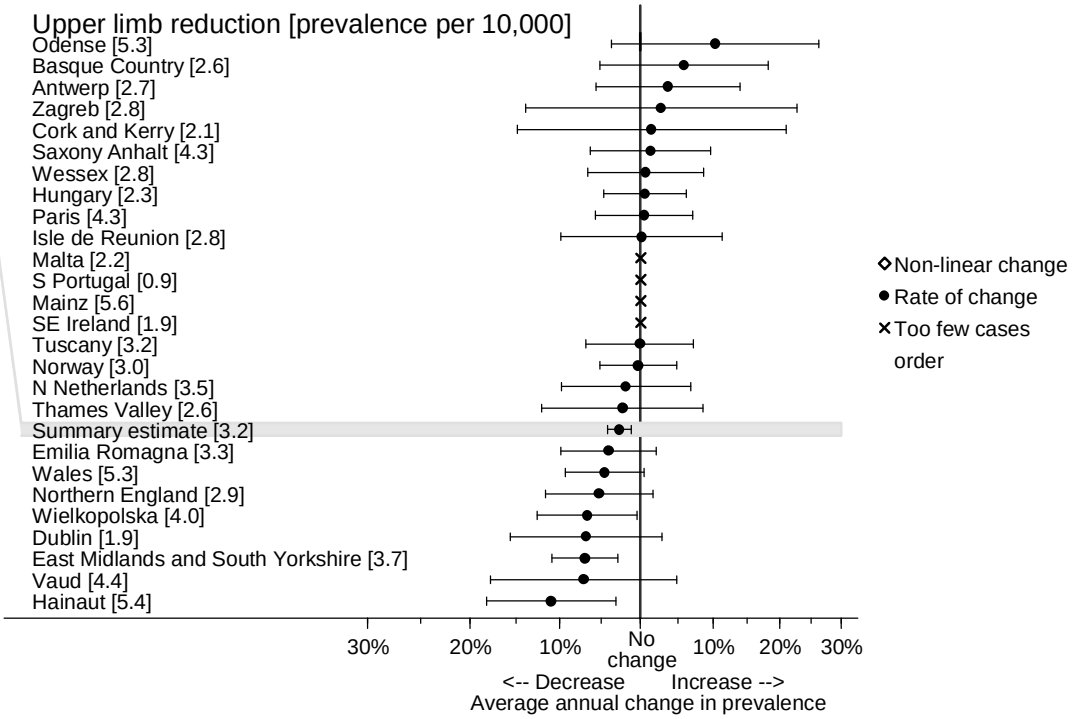

Bladder exstrophy and/or epispadias [prevalence per 10,000]
Paris [1.0]
Hungary [0.4]
Norway [0.5]
Summary estimate [0.6]
Hainaut [0.5]
Odense [0.9]
Tuscany [0.3]
Dublin [0.6]
N Netherlands [1.0]
Emilia Romagna [0.4]
Vaud [1.2]
Zagreb [0.1]
Malta [0.0]
S Portugal [0.2]
Antwerp [0.5]
Basque Country [0.6]
Saxony Anhalt [0.5]
Mainz [0.3]
Cork and Kerry [0.9]
Wales [0.6]
Isle de Reunion [0.5]
Wielkopolska [0.3]
Thames Valley [0.7]
Northern England [0.6]
SE Ireland [0.4]
East Midlands and South Yorkshire [0.8]
Wessex [0.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

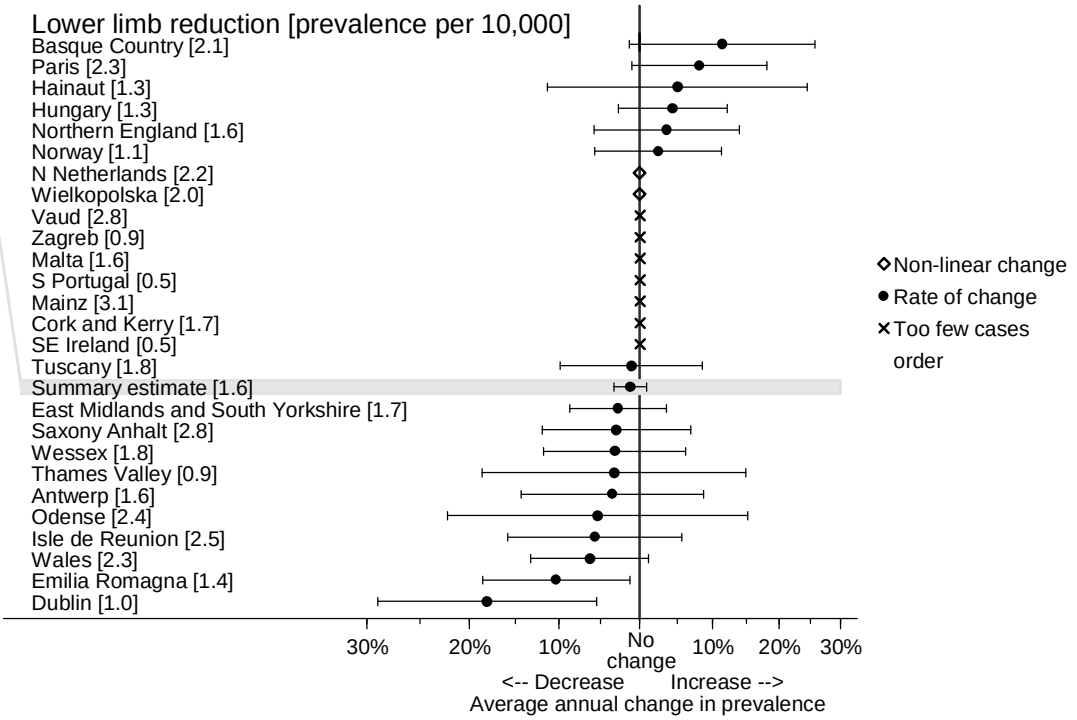

Posterior urethral valve and/or prune belly [prevalence per 10,000]
East Midlands and South Yorkshire [0.4]
Wessex [1.1]
Antwerp [1.5]
Summary estimate [0.8]
Isle de Reunion [2.8]
Paris [1.6]
Emilia Romagna [0.6]
Wales [2.2]
Hainaut [0.5]
Odense [1.7]
Dublin [0.5]
N Netherlands [1.1]
Vaud [2.2]
Zagreb [0.0]
Malta [0.8]
S Portugal [0.1]
Saxony Anhalt [1.2]
Mainz [1.2]
Cork and Kerry [0.9]
Norway [0.1]
Wielkopolska [0.6]
Hungary [0.1]
SE Ireland [0.6]
Northern England [0.7]
Tuscany [0.6]
Thames Valley [1.2]
Basque Country [1.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

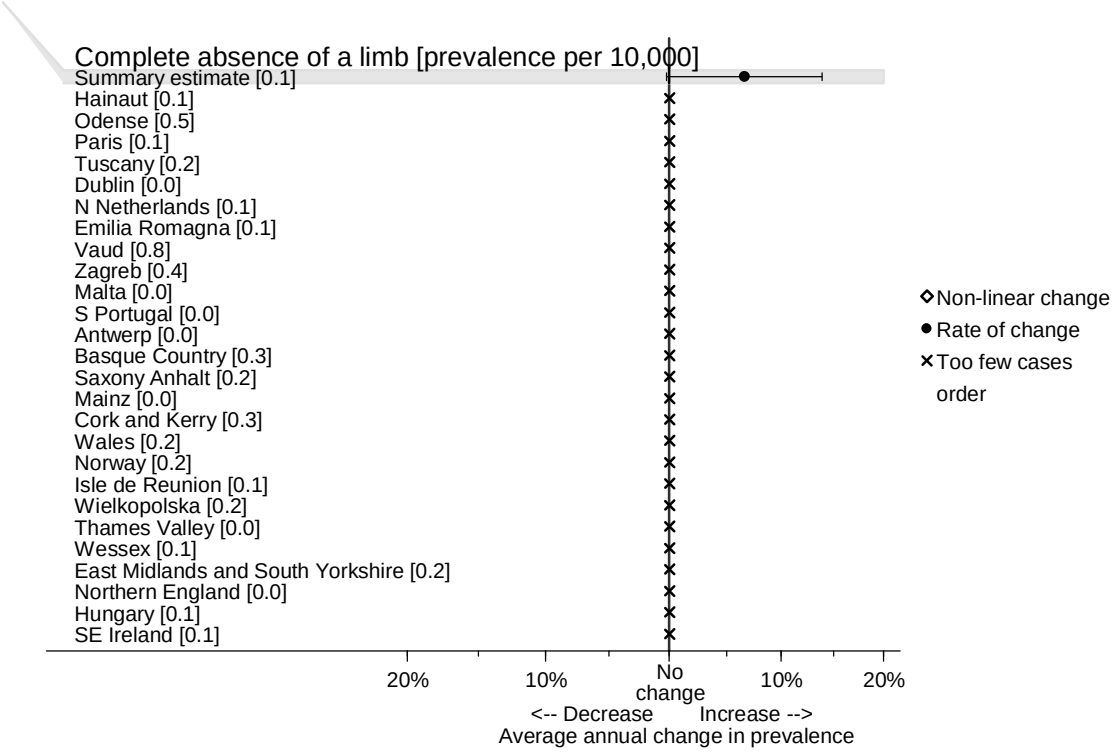

Hypospadias [prevalence per 10,000]
Northern England [3.7]
Isle de Reunion [14]
Emilia Romagna [13]
Hainaut [12]
Summary estimate [16]
Paris [16]
Tuscany [19]
N Netherlands [19]
Zagreb [20]
S Portugal [5.4]
Antwerp [16]
Basque Country [7.5]
Cork and Kerry [16]
Thames Valley [9.9]
Wessex [13]
Hungary [25]
SE Ireland [8.8]
Norway [22]
Saxony Anhalt [18]
Mainz [34]
Wales [27]
Wielkopolska [13]
Odense [20]
Dublin [10]
East Midlands and South Yorkshire [15]
Vaud [23]
Malta [34]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

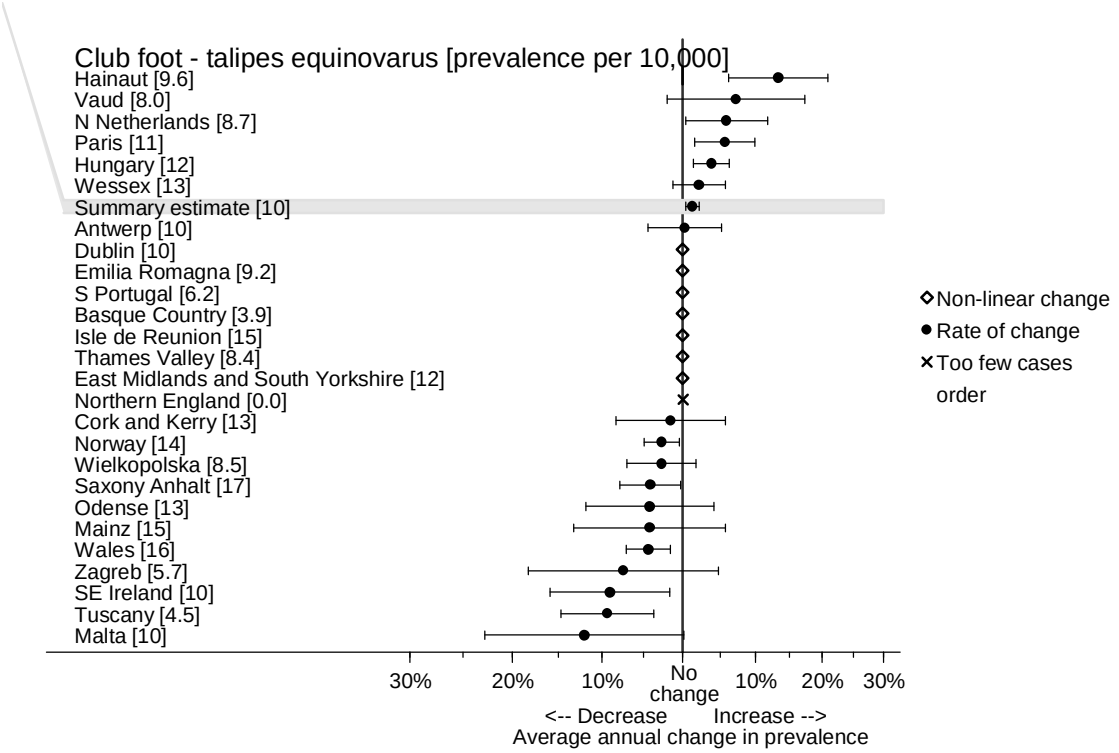

Indeterminate sex [prevalence per 10,000]
Norway [0.4]
Isle de Reunion [1.7]
Wessex [1.2]
Tuscany [0.8]
Emilia Romagna [0.4]
Summary estimate [0.6]
Hainaut [1.1]
Odense [0.5]
Paris [0.5]
Dublin [0.3]
N Netherlands [0.5]
Vaud [0.6]
Zagreb [0.7]
Malta [1.1]
S Portugal [0.3]
Antwerp [0.4]
Basque Country [0.2]
Saxony Anhalt [0.2]
Mainz [0.3]
Cork and Kerry [0.8]
Wales [0.4]
Thames Valley [0.9]
SE Ireland [1.3]
East Midlands and South Yorkshire [0.7]
Wielkopolska [0.4]
Hungary [0.4]
Northern England [0.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

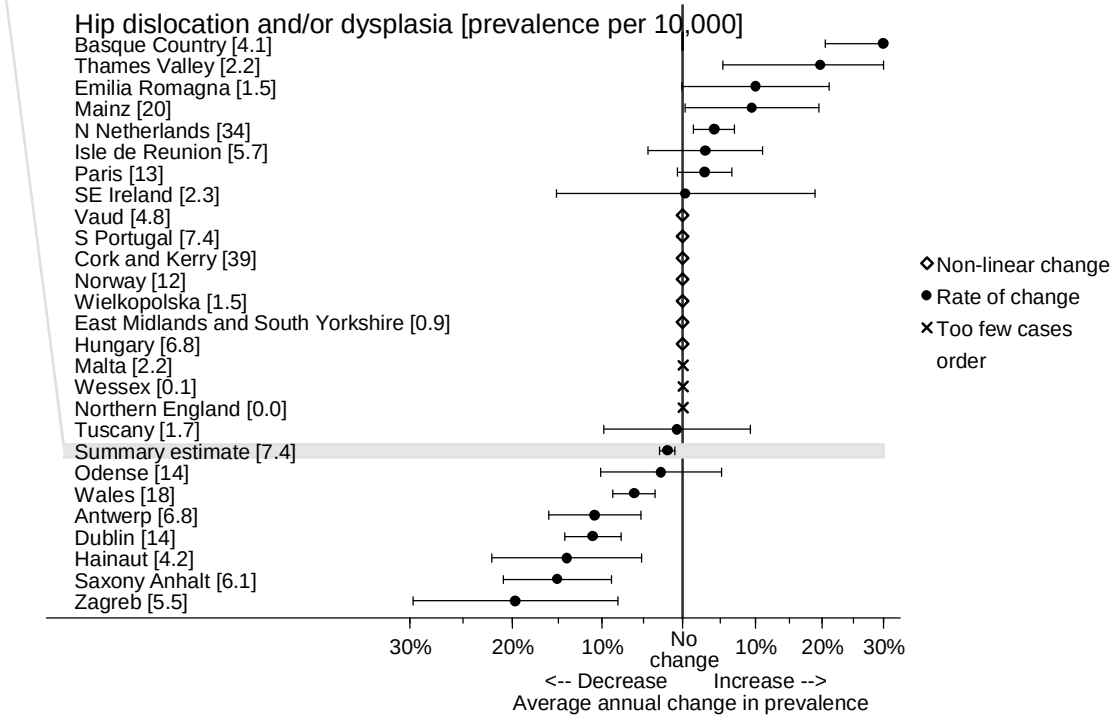

Limb reduction [prevalence per 10,000]
Basque Country [4.1]
Zagreb [3.8]
Cork and Kerry [3.5]
Odense [7.8]
Hungary [3.5]
Norway [4.0]
Paris [6.0]
Antwerp [4.3]
SE Ireland [2.2]
Isle de Reunion [5.4]
Saxony Anhalt [6.0]
Emilia Romagna [4.4]
Malta [3.8]
Wessex [4.3]
Tuscany [4.7]
Northern England [4.1]
N Netherlands [5.5]
Summary estimate [4.6]
Thames Valley [3.3]
Wales [7.0]
Wielkopolska [5.5]
East Midlands and South Yorkshire [5.7]
S Portugal [1.6]
Dublin [2.9]
Vaud [6.0]
Hainaut [6.4]
Mainz [8.4]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

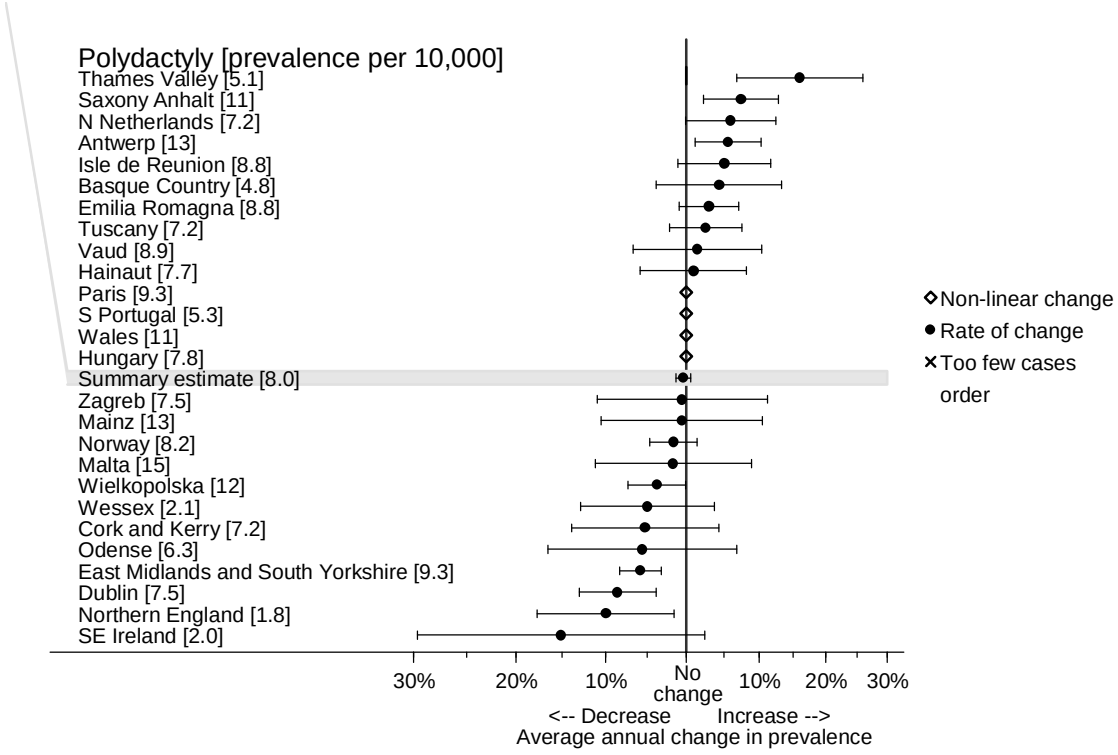

Upper limb reduction [prevalence per 10,000]
Odense [5.3]
Basque Country [2.6]
Antwerp [2.7]
Zagreb [2.8]
Cork and Kerry [2.1]
Saxony Anhalt [4.3]
Wessex [2.8]
Hungary [2.3]
Paris [4.3]
Isle de Reunion [2.8]
Malta [2.2]
S Portugal [0.9]
Mainz [5.6]
SE Ireland [1.9]
Tuscany [3.2]
Norway [3.0]
N Netherlands [3.5]
Thames Valley [2.6]
Summary estimate [3.2]
Emilia Romagna [3.3]
Wales [5.3]
Northern England [2.9]
Wielkopolska [4.0]
Dublin [1.9]
East Midlands and South Yorkshire [3.7]
Vaud [4.4]
Hainaut [5.4]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

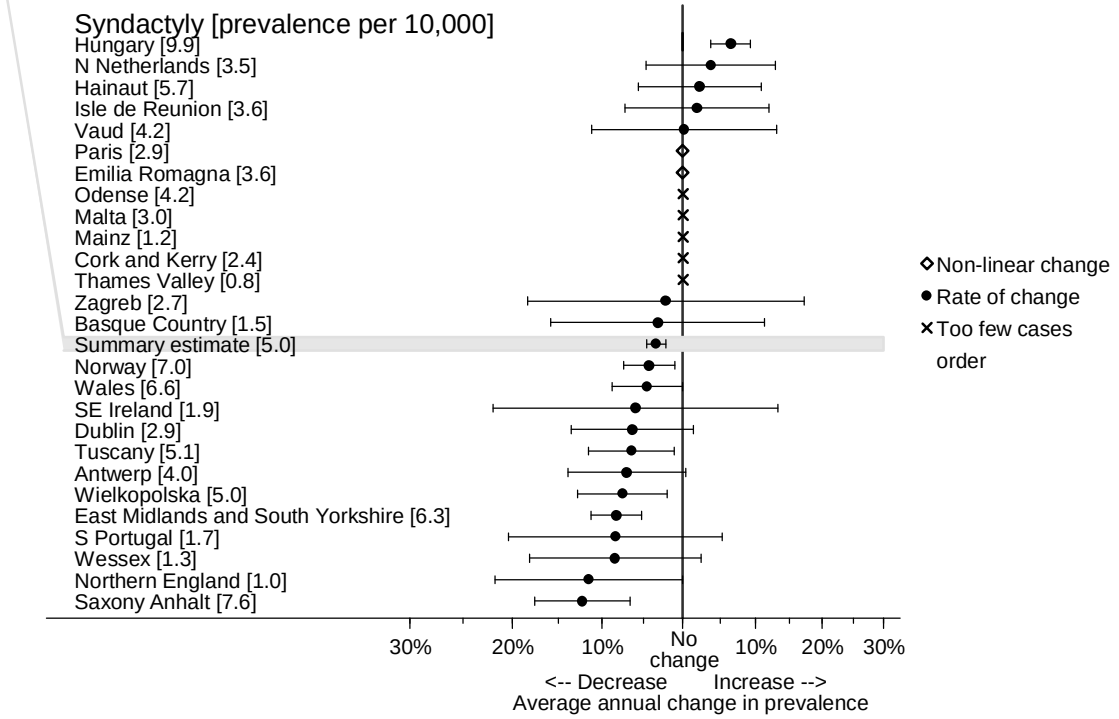

Lower limb reduction [prevalence per 10,000]
Basque Country [2.1]
Paris [2.3]
Hainaut [1.3]
Hungary [1.3]
Northern England [1.6]
Norway [1.1]
N Netherlands [2.2]
Wielkopolska [2.0]
Vaud [2.8]
Zagreb [0.9]
Malta [1.6]
S Portugal [0.5]
Mainz [3.1]
Cork and Kerry [1.7]
SE Ireland [0.5]
Tuscany [1.8]
Summary estimate [1.6]
East Midlands and South Yorkshire [1.7]
Saxony Anhalt [2.8]
Wessex [1.8]
Thames Valley [0.9]
Antwerp [1.6]
Odense [2.4]
Isle de Reunion [2.5]
Wales [2.3]
Emilia Romagna [1.4]
Dublin [1.0]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

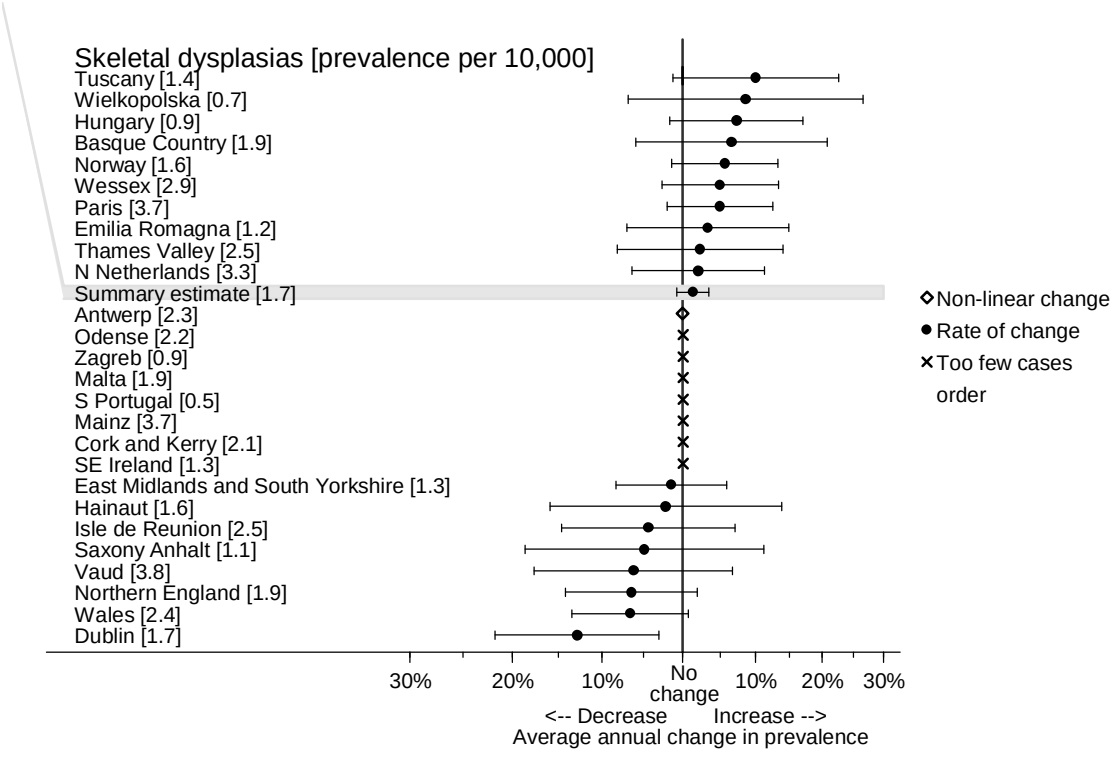

Complete absence of a limb [prevalence per 10,000]
Summary estimate [0.1]
Hainaut [0.1]
Odense [0.5]
Paris [0.1]
Tuscany [0.2]
Dublin [0.0]
N Netherlands [0.1]
Emilia Romagna [0.1]
Vaud [0.8]
Zagreb [0.4]
Malta [0.0]
S Portugal [0.0]
Antwerp [0.0]
Basque Country [0.3]
Saxony Anhalt [0.2]
Mainz [0.0]
Cork and Kerry [0.3]
Wales [0.2]
Norway [0.2]
Isle de Reunion [0.1]
Wielkopolska [0.2]
Thames Valley [0.0]
Wessex [0.1]
East Midlands and South Yorkshire [0.2]
Northern England [0.0]
Hungary [0.1]
SE Ireland [0.1]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

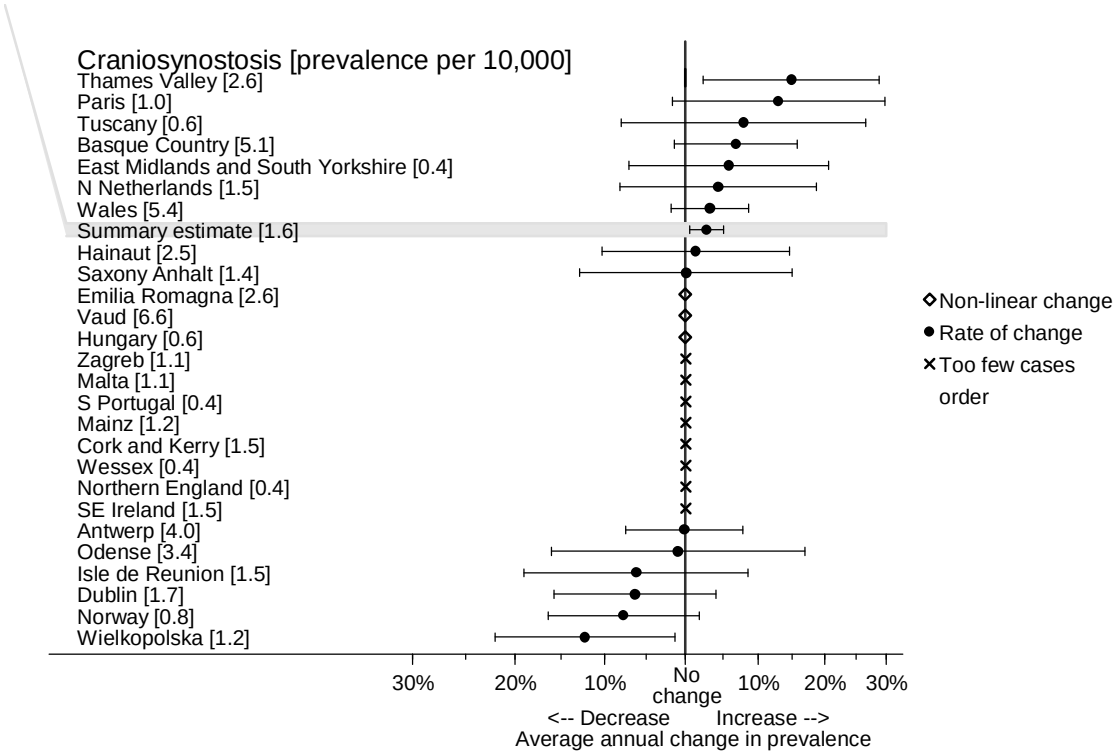

Club foot - talipes equinovarus [prevalence per 10,000]
Hainaut [9.6]
Vaud [8.0]
N Netherlands [8.7]
Paris [11]
Hungary [12]
Wessex [13]
Summary estimate [10]
Antwerp [10]
Dublin [10]
Emilia Romagna [9.2]
S Portugal [6.2]
Basque Country [3.9]
Isle de Reunion [15]
Thames Valley [8.4]
East Midlands and South Yorkshire [12]
Northern England [0.0]
Cork and Kerry [13]
Norway [14]
Wielkopolska [8.5]
Saxony Anhalt [17]
Odense [13]
Mainz [15]
Wales [16]
Zagreb [5.7]
SE Ireland [10]
Tuscany [4.5]
Malta [10]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

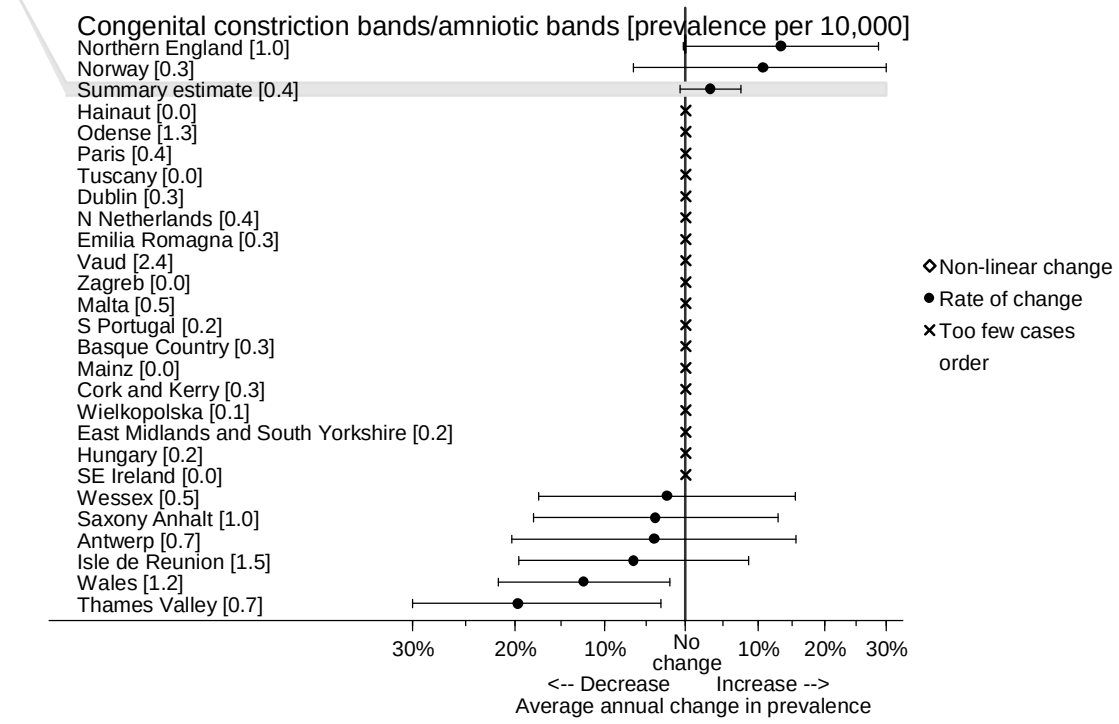

Hip dislocation and/or dysplasia [prevalence per 10,000]
Basque Country [4.1]
Thames Valley [2.2]
Emilia Romagna [1.5]
Mainz [20]
N Netherlands [34]
Isle de Reunion [5.7]
Paris [13]
SE Ireland [2.3]
Vaud [4.8]
S Portugal [7.4]
Cork and Kerry [39]
Norway [12]
Wielkopolska [1.5]
East Midlands and South Yorkshire [0.9]
Hungary [6.8]
Malta [2.2]
Wessex [0.1]
Northern England [0.0]
Tuscany [1.7]
Summary estimate [7.4]
Odense [14]
Wales [18]
Antwerp [6.8]
Dublin [14]
Hainaut [4.2]
Saxony Anhalt [6.1]
Zagreb [5.5]
Non-linear change
Rate of change
Too few cases
order
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence

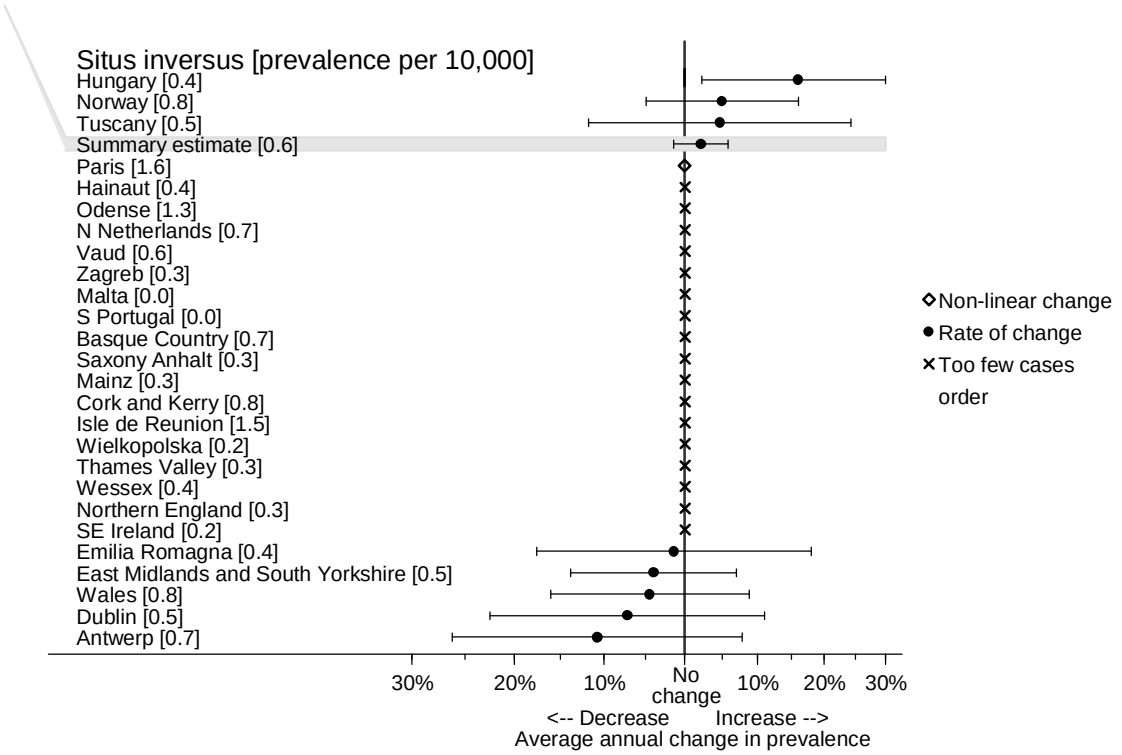

Polydactyly [prevalence per 10,000]
Thames Valley [5.1]
Saxony Anhalt [11]
N Netherlands [7.2]
Antwerp [13]
Isle de Reunion [8.8]
Basque Country [4.8]
Emilia Romagna [8.8]
Tuscany [7.2]
Vaud [8.9]
Hainaut [7.7]
Paris [9.3]
S Portugal [5.3]
Wales [11]
Hungary [7.8]
Summary estimate [8.0]
Zagreb [7.5]
Mainz [13]
Norway [8.2]
Malta [15]
Wielkopolska [12]
Wessex [2.1]
Cork and Kerry [7.2]
Odense [6.3]
East Midlands and South Yorkshire [9.3]
Dublin [7.5]
Northern England [1.8]
SE Ireland [2.0]
Non-linear change
Rate of change
Too few cases
order
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence

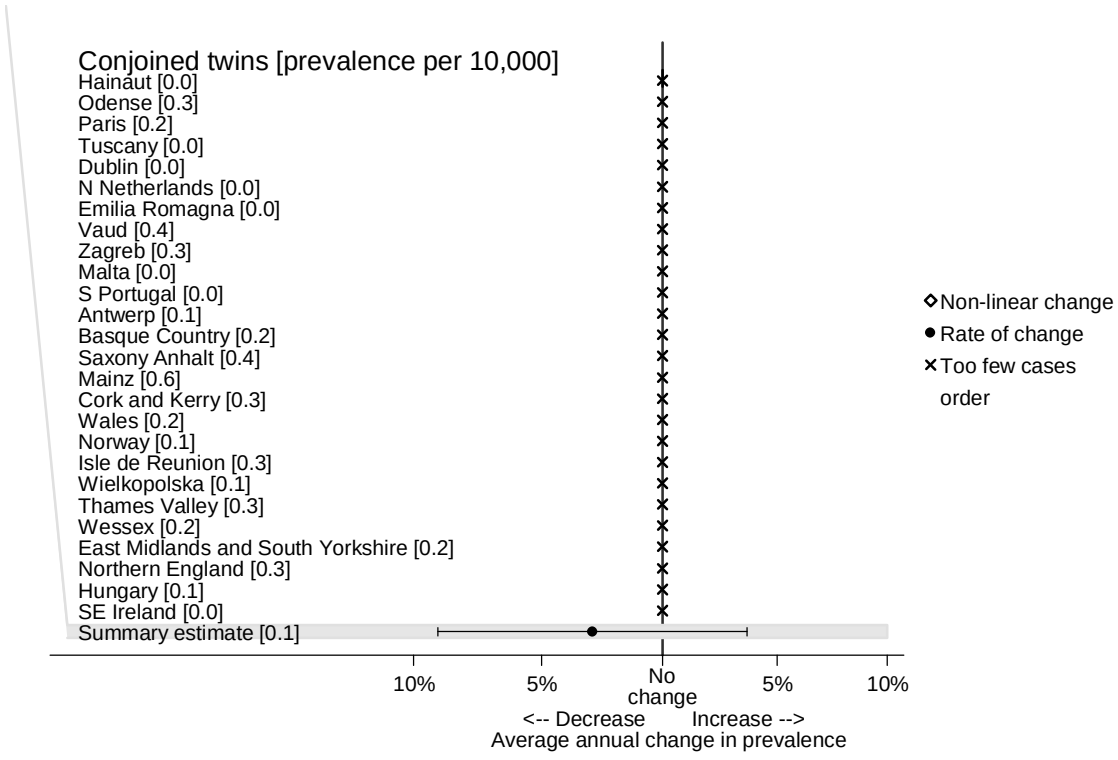

Syndactyly [prevalence per 10,000]
Hungary [9.9]
N Netherlands [3.5]
Hainaut [5.7]
Isle de Reunion [3.6]
Vaud [4.2]
Paris [2.9]
Emilia Romagna [3.6]
Odense [4.2]
Malta [3.0]
Mainz [1.2]
Cork and Kerry [2.4]
Thames Valley [0.8]
Zagreb [2.7]
Basque Country [1.5]
Summary estimate [5.0]
Norway [7.0]
Wales [6.6]
SE Ireland [1.9]
Dublin [2.9]
Tuscany [5.1]
Antwerp [4.0]
Wielkopolska [5.0]
East Midlands and South Yorkshire [6.3]
S Portugal [1.7]
Wessex [1.3]
Northern England [1.0]
Saxony Anhalt [7.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

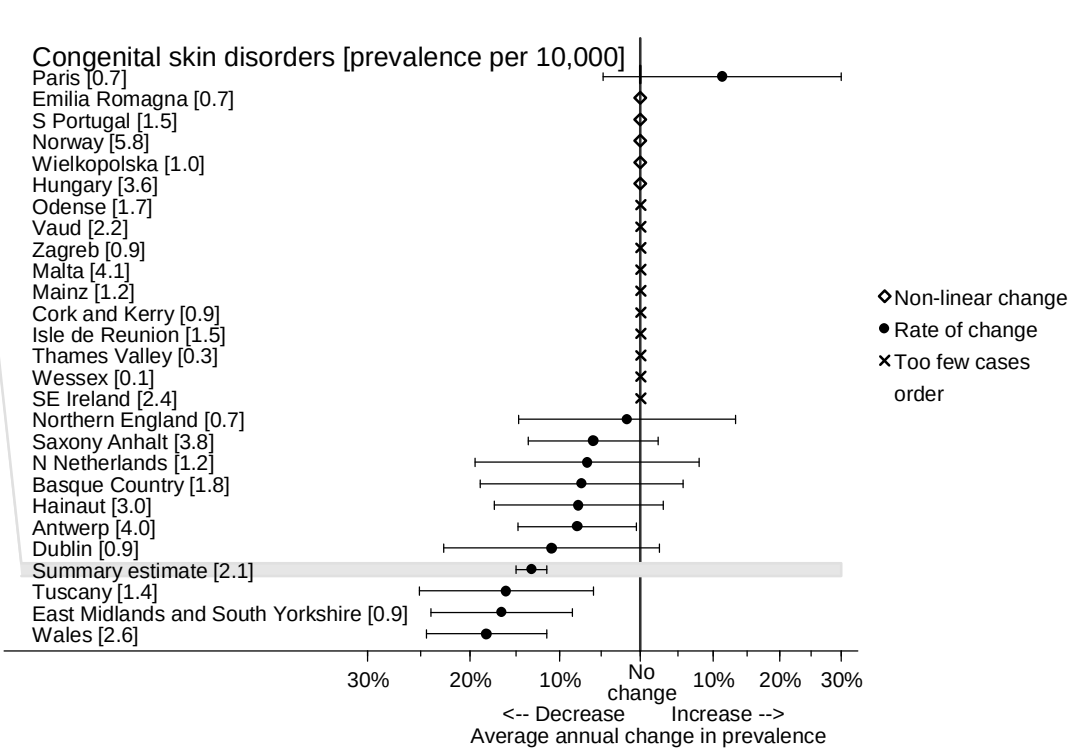

Skeletal dysplasias [prevalence per 10,000]
Tuscany [1.4]
Wielkopolska [0.7]
Hungary [0.9]
Basque Country [1.9]
Norway [1.6]
Wessex [2.9]
Paris [3.7]
Emilia Romagna [1.2]
Thames Valley [2.5]
N Netherlands [3.3]
Summary estimate [1.7]
Antwerp [2.3]
Odense [2.2]
Zagreb [0.9]
Malta [1.9]
S Portugal [0.5]
Mainz [3.7]
Cork and Kerry [2.1]
SE Ireland [1.3]
East Midlands and South Yorkshire [1.3]
Hainaut [1.6]
Isle de Reunion [2.5]
Saxony Anhalt [1.1]
Vaud [3.8]
Northern England [1.9]
Wales [2.4]
Dublin [1.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

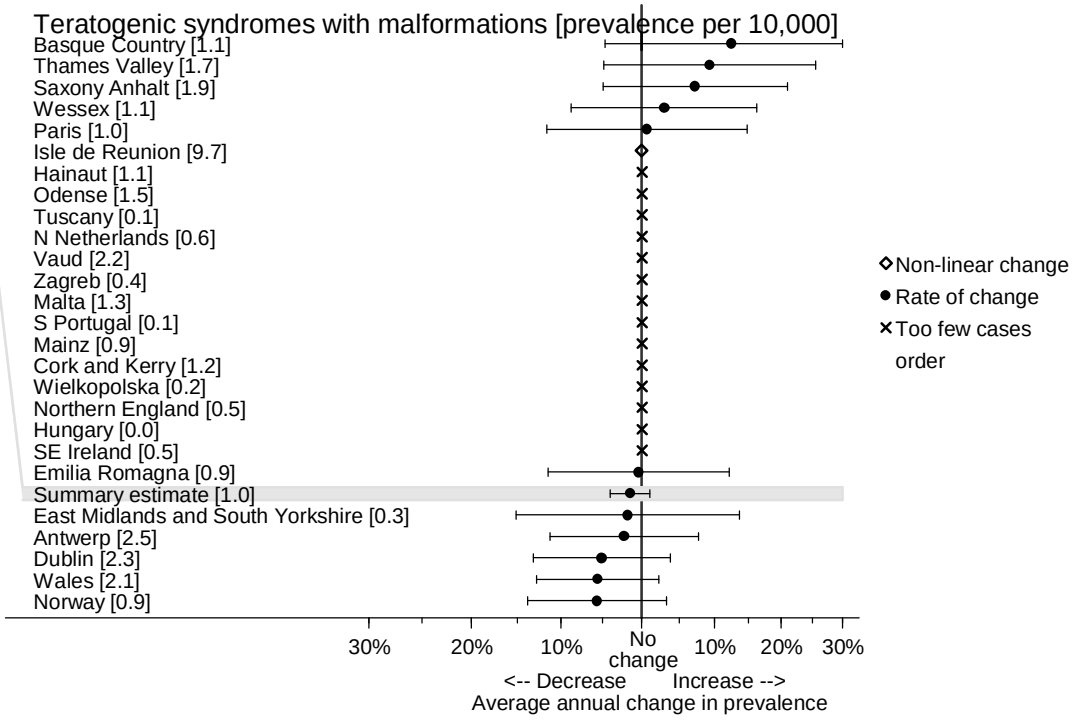

Craniosynostosis [prevalence per 10,000]
Thames Valley [2.6]
Paris [1.0]
Tuscany [0.6]
Basque Country [5.1]
East Midlands and South Yorkshire [0.4]
N Netherlands [1.5]
Wales [5.4]
Summary estimate [1.6]
Hainaut [2.5]
Saxony Anhalt [1.4]
Emilia Romagna [2.6]
Vaud [6.6]
Hungary [0.6]
Zagreb [1.1]
Malta [1.1]
S Portugal [0.4]
Mainz [1.2]
Cork and Kerry [1.5]
Wessex [0.4]
Northern England [0.4]
SE Ireland [1.5]
Antwerp [4.0]
Odense [3.4]
Isle de Reunion [1.5]
Dublin [1.7]
Norway [0.8]
Wielkopolska [1.2]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

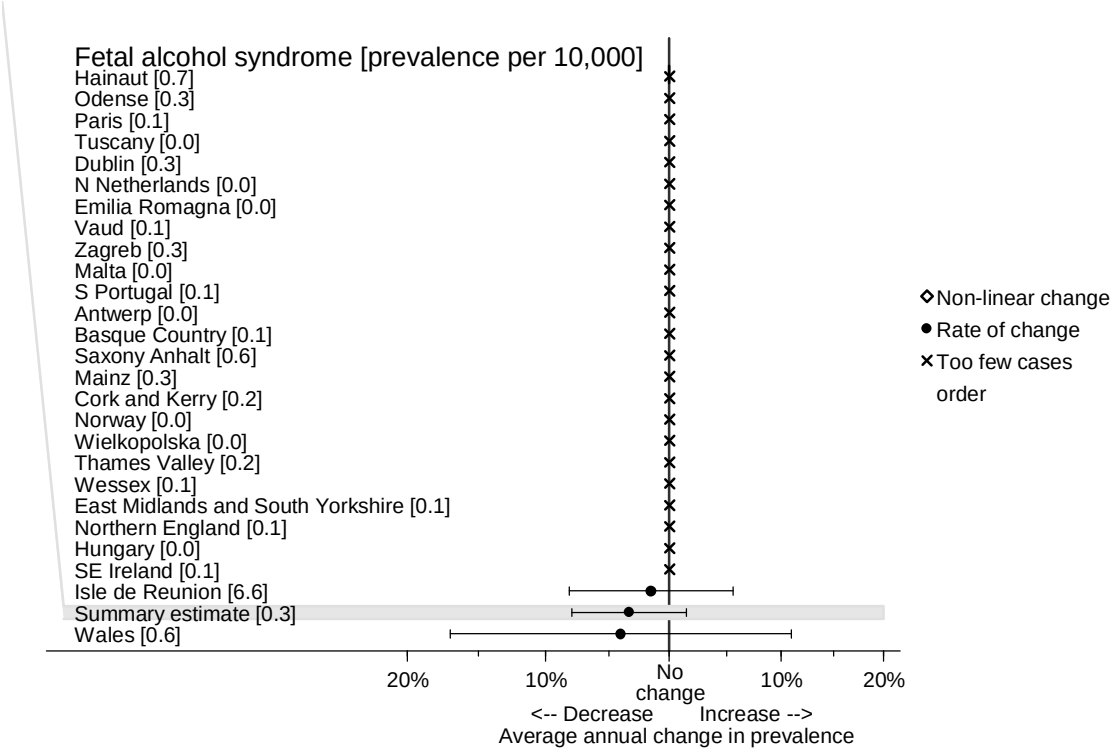

Congenital constriction bands/amniotic bands [prevalence per 10,000]
Northern England [1.0]
Norway [0.3]
Summary estimate [0.4]
Hainaut [0.0]
Odense [1.3]
Paris [0.4]
Tuscany [0.0]
Dublin [0.3]
N Netherlands [0.4]
Emilia Romagna [0.3]
Vaud [2.4]
Zagreb [0.0]
Malta [0.5]
S Portugal [0.2]
Basque Country [0.3]
Mainz [0.0]
Cork and Kerry [0.3]
Wielkopolska [0.1]
East Midlands and South Yorkshire [0.2]
Hungary [0.2]
SE Ireland [0.0]
Wessex [0.5]
Saxony Anhalt [1.0]
Antwerp [0.7]
Isle de Reunion [1.5]
Wales [1.2]
Thames Valley [0.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

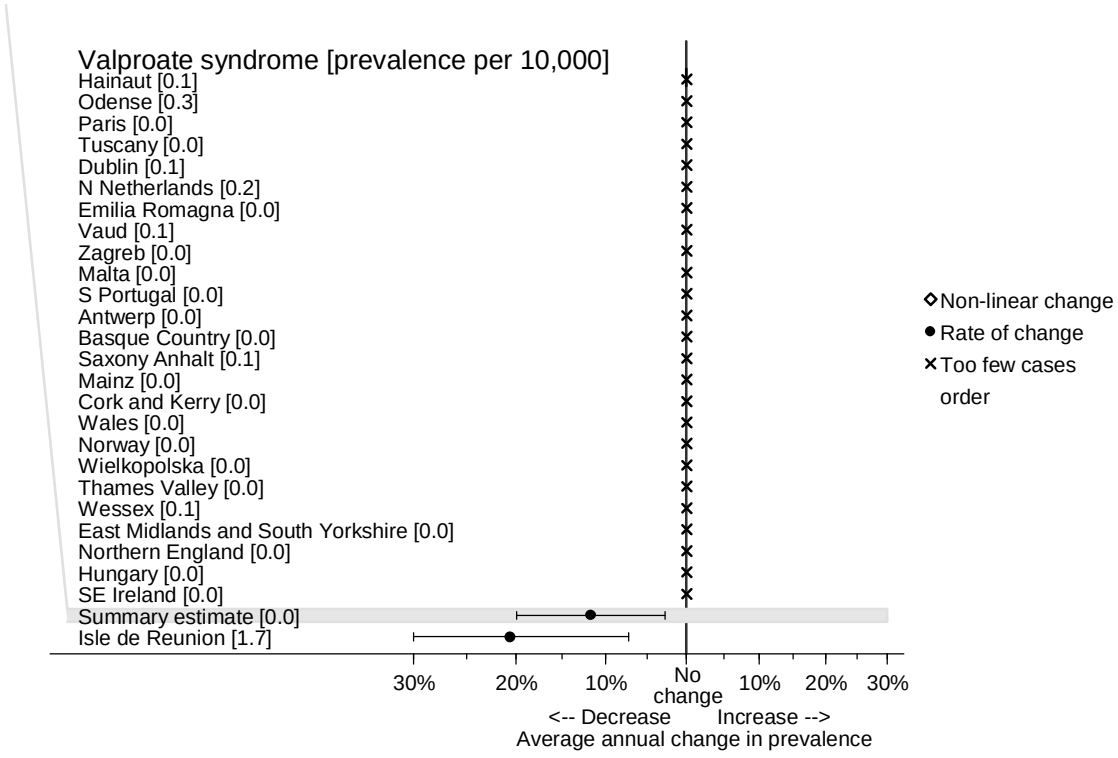

Situs inversus [prevalence per 10,000]
Hungary [0.4]
Norway [0.8]
Tuscany [0.5]
Summary estimate [0.6]
Paris [1.6]
Hainaut [0.4]
Odense [1.3]
N Netherlands [0.7]
Vaud [0.6]
Zagreb [0.3]
Malta [0.0]
S Portugal [0.0]
Basque Country [0.7]
Saxony Anhalt [0.3]
Mainz [0.3]
Cork and Kerry [0.8]
Isle de Reunion [1.5]
Wielkopolska [0.2]
Thames Valley [0.3]
Wessex [0.4]
Northern England [0.3]
SE Ireland [0.2]
Emilia Romagna [0.4]
East Midlands and South Yorkshire [0.5]
Wales [0.8]
Dublin [0.5]
Antwerp [0.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

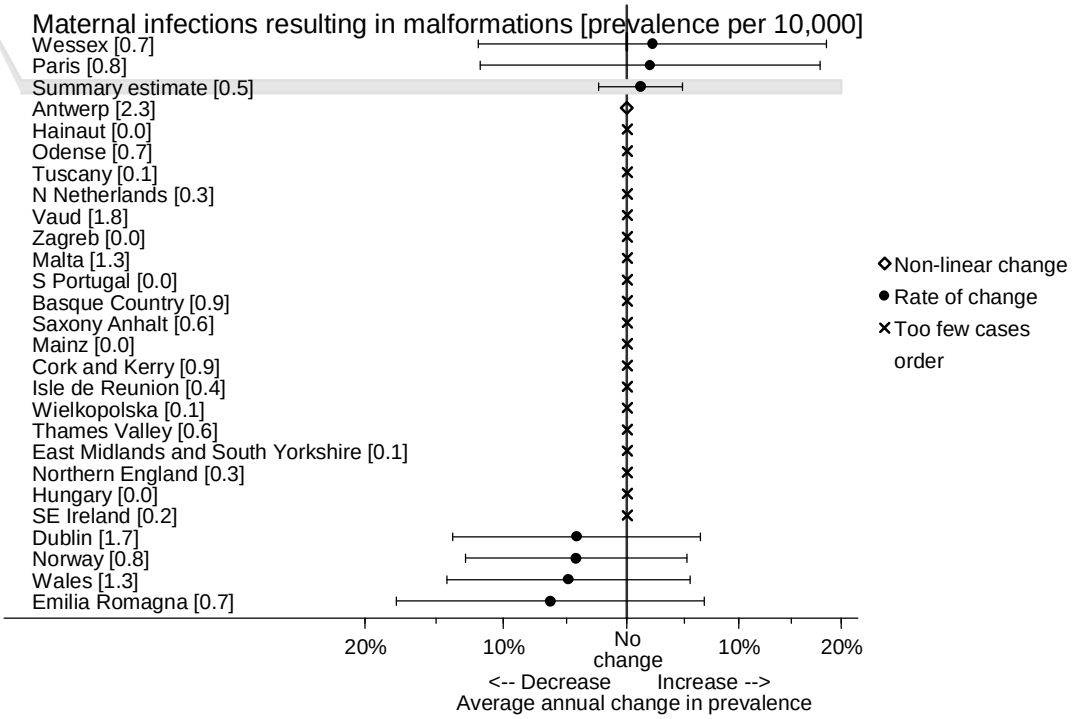

Conjoined twins [prevalence per 10,000]
Hainaut [0.0]
Odense [0.3]
Paris [0.2]
Tuscany [0.0]
Dublin [0.0]
N Netherlands [0.0]
Emilia Romagna [0.0]
Vaud [0.4]
Zagreb [0.3]
Malta [0.0]
S Portugal [0.0]
Antwerp [0.1]
Basque Country [0.2]
Saxony Anhalt [0.4]
Mainz [0.6]
Cork and Kerry [0.3]
Wales [0.2]
Norway [0.1]
Isle de Reunion [0.3]
Wielkopolska [0.1]
Thames Valley [0.3]
Wessex [0.2]
East Midlands and South Yorkshire [0.2]
Northern England [0.3]
Hungary [0.1]
SE Ireland [0.0]
Summary estimate [0.1]
10%
5%
No change
5%
10%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

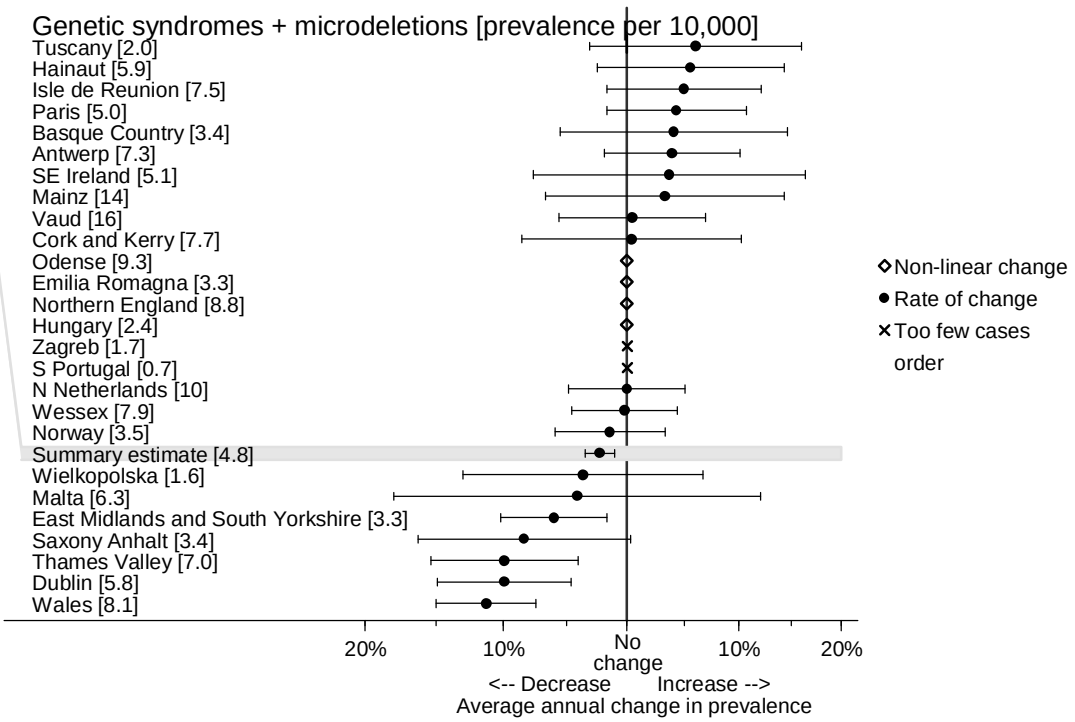

Congenital skin disorders [prevalence per 10,000]
Paris [0.7]
Emilia Romagna [0.7]
S Portugal [1.5]
Norway [5.8]
Wielkopolska [1.0]
Hungary [3.6]
Odense [1.7]
Vaud [2.2]
Zagreb [0.9]
Malta [4.1]
Mainz [1.2]
Cork and Kerry [0.9]
Isle de Reunion [1.5]
Thames Valley [0.3]
Wessex [0.1]
SE Ireland [2.4]
Northern England [0.7]
Saxony Anhalt [3.8]
N Netherlands [1.2]
Basque Country [1.8]
Hainaut [3.0]
Antwerp [4.0]
Dublin [0.9]
Summary estimate [2.1]
Tuscany [1.4]
East Midlands and South Yorkshire [0.9]
Wales [2.6]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

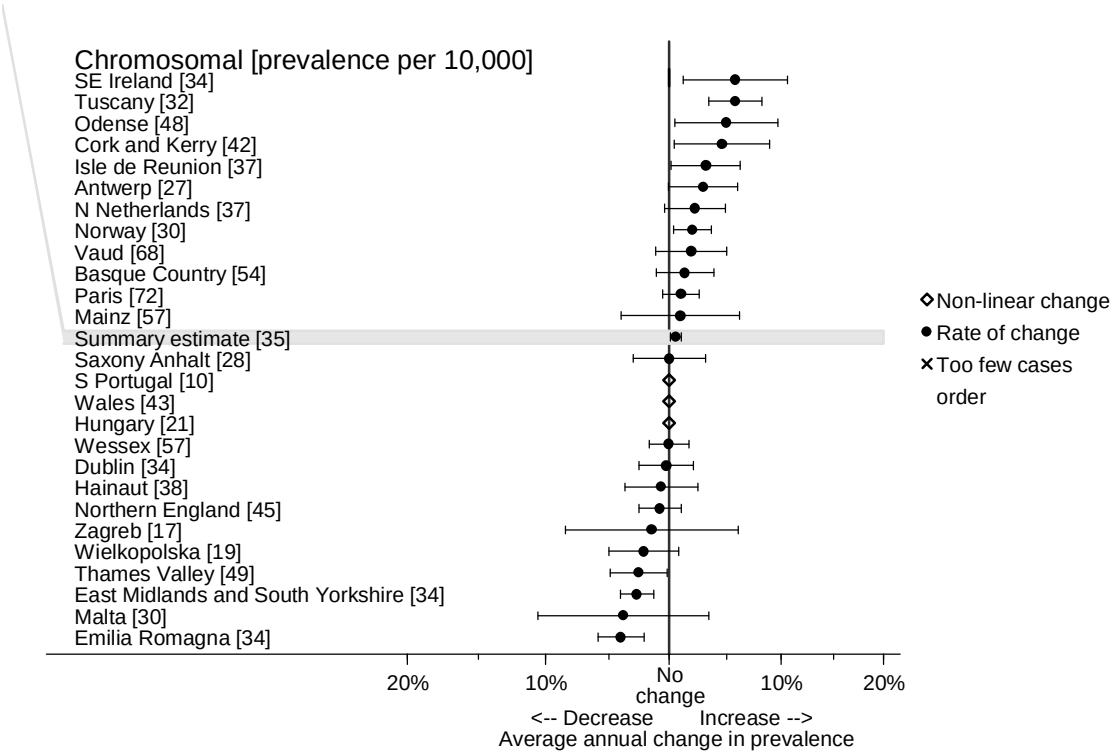

Teratogenic syndromes with malformations [prevalence per 10,000]
Basque Country [1.1]
Thames Valley [1.7]
Saxony Anhalt [1.9]
Wessex [1.1]
Paris [1.0]
Isle de Reunion [9.7]
Hainaut [1.1]
Odense [1.5]
Tuscany [0.1]
N Netherlands [0.6]
Vaud [2.2]
Zagreb [0.4]
Malta [1.3]
S Portugal [0.1]
Mainz [0.9]
Cork and Kerry [1.2]
Wielkopolska [0.2]
Northern England [0.5]
Hungary [0.0]
SE Ireland [0.5]
Emilia Romagna [0.9]
Summary estimate [1.0]
East Midlands and South Yorkshire [0.3]
Antwerp [2.5]
Dublin [2.3]
Wales [2.1]
Norway [0.9]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

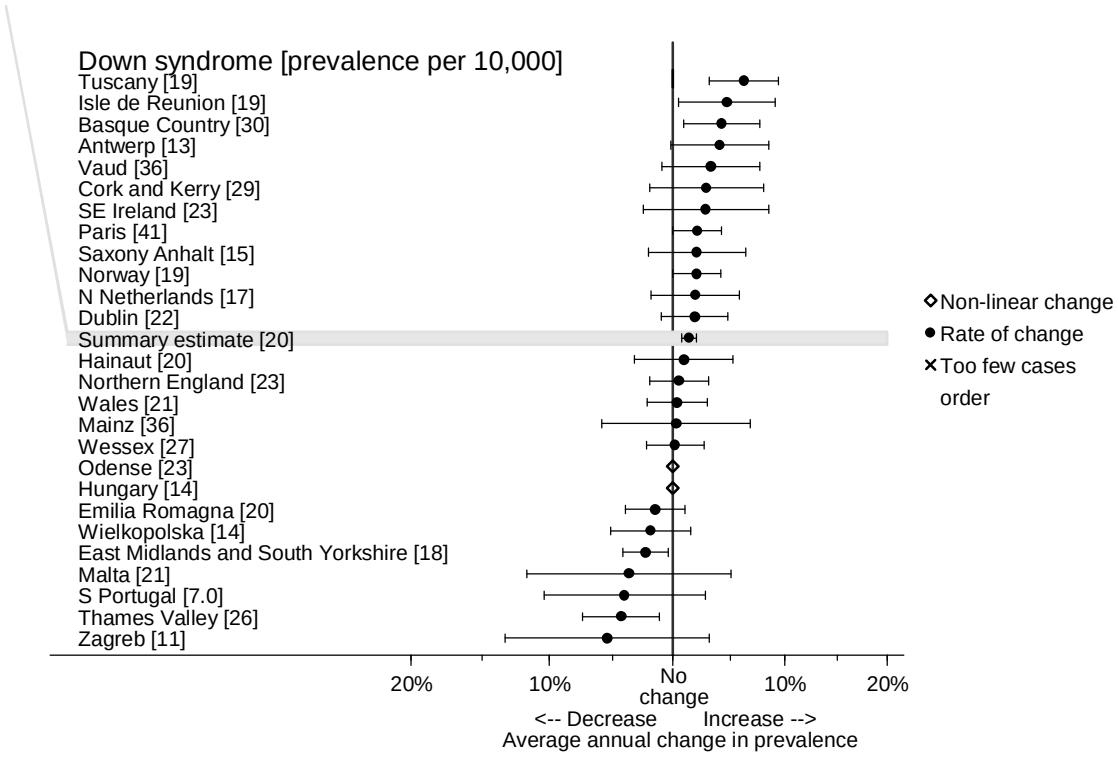

Fetal alcohol syndrome [prevalence per 10,000]
Hainaut [0.7]
Odense [0.3]
Paris [0.1]
Tuscany [0.0]
Dublin [0.3]
N Netherlands [0.0]
Emilia Romagna [0.0]
Vaud [0.1]
Zagreb [0.3]
Malta [0.0]
S Portugal [0.1]
Antwerp [0.0]
Basque Country [0.1]
Saxony Anhalt [0.6]
Mainz [0.3]
Cork and Kerry [0.2]
Norway [0.0]
Wielkopolska [0.0]
Thames Valley [0.2]
Wessex [0.1]
East Midlands and South Yorkshire [0.1]
Northern England [0.1]
Hungary [0.0]
SE Ireland [0.1]
Isle de Reunion [6.6]
Summary estimate [0.3]
Wales [0.6]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

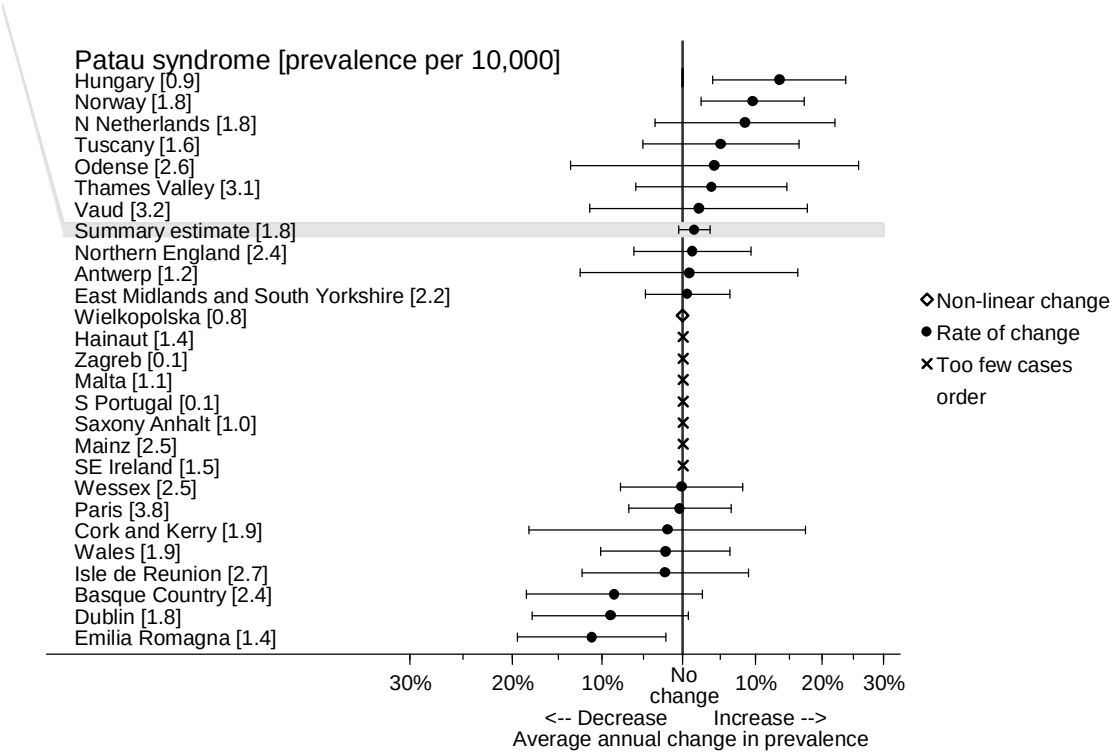

Valproate syndrome [prevalence per 10,000]
Hainaut [0.1]
Odense [0.3]
Paris [0.0]
Tuscany [0.0]
Dublin [0.1]
N Netherlands [0.2]
Emilia Romagna [0.0]
Vaud [0.1]
Zagreb [0.0]
Malta [0.0]
S Portugal [0.0]
Antwerp [0.0]
Basque Country [0.0]
Saxony Anhalt [0.1]
Mainz [0.0]
Cork and Kerry [0.0]
Wales [0.0]
Norway [0.0]
Wielkopolska [0.0]
Thames Valley [0.0]
Wessex [0.1]
East Midlands and South Yorkshire [0.0]
Northern England [0.0]
Hungary [0.0]
SE Ireland [0.0]
Summary estimate [0.0]
Isle de Reunion [1.7]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

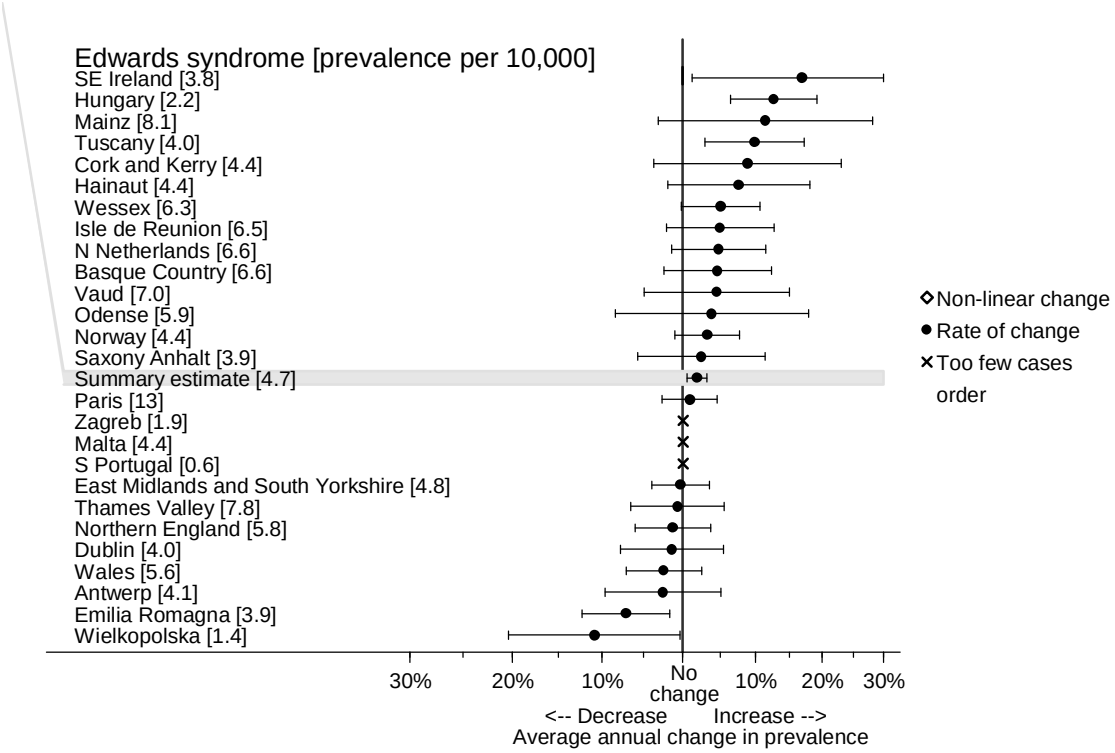

Maternal infections resulting in malformations [prevalence per 10,000]
Wessex [0.7]
Paris [0.8]
Summary estimate [0.5]
Antwerp [2.3]
Hainaut [0.0]
Odense [0.7]
Tuscany [0.1]
N Netherlands [0.3]
Vaud [1.8]
Zagreb [0.0]
Malta [1.3]
S Portugal [0.0]
Basque Country [0.9]
Saxony Anhalt [0.6]
Mainz [0.0]
Cork and Kerry [0.9]
Isle de Reunion [0.4]
Wielkopolska [0.1]
Thames Valley [0.6]
East Midlands and South Yorkshire [0.1]
Northern England [0.3]
Hungary [0.0]
SE Ireland [0.2]
Dublin [1.7]
Norway [0.8]
Wales [1.3]
Emilia Romagna [0.7]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

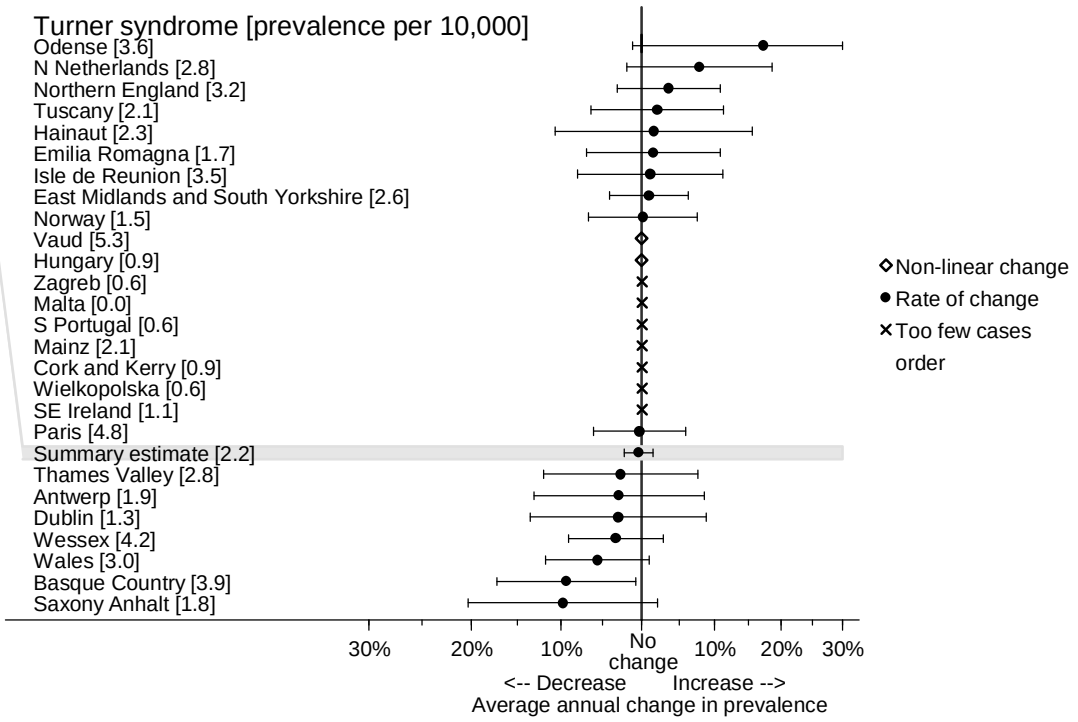

Genetic syndromes + microdeletions [prevalence per 10,000]
Tuscany [2.0]
Hainaut [5.9]
Isle de Reunion [7.5]
Paris [5.0]
Basque Country [3.4]
Antwerp [7.3]
SE Ireland [5.1]
Mainz [14]
Vaud [16]
Cork and Kerry [7.7]
Odense [9.3]
Emilia Romagna [3.3]
Northern England [8.8]
Hungary [2.4]
Zagreb [1.7]
S Portugal [0.7]
N Netherlands [10]
Wessex [7.9]
Norway [3.5]
Summary estimate [4.8]
Wielkopolska [1.6]
Malta [6.3]
East Midlands and South Yorkshire [3.3]
Saxony Anhalt [3.4]
Thames Valley [7.0]
Dublin [5.8]
Wales [8.1]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

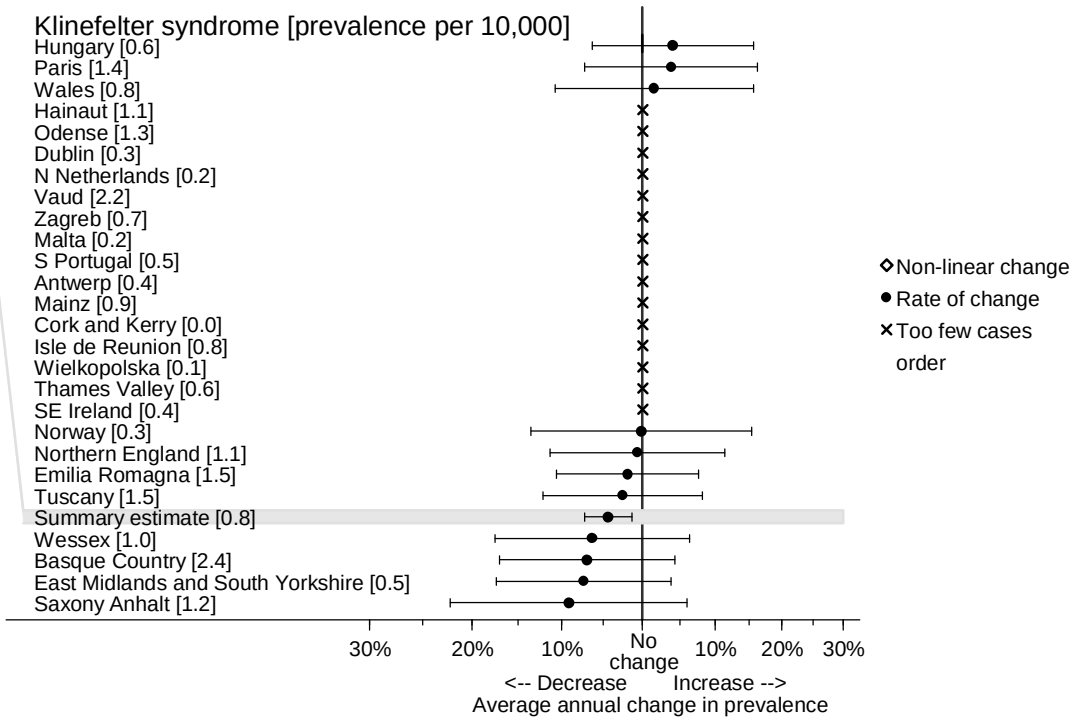

Chromosomal [prevalence per 10,000]
SE Ireland [34]
Tuscany [32]
Odense [48]
Cork and Kerry [42]
Isle de Reunion [37]
Antwerp [27]
N Netherlands [37]
Norway [30]
Vaud [68]
Basque Country [54]
Paris [72]
Mainz [57]
Summary estimate [35]
Saxony Anhalt [28]
S Portugal [10]
Wales [43]
Hungary [21]
Wessex [57]
Dublin [34]
Hainaut [38]
Northern England [45]
Zagreb [17]
Wielkopolska [19]
Thames Valley [49]
East Midlands and South Yorkshire [34]
Malta [30]
Emilia Romagna [34]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

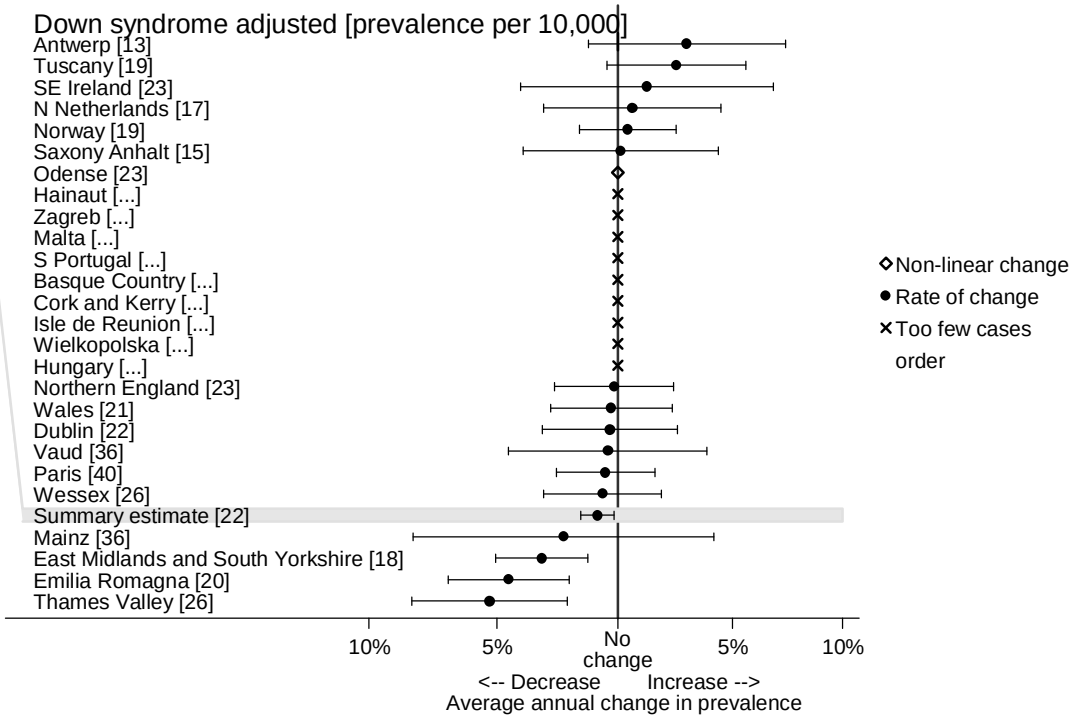

Down syndrome [prevalence per 10,000]
Tuscany [19]
Isle de Reunion [19]
Basque Country [30]
Antwerp [13]
Vaud [36]
Cork and Kerry [29]
SE Ireland [23]
Paris [41]
Saxony Anhalt [15]
Norway [19]
N Netherlands [17]
Dublin [22]
Summary estimate [20]
Hainaut [20]
Northern England [23]
Wales [21]
Mainz [36]
Wessex [27]
Odense [23]
Hungary [14]
Emilia Romagna [20]
Wielkopolska [14]
East Midlands and South Yorkshire [18]
Malta [21]
S Portugal [7.0]
Thames Valley [26]
Zagreb [11]
20%
10%
No change
10%
20%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

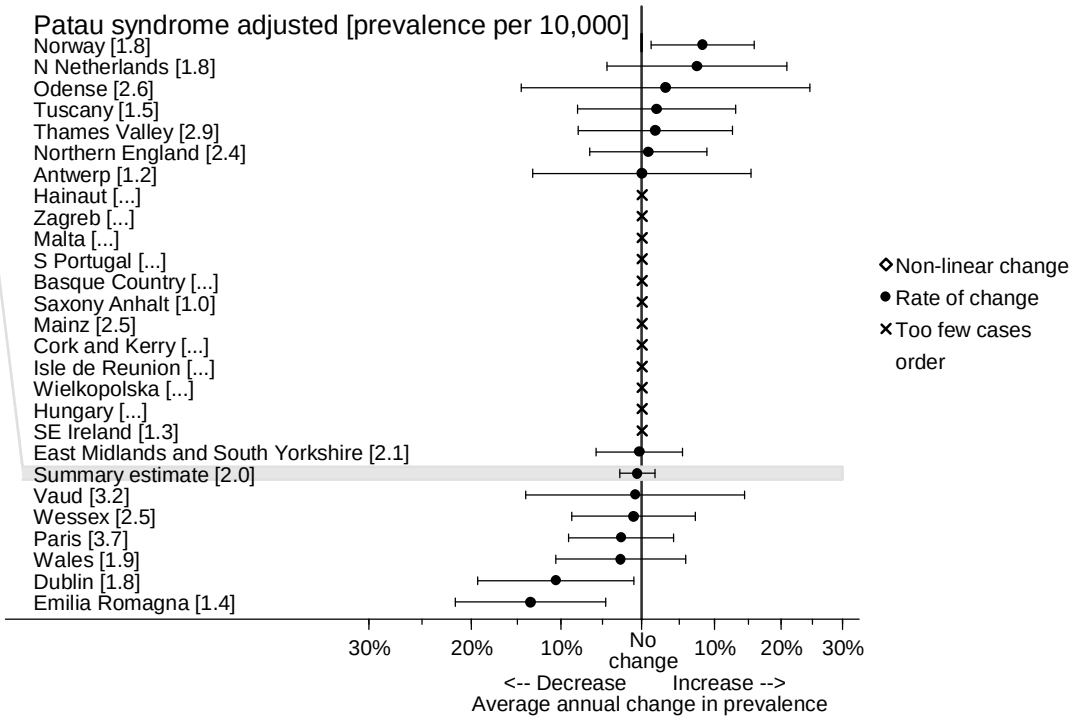

Patau syndrome [prevalence per 10,000]
Hungary [0.9]
Norway [1.8]
N Netherlands [1.8]
Tuscany [1.6]
Odense [2.6]
Thames Valley [3.1]
Vaud [3.2]
Summary estimate [1.8]
Northern England [2.4]
Antwerp [1.2]
East Midlands and South Yorkshire [2.2]
Wielkopolska [0.8]
Hainaut [1.4]
Zagreb [0.1]
Malta [1.1]
S Portugal [0.1]
Saxony Anhalt [1.0]
Mainz [2.5]
SE Ireland [1.5]
Wessex [2.5]
Paris [3.8]
Cork and Kerry [1.9]
Wales [1.9]
Isle de Reunion [2.7]
Basque Country [2.4]
Dublin [1.8]
Emilia Romagna [1.4]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

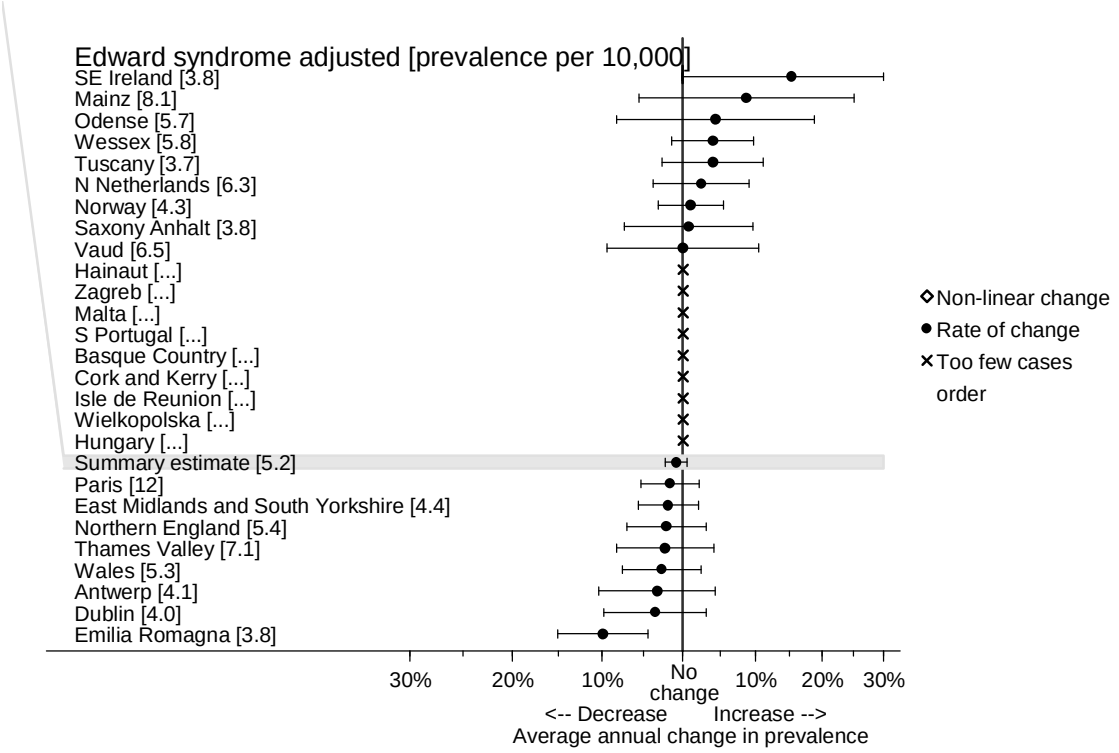

Edwards syndrome [prevalence per 10,000]
SE Ireland [3.8]
Hungary [2.2]
Mainz [8.1]
Tuscany [4.0]
Cork and Kerry [4.4]
Hainaut [4.4]
Wessex [6.3]
Isle de Reunion [6.5]
N Netherlands [6.6]
Basque Country [6.6]
Vaud [7.0]
Odense [5.9]
Norway [4.4]
Saxony Anhalt [3.9]
Summary estimate [4.7]
Paris [13]
Zagreb [1.9]
Malta [4.4]
S Portugal [0.6]
East Midlands and South Yorkshire [4.8]
Thames Valley [7.8]
Northern England [5.8]
Dublin [4.0]
Wales [5.6]
Antwerp [4.1]
Emilia Romagna [3.9]
Wielkopolska [1.4]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order


Turner syndrome [prevalence per 10,000]
Odense [3.6]
N Netherlands [2.8]
Northern England [3.2]
Tuscany [2.1]
Hainaut [2.3]
Emilia Romagna [1.7]
Isle de Reunion [3.5]
East Midlands and South Yorkshire [2.6]
Norway [1.5]
Vaud [5.3]
Hungary [0.9]
Zagreb [0.6]
Malta [0.0]
S Portugal [0.6]
Mainz [2.1]
Cork and Kerry [0.9]
Wielkopolska [0.6]
SE Ireland [1.1]
Paris [4.8]
Summary estimate [2.2]
Thames Valley [2.8]
Antwerp [1.9]
Dublin [1.3]
Wessex [4.2]
Wales [3.0]
Basque Country [3.9]
Saxony Anhalt [1.8]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

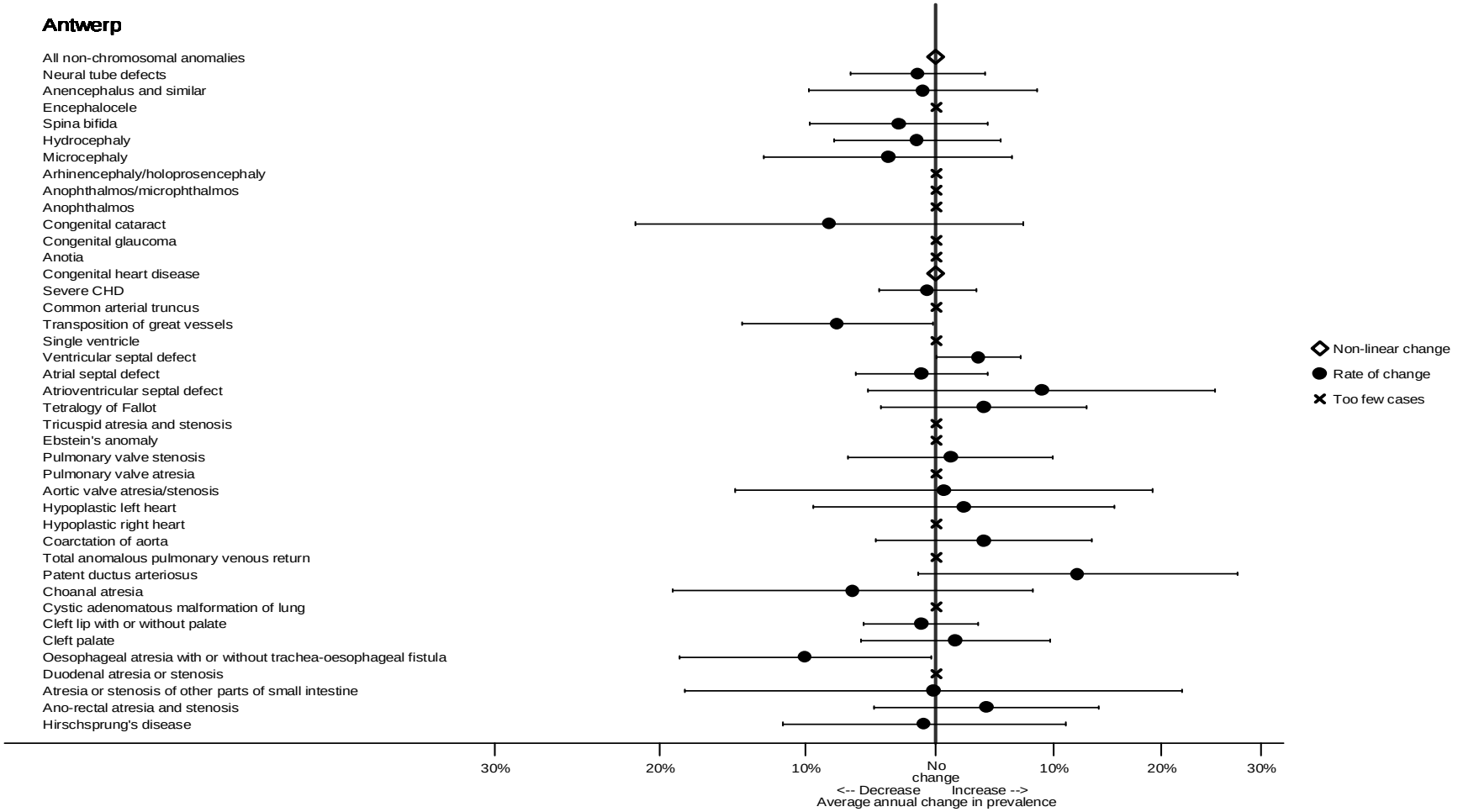

Klinefelter syndrome [prevalence per 10,000]
Hungary [0.6]
Paris [1.4]
Wales [0.8]
Hainaut [1.1]
Odense [1.3]
Dublin [0.3]
N Netherlands [0.2]
Vaud [2.2]
Zagreb [0.7]
Malta [0.2]
S Portugal [0.5]
Antwerp [0.4]
Mainz [0.9]
Cork and Kerry [0.0]
Isle de Reunion [0.8]
Wielkopolska [0.1]
Thames Valley [0.6]
SE Ireland [0.4]
Norway [0.3]
Northern England [1.1]
Emilia Romagna [1.5]
Tuscany [1.5]
Summary estimate [0.8]
Wessex [1.0]
Basque Country [2.4]
East Midlands and South Yorkshire [0.5]
Saxony Anhalt [1.2]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

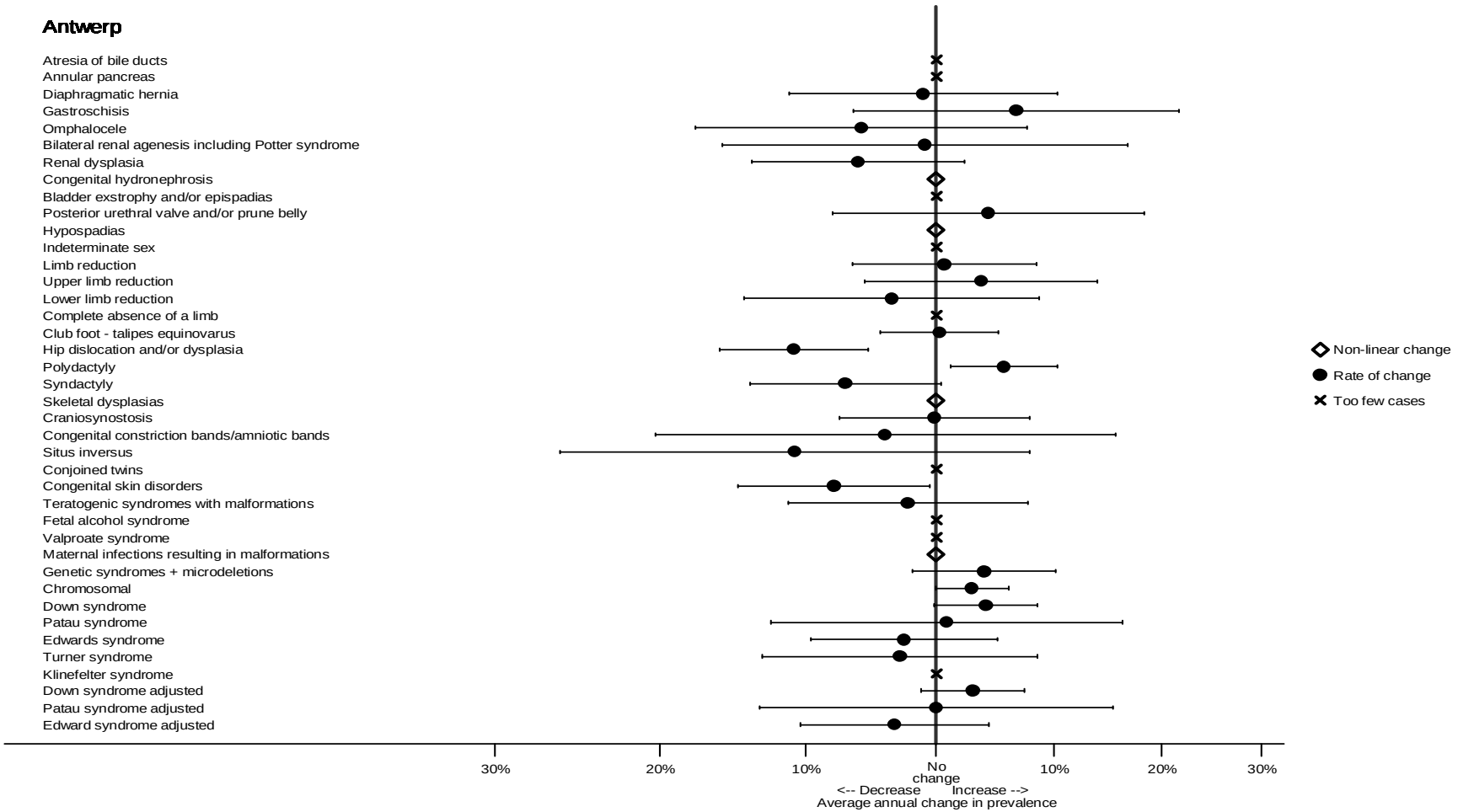

Down syndrome adjusted [prevalence per 10,000]
Antwerp [13]
Tuscany [19]
SE Ireland [23]
N Netherlands [17]
Norway [19]
Saxony Anhalt [15]
Odense [23]
Hainaut [...]
Zagreb [...]
Malta [...]
S Portugal [...]
Basque Country [...]
Cork and Kerry [...]
Isle de Reunion [...]
Wielkopolska [...]
Hungary [...]
Northern England [23]
Wales [21]
Dublin [22]
Vaud [36]
Paris [40]
Wessex [26]
Summary estimate [22]
Mainz [36]
East Midlands and South Yorkshire [18]
Emilia Romagna [20]
Thames Valley [26]
10%
5%
No change
5%
10%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

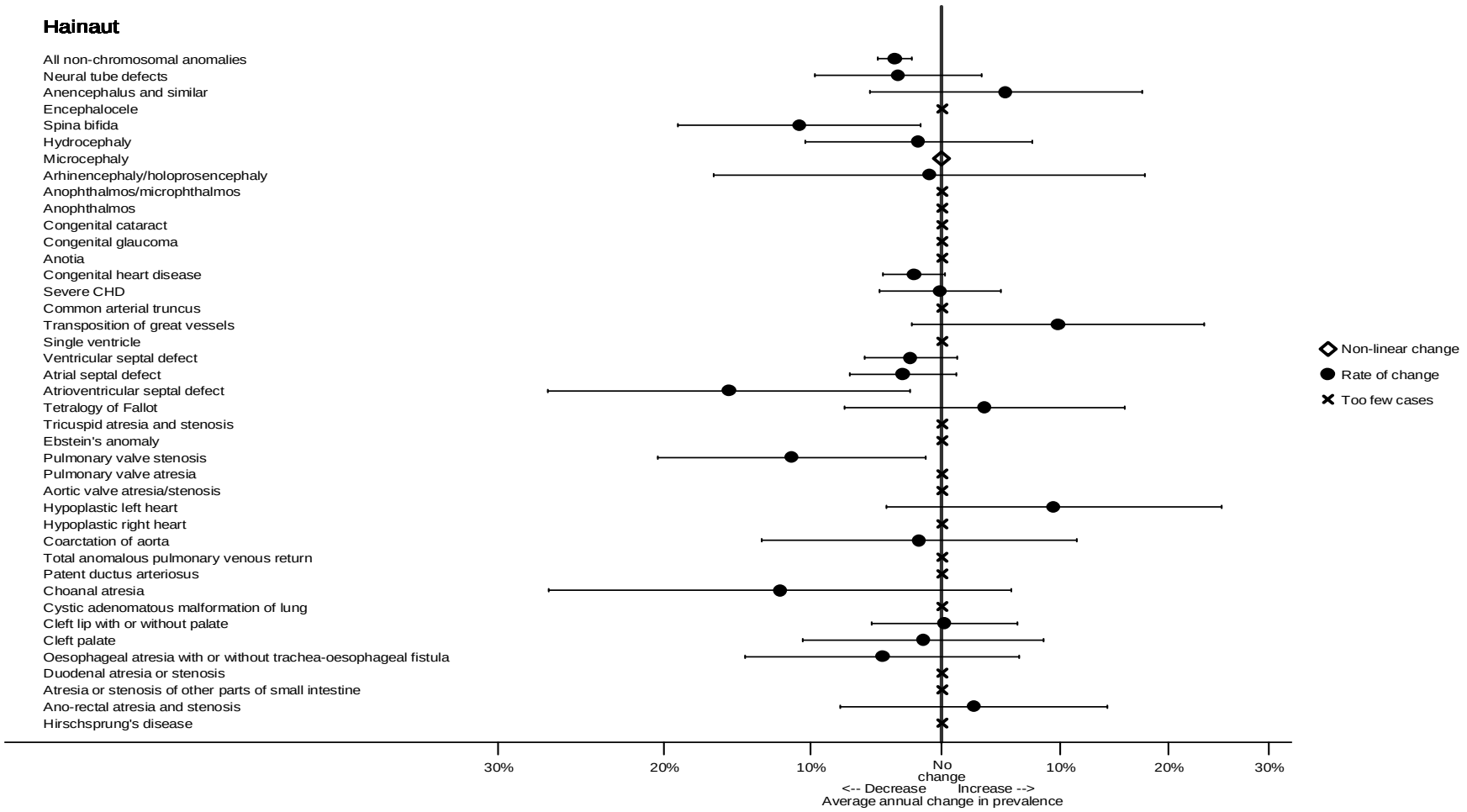

Patau syndrome adjusted [prevalence per 10,000]
Norway [1.8]
N Netherlands [1.8]
Odense [2.6]
Tuscany [1.5]
Thames Valley [2.9]
Northern England [2.4]
Antwerp [1.2]
Hainaut [...]
Zagreb [...]
Malta [...]
S Portugal [...]
Basque Country [...]
Saxony Anhalt [1.0]
Mainz [2.5]
Cork and Kerry [...]
Isle de Reunion [...]
Wielkopolska [...]
Hungary [...]
SE Ireland [1.3]
East Midlands and South Yorkshire [2.1]
Summary estimate [2.0]
Vaud [3.2]
Wessex [2.5]
Paris [3.7]
Wales [1.9]
Dublin [1.8]
Emilia Romagna [1.4]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

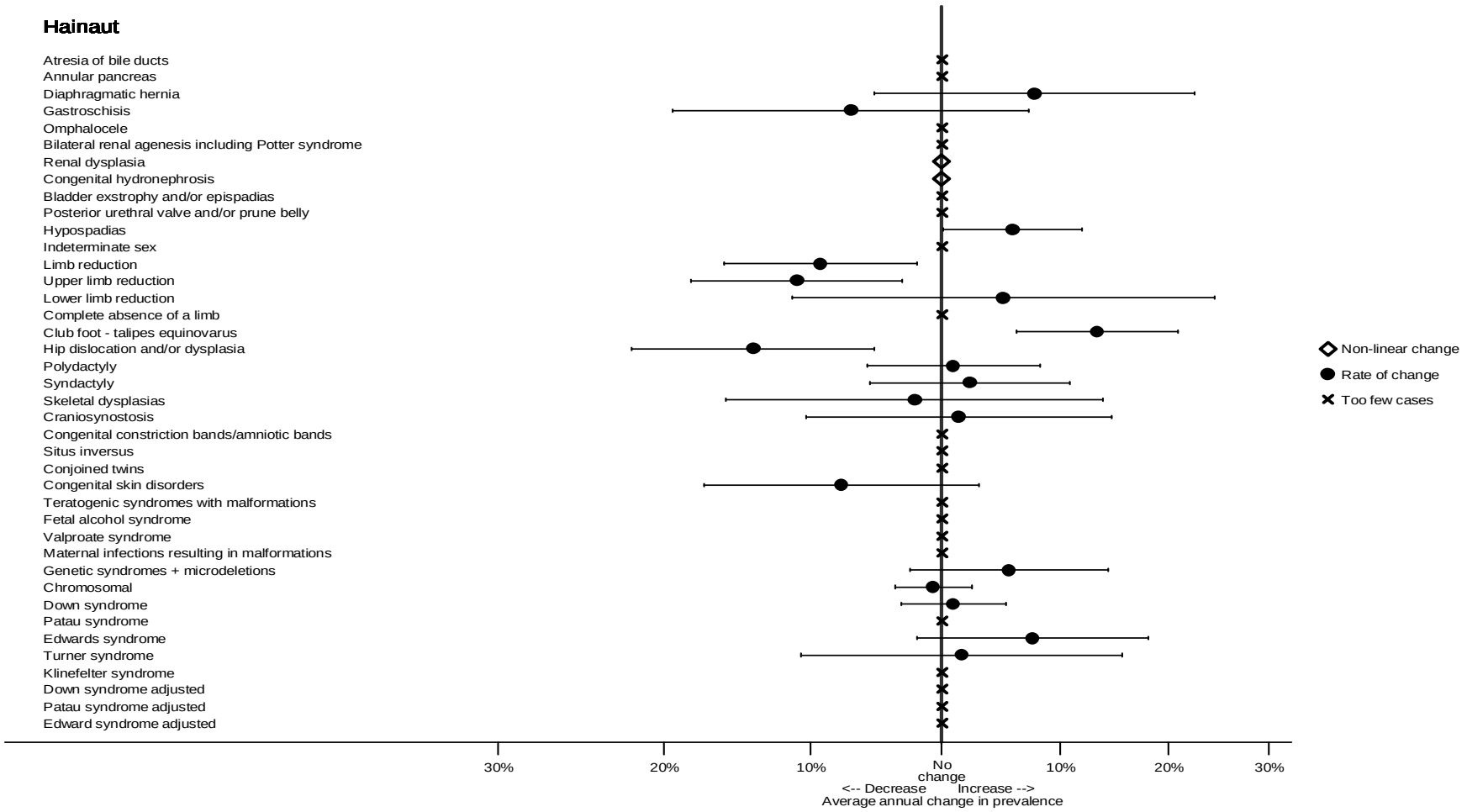

Edward syndrome adjusted [prevalence per 10,000]
SE Ireland [3.8]
Mainz [8.1]
Odense [5.7]
Wessex [5.8]
Tuscany [3.7]
N Netherlands [6.3]
Norway [4.3]
Saxony Anhalt [3.8]
Vaud [6.5]
Hainaut [...]
Zagreb [...]
Malta [...]
S Portugal [...]
Basque Country [...]
Cork and Kerry [...]
Isle de Reunion [...]
Wielkopolska [...]
Hungary [...]
Summary estimate [5.2]
Paris [12]
East Midlands and South Yorkshire [4.4]
Northern England [5.4]
Thames Valley [7.1]
Wales [5.3]
Antwerp [4.1]
Dublin [4.0]
Emilia Romagna [3.8]
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases
order

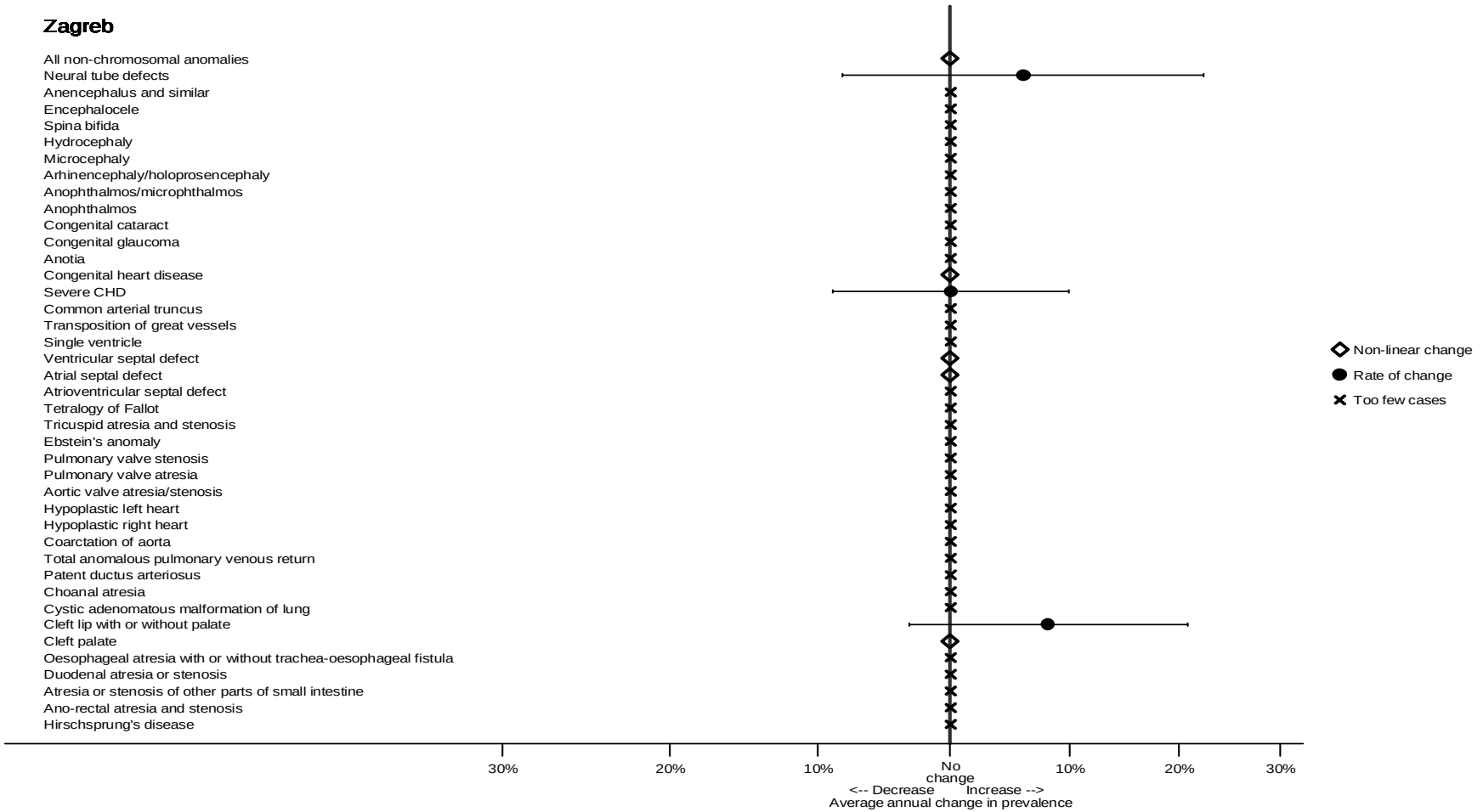
Appendix F: Forest plots showing ten year increasing and decreasing trends detected in the pan-Europe analysis by registry

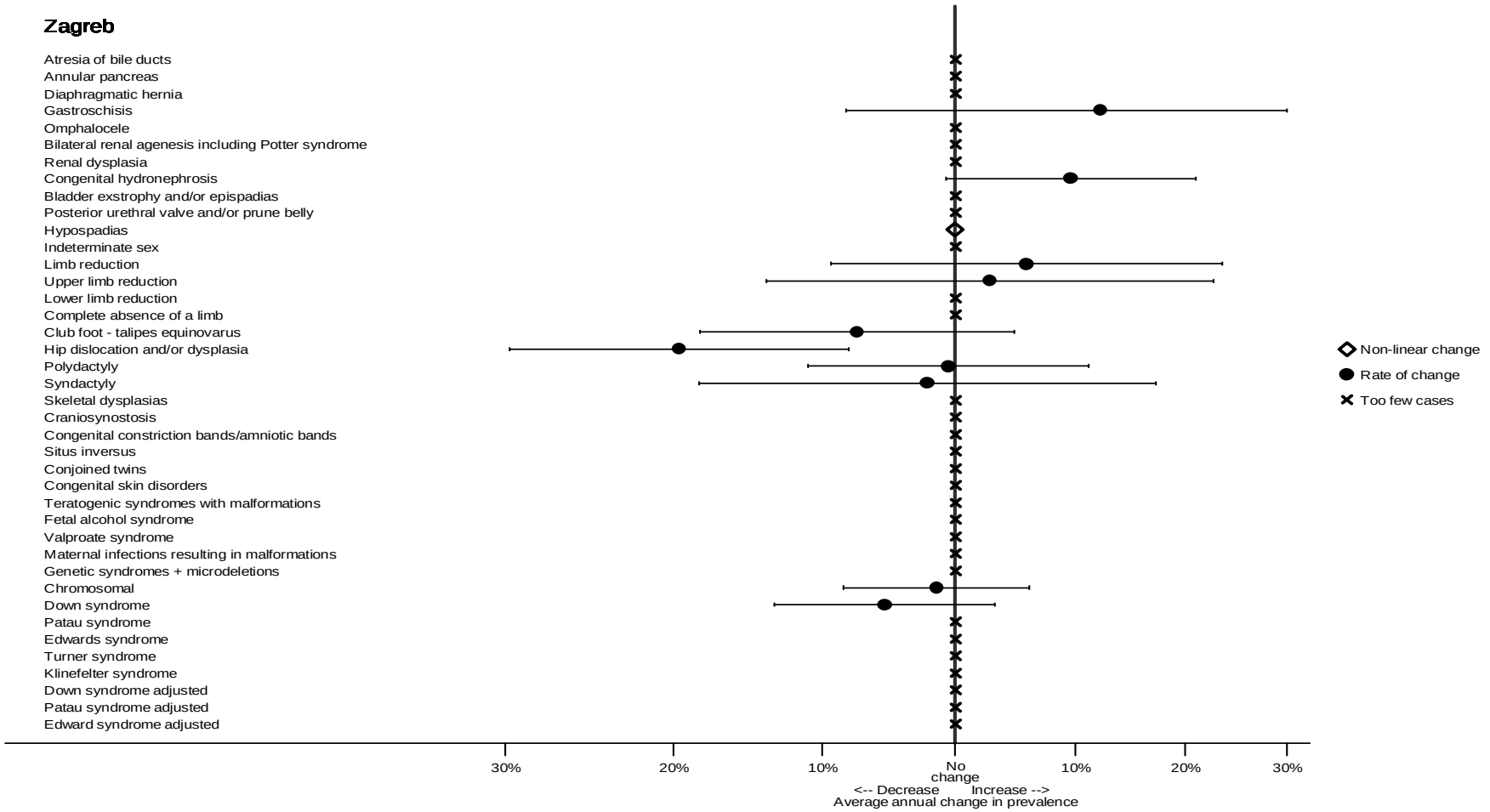


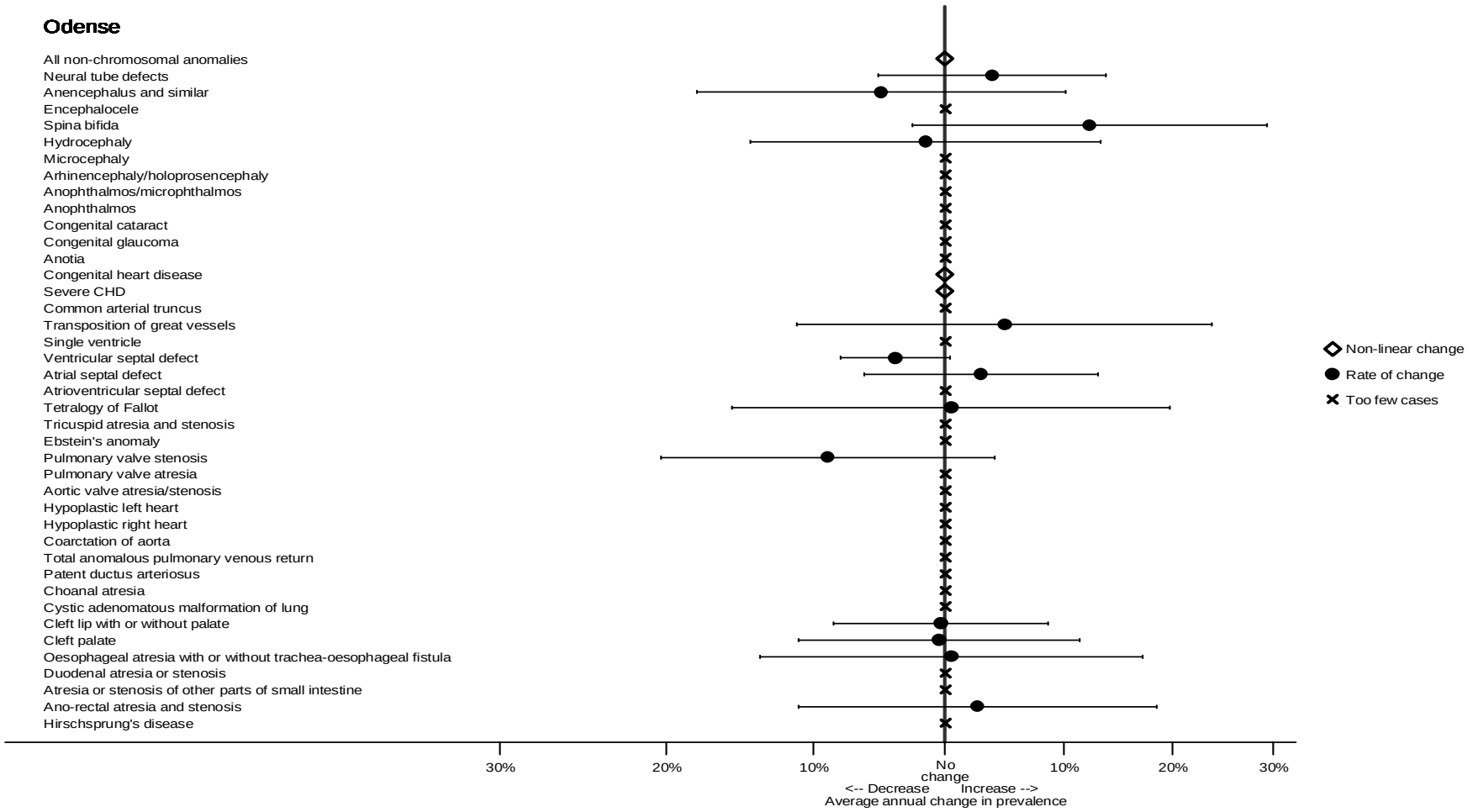

Antwerp
Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb 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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases

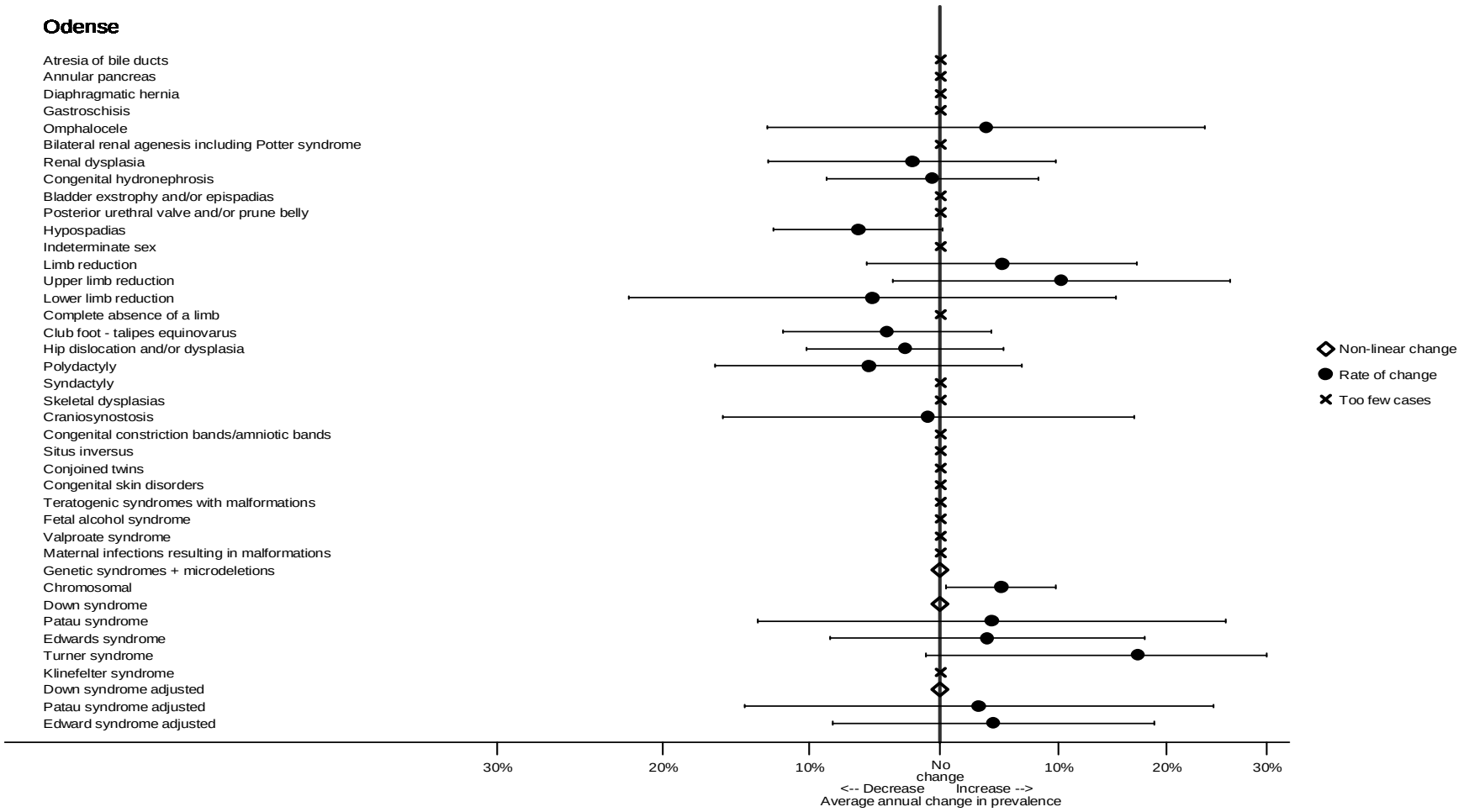

Hainaut
All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
Anophthalmos/microphthalmos
Anophthalmos
Congenital cataract
Congenital glaucoma
Anotia
Congenital heart disease
Severe CHD
Common arterial 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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases

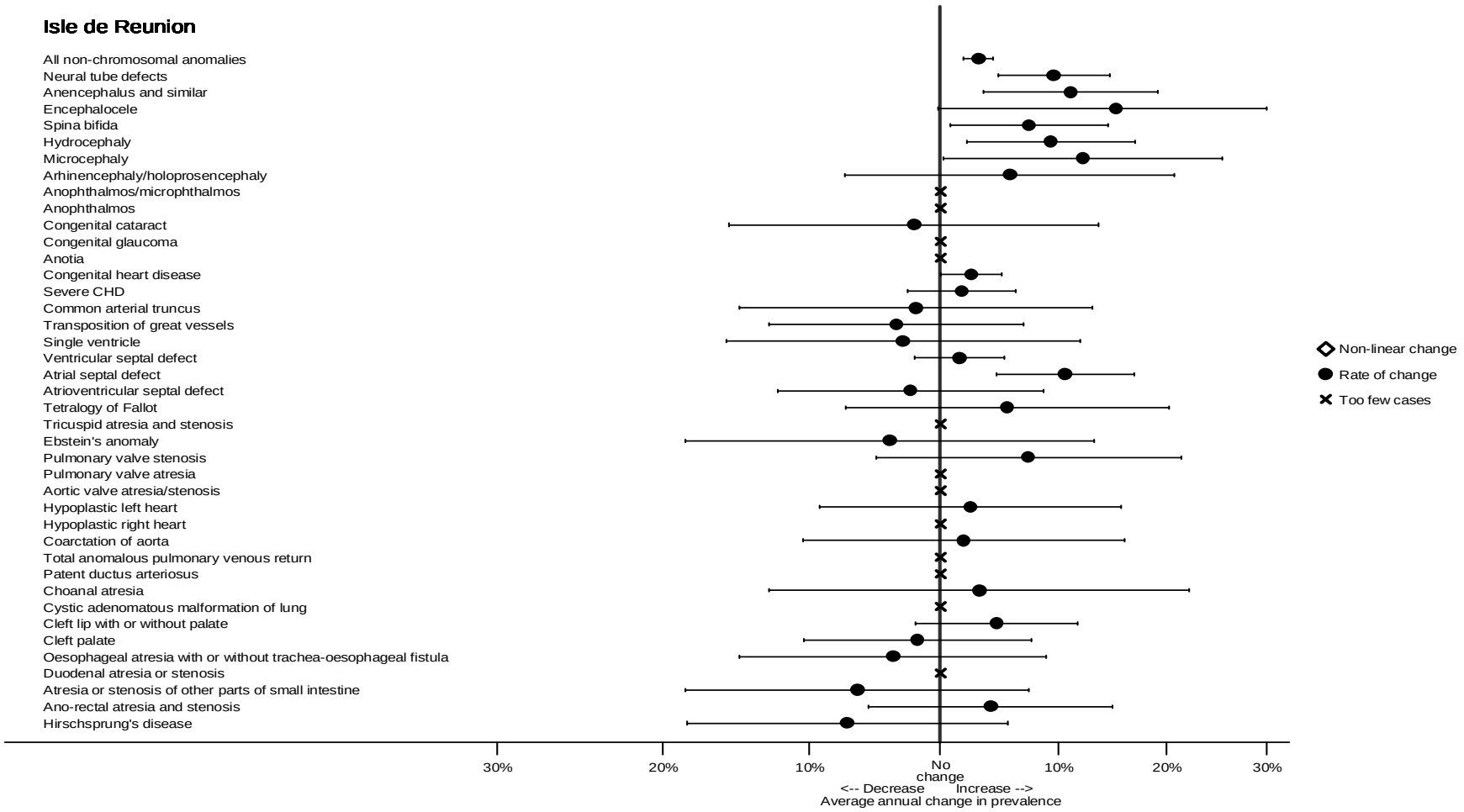

Hainaut
Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb 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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases

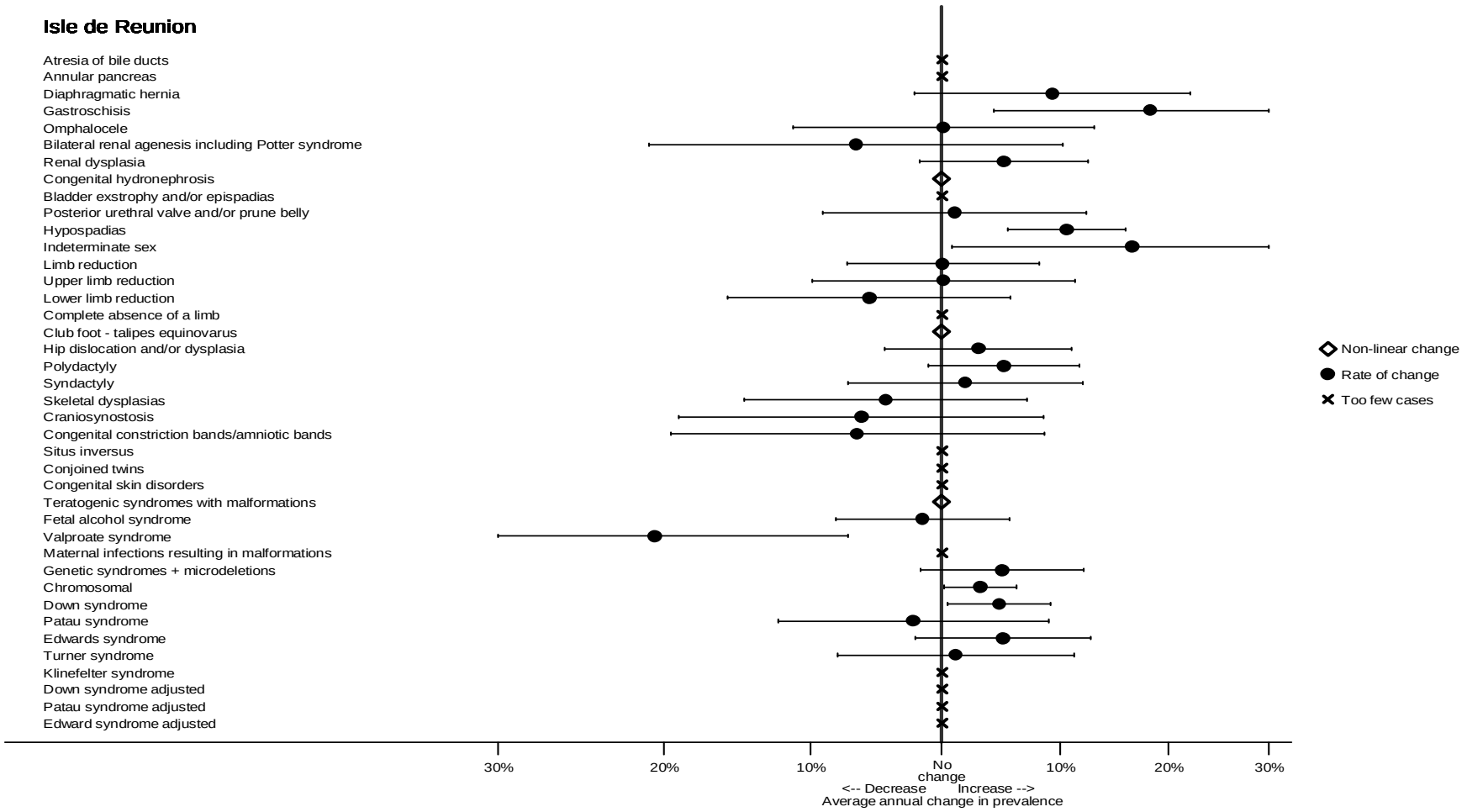

Zagreb
All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
Anophthalmos/microphthalmos
Anophthalmos
Congenital cataract
Congenital glaucoma
Anotia
Congenital heart disease
Severe CHD
Common arterial 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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases

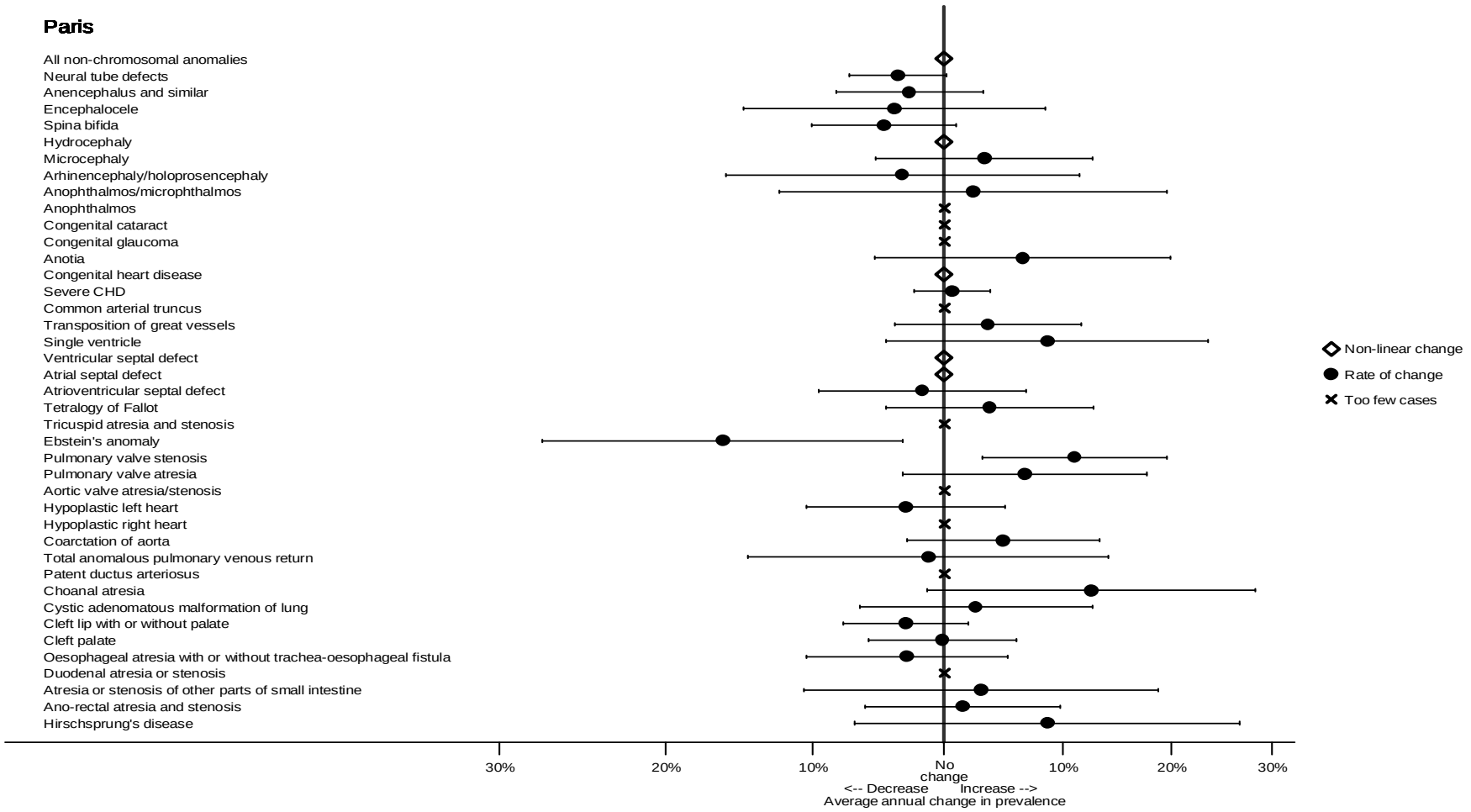

Zagreb
Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
Bladder exstrophy and/or epispadias
Posterior urethral valve and/or prune belly
Hypospadias
Indeterminate sex
Limb 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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Isle de Reunion
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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Isle de Reunion
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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Paris
All non-chromosomal anomalies
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30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
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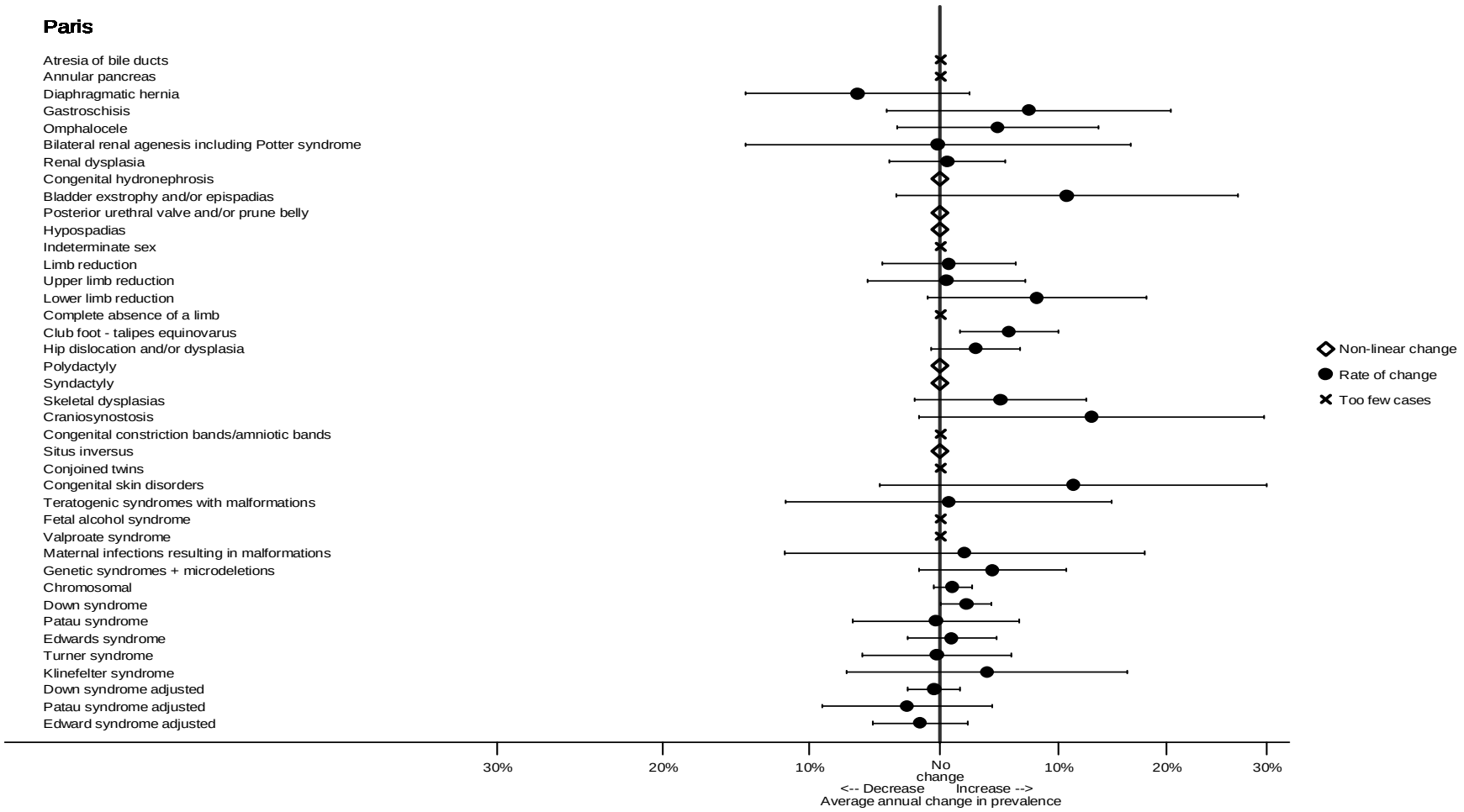
Paris
Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
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Renal dysplasia
Congenital hydronephrosis
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Patau syndrome adjusted
Edward syndrome adjusted
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20%
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Average annual change in prevalence
Non-linear change
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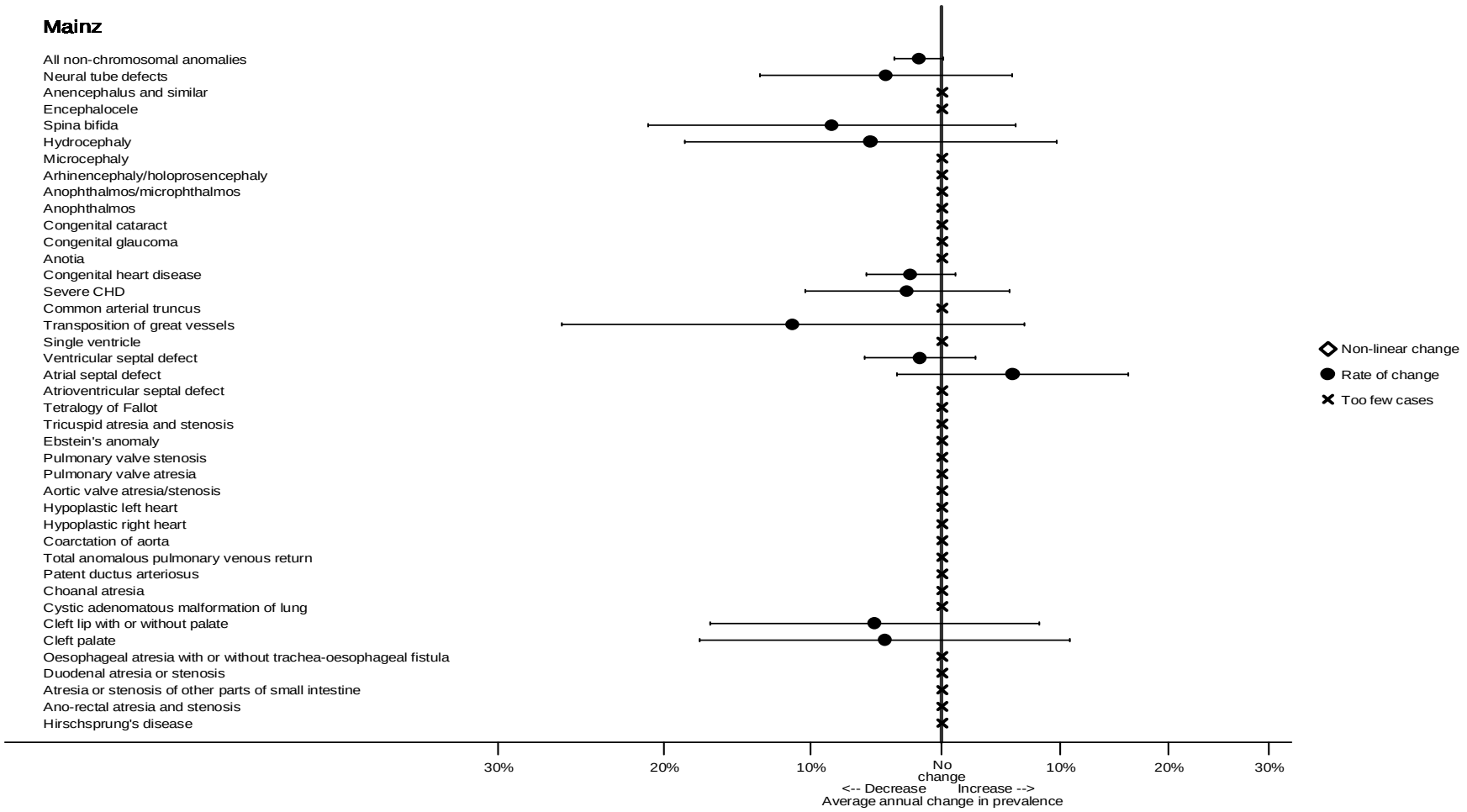
Mainz
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10%
20%
30%
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Increase -->
Average annual change in prevalence
Non-linear change
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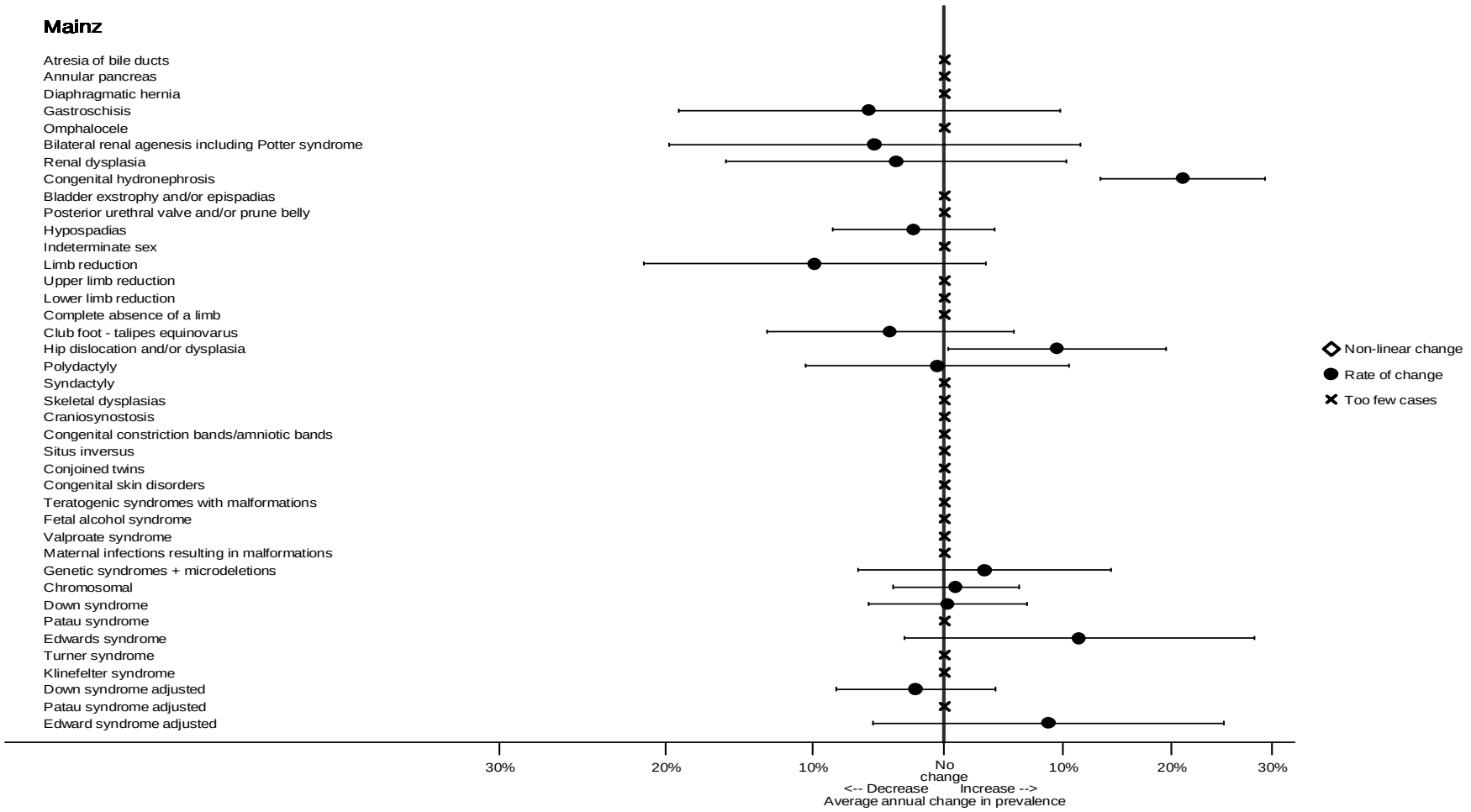
Too few cases


Mainz
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Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
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Renal dysplasia
Congenital hydronephrosis
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Maternal infections resulting in malformations
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Edward syndrome adjusted
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No change
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Average annual change in prevalence
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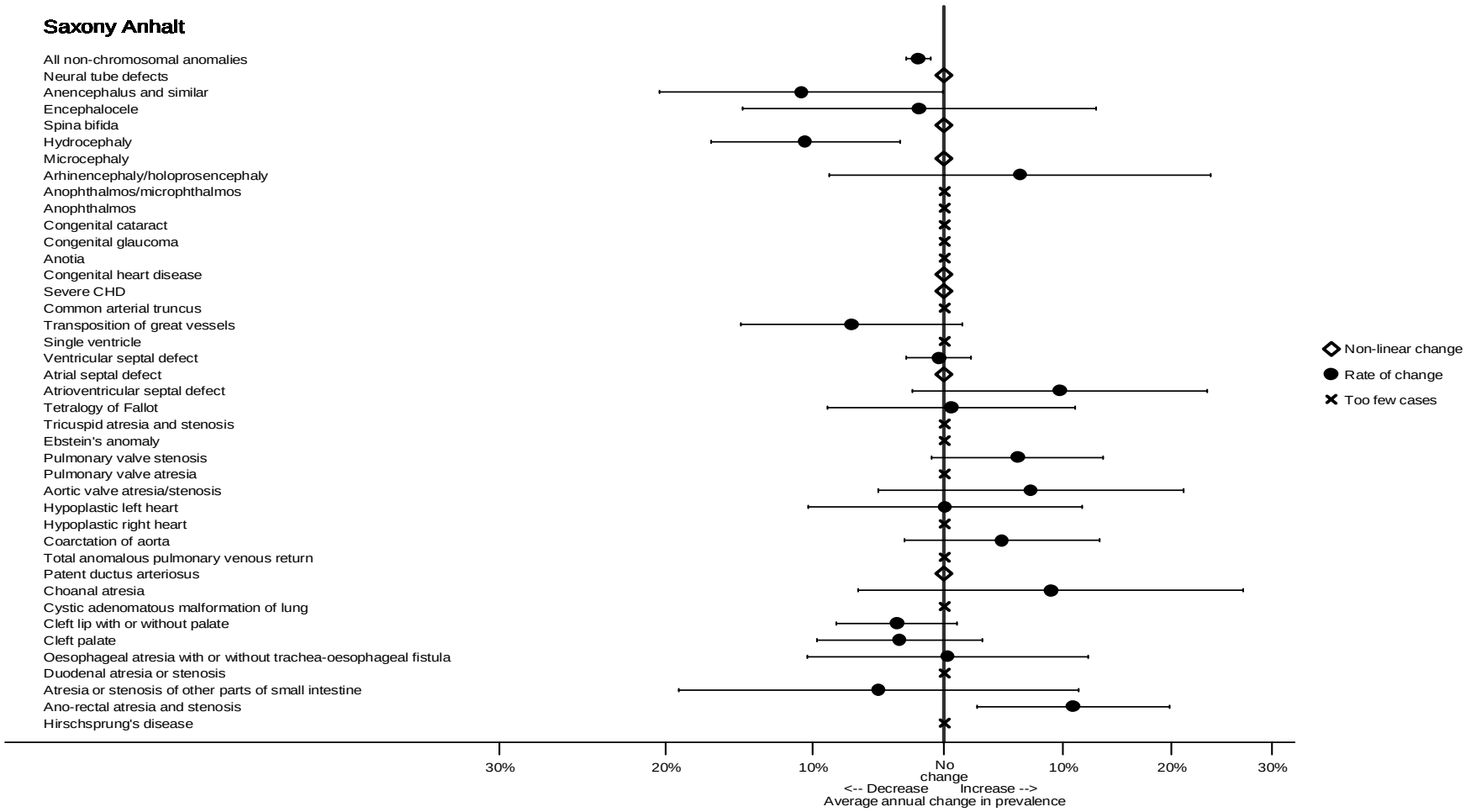
Rate of change
Too few cases


Saxony Anhalt
All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
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Microcephaly
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Ano-rectal atresia and stenosis
Hirschsprung's disease
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20%
10%
No change
10%
20%
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<-- Decrease
Increase -->
Average annual change in prevalence
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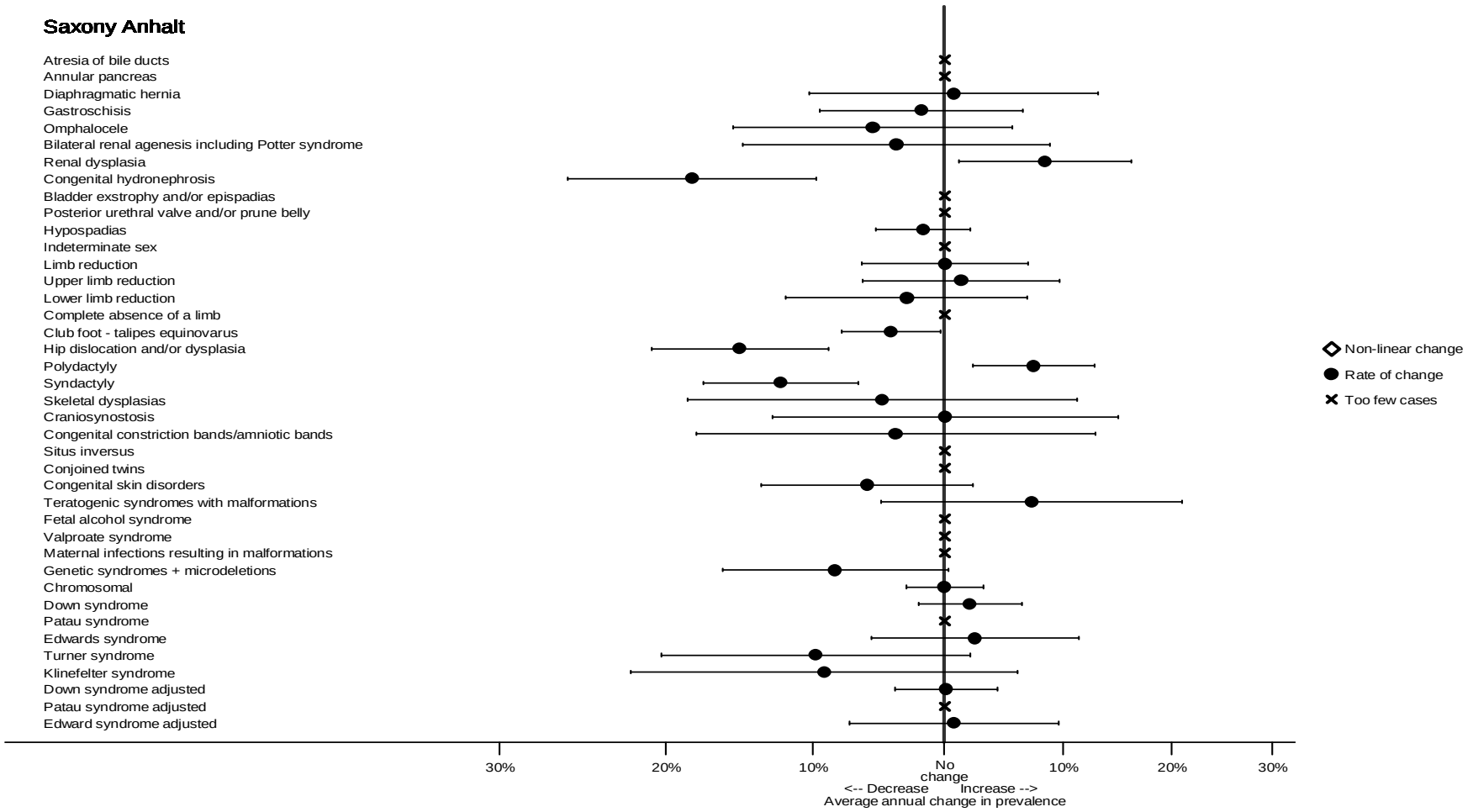
Too few cases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Omphalocele
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Valproate syndrome
Maternal infections resulting in malformations
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Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted
30%
20%
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Average annual change in prevalence
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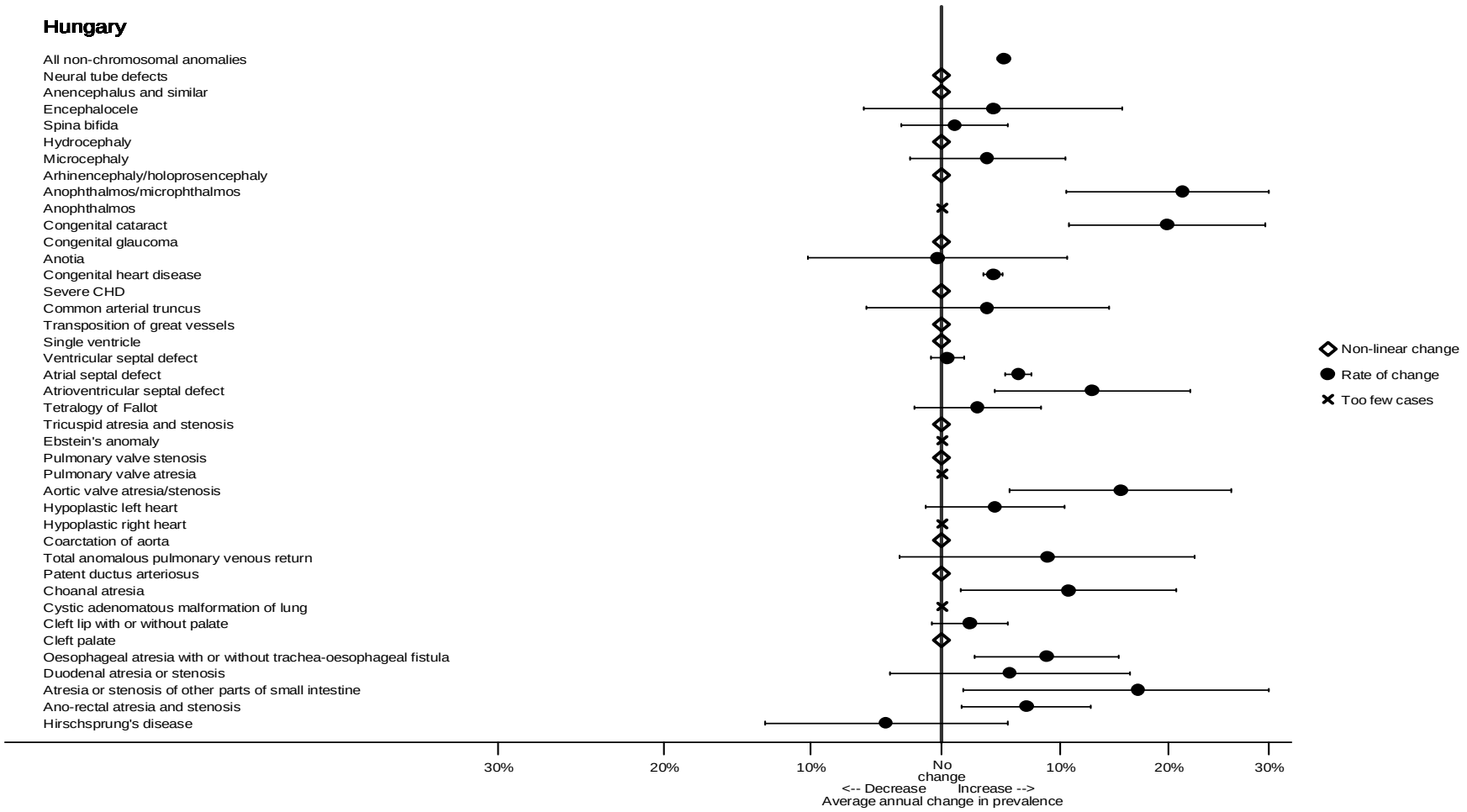
Hungary
All non-chromosomal anomalies
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Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
Anophthalmos/microphthalmos
Anophthalmos
Congenital cataract
Congenital glaucoma
Anotia
Congenital heart disease
Severe CHD
Common arterial truncus
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Hirschsprung's disease
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Average annual change in prevalence
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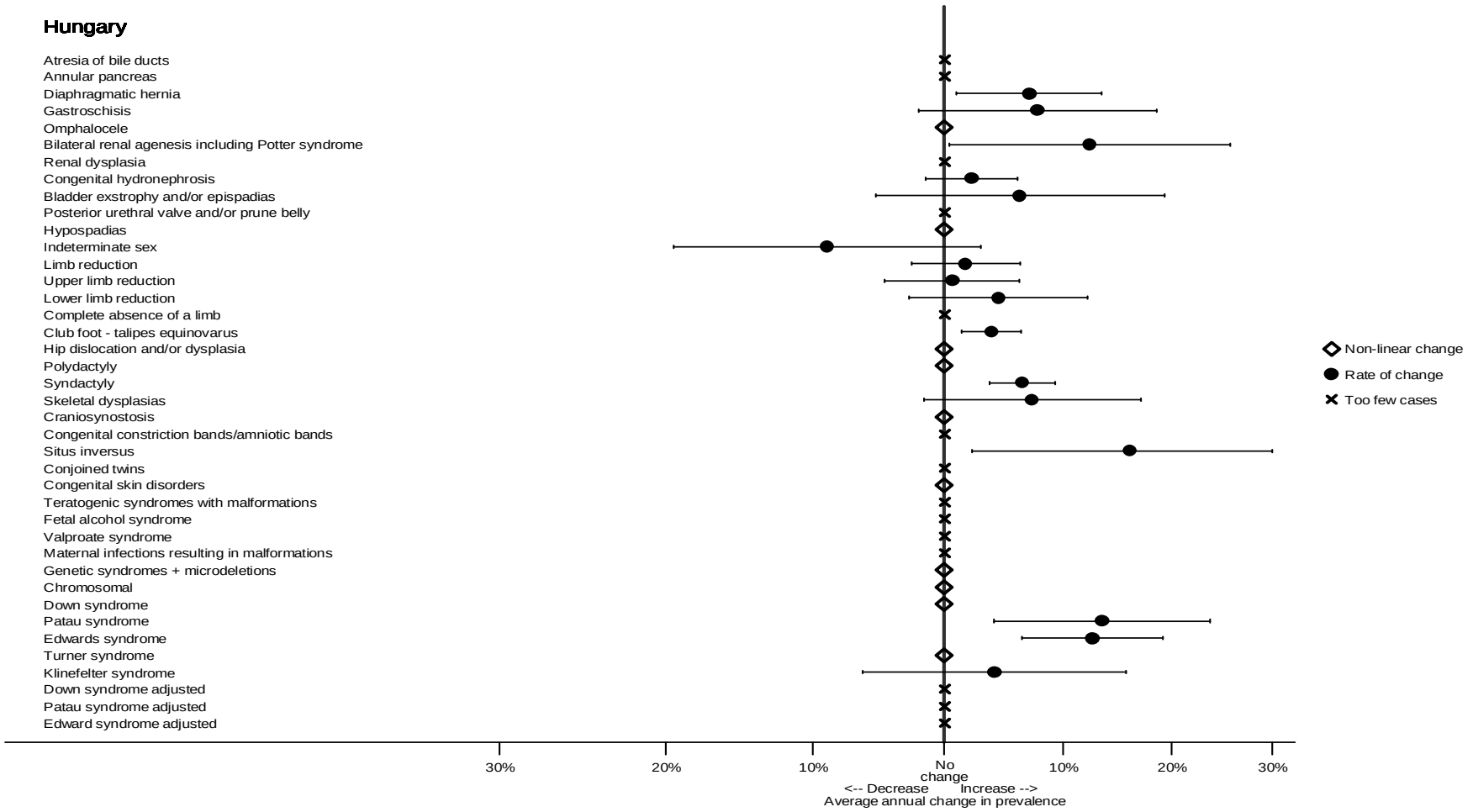
Hungary
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Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
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Renal dysplasia
Congenital hydronephrosis
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Congenital skin disorders
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Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
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Patau syndrome
Edwards syndrome
Turner syndrome
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Edward syndrome adjusted
30%
20%
10%
No change
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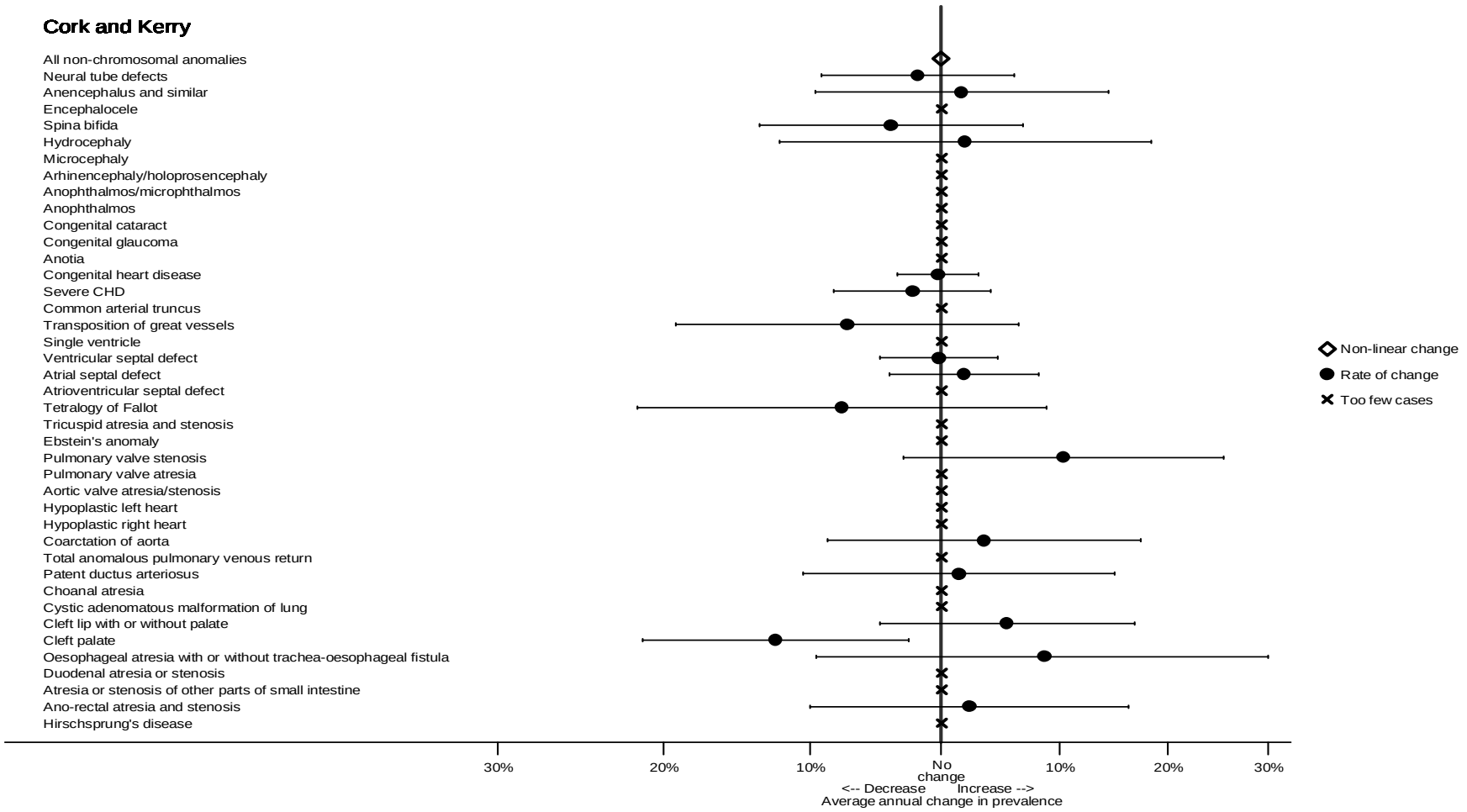
30%
<-- Decrease Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Cork and Kerry
All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
Anophthalmos/microphthalmos
Anophthalmos
Congenital cataract
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Transposition of great vessels
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Hirschsprung's disease
30%
20%
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<-- Decrease
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Average annual change in prevalence
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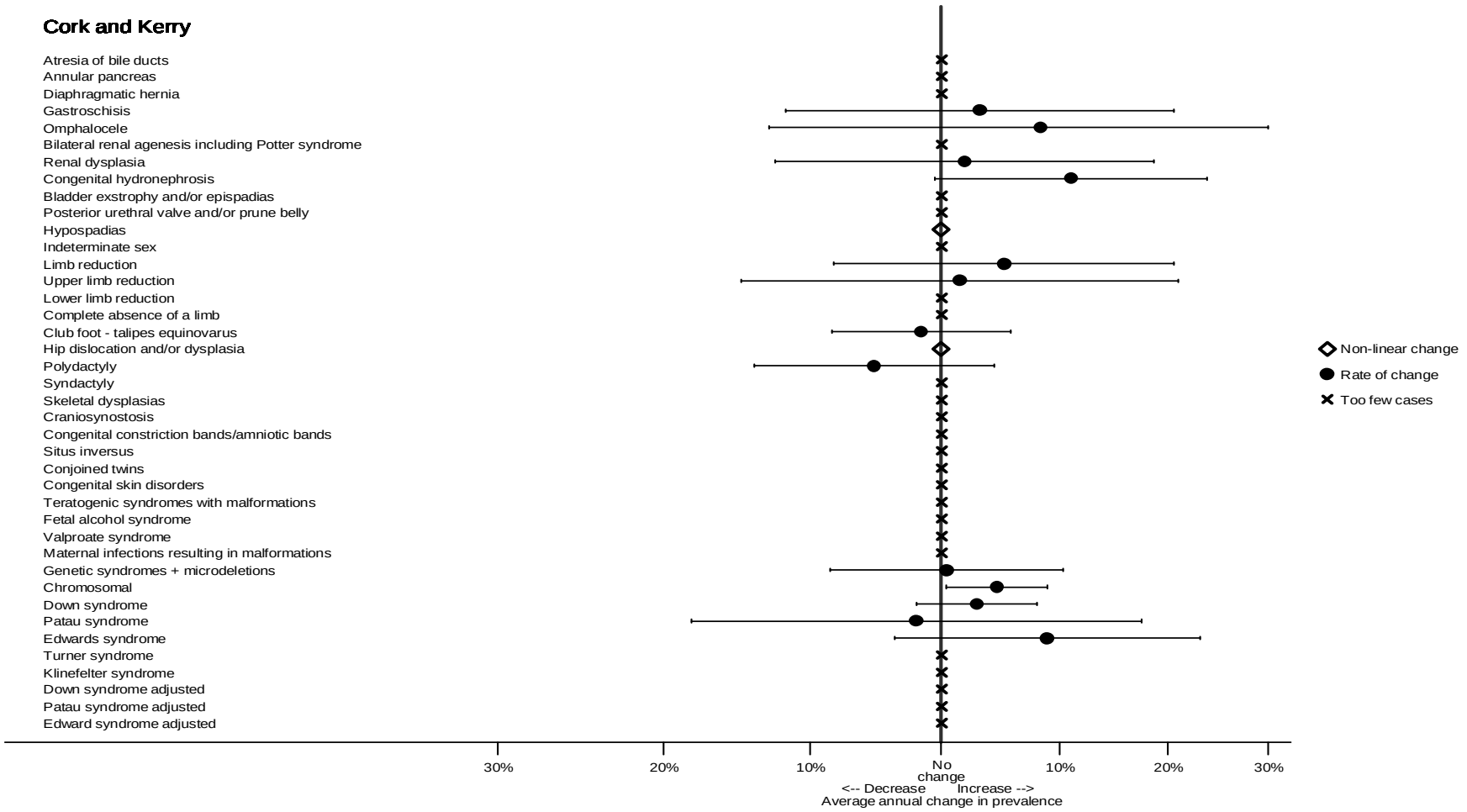
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Congenital hydronephrosis
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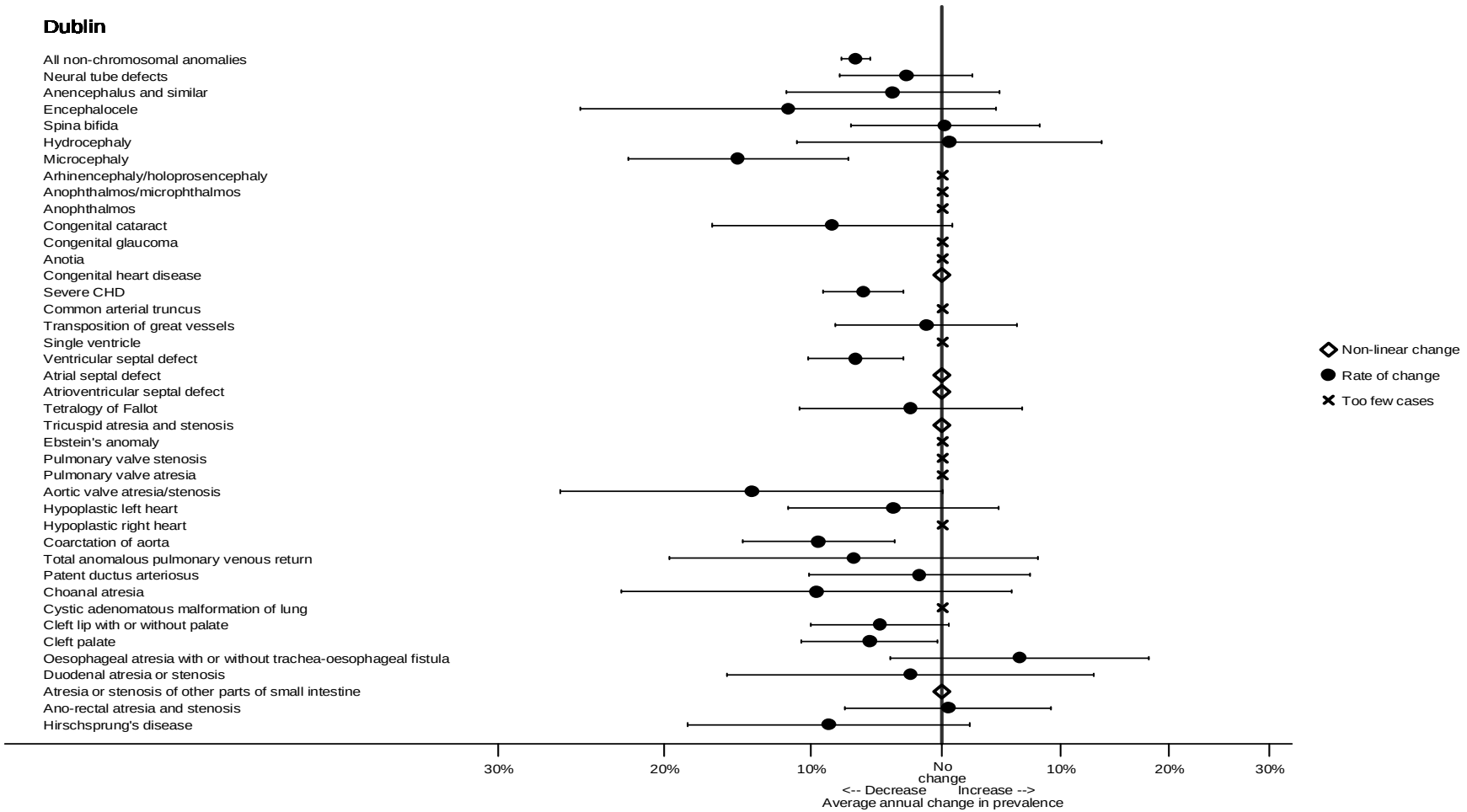
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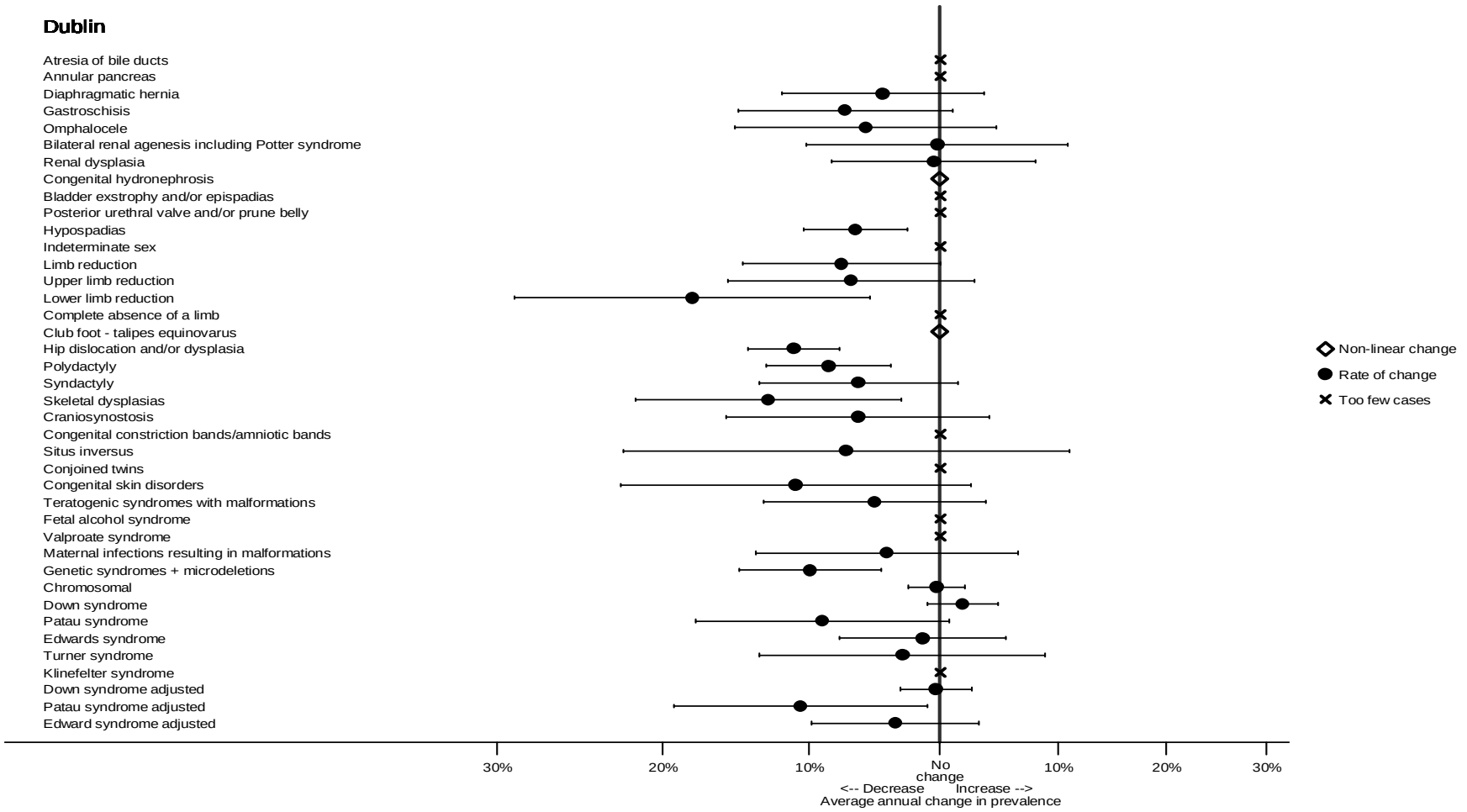
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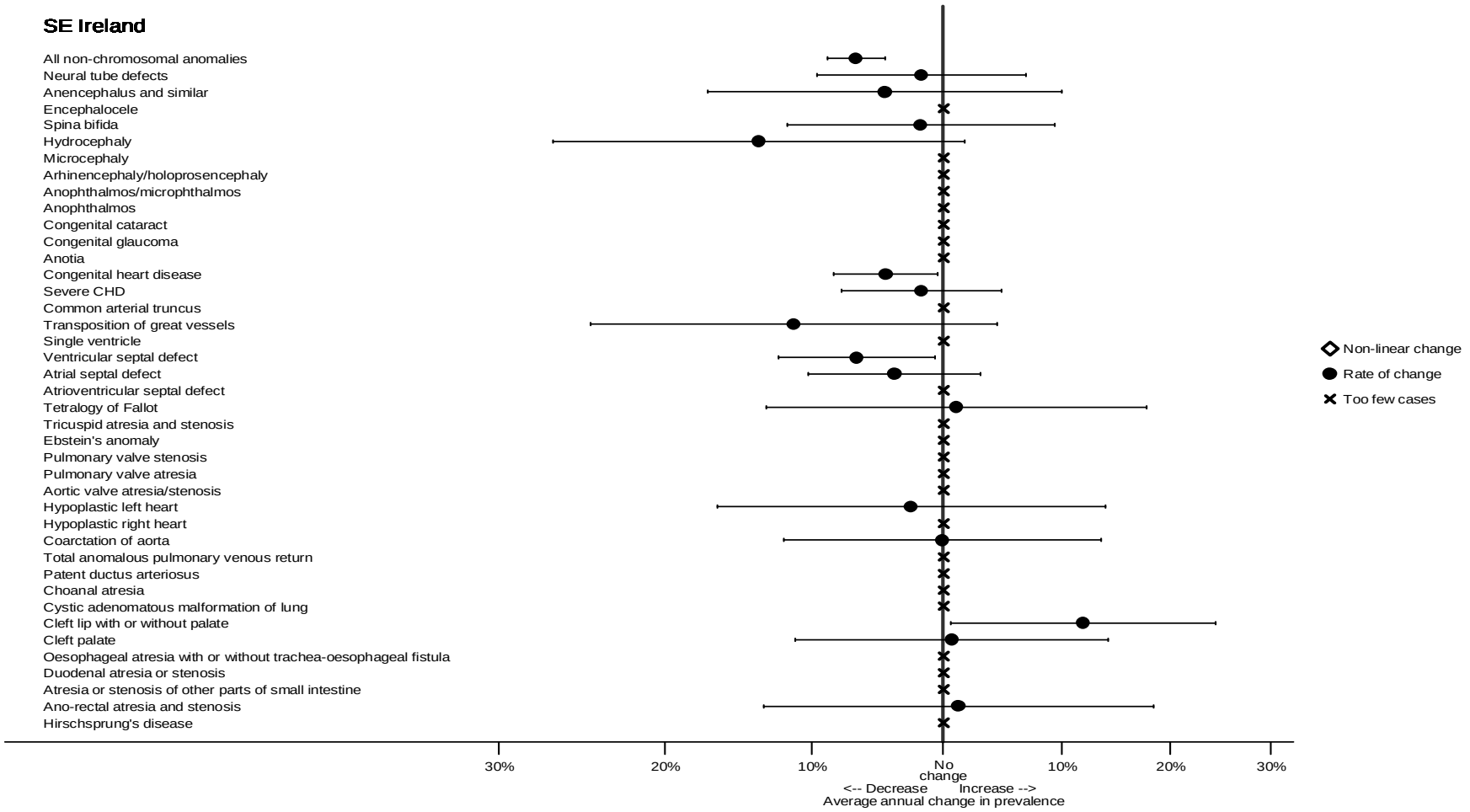
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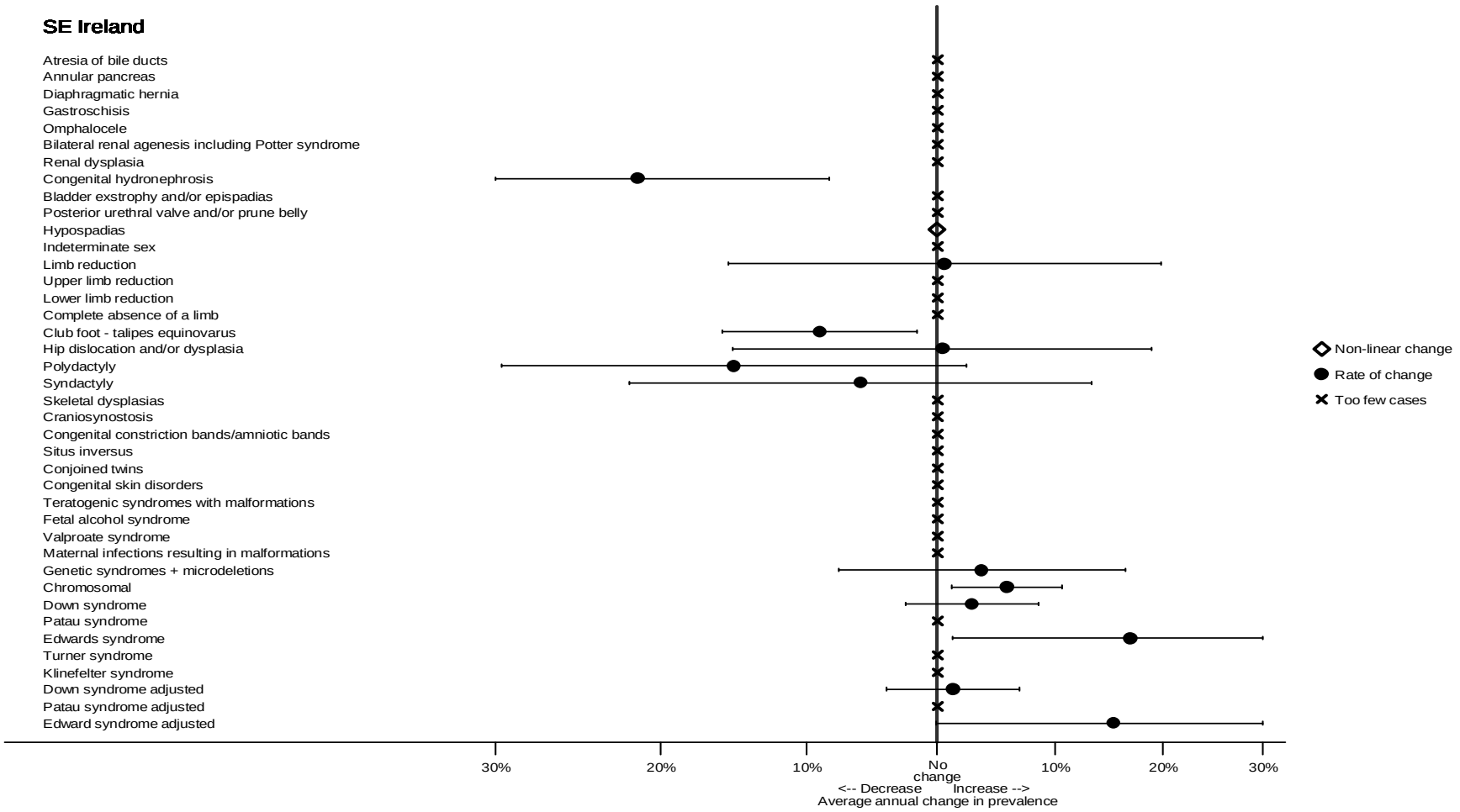
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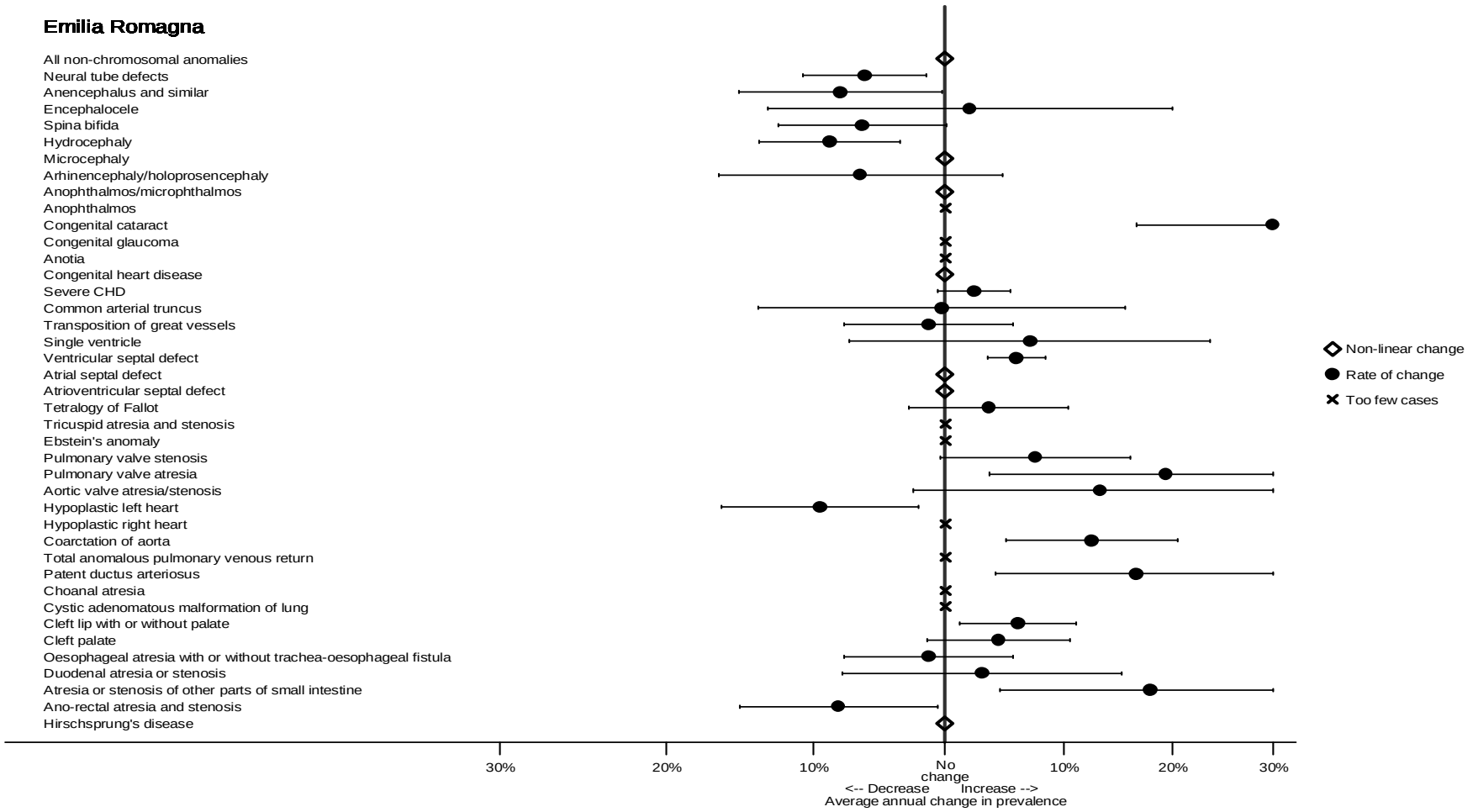
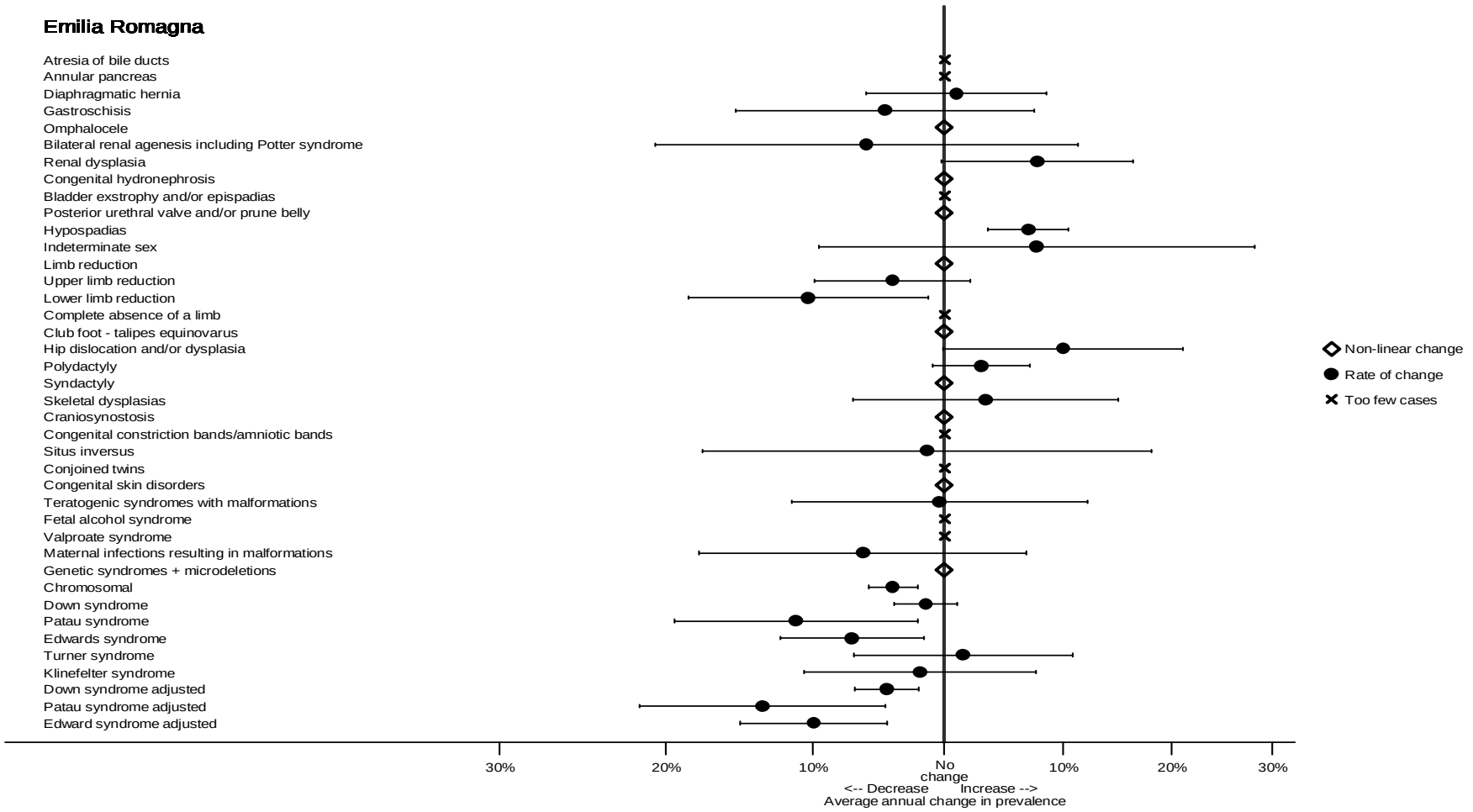
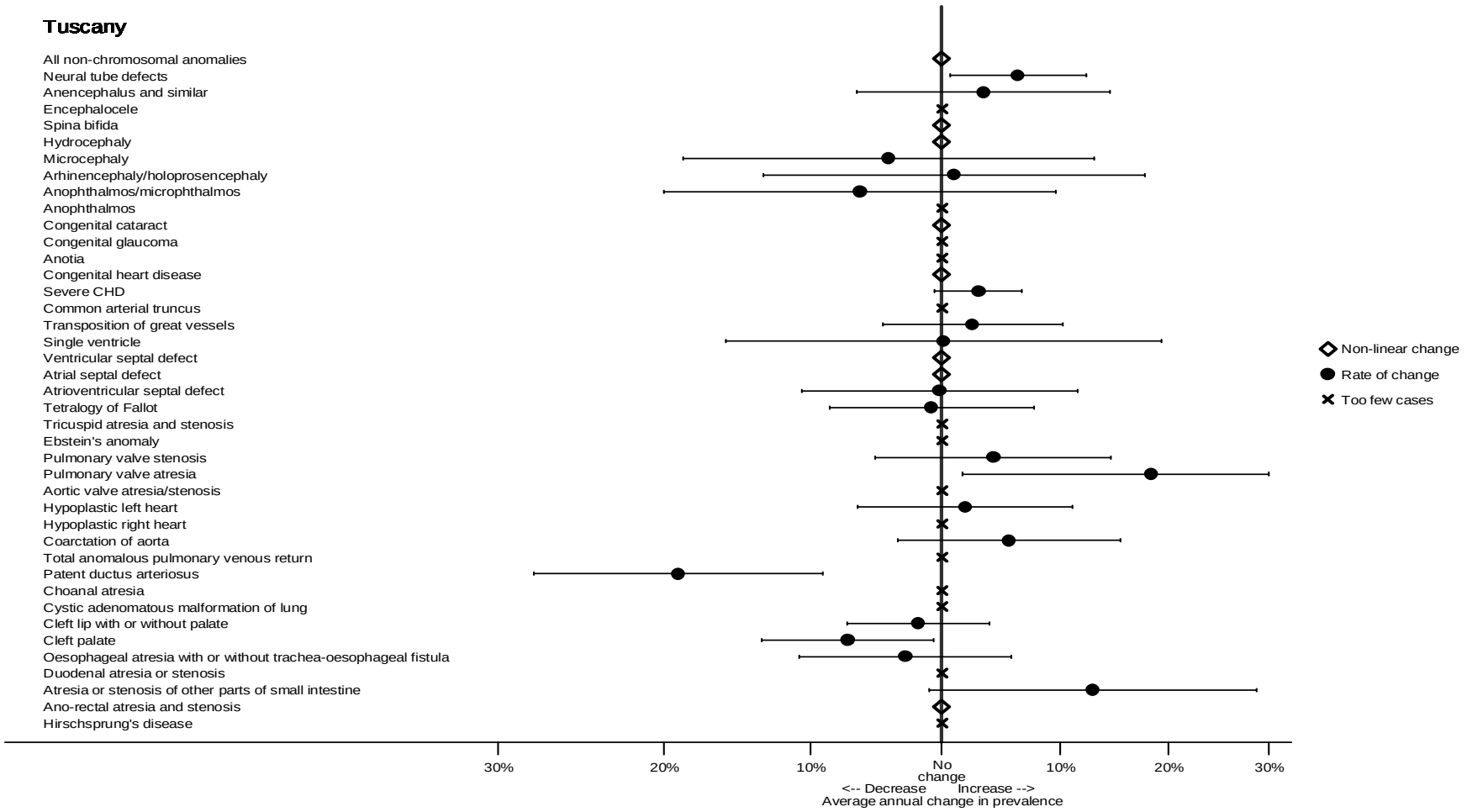
Rate of change
Too few cases


Emilia Romagna
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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Emilia Romagna
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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Tuscany
All non-chromosomal anomalies
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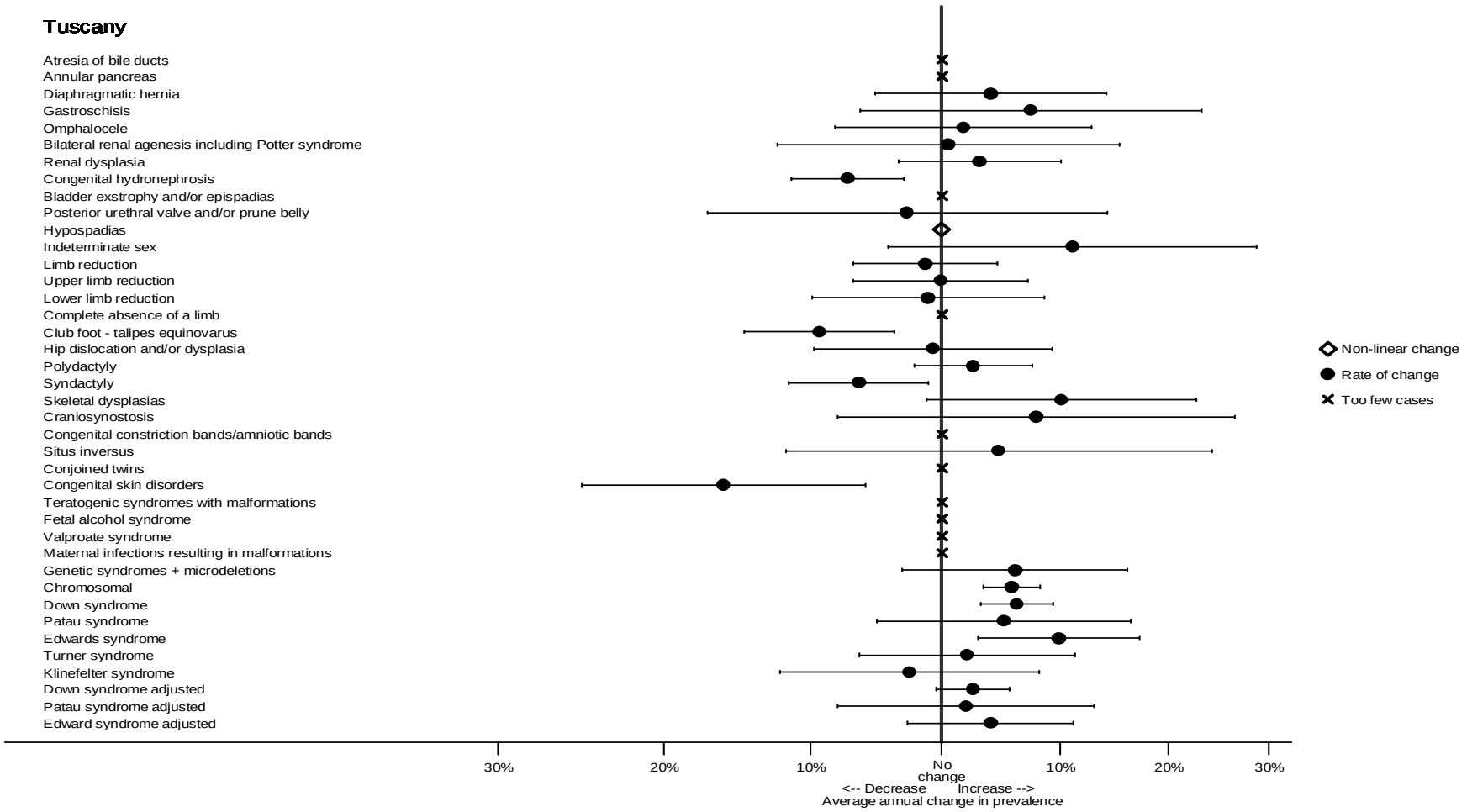
Hirschsprung's disease
30%
20%
10%
No change
10%
20%
30%
<-- Decrease Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases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Diaphragmatic hernia
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Edward syndrome adjusted
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20%
10%
No change
10%
20%
30%
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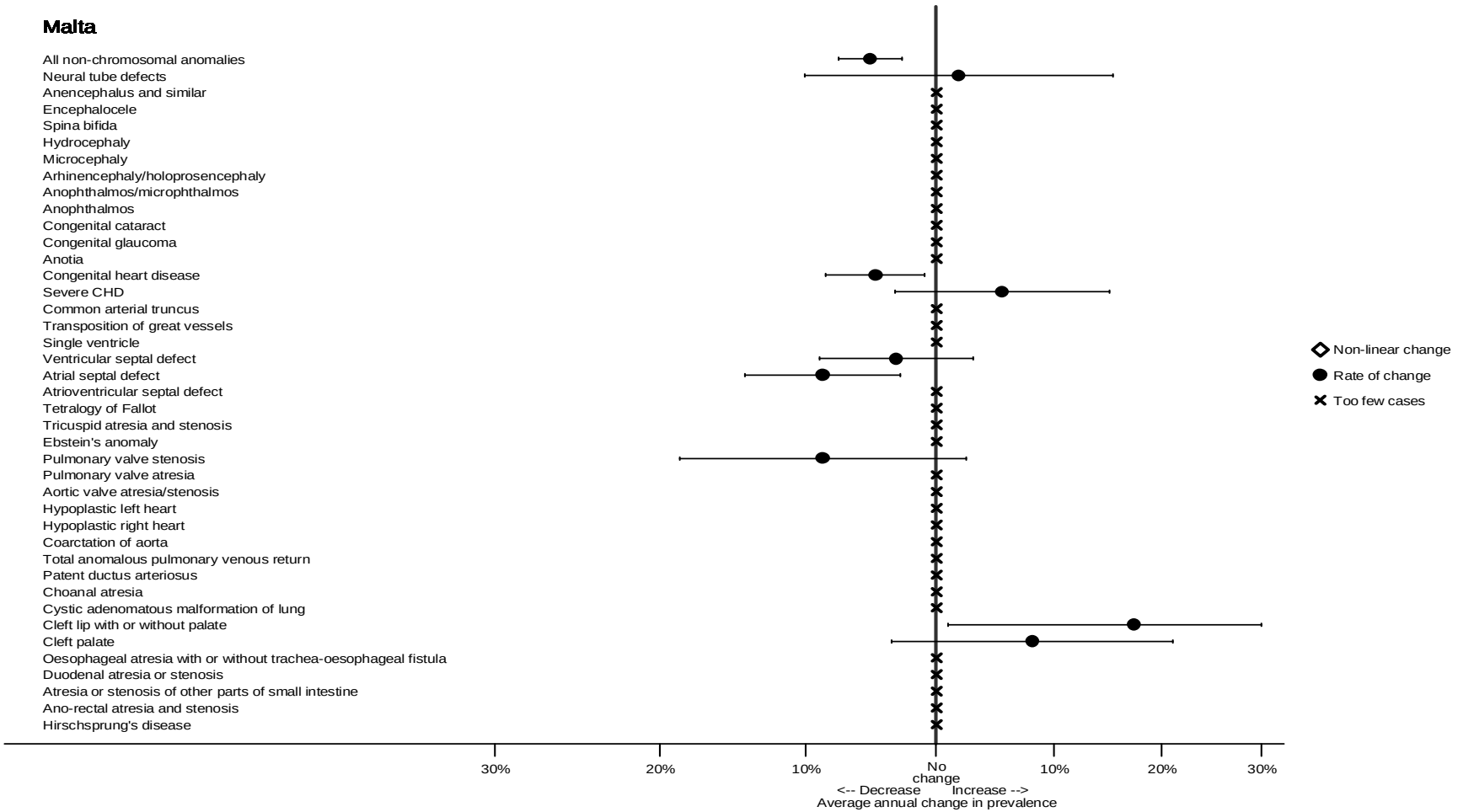
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Malta
All non-chromosomal anomalies
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20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
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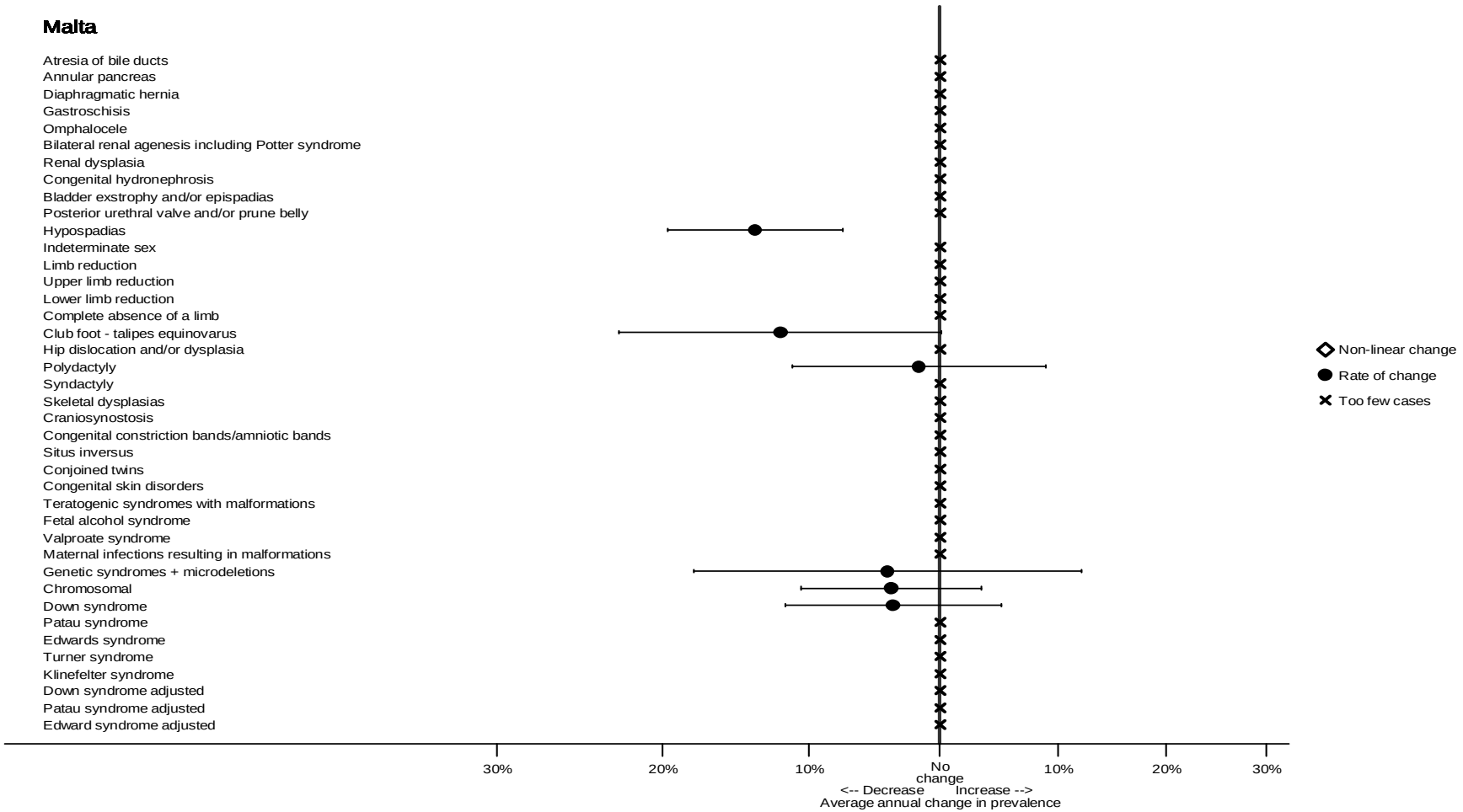
Rate of change
Too few cases


Malta
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Annular pancreas
Diaphragmatic hernia
Gastroschisis
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Renal dysplasia
Congenital hydronephrosis
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Maternal infections resulting in malformations
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Increase -->
Average annual change in prevalence
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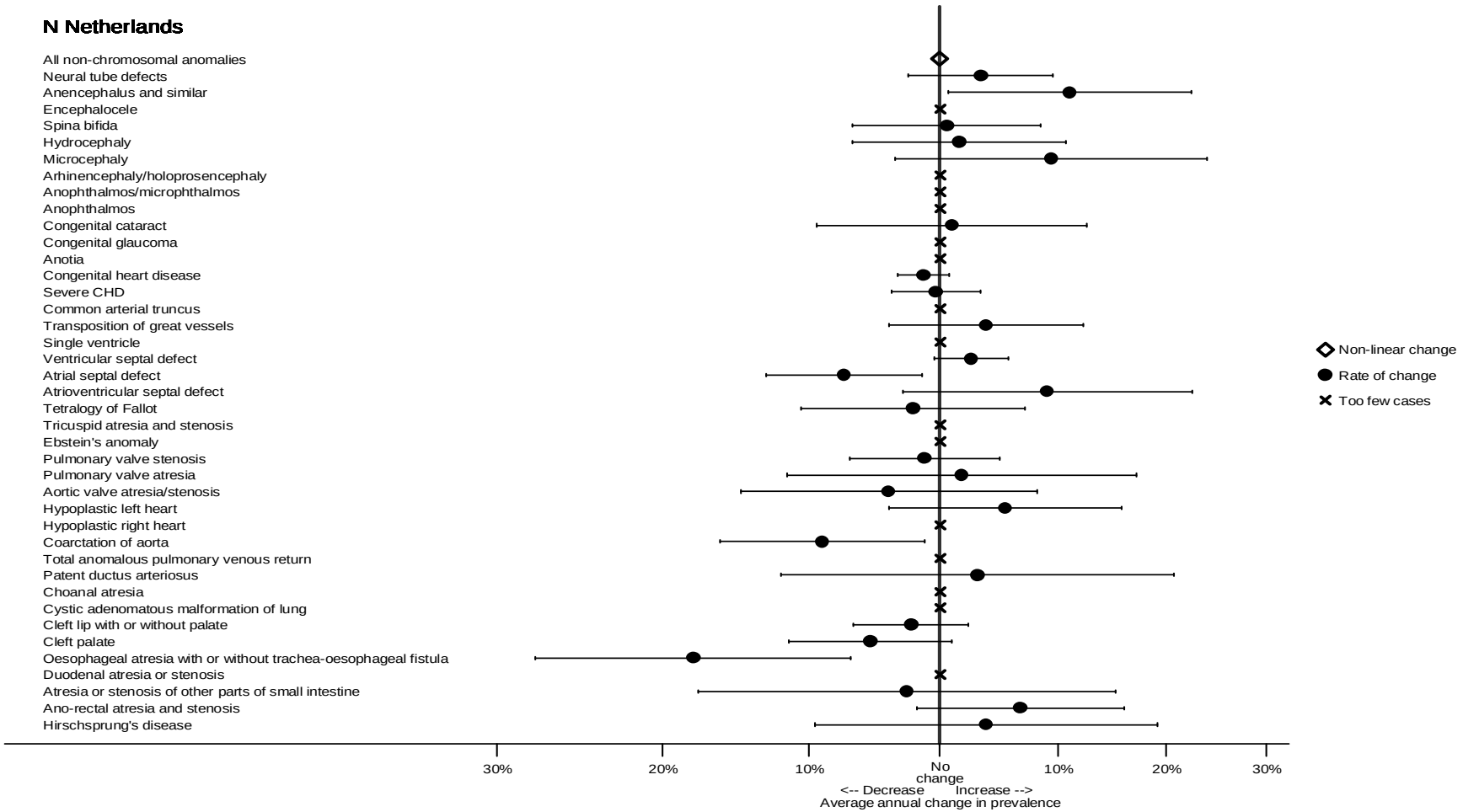
N Netherlands
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Hirschsprung's disease
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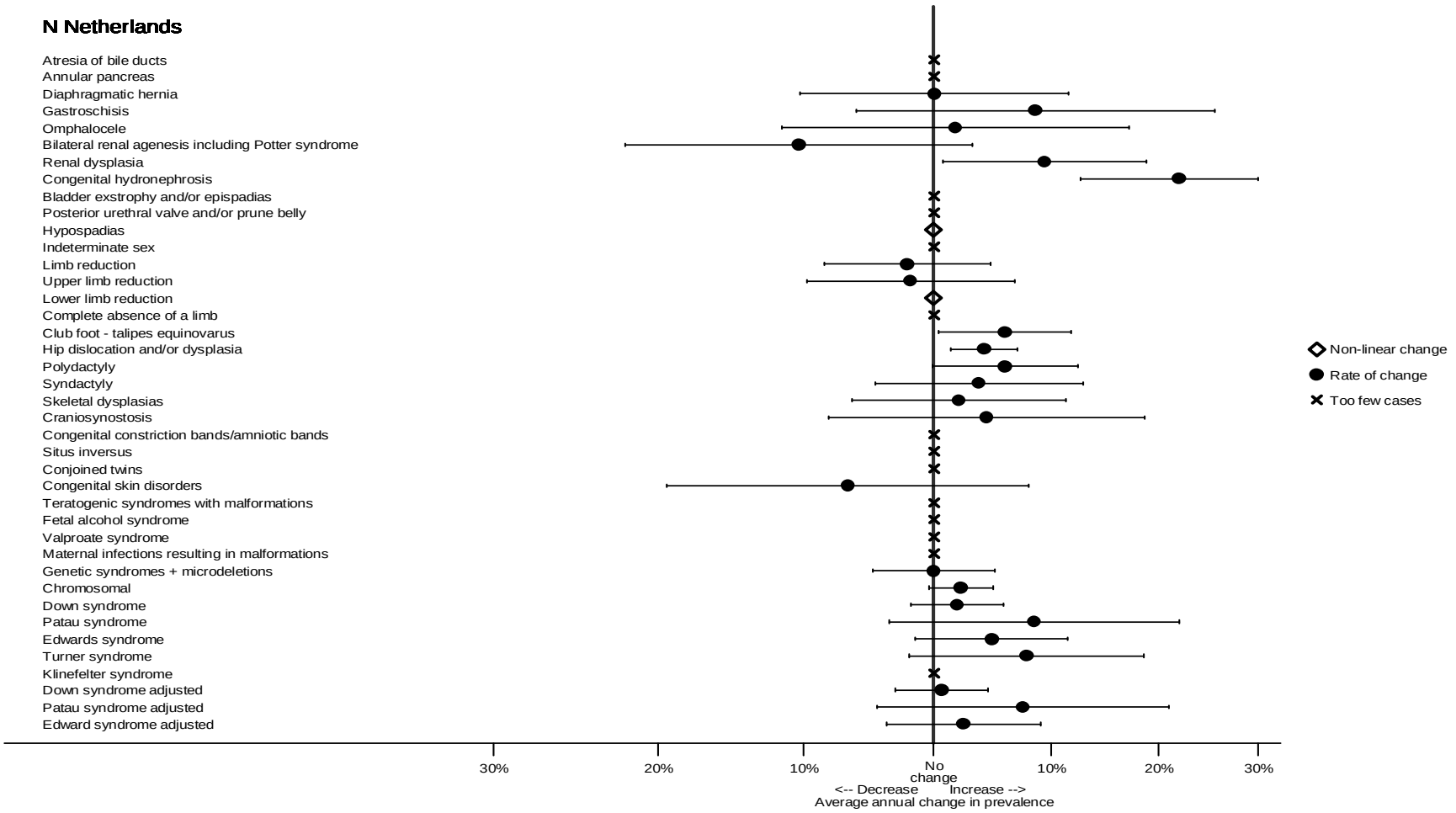
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases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20%
10%
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30%
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Average annual change in prevalence
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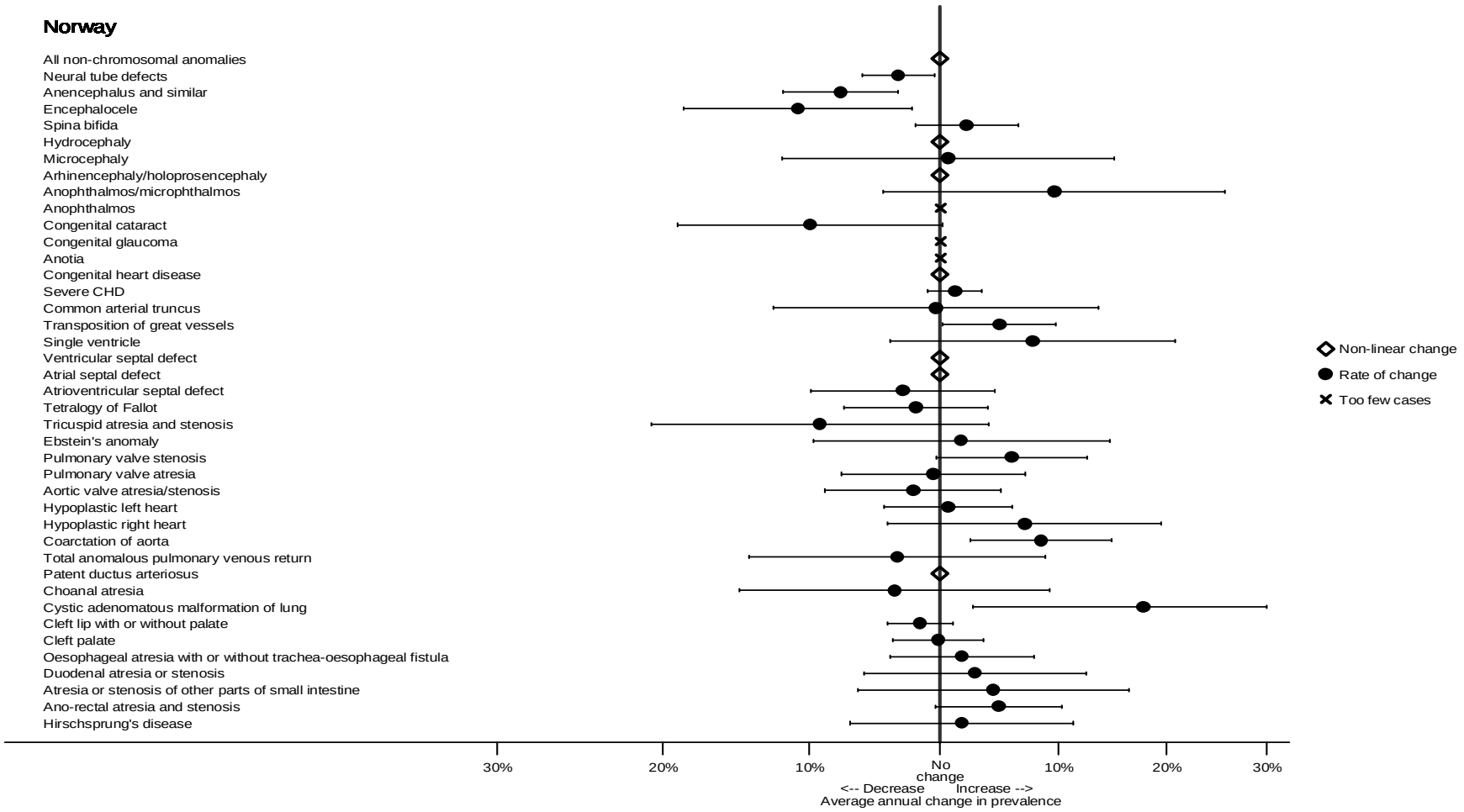
Norway
All non-chromosomal anomalies
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Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
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Anophthalmos/microphthalmos
Anophthalmos
Congenital cataract
Congenital glaucoma
Anotia
Congenital heart disease
Severe CHD
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30%
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10%
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Increase -->
Average annual change in prevalence
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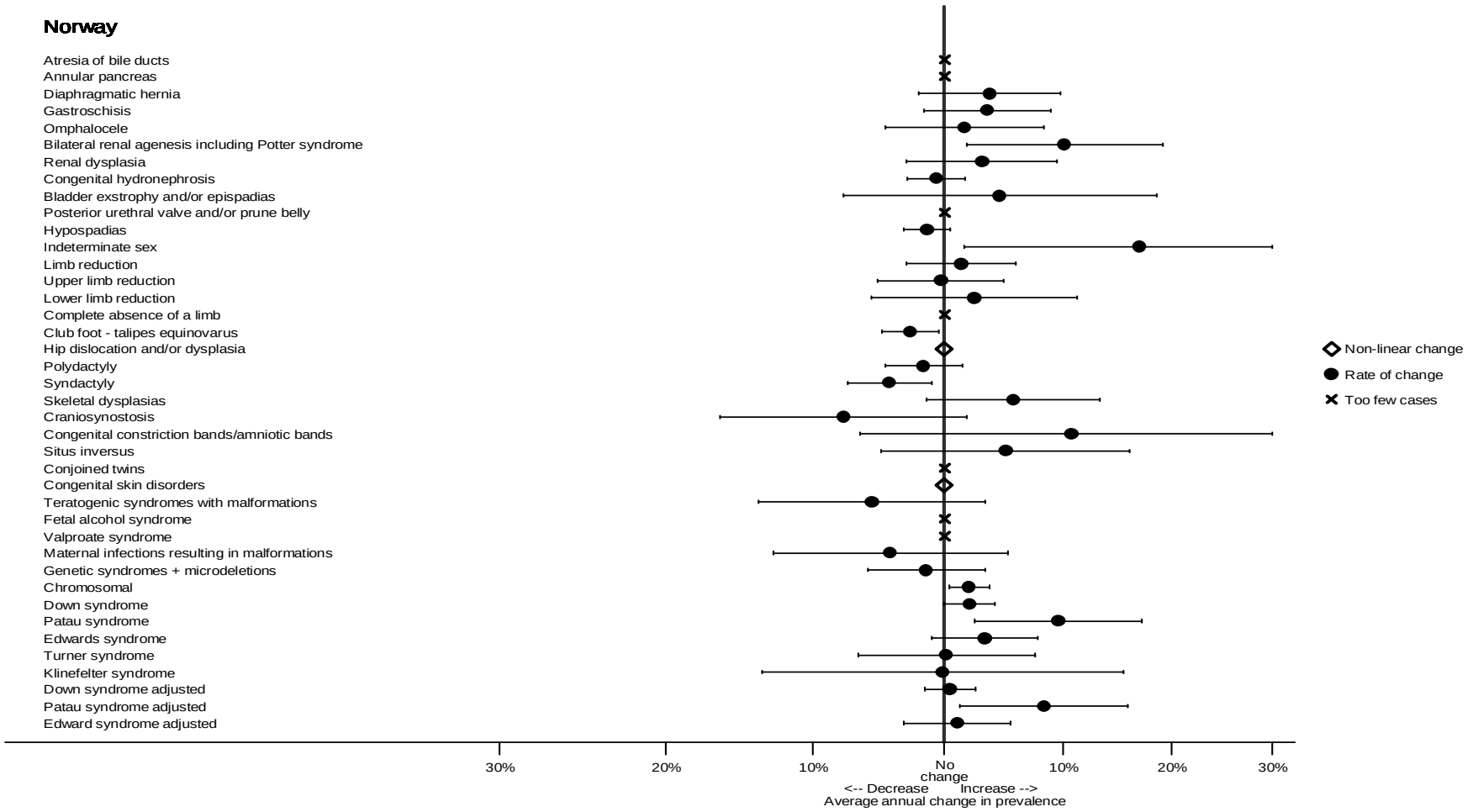
Too few cases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Renal dysplasia
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Congenital skin disorders
Teratogenic syndromes with malformations
Fetal alcohol syndrome
Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
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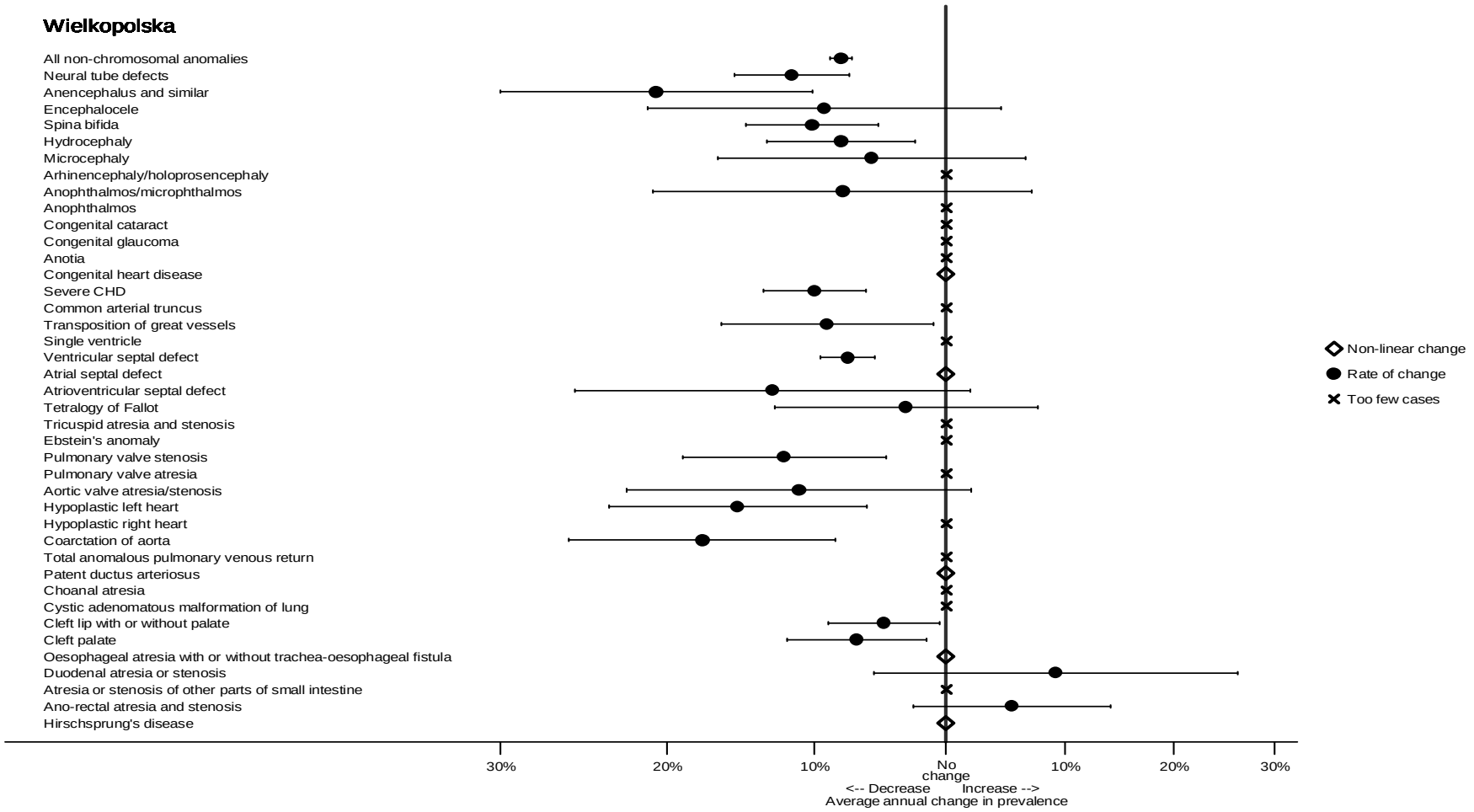
Down syndrome
Patau syndrome
Edwards syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted
Non-linear change
Rate of change
Too few cases
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence


Wielkopolska
All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
Anophthalmos/microphthalmos
Anophthalmos
Congenital cataract
Congenital glaucoma
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Hirschsprung's disease
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20%
10%
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30%
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Average annual change in prevalence
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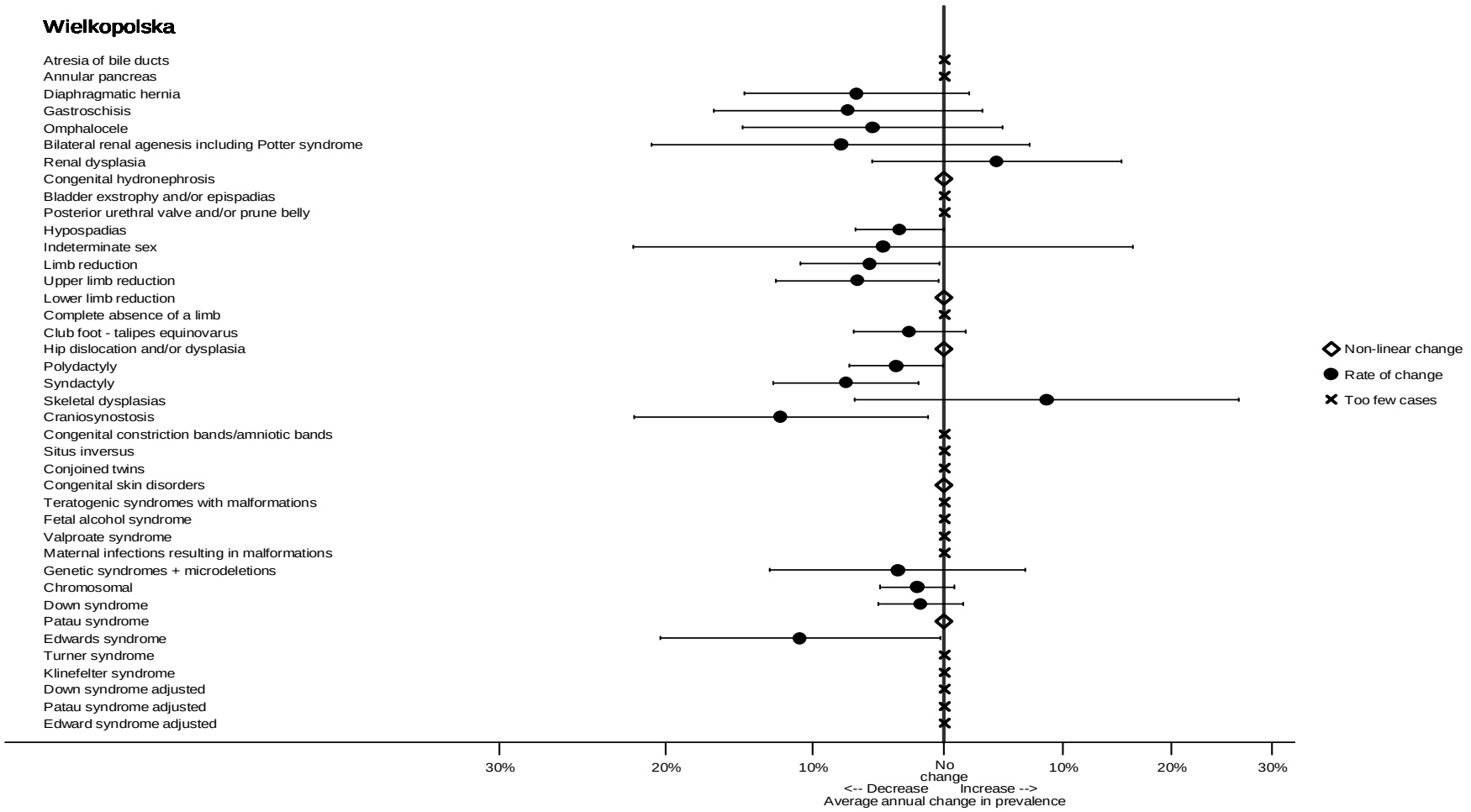
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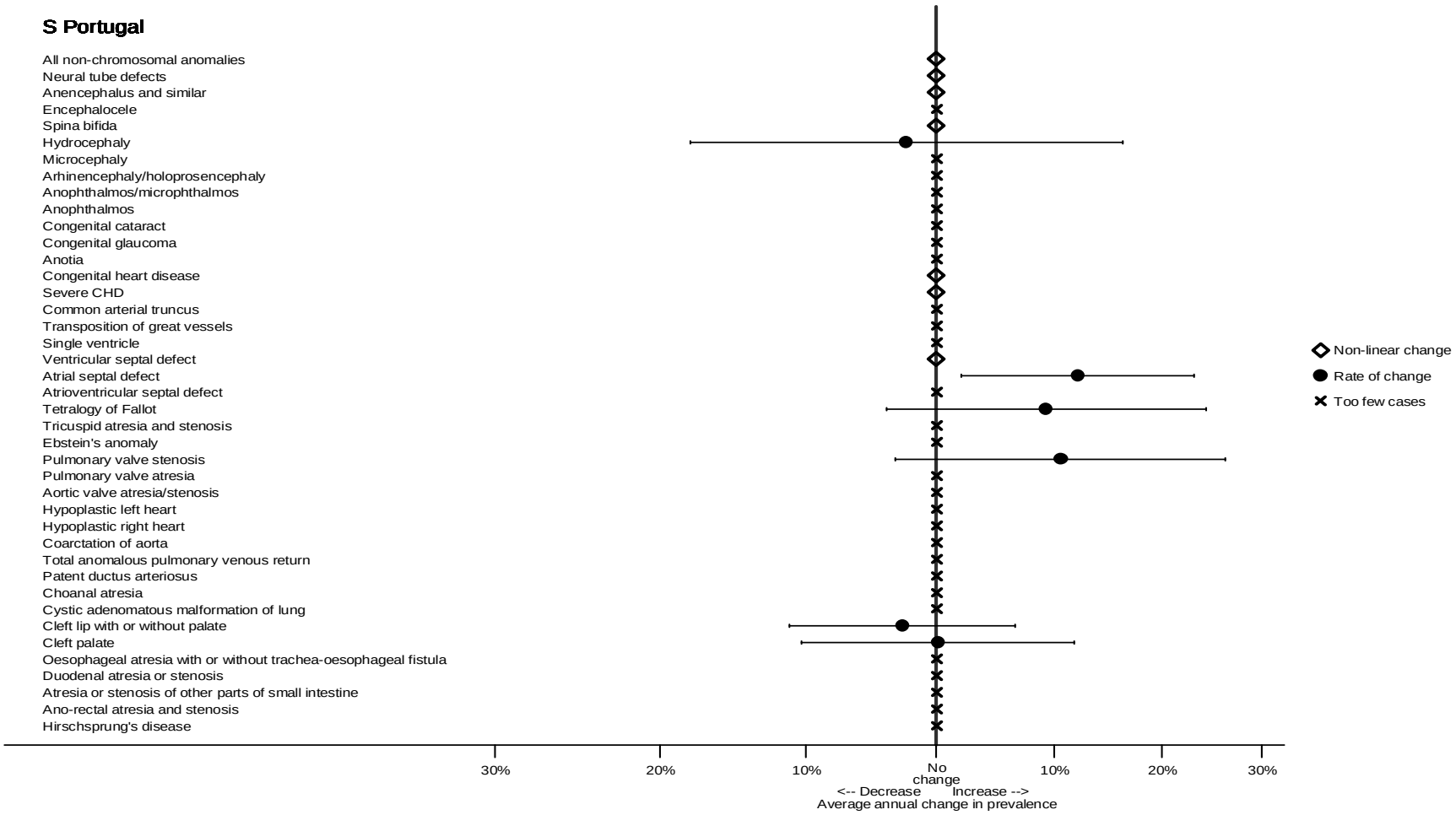
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10%
20%
30%
<-- Decrease Increase -->
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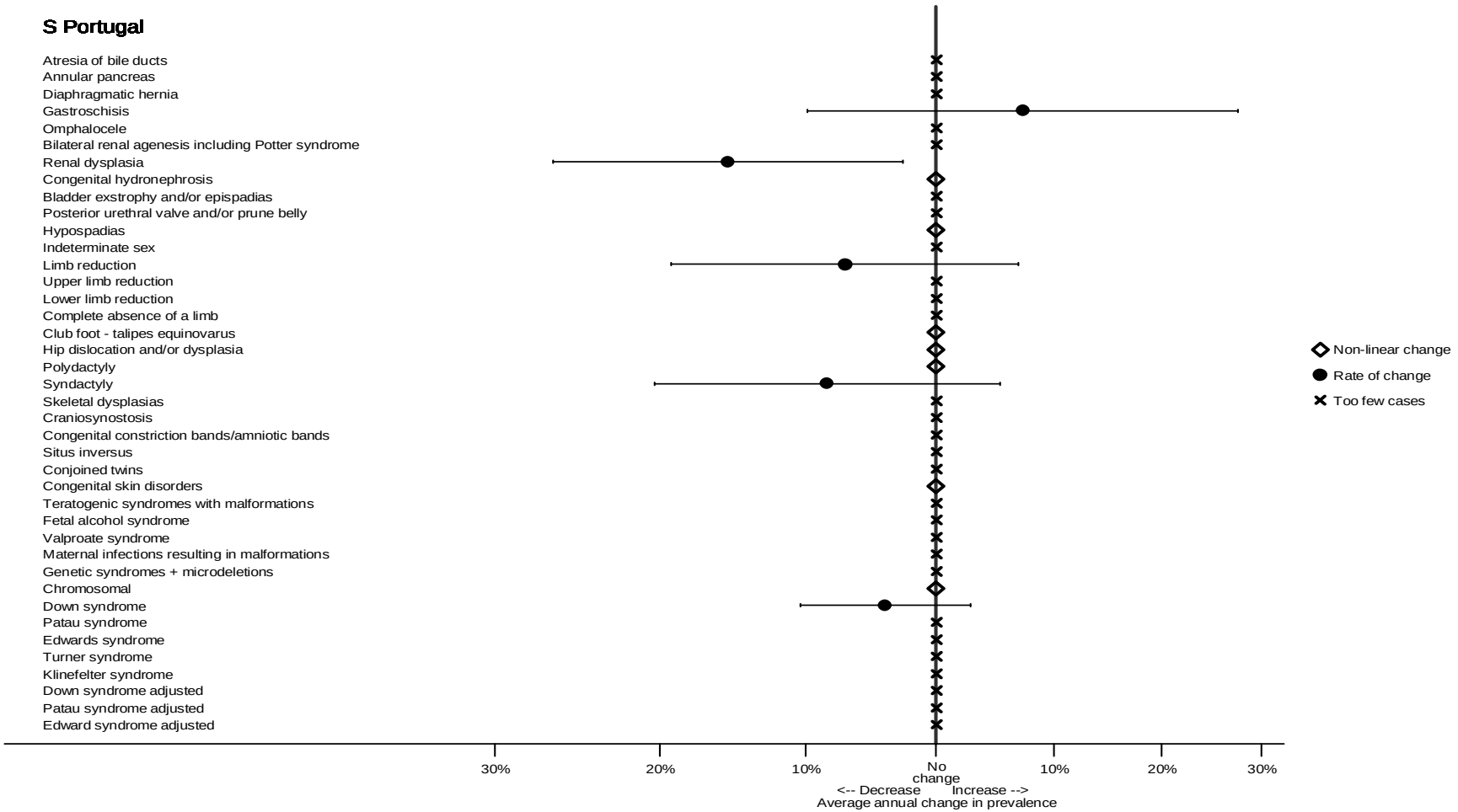
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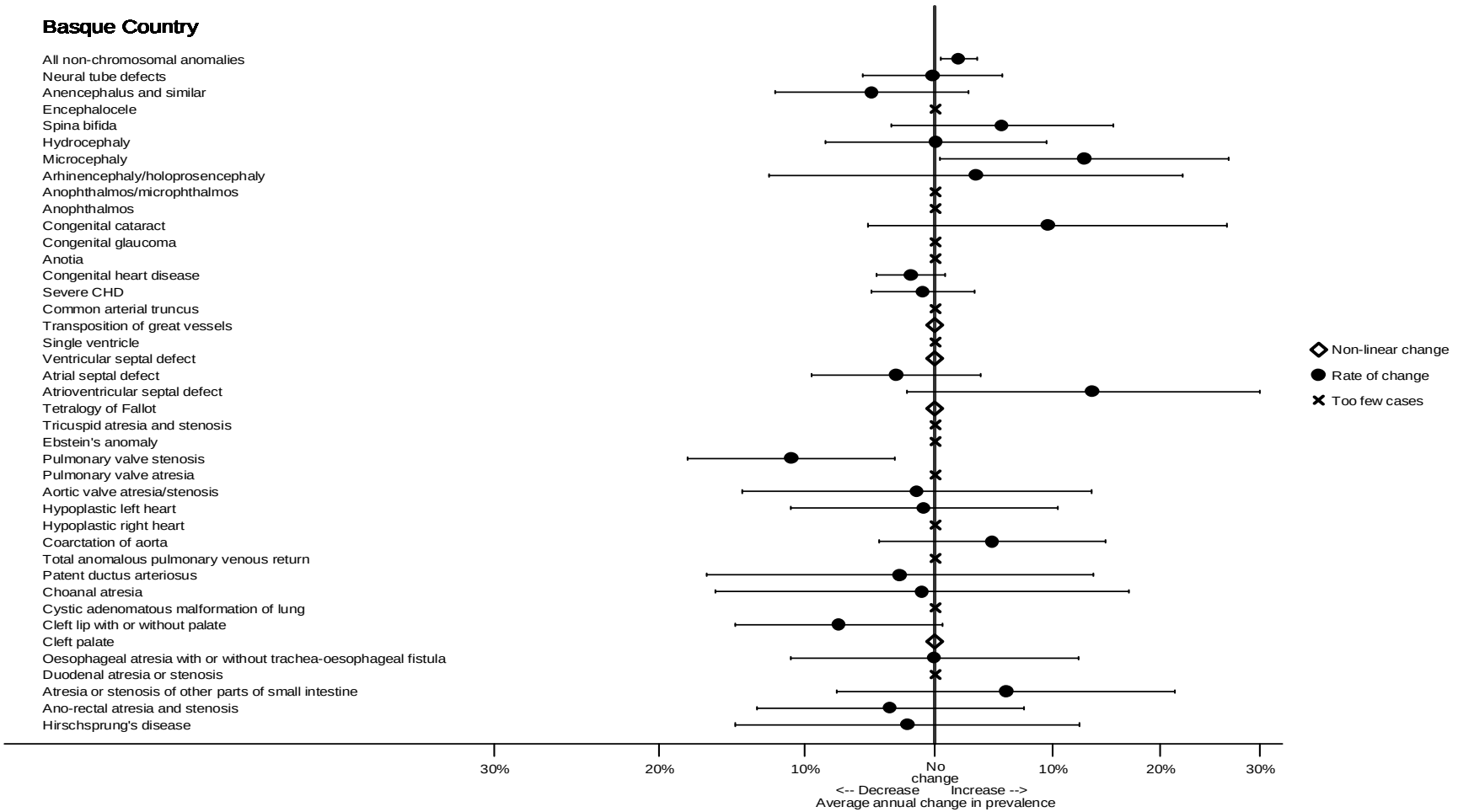
Basque Country
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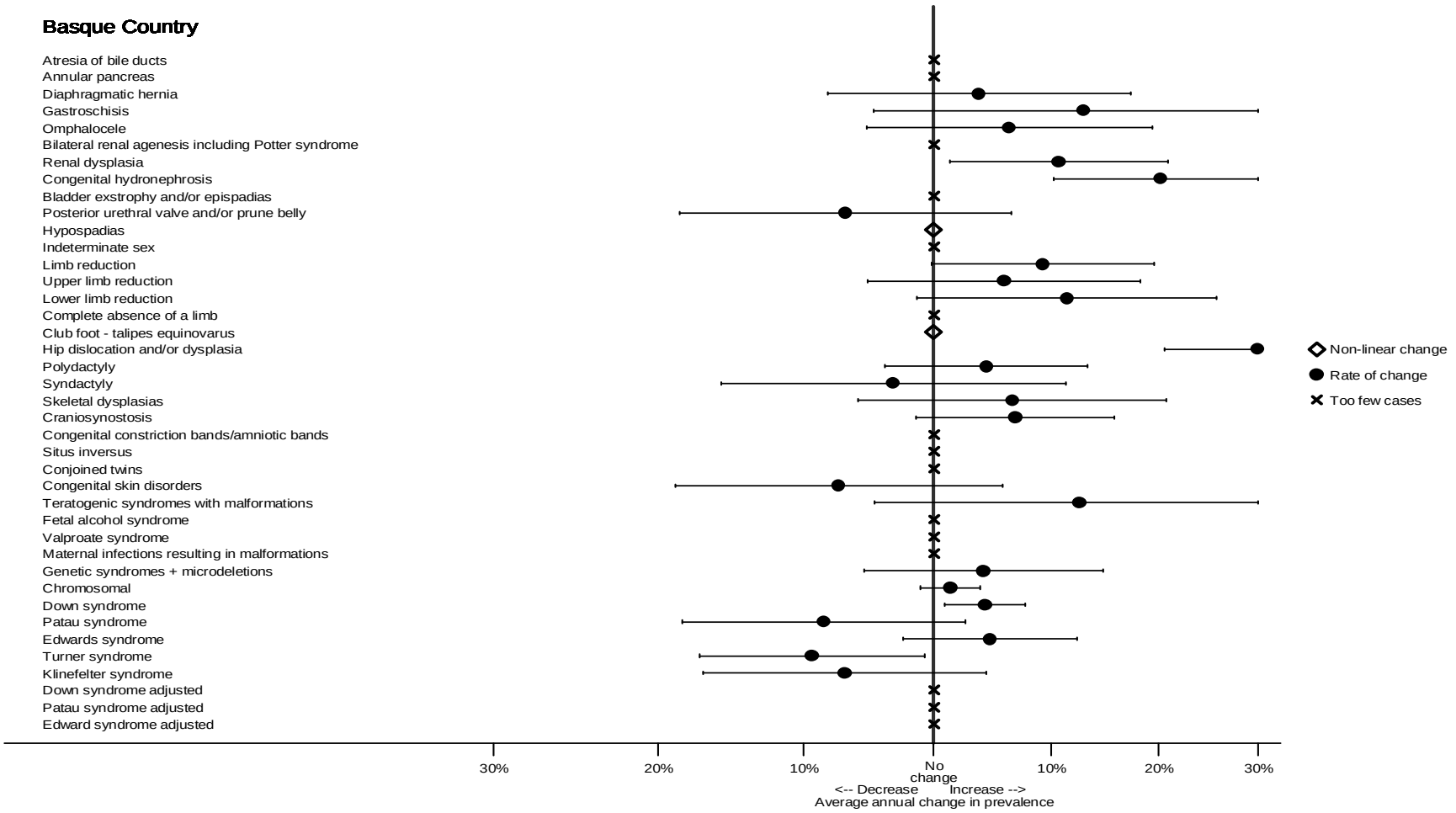
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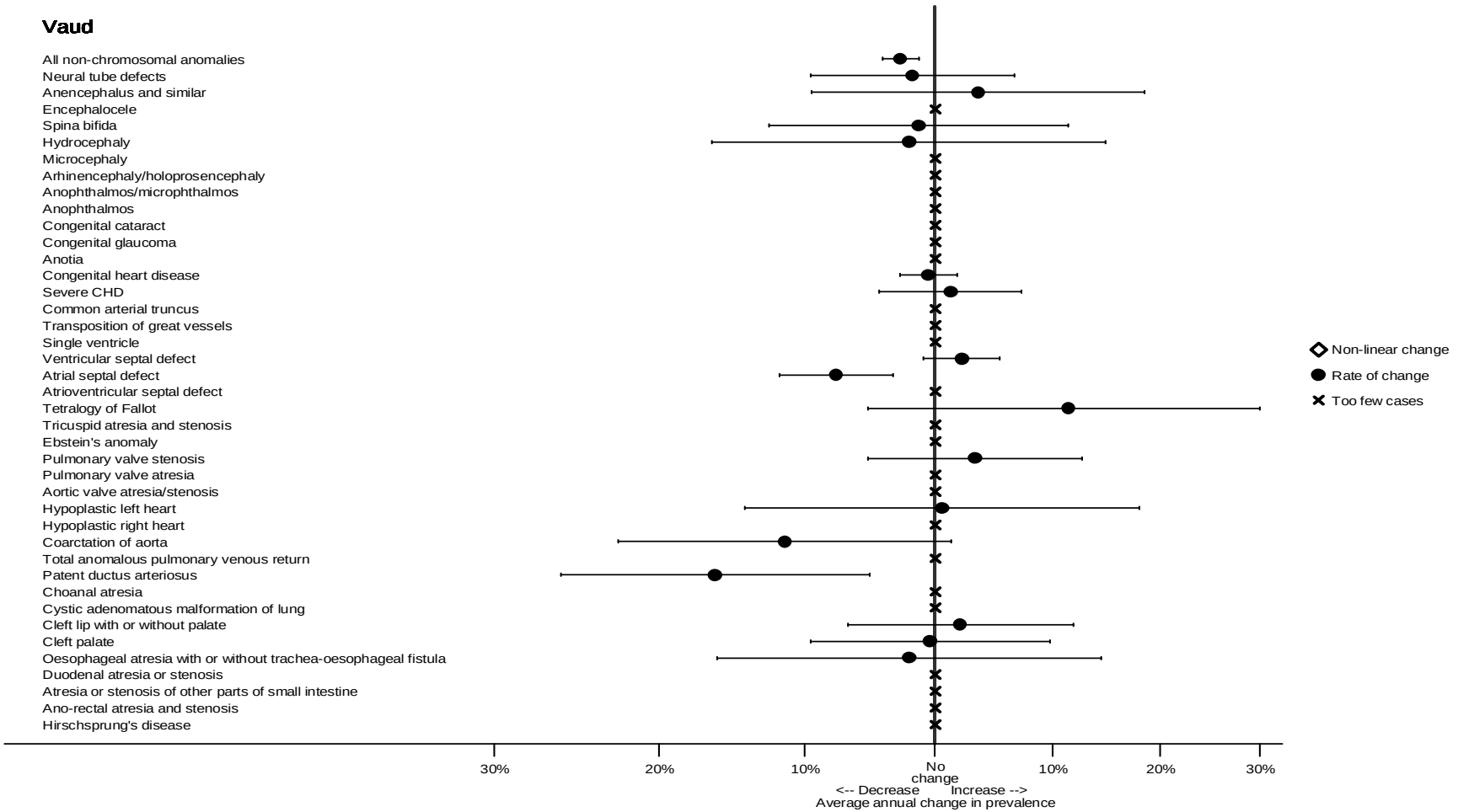
Rate of change
Too few cases


Vaud
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
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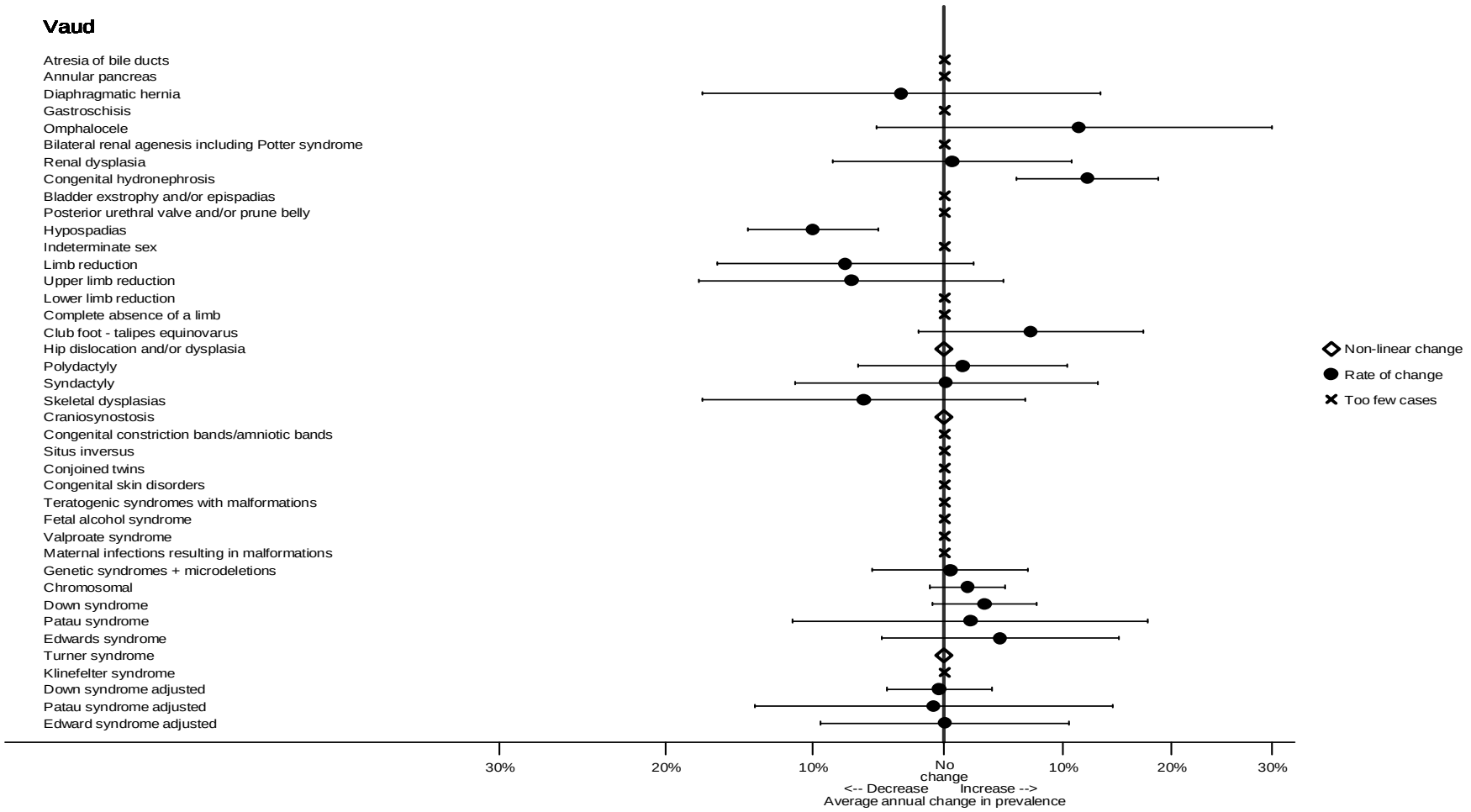
Pulmonary valve stenosis
Pulmonary valve atresia
Aortic valve atresia/stenosis
Hypoplastic left heart
Hypoplastic right heart
Coarctation of aorta
Total anomalous pulmonary venous return
Patent ductus arteriosus
Choanal atresia
Cystic adenomatous malformation of lung
Cleft lip with or without palate
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
30%
20%
10%
No change
10%
20%
30%
<-- Decrease Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Vaud
Atresia of bile ducts
Annular pancreas
Diaphragmatic hernia
Gastroschisis
Omphalocele
Bilateral renal agenesis including Potter syndrome
Renal dysplasia
Congenital hydronephrosis
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Hypospadias
Indeterminate sex
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Lower limb reduction
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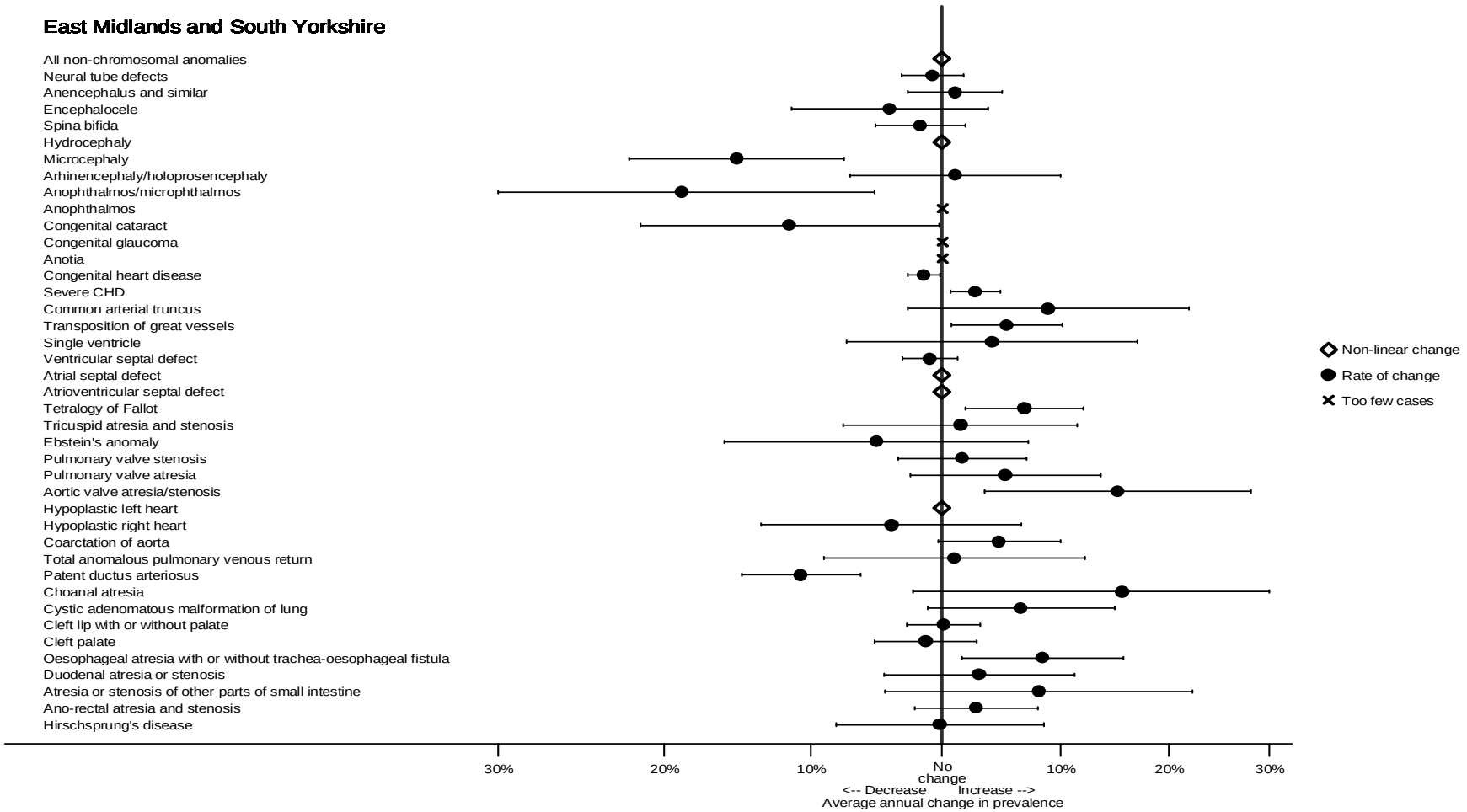
Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
Chromosomal
Down syndrome
Patau syndrome
Edwards syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


East Midlands and South Yorkshire
All non-chromosomal anomalies
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Spina bifida
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Microcephaly
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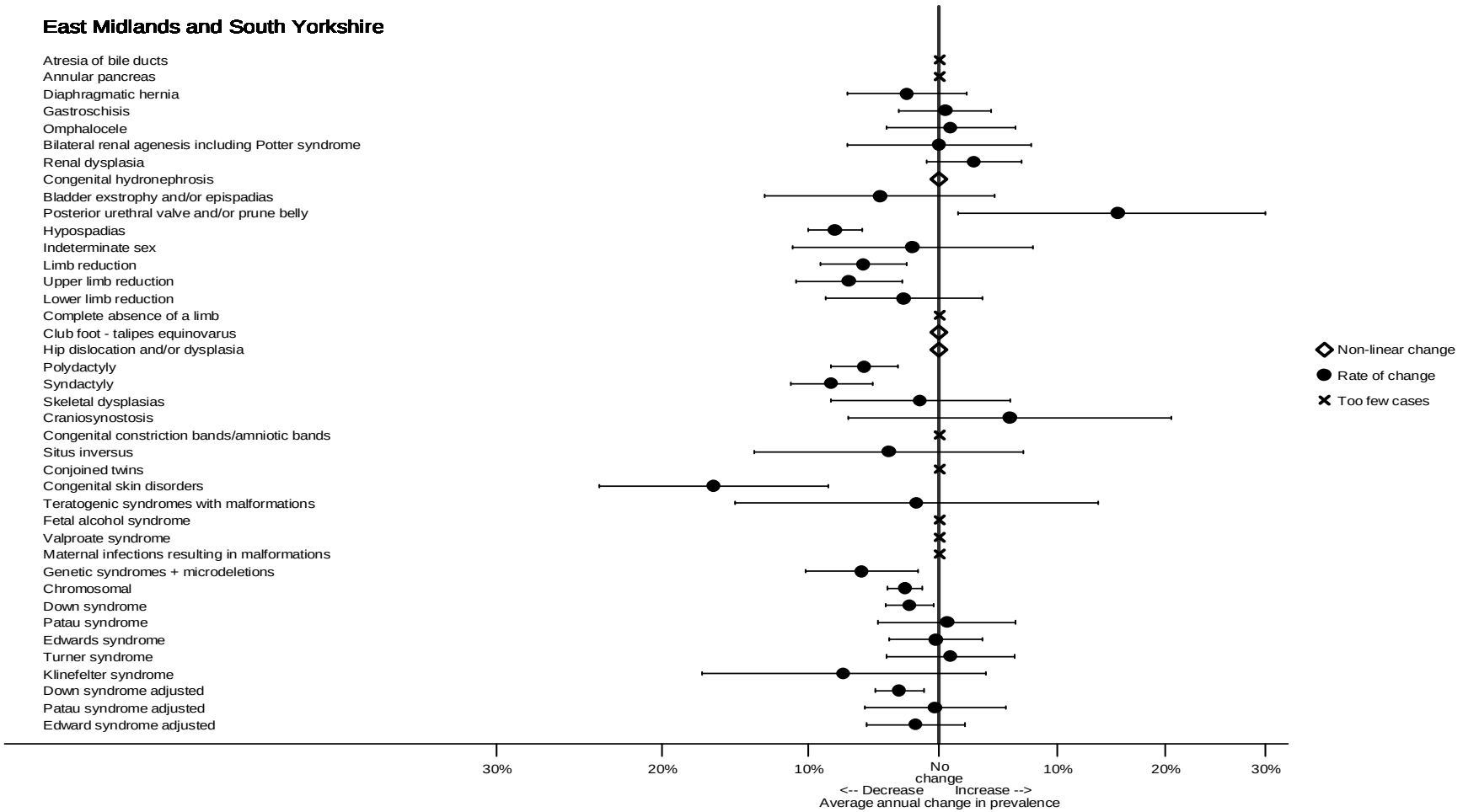
Ano-rectal atresia and stenosis
Hirschsprung's disease
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


East Midlands and South Yorkshire
Atresia of bile ducts
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Turner syndrome
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Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted
30%
20%
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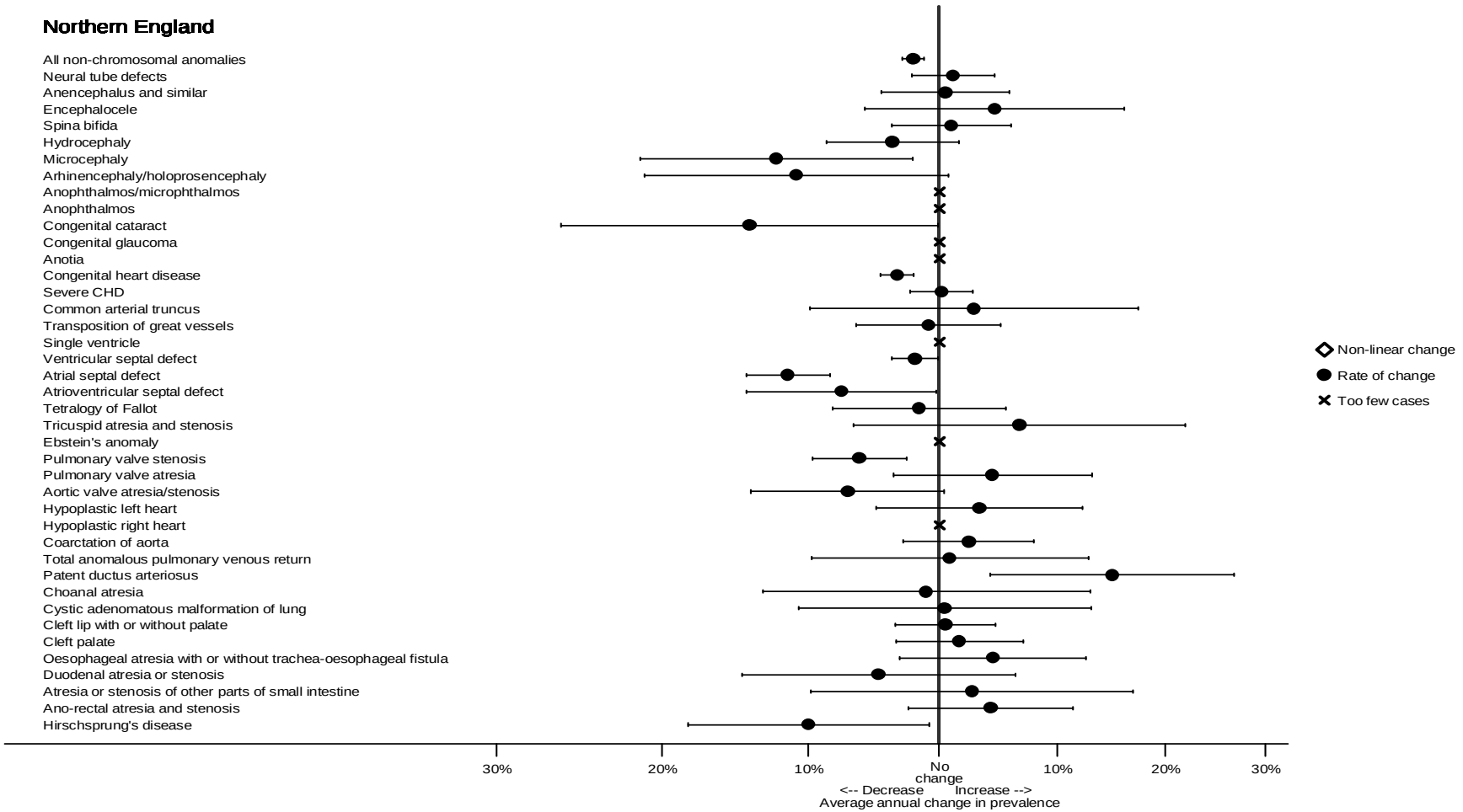
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Northern England
All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
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Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
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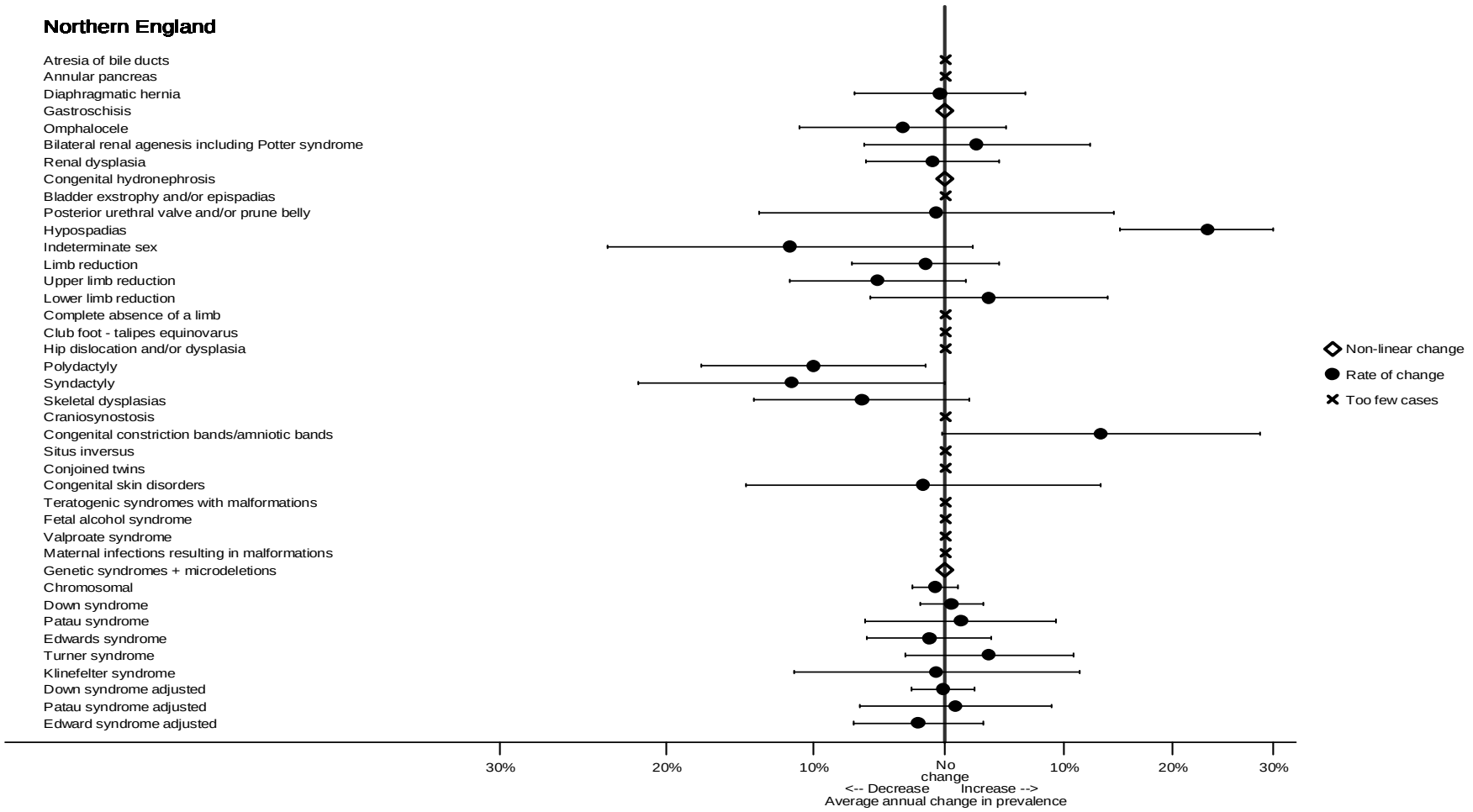
Hirschsprung's disease
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


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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Valproate syndrome
Maternal infections resulting in malformations
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Patau syndrome
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Turner syndrome
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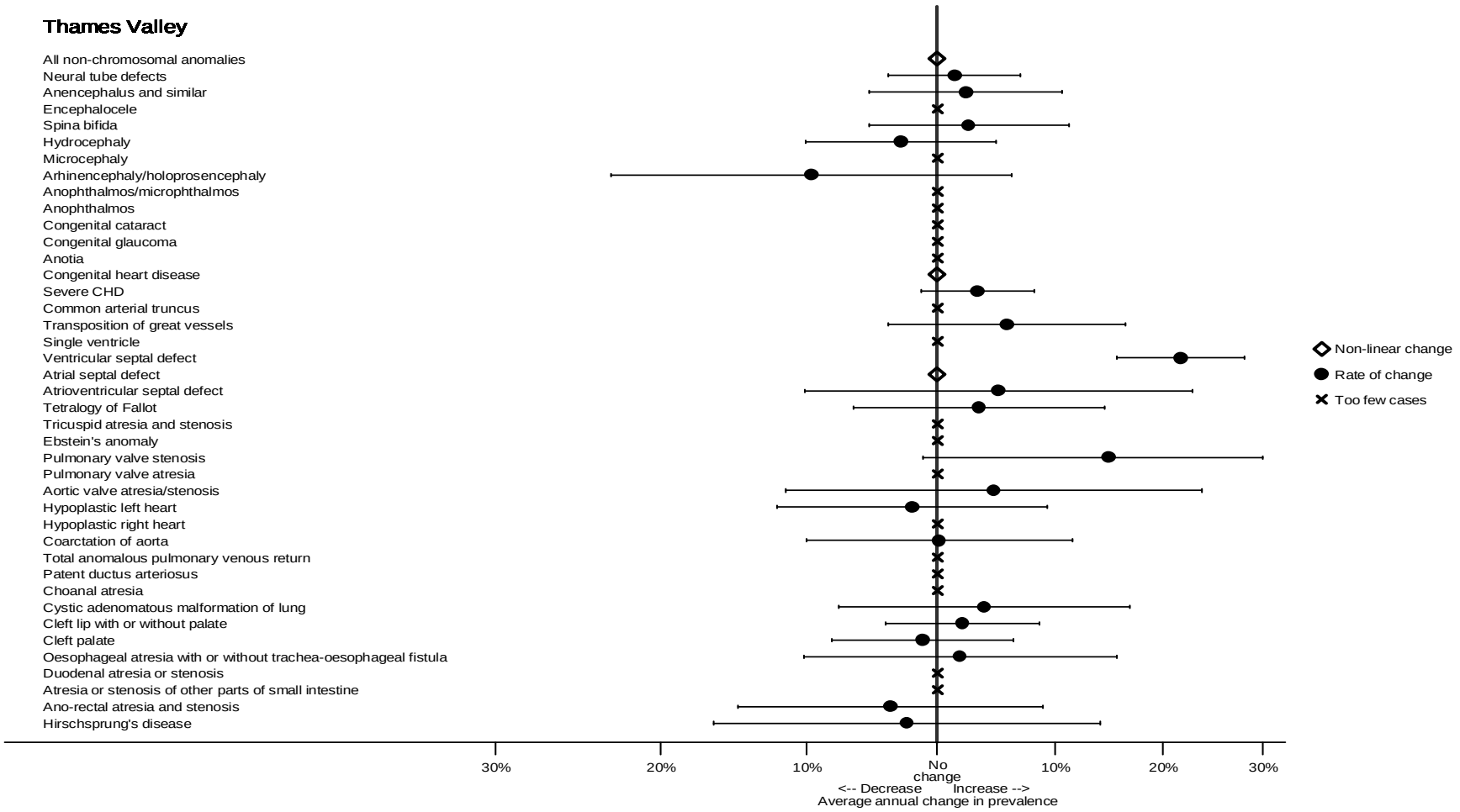
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Thames Valley
All non-chromosomal anomalies
Neural tube defects
Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
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30%
20%
10%
No change
10%
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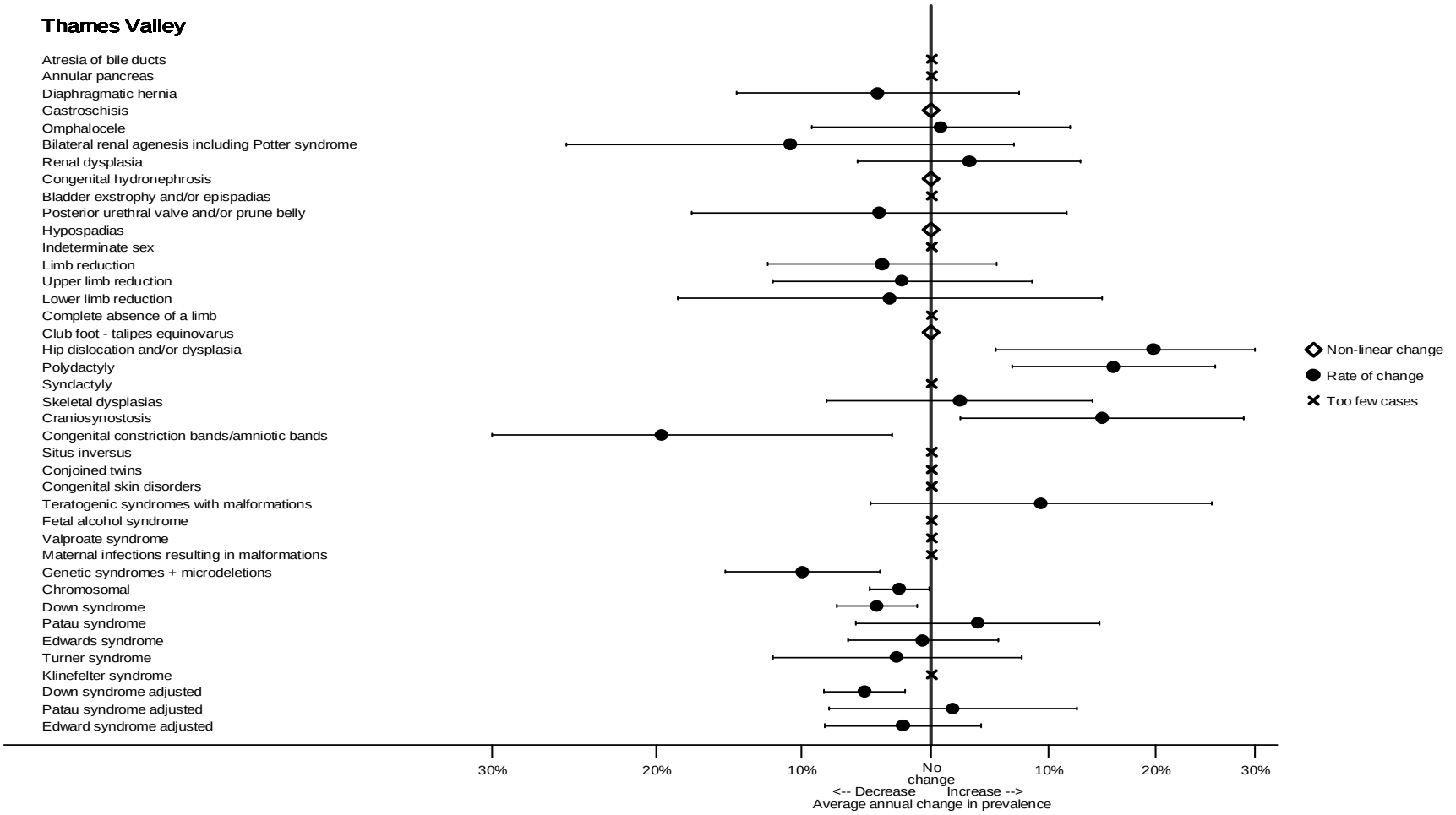
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Thames Valley
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Turner syndrome
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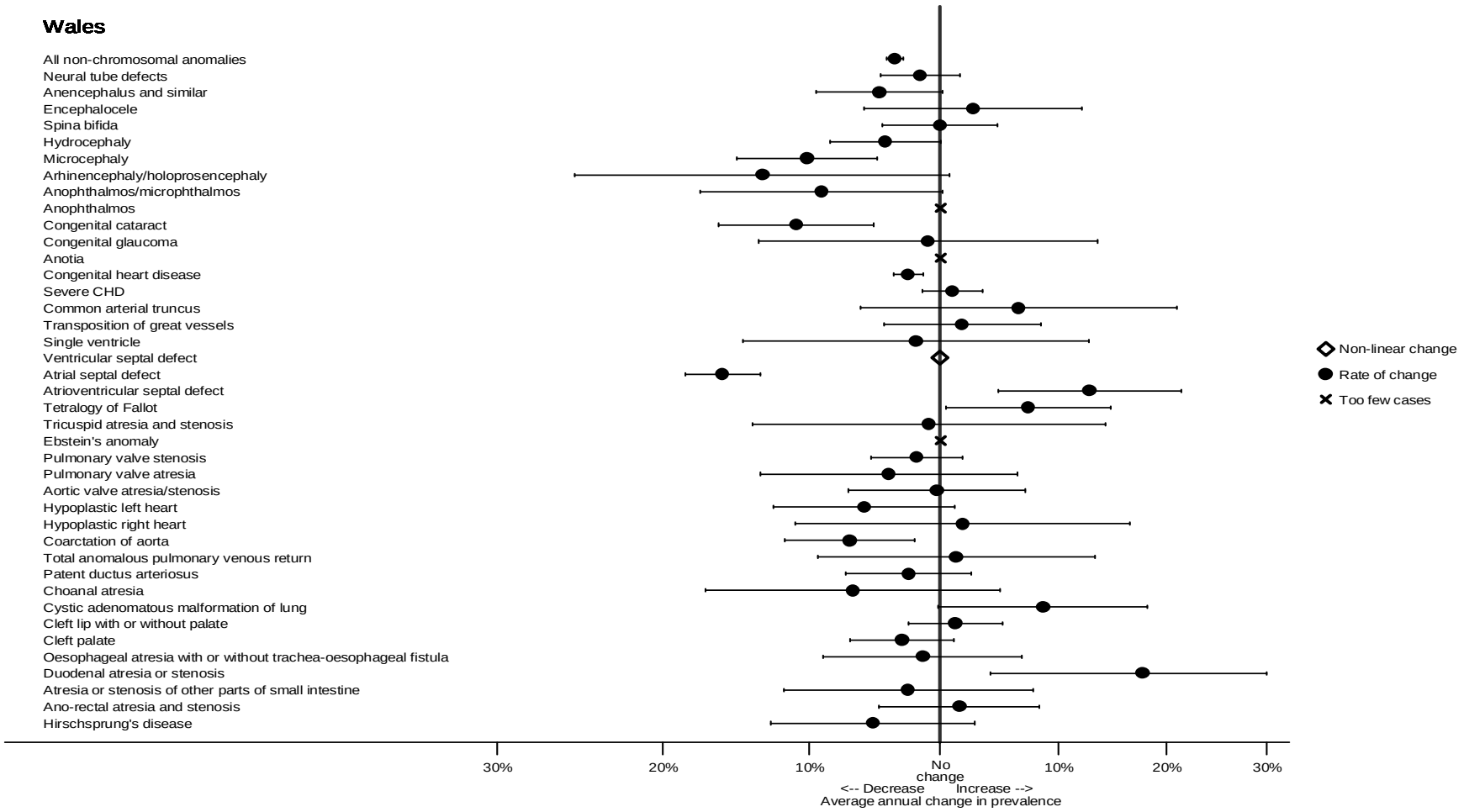
Edward syndrome adjusted
30%
20%
10%
No change
10%
20%
30%
<-- Decrease Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Wales
All non-chromosomal anomalies
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Anencephalus and similar
Encephalocele
Spina bifida
Hydrocephaly
Microcephaly
Arhinencephaly/holoprosencephaly
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Anotia
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Transposition of great vessels
Single ventricle
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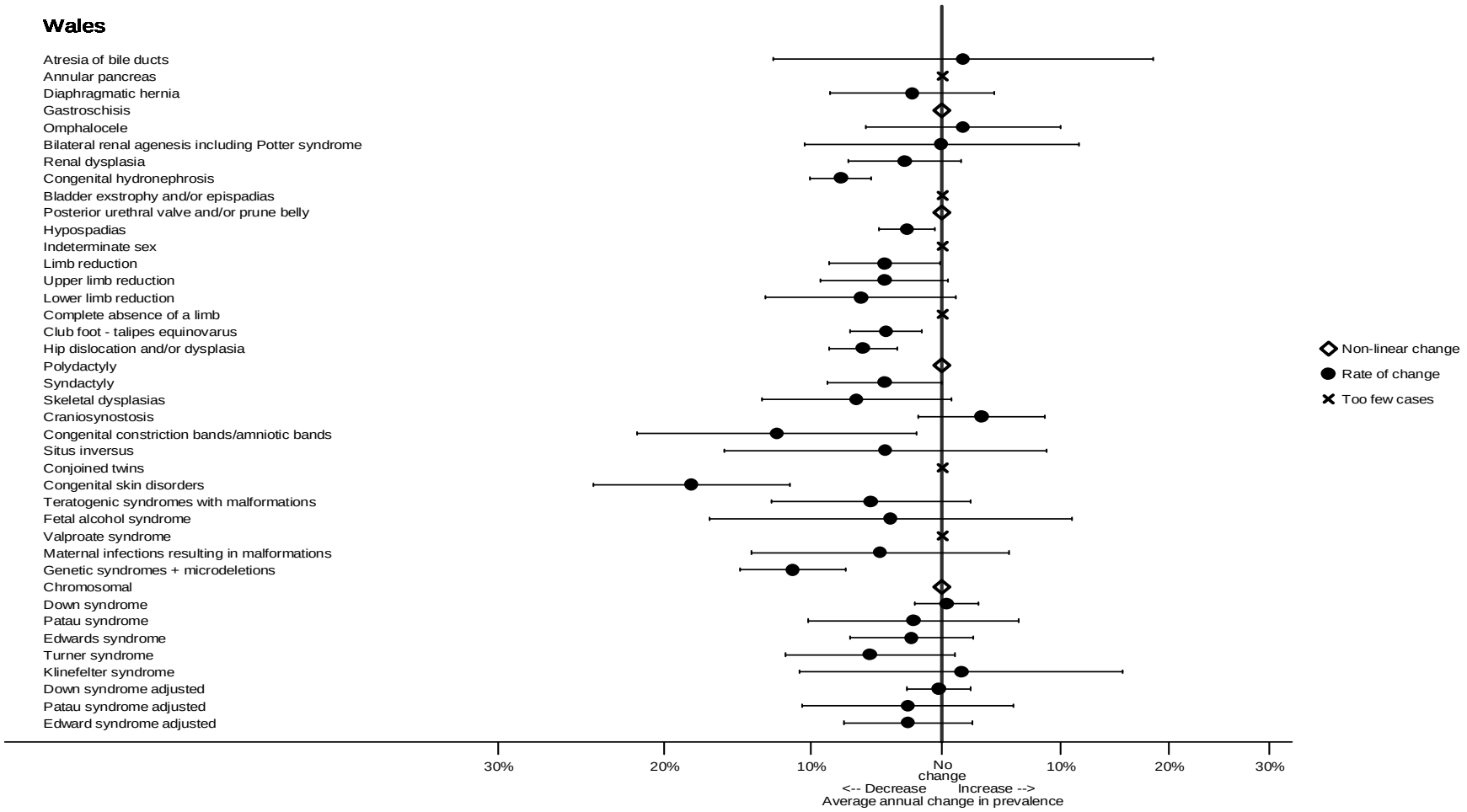
Hirschsprung's disease
Non-linear change
Rate of change
Too few cases
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence


Wales
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Conjoined twins
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Valproate syndrome
Maternal infections resulting in malformations
Genetic syndromes + microdeletions
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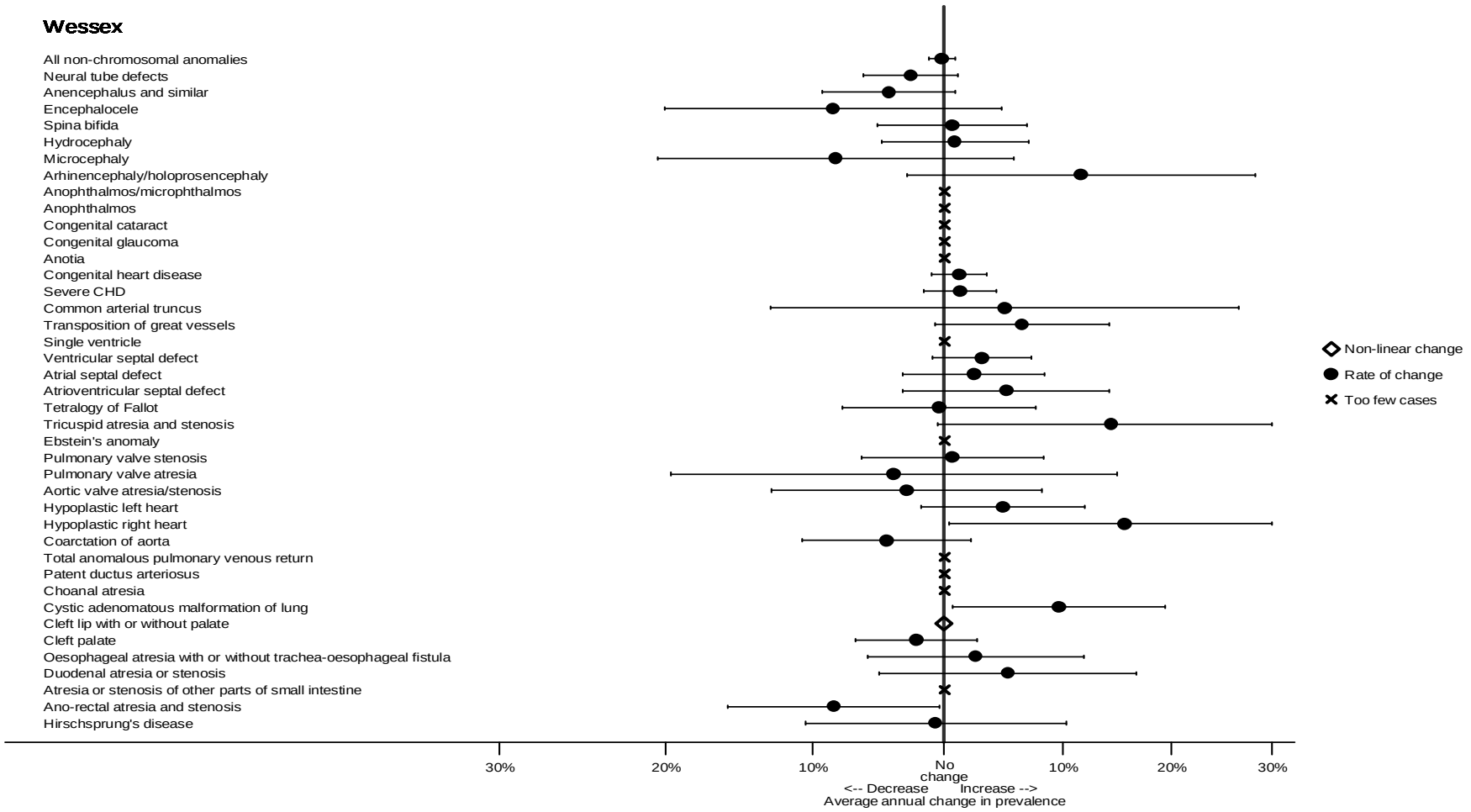
Down syndrome
Patau syndrome
Edwards syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted
30%
20%
10%
No change
10%
20%
30%
<-- Decrease
Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases


Wessex
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Microcephaly
Arhinencephaly/holoprosencephaly
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30%
20%
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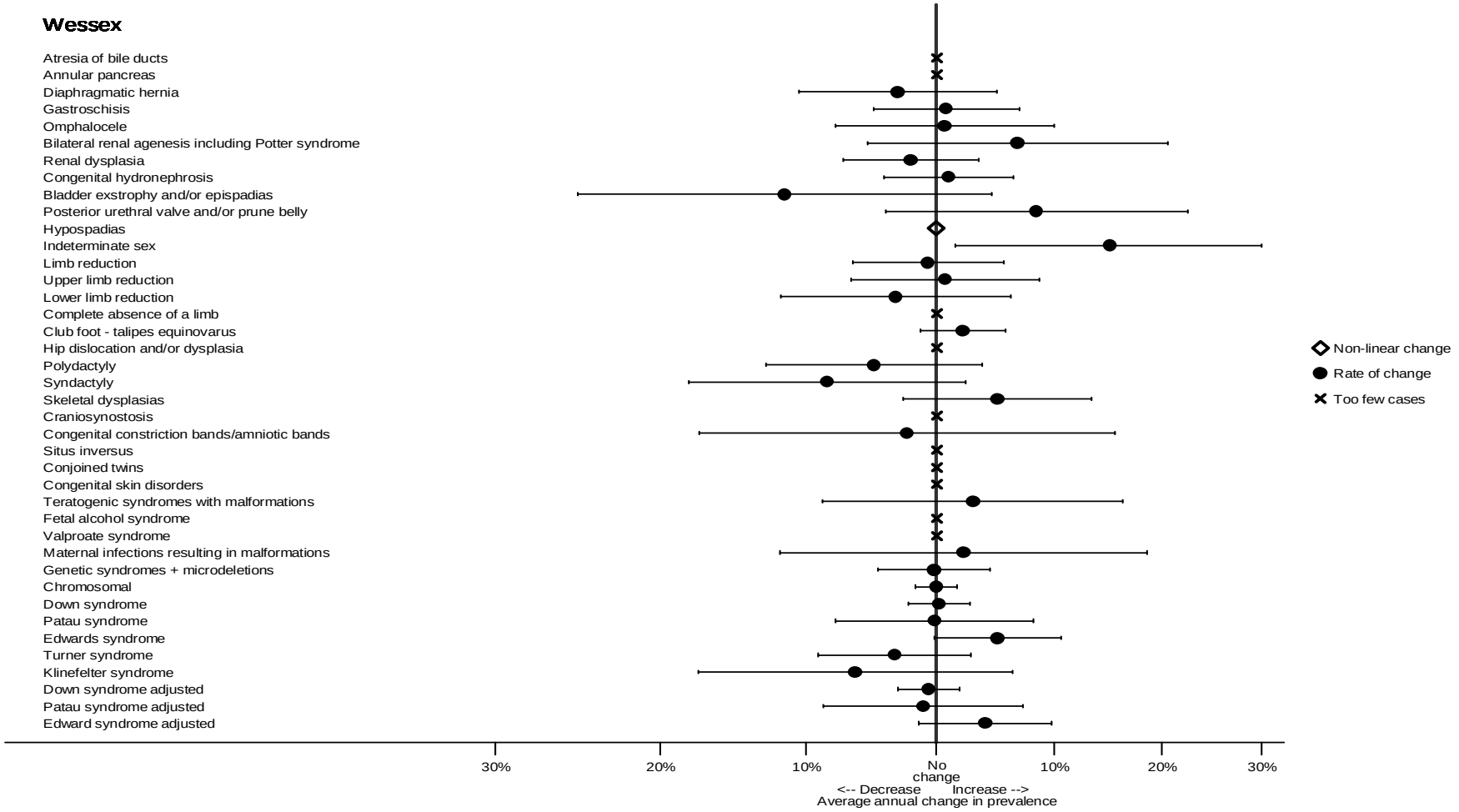
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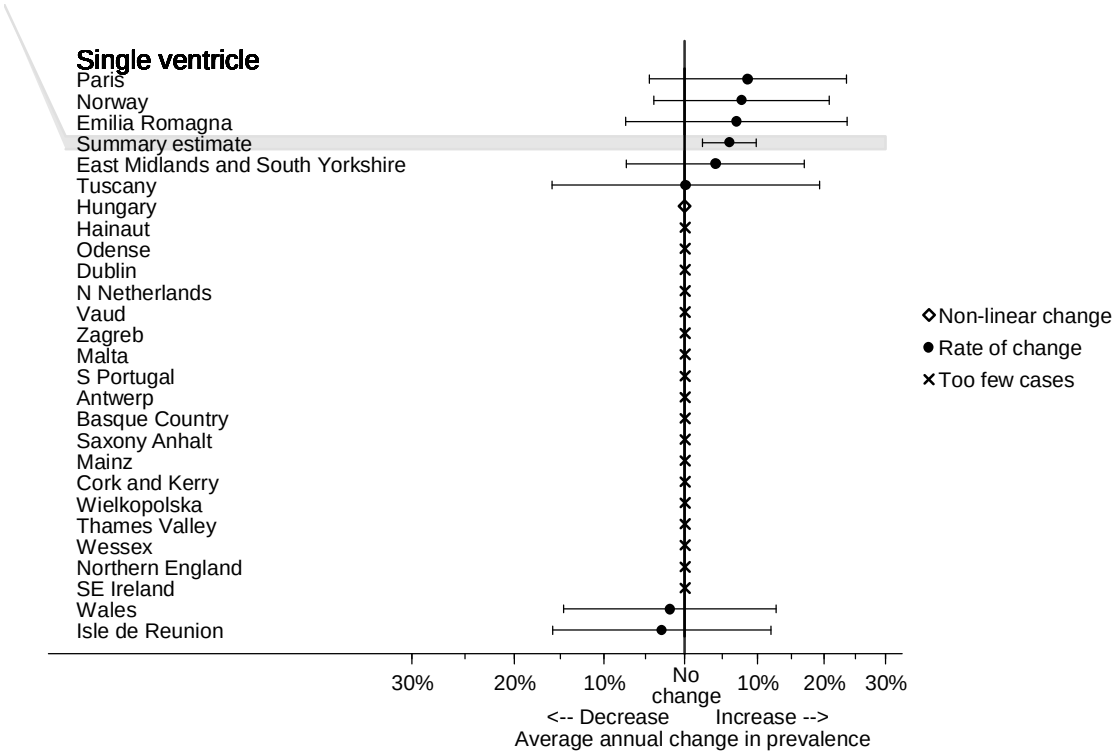
Down syndrome adjusted
Patau syndrome adjusted
Edward syndrome adjusted
30%
20%
10%
No change
10%
20%
30%
<-- Decrease Increase -->
Average annual change in prevalence
Non-linear change
Rate of change
Too few cases

Appendix G: Central registry reports of pan-Europe trends

Single Ventricle: Increasing trend

Three registries, Paris, Norway and Emilia-Romagna, show a trend moving in the same direction and which therefore may be contributing are, none of which independently show a statistically significant increase. There is a non-statistically significant decrease in prevalence in Ile de Reunion and Wales.

***Figure 1**. The trend in prevalence of Single Ventricle, showing individual registries and the pan European trend, 2002-2011*



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 requiring 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 412 cases registered over the 10 year period with prevalence rates ranging from zero in Mainz to 1.64 per 10,000 births in Ile de Reunion. It is worth noting that Ile de Reunion shows a non-statistical decrease in prevalence as their rate peaked at 3.33 cases per 10,000 births in 2007. This was based on 5 cases. As with every registry, their prevalence is variable from year to year as it is built on small numbers of this rare congenital anomaly. There is not consistency between registries in the way that this anomaly is coded as many registries code single ventricle with another anomaly such as hypoplastic left heart or pulmonary valve atresia or stenosis while others code only the full diagnosis. This is not usually the case in either Paris where only one case of their 30 is coded with pulmonary valve stenosis and single ventricle and in Ile de Reunion data none of their 24 cases have a second anomaly. Coding issues therefore does not explain the high prevalence in these registries. Prevalence has increased by an average of 6.03% per year from 0.49 to 0.65 per 10,000 births.

***Figure 2**: Prevalence of Single Ventricle by registry 2002-2011*

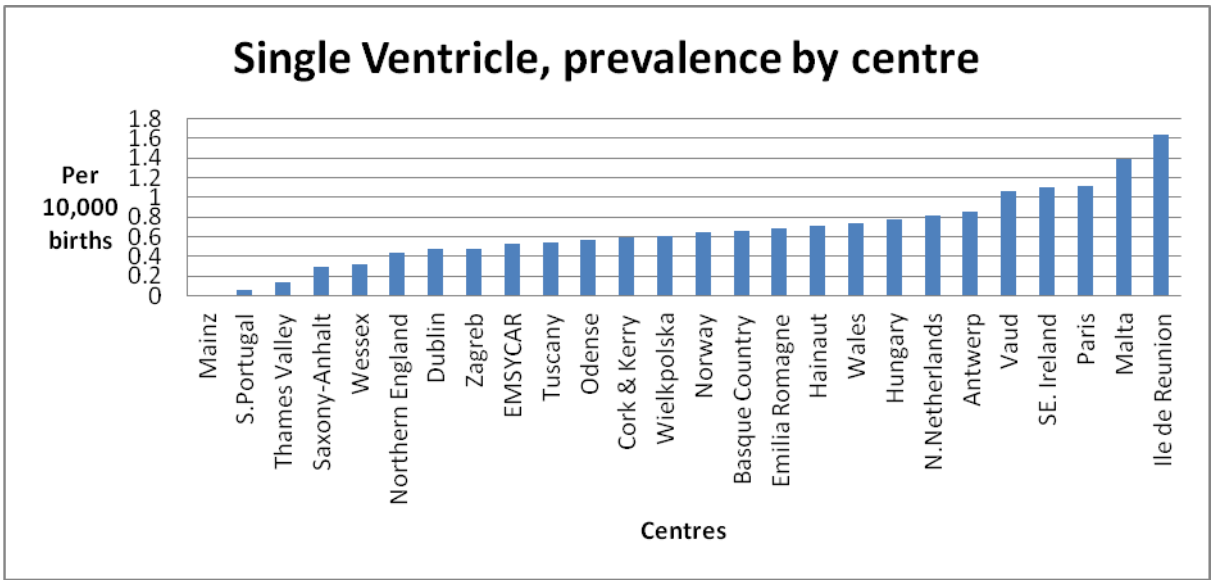
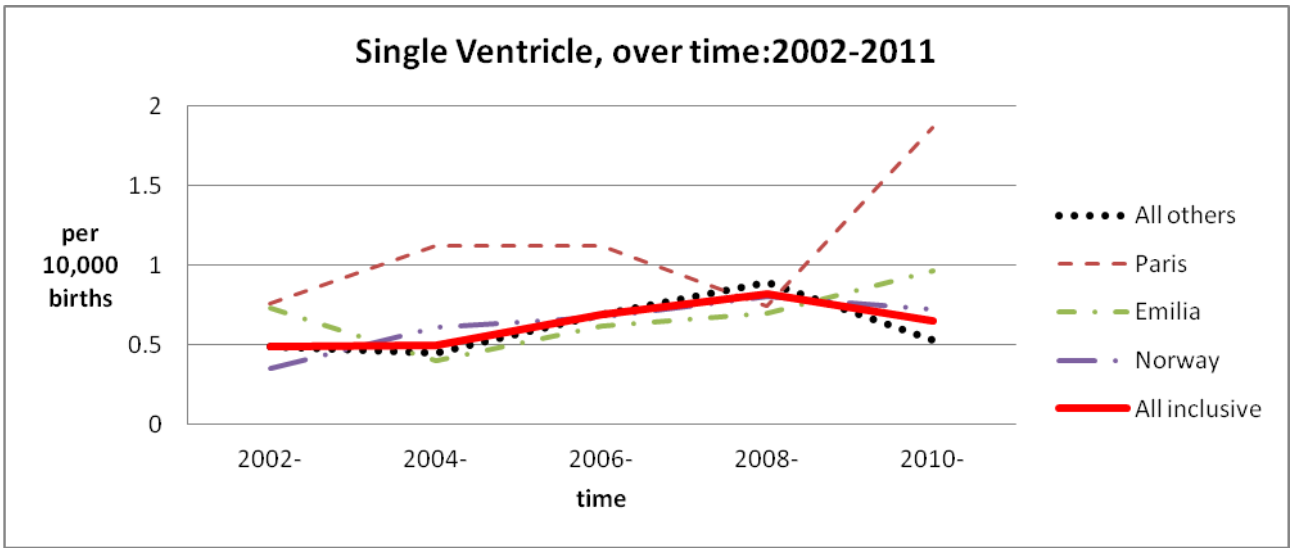


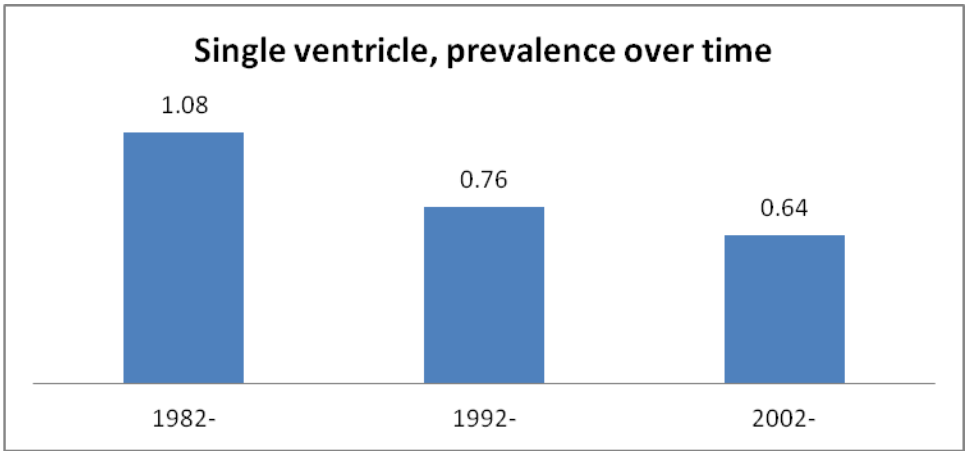
***Figure 3**: Single Ventricle, showing the increasing trend and that trend when the two registries with a statistically significant rise in prevalence are excluded.*



When the three registries which contribute most to the rise in prevalence are removed the increase is less convincing, with Paris contributing most to the pan-European increase.

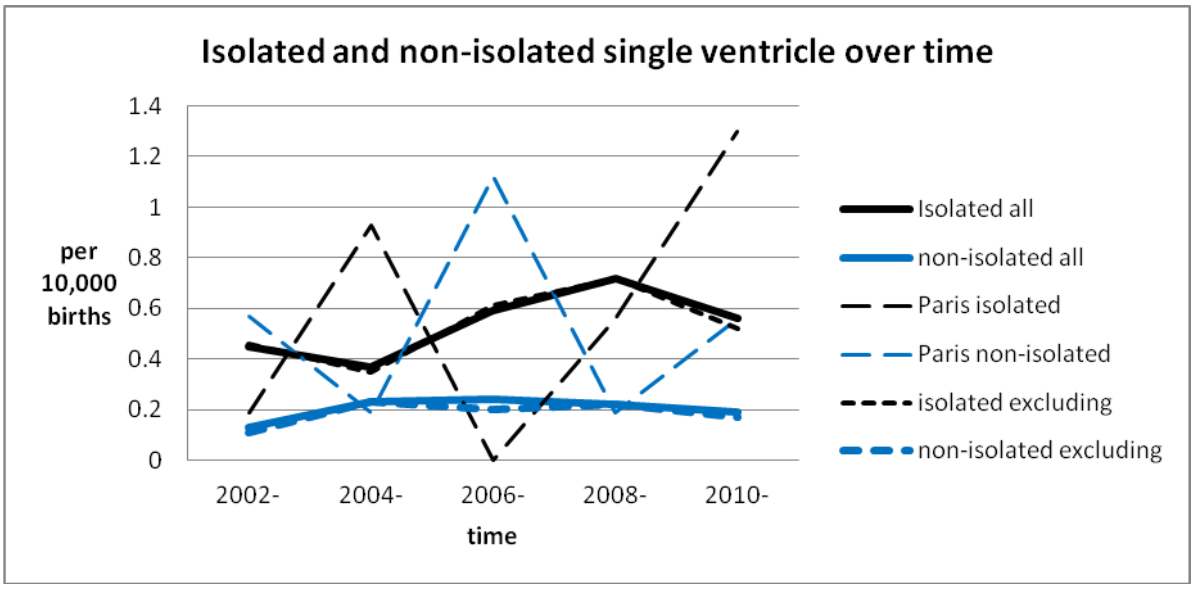
The prevalence of single ventricle appears to have decreased over the past three decades.

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



73.5% of single ventricles are isolated cardiac anomalies, meaning that there are no other anomalies outside the cardiac system. The present rise in prevalence appears to be mainly due to the prevalence of single ventricle as an isolated cardiac anomaly and excluding the Parisian data does not make any difference to the overall trend.

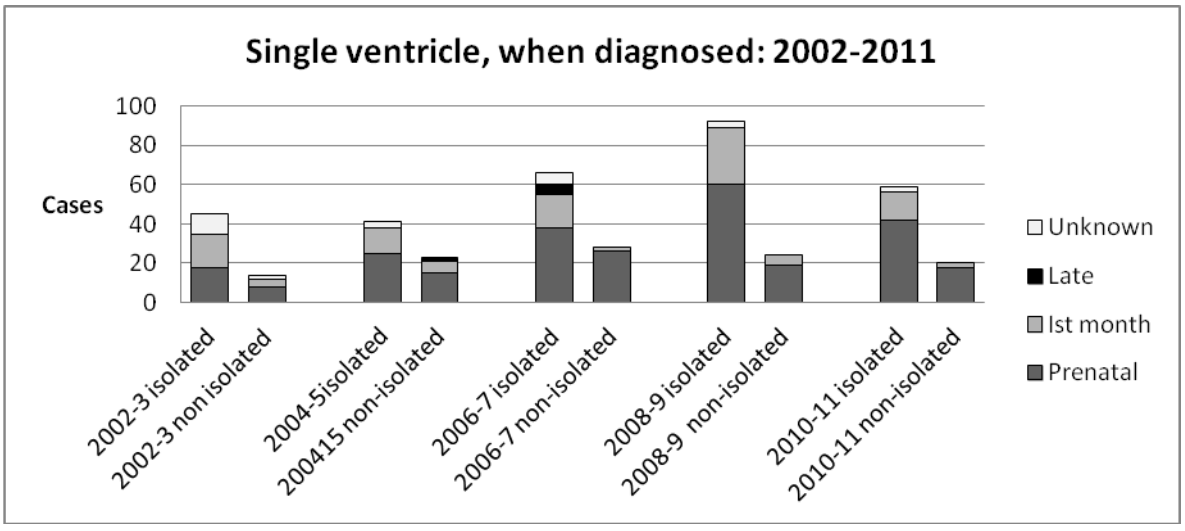
Figure 5: *Prevalence of single ventricle as an isolated and as a non-isolated anomaly, including and excluding data from Paris 2002-2011*



Trend over time in prenatal diagnosis and birth type

The proportion of single ventricle cases which are isolated cardiac anomalies and are prenatally diagnosed has risen from 40 to 71% over the 10 year period. The proportion of single ventricles as part of multiple anomalies which are prenatally diagnosed has risen from 57 to 90% in the same time. As almost 97% of all Parisian cases were prenatally diagnosed this may have contributed to the higher than average prevalence Late diagnosis is unusual with 4 cases recorded as being late diagnosed in Hungary in 2006-7 with a further case in Vaud recorded in 2004.

Figure 6: *When diagnosed for isolated and non-isolated cases, over time.2002-2011*

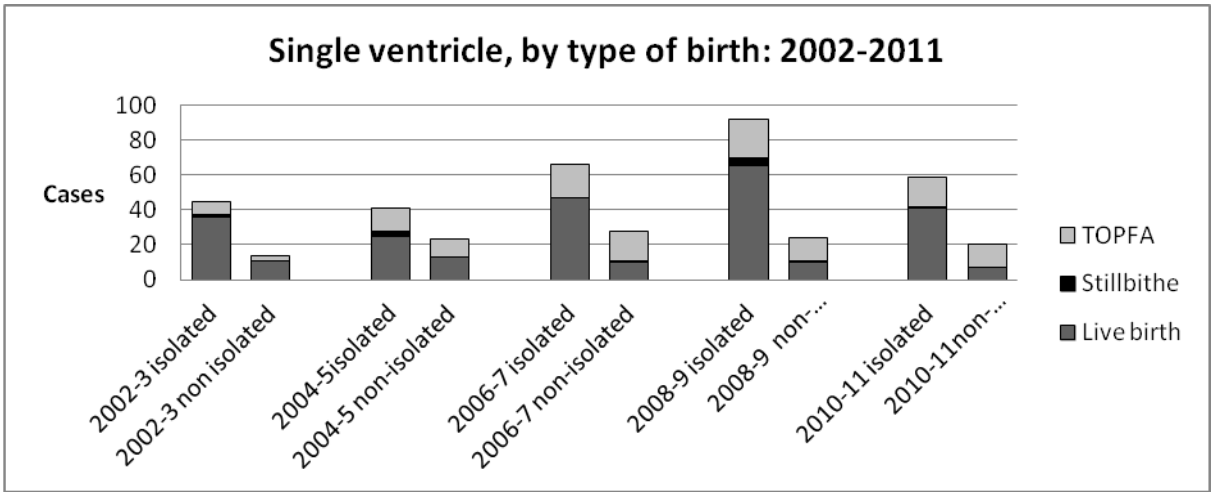


*Late diagnosis refers to more than one month after birth

NB. Data for 7 registries not included for 2011

The proportion of single ventricle as both isolated cardiac and non-isolated anomalies has increased over time with 29% of isolated cardiac and 65% of non-isolated cases now TOPFA.

Figure 7: Type of birth for isolated and non-isolated anomalies, over time 2002-2011



Conclusions

Although the increase in prevalence of single ventricle may be related to an increase in the proportion of cases which are prenatally diagnosed, especially when it occurs as an isolated cardiac anomaly, there are coding issues around whether this should be coded when it is one part of a complex anomaly may need addressing.

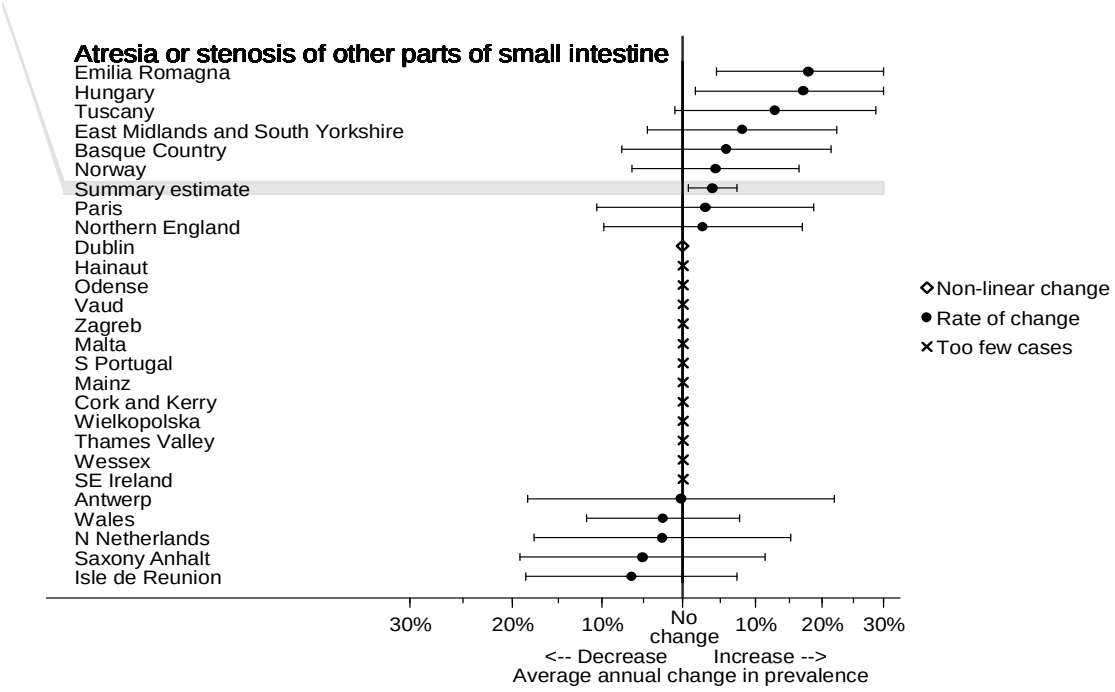
(1) Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy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

Atresia or stenosis of other parts of the small intestine: Increasing trend

The registries which show a trend moving in the same direction and which therefore may be contributing are Emilia-Romagna and Hungary, with a non-statistically significant increase in Tuscany, EMSTCAR, Basque Country, Norway, Paris and Northern England.

The registries which show a trend in the opposite direction are Saxony- Anhalt and Ile de Reunion

***Figure 1**. The trend in prevalence of other intestinal atresia / stenosis showing individual registries and the pan European trend, 2002-2011*



Literature review

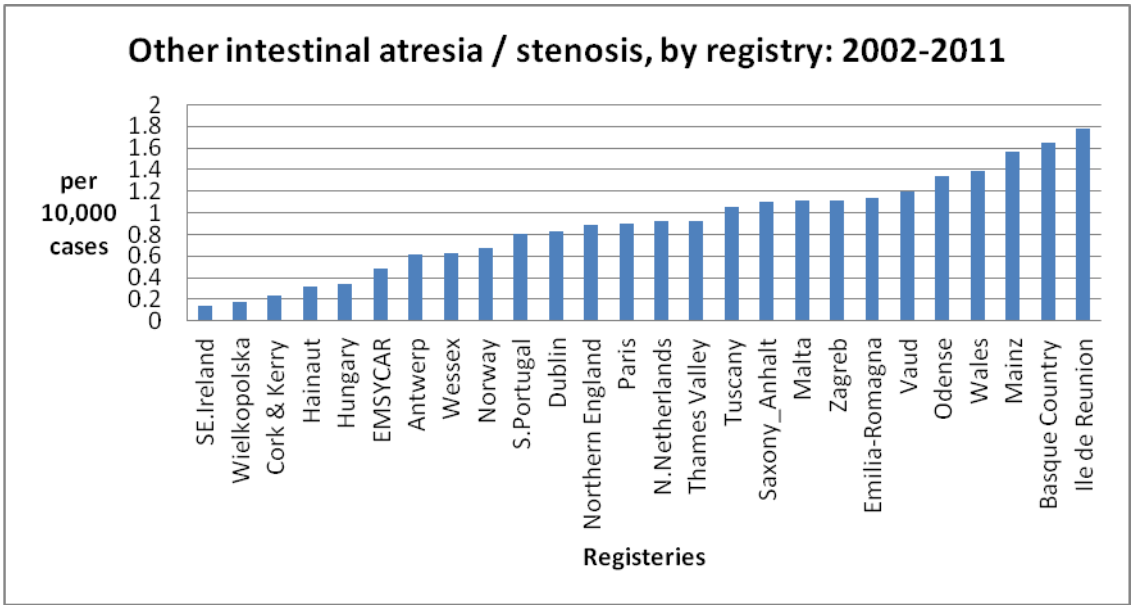
Atresia and stenosis of the jejunum and ileum are attributed to vascular accidents in utero and are usually considered to have a different aetiology than atresia and stenosis of the duodenum(1). The most severe form of these small bowel malformations are known as “apple peel” or “Christmas tree” anomalies where the bowel ends in a blind pouch with small sections wrapped around the blood supply, often with a large section of the bowel missing. All small bowel atresia and most stenosis require surgery in the neonatal period. An association with maternal glomerular nephritis was noted by Hungarian researchers, but they considered this a signal requiring further investigation rather than a definitive risk factor (2). An weak association between these intestinal atresia and stenosis and young maternal age was reported (3,4), but this was not found in a larger EUROCAT analysis of maternal age

and non-chromosomal anomalies (5). There are associations reported between intestinal atresia / stenosis and maternal infection and / or bleeding during pregnancy. Consanguinity has been implicated, but this may be due to the autosomal recessive inheritance which is known for the severs apple peal syndrome (6).

Consistency between registries

There were 501 cases of atresia / stenosis of other parts of the small intestine. Prevalence of "other" intestinal atresia / stenosis ranged from 0.14 per 10,000 births in South East Ireland to 1.78 per 10,000 births in Ile de Reunion.

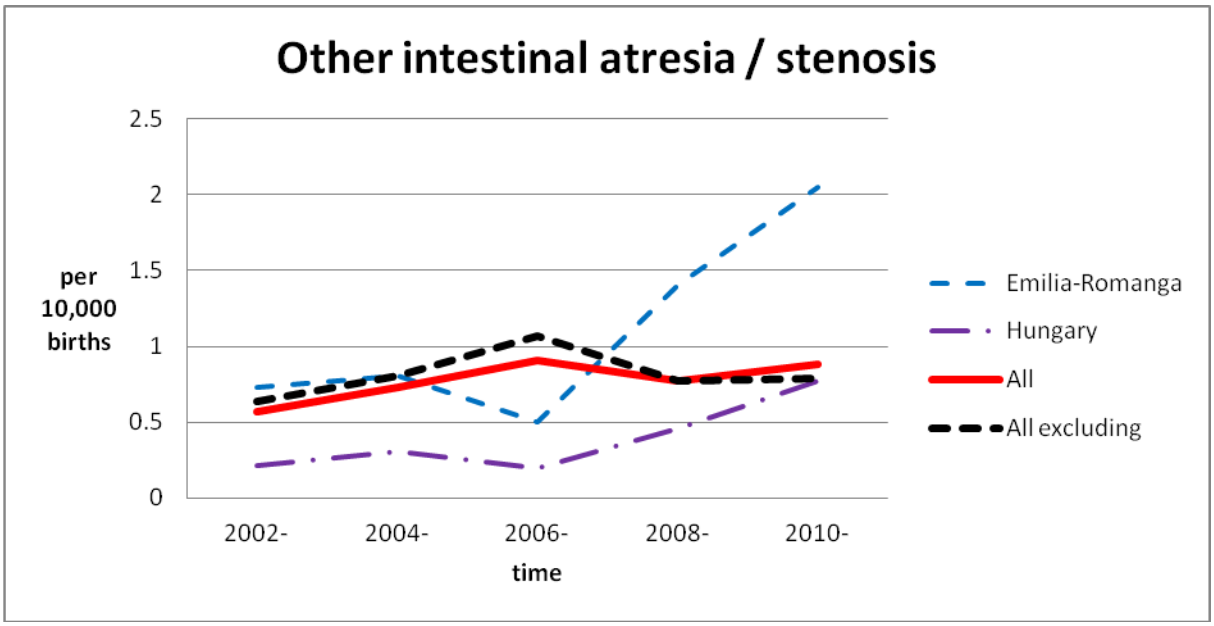
***Figure 2**: Prevalence of Other intestinal atresia / stenosis, by registry 2002-2011*



Trend over time

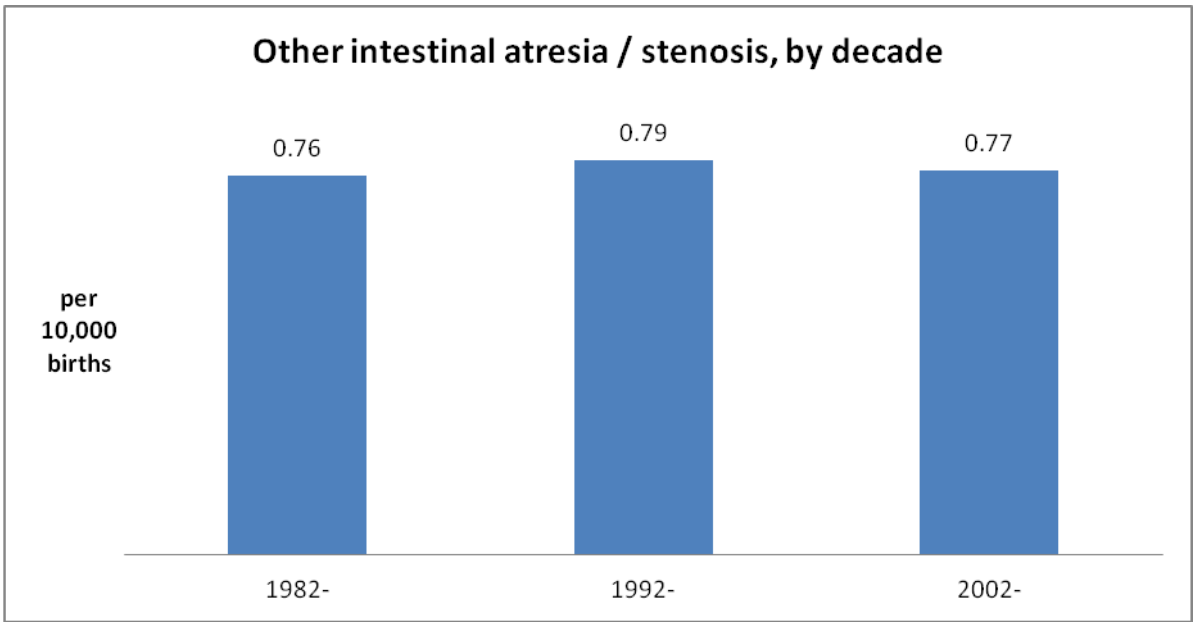
Prevalence increased, on average, by 2.2% per year over the 10 year period from 0.57 per 10,000 births to 0.88 per 10,000 births. The registry which sees to contribute most to the increase is Emilia-Romagna, although it is not the registry with the highest average prevalence. It is worth noting that Hungary, although it has a statistically significant increase in prevalence, has relatively low prevalence over all. Ile de Reunion has the highest average prevalence, but it shows a non-statistical decrease in prevalence over time. Only one SBA cases (0.20%) was associated with diaphragmatic hernia while 22 (4.39%) were associated with gastroschisis, which has also been associated with disturbance in the mesenteric vasculature.

Figure 3: *Other intestinal atresia / stenosis , showing the increasing trend and that trend when the two registries with a statistically significant rise in prevalence are excluded.*



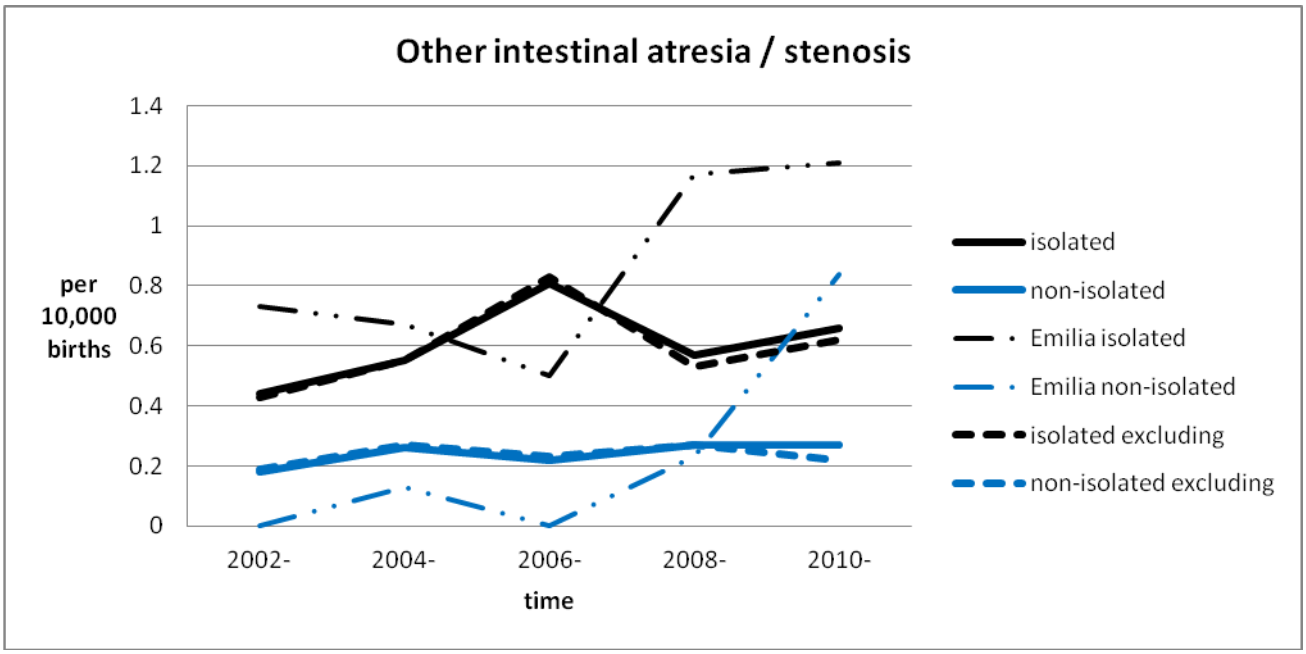
The 10 year prevalence has not changed much over time ranging from 0.76 per 10,000 births to 0.79, with prevalence during the decade from 2002-2011 0.77 per 10,000 births

Figure 4*: The prevalence of other intestinal atresia / stenosis over the past three decades*



When Other intestinal atresia / stenosis is looked at as an isolated anomaly the prevalence is increasing and this increase does not disappear if the data from Emilia Romagna are removed, however, when it is looked at as a non-isolated anomaly, once Emilia Romagna's data are removed the increase disappears.

Figure 5: *Prevalence of other intestinal atresia / stenosis as an isolated and as a non-isolated anomaly, including and excluding data from Saxony-Anhalt: 2002-2011*



There is no convincing trend in the time of diagnosis for either isolated or non-isolated anomalies. Both still birth and TOPFA are unusual for this congenital anomaly.

Figure 6: *When diagnosed, for isolated and non-isolated cases, over time.2002-2011*

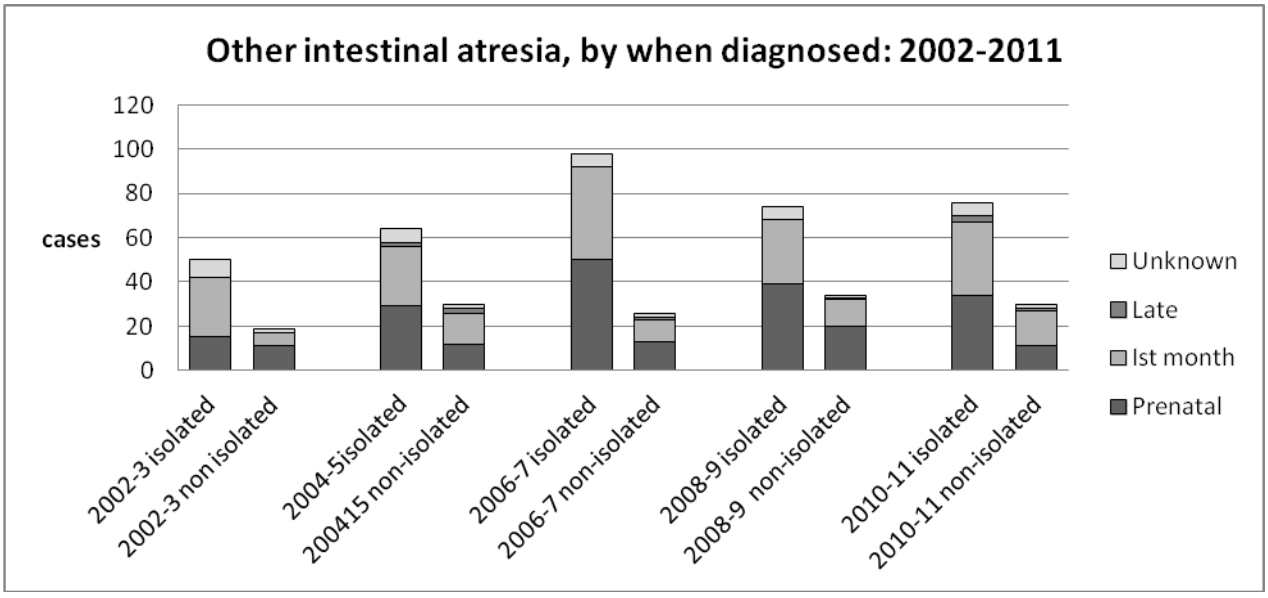
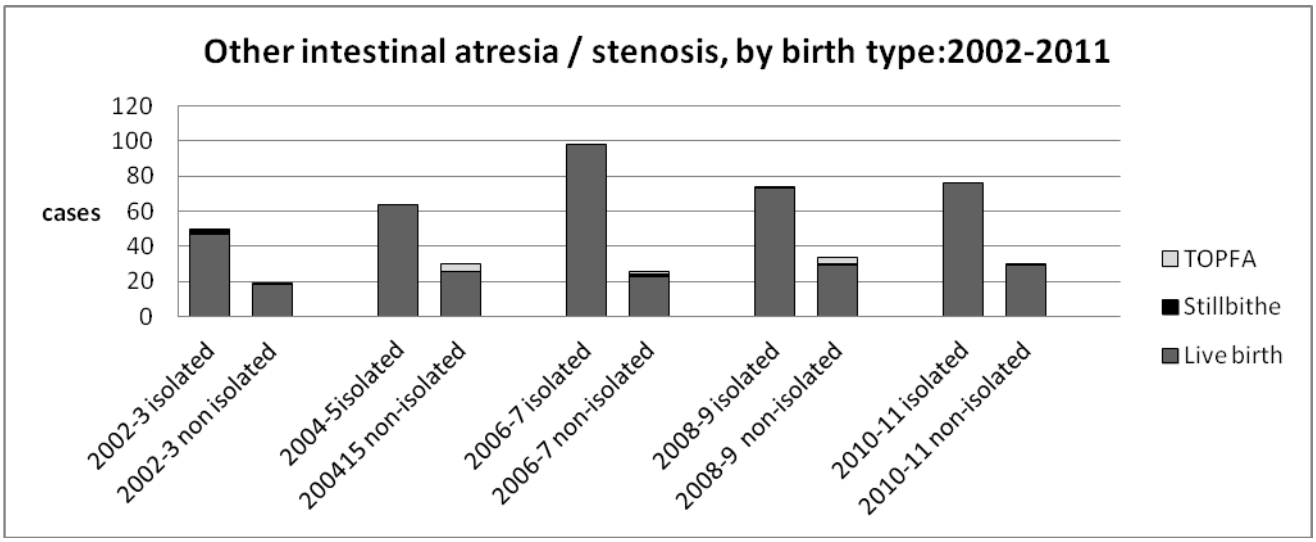


Figure 7: Type of birth for isolated and non-isolated anomalies, over time 2002-2011



Conclusions

There does seem to be an increase over time in “other” intestinal anomalies, and this is mainly in isolated anomalies. There is a significant increase in prevalence in Emilia Romagna, but there are other registries with high prevalence levels which have not changed significantly over time. The registry with the highest prevalence Ile de Reunion is showing a decrease over time.

(1) Barnard CN, Louw JH. The genesis of intestinal atresia. Minn Med 1956 passim; Nov;39(11):745.

(2) Acs N, Banhidy F, Puho EH, Czeizel AE. A possible association between maternal glomerulonephritis and congenital intestinal atresia/stenosis--a population-based case-control study. Eur J Epidemiol 2007;22(8):557-564.

(3) Hemming V, Rankin J. Small intestinal atresia in a defined population: occurrence, prenatal diagnosis and survival. Prenat Diagn 2007 Dec;27(13):1205-1211.

(4) Best KE, Tennant PW, Addor MC, Bianchi F, Boyd P, Calzolari E, et al. Epidemiology of small intestinal atresia in Europe: a register-based study. Archives of Disease in Childhood Fetal & Neonatal Edition 2012 Sep;97(5):F353-8.

(5) Loane M, Dolk H, Morris JK, EUROCAT Working G. Maternal age-specific risk of non-chromosomal anomalies. BJOG: An International Journal of Obstetrics & Gynaecology 2009 Jul;116(8):1111-1119.

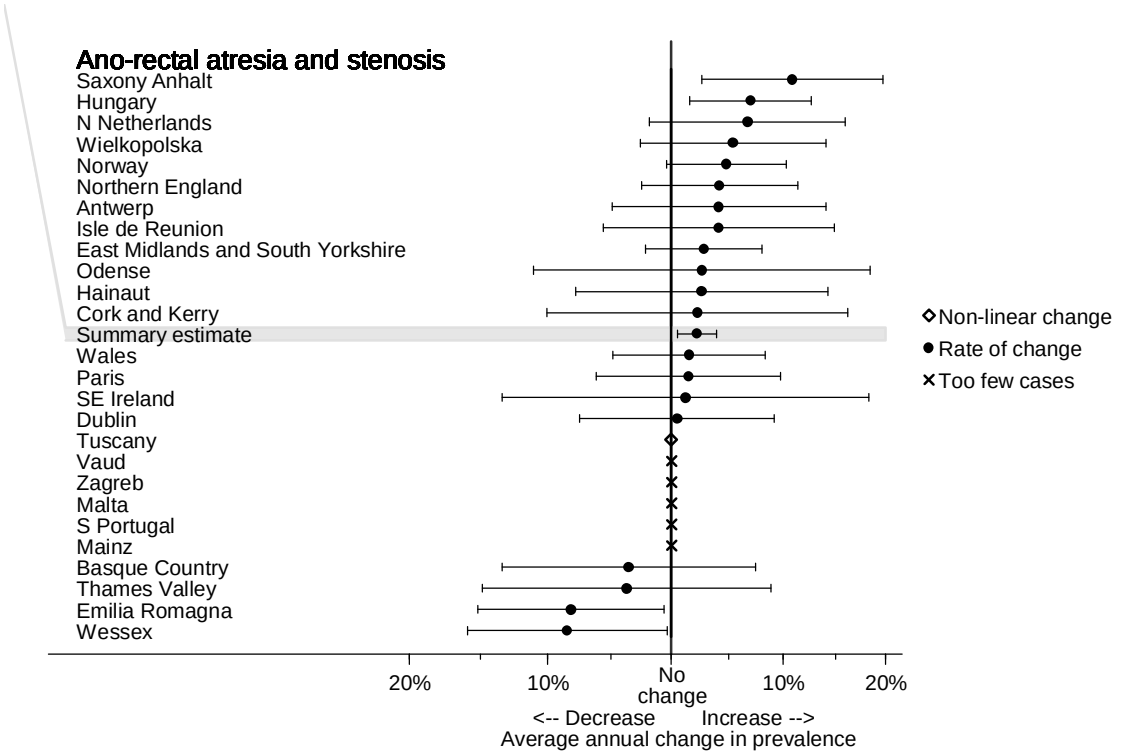
(6) Martinez-Frias ML, Castilla EE, Bermejo E, Prieto L, Orioli IM. Isolated small intestinal atresias in Latin America and Spain: epidemiological analysis. Am J Med Genet 2000 Aug 28;93(5):355-359.

Ano-rectal atresia and stenosis (ARM): increasing trend

The registries which show a statistically significant trend moving in the same direction and which therefore may be contributing are: : Saxony-Anhalt, Hungary, with non-statistically significant increase in prevalence in Northern Netherland Wielkopolska, Norway Northern England, Antwerp, Ile de Reunion, EMSYCAR, Odense, Hainaut, Cork and Kerry, Wales and Paris.

The registries which show a trend in the opposite direction are: Wessex, Emilia-Romagna, Thames Valley and Basque country.

***Figure 1**. The trend in prevalence of ARM showing individual registries and the pan European trend, 2002-2011*



Literature review

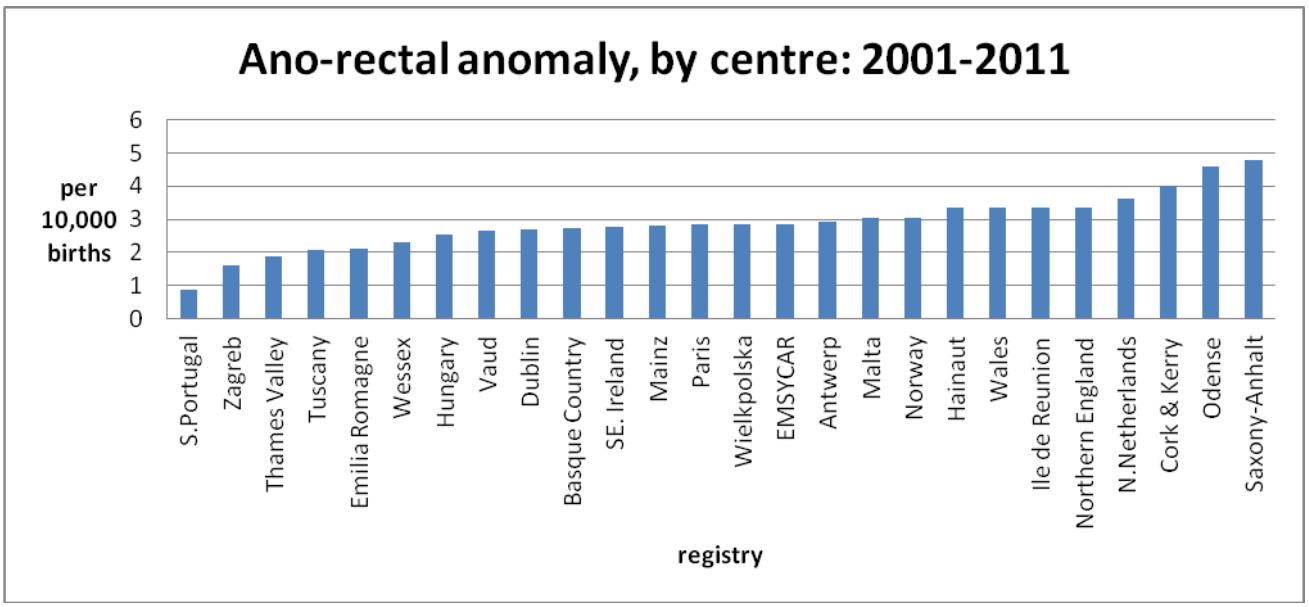
Ano-rectal malformations (ARM) are the group of congenital anomalies which most commonly affect the gastro-intestinal tract (RW.ERROR - Unable to find reference:2762). The anomalies are characterised by a complete failure of the rectum to communicate with the anus or a narrowing of the ano-rectal canal. 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 Trache-Eosophageal, 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 (RW.ERROR - Unable to find reference:2763). There is some evidence that more severe ARM is more likely to be associated with VACTERL and with multiple congenital anomalies in general (RW.ERROR - Unable to find reference:2763). ARM has been theoretically linked with alterations in the Sonic hedgehog pathway (RW.ERROR - Unable to find reference:2781) 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 blastogenitic stage (RW.ERROR - Unable to find reference:2783, RW.ERROR - Unable to find reference:2777). ARM has been strongly associated with multiple birth (RW.ERROR - Unable to find reference:250, RW.ERROR - Unable to find reference:134, RW.ERROR - Unable to find reference:312, RW.ERROR - Unable to find reference:286) and with assisted reproductive technologies (RW.ERROR - Unable to find reference:2629, RW.ERROR - Unable to find reference:2762). 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 (RW.ERROR - Unable to find reference:2762).

Consistency between registries

There were 1,808 ARM cases registered over the ten year period. Prevalence ranged between 0.87 cases per 10,000 births in Southern Portugal and 4.8 per 10,000 births in Saxony-Anhalt.

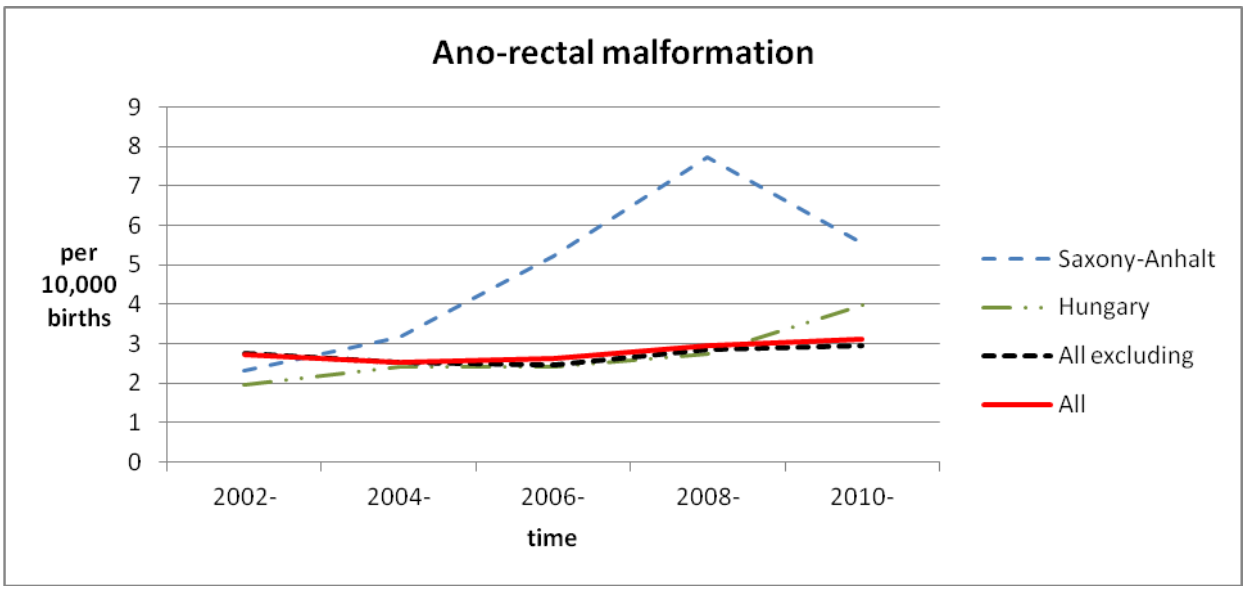
***Figure 2**: Prevalence of ARM by registry 2002-2011*



Trend over time

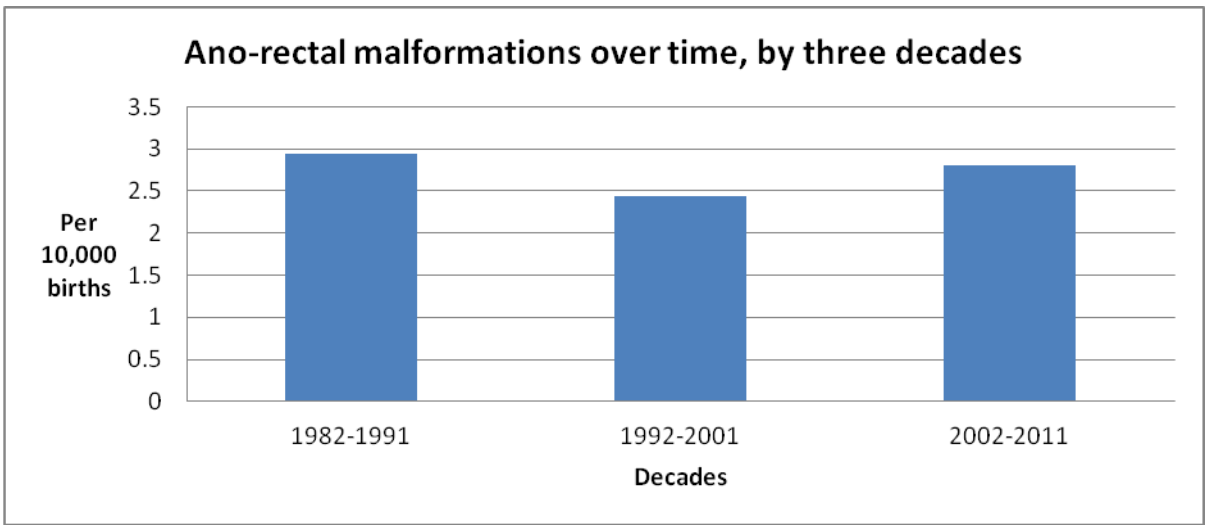
The registry which seems to have contributed most to the increasing trend is Saxony-Anhalt. Hungary started with a relatively low prevalence and ended just above the EUROCAT average. When data from these registries are removed the increasing trend does not disappear, and although the high prevalence rate in Saxony-Anhalt is interesting it does not account for the whole Pan-European rise in prevalence. Prevalence increased, on average, by 2.4% per year over the 10 year period from 2.72 per 10,000 births to 3.13 per 10,000 births and this compares with prevalence of 2.82 per 10,000 births in the 1980 and 2.44 per 10,000 in the 1990s.

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



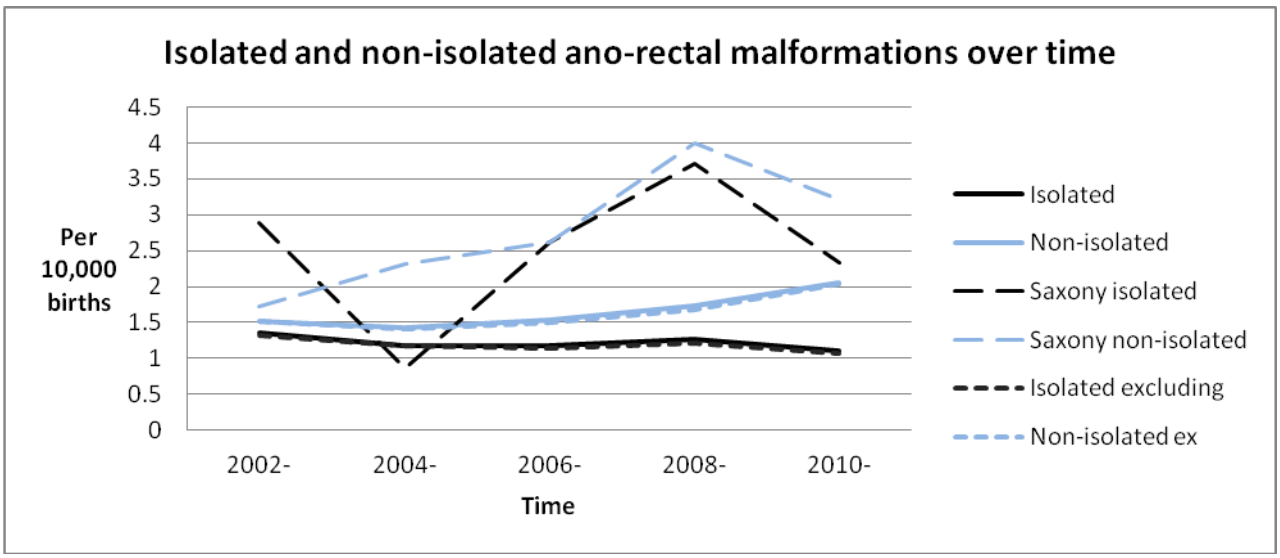
However, when we look at the prevalence of ARM over a longer period of time, prevalence had dropped from 2.95 per 10,000 births in the decade from 1982- 1991 to 2.44 per 10,000 births in the decade from 1992-2001 and has risen to 2.80 per 10,000 births in the last decade.

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



When ARM is divided into an isolated and a non-isolated anomaly (non-isolated includes 3 cases which are part of a teratogenic syndrome and 8 with skin disorders which may have a genetic cause) it becomes obvious that the increase in prevalence is in ARM as a non-isolated anomaly, and that this increase is not attributable to the increase in prevalence in Saxony-Anhalt.

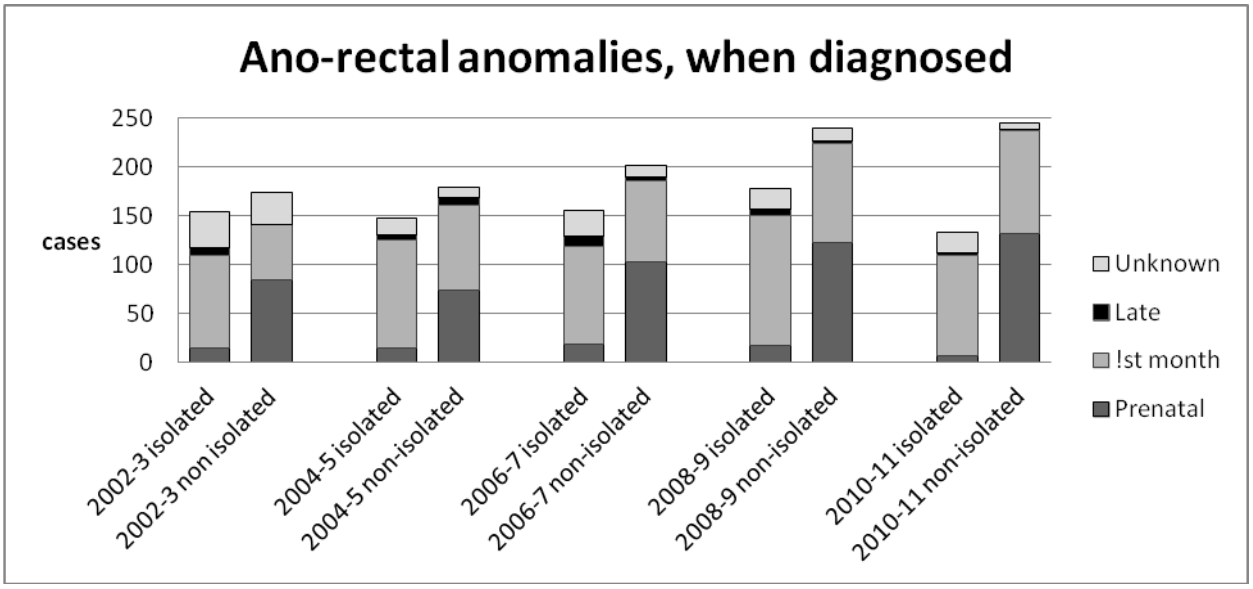
Figure 5: *Prevalence of ARM as an isolated and as a non-isolated anomaly, including and excluding data from Saxony-Anhalt: 2002-2011*



Trend over time in prenatal diagnosis and birth type

Prenatal diagnosis is much more likely if ARM is a non-isolated anomaly with 9.24% of isolated compared with 49.6% of non-isolated ARM cases prenatally diagnosed. These rates were consistent over the ten year period. 4.30% of isolated cases were discovered after 1 months of age compared to 1.35% of non-isolated cases, and late diagnosis does not appear to be increasing over time in either group.

Figure 6: *When diagnosed for isolated and non-isolated cases, over time.2002-2011*

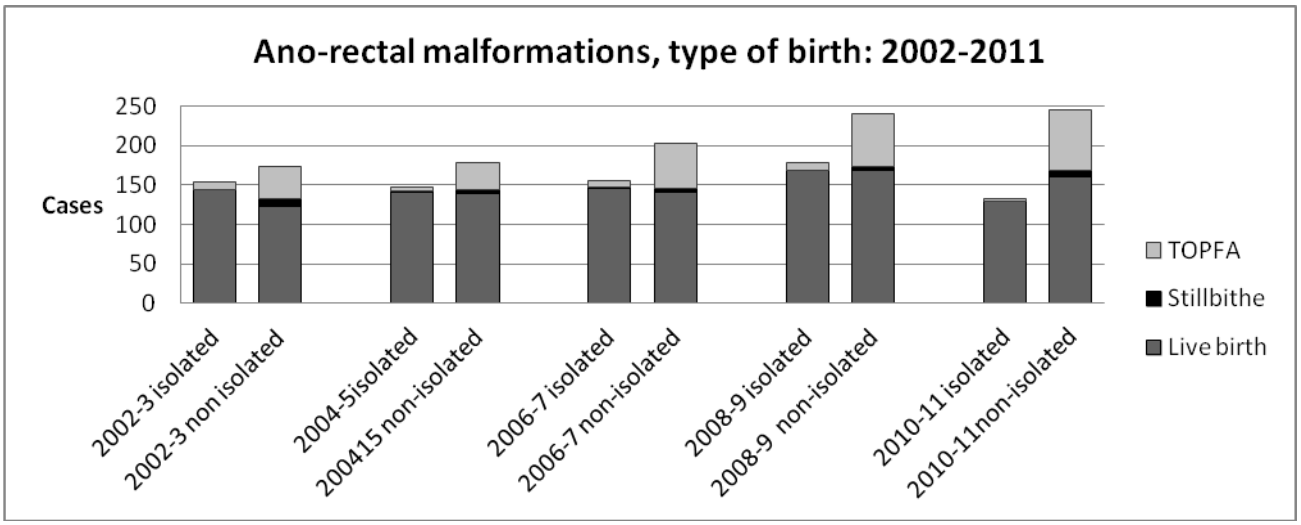


*Late diagnosis refers to more than one month after birth

NB. Data for 7 registries not included for 2011

Stillbirth and TOPFA are both unusual in isolated anomalies. The proportion of non-isolated anomalies which are TOPFA has increased over time. If there is significant attrition in non-isolated cases in the second trimester this may account for some of the increase.

Figure 7: Type of birth for isolated and non-isolated anomalies, over time 2002-2011



NB. Data for 7 registries not included for 2011

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.

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.

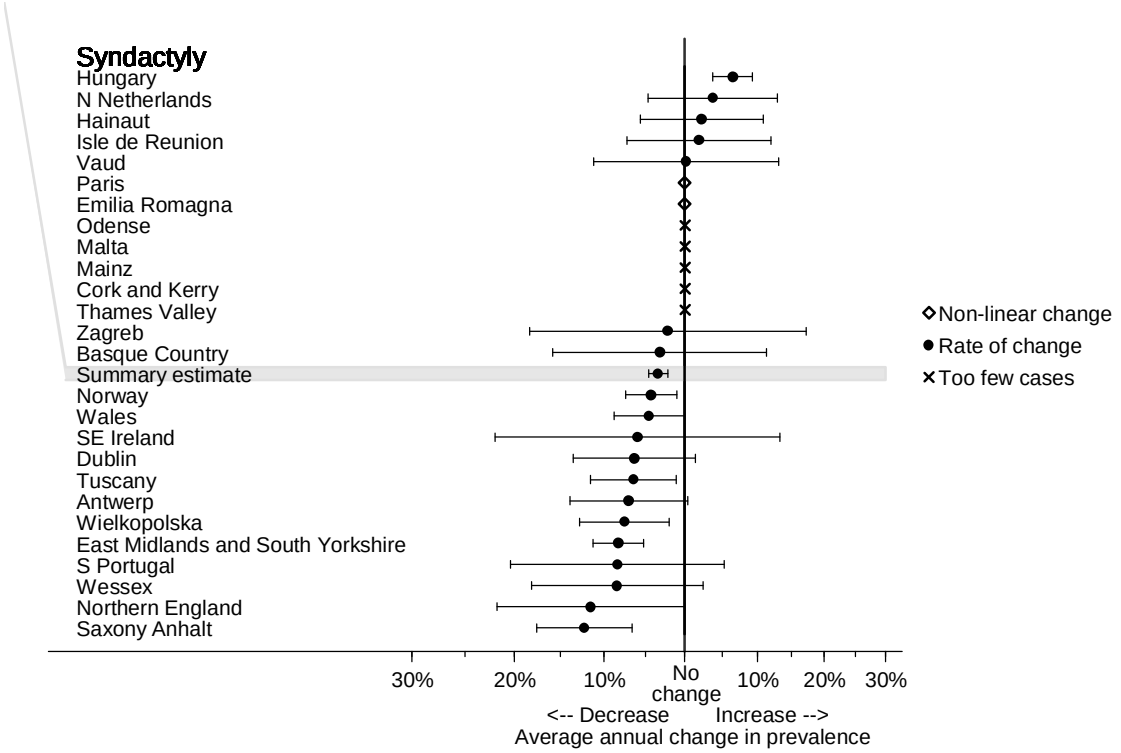
(10) Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Otterblad PO. Congenital malformations in infants born after in vitro fertilization in Sweden. Birth Defects Research 2010 Mar;88(3):137-143.

Syndactyly: decreasing trend

The registries which show a trend moving in the same direction and which therefore may be contributing are Saxony-Anhalt, Northern England, Wielkopolska, Antwerp, Tuscany, Dublin, South East Ireland, Wales and Norway

The registries which show a trend in the opposite direction are Hungary, Northern Netherlands and Hainaut.

***Figure 1**. The trend in prevalence of Syndactyly showing individual registries and the pan European trend, 2002-2011*



Literature review

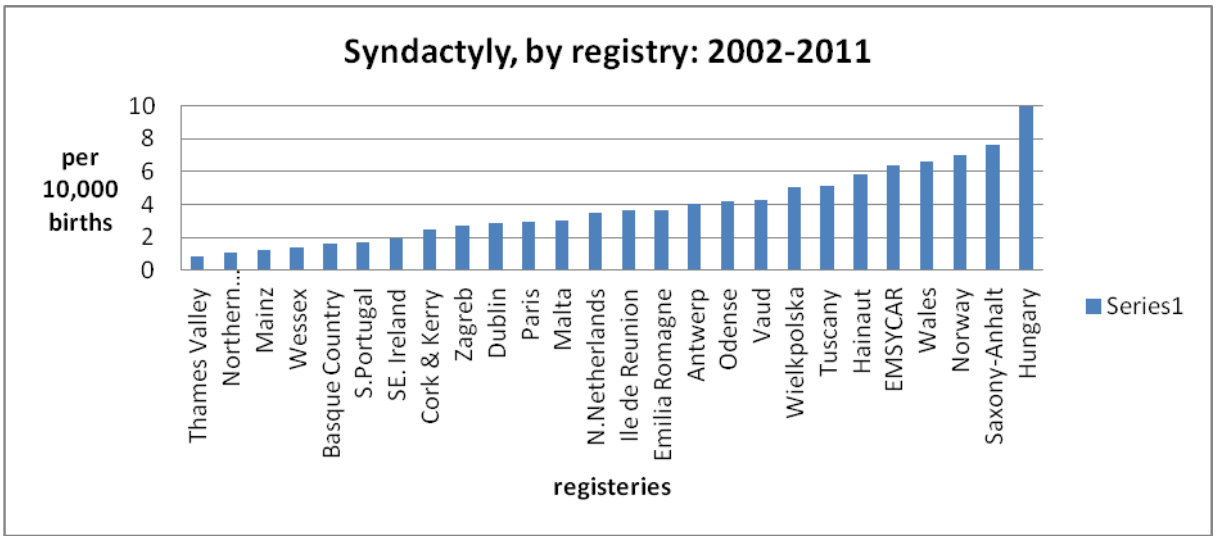
Syndactyly is the most common type of hand deformity involving webbing of adjacent digits (fingers or toe) with the severity ranging from skin webbing to bone involvement. Nine phenotypes of the disease are described with none syndromic syndactyly happening sporadically with a family history noted in 10-15 cases (1). Risk factors include maternal smoking and low socio-economic status which may include poor nutrition. Associations with other congenital anomalies are often seen within syndromes.

There was a change in practice after 2005 when EUROCAT registries stopped registering minor syndactyly cases

Consistency between registries

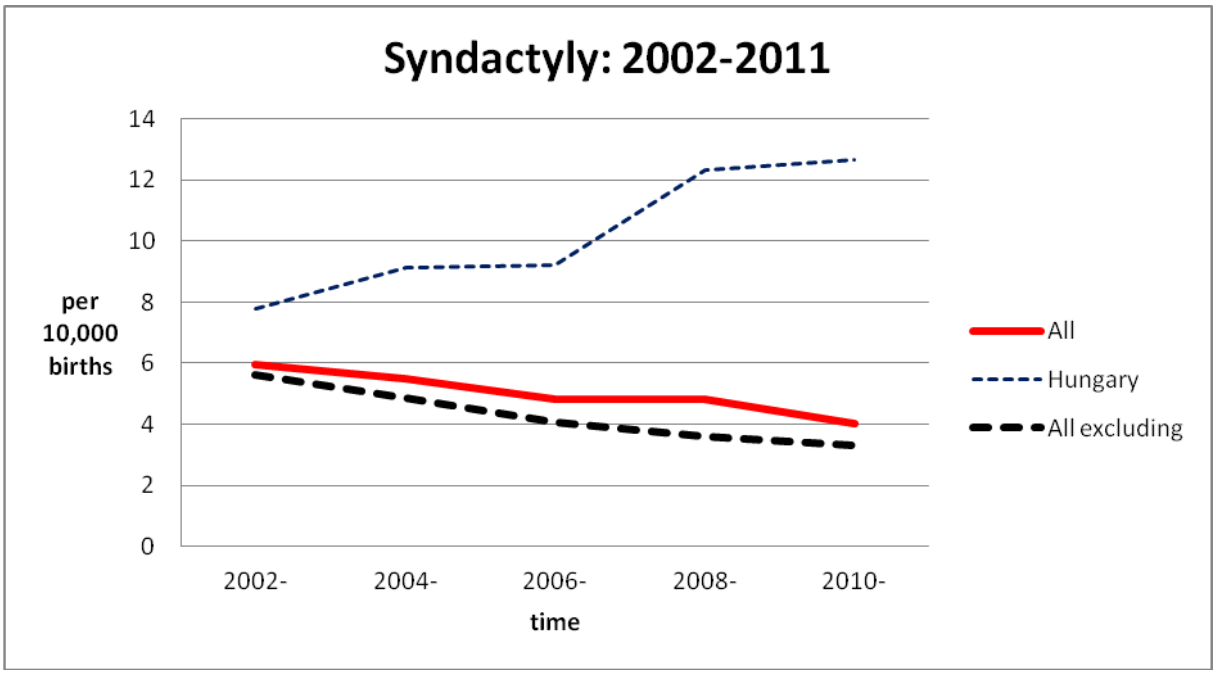
There were 3,245 cases included in the analysis. Prevalence of syndactyly ranged from 0.87 prt 10,000 in Thames Valley to 9.94 per 10,000 in Hungary.

***Figure 2**: Prevalence of Syndactyly, by registry 2002-2011*



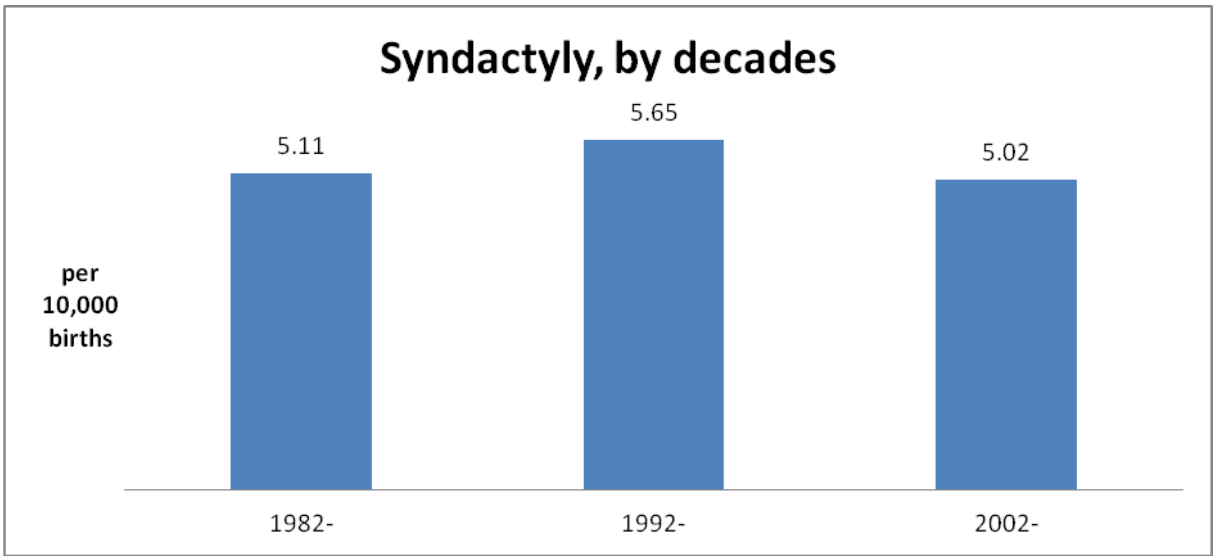
Trend over time (All, those which contribute most, all others

Prevalence decreases, on average, by 3.41% per year over the 10 year period from 5.95 per 10,000 births to 4.03 per 10,000 births. This decrease was seen in most registries, with only Hungary showing a significant increase over time.



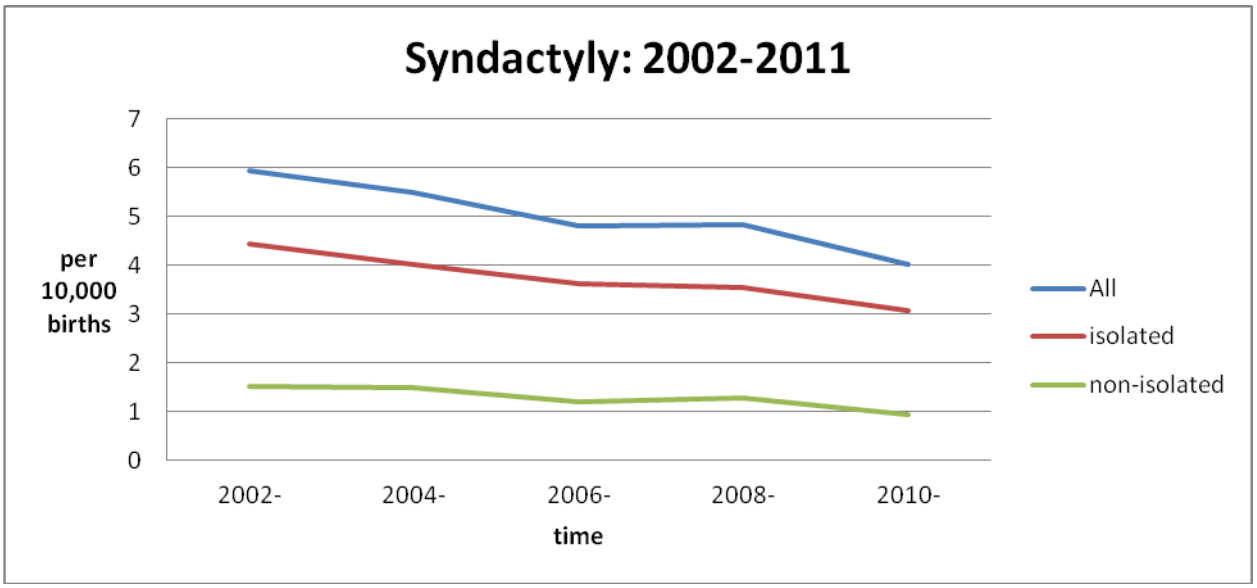
The 10 year prevalence increased from 5.11 per 10,000 births in the decade from 1982-1991 to 5.65 per 10,000 births from 1992-2001 before decreasing again in the decade 2002-2011.

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



The decrease in prevalence of syndactyly was mainly in isolated anomalies, although there was a small decrease in the prevalence of syndactyly as one of multiple anomalies.

***Figure 5:** Prevalence of syndactyly as an isolated and as a non-isolated anomaly, including and excluding data from Saxony-Anhalt: 2002-2011*



Syndactyly is usually prenatally diagnosed when it is one of multiple anomalies, but the frequency of late diagnosis has decreased over time. TOPFA and stillbirth are both very unusual in isolated cases of syndactyly with no trend over time in ether.

Figure 6: *When diagnosed, for isolated and non-isolated cases, over time.2002-2011*

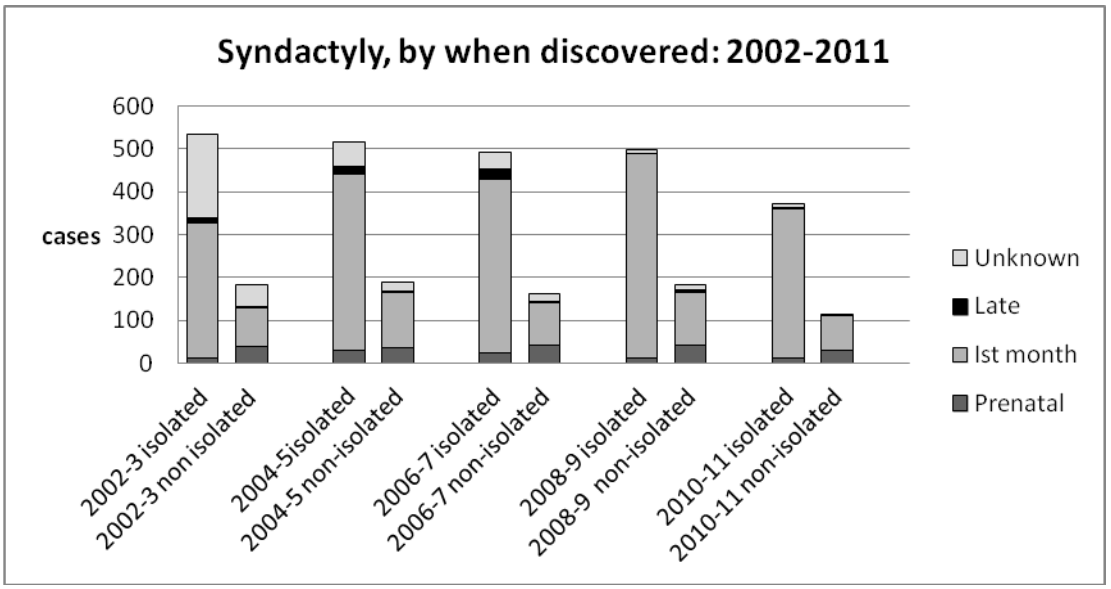
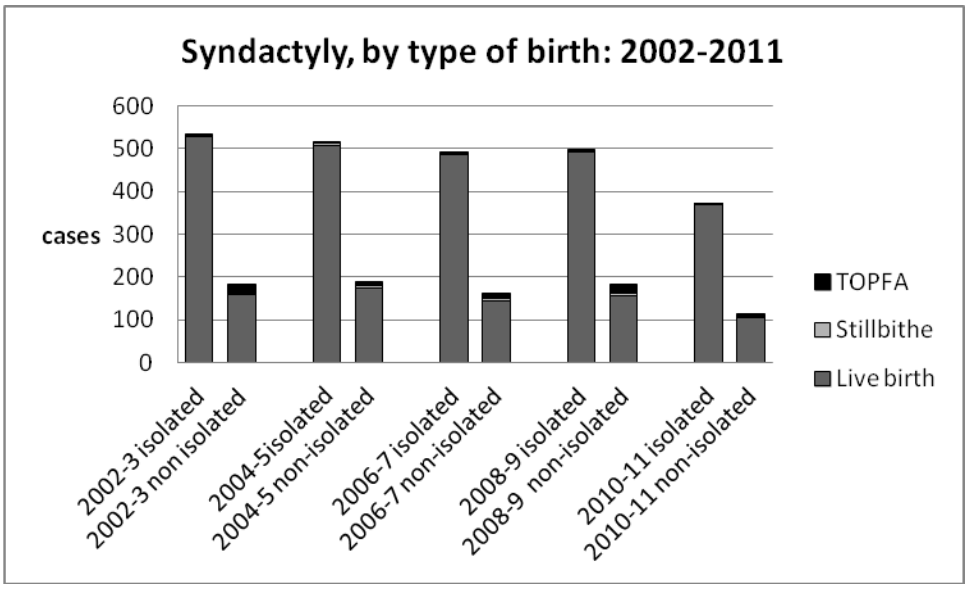


Figure 7: Type of birth for isolated and non-isolated anomalies, over time 2002-2011



Conclusions

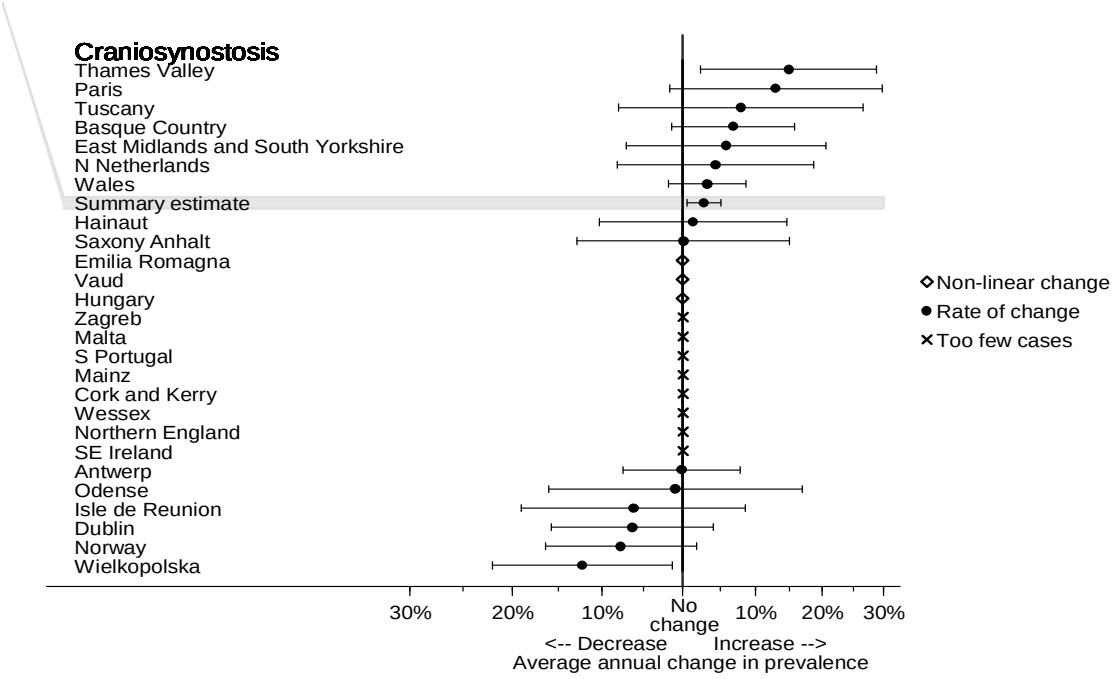
As the decrease in prevalence of syndactyly continued after 2005 changes in registration practices may not fully explain the overall decrease. Some of this may be due to the way in which syndactyly is now classified.

(1) Jordan, d. Hindocha, S. Dhital, M. Saleh, M. Khan, W The epidemiology, genetics and future management of syndactyly. The Open Orthopaedics Journal 2012 (supplement 1:M2) 14-27

Craniosynostosis: increasing trend

The registries which show a trend moving in the same direction and which therefore may be contributing are Thames Valley which is the only registry where the increase is statistically significant, with Paris, Tuscany, Basque Country, EMSYCAR, Northern Netherlands and Wales showing an non-statistically significant increase. Wielkopolska shows a statistically significant decrease in prevalence.

***Figure 1**. The trend in prevalence of Craniosynostosis showing individual registries and the pan European trend, 2002-2011*



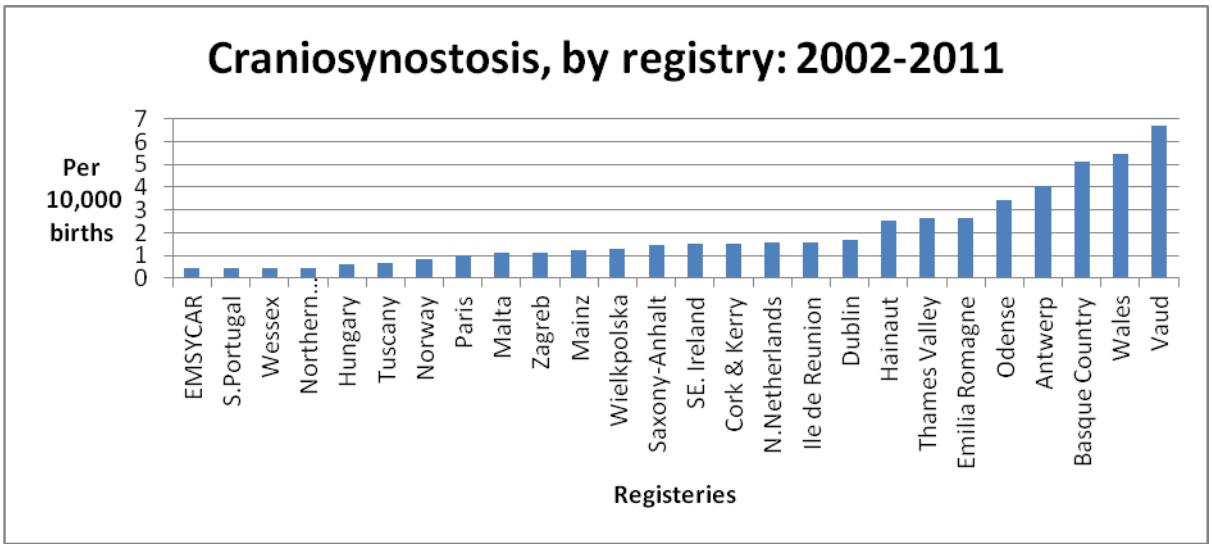
Literature Review

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 of 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

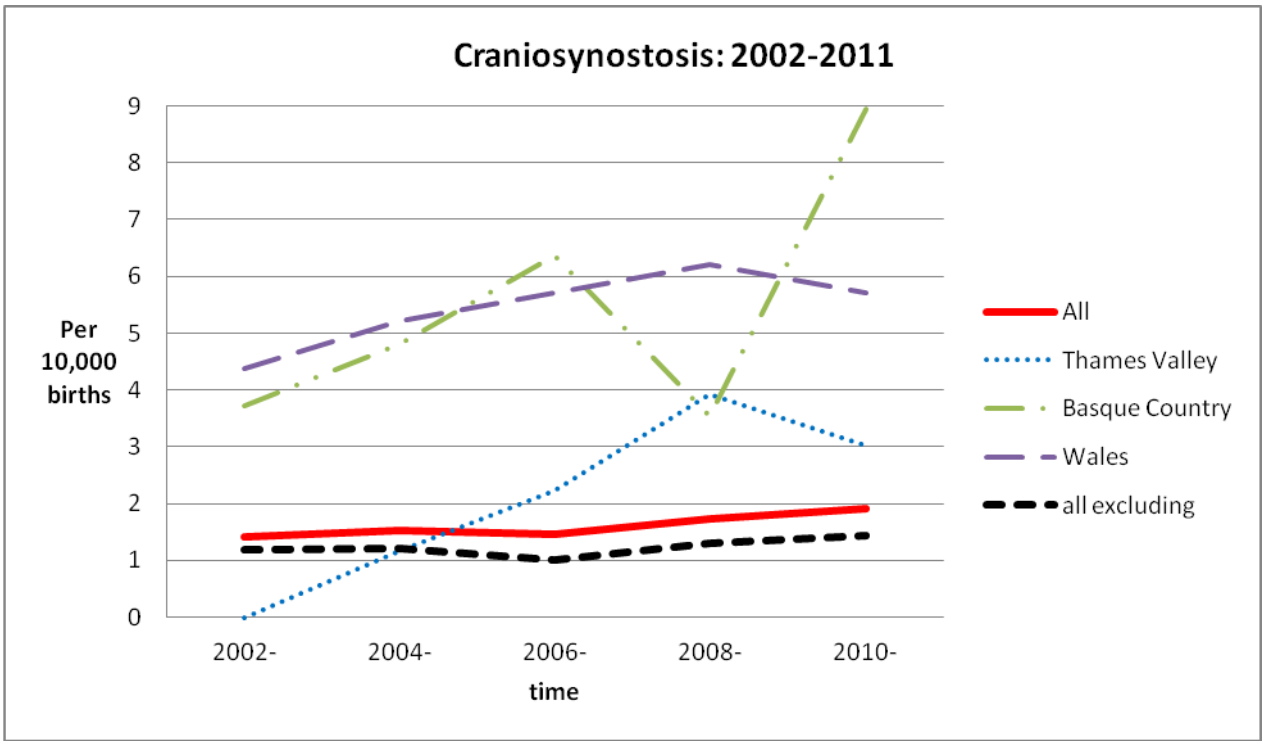
There were 1,039 craniosynostosis cases registered in the 10 year period. There was a wide range in prevalence over the ten year period, from 0.43 per 10,000 births in EMSYCAR to 6.68 per 10,000 births in Vaud.

***Figure 2**: Prevalence of Craniosynostosis, by registry: 2002-2011*



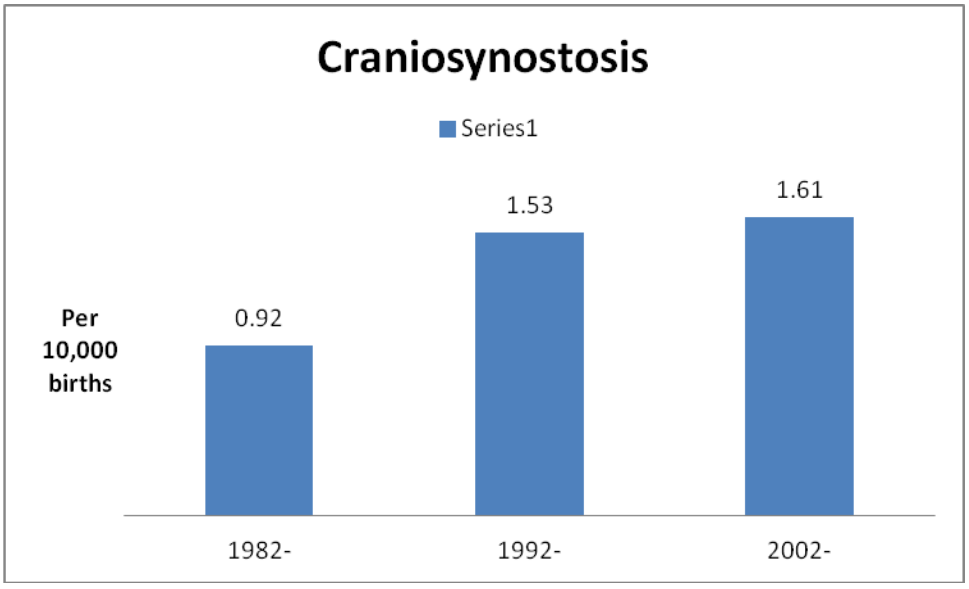
The three registries considered to have an increasing trend and a high enough overall prevalence to be contributing to the increasing trend were Thames Valley, Basque Country and Wales, When the data from these three registries were excluded the overall prevalence dropped, but the increasing trend did not fully disappear.

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



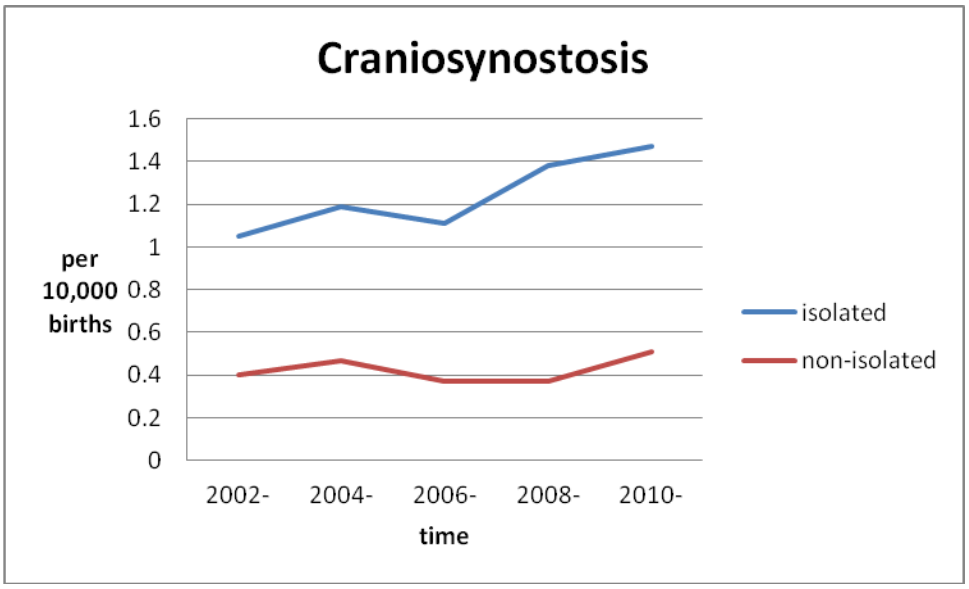
When data are examined across the three decades for which they are available, it becomes clear that the prevalence, or at least the ascertainment, of CS has increased over time. Prevalence has risen from 0.92 per 10,000 births in the decade from 1982-1991 to 1.61 in the decade from 2002-2011.

Figure 4: The prevalence of Craniosynostosis, over the past three decades



When Craniosynostosis is looked at as an isolated and a non-isolated anomaly, although there is a small in rise in prevalence of the condition as a non-isolated anomaly, the main increase seems to be in Craniosynostosis as an isolated anomaly.

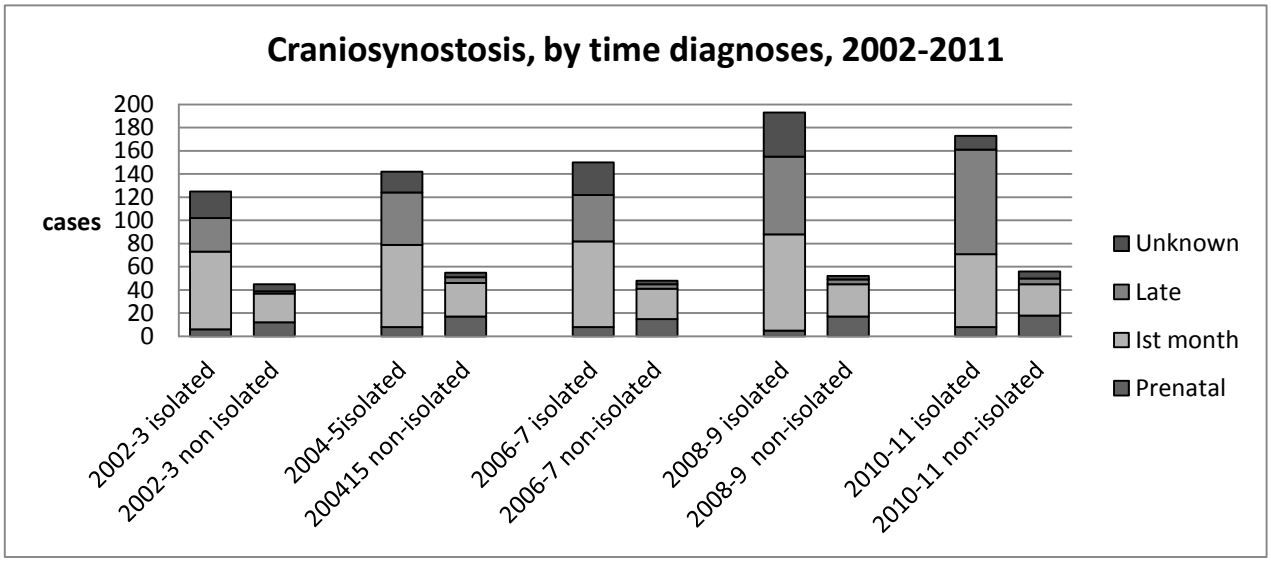
Figure 5: *Prevalence of craniosynostosis as an isolated and as a non-isolated anomaly*



Trend in when diagnosed and in type of birth

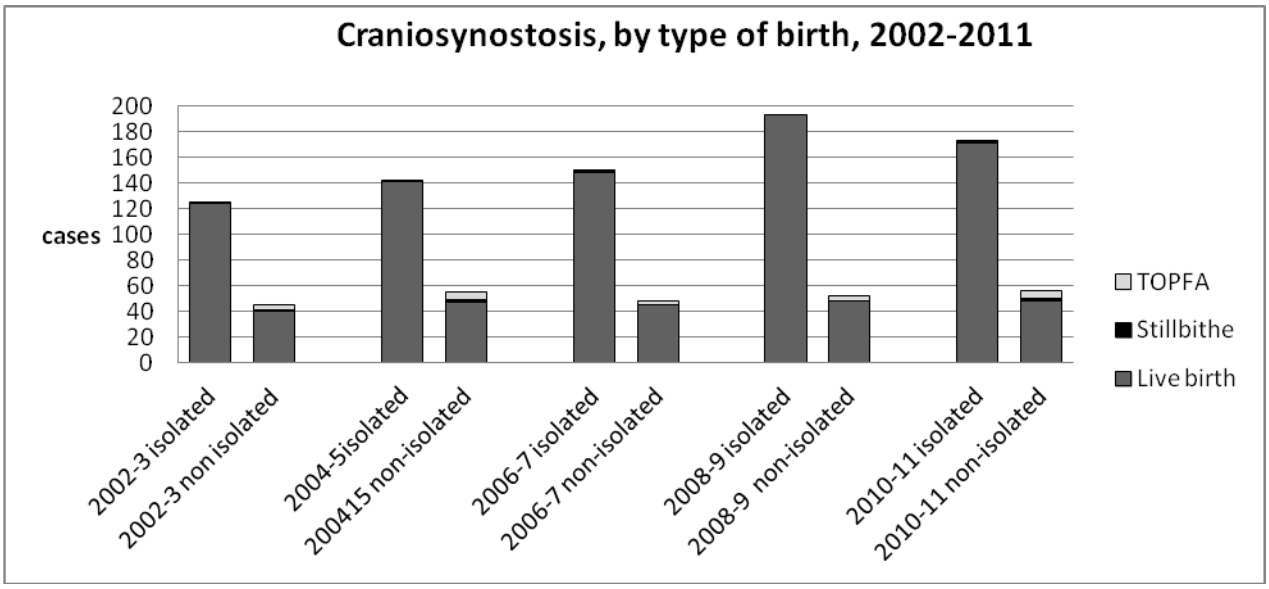
It is relatively unusual for an isolated Craniosynostosis case to be prenatally diagnosed if it is not associated with another congenital anomaly. The proportion of cases which were diagnosed after one month of life has increased over time for both isolated and non-isolated cases with 52% of cases in the 2010 to 2011 period diagnosed after one month of life. Overall prevalence may increase further as cases born in 2011 are diagnosed and ascertained by the registries.

Figure 6: *When diagnosed for isolated and non-isolated cases, over time.2002-2011*



Both TOPFA and stillbirth are unusual in craniosynostosis cases, and this has not altered over time

Figure 7: Type of birth for isolated and non-isolated anomalies, over time 2002-2011



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.

(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.

Valproate acid syndrome: Decreasing trend

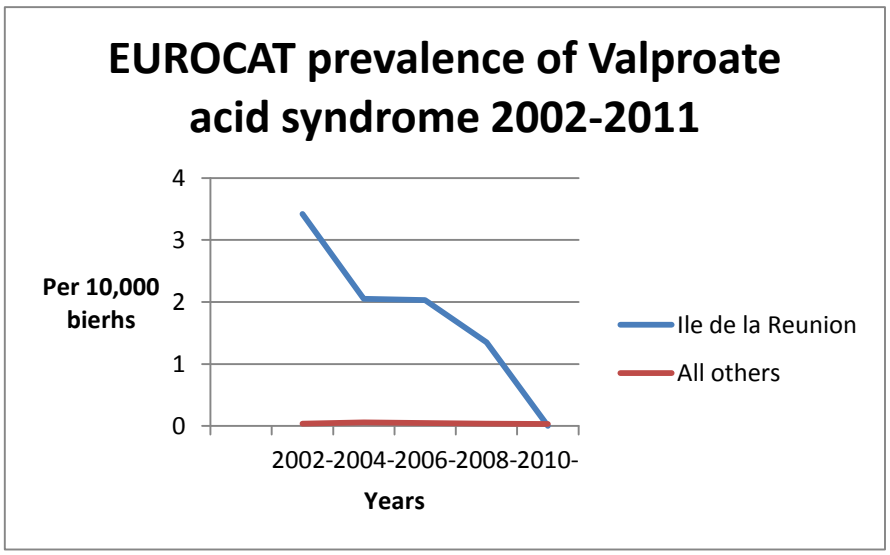
The decreasing trend in the prevalence of Valproate acid syndrome is due to a fall in the number of cases from Ile de la Reunion. Of the 27 cases registered by Ile de la Reunion:

- One also had trisomy 13
- 15 have other congenital anomalies registered
- 11 have no other congenital anomaly registered although one mentions stenosis of the aorta in free text.

Table 1: Numbers and prevalence per 10,000 births of cases with Valproate acid syndrome in Ile de la Reunion and in the rest of EUROCAT: 2002-2011

	Ile de La Reunion		All other registries	
	No	Prevalence per 10,000 births	No	Prevalence per 10,000 births
2002-	10	3.42	5	0.04
2004-	6	2.05	8	0.06
2006-	6	2.03	6	0.05
2008-	4	1.35	5	0.04
2010-	0	0	4	0.03
Total	27	1.78	28	0.04

Figure 1 1: Prevalence per 10,000 births of cases with Valproate acid syndrome in Ile de la Reunion and in the rest of EUROCAT: 2002-2011



Conclusions

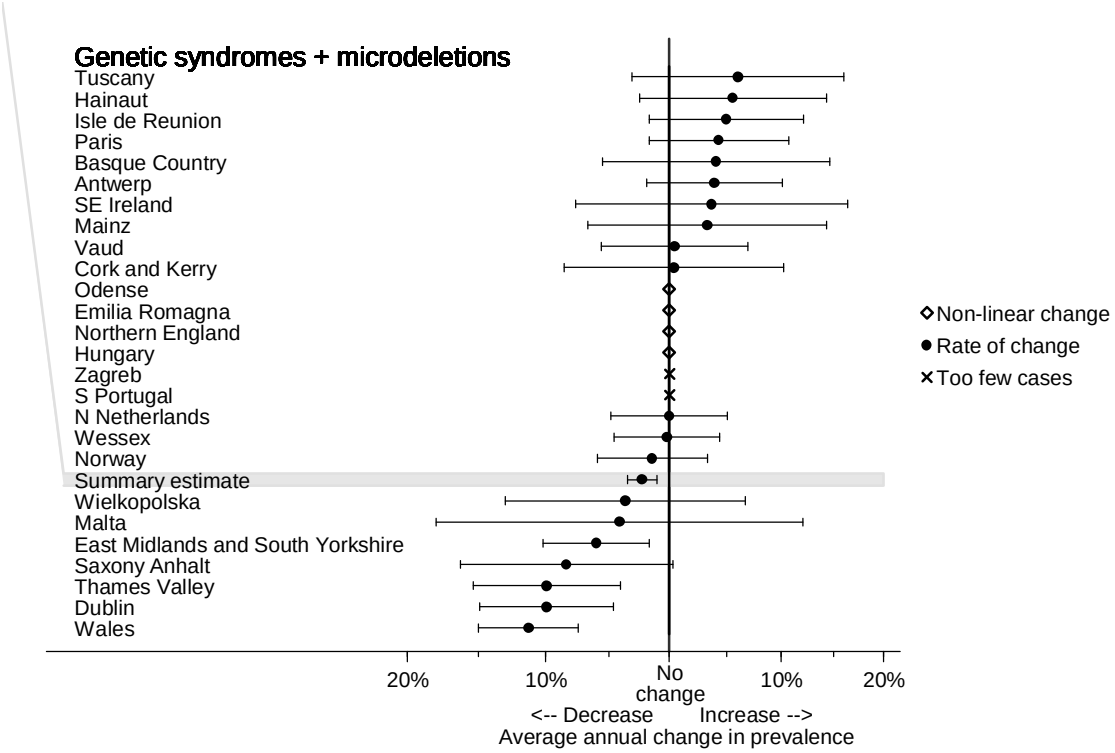
During a discussion at the Registry Leaders Meeting it was reported that there has been a change in prescribing practices in Ile de la Reunion and that this is a true change in prevalence. There was some discussion on the diagnosis of Valproate acid syndrome and the trend will be monitored.

Genetic Syndromes & microdeletions: decreasing trend

The registries which show a statistically significant trend moving in the same direction and which therefore may be contributing are Wales, Dublin, Thames Valley and EMSYCAR, with Saxony-Anhalt showing a decrease which almost reached significance.

Although eight registries showed an increasing trend, none of these were strong enough to be statistically significant.

***Figure 1**. The trend in Genetic syndromes showing individual registries and the pan European trend, 2002-2011*



Literature review

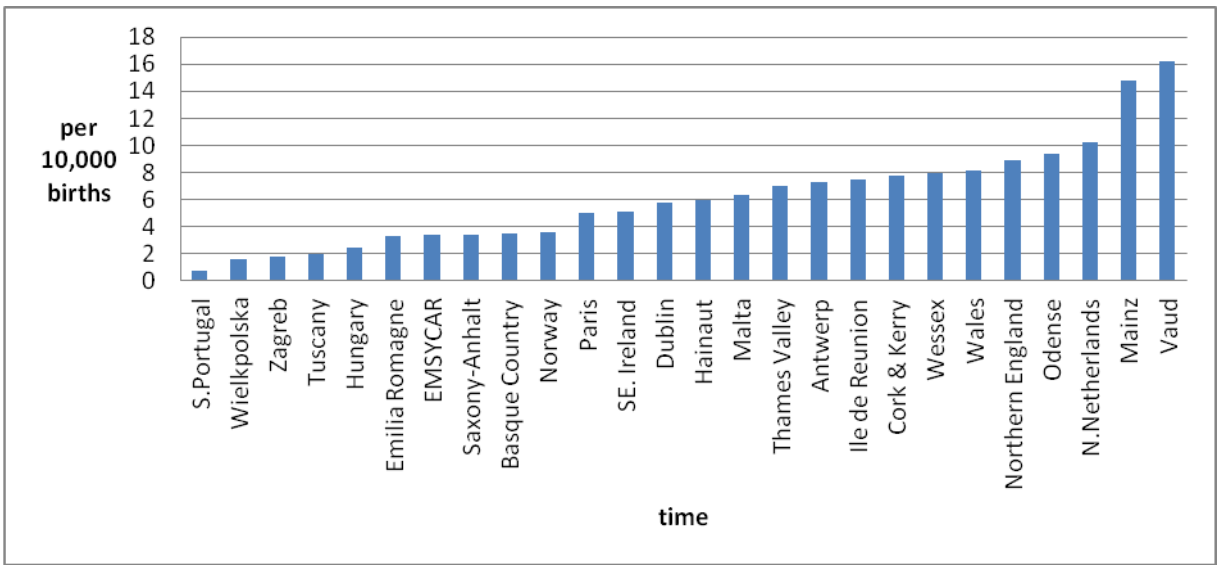
Cases coded to the EUROCAT subgroup Genetic syndromes and micro deletions fulfil the Opitz's definition (1) of conforming to a recognisable pattern of anomalies which are known or "thought" to be causally related. Syndromes are coded using their ICD 10 codes rather than their "Online Mendelian Inheritance in Man (OMIM) codes, and it is recommended that coding is carried out by a geneticist. Many so called syndromes which are really sequences or associations (2), in that their aetiology is not fully understood, are not coded to this variable. (See EUROCAT Syndrome Guide (2004) revised 2008).

It is difficult to discuss risk factor for such a large group of anomalies, with many of them inherited from one or both parents, but epigenetic changes which are implicated in some of these syndromes have been associated with assisted reproductive therapies (3) and with advanced parental age (4).

Consistency between registries

There were 3139 cases registered over the 10 year period. There was a wide range in prevalence over the ten year period, from o.76 per 10,000 births in Portugal to 16.2 per 10,000 births in Vaud.

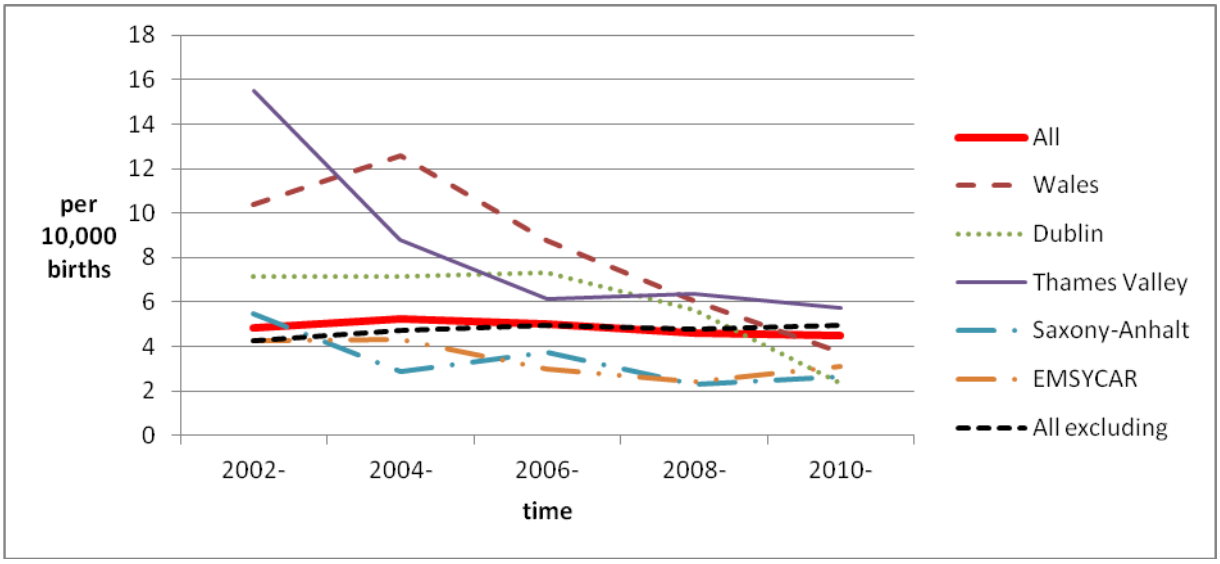
***Figure 2**: Prevalence of Genetic Syndrome, by registry: 2002-2011*



Trend over time

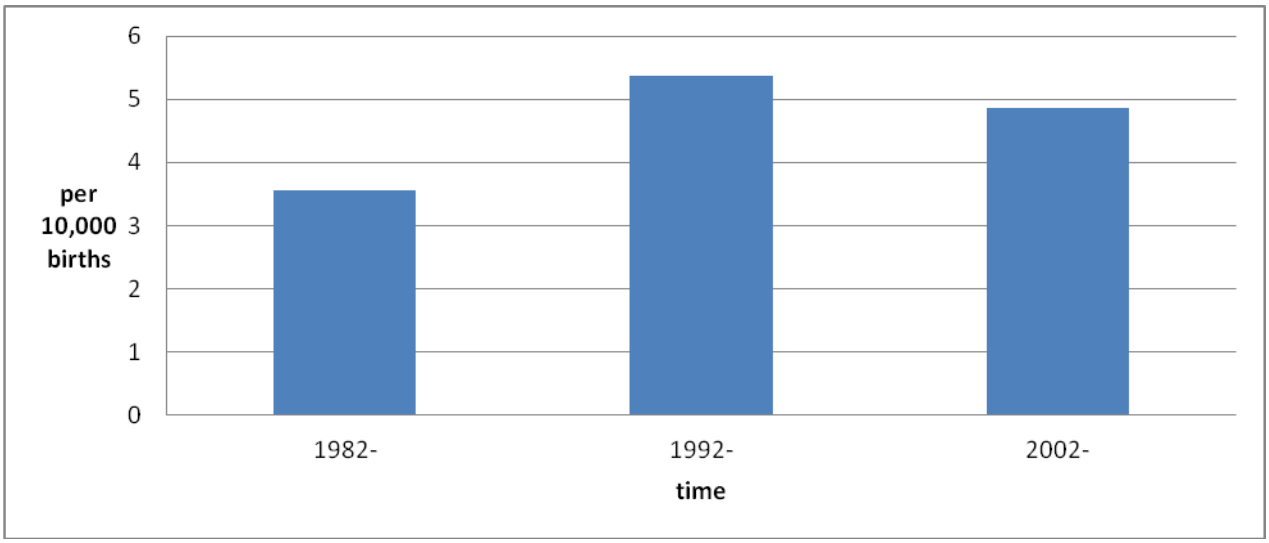
The prevalence fell by an average of 2.29% per year to 4.51 per 10,000 births in 2010-2011. Both Wales and Thames Valley, and to a lesser extent Dublin, had high ascertainment which has dropped sharply toward the end of the time studied. Saxony-Anhalt and EMSYCAR started closer to the EUROCAT average and have also decreased in prevalence. If the data from these registries are excluded, the Pan-European trend actually increases.

Figure 3: *Genetic Syndromes, showing the increasing trend and that trend when the two registries with a statistically significant rise in prevalence are excluded.*



The prevalence rose in the decade from 1992-2001 to 5.38 per 10,000 dropped to 4.86 per 10,000 births in the decade under investigation.

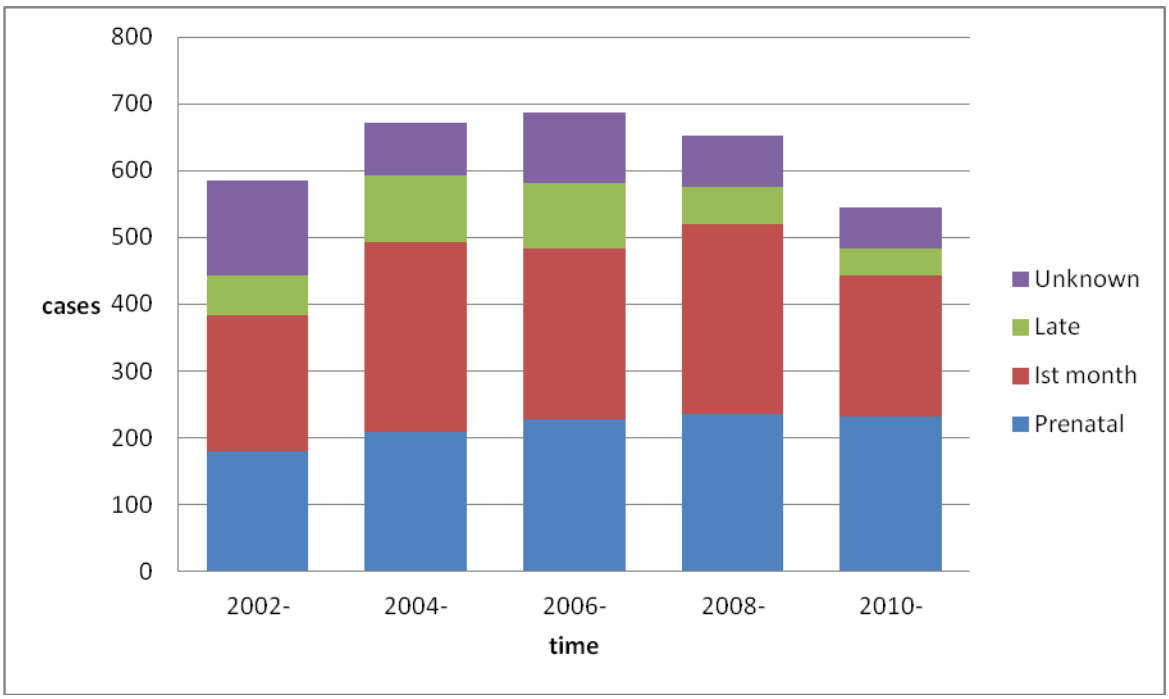
Figure 4*: The prevalence of Genetic Syndromes over the past three decades*



Trend over time in when diagnosed and in birth type

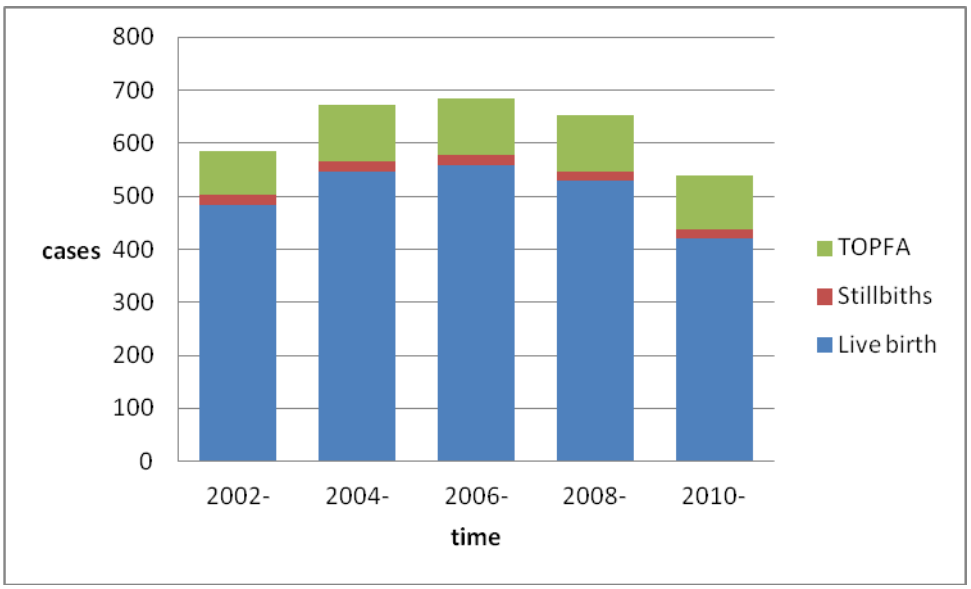
The proportion of cases which were diagnosed late rose toward the middle of the ten year period studied and dropped toward the end. This may be because not all the cases which are diagnosed in childhood have been ascertained by the registries as yet. This may also explain why the proportion of cases which are prenatally diagnosed has risen. It does not fully explain the decrease in prevalence over time, especially in the registries which have shown such a dramatic decrease in prevalence. There was a small increase in the proportion of cases prenatally diagnosed over time.

Figure 5: *When diagnosed, for Genetic Syndromes, over time.2002-2011*



The proportion of cases which were TOPFA or stillbirths does not seem to have dramatically changed over time.

Figure 6: Type of birth for genetic syndromes, over time 2002-2011



Conclusions

The decrease in prevalence seems to be related to a decrease in prevalence in the five registries mentioned, and is particularly related to the change in prevalence in Thames Valley and Wales. This may be related to ascertainment rather than an actual decrease.

References

(1) Opitz JM. Associations and syndromes: terminology in clinical genetics and birth defects epidemiology: comments on Khoury, Moore, and Evans. Am J Med Genet 1994 Jan 1;49(1):14-20.

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(3) Amor DJ, Xu JX, Halliday JL, Francis I, Healy DL, Breheny S, et al. Pregnancies conceived using assisted reproductive technologies (ART) have low levels of pregnancy-associated plasma protein-A (PAPP-A) leading to a high rate of false-positive results in first trimester screening for Down syndrome. Human Reproduction 2009 Jun;24(6):1330-1338.

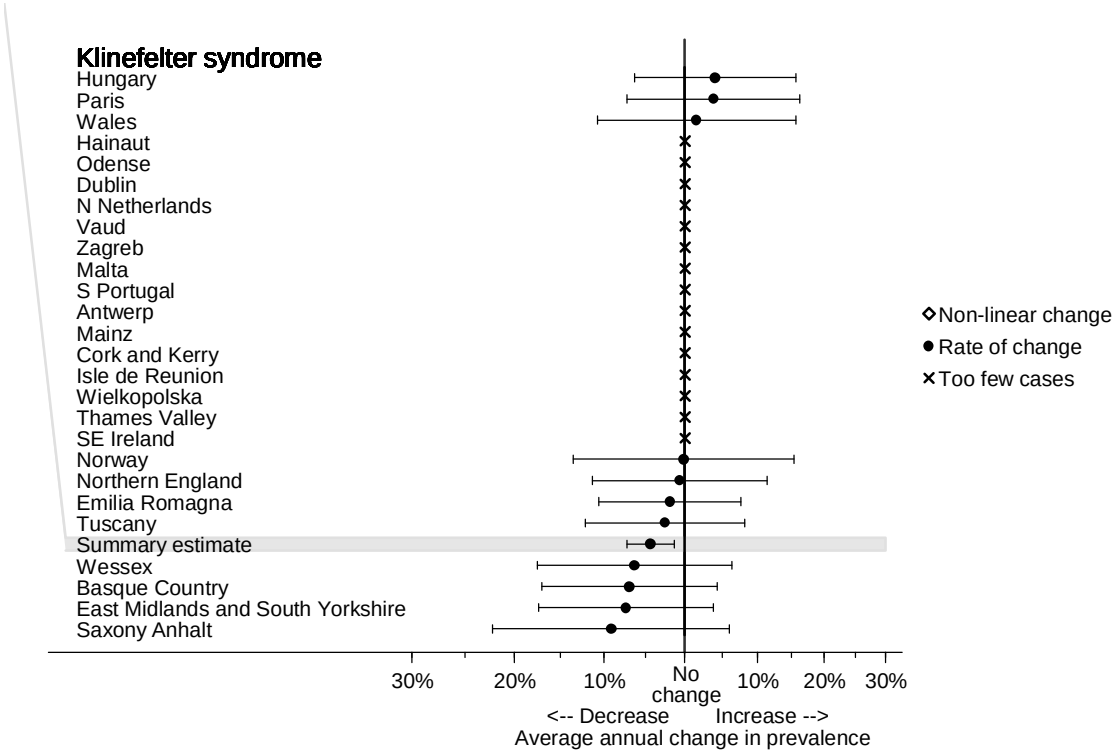
(4) Zhu JL, Madsen KM, Vestergaard M, Olesen AV, Basso O, Olsen J. Paternal age and congenital malformations. Human Reproduction 2005 Nov;20(11):3173-3177.

Klinefelter syndrome: decreasing trend

The registries which show a trend moving in the same direction and which therefore may be contributing are Saxony-Anhalt, EMSYCAR, BASQUE Country and Wessex, none of them independently showing a statistically significant decrease.

The registries which show a trend in the opposite direction are Hungary and Paris

***Figure 1**. The trend in Klinefelter syndromes showing individual registries and the pan European trend, 2002-2011*



Literature review

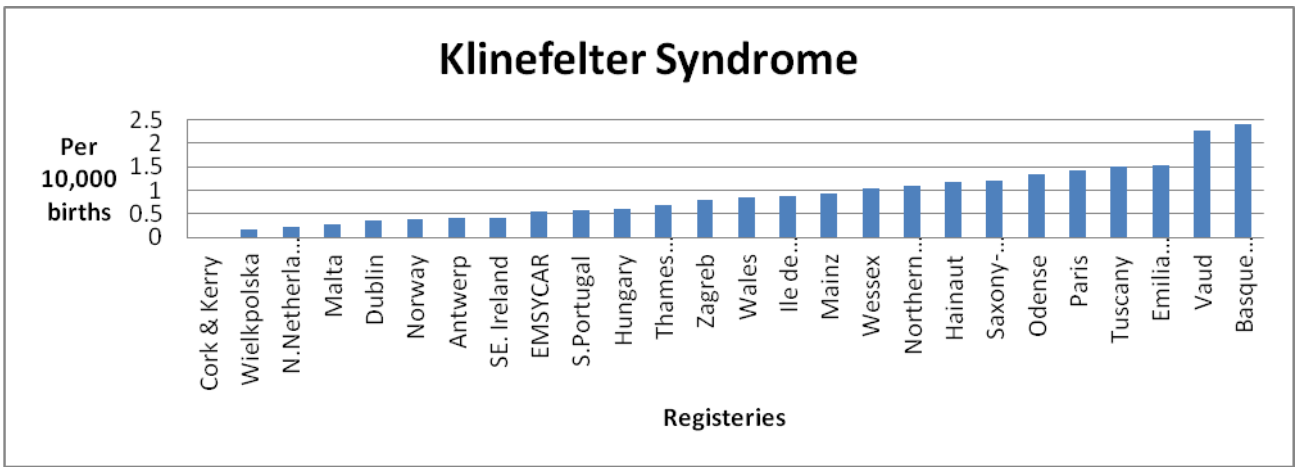
Klinefelter syndrome is caused by a sex chromosome trisomy (XXY) and is associated with increased maternal age. There are few dysmorphic features associated with the syndrome and, while there is an intellectual deficit, this is mild with most cases falling 10 points below their siblings but remaining in the normal range (RW.ERROR - Unable to find reference:2418). As the expected prevalence of Klinefelter syndrome is based on work from the 1970s one could assume that the prevalence should have increased with the recent increase in maternal age (RW.ERROR - Unable to find reference:2803). Prevalence is difficult to ascertain however as many cases are prenatally diagnosed only because their mothers' are considered to be at risk of Down Syndrome and so have an invasive test. Those who are not prenatally diagnosed are often not diagnosed until after the onset of

puberty or even in adulthood when they present with infertility problems, with a large proportion never diagnosed at all (RW.ERROR - Unable to find reference:2800). As the prevalence of Klinefelter syndrome was perceived to be increasing more quickly than that of other sex chromosome related syndromes, in studies which do not overlap the present 10 year trend, there has been speculation that this particular condition is associated with environmental pollution as well as maternal age (RW.ERROR - Unable to find reference:2803).

Consistency between registries

There were 532 cases in this analysis and there was a wide range in prevalence between registries with no cases in Cork and Kerry and 2.42 per 10,000 births in Basque Country.

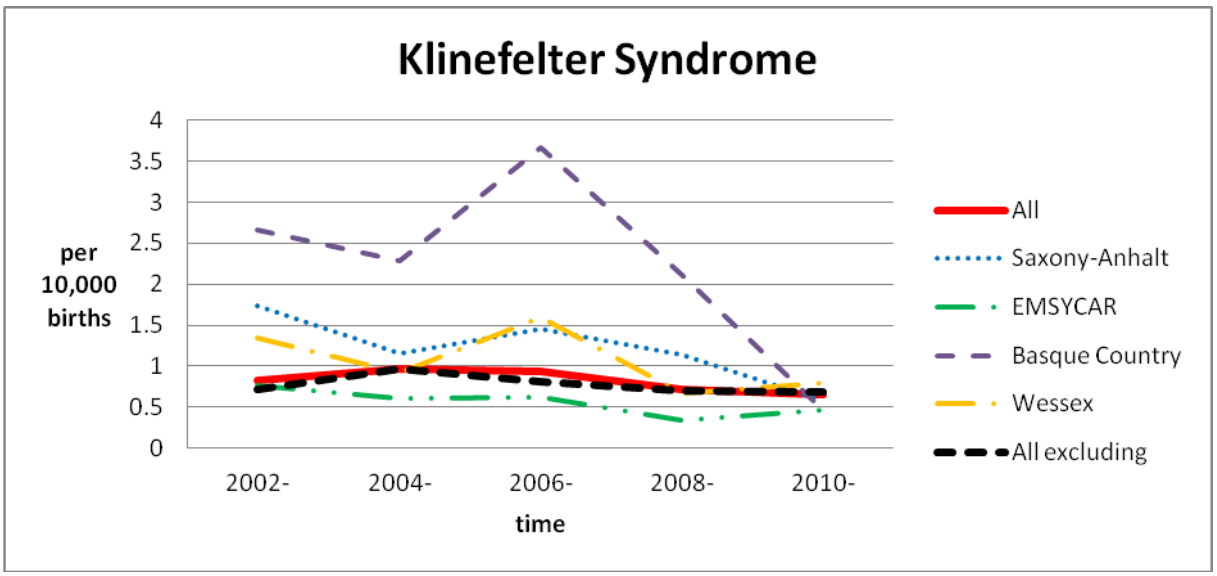
***Figure 2**: Prevalence of Klinefelter syndrome, by registry: 2002-2011*



Trend over time

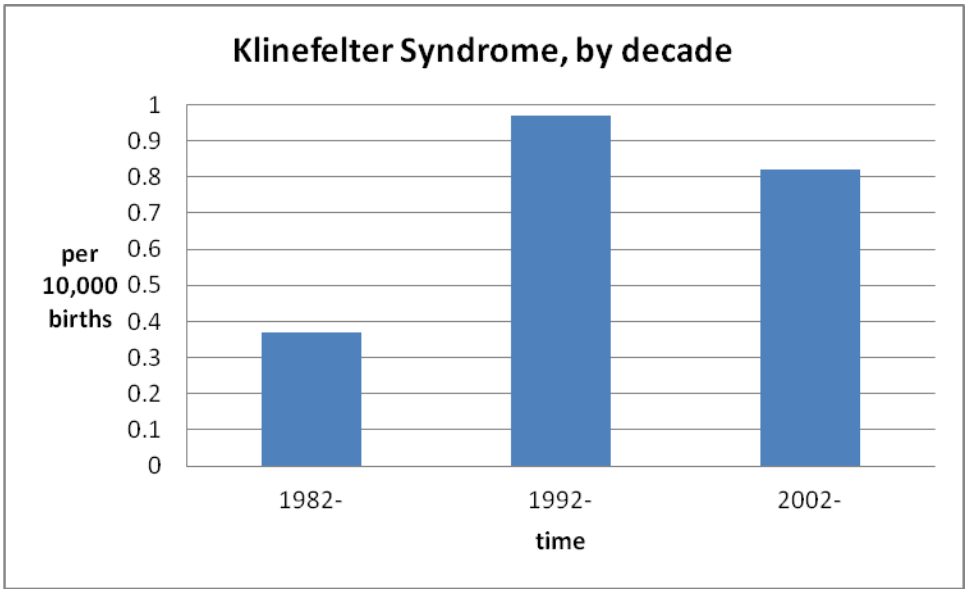
The Pan-European prevalence of Klinefelter syndrome decreased by approximately 4.37% per year from 0.83 per 10,000 births to 0.66 per 10,000 births over the ten year period. This was mainly due to the five registries mentioned above, with Basque Country and Saxony-Anhalt showing particularly high prevalence at the beginning of the time period. Both these registries only collect data relating to children up to the age of one year so their high prevalence is not explained by ascertainment of very late diagnosed cases .Wessex also showed a higher than average prevalence, but there is no upper age limit to ascertainment of cases for that registry. When the data from these five registries was excluded the decrease also disappeared, but that was related to their high prevalence at the beginning which was closer to the EUROCAT average at the end of the time period.

Figure 3: *Klinefelter Syndrome, showing the increasing trend and that trend when the two registries with a statistically significant rise in prevalence are excluded.*



The EUROCAT prevalence of Klinefelter syndrome rose sharply from 0.37 per 10,000 births during the decade from 1982-1991 to 0.97 per 10,000 births in the decade from 1992-2001. It has decreased to 0.82 per 10,000 births in the decade under review.

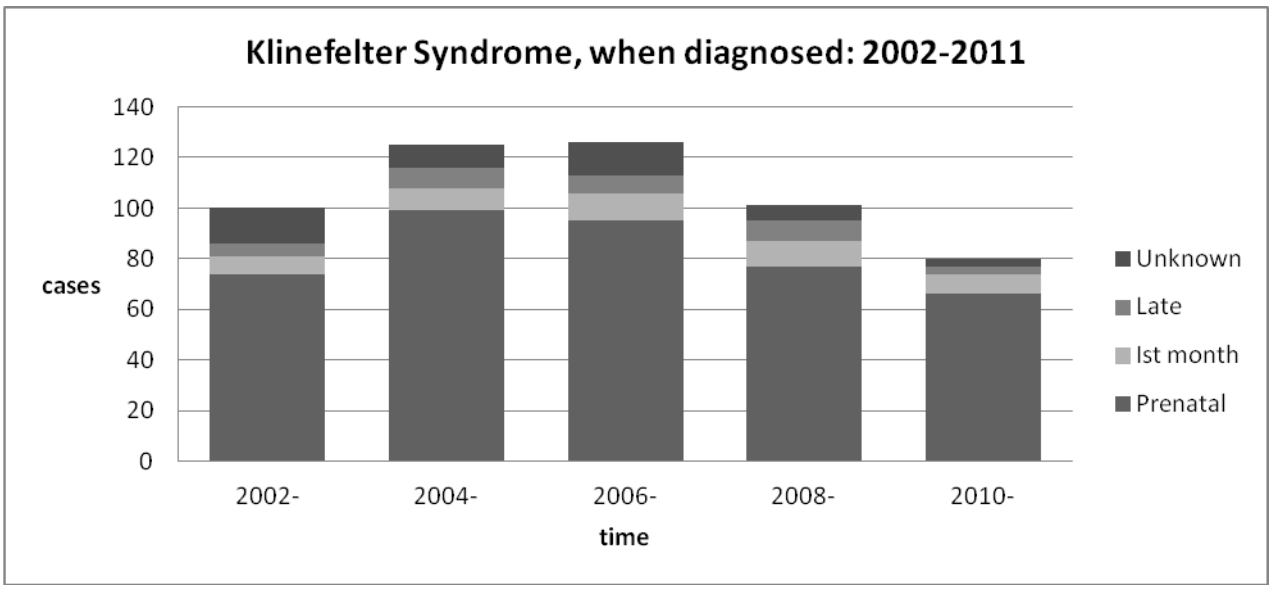
Figure 4*: The prevalence of Klinefelter Syndrome over the past three decades*



The trend in prenatal diagnosis and birth type

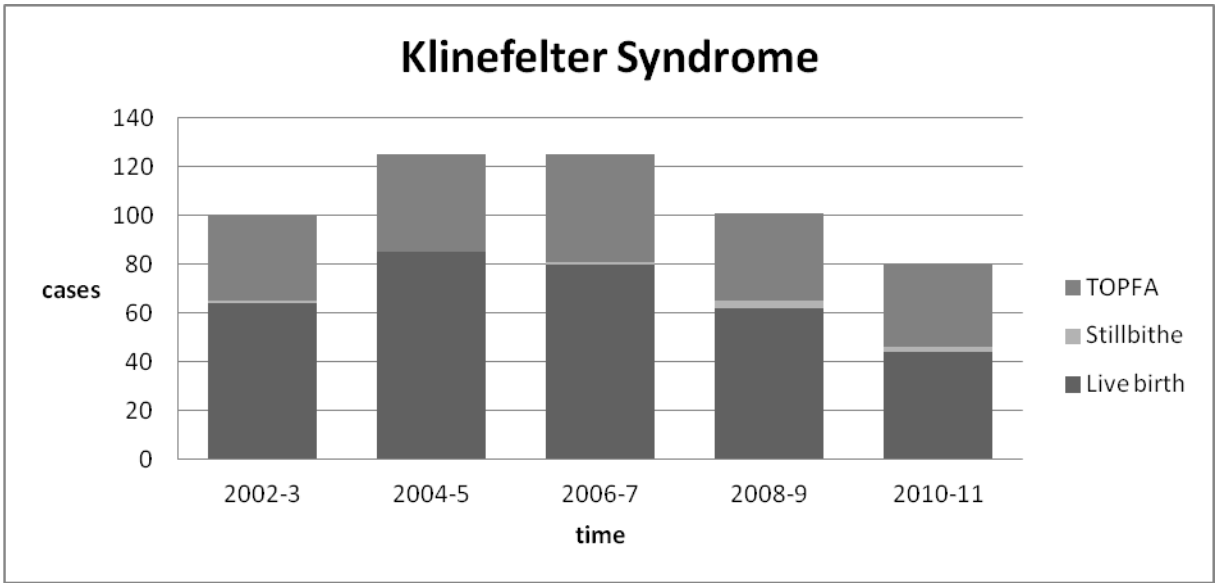
The data suggest that the proportion of cases which were prenatally diagnosed is increasing and that late diagnosis has dropped. This is difficult to interpret. It may simply mean that a lot of cases which are diagnosed late have not been ascertained by the registries yet. However, if it is still unusual for cases to be diagnosed between the neonatal period and puberty, even the boys born in 2002 are only reaching that age now, and so those undiagnosed cases born in-between would not be expected to receive a diagnosis yet.

Figure 5: *When diagnosed, for Klinefelter Syndromes, over time.2002-2011*



There is no obvious change in the proportion of cases which are prenatally diagnosed and result in TOPFA.

Figure 6: Type of birth for genetic syndromes, over time 2002-2011



Conclusions

The decreasing trend in prevalence of Klinefelter syndrome seems to be related to the high ascertainment of cases early in the time period by Saxony-Anhalt and the Basque Country. The drop may be due to a change in either their ascertainment or diagnostic methods, or to a lag while we wait for late diagnosed cases to be added to the data base.

References

(1) Boyd PA, Loane M, Garne E, Khoshnood B, Dolk H, EUROCAT working g. Sex chromosome trisomies in Europe: prevalence, prenatal detection and outcome of pregnancy. European Journal of Human Genetics 2011 Feb;19(2):231-234.

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

Table H1: Increasing trends

Anomaly	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Isle de Reunion (FR)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	Basque Country (ES)	S Portugal (PT)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)		
Neural Tube Defects				E								F													
Anencephalus and similar				E									C/A												
Encephalocele				E				NR																	
Spina Bifida				E																					
Hydrocephalus				F																					
Microcephaly				F																					
Anophthalmos/microphthalmos								NR																	
Congenital cataract								NR			NI														
Congenital glaucoma								NR																	
Congenital heart defects				F				NR																	

Severe CHD §																			A						
Transposition of great vessels								NR						E					A						
Ventricular septal defect	A/ C										NI										A				
Atrial septal defect				B				NR									A								
Atrioventricular septal defect								NR								NR						F			
Tetralogy of Fallot																	A		A			E			
Pulmonary valve stenosis					F			NR	A/F																
Pulmonary valve atresia								NR			NI	NI													
Aortic valve atresia/stenosis §								NR											A						
Hypoplastic right heart §																							C		
Coarctation of aorta											NI			E											
PDA as only CHD in term infants (>=37 weeks)											NI									F					
Cystic adenomatous malf of lung §														F/B									F		
Cleft lip with or without palate								NR		F	NI														
Cleft palate								NR																	

Oesophageal atresia with or without tracheo-oesophageal fistula								NR											NI						
Duodenal atresia or stenosis																						F			
Atresia or stenosis of other parts of small intestine											NI														
Ano-rectal atresia and stenosis							E	NR																	
Diaphragmatic hernia								NR																	
Gastroschisis				F																					
Bilateral renal agenesis including Potter syndrome														F											
Renal dysplasia							A	NR					C												
Congenital hydronephrosis						NI							C			NR		NI							
Posterior urethral valve and/or prune belly																			G						
Hypospadias		A		F				NR			NI									B					
Indeterminate sex				A										A									G		
Limb reduction																NR									

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Upper limb reduction																NR									
Lower limb reduction																NR									
Club foot - talipes equinovarus		A/ E			F			NR					B			NR									
Hip dislocation and/or dysplasia						NI							B			NR					A				
Polydactyly	F						F	NR													A				
Craniosynostosis																					A				
Congenital constriction bands/amniotic band								NR																	
Teratogenic syndromes with malformations §																NR									
Maternal infections resulting in malformations																NR									
Chromosomal			C	F					D	A/D		A		D/A											
Down Syndrome				E	D							A				NR									
Patau syndrome/trisomy 13								NR						D/A	NR										
Patau syndrome/trisomy 13 Adjusted								NR						D/A	NR										

Edward syndrome/trisomy 18								NR		A/D		A												
Edward syndrome/trisomy 18 Adjusted								NR		A														

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

Table H2: Decreasing trends

Anomaly	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Isle de Reunion (FR)	Paris (FR)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
All Non-chromosomal Anomalies		F				A	A	A			NI			NR		NI		A		A	
Neural Tube Defects									NI				D	NR							
Anencephalus and similar						G			NI				D	NR							
Encephalocele													D								
Spina Bifida		G												NR							
Hydrocephalus						F			NI					NR							
Microcephaly							A										G	E		A	
Anophthalmos/micropthalmos																	G				
Congenital cataract																	G	A		F	
Congenital heart defects								A			B			NR			G	G		A	

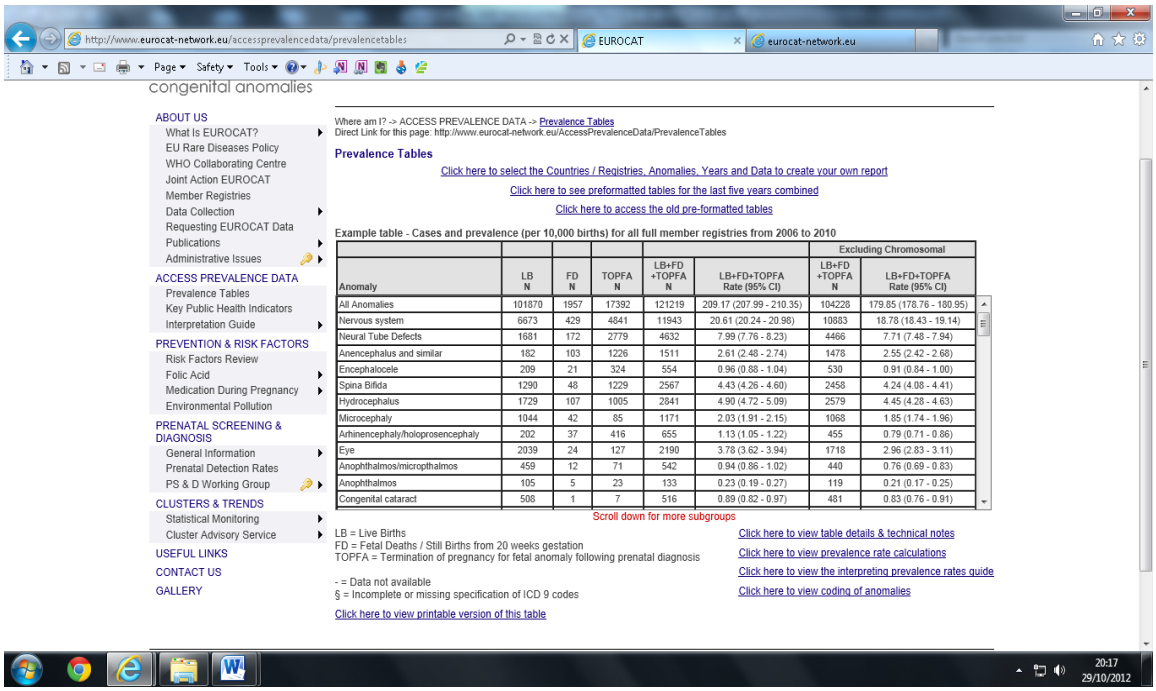
Severe CHD §							A							NR							
Transposition of great vessels	F																				
Ventricular septal defect							A	A						NR				A			
Atrial septal defect											B	B				F		A		B	
Atrioventricular septal defect		E																A			
Ebstein's anomaly					G																
Pulmonary valve stenosis		E												NR	NR			A			
Pulmonary valve atresia															NR						
Aortic valve atresia/stenosis §							A							NR							
Hypoplastic left heart									NI					NR							
Coarctation of aorta							A					F		NR						G	
PDA as only CHD in term infants (>=37 weeks)										NI						NI	A				
Cleft lip with or without palate														NR							
Cleft palate							A			NI				NR							
Oesophageal atresia with or without tracheo-oesophageal	F											F									

fistula																				
Ano-rectal atresia and stenosis									NI											A
Hirschsprung's disease																	E			
Diaphragmatic hernia													NR							
Congenital hydronephrosis						B		A		NI									B	
Posterior urethral valve and/or prune belly														NR						
Hypospadias							A				A					NI	G			B	
Limb reduction		G					A							NR			G			F	
Upper limb reduction		E												NR			G				
Club foot - talipes equinovarus						F		A		NI			F							F	
Hip dislocation and/or dysplasia	B	C	A/ B			C	A													B/ F	
Polydactyly							A							NR			G	E			
Syndactyly						B				NI			F	NR			A	E		F	
Skeletal dysplasias §							A														
Craniosynostosis														NR							

Congenital constriction bands/amniotic band																			A	F
Congenital skin disorders	B									NI							B			A
Valproate syndrome §				E																
Genetic syndromes + microdeletions							A										G		F	A
Chromosomal									NI								?		F	
Down Syndrome																	?		F	
Down Syndrome Adjusted									NI					NR			?		F	
Patau syndrome/trisomy 13									NI											
Patau syndrome/trisomy 13 Adjusted							A		NI											
Edward syndrome/trisomy 18									NI											
Edward syndrome/trisomy 18 Adjusted									NI											

Appendix I: 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)



You can also access the old style formatted tables

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Appendix J: Central Registry Statistical Monitoring Results: Summary table of detected clusters by registry and by anomaly 2010-2011

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Isle de Reunion (FR)	Paris (FR)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	Ukraine (UA)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)	SW England (UK)
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	1	0	1			*					C	*		*							
Arhinencephaly/holoprosencephaly	1	0	1	*	*	*			*	*			*	*	C						
Anophthalmos/micropthalmos	0	0	0	*	*	*			*	*				*		*	*			*	
Anophthalmos	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	0	0	0	*	*	*				*				*			*	*		*	
Congenital glaucoma	0	0	0	*	*	*		*	*	*		*	*	*	*	*	*	*		*	
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	1	0	1															C			
Atrial septal defect	3	0	3					C			C							C			
Atrioventricular septal defect	0	0	0		*	*				*											
Tetralogy of Fallot	0	0	0																		
Tricuspid atresia and stenosis	0	0	0	*	*	*				*	*	*		*	*			*			
Ebstein's anomaly	0	0	0	*	*	*		*		*	*	*	*	*			*	*			*
Pulmonary valve stenosis	0	0	0																		
Pulmonary valve atresia	1	0	1	*	*	*	*		*	*	C			*	*					*	
Aortic valve atresia/stenosis §	0	0	0			*	*			*		*									
Hypoplastic left heart	0	0	0			*															
Hypoplastic right heart §	0	0	0	*	*	*	*	*	*	*	*	*	*				*	*			
Coarctation of aorta	1	0	1			*				C											
Total anomalous pulm venous return	2	0	2	*	*	*	*			*	C	*	*	*	*						C

PDA as only CHD in term infants (>=37 weeks)	1	0	1		*	*		*		*								*			C
Choanal atresia	0	0	0	*	*	*				*				*	*					*	
Cystic adenomatous malf of lung §	0	0	0		*	*	*		*	*		*	*	*							
Cleft lip with or without palate	2	1	3		B							C				C					
Cleft palate	1	0	1		C																
Oesophageal atresia with or without tracheo-oesophageal fistula	0	0	0							*			*								
Duodenal atresia or stenosis	1	0	1	*	C	*				*			*	*							
Atresia or stenosis of other parts of small intestine	1	0	1	*	*	*			*	*			*	*		C					
Ano-rectal atresia and stenosis	1	0	1							C											
Hirschsprung's disease	1	0	1		*	*				*	C	*		*							
Atresia of bile ducts	0	0	0	*	*	*	*	*	*	*		*	*	*		*	*	*		*	
Annular pancreas	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	0	0			*				*											
Gastroschisis	0	0	0							*				*							
Omphalocele	1	0	1							*			C								

Bilateral renal agenesis including Potter syndrome	0	0	0			*				*				*							
Renal dysplasia	1	0	1							*								C			
Congenital hydronephrosis	3	0	3				C			*	C						C				
Bladder exstrophy and/or epispadia	0	0	0	*	*	*	*		*	*		*		*						*	
Posterior urethral valve and/or prune belly	0	0	0		*	*			*	*			*		*						
Hypospadias	1	0	1									C									
Indeterminate sex	1	0	1	*	*	*		*	*	*			*	*	*		*		*	C	
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	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*	*
Club foot - talipes equinovarus	1	0	1					C									*				
Hip dislocation and/or dysplasia	1	0	1				C										*			*	
Polydactyly	1	0	1					C		*											
Syndactyly	0	0	0							*											
Craniosynostosis	0	0	0			*				*							*				

Congenital constriction bands/amniotic band	0	0	0	*	*	*			*	*	*	*						*	*		
Situs inversus	0	0	0	*	*	*			*	*				*	*		*	*		*	
Conjoined twins	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*	*
Congenital skin disorders	1	0	1			*				*			*	*				*		*	C
Fetal alcohol syndrome	0	0	0	*	*	*		*	*	*	*	*	*	*		*	*	*		*	*
Valproate syndrome §	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Maternal infections resulting in malformations	0	0	0		*	*	*			*		*	*		*	*	*				*
Down Syndrome	1	0	1																		C
Patau syndrome/trisomy 13	1	0	1			*										C					
Edward syndrome/trisomy 18	0	0	0																		
Turner syndrome	1	0	1							*					*	C					
Klinefelter syndrome	0	0	0	*	*	*	*		*	*			*	*	*			*			
	33			0	2	0	2	4	0	2	6	2	1	0	1	4	1	3	0	1	4
		1		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			34	0	3	0	2	4	0	2	6	2	1	0	1	4	1	3	0	1	4
		395		26	33	44	15	13	25	51	11	21	24	32	17	9	19	20	8	18	9

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

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Appendix K: 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
Microcephaly	Italy	Emilia Romagna	14	23/02/2009	01/07/2010	5.73	0.028	18	5.6	*	New
Arhinencephaly /holoprosencephaly	Ukraine	Ukraine	23	26/03/2008	05/07/2009	10.54	0.02	35	0	Decreasing Trend	Continuing
Severe CHD §	France	Paris	5	28/04/2010	29/04/2010	0.28	0.01	220	0	No Sig. Change	New
Ventricular septal defect	UK	Thames Valley	5	28/08/2009	29/08/2009	0.31	0.015	241	3.3	Non-linear change	Same
Atrial septal defect	France	Paris	46	03/04/2009	29/09/2010	27.41	0.048	78	0	Increasing Trend	New
Atrial septal defect	UK	Thames Valley	97	28/07/2008	22/01/2010	64.54	0.013	184	4.9	Increasing Trend	Continuing
Atrial septal defect	Italy	Emilia Romagna	95	18/10/2009	06/12/2010	56.99	<0.001	213	2.3	Increasing Trend	Continuing
Pulmonary valve atresia	Italy	Emilia Romagna	10	25/03/2009	29/08/2009	2.24	0.017	22	4.5	*	Same
Coarctation of aorta	Ireland	SE Ireland	12	24/04/2008	30/08/2009	4.78	0.036	15	0	*	New
Total anomalous pulm venous return	UK	SW England	5	25/01/2011	23/03/2011	0.057	0.034	14	7.1	*	New

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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
Total anomalous pulm venous return	Italy	Emilia Romagna	5	22/06/2010	20/10/2010	0.78	0.045	10	0	*	New
PDA as only CHD in term infants (>=37 weeks)	UK	South West England	14	04/05/2008	17/10/2009	5.83	0.021	17	5.9	*	New
Cleft lip with or without palate	Belgium	Hainaut	9	14/01/2010	16/02/2010	1.23	0.012	66	3	No Sig. Change	Same
Cleft lip with or without palate	UK	East Mid & South York	5	29/10/2009	30/10/2009	0.32	0.017	248	0.8	No Sig. Change	Same
Cleft lip with or without palate	Italy	Tuscany	38	30/01/2008	12/07/2009	20.5	0.014	60	0	Non-linear change	New
Cleft Palate#	Belgium	Hainaut	7	13/02/2009	17/04/2009	0.91	0.014	22	4.5	No Sig. Change	Same
Duodenal atresia or stenosis	Belgium	Hainaut	6	06/09/2009	03/05/2010	1.39	0.045	9	0	*	New
Atresia or stenosis of other parts of small intestine	UK	E Mid & S York	14	30/01/2009	12/07/2010	5.8	0.02	17	5.9	*	New
Ano-rectal atresia and stenosis	Ireland	SE Ireland	5	25/11/2009	14/04/2010	0.82	0.039	9	0	*	New

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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
Hirschsprung's disease	Italy	Emilia Romagna	15	16/04/2009	13/03/2010	4.71	<0.001	22	4.5	*	Same
Omphalocele	Netherlands	N Netherlands	8	07/07/2008	14/08/2009	2.6	0.041	10	0	*	Same
Renal dysplasia	UK	Thames Valley	7	16/09/2009	07/10/2009	0.7	0.012	49	0	No Sig. Change	Same
Congenital hydronephrosis	France	Isle de Reunion	29	18/07/2008	03/01/2010	12.76	<0.001	37	0	Non-linear change	Continuing
Congenital hydronephrosis	Italy	Emilia Romagna	9	20/12/2009	02/01/2010	1.35	0.042	150	0.7	Non-linear change	New
Congenital hydronephrosis	UK	Northern England	78	21/12/2009	09/03/2011	49.81	0.043	174	2.3	Increasing trend	Continuing
Hypospadias	Italy	Tuscany	37	28/10/2009	10/02/2010	15.86	0.024	232	0.4	Non-linear change	New
Indeterminate sex	UK	Wessex	5	26/04/2010	03/06/2010	0.5	0.04	20	0	No Sig. Change	New
Club foot - talipes equinovarus	France	Paris	6	04/08/2010	09/08/2010	0.56	0.049	144	0	Increasing Trend	New
Hip dislocation	France	Isle de Reunion	5	02/06/2009	11/06/2009	0.25	0.007	39	0	No Sig.	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
and/or dysplasia										Change	
Polydactyly	France	Paris	60	11/08/2009	05/02/2011	27.71	<0.001	79	0	Non-linear change	Continuing
Congenital skin disorders	UK	South West England	5	15/10/2009	28/10/2009	0.36	0.028	40	5	Decreasing Trend	New
Down Syndrome	UK	SW England	5	02/04/2010	02/04/2010	0.39	<0.001	599	9.5	No Sig. Change	New
Patau syndrome/trisomy 13	UK	East Mid & South York	5	28/07/2010	03/08/2010	0.35	0.037	77	0	No Sig. Change	New
Turner syndrome	UK	East Mid & South York	14	20/01/2011	24/02/2011	2.14	<0.001	92	4.3	No Sig. Change	New

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 country cluster analysis

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	15/05/2009	15/05/2009	0.79	0.046	1226	0.7	
Microcephaly	Italy	18	08/01/2009	01/07/2010	8.36	0.036	24	4.2	
Ventricular septal defect	Italy	5	21/09/2010	21/09/2010	0.69	0.025	1072	1.7	Significant upward trend
Atrial septal defect	Italy	91	10/03/2010	06/12/2010	52.79	<0.001	301	2.7	Significant upward trend
Total anomalous pulm venous return	Italy	11	06/08/2009	19/01/2011	4.46	0.038	13	7.7	
Cleft lip with or without palate	Belgium	13	16/04/2009	12/05/2009	2.63	0.021	151	7.9	
Cleft palate	UK	5	26/11/2010	26/11/2010	0.37	<0.001	580	3.4	
Duodenal atresia or stenosis	Belgium	6	31/03/2010	19/05/2010	0.48	<0.001	15	0	
Ano-rectal atresia and stenosis	UK	5	15/12/2010	16/12/2010	0.4	0.045	307	1.6	Significant upward trend
Ano-rectal atresia and stenosis	Italy	7	24/08/2009	16/09/2009	0.87	0.038	56	3.6	
Hirschsprung's disease	Italy	22	11/05/2009	05/11/2010	9.82	<0.001	28	3.6	Significant non-linear change
Club foot - talipes equinovarus	UK	5	27/03/2010	27/03/2010	0.68	0.028	1056	0.6	Significant downward trend
Polydactyly	France	66	23/09/2009	18/10/2010	33.78	<0.001	134	0	Significant upward trend
Situs inversus	Belgium	5	19/09/2009	07/06/2010	1.18	0.047	7	0	