Estimation of the number of people with Down syndrome in Canada

SUPPLEMENTARY MATERIALS

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Supplementary Methods 1: Number of potential and actual live births (LBs) of children with Down syndrome (DS)

S1A. Estimates of nonselective LBs of children with DS

For the period 1991–2020, data on the number of live births (LBs) in the general population in Canada, total and by maternal age (5-year groupings), are available at Statistics Canada. For 1936–1990, information on the distribution of LBs by maternal ages is available (also in 5-year age bands) in the Demographic Yearbooks (DYB) of the United Nations. Finally, data from 1950 onwards on LBs by maternal age in single years is available at the World Population Prospects (WPP) of the United Nations.

Total number of LBs in the general population
Data on the total number of LBs in the general population from 1900 onwards can be found at https://en.wikipedia.org/wiki/Demographics_of_Canada#Vital_statistics. These data are based on Statistics Canada and the DYB of the United Nations. The same data from 1920 onwards can also be found in"Population growth in Canada: From 1851 to 2061 Population and dwelling counts, 2011 Census" at https://www12.statcan.gc.ca/census-recensement/2011/as-sa/98-310-x/98-310-x2011003_1-eng.pdf.

For 1991–2020, the reported total numbers of LBs in the general population from the WPP are on average 1.4% lower than from Statistics Canada. We don't know why this discrepancy exists. As Statistics Canada is the primary source, we have used their data on the total number of LBs for 1991–2020. If we compare the data for 1950–1990 on total numbers of LBs from the DYB with the data from WPP, the former turns out to be 0.2% lower, which is highly similar. We have used the data from DYB (which also can be found on Wikipedia: Demographics of Canada. Vital Statistics) as the source for the total number of live births in the general population.

Maternal age distribution
In regards to the distribution of maternal ages, from 1950 onwards, we have used the information from WPP, as they report in single-year bands, which makes an estimation of the potential LB-prevalence of DS more precise. To estimate the potential LB prevalence of children with DS or nonselective LB prevalence, which is the prevalence that would have occurred without DS-related elective terminations of pregnancies, we have used the model of maternal-age specific chances for a LB of a child with DS that was developed by Morris et al.[1] Subsequently, we have applied these estimates of nonselective prevalence to the total numbers of LBs to estimate the potential number of live-born children with DS in Canada.

Alternatively, we could have used the 5-year maternal age bands information from DYB (1950–1990) and Statistics Canada (1991–2020). Earlier, de Graaf et al. estimated 5-year maternal age-specific chances based on U.S. birth data (https://www.cdc.gov/nchs/products/vsus.htm), available in single-year maternal age bands for 1931–1937, and from 1946 onwards.[2] For 1938–1945, interpolation was used. These 5-year maternal age chances evolve slightly over the years, as inside the 5-year bands the maternal age distribution changes over time. The use of these constructed 5-year maternal age-specific chances by year of birth is fine-tuning.

We have applied these 5-year maternal age chances (as constructed for the different years of birth) to the Canadian data for the corresponding years, assuming that these small demographic developments were similar in Canada. This is corroborated by constructing Canadian-specific 5-year maternal age chances by year of birth based on the WPP data. Applying these to the 5-year maternal

age bands information from DYB (1950–1990) and Statistics Canada (1991–2020) to estimate Canadian nonselective prevalence of children with DS leads to an estimation that is 0.15% lower for 1950–2020 than applying the US-based 5-year maternal chances. We proceed with the estimates based on the Canadian-specific 5-year maternal age chances. These estimates are 0.4% lower for 1950–2020 in comparison with the estimates based on 1-year maternal age bands (WPP), which are highly similar. From 1950 onward, we use the estimates of nonselective prevalence based on the 1-year maternal age bands (WPP). However, the total number of LBs by year was estimated as reported by Statistics Canada (1991–2020) and DYB (1900–1990).

For 1936–1949, information on the distribution of maternal ages in general live births is available in DYB in 5-year maternal age groups. As information on 1-year maternal age bands is not available for this period in Canada, we applied the 5-year maternal age-specific chances, estimated based on U.S. birth data, to the Canadian maternal age data. These estimates of nonselective prevalence for 1936–1949 were used in the model.

We have not found data on maternal age distribution before 1936. Previously, de Graaf et al. designed a procedure to estimate nonselective prevalence for DS before 1950 based on the female population by 5-year age group in 1950 and 1955, and the age-specific fertility in 1960, 1955, and 1950, data available at WPP, projecting backward in time.[3] We used this procedure to estimate nonselective prevalence for 1915–1949. However, for the years 1936–1949, these estimates were 8% lower than the estimates based on DYB for the same period. So probably the procedure will lead to some underestimation for 1915–1935 as well. With a linear regression, it is possible to transform the first estimates for 1936–1949 (based on the procedure) into the second (based on DYB data) fairly well (R^2=0.63). Applying this regression to the first estimates for 1915–1935 produces the estimates we have used in our model for this period. Before 1915, we assumed that prevalence was similar to our 1915 estimate.

S1B. Sources for number of LBs by maternal age in the general population

1991–2020
Statistics Canada. Table 13-10-0416-01 Live births, by age of mother. https://doi.org/10.25318/1310041601-eng Retrieved January 20, 2024

1936–1990
United Nations, Department of Economic and Social Affairs, Statistic Division. Demographic Yearbook System. https://unstats.un.org/unsd/demographic-social/products/dyb/#statistics Retrieved October 10, 2021

1950–2020
United Nations, Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022, Online Edition. https://population.un.org/wpp/ Retrieved November 8, 2023.

1900–2020
Wikipedia: Demographics of Canada. Vital Statistics. https://en.wikipedia.org/wiki/Demographics_of_Canada#Vital_statistics. Retrieved November 8, 2023.

1921–2008
Population growth in Canada: From 1851 to 2061 Population and dwelling counts, 2011 Census.

https://www12.statcan.gc.ca/census-recensement/2011/as-sa/98-310-x/98-310-x2011003_1-eng.pdf Retrieved January 20, 2024

S1C. Estimates of actual LBs of children with DS

For 2008–2020, by e-mail from the Public Health Agency of Canada (on December 4, 2023), we received full data on LBs (and separately on stillbirths (SBs) too) of the total number of children in the surveillance system and of children with DS. If we compare the data on total LBs in the system with the data from Statistics Canada, the surveillance appears to cover 97.4% of all LBs in Canada. We have used the actual LB prevalence (number of LBs with DS divided by total number of LBs x 10,000) from this system in our model. Earlier, we got the same information (September 15, 2023), however those data excluded Quebec.

For 2005–2013, data (LBs and LBs+SBs) can be found in Down Syndrome Surveillance in Canada 2005–2013 at https://www.canada.ca/en/public-health/services/publications/healthy-living/down-syndrome-surveillance-2005-2013.html. However, Quebec is excluded, as this region had not reported data. For the period 2008–2013, the estimates of actual prevalence based on the data including Quebec (from the e-mail of the Public Health Agency of Canada) are 9% lower than the estimates based on the data excluding Quebec. So, using these data for 2005–2007 might lead to an overestimation.

Alternatively, we have (almost) full data from the Annual Reports of the International Clearinghouse Centre for Birth Defects. They report for 2002, only excluding Nova Scotia (thus covering 96% of all Canadian births), 2004 (excluding Nova Scotia; covering 97%), 2005–2007 (including Nova Scotia, covering more than 99%), both LBs and LBs+SBs of children with DS in Canada. For 2003, only SBs+LBs were available. In 2002, of the total number of reported births of children with DS, 90% were LBs. In 2004, this was 92%. We have assumed 91% for 2003.

For 1995–2004, we could find data on the total number of births (sum of LBs and SBs) of children with DS in the Canadian Perinatal Health Report of the Public Health Agency, 2008 Edition. The data include Quebec (and from 1996 also Nova Scotia). For 1989–1994, Health Canada made these data available in “Congenital Anomalies in Canada — A Perinatal Health Report, 2002.” We have to estimate how many of these are LBs.

In the period 2008–2020, Quebec only reported LBs of children with DS, and not SBs (e-mail from the Public Health Agency of Canada on December 4, 2023). We assume that this also applies before 2008. We have estimated the percentage of LBs in the total number of reported births for 2008–2020 in the dataset including Quebec, and for 2002-2007 based on the data from Clearinghouse (which also includes Quebec). These percentages show a slight upward trend from 2002–2020 (probably because the SBs may contain some (late) elective terminations, and these numbers may have slightly increased). We have interpolated this trend backward in time to transform the total annual numbers of births of children with DS into an estimate of the annual numbers of LBs of children with DS. These were used to estimate DS LB prevalence for 1989–2004.

For the period 1980–1988, we have data available from the Clearinghouse reports for two Canadian regions, i.e., Alberta and British Columbia (BC). These data are also available for 1989–2000. The data report the sum of LBs and SBs with DS. We have used the procedure that we explained in the preceding paragraph to transform these to the likely LB prevalences of DS. For 1989–2000, we compared the average of these estimates for Alberta and BC with the estimates we had made earlier

on (almost) full Canadian surveillance data. For the whole period, the average difference was less than 3%. For 1989–1993, the average was less than 1%. We therefore expect that the estimates for 1980–1988 based on the average of Alberta and BC probably will be a good approximation.

For 1974–1979, only data for BC are available. We deem this too small a basis to construct national estimates. Alternatively, we have projected the trend in reduction from 1980–1990 backward in time. Reduction is defined as:

$$\left[1 - \left(\frac{the\ number\ of\ actual\ LBs\ with\ DS}{number\ of\ potential\ LBs\ with\ DS}\right)\right] x\ 100\%)$$

The results of projecting the development in reduction backward in time suggest the first effect of DS-related elective terminations in 1972, with a reduction growing from 0.5% in 1972 to 6% in 1979. This small effect of elective terminations in the early 1970s is corroborated by a study by Simpson et al. from 1976, looking into amniocenteses in this period.[4] Based on the information, they provide on the number of amniocenteses per 1,000 pregnancies in different age groups in Canada—and their information on the number of DS diagnoses per 1,000 amniocenteses—we estimate that indeed the reduction will have been around 0.5% in 1972.

S1D. Sources of actual LBs of children with DS

2008–2020
E-mail from the Public Health Agency of Canada (December 4, 2023 and September 15, 2023).

2005–2013 (excluding Quebec)
Down Syndrome Surveillance in Canada 2005-2013
https://www.canada.ca/en/public-health/services/publications/healthy-living/down-syndrome-surveillance-2005-2013.html

2002–2007 nationwide data; 1980–1988 for Alberta and BC; 1974–1979 BC.
International Clearinghouse Centre for Birth Defects. Annual reports. Published 2010. International Clearinghouse Centre for Birth Defects Surveillance and Research. Accessed October 30, 2021.
http://www.icbdsr.org/resources/annual-report/

1995–2004
Public Health Agency of Canada. Canadian Perinatal Health Report, 2008 edition. TABLE G28.1 Rate of Down syndrome (DS) Canada.
https://www.phac-aspc.gc.ca/publicat/2008/cphr-rspc/pdf/cphr-rspc08-eng.pdf

1989–1999
Health Canada. Congenital Anomalies in Canada — A Perinatal Health Report, 2002. Table D1.1 Down syndrome (DS) rate, Canada (excluding Nova Scotia). Ottawa: Minister of Public Works and Government Services Canada, 2002.
https://publications.gc.ca/collections/Collection/H39-641-2002E.pdf

1972–1975
Info on amniocenteses, prenatal diagnoses and elective terminations in Canada:
Simpson NE, Dallaire L, Miller JR, Siminovich L, Hamerton JL, Miller J, McKeen C. Prenatal diagnosis of genetic disease in Canada: report of a collaborative study. Can Med Assoc J. 1976 Oct 23;115(8):739-48. PMID: 61796; PMCID: PMC1878820.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1878820/?page=1

Supplementary Methods 2: Modeling survival in DS

S2A. Constructing survival curves for DS

Earlier, based on multiple historical studies from developed countries, de Graaf et al. constructed DS-specific survival curves by year of birth.[3,5–7] These curves were adapted for different U.S. ethnic groups, based on the relationship between 1-year survival in these ethnic groups in the general population and the 1-year survival in children with DS during the period 1983–2003. This relation was projected back in time.[5] Survival curves were adapted in the same way for different U.S. states and countries in Europe.[3,6] The assumption is that a lower 1-year survival in the general population will be indicative of a less well-developed medical care system, which will also negatively affect the survival of children with DS. Details of the procedure are presented in the Supplementary materials of de Graaf et al., which can be downloaded at https://www.nature.com/articles/s41431-020-00748-y.[3]

Using data on survival rates in DS from historical studies, de Graaf et al. fitted a linear relation between 1-year survival in DS and 5-year and 10-year survival, respectively.[3] De Graaf et al. applied these equations to the estimated 1-year survival rates for DS for the different countries.[3,5,7] However, for this article, we have reconsidered these associations. In comparison to a linear equation, a quadratic equation for predicting 5-year survival rates in DS based on 1-year survival rates in DS has a slightly higher fit (R^2 of 96% instead of 94%), and the same applies to a quadratic equation predicting 10-year survival in DS based on 1-year DS survival rates (R^2 of 97% instead of 95%). We applied these quadratic functions. If the estimated 1-year survival rates were lower than 33% (in Canada before 1925), the quadratic projections of 5-year and 10-year survival would be higher than the 1-year survival rates. As this is not possible, we have decided to use the initial linear equation for the years before 1925. At the other side of the value range, 1-year survival values above 98% would yield 5-year and 10-year survival rates higher than 98%. Thus, the highest possible value for 1-year survival that our model would accommodate is 98%. As of 2020 in Canada the highest value actually was lower at 96.3 %.

For modeling survival rates beyond 10 years of age from 1950 onwards, de Graaf et al. made use of the average of (highly similar) survival curves for DS from 7 different historical studies.[3,5–7] For the period up to 1950, de Graaf et al. used a more hazardous curve based on Penrose.[8] In 1950, 60% of children with DS in the U.S. were estimated to survive their first year of life.[5] If in a European country, the estimated 1-year survival rate for DS was <60%, de Graaf et al. have assumed that survival beyond 10 years of age in earlier cohorts followed the more hazardous survival age up to that year.[3] The same procedure has been followed in the Canadian study.

De Graaf et al. validated their results by making a comparison of the distribution of age at death of people with DS, as predicted by the model, with this distribution as reported in The WHO Mortality DataBase (MDB).[3,7] In 2019, we downloaded the raw data at https://www.who.int/healthinfo/statistics/mortality_rawdata/en/ (accessed September 17, 2019). The current link for these files is https://www.who.int/data/data-collection-tools/who-mortality-database, however DS-specific information appears to have been taken out of the files since. For 1994–2016, the MDB reports deaths registered in national vital registration systems by underlying primary cause of death. In the studies of de Graaf et al., comparing the years 2005– 2015, it appears that in West European countries and in Australia and New Zealand (NZ) in the modeled distribution of age at death by

5-year age groups, the percentages of the four age groups in the 10–30 years range are estimated higher than found in the MDB.[3,7] Probably, in developed countries, from the 1990s onward the survival in these age groups has improved in comparison with the on-average curve for survival beyond 10 years of age. To accommodate, in the current study, we have for everyone born from 1980 onwards (10 years of age or older in 1990) halved the constructed mortality rates for all years between 10–30 years of age, thus making the line between 10–30 years of age more horizontal. For Canada, this implies that of every 100 people with DS alive at age 10 around 96.3% are still alive at age 30, instead of around 92.8%.

To summarize, we apply the earlier model of de Graaf et al. with two adaptations.[3,7]

S2B. Sources for infant mortality in general population

1950–2020
United Nations, Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022, Online Edition. Combining File MORT/01-1: Deaths (both sexes combined) by single age, region, subregion and country, annually for 1950–2100 (thousands) and File FERT/03: Births by single age of mother, region, subregion and country, annually for 1950–2100 (thousands)

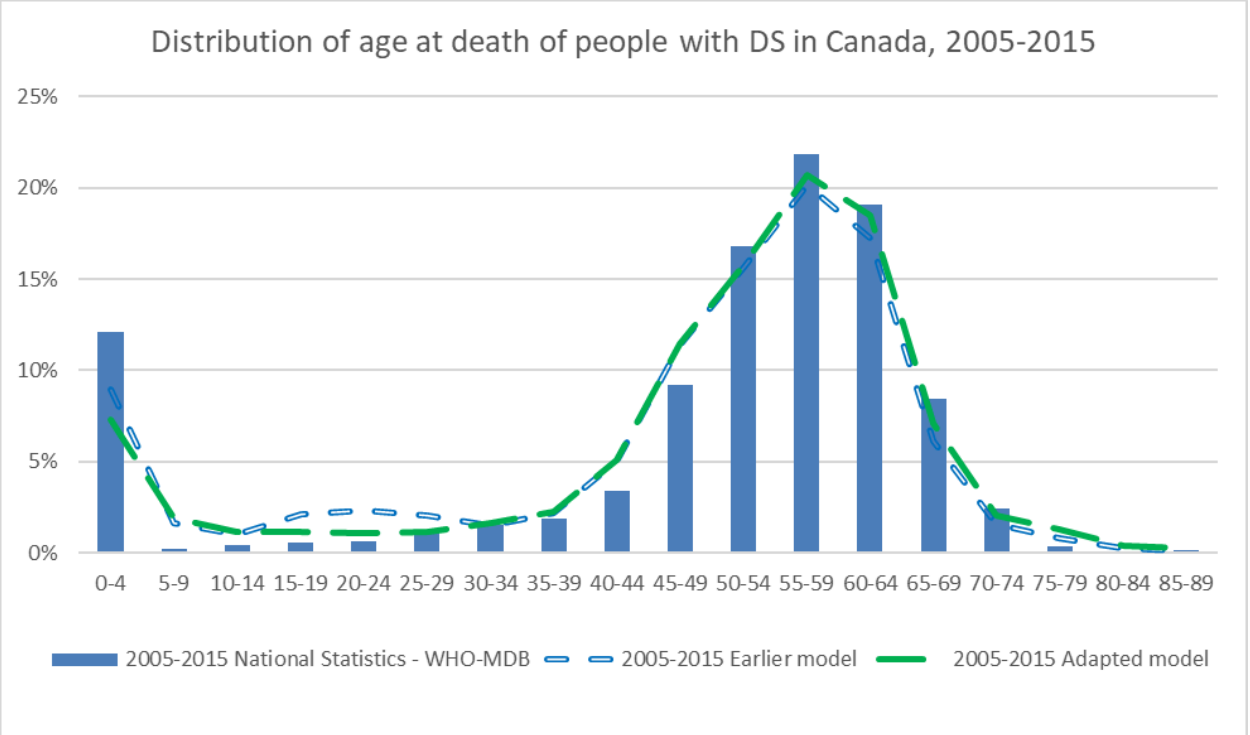
Before 1950
For the period before 1950, for many different countries (including Canada), data on 1-year mortality rates can be found at https://www.gapminder.org/data/ (accessed October 8, 2019).

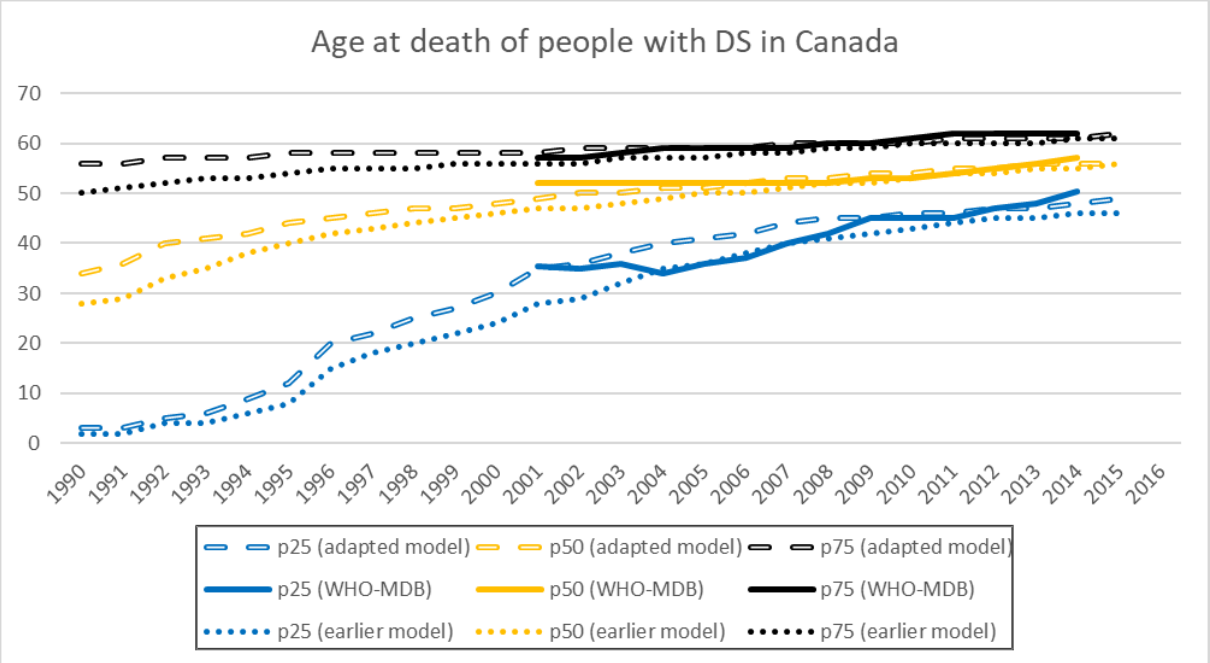
Supplementary Methods 3: Validating the model

Comparison of age at death of people with DS
We have not found data on the number of people with DS alive in Canada to compare with our model. However, it is possible to compare the distribution of the age of death, as modeled, with this same distribution based on The WHO Mortality DataBase (MDB), as explained in S2A.

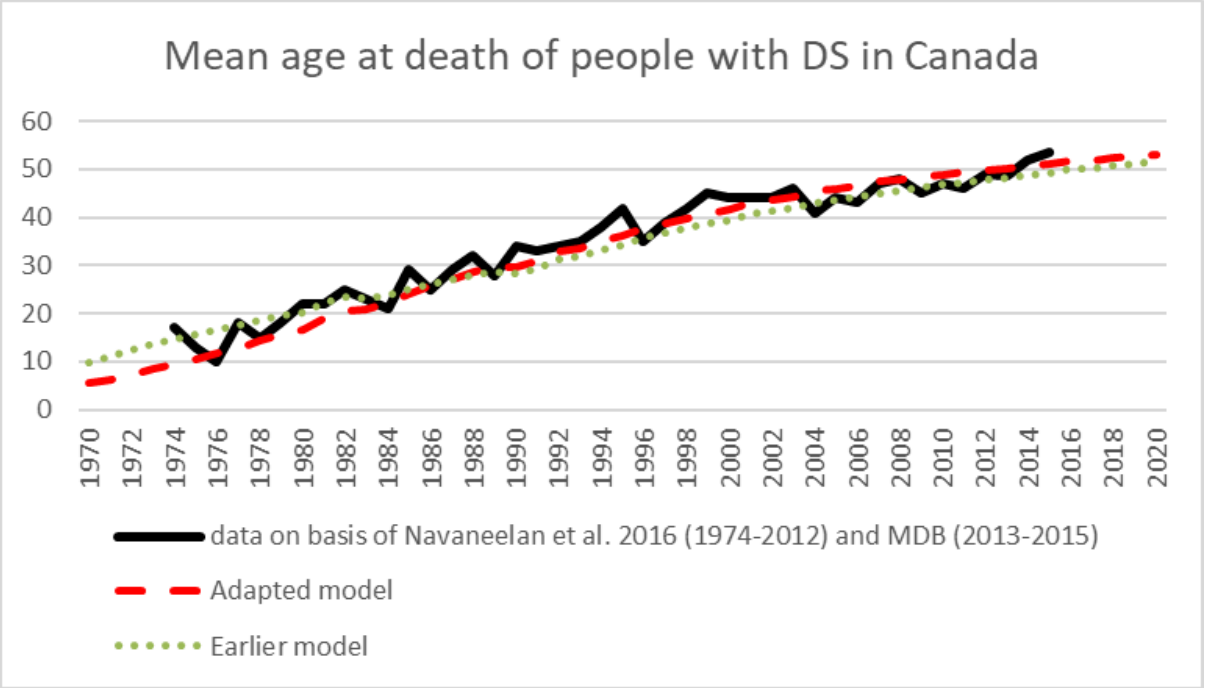
These data cannot be interpreted as complete coverage of every person with DS who is deceased. This is because national systems can be incomplete. Additionally, DS, as a diagnosis, will not always be registered as a primary cause of death, as the death could alternatively be attributed to another primary cause of death (e.g., Alzheimer's disease or pneumonia). Assuming "under-registration" is not dependent on the age of the person, we consider these data as a depiction of the age distribution of deaths of people with DS, which can be compared to the distribution of the age at death as predicted by our model.

The adapted model (with the adaptations as described in S2A) appears to have a slightly better fit.

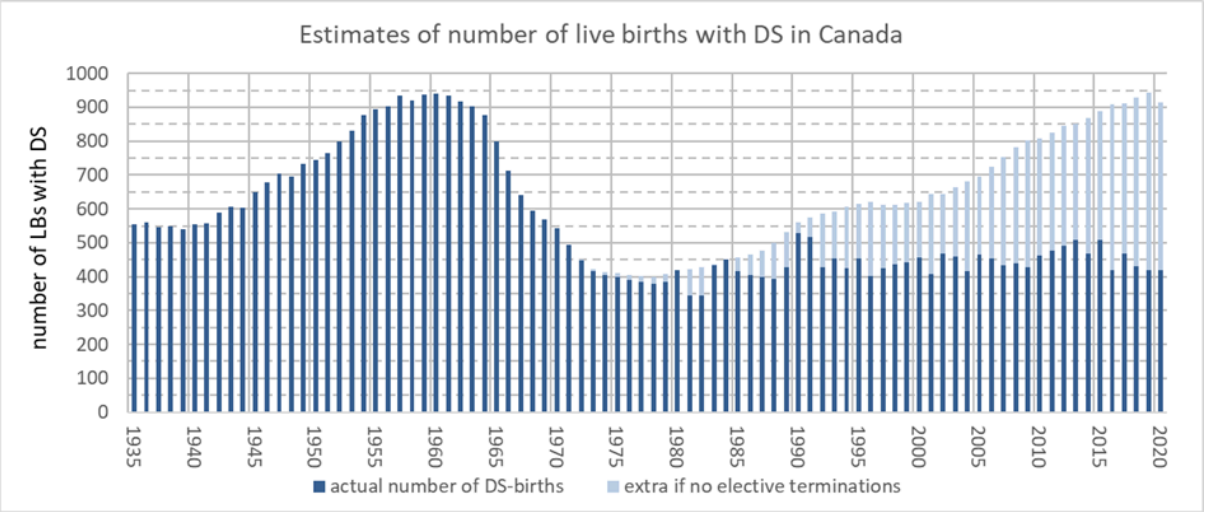


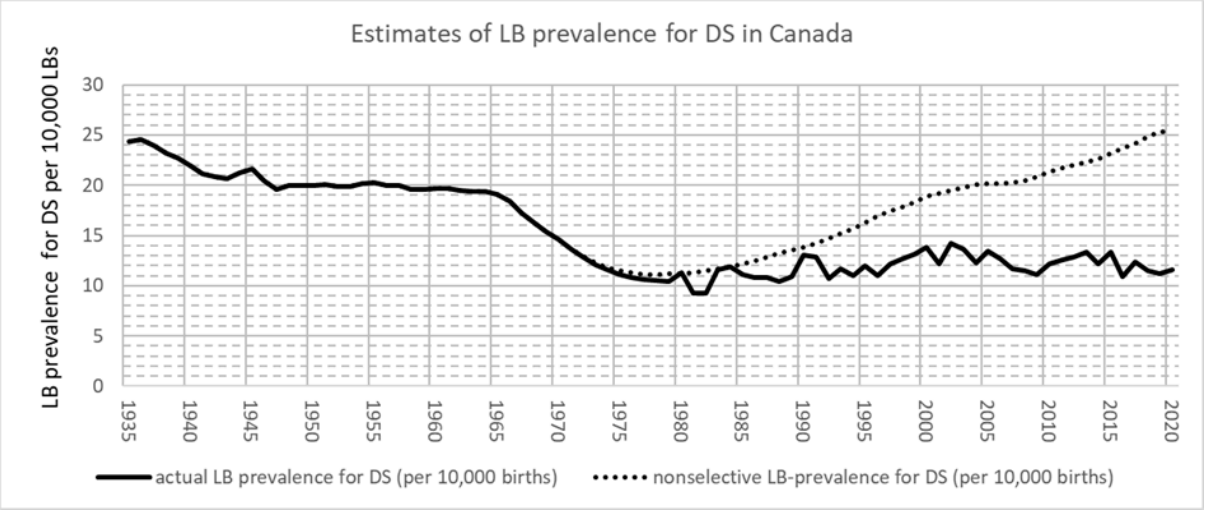


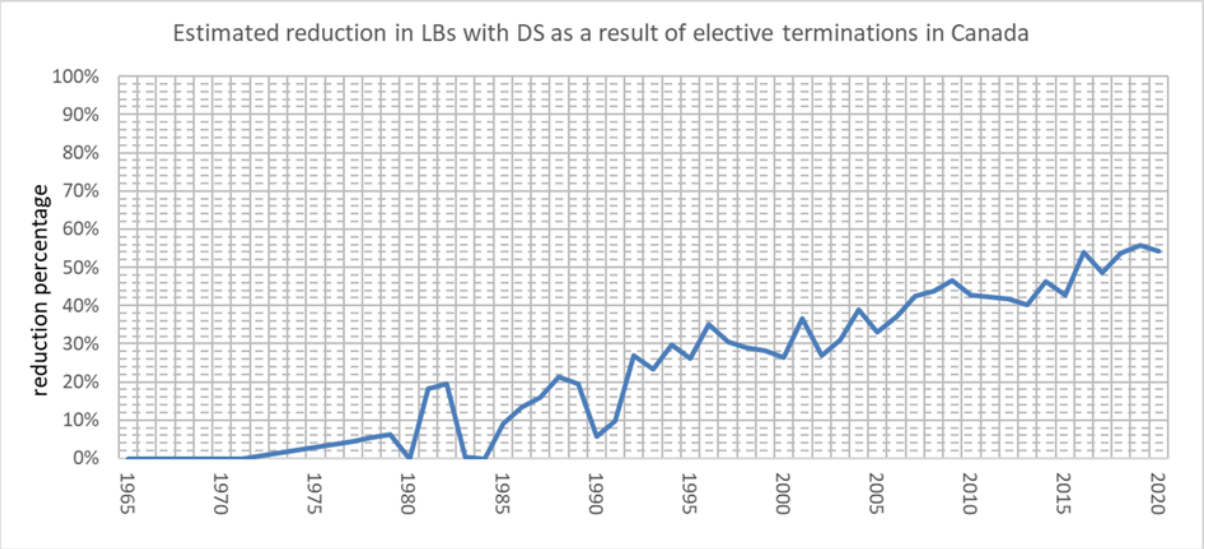
Interestingly, we found an article—based on national statistics on the cause of death—that reported the mean age of death of people with DS in Canada from 1974 to 2012 [9]. We have supplemented the data for 2013–2015 based on the MDB. We would argue that both models have a very good fit. From the 1990s onwards, the adapted model appears to have a slightly better fit.


Mean age at death of people with DS in Canada
60
50
40
30
20
10
0
1970
1972
1974
1976
1978
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
2020
data on basis of Navaneelan et al. 2016 (1974-2012) and MDB (2013-2015)
Adapted model
Earlier model

Supplementary Findings 1



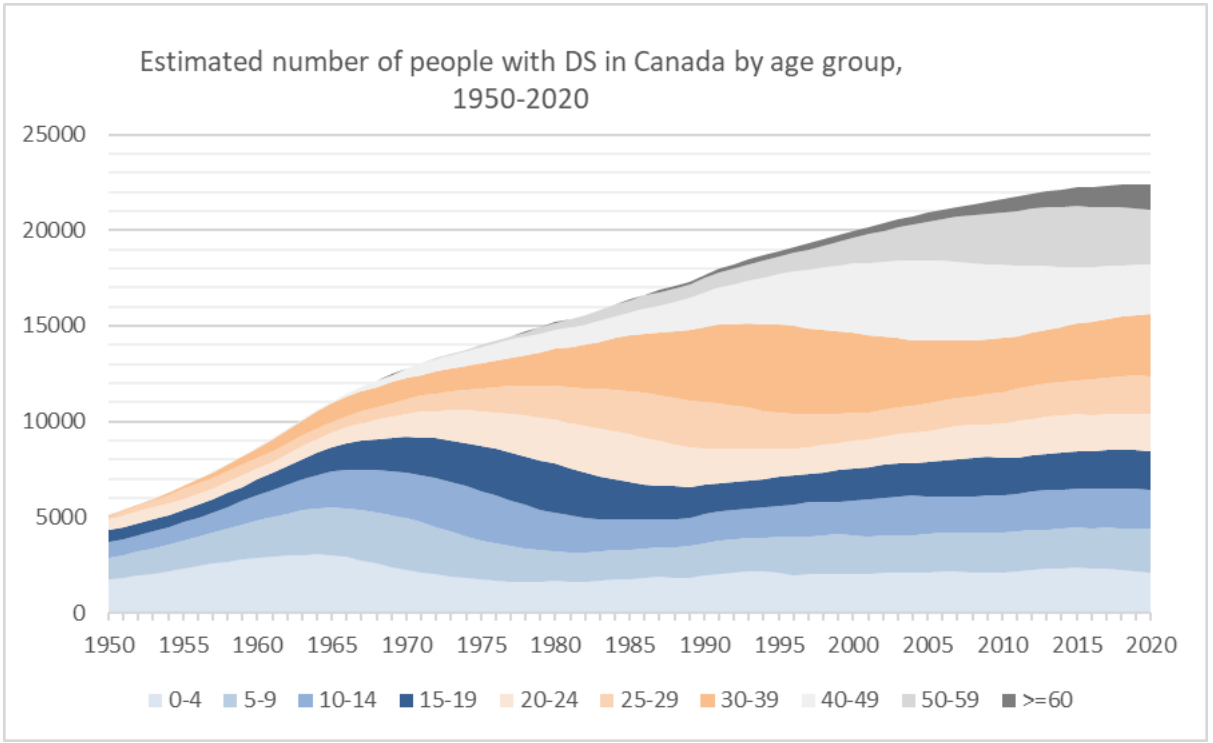


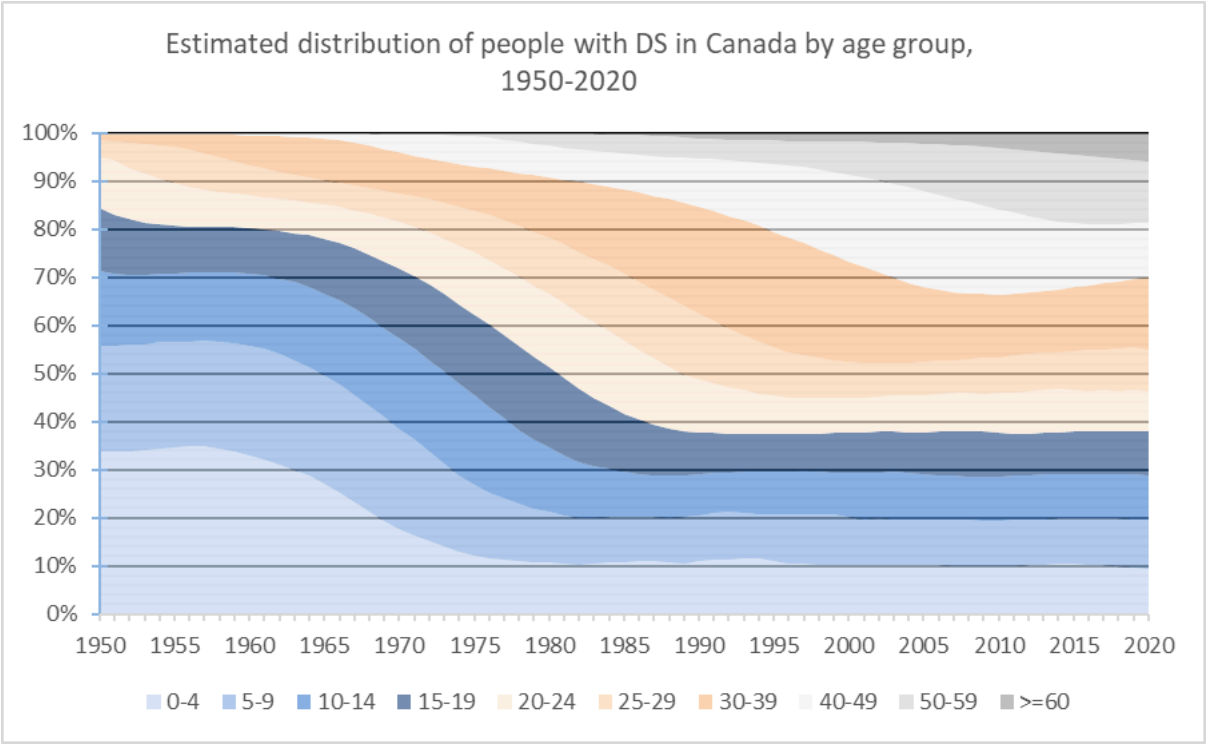


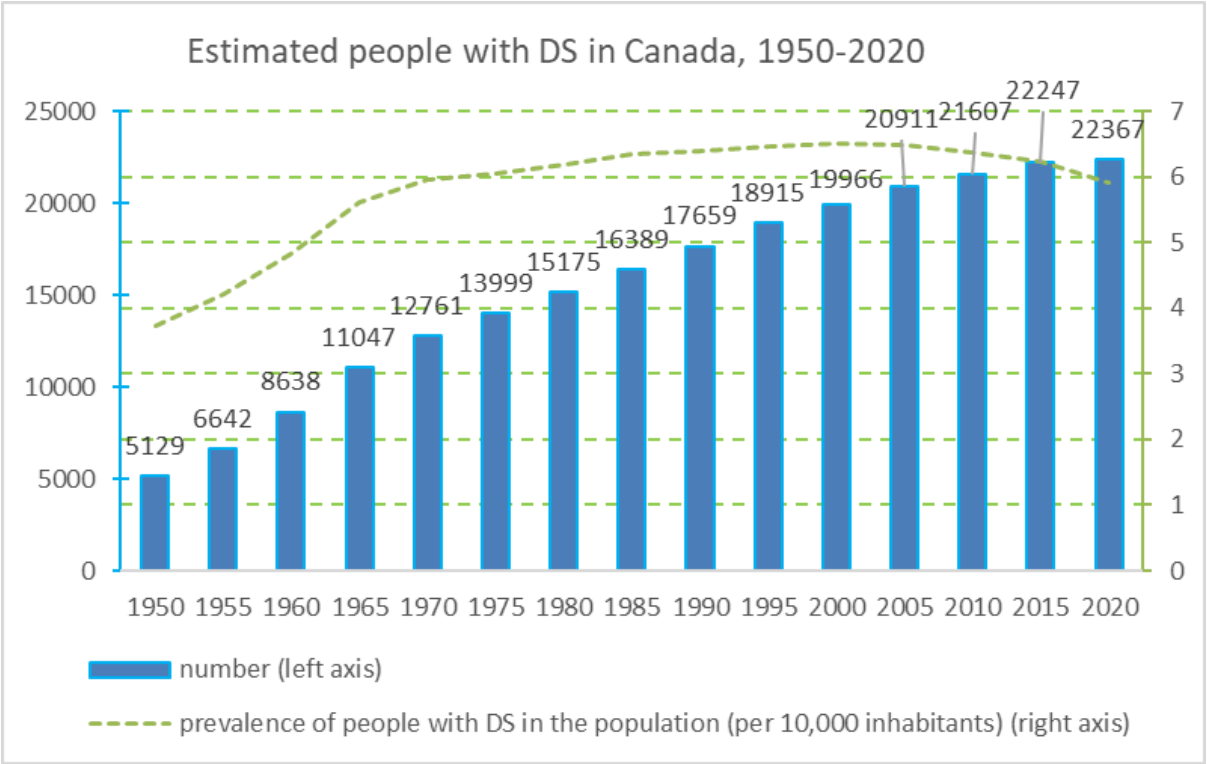
Below we present the estimated number of people with DS in Canada by age group, as of 2020. The models are almost identical in the estimated total number. The adapted model has slightly higher numbers in the age range 0–39 years and slightly lower numbers in the range 40–69 years of age.

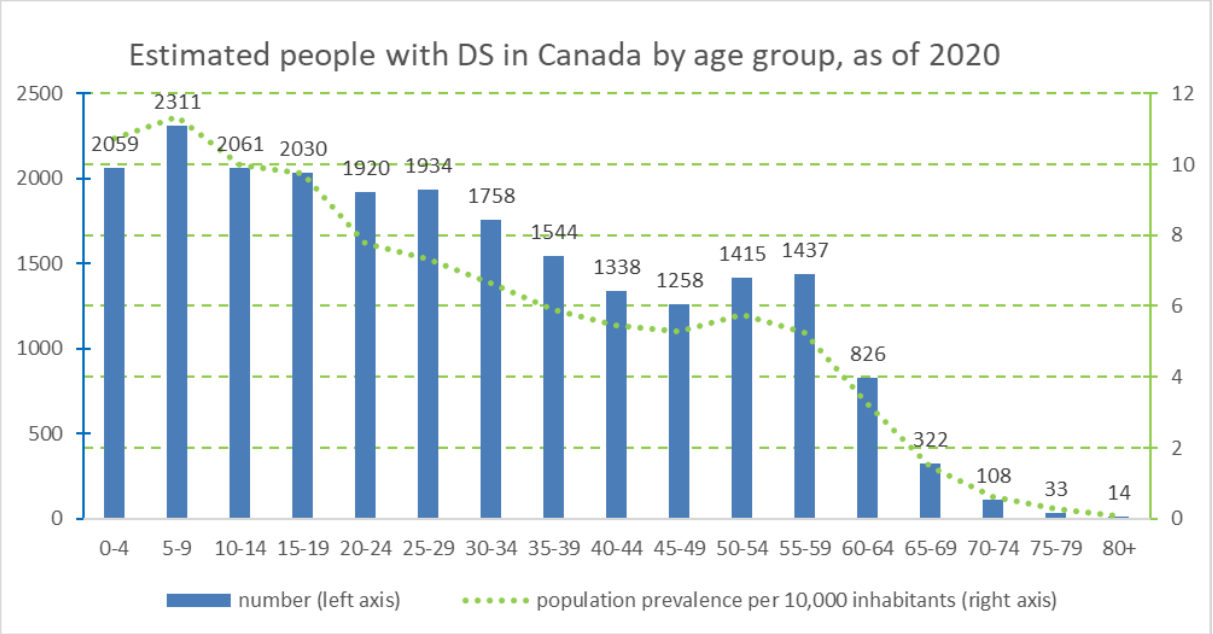
Age	Earlier model	Adapted model
0-4	2040	2059
5-9	2271	2311
10-14	2026	2061
15-19	1985	2030
20-24	1868	1920
25-29	1878	1934
30-34	1706	1758
35-39	1504	1544
40-44	1364	1338
45-49	1312	1258
50-54	1498	1415
55-59	1539	1437
60-64	885	826
65-69	338	322
70-74	109	108
75-79	31	33
80+	11	14
Total	22365	22367

As we have seen in S3 that the adapted model has a slightly better fit with empirical data, we will proceed in presenting only the results for the adapted model.




Estimated distribution of people with DS in Canada by age group, 1950-2020
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60


Estimated people with DS in Canada, 1950-2020
25000
20000
15000
10000
5000
0
7
6
5
4
3
2
1
0
5129
6642
8638
11047
12761
13999
15175
16389
17659
18915
19966
20911
21607
22247
22367
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)



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3. De Graaf G, Buckley F, Skotko BG. Estimation of the number of people with Down syndrome in Europe. *Eur J Hum Genet*. 2021;29(3):402-410. doi:10.1038/s41431-020-00748-y
4. Simpson NE, Dallaire L, Miller JR, et al. Prenatal diagnosis of genetic disease in Canada: report of a collaborative study. *Can Med Assoc J*. 1976;115(8):739-748.
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6. de Graaf G, Buckley F, Dever J, Skotko BG. Estimation of live birth and population prevalence of Down syndrome in nine U.S. states. *Am J Med Genet A*. 2017;173(10):2710-2719. doi:10.1002/ajmg.a.38402
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9. Navaneelan T, Pearson C, Janz T. Deaths from congenital anomalies in Canada, 1974 to 2012. Published online September 29, 2016.