Congenital Heart Disease

Congenital Heart Defects in Europe
Prevalence and Perinatal Mortality, 2000 to 2005

Helen Dolk, DrPh; Maria Loane, MA; Ester Garne, MD; and a European Surveillance of Congenital Anomalies (EUROCAT) Working Group

Background—This study determines the prevalence of Congenital Heart Defects (CHD), diagnosed prenatally or in infancy, and fetal and perinatal mortality associated with CHD in Europe.

Methods and Results—Data were extracted from the European Surveillance of Congenital Anomalies central database for 29 population-based congenital anomaly registries in 16 European countries covering 3.3 million births during the period 2000 to 2005. CHD cases (n=26,598) comprised live births, fetal deaths from 20 weeks gestation, and terminations of pregnancy for fetal anomaly (TOPFA). The average total prevalence of CHD was 8.0 per 1000 births, and live birth prevalence was 7.2 per 1000 births, varying between countries. The total prevalence of nonchromosomal CHD was 7.0 per 1000 births, of which 3.6% were perinatal deaths, 20% prenatally diagnosed, and 5.6% TOPFA. Severe nonchromosomal CHD (ie, excluding ventricular septal defects, atrial septal defects, and pulmonary valve stenosis) occurred in 2.0 per 1000 births, of which 8.1% were perinatal deaths, 40% were prenatally diagnosed, and 14% were TOPFA (TOPFA range between countries 0% to 32%). Live-born CHD associated with Down syndrome occurred in 0.5 per 1000 births, with >4-fold variation between countries.

Conclusion—Annually in the European Union, we estimate 36,000 children are live born with CHD and 3000 who are diagnosed prenatally or in infancy in Europe.1,2 Great advances in birth and the neonatal period,9 –11 and methods of fetal cardiac intervention are under development.12 For severe CHD, prenatal diagnosis may lead to a decision to terminate the pregnancy. There is a need for updated CHD prevalence data taking these developments into account.13

Primary prevention measures currently include rubella vaccination, good diabetic control, and avoidance of known teratogenic drugs such as some antiepileptic drugs and isotretinoin.14 There is also increasing evidence that folic acid may be protective,14 –16 and recent recommendations include avoiding contact with influenza and febrile illnesses and avoidance of exposure to organic solvents.14 There is growing evidence of a link with maternal obesity18,19 and limited evidence of a link with maternal smoking and exposure to air pollution.14 Primary prevention is particularly difficult because the heart may be fully formed before the mother knows she is pregnant and many pregnancies are unplanned. Monitoring of the prevalence of CHD is needed to determine the overall impact of changes in risk factors and the implementation of primary preventive measures based on current and future research evidence.

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From the EUROCAT Central Registry, Centre for Maternal, Fetal and Infant Research, Institute of Nursing Research, University of Ulster, UK (H.D., M.L.); and Department of Pediatrics, Hospital Lillebaelt, Kolding, Denmark (E.G.).

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Correspondence to Helen Dolk, Professor of Epidemiology and Health Services Research, University of Ulster, Jordanstown Campus, Shore Rd, Co Antrim, BT370QB, Northern Ireland, UK; E-mail h.dolk@ulster.ac.uk

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Table 1. Population* (No. EUROCAT Registries, Births, Percentage National Coverage) and Total Prevalence† (95% CI) of All, Nonchromosomal and Nonchromosomal SI and SII CHDs per 1000 Births by Country, 2000 to 2005

<table>
<thead>
<tr>
<th>Countries*</th>
<th>Registries,* n</th>
<th>Registry Regions, n</th>
<th>Annual National Births Covered, 2005, %</th>
<th>Total Births, 2000 to 2005, in Europe</th>
<th>Prevalence per 1000 Births (95% CI)</th>
<th>No.</th>
<th>Prevalence per 1000 Births (95% CI)</th>
<th>No.</th>
<th>Prevalence per 1000 Births (95% CI)</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>2</td>
<td>182 467</td>
<td>27</td>
<td>1212</td>
<td>6.64 (6.27–7.03)</td>
<td>1058</td>
<td>5.80 (5.45–6.16)</td>
<td>343</td>
<td>1.88 (1.69–2.09)</td>
<td></td>
</tr>
<tr>
<td>Croatia‡</td>
<td>1</td>
<td>33 933</td>
<td>14</td>
<td>182</td>
<td>5.36 (4.61–6.20)</td>
<td>161</td>
<td>4.74 (4.04–5.54)</td>
<td>41</td>
<td>1.21 (0.87–1.64)</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>1</td>
<td>32 003</td>
<td>8</td>
<td>291</td>
<td>9.09 (8.08–10.20)</td>
<td>265</td>
<td>8.28 (7.31–9.34)</td>
<td>65</td>
<td>2.03 (1.57–2.59)</td>
<td></td>
</tr>
<tr>
<td>France‡</td>
<td>3</td>
<td>343 715</td>
<td>8</td>
<td>2853</td>
<td>8.30 (6.00–8.61)</td>
<td>2447</td>
<td>7.12 (6.84–7.41)</td>
<td>879</td>
<td>2.56 (2.39–2.73)</td>
<td></td>
</tr>
<tr>
<td>Germany‡</td>
<td>2</td>
<td>124 952</td>
<td>3</td>
<td>1457</td>
<td>11.66 (11.07–12.28)</td>
<td>1315</td>
<td>10.52 (9.96–11.11)</td>
<td>269</td>
<td>2.15 (1.90–2.43)</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>3</td>
<td>215 021</td>
<td>63</td>
<td>1423</td>
<td>6.62 (6.28–6.97)</td>
<td>1083</td>
<td>5.04 (4.74–5.35)</td>
<td>476</td>
<td>2.21 (2.02–2.42)</td>
<td></td>
</tr>
<tr>
<td>Italy‡</td>
<td>3</td>
<td>431 727</td>
<td>15</td>
<td>2944</td>
<td>6.82 (6.58–7.07)</td>
<td>2744</td>
<td>6.36 (6.12–6.60)</td>
<td>754</td>
<td>1.75 (1.62–1.88)</td>
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</tr>
<tr>
<td>Malta</td>
<td>1</td>
<td>23 668</td>
<td>100</td>
<td>348</td>
<td>14.70 (13.20–16.33)</td>
<td>307</td>
<td>12.72 (11.32–14.24)</td>
<td>51</td>
<td>2.15 (1.60–2.63)</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>1</td>
<td>119 104</td>
<td>10</td>
<td>732</td>
<td>6.15 (5.71–6.61)</td>
<td>639</td>
<td>5.37 (4.96–5.80)</td>
<td>272</td>
<td>2.28 (2.02–2.57)</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>1</td>
<td>346 838</td>
<td>100</td>
<td>3538</td>
<td>10.20 (9.87–10.54)</td>
<td>3236</td>
<td>9.33 (9.01–9.66)</td>
<td>611</td>
<td>1.76 (1.63–1.91)</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>1</td>
<td>206 170</td>
<td>9</td>
<td>2304</td>
<td>11.18 (10.72–11.64)</td>
<td>2116</td>
<td>10.26 (9.83–10.71)</td>
<td>297</td>
<td>1.44 (1.28–1.61)</td>
<td></td>
</tr>
<tr>
<td>Spain‡</td>
<td>2</td>
<td>194 234</td>
<td>7</td>
<td>1080</td>
<td>5.56 (5.23–5.90)</td>
<td>904</td>
<td>4.65 (4.36–4.97)</td>
<td>399</td>
<td>2.05 (1.86–2.27)</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
<td>42 874</td>
<td>10</td>
<td>576</td>
<td>13.43 (12.36–14.58)</td>
<td>512</td>
<td>11.94 (10.93–13.02)</td>
<td>105</td>
<td>2.45 (2.00–2.97)</td>
<td></td>
</tr>
<tr>
<td>Ukraine‡</td>
<td>1</td>
<td>25 835</td>
<td>6</td>
<td>201</td>
<td>7.78 (6.74–8.93)</td>
<td>180</td>
<td>6.97 (5.99–8.06)</td>
<td>46</td>
<td>1.78 (1.30–2.38)</td>
<td></td>
</tr>
<tr>
<td>UK‡</td>
<td>5</td>
<td>951 001</td>
<td>26</td>
<td>6497</td>
<td>6.83 (6.67–7.00)</td>
<td>5516</td>
<td>5.80 (5.65–5.96)</td>
<td>1974</td>
<td>2.08 (1.99–2.17)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>3 336 209</td>
<td>13</td>
<td>26 598</td>
<td>7.97 (7.88–8.07)</td>
<td>23 348</td>
<td>7.00 (6.91–7.09)</td>
<td>6745</td>
<td>2.02 (1.97–2.07)</td>
<td></td>
</tr>
</tbody>
</table>

†Only registries include LBs, fetal deaths from 20 weeks and TOPFAs. Prevalence tables for CHD subgroups can be found at http://www.eurocat-network.eu/ACCESSPREVALENCDATA/PrevalenceTables.
‡Twenty-one registries ascertained cases of CHD diagnosed until at least 1 year of life. Exceptions were Croatia (1 week), Paris (discharge from maternity or neonatal unit), Mainz (1 week, but all newborns submitted to standard registry examination and followed up if murmur detected), Barcelona (3 days), and Ukraine (1 month). Ascertainment in Emilia Romagna and Thames Valley was more systematic for cases diagnosed in the first week, and Wessex ascertained cardiac cases diagnosed after 1 week only if they had surgery.

European Surveillance of Congenital Anomalies (EUROCAT) is a population-based surveillance system based on a network of congenital anomaly registers in Europe covering more than one quarter of births in 20 European countries. The great advantage of such a population-based system is that prevalence can be estimated without biases caused by referral of high-risk pregnancies or babies between hospitals, and ascertainment includes fetal and early neonatal deaths as well as terminations of pregnancy for fetal anomaly (TOPFA) after prenatal diagnosis who do not reach pediatric cardiology referral centers.

In this article, we present recent EUROCAT data on the prevalence of CHD in Europe, diagnosed prenatally or in infancy, and on the outcome of pregnancy in terms of fetal and early postnatal survival. This information is needed as a baseline from which to monitor future progress in primary prevention; to monitor the impact of termination of pregnancy for fetal anomaly on prevalence; to plan for high-quality services; and to allow individual regions to compare their rates with the European average and range. This article therefore investigates CHD from a public health rather than a clinical perspective.

Methods

Data were extracted from the EUROCAT database, which is fully described elsewhere and was last updated in February 2009. Twenty-nine population-based registries in 16 European countries (including 3 non-European Union [EU] countries) contributed data (Table 1). The total population coverage for 2000 to 2005 was 3.3 million births. From 12% to 100% of annual births in each country were covered by ≥1 EUROCAT registries (Table 1).

Registries contributing individual-anonymized case data to the EUROCAT central database at least as recent as 2004 were included. Registries use multiple sources of information to ascertain cases in order to cover all types of cases (live birth [LB], late fetal death, and termination of pregnancy; surgical and nonsurgical; and with and without additional major non-CHD anomalies). Sources, depending on registry, include maternity, neonatal, and pediatric records; fetal medicine, cytogenetic, pathologist, and medical genetics records; specialist services including pediatric cardiology; and hospital discharge and child health records. Twenty-one of the registries (covering 2.6 million births) included in the study ascertained cases of CHD diagnosed up to at least 1 year of life. The exceptions are noted as a footnote to Table 1.

Cases of CHD occurring in LBs, late fetal deaths/stillbirths from 20 weeks of gestation (FDs), and TOPFA after prenatal diagnosis at any gestational age were included.

All cases were coded to the International Classification of Diseases (ICD) version 9 or 10 with 1-digit BPA extension. Cases of CHD occurring in LBs, late fetal deaths/stillbirths from 20 weeks of gestation (FDs), and TOPFA after prenatal diagnosis at any gestational age were included.
can have up to 9 syndrome or malformation codes. The ICD codes defining CHD were Q20–26 (ICD10) and 745, 746, and 7470 to 7474 (ICD9-BPA). Cases of patent ductus arteriosus in preterm babies (<37 weeks) and patent foramen ovale as the only CHD were excluded.20

EUROCAT defines 16 standard subgroups of CHD.20 We used a previously defined hierarchical severity ranking20 based on the perinatal mortality rate for each of these subgroups among nonchromosomal cases (see online-only Data Supplement Figure 1), with 3 classes, from I (high perinatal mortality) to III (low perinatal mortality):

Severity I (SI): single ventricle, hypoplastic left heart, hypoplastic right heart, Ebstein anomaly, and tricuspid atresia
Severity II (SII): pulmonary valve atresia, common arterial truncus, atrioregional septal defects, aortic valve atresia/stenosis, transposition of great vessels, tetralogy of Fallot, total anomalous pulmonary venous return, and coarctation of aorta, without additional CHD subgroups classified as severity I. The following anomalies not classified to any of the 16 EUROCAT subgroups were added to SII (finally accounting for 6% of SII cases): double outlet right or left ventricle, discordant atrioregional connections, interventricular and intraventricular connection, Ivemark atrial isomerism, other abnormal cardiac connections, aortopulmonary window, cri triatriatum, subaortic valve stenosis, malformations of coronary arteries, atresia of aorta and interrupted aortic arch, supravalvular aortic stenosis, and abnormal pulmonary venous connections.

Severity III (SIII): ventricular septal defect (VSD), atrioregional defect, and pulmonary valve stenosis, without additional CHD subgroups classified as SII or SIII.

Eleven percent of all CHD cases where the ICD code was for a poorly specified CHD of unknown severity or patent ductus arteriosus in term infants were not classified to a severity group. These cases were included in counts relating to all CHD but not in severity category counts.

Cases were classified according to the presence or absence of an associated chromosomal anomaly (ICD10 codes Q90–93 and 96 to 99 excl Q936). Nonchromosomal cases were classified by the presence or absence of an additional major non-CHD anomaly, the latter labeled “isolated.” Each case is counted once only in any given prevalence rate (ie, prevalence is based on cases, not anomalies). Prevalence rates averaged across Europe were calculated by adding up EUROCAT regions across Europe, without extrapolation to country for partially covered countries. Prevalence rates were calculated as:

\[
\text{LB prevalence rate} = \frac{(\text{No. LB cases})}{(\text{total births live and still})}
\]

\[
\text{FD prevalence rate} = \frac{(\text{No. FD cases})}{(\text{total births live and still})}
\]

\[
\text{TOPFA prevalence rate} = \frac{(\text{No. TOPFA})}{(\text{total births live and still})}
\]

\[
\text{Total prevalence rate} = \frac{(\text{LB} + \text{FD} + \text{TOPFA})}{(\text{total births live and still})}
\]

We present TOPFA mainly as a prevalence per 1000 births rather than as a proportion of all CHD cases because differences in ascertainment of milder postneonatally diagnosed CHD can distort proportions greatly. The “perinatal mortality” rate was defined as (FD from 20 weeks gestation + first week deaths)/ (total births live and still).

Data extracted for registered cases were date of birth, registry, pregnancy outcome (LB, FD, or TOPFA), all diagnosed malformations and syndromes, age at diagnosis (defined as first suspicion of any congenital anomaly, whether CHD or associated non-CHD anomaly), and whether the neonate survived the first week of life. Whether a LB/FD case had been prenatally diagnosed was not recorded in the central database for 4 registries (see footnote to Table 2), which were excluded from analysis of prenatal diagnosis. Confidence intervals (CIs) for prevalence rates were calculated in StatsDirect statistical software version 2.7.7 (StatsDirect Ltd, Cheshire, UK).

Results

All CHD Cases

The reported total prevalence of CHD in Europe was 8.0 per 1000 births (95% CI 7.9 to 8.1) based on 26 598 cases (Table 1), including LBs (89.7%), FDs (1.6%), and TOPFA (8.7%). The range in total prevalence across countries was 5.36 to 15.32 per 1000, with 5 countries reporting prevalence >10 per 1000 (Table 1). The average LB prevalence was 7.2 per 1000 (95% CI 7.1 to 7.3).

Nonchromosomal CHD Cases

Eighty-eight percent of CHD were not associated with a chromosomal anomaly, giving an average total prevalence of 7.0 per 1000 (95% CI 7.0 to 7.1), varying considerably between countries (Table 1) and registries within countries (Figure 1). Most were LBs (6.5 per 1000, Table 2), and 82% were isolated CHD (Table 2). SIII cases were more than twice as common as SI and SII combined (Table 2). The prevalence of VSD without other associated CHD or non-CHD anomalies was 1.9 per 1000.

Age at diagnosis was known for 66% of live-born nonchromosomal CHD cases. Twenty-three percent of cases with known age at diagnosis were diagnosed after 1 week of age: 83% 1 week to 1 month, 12.5% 1 month to 1 year, and 1.9% after 1 year. This proportion was highest for the less severe cases: 5.8% for SI, 15.5% for SII, and 26.2% for SIII. Ascertainment of SIII cases diagnosed after 1 week of age, as indicated by their prevalence, varied between registries (Figure 1). The 3 registries recording the highest prevalence of SIII diagnosed after 1 week of 4 to 5 per 1000 (Figure 1) were from the 3 countries recording the highest overall CHD prevalence (Table 1). Average total SIII prevalence was 0.5 per 1000 births higher in the 21 registries with ascertainment up to 1 year (4.68 per 1000) than the average for all registries (4.18 per 1000, Table 2).

Perinatal mortality was 0.25 per 1000 births (95% CI 0.24 to 0.27, Table 2), varying from 0.07 in Italy to a range of 0.20 to 0.38 in all other countries except Ukraine at 0.93 per 1000 (Figure 2 and online-only Data Supplement Table I). SI and SII contributed approximately a third each to CHD perinatal deaths (Table 1) whereas SIII contributed 19%. CHD of unclassified severity contributed disproportionately to CHD perinatal mortality (16%) probably because of the lower level of diagnostic specificity available from death records. Perinatal deaths were less likely to be isolated CHD (Table 2).

Prenatal Diagnosis and TOPFA for Nonchromosomal Cases

A total of 20.2% of nonchromosomal CHD cases had prenatal diagnosis of a congenital anomaly (Table 2, data from 25/29 registries, being the majority of SI (63.7%), nearly a third of SII (or 40% of SI/SII combined), and less than one tenth of SIII (Table 2). Prenatally diagnosed cases were less likely to be isolated CHD, especially for SIII (Table 2). Prenatal diagnosis proportions for SI/SII varied by country (Figure 3).
A total of 31% of prenatally diagnosed nonchromosomal CHD resulted in TOPFA (54.6% for SI, 27.5% for SII, and 15.9% for SIII, data from 25/29 registries), this proportion also varying by country (Figure 3). TOPFA were less likely to be isolated CHD than other prenatally diagnosed or non–prenatally diagnosed cases, especially for SIII (Table 2).

TOPFA were more frequent than perinatal deaths, at 0.39 per 1000. This rate varied strongly between countries (Figure 2, online-only Data Supplement Table I): from 0 in Ireland, Malta, and Poland to a maximum of 1.06 per 1000 in France (Figure 2).

Table 2. No., Prevalence per 1,000 births (95% Cl), and Proportion of Nonchromosomal CHD by Pregnancy Outcome, Whether CHD was an Isolated Anomaly, and Whether Prenatally Diagnosed, in 29 European Registries, 2000 to 2005

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No.</th>
<th>Prevalence per 1000 Births (95% CI)</th>
<th>Total Cases, %</th>
<th>Isolated Within Category, %</th>
<th>No.</th>
<th>Prevalence per 1000 Births (95% CI)</th>
<th>Total Cases, %</th>
<th>Isolated Within Category, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>23348</td>
<td>7.00 (6.96–6.14)</td>
<td>100.0</td>
<td>82.4</td>
<td>1556</td>
<td>0.47 (0.44–0.49)</td>
<td>100.0</td>
<td>82.8</td>
</tr>
<tr>
<td>LBs</td>
<td>21749</td>
<td>6.52 (6.48–6.65)</td>
<td>93.2</td>
<td>84.6</td>
<td>973</td>
<td>0.29 (0.27–0.31)</td>
<td>62.5</td>
<td>86.1</td>
</tr>
<tr>
<td>Fetal deaths</td>
<td>291</td>
<td>0.09 (0.08–0.10)</td>
<td>1.2</td>
<td>52.9</td>
<td>63</td>
<td>0.02 (0.02–0.02)</td>
<td>4.0</td>
<td>76.2</td>
</tr>
<tr>
<td>TOPFA</td>
<td>1308</td>
<td>0.39 (0.37–0.41)</td>
<td>5.6</td>
<td>52.4</td>
<td>520</td>
<td>0.16 (0.14–0.17)</td>
<td>33.4</td>
<td>77.5</td>
</tr>
<tr>
<td>First–week deaths</td>
<td>554</td>
<td>0.17 (0.15–0.18)</td>
<td>2.4</td>
<td>63.2</td>
<td>191</td>
<td>0.06 (0.05–0.07)</td>
<td>12.3</td>
<td>83.2</td>
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<tr>
<td>Perinatal deaths†</td>
<td>845</td>
<td>0.25 (0.24–0.27)</td>
<td>3.6</td>
<td>59.6</td>
<td>254</td>
<td>0.08 (0.07–0.09)</td>
<td>16.3</td>
<td>81.5</td>
</tr>
<tr>
<td>Prenatally diagnosed‡</td>
<td>3041</td>
<td>1.27 (1.23–1.32)</td>
<td>20.2</td>
<td>58.3</td>
<td>698</td>
<td>0.29 (0.27–0.32)</td>
<td>63.7</td>
<td>77.8</td>
</tr>
</tbody>
</table>

*SI: single ventricle, hypoplastic left heart, hypoplastic right heart, Ebstein anomaly, tricuspid atresia. SII: mainly pulmonary valve atresia, common arterial truncus, atrioventricular septal defects, aortic valve atresia/stenosis, transposition of great vessels, tetralogy of Fallot, total anomalous pulmonary venous return, coarctation of aorta, and without additional CHD subgroups classified as SI or SII.

†Perinatal deaths = fetal deaths from 20 weeks gestation + first week deaths.

‡Prenatal diagnosis of CHD and/or an associated congenital anomaly. Data excludes Norway, and UK: East Midlands and South Yorkshire, Northern England, and Thames Valley.

Chromosomal CHD Cases

Twelve percent of CHD cases were associated with chromosomal anomalies (7% Down Syndrome [DS], 2% Trisomy 18, and 1% Trisomy 13), for an average total prevalence of 0.97 per 1000 births. In the study population, the total prevalence of DS was 2.1 per 1000, of which 48.1% were TOPFA, and the prevalence of DS among LBs was 1.0 per 1000 births. Of these LB DS cases, 45% (n=1521) had a recorded CHD (17.4% SI/SII, 23.8% SIII, and 3.8% unclassified severity), giving a LB prevalence of Down syndrome with CHD of 0.46 per 1000 births (95% CI 0.43 to 0.48). Rates of LB Down syndrome with CHD varied from <0.25 per 1000 in France, Italy, and Switzerland to >1 per 1000 in Ireland and Malta (Figure 4). A total of 1.2% of LB Down syndrome with CHD died in the first week of life.

We estimate the contribution of Down syndrome with CHD to the total pediatric CHD case load to vary from 3% to 4% (Italy, France, and Switzerland) to 15% to 19% (Ireland and Malta), assuming an average nonchromosomal CHD LB prevalence of 6.5 per 1000 for all countries.

Discussion

We found the total prevalence of CHD in Europe during 2000 to 2005 to be 8.0 per 1000 births, with variation between countries and registries within countries, and LB prevalence to be 7.2 per 1000 births. A review of 62 studies published in 2002 found a median LB prevalence of 7.5 per 1000, similar to our study, with an interquartile range of 6.0 to 10.6 per 1000. Variation between the studies reviewed was mainly explained by variation in the inclusion of small VSDs and indication for echocardiography. In our European population, on the basis of diagnoses reached under normal health service conditions, up to half of SIII cases, depending on registry, were first detected after the first week of life, and the prevalence estimate would be 0.5 per 1000 higher if registries not ascertaining up to 1 year of life were excluded. However, it is not possible to standardize comparisons between regions or countries by using age at diagnosis in order to find “real” underlying variation in prevalence, given that average age at diagnosis itself varies according to the intensity of prenatal and early neonatal screening and follow-up taking place in each region. Moreover, even with complete ascertainment of cases diagnosed up to 1 year of age, variation in prevalence relating to echocardiography referral practice and registry inclusion of smaller muscular cases that close spontaneously would remain. During the decade preceding our study, an increase in the prevalence of CHD, particularly SIII, was reported in a number of European and other countries and attributed mainly to diagnostic factors.

The total prevalence of severe (SI/SII) nonchromosomal CHD cases in our population was 2.0 per 1000. These cases are more uniformly ascertained and were mainly diagnosed by the end of the first week of life, including a significant proportion of prenatally diagnosed cases. To what extent country variation in the rate of severe (SI/SII) CHD, the highest rate being recorded in Austria, reflects variation in risk factors requires further investigation. Recent evidence of a decline in severe CHD in this decade, including in
EUROCAT regions,²² lends support to the potential for variation between populations in severe CHD (and by implication less severe CHD) prevalence related to underlying risk factors.

Our severity ranking was based on the proportion of affected births that were perinatal deaths.²⁸ The division between SI and SII on this basis corresponds to whether there are 1 or 2 functioning ventricles. The division between SI/SII and SIII corresponds well with the likelihood that surgery is needed: data from 2 EUROCAT regions show that 80% of isolated SI/SII cases require surgery (and a further 7% are too severe for surgery), compared to 7% of SIII cases requiring surgery.³⁰ The ranking is also pragmatic in that it is based on ICD codes and preexisting EUROCAT subgroup classifications, without the need for further expert review to assess combinations of codes or pediatric cardiology records as needed.

### Table 2. Continued

<table>
<thead>
<tr>
<th>No.</th>
<th>Prevalence per 1000 Births (95% CI)</th>
<th>Total Cases, %</th>
<th>Isolated Within Category, %</th>
<th>No.</th>
<th>Prevalence per 1000 Births (95% CI)</th>
<th>Total Cases, %</th>
<th>Isolated Within Category, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5189</td>
<td>1.56 (1.52–1.60)</td>
<td>100.0</td>
<td>78.6</td>
<td>13 960</td>
<td>4.18 (4.13–4.23)</td>
<td>100.0</td>
<td>85.5</td>
</tr>
<tr>
<td>4671</td>
<td>1.40 (1.36–1.44)</td>
<td>90.0</td>
<td>82.1</td>
<td>13 714</td>
<td>4.11 (4.06–4.20)</td>
<td>98.2</td>
<td>86.5</td>
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<tr>
<td>93</td>
<td>0.03 (0.02–0.03)</td>
<td>1.8</td>
<td>51.6</td>
<td>73</td>
<td>0.02 (0.02–0.03)</td>
<td>0.5</td>
<td>46.6</td>
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<tr>
<td>425</td>
<td>0.13 (0.12–0.14)</td>
<td>8.2</td>
<td>45.4</td>
<td>173</td>
<td>0.05 (0.04–0.06)</td>
<td>1.2</td>
<td>20.9</td>
</tr>
<tr>
<td>197</td>
<td>0.06 (0.05–0.07)</td>
<td>3.8</td>
<td>63.5</td>
<td>88</td>
<td>0.03 (0.02–0.03)</td>
<td>0.6</td>
<td>35.2</td>
</tr>
<tr>
<td>290</td>
<td>0.09 (0.08–0.10)</td>
<td>5.6</td>
<td>59.7</td>
<td>161</td>
<td>0.05 (0.04–0.06)</td>
<td>1.2</td>
<td>40.4</td>
</tr>
<tr>
<td>1115</td>
<td>0.47 (0.44–0.50)</td>
<td>32.1</td>
<td>64.2</td>
<td>775</td>
<td>0.32 (0.30–0.35)</td>
<td>8.6</td>
<td>38.2</td>
</tr>
</tbody>
</table>

**Figure 1.** Total prevalence of nonchromosomal SI/SII/SIII congenital heart defects by severity grouping,* age at detection** of SIII cases, and registry;† 2000 to 2005. *Severity is ranked from greatest severity (SI) to least severity (SIII) on the basis of perinatal mortality (see footnote to Table 2). Unclassified by severity are not included. **Age at which a congenital anomaly is first suspected, shown only for SIII cases: <1 week—perinatally or up to 1 week of age; >1 week is 1 week to registration age limit; and NK, age at detection not recorded in EUROCAT central database. †Registries with incomplete ascertainment after 1 week (see footnote to Table 1).
would be needed for other classification schemes.\textsuperscript{13,33,34} However, our SIII category combined VSD, atrial septal defect, and pulmonary valve stenosis of all sizes because in most cases we had no further specification. Therefore, we have tended to underestimate the prevalence of the more severe cardiac conditions with high mortality by including, for example, large VSD without associated SI/SII defects in SIII. These are most likely represented among the small proportion of SIII cases that have surgery.\textsuperscript{30} Efforts by International Nomenclature Committee for Pediatric and Congenital Heart Disease,\textsuperscript{34} EUROCAT, and others to improve the World Health Organization ICD11 coding system for CHD are important for improving quality and comparability of classifications and interpretability of CHD data in future.

Twelve percent of CHD cases in the EUROCAT series were chromosomal, the majority Down syndrome. Variation in total prevalence of chromosomal CHD cases can be explained by large differences in the maternal age profile of European populations. However, ascertainment of CHD among TOPFA for chromosomal anomaly is likely to be incomplete, especially for early terminations. CHD may also go undetected in perinatal deaths with chromosomal syndromes without full autopsy. We therefore concentrated our analysis of chromosomal cases on LBs. Approximately half of live-born children with Down syndrome are usually considered to have a cardiac defect, 45% in our data set. We found 4-fold country variation in LB prevalence of Down syndrome with CHD, which can be explained by differences in maternal age profile of births together with differences in prenatal detection and TOPFA rates for Down syndrome.\textsuperscript{2,8,35} This needs to be taken into account in planning pediatric cardiology services.

Microdeletions (such as 22q11.2) were included among nonchromosomal cases in our study because testing for microdeletions was variable across regions and registry coding of microdeletions was not yet standardized. The prevalence of CHD with 22q11.2 for 16 of the registers for the same time period was 0.74 per 10 000, of which one third were tetralogy of Fallot (Dr Diana Wellesley, BM, personal communication). If extrapolated, this suggests that during this period <1% of CHD cases had a diagnosed 22q11.2 microdeletion, or 8% of tetralogy of Fallot. Microdeletion 22q11.2 has been estimated to be associated with up to 20% of some severe cardiac defects such as truncus arteriosus and tetralogy of Fallot in fully tested case series.\textsuperscript{36}

Most regions/countries reported prenatal detection rates considerably less than those reported by tertiary centers,\textsuperscript{37} demonstrating the value of population-based appraisal. Only for SI cases were the majority (64%) prenatally diagnosed.
For SI cases, the majority (55%) of prenatal diagnoses led to TOPFA, and thus TOPFA had a significant impact on birth/LB prevalence. As CHD treatment success and quality of life of CHD survivors improves, the number of CHD TOPFA may decrease. Currently, CHD TOPFA prevalence in countries, as represented by their EUROCAT coverage, falls into 3 groups: the maximum of 1.1 per 1000 births in France, a group of countries at 0.3 to 0.5 per 1000 (Italy, Spain, UK, Germany, and Switzerland), and all other countries at <0.3 per 1000.

Perinatal mortality, mainly first week mortality, associated with CHD is significant in relation to overall perinatal mortality, despite a fall in infant mortality due to CHD during the 1990s.23,26,38,39 In the EU in 2004, about one quarter of early neonatal deaths were due to congenital anomalies, and of these, in EUROCAT regions, 25% were CHD and a further 18% chromosomal with or without CHD.1 The high nonchromosomal CHD perinatal mortality rate of 0.93 per 1000 births in the Ukraine is probably related to low treatment success. This suggests that it may not be possible to extrapolate EUROCAT data on mortality to all other Eastern European countries. Other countries at the higher end of the range of perinatal mortality (0.37 to 0.38 per 1000) are Ireland, Malta, and the Netherlands where there are no or very few TOPFA; TOPFA are illegal in Malta and Ireland, and the Netherlands did not carry out routine anomaly ultrasound scanning during this period. The deficit in perinatal mortality below 0.4 per 1000 in other countries (Figure 2) needs to be assessed for each country in terms of whether it is due to TOPFA, lower total prevalence of severe CHD, better treatment outcomes (possibly related to higher prenatal diagnosis rates among LBs), low autopsy rates, and/or poor cause of death recording (the last known to be a factor in Italy, which records the lowest perinatal mortality1).

The present study has a number of limitations. Although we analyzed nearly all the population-based information on CHD available in the countries covered, this information is not completely representative of the European population. In countries only partially covered by EUROCAT registries, the results from 1 region may not reflect the situation for the entire country, and some differences between countries may be over- or underestimated as a result. In terms of Europe as a whole, the countries included are mainly EU countries, and the average results cannot necessarily be extrapolated beyond these countries. Secondly, caution should be exercised in interpreting the prevalence of diagnosed cases as the underlying prevalence, given the range of ascertainment problems discussed. A third limitation relates to information recorded on the age at diagnosis: The data set includes whether a congenital anomaly was prenatally diagnosed or postnatal at first detection, but if the neonate is multiply malformed it does not specify which anomaly was first diagnosed. Some of these limitations relate to compromises that were necessary to obtain a large European data set bringing together many regions. On the other hand, the strengths are the population-based data from many countries, all collecting a common data set and including all pregnancy outcomes.

In the 27 countries of the present EU we have ~5 million births per year. Assuming the data we present here are reasonably representative for the EU, by simple extrapolation we can estimate that there are 36 000 LBs diagnosed with CHD each year, 1250 perinatal deaths with nonchromosomal CHD, and nearly 2000 nonchromosomal TOPFA with CHD. Investing in primary prevention is essential to reduce this burden. Such measures need to be both at an individual level (advice to women before they become pregnant) and at the population level (regulation of exposures in the domestic, occupational, and community environment) to protect women who do not yet know they are pregnant and to address exposures beyond the control of individuals. Investing in pathogenetic research can further increase the potential of primary prevention. The data presented here also allow the impact of prenatal diagnosis and termination of pregnancy on CHD prevalence and perinatal mortality to be further monitored and inform the continuing substantial investment needed in cardiac services from in utero to adulthood.
Appendix

Members of the EUROCAT Working Group

Marie-Claude Addor (Division of Medical Genetics, University of Lausanne, Switzerland)
Marian Bakker (Department of Genetics, University Medical Centre Groningen, Northern Netherlands)
Ingeborg Barisic (Department of Paediatrics, Children’s Hospital Zagreb Croatia)
Sebastiano Bianca (ISMAC, Catania, Sicily, Italy)
Patricia Boyd (National Perinatal Epidemiology Unit, University of Oxford, UK)
Elisa Calzolari (University of Ferrara, Emilia Romagna, Italy)
Berencie Doray (Hôpitaux de Hautepiere, Strasbourg, France)
Miriam Gatt (Malta Department of Health Information and Research, Malta)
Martin Haeusler (University of Graz, Styria, Austria)
Babak Khoshnood (INSERM U953, St Vincent de Paul Hospital, Paris, France)
Kari Klangsoy Melve (Norwegian Institute of Public Health, Bergen, Norway)
Anna Latos-Bielsenka (Poznan University of Medical Sciences, Poland)
Bob McDonnell (Health Service Executive, Dr Steeven’s Hospital, Dublin, Ireland)
Carmel Mullaney (Department of Public Health, Health Service Executive - South East, Kilkenny, Ireland)
Vera Nelen (Provincial Institut voor Hygiene, Antwerp, Belgium)
Mary O’Mahony (Department of Public Health, Health Service Executive - South, Cork, Ireland)
Anna Pietri (CNR Institute of Clinical Physiology, Tuscany, Italy)
Simone Poetzsch (Medical Faculty, Otto-van-Guericke University, Magdeburg, Germany)
Annette Queisser-Luft (University Children’s Hospital, Mainz, Germany)
Hanitra Randrianaivo (Naıˆtre Aujourd’hui, Ile de la Réunion, France)
Judith Rankin (Institute of Health and Society, University of Newcastle, UK)
Joaquín Salvador (Public Health Agency of Barcelona, Spain)
David Tucker (Swansea NHS Trust, Congenital Anomaly Register and Information Service for Wales, UK)
Christine Verellen-Dumoulin (Institut de Morphologie Pathologique, Hainaut-Namur, Belgium)
Diana Wellesley (Wessex Clinical Genetics Service, Princess Anne Hospital, UK)
Wladimir Wertelecki (OMNI-Net, Ukraine)

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Disclosures

None.

References

Information on prevalence and fetal and perinatal mortality associated with Congenital Heart Defects (CHD) in Europe is needed as a baseline from which to monitor future progress in primary prevention, to monitor the impact of termination of pregnancy for fetal anomaly (TOPFA) on prevalence, to plan for high-quality services, and to allow individual regions to compare their rates with the European average and range. We analyzed data from 29 population-based congenital anomaly registries in 16 European countries covering 3.3 million births from 2000 to 2005. The total prevalence of CHD was 8.0 per 1000 births, and live birth prevalence was 7.2 per 1000 births, varying between countries. The total prevalence of nonchromosomal CHD was 7.0 per 1000 births, of which 3.6% were perinatal deaths and 5.6% TOPFA. Severe nonchromosomal CHD (ie, excluding ventricular septal defects, atrial septal defects, and pulmonary valve stenosis) occurred in 2.0 per 1000 births, of which 8.1% were perinatal deaths, 40% were prenatally diagnosed, and 14% were TOPFA. The TOPFA proportion for severe CHD varied from 0 to 32% between countries. The live-birth prevalence of Down syndrome with CHD (average 0.5 per 1000) varied >4-fold between countries because of differences in maternal age profile of births and differences in TOPFA rates for Down syndrome. There are an estimated 36 000 children live born with CHD in the European Union each year and 3000 TOPFA, stillbirth, or early neonatal deaths with CHD. Investing in primary prevention and in cardiac services from in utero to adulthood is essential.
Congenital Heart Defects in Europe: Prevalence and Perinatal Mortality, 2000 to 2005
Helen Dolk, Maria Loane, Ester Garne and a European Surveillance of Congenital Anomalies
(EUROCAT) Working Group

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Supplemental Table 1 (basis for Figure 2): Perinatal mortality and TOPFA associated with non-chromosomal CHD by country, 2000-2005

<table>
<thead>
<tr>
<th>Country</th>
<th>Perinatal Mortality *</th>
<th>TOPFA†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Prevalence per 1,000 births (95% CI)</td>
<td>No Prevalence per 1,000 births (95% CI)</td>
</tr>
<tr>
<td>Austria</td>
<td>21 0.34 (0.21-0.51)</td>
<td>8 0.13 (0.06-0.25)</td>
</tr>
<tr>
<td>Belgium</td>
<td>49 0.27 (0.20-0.36)</td>
<td>48 0.26 (0.19-0.35)</td>
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<tr>
<td>Croatia</td>
<td>7 0.21 (0.08-0.43)</td>
<td>0 0.00</td>
</tr>
<tr>
<td>Denmark</td>
<td>10 0.31 (0.15-0.58)</td>
<td>8 0.25 (0.11-0.49)</td>
</tr>
<tr>
<td>France</td>
<td>96 0.28 (0.23-0.34)</td>
<td>366 1.06 (0.96-1.18)</td>
</tr>
<tr>
<td>Germany</td>
<td>34 0.27 (0.19-0.38)</td>
<td>62 0.50 (0.38-0.64)</td>
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<td>Ireland</td>
<td>82 0.38 (0.30-0.47)</td>
<td>0 0.00</td>
</tr>
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<td>Italy</td>
<td>31 0.07 (0.05-0.10)</td>
<td>151 0.35 (0.30-0.41)</td>
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<td>Malta</td>
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<td>Netherlands</td>
<td>44 0.37 (0.27-0.50)</td>
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<tr>
<td>Norway</td>
<td>69 0.20 (0.16-0.25)</td>
<td>97 0.28 (0.23-0.34)</td>
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<td>Poland</td>
<td>69 0.33 (0.26-0.42)</td>
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<tr>
<td>Spain</td>
<td>42 0.22 (0.16-0.29)</td>
<td>85 0.44 (0.35-0.54)</td>
</tr>
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<td>Switzerland</td>
<td>10 0.23 (0.11-0.43)</td>
<td>22 0.51 (0.32-0.78)</td>
</tr>
<tr>
<td>Ukraine</td>
<td>24 0.93 (0.60-1.38)</td>
<td>2 0.08 (0.01-0.28)</td>
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<td>UK</td>
<td>248 0.26 (0.23-0.30)</td>
<td>450 0.47 (0.43-0.52)</td>
</tr>
<tr>
<td>Total</td>
<td>845 0.25 (0.24-0.27)</td>
<td>1308 0.39 (0.37-0.41)</td>
</tr>
</tbody>
</table>

* Perinatal mortality=fetal deaths from 20 weeks gestation and 1st week deaths  
†TOPFA = termination of pregnancy for fetal anomaly following prenatal diagnosis
Supplemental Figure 1: Proportion of cases resulting in mortality by severity, type of non-chromosomal CHD and type of mortality, 2000-2005