COMPLETE TECHNICAL REPORT

THE WHAM REPORT

Societal Impact of Research Funding for Women's Health

IN RHEUMATOID ARTHRITIS

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RAND CORPORATION

Women's Health Access Matters®

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WHAM, whamnow.org, is a 501c3 dedicated to funding women's health research to transform women's lives.

This report was conceived by WHAM in response to the considerable funding gap, historical exclusion, and under representation of women in health research.

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 by quantifying costs and economic benefits will 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 wellbeing and hence the wellbeing 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 Dementia, Rheumatoid Arthritis as representative of Autoimmune Disease, and Coronary Artery Disease. In the future, we plan to include Lung Cancer and also study different socioeconomic groups to the extent that the data are available and detail the global data which 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 R&D 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, business leaders, public health experts and policy makers to draw from and act upon the results of this report. Together, we can drive meaningful change.

Carolee Lee
Founder and CEO, WHAM
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** to learn more about using these data and citing this report.

WHAM's LEAD COLLABORATORS

WHAM's leadership of this research project was encouraged through the generous support and collaboration from the following organizations:

American Heart Association
The American Heart 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 American Heart Association's signature women's initiative, Go Red for Women® (GRFW), has been the trusted, passionate, relevant force for change to end heart disease and stroke in women all over the world for nearly two decades. Go Red for Women 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 (LJI) is one of the top five research institutes in the world focused on the study of the immune system. LJI is home to three research centers that harness 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, LJI and WHAM will create a framework for researchers to re-analyze 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.

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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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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 Rheumatoid Arthritis (RA). We quantified the potential impact of increasing funding on women's health on health outcomes and ultimate societal costs including healthcare expenditures, labor productivity for patients, and quality-adjusted life years (QALYs). We calculated impacts across 30 years of two funding scenarios: doubling the current National Institutes of Health extramural RA portfolio devoted to women's health, estimated at 7% of the total portfolio, 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 RA 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 0.1 percent or less total health improvement based on reduced age incidence of RA and reduced disease severity has the following results:
    - For the US population, over 70,000 years with RA can be saved across 30 years, with substantial gains in health-related quality of life.
    - Return on investment is 174,000 percent for doubled investment in women's health research with an assumption of only 0.1 percent improvement in health outcomes.
- Doubling the investment would have an expected ROI of 15 percent if it succeeded in generating health improvements of 0.1 percent with a 0.07 percent probability, or a 1 percent health improvement with only a 0.01 percent probability.

The results establish the potential for investment in women's health research on RA 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 RA. 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 RA. Given the limitations in knowledge about women and RA relative to men, the potential gains from women-focused research are substantial.
2) Pursue research on biology of RA in women, including early identification, and identify barriers to diagnosis in women.
3) Expand research agendas to address relationships between RA and work productivity impacts. Ways in which RA limits work productivity could be a useful lens through which to evaluate current and potential future treatment effectiveness. Given evidence of societal gains based on the work productivity gains possible with research, this is a fruitful area for study.

By raising awareness of the current state of funding directed toward women's health in RA 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 RA. 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 purse 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 RA. These communities are key to informing future research investment strategies.

The results can inform funding prioritization by funders, legislators, and the business community, demonstrating the potential for improving research on women's health, and demonstrating the impact of doing nothing - making no change from the current *status quo*.

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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. Over the last three decades some positive changes have been made, most notably placement of knowledge gaps in sharp relief, helpful for setting research agendas. Increased awareness of the impact of gender exclusion on health research has led to some efforts to include more sex- and gender-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, 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.

Quantifying the impact of research funding investment is a relatively new area of inquiry.[1] 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,[1] 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, and to specifically examine impacts of additional investments (see for example, Grant and Buxton, 2018[2]) s. 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.[2] For RA, 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 as part of an examination of the impact of funding for women's health research. We used microsimulation modeling 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. Women's health research as used here refers

both to analyses that address sex/gender within general sample or population studies, and to research focusing on women specifically, and to research focusing on women specifically.[a]

RA is an autoimmune disease with higher prevalence in women than men.[3] Prevalence estimates in the US have ranged from approximately 4 percent to 6 percent (National Health and Nutrition Examination Survey).[4] Over 52 million adults in the US have been diagnosed with arthritis, and over 20 million adults had arthritis-attributable activity limitation in 2010-2012.[5] Some symptom profiles differ by sex, with more women than men reporting hand pain and disability.[6] Current estimates project that women will continue to account for the majority of RA cases, accounting for over 58 percent of all cases in 2040.[5]

Within the portfolio of extramural funding for RA research from the National Institutes of Health (NIH) over the last five fiscal years, funding with a specific focus on women's health research accounted for 8.2 percent of total funding.[7] The disease burden is high[5] and greater investments are likely to yield a favorable return on the investment, for women – particularly given higher prevalence among women - and 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 attention to the medical gender gap. To address these challenges, microsimulation modeling was used to explore the potential for enhanced investment in women's health research, in terms of the economic outcomes for the US population.

Few studies have employed models stratified by sex or gender to test the sex/gender differences of RA, while the majority of RA-focused studies used sex/gender as a descriptive or control variable. Of the 42 articles included in a recent review of research in RA with a focus on women, only 5 studies tested sex/gender differences or conducted other sex/gender analyses such as models stratified by gender. None of these articles discussed societal costs related to the disease, such as lost workforce productivity.[8] Through a microsimulation model approach,

[a] 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)." We combine sex and gender research in our examination.

we examine the impact of funding on health outcomes and economically quantified societal burden from RA.

The analyses quantify costs and benefits of investment in women's research, with a focus on research for RA. The models used for this examination address contribution of research to disease burden and to societal productivity costs and benefits. We used current levels of funding from the 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, reduce disease severity, and improve health-related quality of life. We quantified the innovation impact through costs of medical care, work productivity and healthy life-years gained or lost. These models examine the impact of increased sex- and gender-based health research on women, their families, and the economy. 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 RA. The models followed a cohort representing adults ages 25 to 65 years within the U.S. population, and 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. The first model reflected the *status quo* of the disease, and then we 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 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 the efficiency of not requiring us to estimate each function in the model from underlying data.

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. Of the three final options, it has the largest sample and range of ages, the clearest diagnosis indicators, and comprehensive data on medical expenditures. It also meets our primary criterion of having detailed employment and income data for all household members. We use the MEPS data in several instances to parameterize functions we could not observe in the literature. See the Technical Appendix for more information about selection of dataset.

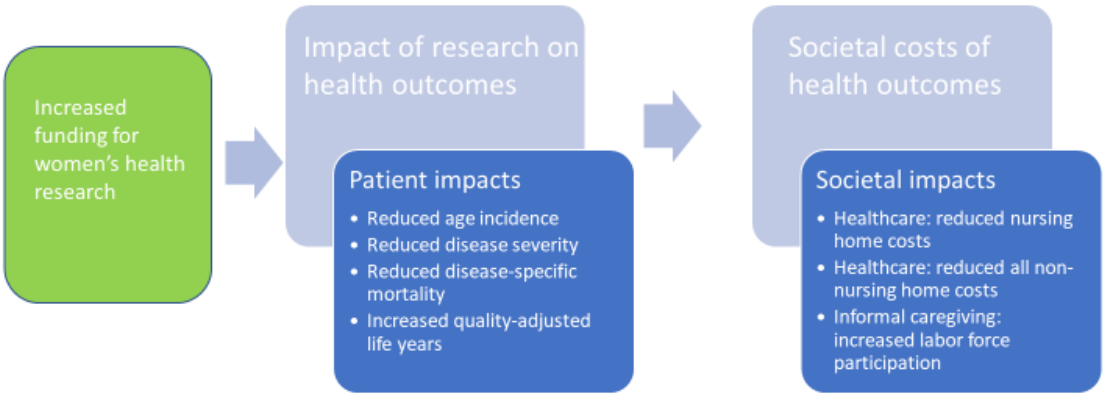
We estimated baseline healthcare costs from the *status quo* simulation model. Note that these baseline healthcare costs are not intended to capture all potential healthcare costs, direct and indirect. Instead, the baseline healthcare costs are with respect to the relevant inputs. We focus on individuals ages 25-65 at the start of the simulation and model their health and costs over a 30-year horizon. The decision to focus on the working-age population was in recognition of the impact that RA has on ability to work.

RA 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 for patients, through the economic microsimulation model. By tying different funding scenarios to incurred societal burden, the model quantifies how funding amounts impact societal burden of RA including health expenditures, productivity loss, and decreased quality of life. The impact on quality-adjusted life years (QALYs), and not just on absolute lost life years, is important to quantify for RA, given the ways in which the disease

affects individuals and the long duration of disease for many patients. The QALY is one way in which monetary value can be assigned to disease impact.[2] 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 impacts on patient and societal burden of rheumatoid arthritis



Background on Model Components

This model was built on six components: age incidence profiles, disease severity progression, earnings from labor, mortality, non-nursing home healthcare costs, and care status (informal care and nursing home). See Figure 2. The earnings profiles, stratified by age, quantify what a given person's earnings look like over their working career, and enable us to see the effect of personal and family health issues on earnings.

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 affect quality of life, care, and employment. This is a function of age and gender. We structure RA onset following Norton et al. (2014),[9] where using

latent class group modeling, they separate individuals with RA into four different classes, indexed by the severity at onset and progression.

Disease Severity Progression

We similarly use Norton et al.'s findings to model disease severity progression by age and gender and by assigned class. Severity is measured using HAQ scores. The severity impacts earnings loss, quality of life, probability and type of care, and mortality. Care status and mortality are functions of age, gender, disease status and severity.

Details of all model components are presented in Technical Appendix B.

Earnings from Labor

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.

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, the 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.

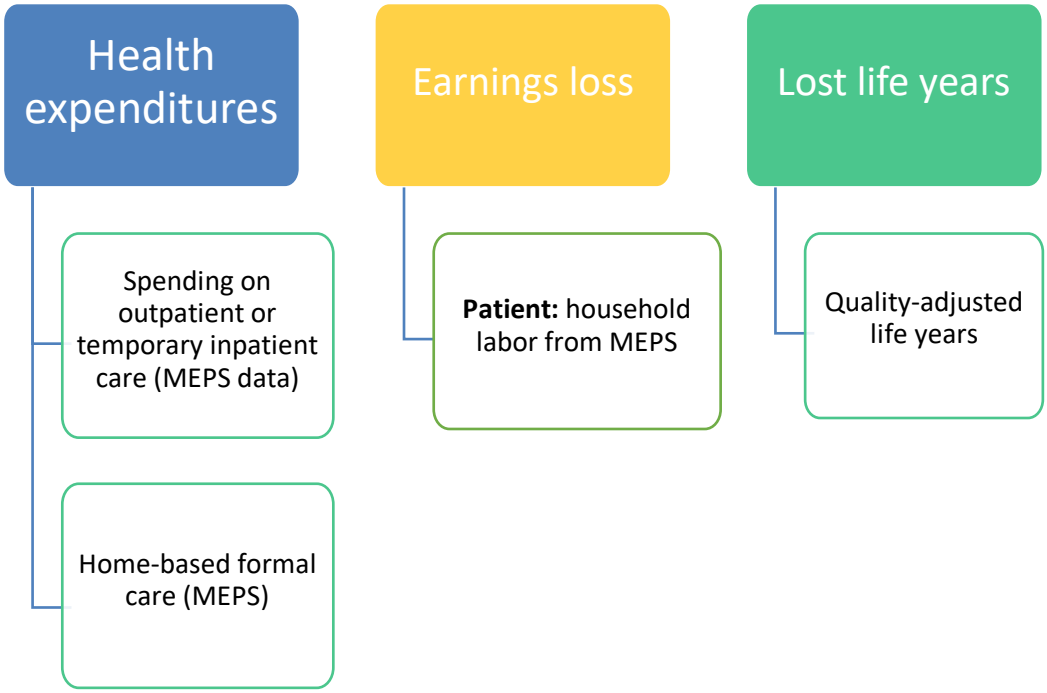
We based assumptions on return on research investment, that is, the impact of funding levels on health outcomes, on prior research on funding investment return.[2] We calculated the return on research investment based on the following specific health outcomes: age incidence of disease, improved detection 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.

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 include the monetary value of patients being able to stay in the labor force longer as a result of decreased disease burden, and reduced productivity loss for informal caregivers.

Time Horizon

The representative cohort of around 1,000,000 lives is moved through a 30-year time horizon, with impact of investment expected to be realized in10 years from initiation. We created the representative sample based on the U.S. age and gender distribution, as well as initial existing disease rates by age and gender. The 10-year investment impact time point is based on existing research on time from investment to healthcare impact.[10-12] 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.

Figure 2. Quantifying Societal Burden of Rheumatoid Arthritis



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, then in pairs, 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: 0.1 percent, 0.2 percent, and 1 percent improvement. Furthermore, we simulated the model and estimated the costs and ROIs under two assumptions of how those health improvements were realized. The first assumption was for a targeted investment in women's RA research, with an impact for women three times larger than that for men. Any investment in research focused on women is expected to yield results relevant for women, but this assumption includes the likelihood that a portion of that research will benefit both women and men. The second assumption was a representation of general investment in RA 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 assumed 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 how the impact is distributed by sex creates six scenarios. These are shown in Table 1. We will use Scenario 1 (0.1 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 1: Health Improvement Scenarios

Health improvement	Women's impact 3x men's	Equal impact by sex
0.1%	Scenario 1	Scenario 2
0.2%	Scenario 3	Scenario 4
1%	Scenario 4	Scenario 6

Value of Investing in Women's Health Research

Using the simulated health and cost outcomes, we examined ROIs under either doubling or tripling the NIH portfolio of women-targeted RA 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 calculate the minimum probability of success of the investment to generate an expected ROI of 15 percent 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 will primarily contrast Scenarios 1 and 2 (0.1 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 RA research within the funded portfolio of the NIH. To estimate this level we retrieved all titles and abstracts for RA area using NIH RePORTER, the publicly available interface of funded extramural NIH projects.[7] The following terms were used to search the retrieved titles and abstracts to determine the total number of women-focused projects: "women", "sex", "gender", and "female." Projects without these terms in the title or abstract were excluded from the "women-focused research" set examined.

Total RA project funding level was based on the allocations using the NIH Research, Condition, and Disease Categorization (RCDC) codes.[13] There were 880 extramural funded projects in RA from 2015 through 2019. Of those, 6.6 percent were focused on women's health specifically, representing 8.2 percent of all NIH extramural funding for RA. The average annual funding level between 2015 and 2019 for RA was $85.7 million dollars. We used 7 percent as the baseline proportion of women-focused funding in the RA portfolio. The 7 percent increment was added to the 2019 amount of $85.7 million to double the level of investment in women's health research to $91.7 million (an increase of $6.0 million), and a 14 percent increment was used to triple the level of investment. All costs are presented in 2017 USD.

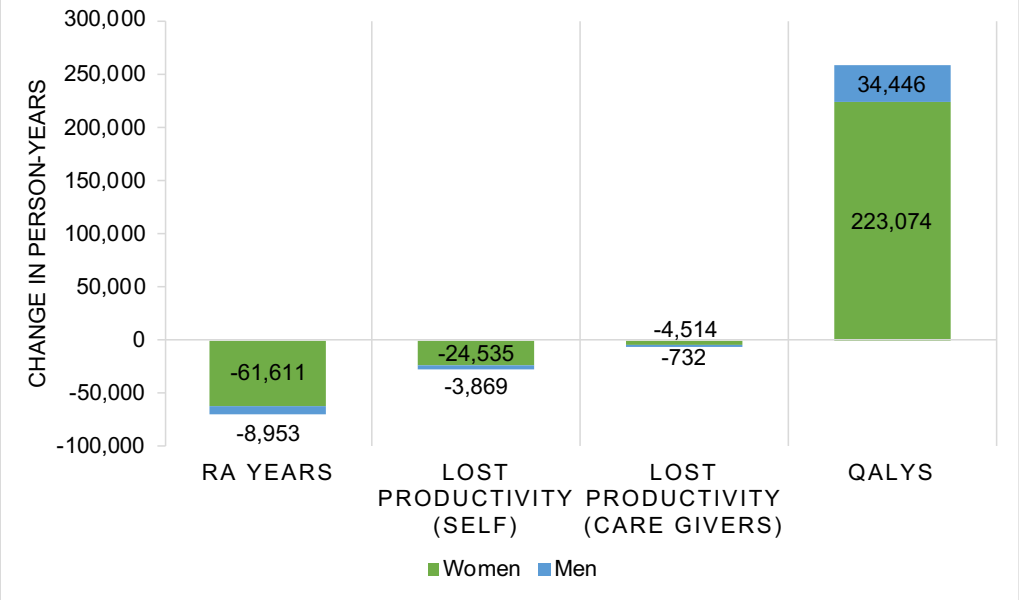
Results

We present the health and economic improvements and resulting impact on costs for the primary specification, Scenario 1 (a 0.1 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 in the next section consider the resulting impact on costs scaled up from the model cohort to the US population, ages 25-65, of approximately 175 million people. We discuss each cost impact in turn below.

Figure 3: Health and economic improvements under Scenario 1 (0.1% impact, three times larger for women than men)



Life expectancy:

While we allowed for RA to potentially impact life expectancy following the methodology of the IVI-RA model,[14] the change in probabilities from RA and the examined 0.1 percent health improvement were not sufficient to lead to differences in mortality. We do not report them in Figure 3.

Decreased disease burden:

Scenario 1's health improvements generated a reduction in RA disease burden in terms of life years with RA. Women have over 61,600 fewer life years with RA, and men have around 9,000 fewer life years with RA. The impact on women's years of RA is over six times that of men's under Scenario 1.

Lost productivity (self):

Scenario 1's health improvements generated fewer lost years of work for the RA patients. Delaying onset or the progression of the disease allowed individuals to have more productive careers, resulting in around 24,500 more equivalent years of full time employment for women, and around 3,900 more for men. Thus, the impact for women is around six times larger than that of men's for labor productivity.

Lost productivity (caregivers):

With reduction in RA burden from the health improvement in Scenario 1, there is also less informal care given. This allows those caregivers to spend more time in paid labor. We estimate that the health improvement leads to 4,500 fewer lost life years of work provided to women, and nearly 1,000 fewer years provided to men.

Increased quality of life (measured in equivalent QALYs):

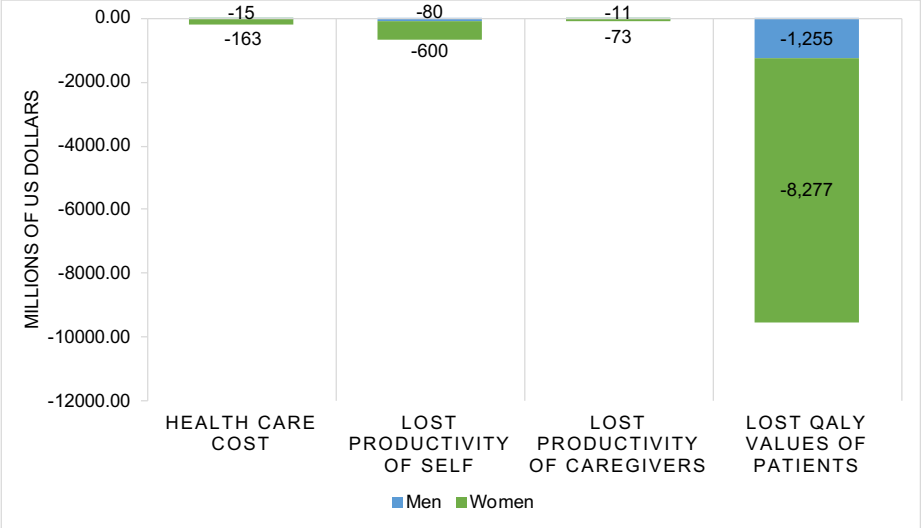
Unlike the prior metrics, this is the only one that is affected by each of the three health improvements. Delayed onset reduces the years of RA burden, which increases quality of life. Slowed progression of the diseases also improves quality of life, as people spend more years in less severe states. Finally, we directly decrease the reduction in quality of life for 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, this captures a much larger effect, which is represented for women by approximately 223,000 more year-equivalent of a fully-healthy adult, measured by QALY, and 34,000 for men. The impact on QALYs for women is substantial relative to men, but both are positive.

Impact on Cost Outcomes for Scenario 1

With the health and economic outcomes in the *status quo* and improved health (Scenario 1) estimated, the costs and changes in costs are estimated). The largest driver of gains is reduction in lost QALYs. Patient work productivity is the next largest driver. See Figure 4.

Figure 4: Change in costs under Scenario 1

0.1% health impact, three times larger impact for women than men

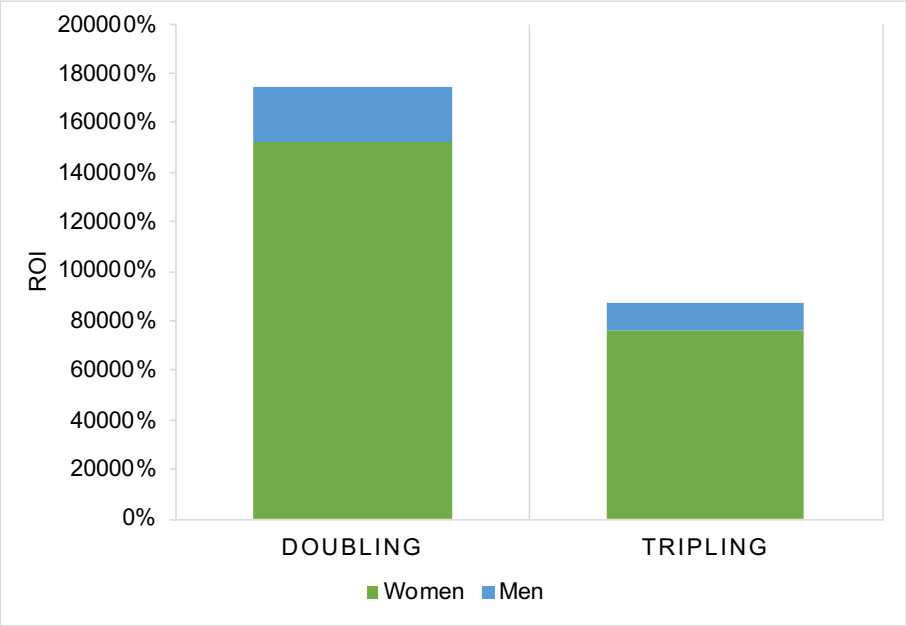


The overall reduction in costs was around $10.5 billion net present value across the 30 years. Around 87 percent of the costs are from female patients, and 13 percent from male patients. Furthermore, as shown in Figure 4, around 90 percent of the cost-reductions arise from fewer lost QALYs (from improved quality of life), with the next most important improvement from reduction in lost productivity of self (RA patients), with the latter representing over $680 million. Thus, while there are very large and important gains from improvement in quality of life, even if we ignored those as cost savings from the health improvement and only examined the health care cost reductions and increased labor productivity, the total across these three categories is around $940 million. Given we are benchmarking these health improvements relative to increases of either $6 million (doubling women's investment in RA) or $12 million (tripling), if these investments bring about the 0.1 percent improvement in health, the cost savings from decreased health care expenditures and increased labor productivity of $940 million easily cover the investment alone, not including the much larger improvement in quality of life.

ROI under Different Scenarios

With the estimated status quo cost and reduced costs under each health improvement scenarios, we calculated the ROI that would result from doubling or tripling the women's portion of the RA portfolio under the health improvements of Scenario 1. Under this scenario of a 0.1 percent health improvement, if it required doubling the women-targeted portion of the portfolio, the ROI would exceed 174,000 percent, as shown in Figure 5. Even with the same level of health improvement, the larger tripled investment would yield a large ROI. Further, as noted in the prior section, while most of these returns are driven by improvements to quality of life, there would still be a large return on investment if only the more direct economic cost reductions (health care cost decreases and increased labor productivity) were included in the ROI calculation. In that case, the ROI would be around 15,000 percent under doubling the investment, and around 7,500 percent under tripling the investment: still quite large, although smaller than if QALY improvements are included.

Figure 5: Return on Investment for Scenario 1



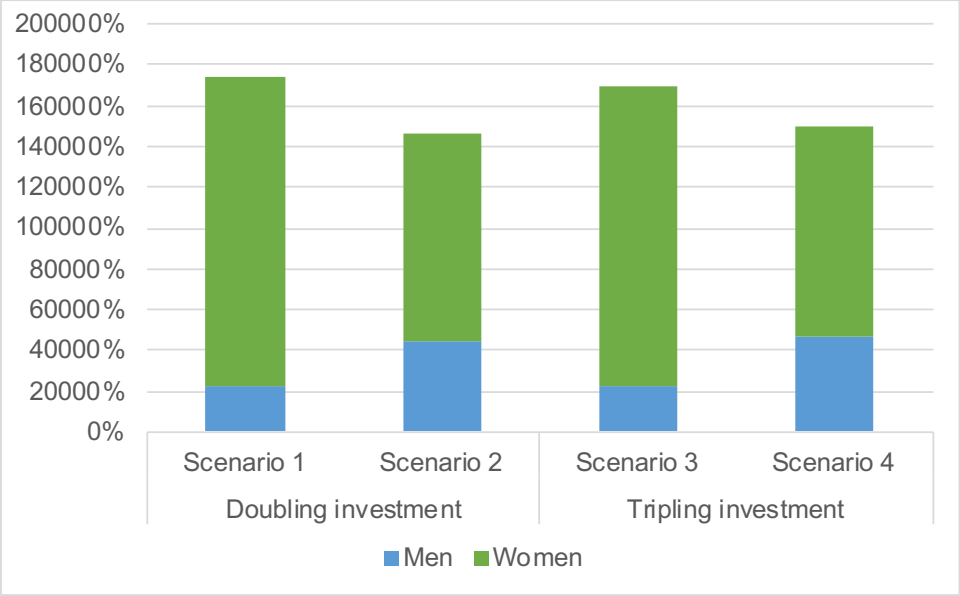
Next, we allowed the health improvement to increase with the increase in the level of investment. We thus examined Scenarios 1 and 2 (average improvement of 0.1 percent) for a doubling of investment and Scenarios 3 and 4 for a tripling of investment (average improvement of 0.2 percent). Scenarios 1 and 3 assume that the health impact is three-times larger for women than men, while Scenarios 2 and 4 assume an equal health impact between women and

men. Comparing Scenario 1 to Scenario 2 (or 3 to 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. Investment in research with a focus on women's health yields larger returns than investment in research without the focus on sex or gender. See Figure 6.

Calculation of Probability of Success Needed for an Expected ROI of 15 Percent

The returns on investment presented above implicitly assume that the investment *will be* successful. In reality, investments bear risk, and this holds true for investments into RA health research. We thus reframed the returns into a simple model of uncertainty, where with probability (P) that investment succeeds in bringing to bear the scenario's health improvement, and with

Figure 6: Return on Investment across scenarios



Scenario 1: 0.1% improvement, women 3x men; Scenario 2: 0.1% improvement, women equal men
Scenario 3: 0.2% improvement, women 3x men; Scenario 4: 0.2% improvement, women equal men

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. A small probability of success is required to return an ROI of approximately 15 percent, and the probability does not vary substantially by nature of the investment – women's health focused or general. The target of 15 percent was chosen based on similar return on research investment in a range of therapeutic areas.[2] See Table 2.

Table 2. Minimum probability of success for 15% expected rate of return.

Scenario	Health improvement under success	Impact for women compared to men	*Minimum probability of success needed under:* Doubling investment	Tripling investment
1	0.1%	3 to 1	0.07%	0.13%
2	0.1%	Equal	0.08%	0.16%
3	0.2%	3 to 1	0.03%	0.07%
4	0.2%	Equal	0.04%	0.08%
5	1%	3 to 1	0.01%	0.01%
6	1%	Equal	0.01%	0.02%

This provides a useful framework under which to consider these risks. In particular, while we saw that if the investment definitely succeeded, the ROI would be very large (over 174,000 percent for Scenario 1). However, the increase in investment under doubling is only an addition $6 million. How likely is it that that small increase in investment could yield a health improvement in RA of around 0.1 percent? It is of course unknown, but Table 2 informs us that it has to succeed with at least a probability of under one-tenth of one percent.

The table also reinforces 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, by the time we move to a much more significant health improvement in Scenario 5 (1 percent improvement), even under a tripling of the budget, it would only take a very small probability of success for the investment to pay off and have a 15 percent expected ROI. However, it is even less likely that that same $6 million increase in investment would result in a 1 percent overall improvement in the three health metrics.

Table 2 can be viewed as a set of potential pathways to a 15 percent ROI. For example, focusing on the doubling of investment scenario for the women's impact being larger than men's, we can frame the discussion of the return on that $6 million increase in women's-targeted research on RA as having an expected ROI of 15 percent if it had a small probability (0.07 percent) of succeeding in a small health improvement (0.1 percent), *or* a slightly smaller probability of success (0.03 percent) of a slightly larger health improvement (0.2 percent), *or* a

very small probability of success (0.01 percent) of a relatively large health improvement (1 percent).

While these very large ROIs and very small necessary probabilities of success of the investment are encouraging, and can be seen as evidence in favor of budget increases, we should recognize that there are inherent trade-offs in investments. We are not including the opportunity cost of investment in these cost calculations. If investing in research for a different disease yielded higher reduction in costs, then arguably increases of investment dollars should first be directed there. For example, we may contrast the cost savings here in RA against those from Alzheimer's Disease and related dementias research in the companion report.[15] While the ROIs are much larger for RA here, it is for a much smaller investment and affects far fewer people and for a much less expensive baseline. Thus, the $940 million reduced net present value costs in this RA model from a 0.1 percent improvement in health are dwarfed by the $930 billion in cost savings for a smaller health improvement (0.01 percent) in the AD/ADRD model.

Discussion

For rheumatoid arthritis, investment in research has the largest impact on improved quality of life. That is, health-related quality of life impacts from modest improvements are large, given the impact of rheumatoid arthritis on quality of life. Even if only labor productivity and reduced health care costs are included in the gains, return on investment is still positive.

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. The model assumptions were purposefully kept conservative, assuming relatively small health impacts from research investment. More optimistic scenarios are not unreasonable.

Based on the models developed to examine the impact of increasing investment in women's health research in RA, for investments that yield very small overall increments in health improvement, large societal gains would result. Overall magnitude of impact is in line with similar research on impact of research investment.[16] Investing in research targeted to women's health has somewhat higher returns on investment than general research that affects women and men equally.

The potential to recognize societal gains is amplified for research devoted to women's health relative to general research, based on the specifications used here. It is important to note that 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 and the return on investment is a function of assumptions not just of the size of the investment but also of the magnitude of health improvements that investment yields. Smaller overall increments in investment 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 examined 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.[10-12] 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 are relatively small compared to the size of the extramural AD portfolio of research funded by the NIH. 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. Given similar and extremely large magnitude of return for both doubling and tripling scenarios, the potential is high for modest investments to yield large returns.

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.

Limitations

This examination should be interpreted with reference to potential limitations. First, while the keyword approach for identifying women-focused research was simple, comprehensive and consistent with other literature searches targeting gender/sex differences, 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 increments used to project the impacts of doubled and tripled funding scenarios on health and societal outcomes are conservative. Given higher prevalence of RA in women, the estimate used here for the percentage of the funded NIH portfolio dedicated to women's health research in RA may be an undercount.

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. Further, 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 further 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.

Additionally, our incidence and prevalence of RA parameters are based on our own estimates from the MEPS, so as to get age-by-gender estimates needed for our analysis. In inspecting these, our estimates for incidence are about 2-3 times as large as in the literature. We decided to use these rates, as we have evidence that in the MEPS there was a parallel increase in RA diagnosis rates between 2006 and 2010. However, we did alternatively test a model with incidence rates in line with the literature, or about 2-3 times smaller than that used in the results presented here. In this version with smaller incidence rates, there are still large returns on the investment, although of smaller magnitude than those reported here. The overall conclusions of the report are the same as well, including comparisons of where the benefits arise from and if the ROIs for women-targeted research exceed those for general investment.

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

1) Increase research funding directed at women's health within RA. Given the limitations in knowledge about women and RA relative to men, the potential gains from women-focused research are substantial.
2) Pursue research on biology of RA in women, including early identification, and identify barriers to diagnosis in women.

3) Expand research agendas to address relationships between RA and work productivity impacts. Ways in which RA limits work productivity could be a useful lens through which to evaluate current and potential future treatment effectiveness.

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 RA and the potential for such funding to yield a range of societal benefits. Specifically we recommend the following:

1) Raise awareness of the potential value of investment in women's health research in RA. 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 purse 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 RA. These communities are key to informing future research investment strategies.

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. Future investment in women's health may result in large gains in condition status with resulting gains in health-related quality of life. While the higher prevalence of RA among women has led to health research with impacts for women as well as men, a focused investment on women's health research could yield large impacts on women's health-related quality of life in particular.

The limitations that result from RA impact work productivity, and this represents another important avenue to realize impacts of health research innovation. To inform a research agenda, the financial investment needed to realize the goals of that agenda requires planning. These analyses suggest that investing more in research on women's health in RA 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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Technical Appendix A: Selection of Data Sources

Table A1. Availability of key variables among potential data sources

	Panel Study of Income Dynamics	**National Longitudinal Survey of Youth, 1979**	**Medical Expenditure Panel Survey**
N	24,000 people	12,686 people	30,000 households
Age ranges	Born 1951-present	Born 1957-1964	Range of ages
Received diagnosis of			
Rheumatoid arthritis	Yes	Snapshot	Yes (aggregated)
Health spending	Yes (aggregated)	No	Yes
Health condition limits activities	Yes	Snapshot	Yes
Extra care needed	Snapshot	No	Yes
Disability insurance participation	Yes	Yes	No
Paid nurse to come to home this year	Yes	No	Yes

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 999,996 individuals aged 25-65. We use the fraction of individuals that are each age and gender in the U.S. population from the Census Bureau,[22] and multiple that fraction by 1,000,000 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 first sorted into one of 5 states:

1. Alive without Rheumatoid Arthritis (RA)
2. Alive with RA class 1
3. Alive with RA class 2
4. Alive with RA class 3
5. Alive with RA class 4

The distribution of the 5 states in the population is derived by simulating a cohort of 100,000 females and 100,000 males aged 24 for 41 years through our health model until everyone reaches 65 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 RA status and RA class. This determines by age and gender the fraction of individuals within each of the 5 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 999,996 individuals for the starting cohort due to the discrete nature of the states.

Outside of the simulation that assigns the five states, we use the distribution of RA duration from Medical Expenditure Panel Survey (MEPS) to assign the duration of RA to individuals living with RA in the starting cohort. We derive the duration of RA by subtracting the age of diagnosis from current age for RA patients in MEPS. The distribution of RA duration is right-skewed and

resembles a gamma distribution; therefore, we fit a two-parameter gamma distribution on the durations conditional on age bins 25-34, 35-44, 45-54, 55-64 and use the fitted results to assign durations conditional on age bins accordingly. With RA class and duration assigned, we are able to calculate the Health Assessment Questionnaire (HAQ) scores for RA patients in the starting cohort using the methods described in Innovation and Value Initiative Rheumatoid Arthritis (IVI-RA) Value Model, Appendices part D. HAQ scores are used as the measure of RA severity in the model. Individuals without RA are assigned with a HAQ score of 0.25.

There are three components in this model:

1. Simulating the model for 30 years and assuming the health improvement happens at 10 years out. Predicting the proportion of people diagnosed with RA, which latent class of RA severity they have, the progression of the disease, effects on employment, 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 the patient and of their 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.[23] 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 only use the MEPS to estimate health care costs 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. 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.

3. Modeling health and economics statuses

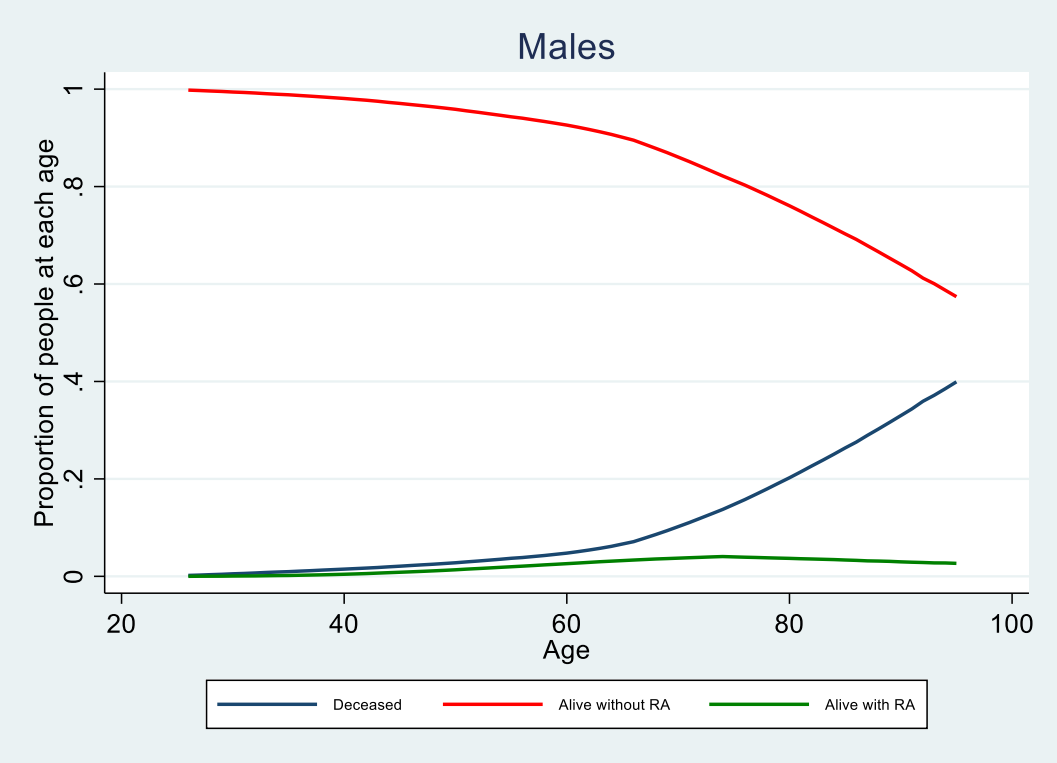
3.1 Incidence of RA

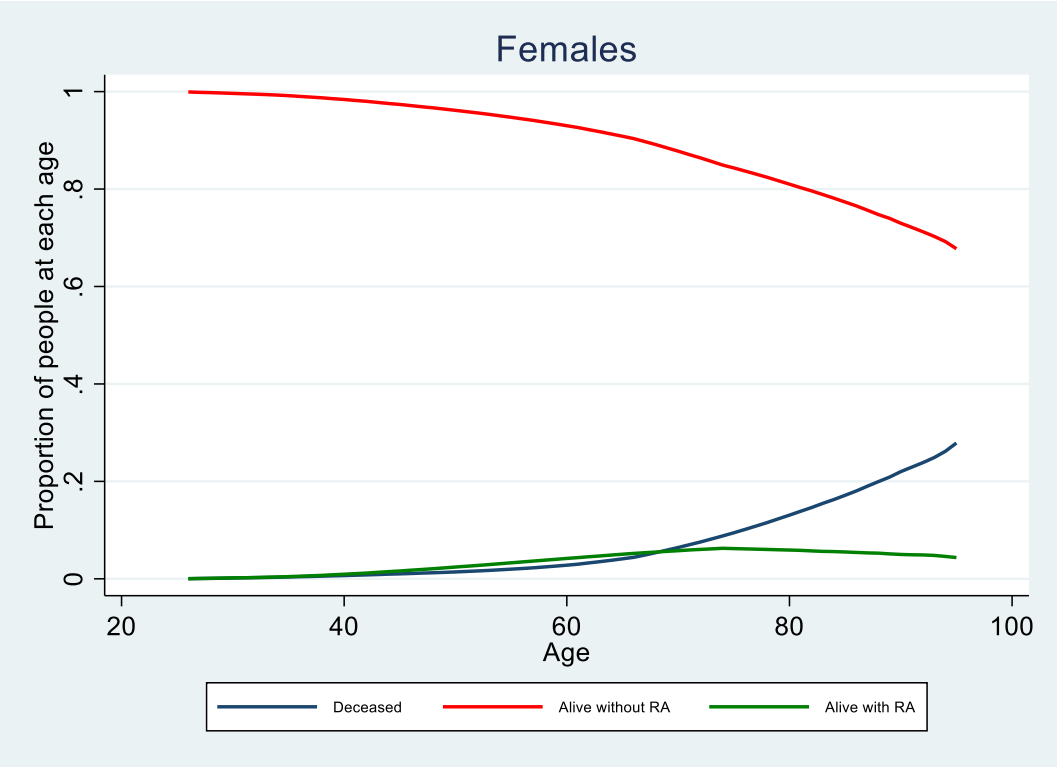
We model the probability of having onset of RA for each individual. To do so, we estimated the following probability in equation B.1 for each gender g and age t using MEPS. The age of diagnosis was collected for RA patients in MEPS, and we use it as a proxy of onset of RA. For an individual aged 65 years old who was diagnosed at age 55, we expand this one cross-sectional observation at age 65 to age 25, and flagged age 55 to age 65 as having RA.

$$\psi_{gt} = \frac{number\ of\ indiciduals\ who\ had\ been\ diagnosed\ with\ RA\ at\ age\ t \mid gender}{number\ of\ individuals\ who\ have\ lived\ through\ age\ t \mid gender} \quad \text{(B.1)}$$

RA 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 RA in the prior year, model them as having been diagnosed with RA 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 RA, alive without RA, and deceased. The fraction of people with RA peaks shortly after age 80.

Figure B1: RA case trend in males and females





3.2 Duration of RA

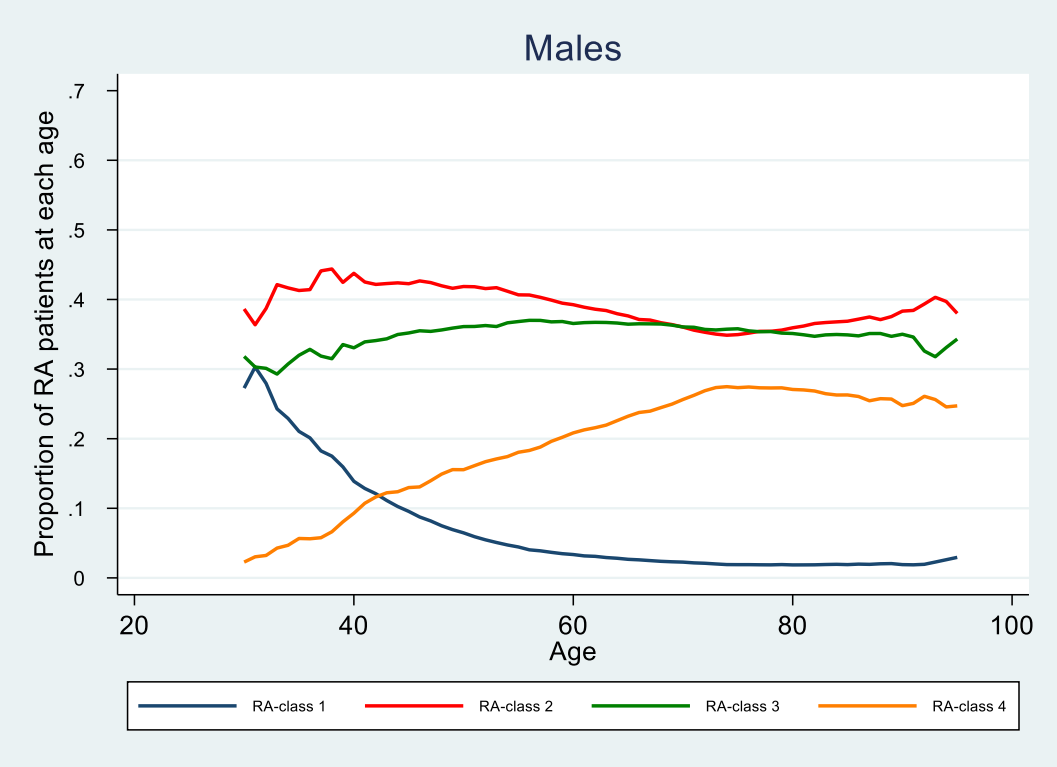
Newly diagnosed RA patients in our model are assigned with symptom duration of 6 months. For every year onward, 12 months is added to the durations for RA patients.

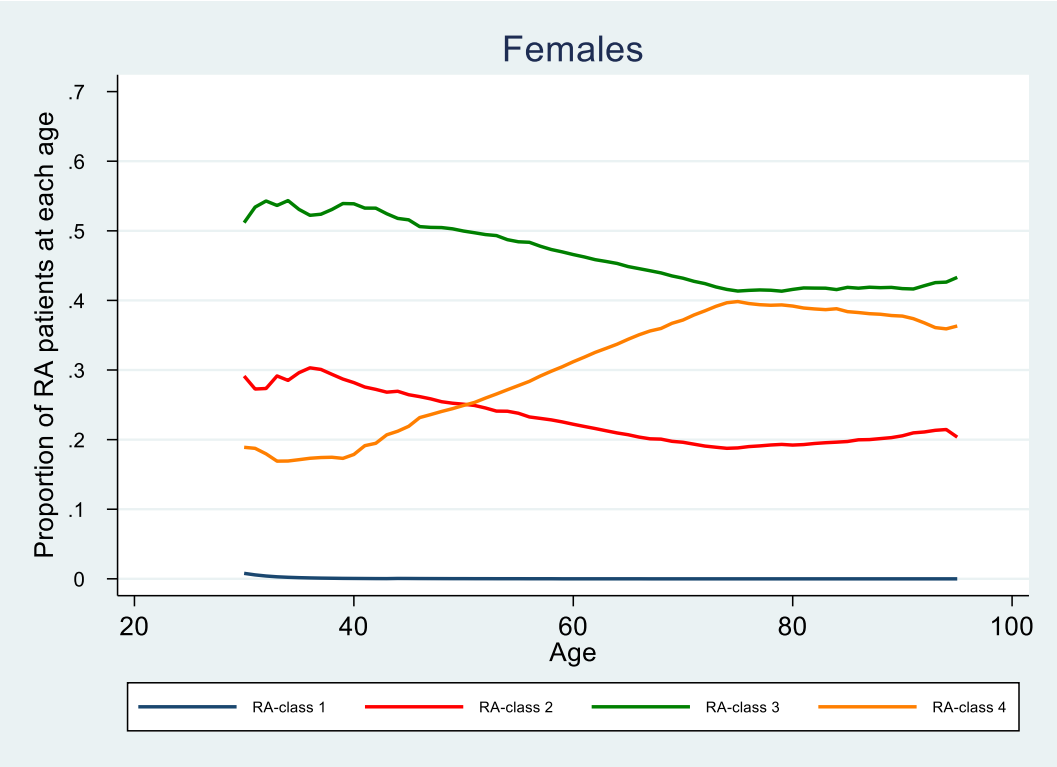
3.3 Severity of RA

Progression of severity among RA patients are determined by four classes and the severity is expressed in HAQ score, which is a self-report functional status measure ranging from 0 to 3, as 0 represents no disability at all and 3 represents the highest disability. We use the same approach to predict RA classes and HAQ scores as the IVI-RA model (Appendices part D). The estimates used in the IVI-RA model are mainly drawn from Norton et al.'s (2014) latent class growth model of HAQ trajectory among RA patients. Norton and colleagues first determined class membership using variables including age, gender, baseline DAS28, symptom duration, rheumatoid factor, ACR criteria, and socioeconomic status. Females and patients who had RA onset later in life are more likely to be assigned to class 3 and 4 (higher risk classes). For

variables that are not modelled in our model, i.e. baseline DAS28, rheumatoid factor, ACR criteria, and socioeconomic status, we follow the approach of Incerti and Jansen (2020) and use the simulated population mean in IVI-RA model appendix table A1. Next, based on the class membership, different coefficients and standard errors are applied to predict HAQ score progression. Under no circumstances can a patient switch to another RA class in our model, and trends of HAQ score between classes do not intersect. That is, patients in class 1 (the lowest risk class) will always have lower HAQ scores than patients in the other three classes. Figure B2 presents the simulated proportions of individuals in each RA class, conditional on being diagnosed with RA.

Figure B2: RA class trend in males and females





3.4 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 RA each year, conditional on age and gender.[2] For patients with RA, probability of dying is assigned based on HAQ score, age, and gender using similar approach as the IVI-RA model, appendix part E. The probabilities of dying for RA patients are not always higher than people without RA conditional on age and gender. For RA patients with lower HAQ score than the general population (HAQ<0.25), they will have a lower mortality rate, although the difference is very small.

As with the probability of RA onset, we took random uniform draws between 0 and 1, and if the uniform draw was below the probability of dying, we assigned that person in the simulation to die that year.

3.5 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 estimated the probability of moving into a nursing home for the general 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.

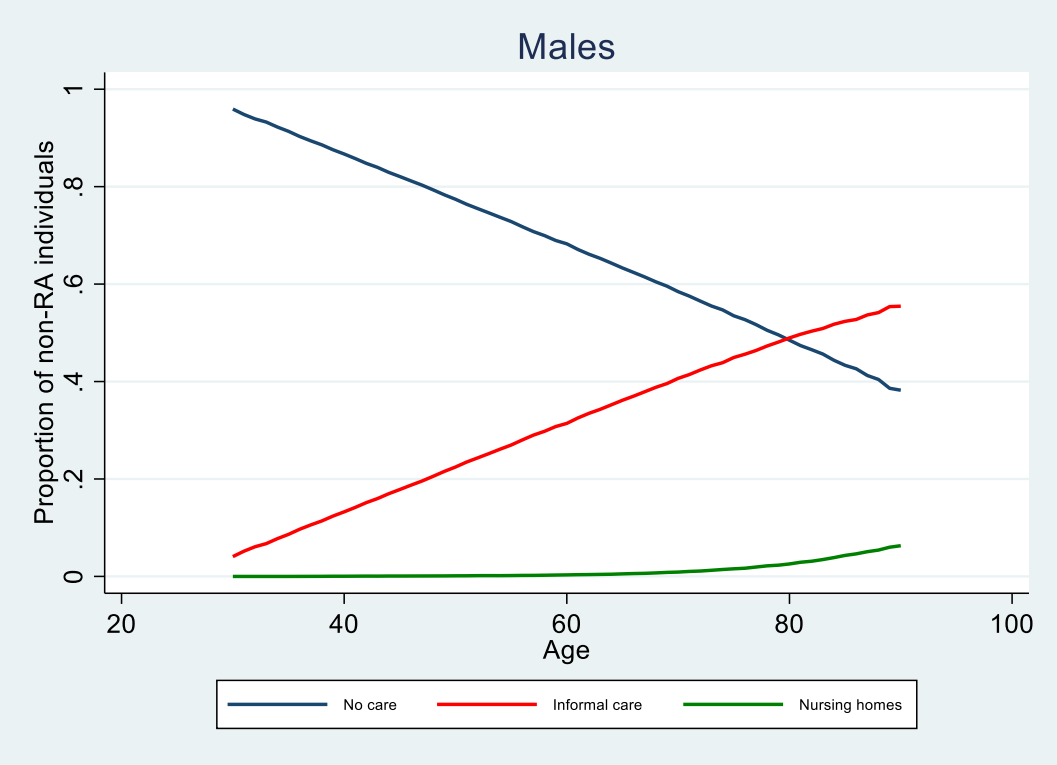
$$\Pr(NH|gender, age) = b_0 + \frac{b_1}{1+exp(-b_2*(age-b_3))} \qquad (B.2)$$

Where $\Pr(NH|gender, age)$ is the probability of nursing home entry. 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 for the general populations.

We did not find any literature on different probability of nursing home entry for RA patients and the general population. Therefore, all individuals in our model, with or without RA, are assigned with probability of nursing home entry solely conditional on their age and gender. People younger than 65 years old are assigned with zero probability of nursing home entry. Again, we took random uniform draws between 0 and 1, and if the uniform draw was below the probability of nursing home entry, we assigned that person in the simulation to be institutionalized that year.

Figure B3 and B4 present the simulated care trends.

Figure B3: care trend in non-RA males and females



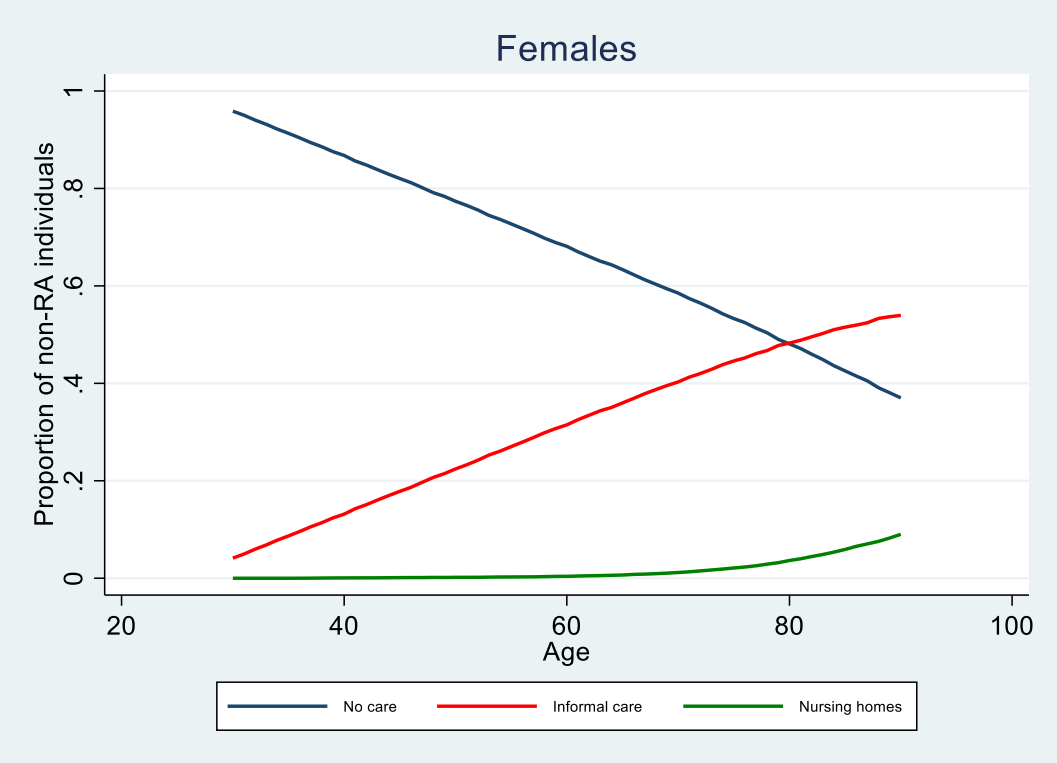
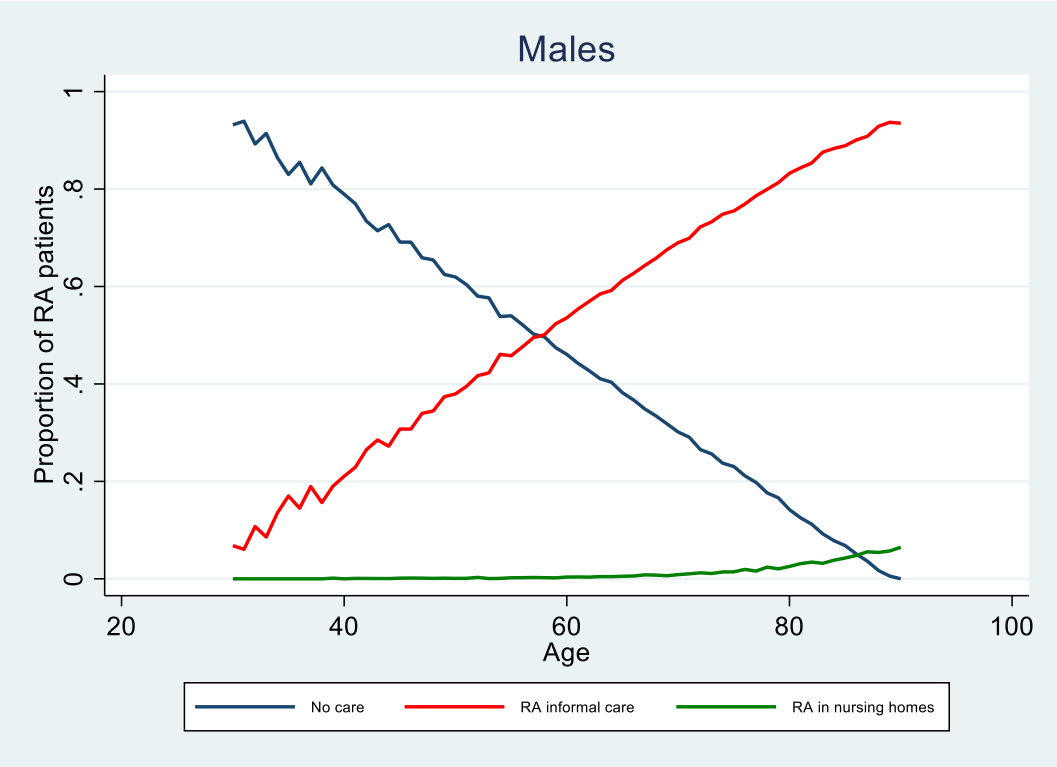
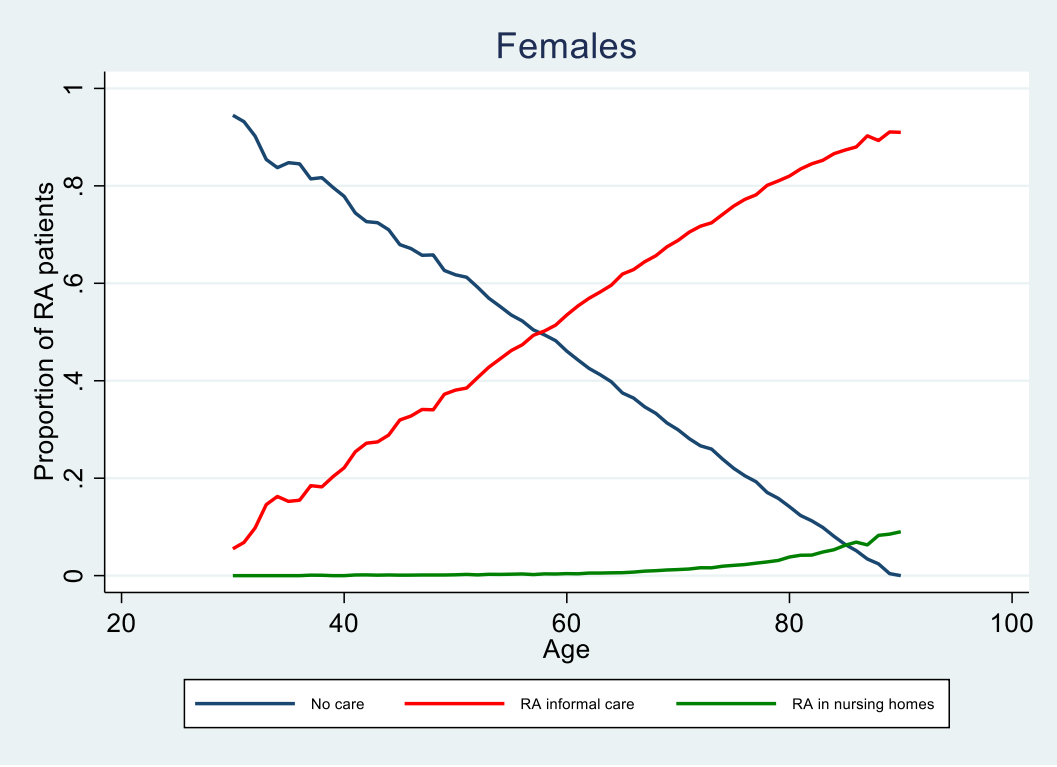


Figure B4: care trend in RA males and females


Males
Proportion of RA patients
0
.2
.4
.6
.8
1
20
40
60
80
100
Age
No care
RA informal care
RA in nursing homes


Females
Proportion of RA patients
0
.2
.4
.6
.8
1
20
40
60
80
100
Age
No care
RA informal care
RA in nursing homes

3.6 Receiving Informal Home Care

For non-RA individuals living in the communities, we anticipate the probability of receiving informal care is the same as the general population. Based on Kaye (2013) exhibit 1 and 2, we know that 15% of working-age adults and 45% of individuals older than 65 years old have functional limitations, and we assume all people with functional limitations have received informal home care. We fit a linear function of age on the probability of having functional limitations to meet these prevalence rates. For RA, Kobelt and colleagues estimated 61.5% of community-dwelling RA patients (mean age=62.7, standard deviation=12.5) had received some informal care. We divide this number by the weighted average of the probability of having functional limitations among general population aged 36 to 93 (36.2%) and get an inflation factor of 1.7 (Equation B.3).

$$\frac{prevalence\ of\ RA\ patients\ receiving\ informal\ home\ care = 0.615}{prevalence\ of\ general\ population\ receiving\ informal\ home\ care = 0.362} = 1.7 \qquad (B.3)$$

We then use the inflation factor to multiply the linear probability of having functional limitations as the probability of receiving informal home care for RA patients. RA patients older or equal to 90 years old have probabilities of receiving informal home care larger than 1 after applying the inflation factor, and are replaced with probabilities equal to 1 instead. Same as above, we took random uniform draws between 0 and 1, and if the uniform draw was below the probability of receiving informal home care, we assigned that person in the simulation to receive informal home care that year.

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%. Figures B.5 and B.6

show the average costs—across both RA and non-RA patients—by age, based on our simulations. We describe each in turn.

Figure B5: average cost conditional on age for males

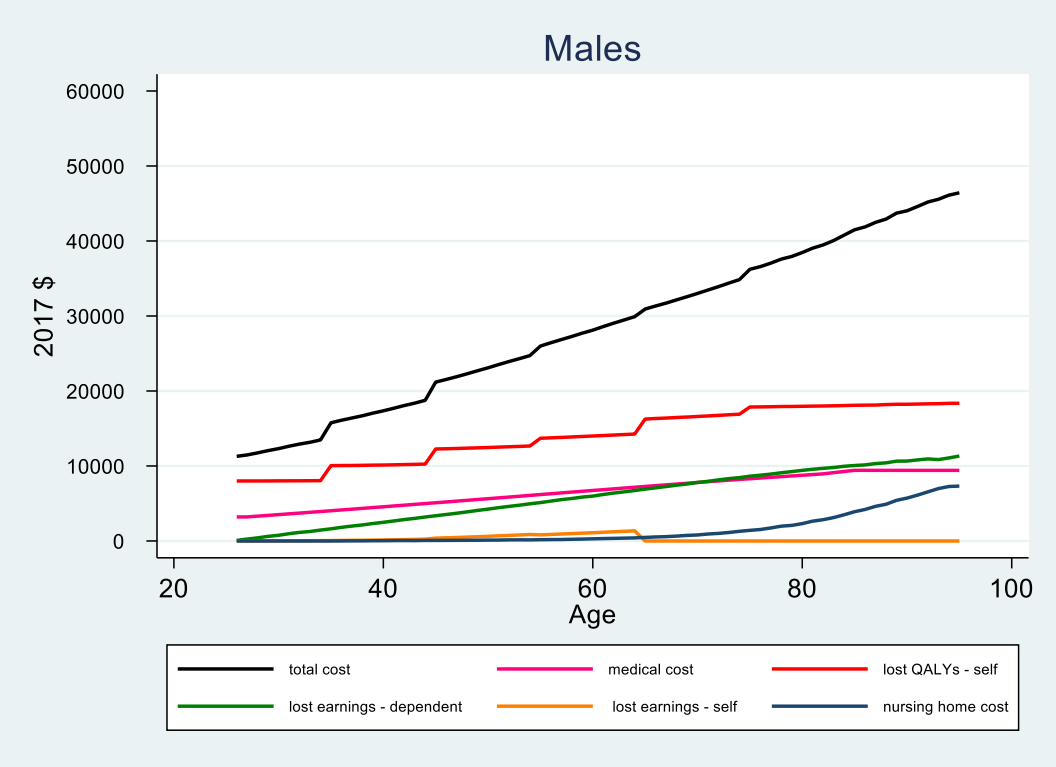
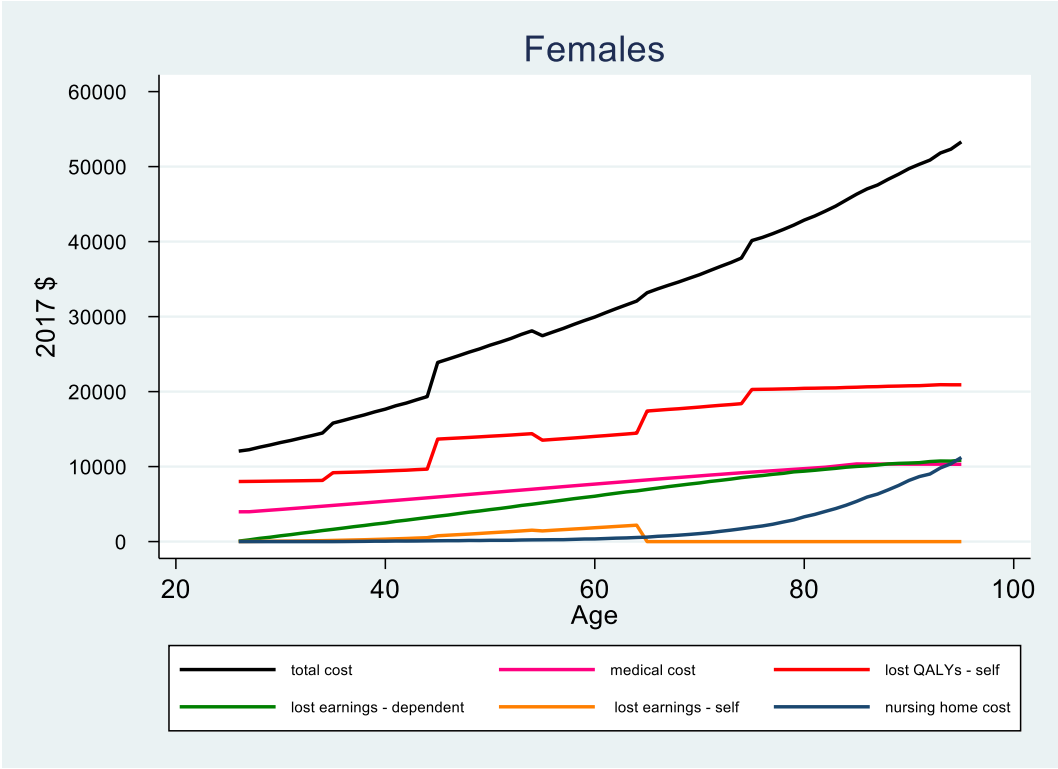


Figure B6: average cost conditional on age for females



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 RA. For RA patients, we assigned them the average health care costs of RA patients conditional on age bins and gender, also calculated from the MEPS. 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, 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 from MEPS but estimated using productivity loss of caregivers in section 4.2 below. Since MEPS is only representative for 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 Self

We estimate the productivity loss of the patients who have RA as a function of RA status and severity, as measured by their simulated HAQ score as described above in section 3.3. We start with estimates from Wolfe et al. (2005), who estimate that (not conditioning on age) an increase in 0.25 HAQ score for RA patients is associated with a loss of $1,095. Normalizing to 2017 dollars, we use a value of $6,000 per unit change in HAQ. Thus, the difference in earnings between two patients with RA of differing severities of HAQ given by h and h' is given by equation B.4.

$$E[W|RA, H = h] - E[W|RA, H = h'] = 6000 * (h - h') \qquad (B.4)$$

We ultimate want to estimate equation B.5 so as to allow the lost earnings to depend on RA status and HAQ score by age group G:

$$\theta_{gh} = E[W|no\ RA, G = g] - E[W|RA, G = g, H = h] \qquad (B.5)$$

To get to the change by age, we estimate from the MEPS the following for each age group g:

$$\psi_g = E[W|no\ RA, G = g] - E[W|RA, G = g] \qquad (B.6)$$

We do this by estimating the following regression for individuals between age 25 and 65

$$W = \sum_g \psi_g RA * 1(G = g) + \sum_g \delta_g 1(G = g) \qquad (B.7)$$

We now want to integrate together this estimate, which depends on age, and Wolfe et al.'s, which depends on severity. In order to do so, we make the simplifying assumption that the difference in lost earnings for an increase in severity does not depend on age group. We have no way to calibrate how this difference would increase, and there are infinite solutions that would yield the age gradient (irrespective of severity) and the severity gradient (irrespective of age). With this, we use the law of total probability for a given age group g for equation B.7. Using the above estimation of ψ_g, the average difference across RA-diagnosed individuals, we can separate this out into

$$\psi_g = E[W|no\ RA, G = g] - E[W|RA, G = g] = E[W|no\ RA, G = g] - \sum_{\forall h} E[W|RA, G = g, H = h] \Pr(H = h|G = g) \qquad (B.8)$$

Using our simplifying assumption that the severity gradient on lost earnings does not differ by age, we choose to base off of H=3 (most severe), and recognizing that the results are identical in the end no matter which base point to choose, then we can substitute

$$E[W|RA, G = g, H = h] = E[W|RA, G = g, H = 3] + 18 - 6h \qquad (B.9)$$

Substituting equation B.9 into equation B.8, we have

$$\psi_g = E[W|no\ RA, G = g] - \sum_{\forall h} (E[W|RA, G = g, H = 3] + 18 - 6h) \Pr(H = h|G = g)$$

$$\Rightarrow E[W|RA, G = g, H = 3] = E[W|no\ RA, G = g] - \psi_g - 18 + 6E[h|G = g] \qquad (B.10)$$

Everything on the right-hand side of equation B.10 is observable or estimable. The left-hand side is thus estimated using these parameters. From there, we can estimate it for *any* h at that age group by using equation B.9. To do so, note that

$$\theta_{gh} = E[W|no\ RA, G = g] - E[W|RA, G = g, H = h]$$

$$= E[W|no\ RA, G = g] - (E[W|RA, G = g, H = 3] + 18 - 6h)$$

$$= \psi_g + 6h - 6E[h|G = g] \qquad (B.11)$$

This provides our final equation to estimate the earnings loss. Positive numbers represent larger earnings loss, and this is increasing in h according to the necessary calculation. Concretely, we do so in the following steps:

1. Estimate $\psi_g = E[W|no\ RA, G = g] - E[W|RA, G = g]$ for each g either by regression with dummy variables or collapsing (will yield identical answers)
2. Calculate $E[h|G = g]$ by collapsing h within age group
3. Set up the formula for each age group g where the earnings penalty is given by equation X: $\widehat{\theta_{gh}} = \widehat{\psi_g} + 6h - 6E[h|G = g]$

4.3 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% of caregivers for individuals receiving informal home care to be older than age 65, regardless of patients' RA status or disease severity.

2. The average hours spent on caretaking for RA patients, conditional on receiving informal home health care is based on Kobelt et al. (2008). They estimated the annual cost of informal care for RA patients using the replacement method, where an hour of family care is valued at the hourly rate of home help, but they did not report the rate they used. We assume the hourly rate of home help is close to the minimum wage in France (the country studied) 2005 (€8.03), and use equation B.12 below to get the unconditional informal care hours. Using the minimum wage gives the lower bound on what the pay rate would be, and an upper bound on the number of hours that RA patients are receiving in their study.

$$informal\ care\ hours\ per\ year = \frac{cost\ of\ informal\ care/year}{cost\ of\ home\ help/hour} = \frac{€3{,}388/year}{€8.03/hour}$$

$$= 421.9\ hours/year \quad (B.12)$$

The unconditional informal care hours per month is therefore 421.9 hours/year divided by 12 months/year=35 hours/month. We can divide this number by the proportion of RA patients receiving informal care to get the conditional informal care hours (equation B.13).

$$E[informal\ care\ hours\ |receiving\ informal\ care, RA]$$

$$= \frac{E[informal\ care\ hours/month|RA] = 35}{Pr(receive\ informal\ care|RA) = 0.615} = 59.6\ hours/month \quad (B.13)$$

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 RA patients and non-RA individuals, calculated as follows:

non-RA, caregivers younger than 65: $23.86 \times 65.8 \times 12 = 18839.856$

non-RA, caregivers older than 65: $23.58 \times 65.8 \times 12 = 18618.768$

RA, caregivers younger than 65: $23.86 \times 59.6 \times 12 = 17064.672$

RA, caregivers older than 65: $23.58 \times 59.6 \times 12 = 16864.416$

Note that the loss is slightly lower for an RA patient receiving RA care given slightly fewer expected hours. However, RA patients are 1.7 times more likely to receive informal care, leading to a higher unconditional expectation of cost from informal care for RA patients than non-RA patients.

4.4 Nursing Home Costs

The cost of living in nursing homes is set at $90,520 annually for non-RA individuals and RA patients. 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.[31]

4.5 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, 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 the EuroQol five-dimensions questionnaire (EQ-5D) to the general population conditional on age and gender from Clemens et al. (2014) table 3, and RA patients conditional on disease severity, i.e. HAQ scores based on Kobelt et al. (2005) table 2. We calculated lost QALYs for both RA and non-RA 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.[34] 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 RA and a HAQ score of 2.1 not living in a nursing home.

$$1 - 0.229\ (EQ - 5D\ for\ RA\ patients\ with\ HAQ = 2.1) = 0.771$$

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

$$1 - 0.229\ (EQ - 5D\ for\ RA\ patients\ with\ HAQ = 2.1) + 0.1 = 0.871$$

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%, 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 prechosen health improvements, and evaluated the (typically much larger than 10-15%) 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%. 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.14:

$$ROI = 100 * \left(\frac{cost_s - cost_n - Investment}{Investment} - 1\right) \qquad (B.14)$$

Where

$cost_s$: 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.

$$E[cost_i] = P * cost_n + (1 - P) * cost_s \qquad \text{(B.15)}$$

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% by

$$15 = E\left[\, 100 * \left(\frac{cost_s - cost_i - Investment}{Investment} - 1\right)\right] \qquad \text{(B.16)}$$

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

$$E[cost_i] = cost_s - 2.15 * Investment \qquad \text{(B.17)}$$

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

$$cost_s - 2.15 * Investment = P * cost_n + (1 - P) * cost_s$$

$$\Rightarrow P = \frac{2.15 * Investment}{cost_s - cost_n}$$

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SOCIAL AND ECONOMIC WELL-BEING

Women's health has suffered from insufficient research addressing women. The research community has not widely embraced the value of this research, and 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.

As part of an initiative of the Women's Health Access Matters (WHAM) nonprofit foundation, RAND Corporation researchers examined the impact of increasing funding for women's health research on rheumatoid arthritis (RA). RA was chosen partly because of its higher prevalence in women than men, with some symptom profiles differing by sex. In this report, the authors present the results of microsimulation models used to explore the potential for enhanced investment in women's health research, in terms of the economic well-being of women and for the U.S. population.

For more information on this publication, visit www.rand.org/t/RRA708-3.

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