The heart in Down syndrome

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Assessment of prevalence of persons with Down Syndrome; a theory-based demographic model


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ABSTRACT

Background The Netherlands are lacking reliable empirical data in relation to the development of birth and population prevalence of Down syndrome. For the UK and Ireland there are more historical empirical data available. A theory-based model is developed for predicting Down syndrome prevalence in the Netherlands from the 1950’s onwards. It is likewise applied to Ireland and the UK for the purpose of validation. Furthermore, a prediction to 2050 is constructed.

Materials and Methods Maternal age births data in the general population, maternal age related risk of Down syndrome, data on selective terminations of Down syndrome pregnancies and mortality rates (from 35 studies from the 1930’s until today) were obtained to create this model.

Results For the Netherlands, nowadays birth prevalence is estimated at 14 per 10,000 with around 275 total annual births. The impact of selective abortion is lower than in the UK. Present Dutch Down syndrome population prevalence is estimated, according to this theory-based model, at 7.7 per 10,000 and the grand total at 12,600 individuals. The prevalence of ‘older’ persons with Down syndrome (over 40 years of age) in the Netherlands will reach a peak in 2010, a doubling compared to 1990, implying an increased demand on medical care and counseling. Validity of this theory-based model was examined by comparison with relevant available empirical data from the three countries. The model shows a good fit with historical empirical research, notably four UK and two Irish population prevalence studies and eight birth prevalence studies.

Conclusions A theory-based model for Down syndrome prevalence provides supplementary data in situations with a lack of empirical material and can be used for understanding and predicting long-term developments.
INTRODUCTION

Down syndrome is the most common chromosomal anomaly among live born infants and the most frequent form of intellectual disability in industrialized countries. The birth prevalence of Down syndrome has been studied extensively and according to most studies lies between 1 - 3 per 1000 live births, where the differences are depending on maternal age distribution in general population and selective abortion rates. In recent years, more and more precise techniques for screening on Down syndrome during pregnancy have been developed. Of course, the expansion of prenatal services has a decreasing influence on Down syndrome birth prevalence.

On the other hand, in the Netherlands, as in other Western countries, in the last decades maternal age at birth has been rising. As the chance of giving birth to a child with Down syndrome rises sharply with maternal age, this latter property has a huge influence on Down syndrome birth prevalence. Furthermore, over the past 100 years, society has changed dramatically in terms of living conditions, medical science and wealth. Also, public attitudes towards persons with Down syndrome have changed. Both developments will have an effect on preterm and long term mortality trends in persons with Down syndrome and its population prevalence.

Yet, the aforementioned developments have different impacts on Down syndrome prevalence. The questions of this article are; (1) what are the contributions of those factors separately to prevalence of Down syndrome? (2) Is it possible to combine those operationalized factors in a valid model? (3) What are the results of this model for the prognosis of prevalence figures of persons with Down syndrome for the Netherlands? In this article a theory-based epidemiological model will be presented for predicting Down syndrome population prevalence figures, according to age, in the Netherlands from the 1950's onwards till 2050. Maternal age births data in the general population, maternal age-related risk of Down syndrome, data on selective abortions and mortality rates (from 35 studies from developed countries from the 1930's until today) were obtained to create this model.

In the Netherlands, as in most other European countries, data about Down syndrome population prevalence and its age distribution are not available. As a consequence, it was decided to add England/Wales and Ireland for reasons of model development and validation, because in those two European countries reasonably reliable historical data on Down syndrome population prevalence and age distribution
have been published. Moreover, living conditions and quality of health care are to a large extent comparable with the Netherlands. For both countries, too, data are available on maternal age distribution in general population and on the amount of selective abortions of Down syndrome pregnancies. These data are necessary for developing the model.

Relevance of the theory-based model
Prevalence data on a national level can be highly relevant for at least four reasons. Firstly, a national prevalence figure of disability can be an indicator of relevance. Together with incidence-assessments, it shows the number of affected persons in society. Secondly, it can be used to ascertain and control, if samples are biased in outcomes of age distribution. Thirdly, epidemiological data can provide some insights in special characteristics and life circumstances of the persons involved. Finally, knowledge of prevalence and age distribution of a special population, like persons with Down syndrome, can be helpful in terms of long-term planning for medical and social welfare.

POMONA was a European Commission-funded public health project that aimed to develop and implement a set of health indicators specific to Europeans with intellectual disabilities. Data on prevalence and life expectancy are two of a set of 18 health indicators which are necessary, but in most European countries not available, in assessing the health situation for this section of society.

Also with regard to the specific subgroup of individuals with Down syndrome, data on prevalence are far from complete. This is certainly the case in the Netherlands. In this country, three professional registers record the births of children with Down syndrome, notably:

1. The National Perinatal Database LVR (Landelijke Verloskunde Registratie), since 1994 combined with the National Neonatology Registration LNR (Landelijke Neonatologie Registratie).
2. The Dutch Pediatric Surveillance Unit NSCK (Nederlands Signalerings Centrum Kindergeneeskunde), which is in operation since 2003.
3. The European Registration Of Congenital Anomalies (EUROCAT), which is in operation since 1981. As a regional register in an European consortium EUROCAT is only active in the Northern part of the Netherlands.

Because children with Down syndrome are reported in all centers by health care
professionals on a voluntary basis, it is likely that the three registers suffer from under-ascertainment.

This was also a conclusion of a study by Weijerman and his colleagues. Weijerman et al (2008) combined the relevant data from the LVR/LNR and the NSCK registers for 2003 and found that Down syndrome birth prevalence was 16 per 10 000, using the Capture-Recapture method. This prevalence assessment exceeds the reported levels of all three registers, taken separately. However, combining the LVR/LNR and NSCK registers has only been carried out for the year 2003. As a consequence the results from this study do not allow conclusions about changes and long-term trends.

As information on Dutch Down syndrome population prevalence is missing, it is an alternative approach to estimate Down syndrome prevalence by a theory-based epidemiological model. In regard to Down syndrome this has been done by De Graaf (1998) for birth prevalence, by Scheepstra (1998) for elementary school aged population prevalence of children with Down syndrome, and by Steffelaar & Evenhuis (1989) for senior population prevalence in the Netherlands, and by Steele & Stratford (1995) for population prevalence and age distribution in the UK. In the three Dutch studies the model was not validated by any empirical data, and in the UK study only data for one specific year were used. In the British study and in two of the Dutch studies, population prevalence and age distribution were estimated. The huge changes in mortality rates in Down syndrome, however, during the twentieth century were not taken into account or only roughly modeled. It was our goal to validate an evidence-based theoretical model for prevalence of Down syndrome using social-demographic and statistical-medical data about birth prevalence and mortality for a long period and for several countries.

MATERIALS AND METHODS

In the methods section the separate steps to build the model, but also methods and sources of the information of each of the included variables are discussed.

Natural birth prevalence

Natural birth prevalence of Down syndrome is the total amount of births in the absence of prenatal testing and induced abortion of affected pregnancies.
There is an extensive body of research regarding maternal age-specific risk for Down syndrome live births. Researchers have developed slightly different models.\textsuperscript{10} We have decided to apply the most recent model of maternal age-specific risk for Down syndrome developed by Morris et al (2002) using data from the National Down Syndrome Cytogenetic Register (NDSCR).\textsuperscript{11,12} The NDSCR has been collecting information on prenatally and postnatally karyotyped Down syndrome cases from all cytogenetic laboratories in England and Wales since 1989.

Data on births by maternal age in general population are available for the Netherlands from 1936 onwards, from the National Office for Statistics (CBS)\textsuperscript{13}, for Ireland from 1955 onwards, from the Central Statistics Office (CSO)\textsuperscript{14} and for England/Wales from 1938 onwards, from the Office for National Statistics (ONS).\textsuperscript{15} In our model, natural Down syndrome birth prevalence was assessed by combining these data for each country with the Morris model of Down syndrome maternal age-related risk. It was assumed that maternal age distribution in the general population before 1936 in the Netherlands, before 1955 in Ireland, and before 1938 in England/Wales, would be similar to the average in the five following years from which data were available.

**Actual birth prevalence**

To determine actual birth rates instead of potential birth rates of children with Down syndrome according to maternal age, the effect of prenatal testing and subsequent selective abortion of Down syndrome pregnancies is an important variable.

However, induced abortions of, say, 100 Down syndrome pregnancies do not lead to a reduction of a 100 live births. According to the literature 23 to 25% would have ended in a natural miscarriage.\textsuperscript{6,16} Savva et al (2006) used the aforementioned English/Welsh NDSCR database to investigate more precisely the correlation between natural miscarriages and maternal age versus type of prenatal testing (amniocentesis or chorionic villus sampling (CVS)).\textsuperscript{17} In our study this information was used to construct a more precise correction factor for natural fetal loss. The natural fetal loss was estimated to be 34% in case of CVS and 27% in case of amniocentesis in women older than 35 years of age and 25% and 20% in women younger than 35 years of age, respectively. By making use of information from the NDSCR database from 1989 onwards on terminations of Down syndrome
pregnancies, type of prenatal testing and maternal age, we could estimate that every 100 induced Down syndrome abortions leads to a net result of 73 prevented births of children with Down syndrome, with a range from 71 to 77 for different years. In their study, Buckley & Buckley (2008) used a slightly different correction factor for natural fetal loss in CVS and estimated the net result of 100 induced abortions in the NDSCR database to be 70 prevented births, with a range of 67 to 75 for different years.18

From 1989 onwards, reliable data on terminations of Down syndrome pregnancies are available from the NDSCR. For the period 1974-1988 data were used on induced abortions of Down syndrome pregnancies published by the Office for National Statistics (ONS) and the Government Statistical Service of the Department of Health. Finally, we assumed that Down syndrome birth reduction due to selective abortion proportionally increased from 0% in 1969 to the situation of 1974 (10.5%).

For the Dutch situation, the annual reports on terminations of Down syndrome pregnancies, including data on prenatal testing method and maternal age, from the Working Party Prenatal Diagnosis and Therapy (WPDT) were used for the period 1991-2004.19 For the Netherlands we estimated a net prevention of 71 births per 100 induced terminations, with a range from 70 to 73. This is somewhat lower than in England/Wales, as in the Netherlands both the percentage CVS and maternal age of women making use of prenatal services were slightly higher.

From 1991 onwards, reliable data on terminations of Down syndrome pregnancies in the Netherlands are available from the WPDT. For 1981-1990 we used data from EUROCAT on induced terminations of Down syndrome pregnancies. Finally, we assumed that Down syndrome birth reduction due to selective abortion proportionally increased from 0% in 1970 to the situation of the early eighties (6.5%).

Ireland is in a special position compared to the Netherlands and England/Wales because termination of pregnancy is illegal in this country. Therefore it was assumed that the actual birth prevalence will be similar to (or at least close to) the natural birth prevalence.

Mortality
Results from 35 studies were used to estimate 10-years-survival rates for the respective years of birth (figure 1 and table 1). For each study the survival rate was plotted against the year of birth and a regression line was drawn with the non-
parametric SPSS LOESS function. If the authors of a study did not specify this, it was assumed that the survival rate mentioned in the study applied to the most recent year of birth. Particularly in research concerning longer periods of time some researchers report higher under-registration of neonatal mortality in Down syndrome in the beginning of the research period.\textsuperscript{20,21} According to such information, it is safer to assume that survival rates are more correct for the end of the research period. The same procedure was used for estimating 1- and 5-year survival rates. The rates for intermediary ages were extrapolated. In table 1, underlined figures are directly derived from or calculated on the basis of the cited study. The other (not-underlined) figures are estimated on the basis of the relation between (similar) 1-year, 5-year and 10-year survival rates as found in studies in which more than one of these figures is given. Some studies in table 1 are marked with an asterisk (*). In that case we estimated the survival rates on the basis of a combination of the Down syndrome population prevalence in relation to a certain age group as given in the study and the birth prevalence as derived from the present model. The studies show that survival of young children with Down syndrome dramatically improved during the twentieth century.

A final slight adjustment to the modeled survival rates was made by assuming that from the early nineties until now 10-years survival rates not have risen gradually from 85\% to 93\% as shown in figure 1, but more sharply in the early nineties to reach 93\% from 1993 onwards. This assumption is based on the findings of Yang et al (2002).\textsuperscript{22} In their analysis of almost 18 000 death certificates of persons with Down syndrome in the USA from 1983 to 1997, they found an sharply increased median age at death in white persons with Down syndrome and additional congenital heart defects after 1992, from 0 year of age in 1992 to 18 years of age in 1994. As half of children with Down syndrome have a congenital heart defect, this implies that survival of young children with Down syndrome substantially and rapidly improved in the early nineties.

For modeling survival rates above 10-years of age, data were used from studies of Glasson et al (2002), Maaskant (1993), Baird & Sadovnick (1987) and Dupont et al (1986) (figure 2).\textsuperscript{20,21,23} The survival curves above 10 years of age from these studies are highly similar. It was decided to make use of the average of these four curves. For the period before 1955 a survival curve above 10 years of age was used showing a more rapid decrease, based on the work of Penrose (1949).\textsuperscript{24} This
more hazardous survival curve was used for predicting the survival of cohorts born before 1945 until the calendar year 1955. After 1955 it was assumed that the survivors of these cohorts would also follow the survival curve constructed for the period 1955 onwards.

Figure 1 Ten years survival rates for children with Down syndrome.

Figure 2 Down syndrome survival curve above 10 years of age.
# Table 1: 1-, 5-, and 10-year Down syndrome survival rates

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Superscript numbers in the table are references of the articles, not mentioned in the text.
**Population prevalence**

By combining the modeled actual birth prevalence with the constructed survival curves for each year of birth, the population prevalence and age distribution for each calendar year from the 1950's onwards could be computed.

**Predicting future prevalence rates**

In order to apply this model for future predictions, it was necessary to make some additional assumptions:

- The distribution of maternal age at birth in the general population will stay unchanged (with a high percentage of older mothers).
- The total amount of births in general and the development of the total population in future years can be based on prognostic models of CBS, CSO and ONS.
- The reduction percentage due to selective terminations of Down syndrome pregnancies will only be slightly higher than nowadays, and will be 40% in the Netherlands and 50% in England/Wales in coming decades. Selective termination of Down syndrome pregnancies in Ireland will remain practically absent.
- The 10-years-survival rates will only slightly improve to 95% for the next decades.
- The survival curve above 10 years of age will be stable and unchanged for the next decades.

Only a slight increase was assumed in the reduction percentage due to selective abortion in the Netherlands and England/Wales because, according to the theory-based model, the reduction percentage for women above the age of 35 has been nearly constant for the last fifteen years (around 45% in the Netherlands and around 55% in England/Wales). For the subgroup of women younger than 35, the reduction percentage in England/Wales increased from 1989 to 1997 from 7 to 35% and stayed nearly constant in subsequent years. In the Netherlands, the reduction percentage gradually grew from nearly zero in 1991 to 20% in 2004. There seems to be more recently a fairly consistent quantitative subgroup of women in both countries that do not want to make use of prenatal testing services. The increase in Down syndrome
reduction percentage due to selective abortion for all pregnant women (from 20 to 35% in the period 1991-2004 in the Netherlands; from 25 to nearly 50% in 1989-2004 in England/Wales) is for a very large part the consequence of rising maternal age and only for a small part the result of a higher percentage making use of prenatal services in pregnant women under 35. The assumption of an unchanged maternal age distribution will result in only a slight increase in reduction percentages due to selective abortion in coming years.

RESULTS

Validating the model
The next step is validating the theory-based model and, if necessary, adapting the model by comparing the predicted birth prevalence, life expectation and mortality rates, population prevalence, and age distribution with empirical data from the three countries. However, 14 of the 26 empirical datasets in these comparisons were actually also used in developing the model. The issue whether these comparisons can be considered to be a real external validation of the model will be elaborated upon in the discussion.

Comparison with empirical data on birth prevalence of children with Down syndrome
For the purpose of validation, results on assessed birth prevalence on Down syndrome of the theoretical model were compared with data on actual birth prevalence from eight studies (figure 3) from the UK (3), Ireland (2) and the Netherlands (3). The model fits the empirical data fairly well. For the UK, the theoretically-based results on average are 2% higher than the 1978-1992 data of Huether et al (1996), 5% lower than the 1991-2003 combined UK EUROCAT data and 2% higher than the 1990-2004 NDSCR data (see for the NDSCR data also Morris & Alberman, 2009). For Ireland, the theoretically-based results on average are 2% higher than the 1966-1983 data of Mulcahy & Reynolds (1985) and 6% higher than the 1980-2003 combined Irish EUROCAT data. For the Netherlands, the theoretically-based results are slightly higher (8%) than the actual 1996-2003 LVR/LNR data, and the NSCK-data. Furthermore, the theoretically-based results on average are 5% higher than the 1980-1989 Dutch EUROCAT data. However, for the
period 1990-2004 the theoretically-based results on average are even much higher (28%) than the Dutch EUROCAT data. But, as has been stated before, the LVR/LNR, NSCK and Dutch EUROCAT register are likely to suffer from under-ascertainment. Correcting for this bias, Weijerman et al (2008) estimated live birth prevalence in 2003 even to reach 16 per 10,000, which is 2 points (14%) higher than our theory-based estimation for 2003.

Comparison with empirical data on mortality and life expectancy
The theoretically-based model outcomes on mortality were compared with data from a Dutch study of Coppus et al (2006). From 2000 onwards, they did a follow-up of 506 persons with Down syndrome over 45 years of age. Mortality after a mean 3.3 years of follow-up was in the age group 45 to 50 8%, age 50-54 14%, age 55-60 28% and age >60 49%. Our model would predict comparable mortality rates for a similar period of 3.3 years, respectively 7, 13, 25 and 39%. The difference between the model outcome on mortality in the age group >60 and the empirical data of Coppus et al could very well be the result of chance, as Coppus et al studied a fairly small group (of 39 persons) in this age range, which results in a 95% confidence interval of approximately 33-64%.

Figure 3. Down syndrome birth prevalence; comparison of model with other studies
According to results of the study of Yang et al (2002) in the USA median age at death for persons with Down syndrome increased from 25 years in 1983 to 49 years in 1997.22 Our model would predict a similar increase in median age of death from 24 to 50 years in the same period.

For each year of birth a survival curve was constructed and life expectancy for the respective years of birth was estimated. The theoretically-based model outcomes were compared with empirical studies on Down syndrome life expectancy at birth. Penrose (1949) estimated Down syndrome life expectancy to be 9 years in 1930 and 12 years in 1949.24 On the basis of our model for the same years, this would be 11 and 22 years, respectively. Collman & Stoller (1963a;b) estimated a life expectancy of 10 years for the year of birth 1955 and 16 years for 1963.28,29 Our model would predict for the same period 25 and 28 years, respectively. Deaton (1973) estimated 30 years for 197026, our model would predict 35 years. Masaki (1981) and Maaskant (1993) both estimated life expectancy to be 49 years for 198021,23 our model would predict 43 years. Dupont et al (1986) estimated 46 years for 198932, our model exactly the same. Glasson et al (2002) estimated median life expectancy for 2000 to be 59 years.21 On basis of Glasson et al’s survival curve it could be estimated that this results in a mean life expectancy of 54 years21, which is comparable with the 52 years of our model for 2000. Both the historical empirical data and the model-based results show a clear increase of Down syndrome life expectancy from around 10 years in 1930 to more than 50 years nowadays. This is a sharp increase compared to the development of life expectancy in general population with an increase of 20 years in the same period to an age of 78.33-35,13 Some of the older historical studies estimate Down syndrome life expectancy to be lower than our model predicts for the year of birth concerned. A possible explanation for these differences is that in assessing life expectancy these studies used survival data from those born in earlier years, which could lead to a huge underestimation of life expectancy when survival rates actually significantly improve in successive years.

Comparison with empirical data on population prevalence and age distribution

The most important question in validating the theoretically-based model is with regard to the central question: does the model represent similar data compared to representative population-based empirical data on Down syndrome prevalence and age distribution? For the Netherlands, complete empirical studies on population
prevalence are absent. However, it proved possible to make a comparison between the model and the outcomes of three recent Dutch studies, however, with limited samples. Coppus et al (2006) studied a population-based sample of 506 persons with Down syndrome over 45 years of age in the Dutch regions of Rotterdam, Zeeland, Noord-Brabant and Gelderland.27 Four age groups were distinguished: <50, 50-54, 55-59 and >60 years. The correlation between these empirical and the modelled data in age distribution is $r=0.998$ ($p<0.002$). The second author of this article collected information in 2008 on 1073 persons (30+ years of age) with Down syndrome in Dutch institutions. The correlation between empirical and modelled data in age distribution in ten age groups is $r=0.93$ ($p<0.001$). Finally, on the basis of a count by 21 out of 116 SLD-schools in the Netherlands of pupils with Down syndrome (4-13 years of age) in their region (in special as well as regular education), the first author of this article could estimate the grand total of Down syndrome in the Netherlands in primary school age to be about 2200, whereas the model predicts about 2100. Although all of these more recent studies are limited in scope, their results are in good accordance with the model.

For England/Wales, there are four complete studies on Down syndrome population prevalence and age distribution available. In 1949, in the London region, Penrose counted a total of 138 persons with Down syndrome in a population out of 773 000 inhabitants. This would equal a population prevalence of 1.8 per 10 000. Penrose stated in his publication that under-ascertainment in the age range 0-10 years was extremely high.24 After correcting for under-ascertainment Penrose assumed population prevalence to be 3.2 per 10 000. Our model predicts a comparable figure with 3.1 per 10 000 for England/Wales in 1949. Midwinter counted in 1968 in the Bristol region 229 persons with Down syndrome in a population of 427 780 inhabitants. This study equals a population prevalence of 5.4 per 10 000.36 Our model predicts a slightly lower prevalence figure of 4.6 per 10 000. In 1982, in the combined Sheffield and Buckingham region, Stratford and Steele (1985) counted 530 persons with Down syndrome in a population of 1 145 200 inhabitants.37 Population prevalence would be 4.6 per 10 000 for the combined regions. Our model predicts a somewhat higher prevalence of 5.5 per 10 000 for England/Wales in 1968. Between the two regions, population prevalence differed widely, with 5.1 in Sheffield and 4.2 in Buckingham. This difference suggests that there might be under-registration in certain age groups. In 1987 Steele & Stratford (1995) in 30 different
Social Service and Health Authority registers across the UK identified about 3700 persons with Down syndrome in a total population of approximately 7 million. According to Steele & Stratford, following adjustment for under-ascertainment in 0-4 years, this would equal a total of 30 099 persons with Down syndrome for England, Wales and Scotland. The authors claim a population prevalence figure in 1987 of 6.7 per 10 000. This last assessment must be a computational error. According to ONS, the resident population in 1987 was 55 222 million in England, Wales and Scotland. With an estimated total of 30 099 persons with Down syndrome, this would yield a population prevalence of 5.5 per 10 000 (and not 6.7 per 10,000). Our model predicts a comparable 5.7 per 10 000 for 1987.

It can be concluded that the results of the theory-based model are quite consistent with the empirical data on total population prevalence of the four UK studies. Quite similar results are also achieved with regard to age distribution. Correlations between modelled age distribution and empirical data are respectively $r=0.99$ ($p<0.001$) for the 1949 data on age-distribution in 8 age groups of Penrose (after correcting by Penrose for under-ascertainment in the age range 0-10 years), $r=0.76$ ($p<0.004$) for the 1968 data on age-distribution in 12 age groups of Midwinter, $r=0.97$ ($p<0.001$) for the 1982 data on age-distribution in 8 age groups of Stratford & Steele, and $r=0.99$ ($p<0.001$) for the 1987 data on age-distribution in 14 age groups of Steele & Stratford. In the counts of Midwinter there is a clear under-registration in the age range 0-4 years. If we exclude the data for the age range 0-4 years, the correlation coefficient between modelled and empirical data reaches $r=0.97$ ($p<0.0001$).

**Adjustments of the model after the validation process**

Our initial model does fit the Dutch and British empirical data fairly well and no adjustments have to be made. With regard to the republic of Ireland, Mulcahy & Reynolds (1985) published data from the Irish census of 1974 and 1981. For 1974 a total of 2992 persons with Down syndrome were counted in the Irish population of 31 239 million inhabitants. In 1981 the respective figures were 3559 in 34 434 million. The Down syndrome population prevalence figures are 9.6 per 10 000 for the year 1974 and 10.3 for 1981. The theory-based model shows higher values with 12.2 and 12.6 respectively. This difference is partly due to a higher estimation of children with Down syndrome in the age range 0-4 years in our model. This discrepancy could be
again the result of under-ascertainment in the empirical data. However, our model also shows much higher prevalence rates in the age range 20-54 in 1974 and in the age range 35-54 in 1981. All of these are Irish persons born between 1920 and 1955. By comparing information from CBS, CSO, ONS and the Registrar General Northern Ireland Annual Report (2004) on infant mortality in general population in the Netherlands, the UK and Ireland respectively, it could be demonstrated that infant mortality in the period 1920-1955 was almost twice as high in Ireland in comparison with both other countries. This gap between countries is closing in more recent years. It can be expected, that a higher general infant mortality will co-occur with a much higher infant mortality in Down syndrome, as these children often are more vulnerable. Therefore an adapted model for Ireland was constructed with a lower 10 year survival rate for persons with Down syndrome born between 1920 and 1955. Assuming 10 year survival for persons with Down syndrome in Ireland for 1950-1955 was 84% and for 1920-1949 60% of the values used in our model for both other countries, the adjusted model predicts numbers in the corresponding age ranges that are in more accordance with the census data. Predicted population prevalence rates on basis of the adjusted model are 10.5 per 10 000 in 1974 and 11.1 in 1981. Age distribution of the initial model showed a correlation coefficient of $r=0.91$ ($p<0.005$) with Irish census data on age distribution in 7 age groups of 1974 and $r=0.93$ ($p<0.002$) with 1981 census data. After correction the concordance was $r=0.98$ ($p<0.001$) and 0.93 ($p<0.002$) respectively. In comparison with the initial model the adjusted model predicts a slightly lower population prevalence, ranging from 14% lower in 1974 to only 3.5% in 2005.

Assessments of prevalence rates with the model

In regard to birth prevalence, the present model shows similar trends and results in all three countries (figure 3). Until the early eighties, there is a sharp decrease in Down syndrome live birth prevalence caused by a decreasing percentage of older mothers, due to smaller family size. From the early eighties onwards, as a consequence of postponed motherhood, the percentage of mothers older than 35 years of age is growing again. This demographic trend produced a clear increase in natural Down syndrome live birth prevalence. However, from the early eighties onwards prenatal services have been developed and expanded in the Netherlands and England/Wales, resulting in a small increase in actual live birth prevalence in the
Netherlands, and with only a very slight growth since the nineties in England/Wales.

If we look in more detail at the timing of events and the corresponding values of live birth prevalence, some cultural differences between the three countries emerge. A pattern of large families can particularly be observed in Ireland, where the percentage of 35+ mothers has always been higher than in both other countries and where the onset of a decrease in this percentage fell some 15 years later. Also, some difference between England/Wales and the Netherlands existed before 1975 with a higher percentage 35+ mothers and a corresponding higher natural live prevalence in the Netherlands. Starting in the early seventies the gap in percentage of older mothers and natural birth prevalence rates has disappeared between both countries. The differences in actual birth prevalence between both countries since the early seventies are caused by differential use of selective abortion. England/Wales has a policy of a more active approach since the early nineties by offering prenatal screening services to all pregnant women. There also seems to be a different attitude towards abortion between both countries. The abortion rate in the general population is twice as high in England/Wales as compared to the Netherlands.\(^{39}\) It is expected that also in the Netherlands a small increase in Down syndrome birth reduction due to selective abortion will take place in future years, since screening is offered more actively in most recent years.

Down syndrome reduction rates due to selective abortion have been increasing in the Netherlands from approximately 20% in the early nineties to some 35% in 2003, and in England/Wales in the same period of time from around 25% to over 45%. Therefore, one might conclude that children with Down syndrome are less welcome nowadays. However, this conclusion would be premature, since increasing reduction rates are to a large extent a function of a growing proportion of mothers above the age of 35 years in the general population. Within this group of elder women the reduction rates have been nearly constant in both countries throughout the last 15 years.

Population prevalence of persons with Down syndrome is a function of incident cases at birth and life expectancy. Life expectancy for persons with Down syndrome has been dramatically improved during the twentieth century. Figure 4 shows predicted population prevalence rates for the period 1950-2050 in the three countries concerned. It shows also prevalence estimates, if there had never been any prenatal testing and selective abortion. These figures give an impression of the
The estimates of population prevalence of persons with Down syndrome in the Netherlands (figure 4) show a sharp increase until 1970. After this year it reaches a more or less stable level. In England/Wales and Ireland Down syndrome population prevalence was clearly rising till 1990 and reached a relatively stable level in following years. Nowadays, in absence of selective abortion, population prevalence of persons with Down syndrome would have been 14% higher in the Netherlands and 25% in England/Wales. As a result of selective abortion, Down syndrome population prevalence in the Netherlands and England/Wales has been more or less stable since 1990. Recent Down syndrome population prevalence rates are assessed by this model as 13.1 per 10 000 persons in Ireland, 7.7 in the Netherlands and 6.1 in England/Wales. Within its assumptions, for the Netherlands and England/Wales a slight decrease to respectively 7.1 per 10 000 persons and 5.6 per 10 000 persons in 2030, and for Ireland a small increase to 13.5 in 2015 is expected.

Changes in birth prevalence and in childhood survival have altered the age distribution of the Down syndrome population. Using the outcomes of the model in 1950 only 20% of Dutch persons with Down syndrome were older than 20 years of age and 3% older than 40 years, compared to respectively 65% and 36% nowadays. For England/Wales the age distribution is quite similar. However, the model estimates show that in Ireland only 25% of the recent Down syndrome population is older than 40 years, due to higher birth prevalence rates in recent decades in comparison with both other countries.

The predicted numbers of persons with Down syndrome by age group for the period 1950-2050 in the Netherlands based on the theoretical model are shown in figure 5. These results demonstrate that the numbers of ‘older’ persons with Down syndrome (over 40 years of age) in the Netherlands will reach a peak in the year 2010 with about 4600 persons. This is twice as much compared to the number of persons with Down syndrome in 1990.
Figure 4  Down syndrome population prevalence; past and future expectation with or without selective abortion

Figure 5  Age distribution of persons with Down syndrome in the Netherlands; past and future expectations
DISCUSSION

Some of the empirical datasets in the validation process were actually also used in developing the model. In regard to our estimation of actual birth rates, this applies to the NDSCR-database. We used the model of Morris et al (2002) of Down syndrome maternal age-related risk. In addition, we used data of Savva et al (2006) in constructing a precise correction factor for natural fetal loss. Both Morris and Savva, however, based their investigations on the NDSCR-database. This implies that the comparison of our modeled results with the birth prevalence rates in the NDSCR-database should not be considered to be a truly external validation, but rather only shows a goodness of fit. However, the comparisons with the other seven studies of Down syndrome birth prevalence are genuinely external validations, as these studies were not used at all in constructing our modeled birth prevalence rates.

Four out of the seven comparisons with empirical studies on Down syndrome life expectancy at birth should not be considered truly external validations. Survival curves of Glasson et al (2002), Maaskant (1993), Dupont et al (1986) and Penrose (1949) were used both in constructing the survival curves above 10 years of age as in estimating 1-year, 5-year and 10-year survival rates in our model. Since the estimation of life expectancy at birth is derived from survival curves, it would be surprising if in this regard model and empirical data from these studies would not converge. However, data of Collman & Stoller (1963a,b) and of Masaki (1981) were only used in estimating 1-year, 5-year and 10-year survival rates in our model, amongst many other studies. Leaving out the data of Collman & Stoller and of Masaki in constructing our model, and in doing so making their data actually external to our model, does not make any difference for the derived parameters (the 1-year, 5-year and 10-year survival rates). Following this line of thought, we would argue that the comparisons with these two studies could be considered to be external validations. Data of Deaton (1973), finally, were not used at all in constructing the model. So the comparison with this study is indisputably an external validation. In constructing our model, with regard to studies on mortality, not on life expectancy at birth, the study of Yang et al (2002) was only used to make a small adjustment in the 1-year, 5-year and 10-year survival rates in the early nineties. However, also without this adjustment, the model would predict a similar increase in median age of death from 24 years in 1983 to 50 years in 1997. Finally, the comparison between the
study of Coppus et al (2006) and our model, regarding mortality rates in persons with Down syndrome over 45 years of age, should be considered a genuinely external validation. The work of Coppus was not used at all in constructing our model.

In regard to our estimations of population prevalence, the comparison of our model with the data of Penrose (1949) should not be considered a truly external validation, as the data of Penrose were used both in constructing the survival curves above 10 years of age (for the period before 1955) as in estimating 1-year, 5-year and 10-year survival rates in our model. However, the data of Midwinter (1972), Stratford & Steele (1985), Steele & Stratford (1995) and Mulcahy & Reynolds (1985) were used only in estimating 1-year, 5-year and 10-year survival rates in our model, amongst many other studies. Leaving out the data of one of these four studies in constructing our model, and in doing so making the data of that specific study actually external to our model, does not make any difference for the derived parameters (the 1-year, 5-year and 10-year survival rates). Even leaving out all of the data of these four studies leads to only a small difference in the derived parameters, with 1-year, 5-year and 10-year survival that are approximately 6% higher for the period 1960-1980 and unaltered for other periods. Since eventually almost the same model is constructed, if we leave out all the data of these four studies in the constructing process, we would argue that the comparisons with these studies could be considered to be external validations. Finally, the comparisons with the three Dutch studies (on more limited samples) are without doubt genuinely external validations, since none of these studies were used in constructing the model.

The theory-based model for Down syndrome prevalence has a fairly good fit with available empirical studies. In addition, it provides supplementary data in situations with a clear lack of empirical material, for instance in regard to Down syndrome population prevalence in the Netherlands and for recent years for England/Wales and Ireland as well. Moreover, the model can be used for understanding and predicting long-term developments. It provides detailed information on developments in birth prevalence, population prevalence and age distribution of Down syndrome. The theory-based model also yields more insights in the effects on birth and population prevalence and age distribution of changes in maternal age, the growing use of prenatal testing, cultural differences between countries in both these properties, as well as changes in mortality.

For the Netherlands, birth prevalence (in 2003) is estimated at 14 per 10 000
with a total of around 275 births annually. The impact of selective abortion is lower than in the UK. Present Dutch Down syndrome population prevalence is estimated at 7.7 per 10,000 and the grand total at 12,600 individuals, of whom approximately 4,600 are under the age of 20 and 4,500 above 40 years old. The prevalence of ‘older’ persons with Down syndrome (over 40 years of age) in the Netherlands will reach a peak in 2010, a doubling compared to 1990, implying an increased demand on medical care and counseling.

Constructing and validating a theoretically-based model is an inductive task with many methodological challenges and assumptions. Important variables have to be defined and selected, and the model outcomes have to be externally validated with empirically based outcomes.

Natural birth prevalence, total amount of abortions, and the correction factor for natural miscarriages can be estimated fairly accurately and this will not lead to a large contrast with reality. In estimating natural birth prevalence, the model for maternal age-specific risk for Down syndrome was used as developed by Morris et al (2002). Their model is the most recent one and is based on a large dataset with a high level of ascertainment. However, predicted birth and population prevalence would be 5 to 11.5% higher if one of the other recent models for maternal age-specific risk for Down syndrome had been used. The choice for the Morris model, instead of one of the other models, might possibly give some explanation for the higher Dutch Down syndrome birth prevalence rate that Weijerman et al estimated for the year 2003.

The Capture-Recapture method, as used by Weijerman and colleagues, could also lead to a small overestimation by missed true matches and/or false positive cases. Consequently, there remains a possibility that the prediction of Weijerman et al is too high. The model-predicted birth prevalence rates for England/Wales are in almost perfect accordance with the reliable counts from 1989 onwards of the NDSCR (the theory-based model even predicts slightly higher values). The NDSCR has a verified high level of ascertainment of 95%. Therefore, it appears unlikely that another model of maternal age-specific risk would yield better fitting results in regard to birth prevalence.

In regard to population prevalence, the accuracy of predictions is dependent on an accurate model for mortality. In this study a model was developed in which 10-year-survival rates have been gradually increasing during last century. Perhaps in reality these changes were more intermittent, like it was modeled for the early
nineties. Furthermore, in the theory-based model the same survival curve after 10 years of age was used from 1955 onwards whereas survival above ten years of age might have increased in recent years. However, the theory-based model predicts mortality rates in accordance with recent empirical findings of Coppus et al (2006) in the age range 45+.[27] Moreover, the age-distribution of Down syndrome deaths of the theory-based model for the period 1996-2005 fits fairly well data on age distribution in 19 age groups of the National Office for Statistics (CBS) in the same period on deceased persons with Down syndrome as primary cause of death. The correlation coefficient between modelled and empirical data is $r= 0.96$ (p<0.001).[13]

The theory-based model is not directly applicable to every country. In assessing Down syndrome birth prevalence rates, it is necessary to collect valid historical statistical information on maternal age births data in the general population and data on selective terminations of Down syndrome pregnancies. In assessing Down syndrome population prevalence rates, as can be learned from the example of Ireland in the period 1920-1955, historical and regional differences in infant mortality rates, with corresponding effects on Down syndrome survival, have to be taken into account, especially in regard to countries with a less well-developed medical system and more poverty. The mortality rates in the present model are based on studies from developed countries and as a consequence the model only is applicable to those countries. Down syndrome population prevalence in a less developed country can only be estimated if valid information on Down syndrome survival in the relevant country is available.

In regard to population prevalence, the most recent empirical study for validating the present theory-based is over 20 years old. More recent complete studies in Down syndrome population prevalence from the three countries are lacking. However, it proved possible to make a comparison with three recent Dutch studies with more limited samples. Their results are in good accordance with the model.

The best way of assessing the prognostic validity of the model would be a comparison with future empirical data. It is important to note that the present model is a dynamic model. It can and has to be adapted to changes in future demographic trends.

In predicting future population prevalence rates, it was assumed that the distribution of maternal age at birth will stay unchanged for the next decades. This
assumption could prove to be false as maternal age at birth has been rising during the last decades. However, in their prognostic projections, CBS, CSO and ONS assume that this trend will not continue into the next decennia.13-15

Future development of birth prevalence is largely dependent on how many pregnant women will make use of prenatal screening, testing and selective abortion. If, in contrast with the assumptions, this would increase to a large extent, the model needs to be adjusted. Another assumption is that ten-years-survival rates will only slightly improve to 95% for the next decades. However, a larger improvement would only have a marginal effect on population prevalence since in the three countries for which the model was developed ten-years-survival rates are already very high. More or less the same applies to survival rates in older children and young adults. Improvement in their survival would also only have a small effect on predicted future population prevalence. Nowadays, many persons with Down syndrome die between 50 and 60 years of age. If medical advancement would change this, the model certainly needs adjustment, especially for the number of persons above 40 years of age. An important question is whether these uncertainties in the future predictions can be quantified. Ascribing error terms to the various parameters, and using these to derive error bounds on the predictions would be ideal but is beyond the scope of our present approach. However, it is possible to provide some idea of the effect of varying parameters. The future development in Down syndrome population prevalence largely depends on the future development in maternal age and in uptake of prenatal services. We could construct a minimum and a maximum variant. In the following explanation, we will limit ourselves to the Dutch predictions. In a minimum variant, maternal age does not rise in the next decades, and the reduction percentage due to selective terminations in the Netherlands increases to 50% instead of 40%. This variant leads to a birth prevalence in the next decennia that is 17% lower than assumed in the original model and to an estimation of population prevalence that, in comparison with the original model, is 6% lower in 2030 (6.7 per 10 000 instead of 7.1). In a maximum variant, maternal age increases, while the reduction percentage for women above the age of 35 and this percentage for women below age 35 stay constant. Actually, this has been more or less the situation in the Netherlands from the early nineties till at least 2003. The resulting increase in actual birth prevalence has been on average 0.2 per 10 000 per year. We could assume this trend to continue in next decades, starting with an actual birth prevalence of around
14 in 2005 till in 2030 a peak value is reached of 19. This variant leads to an estimation of population prevalence that, in comparison with the original model, is 14% higher in 2030 (8.1 per 10 000 instead of 7.1).

The most important strengths of our modelling method are (1) the fact that it can provide supplementary data on Down syndrome prevalence in situations with a clear lack of empirical material and (2) it can be used in predicting long-term developments. The most important limitations are (1) the necessity of valid data on maternal age at birth in the general population and on selective abortions and (2) the fact that the survival curves need adjustment for the model to be applied to countries with a less well-developed medical system and more poverty.

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Appendix: How does the model operate?

**Step 1: natural live birth numbers and prevalence**

Data on births by maternal age in general population are available from national statistical offices. Morris formula is: risk = \(1/(1+\exp(7.330-4.211/(1+\exp(-0.282*(\text{maternal age}-37.23))))))\). In this formula a maternal age of for instance 36 actually means an age range of 36-37 (so on average: 36.5). Statistical offices can use different definitions for maternal age. It is important to make sure which range is meant with for instance an age of 36. The first step is combining these maternal age data with the formula. For instance in the Netherlands in 2000, 8079 children were born by women of 36 years of age (CBS, in this table, uses a definition in which 36 year is indeed the range 36-37). The natural risk for Down syndrome is for the maternal age range 36-37: \(1/(1+\exp(7.330-4.211/(1+\exp(-0.282*(36-37.23)))))) = 0.003758\). So in 2000, in the absence of prenatal services, \(0.003758 \times 8979 = 30.2\) children with Down syndrome would have been born in women of 36 years of age. By combining these data for each maternal age, it can be estimated that in 2000 401 children with Down syndrome would have been born in the absence of prenatal services. By dividing the estimated number of children with Down syndrome for each year of birth by the total annual number of children born in the Netherlands (CBS-data), and multiplying this with 10 000, we arrive at the annual natural birth prevalence per 10 000 births.
Step 2: actual live birth numbers and prevalence
We need data on selective terminations of pregnancies, available for instance from WPDT and NDSCR. Because the period between a prenatal diagnosis and birth is approximately half a year, we assumed that half of the children aborted in a particular calendar year, if not aborted, would have been born in that same calendar year and the other half in the next calendar year. If we want to know the actual number of Down syndrome births in for instance 2000, we need to know the number of selective TOP’s in 1999 and in 2000. We estimated that every 100 induced Down syndrome abortions leads to a net result of 73 prevented births of children with Down syndrome (if more details were available about maternal age at prenatal diagnosis and type of prenatal testing, we constructed a more precise correction factor, see the article). In the Netherlands for instance, in 1999 and 2000, 149 and 162 Down syndrome pregnancies were terminated, respectively. This implies that the net reduction of Down syndrome births in 2000 was around 0.73x ((149+162)/2) = 114 children. So the estimated actual number of Down syndrome births in 2000 would be 401-114 = 287. By dividing the estimated number of children with Down syndrome for each year of birth by the total annual number of children born in the Netherlands (CBS-data), and multiplying this with 10 000, we arrive at the annual actual birth prevalence per 10 000 births.

Step 3: population prevalence
For each year of birth we have estimated 1-, 5- and 10-year survival rates (for the 10-year rates, see figure 1). For instance of the 287 children born in 2000, 96% will still be alive in 2001 (1-year survival of 96%), 94% in 2005 and 93% in 2010 (267 children). The numbers for intermediary ages are extrapolated. For the survival above 10 years of age the curve in figure 2 is applied. For instance in 2020, of the children born in 2000 and still alive in 2010 (n=267), 94.4% (percentages taken from figure 2) will still be alive in 2020 (at age 20), 90.8% in 2030 and 76.3% in 2050 (204 persons). Using this same approach for each year of birth the number of persons still alive in following calendar years can be estimated. By adding up for each calendar year the estimated number of persons from preceding years that are still alive, and dividing this total by the total number of inhabitants (data from national statistical offices) and multiplying this with 10 000, we arrive at the estimated population prevalence per 10 000 inhabitants per calendar year.