

SUPPLEMENTARY MATERIALS

Estimation of Live Birth and Population Prevalence of Down Syndrome in 9 U.S. States

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S1. Estimating the number of nonselective live births by ethnic group and U.S. state

Nonselective live birth prevalence for Down syndrome (DS) is the live birth prevalence that would have occurred in the absence of DS-related elective terminations. The number of nonselective births of children with DS can be estimated on basis of the maternal age distribution in general population in combination with a model for maternal age-related chance of a live born child with DS absent elective terminations. Like de Graaf et al.,¹⁻³ we used the most recent model for maternal age-related chance for DS, developed by Morris et al.⁴

Data on births by state, maternal age, and maternal ethnic group can be acquired at the Centers for Disease Control and Prevention (CDC).^{5,6} For the period 1990–2010, these data specify non-Hispanic whites (NHW), non-Hispanic blacks (NHB), Hispanics (HIS), Asians and Pacific Islanders (AS/PI) and American Indian and American Natives (AI/AN).⁵ For the period 1968–1989, the natality files of CDC specify Whites, Blacks, AS/PI and AI/AN for the different states; Hispanic ethnicity is not reported until 1978 (AZ, NJ, NY), 1979 (FL, IL), 1988 (KY) and 1989 (MA, MI).⁵ For the period 1931–1967, in the annual reports of the Vital Statistics of the United States at CDC, births are only specified as occurring to “White” or “Non-white” mothers.⁶ We corrected these numbers (1931–1968) for under-registration in relation to fertility by maternal age group, information which can be found in the Vital Statistics.⁶

Alternatively, the number of births by state, maternal age, and maternal ethnic group can be estimated on basis of data from the 1850–2013 sample in the Integrated Public Use Microdata Series (IPUMS-USA).⁷ We analyzed information from the census years 1890, 1900, 1910, 1920, 1930, 1940, 1950, 1960, 1970, 1980, 1990, 2000, and 2010 in relation to age of mother (15–60 years) and age of child (0–9 years), separately for the five ethnic groups, for the 9 U.S. states and the U.S. as a whole. Like de Graaf et al.,³ we determined the age of the mother at time of birth by subtracting the age of the child from the age of the mother. The maternal age information in relation to the children <1 year of age gives an estimation of the maternal age distribution in the census year. The maternal age information in relation to the children between 1–2 years old provides an estimation of the maternal age distribution in the year before the census year, and so on. By applying to these estimates the model of maternal age-related chance for a live birth with DS absent elective terminations, we could then produce a first estimate of the nonselective numbers of births of children with DS by ethnic group and U.S. state. Subsequently, for each ethnic group separately, again on basis of the IPUMS-data, we estimated the percentage of all live births of children with DS in the U.S. that were born in that specific state. Earlier, de Graaf et al. had estimated the total number of nonselective births by ethnic group for the U.S. as a whole.³ We applied our estimates of the proportion of children with DS by ethnic group born in a specific state to these earlier estimates of de Graaf et al. to construct our final IPUMS-based estimates of the numbers of children with DS by ethnic group and state.

We compared our CDC-based estimates with our IPUMS-based estimates for the different ethnic groups for overlapping years in which specific information on ethnicity was available. These comparisons showed that CDC-based estimates and IPUMS-based estimates are highly similar.

For years in which CDC-based estimates of nonselective births of children with DS by ethnic group were available, we used these estimates in our modeling; for years in which these CDC-based estimates were not available, we used IPUMS-based estimates instead. Finally, to smooth out random fluctuations, we calculated 5-year running averages for each year of birth.

S2. Estimating the number of actual live births by ethnic group and state

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.⁸⁻¹⁹ So, for example, the data for 2010 are the average of the births in the period 2008–2012. For some U.S. states, elective terminations are included in these counts; as these are not specified separately, we could not use the data of these programs. Some programs counted in natural loss (miscarriage and stillbirths); we corrected for these assuming that around 4% of the sum of live births and natural loss are natural loss on basis of data of three programs (Texas, Utah and Georgia) which specify this in the annual reports of the International Clearinghouse for Birth Defects.²⁰ Finally, some programs only counted live births, and these data could be used without any modification. Ultimately, there were 9 U.S. states for which we could obtain the relevant data on live births with DS for a substantial number of years. These were MA (1998–2010), NJ (1998–2010), NY (1997–2010), IL (1997–2004 and 2006–2010), IN (1999 and 2001–2008 and 2010), MI (1999–2009), FL (2000–2010), KY (1997–1998 and 2004 and 2006–2010), and AZ (1997–2002 and 2004–2010). Data from in-between years were interpolated. See Table S1.

For the period before these years with data from the 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. in modeling a reduction percentage of 0% before 1968, 0.5% for 1969, 5% in 1978, growing to 7.5% in 1979 and 10% in 1980.¹ De Graaf et al. found a linear increase of reduction percentage between 1980-1996.¹ Reduction percentage was more or less stable from 1996 onward.¹ Between 1980 and 1996, we modeled a linear increase in reduction percentage for each ethnic group separately. If program data for one or more of the years between 1996-1999 were missing, we assumed that the reduction percentage in those years was similar to that in following years. For some ethnic groups (in some U.S. states), reduction percentage in recent years was lower than 10%. In these situations, we substituted the 1980 value of 10% reduction (and all values between 1980 and the first year with program data) with this lower value. If the value in recent years was below 7.5%, we assumed that all values between 1979 and the first year with data were at this lower level, and so on. In Figure S1, we present the modeled reduction percentages by U.S. state and ethnic group. 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 in the main article). In addition, in Figure S2, we present the historical development in ethnic distribution of live births estimates of children with DS as percentages.

Table S1 Study data on live births of children with DS

Region and State	Years for which data are available in the U.S. Birth Defects Surveillance Programs*
Northeast	
Massachusetts	1998–2010
New Jersey	1998–2010
New York	1997–2010
Mid-West	
Illinois	1997–2004 and 2006–2010
Indiana	1999 and 2001–2008 and 2010
Michigan	1999–2009
South	
Florida	2000–2010
Kentucky	1997–1998 and 2004 and 2006–2010
West	
Arizona	1997–2002 and 2004–2010

* If data are available for 2008–2010, these represent the data for, respectively, 2006–2010 (=2008), 2007–2011 (=2009) and 2008–2012 (=2010), as the U.S. Birth Defects Surveillance Programs present data as 5-year averages.

Figure S1

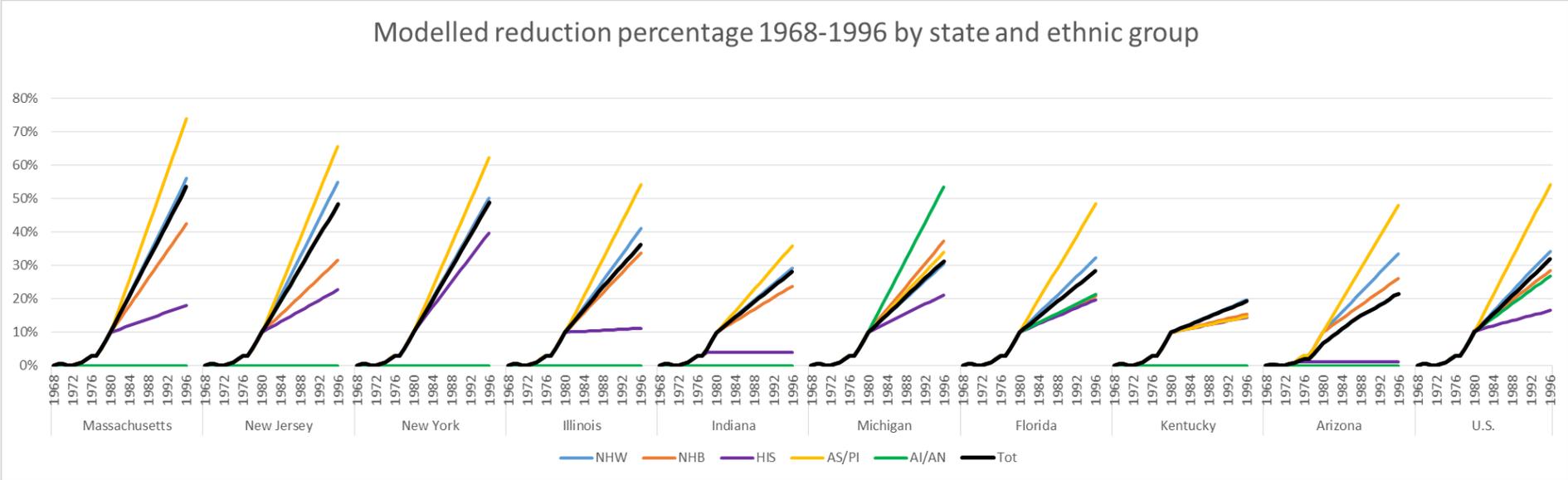
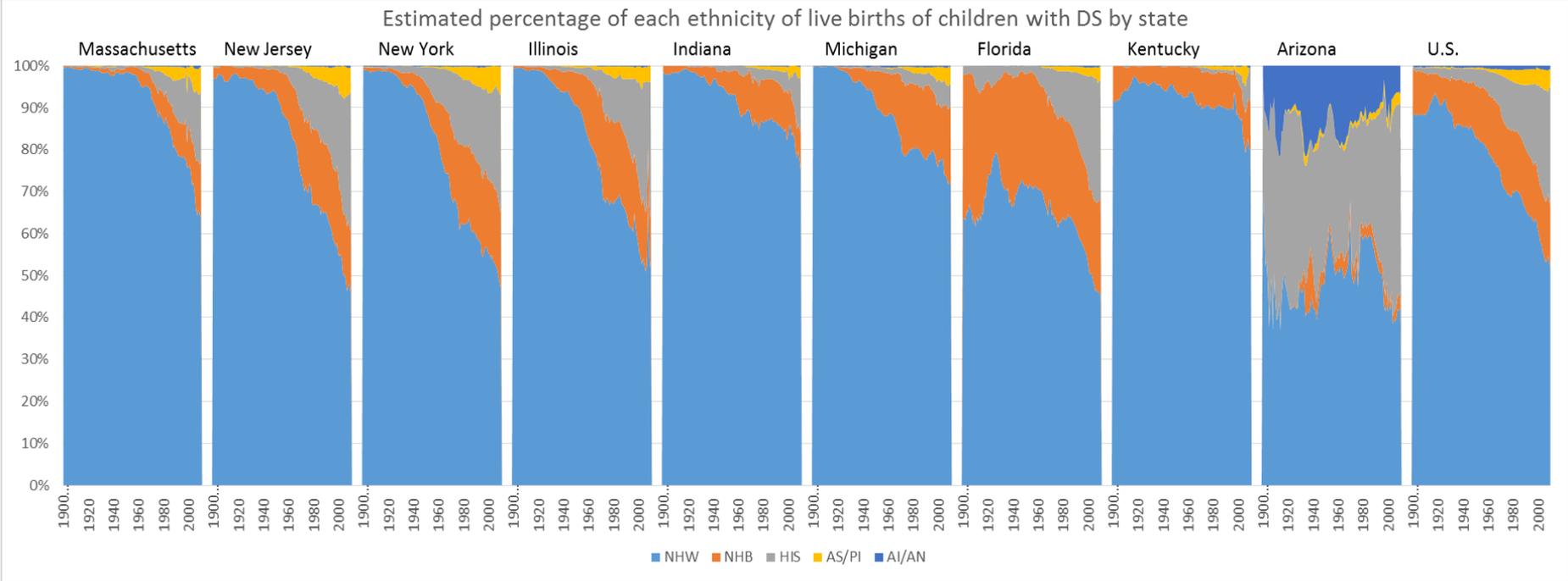


Figure S2



S3. Nonselective and actual live birth prevalence for DS and the effects on population prevalence for DS in 9 U.S. states

Figure 2 (in the main article) shows the historical development of nonselective and actual live birth prevalence estimates for DS in 9 U.S. states. In Figure S3, for both nonselective LB prevalence for DS and actual LB prevalence for DS, we present the average of the 9 U.S. states, in combination with the minimum value and the maximum value per year of birth. In Figure S4, the extent to which this minimum and maximum value diverges from the average value is shown as percentages (plus or minus). Figure S5 presents the standard deviation of the values for the 9 U.S. states.

Historically, for nonselective prevalence for DS, the differences between the 9 U.S. states were not large. Before 1985, the difference in relation to the average was around -10% and +10%. However, these differences in nonselective LB prevalence for DS increased after 1985 to around -25% and +30% in the 2000s (Figure S4). This is a result of differences in maternal ages in different states in recent decades. Maternal ages were relatively high, for instance, in NY, NJ, and MA, and relatively low, for instance, in AZ, IN, KY, and MI. This implies that the postponement of motherhood since the 1980s (visible in all 9 states in the nonselective LB prevalence for DS estimates in Figure 2 in the main article) shows a clearly different pace in different U.S. states.

In the older age groups, differences between population prevalence for the 9 U.S. states are influenced by differences in nonselective live birth prevalence for DS (resulting from differences in maternal age distribution) to a limited extent (-10% to +10% only). However, in the younger age groups (born after 1985), differences in nonselective live birth prevalence of DS potentially could have had more impact on population prevalence (-25% to +30% in recent years). However, this impact is strongly moderated by the differential effect of elective DS-related terminations of pregnancies on actual live birth prevalence.

The direct effect of this reduction of live births with DS (resulting from DS-related elective terminations) 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 ranges 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, with the impact on population prevalence for these 9 U.S. states, on average when combined, being around a 22% reduction of population size of people with DS. The highest impact was for AS/PI (51% reduction), followed by NHW (22%), NHB (21%), HIS (17%) and AI/AN (4%). It is important to understand that these percentages do not directly refer to the reduction in live births (which is higher), but are our estimates of the net effect of the reduction in live births on population numbers. So, for example, in MA, the reduction of live births as a result of DS-related elective terminations 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 prevalence (linked to advanced maternal ages) than in U.S. states with a relatively low nonselective prevalence, as can be inferred from Figure 2 in the main article (see also Figure S1). As a result of these differences in elective DS-related

terminations being linked to the height of nonselective prevalence estimates for DS, differences between U.S. states' actual live birth prevalences for DS (in comparison to the differences in nonselective prevalence in recent years) are much less pronounced (Figure S3 and S4), around minus 10-12% to plus 10-12% for most years. An exception is 2009 and 2010, which show a higher negative value (around 30%). However, this is due to only one state (KY), which had a remarkably low actual LB prevalence for DS in those two years. As this might be a coincidental result, we present the standard deviation (SD) of the values in Figure S5, including and excluding KY.

In conclusion, for people with DS born before 1985, historical differences in nonselective live birth prevalence, resulting from differences in maternal age distribution, have a limited impact on differences in current population prevalence between U.S. states. For people born after 1985, this effect would have been much more pronounced, had it not been counterbalanced by huge differences between U.S. states with the impact of DS-related elective terminations, which are linked to these differences in nonselective prevalence. So, both differences in nonselective prevalence and differences in reduction in live births of children with DS, as a result of DS-related elective terminations, have a large impact on population prevalence. However, these effects counterbalance. As a result, differences in actual live birth prevalence for DS between the 9 U.S. states with available data turn out to be limited. So, historical and current differences in actual live birth prevalence in fact only have a relatively small effect on differences in population prevalence between these U.S. states.

Figure S3

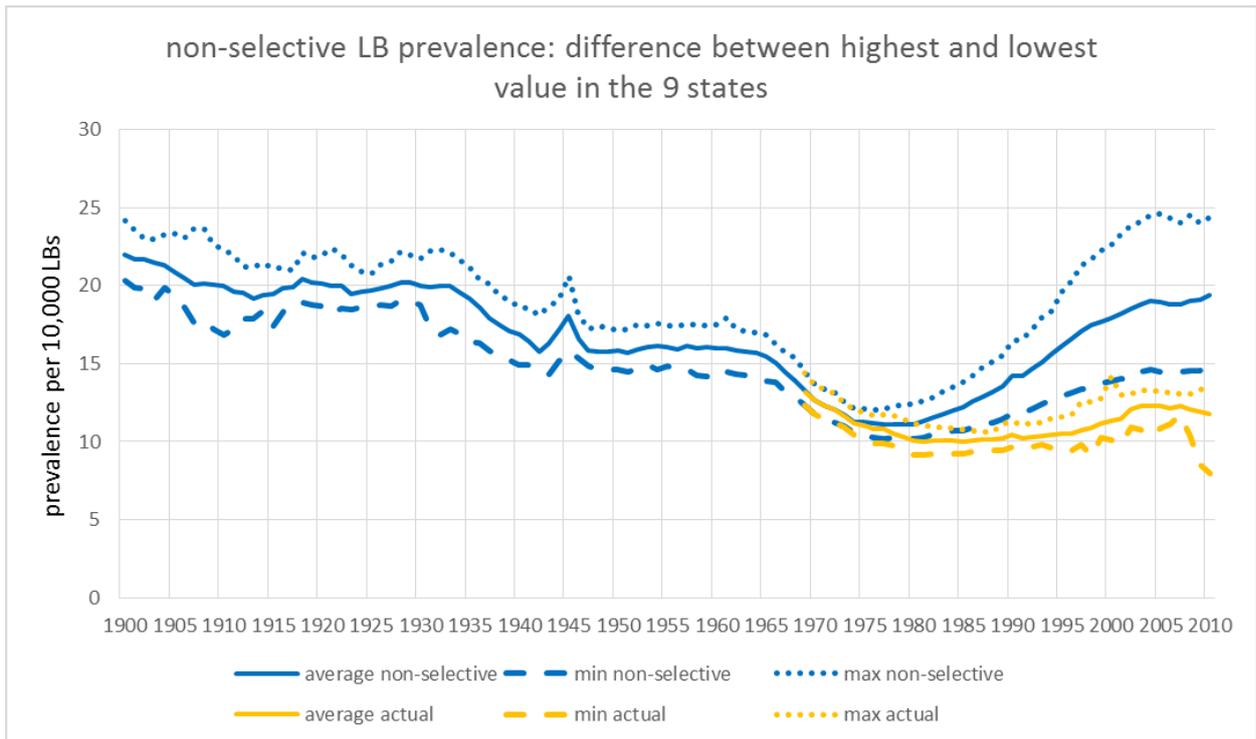


Figure S4

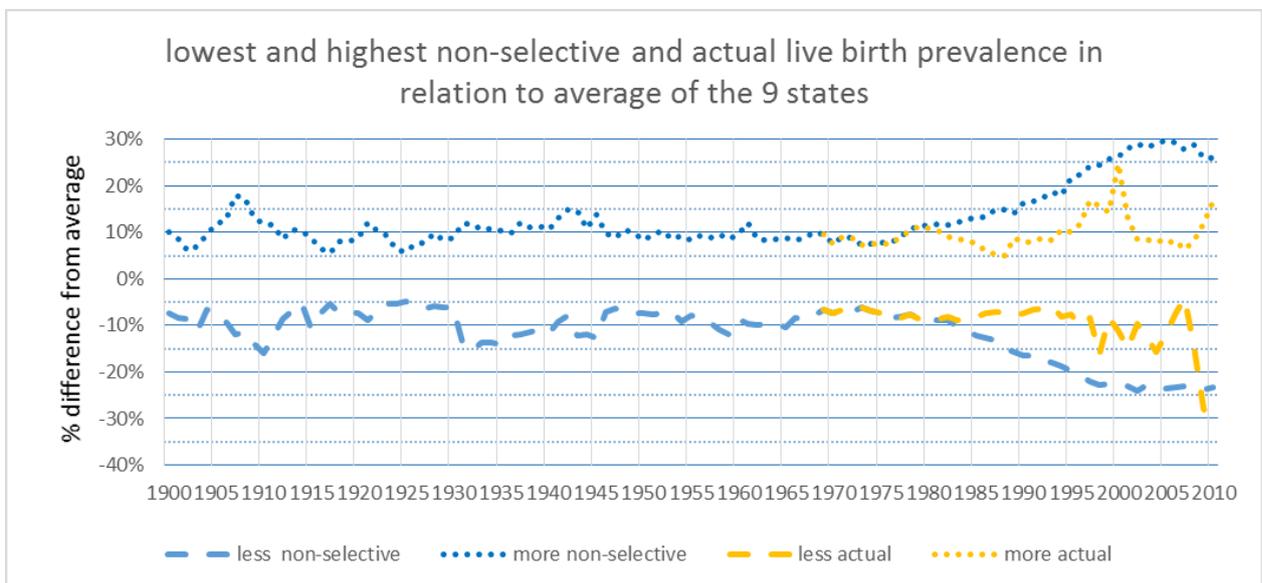
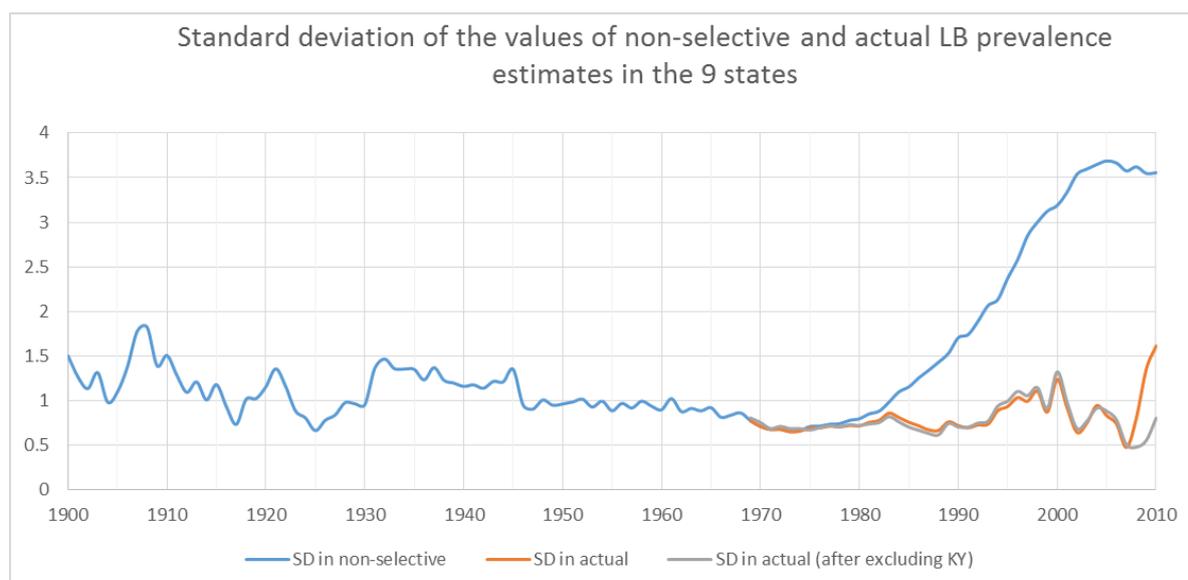


Figure S5



S4. Modeling survival

We adapted an earlier model from de Graaf et al.²¹ On the basis of multiple historical studies on the survival in persons with DS, de Graaf et al. constructed and validated a model with different survival curves for people with DS for each year of birth in addition to constructing separate curves for NHB and AI/AN (with a lower survival) versus NHW, HIS, and AS/PI.³

We applied these curves to our constructed numbers of live births with DS to estimate population numbers and population prevalence for DS by state, age, and ethnic group.

S5. Effects of differences in survival between U.S. states on population prevalence

As there are some differences between U.S. states in the ethnic composition of the births of children with DS (Figure 1 in the main article and Figure S2), the differential survival in NHB and AI/AN versus the other ethnic groups will have some effect on population prevalence. However, this effect is very small. First, in all of these states, NHB and AI/AN are relatively small groups. Second, the effect of using differential survival curves by ethnic group is not large. To illustrate this point, if we had estimated the NHB population of people with DS using the NHW-HIS-AS/PI curves, the estimate would have been only 6% higher than using the NHB-AI/AN curve.

Data on 1-year mortality by U.S. state can be found in the reports of the Vital Statistics of the United States at CDC and, for recent years, at the CDC WONDER database.^{6,22} We checked whether 1-year mortality in the 9 U.S. states was different from that in the general U.S. population. Figure S6 shows that this is not the case to a high extent with the exception of AZ before 1950. In the other 8 states, 1-year mortality is similar to that in the U.S. as a whole. The differences between these states are much smaller than the difference between “Whites” and “Non-whites” in the U.S. as a whole. However, in AZ before 1950, 1-year mortality resembles that of “Non-whites” in the U.S. As an alternative analysis, we have constructed 1-

year mortality rates for children with DS, and corresponding 5- and 10-year mortality rates for AZ on the basis of the 1-year mortality rates in the general population in AZ following the method of de Graaf et al. (2016b). Figure S7 shows the constructed 1-year mortality rates for DS. If we use these alternative 1-year survival rates for children with DS in AZ to construct alternative survival curves for the life span, this leads to a 0.4% lower prediction of the number of people with DS in AZ as of 2010. This alternative prediction would have been 23% lower as of 1950, 16% as of 1960, 8% as of 1970, 4% as of 1980, 2% as of 1990, and 0.6% as of 2000. As such, the fact that in AZ survival was less favorable before 1950 had almost no impact on the prediction of numbers of people with DS living in AZ in recent years.

Figure S6

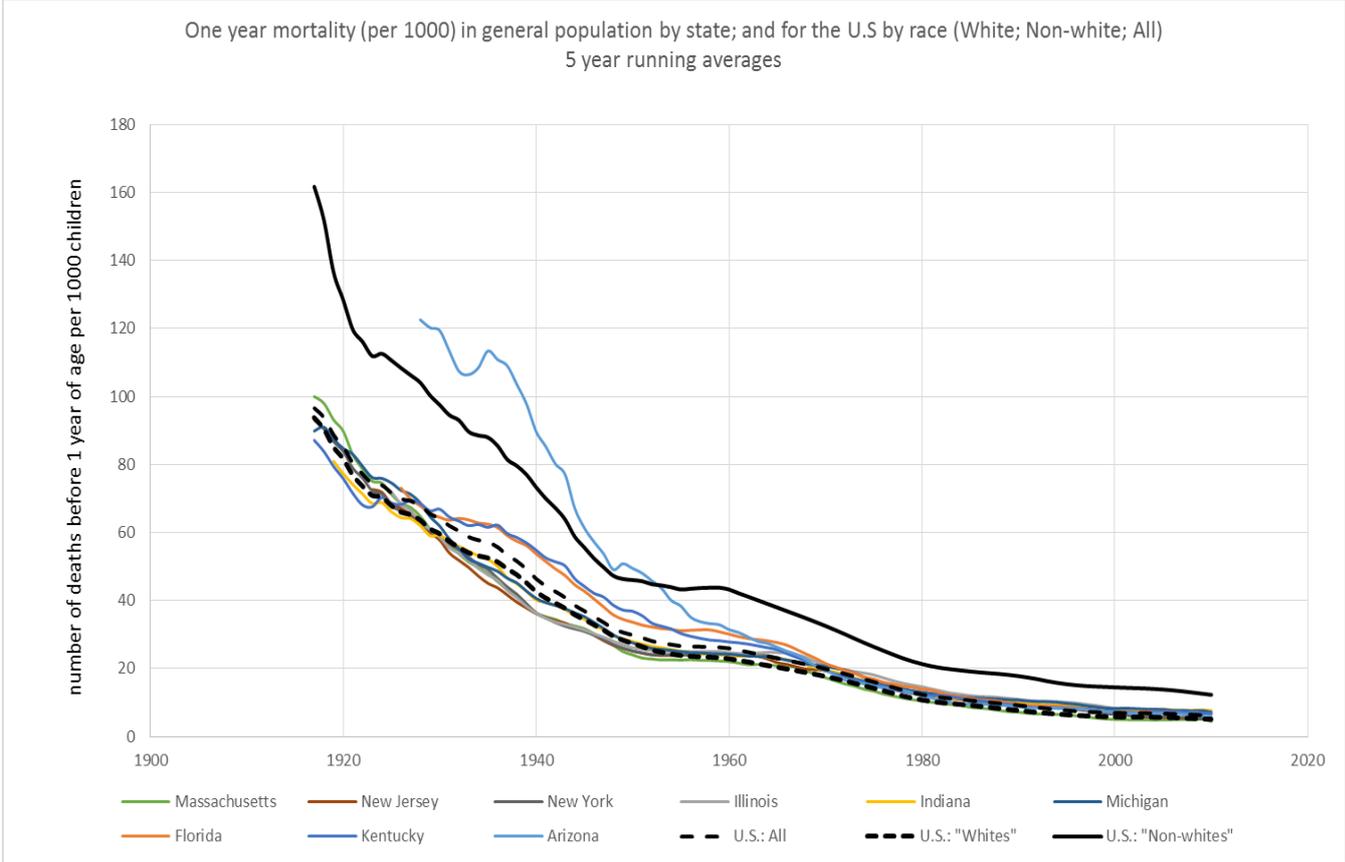
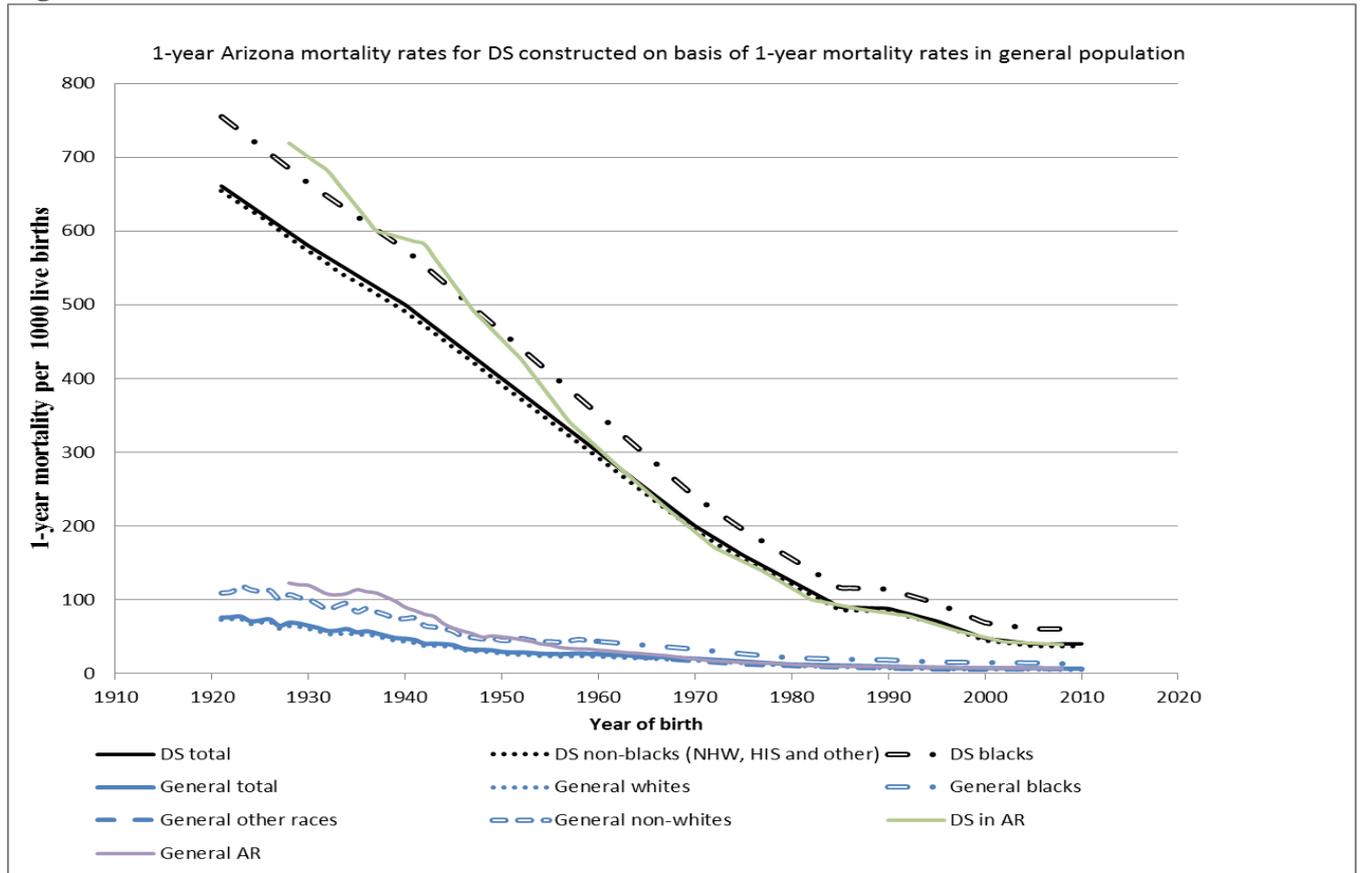


Figure S7



S6. Estimating interstate migration

To estimate the effect of interstate migration on population numbers of people with DS, we used data on DS as a cause of death from the Death Certificate Files 1997–2004, as these are the last 8 years in which data on state of birth and state of residence were available.²³ To begin, for each separate age of death (in years), we divided the number of reported deaths of people with DS who were residents of a specific U.S. state by the number of reported deaths of people with DS who were born in that specific state. This yields an estimate of a first correction factor for interstate migration of people with DS. For instance, if 20 people with DS with a certain age of death born in AZ were reported to have died in the period 1997–2004, but 30 deceased people with DS with that age of death were reported to be residents of AZ in that period, a first estimation of the net effect of migration would be that 1.5 more people with DS must have lived in AZ than we would have modelled on basis of the number of births of DS in AZ from that specific years of birth. We followed this procedure for all 9 U.S. In this analysis, running 7-year averages of death by year of birth were used to ensure large numbers. We then repeated the same procedure for all people (with or without DS) to estimate a correction factor for interstate migration in the general population.

Subsequently, we checked whether these analyses for the general population based on mortality files is a valid measure for interstate migration by comparing the constructed general population correction factors by age of death and state with corresponding correction factors (constructed in the same way) based on the Integrated Public Use Microdata Series (IPUMS-USA) for the census year 2000, which fits best the time frame 1997–2004.⁷ These two constructed variables turn out to have a high correlation (0.984; $p < 0.000$). That means that we can use the census-based factors instead of the mortality files-based factors. An advantage is that the census-data are available for 2010 (whereas the mortality files don't specify state of birth after 2004).

The next step is predicting the DS-specific correction factors on basis of the general population correction factors (for which we used the factors based on the 2000 Census data, as explained above). We constructed a linear relation in such a way that the line crosses the point (1,1), which means that if the general net migration is zero, we assume the DS net migration is zero too. The relation is estimated by $y = 0.2211x + 0.7789$, in which y is the constructed DS-migration correction factor and x is the general population migration factor (based on the 2000 Census). This formula implies that people with DS are less likely to migrate from one state to another than people in general.

Subsequently, we used the 2010 Census data from the Integrated Public Use Microdata Series (IPUMS-USA) separately for the five ethnic groups under observation to construct general population migration correction factors by age, ethnicity, and U.S. state.⁷ We subsequently used these general population correction factors to predict the DS migration correction factors by state, ethnicity, and age, using the formula above.

This is a more indirect way of correcting than using the first correction factor for DS migration directly. However, in constructing this first correction factor for DS by state and ethnic group, one runs into very small numbers of deaths of people with DS in the subgroups. This problem is circumvented by constructing these correction factors indirectly on the basis of the general migration correction factors. These indirectly derived correction factors for DS—constructed separately by U.S. state, ethnic group, and year of birth—were applied to

our estimated numbers of births of people with DS by state, ethnic group, and year of birth. In this way, we estimated the numbers of births of children with DS corrected for migration, which we subsequently used as an input in our model for survival to estimate the number of people with DS by state, ethnic group, and age, corrected for interstate migration. In this approximation, we assume the interstate migration usually occurs shortly after birth, which, of course, isn't always the case, though we would expect that migration to be higher in families with a young child with DS than it would be in adults with DS. However, this assumption will not affect our DS population estimates for recent years; and as the direct effect of migration of people with DS on population estimates turns out to be small altogether, only historical estimates are affected to a minor extent.

S7. Effects of interstate migration on the population number and population prevalence of people with DS in the 9 U.S. states

For most U.S. states and for most ethnic groups in each U.S. state, the direct effect of interstate migration of people with DS on the number of people with DS living in that state is small. 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, 3% higher in NJ, and less than 1% difference for the other states under observation. For NHW, the estimates for AZ and FL also turn out to be higher after correction for migration, respectively +14% and +10%, whereas for the other states the differences are smaller (between -3% and +3%). NHB shows more or less the same picture: +18% for AZ and +7% for FL, +7% for MA, and all other states less than 3% difference. For HIS, a relatively young ethnic group in the U.S., for all states under observation the correction leads to higher estimates of the DS population number, varying from +6% in MI, +7% in NY, +25% in KY, and +28% in FL. The AS/PI group shows a similar picture, with percentages between +25% for IN to +60% for AZ. For AI/AN the effects are small, less than $\pm 6\%$ for the different U.S. states, with KY as an exception with +21%. However, the AI/AN form an extremely small ethnic group in almost all states under observation, with less than 0.3% of the people with DS having an AI/AN background in 7 out of the 9 states. Only in AZ, an estimated 9% of people with DS come from this ethnic group and in MI around 2%.

Whereas the direct effect of interstate migration on the population number of people with DS is very small for most states (and relatively small even for AZ and FL)—and for most ethnic groups in each state (with the exception of HIS and AS/PI)—interstate migration in the general population has indirect strong effects on population prevalence estimates of people with DS.

In Figure S8A, we present population prevalence estimated 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 in general population and born in that specific state as the denominator. The last estimates are based on the IPUM-CENSUS-data for 2010.⁷ 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, again based on the IPUM-data. In Figure S8B, we present these same data constructed for 3 ethnic groups (NHW, NHB, and HIS). We consider the

AS/PI and AI/AN group in most of these U.S. states to be too small to construct reliable population prevalence estimates by state.

Interestingly, the non-corrected estimates (for all ethnic groups combined) are more or less the same for most U.S. states, with around 7 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 necessarily due to higher live birth prevalence estimates for DS in these states, historically or recently (as can be inferred from Figure 2 in the main article and Figure S9), but this is the result of a different age distribution of people, in general, born in these states. This is an indirect effect of relatively high levels of immigration of younger people, in general, into these states. Immigrants are relatively more often young people in their fertile years who, after immigration, give birth to their children. (Although DS is more likely to occur in women of advanced maternal age, a large base of younger fertile mothers will still statistically result in larger numbers of children with DS.) Their children count as being born in that specific state, whereas the parents themselves 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 (under the condition that we don't correct the denominator for interstate migration as with our first estimates in Figure S8A and S8B).

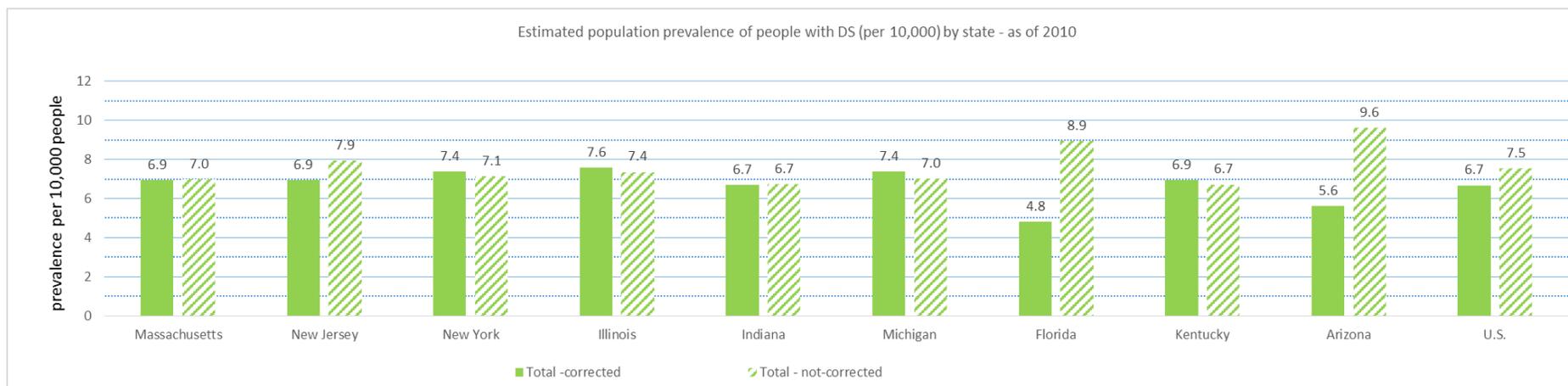
A population pyramid, with a wider base, will also occur for people *born* in immigration states. To illustrate this point, of people in the general population *born* in AZ, 50% were younger than 21 as of 2010. In FL, this percentage is 46%. In the other 7 states, this percentage is between 25–30%.

The same phenomenon is found for the Hispanic group (Figure S8B) (and also for the AS/PI group, which we consider too small for a separate analysis). In most of the 9 U.S. states, the uncorrected population prevalence for DS tends to be higher for HIS than for NHW. HIS are a young immigration group. Of people in the general population (all ethnicities combined) born in these 9 U.S. states, 30% were younger than 21 as of 2010. In the HIS group, this percentage is 60%.

When we correct for interstate migration, the high estimates of population prevalence for DS in immigration states and in ethnic immigration groups drop, as the denominator (estimate of people in general living in that specific state) is much more strongly influenced by this correction than the numerator (estimate of people with DS living in that state). In Figure S8A, we can see that the population prevalence for DS in most U.S. states is relatively unchanged by this correction. 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. This is a very strong indirect effect of interstate immigration in the general population on population prevalence for DS. The same phenomenon applies to the HIS group (and the AS/PI group), which is a young immigrant group. In most U.S. states, the population prevalence for HIS, after correction (which especially changes the denominator) for migration, drops below the values for NHW. Only in AZ and FL, NHW population prevalence for DS is relatively low, too, as apparently these states are immigration states for NHW as well. If the population prevalence estimates increase after correction, there is a net emigration of people in general population from that state, as is clearly the case for the NHW group in MA, NY, IL, and MI.

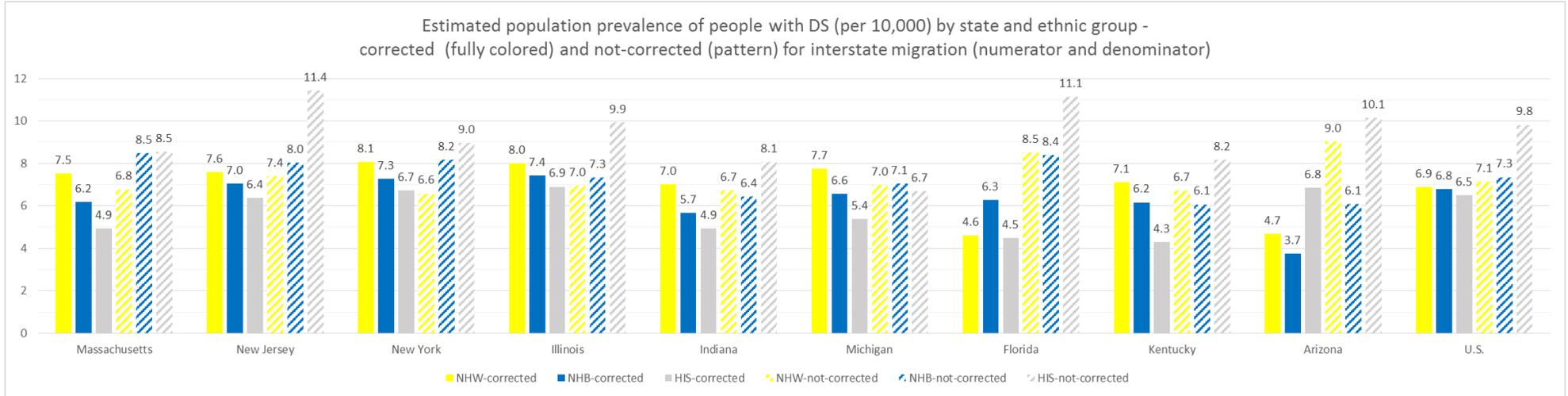
Figure S9, S10, and Figure 3 (main article) show that the correction for interstate migration (especially changing the denominator by using people *living* in the state instead of people *born* in the state as the denominator) has a large effect in AZ and FL on the estimates of population prevalence by age for the age groups above 25 years.

Figure S8A



* 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* the U.S. as numerator (DS) and denominator (general population). Denominators are based on the Integrated Public Use Microdata Series (IPUMS-USA).⁷

Figure S8B



* 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* the U.S. as numerator (DS) and denominator (general population). Denominators are based on the Integrated Public Use Microdata Series (IPUMS-USA).⁷

Figure S9

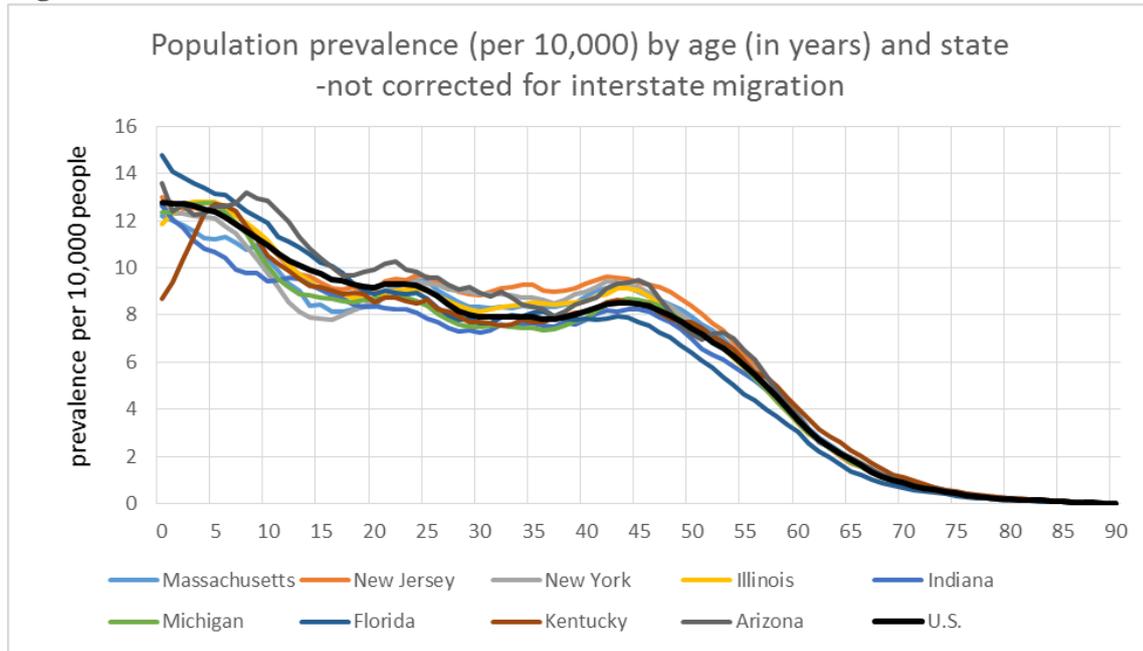
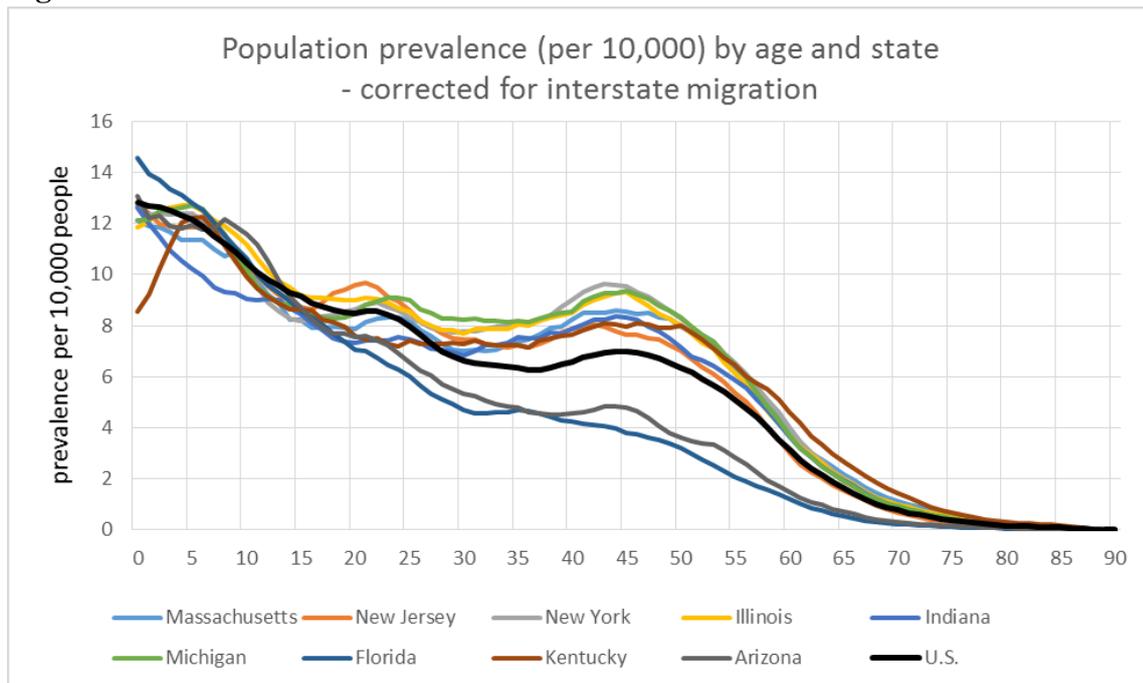


Figure S10



* 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* the U.S. as numerator (DS) and denominator (general population). Denominators are based on the Integrated Public Use Microdata Series (IPUMS-USA).⁷

S8. Estimates of the number of people with DS by age group, ethnicity and U.S. state, corrected for migration.

As for planning of services and for research, the estimates of the number of people with DS by age, ethnicity, and U.S. state are important, we present these in detail in Figure 4 (main article). The excel file with the information from this Figure can be downloaded as a Supplementary material (file: “Supplement estimates of numbers of people with DS by age as of 2010 – Figure 4”). We present the numbers corrected for interstate migration.

S9. Historical development of the numbers of people with DS by age group and U.S state, corrected for interstate migration

In Figure 5 (main article), we present the historical development between 1950–2010 for the estimates of the number of people with DS by state. The information for this Figure can be found as a Supplementary material (file: “Supplement historical development in numbers of people with DS by age and ethnic group - Figure 5”). In this file, we also present the historical development for each ethnic group separately.

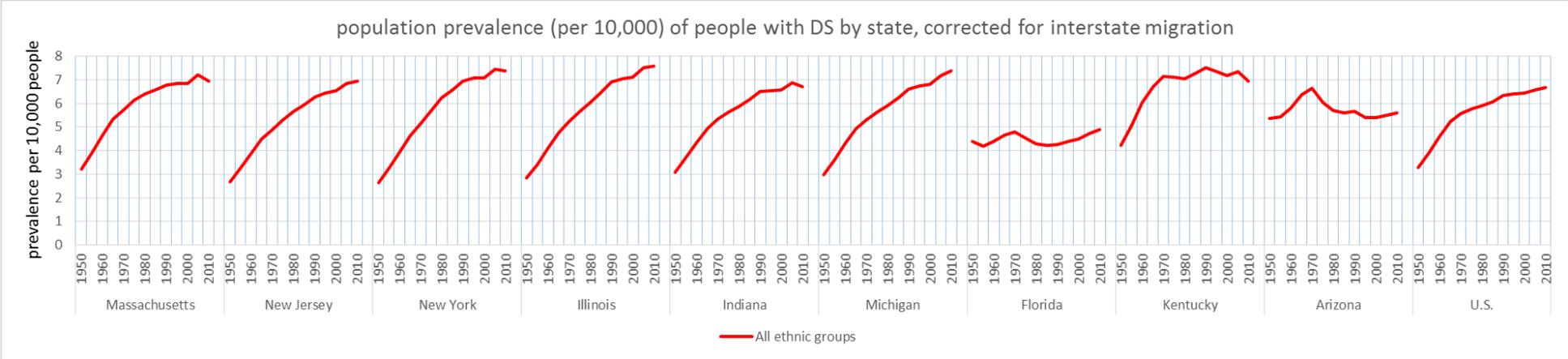
In most states, as can be inferred from Figure 5 (main article), the increase in numbers of people with DS plateaus in recent decades. However, in the immigration states AZ and FL, the increase doesn't level off; to the contrary, the increase seems to get somewhat stronger (more or less an exponential curve). The explanation is the fact that many young people in their fertile years move into these immigration states. This leads to more births, and thus to more births of children with DS as well. The same phenomenon can be observed in the young immigrant groups (HIS and AS/PI). In all 9 U.S. states under observation, the growth of the number of people with DS from these ethnic groups follows an exponential curve, whereas the curves of the NHW level off in all states except the immigration states AZ and FL. The development in NHB appears to be linear (not leveling off as in NHW), as the reduction in live births as a result of DS-related elective terminations of pregnancies is lower than in NHW.

S10. Historical development of the population prevalence of people with DS by state, corrected for interstate migration

Figure S11 shows the development of population prevalence estimates of people with DS between 1950–2010. In 7 out of the 9 U.S. states, population prevalence has increased during this period from around 3 per 10,000 inhabitants (or 4 in KY) in 1950 to values between 6.5 and 7.5 per 10,000 as of 2010. In the immigration states AZ and FL, population prevalence, as expected, has followed a different path. In AZ, population prevalence estimates for DS increased from 5.4 per 10,000 in 1950 to 6.7 per 10,000 in 1970, decreasing in following years to around 5.6 per 10,000 as of 2010. In FL, population prevalence for DS has been between 4 and 5 per 10,000 for the period 1950–2010. The relatively strong increase of the population of people with DS (as a result of many births in young immigrant families) 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 1950–2010 in FL.

We have abstained from presenting these historical developments by ethnic group. In many states the different ethnic groups (except NHW, but this group follows the same trends as the total of all ethnic groups combined) are too small for a reliable estimation of population prevalence by ethnic group and state.

Figure S11



S11. Validating the model by comparison of the age distribution of expected deaths with the age distribution in death certificates

The model can be used to predict numbers of deaths of people with DS by age and year of occurrence. The age distribution of these deaths can be compared to the corresponding age distributions found in the Death Certificate data of CDC.²³ We use the age distribution and not the raw numbers. The Death Certificates under-report DS.^{3,24} However, as long as this under-reporting is not systematically different for different years of age, the age distribution is not affected by under-reporting.

In Figure S12, we present the results of this analysis. We consider the match to be reasonably good. In most states, a mean age at death of 30 years of age* is reached in the early 1980s, both according to our model and to the Death Certificates.²³ In AZ and FL, both according to the model and in the Death Certificates, the 30-years are reached later in FL (in the 1990s) and AZ (the early 2000s).²³ This is the result of the age pyramid of the people with DS living in these immigration states, containing relatively many children and relatively few older people.

Again, we abstain from an analysis by ethnic group and state, as the different ethnic groups are too small in many of the states to do a reliable analysis by ethnic group and state (and as the NHW group follows the same trends as all ethnic groups combined).

Of note, de Graaf et al. have already done this same validation analysis by ethnic group for the U.S., as a whole.³ Following the same strategy for only these 9 U.S. states combined does not show a different picture (and we actually have too little data for AS/PI and AI/AN in only these 9 U.S. states to do a reliable analysis); as such, we refer the readers to de Graaf et al.³

Applying the alternative survival curves to AZ (See Supplementary Section 5) leads to some changes in modeled age of death (Figure S13). The alternative has a slightly better fit to the Death Certificate data.²³ However, as we have seen in Section 5, the estimated number of people with DS living in AZ as of 2010 is almost the same.

* Mean “age at death” is a different concept than “life expectancy,” and it is important to distinguish these two concepts. Mean age at death refers to the age distribution of people who died in a specific calendar year, which is heavily influenced by the age distribution of the live population under observation. Life expectancy is the number of years children born in a specific year of birth on average will live. For example, modeled mean life expectancy for DS in the U.S. as of 2010 is around 53 years in all 9 U.S. states under observation. However, modeled mean age at death varies between U.S. states, around 41 years of age in the immigration states of AZ and FL and around 50 years of age in the other U.S. 7 states, as of 2010. The reason that mean age at death is lower in AZ and FL is not because of less survival in people with DS in these states, but instead is due to the fact that the population of people with DS is relatively young in immigration states. As a result of this age distribution of live persons, there are relatively fewer older deceased people, too, and so the mean age of death is consequently lower.

Figure S12

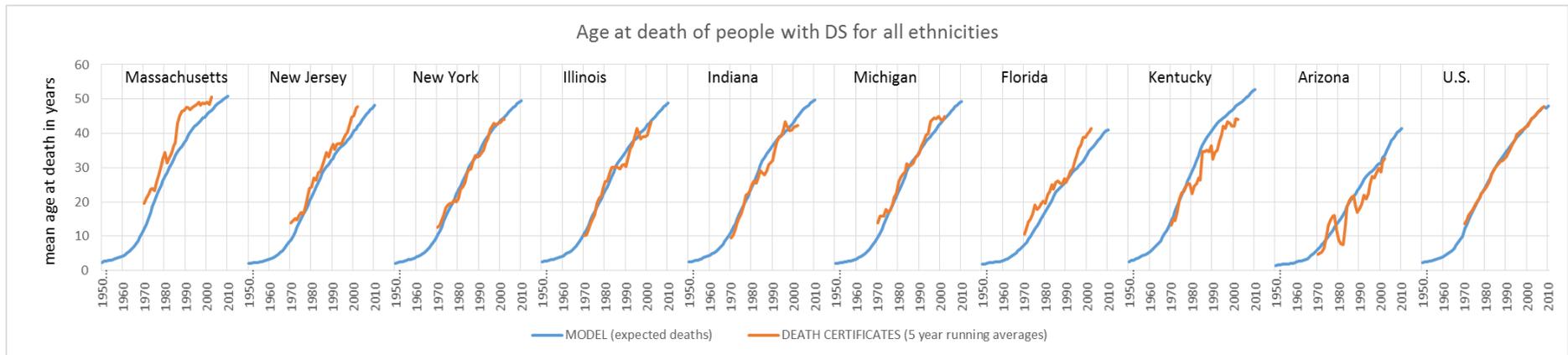
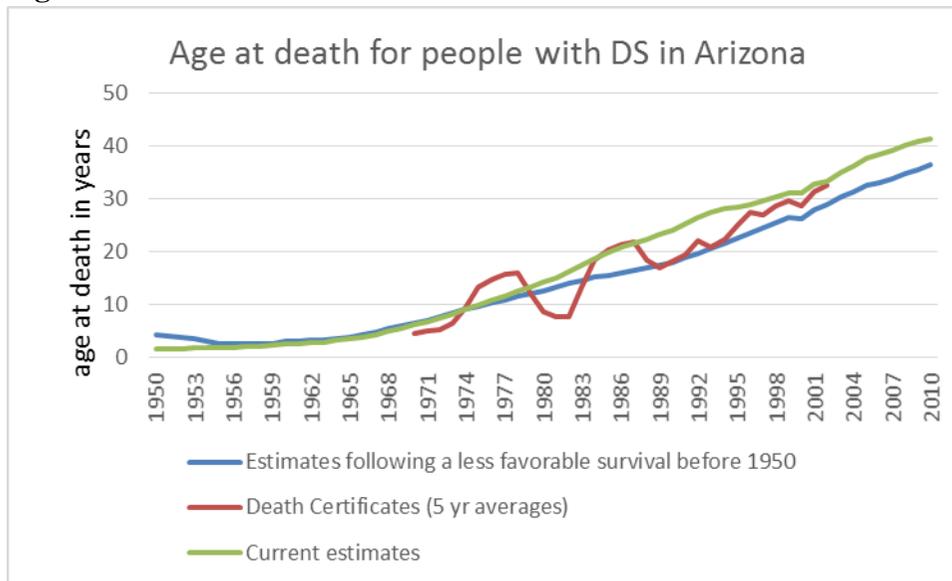


Figure S13



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