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Estimation of live birth and population prevalence of Down syndrome in nine U.S. states

Gert de Graaf[1] | Frank Buckley[2,3] | Jennifer Dever[4] | Brian G. Skotko[4,5]

[1] Dutch Down Syndrome Foundation, Meppel, The Netherlands

[2] Down Syndrome Education International, Kirkby Lonsdale, Cumbria, UK

[3] Down Syndrome Education USA, Newport Beach, California

[4] Down Syndrome Program, Division of Medical Genetics, Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts

[5] Department of Pediatrics, Harvard Medical School, Boston, Massachusetts

Correspondence
Brian Skotko, MD, MPP, Down Syndrome Program, Division of Medical Genetics, Department of Pediatrics, Massachusetts General Hospital, 125 Nashua Street, Suite 821, Boston, MA 02114.
Email: bskotko@mgh.harvard.edu

For all of the U.S. states with sufficient data, we estimated live birth and population prevalences for Down syndrome (DS). As social service resources vary between states, such data are important for public policy discussions and state planning. We predicted the actual and nonselective live birth prevalence, and population prevalence, for DS in nine U.S. states based on publicly available datasets from the Centers for Disease Control and Prevention and the Integrated Public Use Microdata Series. As of 2010, we estimated a population size for people with DS of 4,554 in MA (population prevalence 1 in 1,440), 6,101 in NJ (1 in 1,443), 14,315 in NY (1 in 1,355), 9,739 in IL (1 in 1,319), 4,354 in IN (1 in 1,491), 7,295 in MI (1 in 1,354), 9,099 in FL (1 in 2,071), 3,014 in KY (1 in 1,442), and 3,596 in AZ (1 in 1,784). The number of people living with DS has steadily increased from 1950 until 2010 in these nine U.S. states. Population prevalence would have been higher absent DS-related elective terminations. Racial and ethnic groups, other than non-Hispanic whites, comprise a growing proportion within these DS communities, particularly among younger-aged persons.

KEYWORDS
Down syndrome, epidemiology, health policy, population health, prevalence, trisomy 21

1 | INTRODUCTION

As noninvasive prenatal testing expands within the United States, Down syndrome (DS) has been placed under an epidemiological microscope. Previous studies have suggested that around 74% of expectant parents in the U.S. who learn of a DS diagnosis prenatally choose to terminate (Natoli, Ackerman, McDermott, & Edwards, 2012). However, many expectant couples choose not to pursue prenatal screening or diagnostic testing altogether. As a consequence of elective terminations, de Graaf, Buckley, and Skotko (2015) estimate there was an overall 30% reduction in the numbers of babies with DS that could have been born in 2006–2010. During this period, the United States had about 3,100 DS-related elective pregnancy terminations and 5,300 live births with DS annually (de Graaf et al., 2015).

At the same time, thanks to advances in medical care, the median life expectancy for people with DS has been rising in the United States from an estimated 4 years in 1950 to 58 years in 2010 (de Graaf, Buckley, & Skotko, 2016a). Taking this into consideration, de Graaf et al. (2016a) estimated that the number of people with DS living in the U.S. (including those foreign born) grew from 49,923 in 1950 to 206,366 in 2010. To date, only one study has reported the number of live births, terminations, and natural losses (miscarriages and stillbirths) with DS for an individual state (de Graaf, Buckley, & Skotko, 2016b). De Graaf et al. (2016b) estimated the live birth prevalence for DS in Massachusetts at 12.4 per 10,000 live births for 2006–2010. As of 2008, the estimated reduction rate as a consequence of DS-related elective pregnancy terminations was 49%.

In this current study, we extend these analyses to all of the remaining U.S. states that have sufficient data. Estimates of live birth and population prevalence are important for public policy discussions and state planning. Non-profit DS advocacy groups also benefit from accurate data so that outreach efforts can be measured and targeted. Further, as prenatal testing becomes more widespread, having solid baseline data enable future trends within states to be appreciated and compared. In our study, we analyze state data by racial/ethnic groups and by age. We then ask which epidemiological factors—age of

mothers, reduction rates by terminations, age structure of the general population, interstate migration of people with DS, and/or interstate migration in general population—might account for any variations between states?

2 | MATERIALS AND METHODS

Technical terms used in this paper are defined in Table 1.

2.1 | Estimating nonselective live birth prevalence

Nonselective live birth prevalence for DS is the live birth prevalence that would have occurred in the absence of DS-related elective terminations. Following the method of de Graaf et al. (2015 and 2016a, 2016b), we estimated the number of nonselective births of children with DS on the basis of the maternal age distribution in the general population. Data on births by state, maternal age, and maternal ethnic group are available from the Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention, 2015, 2016c). For years in which CDC data were not available, we used data from the 1850–2013 sample in the Integrated Public Use Microdata Series (IPUMS-USA) (Ruggles, Genadek, Goeken, Grover, & Sobek, 2015). Details on the sources and procedures can be found in Supplementary Materials S1.

2.2 | Estimating actual live birth prevalence

For recent years, data on number of live births of children with DS by ethnic group are available in the reports of U.S. Birth Defects Surveillance Programs as 5-year running averages (National Birth Defects Prevention Network, 2003, 2004, 2005, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015; National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 2006). For some states, elective terminations are included; as these are not specified separately, we could not use these data. Some programs counted in natural loss (i.e., miscarriages and stillbirths); we corrected for these assuming that natural losses constituted around 4% of the sum of live births and natural loss on the basis of data of three programs (Texas, Utah, and Georgia), which enumerate these details (International Clearinghouse Centre for Birth Defects, 2010). To summarize, for our purpose, a state must collect the number of live births with DS, distinguishable from terminations with DS, over a period of time. In addition, we excluded programs with an entirely passive surveillance approach. Data from 41 states were either insufficient—that is, not meeting the criteria above—or altogether lacking. Ultimately, there were nine U.S. states for which we could obtain the relevant data on live births with DS for a substantial number of years (Supplementary Table S1). For the period of time before data were available from these programs, we interpolated the reduction percentage (i.e., the reduction in live births as a result of elective terminations). We followed de Graaf et al. (2015) in modeling a reduction percentage of 0% before 1968, 0.5% for 1969, 5% in 1978, and 10% in 1980. De Graaf et al. (2015) found a linear increase of reduction percentage between 1980 and 1996. Reduction percentage was more or less stable from 1996 onward (de Graaf et al., 2015). Between 1980–1996, we modeled a linear increase in reduction percentage for each ethnic group separately (Supplementary Materials S2 and Figure S1). Applying these reduction percentages to the estimated numbers of nonselective births yields the estimates of the number of actual live births with DS by ethnic group and U.S. state (Figure 1).

2.3 | Modeling survival

On the basis of historical studies on survival in DS, de Graaf et al. (2016a) constructed and validated a model with different survival curves for people with DS for each year of birth. These researchers also constructed separate curves for Non-Hispanic Blacks (NHB) and American Indians/American Natives (AI/AN) (with a lower survival) versus Non-Hispanic Whites (NHW), Hispanics (HIS), and

TABLE 1 Definition of terms

Actual live birth prevalence	Number of live births with DS per 10,000 live births in general population
Actual population prevalence	Number of people with DS alive per 10,000 people in general population
DS-related elective termination	Termination of pregnancy after a prenatal diagnosis of DS
Mean age at death	Average age of people who died in a specific calendar year
Median life expectancy	Number of years that half of the people from a specific year of birth are expected to live
Nonselective live birth prevalence	Modeled number of live births with DS per 10,000 live births in general population that would be expected in absence of DS-related elective terminations
Nonselective population prevalence	Modeled number of people with DS alive per 10,000 people in general population that would be expected if there had been no DS-related elective terminations
Reduction rate	Net effect of screening: $\left(\frac{\text{nonselective prevalence}-\text{actual prevalence}}{\text{nonselective prevalence}}\right) \times 100\%$
Termination rate	Percentage of expectant parents opting for elective termination after a prenatal diagnosis of DS: $\left(\frac{\text{number of DS-related terminations}}{\text{number of prenatal diagnoses of DS}}\right) \times 100\%$

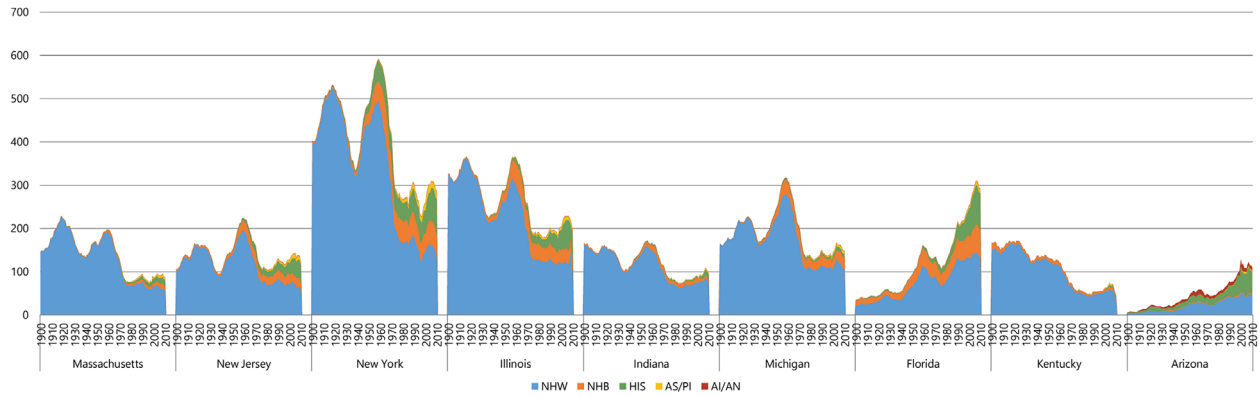

FIGURE 1 Live births: Estimates of the number of actual live births of children with DS by state and ethnicity. NHW, non-Hispanic whites; NHB, non-Hispanic blacks; HIS, Hispanics; AS/PI, Asians/Pacific Islanders; AI/AN, American Indians/American Natives. [Color figure can be viewed at wileyonlinelibrary.com]

Asian/Pacific Islanders (AS/PI). As survival of children with DS might be associated to survival of children in the general population, we checked to see if there were considerable differences in 1-year mortality in the general population between the nine U.S. states under observation (Supplementary Materials S5 and Figure S6) (Centers for Disease Control and Prevention, 2015, 2016).

2.4 | Modeling interstate migration

To estimate the effect of interstate migration, we used data on DS from the Death Certificate Files 1997–2004 (National Center for Health Statistics, Centers for Disease Control and Prevention, 2015), as these are the last 8 years in which data on state of birth and state of residence were available. In a stepwise procedure, which is described in Supplementary Materials S6, we combined these data with data for all people (with or without DS) in the Death Certificate Files (1997–2004) (National Center for Health Statistics, Centers for Disease Control and Prevention, 2015) and with data from the Integrated Public Use Microdata Series (IPUMS-USA) (Ruggles et al., 2015) for the census year 2000 and 2010 of people alive in the general population. Following the procedure described in Supplementary Materials S6, we estimated the numbers of births of children with DS by state, ethnic group, and year of birth corrected for migration, which we subsequently used as an input in our model. In this approximation, we assume that interstate migration usually occurs shortly after birth, which, of course, is not always the case, though we would expect migration to be higher in families with a young child with DS than it would be in adults with DS. In general, people with DS are more dependent on support from family and professionals than people without an intellectual disability. If they migrate, this typically will be with their parents and not often independently. Additionally, the social network of people with intellectual disability is more vulnerable. We would expect that parents of teenagers or adults with DS would be more hesitant to migrate and disrupt their child's social network, which was undoubtedly cultivated over many years. However, if this assumption of migrating at a young age would be false, this would have no influence on the estimates as of 2010. It would have a small effect on the estimates of population numbers of DS for earlier years—that is, our modeled estimates for net immigration states would be slightly too high for these earlier years, as the influx of some of the migrators with DS would have been later in time.

2.5 | Validating the model

The model can be used to predict numbers of deaths of people with DS by age and year of occurrence. Following the method of de Graaf et al. (2016a), we compared the age distribution of these deaths (by state) to the corresponding age distributions found in the Death Certificate data of CDC (National Center for Health Statistics, Centers for Disease Control and Prevention, 2015).

3 | RESULTS

3.1 | Nonselective and actual live birth prevalence

As of 2010, in all nine states combined, there were an estimated 1,386 live births with DS, corresponding to an actual live birth prevalence of 1 in 824. Estimates of actual live birth prevalence by state range from 1 in 729 in FL to 1 in 1256 in KY. As of 2010, in all nine states combined, we estimated the reduction percentage at 39%, ranging from 26% in IN and MI to 52% in NJ. Put another way, without DS-related terminations, in all nine states combined, we estimate there would have been 898 additional live births. Results by state are summarized in Table 2.

The estimates of the number of actual live births with DS by ethnic group and U.S. state are presented in Figure 1, with ethnic distribution as percentages in Supplementary Figure S2. The historical development of nonselective and actual live birth prevalence estimates is presented in Figure 2. Before 1985, differences between the nine states in nonselective live birth prevalence were not large (~±10%) compared to the average (Figure S3 and S4 in Supplementary Materials S3). However, after 1985, these differences begin to widen, reaching about ±25–30% in the 2000s (Figure S4). This is a result of differences

TABLE 2 Estimates of live birth prevalence of children with DS in 2010

State	Actual DS LBs	Actual DS LB prev. per 10,000	Actual DS LB prev. as 1 in X	LB reduction rate (%)	Prevented LBs	Nonselective LB prev. per 10,000	Nonselective DS LB prev. as 1 in X
MA	87	12.0	833	51	91	24.6	407
NJ	121	11.3	882	52	133	23.8	420
NY	287	11.8	844	49	274	23.2	432
IL	199	12.0	832	38	124	19.5	513
IN	97	11.5	871	26	34	15.5	645
MI	148	13.0	770	26	51	17.5	573
FL	294	13.7	729	27	111	18.9	529
KY	44	8.0	1256	47	39	15.0	666
AZ	109	12.5	797	27	41	17.3	579
All 9 states	1386	12.1	824	39	898	20.0	500

Actual DS LBs: Actual number of livebirths of children with DS.
Actual DS LB prev. per 10,000: Actual livebirth prevalence per 10,000 livebirths.
Actual DS LB prev. as 1 in X: Actual live birth prevalence as 1 in X.
LB reduction rate: Net effect of elective terminations—that is, prevented LBs divided by (Actual DS LBs + prevented LBs) multiplied by 100%.
Prevented LBs: Number of extra children with DS that would have been born, absent elective terminations.
Nonselective LB prev. per 10,000: Nonselective livebirth prevalence per 10,000 livebirths.
Nonselective LB prev. as 1 in X: Nonselective live birth prevalence as 1 in X.

in maternal ages between states (Supplementary Materials S3), as nonselective live birth prevalence is explained fully by maternal age distribution alone.

The direct effect of elective terminations in recent decades on the total number of people with DS within population varies between U.S. states. According to our model, the reduction of population size of people with DS in the nine states was around 22%, ranging from around 11% in KY, 15% in IN and MI, 16% in AZ, 20% in IL, 21% in FL, 26% in NY, 29% in NJ, and 30% in MA. There are also ethnic differences. The highest impact was for AS/PI (51% reduction), followed by NHW (22%), NHB (21%), HIS (17%), and AI/AN (4%). These percentages do not directly refer to the reduction in live births, but are the estimates of the net effect of the reduction in live births on population numbers. So, for example, in MA, the reduction of live births is estimated at 51% as of 2010; whereas for 2010, the reduction of population size of people with DS in MA as a result of DS-related elective terminations in recent decades is around 30%.

Though the direct net effect of reduction of births with DS as a result of DS-related elective terminations is relatively strong, this effect tends to be far stronger in U.S. states with a relatively high nonselective live birth prevalence (linked to advanced maternal ages) (Figures 2 and S1). As a result, the differences between states' actual live birth prevalences for DS are much less pronounced (Figures S3, S4, and S5), around ±10–12% for most years.

3.2 | Effects of differences in survival between states

As some differences exist between U.S. states in the ethnic composition of live births with DS (Figures 1 and S2), the differential survival—particularly in NHB and AI/AN versus the other ethnic groups— will have some effect on population prevalence. However, this effect is very small (Supplementary Materials S5).

When compared with the other eight states, AZ had a much higher 1-year mortality for the general population before 1950. Therefore, we

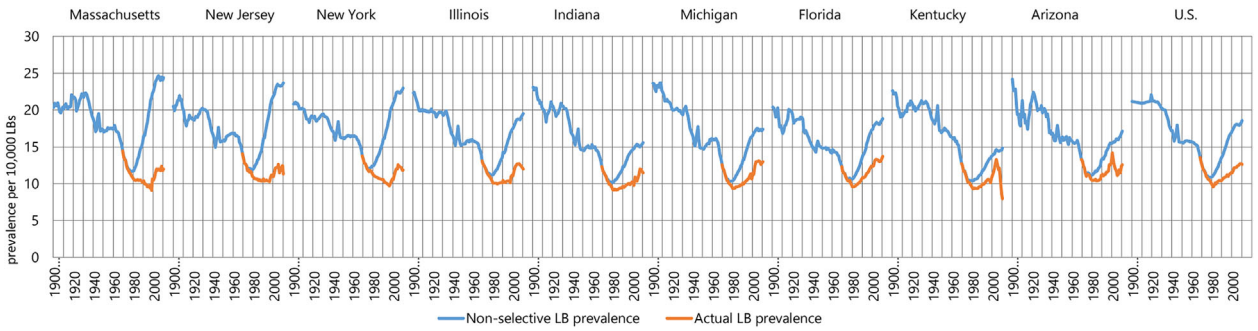

FIGURE 2 Nonselective and live birth prevalence (per 10,000) estimates. LB, live birth. [Color figure can be viewed at wileyonlinelibrary.com]

constructed differential survival curves for people with DS in AZ (Supplementary Materials S5). Applying these curves would have led to a 0.4% lower prediction of the number of people with DS in AZ as of 2010.

3.3 | The effects of interstate migration

For most U.S. states, the direct effect of interstate migration of people with DS on the number of people with DS living in that state is small (Supplementary Materials S7). For all ethnic groups combined, our correction for interstate migration of people with DS leads to a 13% higher estimate of the population number of people with DS in AZ and FL, and less than 3% difference for the other states under observation. For HIS—in comparison to NHW, NHB, and AI/AN—the correction leads to relatively higher estimates of the population number for all states under observation, varying from +6% in MI, +7% in NY, +25% in KY, and +28% in FL. HIS are a relatively young ethnic group in the U.S, both in regards to time of immigration and age distribution. The AS/PI group shows a similar picture with percentages between +25% for IN to +60% for AZ.

Whereas the direct effect of interstate migration on the population of people with DS is very small for most states (and relatively small even for AZ and FL)—and for most ethnic groups (with the exception of HIS and AS/PI)—interstate migration in the general population has strong indirect effects on population prevalence. We estimated population prevalence in two different ways. In the first "uncorrected" way, we use the estimated number of people with DS alive in 2010 and born in a specific U.S. state (i.e., not corrected for migration) as the numerator and the number of people living at large in general population but born in that specific state as the denominator. In the second way where we correct for migration, we use the estimated number of people with DS living in that state as the numerator (i.e., corrected for migration) and the number of people, in general, living in that U.S. state as the denominator (Supplementary Figures S8A and S8B).

Interestingly, the non-corrected estimates (for all ethnic groups combined) are more or less the same for most U.S. states, with around seven people with DS per 10,000 inhabitants. Only AZ (9.6 per 10,000) and FL (8.9 per 10,000) have clearly higher estimates. This is not due to higher live birth prevalence estimates for DS in these states (Figures 2 and S9). It results from AZ and FL being net immigration states. The children born after immigration count as being born in that specific state, whereas their parents were not born in that state, and consequently are not counted as such. This results in a higher total population prevalence of people with DS (if uncorrected for interstate migration). The same phenomenon is found for the Hispanic group (Figure S8b), and the AS/PI group.

When we correct for interstate migration, the high estimates of population prevalence in immigration states and in ethnic immigration groups drop, as the denominator (i.e., people in general) is much more strongly influenced by this correction than the numerator (i.e., people with DS). The population prevalence for DS in most U.S. states is relatively unchanged by this correction (Figure S8a). However, in the immigration states of AZ and FL, these estimates drop to 5.6 per 10,000 and 4.8 per 10,000, respectively. The same phenomenon applies to the HIS group (and the AS/PI group), which is a young immigrant group. Furthermore, this correction has the most pronounced effect in AZ and FL on the estimates of population prevalence by age for the age groups above 25 years (Supplementary Figures S9 and S10 and Figure 3). If, in contrast, the population prevalence estimates increase after correction, there is a net emigration of people in general population from that state, as is the case for the NHW group in MA, NY, IL, and MI (Figure S8b).

3.4 | Estimates of the number of people with DS by age, ethnicity, and U.S. state, corrected for migration

In Figure 4a, we present the number of people with DS in U.S. states, as of 2010, by age and ethnicity, corrected for interstate immigration in the process detailed previously. Figure 4b presents the estimates for the U.S. as a whole. The excel file with the information from this Figure can be downloaded as a Supplementary material (file: "Supplement estimates for Figure 4"). Comparison data from the U.S., as a whole, were used with permission from the same authors' previous publication (de Graaf et al., 2016a). As of 2010, our model results in an estimated population size for people with DS of 62,067 in all nine states combined, corresponding to a population prevalence of 1 in 1,508. Estimates of actual population prevalence by state range from 1

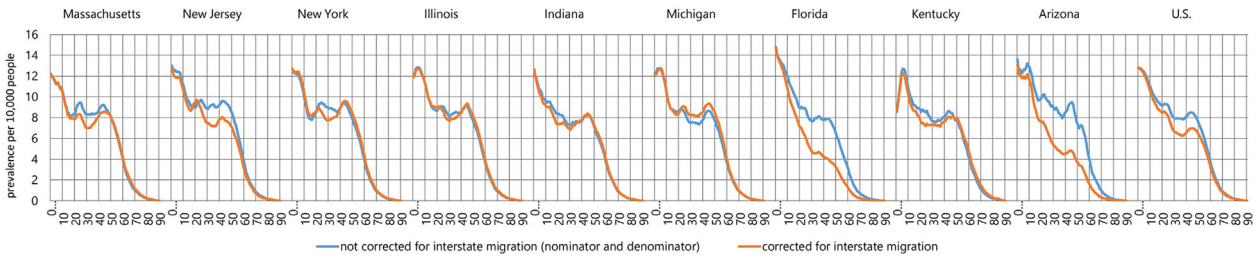

FIGURE 3 Population prevalence (per 10,000) estimates of DS by age (in years) and state as of 2010. "Not corrected" values result from taking the estimated number *born* in a state as the numerator (DS) and denominator (general population); "corrected" values result from taking the estimated number *living* in a state as numerator (DS) and denominator (general population). For the U.S. as a total, not corrected values result from taking the estimated number *born* in the U.S. as the numerator (DS) and denominator (general population); corrected values result from taking the estimated number *living* in the U.S. as numerator (DS) and denominator (general population). Denominators are based on the Integrated Public Use Microdata Series (IPUMS-USA) (Ruggles et al., 2015). [Color figure can be viewed at wileyonlinelibrary.com]

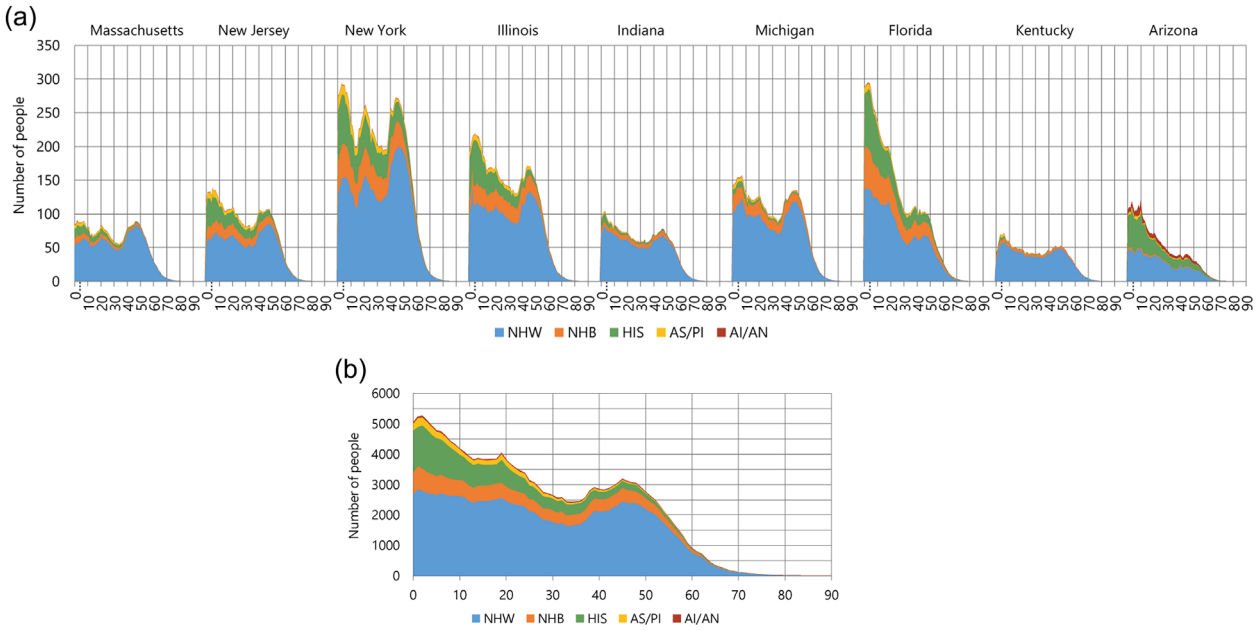

FIGURE 4 (a) State population numbers: People with DS in 9 states by age (in years) and ethnic group (as of 2010) corrected for interstate migration. "Corrected" values result from taking the estimated number *living* in a state as numerator (DS) and denominator (general population). NHW, non-Hispanic whites; NHB, non-Hispanic blacks; HIS, Hispanics; AS/PI, Asians/Pacific Islanders; AI/AN, American Indians/American Natives. (b) U.S. population numbers: People with DS in the U.S. by age (in years) and ethnic group (as of 2010) including foreign-born persons. NHW, non-Hispanic whites; NHB, non-Hispanic blacks; HIS, Hispanics; AS/PI, Asians/Pacific Islanders; AI/AN, American Indians/American Natives. [Color figure can be viewed at wileyonlinelibrary.com]

in 1,319 in IL to 1 in 2,071 in FL. By comparison, de Graaf et al. (2016a) estimated 206,366 people with DS in the U.S. as a whole (1 in 1,499). Results by state are summarized in Table 3.

3.5 | Historical development of the numbers and population prevalence for DS

In Supplementary Materials S9 and S10, we elaborate upon the historical development in numbers and population prevalence. Figure 5a presents the estimates of the number of people with DS by age and by state for the period 1950–2010. Figure 5b presents the estimates for the U.S. as a whole. The information for this Figure can be found as a Supplementary material (file: "Supplement estimates for Figure 5"). In this file, we also present the historical development for each ethnic group separately. Comparison data from the U.S., as a whole, were used with permission from the same authors' previous publication (de Graaf et al., 2016a). In most states, the increase in numbers of people with DS plateaus in recent decades. However, in the immigration states AZ and FL, the increase does not level off (Figure 5). Many young people in their fertile years move into these immigration states, as interstate migration in the United States is relatively high in young adults (Hernandez-Murillo, Ott, Owyang, & Whalen, 2011; Mateyka, 2015; Ruggles et al., 2015). This leads to more births and, thus, to more births of children with DS. The same phenomenon can be observed in the young immigrant groups (HIS and AS/PI).

In seven out of the nine U.S. states, population prevalence has increased from around 3 per 10,000 inhabitants (4 in KY) in 1950 to values between 6.5 and 7.5 per 10,000 as of 2010 (Supplementary Figure S11). However, in the immigration states AZ and FL, the relatively strong increase of the population of people with DS has been more or less counterbalanced by the strong growth of the general population (as a result of immigration, in general) between 1970 and 2010 in AZ and between 1950 and 2010 in FL.

3.6 | Validating the model

We compared the age distribution of deaths of people with DS by year, age, and state as predicted by our model with the corresponding age distributions found in the Death Certificate data of CDC (Supplementary Materials S11) (National Center for Health Statistics, Centers for Disease Control and Prevention, 2015). We consider the match to be reasonably good (Supplementary Figure S12). Mean age of death is lower in AZ and FL, in comparison to the other seven U.S. states, a direct result of the relative young population in these immigration states.

Applying the alternative survival curves to AZ (Supplementary Materials S5) leads to some changes in modeled age of death (Figure S13). The alternative appears to have a slightly better fit to the Death Certificate data (National Center for Health Statistics, Centers for Disease Control and Prevention, 2015). However, as we have demonstrated above, the estimated number of people with DS living in AZ as of 2010 is almost the same.

4 | DISCUSSION

In nine U.S. states located in four U.S. regions, the number of people living with DS has steadily increased from 1950 until 2010. However, in all of

TABLE 3 Estimates of population prevalence of people with DS in 2010

State	Actual DS pop	Actual DS pop prev. per 10,000	Actual DS pop prev. as 1 in X	Reduction of DS pop (%)
MA	4,554	6.9	1,440	30
NJ	6,101	6.9	1,443	29
NY	14,315	7.4	1,355	26
IL	9,739	7.6	1,319	20
IN	4,354	6.7	1,491	15
MI	7,295	7.4	1,354	15
FL	9,099	4.8	2,071	21
KY	3,014	6.9	1,442	11
AZ	3,596	5.6	1,784	16
All 9 states	62,067	6.6	1,508	22

Actual DS pop: Number of people with DS alive.
Acutal DS pop prev. per 10,000: Actual population prevalence per 10,000 people.
Acutal DS pop prev. as 1 in X: Actual population prevalence as 1 in X.
Reduction of DS pop: Net effect of screening, that is: (the potential number of people with DS if there had not been any elective terminations minus the number of people with DS alive) divided by the potential number of people with DS multiplied by 100%.

these states, the population prevalence could have been even higher, absent DS-related elective terminations. Racial and ethnic groups, other than non-Hispanic whites, comprise a growing proportion within these DS communities, particularly among younger-aged persons.

Regional differences are distinctive, though. As of 2010, reduction in live births as a result of DS-related elective terminations was highest in the Northeast (MA, NY, NJ) and KY, at around 50%, and more or less the same for the remaining states in the Mid-West, South, and West (26–38%). Advanced maternal age—and the willingness to terminate—was highest in the Northeast, accounting for much of this difference. By comparison, as of 2010, de Graaf et al. (2015) estimated a reduction percentage for the U.S., as a whole, to be 32%, which corresponds to 2,376 additional live births absent DS-related elective terminations.

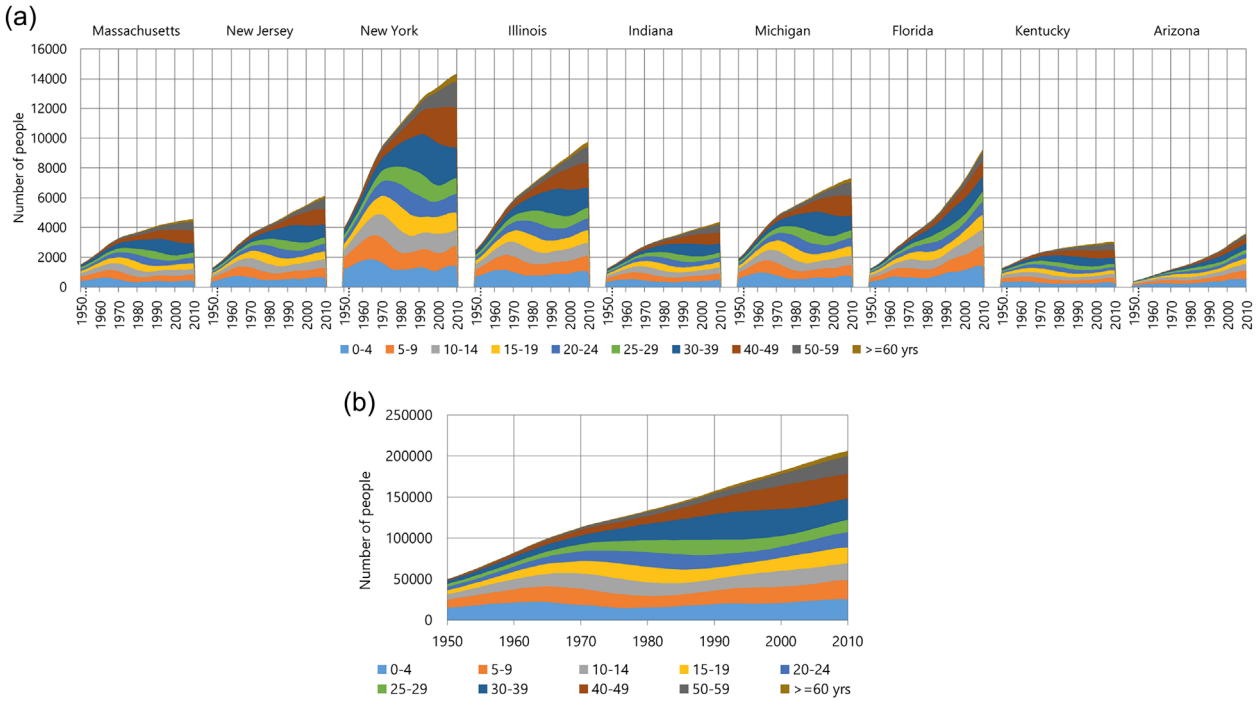

FIGURE 5 (a) Historical populations: Number of people with DS by age group and state (all ethnic groups combined), corrected for interstate migration, from 1950 to 2010. "Corrected" values result from taking the estimated number *living* in a state as numerator (DS) and denominator (general population). (b) Historical populations: Number of people with DS in the U.S. by age group from 1950 to 2010. [Color figure can be viewed at wileyonlinelibrary.com]

These reductions in live births also had the biggest impact on the population size of people with DS in the Northeast leading to a 26–30% reduction, followed by FL and IL (20–21%), and then comparable within the other states (10–16%). For the U.S., as a whole, there was a 19% reduction in overall population prevalence as of 2010 (de Graaf et al., 2016a). Ethnic differences in historical survival of children with DS had a very small impact on population prevalence variation between states.

Interstate migration of people with DS had a small effect on the overall *number* of people DS in these states. Future survey studies among people with DS, elucidating whether they were born in the state they are living, could further corroborate this finding. Though the effect of migration of people with DS appears to be small, interstate migration from the general population significantly reduced the *population prevalence* for DS in some states (AZ and FL). Accounting for the influx of U.S. citizens into these states dilutes the proportion of people with DS living there. This same trend holds true for HIS and AS/PI ethnic groups, which consist of mostly younger people in their fertile years who are immigrating into U.S. states, some for the first time. By contrast, MA, NY, IL, and MI show an emigration pattern, with the DS population prevalence slightly increasing when accounting for migration.

Historical trends in the United States are also reflected in individual states over the years. Between 1920–1940, birth control and family planning was introduced in the United States, resulting in a decrease in the number of children overall, including those with DS (Centers for Disease Control and Prevention, 1999). From 1940–1957, the fertility rate and family size increased surrounding World War II, also boosting the numbers of babies with DS (Centers for Disease Control and Prevention, 1999; Wetzel, 1990). During the 20th and early 21st century, survival of young children with DS steadily increased. Beginning in the 1950s, the survival for adults with DS increased, consequent to advances in medical treatments. Those already alive with DS could now expect to live longer. Beginning in 1960, modern birth control pills and intrauterine devices (IUDs) were introduced, leading to a reduction in family size within the United States again (Centers for Disease Control and Prevention, 1999). In the 1980s, women began waiting until later years to have children. As DS is more common among women of advanced maternal age, there was an observable increase in the numbers of children with DS from the 1980s onwards. At this same time, children with DS were now mandated by federal law to have their congenital heart defects repaired, leading to another boost in childhood survival rates.

In more recent decades, advanced maternal age has been counterbalanced by increased utilization of DS-related selective terminations. While non-selective live birth prevalence strongly increased, actual live birth prevalences only slightly increased in the period 1980–2010. In most recent years, in many states, both actual live birth prevalence for DS and actual numbers of births with DS have slightly decreased. Those who are born, though, have a median life expectancy of nearly 58 years, meaning that the overall population of people with DS within states is still increasing (de Graaf et al., 2016a). Unclear is how much of an impact the new cell-free DNA NIPS will have on birth prevalence and, ultimately, population prevalence. As there is generally a ~6 year lag in birth data becoming publicly available, the initial impact will be first measurable around 2018.

For this study, we analyzed nine U.S. states. Data from the remaining 41 states were either insufficient or altogether lacking. To make a calculation of the actual live birth and population prevalence, a state must collect the number of live births with DS, distinguishable from terminations with DS, over a period of time. In addition, we would recommend these data be categorized by race and ethnicity, as done in the United States Birth Defects Surveillance Programs, but not in the reports of the International Clearinghouse for Birth Defects. In the future, a national database or registry would also be of great use to expand this study.

In the United States, 41 states have birth defects tracking programs; however, the majority of these datasets are not population-based, and some use an entirely passive surveillance approach (Centers for Disease Control and Prevention, 2016b). The CDC has been funding 14 birth defects tracking systems in 10 different U.S. states (Centers for Disease Control and Prevention, 2016a). Out of these states, we included six (AZ, FL, IL, KY, MI, NJ) in our study. We had to exclude four, as the surveillance programs in Colorado, Oklahoma, and Rhode Island include elective terminations, and data from Minnesota only cover most recent years. We included another three programs that are not funded by the CDC (IN, MA, NY).

Taking everything into account, as of 2010, the estimated population prevalence of people with DS was greatest in IL (at 1 in 1,319), followed by MI, NY, MA, KY, NJ, IN, AZ, and FL (at 1 in 2,071). By comparison, de Graaf et al. (2016a) estimated the population prevalence for DS to be 1 in 1,499 for the U.S. as a whole, representing about 206,366 people with DS. While people with DS are living longer than they have ever before, increased utilization of prenatal testing and DS-related elective terminations are having counterbalancing effects on population statistics, resulting in a plateauing of numbers of people with DS in most states with the exception of the two immigration states (FL and AZ) with their relatively young and fertile general population.

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B.G.S. occasionally consults on the topic of DS through Gerson Lehrman Group. He receives remuneration from DS non-profit organizations for speaking engagements and associated travel expenses. B.G.S. receives annual royalties from Woodbine House, Inc., for the publication of his book, *Fasten Your Seatbelt: A Crash Course on Down Syndrome for Brothers and Sisters*. Within the past 2 years, he has received research funding from F. Hoffmann-La Roche, Inc., and Transition Therapeutics to conduct clinical trials on study drugs for people with DS. B.G.S. is occasionally asked to serve as an expert witness for legal cases where DS is discussed. G.deG. works for the Dutch DS Foundation, a nonprofit organization. F.B. works for DS Education International and DS 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 DS.

CONFLICTS OF INTEREST

Beyond the items mentioned in the financial disclosures above, B.G.S. serves in a non-paid capacity on the Honorary Board of Directors for the Massachusetts Down Syndrome Congress, the Board of Directors for the Band of Angels Foundation, and the Professional Advisory Committee for the National Center for Prenatal and Postnatal Down Syndrome Resources. B.G.S. has a sister with DS. G.deG had a daughter with DS, who passed away in 2005 at the age of 15. F.B. serves in an unpaid capacity as vice president of the European Down Syndrome Association and as a member of the Professional Advisory Committee of the US National Center for Prenatal and Postnatal Down Syndrome Resources. He has a sister with DS.

ORCID

Gert de Graaf http://orcid.org/0000-0002-4990-5711
Brian G. Skotko http://orcid.org/0000-0002-5232-9882

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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