Modeling the Impact of Research Investment on Down Syndrome–Associated Alzheimer's Disease

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About This Report

Individuals with Down syndrome (DS) are living longer than they used to. This trend has led to a heightened prevalence of DS-associated Alzheimer's disease (DS-AD) in the adult DS population. Information about the impacts of longer lives and increased DS-AD prevalence is lacking. This information is needed to inform both investment in research development programs for new treatments for DS-AD and policies related to health care and caregiving for aging adults with DS. To begin addressing the knowledge gap, we developed a multistate population simulation and projection model to study trends in DS-AD and the associated impact on caregiving. The study was funded by the LuMind IDSC Foundation, the Alliance for Aging Research, BrightFocus Foundation, and the National Down Syndrome Society.

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Acknowledgments

Summary

Increasing numbers of people with Down syndrome (DS) are reaching older ages, a positive trend that brings novel challenges. Individuals with DS face a much higher rate of Alzheimer's disease (AD) than the general population. Treatments for AD among those with DS are needed, as are strategies for addressing the changing caregiving needs that AD brings to those with DS and those who care for them.

Recent innovations in AD treatment draw into focus critical issues of health care access, equity, and inclusion for those with DS. This study focuses on the uniquely disparate health and social costs of AD in the DS population. Through modeling, this study addresses the limited information about potential impacts of DS-associated Alzheimer's disease (DS-AD) given longevity gains for those with DS and the potential for research investment to alter prevalence of DS-AD and related caregiving impacts.

Key Findings

- Prevalence of AD among adults aged 65 and older is about six times higher among Americans with DS than in the general population (65 percent versus 11 percent).
- Caregiving for the adult DS population aged 45 or older is currently estimated to require 35,000 full-time equivalent (FTE) hours per year. Assuming this care is provided at the national average rate for home health and personal care aides or entails lost wages of equal value for family and other unpaid caregivers, DS caregiving is estimated to cost about $1 billion annually.
- Over the past 50 years, the percentage of the DS population aged 50 and older quadrupled from about 5 percent to nearly 20 percent of the population by 2020.
- Improvement in DS survival and four decades of declining births following the baby boom have dramatically increased the likelihood that individuals with DS survive to develop DS-AD.
- With continued improvements in survival and without investments that would yield improvements in DS-AD, the additional gains in life years will predominantly be spent living with DS-AD. Adults with DS are projected to have more than double the increase in the expected years of life with DS-AD than without DS-AD (respective increases of 40 percent versus 15 percent).
- Treatment innovations reducing the onset of AD in the general population could improve health, survival, and caregiving outcomes by as much as 40 percent over the next 50 years if made available to the DS population. Among the impacts are the following:
  - Years of life without DS-AD is expected to increase by five years.
  - Prevalence of DS-AD is expected to decrease by 10 percentage points.
  - Caregiving for adults with DS-AD is expected to decline by 12,500 FTE hours.

Recommendations

To realize these benefits, access to treatments for AD would need to be expanded to include individuals with DS-AD. Multiple system-level policy improvements are needed to support this access:

- AD treatment approvals should include DS-AD, which requires inclusion of individuals with DS-AD in clinical trials along with attention to adequacy of sample sizes.
- Clinician education about these treatments should address guidance for use with patients with DS-AD.
- Timely detection of AD among individuals with DS requires clinician and caregiver education. Initiatives to improve early detection of treatable AD should include attention to those with DS-AD.

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Modeling the Impact of Research Investment on Down Syndrome–Associated Alzheimer's Disease

Background

The longevity of individuals with Down syndrome (DS) has increased dramatically over the 20th century (de Graaf, Buckley, and Skotko, 2017; Iulita et al., 2022). More individuals with DS are reaching adulthood and older adulthood. The increase in life expectancy presents novel challenges, including increased prevalence of Alzheimer's disease (AD) among those with DS and related changes to caregiving needs. The prevalence of AD among those with DS is higher than the prevalence in the non-DS population, with some estimates of 75 percent or above for those over 60 (Lai and Williams, 1989; McCarron et al., 2014; Strydom et al., 2018). Although the causes of AD in the general population and in the DS population are not fully known, the genetics associated with DS relate to increased production of amyloid precursor protein, which is a known risk factor for AD (Wiseman et al., 2015).

In the United States, improvements in survival over the first half of the 20th century have combined with the aging of the baby boom birth cohort—generally considered to be composed of those born between 1946 and 1964—to magnify the population impact of AD as a public health problem (Alzheimer's Association, 2018; Hebert et al., 2001; Knickman and Snell, 2002). However, growth in the population of individuals at younger ages within the DS population over the past 50 years might be dampening this impact. This is because the rebound in births from historic lows after the baby boom has been greater in the DS population than in the total U.S. population. It is unknown how population aging and increasing numbers of births affect trends in DS-associated Alzheimer's disease (DS-AD). Without this information, planning for the future health of people with DS is severely limited.

DS is associated with lifelong care needs for most individuals. Unpaid caregivers for individuals with DS are mainly family members and usually parents, with some caregiving transitioning to siblings as the ability for parents to provide physical care declines with their own increasing functional limitations (Watchman et al., 2019). The addition of AD to DS (1) adds to caregiving challenges and changes health care utilization and (2) has consequences for overall health care costs for individual families and for society. Features of AD, such as neuropsychiatric symptoms, add to caregiver challenges (Fonseca et al., 2021).

Despite high DS-AD prevalence, the challenges for family caregivers of individuals with DS-AD have been substantially understudied (Ilacqua et al., 2020). Even less is known about the costs to caregivers of caring for a family member with DS-AD. The lives of individuals with AD—and those that care for them—have changed with the approval of two new treatments, aducanumab and lecanemab, in 2021 and 2022, respectively. More treatments are in the pipeline,

and in the United States, the Institute for Clinical and Economic Review (ICER) is examining treatment value (ICER, 2023; Lin et al., 2021). ICER's analyses are intended to use health economic modeling to aid with the determination of value and ultimately are intended to inform coverage decisions by health insurers.

Although attention to the downstream impacts of treatment developments tied to research investment has increased for AD in the general population (e.g., Baird et al., 2021), few studies examine the research investment impacts for individuals with DS, particularly individuals with both DS and AD. Public health planning, along with planning for research investments, requires more-detailed information about the potential impacts of treatments for AD among those with DS, including the impact of decreased prevalence of DS-AD, the impact of changes in life span, and the impact on caregiving.

To begin addressing this knowledge gap, we sought to answer three research questions:

- What is the status of the cognitive health and longevity of the older adult DS population?
- What is the status of caregiving associated with DS-AD for the older adult DS population?
- How could research investment affect trends in cognitive health, longevity, and caregiving in the next 50 years?

Approach

We used a multistate life table (MSLT) modeling approach to address the research questions. The MSLT modeling approach can be used to estimate population health metrics to summarize the dynamic changes in population health that arise when the incidence of a disease, such as AD, changes across ages and over time and is potentially independent of changes in survival with and without the disease (Ewbank, 2004; Reuser, Bonneux, and Willekens, 2010; Reuser, Willekens, and Bonneux, 2011). The framework we developed to answer the research questions using the MSLT model is depicted in Figure 1. This figure shows how the MSLT model is used to relate inputs to outputs and generate new evidence about the status of the DS population and alternative projected scenarios for the future. We use the MSLT model to simulate conditions for 2020 and to project 50 years to 2070.

Figure 1. Framework for Multistate Population Simulation and Projection

Model Inputs	Multistate Life Table Model	Model Outputs	

Simulation inputs:
1. DS-AD incidence by age
2. Survival by age with DS-AD
3. Survival by age with no DS-AD
4. Size of birth cohort
 	
Projection inputs:
Expected change in inputs 1-4
		Survival & Cognitive Health
		• Population size by age and DS-AD status
		• Prevalence of DS-AD in total and by age
		• Total life expectancy
		• Years of life with & without DS-AD
			Caregiving
			• Total expected caregiving hours and FTEs:
			  • for the population with DS-AD
			  • for the population without DS-AD

The Multistate Life Table Model

In the three-state MSLT model we developed, we consider transitions between the three statuses of (1) no DS-AD, (2) DS-AD, and (3) death. The model simulates states of the life trajectory of the DS population from (1) being born into the no DS-AD status, (2) aging and being subjected to age-varying risks of incident DS-AD (i.e., remaining in State 1 with increasing age or transitioning from State 1 to 2 with increasing age), and (3) aging and being subjected to age-varying risks of mortality either directly from the status of no DS-AD or after the onset of DS-AD (i.e., transitioning from State 1 to 3 or from State 2 to 3 with increasing age). The MSLT model is explained in detail in Appendix B.

Development of the MSLT model proceeded iteratively through identification of an initial set of age-specific input probabilities that fell within the boundaries of prior literature, estimation of the MSLT, and evaluation of the MSLT to assess whether the output was consistent with calibration targets from the prior literature, most notably a recent meta-analysis (Iulita et al., 2022). For the initial set of inputs, we harmonized prior estimates from the literature into age-specific input probabilities for equivalent age intervals. With few exceptions, prior studies had been conducted with small convenience samples of DS adults receiving clinical care. We focused on high-quality, recent studies with large samples of adults that provided the required analytical detail on age-varying change in input parameters (Lai et al., 2020; Mhatre et al., 2021; Rubenstein, Hartley, and Bishop, 2020). In addition, the research team conducted primary data analyses of input probabilities using administrative registry and surveillance data available from the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC).

For the primary data analysis, we identified all adults with DS in the CMS's Minimum Data Set (MDS) for Nursing Homes and Swing Bed Providers (MDS 3.0) (Centers for Medicare and

Medicaid Services, undated) and linked this sample with the Master Beneficiary Summary File (MBSF) (Research Data Assistance Center, undated-b) to obtain clinical assessment of the onset of DS-AD and the age of death. Detailed description of these health and health care microdata produced by the CMS are described in Appendix D. We also employed data on the number of births with DS reported on birth certificates and compiled by the CDC through the National Vital Statistics System.[1] Federal surveillance data of similar quality on DS deaths is not available because U.S. death certificates report DS only if it is identified as a primary or secondary cause of death. In addition, use of CDC data on DS deaths without attention to the changing birth cohort sizes over time generates critical bias in any inferences about mortality, such as mean age of death, and it exacerbates well-established numerator-denominator bias that can arise when death counts and population counts come from different sources.

The process of finalizing the parameterization and model structure of the MSLT required balancing the granularity of available data for the inputs against desired granularity of the outputs required for meaningful evidence about the research questions. After evaluating data sources, examining existing published literature, and obtaining feedback from the project's key informants on the initial MSLT models (see later section for discussion of key informant methods), we determined that the most parsimonious structure that achieved this balance was a three-state model that adjusted simulated and projected population counts by age for historical changes in the number of DS births. We determined that either differences were too small or there were insufficient data to distinguish differences by gender, race and ethnicity, geography, or type of caregiving arrangement without collapsing age groups and sacrificing larger differences in inputs by age.[2]

Projection Scenarios

We describe the projection scenarios in Table 1. We make a set of assumptions about annual change in age-specific DS survival probabilities, and we make a separate set of assumptions about annual change in age-specific DS-AD incidence. These assumptions are grounded in a review of prior literature and analyses of demographic and epidemiological trends we conducted, with feedback from key informants.

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[1] We gratefully acknowledge historical data on DS birth counts provided by Gert de Graaf.

[2] Reviews of the published literature showed small, inconsistent, or null findings on gender differences in age-specific risks of DS-AD incidence, total mortality, and DS-AD mortality (Iulita et al., 2022; Andrews, Martini, and Head, 2022).

Table 1. Scenarios for Projected Population Trends in DS-AD Incidence and DS Survival

| | Trends in DS-AD Incidence | | | |
| | 2020 | 2070 | | |
Trends in DS Survival	Stable Incidence (No Change)	Stable Incidence (No Change)	Innovation 1: Decreasing Incidence (−0.5% per Year)	Innovation 2: Rapidly Decreasing Incidence (−1% per Year)
Scenario A: No change in survival	Baseline A	Status Quo A	Innovation 1A	Innovation 2A
Scenario B: Survival improving	Baseline B	Status Quo B	Innovation 1B	Innovation 2B

The rows of Table 1 define the two sets of assumptions about DS survival. Scenario A assumes that age-specific mortality has remained the same since 2005. Scenario B assumes that age-specific mortality for DS adults has and will continue to decrease at a rate similar to the decline in the general population (i.e., a decline of 0.7 percent every year for DS adults aged 40 and older).[3] These two scenarios could be interpreted as upper and lower bounds for DS survival.

The columns of Table 1 define the four projections we make that vary the year and the projected trend in DS-AD incidence. For the assumption of stable incidence, we define a baseline projection for 2020 and a status quo projection for 2070 with no change in DS-AD incidence. In addition, for 2070, we define Innovation 1 in which we project annual decreases in DS-AD incidence of 0.5 percent per year and Innovation 2 with annual decreases in DS-AD incidence of 1 percent per year.

The assumptions for expected change in incidence inputs over the next 50 years are based on a prior study on the expected change in AD incidence in the total U.S. population over the next 50 years with research and scientific innovation (Sloane et al., 2002). This study used improvements in congestive heart failure and Parkinson's disease over the latter half of the 20th century as prototype success stories for the types of changes that would be needed for AD to achieve similar reductions. The rate of reduction we employ in Innovations 1 and 2 generates a 50-year reduction in the age-specific incidence of DS-AD that are, respectively, slightly lower and slightly higher than the average rate of change in incidence from Sloane et al. (2022).[4]

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[3] The Social Security Administration found that, over the 20th century, age-adjusted mortality rates declined on average by about 1.0 percent for men and women and by 0.6 percent for men and 0.8 percent for women over age 65 (Bell and Miller, 2005).

[4] We estimated an average annual rate of reduction of 0.8 percent for Sloane et al. (2002) by averaging across age-specific reductions in incidence for the delayed disease onset model. We calculated age-specific incidence for the baseline and the final projected time point using the authors' equation for age-specific incidence (which defines incidence to be exponentially increasing with age) with their assumptions about change in the parameters of this

Stakeholder and Informant Input

In alignment with principles of engaged research, we consulted with content area experts and those with relevant lived experience at several points. Prior to finalizing the model, we conducted a stakeholder-convening to broaden input and bring in perspectives valuable to methods decisions. The six stakeholders who were invited to participate were experts in DS-AD research and health care coverage and reimbursement. The stakeholders represented a variety of perspectives: experts in and funders of dementia and intellectual and developmental disability research, drug developers, federal payers, and relatives and friends of adults with DS, including a participant with experience managing a group home for adults with DS. The convening was held in January 2023.

The stakeholder group was provided with an overview of the project goals and methods and asked to comment on the appropriateness and comprehensiveness of proposed model outputs for informing research funders, drug developers, and policymakers. Participants were also asked to discuss the potential influence of this work on the larger field of dementia research.

Several participants noted the increased attention to clinical trial participation for individuals with DS-AD, acknowledging that the limitations of data on DS-AD and caregiving make the modeling approach of this project valuable. The group discussed implications of sparse data on DS and DS-AD for modeling efforts—particularly for racial and ethnic groups other than Whites—and the limited clinical trial representation of rural communities and communities with low socioeconomic status.

The group endorsed the model inputs as appropriate and sufficiently comprehensive. They also expressed strong support for adding data about caregiving costs because this information will be valuable for multiple audiences. The stakeholders identified some often overlooked advantages of including individuals with DS in AD treatment trials, such as the potential for streamlined proof-of-concept studies and focused biomarker exploration. Participants noted that some AD research consortia—including the Alzheimer's Disease Research Centers, which is funded by the National Institutes of Health—are now pursuing more work with DS. All participants agreed that improving the evidence base by accruing more data on life span and median age of death by race would be desirable.

The participants were enthusiastic about the contributions our work could make, particularly given the lack of empirical data and the lack of modeling studies examining the impact of research investment on individuals with DS, on those who care for individuals with DS, and on the wider societal costs and benefits.

Following the discussion with these stakeholders and additional analytic work, we consulted with key informants, clinicians, and researchers who had substantial expertise in DS. The goals of these discussions were to address technical aspects of the model and inform model refinement.

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equation under the delayed disease onset model (specifically, that the rate of the exponential increase in incidence with age would change from 0.149 to 0.109).

We held individual interviews with five informants that included clinicians and scientists from academic medical centers and research advocacy organizations. The informants had expertise in neurology, genetics, epidemiology, dementia, intellectual and developmental disabilities, and public health. Four informants were based in the United States, and one worked in Europe with U.S. collaborators.

These experts provided input on the structure and parameterization of our model, and they provided input on the accuracy and appropriateness of data used in parameterization. The discussions included reviews of the variation in the published estimates related to DS-AD and DS and the credibility of our estimates relative to various published estimates. These discussions also addressed the benefits and risks of examining gender, setting of care and care types, changes in birth cohort size as part of the model, and accuracy of different projection assumptions (i.e., change in survivorship and change in incidence). In our earlier description of the MSLT model, we discussed how we determined the extent of granularity supported by the data and prior evidence.

Key informant input led us to reevaluate some of the simplifying assumptions we were making by using conventional MSLT methods for the projections. Specifically, we conducted additional analyses of changes in birth cohort size (see Appendix A), and we determined that the assumption of equal birth cohort sizes to estimate population composition and population DS-AD rates was not appropriate. Thus, we developed a novel extension of the conventional MSLT methods (e.g., see Preston, Heuveline, and Guillot, 2000; Schoen, 2013) to adjust the survivorship function for changes in birth cohort size across age groups in a given simulated year (see Appendix B). This innovation allowed us to incorporate required analytic detail that would otherwise be accomplished using a more complex and data-intensive method (such as population microsimulation) while maintaining the analytical parsimony of the MSLT method.

Findings

Projected Life Expectancy and Age Composition of the DS Population from 2020–2070

As shown in Figure 2, we estimate that life expectancy at birth for individuals with DS will be about 54 years and that it will increase by about four years if age-specific improvements in survival continue to accumulate incrementally as assumed in Scenario B. Scenario A assumes that age-specific risks of mortality—and consequently trends in life expectancy—are unchanged after 2005.

Figure 2. Estimates of Historical and Projected Trends in Life Expectancy for Individuals with DS
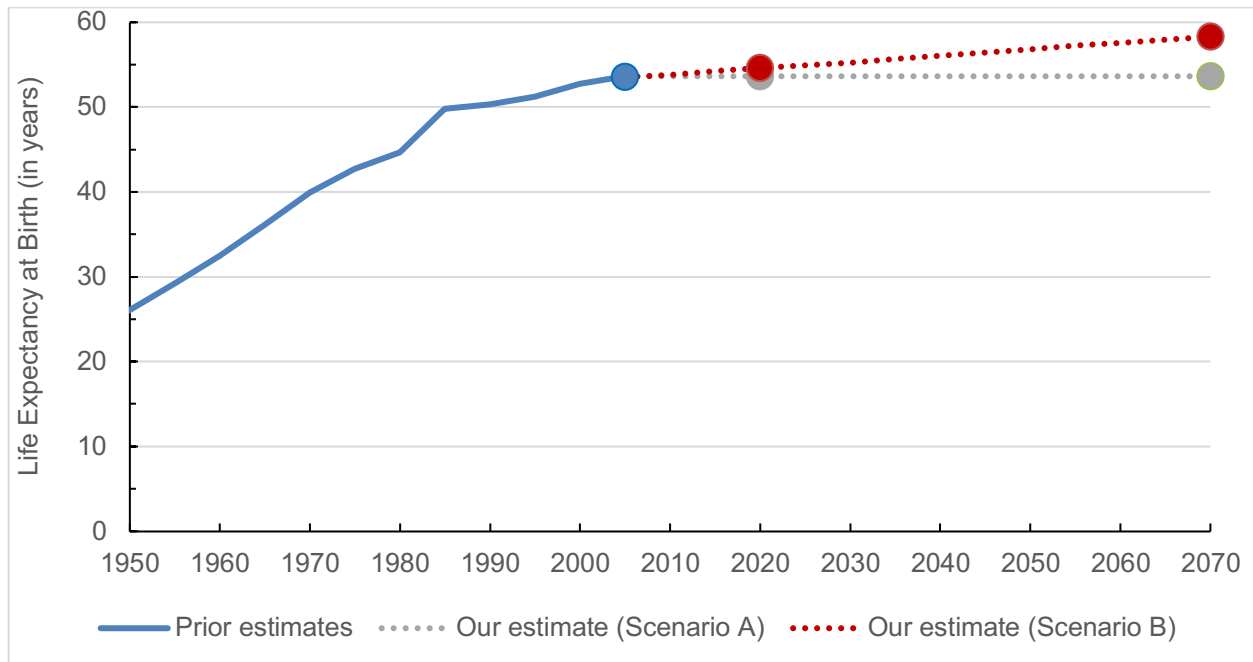
SOURCE: Life expectancy is calculated using age-specific DS survival probabilities. The "Prior estimate" series (solid line) uses published probabilities (de Graaf, Buckley, and Skotko, 2017). The series labeled "Our estimate" is generated by the authors.
NOTE: The dotted lines connect the most recent point from the prior estimate series for 2005 with the first "Our estimate" series for 2020. Scenario A assumes no change in DS mortality after 2005. Scenario B assumes age-specific mortality probabilities decline by 0.1 percent and 0.7 percent annually for individuals younger than 40 years and 40 years or older, respectively.

Between 2010 and 2020, we estimate that continuation of the improvements in survival and diminishing size of the birth cohorts (from the 1960 to 1970 birth cohort) will generate continued growth in the older adult population (see Figure 3). From the historical estimate of nearly 14 percent in 2010, the percentage of the DS population at age 50 or older in 2020 is expected to increase to about 17 percent and 19 percent under Scenarios A and B, respectively. After 2020, the change in the composition of the population is assumed not to change under Scenario A. In Scenario B, the growth in the older adult population because of continued improvements in survival is increasingly dampened over time by the growth in the birth cohort size after 1970. The rate in 2070 is expected to be about 23 percent.

Figure 3. Historical and Projected Estimates of the Percentage of the Total Population with DS Who Survive to Age 50 or Older
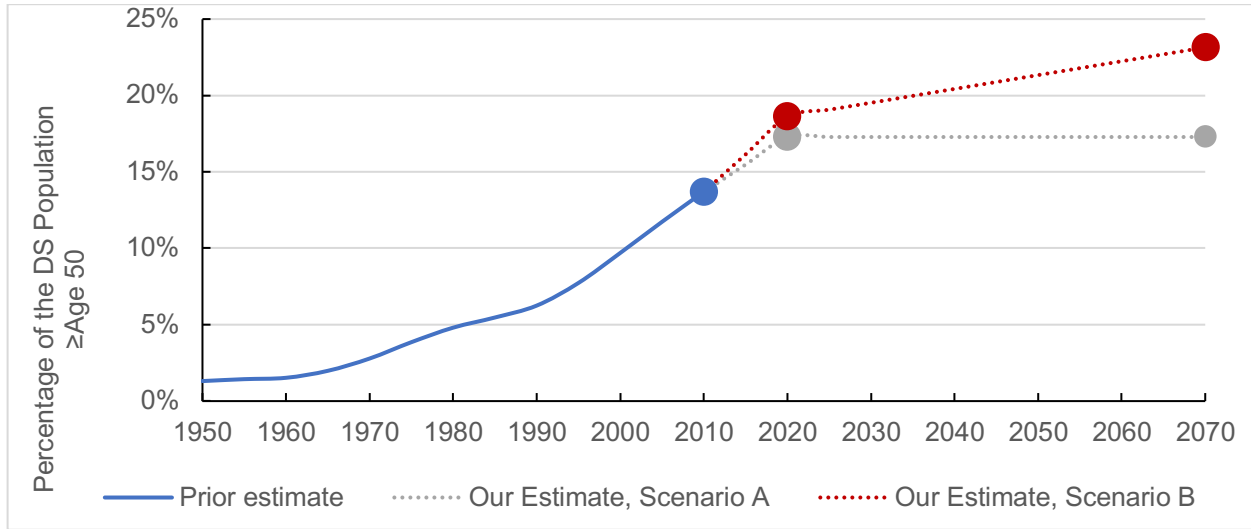
SOURCE: Percentage of the total population with DS aged 50 or older is calculated using age-specific DS population counts. The "Prior estimate" series (solid line) uses published population counts (de Graaf, Buckley, and Skotko, 2017). The series labeled "Our estimate" is generated by the authors.
NOTE: The dotted lines connect the most recent point from the prior estimate series for 2010 with the first "Our estimate" series for 2020. Scenario A assumes no change in DS mortality after 2005. Scenario B assumes age-specific mortality probabilities decline by 0.1 percent and 0.7 percent annually for individuals younger than 40 years and 40 years or older, respectively.

The discontinuous trend we observe in Scenario A and Scenario B—despite a constant change in survival—arises because of the changes in the birth cohort sizes reaching adulthood by, respectively, 2010, 2020, and 2070. In 2010, the older adult DS population was almost entirely composed of the baby boom birth cohort (e.g., individuals reaching age 50 were born in 1960, roughly the peak of the baby boom [see Appendix A]). For the next 15 years after 2010, the adults who survive to older ages come from smaller and smaller birth cohorts (e.g., the historically smallest birth cohort over the past 50 years occurred in about 1975; adults from that cohort reached age 45 in 2020). As smaller and smaller cohorts entered the older ages, the age composition of adults aged 45 and older shifted to older ages as baby boomers with DS aged (see Appendix A). The increase in the percentage of adults aged 50 and older in Scenario A was driven by the changes in birth cohort size, whereas the larger increases in Scenario B were driven by both birth cohort size and improvements in survival. After 2020, however, trends in birth cohort size reversed: Adults from increasingly larger birth cohorts began to enter older age and to increasingly counterbalance the larger birth cohort sizes at the oldest of the older ages. The unestimated points between 2020 and 2070 are linked with straight lines; however, the changes in birth cohort size imply that the path is nonlinear.

Projected Cognitive Health and Caregiving Needs of the Adult DS Population from 2020–2070

In Figure 4, we depict the age-specific rates of DS-AD in 2020 using the MSLT method and age-specific counts and prevalence of DS-AD in 2020. The prevalence increases from about 20 percent at ages 50 through 54 to more than triple that rate (64 percent) for ages 65 and older. It is noteworthy that, in Figure 4, we depict the age-specific rates under Scenario A; however, the age-specific rates under Scenario B are nearly identical or, in the last age group, differ by less than two percentage points.[5]

Figure 4. Total Number of Adults With DS and the Number With and Without DS-AD by Age Group, 2020
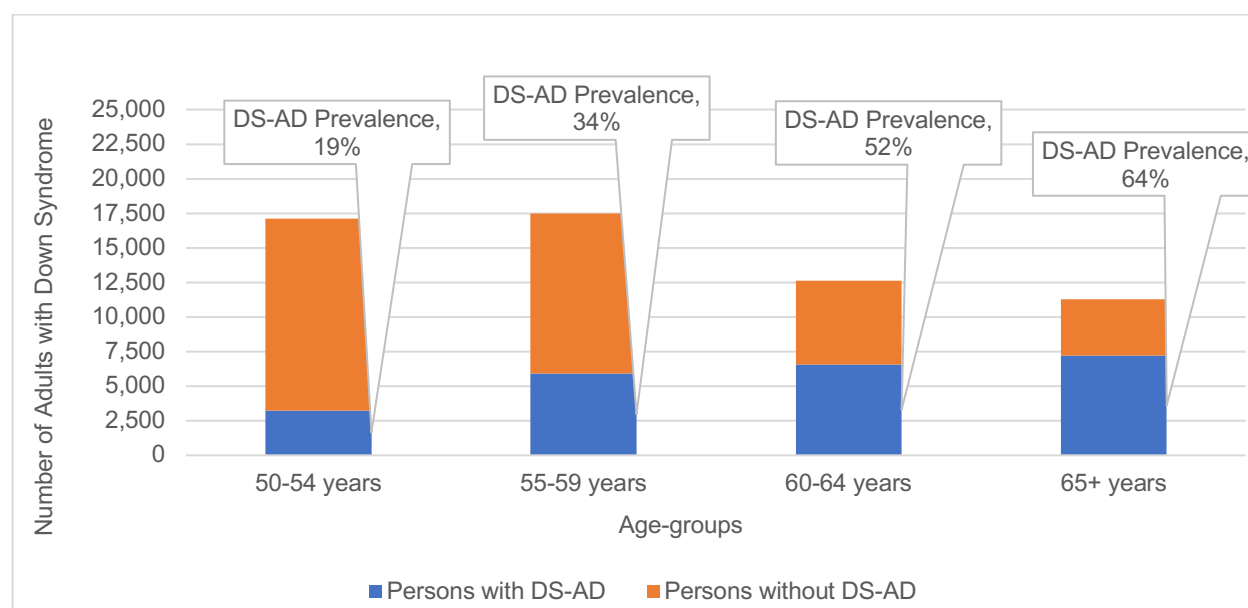
NOTE: Estimates are produced by the authors using MSLT methods. We depict the age-specific rates for Scenario B. The use of age-specific prevalence rates almost entirely age-adjusts for differences in age composition of the populations simulated under the two scenarios, with the exception of the open-ended group age 65 and older, which has a prevalence of 66 percent in Scenario A.

Next, in Figure 5, we project the prevalence of DS-AD among individuals aged 45 and older in 2020 to 2070 if there is no change in research investments and no innovations in DS-AD treatment. Then, we calculate the amount of change in prevalence between 2020 and 2070. In the baseline 2020 projections, we find that the rate is 32 percent under Scenario A (which assumes

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[5] In Scenario B, the rates are 19 percent at ages 50 through 54, 34 percent at ages 55 through 59, 52 percent at ages 60 through 64, and 66 percent at ages 65 and older. The lack of difference between Scenarios A and B is expected given the lack of differences in the age-specific incidence between the two alternative projections for 2020 and the fact that differences in survival between the two models will only make changes to the proportion of DS-AD versus no DS-AD in the open-ended age group.

no change in DS survival) and 33 percent under Scenario B (which assumes continuing improvements in DS survival).

Figure 5. Projected Estimates of DS-AD Prevalence for Adults Aged 45 Years and Older
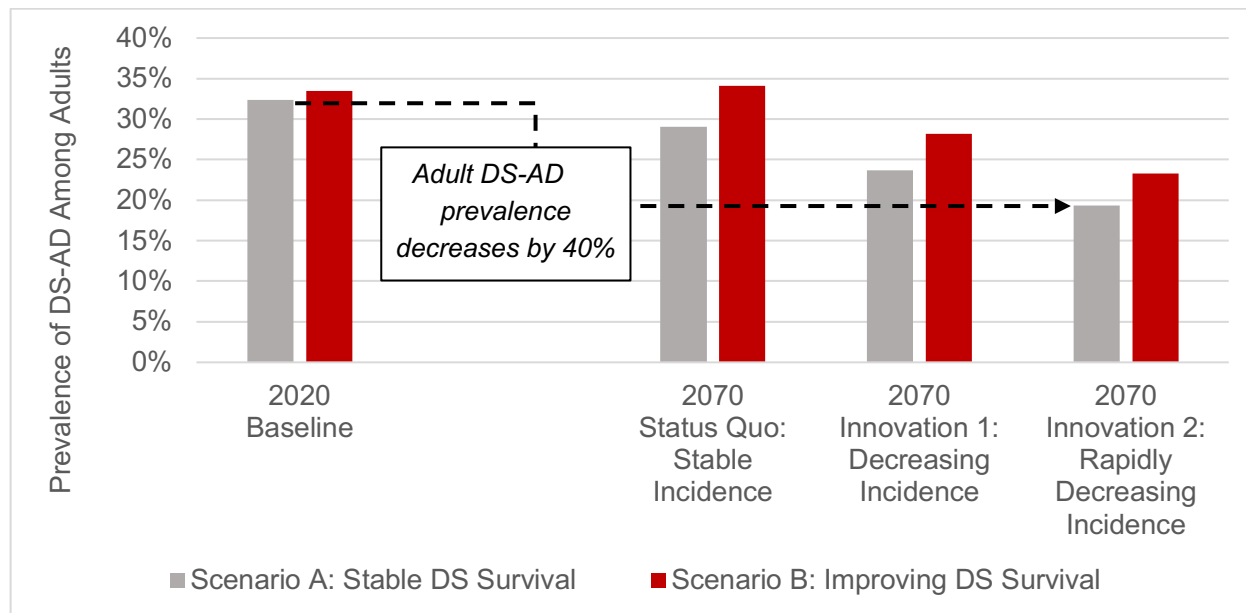
NOTE: Estimates are produced by the authors using MSLT methods. Assumptions about change in age-specific DS survival probabilities are defined by Scenario A (no change in DS survival) and Scenario B (continued improvement in DS survival). Assumptions about change in age-specific DS-AD incidence are as follows: 2020 baseline and 2070 status quo assumes stable DS-AD incidence with no change over time, Innovation 1 assumes DS-AD incidence decreases by 0.5 percent per year, and Innovation 2 assumes DS-AD incidence decreases by 1 percent per year.

Moving forward to the status quo projection in 2070, we find that prevalence is changed very little (34 percent) under Scenario B (improving DS survival). Recall that the status quo projection assumes that there has been no change in the age-specific incidence of DS-AD between 2020 and 2070. Under the status quo Scenario A projection, however, there is a small decline in the rate by three percentage points to 29 percent. Although this reduction in prevalence is small, it illustrates the importance of the changes in birth cohort sizes in influencing the projection results.

The decline in prevalence under status quo Scenario A—despite the absence of any changes in DS-AD incidence—results from the change in the birth cohort sizes reaching adulthood between 2020 and 2070. In this scenario, the age composition of the DS population aged 45 and older has shifted to younger ages with lower risks of developing DS-AD because of the relatively larger sizes of the more recent birth cohorts. Consequently, the number of individuals with DS-AD aged 45 and older is a smaller percentage of the total number of individuals with DS aged 45 and older. A similar change in the age composition is projected to occur in Scenario B; however, we estimate that the downward pressure on prevalence because of the changing size of the birth cohorts is completely reversed by the upward pressure on prevalence because of improvements

in survival. Taken in isolation, improvements in survival will generate larger numbers of adults at older ages (i.e., population aging, which is defined by a shift in age composition to older ages). In this scenario, population aging because of improvements in survival is balanced by the increases in birth cohort size that increase the numbers of adults at younger ages.

We next consider the projected changes in the prevalence of DS-AD among adults aged 45 and older under the two scenarios for potential innovation in DS-AD treatment (see Figure 5). Recall that Innovation 1 and Innovation 2 are projected to generate either a 0.5-percent or 1-percent reduction, respectively, in age-specific DS-AD incidence in each year, with the reductions in incidence accumulating annually over the 50 years from 2020 to 2070. We estimate that prevalence is 24 to 28 percent under the conditions of Innovation 1 (depending on the assumptions about change in survival) and 19 to 23 percent under the conditions of Innovation 2. The upper and lower bounds of the prevalence for Innovations 1 and 2 correspond, respectively, with Scenario A (no change in survival) and Scenario B (ongoing improvements in survival).

In summary, we show in Figure 5 that there is projected to be as much as a 40-percent reduction in the prevalence of DS-AD among adults aged 45 and older (i.e., a change from a DS-AD prevalence of 32 percent in 2020 to 19 percent in 2070). This change occurs in the 2070 Innovation 2, Scenario A conditions, in which DS-AD incidence is reduced by 1 percent per year and age-specific mortality for individuals with DS remains stable.

The next set of cognitive health and survival outcomes we project are depicted in Figure 6, and they entail the projections of the expected years of life with and without DS-AD among adults aged 45 and older. We first report the baseline 2020 simulations under the two scenarios for mortality change, where Scenario A entails no change in age-specific DS survival probabilities and Scenario B entails ongoing change in age-specific DS survival probabilities of 0.7 percent every five years at ages younger than 40 and of 3.5 percent every five years for individuals aged 40 or older.

Figure 6. Projected Estimates of Expected Years of Life With and Without DS-AD for Individuals Surviving to Age 45
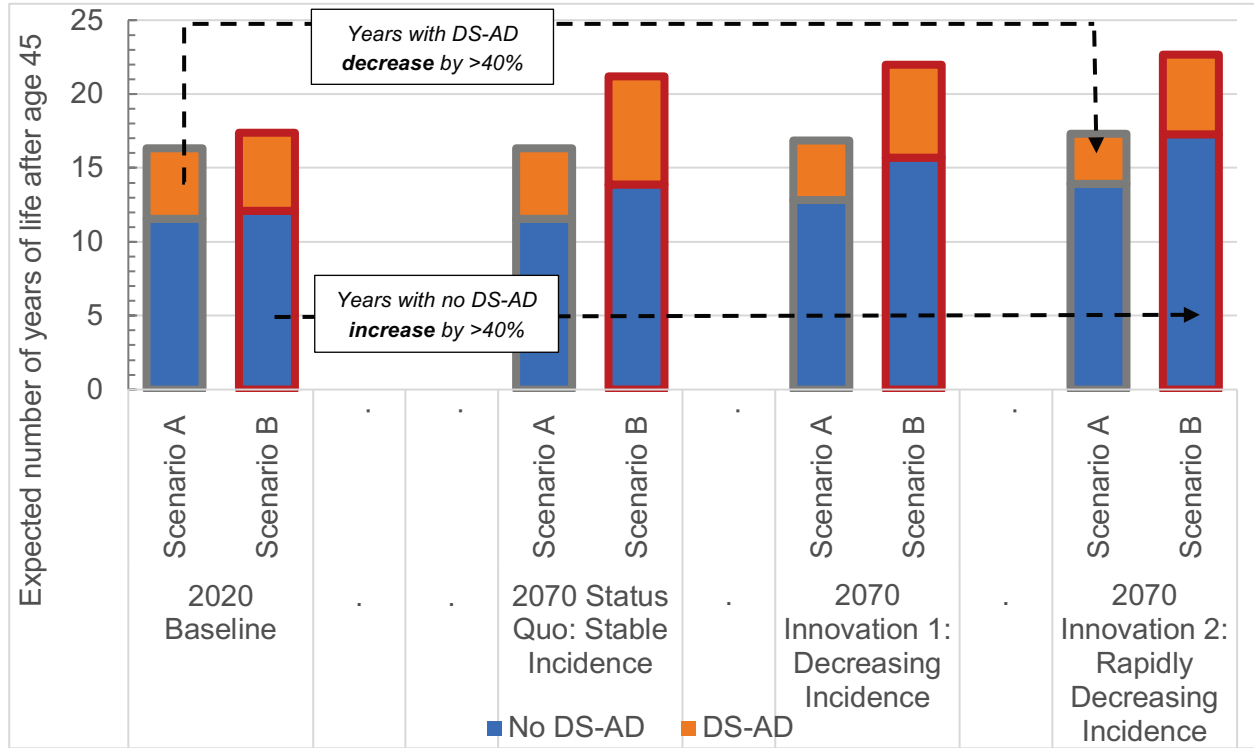
NOTE: Estimates are produced by the authors using MSLT methods. Assumptions about change in age-specific DS survival probabilities are defined by Scenario A (no change in DS survival) and Scenario B (continued improvement in DS survival). Assumptions about change in age-specific DS-AD incidence are as follows: 2020 baseline and 2070 status quo assumes stable DS-AD incidence with no change over time, Innovation 1 assumes DS-AD incidence decreases by 0.5 percent per year, and Innovation 2 assumes DS-AD incidence decreases by 1 percent per year.

For the 2020 baseline projections, we find that the expected years of life after age 45 range from about 16 to 18 years depending on the survival assumption, and this total life expectancy after age 45 is divided into about 11.6 to 12.1 years with no DS-AD and 4.8 to 5.3 years of life with DS-AD.

For the 2070 status quo projections, we make alternative estimates assuming either that (1) age-specific DS-AD incidence and age-specific DS survival have remained unchanged since 2020 and only the birth cohort sizes have changed (Scenario A) or (2) age-specific DS-AD incidence has remained unchanged but DS survival has improved continuously (with reductions of 0.7 percent every five years for ages younger than 40 and reductions of 3.5 percent every five years for ages 40 and above). As expected, we find that the projected years of life with and without DS-AD do not change when there are no changes in DS-AD incidence (i.e., expected years of life with and without DS-AD are 4.8 and 11.6 years, respectively, for the 2070 status quo Scenario A).

For status quo Scenario B, the continued improvements in DS survival in the context of no change in DS-AD incidence means that there will be increases in years of life with and without

DS-AD. This is a 15-percent increase (to a value of 13.8 years) for years with no DS-AD but nearly a 40-percent increase (to a value of 7.3 years) for years with DS-AD.

For Innovation 1, years of life *with no* DS-AD are increased slightly, and years of life *with* DS-AD are reduced slightly. For Innovation 2, years of life *with no* DS-AD are also increased, and these increases are especially notable in Scenario B (compare a 43-percent increase from 12.1 to 17.3 years in Scenario B with the 21-percent increase from 11.6 to 13.9 years in Scenario A). On the other hand, years of life with DS-AD are reduced in Scenario A (i.e., a 45-percent reduction from 4.8 to 3.4 years) and essentially unchanged in Scenario B (i.e., 5.3 to 5.5 years).

Our last set of projections considers the impact of changes in the MSLT inputs over time and across different projection scenarios for caregiving outcomes. In Figure 7, we report the projected full-time equivalent (FTE) hours for caregiving that the previously described changes in the numbers of individuals with and without DS-AD are expected to require. These figures are estimated from the projected size of the DS population with and without DS-AD aged 45 years and older using prior evidence of about three times greater caregiving hours for adults with DS-AD (see Appendix B).

We find that caregiving for adults with DS-AD in 2020 is estimated to require upward of about 35,000 FTE hours (31,983 under Scenario A and 35,743 under Scenario B). Assuming that caregiving for individuals with DS is provided at the national average rate for home health and personal care aides, which is $14.87 per hour (U.S. Bureau of Labor Statistics, 2023), or that the care entails lost wages of equal value for unpaid caregivers, DS caregiving is estimated to cost about $1 billion annually.

Consistent with the findings on the cognitive health and survival outcomes, we find that there is little change in the projected estimates of caregiving from 2020 to 2070 under the status quo Scenario A conditions. But under the status quo Scenario B conditions (of no change in DS-AD incidence but ongoing improvements in DS survival) there is as much as a 17- to 20-percent increase in caregiving with or without DS-AD (with the larger increase of 20 percent for individuals with DS-AD).

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Figure 7. Projected Caregiving Full-Time Equivalent Hours for Individuals With and Without DS-AD Ages 45 Years and Older
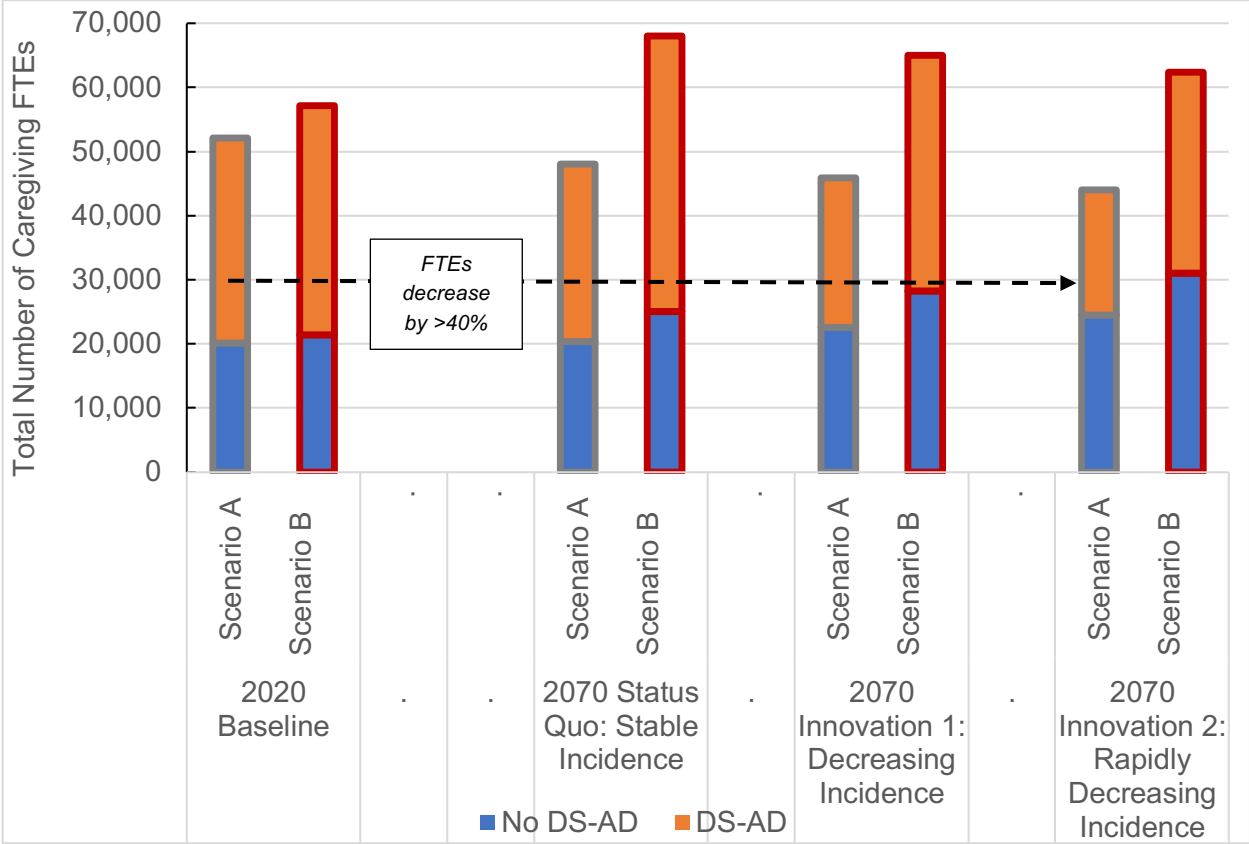
NOTE: Estimates are produced by the authors using MSLT methods. Assumptions about change in age-specific DS survival probabilities are defined by Scenario A (no change in DS survival) and Scenario B (continued improvement in DS survival). Assumptions about change in age-specific DS-AD incidence are as follows: 2020 baseline and 2070 status quo assumes stable DS-AD incidence with no change over time, Innovation 1 assumes DS-AD incidence decreases by 0.5 percent per year, and Innovation 2 assumes DS-AD incidence decreases by 1 percent per year.

For Innovations 1 and 2, we project that caregiving FTE hours for individuals with DS-AD will be reduced at most by 45 percent for Innovation 2 and Scenario A. Specifically, there is a reduction from 2020 to 2070 of about 12,500 FTE hours (i.e., 31,983 − 19,524 = 12,459).

Summary of Findings

The following is a summary of our findings for each of the research questions.

1. What is the status in 2020 of the cognitive health and longevity of the older adult DS population?

    – Prevalence of DS-AD is estimated to triple over the 15 years of older adulthood from age 50 to age 65.
    – Age-specific rates are 19 percent for ages 50 to 54, 34 percent for ages 55 to 59, 52 percent for ages 60 to 64, and 64 percent for ages 65 and older. These rates

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reach upward of six times the rate of AD in the general population (10.8 percent for age 65 and older; see Alzheimer's Association, 2023, p. 20).
   – Life expectancy for individuals with DS is estimated to be about 54 to 55 years.
   – Individuals with DS are expected to survive for about five years after developing DS-AD.

2. What is the status in 2020 of caregiving associated with DS-AD for the older adult DS population?

   – About 35,000 FTE hours are expected to be devoted annually to caring for individuals with DS-AD.

3. How could research investment affect trends in cognitive health, longevity, and caregiving in the next 50 years?

   – DS-AD prevalence is projected to decline by upward of about 40 percent of the 2020 prevalence rate.
   – The change in years of life with and without DS-AD and change in caregiving FTE hours for individuals with and without DS-AD also depend strongly on assumptions about projected change in survival.
   – The largest improvements in *years of life with DS-AD* and *DS-AD caregiving FTE hours* are observed for simulations in which survival is assumed to remain unchanged.
   – The largest improvements in *expected years with no DS-AD* and *life expectancy at birth* are observed for simulations in which survival is assumed to continue to improve.

Recommendations

The findings suggest some health care, research, and policy action steps to ensure fair AD treatment access for individuals with DS-AD. To support this access,

- AD treatment approvals should include DS-AD, which requires inclusion of individuals with DS-AD in clinical trials along with attention to adequacy of sample sizes.
- Clinician education about these treatments should address guidance for use with patients with DS-AD.
- Timely detection of AD among individuals with DS requires clinician and caregiver education. Initiatives to improve early detection of treatable AD should include attention to those with DS-AD.

Discussion

The results of the study demonstrate the potential for investment in DS and DS-AD research to increase years of life without DS-AD among those living with DS, with concomitant improvements in caregiving time investments. Specific projections depend on assumptions about DS longevity, which itself might improve with increased research investment. The magnitude of the caregiving impact is notable, given that, unlike in the general population, DS caregiving is ongoing for many individuals with DS whether or not they have AD.

The results from this MSLT approach support calls for increased research investment in DS-AD. Practically, leveraging existing drug development efforts in AD for the general population could—with just a marginal investment—yield information about treatment efficacy for AD broadly and for those with DS at high risk of developing AD. In prior work, researchers concluded that prevention studies for AD benefit from the inclusion of individuals with DS and that study of AD in the general population would benefit from increased inclusion of individuals with DS-AD in clinical trials (Boerwinkle et al., 2023; Iulita et al., 2022).

The projected innovations simulated in this study are conceived broadly as arising from any number of potential improvements in DS-AD treatment resulting from increased investment in clinical research. Although the projections have been made without reference to specific mechanisms for the improvements in treatment, there is evidence to support increases in research investment in several areas. Early intervention is a promising avenue for reducing DS-AD prevalence and attendant family, health system, and societal burden (Boerwinkle et al., 2023; Silverman et al., 2022). Another question to address in future work is whether there are gender differences in DS-AD. Although some prior work suggests DS-AD might be more common among women, studies have not consistently observed statistically significant differences; some studies have even observed higher risks of DS-AD among men (Andrews, Martini, and Head, 2022; Lai et al., 2020; Mhatre et al., 2021; Schupf et al., 2008). Another area for further examination relates to the potential for long-term care policy to (1) improve provision of care for individuals with DS-AD and (2) reduce the impact of DS-AD on family and other unpaid caregivers (Boerwinkle et al., 2023; Iulita et al., 2022).

The limitations in available data for individuals with DS represent a major challenge for completing this type of modeling. Existing data resources available from the CDC and CMS are important for understanding the health of populations. However, these sources are inadequately developed for the DS population and thus are underused in research on the DS population. In this study, we have developed methods to employ surveillance data in conjunction with data from clinical populations to leverage the respective strengths of each source.

Limitations

The present study highlights the lack of accurate data about individuals with DS and the consequences for guiding health policy for this population and those that care for them. The limited data on DS and on DS-AD was a major challenge for completion of this work, requiring repeated and careful review of the value of estimates for informing decisionmaking, balanced against the robustness of the estimates given the limited evidence.

In parallel with the investment in clinical research on DS-AD, investment in population-based data infrastructure for individuals with DS would yield meaningful returns. As of this writing, there is no ongoing surveillance of the changing size and composition of the DS population by age, let alone by gender, race and ethnicity, geography, socioeconomic status, or residential status and caregiving arrangements. Although there is some published evidence to

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suggest that differences in the onset and survival with DS-AD may exist by gender and other sociodemographic characteristics, our review of the data and evidence is that better data infrastructure is required to support robust estimates of the potential social and spatial disparities in DS-AD. It is also possible that the dramatic changes in medical care, living conditions, and educational opportunities that have been experienced by DS birth cohorts who have not yet reached adulthood have generated widening opportunity for the early life and life-course determinants of AD to become socially and spatially stratified to an extent not previously possible. The importance of tracking the potential emergence of these disparities underscores the value of expanded investment in demographic, population health, and health services data infrastructure for the DS population.

Conclusion

Against a backdrop of limited empirical information about DS-AD costs and impact on family and unpaid caregivers, modeling of potential future impacts of increased research investment can inform research and public health planning and guide clinical and family decisionmaking. In this study, we used a novel method for examining the health and survival of the DS population to estimate the societal impact of increased research investment in DS-AD, implemented through incidence reduction and delayed mortality. The results from this novel MSLT approach to projections for DS and DS-AD underscore the urgency of research and understanding of DS-AD and the need for this work to continue.

Appendix A. Background on Novel Demographic Inputs Established for the Model

Since at least the 1970s, trends in DS survival—like all other data on the characteristics of the DS population in the United States—have been documented in typically small, clinic-based samples of individuals with DS. The most recent study to synthesize these data for changes in survival over the 20th century suggests that improvements in survival were very large (de Graaf, Buckley, and Skotko, 2017). We calculate life expectancy at birth from the estimates synthesized by de Graaf, Buckley, and Skotko (2017) and find that life expectancy increases from under 30 years prior to 1950 to over 50 years by 2005 (see Figure A.1).

Figure A.1. Estimates of Life Expectancy at Birth and Mean Age at Death of the U.S. Population with DS, 1940–2005
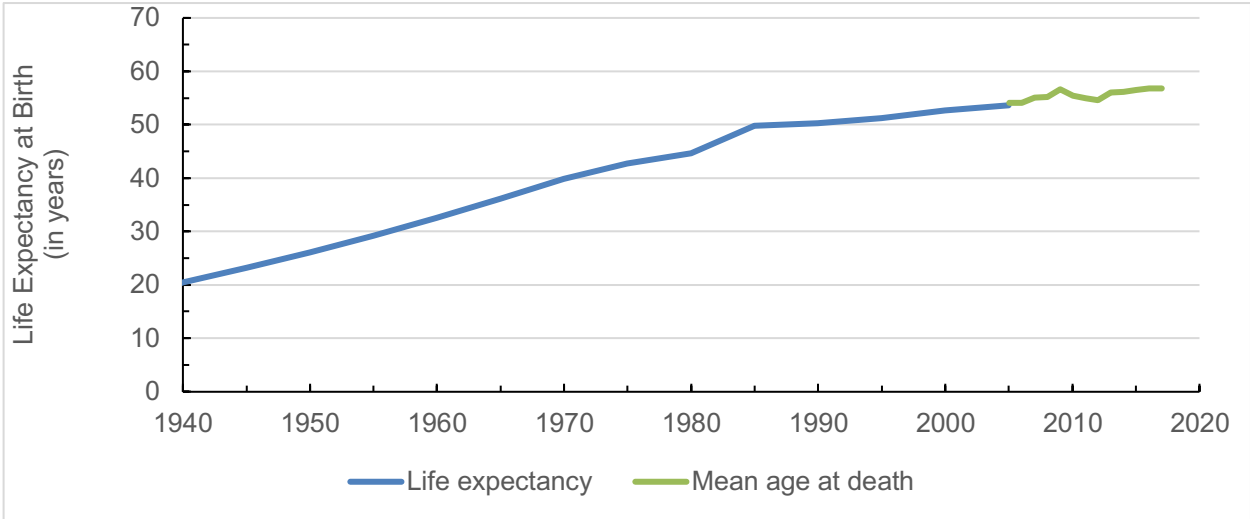
SOURCES: Life expectancy at birth is calculated by the authors using conventional methods for an abridged life table and age-specific survival probabilities estimated by de Graaf, Buckley, and Skotko (2017) (mean age at death is reported from U.S. vital statistics counts of deaths by Landes et al., 2021).

There are no published estimates of the DS population's life expectancy after 2005. However, as we show in Figure A.1, some studies have estimated that longevity has continued to increase on the basis of historical and recent changes in the median or mean age of deaths from the CDC's National Vital Statistics System (see, respectively, Iulita et al., 2022; Landes et al., 2021). There are two critical problems with these estimates: (1) The vital statistics data might be an incomplete and selective sample of all individuals with DS because DS is distinguished on the death certificate only when the reporting physician identifies DS as a primary or contributing cause of death, and (2) the mean age of death is a less precise measure of changes in longevity

than life expectancy because it captures not only trends in survival over time but also changes in birth cohort sizes over time.

In Figure A.2, we report the number of births with DS from the CDC's National Vital Statistics System (Martin et al., 2012; Osterman et al., 2023). The number of births with DS show peaks and troughs that correspond with the peaks and troughs in births in the total U.S. population because of the baby boom and baby boomlet. In 1957, DS births reached a historic high of 6,777; in 1976, they reached a historic low of 3,365.

Figure A.2. Peaks and Troughs in Births with DS and in Total Births in the United States
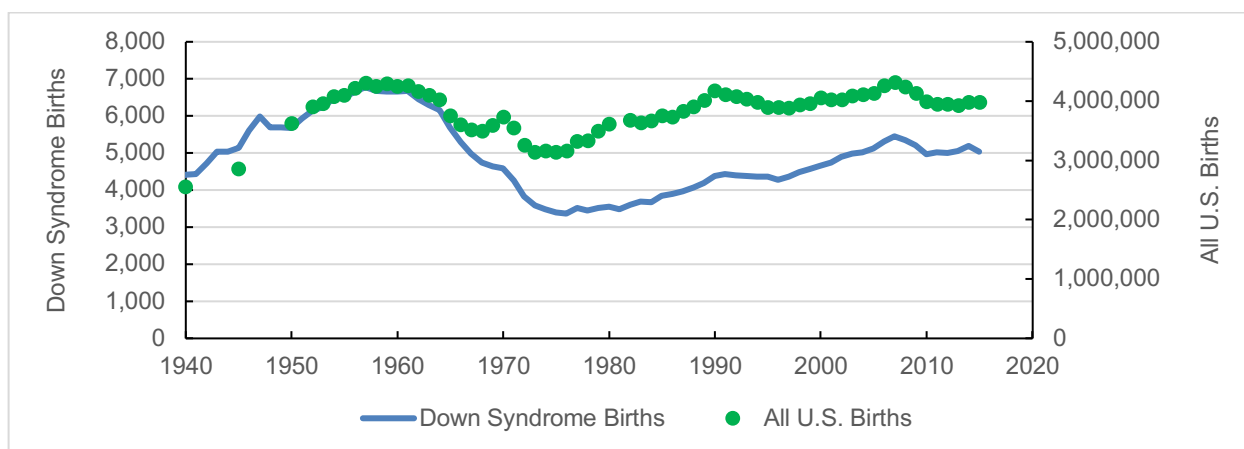
SOURCES: Births with DS were provided by Gert de Graaf based on prior work (de Graaf, Buckley, and Skotko, 2017). Total U.S. births were obtained from the CDC's National Vital Statistics System (Martin et al., 2012; Osterman et al., 2023).

Births with DS have been increasing steadily after hitting a historically low trough in the 1970s. The magnitude of changes in birth cohort sizes for the DS population is larger than observed for the total U.S. population. It is unclear how these trends in the birth cohort sizes compare with the changes in health and longevity of the DS population. But the decreases and increases in birth cohort size operate in conjunction with trends in health and survival to determine the size and composition of the DS population by age.

A typical demographic consequence of increasing longevity is that it will shift the age composition of a population toward older ages. Increasing numbers of births shift the age composition to younger ages, whereas improvements in survival shift the composition to older ages (i.e., they generate population aging).

In the DS population, an increasing proportion of the population at older ages has been estimated with an increase in the proportion of the total DS population at ages 50 and older from less than 4 percent prior to 1970 to nearly 14 percent by 2010 (Figure A.3).

Figure A.3. Increase over Time in the Percentage of the Total Population with DS Who Survive to Older Adult Ages
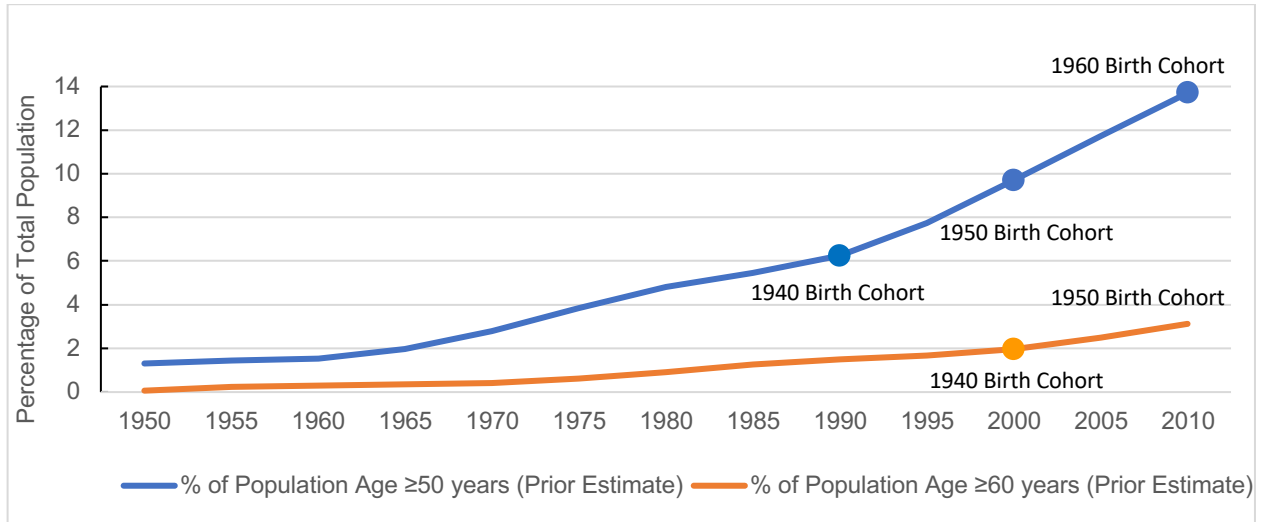
SOURCE: The prior estimates come from de Graaf, Buckley, and Skotko (2017).

Appendix B. Multistate Life Table and Outcome Calculations

Increment-Decrement Multistate Life Table Methods

We define our MSLT model to have a three-state, increment-decrement structure. Individuals can belong to one of the following three states: no DS-AD, DS-AD, or death. Transitions are possible as follows: from no DS-AD to DS-AD (i.e., DS-AD incidence), from no DS-AD to death (i.e., non-DS-AD mortality), and from DS-AD to death (i.e., DS-AD mortality). These transitions are depicted in Figure B.1.

We define the transitions as occurring between age groups defined using conventional abridged life table intervals with two exceptions in which we group individuals into larger age groups than the conventional intervals. Our definition of age groups is based on the limitations of data availability, with the larger age groups defined for childhood and adolescence (ages 5–19) and young adulthood (ages 20–39). The age groups thus are as follows: 0, 1–4, 5–19, 20–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, and 90 and above. The latter three age groups are included for modeling purposes and to accommodate the potential for individuals with DS to survive to ages above 75 in the future.

Figure B.1. Three-State Increment-Decrement Multistate Model
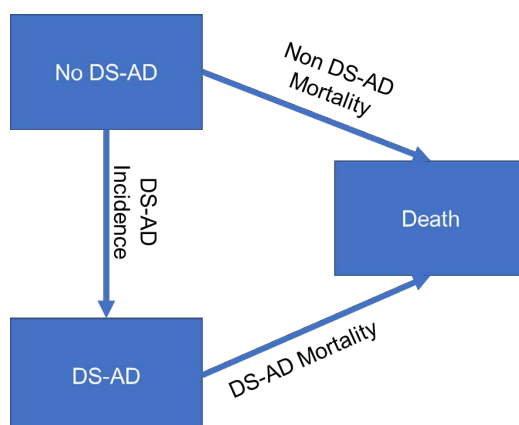
For each age interval listed above, the MSLT model allows us to fully characterize the transitions between the states depicted in Figure B.1. More specifically, this consists of the following decrements: the number of people developing DS-AD, $_yd^D(x)$, the number of people who died during the non-DS-AD state, $_yd^0(x)$, and the number of people who died during the DS-AD state, $_yd^1(x)$, from exact age x to $x + y$. We use the formulas below:

$$_yd^D(x) = l^0(x) * {}_yq^D(x)$$
$$_yd^0(x) = l^0(x) * {}_yq^0(x)$$

$$_yd^1(x) = l^1(x) * {}_yq^1(x)$$
$$x = 0,1,5,20,40,45,50,\ldots,85.$$

Note that the last age interval, where $x = 85$, is an open-ended interval. In other words, it includes all individuals at age 85 or older. In addition, $l^0(x)$ and $l^1(x)$ are defined as the number of people without and with DS-AD surviving to exact age x, respectively.

We assign $l^0(0) = 5,033$ and $l^1(0) = 0$ on the basis of the number of DS births in 2020 reported in the CDC's National Vital Statistics System and the assumptions, respectively, that the number of births defined by $l^0(0)$ remains unchanged after 2020 (which was informed by the trends observed in Figure A.2) and that there are no individuals with DS-AD at birth (i.e., $l^0(0) = 0$). The quantity $_yq^D(x)$ represents the probability that an individual without DS-AD at exact age x will develop DS-AD within y years. The quantity $_yq^0(x)$ and $_yq^1(x)$ represent the probability that an individual without DS-AD or with DS-AD, respectively, at exact age x will die within y years. We define y as the length of each age interval, and it is determined by how the age interval is specified. In the following equations, we define $y = 1$ for age interval 0, $y = 4$ for interval 1–4, $y = 15$ for interval 5–19, $y = 20$ for interval 20–39, and $y = 5$ for all remaining intervals.

The calculations are conducted for each age interval, with $l^0(x + y)$ and $l^1(x + y)$ provided as examples as follows:

$$l^0(x + y) = l^0(x) - {}_yd^D(x) - {}_yd^0(x)$$
$$l^1(x + y) = l^1(x) + {}_yd^D(x) - {}_yd^1(x)$$
$$x = 0,1,5,20,40,45,50,\ldots,85.$$

Note again that for the last age interval, where $x = 85$, the interval is open ended. In other words, it contains all individuals at age 85 or older.

Calculating Outcomes of Interest Using Multistate Life Table

Population Size by Age and DS-AD Status

We calculated the number of individuals alive without and with DS-AD at age x at any time in the stationary population, $L^0(x)$ and $L^1(x)$, respectively, using the formula below:

$$L^0(x) = y * [l^0(x) - \left(1 - {}_yf(x)\right) * {}_yd^0(x) - 0.5 * {}_yd^D(x)]$$
$$L^1(x) = y * [l^1(x) - \left(1 - {}_yf(x)\right) * {}_yd^1(x) + 0.5 * {}_yd^D(x)]$$
$$x = 0,1,5,20,40,45,50,\ldots,85.$$

In these equations, $_yf(x)$ is the separation factor, representing the average number of years not lived between exact ages x and $x + y$ for those who died between exact ages x and $x + y$.

Following conventional methods for an abridged life table, we assign $_1f(0) = 0.1$, $_4f(1) = 0.4$, and $_{15}f(5) = _{20}f(20) = _5f(40) = _5f(45) = \cdots = _5f(85) = 0.5$.

To capture the population size in 2020 more accurately, we adjusted the stationary population calculated above by relative birth cohort size of each age-group. For example, to estimate DS population size for those aged 1–4 in 2020, we need to take into account the birth cohort size of this age group who were born between 2016 and 2019. Similarly, for age group 40–44 in 2020, we need to factor in the size of the DS birth cohort in 1976–1980. For each age group, we calculated a relative cohort size factor by first taking the average of birth cohort sizes between corresponding years (e.g., for age group 40–44, we took the average of birth cohort sizes in years 1976 through 1980) and dividing that with the cohort size in 2020. Data on DS birth cohort size were obtained from the CDC's National Vital Statistics System. Because the latest birth cohort size data available at the time of the MSLT development were from 2015, we assumed that birth cohort size has remained stable since then. As noted above, this assumption was informed by Figure A.2.

The final adjusted age-specific population size without and with DS-AD, $L^0_{adj}(x)$ and $L^1_{adj}(x)$, respectively, was calculated as follows:

$$L^0_{adj}(x) = L^0(x) * k_x$$
$$L^1_{adj}(x) = L^1(x) * k_x$$
$$k_x = \frac{n_{2020-x} + n_{2020-(x+y)}}{2} / n_{2020}$$
$$x = 1,5,20,40,45,50,\ldots,85$$

where k_x is the age group–specific relative cohort size factor and n_t is the DS birth cohort size in year t.

Prevalence of DS-AD

Age-specific prevalence of DS-AD was calculated using the formula below:

$$Prev(x) = \frac{L^1_{adj}(x)}{L^0_{adj}(x) + L^1_{adj}(x)}.$$

Total prevalence of DS-AD for individuals aged 45 and older was calculated using the formula below:

$$Prev(x) = \frac{L^1_{adj}(x)}{T^0_{adj}(x) + T^1_{adj}(x)}.$$

Total Life Expectancy and Life Expectancy With and Without DS-AD

Life expectancy for population s at exact age x, $e^s(x)$, was calculated by dividing the number of person-years with status s lived after exact age x, $T^s(x)$, by the number of individuals with status s surviving to exact age x, $l^s(x)$:

$$e^s(x) = \frac{T^s(x)}{\sum_{s=0}^{1} l^s(x)}.$$

$T^s(x)$ was calculated by summing the number of person-years lived between exact ages x and $x + y$, $L^s(x)$ for all age intervals starting with x:

$$T_s(x) = L^s(x) + L^s(x + y) + \cdots + L^s(85),$$
$$x = 0,1,5,20,40,45,50,\ldots,85.$$

Status-specific life expectancy at age x, $e^s(x)$, is defined for the expected years of life with DS-AD, $e^1(x)$, and without DS-AD, $e^0(x)$. These quantities are one of our outcomes of interest.

We can also calculate total life expectancy for individuals with DS at birth as follows:

$$e(0) = e^0(0) + e^1(0).$$

Total Expected Caregiving FTE Hours for the Population With and Without DS-AD

Using our review of the literature and discussions with key informants, we identified inputs for the expected caregiving hours per day for an individual with and without DS-AD. Specifically, we assume 2.5 hours per day (or 912.5 hours per year) for taking care of individuals without DS-AD and 8.3 hours per day (or 3,029.5 hours per year) for taking care of individuals with DS-AD (Janicki et al., 2005). Other studies found similar estimates in the range of 8 to 10 hours for DS-AD and 2.5 hours for no DS-AD (Cleary and Doody, 2017; Courtenay, Jokinen, and Strydom, 2010; McCarron et al., 2005). Total annual expected caregiving FTE hours for populations older than 45 years old without and with DS-AD were calculated by multiplying the relative cohort size–adjusted total person-years lived after age 45 without and with DS-AD with respective annual caregiving hours:

$$H^s(45) = T^s_{adj}(45) * r^s, s = 0,1$$
$$T^s_{adj}(45) = L^s_{adj}(45) + L^s_{adj}(50) + \cdots + L^s_{adj}(85)$$
$$r^0 = 912.5, r^1 = 3029.5.$$

Appendix C. Parameterizing the Multistate Life Table

Our extension of the MSLT approach requires three sets of input: (1) age-specific likelihood of developing DS-AD, (2) age-specific likelihood of death without DS-AD and with DS-AD, and (3) historical patterns in the size of the DS birth cohort (i.e., average number of DS births) for all age groups in the DS population observed in a given year. Given the limited data and relatively small population size, we specified the inputs based on a synthesis and qualitative assessment of all existing estimates from the research literature, experts' opinion, and our primary analysis using the CMS's Minimum Data Set (MDS) 3.0 (Centers for Medicare and Medicaid Services, undated).

Determining Age-Specific DS-AD Incidence

First, we conducted our primary analysis of MDS 3.0 and generated our own estimation of DS-AD incidence. Because of the limitation of MDS 3.0, we also identified three articles that provided estimates of DS-AD incidence and compared all the estimates in Figure C.1 (Lai et al., 2020; Mhatre et al., 2021; Rubenstein, Hartley, and Bishop, 2020). We tested different sets of DS-AD incidence probabilities in the MSLT and identified a final set (see the Model Input series in Figure C.1) that fell within the boundaries of prior literature estimates and that produced output of DS-AD prevalence among older adults and DS-AD expected number of years duration that best reflected calibration targets from the prior literature on mean age of DS-AD onset and expected duration of DS-AD. In a recent meta-analysis (Iulita et al., 2022), the mean age of onset of DS-AD was 53.8 years (95-percent confidence interval: 53.1, 54.5) and the mean disease duration was 4.6 years (95-percent confidence interval: 3.7, 5.5). Our estimates of the 2020 baseline fit well within these confidence intervals, with a mean age of DS-AD onset in Scenario A and B of 53.4 and 53.7 years, respectively, and a mean expected number of years of DS-AD in Scenario A and B of 4.7 and 5.2 years, respectively. We purposefully selected inputs that generated mean disease duration toward the upper end of the meta-analysis distribution because all studies with a mean duration lower than 4.6 years included in the meta-analysis were from non-U.S. samples and had very small sample sizes (ranging from 8 to 20 adults).

Figure C.1. Age-Specific Incidence of Developing DS-AD
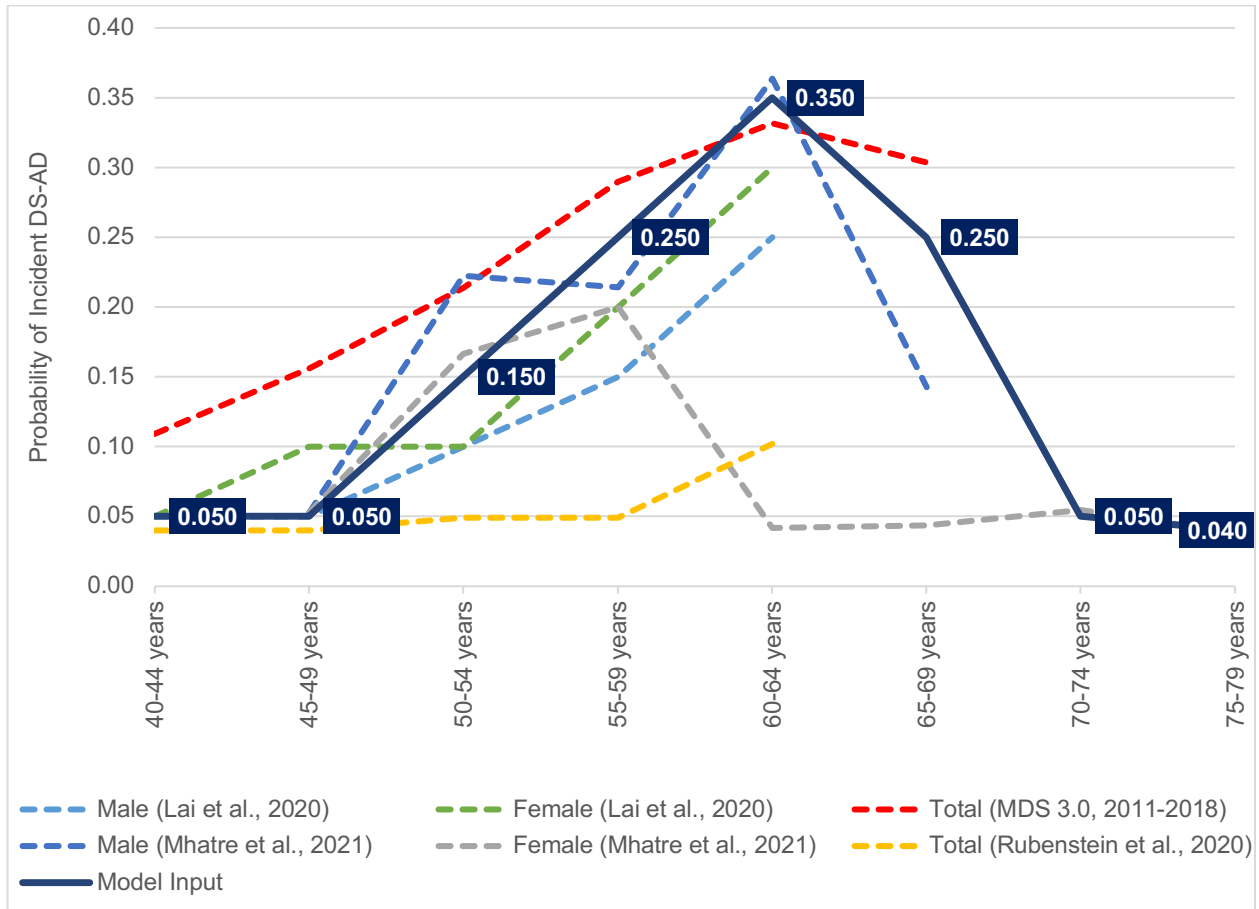
SOURCES: Lai study estimates come from visual inspection (see Lai et al., 2020); Mhatre study estimates are calculated from cumulative incidence that come from visual inspection (see Mhatre et al., 2021); Rubenstein study estimates are reported from Rubenstein, Hartley, and Bishop (2020, Table 1); MDS estimates are produced by the authors using CMS claims data from over 16,000 adults with DS that visited nursing facilities during 2011 through 2018 (Centers for Medicare and Medicaid Services, undated); model input estimates are a qualitative summary of all these data.

Determining Age-Specific Mortality Probabilities by DS-AD Status

We estimated age-specific mortality probabilities with and without DS-AD through an iterative calibration approach in the MSLT until we found estimates for DS-AD and non-DS-AD values of age-specific mortality that hit two calibration targets: (1) age-specific total mortality for the DS population (irrespective of DS-AD status) and (2) ratios of DS-AD versus non-DS-AD mortality.

Given limited data on the most recent estimates and mixed results from key informant interviews, we established two base cases in 2020 under different assumptions for the trend in mortality probabilities for the general DS population: Scenario A assumed a stable mortality probability since 2005, and Scenario B assumed an improving mortality probability since 2005. Specifically, Scenario B assumed that the general mortality probabilities followed the trend of

the U.S. general population and decreased by 0.7 percent per five years for individuals younger than 40 and decreased by 3.5 percent per five years for individuals 40 and older.

The calibration target of age-specific ratios of mortality probabilities with versus without DS-AD were obtained using data from the MDS 3.0. Details on obtaining this calibration target can be found in Appendix D. We estimated ratios of about three times higher mortality for individuals with DS-AD, ranging from 2.7 to 3.6. Throughout the calibration process, we assume that these age-specific ratios remain unchanged in all scenarios.

The calibration process works as follows: We start by feeding the MSLT our best guess (incorporating the calibration targets of ratios of DS-AD and non-DS-AD mortality probabilities) of age-specific mortality probabilities for individuals with DS-AD and individuals without DS-AD. Then, we compare the total mortality probabilities calculated by the MSLT with the calibration target and adjust our guesses accordingly. We repeated the above process until we found the set of age-specific mortality probabilities for DS-AD and non-DS-AD individuals such that the total mortality probabilities hit the calibration targets.

Appendix D. Statistical Analysis of the MDS 3.0

The MDS 3.0 contains clinical assessment records of all residents in Medicare or Medicaid–certified nursing homes (Centers for Medicare and Medicaid Services, undated). Residents are screened for DS at their initial assessment upon nursing home admission (question A1550A, "Conditions Related to Down Syndrome"), which is how we identified all residents with DS. This dataset captures virtually all nursing home residents in the United States because reporting to CMS is required for certification and reimbursement from CMS. Using MDS 3.0 data from 2011 through 2018, we were able to identify 16,679 unique nursing home residents with DS who received at least one initial assessment during the period from 2011 through 2018.

To use the more accurate measures of diagnosis of AD that are available in the MBSF and not on the MDS, we matched the MDS respondents to the MBSF. Because the MDS identifiers for individuals are reused over time within a state and change if an individual moves to a different state, the crosswalk for merging the data is many-to-many. We successfully matched 14,489 respondents with DS (87 percent), which is slightly higher than the match we achieved elsewhere for the general population. The retained sample included the majority of older adult residents with DS (89 percent remained in age group 40–64 and 94 percent in age group 65 and above; see Table D.1). We found that more than one-quarter of respondents not matched with MBSF were younger than 40. However, we determined that the poor match for respondents aged 40 and younger would have minimal impact on our assessment of the MSLT inputs in the matched sample because incidence of DS-AD is first assessed in the MSLT at age 40 and differences in mortality are first distinguished at age 40. To the extent that the mismatched observations are random, the loss of observations (13 percent) would not introduce a bias; however, we do not know whether those lost to relocation across states or reuse of MDS identifiers over time introduce a bias.

Table D.1. Comparing Age Composition Between MDS 3.0 Residents Matched and Not Matched with MBSF

	Not Matched with MBSF	Matched with MBSF	Total
Sample Count, Ages <40 years	558	584	1,142
Row Distribution	49%	51%	100%
Column Distribution	26%	4%	7%
Sample Count, Ages 40–64 years	1,423	10,948	12,371
Row Distribution	12%	89%	100%
Column Distribution	66%	76%	74%
Sample Count, Ages ≥65 years	184	2,957	3,141
Row Distribution	6%	94%	100%
Column Distribution	9%	20%	19%
Total Sample Count	2,165	14,489	16,654
Row Distribution	13%	87%	100%
Column Distribution	100%	100%	100%

By linking these individuals with MBSF (Research Data Assistance Center, undated-b) and the Chronic Conditions segment of MBSF (Research Data Assistance Center, undated-a), we obtained their date of death (the *bene_death_dt* variable) and first date of AD and related disorders or senile dementia diagnosis (the *alzh_demen_ever* variable). These data include individuals with DS aged 75 and older and individuals with DS and age at first dementia diagnosis of 75 or older. Multiple sources indicate that these observations for individuals older than 75 are not plausible. Discussion with key informants confirmed that the presence of these cases likely reflects error. For these reasons, we dropped residents (1) who entered a nursing home at age 75 or older, (2) whose age at death as indicated by *bene_death_dt* was equal to or greater than 75 years old, or (3) whose age at first dementia diagnosis as indicated by *alzh_demen_ever* was equal to or greater than 75. The final dataset consisted of 13,150 residents with DS.

Estimating Age-Specific DS-AD Incidence Probability Using MDS 3.0

Age-specific DS-AD incidence probabilities were estimated using a discrete time survival analysis approach. We constructed a person-year dataset for the 13,150 residents with years spanning from the year of nursing home entry to the year of first dementia diagnosis. The outcome variable was D_{it}, an indicator for the first dementia diagnosis in that year. Therefore, each resident was observed from the year they entered nursing home until they were first

diagnosed with dementia ($D_{it} = 1$ in the year of first diagnosis and equals 0 in years prior) or they were censored because of death or the end of the study period (in either case of censoring, $D_{it} = 0$ in all years for individual i). Individuals who were first diagnosed with dementia in the same year they entered nursing home were dropped, which left a final sample of 4,236 unique residents and 16,897 person-year observations for the incidence analysis.

We fitted a logit model of D_{it} on age splines, controlling for gender and year of entry:

$$ln\left(\frac{D_{it}}{1 - D_{it}}\right) = \sum_{g=1}^{8} \beta_g Age_{it}^g + \alpha_1 female_i + \alpha_2 entry_i + \epsilon_{it} \qquad (1)$$

where

- D_{it} represents whether a resident i was diagnosed with dementia for the first time in year t
- Age^g represents different age spline variables with knots at 40, 45, 50, 55, 60, 65, and 70. For example, for an individual aged 35 at time t, $Age^1 = 35$ and Age^2 through $Age^8 = 0$; for an individual aged 73 at time t, $Age^1 = 40$, $Age^2 = 5$, $Age^3 = 5$, $Age^4 = 5$, $Age^5 = 5$, $Age^6 = 5$, $Age^7 = 5$, $Age^8 = 3$ ($73 = 40 + 5 + 5 + 5 + 5 + 5 + 5 + 3$)
- $female_i$ is the indicator for female residents
- $entry_i$ is a categorical variable indicating the year of nursing home entry for resident i.

After the model (1) was fitted, we then predicted the probability of developing dementia within a year at each single age x from 40 to 74, q_x^D. Assuming individuals with DS do not develop dementia until age 40, we set the survivorship function at age 40 (the proportion of population without DS-AD at the beginning of age 40), specifically $l^D(40) = 100\%$. We then calculated $l(x)$ at each age from 41 to 74 using the following formula:

$$l^D(x + 1) = l^D(x) * (1 - q_x^D).$$

Lastly, we calculated the desired input for our main MSLT model—the incidence probability of developing dementia within five years, specifically $5q_x^D$—following the formula below:

$$5q_x^D = 1 - \frac{l^D(x + 5)}{l^D(x)}, x = 40, 45, 50, \ldots, 70.$$

Estimating Age-Specific DS-AD Mortality Probability Using MDS 3.0

We estimated age-specific DS-AD mortality probability with and without DS-AD using a similar method for estimating incidence probability described above. We constructed another person-year dataset for the 13,150 residents with years spanning from the year of nursing home entry to the year of observed death. The outcome variable was M_{it}, an indicator for observed death in year t derived from variable *bene_death_dt*. Therefore, each resident was observed from the year they entered nursing home until either the year of their death (M_{it} equals 1 in the year of death and equals 0 for years prior) or the end of the study period ($M_{it} = 0$ in all periods for

individual i). A binary variable $DSAD_{it}$ was created to indicate DS-AD status for each individual i in year t. $DSAD_{it}$ was set to 1 in the year when individual i was first diagnosed with dementia and remained 1 for following years; it was set to 0 otherwise. The final dataset for the mortality probability analysis consisted of 13,150 unique residents and 40,913 person-year observations.

We fitted a logit model of M_{it} on age splines and DS-AD status controlling for gender and year of entry:

$$ln\left(\frac{M_{it}}{1-M_{it}}\right) = \sum_{g=1}^{8} \tau_g Age_{it}^g + \gamma_1 DSAD_{it} + \gamma_2 female_i + \gamma_3 entry_i + \epsilon_{it} \qquad (2)$$

where

- M_{it} represents whether a resident i was recorded dead in year t
- Age^g represents different age spline variables with knots at 40, 45, 50, 55, 60, 65, and 70
- $DSAD_{it}$ represents whether individual i had DS-AD in year t
- $female_i$ is the indicator for female residents
- $entry_i$ is a categorical variable indicating the year of nursing home entry for resident i

After the model (2) was fitted, we then predicted the mortality probability within a year at each single age x from 40 to 74 for individuals without DS-AD, q_x^0, and with DS-AD, q_x^1. Because MDS 3.0 captures only individuals with DS who entered a nursing home (which can be late in the life stage), our sample might not have captured the majority of deaths happening in early ages of individuals with DS (which should occur mostly outside nursing homes). Because of this limitation, we disregarded the mortality probability estimates from MDS 3.0 for ages under 40 and used the survivorship function estimate from de Graaf, Buckley, and Skotko (2017) to set the survivorship function at age 40 and above for individuals without and with DS. At age 40, this was $l^0(40) = l^1(40) = 79\%$.

For ages above 40, we then calculate $l(x)$ at each age from 41 to 74 using the formula:
$$l^s(x+1) = l^s(x) * (1 - q_x^s), s = 0,1.$$

The mortality probability at five-year age intervals for individuals without and with DS-AD, specifically $5q_x^0$ and $5q_x^1$, was calculated similarly:
$$5q_x^s = 1 - \frac{l^s(x+5)}{l^s(x)}, s = 0,1; x = 40,45,50,\ldots,70.$$

Next, the age-specific ratios of mortality probability between individuals with and without DS-AD were calculated using this formula:
$$5r_x = \frac{5q_x^1}{5q_x^0}, x = 40, 45, 50, \ldots, 70.$$

These relative risks of mortality, r_x, for DS-AD versus non-DS-AD range from about 2.7 times higher mortality at ages 40 to 44 for adults with DS-AD versus those without DS-AD to a peak of 3.5 and 3.6 times higher mortality at ages 60 to 64 (after which risks remain at about 3.2 to 3.3

times higher for adults with DS-AD versus those without DS-AD). The final mortality inputs for the model are then determined using these relative risks as discussed in Appendix C. Consequently, the final mortality inputs assume that the nursing home population can be used to estimate only the relative risk of mortality associated with DS-AD and not the actual age-specific estimates.

Abbreviations

AD	Alzheimer's disease
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
DS	Down syndrome
DS-AD	Down syndrome–associated Alzheimer's disease
FTE	full-time equivalent
ICER	Institute for Clinical and Economic Review
MBSF	Master Beneficiary Summary File
MDS	Minimum Data Set
MSLT	multistate life table

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