

The five-year survival of children with Down ´s syndrome differed by associated congenital heart defects and extracardiac malformations, Norway, 1994-2009

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Keywords:	Birth Register, population-based cohort study, childhood mortality, congenital anomalies, trisomy 21

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4 **The five-year survival of children with Down's syndrome differed by associated**
5 **congenital heart defects and extracardiac malformations, Norway, 1994-2009**
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45 **Short title:** Childhood survival by malformations in Down's syndrome
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Abstract

Aim: We investigated Down's syndrome prevalence in a nationwide birth cohort, focusing on congenital heart defects, associations between heart defects and extracardiac malformations, and survival.

Methods: All births in Norway, 1994-2009, were identified in the Medical Birth Registry, updated with hospital diagnoses, and followed in the Cause of Death Registry until 2014. We estimated birth defect frequencies in Down's syndrome and the general population; the association between heart defects and extracardiac malformations; and hazard ratios for death for different combinations of heart defects and extracardiac malformations.

Results: Among 953,450 births, 1,672 had Down's syndrome (17.6 per 10,000), including 1,251 live births (13.3 per 10,000). Among live births with Down's syndrome, 58% had heart defects and 9% extracardiac malformations. Heart defects were associated with oesophageal atresia ($p=0.02$) and Hirschsprung's disease ($p=0.03$), but with no other malformations. The five-year survival for Down's syndrome children increased from 91.8% (1994-1999) to 95.8% (2000-2009), $p=0.006$. Overall it was 92.0% with heart defects and 97.4% without. Five-year mortality was 13-28 times higher in those with severe heart defects and extracardiac malformations than in those without malformations.

Conclusion: Childhood survival in Down's syndrome improved, but mortality was still high in children with severe heart defects combined with extracardiac defects.

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3 **Key words:** birth register, childhood mortality, congenital anomalies, population-based cohort
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5 study, trisomy 21
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9 **Key notes:**
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- 11 • Children with Down's syndrome have increased risk of congenital heart defects and
12 extracardiac malformations, potentially affecting their risk of childhood death.
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- 14 • Among live births with Down's syndrome in Norway 1994-2009, the risk of congenital
15 heart defects was not associated with the risk of extracardiac malformations, except for
16 oesophageal atresia and Hirschsprung's disease.
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- 18 • Severe congenital heart defects predicted increased mortality in children with Down's
19 syndrome, especially when combined with extracardiac malformations.
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33 **Word count:** 3,150
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INTRODUCTION

The birth prevalence of Down's syndrome is about one per 1,000 births, with an increasing total birth prevalence explained by increasing maternal age (1). Down's syndrome is associated with congenital heart defects (CHD), in particular atrioventricular septal defect (AVSD) (2–7), and also extracardiac malformations (ECM), especially gastrointestinal malformations (5,6). It has not been established whether the risks of cardiac and extracardiac malformations are associated or independent in Down's syndrome.

Mortality is linked to malformations in Down's syndrome (8–11). Despite increasing proportion of pregnancy termination due to foetal Down's syndrome in Europe, the proportion of live births with associated malformations remains unchanged (6). Therefore, it is important to assess further the association between malformations and childhood mortality in Down's syndrome, to identify individuals at highest risk of premature death.

Norway's national health registers and population registers provide the opportunity to investigate the prevalence of Down's syndrome in live births, stillbirths and terminated pregnancies. We aimed at estimating the specific cardiac phenotypes in Down's syndrome, and the association between CHD and ECM in children with Down's syndrome. Finally, following the cohort in the Cause of Death Registry enabled us to study the influence of CHD and ECM on survival among children with Down's syndrome.

METHODS

Data sources

Since 1967, the Medical Birth Registry of Norway has registered information on live births and stillbirths after 16 weeks of gestation. The registry has received notifications

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3 of every termination of pregnancy for foetal anomaly (TOPFA) since December 1998,
4 and occasionally earlier, reported as stillbirths (12). The unique personal identification
5 number was used to update the Medical Birth Registry with information on CHD from
6 three additional sources: Diagnostic and procedural codes from the hospitals' Patient
7 Administrative System for all hospitalizations in Norway 1994-2009, if at least one
8 diagnosis was related to the cardiovascular system (13); diagnostic and procedural
9 codes in the clinical database for children with heart disease from Oslo University
10 Hospital; and diagnostic codes in the Cause of Death Registry of Norway. This study is
11 part of the Cardiovascular Disease in Norway project (www.cvdnor.no) (13). The study
12 was approved by the Regional Committee for Medical and Health Research Ethics,
13 Western Norway (2009/861-14).

28 **Study population**

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30 Among 954,413 births from 1994 through 2009, we excluded 963 births with
31 chromosomal aberrations other than Down's syndrome (International Classification of
32 Diseases, Eighth Revision 759.1-759.2, 759.4-759.8; Ninth Revision 758.1-758.9,
33 759.3-759.8; Tenth Revision Q91.0-99.9), leaving 953,450 for analysis. Information of
34 Down's syndrome, CHD and ECM was retrieved from the data sources mentioned
35 above until 31 December 2009. Information on date of death was collected from the
36 Cause of Death Registry until 2 May 2014.

47 **Ascertainment of Down's syndrome**

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49 Individuals with Down's syndrome were ascertained from the four data sources
50 mentioned above, using codes in the International Classification of Diseases, Eighth
51 Revision (759.3), Ninth Revision (758.0) and Tenth Revision (Q90.0, Q90.1, Q90.2 or
52 Q90.9).

Congenital heart defects

Information about CHD was retrieved from the four data sources and classified as described in detail by Leirgul et al (14). Individuals with one or more CHD were assigned one cardiac phenotype by using the hierarchical classification system introduced by Botto et al (15) and later modified by Leirgul et al (14). Atrial septal defects (ASD) of the primum type were classified as AVSD, and isolated ASD secundum as ASD. Persistent ductus arteriosus (PDA) and ASD were only ascertained if recorded at postnatal age >6 weeks or if surgically corrected. In this study, we define severe CHD as any CHD except ASD, ventricular septal defect (VSD) and PDA.

Extracardiac malformations

Information on ECM was identified from the Medical Birth Registry and Cause of Death Registry using codes in the International Classification of Diseases (Table S1). ECM diagnoses were classified by organ systems according to the structure in the International Classification of Diseases, Tenth Revision, chapter XVII: malformations of the nervous system; eyes, ears, face, and neck; respiratory system; cleft lip-palate; digestive system; genital organs; urinary system. Subcategories were analysed if there were at least seven children with Down's syndrome.

Statistical analyses

The total birth prevalence of Down's syndrome was calculated for live births, stillbirths, and TOPFA by each year of birth and adjusted for maternal age in years, handled as continuous variables in a generalised linear model with the log-link function for binomial outcome. Prevalence ratios expressed the ratios between birth prevalences of congenital malformations in Down's syndrome, and birth prevalences of the same

malformations in live births without chromosomal aberrations. When adjusting for maternal age and year of birth, prevalence ratios were estimated in generalised linear models with the log-link function for binomial outcome. Time trends were evaluated with generalised linear models, using year of birth as a continuous variable. To estimate associations between CHD and ECM, we used logistic regression to calculate odds ratio with 95% confidence interval (95%CI). For associations between CHD and ECM for which odds ratio were not estimable (due to empty cells), Fisher's exact test was used to calculate a p-value for the association.

We estimated five-year survival for live births, censoring individuals at loss to follow-up (5.5% of live births were lost to follow-up before five years of age) due to emigration or birth after May 2009 (non-informative censoring). When comparing different mortality rates, Poisson regression was used to calculate p-values. We estimated childhood death risk by CHD and ECM groups, using Nelson-Aalen's cumulative hazard and Cox' proportional hazard regression, adjusted for year of birth as (one-year categories). Survival was displayed with Kaplan-Meier curves. All statistical analyses were performed with Stata 14.0 (StataCorps, Texas, USA).

RESULTS

Among 953,450 births in the period 1994-2009, there were 943,477 live births, 7,914 stillbirths and 2,059 TOPFAs. Down's syndrome was diagnosed in 1,672 births (total birth prevalence 17.6 per 10,000) and in 1,251 live births (live birth prevalence 13.3 per 10,000 births). The total birth prevalence of Down's syndrome gradually increased throughout the 16-year period: the annual increase in relative risk was 1.04 (95% confidence interval (CI) 1.03-1.05). However, there was no significant time trend in the total birth prevalence of Down's syndrome, when adjusting for maternal age and stratifying on the time periods without (1994-1998) and with (1999-2009) mandatory

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3 reporting of TOPFA (relative risk 1.03; 95%CI 0.96-1.10 and relative risk 1.01; 95%CI
4 0.99-1.02, respectively). Since 1999, the proportion of Down's syndrome pregnancies
5 being terminated has increased with an average of 7.2% annually ($p=0.000$).

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7 Throughout the study period, there was a weak, annual increase in the live birth
8 prevalence of Down's syndrome (relative risk 1.01; 95%CI 1.00-1.03) (Figure 1).

13 14 15 **Proportion with CHD in births with Down's syndrome**

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17 CHD were highly prevalent among births with Down's syndrome: 786/1,672 (47.0%)
18 had CHD among all births, 724/1,251 (57.9%) among live births, 12/49 (24.5%) among
19 stillbirths and 50/372 (13.4%) among terminated pregnancies. In stillbirths/TOPFA with
20 Down's syndrome, the probability of a CHD diagnosis decreased by shorter gestational
21 age ($P<0.001$). Due to a probable underreporting of CHD in stillbirths/TOPFA the
22 following analyses were restricted to live births.

23 24 25 **Specific types of cardiac defects in Down's syndrome**

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27 In live births, CHD was 47 times more prevalent in Down's syndrome than in births
28 without chromosome aberrations (Table 1). Most types of CHD were overrepresented in
29 Down's syndrome compared to the background population (prevalence ratios ranged
30 2.7-850), except for transposition of the great arteries, hypoplastic left heart syndrome
31 and hypoplastic right heart syndrome. The prevalence ratios were unchanged after
32 adjusting for maternal age and year of birth. AVSD was particularly prevalent, found in
33 20.3% of Down's syndrome live births, which means that the birth prevalence was 850
34 times greater than the AVSD prevalence in live births without chromosomal aberrations.
35 In Down's syndrome, AVSD was recorded as an isolated cardiac defect in nearly all
36 affected children (254 of 256), in contrast to the background population where 16.4% of
37 the AVSD occurred in combination with another cardiac defect. For children with
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3 Down's syndrome, there were no temporal changes in the prevalence of CHD overall,
4 AVSD, ASD, VSD, nor for PDA (p values 0.638, 0.905, 0.845, 0.250 and 0.533,
5 respectively).
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10 11 **Extracardiac malformations**

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13 ECMs were diagnosed six times more frequently in live births with Down's syndrome
14 than without chromosomal aberrations (911 per 10,000 versus 146 per 10,000, Table
15 2). Malformations of the gastrointestinal tract were particularly frequent in Down's
16 syndrome (prevalence ratio 19, 95% CI 15-24).
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24 **Association between congenital heart defects and extracardiac malformations**

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26 The co-occurrence between CHD and ECM was estimated among individuals with
27 Down's syndrome and in the general population; the CHD risk was calculated for
28 subgroups defined by presence or absence of ECM (Table 3). In live births without
29 chromosomal aberrations there was a strong association between CHD and ECM (odds
30 ratio 5.6; 95%CI 5.2-6.0), with CHD associated with every type of ECM. In Down's
31 syndrome, however, 7/7 cases of oesophageal atresia and 10/11 cases of
32 Hirschsprung's disease were associated with CHD (p-value 0.02 and p-value 0.03,
33 respectively, on Fisher's exact test).
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45 **Childhood mortality in Down's syndrome**

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47 During follow-up of 1,251 live births with Down's syndrome until 2 May 2014 (mean
48 follow-up time 11.2 years), 16 emigrated and 78 died, of whom 68 died before 5 years
49 of age and 5 died between five years and 15 years of age. Among the children with
50 CHD who died, more than half (31 of 58) had undergone cardiac surgery or other type
51 of cardiac intervention at least once. The overall one-year survival for children with
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Down's syndrome was 96.3% (46 deaths). In those with CHD the one-year survival was 94.9%, and in those without CHD 98.3% ($p=0.003$). The five-year survival for children with Down's syndrome increased from 91.8% for births 1994-1999 to 95.8% for births 2000-2009 ($p=0.006$). Overall, the five-year survival was 94.2%, with lower survival for children with CHD (92.0%) than without CHD (97.4%) ($p<0.001$). For comparison, five-year survival in the general population was 93.1% for individual with CHD and 99.6% for individuals without CHD. Comparing with the general population, survival was significantly poorer for children with Down's syndrome without CHD ($p<0.001$), but not for those with CHD ($p=0.294$).

Mortality estimates in Down's syndrome by CHD and ECM

In children with Down's syndrome, the hazard ratio of death before age five years was similar for those with septal defects or PDA, as compared with children with Down's syndrome without CHD (Table 4). The five-year hazard ratios of death was highest for children with conotruncal defects, followed by AVSD and remaining types of CHDs. Mortality was especially high for children with Down's syndrome who had CHD in combination with ECM. In this category, 93% of the childhood deaths occurred before the first birthday. Most childhood deaths occurred before five years of age, for all children with Down's syndrome and any combination of CHD and ECM. Very few children with Down's syndrome died between five and 15 years of age (Figure 2), but with complete follow-up for 28% of the cohort; that is children born before 1999.

DISCUSSION

In a national cohort of around 950,000 births 1,672 were identified with Down's syndrome over a 16 year period. The total birth prevalence of Down's syndrome was 17.6 per 10,000, and the live birth prevalence 13.3 per 10,000. These numbers were

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3 comparable to previous estimates (2,3,5). In Down's syndrome live births, more than
4 half had CHD, among them one-third had AVSD. Extracardiac malformations (ECM)
5 were found in 9%. Most of the ECMs were malformations of the gastrointestinal tract.
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7 Generally, CHD and ECM were *not* associated in children with Down's syndrome, as
8 opposed to what was seen in the general population. Survival beyond five years of age
9 was 94.2% for children with Down's syndrome overall, but differed by CHD and ECM
10 subgroups, and was poorest for those with severe types of CHD combined with ECM.
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18 The total birth prevalence of Down's syndrome gradually increased through the
19 study period, mainly attributable to an increasing maternal age. The stable live birth
20 prevalence of Down's syndrome may be explained by more frequent use of termination
21 of pregnancies with foetal Down's syndrome (1,6). In Norway, pregnant women aged
22 38 years or older at due date qualify for prenatal screening for foetal aneuploidy. In the
23 present study, the proportion of Down's syndrome fetuses with a registered CHD
24 diagnosis was low if the pregnancy was terminated or ended in stillbirth. This lower
25 proportion of CHD could be explained by diagnostic inaccuracy in early foetal life (6,16),
26 and/ or by lower autopsy rates in Down's syndrome stillbirths and terminations. Due to
27 this possible underreporting, analyses of CHD and ECM were restricted to live births.
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39 The proportion of children with Down's syndrome having CHD (58%) showed no
40 temporal change; neither did the prevalence of the most frequent groups of CHD
41 (AVSD, ASD, VSD, and PDA), as opposed to what was seen in a recent Swedish study
42 (17). Children with Down's syndrome had increased risk of most types of CHD.
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45 However, transposition of the great arteries was not identified in any individual with
46 Down's syndrome in our study. This is consistent with findings pointed out in most other
47 studies (5). We found AVSD (20.3%), isolated ASD (10.8%) and isolated VSD (10.6%)
48 to be the dominating types of CHD in Down's syndrome. Expressed as proportions of
49 children with CHD and Down's syndrome AVSD, ASD and VSD accounted for 35.1%,
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3 18.7% and 18.4%, respectively. These proportions were within the range of most
4 previous estimates (3–5,7). One in every six chromosomally normal individuals with
5 AVSD had an additional CHD, whereas AVSD was isolated in most of those with
6 Down's syndrome in our study. Similar findings have been reported previously (18).
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11 In the general population, CHD is known to be associated with ECM (19) which
12 we confirmed in our cohort, but to our knowledge this association has not been studied
13 in Down's syndrome previously. All children with Down's syndrome and oesophageal
14 atresia had CHD, and 10 of 11 children with Down's syndrome and Hirschsprung's
15 disease had CHD. In the general population, the association between oesophageal
16 atresia and CHD is well known as part of the VACTERL association, which stands for
17 vertebral defect, anorectal malformation, cardiac defect, tracheoesophageal fistula,
18 renal anomaly, radial dysplasia and limb defects (20). But in the present study none of
19 the seven children with Down's syndrome, oesophageal atresia and CHD had other
20 diagnoses related to the VACTERL association. The association between
21 Hirschsprung's disease and CHD in children with Down's syndrome was consistent
22 with numbers reported in other studies (7,8), but the association has not been tested
23 statistically previously. Other types of ECM were not significantly associated with CHD
24 in children with Down's syndrome. This finding could indicate that the trisomy is so
25 strong a risk factor that other risk factors that differ among individuals with Down's
26 syndrome become relatively unimportant for the development of congenital
27 malformations.
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47 The five-year mortality for children with Down's syndrome was 5.8%. The
48 mortality was significantly increased for those with CHD, in line with previous studies
49 (9,11,21–24). We found that the risk of death in early childhood was further increased if
50 the CHD was combined with an ECM, a finding which to our knowledge has not
51 previously been described. The mortality was especially high for children with Down's
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3 syndrome and conotruncal defects, AVSD, or other severe types of CHD; that is, any
4 CHD except PDA, ASD and VSD. But 89% of these children were still alive at five years
5 of age.
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9 We found increased early childhood mortality for children with Down's
10 syndrome, compared to the general population, but not when comparing children with
11 Down's syndrome and CHD with chromosomally normal children with CHD. The one-
12 year survival for children with Down's syndrome in our cohort was 96%. This is higher
13 than what was found for children with Down's syndrome in northern Sweden 1973-80
14 (85.4%) (8,24), Italy 1978-84 (80%) (22), Ireland 1980-89 (88%) (25), Denmark 1968-
15 2009 (89%) (9), Western Australia 1980-96 (92%) (11) and the United States 1983-
16 2003 (93%) (10), but it is similar to what was found in northern Sweden 1995-98
17 (97.7%) (24), the Netherlands 2003 (96%) (23) and Thailand 2007-12 (96%) (21).
18 Survival of children with Down's syndrome improved over time in our study, and
19 extrapolation of this time trend to the aforementioned studies can possibly explain
20 different estimates. This time trend might reflect changing attitude to surgical repair of
21 congenital malformations in children with Down's syndrome over the past decades (26).
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37 The major strengths of this study were the large number of individuals with
38 Down's syndrome and inclusion of stillbirths and TOPFA for prevalence rates. Further,
39 our study was strengthened by health information collected from population based
40 registers with compulsory notification and updated with diagnoses from clinical
41 registers. Because health care is essentially free of charge in Norway there is universal
42 access ensuring completeness of the data.
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49 Individuals with Down's syndrome were predominantly ascertained from the
50 Medical Birth Registry (90.3%). The registration of Down's syndrome in this registry has
51 been validated for the period 2001-2005 by comparing with laboratory data from the
52 departments of medical genetics in Norway (27). The Medical Birth Registry had
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3 registered Down's syndrome for 81.6% of the laboratory confirmed cases, and 90.2% of
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5 Down's syndrome cases in the Medical Birth Registry had laboratory verification.
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7 Presumably, our ascertainment has identified 91% of the total number of individuals
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9 with Down's syndrome, based on an estimation method for the expected proportion of
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11 Down's syndrome in a specified birth cohort (28). A weakness, however, was the lack of
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13 information about karyotype, preventing us from distinguishing between complete
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15 trisomy 21, translocations and mosaicism.
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18 Limitations in the present study included a likely underreporting of congenital
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20 malformations in stillbirths and terminations due to foetal anomalies. For this reason, we
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22 restricted the main analyses to live births, which might have introduced *live birth bias*
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24 (29). Misclassifications were possible, particularly regarding ECM which has not been
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26 fully validated in the Medical Birth Registry, but misclassification was not likely to be
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28 extensive, since we found prevalence of ECM in Down's syndrome similar to previous
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30 studies (6,7). Finally, increased mortality associated with multiple birth defects in
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32 children with Down's syndrome could be due to complications of the birth defects, but it
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34 could also be explained by clinicians withholding treatment for children with multiple
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36 medical challenges. We missed data that could have distinguished between these two
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38 explanations.
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43 **CONCLUSION**

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45 In a complete national birth cohort, the total birth prevalence of Down's syndrome
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47 increased in Norway, 1994-2009. The live birth prevalence, however, was stable around
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49 13.3 per 10,000, due to the increasing proportion of pregnancy termination for
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51 prenatally diagnosed Down's syndrome. More than half of live births with Down's
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53 syndrome had CHD, of which AVSD was the most frequent, followed by ASD and VSD.
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55 In children with Down's syndrome, CHD was associated with oesophageal atresia and
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3 Hirschsprung's disease, but *not* with any other ECM, as opposed to births without
4 chromosomal aberrations. The five-year survival for children with Down's syndrome
5 improved during the study period, and overall it was 97.4% for those without CHD,
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10 93.3% for those with CHD without ECM and 80.6% for those with both CHD and ECM.
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For Peer Review Only

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List of abbreviations

ASD – atrial septal defect

AVSD – atrioventricular septal defect

CHD – congenital heart defect

CI – Confidence interval

ECM –extracardiac malformations

PDA – isolated persistent ductus arteriosus

TOPFA – termination of pregnancy for foetal anomaly

VSD – ventricular septal defect

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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3 **Figure Legends**
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6 **Figure 1:**
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9 **Legend:** Time trend for total birth prevalence (per 10,000 births) of Down's syndrome by year of
10 birth, based on 953,450 births in Norway 1994-2009.
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15 **Footnote:** AVSD, atrioventricular septal defect; CHD, congenital heart defects; TOPFA:
16 Termination of Pregnancy for Foetal Anomaly.
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24 **Figure 2:**
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26 **Legend:** Kaplan-Meier survival estimates for children with Down's syndrome born in Norway
27 1994-2009. The estimates are based on 1,251 live births with Down's syndrome follow-up until
28 May 2nd 2014.
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35 **Footnote:** Severe CHD is defined as any CHD, excluding ASD, VSD and PDA.

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37 ASD, atrial septal defect; CHD, congenital heart defects; ECM, extracardiac malformations;
38 PDA, persistent ductus arteriosus; VSD, ventricular septal defect.
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Table 1: Prevalence of specific cardiac phenotypes in births with Down's syndrome versus births without chromosomal aberrations, 953,450 live births, Norway 1994-2009.

Cardiac phenotype	Down's syndrome 1,251		Normal chromosomes 942,226		PR ^a	(95% CI)
	N	Prevalence per 10,000 births				
With any type of CHD	724	5,787	124	47	(44 – 49)	
Heterotaxia	1	8.0	1.4	5.7	(0.8 – 41)	
Conotruncal defect	39	312	10	30	(22 – 42)	
Transposition of the great arteries	0		3.2			
Tetralogy of Fallot ^b	14	112	2.4	48	(28 – 81)	
Double outlet right ventricle	2	16	0.6	26	(6.5 – 108)	
Conotruncal VSD	12	96	1.5	66	(37 – 119)	
Aortic hypoplasia	7	56	1.8	32	(15 – 67)	
Other conotruncal defects ^c	4	32	0.9	37	(14 – 101)	
Atrioventricular septal defect	254	2,030	2.4	850	(717 – 1008)	
Anomalous pulmonary venous return	2	16	1.1	15	(3.6 – 60)	
Left ventricular outflow tract obstruction	11	88	7.3	12	(6.6 – 22)	
Hypoplastic left heart syndrome	0		1.6			
Aortic valve stenosis	1	8.0	3.0	2.7	(0.4 – 19)	
Coarctation of the aorta	10	80	2.7	30	(16 – 56)	
Right ventricular outflow tract obstruction	3	24	5.3	4.5	(1.5 – 14)	
Hypoplastic right heart syndrome	0		0.7			
Ebstein's anomaly	1	8.0	0.6	14	(1.9 – 99)	
Pulmonary valve stenosis/ atresia	2	16	4.0	4.0	(1.0 – 16)	
Septal defects	322	2,574	61	43	(39 – 47)	
ASD, isolated	135	1,079	13	85	(72 – 101)	
VSD, isolated, any type	133	1,063	46	23	(20 – 27)	
VSD, perimembranous	57	456	4.7	96	(73 – 126)	
VSD, muscular	9	72	4.6	16	(8.1 – 30)	
VSD, unspecified location	67	536	36	15	(12 – 19)	
ASD + VSD	51	408	1.3	326	(235 – 450)	
Unspecified septal defects	3	24	0.9	28	(8.7 – 87)	
Persistent ductus arteriosus, isolated	60	480	24	20	(15 – 25)	
At term gestation	44	440	11	41	(30 – 55)	
In preterm birth	16	640	208	3.1	(1.9 – 5.0)	
Other specified congenital heart defects	12	96	6.2	16	(8.8 – 27)	
Unspecified congenital heart defects	20	160	5.0	32	(20 – 50)	

a) Unadjusted prevalence ratio (PR) with 95% confidence interval (CI), comparing the prevalence of CHD in live births with Down's syndrome with the prevalence of the same type of CHD in live births without chromosomal aberrations (reference). Adjusted PR for maternal age and year of birth were unchanged (not shown).

b) Including tetralogy of Fallot in combination with atrioventricular septal defect

c) Including truncus arteriosus, aortopulmonary window, and interrupted aortic arch type B and C.

Table 2: Prevalence of extracardiac malformations in births with Down's syndrome versus births without chromosomal aberrations, 953,450 live births, Norway 1994-2009.

	Down's syndrome 1,251		Normal chromosomes 942,226		Prevalence ratio ^a	(95%CI)
	N	Per 10,000	N	Per 10,000		
One or more extracardiac malformations	114	911	13,741	146	6.2	(5.2-7.4)
Nervous system malformations	2	16	819	8.7	1.8	(0.5-7.4)
Eyes, ears, face, neck malformations	5	40	1,407	15	2.7	(1.1-6.4)
Respiratory system malformations	10	80	774	8.2	9.7	(5.2-18)
Cleft lip-palate	3	24	1,714	18	1.3	(0.4-4.1)
Digestive system malformations	81	647	3,211	34	19	(15-23)
Oesophageal atresia/ stenosis	7	56	204	2.2	26	(12-55)
Small intestine	43	344	146	1.5	222	(159-310)
Duodenal atresia/ stenosis ^b	30	240	63	0.7	341	(222-524)
Large intestine	14	112	196	2.1	54	(31-92)
Rectal/ anal atresia/ stenosis ^b	13	104	137	1.5	68	(39-120)
Hirschsprung's disease	11	88	135	1.4	61	(33-113)
Genital organs malformations	9	72	4,746	50	1.4	(0.7-2.7)
Urinary system malformations	8	64	1,632	17	3.7	(1.8-7.4)

a) Unadjusted prevalence ratio (PR) with 95% confidence interval (CI), comparing the prevalence of extracardiac malformation in live births with Down's syndrome with the prevalence of the same type of extracardiac malformation in live births without known chromosomal aberrations (reference).

b) Registered for births from 1999 to 2009.

CI, confidence interval.

Table 3: Associations between extracardiac malformations and congenital heart defects among births with Down's syndrome and among births without chromosomal aberrations, 953,450 live births, Norway 1994-2009.

		Down's syndrome 1,251: 724 with CHD, 527 without CHD 114 with ECM, 1,137 without ECM				Normal chromosomes 942,226: 11,676 with CHD, 930,550 without CHD 13,741 with ECM, 928,485 without ECM				Interaction ^b
Extracardiac malformation	CHD	Per 10,000				Per 10,000				
		N	OR ^a	(95%CI)		N	OR ^a	(95%CI)		
One or more extracardiac malformations	Yes	75	1,036	1.4	(1.0-2.2)	849	727	5.6	(5.2-6.0)	<0.0001
	No	39	740			12,892	139			
Nervous system malformations	Yes	1	14	0.7	(0.0-12)	104	89	12	(9.5-14)	0.045
	No	1	19			715	7.7			
Eyes, ears, face, neck malformations	Yes	3	41	1.1	(0.2-6.6)	65	56	3.9	(3.0-5.0)	0.17
	No	2	38			1,342	14			
Respiratory system malformations	Yes	8	110	2.9	(0.6-14)	100	86	12	(9.7-15)	0.061
	No	2	38			674	7.2			
Cleft lip-palate	Yes	2	28	1.5	(0.1-16)	113	97	5.7	(4.7-6.9)	0.27
	No	1	19			1,601	17			
Digestive system malformations	Yes	54	746	1.5	(0.9-2.4)	350	300	10	(9.0-11)	<0.0001
	No	27	512			2,861	31			
Oesophageal atresia/ stenosis	Yes	7	97	NE		91	78	65	(49-85)	NE
	No	0	0			113	1.2			
Small intestine	Yes	26	359	1.1	(0.6-2.1)	34	29	24	(17-36)	<0.0001
	No	17	323			112	1.2			
Duodenal atresia/ stenosis ^c	Yes	17	235	1.0	(0.5-2.1)	16	14	25	(14-44)	<0.0001
	No	13	247			47	0.5			
Large intestine	Yes	7	97	0.7	(0.3-2.1)	42	36	22	(16-31)	<0.0001
	No	7	133			154	1.7			
Rectal/ anal atresia/ stenosis ^c	Yes	7	97	0.9	(0.3-2.6)	35	30	25	(17-37)	<0.0001
	No	6	114			102	1.1			
Hirschsprung's disease	Yes	10	138	7.4	(0.9-58)	17	15	11	(6.9-19)	0.60
	No	1	19			118	1.3			
Genital organs malformations	Yes	6	83	1.5	(0.4-5.9)	149	128	2.6	(2.3-3.1)	0.42
	No	3	57			4,597	49			
Urinary system malformations	Yes	5	69	1.2	(0.3-5.1)	127	109	6.8	(5.7-8.1)	0.017
	No	3	57			1,505	16			
Without extracardiac malformation (Reference)	Yes	649				10,827				0.017
	No	488				917,658				

a) Unadjusted odds ratio (OR) with 95% confidence interval (CI), comparing the odds of extracardiac malformations live births with CHD with the odds of the same type of extracardiac malformations live births without CHD, calculated separately for births with Down's syndrome and births without known

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chromosomal aberrations.
b) P-value for homogeneity between the OR values in births with Down's syndrome and the OR values in births without chromosomal aberrations, calculated with the Mantel-Haenszel's test.
c) Registered for births from 1999 to 2009.
CHD, congenital heart defect; CI, confidence interval; NE, not estimable; OR, odds ratio.

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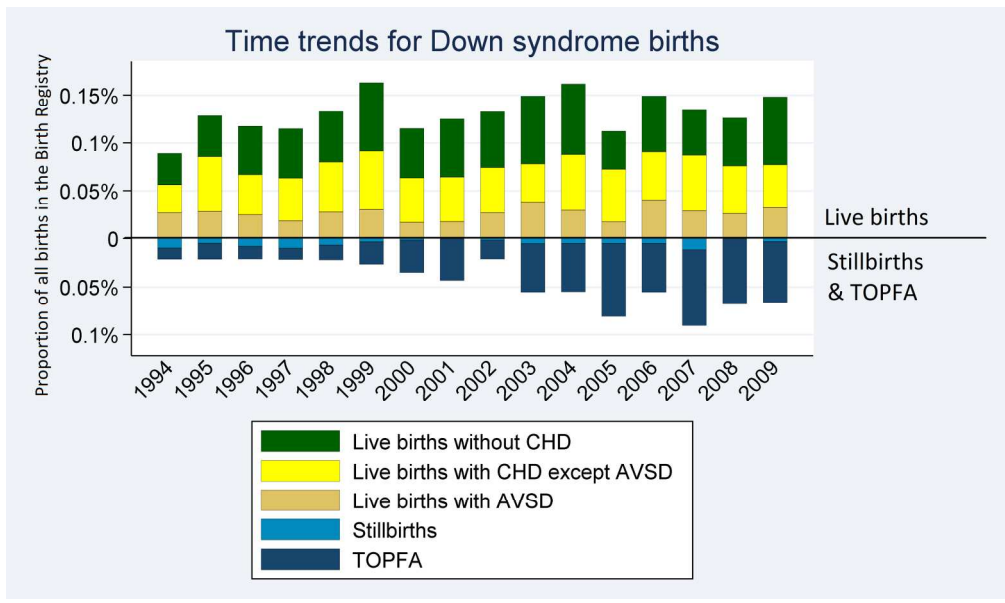
Table 4: Hazard ratios of death before five years of age in children with Down's syndrome by cardiac and extracardiac malformations, based on 1,251 live births with Down's syndrome in Norway 1994-2009.

Malformations	ECM	Deaths	N at risk ^a	Risk of death ^b	(95%CI)	HR ^c	(95%CI)
No CHD	No	11	488	2.3%	(1.3 - 4.1%)	1	(Reference)
	Yes	2	39	5.2%	(1.3 - 21%)	2.6	(0.6-12)
Isolated persistent ductus arteriosus	No	1	48	2.1%	(0.3 - 15%)	0.9	(0.1-6.7)
	Yes	0	12	-		-	
Septal defects ^d	No	9	296	3.1%	(1.6 - 6.0%)	1.5	(0.6-3.5)
	Yes	3	26	12%	(3.9 - 37%)	3.8	(0.8-17)
Atrioventricular septal defect	No	22	234	9.9%	(6.5 - 15%)	4.2	(2.0-8.7)
	Yes	4	20	22%	(8.1 - 58%)	13	(3.9-40)
Conotruncal defects ^e	No	5	31	17%	(7.2 - 42%)	7.4	(2.6-21)
	Yes	4	8	63%	(23 - 100%)	28	(8.9-88)
CHD, remaining types ^f	No	4	40	10%	(3.9 - 28%)	4.3	(1.4-13)
	Yes	3	9	38%	(12 - 100%)	19	(5.2-67)
Total		68	1,251	5.6%	(4.4 - 7.1%)		

- a) Due to emigration or limited follow-up time, 72 individuals were censored in the analysis.
- b) Estimated risk of death before five years of age, calculated by the Nelson-Aalen's cumulative hazard estimate. For comparison, the risk of death before five years of age in children without chromosomal aberration was 0.3% for individuals without CHD, 4.0% for individuals with persistent ductus arteriosus, atrial septal defect or ventricular septal defect, and 18% for those with remaining types of CHD.
- c) Cox' proportional hazard ratio estimate, using live births with Down's syndrome without CHD and without ECM as reference. Estimates are adjusted for year of birth.
- d) Isolated atrial septal defects, isolated ventricular septal defects, and combined atrial septal defects and ventricular septal defects.
- e) Tetralogy of Fallot, double outlet right ventricle, conotruncal ventricular septal defects, aortic hypoplasia, truncus arteriosus, and interrupted aortic arch.
- f) Heterotaxia, anomalous pulmonary venous return, aortic valve stenosis, aortic valve insufficiency, other malformations of the aortic valve, coarctation of the aorta, Ebstein's anomaly, pulmonary atresia, pulmonary valve stenosis, mitral valve insufficiency, and unspecified CHD.

CHD, congenital heart defect; CI, Confidence interval; ECM, extracardiac malformations; HR, hazard ratio.

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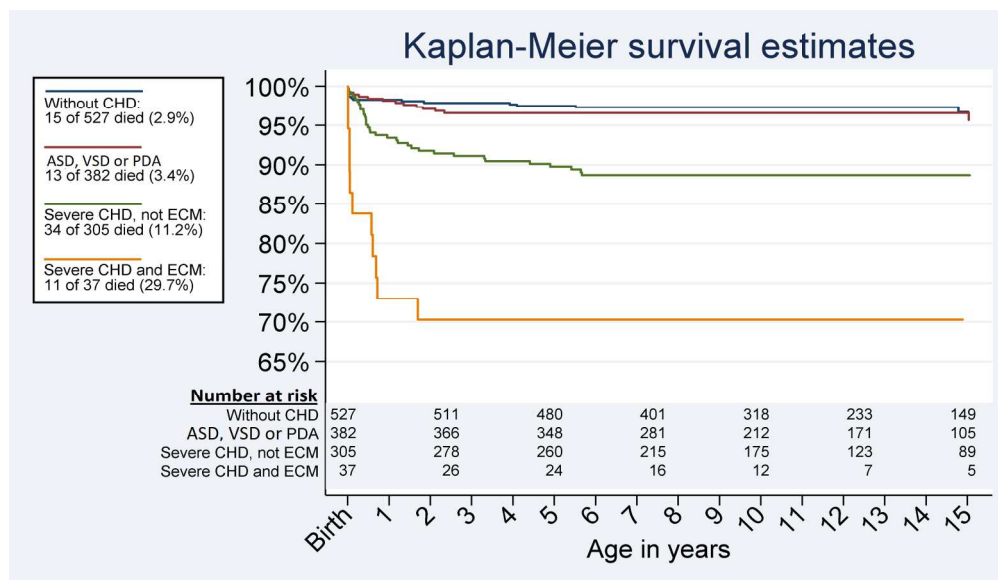


Time trend for total birth prevalence (per 10,000 births) of Down 's syndrome by year of birth, based on 953,450 births in Norway 1994-2009.

Footnote: AVSD, atrioventricular septal defect; CHD, congenital heart defects; TOPFA: Termination of Pregnancy for Foetal Anomaly.

465x275mm (120 x 120 DPI)

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Kaplan-Meier survival estimates for children with Down's syndrome born in Norway 1994-2009. The estimates are based on 1,251 live births with Down's syndrome follow-up until May 2nd 2014.

Footnote: Severe CHD is defined as any CHD, excluding ASD, VSD and PDA.
ASD, atrial septal defect; CHD, congenital heart defects; ECM, extracardiac malformations; PDA, persistent ductus arteriosus; VSD, ventricular septal defect.

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Table S1: Definitions and categorizations of extracardiac malformations.

Extracardiac malformation^a	ICD-10	ICD-9	ICD-8
Any extracardiac malformations	Q00-Q18, Q30-Q64	740.0-744.9, 748.0-749.9, 759.0-759.2	740.0-745.9, 748.0-749.9, 758.0-758.3
Nervous system malformations	Q00-Q07	740.0-742.9	740.0-743.9
Eyes, ears, face, neck malformations	Q10-Q18	743.0-744.9	744.0-745.9
Respiratory system malformations	Q30-Q34	748.0-748.9	748.0-748.9
Cleft lip-palate	Q35-Q37	749.0-749.9	749.0-749.9
Digestive system malformations	Q38-Q45	750.0-751.9	750.0-751.9
Oesophageal atresia/ stenosis	Q39	750.3-750.4	750.2
Small intestine	Q41	751.1	751.1
Duodenal atresia/ stenosis	Q41.0	^b	^b
Large intestine	Q42	751.2	751.2
Rectal/ anal atresia/ stenosis	Q42.0-Q42.3 ^c	^b	^b
Hirschsprung's disease	Q43.1, P76.1, P76.8, P76.9 ^d	751.3	751.3
Genital organs malformations	Q50-Q56	752.0-752.9	752.0-752.9
Urinary system malformations	Q60-Q64	753.0-753.9	753.0-753.9

- a) Malformations of the musculoskeletal system (Q65-Q79) were not included, due to perceived low completeness among children with Down's syndrome. Other malformations (Q80-Q89) were not included because too few cases were identified among children with Down's syndrome.
- b) No representative codes in ICD-8 and ICD-9
- c) Rectal and anal stenoses and atresia, with and without fistulas, were combined into one category.
- d) ICD-10 codes suggesting transitory intestinal obstruction of new-born (P76.1, P76.8, and P76.9) were included to identify possibly misclassified Hirschsprung's disease, because the clinical presentation may be unspecific initially. One infant with Down's syndrome with P76.1 was identified, and for this child the diagnosis Hirschsprung's disease was verified in the CVDNOR.

ICD-8, ICD-9, ICD-10: International Classification of Diseases, Eighth, Ninth, and Tenth Revisions, respectively.