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Estimation of the number of people with Down syndrome in the United States

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Purpose: An accurate accounting of persons with Down syndrome (DS) has remained elusive because no population-based registries exist in the United States. The purpose of this study was to estimate this population size by age, race, and ethnicity.

Methods: We predicted the number of people with DS in different age groups for different calendar years using estimations of the number of live births of children with DS from 1900 onward and constructing DS-specific mortality rates from previous studies.

Results: We estimate that the number of people with DS living in the United States has grown from 49,923 in 1950 to 206,366 in 2010, which includes 138,019 non-Hispanic whites, 27,141 non-Hispanic blacks, 32,933 Hispanics, 6,747 Asians/Pacific Islanders, and 1,527 American Indians/American Natives. Population prevalence of DS in the United States, as of 2010, was estimated at 6.7 per 10,000 inhabitants (or 1 in 1,499).

Conclusion: Until 2008, DS was a rare disease. In more recent decades, the population growth of people with DS has leveled off for non-Hispanic whites as a consequence of elective terminations. Changes in childhood survival have impacted the age distribution of people with DS, with more people in their fourth, fifth, and sixth decades of life.

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Key Words: births; deaths; Down syndrome; prevalence; trisomy 21

INTRODUCTION

Although Down syndrome (DS) is the most common single cause of intellectual disability, an accurate accounting of such persons in the United States has been elusive. Population prevalence data can be helpful in long-term planning for medical and social welfare.[1] The best option for obtaining these data would be a well-functioning national registration system of births and deaths of people with disabilities. However, only a few countries have established such systems, including Denmark,[1,2] Sweden,[3,4] and, to a more limited extent, the United Kingdom and Portugal.[5] No population-based registry exists for people with DS in the United States, although the need has been highlighted at national conferences.[6,7]

In a recent study, de Graaf et al.[8] used and validated an alternative approach for the United Kingdom, the Netherlands, and Ireland. In estimating population prevalence, the model uses maternal-age birth data in the general population, maternal age–related chances for a live birth with DS, data regarding elective terminations, and DS-specific mortality rates. Other researchers replicated this approach for England/Wales, with slightly different assumptions.[9]

In the United States, DS *birth prevalence* was estimated by de Graaf et al.[10] at 12.6 per 10,000 (or 1 in 792) as of 2010. However, only a few studies have estimated US *population prevalence*. Two previous US studies targeted the age group 0–19 years. For this age group, Shin et al.[11] estimated a population prevalence of 10.3 per 10,000 (or 1 in 971) as of 2002. Besser et al.[12] estimated 8.3 per 10,000 (or 1 in 1,205) as of 2003. Recently, Presson et al. adopted a strategy related to that of de Graaf et al.[8,13] For the period 1909–2007, the number of births of children with DS was estimated based on counts of births by maternal age. Presson et al.[13] adjusted for the effect of elective pregnancy terminations by assuming a constant rate of 13% reduction in live births with DS from 1980 to 2007. Additionally, they modeled the survival of people with DS using proportions of deaths by age obtained from death-certificate data from the Centers for Disease Control and Prevention.[13] Death-certificate data, however, might be unreliable for modeling the population size of people with DS. According to Presson et al.[13], there is underreporting of DS in death certificates. The authors further state that their "life table approach incorrectly assumes that the population size and the age-structure are constant over time."

In our study, we estimated the population size of DS in the United States by adapting the approach taken by de Graaf et al.,[8] modeling survival on the basis of mortality rates derived from historical studies and distinguishing our approach from that of previous researchers (**Table 1**).

MATERIALS AND METHODS

Live births

Estimated numbers of live births of children with DS in the United States by year for 1900–2010 were derived from previous work.[10]

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Table 1 Methodological differences between the current study and the study by Presson et al.[13]

	Current study	Study by Presson et al.[13]
Input	• For 1900–2010, estimates of number of births by maternal age, specified by ethnic group (CDC data and IPUMS-USA data). • From 1980 onward, counts of LB of children with DS in surveillance programs not specified by ethnic group (CDC data). • For 1998–2010, counts of LB of children with DS in surveillance programs specified by ethnic group (CDC data). • DS-specific mortality rates for different age groups from previous studies in the United States and in other developed countries (some US studies differentiating by ethnic group). • DS in US death-certificate data for 1968–2010 (CDC data).	• For 1909–2007, estimates of number of births by maternal age (CDC data). • DS in US death-certificate data for 1968–2007 (CDC data).
Method	• For 1998–2010, the number of LB of children with DS by ethnic group was estimated on the basis of counts in surveillance programs. • For 1969–1997, the number of LB of children with DS by ethnic group was estimated on the basis of maternal-age distribution in the general population and on the basis of trends in reduction percentages as constructed by de Graaf et al.[10] • For each year of birth, a different survival curve was constructed on the basis of the data from previous studies on survival in DS, thus taking into account the huge changes in 1-, 5-, and 10-year survival rates over time. In addition, specific curves were constructed for different ethnic groups. These survival curves were applied to the estimates of number of LB by ethnic group for the corresponding years of birth. • The number of foreign-born people with DS by ethnic group was estimated on the basis of death-certificate data by using the proportion of deaths (per birth decade) of foreign-born people with DS in the total number of deaths of people with DS by ethnic group/race, making use of the past 8 years for which this information was available (1997–2004).	• For 1909–2007, the number of LB of children with DS was estimated by applying a model of maternal age–specific chance for DS to counts of births by maternal age, adjusting for the effect of elective pregnancy terminations by assuming a constant rate of 13% reduction in LB with DS from 1980 to 2007. • One survival curve for all years of birth was constructed on the basis of the proportions of deaths by age in people with DS obtained from the two most recent years (2006–2007) of death-certificate data. This curve was applied to the estimated number of LB of children with DS for the different years of birth.
Output	• Estimation of the number of people with DS by age, ethnic group, and nativity (native-born or foreign-born) in 2010. • Estimated population prevalence of people with DS, as of 2010, by age group, ethnic group, and nativity. • Construction of historical changes in number of people with DS by age group, ethnic group, and nativity for 1950–2010. • Estimation of the effect of elective terminations of pregnancies on the population size of people with DS.	• Estimation of the number of (native born) people with DS by age in 2007. • Estimated population prevalence for (native born) people with DS in 2007.
Sensitivity analysis[a]	The results of the current model were compared with the results if survival had been modeled according to the models by de Graaf et al.[8] or Wu and Morris.[9] The current model estimated the total number of people with DS in the US (excluding foreign-born people with DS) to be 199,720; the model by de Graaf et al. estimated 192,456 (4% lower); the model by Wu and Morris estimated 205,089 (3% higher). The estimated age distribution of the three models was slightly different.	Presson et al. present four variant calculations for population size estimates: (i) using the two most recent years of death-certificate data (2006–2007), the population size was estimated to be 250,700; (ii) using the final 10 years of data (1998–2007) gave 241,000; (iii) using death-certificate data from 2006 to 2007 for births from 1970 to 2007 and death-certificate data from 1968 to 1969 for births from 1909 to 1968 estimated 180,400; and (iv) matching death-certificate years with birth-certificate years yielded 133,200.
Validation approach	All three models (the current model and those by de Graaf et al.[8] and Wu and Morris[9]) can be used to predict the number of deaths of people with DS by age group for different calendar years. These predictions were compared with the age distribution of people with DS in the death-certificate data of the CDC (1986–2010) by comparing the mean, 25th percentile, 50th percentile, and 75th percentile of these distributions for the corresponding calendar years. The current model has a better fit than both alternative models. In addition, the current model also fits well with the age distribution at death found in the death-certificate data, if analyzed in detail or by ethnic group.	As a validation approach, Presson et al. applied the same method to estimate the total US population. The population size estimates for the full US population for the four variants were (i) 258,832,900, (ii) 258,881,900, (iii) 240,870,100, and (iv) 236,617,200. The first method estimate was approximately 14.6% lower than the actual US population size, which was 302,977,371, but it gave the closest estimate.

CDC, Centers for Disease Control and Prevention; DS, Down syndrome; IPUMS-USA, Integrated Public Use Microdata Series–USA; LB, live births.

[a]Whereas Wu and Morris[9] in constructing 1-, 5-, and 10-year survival rates only included studies that followed a defined cohort of people with DS over time, de Graaf et al.[8] included a second type of study. In these eight additional studies, survival estimates were based on the difference between the population prevalence of a certain age group in the study compared with the estimated birth prevalence of the people in this age group. In our current model, like de Graaf et al., we utilized both types of studies. Second, de Graaf et al. assumed that the survival rate mentioned in a study applied to the most recent year of birth in the study because some researchers reported higher underregistration of neonatal mortality in DS at the beginning of their research period. By contrast, the model by Wu and Morris applied the survival rate to the midpoint of the study period and argued that this may be closer to the true survival rate in that birth cohort. In our current model, we followed this assumption of Wu and Morris.

Born after 1983: survival up to 20 years of age

We constructed 1-, 5-, 10-, and 20-year survival rates and interpolated survival between years based on the US survival rates from Kucik et al.[14] (**Supplementary Materials S1** online).

Born after 1983: survival to more than 20 years of age

For modeling survival beyond 20 years of age after 1983 (and for modeling survival of all ages before 1983), no comprehensive US studies are available. To fill the gap, we adapted the approach taken by de Graaf et al.[8] (**Supplementary Materials S1** online).

Born before 1983: survival up to 10 years of age

We adapted the approach of de Graaf et al., who used the results from multiple historical studies to estimate 1-, 5-, and 10-year survival rates[8] (**Supplementary Table S1** online and **Supplementary Material S1** online). **Figure 1** shows the 1-, 5-, and 10-year survival rates.

Born before 1983: survival over 10 years of age

For modeling survival beyond 10 years of age, de Graaf et al.[8] used data from four studies.[15–18] Wu and Morris[9] added two studies.[19,20] In our modeling of survival to more than 10 years of age before 1983 (and more than 20 years of age after 1983), we made use of the average of these very similar curves. Like de Graaf et al.,[8] we used a more hazardous survival curve based on the previous work of Penrose[21] for predicting the survival of cohorts born before 1940 until the calendar year 1950.

Predicting population prevalence

By combining the estimated numbers of births of people with DS in the United States by year with the constructed survival curves (**Supplementary Table S2A** online and **Supplementary Figure S1** online), we estimated the population prevalence and age distribution for each calendar year from 1950 onward.

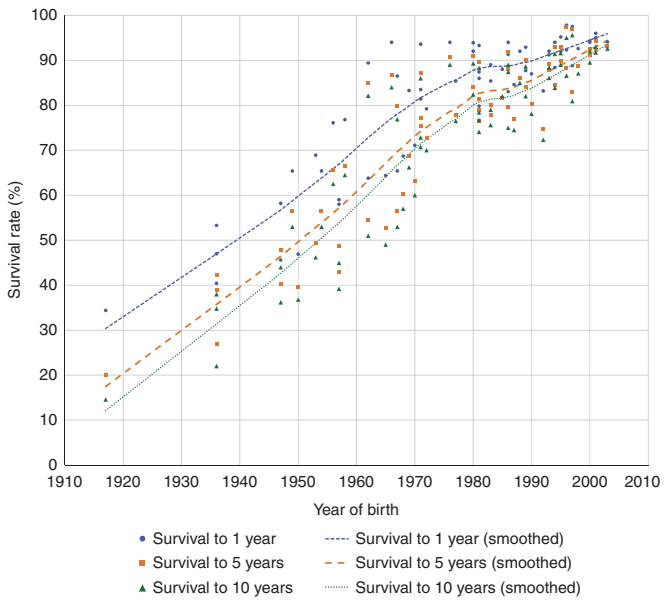

Figure 1 Estimates of 1-, 5-, and 10-year survival rates for children with Down syndrome, 1917–2003.

Predicting nonselective birth prevalence by race/ethnic group

Birth prevalence in the absence of DS-specific terminations of pregnancy ("nonselective birth prevalence") can be estimated on the basis of maternal-age distribution in the general population by following the strategy described by de Graaf et al.[10] (**Supplementary Materials S2** online). For the period 1900–2010, we constructed the nonselective number of births of children with DS for five groups: non-Hispanic whites (NHW), non-Hispanic blacks/Africans (NHB), Hispanics (HIS), Asians/Pacific Islanders (AS/PI), and American Indians/American Natives (AI/AN).

Predicting live birth prevalence by race/ethnic group

For the period 1998–2010, the number of live births of children with DS by race/ethnic group can be estimated based on counts in surveillance programs.[22–34] For the period 1969–1997, numbers of live births by ethnic group were extrapolated on the basis of trends in reduction percentages, as constructed by de Graaf et al.[10] (**Supplementary Materials S2** online).

Estimating survival by race/ethnic group

There is evidence that survival rates for children with DS differ by race/ethnic group.[14,35] Previously published data specify 1-year mortality rates by race/ethnic group and by birth cohort (1983–1987; 1988–1992; 1993–1997; 1998–2003).[14,36] Combining these data with the data of Wang et al.[35] for 1999–2007, we constructed 1-year mortality rates for NHB children with DS in 1985–2003. For the years before 1985 and after 2003, 1-year mortality rates for NHB were extrapolated (**Supplementary Materials S3** online).

Survival rates between 1 and 8 years are significantly lower for NHB children with DS than for NHW children with DS.[35] There is a significantly lower survival rate for NHB children with DS between 1–5 years and between 5–10 years.[14] Therefore, we constructed 5-year and 10-year rates separately for NHB and for all other races combined (**Supplementary Materials S3** online). We assumed that beyond the age of 10 years there would be no ethnic differences in survival rates. Finally, we also applied the survival curves for NHB to AI/AN because previous data suggested that 1-year survival for DS is highly similar in these two groups.[35]

Estimating the number of foreign-born people with DS

Death-certificate data indicate whether the deceased was native- or foreign-born.[37] We estimated the number of foreign-born persons with DS by using the proportion of deaths (per birth decade) of foreign-born people with DS for the total number of deaths of people with DS by ethnic group/race; we made use of the last 8 years for which this information was available (1997–2004).

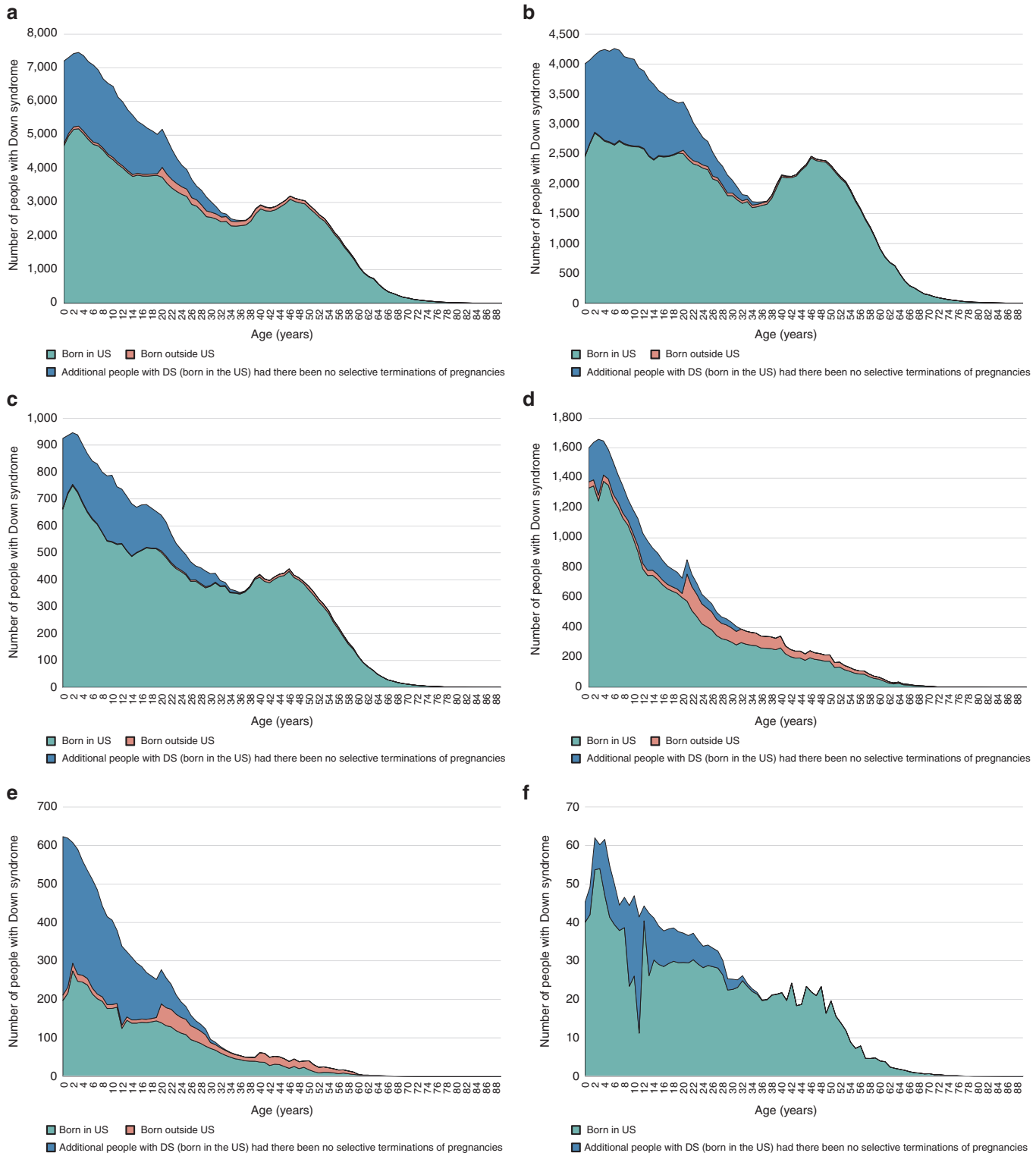

Figure 2 Estimates of the number of people with Down syndrome in the United States in 2010. The estimates are shown by age for (**a**) all persons, (**b**) non-Hispanic whites, (**c**) non-Hispanic blacks, (**d**) Hispanics, (**e**) Asians/Pacific Islanders, and (**f**) American Indians/American Natives. Because no foreign-born American Indian/American Native children were included in the death-certificate data for 1997–2004, we did not estimate foreign-born children for this group.

Validation

As a sensitivity analysis, we estimated outcomes for population prevalence if we had followed other assumptions, including those of previous researchers[8,9] (**Supplementary Materials S7** online). Our current model can be applied to predict the number of deaths of people with DS by age group in different calendar years. As validation, this predicted age distribution was compared with the age distribution of deaths of people with DS in death-certificate data (1968–2010).[37]

RESULTS

Numbers by age and ethnicity in 2010

Excluding foreign-born people, the number of people with DS in the United States, as of 2010, was estimated at 199,720, including 136,318 NHW, 26,827 NHB, 29,387 HIS, 5,663 AS/PI, and 1,527 AI/AN (**Figure 2** and **Supplementary Materials S4** online). In the absence of elective terminations, these predicted numbers would have been 245,981, including 167,992 NHW, 31,836 NHB, 33,620 HIS, 10,716 AS/PI, and 1,817 AI/AN. This corresponds with reductions in population prevalence related to elective terminations, which are estimated to be 19% for all people with DS, 19% for NHW, 16% for NHB, 13% for HIS, 47% for AS/PI, and 16% for AI/AN.

For each ethnic group, younger age groups tend to be larger and are most pronounced in HIS and AS/PI, thus reflecting the fast-growing number of births in these ethnic groups, in general, during the past decades. These age differences are largest for HIS. For AS/PI, the estimated number of live births in the younger age groups is considerably reduced by terminations of pregnancies (**Figure 2e**), whereas for HIS the estimated reduction percentages are relatively low (**Figure 2d**).

For most ethnic groups, there is a peak in predicted numbers at approximately 45 years of age consequent to the relatively large estimated numbers of births of children with DS in the 1950s and 1960s (**Supplementary Material S2** online) and the improvement in survival for young children with DS (**Supplementary Materials S1 and S3** online). For HIS and AS/PI, which are fast-growing immigrant groups, this peak is absent.

Including people born outside of the United States, our estimation of people with DS in the United States is 206,366, including 138,019 NHW, 27,141 NHB, 32,933 HIS, 6,747 AS/PI, and 1,527 AI/AN. Since the 1950s, a few people with DS immigrated into the United States (**Figure 2a**). They were predominantly HIS and AS/PI, and most were born in the 1970s and 1980s (**Figures 2d,e**).

For each ethnic group, including HIS and AS/PI, immigration of people with DS has had only a limited effect on the total predicted number of people with DS (**Figure 2**). However, as a result of immigration, the estimated numbers of births in the HIS and AS/PI groups, many of whom are young people in their fertile years, have increased rapidly over recent decades.

Historical development in numbers

The number of people with DS (including foreign-born) has shown a linear growth from an estimated 49,923 in 1950 to 206,366 in 2010 (**Figure 3a**). Growth has also been more or less linear for the NHB (**Figure 3c**) and AI/AN (**Figure 3f**) groups. Growth for NHW was linear between 1950 and 1975 but has leveled off in recent decades, mainly as a consequence of elective terminations. For HIS and AS/PI, the growth pattern is exponential (**Figure 3d,e**) because these two ethnic groups consist of many young people in their fertile years. For AS/PI, this exponential pattern would have been even stronger in the absence of the high estimated number of elective terminations in recent decades (**Figure 2e**).

Changes in childhood survival have had a substantial impact on the age distribution of people with DS (**Supplementary Materials S5** online). In 1950, only an estimated 27% were older than 20 years of age and 4% were older than 40 years compared with 57 and 28%, respectively, in 2010. However, for HIS and AS/PI—both of which are immigrant groups with many young people—these latter estimated percentages are lower. As of 2010, the percentages for HIS were 39 and 12% and those for AS/PI were 42 and 11%, respectively.

Population prevalence

Population prevalence of DS in the United States as of 2010 was estimated at 6.7 per 10,000 inhabitants (or 1 in 1,499). If only native-born people were included in the numerator and denominator, then population prevalence would be estimated at approximately 7.5 per 10,000 (or 1 in 1,328). In each ethnic group, the estimated population prevalence for foreign-born people is much lower, between 1 or 2 per 10,000 (**Supplementary Materials S6** online). In NHW, NHB, and AI/AN, the population prevalence including only native-born people (in the numerator and denominator) leads to slightly higher estimations of that population prevalence than those including both native- and foreign-born people. However, for HIS and AS/PI, this difference is large because the denominator is strongly influenced by excluding foreign-born people. For HIS, the population prevalence (as of 2010) including foreign- and native-born people is estimated at 6.5 per 10,000 (or 1 in 1,540); when only native-born people are included, it is estimated at 9.8 per 10,000 (or 1 in 1,020). For AS/PI, the corresponding values are an estimated 4.1 per 10,000 (1 in 2,410) and 10.1 per 10,000 (1 in 994), respectively. The values including only native-born people are relatively high for HIS and AS/PI because these immigrant groups consist of many relatively young people in their fertile years.

Using Integrated Public Use Microdata Series–USA estimates for population size,[38] including both native- and foreign-born people (in numerator and denominator), the total population prevalence of DS is estimated at approximately 12.7 per 10,000 (1 in 790) for 0- to 4-year-olds and decreases with age to an estimated 8.6 per 10,000 (1 in 1,169) for 20- to 24-year-olds, 6.4 per 10.000 (1 in 1,567) for 30- to 39-year-olds, 1.9 per 10,000 (1 in 5,273) for 60- to 69-year-olds, and to less than 0.1 per 10,000 (1 in 122,364) for those older than 80 years (**Supplementary Materials S6** online). Population prevalence for adults 18 years of age and older is estimated

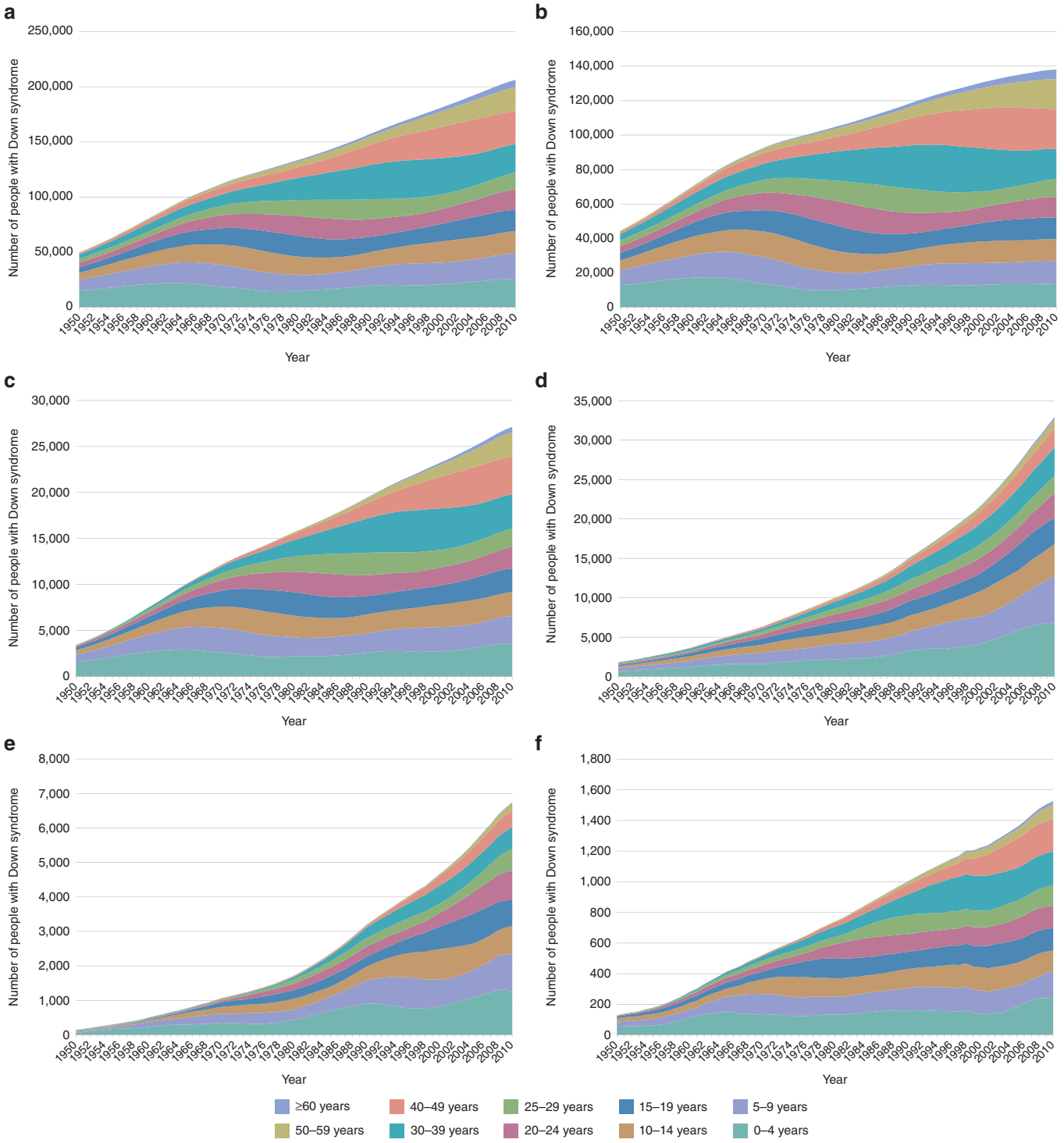

Figure 3 Estimates of the number of people with Down syndrome in the United States, 1950–2010. Estimates are shown by age for (**a**) all persons, (**b**) non-Hispanic whites, (**c**) non-Hispanic blacks, (**d**) Hispanics, (**e**) Asians/Pacific Islanders, and (**f**) American Indians/American Natives.

at approximately 5.3 per 10,000 (1 in 1,875; corresponding to a total estimate of 125,461 persons) in 2010. Including both native- and foreign-born people (in the numerator and denominator), the population prevalence for HIS and AS/PI seems to be lower than that for other ethnic groups, especially for those between 20 and 60 years of age. For HIS groups born before 1985 and for AS/PI groups born before 1995, excluding foreign-born people (from the numerator and denominator) makes a huge difference, leading to estimates 1.5 to 6 times higher and to values of population prevalence by age group that are much more similar to those for other ethnicities.

Historical development in population prevalence

Before 1970, the United Kingdom appeared to have a slightly lower estimated population prevalence in the absence of terminations than did the United States; however, this was reversed after 1980 (**Supplementary Materials S6** online). In comparison to the United States, the effect of elective terminations on population prevalence in the United Kingdom has been more pronounced in recent years. In the United States, in 1995, there were an estimated 8% fewer people with DS than there would have been without elective terminations, and this value increased to approximately 19% in 2010. In the United Kingdom, the corresponding estimated values were 10 and 26%, respectively. As a result, the modeled DS population prevalence is approximately 6.7 per 10,000 in the United States (1 in 1,499) and 6.4 per 10,000 in the United Kingdom (1 in 1,553) as of 2010. In comparison, historically and currently, the Netherlands has considerably higher estimated population prevalence in the absence of elective terminations. The impact of elective terminations on population prevalence is similar to that in the United States, rising from an estimated 5% fewer people with DS as a result of elective terminations in 1995 to 15% as of 2010. The population prevalence of DS in the Netherlands was estimated at approximately 8.2 per 10,000 (1 in 1,223) as of 2010.

Sensitivity analysis and validation

We compared the results of our current model with the results of survival modeled according to the models by de Graaf et al.[8] and Wu and Morris,[9] respectively (**Supplementary Materials S7** online). Our current model estimated the total number of people with DS (excluding foreign-born people with DS) to be 199,720. The model by de Graaf et al.[8] estimated that number to be 192,456 (4% lower), and Wu and Morris's model[9] estimated 205,089 (3% higher). The age distributions are slightly different. In the age range of 0–20, the model by de Graaf et al. predicts higher numbers than the current model[8] and the model by Wu and Morris predicts lower numbers.[9] However, between ages 25 and 59 years, this pattern reverses. For those more than 60 years of age, both alternative models predict lower numbers than the current model does.

In **Supplementary Materials S7** online, the age distribution at death of people with DS, as predicted by the three models, is compared with the age distribution of people with DS in the death-certificate data (1986–2010)[37] by comparing the mean, 25th, 50th, and 75th percentiles of these distributions for the corresponding calendar years.

DISCUSSION

Previously, Presson et al.[13] predicted the best estimate of native-born people with DS in the United States to be 250,700. Our estimates are considerably lower at 206,366 (which includes people born outside the United States) and 199,720 (which excludes those individuals). Up to 20 years of age, model differences can be explained mainly by the input of different live birth numbers. For recent years, we based our estimates on counts in surveillance programs, whereas Presson et al.[13] estimated the number of expected births in the absence of terminations, and adjusted these by an assumed rate of 13% reduction from 1980 onward. For ages more than 30 years, as a result of using different survival curves, our model predicts considerably lower numbers than Presson et al did. Both models predict a peak at approximately 45 years of age. However, in the work by Presson et al., this peak occurs for approximately 4,600 people; in our model, it occurs for approximately 3,200 (30% lower). In summary, the models differ in both total number and estimates for specific age groups.

De Graaf et al.[10] previously demonstrated that systematic changes of some input variables had only limited outcome effects on the constructed birth rates. Regarding survival rates, we compared the results of our current model with those of two alternatives: those of de Graaf et al. and those of Wu and Morris (**Supplementary Materials S7** online).[8,9] Prediction of the total number of people with DS is only slightly different; however, there are differences in the predicted age distribution. As validation, we compared the age distribution at death for people with DS as predicted by these models with this age distribution in the death-certificate data (**Supplementary Material S7** online).[37] Our current model has a better fit than both alternatives. In addition, our current model also fits very well with the age distribution in the death-certificate data, if analyzed in detail (**Supplementary Figure S7C** online) or by ethnic group (**Supplementary Figure S7D** online).

Without a valid estimate of DS population size by age group, it is impossible to construct reliable survival rates on the basis of death-certificate data. Presson et al.[13] circumvented this problem by assuming a constant size of the birth cohorts of children with DS over time—and a constant rate of childhood survival—thus constructing an approximation with the same survival curve for each year of birth. By contrast, we constructed both population size by age and differential survival curves for each year of birth using other sources of information (**Table 1**). Subsequently, our model was used to predict the age distribution at death for people with DS, which as a validation was compared with the actual age distribution in the death-certificate data, assuming that underreporting of DS is similar for different age groups. This last assumption might not be entirely true; however, the close fit in age distribution at death between our model and the death-certificate data seems to support the notion that these two approaches validate each other.

DS has changed from a predominantly childhood disability in the 1950s, with only an estimated 27% older than 20 years of age and 4% older than 40 years, to a disability that also affects many people in older age groups. As of 2010, approximately 57% were older than 20 years and an estimated 28% older than 40 years. However, for HIS and AS/PI, both of which are fast-growing immigrant groups with many young people, these latter percentages are lower. The substantial growth in the number of adults and elderly people with DS living in the United States indicates the importance of advocating adult- and senior-specific services and research.

In contrast to the work by Presson et al.,[13] our study offers a detailed picture of the changing ethnic composition of the population of people with DS. For each ethnic group, the direct effect of immigration of people with DS is small. However, as a result of immigration of many HIS and AS/PI people in their fertile years, the estimated number of births (of children with and without DS) in these two groups has increased substantially in recent decades. Consequently, the estimated percentage of young HIS and AS/PI people with DS has increased, whereas the percentage of young NHW people with DS has decreased (**Supplementary Figure S4B** online), mainly reflecting the change in the ethnic composition of the United States, in general, and—to a lesser extent—ethnic differences regarding elective terminations. We consider it important to differentiate between ethnic groups because our model negates the, perhaps, "easy" assumption that population prevalence by age group will be more or less similar for all ethnic groups.

As a consequence of elective terminations, the (native-born) population of DS had been reduced by an estimated 19% as of 2010. This effect is lower than that in the United Kingdom (26%) and slightly higher than in the Netherlands (15%). Although the effect of elective terminations on the number of people with DS in the US population is limited, large ethnic differences exist. The reduction of the number of (native-born) people with DS, consequent to elective terminations, is as low as an estimated 13% for HIS and as high as an estimated 47% for AS/PI, reflecting the large ethnic differences in reduction percentages of births in recent decades, as explored by de Graaf et al.[10] Noninvasive prenatal screening with cell-free DNA was introduced in the United States at the end of 2011; it remains an open question how many more elective terminations will result from expanded prenatal diagnoses.

The historical changes in age distribution in the DS population are due in part to longer adulthood survival after 1950. However, the most substantial explanation is the ever-increasing survival of young children with DS over the past 100 years. This has led to increasing mean and median life expectancy rates, which have risen from an estimated 26 years (mean) and 4 years (median) in 1950 to 53 years (mean) and 58 years (median) in 2010 (**Supplementary Figure S3B** online). There are also some ethnic differences in life expectancy. For NHB (and AI/AN), estimates of mean and median life expectancy were slightly lower, at 22 and 2 years, respectively, in 1950 and 50 and 57 years in 2010.

Importantly, there is a difference between "life expectancy" and "mean age of death." Life expectancy is the prediction of how many years a person born in a specific year will probably live, whereas mean age of death is the average age of death in the calendar year under observation. Mean age of death is strongly influenced by the age distribution of people living in the specific population, which is a result of the relative sizes of birth cohorts and of historical childhood survival rates within these cohorts. According to our model, the mean and median age of death also increased, and even more rapidly, from an estimated 3 and 0 years, respectively, in 1950 to 12 and 2 years in 1970 to 35 and 38 years in 1990 to 48 and 54 years in 2010 (**Supplementary Figure S7B–D** online), similar to the rapid changes in age of death found in death certificates by Yang et al.[39] and Presson et al.[13] for the United States and by Englund et al.[40] for Sweden.

In comparison to the differences in life expectancy, ethnic differences in age of death are much more pronounced (**Supplementary Figure S7D** online) because this construct is influenced not only by differences in age-specific survival at that moment of time but also by the age distribution of the living population. Therefore, the substantial differences in the historical development of age of death by ethnicity, as found in the death certificates[37] by other researchers,[39] only partly reflect real differences in survival rates at the time.

One important consequence of our results is the identification of DS as a rare disease according to the definition of the Rare Diseases Act of 2002. Including foreign-born people, estimations up to 2008 were less than 200,000. Excluding foreign-born people, estimations for all years were less than 200,000. Furthermore, DS is no longer a childhood disability. Within the United States, there are many adults with DS and the estimated median life expectancy is now approaching 58 years.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

DISCLOSURE

B.G.S. serves in a nonpaid capacity on the board of directors or scientific advisory boards for the Massachusetts Down Syndrome Congress, the Band of Angels Foundation, and the National Center for Prenatal and Postnatal Down Syndrome Resources (all nonprofit organizations). B.G.S. is codirector of the Massachusetts General Hospital Down Syndrome Program and occasionally gets remunerated by Down syndrome nonprofit organizations for speaking engagements about Down syndrome. He receives support for clinical drug trials involving people with Down syndrome from Hoffmann–La Roche, Inc. He has a sister with Down syndrome. G.G. works for the Dutch Down Syndrome Foundation, a nonprofit organization. He had a daughter with Down syndrome who passed away in 2005 at the age of 15. F.B. works for Down Syndrome Education International and Down Syndrome Education USA. The charities receive donations and grants from individuals and organizations to conduct research and develop resources and services to improve early intervention and education for children with Down syndrome. He also serves in an unpaid capacity as vice president of the European Down Syndrome Association and as member of the Professional Advisory Committee of the US National Center for Prenatal and Postnatal Down Syndrome Resources. He has a sister with Down syndrome. The other authors declare no conflict of interest.

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