Use of hierarchical models to analyse European trends in congenital anomaly prevalence

Journal:	*Birth Defects Research Part A: Clinical and Molecular Teratology*
Manuscript ID	Draft
Wiley - Manuscript type:	Original Research Article
Date Submitted by the Author:	n/a

Complete List of Authors:	Cavadino, Alana; Queen Mary University of London, Centre for Environmental and Preventive Medicine Prieto, David; London School of Hygiene and Tropical Medicine, Department of Medical Statistics; University College London, Farr Institute of Health Informatics Research; Universidad Catolica San Antonio de Murcia Addor, Marie-Claude; Division of Medical Genetics Arriola, Larraitz; Subdireccion de Salud Publica Bianchi, Fabrizio; CNR Institute of Clinical Physiology, G Monasterio Tuscany Foundation Draper, Elizabeth; University of Leicester Garne, Ester; Hospital Lillebaelt-Kolding, Paediatrics Greenlees, Ruth; University of Ulster, EUROCAT Central Registry Haeusler, Martin; Medical University of Graz Khoshnood, Babak; The Paris Registry of Congenital Malformations Kurinczuk, Jenny; University of Oxford Nuffield Department of Population Health, National Perinatal Epidemiology Unit McDonnell, Robert; Health Service Executive Nelen, Vera; Provincial Institute for Hygiene O'Mahony, Mary; Health Service Executive Randrianaivo, Hanitra; Medical Genetics Unit of CHU Sud Réunion Rankin, Judith; Newcastle University, UK, Institute of Health & Society Rissmann, Anke; Otto-von-Guericke University Tucker, David; Public Health Wales Verellun-Dumoulin, Christine; Institut de PAthologie et de Genetique Walle, Hermien; EUROCAT, Medical Genetics Wellesley, Diana; Princess Anne Hospital, Wessex Clinical Genetics Service Morris, Joan; Queen Mary University of London, Wolfson Institute of Preventive Medicine

Key Words:	congenital anomalies, trends, prevalence, hierarchical models, Bayesian analysis

Use of hierarchical models to analyse European trends in congenital anomaly prevalence

Alana Cavadino[1], David Prieto-Merino[2, 3, 4], Marie-Claude Addor[5], Larraitz Arriola[6], Fabrizio Bianchi[7], Elizabeth Draper[8], Ester Garne[9], Ruth Greenlees[10], Martin Haeusler[11], Babak Khoshnood[12], Jenny Kurinczuk[13], Bob McDonnell[14], Vera Nelen[15], Mary O'Mahony[16], Hanitra Randrianaivo[17], Judith Rankin[18], Anke Rissmann[19], David Tucker[20], Christine Verrelen-Dumoulin[21], Hermien de Walle[22], Diana Wellesley[23], Joan K. Morris[1]

[1]Wolfson Institute of Preventive Medicine, Queen Mary University of London, United Kingdom

[2]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom

[3]Farr Institute of Health Informatics Research, University College London, United Kingdom

[4]Catholic University of Murcia (UCAM), Spain

[5]Service de Genetique Medicale Maternite, CHUV, Lausanne, Switzerland

[6]Public Health Division of Gipuzkoa, Instituto BIO-Donostia Basque Government CIBER Epidemiología y Salud Pública - CIBERESP, San Sebatian, Spain

[7]CNR Institute of Clinical Physiology and Tuscany Registry of Congenital Defects, "Gabrielle Monasterio" Foundation, Pisa, Italy

[8]Department of Health Sciences, University of Leicester, Leicester, United Kingdom

[9] Paediatric Department, Hospital Lillebaelt-Kolding, Denmark

[10]Institute of Nursing and Health Research, Ulster University, Newtownabbey, United Kingdom

[11]Medical University of Graz, Austria

[12]Obstetrical, Perinatal and Pediatric Epidemiology Research Team, Center for Biostatistics and Epidemiology, INSERM U1153, Maternité de Port-Royal, 75014 Paris, France

[13]National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, United Kingdom

[14]Health Service Executive, Dublin, Ireland

[15]Provincial Institute for Hygiene, Antwerp, Belgium

[16]Department of Public Health, Health Service Executive - South, Ireland

[17]Medical Genetics Unit of CHU Sud Réunion, Ile de la Reunion, France

[18]Institute of Health & Society, Newcastle University, Newcastle, UK

[19]Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty Otto-von-Guericke University, Magdeburg, Germany

[20]Public Health Wales, Swansea, United Kingdom

[21]Center for Human Genetics, Institut de Recherche Scientifique en Pathologie et en Génétique, Charleroi, Belgium

[22]University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, Netherlands

[23]University Hospitals Southampton, Faculty of Medicine and Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, United Kingdom

Grant information and grant numbers

This work was supported by the Medical Research Council [grant number 1504916]

Running title: Analysis of trends in congenital anomalies

Corresponding author: Professor Joan K Morris

Centre for Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ

Telephone: +442078826274

Fax: +442078826270

Email: j.k.morris@qmul.ac.uk

Word count: 3246

Number of tables: 1

Number of figures: 4

Number of supplementary files: 1 appendix

Abstract

Background: Surveillance of congenital anomalies is important to identify potential teratogens. Despite known associations between different anomalies, current surveillance methods examine trends within each subgroup separately. We aimed to evaluate whether hierarchical statistical methods that combine information from several subgroups simultaneously would enhance current surveillance methods using data collected by EUROCAT, a European network of population-based congenital anomaly registries.

Methods: Ten year trends (2003 to 2012) in 18 EUROCAT registries over 11 countries were analysed for the following groups of anomalies: neural tube defects, congenital heart defects, digestive system and chromosomal anomalies. Hierarchical Poisson regression models that combined related subgroups together according to EUROCAT's hierarchy of subgroup coding were applied. Results from hierarchical models were compared to those from Poisson models that consider each congenital anomaly separately.

Results: Hierarchical models gave similar results as those obtained when considering each anomaly subgroup in a separate analysis. Hierarchical models that included only around three subgroups showed poor convergence and were generally found to be over-parameterised. Larger sets of anomaly subgroups were found to be too heterogeneous to group together in this way.

Conclusions: There were no substantial differences between independent analyses of each subgroup and hierarchical models when using the EUROCAT anomaly subgroups. Considering each anomaly separately therefore remains an appropriate method for the detection of potential changes in prevalence by surveillance systems. Hierarchical models do, however, remain an interesting alternative method of analysis when considering the risks of specific exposures in relation to the prevalence of congenital anomalies, which could be investigated in other studies.

Keywords: congenital anomalies, trends, prevalence, hierarchical models

Introduction

Congenital anomalies are structural or functional abnormalities that are present at birth. They are a leading worldwide cause of fetal and infant death, chronic illness and disability in childhood; a diverse group of disorders for which only around 50% can be linked to a specific known cause or risk factor (World Health Organization, 2014). Causes of congenital anomaly include a wide range of both genetic and environmental factors such as maternal age, nutritional status or exposure to certain medications. It is important to identify risk factors for congenital anomalies, in particular the early identification of new potentially teratogenic exposures. Following the Thalidomide disaster, congenital anomaly registries were established worldwide in order to facilitate surveillance and research into the causes of birth defects (Khoury and others, 1994; McBride, 1961). A European network of such population-based registries, EUROCAT, provides important epidemiologic information on congenital anomaly by collecting data on over 1.7 million births from 43 registries in 23 countries across Europe (EUROCAT, 2016). EUROCAT annually monitors the birth prevalence of specific anomalies in order to detect new or continuing trends, identifying new potentially teratogenic exposures and evaluating the effectiveness of primary prevention policies (Dolk, 2005).

Surveillance of congenital anomalies is often performed using defined sets of subgroups, such as the EUROCAT anomaly subgroups (EUROCAT, 2005). Many of these subgroups overlap, for example the congenital heart defects (CHD) subgroup includes further subgroups such as ventricular septal defects, atrial septal defects and tetralogy of Fallot (ToF). Despite known relationships amongst many of the subgroups, current surveillance methods examine trends, clusters or associations between risk factors and anomalies within each subgroup separately (EUROCAT, 2015; Loane and others, 2011b). Relevant information on relationships between anomalies across the different subgroups is therefore not currently being incorporated in surveillance analyses; hence it is possible that important associations or trends are not being detected by the current methods. Congenital anomaly surveillance methods that combine information from several subgroups simultaneously

may enhance the analysis of any particular anomaly by considering what is happening in related or similar anomalies. The aim of this paper is to evaluate whether hierarchical statistical methods that combine information from several subgroups within the same congenital anomaly group simultaneously increase the power to detect trends in congenital anomalies.

Methods

EUROCAT dataset

This study is based on routinely collected EUROCAT data from 18 full member registries in 11 European countries: Austria (Styria registry), Belgium (Antwerp and Hainaut), Denmark (Odense) France (Paris and Isle de la Reunion), Germany (Saxony-Anhalt) Ireland (Cork & Kerry and Dublin), Italy (Tuscany) Netherlands (Northern Netherlands), Spain (Basque Country), Switzerland (Vaud) and the UK (East Midlands & South Yorkshire, Northern England, Thames Valley, Wales and Wessex). Data was extracted from the EUROmediCAT central database in February 2015, including only registries with a total prevalence of all anomalies greater than 2% and available data for at least nine years of the ten year period from 01 January 2003 to 31 December 2012. All coding was done according to EUROCAT guide 1.3 (www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf) (EUROCAT, 2005), which uses a hierarchy of codes to classify all cases of non-minor congenital anomaly into 89 EUROCAT anomaly subgroups. EUROCAT anomaly subgroups are grouped in a hierarchical structure, with the highest level being the major organ groups, within which there are further classes. Spina bifida, for example, is in the neural tube defects (NTD) subgroup, which is within the Nervous System group of anomalies. A case may be counted only once in each of the lowest level EUROCAT subgroups, but if it has multiple anomalies it will be counted in multiple subgroups. Cases with genetic conditions (genetic syndromes/ microdeletions, teratogenic syndromes with malformations, or chromosomal anomalies) were excluded from all analyses of non-chromosomal anomaly. Data are collected for all birth outcomes, including live and still births and terminations of pregnancy for fetal anomaly. Further details regarding the registries, methods of

case ascertainment and data collection and processing are described elsewhere (Boyd and others, 2011; EUROCAT, 2005; Greenlees and others, 2011).

Statistical Methods

The most recent ten years of data available were assessed for changes in prevalence for the following groups of anomalies: NTDs, autosomal chromosome anomalies, CHDs and digestive system anomalies. Poisson regression was used to model prevalence rates for the number of congenital anomaly cases each year, with the log total births included as an offset to account for the differing population size each year. Estimated average yearly ten year trends in prevalence obtained from **individual models** (separate Poisson models for each anomaly subgroup with no information sharing between anomaly subgroups) were compared to those obtained from **hierarchical models** (one Poisson model fitting related anomaly subgroups simultaneously with sharing of information between anomaly subgroups). For CHDs there are sixteen standard subgroups (EUROCAT, 2005) that have previously been grouped using a hierarchical severity ranking according to perinatal mortality rates in non-chromosomal cases, formed of three ordered groups from severity I (high perinatal mortality) to severity III (low perinatal mortality) (EUROCAT, 2009) (**Table 1**). A two level hierarchy that includes the grouping of CHDs by these severity subgroups was also considered. A data-level variance component was used to directly model potential overdispersion in the data for hierarchical models (Gelman and Hill, 2007). Models were also repeated with the inclusion of a term to take account of the random effects of registry. All statistical analyses were conducted in R (R Development Core Team, 2008). Markov Chain Monte Carlo sampling methods were used to obtain estimates of variability around the random effects in hierarchical models by using Gibbs sampling (Casella and George, 1992) in the Bayesian analysis programme JAGS via the R package rjags (Plummer, 2003). Results from hierarchical models are presented as annual percentage changes in prevalence and their 95% posterior credible intervals (PCIs), which can be thought of as the Bayesian equivalent of 95% confidence intervals (CIs) and where we say there is a 95% probability that the

true trend in prevalence lies within this interval. If the 95% CI or PCI doesn't include zero then we consider this a "statistically significant" average annual change in prevalence or a "signal". The resulting estimates are only valid if convergence has occurred, which is assessed graphically and by using convergence diagnostics in the R package coda (Plummer and others, 2003). Further details on the use of the Bayesian hierarchical models in JAGs can be found in the Appendix.

Results

A total of 103,507 cases of congenital anomaly (81,147 cases excluding genetic conditions) were available for analysis from a combined population of 4,097,142 births over 18 registries during the 10 year study period. Trends were assessed in 4,167 NTD, 13,358 chromosomal, 25,273 CHD and 7,683 digestive system anomaly cases (**Table 1**). The rarest subgroup included in these analyses was the digestive system anomaly annular pancreas, with only 57 cases in the combined population over the ten years giving an estimated total prevalence of 0.1 cases per 10,000 births. The most common anomaly subgroup was the CHD ventricular septal defect, with an estimated total prevalence of almost 28 cases per 10,000 births (**Table 1**).

Models for neural tube defects

There were no changes in prevalence for any of the NTD subgroups, with estimated average annual trends remaining very similar for individual and hierarchical models and 95% CIs and PCIs including zero (no change) for all estimates (**Figure 1**). There was some "shrinkage" in the estimates towards the group mean in the hierarchical model, in particular for encephalocele, although this estimated trend was not significant in either model.

Models for chromosomal anomalies

In individual models, an increasing trend of 1.7% (95% CI: 0.7% to 2.6%) and 1.8% (95% CI: 0.4% to 3.1%) per year on average was observed for Down and Edwards syndrome, respectively (**Figure 2**), but there was no significant change in prevalence of Patau syndrome. Trends in prevalence were

similar when combining the three anomalies together in a hierarchical model; the estimated trend for Patau syndrome increased slightly towards the average of the three trends but the 95% PCI still included zero (**Figure 2**).

Models for congenital heart defects

Of all cases with CHD, 85.5% were counted in one of the three EUROCAT severity groups for CHDs, excluding those with patent ductus arteriosus in term infants as well as a number of other CHDs that are not assigned a specific subgroup code according to EUROCAT's coding hierarchy. In individual models, decreasing trends for atrial septal defect (ASD) and pulmonary valve stenosis (PVS), and an increasing trend for ToF were observed (**Figure 3**). When using a hierarchical model that combined all CHDs (**Figure 3**), the estimated trends for PVS and ToF attenuated towards the null. The only significant change in prevalence in a hierarchical model was for ASD, which attenuated slightly to 3.0% on average from the estimated 4.1% in an individual model. Average annual changes in prevalence for the other CHD subgroups were a mix of increasing and decreasing trends, none of which were statistically significant in either model. When including severity subgroup as an additional level in a hierarchical model for CHDs (**Figure 3**), the trends for ASD and PVS remained significant, with estimated average changes in prevalence very similar to those obtained in individual models. The increasing trend for ToF was not statistically significant when grouping all CHDs together, whether including the severity grouping or not.

Models for digestive system anomalies

There were no significant trends in prevalence for any of the digestive system subgroups for individual or hierarchical models (**Figure 4**), with estimated trends in the hierarchical model generally attenuating towards the mean of the estimated trends across the eight subgroups, which was again close to the null value of no trend. Subgroups that were less precisely estimated were more affected by the information in other subgroups, giving more marked differences in estimated trends in the less common anomalies for individual models compared to a hierarchical model.

Model assessment for hierarchical models

Parameters for hierarchical models that included a reasonable number of subgroups (i.e. eight or more for the digestive system anomalies) displayed good convergence. Hierarchical models for smaller groups of anomalies (e.g. models for NTDs and autosomal anomalies including only three subgroups) showed poor convergence due to over parameterisation in the model. Further details on model diagnostics for hierarchical models are given in the appendix.

Including a registry effect

All models were repeated with the inclusion of a random effect for registry to assess the effect of accounting for differences at the registry level. The estimated trends in prevalence of each anomaly subgroup remained very similar to those described above when including the effect of registry for all models (data not shown). Hierarchical models that included a registry effect, in particular those with only a small number of subgroups, demonstrated an overall lack of convergence.

Discussion

For all examples of congenital anomaly subgroups considered in these analyses, estimated trends in prevalence were similar whether considering anomalies separately (individual models) or together (hierarchical model). Identified trends were consistent with other studies. Increasing trends in chromosomal anomalies were observed, which are known to be due to maternal age and changes in prenatal screening practices (Cocchi and others, 2010; Loane and others, 2013). NTD prevalence remained stable in EUROCAT registries, as has been observed elsewhere (Botto and others, 2006; Khoshnood and others, 2015). This might be explained by the lack of folic acid fortification in Europe and poor uptake of folic acid supplementation; in the UK, for example, under 30% of women took folic acid prior to their pregnancy in 2011–2012 (Bestwick and others, 2014). Prevalence in three of the digestive system anomaly subgroups was found to be significantly increasing in the latest EUROCAT statistical monitoring report (EUROCAT, 2015). A similar estimated increase in prevalence

in these three subgroups was observed here, although these trends did not reach statistical significance in independent models due to the smaller number of registries included. Increases in the prevalence of the CHDs single ventricle (severity group I), ToF and atrioventricular septal defect (severity group II) were consistent with previous findings (EUROCAT, 2015). Estimated decreases in prevalence of ASD and PVS, however, were not consistent with those observed in other studies, where either no significant changes or increasing trends have been observed (EUROCAT, 2015; van der Linde and others, 2011). Published prevalence estimates in CHDs are known to vary substantially due to differing definitions of cases across studies, and it is likely that the differences in estimated trends here reflect changes in reporting for these anomalies (in recent years EUROCAT have focused on only reporting ASD cases that have been confirmed after 6 months of age) or differing prenatal screening practices in this particular set of registries (Baardman and others, 2014; Garne and others, 2012; Hoffman and Kaplan, 2002).

Hierarchical models have proven useful in the field of pharmacovigilance, where they have been used in the detection of potential adverse drug reactions (Berry and Berry, 2004; Crooks and others, 2012; Xia and others, 2011). Natural hierarchies in drug and adverse event coding have been used to group similar drugs or adverse events together, such that models for each drug-adverse event combination incorporate information from analyses of other similar drugs and adverse events (Prieto-Merino and others, 2011). In this paper, the same rationale was applied to congenital anomalies; however, the situation here was different compared to that for adverse drug reactions, where the hierarchical classification systems may provide more natural hierarchies than the grouping of anomalies according to the defined subgroups. Indeed, the EUROCAT subgroup coding hierarchy provides sets of anomalies that are too heterogeneous in practice to be grouped together when analysing changes in prevalence. This is because the “shrinkage”, a key feature of hierarchical models (Gelman and Hill, 2007) whereby the estimated trend for each subgroup is influenced towards the average trend over all subgroups in the model, will largely pull estimates towards the null if there is a mixture of increasing and decreasing trends, as was the case for CHD and digestive

anomalies. It is possible, therefore, that potential changes in prevalence in analyses of groups of anomalies such as these could actually be masked by hierarchical models. On the other hand, this shrinkage can help control estimates based on small counts by including information from the rest of the group. Moreover, this can be thought of as a natural "penalisation" considering that a hierarchical model is simultaneously looking for changes in prevalence in numerous subgroups, compared to individual models where this multiple testing aspect is not taken into account (and a number of false positive results are therefore likely). For a group where the mean trend across subgroups is close to the null, this penalisation will mean that the estimated trend is no longer a "signal" in the hierarchical model, for example as seen for the CHD ToF in severity group II (**Figure 3**). For a group where the mean trend is not so close to the null, however, this penalisation might actually lead to an increase in the strength and precision of a signal, for example for ASD in severity group III (**Figure 3**). Furthermore, the same signal might be reduced or enhanced depending on which grouping is used; for example, the trend in PVS is attenuated if considering all CHD groups together but maintained if also including the severity grouping in the hierarchical model (**Figure 3**). This highlights how the posterior distribution is sensitive to the prior information, which here is the way the groups have been defined.

EUROCAT subgroups that were considered to be related, for example aetiologically similar or in the same organ system class, were still found to vary considerably in terms of their differing proportional yearly changes in prevalence. It is well known (Gelman and Hill, 2007; Greenland, 2000), and has been seen here in the case of NTDs and autosomal trisomy groups of anomalies, that a random effects model with only three levels for the random effect parameter does not perform well, with such models showing poor convergence and over-parameterisation. There may be other larger groups of anomalies that are similar enough to be analysed together that were not considered here, and in fact there are known relationships between anomalies that lie within different groups of the EUROCAT hierarchy. In addition to NTDs, for example, there are a number of other anomalies across different body systems that are known to be sensitive to folate levels during pregnancy,

including CHDs, clefts and limb reduction defects (Wilson and others, 2015). If there was evidence that folate levels had been increasing in Europe, then it would have been useful to have analysed all these anomalies as a hierarchical model. However, from examining the NTDs alone here and in other studies, no such change has occurred in Europe and hence such models were not further investigated. Similarly, EUROCAT now includes a VATER/VACTERL association subgroup that comprises anomalies of the vertebra, anal atresia, CHDs, trachea-esophageal fistula, esophageal atresia, radial anomaly and limb defect, which are known to occur together more frequently than expected by chance. However, the heterogeneity of trends in just the CHD component of this subgroup indicates that hierarchical models are not likely to add any useful information to such an analysis. When examining congenital anomaly prevalence there are many factors that are likely to have an influence, such as reporting, case ascertainment or screening practices. Hierarchical models might be more relevant, then, when considering the risks of specific exposures in relation to prevalence of congenital anomalies. It would therefore be worthwhile investigating the application of hierarchical models in such situations, for example when looking at the risk of medications taken during the first trimester of pregnancy.

Strengths and limitations of this study

EUROCAT registries collect data that is ascertained from multiple sources and includes information on all major structural congenital and chromosomal anomalies (Boyd and others, 2011; Loane and others, 2011a), providing high quality population-based data across multiple European countries and allowing the inclusion of a large number of congenital anomaly cases covering over four million births over ten years for this study. EUROCAT registries include information on cases of prenatal diagnosis followed by termination of pregnancy, enabling the inclusion of cases that would otherwise have gone undiagnosed, or unreported amongst spontaneous abortions or stillbirths. One potential limitation of this study is that it was not possible to include data from all of the EUROCAT member registries in these analyses, hence some trends that were seen in the latest statistical

monitoring report did not reach statistical significance here, likely due to the smaller sample sizes included. However, it does not seem likely that increasing the sample size would have improved the performance of hierarchical models.

Conclusions

In summary, the hierarchical models considered here demonstrated that sharing information between subgroups of anomalies can provide a sensible "penalisation", helping to avoid false positive signals by shrinking the estimated trends towards the null when there is no evidence of other trends in the rest of the group, whilst maintaining signals of changes in prevalence when there are others in the group. Using the EUROCAT hierarchy of anomaly subgroups, however, presented no substantial differences between the independent analyses of each subgroup and hierarchical models. When using EUROCAT subgroups for analysis, therefore, considering each congenital anomaly separately remains an appropriate method for the detection of potential changes in prevalence by relevant surveillance systems. Hierarchical models do, however, remain an interesting and potentially useful alternative method of analysis when considering the risks of specific exposures in relation to the prevalence of congenital anomalies, and this could be investigated in other studies.

Acknowledgements

EUROCAT registries are funded as described in Paper 6 of Report 9 "EUROCAT Member Registries: Organization and Activities" (http://onlinelibrary.wiley.com/doi/10.1002/bdra.20775/pdf). We thank the people throughout Europe involved in providing and processing information, including affected families, clinicians, health professionals, medical record clerks and registry staff.

References

Baardman ME, du Marchie Sarvaas GJ, de Walle HE, Fleurke-Rozema H, Snijders R, Ebels T, Bergman JE, Bilardo CM, Berger RM, Bakker MK. 2014. Impact of introduction of 20-week ultrasound scan on prevalence and fetal and neonatal outcomes in cases of selected severe congenital heart defects in The Netherlands. Ultrasound Obstet Gynecol 44(1):58-63.

Berry SM, Berry DA. 2004. Accounting for multiplicities in assessing drug safety: a three-level hierarchical mixture model. Biometrics 60(2):418-426.

Bestwick JP, Huttly WJ, Morris JK, Wald NJ. 2014. Prevention of neural tube defects: a cross-sectional study of the uptake of folic acid supplementation in nearly half a million women. PLoS One 9(2):e89354.

Botto LD, Lisi A, Bower C, Canfield MA, Dattani N, De Vigan C, De Walle H, Erickson DJ, Halliday J, Irgens LM, Lowry RB, McDonnell R, Metneki J, Poetzsch S, Ritvanen A, Robert-Gnansia E, Siffel C, Stoll C, Mastroiacovo P. 2006. Trends of selected malformations in relation to folic acid recommendations and fortification: an international assessment. Birth Defects Res A Clin Mol Teratol 76(10):693-705.

Boyd PA, Haeusler M, Barisic I, Loane M, Garne E, Dolk H. 2011. Paper 1: The EUROCAT network--organization and processes. Birth Defects Res A Clin Mol Teratol 91 Suppl 1:S2-15.

Casella G, George EI. 1992. Explaining the Gibbs Sampler. American Statistician 46(3):167-174.

Cocchi G, Gualdi S, Bower C, Halliday J, Jonsson B, Myrelid A, Mastroiacovo P, Amar E, Bakker MK, Correa A, Doray B, Melve KK, Koshnood B, Landau D, Mutchinick OM, Pierini A, Ritvanen A, Ruddock V, Scarano G, Sibbald B, Sipek A, Tenconi R, Tucker D, Anneren G. 2010. International trends of Down syndrome 1993-2004: Births in relation to maternal age and terminations of pregnancies. Birth Defects Res A Clin Mol Teratol 88(6):474-479.

Crooks CJ, Prieto-Merino D, Evans SJ. 2012. Identifying adverse events of vaccines using a Bayesian method of medically guided information sharing. Drug Saf 35(1):61-78.

Dolk H. 2005. EUROCAT: 25 years of European surveillance of congenital anomalies. Arch Dis Child Fetal Neonatal Ed 90(5):F355-358.

EUROCAT. 2005. EUROCAT Guide 1.3: Instructions for the registration and surveillance of congenital anomalies. EUROCAT Central Registry, University of Ulster.

EUROCAT. 2009. Special Report, Congenital Heart Defects in Europe: 2000-2005.

EUROCAT. 2015. EUROCAT Statistical Monitoring Report 2012. [ONLINE] Available at: http://www.eurocat-network.eu/content/Stat-Mon-Report-2012.pdf.

EUROCAT. 2016. What is EUROCAT? [ONLINE] Available at: http://www.eurocat-network.eu/aboutus/whatiseurocat/whatiseurocat. 23/02/16

Garne E, Olsen MS, Johnsen SP, Hjortdal V, Andersen HO, Nissen H, Sondergaard L, Videbaek J. 2012. How do we define congenital heart defects for scientific studies? Congenit Heart Dis 7(1):46-49.

Gelman A, Hill J. 2007. Data analysis using regression and multilevel/hierarchical models. Cambridge; New York: Cambridge University Press.

Greenland S. 2000. Principles of multilevel modelling. Int J Epidemiol 29(1):158-167.

Greenlees R, Neville A, Addor MC, Amar E, Arriola L, Bakker M, Barisic I, Boyd PA, Calzolari E, Doray B, Draper E, Vollset SE, Garne E, Gatt M, Haeusler M, Kallen K, Khoshnood B, Latos-Bielenska A, Martinez-Frias ML, Materna-Kiryluk A, Dias CM, McDonnell B, Mullaney C, Nelen V, O'Mahony M, Pierini A, Queisser-Luft A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Ritvanen A, Salvador J, Sipek A, Tucker D, Verellen-Dumoulin C, Wellesley D, Wertelecki W. 2011. Paper 6: EUROCAT member registries: organization and activities. Birth Defects Res A Clin Mol Teratol 91 Suppl 1:S51-s100.

Hoffman JI, Kaplan S. 2002. The incidence of congenital heart disease. J Am Coll Cardiol 39(12):1890-1900.

Khoshnood B, Loane M, Walle H, Arriola L, Addor MC, Barisic I, Beres J, Bianchi F, Dias C, Draper E, Garne E, Gatt M, Haeusler M, Klungsoyr K, Latos-Bielenska A, Lynch C, McDonnell B, Nelen V, Neville AJ, O'Mahony MT, Queisser-Luft A, Rankin J, Rissmann A, Ritvanen A, Rounding C, Sipek A, Tucker D, Verellen-Dumoulin C, Wellesley D, Dolk H. 2015. Long term trends in prevalence of neural tube defects in Europe: population based study. Bmj 351:h5949.

Khoury MJ, Botto L, Mastroiacovo P, Skjaerven R, Castilla E, Erickson JD. 1994. Monitoring for multiple congenital anomalies: an international perspective. Epidemiol Rev 16(2):335-350.

Loane M, Dolk H, Garne E, Greenlees R. 2011a. Paper 3: EUROCAT data quality indicators for population-based registries of congenital anomalies. Birth Defects Res A Clin Mol Teratol 91 Suppl 1:S23-30.

Loane M, Dolk H, Kelly A, Teljeur C, Greenlees R, Densem J. 2011b. Paper 4: EUROCAT statistical monitoring: identification and investigation of ten year trends of congenital anomalies in Europe. Birth Defects Res A Clin Mol Teratol 91 Suppl 1:S31-43.

Loane M, Morris JK, Addor MC, Arriola L, Budd J, Doray B, Garne E, Gatt M, Haeusler M, Khoshnood B, Klungsoyr Melve K, Latos-Bielenska A, McDonnell B, Mullaney C, O'Mahony M, Queisser-Wahrendorf A, Rankin J, Rissmann A, Rounding C, Salvador J, Tucker D, Wellesley D, Yevtushok L, Dolk H. 2013. Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening. Eur J Hum Genet 21(1):27-33.

McBride WG. 1961. Thalidomide and congenital abnormalities. The Lancet 278(7216):1358.

Plummer M. JAGS: A Program for Analysis of Bayesian Graphical Models Using Gibbs Sampling; 2003 March 20–22.

Plummer M, Best N, A Cowles K, A Vines K. 2003. CODA: convergence diagnosis and output analysis for MCMC.

Prieto-Merino D, Quartey G, Wang J, Kim J. 2011. Why a Bayesian approach to safety analysis in pharmacovigilance is important. Pharm Stat 10(6):554-559.

R Development Core Team. 2008. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing.

van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. 2011. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 58(21):2241-2247.

World Health Organization. 2014. Fact sheet N° 370 Congenital anomalies. [ONLINE] Available at: http://www.who.int/mediacentre/factsheets/fs370/en/.

Xia HA, Ma H, Carlin BP. 2011. Bayesian hierarchical modeling for detecting safety signals in clinical trials. J Biopharm Stat 21(5):1006-1029.

Table and figure legends

Table 1. Total prevalence of selected groups and subgroups of congenital anomalies per 10,000 births, using data covering 4,097,142 births from 18 EUROCAT registries, 2003 to 2012.

Figure 1. Estimated average annual trends in prevalence of neural tube defects with 95% Posterior Credibility Intervals.

Figure 2. Estimated average annual trends in prevalence of chromosomal anomaly subgroups with 95% Posterior Credibility Intervals.

Figure 3. Estimated average annual trends in prevalence of congenital heart defect subgroups with 95% Posterior Credibility Intervals.

Figure 4. Estimated average annual trends in prevalence of digestive system subgroups with 95% Posterior Credibility Intervals.

Table 1. Total prevalence of selected groups and subgroups of congenital anomalies per 10,000 births, using data covering 4,097,142 births from 18 EUROCAT registries, 2003 to 2012.

Anomaly group and subgroup	Total cases[a]	Prevalence (95% CI)
Neural Tube Defects	4,167	10.2 (9.9, 10.5)
Anencephaly	1,709	4.2 (4.0, 4.4)
Encephalocele	430	1.0 (1.0, 1.2)
Spina Bifida	2,028	4.9 (4.7, 5.2)
Autosomal chromosome anomalies	13,358	32.6 (32.1, 33.2)
Down syndrome / trisomy 21	9,854	24.1 (23.6, 24.5)
Patau syndrome / trisomy 13	942	2.3 (2.2, 2.5)
Edwards syndrome / trisomy 18	2,562	6.3 (6.0, 6.5)
Congenital heart defects	25,273	61.7 (60.9, 62.4)
Severity group I:		
Single ventricle	249	0.6 (0.5, 0.7)
Tricuspid atresia and stenosis	286	0.7 (0.6, 0.8)
Ebstein's anomaly	212	0.5 (0.5, 0.6)
Hypoplastic left heart	1,127	2.8 (2.6, 2.9)
Hypoplastic right heart	205	0.5 (0.4, 0.6)
Severity group II:		
Common arterial truncus	233	0.6 (0.5, 0.6)
Transposition of great vessels	1,467	3.6 (3.4, 3.8)
Atrioventricular septal defect	838	2.0 (1.9, 2.2)
Tetralogy of Fallot	1,187	2.9 (2.7, 3.1)
Pulmonary valve atresia	425	1.0 (0.9, 1.1)
Aortic valve atresia/stenosis	540	1.3 (1.2, 1.4)
Coarctation of aorta	1,488	3.6 (3.4, 3.8)
Total anomalous pulmonary venous return	299	0.7 (0.6, 0.8)
Severity group III:		
Ventricular septal defect	11,262	27.5 (27.0, 28.0)
Atrial septal defect	5,226	12.8 (12.4, 13.1)
Pulmonary valve stenosis	1,850	4.5 (4.3, 4.7)
Digestive system anomalies	7,683	18.8 (18.3, 19.2)
Oesophageal atresia with or without tracheo-oesophageal fistula	890	2.2 (2.0, 2.3)
Duodenal atresia or stenosis	377	0.9 (0.8, 1.0)
Atresia or stenosis of other parts of small intestine	393	1.0 (0.9, 1.1)
Ano-rectal atresia and stenosis	1,157	2.8 (2.7, 3.0)
Hirschsprung's disease	548	1.3 (1.2, 1.5)
Atresia of bile ducts	122	0.3 (0.2, 0.4)
Annular pancreas	57	0.1 (0.1, 0.2)
Diaphragmatic hernia	1,030	2.5 (2.4, 2.7)

[a] *Including livebirths, stillbirths and terminations of pregnancy after prenatal diagnosis*

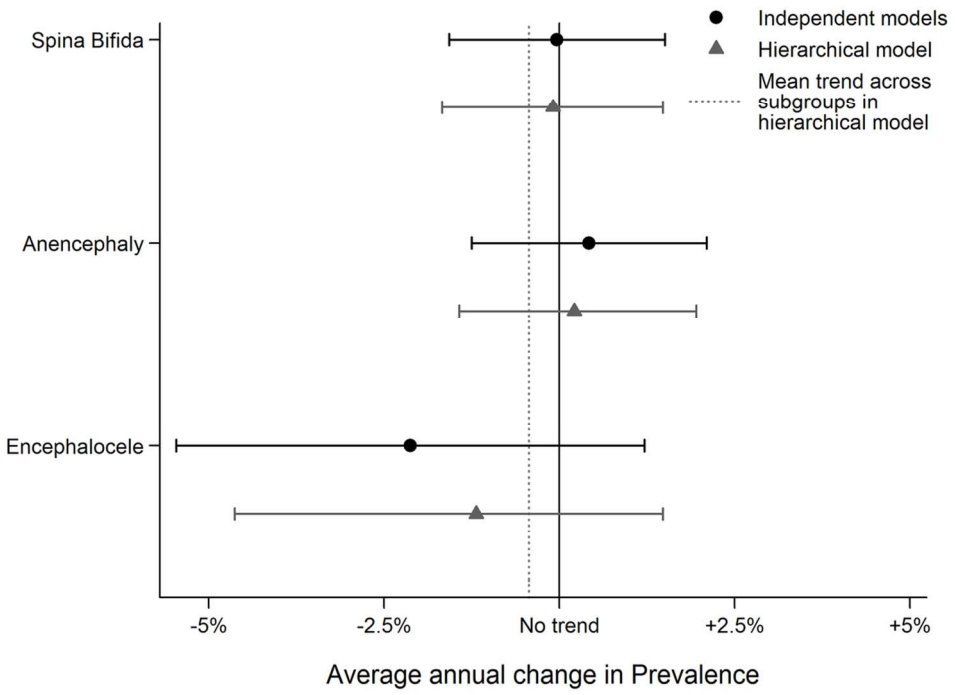

Figure 1. Estimated average annual trends in prevalence of neural tube defects with 95% Posterior Credibility Intervals.
112x84mm (300 x 300 DPI)

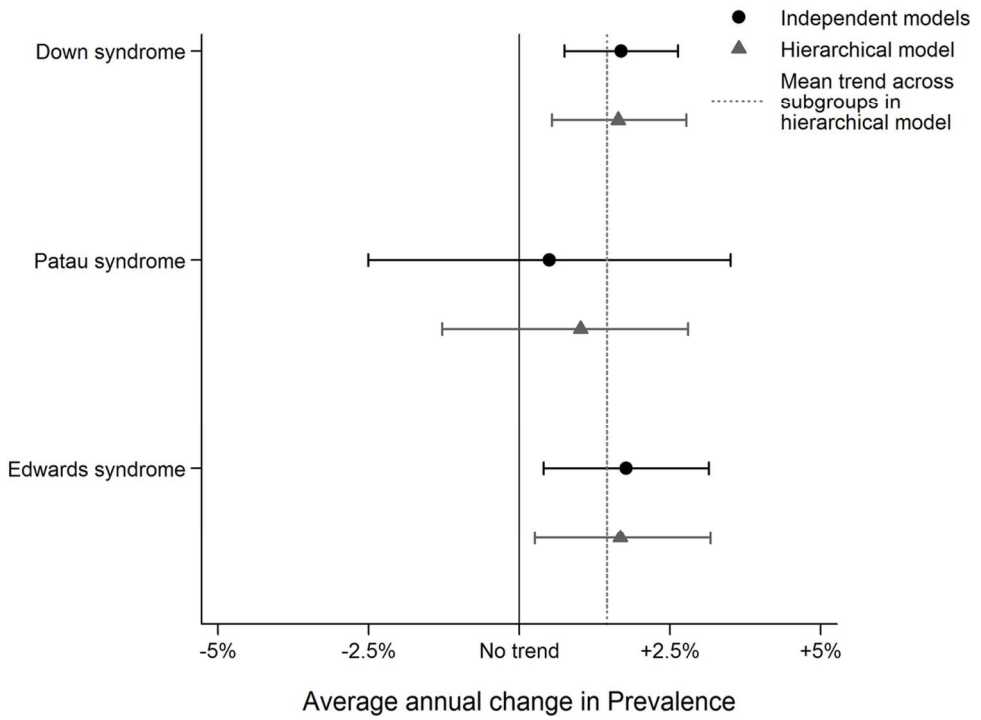

Figure 2. Estimated average annual trends in prevalence of chromosomal anomaly subgroups with 95% Posterior Credibility Intervals.
112x84mm (300 x 300 DPI)

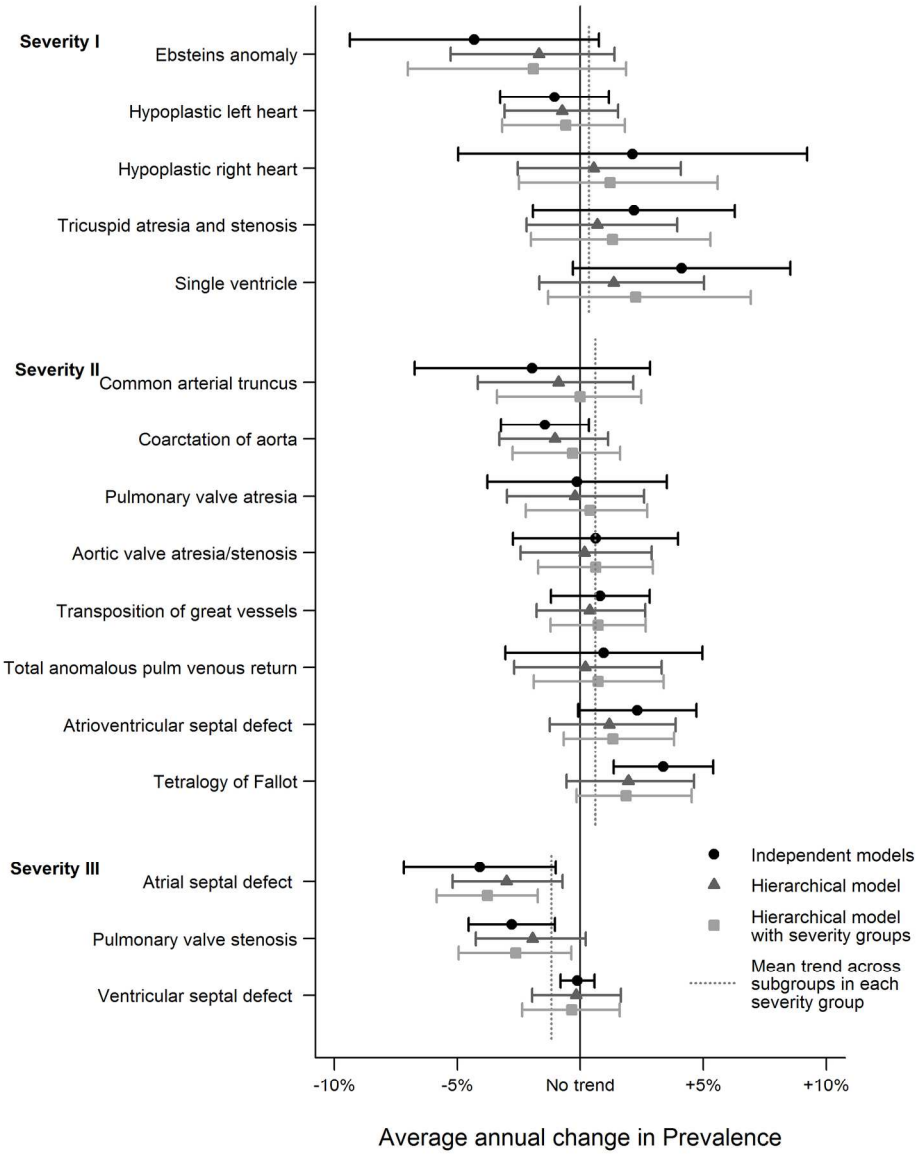

Figure 3. Estimated average annual trends in prevalence of congenital heart defect subgroups with 95% Posterior Credibility Intervals.
187x234mm (300 x 300 DPI)

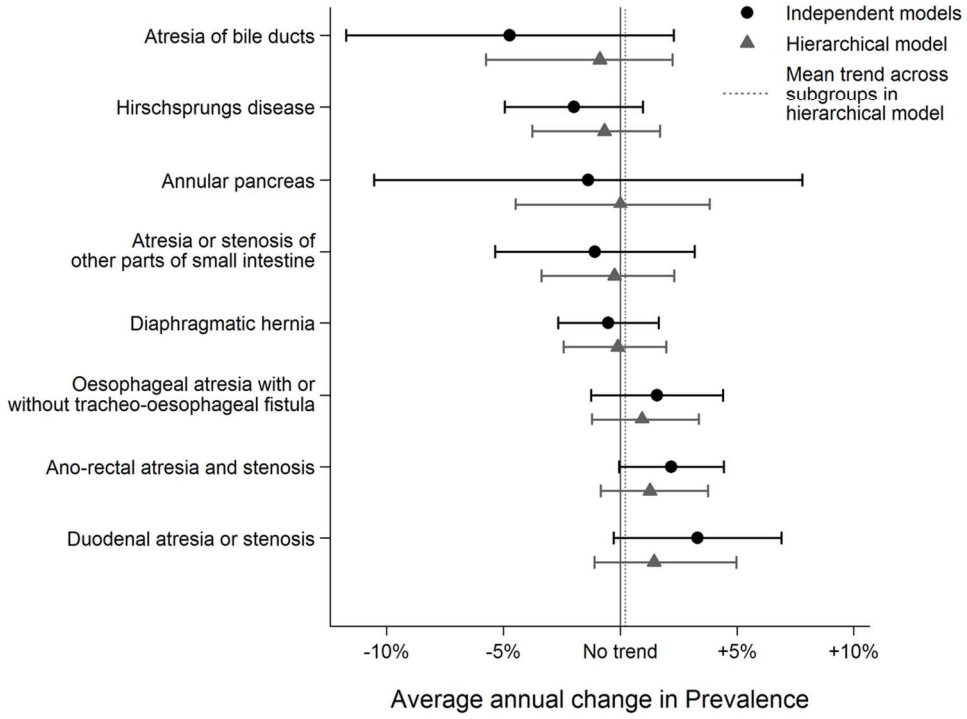

Figure 4. Estimated average annual trends in prevalence of digestive system subgroups with 95% Posterior Credibility Intervals.
117x88mm (300 x 300 DPI)