

# THE WHAM REPORT

## Societal Impact of Research Funding for Women's Health

### IN CORONARY ARTERY DISEASE

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Women's  
Health  
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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

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Please find additional infographics and social media toolkits on [www.thewhamreport.org](http://www.thewhamreport.org).

The technical specifications for the models are publicly available. Please visit [www.thewhamreport.org](http://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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**Marsha Henderson**, Associate Commissioner for Women's Health, FDA (retired)

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## 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.

**Soo Borson, MD**, Professor of Clinical Family Medicine, University of Southern California; Professor Emerita, University of Washington School of Medicine

**Roberta Brinton, PhD**, Director, Center for Innovation in Brain Science, University of Arizona Health Sciences

**Susan Dentzer**, Senior Policy Fellow, Duke-Margolis Center for Health Policy

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**Julie Wolf-Rodda**, Senior Vice President of Development, Foundation for NIH

## 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 Coronary Artery Disease (CAD). 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 percent of the National Institutes of Health extramural CAD 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:

- Large returns result from very small health improvements. Assuming health improvements of 0.01 percent or less in terms of age incidence and mortality and quality of life yields the following results:
  - For the US population age 25 and older, over 53,000 years with CAD can be saved across 30 years, with substantial gains in health-related quality of life.
  - Almost 12,000 more years (and \$236 million) more in labor productivity, both from higher labor and earnings from having fewer years of CAD and more years alive.
  - Return on investment is 9,500 percent for doubled investment in women's health research amid that only 0.01 percent improvement in health outcomes.
- Doubling the investment would have an expected ROI of 15 percent if it succeeded in generating health improvements of 0.01 percent with a 1.2 percent probability.
- Investing in women's health research for CAD yields benefits similar to investing in general research, with improved health-related quality of life for women from women-focused research.

The results establish the potential for investment in women's health research on CAD 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 CAD. 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. Expand the research agenda to address:

- a. The unknown interactions of sex and gender with cardiovascular disease antecedents and disease progression to inform treatment and prevention research.
- b. Under-studied interactions of gender and race with cardiovascular disease risk, health care, and disease progression. In particular examine obstacles to access to and use of medical provider visits, prescription drugs, and relevant devices.
- c. Differences by sex and gender in dietary impacts on disease and adherence to dietary recommendations.
- d. Differences in disease course and outcomes by sex and gender based on different patterns of use of formal and informal caregiving.
- e. Health-related quality of life of women with coronary artery disease and the potential for earlier detection to positively impact health and quality of life outcomes.

By raising awareness of the current state of funding directed toward women's health in CAD and the potential for such funding to yield 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 differences between the coronary artery disease course for women and men and the potential for investment to improve disease outcomes.
2. Raise awareness among the business community of the potential return on investment for women in the workforce of investment in women's health research.

## Table of Contents

<b>Executive Summary .....</b>	<b>1</b>
<b>Introduction .....</b>	<b>4</b>
<b>Methods.....</b>	<b>6</b>
Base case: .....	7
CAD Model .....	8
Background on Model Components .....	9
Time Horizon .....	11
Investment Impacts .....	11
Value of Investing in Women's Health Research.....	12
<b>Results .....</b>	<b>13</b>
Impact on Health and Economic Outcomes for Scenario 1 .....	13
Impact on Cost Outcomes for Scenario 1 .....	15
ROI under Different Scenarios.....	16
Calculation of Probability of Success Needed for an Expected ROI of 15 Percent .....	18
<b>Discussion .....</b>	<b>19</b>
Limitations .....	22
Policy Implications: .....	23
<b>Conclusion.....</b>	<b>24</b>
<b>Acknowledgments.....</b>	<b>24</b>
<b>Technical Appendix: Selection of Data Sources .....</b>	<b>25</b>
<b>References .....</b>	<b>26</b>

## 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,<sup>1</sup> 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.

Physiological differences between men and women affect factors that relate to development and progression of cardiovascular disease. For example, hormonal status influences renal sodium reabsorption and water retention and change in blood pressure in response to changes in sodium intake is greater for women than men.<sup>2</sup> Dietary changes may impact mortality differentially for women and men.<sup>2</sup> Access and use of health services related to CAD differ by gender. More women than men are prescribed diuretics and more men than women are prescribed aspirin, statins, and angiotensin-converting enzyme (ACE) inhibitors.<sup>3</sup> Incidence of death is higher for women than men during disease follow-up despite more healthcare visits and prescription fills.<sup>4</sup>

Differences between men and women are also evident in availability of informal caregivers for patients with CAD. More men than women CAD patients have informal caregivers and having a caregiver is associated with better attainment of treatment goals.<sup>5,6</sup> Risks of cardiovascular disease differ by gender and extent of neighborhood disadvantage.<sup>7</sup> Still mostly unexplored are the complex interactions of gender-based biology, individual physiology, and cultural factors in terms of cardiovascular disease risks and disease course.<sup>7,8</sup>

Given known differences and the potential for unknown differences to affect morbidity and mortality, investment in women's health could be expected 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 CAD 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.<sup>9</sup> 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, and valuing different impacts in a common currency.<sup>9</sup> 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 CAD and to specifically examine impacts of additional investments (see for example, Grant and Buxton 2018<sup>10</sup>). 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.<sup>10</sup> For CAD, understanding the impact of the disease and potential disease mitigation on health-related quality of life as well as other health outcomes ensures outcomes beyond those that are readily monetized are appropriately considered and included.

To address this gap, 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. Few studies have employed models stratified by sex or gender to test the sex/gender differences of CAD. Instead the majority of studies use sex/gender as a population variable, descriptive variable, or control variable.<sup>11</sup> 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. 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 CAD.

The analyses presented here quantify costs and benefits of investment in women's health research in CAD. 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.

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 mortality 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.

In the US, the universe of funding for research on cardiovascular disease extends beyond NIH and includes other major funders and advocacy organizations like the American Heart Association, the biopharmaceutical industry, and philanthropic organizations.<sup>12</sup> NIH's share of CAD research investment is large, however, and provides a starting point for understanding investments in health research generally and women's health research in particular.<sup>1</sup>

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 CAD. The models followed a cohort representing the U.S. population of individuals who have or could develop CAD, age 25 and older. The youngest age of 25 reflects the fact that CAD affects adults, and this captures the working-age population and older. The cohort assumed 100 percent mortality at age 99. The model simulated the progression of each person's health in the

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<sup>1</sup> 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.

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.

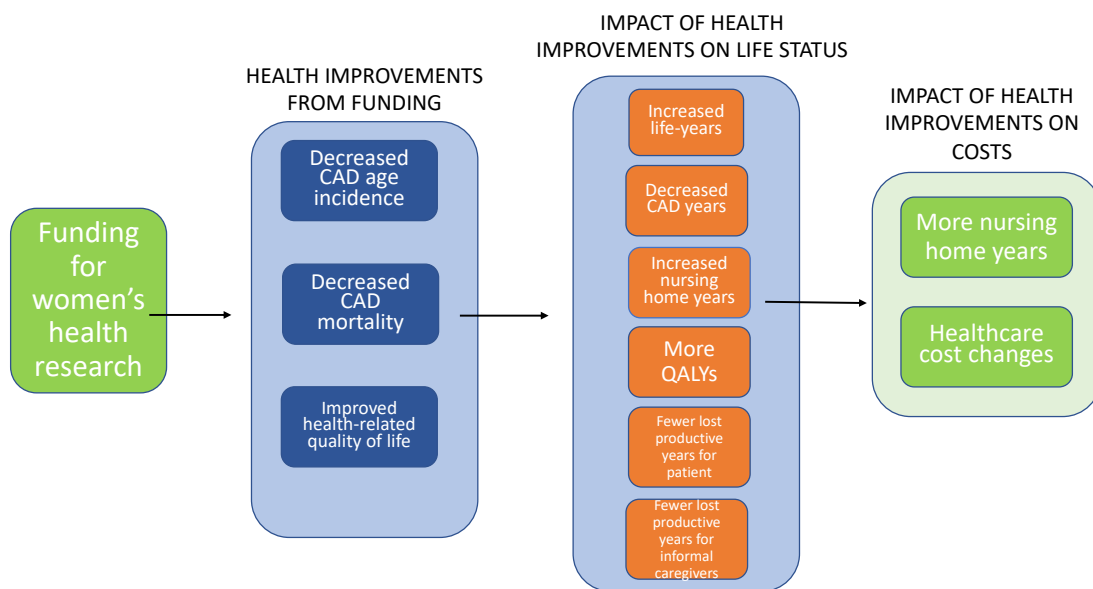
We considered several data sources; the Medical Expenditure Panel Survey (MEPS) best fit these criteria. Among our options, the MEPS has the largest sample and range of ages, the clearest diagnosis indicators, and detailed data on medical expenditures. It also meets our primary criterion of having detailed 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. We also used data from the Centers for Medicaid & Medicare Services (CMS) Medicare Beneficiary Summary File to estimate age-specific incidence and mortality rates for patients. 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.

## CAD 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 CAD 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, given the ways in which the disease affects individuals. The QALY is one way in which monetary value can be assigned to disease impact<sup>10</sup>. The approach to relating funding to health improvements, life status, and costs is summarized in Figure 1 as the conceptual model guiding this work. The model represents the hypothesis of improved health as a result of increased funding for women's health research – decreased age incidence of CAD, decreased mortality, and improved health-related quality of life. While the hypotheses related to improved health relate to lower costs for some aspects of healthcare, we are associating decreased mortality with more time in nursing homes.

**Figure 1. Conceptual model of research funding impacts for CAD**



## Background on Model Components

The model was built with the following components: age incidence profiles, mortality, non-nursing home healthcare costs, informal care status, and nursing home care costs. Patient-level disease burden components were the age incidence 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.

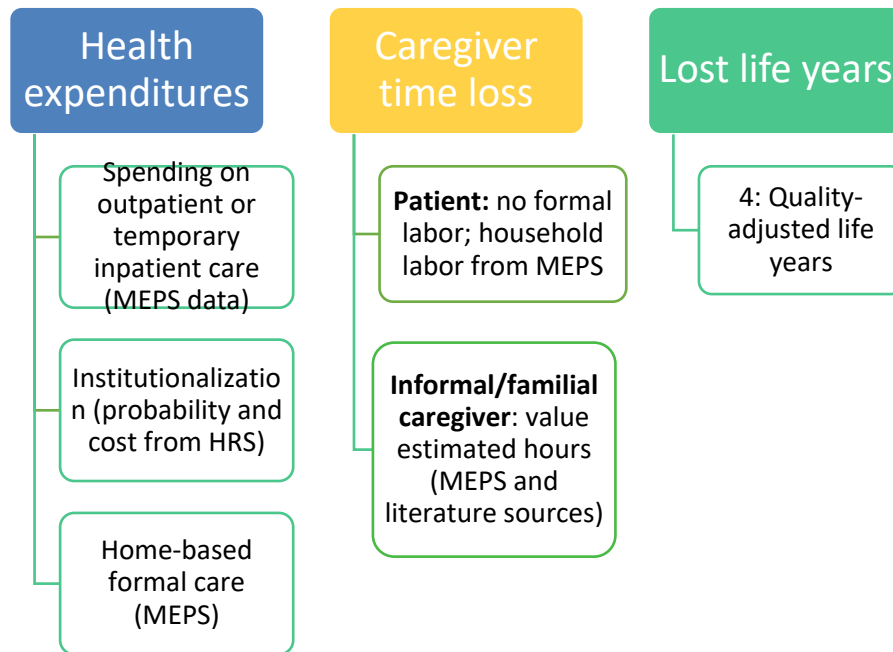
Disease burden extends to other family members beyond the patient and was represented as lost labor force participation in the model.<sup>13</sup> The earnings profiles, stratified by age, quantify earnings over a working career and enabled us to see the effect of personal and family health issues as well as caregiving responsibilities on earnings.

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, the earnings used for self and 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. 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, and disease status.

**Figure 2. Quantifying Societal Burden of CAD**



Finally, expenditures were a function of age, gender, CAD status, and care status. 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. Reductions in own-earnings due to CAD may occur for two reasons: first, we accounted for reduction in earnings for all individuals below age 65 based on estimates in earnings differentials for CAD and non-CAD individuals. Second, those that die before age 65 are assumed to additionally have an earnings loss equal to the unconditional average earnings for non-Hispanic white men (that is, including the fact that some individuals do not work, and have zero earnings).

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.<sup>10</sup> 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, 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.<sup>11</sup>

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 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 25 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.<sup>14-16</sup> 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) decreased mortality rates for CAD patients given age and gender
- 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 CAD 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 CAD 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 1: Investigated Health Improvement Scenarios**

Health improvement	Women’s impact 3x men’s	Equal impact by sex
0.01%	Scenario 1	Scenario 2
0.02%	Scenario 3	Scenario 4
1%	Scenario 5	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 of the NIH portfolio of women-targeted CAD 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 CAD research within the funded portfolio of the NIH. To estimate this level we retrieved all titles and abstracts for the CAD area using NIH RePORTER, the publicly available interface of funded extramural NIH projects.<sup>17</sup> 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). The RePORTER search identified 10,685 Coronary Artery Disease projects from 2008 to 2019; 3.8% of the total number, and 4.5% of the total dollar amount of the portfolio was women-focused. Total project funding level was calculated based on the NIH Research, Condition, and Disease Categorization (RCDC) codes<sup>18</sup>.

The total funding level between 2008 and 2019 for CAD was \$ 5,329,071,325 dollars (for an annual average of \$444,089,277, with 4.5 percent of the budget allocated to women-focused projects.<sup>18,19</sup> The 4.5 percent increment was added to the 2019 amount to double the level of investment in women's health research by \$20.1 million to \$40.2 million, and a 9 percent increment was used to triple the level of investment to \$60.3 million. All costs are presented as 2017 USD.

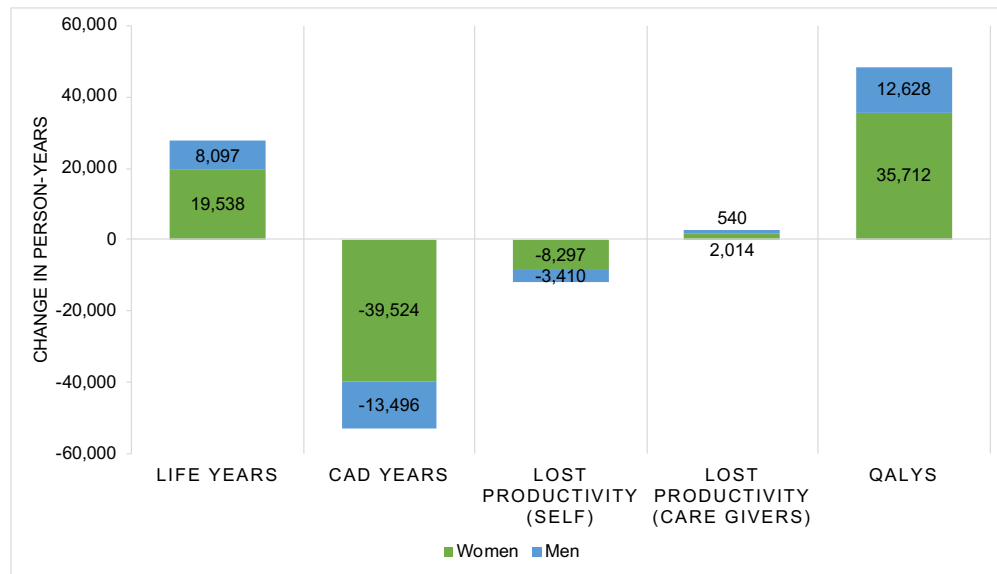
## Results

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 25 and older, of approximately 225 million people, of which around 24 million people had CAD 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 25 and older**



Note: Based on US population age 25 and older of around 225 million.

### Increased life expectancy:

We estimated that the scenario 1 health improvement results in more years of life from lowering the onset of CAD and the mortality rate for CAD patients. Specifically, we found that women realize almost 20,000 more life years from innovations, while men realized over 8,000 more life years from innovations, for a total of almost 28,000 more life years. This is small for the overall US population over age 24, approximately 225 million people, tracked through 30 years. Put another way, this represents an average additional extension of life by fourth-tenths of a day per CAD patient, or one additional life year for one out of every approximately 900 CAD patients.

### Decreased disease burden:

Scenario 1 health improvements also generated a reduction in CAD disease burden in terms of life years with CAD, a function of both shorter disease duration as well as a reduction in age incidence. Women have nearly 40,000 fewer life years with CAD, and men had over 13,000 fewer life years with CAD. These are again relatively small compared to the underlying population, with around 0.8 fewer days with CAD per patient, or one fewer year of CAD for one out of every around 500 patients. Similar to life expectancy increases, although these numbers are relatively small, they represent real gains for people.

**Lost Productivity (Self):**

We examine the impact of the CAD health improvements on employment productivity for the patients. There are two ways in which the health improvements increase employment and earnings of the CAD population. First, fewer years of CAD create less lost earnings given the earnings penalty for CAD patients. Second, more years of life also allows for more years of work. In both cases, the effect is limited to those that are age 65 or younger. We estimate that these effects yield around 8,000 more equivalent years of work for women, and 3,000 for men.

**Caregiver Productivity:**

We also investigated the change in productive years of caregivers, which is a function of changes in formal and informal care. We find the effect to be small but in the direction opposite of that hypothesized in the conceptual model: the increase in lost years (or fewer productive years) is around 2,000 for women and 500 for men. These are due to more years of life given the health improvements, but more of those years at a functional level requiring informal caregiving.

**Increased quality of life (measured in equivalent QALYs):**

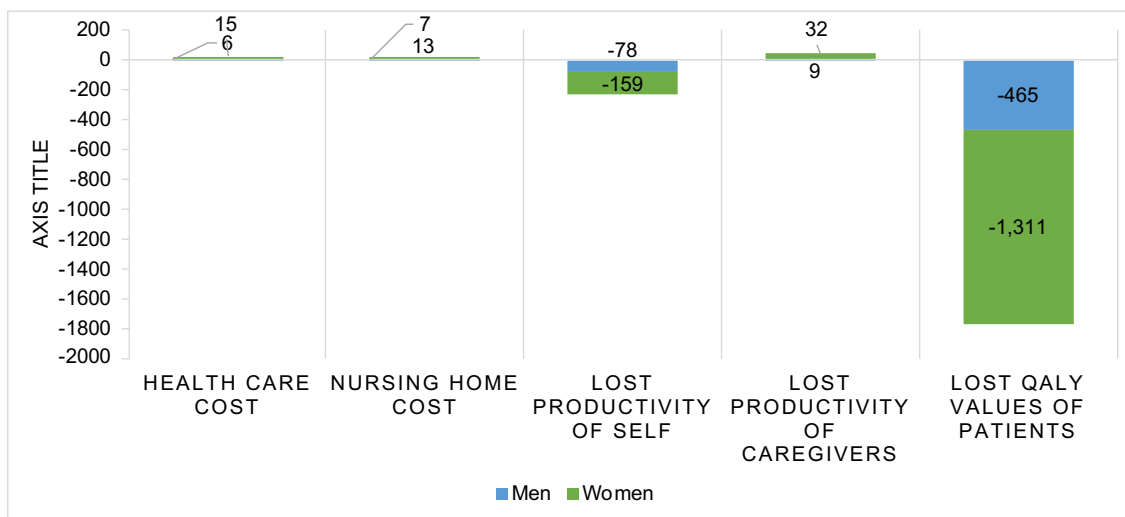
While we measured an increase of around 28,000 total life years due to the health improvement in scenario 1, this does not capture the fact that these health improvements are also related to higher quality of life. In fact, unlike the prior metrics, this is the only one affected by each of the three health improvements. Delayed onset reduces the years of CAD burden, which increases quality of life. Decreased mortality rates leads to more years alive, which increases quality of life. Finally, we directly decreased the reduction in quality of life for CAD patients from the health improvements, representing potential innovations that decrease the burden of the disease. For these reasons, the QALYs represent a large effect, with around 48,000 more year-equivalent of a fully-healthy adult. Of these, approximately 74 percent are from women patients, and 26 percent from men.

**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.

**Figure 4: Change in costs under Scenario 1**

**0.01% health impact, three times larger impact for women than men**



The overall reduction in costs was around \$1.9 billion net present value across the 30 years. Around 73 percent of the costs are from female patients, and 27 percent from male patients. Furthermore, as shown in Figure 4, approximately 90 percent of the cost-reductions arise from fewer lost QALYs (from improved quality of life and more life years), while approximately 10 percent come from fewer lost years of workforce productivity of patients. Nursing home costs, direct health care costs, and lost productivity of caregivers are significantly smaller relative to the first two factors.

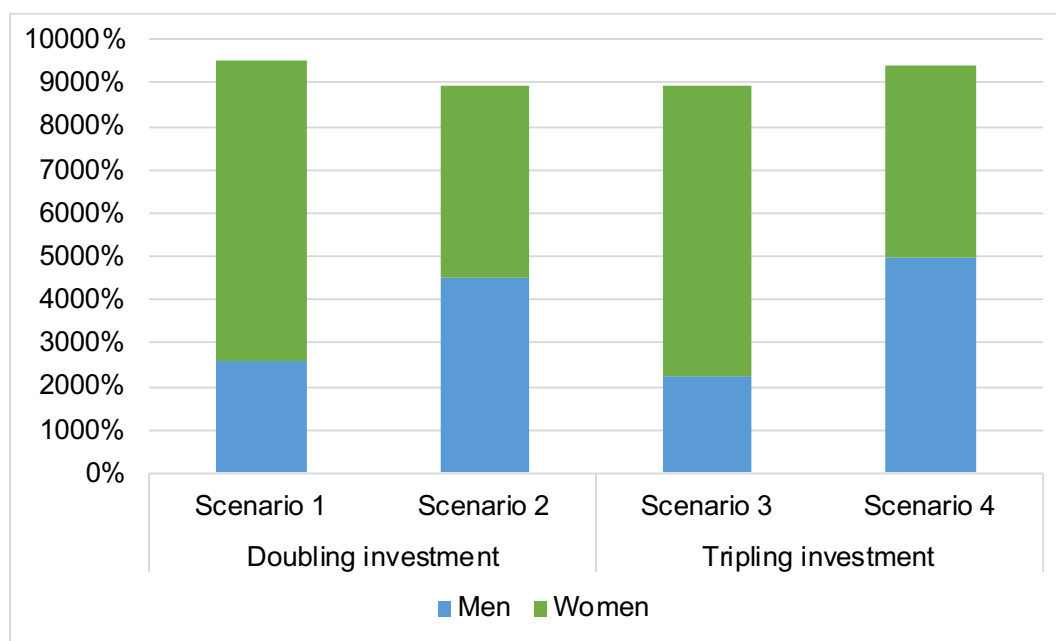
### ROI under Different Scenarios

We calculated the ROI that would result from doubling or tripling the women's portion of the CAD 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 9,500 percent, and 4,700 percent for tripling the budget.

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 \$20 million (doubling women's targeted portfolio) to around \$40 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**



Scenario 1: 0.01% improvement, women 3x men; Scenario 2: 0.01% improvement, women equal men  
 Scenario 3: 0.02% improvement, women 3x men; Scenario 4: 0.02% improvement, women equal men

The return on investment of research on CAD is a function of how the research funds are directed. Overall ROI is very high for any increased funding scenario. Women recognize proportionately more benefits of research directed at women, but all scenarios examined here lead to large returns on investment. For doubling investment, women's targeted investments yield slightly larger overall ROI. For tripling investment, investment in general research yields slightly higher ROI. However, the scenarios are based on the assumption that the same investment increase in dollars focused on women's-targeted research will have the same average health improvement (e.g., 0.01% for doubled investment) as general research. Given that gender-specific CAD research has historically focused more on men than on women, and general research often is actually focused on men, this assumption may not be true. Women's-focused research is likely to have a higher average health improvement than general research.

In that case, given we find equal ROIs in Figure 5, we would find higher ROIs under women's-targeted research than general in that case.

### 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 CAD 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. The target of 15 percent was chosen based on similar return on research investment in a range of therapeutic areas.<sup>10</sup>

**Table 2: Probability of success of investments needed for 15 percent expected ROI**

Scenario	Health improvement under success	Women's impact compared to men	Minimum probability success needed under:	
			Doubling investment	Tripling investment
1	0.01%	3 to 1	1.19%	2.39%
2	0.01%	Equal	1.28%	2.55%
3	0.02%	3 to 1	0.64%	1.27%
4	0.02%	Equal	0.60%	1.21%
5	1%	3 to 1	0.01%	0.03%
6	1%	Equal	0.01%	0.03%

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 around 9,500 percent, the investment would have to succeed with probability 1.19 percent to result in a 15 percent expected ROI. This is a relatively low necessary probability of success, for a very small health improvement. However, bigger health improvements, such as in scenarios 5 and 6, require a much smaller probability of success. 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 0.03 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 from a \$20 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 CAD will have an expected ROI of 15 percent, with a smaller probability of success (1.2 percent) for a very small health improvement (0.01 percent). Alternately, for the same expected ROI of 15 percent, a smaller probability of success (0.6 percent) is associated with a larger health improvement (0.02 percent). A very small probability of success (0.01 percent) would obtain for a relatively large health improvement (1 percent). Altogether, this suggests it is possible to obtain positive returns on increasing the budget for this research.

## Discussion

Small investments in coronary artery disease are likely to yield large societal gains. The very high return on investment from assumptions of relatively small overall health improvement support the potential for these gains from research. The very low probability of success required for research in coronary artery disease to yield a 15% return on investment provide further support. Overall magnitude of impact is greater than similar research on impact of research investment.<sup>20</sup>

The results can aid with establishing the value of new interventions by addressing which stakeholders and which societal payers are impacted.<sup>21</sup> The assumptions used for these microsimulation models yield high return, with healthcare cost and productivity loss reductions but most of the gains are due to improved health-related quality of life.

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. The ROI is a function of the size of the investment and the magnitude of health

improvements. 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 main 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, likely underestimates the 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. That we find approximately equal returns on investment from a women-targeted investment as from a general one is thus indicative of a baseline that suggests if we adopted more realistic parameters (such as women-targeted research having a larger average health improvement than general research), the ROI would thus be higher from women-targeted research.

**Time horizon:** Estimates for the time from investment to discernible impact of investment for health research center on 13 to 25 years.<sup>14-16</sup> 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 CAD 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 impact of health improvements on patient functioning are fundamental to the results for health care costs and caregiver productivity, and the results here, while small, point to slightly more lost caregiver productive years, while the model included the hypothesis of fewer lost productive years for caregivers. The 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 CAD 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. For example, we do not model severity progression or treatment and remission explicitly. A preventive intervention or disease-eliminating intervention 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 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 in 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. We also did not estimate the costs for temporary skilled nursing home stays, including those after exit from hospitalizations. 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.

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.

2. Expand the research agenda to address multiple aspects of sex/gender and coronary artery disease based on the limited evidence base, including
  - a. the unknown interactions of sex and gender with cardiovascular disease antecedents and disease progression to inform treatment and prevention research.
  - b. under-studied interactions of gender and race with cardiovascular disease risk, health care, and disease progression. In particular examine obstacles to access to and use of medical provider visits, prescription drugs, and relevant devices.
  - c. differences by sex and gender in dietary impacts on disease and adherence to dietary recommendations.
  - d. differences in disease course and outcomes by sex and gender based on different patterns of use of formal and informal caregiving.

Given the findings here of potential for impact on health-related quality of life of women with coronary artery disease, further study of the relationship of earlier detection for women and improved disease management, in terms of impact on health and quality of life outcomes, can aid with tracking investment impacts in the future. The following recommendations can provide a foundation for support of research funding allocation decisions:

1. Raise awareness of differences between the coronary artery disease course for women and men and the potential for investment to improve disease outcomes and societal impact.
2. Raise awareness among the business community of the potential return on investment in women's health research, particularly for women in the workforce.

## 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 CAD and can provide specifics to inform an agenda for research on women's health.<sup>22-24</sup> 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.

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## Technical Appendix A: Selection of Data Sources

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

	<b>Panel Study of Income Dynamics</b>	<b>National Longitudinal Survey of Youth, 1979</b>	<b>Medical Expenditure Panel Survey</b>
N	24,000 people	12,686 people	30,000 households
Age ranges	Born 1951-present	Born 1957-1964	Range of ages
Received diagnosis of			
Alzheimer's specifically	No (just diagnosis of permanent loss of memory/ mental ability)	No	Yes
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 1,000,000 individuals aged 25-99. We take the fraction of individuals in each year of age and gender subgroup in the U.S. population from the Census Bureau,<sup>22</sup> and multiply that fraction by 1,000,000 to determine how many individuals in our simulation sample to assign that age and gender at start. Then, conditional on age and gender, individuals in the starting cohort are first sorted into one of two states:

1. Alive without Coronary Artery Disease (CAD)
2. Alive with CAD

The distribution of the two states in the population is determined by the prevalence of CAD conditional on age and gender, which we estimate using Medical Expenditure Panel Survey (MEPS) for individuals age 65 years old or younger and Centers for Medicaid & Medicare Services (CMS) data for those over 65 years old. We identify CAD through ICD-9 (410, 413, 414) and ICD-10 codes (I20, I21, I25) in MEPS, and we further include patients with atherosclerosis (ICD-9 440, ICD-10 I70) and 68% of patients with heart failure (ICD-9 428, ICD-10 I50) to the CAD patient pool. In CMS data, ischemic heart disease is one of the selected chronic conditions reported; therefore, we can identify CAD patients through the indicator for ischemic heart disease.

Although there are respondents older than 65 in MEPS, we choose to use CMS data for elderly population due to the advantages of claims dataset, including larger sample sizes and less sampling and recall bias, and because the MEPS data does not include individuals in skilled nursing facilities, such as nursing homes. Insofar as residence in skilled nursing facilities is both more common for older individuals and correlated with CAD diagnoses, using the MEPS for these older individuals would undercount the rate of CAD. We compare the CAD prevalence

rates in MEPS with the ones in CMS data for females and males aged 66-75, and generate an inflation ratio (1.32 for males, 1.80 for females) for the CAD prevalence rates among respondents aged 25 to 65 in MEPS. Finally, we fit a flexible monotonic increasing function (logistic function symmetric sigmoid shape, Stata's `nl log3`) to the hybrid CAD prevalence rates of:

1. the inflated prevalence rates from respondents aged 25 to 65 in MEPS
2. the prevalence rates from individuals aged 66 or older in CMS data.

We assign a fraction of individuals in each age and gender subgroup to start with an existing CAD diagnosis based on the fitted prevalence rates from that estimated function.

Having the initial conditions of the representative cohort, there are three steps 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 CAD, 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.<sup>23</sup> 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 years old.

## 2.3 Centers for Medicaid & Medicare Services Data

The CMS Medicare Beneficiary Summary File (base and chronic conditions components) is used to estimate the age incidence rate, age prevalence rate and mortality hazard of CAD. 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, one of which is Ischemic Heart Disease, 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 use data of



these annual files from 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 CAD. We use the 2017 data to estimate age-specific mortality rates, conditional on CAD status.

### 3. Modeling health and economics statuses

#### 3.1 Incidence of CAD

We model the probability of having onset of CAD for each individual. To do so, we estimate the following probability in equation B.1 for each gender  $g$  and age  $t$  using MEPS. Similar to prevalence rates we estimate to construct the starting cohort, we utilize both MEPS and CMS data to get the incidence rates. For population age 65 years old or younger, we use the age of diagnosis collected for CAD patients in MEPS as an estimate of the age of onset of CAD. When patients have multiple age of diagnosis for different CAD diseases, we choose the youngest age as the age of onset of CAD. For example, we expand one cross-sectional observation in MEPS of an individual aged 54 years old who was diagnosed at age 45 to 30 observations, one for each year from age 25 to age 54, and flag age 45 to age 54 as having CAD. This person will only appear in the numerator in the calculation of incidence rate at age 45 (equation B.1). The reason we expand one cross sectional observation to 30 observations in this case is that we underestimate the number of individuals who have lived through age  $t$  (denominator in equation B.1) if we do not include person-years that are CAD free.

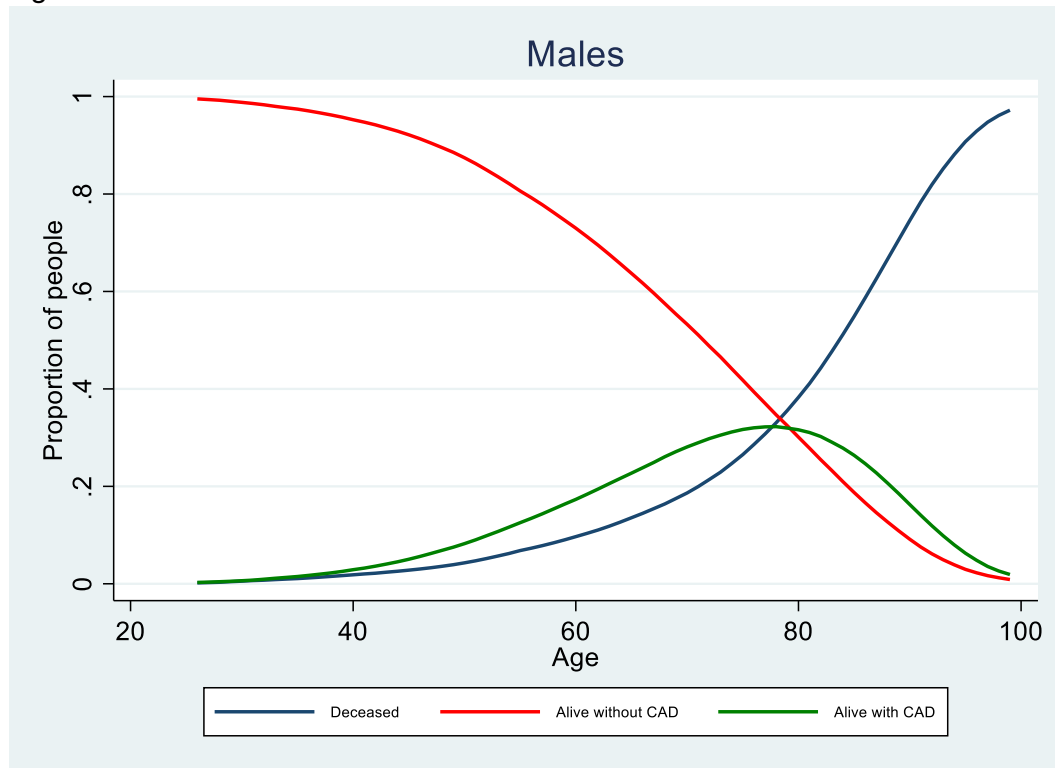
$$\psi_{gt} = \frac{\text{number of individuals who had been newly diagnosed with CAD at age } t \mid \text{gender}=g}{\text{number of individuals who have lived through age } t \mid \text{gender}=g} \quad (\text{B.1})$$

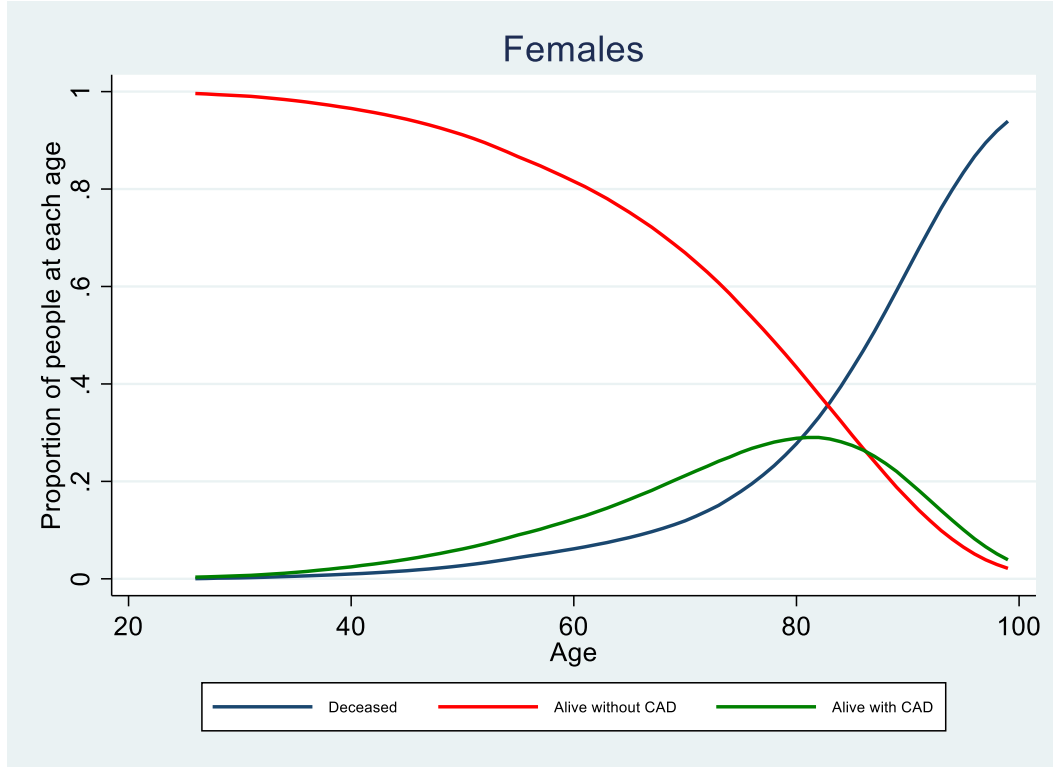
For population age 66 years old or older, we calculate the incidence rates conditional on gender and age from the CMS data using equation B.1. As discussed in section 1 of the appendix, we suspect that MEPS underestimates the incidence rates of CAD across all age groups; therefore, we compare the estimated CAD incidence rates in MEPS with the estimated rates in CMS data for females and males aged 66-75, and generate an inflation ratio (2.70 for males, 3.97 for females) for the incidence rates among respondents aged 25 to 65 in MEPS. Finally, we fit a flexible monotonic increasing function (logistic function symmetric sigmoid shape, Stata's `nl log3`) to hybrid CAD incidence rates of the inflated incidence rates from respondents aged 25 to 65 in MEPS and the rates from individuals aged 66 or older in CMS data. From this, we then predict the incidence rate for each age and gender.

CAD is an absorbing state in our model, which means that once an individual is diagnosed, he/she lives with the condition until death. With the incidence rates estimated for each age and gender, 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 CAD in the prior year, and model them as having been diagnosed with CAD in that year if the random draw is less than the probability of CAD

diagnosis, i.e. if  $u_{gt1} < \psi_{gt}$ . Figure B1 presents our simulated proportion of people at each age in each state of alive with CAD, alive without CAD, and deceased. The fraction of people with CAD peaks shortly after age 80.

Figure B1: CAD case trend in males and females





### 3.2 Probability of Dying

We estimate the probabilities of dying to individuals with and without CAD each year conditional on age and gender using equation B.2 and B.3. We use the United States Life Table in 2017 released by Centers for Disease Control and Prevention (CDC) for the probabilities of dying in the general population in equation B.2,<sup>2</sup> and the CMS data for the mortality hazards of CAD in equation B.3 and B.4. For patients with CAD, probability of dying is the addition of a mortality risk based on age and gender to the baseline probability for individuals without CAD. We calculate the additive mortality hazards of CAD from the CMS data for individuals age 66 years old or older, and fit a monotonic increasing function using Stata command `nl log3`. For individuals younger than 66 years old, we assume they have the same mortality hazard as people age 66 years old. By substituting equation B.3 into B.2, we can derive the probability of dying for individuals without CAD conditional on age and gender using equation B.4.

$$\begin{aligned} \Pr(\text{die}|\text{age} = t, \text{gender}) &= \Pr(\text{die}|\text{age} = t, \text{gender}, \text{CAD}) \times \Pr(\text{CAD}|\text{age} = t, \text{gender}) + \\ &\Pr(\text{die}|\text{age} = t, \text{gender}, \text{no CAD}) \times \Pr(\text{no CAD}|\text{age} = t, \text{gender}) \end{aligned} \quad (\text{B.2})$$

$$\Pr(\text{die}|\text{age} = t, \text{gender}, \text{CAD}) = \Pr(\text{die}|\text{age} = t, \text{gender}, \text{noCAD}) + (\text{predicted mortality hazard}|\text{age} = t, \text{gender}) \quad (\text{B.3})$$

$$\Pr(\text{die}|\text{age} = t, \text{gender}, \text{noCAD}) = \Pr(\text{die}|\text{age} = t, \text{gender}) - (\text{predicted mortality hazard}|\text{age} = t, \text{gender}) \times \Pr(\text{CAD}|\text{age} = t, \text{gender}) \quad (\text{B.4})$$

### 3.3 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) of the RAND HRS version Q. 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 (equation B.5).

$$\Pr(\text{NH}|\text{gender}, \text{age}) = b_0 + \frac{b_1}{1 + \exp(-b_2 * (\text{age} - b_3))} \quad (\text{B.5})$$

Where  $\Pr(\text{NH}|\text{gender}, \text{age})$  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 CAD patients and the general population. Therefore, all individuals in our model, with or without CAD, are assigned with probability of nursing home entry solely conditional on their age and gender, independent of CAD status. People younger than 65 years old are assigned zero probability of nursing home entry. Again, we then took random uniform draws between 0 and 1, and if the uniform draw was below the estimated probability of nursing home entry, we assigned that person in the simulation to be institutionalized that year.

Figure B2 and B3 present the simulated care trends.

Figure B2: care trend in non-CAD males and females

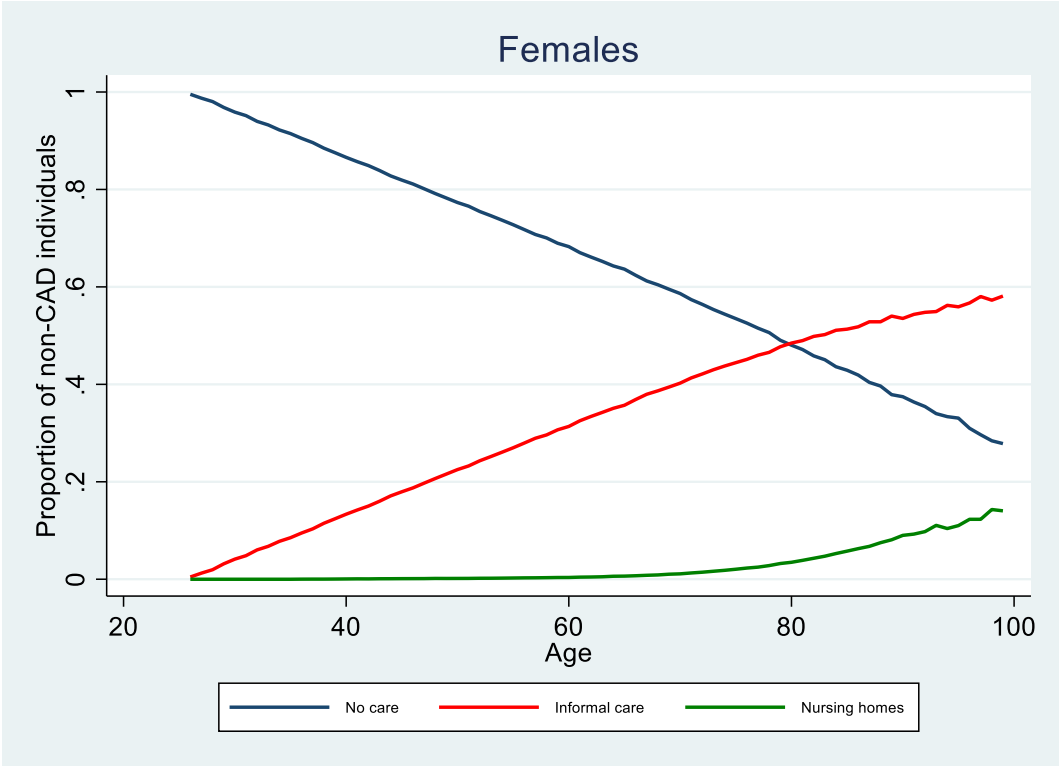
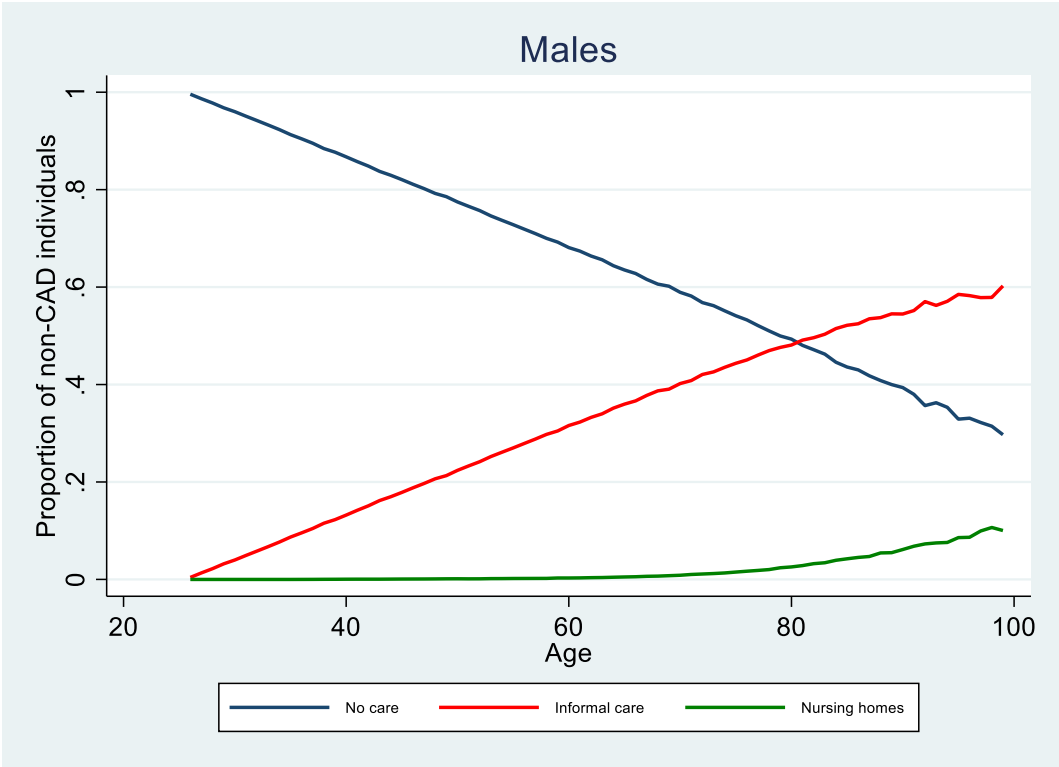
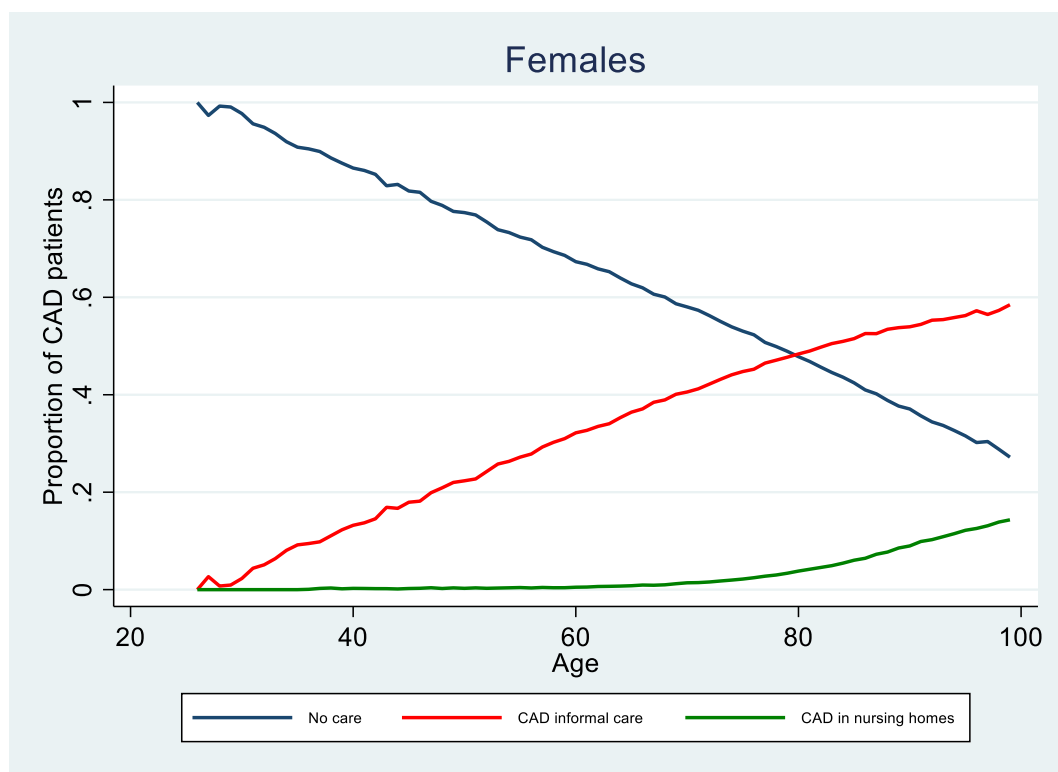
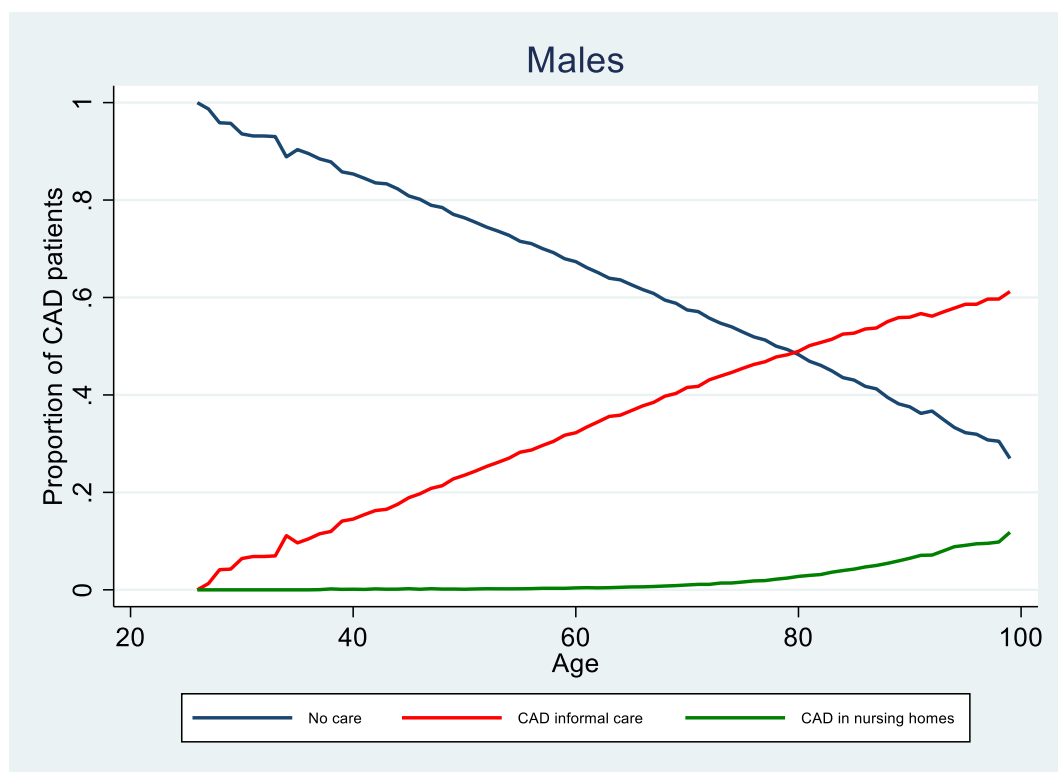


Figure B3: care trend in CAD males and females



### 3.4 Receiving Informal Home Care

To assign the informal home care status for non-CAD and CAD individuals, we use equation B.6 to B.9 below to get the probabilities of receiving informal care and the expected informal care hours conditional on CAD status. We derive the probability of receiving informal care in the general population from Kaye et al. (2013) exhibit 1 and 2, which show 15% of working-age adults and 45% of individuals older than 65 years old have functional limitations. We then assume all people with functional limitations received informal home care. We fit a linear function of age on the probability of having functional limitations to meet these prevalence rates. We assume the expected informal care hours received by the general population is 65.8 hours per month, according to exhibit 2 from Friedman et al. (2015). Using equation B.6, we can calculate the expected informal care hours in the general population unconditional on receiving care or not.

Next, as we already derive the prevalence of CAD patients in each age and gender group, we know the expected informal care hours conditional on not having CAD will be equal to

$E(\text{informal care hours}) - (E(\text{informal care hours}|\text{CAD}) - E(\text{informal care hours}|\text{no CAD}) \times \Pr(\text{CAD}))$  from equation B.7.  $(E(\text{informal care hours}|\text{CAD}) - E(\text{informal care hours}|\text{no CAD}))$  is 0.16 hour/week for males and 0.04 hour/week for females based on Dunbar et al. (2018), and therefore we can calculate out  $E(\text{informal care hours}|\text{CAD})$  for each age and gender group. Once we have estimated  $E(\text{informal care hours}|\text{CAD})$ ,  $E(\text{informal care hours}|\text{no CAD})$  is simply estimated by adding the informal care hours attributable to CAD from Dunbar et al. (2018).

Finally, to estimate the probability of receiving informal home care for CAD and non-CAD individuals, we divide the expected informal care hours conditional on CAD status by the expected informal care hours received conditional on receiving informal care in the general population (equations B.8 and B.9).



$$E(\text{informal care hours}) = E(\text{informal care hours}|\text{receiving care}) \times \Pr(\text{receiving care}) \quad (\text{B.6})$$

$$E(\text{informal care hours})$$

$$= (E(\text{informal care hours} | \text{CAD}) + 0.1) \times \Pr(\text{CAD})$$

$$+ E(\text{informal care hours} | \text{no CAD}) \times \Pr(\text{no CAD})$$

$$\Rightarrow E(\text{informal care hours} | \text{no CAD}) = E(\text{informal care hours}) -$$

$$(E(\text{informal care hours} | \text{CAD}) - E(\text{informal care hours} | \text{no CAD}) \times \Pr(\text{CAD})) \quad (\text{B.7})$$

$$\Pr(\text{informal care hours} | \text{receiving care}, \text{CAD}) = \frac{E(\text{informal care hours} | \text{CAD})}{E(\text{informal care hours} | \text{receiving care}, \text{CAD})} \quad (\text{B.8})$$

$$\Pr(\text{informal care hours} | \text{receiving care}, \text{no CAD}) = \frac{E(\text{informal care hours} | \text{no CAD})}{E(\text{informal care hours} | \text{receiving care}, \text{no CAD})} \quad (\text{B.9})$$

As before, we took random uniform draws between 0 and 1, and if the uniform draw was below the estimated 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.4 and B.5 show the average costs—across both CAD and non-CAD patients—by age, based on our simulations. We describe each in turn.

Figure B4: average cost conditional on age for males

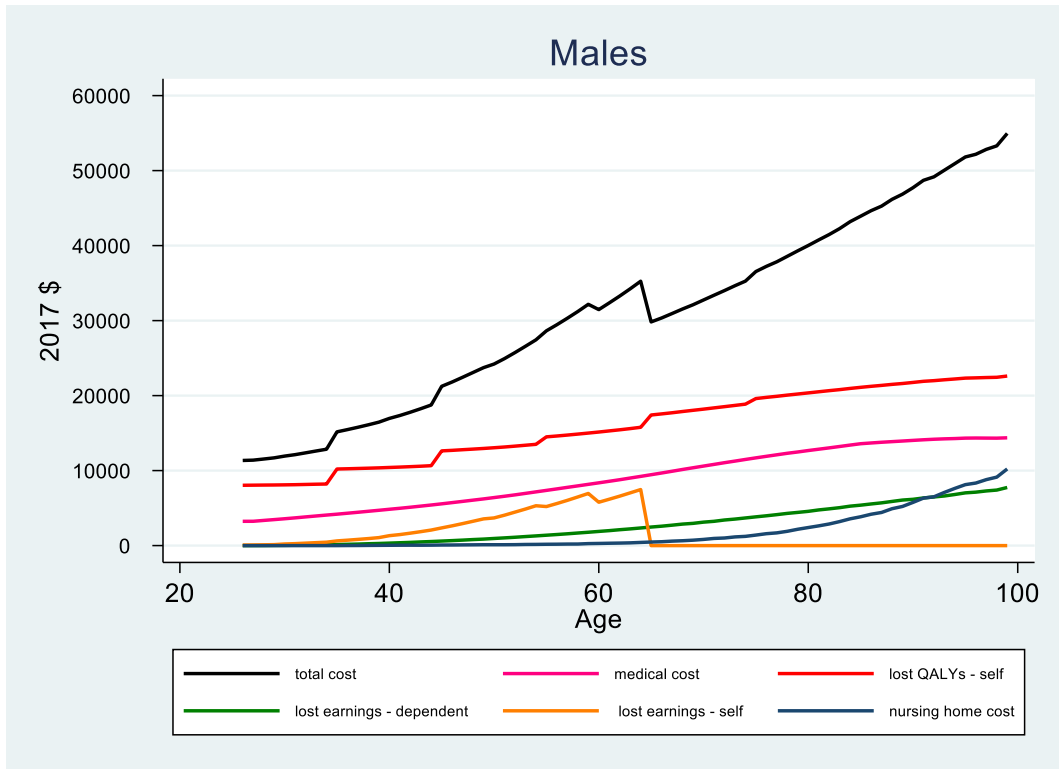
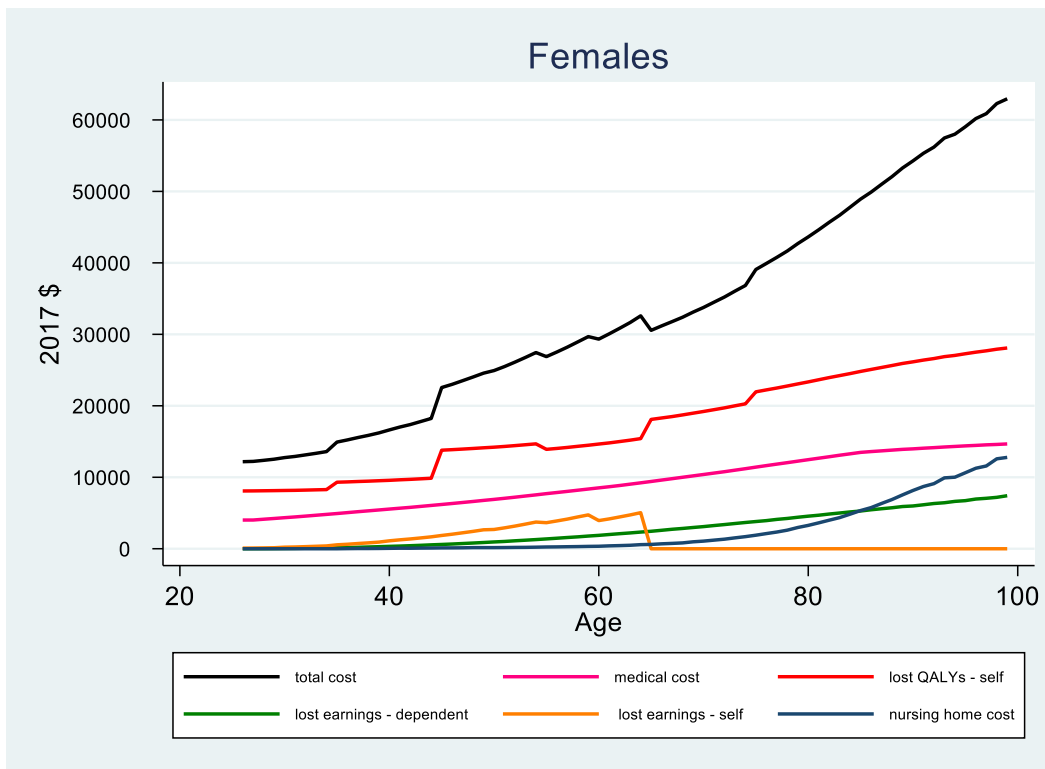


Figure B5: average cost conditional on age for females



#### 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 MEPS separately for individuals with and without CAD. In view of the impact of insurers on medical spending, we used ordinary least squares regression to estimate 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, nursing home costs for individuals in nursing homes were estimated separately. However, we chose to assign the same average total health care costs (not including the costs of the nursing home) 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 CAD using the MEPS. In addition to decreased earnings due to CAD when patients are alive, we categorize any deaths before the age of 65 as premature deaths (with respect to labor productivity) and calculate the potential earnings until age 65 that would have been earned if they were to live. All earnings are based on those of non-Hispanic white males, to correct for gender and race-based labor market discrimination. We start with estimating the gap of earnings between CAD and non-CAD non-Hispanic White males for each age group  $g$  from the MEPS using equation B.10:

$$\pi_g = E[W|no\ CAD, Age = g] - E[W|CAD, Age = g] \quad (B.10)$$

We do this by estimating the following regression using MEPS data for individuals between ages 25 and 65

$$W = \sum_g \pi_g CAD * 1(Age = g) + \sum_g \delta_g 1(Age = g) \quad (B.11)$$

For CAD patients with premature deaths, we use the wage of non-Hispanic White males not conditional on working (including non-CAD and CAD patients) for each age group  $g$  to construct

the expected productivity until age 65. For example, if a CAD patient enters our simulation model at age 45 and dies at age 55, we calculate his/her productivity loss over the 30-year time span of the simulation by accumulating the wage loss for the first ten years of the simulation for having CAD (between ages 45 and 55) and the full productivity loss of wages between ages 55 (when they are estimated to have died) and age 65 (assumed retirement age). This is done by equation B.12.

$$E(\text{Total productivity loss} | \text{CAD age 45, death age 55}) = \sum_{g=45}^{54} \pi_g 1(\text{Age} = g) + \sum_{g=55}^{65} E[W | \text{Age} = g] \quad (B.12)$$

#### 4.3 Productivity Loss of Informal Home Caregivers

Costs of informal home care are calculated using the productivity (earnings) loss of informal home caregivers, to account for the time they spend providing unpaid, informal care instead of doing paid labor. 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' CAD status.
2. The average hours spent on caretaking is derived in section 3.4, conditional on patient's age and gender.
3. We multiply the hourly wage of non-Hispanic white males estimated from MEPS with the average informal caregiving hours from step 2 to get productivity loss in a year of informal home caregivers for CAD patients and non-CAD individuals

#### 4.4 Nursing Home Costs

The cost of living in nursing homes is set at \$90,520 annually for non-CAD individuals and CAD 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.<sup>31</sup>

#### 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 CAD patients conditional on gender based on Xie et al. (2008) table 2.

We calculated lost QALYs for both CAD and non-CAD 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.<sup>34</sup> 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 a female with CAD not living in a nursing home.

$$1 - 0.68 \text{ (health utilities for female CAD patients)} = 0.32$$

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

$$1 - 0.68 \text{ (health utilities for female CAD patients)} + 0.1 = 0.42$$

#### 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 to have the one-million person sample scale up to the US adult population, 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 around \$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.13:

$$ROI = 100 * \left( \frac{cost_s - cost_n - Investment}{Investment} - 1 \right) \quad (B.13)$$

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.

$$E[cost_i] = P * cost_n + (1 - P) * cost_s \quad (B.14)$$

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

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

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

$$E[cost_i] = cost_s - 2.15 * Investment \quad (B.16)$$

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

$$\begin{aligned} cost_s - 2.15 * Investment &= P * cost_n + (1 - P) * cost_s \\ \Rightarrow P &= \frac{2.15 * Investment}{cost_s - cost_n} \end{aligned}$$

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omen'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 coronary artery disease (CAD). CAD was chosen partly because physiological differences between men and women affect factors that relate to the development and progression of cardiovascular disease. 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.

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