Trends in Congenital Heart Defects in Infants With Down Syndrome

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BACKGROUND: As a result of antenatal screening, abortion of fetuses with Down syndrome has become increasingly common. Little is known about the cardiovascular phenotype in infants with Down syndrome born today.

METHODS: Population-based cohort study based on national health registers including 2588 infants with Down syndrome, live-born in Sweden from 1992 to 2012. Risk ratios for congenital heart defects were calculated per 3-year period, adjusted for maternal age, parity, BMI, smoking, diabetes and hypertensive disease, and infant gender.

RESULTS: Any congenital heart defect was diagnosed in 54% of infants with Down syndrome. Overall, year of birth was not associated with risk of any congenital heart defect. However, the risk of complex congenital heart defects decreased over time. Compared with 1992 to 1994, the risk in 2010 to 2012 was reduced by almost 40% (adjusted risk ratio 0.62, 95% confidence interval 0.48–0.79). In contrast, risks for isolated ventricular septal defect (VSD) or atrial septal defect showed significant increases during latter years. Overall, the 3 most common diagnoses were atrioventricular septal defect, VSD, or atrial septal defect, accounting for 42%, 22%, and 16% of congenital heart defects, respectively. Although atrioventricular septal defect was far more common than VSD in 1992 to 1994, they were equally common in 2010 to 2012.

CONCLUSIONS: Complex congenital heart defects have become less common in infants diagnosed with Down syndrome. This phenotypic shift could be a result of selective abortion of fetuses with Down syndrome, or due to general improvements in antenatal diagnostics of complex congenital heart defects.

WHAT'S KNOWN ON THIS SUBJECT: Down syndrome is often associated with a congenital heart defect. With the introduction of antenatal screening, many fetuses diagnosed with Down syndrome are aborted. Little is known about the cardiovascular phenotype in infants with Down syndrome born today.

WHAT THIS STUDY ADDS: In Sweden, the spectrum of congenital heart defects in infants with Down syndrome changed between 1992 and 2012. Complex congenital defects, usually requiring surgery, became less common, suggesting a shift of the cardiovascular phenotype in a more favorable direction.

Antenatal testing enables fetal diagnosis of Down syndrome, the eponym for trisomy of chromosome 21. Being the most common chromosomal disorder associated with severe comorbidities in addition to cognitive impairment, antenatal screening has led to high abortion rates of affected fetuses. In Sweden, most fetuses with Down syndrome are diagnosed and aborted, but the yearly incidence of live-born infants with Down syndrome has remained stable at ~0.1%, probably because the average age of Swedish mothers has increased from 26 to 31 years during the past decades. Other countries, like France, Italy, and Denmark, have reported decreasing rates of live-born infants with Down syndrome, as low as 0.05%, presumably as a result of more extensive antenatal screening programs.

Approximately half of infants with Down syndrome are diagnosed with congenital heart defects, compared with a baseline risk of ~1%. Related complications, such as pulmonary hypertension and heart failure may affect health and survival, but a change in attitudes toward treatment of infants with Down syndrome, corrective heart surgery included, has improved prognosis.

For example, the infant mortality rate among infants with Down syndrome in Sweden has decreased from 41% during 1969 to 1973 to 4% during 1999 to 2003.

Recent studies from Norway and Canada have demonstrated small declines in the incidence of congenital heart defects over time in the general population. Improved diagnostic tools like fetal echocardiography may have led to more pregnancy terminations when severe malformations are diagnosed antenatally. A reduced incidence could also be related to general improvements in reproductive health, for example related to reduced maternal smoking and improved management of morbidities such as diabetes during pregnancy.

It is not known if congenital heart defects have become less common also among infants with Down syndrome. However, such a change is plausible given the trend observed in the general population, and given increasing abortion rates of fetuses diagnosed with Down syndrome. Therefore, using health care registers with nationwide coverage, we investigated whether risks of congenital heart defects changed among infants with Down syndrome, during a period of time in which antenatal screening was introduced in Sweden.

**METHODS**

**Study Population and Data Sources**

This population-based cohort study is based on 3 national health care registries held by the National Board of Health and Welfare in Sweden. The Medical Birth Register, established in 1973, covers almost 99% of all births in Sweden, and includes information from antenatal, obstetric, and neonatal care. The Birth Defect Register, initiated in 1964, contains records of congenital malformations diagnosed within the first 6 months of life, and for congenital heart malformations within the first year of life. Finally, the Patient Register has nationwide coverage of information on diagnoses, for inpatient care since 1987 and for outpatient care since 2001.

Diagnoses in the registers are coded according to the International Classification of Diseases (ICD); International Classification of Diseases, Eight Revision until 1986, International Classification of Diseases, Ninth Revision (ICD-9) from 1987 to 1996, and International Classification of Diseases, Tenth Revision (ICD-10) from 1997. Register data were cross-linked by using the personal identification number given to each Swedish citizen at birth.

Clinical suspicion of Down syndrome is confirmed by chromosome analysis carried out by 1 of 7 regional cytogenetic laboratories, and the information is forwarded to the Birth Defect Register. It has been shown that linkage of the Medical Birth Register, the Birth Defects Registry, and the Patient Register, can identify virtually all infants with Down syndrome in Sweden. During the study period 1992 through 2012 and among 2 077 225 singleton live-born infants, we identified 2588 infants with Down syndrome, born at 24+0 weeks of gestation and onward (0.12%). There was a limited variation of the yearly incidence over the study period (Supplemental Fig 1). The ICD-9 code 758A and ICD-10 codes Q90.0–Q90.9 were used to identify the study population, thus including infants with Down syndrome arising from nondisjunction, mosaicism, translocation, or when coded as unspecified. As no difference has been observed with regard to the presence of congenital heart defects in specific karyotypes, we did not distinguish between the different genetic types in our analyses.

**Outcomes**

National guidelines state that all infants diagnosed with Down syndrome shall be investigated with echocardiography. In this study, congenital heart defects were identified from ICD codes recorded in the previously mentioned registers, and categorized in a classification model used by the Swedish Registry of Congenital heart disease, a quality register held by the Swedish Pediatric Cardiology Society since 2009. The classification is presented in Supplemental Table 4. For the purpose of this study, we grouped congenital heart defects into 4 main categories: (1) complex defects (atrioventricular septal defect [AVSD], aortic arch abnormalities, tetralogy of Fallot, transposition...
of the great arteries, and single ventricle hearts), (2) valve defects (aortic, pulmonary, and mitral-tricuspid valve defects), (3) shunt defects (isolated ventricular septal defect [VSD], isolated atrial septal defect [ASD], and isolated patent ductus arteriosus), and (4) others. All infants were assigned hierarchically to 1 of the 4 categories. A patent ductus arteriosus associated with the circulatory adaptation after birth was not considered a congenital malformation (ICD-9 747.8 and ICD-10 P29.3).

Primary outcome was “any congenital heart defect,” comprising all diagnoses listed in Supplemental Table 4. We also wanted to estimate risks of complex malformations usually requiring surgery and risks of the 3 most prevalent single diagnoses in the cohort. Therefore, secondary outcomes were complex congenital heart defects as defined previously, and occurrence of AVSD, isolated VSD, or isolated ASD.

Exposures

In addition to year of birth, exposure variables included maternal age, parity, smoking, diabetes, hypertensive disease, BMI, and infant gender. Maternal age was recorded at delivery and information on self-reported parity, height, measured weight, and smoking habits was obtained at the first antenatal visit that occurs within the first 12 weeks of gestation for 90% of pregnant women. Diagnoses of maternal diabetes and hypertensive disease were retrieved from the Medical Birth Register. Diabetes, defined by ICD codes (ICD-9: 250, 648A, 648W; ICD-10: 024, E10–E14), included both prepregnancy and gestational diabetes. Hypertensive disease, defined by ICD codes (ICD-9: 401–405, 642C, 642E–642H; ICD-10: 110–115, 010, 011, 014, 150) included chronic hypertension diagnosed before the pregnancy as well as gestational hypertension and preeclampsia. BMI was classified as underweight (≤18.4), normal weight (18.5 to <25.0), overweight (25.0 to <30.0), obese grade 1 (30.0 to <35.0), or obese grade 2 to 3 (≥35.0). For descriptive purposes, we also included information on gestational age and birth weight for gestational age in the Results section. Gestational age in Sweden is primarily based on early second-trimester ultrasound. Birth weight for gestational age was defined according to the Swedish standard curve for normal intrauterine growth as small for gestational age (birth weight <2 SDs below the mean weight for gestational age) and large for gestational age (birth weight >2 SDs above the mean weight for gestational age). The exposure variables were categorized as presented in Table 1.

Statistical Analysis

In addition to tabulations of the distribution of congenital heart defect diagnoses within the cohort, we calculated risk ratios (RRs) with 95% confidence intervals (CIs) in log-binomial regression models. We calculated RRs for any congenital heart defect, and separately for complex congenital heart defects, AVSD, VSD, and ASD, respectively. Multivariate analyses were adjusted for year of birth, maternal age, parity, BMI, diabetes, hypertensive disease, smoking, and infant gender. Maternal age was added to the models as a continuous variable, whereas parity, smoking in first trimester, diabetes, hypertensive disease, and infant gender were included as categorized variables, as presented in Table 1. BMI was investigated both as a categorized and a continuous variable. The reference group in the regression analyses was infants with Down syndrome with no recorded diagnosis of congenital heart defect.

The SAS software package version 9.4 (SAS Institute, Inc, Cary, NC) was used. The study was approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden (reference number: 2013/1748–31/4).

RESULTS

Study Population and Distribution of Congenital Heart Defects

Among 2588 singleton live-born infants with Down syndrome between 1992 and 2012, 549 (21%) were born preterm (<37 completed gestational weeks) and 237 (9%) were born small for gestational age. In total, 1387 infants had a diagnosed congenital heart defect, giving an overall birth prevalence of 54% (Table 2). The 3 most common single diagnoses were AVSD, VSD, and ASD, accounting for 42%, 22%, and 16% of all congenital heart defects, respectively.

Perinatal Characteristics and Rates of Congenital Heart Defects

The overall rates of diagnosed congenital heart defects were similar over year of birth, varying between 51% and 56% (Table 1). Rates decreased with increasing maternal age, whereas rates increased with increasing maternal BMI. Similar rates were found regardless of parity, or presence of diabetes or hypertensive disease. Congenital heart defects were more commonly diagnosed in infants of smoking mothers compared with nonsmoking mothers, and infant girls had a higher rate of congenital heart defects than infant boys.

Risks of Congenital Heart Defects

The overall risk of congenital heart defect among infants with Down syndrome was similar over time (Table 1). Higher maternal age was significantly associated with a lower risk ($P = .03$); the adjusted RR (95% CI) of 0.99 (0.98–1.00) suggested a 1% risk reduction per year of age. Maternal obesity was associated
with an increased risk of congenital heart defect. Compared with normal-weight mothers, maternal obesity grades 1 and 2 to 3 (BMI 30 to <35 and ≥35, respectively) were associated with a 16% and 34% increased risk, respectively. Point estimates were not significant but suggested that also maternal overweight (BMI 25 to <30) increased the risk of infant congenital heart defect. However, as BMI was associated with risks in a dose-dependent fashion, we also entered BMI as a continuous measurement in the adjusted regression model. BMI was significantly associated with risk of congenital heart defect ($P = .001$); the risk increase per BMI unit was 1.4% (adjusted RR 1.01 [1.01–1.02]).

Smoking showed an association with the risk of congenital heart defect, mostly driven by an association with VSD (adjusted RR 1.57 [1.18–2.09]). Neither diabetes nor hypertensive disease during pregnancy was associated with congenital heart defect.

Infant girls faced a 12% higher risk of congenital heart defects compared with infant boys. The association was mostly driven by an increased risk among girls for AVSD (adjusted RR 1.29 [1.12–1.50]).

### Rates and Risks of Specific Congenital Heart Defects Over Year of Birth Period

Although the overall rates and risks of congenital heart defects were not related to year of birth, we found temporal changes with regard to specific defects (Table 3). Between the first (1992–1994) and last (2010–2012) 3-year period,
the distribution of congenital heart defects changed (Table 3). Among infants with a diagnosis of a congenital heart defect born from 1992 to 1994, 46% were diagnosed with AVSD and 14% were diagnosed with VSD. The corresponding rates of AVSD and VSD from 2010 to 2012 were 30% and 31%, respectively.

When we estimated risks for complex congenital heart defects over time, we found that the risk was reduced by almost 40% from 1992 to 1994, to 2010 to 2012 (adjusted RR 0.62 [0.48–0.79]). When we further restricted the analysis to AVSDs, we found a similar risk reduction over time. In contrast, risks of VSD or ASD, usually considered less severe congenital heart defects, seemed to increase over time. The risk of VSD showed a significant increase in the period 2004 to 2006, and risk of ASD showed a significant increase in 2007 to 2009.

Because risks of complex congenital heart defects seemed to decrease successively per 3-year period, we also entered year of birth as a continuous variable in the adjusted regression model. The adjusted odds ratio per year for complex defects and AVSD were 0.98 (0.97–0.99) and 0.98 (0.97–0.99), respectively, indicating a 2% risk reduction per year during the study period.

**DISCUSSION**

In this nationwide cohort study, the overall incidence of congenital heart defects among newborn infants with Down syndrome remained stable over time but the risk of complex malformations declined by almost 40% between 1992 and 2012. The reduced risk of complex heart defects was counterbalanced by increased risks of VSD and ASD during latter years, suggesting that the distribution, but not the overall prevalence of congenital heart defects, changed over time. Interestingly, AVSD, the previously dominating malformation associated with Down syndrome, and VSD became equally common by the end of our study period. During 2010 to 2012, AVSD and VSD accounted for 30% and 31% of diagnosed congenital heart defects, respectively.

The current AVSD rate of 30% among Swedish infants with Down syndrome and co-occurring congenital heart defect is lower than typically reported in other population-based cohorts. In the Netherlands, AVSD constituted 54% of diagnosed congenital heart defects, whereas in the United States, the corresponding rate was 39%. However, the European Surveillance of Congenital Anomalies Central Register, including population-based data from European countries including Sweden, recently reported an AVSD rate of 32%.

We can only speculate about underlying mechanisms for the shift in cardiovascular phenotype observed in Sweden, as we had no information on fetuses from terminated pregnancies. In recent years, congenital heart defects are reportedly less common in the general population, but the magnitude of changes observed among Swedish infants with Down syndrome is unlikely to be explained by factors related to such small general trends. Instead, it is plausible that we are observing the consequences of selection. Although most cardiac malformations are treatable, complex malformations may contribute to parents’ decision to terminate a pregnancy. In Sweden, ~95% of pregnancies are dated by early second-trimester ultrasound when cardiac malformations can be discovered. Fetal echocardiography confirming a heart defect usually leads to antenatal genetic testing, given the high risk of a chromosomal disorder associated with congenital heart defects. Co-occurrence of Down syndrome may add weight to parents’ decision to terminate pregnancy, leading to selective abortion of fetuses with Down syndrome with complex heart defects.

Selection could also operate through antenatal screening, in Sweden primarily targeted at women from 35 years of age. If older women are more closely investigated with regard to fetal chromosomal abnormalities, they also may be more likely to be subjected to fetal echocardiography. Our findings that congenital heart defect risk was 1% lower per maternal year of age support that ascertainment bias may partly explain our findings.
as we lack information on aborted fetuses with Down syndrome, we cannot explore whether maternal age as such affects the risk or whether antenatal diagnoses of congenital heart defects are more common in fetuses with Down syndrome to older mothers.

Increased risks of ASD and VSD during latter years counterbalanced the reduced risk of complex heart defects, resulting in an overall prevalence of congenital heart defects that was similar over time. During the study period 1992 to 2012, the improvement of echocardiographic technology could have introduced some measurement bias, increasing the likelihood of infants being diagnosed with congenital heart defects of minor clinical significance during latter years.

Our results also illustrate the multifactorial nature of congenital heart defects related to Down syndrome. As previously reported, we found that infant girls were more commonly affected than infant boys.27, 28 Similar to findings in the general population, maternal obesity and maternal smoking were associated with increased risk of congenital heart defects of minor clinical significance during latter years.9

Our findings are strengthened by the population-based cohort study design and the use of prospectively recorded data from nationwide health care registers.15–17 We were able to include virtually all infants with Down syndrome born in Sweden over 2 decades.19 Diagnoses of co-occurring congenital heart defects were likely valid as national guidelines included a mandatory echocardiography after the cytogenetic diagnosis of Down syndrome.21 We categorized the severity of congenital heart defect diagnoses according to a classification developed by the Swedish Pediatric Cardiology Society.6

### Table 3. Numbers and RRs Over Time, for Complex Congenital Heart Defects (Including AVSD, Aortic Arch Abnormality, Tetralogy of Fallot, or Transposition of the Great Arteries), and for AVSD, Isolated VSD, and Isolated ASD, Among 2588 Singleton Live-Born Infants With Down Syndrome, Born in Sweden 1992–2012

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>n</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted RR a (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>1992–1994</td>
<td>161</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>1995–1997</td>
<td>125</td>
<td>1.03 (0.86–1.22)</td>
<td>1.02 (0.84–1.24)</td>
</tr>
<tr>
<td>1998–2000</td>
<td>81</td>
<td>0.83 (0.68–1.02)</td>
<td>0.78 (0.61–0.99)</td>
</tr>
<tr>
<td>2001–2003</td>
<td>101</td>
<td>0.81 (0.67–0.98)</td>
<td>0.82 (0.68–1.01)</td>
</tr>
<tr>
<td>2004–2006</td>
<td>107</td>
<td>0.80 (0.66–0.96)</td>
<td>0.79 (0.64–0.98)</td>
</tr>
<tr>
<td>2007–2008</td>
<td>92</td>
<td>0.74 (0.60–0.90)</td>
<td>0.74 (0.59–0.92)</td>
</tr>
<tr>
<td>2010–2012</td>
<td>67</td>
<td>0.62 (0.49–0.78)</td>
<td>0.62 (0.48–0.79)</td>
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</table>

<table>
<thead>
<tr>
<th>n</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted RR a (95% CI)</th>
</tr>
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<tr>
<td>1992–1994</td>
<td>33</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>1995–1997</td>
<td>24</td>
<td>0.99 (0.61–1.60)</td>
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<tr>
<td>1998–2000</td>
<td>36</td>
<td>1.46 (0.95–2.24)</td>
</tr>
<tr>
<td>2001–2003</td>
<td>55</td>
<td>1.85 (1.12–2.44)</td>
</tr>
<tr>
<td>2004–2006</td>
<td>64</td>
<td>1.74 (1.19–2.55)</td>
</tr>
<tr>
<td>2007–2008</td>
<td>38</td>
<td>1.19 (0.77–1.82)</td>
</tr>
<tr>
<td>2010–2012</td>
<td>57</td>
<td>1.71 (1.16–2.52)</td>
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<tr>
<th>n</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted RR a (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>1992–1994</td>
<td>109</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>1995–1997</td>
<td>88</td>
<td>1.06 (0.85–1.33)</td>
</tr>
<tr>
<td>1998–2000</td>
<td>63</td>
<td>0.89 (0.69–1.15)</td>
</tr>
<tr>
<td>2001–2003</td>
<td>89</td>
<td>0.94 (0.75–1.18)</td>
</tr>
<tr>
<td>2004–2006</td>
<td>92</td>
<td>0.91 (0.73–1.14)</td>
</tr>
<tr>
<td>2007–2008</td>
<td>85</td>
<td>0.88 (0.70–1.11)</td>
</tr>
<tr>
<td>2010–2012</td>
<td>55</td>
<td>0.87 (0.51–0.98)</td>
</tr>
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**a** Adjusted for year of birth, maternal age, parity, BMI, smoking, diabetes, hypertensive disease, and infant gender.
Society that reduced the risk of misclassification.22

Our study has several limitations. Our data lacked information on termination of pregnancies and we could not estimate rates and risks of Down syndrome–related congenital heart defects among all fetuses at risk. Consequently, we could not explore whether our findings were influenced by selection mechanisms due to antenatal screening. During the study period 1992 to 2012, the improvement of ultrasound technology could have introduced some measurement bias, increasing the likelihood of infants being diagnosed with congenital heart defects of minor clinical significance during latter years, and thus underestimating changes in risk of congenital heart defects. Furthermore, our data did not allow us to explore the impact of antenatal screening. Antenatal screening was successively introduced during the study period, but there were regional variations within Sweden.38

Finally, our register linkage did not include detailed information on socioeconomic status, such as years of education or profession, and we cannot exclude the possibility of residual socioeconomic confounding. Although antenatal, obstetric, and neonatal care is universally available to families regardless of socioeconomic background in Sweden, we do not know whether individual choices about antenatal screening and pregnancy termination were differentially related to socioeconomic status.

Although half of infants with Down syndrome are still diagnosed with congenital heart defects, our findings of a changed spectrum of diagnoses shed new light on the phenotypic expressions of the Down genotype. Today, risks of more complex congenital heart defects seem to be considerably lower among newborns with Down syndrome, and the previously dominating AVSD defect and VSD are now equally common. Whether infants with Down syndrome also have a reduced need of thoracic surgery warrants further investigation. Likewise, it is important to investigate if risks of other comorbidities, such as cognitive impairment and autoimmune diseases, have also changed in a favorable direction in this new generation of infants and children with Down syndrome.

**ABBREVIATIONS**

ASD: atrial septal defect  
AVSD: atrioventricular septal defect  
CI: confidence interval  
ICD: International Classification of Diseases  
ICD-9: International Classification of Diseases, Ninth Revision  
ICD-10: International Classification of Diseases, Tenth Revision  
RR: risk ratio  
VSD: ventricular septal defect

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