Research Funding for Women’s Health: A Modeling Study of Societal Impact

Findings for Alzheimer’s Disease and Alzheimer’s Disease Related Dementia Model

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A Message from WHAM

The research described in this volume was conceived and sponsored by Women’s Health Access Matters (WHAM—whamnow.org). WHAM was created in response to the considerable funding gap, historical exclusion, and underrepresentation of women in health research. WHAM is a 501(c)(3) (www.whamnow.org) dedicated to funding women’s health research to transform women’s lives.

As businesswomen, we believed that a focused study showing the impact of accelerating sex and gender–based health research on women, their families, and the economy through a study quantifying costs and economic benefits would be an invaluable accountability index. In other words, if more investment is made in women’s health research, the plausible assumption is that women would benefit from sex-specific prevention strategies, diagnoses, and treatments that reduce their burden of disease and thus improve their well-being and the well-being of society.

WHAM commissioned the RAND Corporation to conduct a data-driven study of the economic impact to society of increasing the investment in women’s health research. This first research project comprises three disease modules: Alzheimer’s disease; rheumatoid arthritis as representative of autoimmune disease, and cardiovascular disease. In the future, we plan to include lung cancer, study different socioeconomic groups to the extent that the data are available, and detail the global data that expands this research.

To the best of WHAM’s and RAND’s knowledge, this is the first analysis of its kind to create and calibrate a microsimulation model of investments in health research and development that examines differences for women’s health research investment and should become a seminal part of the arsenal in advocating for increased investment in women’s health research. The research methodology and the microsimulation models have been vetted by a diverse panel of experts convened by RAND.

We are so thankful for the dedicated, invested partnership of the research team at the RAND Corporation who conducted the analysis presented here and brought their findings to life. We encourage other leaders, including advocates, economists, scientists, public health experts, and policymakers, to draw from and act on the results of this report. Together, we can drive meaningful change.

Carolee Lee
Founder and CEO
WHAM Women’s Health Access Matters (www.whamnow.org)
www.thewhamreport.org

Please find additional infographics and social media toolkits on www.thewhamreport.org.

The technical specifications for the models are publicly available. Please visit www.thewhamreport.org/report/brain to learn more about using these data and citing this report.
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WHAM’s sponsorship of this research project was enabled through the generous financial support from the following partners.

**American Heart Association**
The Association is a relentless force for a world of longer, healthier lives dedicated to ensuring equitable health for all—in the United States and around the world. The Go Red for Women® (GRFW) movement is the trusted, passionate, relevant force for change to end heart disease and stroke in women all over the world.

GRFW and WHAM will collaborate to directly address the lack of societal-level evidence on the economic cost, benefits, and social impact due to the underrepresentation of women in cardiovascular research.

**BrightFocus Foundation**
BrightFocus Foundation is a leading source of private research funding to defeat Alzheimer’s, macular degeneration, and glaucoma. Supporting scientists early in their careers to kick-start promising ideas, BrightFocus addresses a full and diverse range of approaches, from better understanding the root causes of the diseases and improving early detection and diagnosis to developing new drugs and treatments. The nonprofit has a longstanding commitment to funding pioneering, sex-based research in Alzheimer’s and related dementias. BrightFocus currently manages a global portfolio of over 275 scientific projects, a $60 million investment, and shares the latest research findings and best practices to empower families impacted by these diseases of mind and sight.

**The Connors Center for Women’s Health and Gender Biology at Brigham and Women’s Hospital/Harvard Medical School** is a leading local and national force in advancing the health of women, with a rich history and strong foundation of women’s health and sex-differences discovery, clinical care, and advocacy for equity in the health of women, and is the Premier Partner and the Lead Scientific Research Partner of the WHAM Collaborative for Women’s Health Research. The Connors Center shares the bold vision of improving the health of women and a commitment to joining forces to advance scientific discovery for the benefit of all women.

**La Jolla Institute for Immunology**
La Jolla Institute is home to three research centers that focus the efforts of collaborative groups of researchers on defined areas of inquiry to accelerate progress toward the development of new treatments and vaccines to prevent and cure autoimmune conditions, cancer, and infectious disease. Together, we will create a framework for researchers to reanalyze existing data with sex as a biological variable, to work together to spark new projects, to hire new faculty to build key research areas, to communicate via the WHAM Report, and to establish an ignition point for new leadership in the scientific field.
The WHAM Collaborative

WHAM convenes thought leaders, researchers, and scientists to work together to identify problems and devise solutions. Our members include:

- Dr. Wendy Bennett, MD, MPH, Associate Professor of Medicine, Johns Hopkins School of Medicine Co-Director, Johns Hopkins Center for Women’s Health, Sex, and Gender Research
- Dr. Antonella Santuccione Chadha, PhD, Co-Founder, Women’s Brain Project Head Stakeholder Liaison, Alzheimer’s Disease, Biogen International Medical Director, Alzheimer’s Disease, Roche Diagnostics Europe
- Dr. Marjorie Jenkins, MD, Dean, University of South Carolina School of Medicine Greenville Chief Academic Officer, Prisma Health Upstate
- Dr. Hadine Joffe, MD, MSc, Founding Member and Lead Scientific Advisor to the WHAM Collaborative Executive Director, Mary Horrigan Conners Center for Women’s Health Research, Brigham and Women’s Hospital, Chair for Research, Department of Psychiatry, Brigham and Women’s Hospital, Paul A. Johnson Associate Professor of Psychiatry in the Field of Women’s Health, Brigham and Women’s Hospital
- Dr. Wendy Klein, MD, MACP, Former Medical Director, Health Brigade
- Dr. Jokann Manson, DrPH, MD, Michael and Lee Bell Professor of Women’s Health, Medicine, Harvard Medical School Co-Director, Women’s Health, Brigham and Women’s Hospital Professor, Epidemiology, Harvard T.H. Chan School of Public Health, Chair, Preventive Medicine, Brigham and Women’s Hospital
- Dr. Alyson McGregor, MD, Associate Professor of Emergency Medicine, The Warren Alpert Medical School of Brown University, Division of Women’s Health, Brigham and Women’s Hospital
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- Dr. Suzanne Steinbaum, DO, Private Practice Cardiologist Co-Founder, Preventive Cardiology at UCI
- Dr. Connie Tyne, Executive Director, Laura W. Bush Institute for Women’s Health

Research Advisory Panel

RAND convened advisory panels to help guide the work and elicit insights on the target case study areas of autoimmune and immune disease, cardiovascular disease, and Alzheimer’s disease. Central to RAND’s work was the creation of health economic models in each case study area. RAND is committed to creating final products with immediate relevance for use by funders, advocacy organizations, researchers, and other stakeholders.

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- Roberta Brinton, PhD Director, Center for Innovation in Brain Science, University of Arizona Health Sciences
- Susan Dientzer Senior Policy Fellow, Duke-Margolis Center for Health Policy
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Executive Summary

The Challenge: Women’s health has suffered from insufficient research addressing women. The research community has not widely embraced the value of this research. The impact of limited knowledge about women’s health relative to men’s is far reaching. Without information on the potential return on investment for women’s health research, research funders, policymakers, and business leaders lack a basis for altering research investments to improve knowledge of women’s health.

What We Did: Research impact analysis is a framework for supporting decision making about research funding allocation. Economic modeling aids with such impact analysis. Microsimulation models provide a method of quantifying the potential future impact of additions to research investment. Using microsimulation analyses, we examined the societal cost impact of increasing research funding in Alzheimer’s Disease and Alzheimer’s Disease related disorders (AD/ADRD). We quantified the potential impact of increasing funding on women’s health on health outcomes and ultimate societal costs including healthcare expenditures, labor productivity of informal caregivers, and quality-adjusted life years (QALYs). We calculated impacts across 30 years of two funding scenarios: doubling the current 12 percent of the National Institutes of Health extramural AD/ADRD portfolio devoted to women’s health and tripling that investment. Impact of a current investment was assumed to occur in 10 years, with benefits accruing after that.

Key Takeaways:
- Investing in women’s health research for AD/ADRD yields benefits beyond investing in general research. Return on investment is higher for scenarios in which research funding has 3 times the impact on women’s health outcomes than men’s. Assuming equal impact of research on women and men results in lower returns.
- Large returns result from very small health improvements. Assuming health improvements of 0.01 percent or less in terms of age incidence and disease severity yields the following results:
  - For the US population, over 6000 years with AD/ADRD can be saved across 30 years, with substantial gains in health-related quality of life.
  - Nursing home costs account for approximately 40 percent of the effect of the return on investment in women’s health, and nursing home costs could drop by over $360M.
  - Return on investment is 224 percent for doubled investment in women’s health research amid that only 0.01 percent improvement in health outcomes.
- Only a 35.5% probability of success in improving health by the very small 0.01% is required to generate an expected return on investment of 15 percent. An investment that is able to improve health instead by 1% would only require a 0.6% probability of success for an expected return of 15%.

The results establish the potential for investment in women’s health research on AD/ADRD to realize gains beyond additional general research investment and point the way to a concrete, actionable research and funding agenda.

Implications: Large societal gains may be possible by increasing investment in women’s health research in AD/ADRD. The potential to recognize societal gains is greater for research devoted to women’s health relative to general research, based on the specifications used here.
We recommend the following policy actions based on this research to inform decisions about research funding allocations:

1) Increase research funding directed at women’s health within AD/ADRD. Given the limitations in knowledge about women and AD/ADRD relative to men, the potential gains from women-focused research are substantial.
2) Pursue research on biological and cultural dimensions of AD/ADRD and women. Clinically actionable knowledge is likely from both spheres. Biologically focused research could address hormonal status on AD/ADRD risk and progression and impact of pregnancy factors on AD/ADRD risk. Cultural research could address marital effects and impact of physical activity and education on AD/ADRD risk and disease course.
3) Expand research agendas to address relationships between AD/ADRD and other health conditions in women. For example, existing research in cardiovascular health and metabolic disease could be “mined” to identify promising signals relevant to AD/ADRD in women.

By raising awareness of the current state of funding directed toward women’s health in AD/ADRD and the potential for such funding to yield a range of societal benefits, researchers and other communities can pursue information relevant for improving funding allocation decisions. Specific ways to connect other communities to the relevant issues include the following:

1) Raise awareness of the potential value of investment in women’s health research in AD/ADRD. The ways in which women’s health research is disadvantaged relative to general research requires further study but investing not just in the research agenda but also the careers of those who can pursue that agenda is critical. Identify obstacles such as career interruption from caregiving burden for women, develop strategies to overcome these and systemic factors such as implicit and explicit bias against women in health research.
2) Raise awareness among the business community of the potential return on investment for women’s health research. Viability of women’s health research agendas and funding depend on understanding of the value on the part of the “market” for such research. Within the pharmaceutical and biotechnology industry, decisions made now by leaders about research investments should be informed by the potential for societal return on investment. Across multiple other business sectors, leaders need to understand the consequences of under-investment workforce productivity and healthcare burden associated with AD/ADRD. These communities are key to informing future research investment strategies.
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Introduction

Historical exclusion and under-representation of women in health research has resulted in an impoverished evidence base about women’s health. Increased awareness of the impact of sex and gender exclusion on health research has led to efforts to include more representative samples. However, the value of this research is not yet widely embraced by the research community, nor is consideration of gender effects part of the culture of science. The impact of this oversight is far-reaching.

Given the evidence that women’s health has been historically underfunded, with resulting negative consequences for diagnosis and treatment of diseases among women (Johnson et al., 2014), tracking the dedicated investment to women’s health research provides information vital to funders, researchers, and policymakers in terms of planning for investments that can yield the greatest public health benefits. Alzheimer’s Disease and Alzheimer’s Disease related dementias (AD/ADRD) are one of the top contributors to illness burden in terms of morbidity and mortality and in terms of socioeconomic impact (Johnson et al., 2014). The investment in AD/ADRD increased substantially beginning in 2017 as the first AD Professional Judgment budget for AD/ADRD was instituted (Consortium of Social Science Associations, 2015; National Institutes of Health, 2019). Despite this increase in funding, the disease burden continues to be high. Still unknown is the potential for gender investment in women’s health to yield a favorable return for society.

The lack of societal-level evidence on the economic costs, benefits, and social impacts of attention to sex and gender in health research is a major obstacle to moving from policies of passive inclusion to active focus on the medical gender gap. Research in AD/ADRD to date has yielded some benefits but lagging attention to women leaves a knowledge gap.

Quantifying the impact of research funding investment is a relatively new area of inquiry (Adam et al., 2018). Hallmarks of ideal systems for comprehensively examining research funding impact include capture of a full set of impacts and benefits, aggregating impacts and also reporting disaggregated impacts (Adam et al., 2018), and valuing different impacts in a common currency. Economic modeling provides a method for achieving these goals. Microsimulation modeling allows a way to address the gap in knowledge about investment in women’s health research in AD/ADRD, and to specifically examine impacts of additional investments (see for
example, Grant and Buxton, 2018). Impacts can be quantified in economic terms. Inclusion of impacts on health-related quality of life is a relatively recent addition to the comprehensive impacts examined in research impact analysis (Grant and Buxton, 2018). For AD/ADRD, understanding the impact of the disease and potential disease mitigation on health-related quality of life ensures that health outcomes beyond those readily monetized are appropriately considered and included.

We report on results of a microsimulation model to explore the potential for enhanced investment in women’s health research, in terms of the economic wellbeing of women and for the US population. Few studies have employed models stratified by sex or gender to test the sex/gender differences of AD/ADRD. Instead the majority of AD/ADRD-focused studies use sex/gender as a population variable, descriptive variable, or control variable (Quigley et al., 2020). Women’s health research\(^1\) as used here refers both to analyses that address sex/gender within general sample or population studies, and to research focusing on women specifically. Our microsimulation model approach contributes to the existing body of literature by allowing us to project the future impact of funding on health outcomes and changes in societal burden from AD/ADRD.

The analyses presented here quantify costs and benefits of investment in women’s health research in AD/ADRD. The models used for this examination address the contribution of research to disease burden and to societal productivity costs and benefits. Quantifying societal costs alongside disease burden is key, as AD/ADRD is related to substantial burden for caregivers (AARP, 2020). As with many diseases, women are more likely than men to be informal caregivers for someone with AD/ADRD. One of the greatest economic challenges of AD/ADRD to women is the cost of the informal care they deliver; women bear substantially more of the cost of that informal caregiving than men (Yang and Levey, 2015).

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\(^1\) Terminology: We follow terminology guidance from the NIH, which states the following: “‘Sex’ refers to biological factors and processes (e.g., sex chromosomes, endogenous hormonal profiles) related to differentiation between males (who generally have XY chromosomes) and females (who generally have XX chromosomes). ‘Gender’ refers to culturally and socially defined roles for people, sometimes but not always along the lines of a gender binary (girls and women, boys and men). Gender incorporates individuals’ self-perceptions (gender identity); the perceptions, attitudes, and expectations of others (gender norms); and social interactions (gender relations).”\(^10\) For the purposes of these analyses, we refer to sex/gender research generally; assumptions are about sex and/or gender research focused on women.
In the US, the universe of funding for AD/ADRD research extends beyond NIH and includes advocacy organizations, the biopharmaceutical industry, and philanthropic organizations (Cummings, Reiber and Kumar, 2018). NIH’s share of AD/ADRD research investment is large, however, and provides a starting point for understanding investments in health research generally and women’s health research in particular.

We used current levels of funding from the National Institutes of Health (NIH) as the "base case" with comparisons to doubling and tripling the level of research funding currently invested in women-focused research. We assumed that impacts of increased funding occur through innovations that reduce age incidence of disease and disease severity and improve health-related quality of life. We quantified the innovations through costs of informal and paid caregiving, work productivity for informal caregivers, and healthy life-years gained or lost.

Through analyses that quantify costs and socio-economic benefits, these models examine the impact of increased sex- and gender-based health research on women, their families, and the economy. The goal of the analyses is to serve as a foundation for developing a concrete, actionable research and funding agenda. The analyses are intended to demonstrate the potential impacts of increased funding for research on women’s health and thereby inform funders’, legislators’, and the business community’s prioritization of research funding allocations.

**Methods**

We used microsimulation models to address the impact of funding for women’s health research in AD/ADRD. The models followed a cohort representing the U.S. population of individuals who have or could develop AD/ADRD, age 65+, along with the working age caregivers for individuals with AD/ADRD onset at age 65+. The youngest age included was therefore age 35, which represents a simplifying and conservative assumption about the lower bound of informal caregiver age, given informal caregiving at all ages. The cohort assumed 100 percent mortality at age 99. The model simulated the progression of each person’s health in the sample over a 30-year time horizon; the models generated the relevant costs associated with the development of health. We generated a model to first reflect the status quo of the disease and then re-simulated the model under the assumption that increased investment improves health outcomes and thus lowers costs. This approach allowed us to directly estimate how costs evolve with health innovation and allows exploration of the associated return on the research investments.
**Base case:** Creating a realistic microsimulation model requires calibrating several functions that define how health evolves and the relationship with changes in health and costs. Where possible, we calibrated these functions using estimates from the research literature. This approach has the primary advantage of relying on best-available, peer-reviewed estimates; an added benefit is efficiency in terms of estimates for each function in the model.

However, we could not calibrate every parameter of the model from the literature; in some cases, we had to create our own estimates. Ultimately, we required data that included measures of employment, medical expenditures, health condition incidence, and baseline demographics such as age and gender. The data set also needed to include a large sample to ensure substantial detection of each condition within the population.

We considered several data sources; the Medical Expenditure Panel Survey (MEPS) best fit these criteria. Among our options, the MEPS has the largest sample and range of ages, the clearest diagnosis indicators, and detailed data on medical expenditures. It also meets our primary criterion of having detailed employment and income data for all household members. We used the MEPS data in several instances to parameterize functions we could not observe in the literature. Two additional data sources used were the Centers for Medicaid & Medicare Services (CMS) Medicare Beneficiary Summary File to estimate age-specific incidence and mortality rates for patients, and the Health and Retirement Survey (HRS) to estimate the proportion of patients being institutionalized. See the Technical Appendix A for details of each dataset.

We estimated baseline healthcare costs from the *status quo* simulation model. Note that these baseline healthcare costs are not intended to capture all potential healthcare costs, direct and indirect. Instead, the baseline healthcare costs are with respect to the relevant inputs. We exclude early-onset AD/ADRD from our examination and thus do not include in the baseline healthcare costs earnings that were lost due to diseases, because the patient population is assumed to be out of the workforce.

**AD/ADRD Model**

Our primary strategy was to create a model that allows us to take assumptions about current funding levels, input what the literature tells us about how funding affects health outcomes and
translate that information into predicted economic outcomes of funding changes. We quantified the impact of funding on health outcomes, and on specific changes in societal burden like reduced workforce participation of informal caregivers, through an economic microsimulation model. By tying different funding scenarios to incurred societal burden, the model quantifies how funding amounts impact societal burden of AD/ADRD in terms of health expenditures, caregiver time loss, and lost life years. The impact on quality-adjusted life years (QALYs), and not just on absolute lost life years, is important to quantify for AD/ADRD, given the ways in which the disease affects individuals. The QALY is one way in which monetary value can be assigned to disease impact (Grant and Buxton, 2018). The approach to relating funding to health improvements, life status, and costs is summarized in Figure 1, as the conceptual model guiding this work.

Figure 1. Conceptual model of research funding impacts for AD/ADRD
Background on Model Components

The model was built with the following components: age incidence profiles, disease severity progression, mortality, non-nursing home healthcare costs, informal care status, and nursing home care costs. Patient-level disease burden components were the age incidence, disease severity, and quality-adjusted life years. Societal-level disease burden components were the healthcare costs associated with institutionalization, all other healthcare costs, and informal caregiver lost productivity. Data sources for model components are presented in Figure 2.

Age Incidence Profiles
The age incidence profiles provided a layer of information regarding when in a person's life the health conditions of interest occur and when they affect quality of life, care, and employment as a function of age and gender. We modeled disease severity progression over years, with probabilities of progression differing by age and gender. The impacts were on informal caregiver earnings loss, quality of life, and probability and type of care. Care status and mortality were functions of age, gender, disease status, and severity.

Disease Severity Progression
Severity levels used in the model were the following: normal, mild cognitive impairment, mild AD, moderate AD, severe AD, non-AD cognitive impairment, and death. Severity is defined based on Clinical Dementia Rating (CDR) scores: CDR <2 for mild AD/ADRD, CDR =2 for moderate AD, and CDR = 3 for severe AD/ADRD (Davis et al., 2018).

Patient-level Disease Burden
Disease burden extends to other family members beyond the patient and was represented as lost labor force participation in the model (Committee on Family Caregiving for Older Adults, 2016). The earnings profiles, stratified by age, quantify earnings over a working career and enabled us to see the effect of personal and family health issues as well as caregiving responsibilities on earnings. Notably, substantially more women than men move from full-time to part-time work among those providing informal AD/ADRD related caregiving (Alzheimer's Impact Movement, March 2020).

Details of all model components are presented in Technical Appendix B.
Calculations involving population earnings ordinarily adjust by race and ethnicity and gender, given differences by these variables in earnings. We chose to instead use earnings of non-Hispanic white males as the basis for the earnings calculations in these models, regardless of gender and race/ethnicity composition of the informal caregiving population. This choice avoids current time disparities in earnings to be propagated into an assumed future. Doing so avoids the gender and race-based labor market discrimination that is inherent in the differential, and lower, earnings for women and for non-Hispanic white males. Specifically, earnings used for informal caregivers were based on those of non-Hispanic white males, instead of on race and gender specific earnings, representing an assumption of earnings equality.

The age incidence profiles provided a layer of information regarding when in a person’s life the health conditions of interest occur and when they affect quality of life, care, and employment as a function of age and gender. We modeled disease severity progression over years, with probabilities of progression differing by age and gender. The impacts were on informal caregiver earnings loss, quality of life, and probability and type of care. Care status and mortality were functions of age, gender, disease status, and severity.

Severity levels used in the model were the following: normal, mild cognitive impairment, mild AD, moderate AD, severe AD, non-AD cognitive impairment, and death. Severity is defined based on Clinical Dementia Rating (CDR) scores: CDR <2 for mild AD/ADRD, CDR =2 for moderate AD, and CDR = 3 for severe AD/ADRD (Davis et al., 2018).
Finally, expenditures were a function of age, gender, care status, and for the AD/ADRD model, disease severity. For example, severe AD/ADRD is associated with higher nursing home costs for memory units. The model accounts for uncompensated costs of labor and household management in the form of informal care, which may represent a spouse or dependents engaged in caregiving.

We used prior research on funding investment return as a basis for assumptions on return on research investment, that is, the impact of funding levels on health outcomes (Grant and Buxton, 2018). The return on research investment calculation was a function of the following specific health outcomes: age incidence of disease, improved detection rates and earlier detection in the disease course, severity with assumption of reduced severity and reduced time in more severe stages of disease, and reduced mortality due to disease. Following analyses in which the return on research investment was permitted to vary, we constrained the model to determine inputs that would yield an expected return on investment of 15 percent, in line with findings from several therapeutic areas (Committee on Family Caregiving for Older Adults, 2016).
Taken together, these components enabled us to simulate the effects of increasing funding for health research on women in terms of economic outcomes. These economic outcomes included the monetary value of workers being able to stay in the labor force longer as a result of decreased caregiving burden.

**Time Horizon**

The representative cohort of around 1,000,000 lives was moved through a 30-year time horizon, with impact of investment expected 10 years from initiation. We created the representative sample based on the U.S. age and gender distribution for individuals age 35 and older as well as initial existing disease rates by age and gender. We chose a 10-year investment impact time point based on existing research on time from investment to healthcare impacts (Cruz Rivera et al., 2017; Hansen et al., 2013; Scott et al., 2014). Given the small health improvement assumed with each scenario, we chose the lower end of the literature estimates of time from investment to impact. The 30-year model time horizon permits accrual of impacts for the 20 subsequent years, within the lifespan of the majority of the cohort.

**Investment Impacts**

The model provides information on return on investment (ROI) associated with multiple innovation impacts. Models address each of the three main impacts separately and then address all three impacts occurring together:

1) decreased age incidence of disease (probability of onset at a given age)
2) delay in progression to more severe levels of disease, with the assumption that innovations will reduce severity and slow progression
3) improvements in health-related quality of life, with the assumption that reduction in symptoms and more functional independence would account for more quality-adjusted life-years (QALYs).

We investigated three different levels of aggregate health improvement in each of the three health inputs described above: 0.01 percent, 0.02 percent, and 1 percent improvement. Furthermore, we simulated the model and estimated the costs and ROIs under two assumptions about health improvements. The first assumption was for a targeted investment in women’s AD/ADRD research with an impact for women three times larger than that for men. Any investment in research focused on women was expected to yield results relevant for women, but
this assumption included the likelihood that a portion of that research will benefit both women and men. The second assumption was a representation of general investment in AD/ADRD research with equal research impact on women and men. Given the limitations of “general” research with regard to understanding women’s health historically, this assumption is a likely overestimation of the impact of “general” research on women’s health. For both differential and equal impact, we assume that the average return is still the same. Thus, when considering an average health improvement of 1 percent, the equal impact assumes that both women and men realize a 1 percent improvement, whereas the three-times larger version assumes that women realize a 1.5 percent improvement and men realize a 0.5 percent improvement, averaging approximately to a population-level 1 percent improvement.

The three levels of health improvement we investigated and the two different assumptions on distribution of impact by sex creates six scenarios. These are shown in Table 1. We use scenario 1 (0.01 percent health improvement and women having three times the impact as men) to show the detailed impacts of the investment on health outcomes and associated costs.

<table>
<thead>
<tr>
<th>Health improvement</th>
<th>Women’s impact 3x men’s</th>
<th>Equal impact by sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01%</td>
<td>Scenario 1</td>
<td>Scenario 2</td>
</tr>
<tr>
<td>0.02%</td>
<td>Scenario 3</td>
<td>Scenario 4</td>
</tr>
<tr>
<td>1%</td>
<td>Scenario 4</td>
<td>Scenario 6</td>
</tr>
</tbody>
</table>

Value of Investing in Women’s Health Research

Using the simulated health and cost outcomes, we examined ROIs under either doubling or tripling of the NIH portfolio of women-targeted AD/ADRD research across the scenarios. To further understand investment impact, we also examined probability of success. To do so, we additionally framed the ROIs in the context of uncertainty of investments. That is, we calculated the minimum probability of success of the investment to generate an expected ROI of 15% for a given health improvement.
Given that higher investment should yield better improvements in health, more money for the same health impact would result in a lower ROI for the tripling scenario (more money put in for the same health improvement). For this reason, results presented below primarily contrasted scenarios 1 and 2 (0.01 percent health improvement) for doubling the women’s portfolio to scenarios 3 and 4 (0.02 percent health improvement) for tripling the women’s portfolio. This assumes a linear relationship between investment and impact in that doubling the amount of money, in turn, doubles the health impact.

The benchmark for the baseline percentage of research on women’s health was funding levels for AD/ADRD research within the funded portfolio of the NIH. To estimate this level we retrieved all titles and abstracts for the AD/ADRD area using NIH RePORTER, the publicly available interface of funded extramural NIH projects (National Institutes of Health, 2020b). The terms used to search the retrieved titles and abstracts to determine the total number of women-focused projects were “women”, “sex”, “gender”, and “female.” Projects without these terms in the title or abstract were excluded from the “women-focused research” set examined (N=56,612).

Total AD/ADRD project funding level was calculated based on the NIH Research, Condition, and Disease Categorization (RCDC) codes (National Institutes of Health, 2020a). The total funding level in 2019 for AD/ADRD was $2.398 billion dollars, and the percentage of funding invested in women-focused projects for AD/ADRD increased from 6 percent in 2015 to 12 percent in 2019 (Sekar; National Institutes of Health, 2020a). The 12 percent increment was added to the 2019 amount of $2.398 billion to double the level of investment in women’s health research to $2.685 billion, and a 24 percent increment was used to triple the level of investment to $2.973 billion. All costs are presented as 2017 USD.

Results

We present the health and economic improvements and resulting impact on costs for the primary specification, scenario 1: a 0.01 percent average health improvement, with three times the impact for women as for men. Different funding scenarios are compared to provide context for these results. Finally, we present the resulting ROIs and probability of success necessary to have an expected ROI of 15 percent.
Impact on Health and Economic Outcomes for Scenario 1

Figure 3 presents the simulated improvements in the health and economic outcomes and the resulting impact on costs, scaled up from the model cohort to the US population, ages 35 and older, of approximately 179 million people, of which around 7 million people had ADRD at baseline. We discuss each cost impact in turn below.

**Figure 3: Health and economic improvements under scenario 1 (0.01% impact, three times larger for women than men), for US population age 35 and older**

Note: based on US population age 35 and older of around 179 million, of which around 7 million had ADRD

**Increased life expectancy:**

We estimated that the scenario 1 health improvement results in more years of life from lowering the onset and progression of AD/ADRD. Specifically, we found that women realize over 2,800 more life years from innovations, while men realized over 1,000 more life years from innovations, for a total of around 4,000 more life years. This is small for the overall US population, approximately 179 million people, tracked through 30 years. Put another way, this represents an average additional extension of life by one-tenth of a day per AD/ADRD patient, or one additional life year for one out of every approximately 3,300 AD/ADRD patients. This represents improvements for thousands of people, without having changed the mortality rate for AD/ADRD patients. Data are scaled up from the model cohort to the US population, ages 35 and older, of approximately 179 million people, of which around 7 million people had ADRD at baseline.
Decreased disease burden:
Scenario 1 health improvements also generated a reduction in AD/ADRD disease burden in terms of life years with AD/ADRD, a function of both shorter disease duration as well as a reduction in age incidence. Women have over 5,500 fewer life years with AD/ADRD, and men had nearly 900 fewer life years with AD/ADRD. These are again relatively small compared to the underlying population, with around two-tenths fewer days with AD/ADRD per AD/ADRD patient, or one fewer year of AD/ADRD for one out of every around 2,000 patients. Similar to life expectancy increases, although these numbers are relatively small, they represent real gains for people.

Reduced institutionalization:
We estimated that due to the examined health improvement in scenario 1, women have over 2,100 fewer life years in nursing homes, while men have over 1,400 fewer life years in nursing homes, for a total of around 3,500 years. This is roughly similar to the numbers of increased life expectancy, and while small, represent real improvements. Note that if all of these costs were incurred in the first year, and so were not discounted for net present value, and the cost was at $100,000 per year, then these 3,500 fewer years represent a cost savings of $350 million, which exceeds the doubling of the women’s health research funding investment.
Increased quality of life (measured in equivalent QALYs):
While we measured an increase of around 4,000 total life years due to the health improvement in scenario 1, this does not capture the fact that these health improvements are related to higher quality of life. In fact, unlike the prior metrics, this is the only one affected by each of the three health improvements. Delayed onset reduces the years of AD/ADRD burden, which increases quality of life. Slowed progression of the diseases also improves quality of life, as people spend more years in less severe states. Finally, we directly decreased the reduction in quality of life for AD/ADRD patients from the health improvements, representing potential innovations that, while not changing the onset or severity of the disease, do decrease the burden of the disease for a given severity. For these reasons, the QALYs represent a large effect, with around 16,000 more year-equivalent of a fully-healthy adult. Of these, approximately 80 percent are from women patients, and 20 percent from men.

Caregiver Productivity:
The final health and economic outcome we investigated is the change in productive years of caregivers, which is a function of changes in formal and informal care. This is the only case where we split results for care for women and men, with around 300 fewer lost years of productivity given in care for women and an increase in lost productive years given to men, at around 500 years. The latter may be a result of keeping some men out of nursing homes, which would have shifted care to formal caregivers, but instead shifts care to informal caregivers. This would have likely also affected women too, attenuating the reduction in care from the health improvement. Overall, there is a small total effect of around 200 more years of lost productive years from caregivers.

Impact on Cost Outcomes for Scenario 1
With the health and economic outcomes in the status quo and improved health scenario 1 estimated, we can calculate the costs and changes in costs. These are presented in Figure 4.
The overall reduction in costs was around $930 million net present value across the 30 years. Around 80 percent of the costs are from female patients, and 20 percent from male patients. Furthermore, as shown in Figure 4, approximately 40 percent of the cost-reductions arise from fewer nursing home stays, while approximately 60 percent come from fewer lost QALYs (from improved quality of life). Non-care healthcare costs actually increase slightly (due to fewer years of formal institutional care), but the effect is negligible. So too is the effect on lost productivity of caregivers compared to the two main cost savings drivers.

**ROI under Different Scenarios**

We calculated the ROI that would result from doubling or tripling the women’s portion of the AD/ADRD portfolio under scenario 1’s health improvements. Under this scenario of a 0.01 percent health improvement, doubling the women-targeted portion of the portfolio results in a ROI of 224 percent. If we assume a tripling of the investment is required to achieve the same health impact of 0.01% improvement, then the ROI is 62 percent in this scenario. This exercise did not model larger health improvements that are likely with larger investment.

Next, we allowed the health improvement to increase with the increase in the level of investment. Specifically, we assumed a linear return to the investment, such that doubling the investment increase from around $288 million (doubling women’s targeted portfolio) to around $575 million (tripling women’s targeted portfolio) would also double the health improvement. We
thus examined scenarios 1 and 2 (average improvement of 0.01 percent) for a doubling of investment and scenarios 3 and 4 for a tripling of investment (average improvement of 0.02 percent). Scenarios 1 and 3 assumed that the health impact is three times larger for women than men, while scenarios 2 and 4 assumed an equal health impact for women and men. Comparing scenario 1 to scenario 2 (or similarly, comparing scenario 3 to scenario 4) thus allows for a comparison of the return on investments for research on women’s health, versus investment in research with no specific sex/gender focus. See Figure 5.

**Figure 5: Return on Investment**

[Figure showing return on investment for scenarios 1 to 4, with women having a higher ROI than men for both doubling and tripling investments.]

There are a number of key takeaways from Figure 5. First, we note that the cost-reductions are greater for women compared to men in scenarios 1 and 3. This follows from the assumption in these scenarios of women having three times the health improvement as men. Second, we note that despite that, there is a higher ROI for the women-targeted research investment scenarios (1 and 3). This result expresses the potential gains to targeting additional research in AD/ADRD towards women’s health rather than to general health research. Third, the tripling investment has a higher ROI than the doubled investment under the constant returns to investment assumption we have made here. The result suggests that, in the face of large potential gains, an aggressive increase in investment may pay off over the several decades. The magnitude is not sufficiently large to draw strong conclusions, however, given our lack of evidence in support of constant returns to investment.
Calculation of Probability of Success Needed for an Expected ROI of 15 Percent

The returns on investment presented in the prior section implicitly assume that the investment will be successful. In reality, investments bear risk, and this holds true for investments into AD/ADRD research. We thus reframe the returns into a simple model of uncertainty, where with probability (P) that the investment succeeds in bringing to bear the scenario’s health improvement, and with probability (1-P) that it fails and costs remain the same, except with the additional borne cost of the investment. We then can calculate the probability of success (P) that equates to an expected return on investment of 15 percent. These results are presented in Table 2. Note that small probabilities are desirable in this exercise, as they indicate that the investment is lower risk. Further, since each row holds the health improvement constant, tripling the investment dollars will require a higher probability of success than doubling to achieve a given ROI. The target of 15 percent was chosen based on similar return on research investment in a range of therapeutic areas (Grant and Buxton, 2018).

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Health improvement under success</th>
<th>Women's impact compared to men</th>
<th>Minimum probability success needed under:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Doubling investment</td>
</tr>
<tr>
<td>1</td>
<td>0.01%</td>
<td>3 to 1</td>
<td>35.5%</td>
</tr>
<tr>
<td>2</td>
<td>0.01%</td>
<td>Equal</td>
<td>39.1%</td>
</tr>
<tr>
<td>3</td>
<td>0.02%</td>
<td>3 to 1</td>
<td>16.2%</td>
</tr>
<tr>
<td>4</td>
<td>0.02%</td>
<td>Equal</td>
<td>16.3%</td>
</tr>
<tr>
<td>5</td>
<td>1%</td>
<td>3 to 1</td>
<td>0.3%</td>
</tr>
<tr>
<td>6</td>
<td>1%</td>
<td>Equal</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

This provides a useful framework under which to consider these risks. For the scenario 1 case under a doubling of investment, with an ROI of 224 percent, the investment would have to succeed with probability 35.5 percent to result in a 15 percent expected ROI. This is a moderate necessary probability of success, not unexpected given the assumption of a very small health improvement. This is the fundamental dynamic in play in this exercise—larger improvements in health require a smaller probability of success to result in the same expected ROI of 15 percent. Thus, for the much larger health improvement in scenario 5 of 1 percent improvement, even under a tripling of the budget, it would take only a 0.6 percent probability of success to result in an expected ROI of 15 percent.
These results provide a set of potential pathways to result in a 15 percent ROI. For example, for Scenarios 1, 3, and 5, in which investment in research is doubled and directed toward women’s health, the probability of success of a $288 million increase in women’s health research funding will vary by size of the health improvement obtained, holding the return on investment constant at 15 percent. Specifically, this women’s health research on AD/ADRD will have an expected ROI of 15 percent. Therefore, a very small health improvement of 0.01 percent requires a larger probability of success (35.5 percent) than a health improvement of 0.02 percent, which requires a probability of success of only 16.2 percent. An even larger health improvement of 1 percent requires only a 0.3 percent probability of success to yield an expected return of 15 percent. Altogether, this suggests it is possible to obtain positive returns on increasing the budget for this research.

Discussion

Large societal gains may be possible by increasing investment in women’s health research in AD/ADRD. The potential to recognize societal gains is greater for research devoted to women’s health relative to general research, based on the specifications used here.

Overall magnitude of impact is in line with similar research on impact of research investment (Luce et al., 2006). The results can aid with establishing the value of new interventions by addressing which stakeholders and which societal payers are impacted (El-Hayek et al., 2019).

All models involve assumptions, by design. The assumptions made for the models reported here were in general selected to return more conservative results, that is, results that bound the lower end of possibilities for investment in women’s health research. These assumptions are discussed in turn.

Investment size: The size of the investment increments examined in these models is relatively small, less than 15 percent addition for the doubled case and less than 25 percent addition in the tripled case. However, the FY2019 AD/ADRD portfolio total, on which baseline investment and the doubled and tripled increments were based, includes the addition of the Professional Judgment budget, the substantial increase in NIH funding dedicated to AD/ADRD research through appropriation legislation (Consortium of Social Science Associations, 2015; National Institutes of Health, 2019). Future size of the portfolio may revert to the lower pre-2016 levels. The ROI is a function of the size of the investment and the magnitude of health improvements. Smaller overall increments in investment, should the AD/ADRD budget revert to a smaller
overall size, would yield larger investment returns with health improvement assumptions held constant. The very small health improvements examined here make the direction of impacts robust to smaller overall investments.

**Accrual of health improvements to women compared to men:** The main results reported here assumed that dollars invested in women’s health research would yield greater benefits for women than men but that all people would recognize health benefit from the investment. The two separate scenarios were one in which the investment in women’s health research was assumed to yield greater benefit for women but some benefit for men in terms of health improvements, and the other in which the research investment was assumed to yield equal benefits for women and men. The second scenario can be considered a “general investment” case and is a form of the *status quo*. A key caveat is that the *status quo* disadvantages women. That is, gender neutral or gender inclusive research yields results that are less applicable to women than to men. The comparison of a 3:1 benefit, favoring women, may underestimate actual benefit to women of research investment in women’s health research, as relative benefit for women may be higher. The overall model assumption also keeps the proportion of the investment in women’s health research to well less than 50 percent of the total portfolio amount. The results are therefore likely an underestimate of the potential societal impacts. The comparison case of equal benefit accruing to women and men is likely an overestimate of the impact of women, given historical disadvantage to women’s health of research that does not expressly address women. The true ratio of benefit for the base case is not known, but the ratio of 1:1 is not an underestimate of the relative benefit to men. For these reasons, the comparison is likely skewed toward understatement of the value of investment in women’s health research.

**Time horizon:** Estimates for the time from investment to discernible impact of investment for health research center on 13 to 25 years (Cruz Rivera et al., 2017; Hansen et al., 2013; Scott et al., 2014). Future research may involve acceleration of that timeline. The speed with which treatments and vaccines are being developed to address the current COVID-19 pandemic may be a bellwether for research time horizons, demonstrating the potential for shorter timelines for peer review and publication of research results. The models examined here assumed 10 years from present day investment to future realization of health impacts. However, the models were based on a single cohort, without replacement. While impacts were scaled up to the US population, cumulative impacts of health improvements may be greater longitudinally than presented here.
The benchmark for additive investments in women’s health research is relatively small compared to the size of the AD/ADRD portfolio of research that NIH funds. The potential for both smaller and larger investments is worth investigating, although the doubling and tripling scenarios examined here provide some benchmarks for interpreting potential benefit relative to investment size.

The potential for differential impacts on informal caregiving depending on size of health improvements points to the importance of identifying policy scenarios to pursue pending different health innovation scenarios. For example, policies that address the transitions between formal long-term care and informal caregiving deserve close attention when planning for future public health impacts of research investment. Home health reimbursement and workforce readiness may be critical to address if innovations increase the informal care burden by extending time in non-severe but highly functionally impaired stages. Longer life span for women may exacerbate the informal caregiving need.

One key consideration in modeling based on labor force participation and earnings is selection of earnings profiles. We chose to apply earnings of non-Hispanic white males for all races/ethnicities and genders in the informal caregiving population. This has the advantage of avoiding assumed ongoing bias but does represent a departure from the strict matching of other economic modeling studies.

Health research investments impact society through many pathways. The models examined here focused on a small but important subset of potential impacts on population health based on investment in women’s health research. While a cure and/or preventive intervention may be possible for AD/ADRD over the coming decades, these analyses assume relatively small health impacts from research investment. More optimistic scenarios are not unreasonable.

Limitations
This examination should be interpreted with reference to potential limitations. These results are dependent on the underlying assumptions about uncertain impact of investment. As noted above, the models present a realistic but not overly optimistic view of the potential for increased research investment. Disease modification that yields a different severity profile – for example, longer time in moderate-to-severe stages with reduced mortality – could yield more negative impacts than those presented here. A preventive intervention or cure is certainly possible as well and could yield more positive impacts than presented here.
While the keyword approach for identifying women-focused research was simple, comprehensive, and consistent with other such searches, the selected keywords may have over- or under-included relevant research. Given the recent requirement to include sex-based analyses in NIH funded research beginning in 2016, many projects may have a women-focused research goal within a set of larger goals, leading to undercounting of women-focused research investment. This suggests that our estimates of overall funding levels for women-focused research are low, and the 12 percent and 24 percent increments used to project the impacts of doubled and tripled funding scenarios on health and societal outcomes are conservative. Future impacts of research may differentially accrue to women based on this requirement.

There were additional limits to the modeling and simulations. Microsimulations are an exercise is trade-offs, where simplifications made for tractability of the model may weaken the ability of the model to capture the relevant dynamics. In some cases, decisions to simplify were reflections of our inability to obtain reliable parameters from the literature or have the necessary data to estimate. For example, while we have estimations of formal home care costs conditional on receiving formal home care, we chose not to simulate the status of receiving formal home care; instead, we use the average health care cost that covers formal home care in our model. Furthermore, our results depend on some of the more subjective model decisions we made, including how many years to simulate the model forward (we chose 30 years), whether to bring new people into the cohort as they age into the relevant time-frame (we modeled without replacement), and how many years after the investment until the impact was realized (we assumed 10 years). We also had to simplify the model to assume that the full health improvements were realized at once at that 10-year mark instead of introducing time-gradient for small improvements and bringing the innovations up to scale.

Another limitation is that we are not reporting results for improvements to mortality rates for AD/ADRD patients. While we ran these in simulations, mortality reductions always increased costs and never yielded positive ROI, based on the standard threshold of $100,000 used for the QALY analysis. Of course, this does not imply that we object to researching innovations that decrease probability of death for AD/ADRD patients; quite to the contrary, we support these and point this out as a limitation of the use of QALYs and the value we set it at. Interestingly, our microsimulation model allowed us to estimate the break-even value of a QALY such that decreasing mortality would be beneficial to society given the modeled costs; we estimate this at around $350,000 per full-health year. However, we do not include this as a formal part of the
innovation analyses here. The multiple assumptions required in QALY-based valuation are dependent on social and cultural factors (Hood, 2017) and warrant further study.

The analyses here do not reference transgender or other sex and gender identities. This is not to deemphasize the importance of wider consideration of sex/gender identities but the focus here is on a first view of the under-resourced area of women’s health.

**Policy Implications:** The results of these analyses suggest several policy actions to inform decision making about research funding allocations.

1) Direct additional research funds toward women’s health within AD/ADRD. The potential for improved return on investment for research directed at women’s health relative to general health research makes such an investment more valuable, from a societal perspective. Information about women and AD/ADRD is limited relative to information about men and AD/ADRD. The potential for research funding to identify new knowledge may therefore be greater than directed toward women’s health, given the substantial lack of knowledge. Among the potentially fruitful women-focused research areas that could yield important clinically actionable knowledge are biological and cultural. Biologically focused research that is likely to uncover new advances include impact of hormonal status on AD/ADRD risk and progression, impact of pregnancy factors (parity, hypertensive pregnancy disorders) to AD/ADRD risk, differing profile of cardiometabolic risks, and relationship of mood disorders with higher prevalence in women to AD/ADRD risk (Lin et al., 2014). Among the cultural areas for research that could positively impact AD/ADRD are marital effects and impact of physical activity and education (Hood, 2017).

2) Establish research agendas that expand beyond existing work, to permit identification of un- and under-studied relationships between AD/ADRD in women and other health conditions, like cardiovascular disease (Lin et al., 2014). Women’s health researchers have been identifying promising “signals” of relevant effects of health conditions on later life cognition. We recommend focused mining of existing research to inform the agenda for future AD/ADRD likely to yield high impact results for women.

Broader actions that could improve decision-making about research funding involve increasing awareness of the current state of funding directed toward women’s health in
AD/ADRD and the potential for such funding to yield a range of societal benefits. Specifically, we recommend the following:

1) Increase outreach to multiple research disciplines to raise awareness of the current limitations of knowledge about women and AD/ADRD and of the potential for research to yield benefits for women and for society. This step requires evaluation of the culture of science and the ways in which women’s health research is disadvantaged relative to other health research. A key focus of this evaluation must be on the ways in which women’s research careers are disadvantaged relative to men’s, based on family factors such as differential caregiving burden for women, and based on systemic factors such as implicit and explicit bias against women in health research.

2) Increase outreach to the business community to raise awareness of the potential return on investment for women’s health research. It is crucial to address and remedy discriminatory practices in terms of research funding allocations and women’s health researcher careers. This is not sufficient, however. Raising awareness among business leaders is critical to ensuring “market pull” for research, which is necessary for the viability of women’s health research agendas and funding. Within the pharmaceutical and biotechnology industry, decisions made now by leaders about research investments should be informed by the potential for societal return on investment. Across multiple other business sectors, the potential for improving workforce productivity and reducing healthcare burden associated with AD/ADRD based on research investment should be known, to inform investment and advocacy for research funding.

Conclusion

Understanding the full range of societal impacts from health research investment requires consideration of multiple factors and, given the uncertainty of the future, requires assumptions. Differences in etiology, detection, care access, and treatment by sex and gender are well documented in AD/ADRD and can provide specifics to inform an agenda for research on women’s health (Nebel et al., 2018). In conjunction with detailing the research agenda, the financial investment needed to realize the goals of that agenda requires planning. Investing more in research on women’s health is likely to deliver net positive societal impacts. Clear
understanding of the potential for investment can improve decisions about where and how to invest, to recognize positive impacts for women and for society as a whole.

Acknowledgments

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## Table A1. Availability of key variables among potential data sources

<table>
<thead>
<tr>
<th></th>
<th>Panel Study of Income Dynamics</th>
<th>National Longitudinal Survey of Youth, 1979</th>
<th>Medical Expenditure Panel Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>24,000 people</td>
<td>12,686 people</td>
<td>30,000 households</td>
</tr>
<tr>
<td>Age ranges</td>
<td>Born 1951-present</td>
<td>Born 1957-1964</td>
<td>Range of ages</td>
</tr>
<tr>
<td>Received diagnosis of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s specifically</td>
<td>No (just diagnosis of permanent loss of memory/ mental ability)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Health spending</td>
<td>Yes (aggregated)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Health condition limits activities</td>
<td>Yes</td>
<td>Snapshot</td>
<td>Yes</td>
</tr>
<tr>
<td>Extra care needed</td>
<td>Snapshot</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Disability insurance participation</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Paid nurse to come to home this year</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Note: “Snapshot” indicates a variable is capture incidentally (e.g. in a single year or at milestone ages) rather than every survey wave (annual/biennial).*
Technical Appendix B: Model

1. Overview of the model

This microsimulation model is based on a synthetic starting cohort with 999,988 individuals aged 35-99. We use the fraction of individuals that are each age and gender in the U.S. population from the Census Bureau (U.S. Census Bureau, 2020) and multiple that fraction by 999,988 to determine how many individuals in our simulation sample are that age and gender. Conditional on age and gender, individuals in the starting cohort are sorted into one of eight states:

1. Alive without AD/ADRD and not institutionalized
2. Alive without AD/ADRD and institutionalized
3. Alive with AD/ADRD in mild stage and not institutionalized
4. Alive with AD/ADRD in mild stage and institutionalized
5. Alive with AD/ADRD in moderate stage and not institutionalized
6. Alive with AD/ADRD in moderate stage and institutionalized
7. Alive with AD/ADRD in severe stage and not institutionalized
8. Alive with AD/ADRD in severe stage and institutionalized

The distribution of the 8 states in the population is derived by simulating a cohort of 100,000 females and 100,000 males aged 34 for 66 years through our health model until everyone dies in our simulation. This is used to calculate the initial conditions of the population. Setting the number of individuals in the starting cohort at 1000,000, we multiply 1000,000 with the distribution to assign individuals with AD/ADRD status, ADRD severity, and nursing home status. This determines by age and gender the fraction of individuals within each of the 8 states. We take each age and gender group and assign the proportion of people in each state reflected by those simulations. We ended up with 999,988 individuals for the starting cohort due to the discrete nature of the states.
There are three components in this model:

1. Simulating and predicting the proportion of people diagnosed with Alzheimer’s Disease/Alzheimer’s Disease and Related Disorders (AD/ADRD), the progression of the disease, care status, and mortality.

2. Generating aggregate projections of individual-level outcomes, including total non-nursing home health care costs (including formal home care), nursing home costs, productivity loss of informal caregivers, and quality of life loss.

3. Estimating the impact of additional research funding on economic costs, using return on research funding investment.

2. Data sources used for estimation

2.1 Medical Expenditure Panel Survey

The Medical Expenditure Panel Survey (MEPS), beginning in 1996, is a set of large-scale surveys of individuals and families, their medical providers (doctors, hospitals, pharmacies, etc.), and employment status across the United States (Agency for Healthcare Research and Quality, 2020). The Household Component (HC) of the MEPS provides data from individual households and their members, which is supplemented by data from their medical providers. The Household Component collects data from a representative sub sample of households drawn from the previous year’s National Health Interview Survey (NHIS). Institutionalized population is not included in the MEPS, which implies that we can use the MEPS to estimate health care costs only for the individuals living in communities. Information collected during household interviews includes demographic characteristics, health conditions, health status, use of medical services, and health insurance status. Each year the household survey includes approximately 12,000 households or 34,000 individuals. We estimate expenditures and utilization using 2011-2017 data.
2.2 Health and Retirement Study
The Health and Retirement Study (HRS) is a longitudinal panel survey of Americans over the age of 50 occurring every two years (The University of Michigan, 2020). It’s a complex and rich source to explore health transitions relating to aging. We used from the waves 1 (1990) through wave 12 (2014-2016) to estimate the proportion of people being institutionalized. We use the dataset created by RAND (RAND HRS, version Q) as our basis for the analysis. When appropriately weighted, the HRS is representative of U.S. households where at least one member is at least 51.

2.3 Centers for Medicaid & Medicare Services Data
The CMS Medicare Beneficiary Summary File (base and chronic conditions components) was used to estimate the age incidence rate of AD/ADRD. The master beneficiary summary file (MBSF) base segment includes Medicare enrollment information for the universe of Medicare beneficiaries. It also contains demographic data (date of birth, date of death, sex, race, and ethnicity) and limited socio-economic information (Medicare/Medicaid dual eligibility status and Part D (drug coverage) cost-sharing status). The MBSF chronic conditions segment contains data on 27 chronic conditions, two of which are Alzheimer’s disease (AD) and Alzheimer’s disease related dementia (ADRD), and for each condition, it includes the date of first diagnosis as well as indicators for whether the diagnosis is active in the current year. With date of first diagnosis, incident cases can be identified separately from prevalent cases in any year. We used data these annual files 2016 and 2017 so we would have one complete year from birthday to birthday for each beneficiary, and from these we identified age-specific incidence rates for AD and ADRD. We used the 2017 data to estimate age-specific mortality rates, conditional on AD/ADRD status and the time since AD/ADRD diagnosis. Thus, estimates of age-specific incidence rate and age-specific mortality rates conditional on AD/ADRD duration were made using the universe of individuals who were at least 65 years of age and enrolled in Medicare (Research Data Assistance Center, 2020a; Research Data Assistance Center, 2020b).
3. Modeling health and economics statuses

3.1 Incidence of AD/ADRD

We model the probability of having onset of AD/ADRD for each individual. To do so, we estimated the following probability in equation B.1 for each gender $g$ and age $t$ using CMS data.

$$
\psi_{gt} = \Pr(AD/ADRD \text{ at age } t + 1 | \text{alive at age } t + 1, \text{no ADRD at age } t, \text{gender})
$$

(B.1)

We do not assign anyone younger than or equal to 65 years old to AD/ADRD state ($i = 66 - 99$); that is, our model does not consider early-onset AD/ADRD patients. AD/ADRD is an absorbing state in our model, which means that once an individual is diagnosed, he/she lives with the condition until death. With these probabilities estimated, in the microsimulation model we take uniform random draws ($u_{gt1}$) from 0 and 1 for each individual at each age that did not have AD/ADRD in the prior year, model them as having been diagnosed with AD/ADRD in that year if the random draw is less than the probability, i.e. if $u_{gt1} < \psi_{gt}$. Figure B1 presents our simulated proportion of people at each age in each state of alive with AD/ADRD, alive without AD/ADRD, and deceased. The fraction of people with AD/ADRD peaks shortly after age 80.

Figure B1: AD/ADRD case trend in males and females
3.2 Severity of AD/ADRD

Transition probabilities between AD/ADRD severity stages are based on Davis et al. (2018), Table 4. Davis et al. model seven states: normal, mild cognitive impairment, mild AD, moderate AD, severe AD, non-AD cognitive impairment, and death. We assign normal, mild cognitive impairment, and non-AD cognitive impairment into a category of non-AD/ADRD. The definition of mild AD/ADRD state by Davis et al. is having a clinical dementia rating (CDR) less than 2, whereas patients in moderate AD state have CDR of 2 and patients in severe AD/ADRD state have CDR of 3.\(^1\) The transition probabilities in Davis et al. (2018)’s Table 4 allow patients transition from more severe stages back to a milder stage to capture measurement noise. For age 65, we use the transition probabilities in Table 4 panel A. For age 75 and older, we use the transition probabilities in Table 4 panel B. For ages between 65 and 75, we use a linear interpolation of the transition probabilities. For example, the unconditional transition probability from mild to moderate for age 68 would be set to \(0.19 + (0.21-0.19)/10\times3=0.196.\)

These represent the unconditional probabilities of transitioning, specifically, allowing for a transition into death. Our model instead is conditional on surviving at that age, and so we must
adjust the transition probabilities. We do so recognizing that \( Pr(\text{transition|alive}) = \frac{Pr(\text{transition,alive})}{Pr(\text{alive})} \). The numerator on the right hand side is contained in the numbers in Davis et al. Table 4. We must divide by the probability the person survives between the two years. We describe in the next section how mortality transition probabilities by age, gender, and AD/ADRD severity are calculated, which we use there.

With the adjustments to represent the conditional probability of transitioning into a different severity of AD/ADRD, we have probabilities of each transition. We take a random uniform draw \( u_{gt2} \) between 0 and 1. Then, for example, for a person who had mild AD/ADRD in the prior year, he/she is assigned to severe AD/ADRD if the random draw is less than the transition probability of mild to severe stage, i.e. if \( u_{gt2} < Pr(\text{mild to severe|alive}) \).

A random draw of people who had mild AD/ADRD in the prior year are assigned to moderate disease severity in an amount that exceeds the transition probability of mild to severe but is less than the sum of the transition probabilities for all transitions from mild: mild to moderate and mild to severe.

\( Pr(\text{mild to severe|alive}) < u_{gt2} < Pr(\text{mild to severe|alive}) + Pr(\text{mild to moderate|alive}) \)

Figure B2 presents the simulated proportions of individuals in each severity group, conditional on being diagnosed with AD/ADRD.
3.3 Probability of Dying

We used the United States Life Table in 2017 released by Centers for Disease Control and Prevention (CDC) to assign probabilities of dying to individuals without AD/ADRD each year, conditional on age and gender. For patients with AD/ADRD, probability of dying is assigned based on AD/ADRD stage, age, and gender. We generated the transition probabilities to death based on Davis et al. (2018) and adjusted for age and gender using the CDC probabilities of
dying for the general population, so that the probabilities of dying for ADRD patients are always higher than people without AD/ADRD conditional on age and gender. Figure B3 compares our simulated death probabilities with the CDC life tables.

Figure B3: Probabilities of dying in simulated cohort and in US general population

In addition to using Davis et al. (2018) to parameterize transitions between severity of AD/ADRD (as discussed in section 3.2), we also use their paper to calculate the probabilities of dying at any given age, depending on gender and AD/ADRD severity. To do so, we use both Table 3 from Davis et al. (to examine differences by gender) and Table 4 (to differences by severity of AD/ADRD).

We start by using the AD/ADRD severity distribution conditional on age groups (65-74, 75-84, 85-94, 95+) from Davis et al. (2018) Table 3. To generate stage distribution for every age, we first assign median age for the severity distribution (70, 80, 90, 97). Next, we get female/male ratio for every severity group using the severity distribution conditional on gender from Davis et
al. (2018). For example, when examining moderate AD/ADRD, Table 3 reports 418 women in the moderate group, and 681–418=263.

\[
\frac{\Pr(\text{moderate}|\text{female})}{\Pr(\text{moderate}|\text{male})} = \frac{418/(4962 + 1684 + 2001 + 418 + 183 + 1088)}{263/(18103 - (4962 + 1684 + 2001 + 418 + 183 + 1088))} = 1.1943 \quad (B.2)
\]

We do this for each of the three severity groups to get the difference for women and men. Next, we use this in combination with the overall CDC life tables for mortality rate. Below is an example using an individual age 70 with moderate disease severity. Using the law of total probability, we can rewrite the probability of having moderate AD/ADRD as in equation B3.

\[
\Pr(\text{moderate}|\text{age} \, 70) = \Pr(\text{moderate}|\text{age} \, 70, \text{female}) \Pr(\text{female}|\text{age} \, 70) + \Pr(\text{moderate}|\text{age} \, 70, \text{male}) \Pr(\text{male}|\text{age} \, 70) \quad (B.3)
\]

We assume that the change in probability of being in a given severity stage by gender is constant over age (as we do not have age-specific values). Therefore, we can use

\[
\Pr(\text{moderate}|\text{female}, \text{age} = 70) = 1.1943 \times \Pr(\text{moderate}|\text{male}, \text{age} = 70) \quad (B.4)
\]

We can substitute equation B.4 into equation B.3. Furthermore, we use the 2017 CDC life tables to calculate \(\Pr(\text{female}|\text{age} = 70)\) and \(\Pr(\text{male}|\text{age} = 70)\). We also use the probability of being in a given severity stage by age from Davis et al.; for example, \(\Pr(\text{moderate}|\text{age} = 70) = 197/(3953 + 1371 + 1352 + 197 + 89 + 1421)\). This leaves us with one unknown in equation B3, namely \(\Pr(\text{moderate}|\text{male}, \text{age} = 70)\). We solve for this and then solve for \(\Pr(\text{moderate}|\text{female}, \text{age} = 70)\).

We repeat the steps above and we have \(\Pr_{i,j}(\text{stage} = i|\text{male}, \text{age} = j)\) and \(\Pr_{i,j}(\text{stage} = i|\text{female}, \text{age} = j)\) where \(i = \text{mild, moderate, severe}\) and \(j = 70, 80, 90, 97\). These values of \(j\) are chosen as the mid-points in the Davis et al. ranges. We perform linear interpolation to get the
probabilities of all ages between 70 to 97 and linear extrapolation for age 65 to 69 and age 98 to 99.

We need these probabilities of being in a given severity stage by age and gender so as to adjust for the mortality rates. Davis et al. (2018) also report transition probabilities to death at age 65 and 75 for women and men combined, given the severity of ADRD. Similar to the approach in part 3.2, we use the transition probabilities to death in Table 4 panel A for patients age 65. For age 75 and older, we use the transition probabilities to death in Table 4 panel B. For ages between 65 and 75, we use a linear interpolation of the transition probabilities.

However, we are still missing the probability of dying in the next year for those without AD/ADRD for a given age and gender for these two ages, as well as more generally, the probability of dying at other ages for each gender and severity. For the former, we combine these transition probabilities to death with the probabilities of dying in any given age conditional on gender from CDC life tables, stage distribution conditional on age and gender from previous steps, and use the equation (B.5) below to get, for a given age and gender,

\[ \Pr(die|\text{no ADRD, at age } = i, \text{gender}). \]

We do so by again using the law of total probability. This is shown in equation B.5.

\[
\Pr_i(die \text{ at age } = i + 1|\text{alive at age } = i, \text{gender}) = \Pr(die|\text{no ADRD, at age } = i + 1, \text{gender}) \times \Pr(\text{no ADRD} \text{ at age } = i, \text{gender}) \\
+ \Pr(die|\text{mild ADRD, at age } = i + 1, \text{gender}) \times \Pr(\text{mild ADRD} \text{ at age } = i, \text{gender}) \\
+ \Pr(die|\text{mod ADRD, at age } = i + 1, \text{gender}) \times \Pr(\text{mod ADRD} \text{ at age } = i, \text{gender}) \\
+ \Pr(die|\text{severe ADRD, at age } = i + 1, \text{gender}) \times \Pr(\text{severe ADRD} \text{ at age } = i, \text{gender}) \quad (B.5)
\]

From equation B.5, we can back out the probability of dying given not having AD/ADRD. We estimated \( \Pr(die|\text{no ADRD, at age } = i, \text{gender}) \) separately at age 65 and age 75.
For the calculation of the probability of death at any age and gender for each severity group, we assume a linear adjustment to the underlying CDC mortality curve by severity, age, and gender. To do so, we calculated the hazard by the following equation (B.6) for \( i = 65, 75 \) and \( j = \text{mild, moderate, severe} \):

\[
\text{Hazard}_{i,j} = \Pr_{i,j}(\text{die at age} = i + 1 | \text{alive at age} = i, \text{stage} = j, \text{gender}) - \Pr(\text{die at age} = i + 1 | \text{alive at age} = i, \text{no ADRD}, \text{gender})
\]

(B.6)

We used linear interpolation to get hazard rates between age 65 and 75 and set constant hazards for age\( \geq 75 \) as the hazard of age 75. Finally, equation (B.7) below gives us the estimation for probabilities of dying conditional on any given age, AD/ADRD stage and gender:

\[
\Pr_{i,j}(\text{die at age} = i + 1 | \text{alive at age} = i, \text{stage} = j, \text{gender}) = \Pr_{i}(\text{die at age} = i + 1 | \text{alive at age} = i, \text{no ADRD}, \text{gender}) + \text{Hazard}_{i,j}
\]

(B.7)

As before, we then took random uniform draws between 0 and 1, and if the uniform draw was below the probability, we assigned that person in the simulation to die that year.

3.4 Living in Nursing Homes

We estimated the probabilities of being institutionalized in a nursing home conditional on age using all available waves (through wave 12) the RAND HRS version Q. We first estimated the probability of moving into a nursing home for the non-AD/ADRD population. We did so separately for women and men by fitting a general, non-linear monotonic increasing function of age on the probability of nursing home entry. Specifically, we used a logistic function (symmetric sigmoid shape) using Stata’s nl package with the log4 model.

\[
\Pr(NH|\text{Non} - \text{AD, gender}) = b_0 + \frac{b_1}{1 + \exp(-b_2(\text{age} - b_3))}
\]

(B.8)

Where \( \Pr(NH|\text{Non} - \text{AD, gender}) \) is the probability of nursing home entry for non-AD/ADRD persons. We estimated this for individuals age 50-94, and then predicted the smooth line from the estimated parameters to calculate the probability of nursing home entry or non-AD/ADRD populations.
We used the same data to calculate the probability of nursing home entry for AD/ADRD patients. Here, we had fewer data points, and so we did not estimate the probability of nursing home entry with a non-linear function. Instead, we estimated how much higher the probability of nursing home entry was for AD/ADRD patients compared to non-AD/ADRD patients with a linear time trend, as described in equation B.9.

\[
\Pr(NH) = a_0 + a_1(Age - 65) + a_2 AD + a_3(Age - 65) \times AD \quad (B.9)
\]

For any age and gender then, we can adjust and calculate the probability of nursing home entry by adding \(\bar{a}_2 + \bar{a}_3(Age - 65)\) to the probability of nursing home entry calculated for the non-AD/ADRD population using the logistic function (symmetric sigmoid shape) described above. However, this does not yet depend on AD/ADRD severity but is the average across severity for any given age/gender. To adjust for severity, we use the transition probabilities of being institutionalized from Spackman et al. (2012), Table 4. Spackman and colleagues provide transition probabilities by severity, but do not allow them to differ by age or gender. We use these to benchmark the difference in the probabilities of nursing home entry. That is, they calculate \(\Pr(NH|Mild AD) = 0.01\), \(\Pr(NH|Moderate AD) = 0.034\), and \(\Pr(NH|Severe AD) = 0.066\).

From this we, calculate the difference in the probabilities. From the law of total probability, we have for any given age and gender

\[
\Pr(NH|AD) = \Pr(NH|mild AD)\Pr(mild AD) + \Pr(NH|mod AD)\Pr(mod AD) + \Pr(NH|severe AD)\Pr(severe AD) \quad (B.10)
\]

The key is that we have \(\Pr(NH|AD)\) calculated from the HRS for each age and gender. We additionally have \(\Pr(mild AD), \Pr(mild AD), \text{ and } \Pr(mild AD)\) estimated for every age and gender from Davis et al. (2018). From the Spackman et al. differences, we have two more equations (the differences between moderate and mild as well as the difference between severe and mild, for example), which leaves us with three equations and three unknowns.
\( \text{Pr}(\text{NH|mild AD}), \text{Pr}(\text{NH|mod AD}), \text{and Pr}(\text{NH|severe AD}) \), which we solve for at each age and gender. This gives us a full set of probabilities of nursing home entry for every age and gender, for non-AD/ADRD, as well as AD/ADRD by severity. Figure B4 and B5 present the simulated care trends.

Figure B4: care trend in non-AD/ADRD males and females
3.5 Receiving Informal Home Care

We assumed that all community-dwelling AD/ADRD patients receive some informal home care, regardless of disease severity. For people without AD/ADRD living in the communities, we randomly assigned 15 percent of non-AD/ADRD individuals in the community younger than 65
years old and 45 percent of non-AD/ADRD individuals older than 65 years old to be receiving informal home care that year, based on Kaye (2013). (Kaye, 2013)

4. Cost Model

All costs were projected over 30 years assuming the investment is a one-time cost incurred in 2019. Future medical costs were normalized to 2017 USD using the Personal Consumption Expenditures (PCE) Health index. We adjusted for time preferences and the opportunity cost of investment by discounting future costs and QALYs at an annual rate of 5 percent. Figures B.6 and B.7 show the average costs—across both AD/ADRD and non-AD/ADRD patients—by age, based on our simulations. We describe each in turn.

Figure B6: average cost conditional on age for males
4.1 Health Care Costs

We estimated the average health care costs (not including nursing home stays) conditional on age and gender using the 2011-2017 Medical Expenditure Panel Survey (MEPS) for individuals without AD/ADRD. For AD/ADRD patients, we assigned them the average health care costs of AD/ADRD patients conditional on gender. There is no variation in the assigned health care costs based on age for AD/ADRD patients because of the difficulty to estimate those from the small sample size of AD/ADRD patients in MEPS (although we also found little difference in the health care costs when we did estimate, likely because the MEPS does not include nursing home stays or costs). In view of the impact of insurers on medical spending, we used ordinary least squares regression to estimated total medical spending (medical spending from all payment sources) controlling for year, age, gender, and insurer type (Medicaid, Medicare, Tricare and private insurers). Instead of modelling the status of receiving formal home care and assigning formal home health care costs conditionally, we assigned the total health care costs that include formal home care. Informal home health care is not included in the total health care costs.
costs from MEPS but estimated using productivity loss of caregivers in section 4.2 below. Since MEPS is representative of only the US civilian non-institutionalized population, health care costs for individuals in nursing homes were estimated separately. However, we chose to assign the same average total health care costs for institutionalized population on the assumption that their health care costs (not including the costs of the nursing home) do not differ from community-dwelling individuals.

4.2 Productivity Loss of Informal Home Caregivers
Costs of informal home care are calculated using the productivity loss of informal home caregivers. All informal caregiver earnings are based on those of non-Hispanic white males to correct for gender and race-based labor market discrimination. The hourly wage for non-Hispanic white males estimated from MEPS is around $23.86 for workers younger than 65 and $23.60 for workers older than 65. The steps of calculating the productivity loss are as follows:

1. We assign 30 percent of caregivers for individuals receiving informal home care to be older than age 65. The percentage of caregivers older than age 65 (30 percent) is similar in individuals without AD/ADRD and AD/ADRD patients who receive informal home care ("2020 Alzheimer’s disease facts and figures," 2020; Spillman et al., 2014).

2. The average hours spent on caretaking for AD/ADRD patients, not conditional on receiving informal home health care is based on Friedman et al. (2015) exhibit 2. For individuals without AD/ADRD and AD/ADRD patients in mild stage receiving informal home care, the hours per month caregivers spent are 65.8. We assign AD/ADRD patients in moderate stage with 89.3 hours per month of informal caregiving and 171.1 hours per month for AD/ADRD patients in severe stage.

3. By multiplying the hourly wage of non-Hispanic white males estimated from MEPS with the average informal caregiving hours from step 2, we get productivity loss in a year of informal home caregivers for AD/ADRD patients in different stages, calculated as follows:
Mild AD/ADRD or non-AD/ADRD, caregivers younger than 65: $23.86 \times 65.8 \times 12 = 18839.856$

Mild AD/ADRD or non-AD/ADRD, caregivers older than 65: $23.58 \times 65.8 \times 12 = 18618.768$

Moderate ADRD, caregivers younger than 65: $23.86 \times 89.3 \times 12 = 25568.376$

Moderate ADRD, caregivers older than 65: $23.58 \times 89.3 \times 12 = 25268.328$

Severe ADRD, caregivers younger than 65: $23.86 \times 171.1 \times 12 = 48989.352$

Severe ADRD, caregivers older than 65: $23.58 \times 171.1 \times 12 = 48414.456$

4.3 Nursing Home Costs

The cost of living in nursing homes is set at $90,520 annually for non-AD/ADRD individuals and AD/ADRD patients in mild and moderate stage. This rate is based on the reported national average for a private room in the Market Survey of Long-Term Care Costs published by MetLife Mature Market Institute in 2012 (MetLife Mature Market Institute, 2012). For AD/ADRD patients in severe stage, we assign the costs of living in nursing homes twice as much as the average rate ($181,040/year). The rise in costs is to reflect the intensity of care and unaccounted health care costs for severe AD/ADRD patients.

4.4 Quality of Life Loss

The value of one quality of life year (QALY) is set between $50,000 to $150,000 by the Institute for Clinical and Economic Review, and we choose to use $100,000 in our model. Although $50,000 threshold is arguably the “rule of thumb” in cost-effectiveness analysis in health care sector, but we believe that this value is an underestimation since it has never been adjusted for advances in technology, increased costs of care, and change in valuations about life over time. We assign health utilities based on Health Utilities Index Mark 2 (HUI2) to the general population conditional on age and gender from Fryback et al. (2007) table 3, and AD/ADRD patients conditional on disease severity based on Neuman et al. (1999) table 2. Although Neuman et al. (1999) also report health utilities of caregivers for AD/ADRD patients, the utility
levels are almost identical to those from Fryback et al. of the general population conditional on age and gender, so we choose to not consider lost QALYs from caregivers in our model.

We calculated lost QALYs for both non-AD/ADRD and AD/ADRD patients by subtracting their health utilities from 1, i.e. perfect quality of life. If someone is living in a nursing home, an additional 0.1 is added to the lost QALYs (Zissimopoulos, Crimmins and St Clair, 2014).

Persons who die in the simulation will have a lost QALY of 1 in the year they die, and for all the subsequent years in the time horizon. Below is an example of the calculation of lost QALYs for an individual with mild AD/ADRD not living in a nursing home.

\[1 - 0.69 \times (\text{HUI2 for mild AD/ADRD patients}) = 0.31\]

If this individual enters a nursing home, the lost QALYs would be:

\[1 - 0.69 \times (\text{HUI2 for mild AD/ADRD patients}) + 0.1 = 0.41\]

If the individual dies, the lost QALYs each year would be 1.

5. Return on Investment

Initially the target return on investment was set between 5 and 15 percent, and parameters were varied to achieve an ROI in this range. This proved a difficult task to calibrate, given small changes in the parameter could generate small changes in the outcomes (that is, only affecting a few people in our simulation), which when multiplied out represented large differences. For example, a small change which resulted in one person out of the one million people in our microsimulation having only one fewer year in a nursing home out of the thirty years simulated would represent a large shift in cost savings. With one million people in our sampling frame, and nearly 200 million in the underlying US population, each individual in the microsimulation sample represents nearly 200 people in the US population. Thus, the one fewer year of nursing home for one person, valued at $100,000, would represent a cost reduction of $100,000 times 200, or $20 million for the economy. Therefore, we instead focused on pre-chosen health improvements, and evaluated the (typically much larger than 10-15 percent) ROIs associated
with those health improvements, as well as the probability of success necessary for that cost improvement to yield an expected ROI of 15 percent. These methods are described below.

5.1 Calculation of Return on Investment

The return on investment, or ROI, is calculated using the following equation B.11:

\[
ROI = 100 \times \left( \frac{cost_x - cost_n - Investment}{Investment} \right)
\]

Where

\(cost_x\): US healthcare costs for age 35 and older under status quo health
\(cost_n\): US healthcare costs for age 35 and older with the new health improvement
\(Investment\): increase in investment

5.2 Expected ROI Under Uncertain Probability of Success

The return on investment process described in section 5.1 assumes that the investment will with certainty yield the health improvement and thus the cost savings. However, this is not a realistic representation of the risky nature of investments into health. We thus additionally frame an investment as a Bernoulli trial, that is, a binary outcome with a probability of success \(P\) achieving the given health improvement (and associated reductions in healthcare costs), or \((1 - P)\) probability of having no health improvement and remaining at the status quo healthcare costs. We write this as follows, where \(cost_i\) is the healthcare cost under investment.

\[
E[cost_i] = P \times cost_n + (1 - P) \times cost_x
\]  

(B.12)

We can combine equation B.12 with the ROI by connecting it to a specific ROI. For example, we can estimate the probability of success that is related to an expected ROI of 15 percent by

\[
15 = E \left[ 100 \times \left( \frac{cost_x - cost_i - Investment}{Investment} \right) \right]
\]

(B.13)

At the investment decision point, the only uncertainty is what the cost under investment \((cost_i)\) will be—either \(cost_n\), the new healthcare cost under health improvement from the investment,
with probability $P$, or $cost_s$, the status quo healthcare cost, with probability $(1 - P)$. Solving for the expected cost in the equation, we have

$$E[\text{cost}_i] = cost_s - 1.15 \times \text{Investment} \quad \text{(B.14)}$$

Putting the two equations together, we can solve for $P$ as

$$cost_s - 1.15 \times \text{Investment} = P \times cost_r + (1 - P) \times cost_s$$

$$\Rightarrow P = \frac{1.15 \times \text{Investment}}{cost_s - cost_r}$$
References


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