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Los Angeles

LEAN ON ME: Spousal and Friendship Social Support Influencing Dementia Among Older  
Adults

A dissertation submitted in partial satisfaction of the  
requirements for the degree Doctor of Philosophy  
in Epidemiology

by

Nicola Ann Marie Churchill

2026

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## ABSTRACT OF THE DISSERTATION

LEAN ON ME: Spousal and Friendship Social Support and Dementia Risk Among Older Adults

by

Nicola Ann Marie Churchill

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2026

Professor Roch Nianogo, Co-Chair

Professor Onyebuchi A. Arah, Co-Chair

This dissertation aims to understand the mechanism through which social support affects dementia, as well as the potential synergistic effect of multiple social support types on dementia, and evaluate potential interventions, particularly for individuals in racial and ethnic and sex/gender subpopulations. Specifically, the aims are as follows: Aim 1: To examine the joint effects of positive spousal social support and closeness to spouse on dementia and cognitive impairment risk overall and by subgroups defined by race/ethnicity and sex/gender; in Aim 2: To identify potential factors that can modify the effect of friendship social support on the risk of dementia and estimate subgroup heterogeneous effects across these factors in the overall and racial/ethnic subgroups; and Aim 3: To examine the extent to which depression mediates the effects of positive spousal social support on dementia and cognitive impairment risk and evaluate if these effects vary by sex/gender subpopulations. These research aims were carried out by

using the 2006-2020 Health and Retirement Study (HRS) cohort of U.S. older adults, age 50 and older and their spouses. The results of these aims demonstrated the complex relationships between social support and dementia/cognitive impairment risk. There is a need for more representation of older adults from racial and ethnic subpopulation. In particular, expanding participation among Black and Hispanic individuals is essential to overcoming the small sample size limitations. Future research should explore the nuanced social mechanisms that govern how support from a partner effects long term cognitive health and whether quality in addition to frequent interactions with friends can affect dementia risk.

The dissertation of Nicola Ann Marie Churchill is approved.

Elizabeth Rose Mayeda

Jin Zhou

Onyebuchi A. Arah, Committee Co-Chair

Roch Nianogo, Committee Co-Chair

University of California, Los Angeles

2026

## DEDICATION

To my husband, Sam — my steady ground and my greatest love.

To my daughter, Diana — my cheerleader, my champion, my heart.

To my parents — my guides through every uncertain road.

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## VITA

Nicola Ann Marie Churchill

### Education

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|------|---------------------------------------------------------------------------------------------------------------------------|
| 2026 | Doctor of Philosophy Candidate, Epidemiology<br>Fielding School of Public Health<br>University of California, Los Angeles |
| 2022 | Master of Public Health, Epidemiology<br>Fielding School of Public Health<br>University of California, Los Angeles        |
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### Positions

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| 2026      | Graduate Student Researcher, Dept. of Epidemiology. PI: Dr. Roch Nianogo                               |
| 2026      | Teaching Assistant, Epi 100: Teaching in Epidemiology                                                  |
| 2025      | Teaching Assistant, Epi 120: Teaching in Epidemiology                                                  |
| 2024      | Graduate Student Researcher, Dept. of Epidemiology. PI: Dr. Roch Nianogo                               |
| 2024      | Graduate Student Researcher, Dept. of Computational Medicine. PI: Dr. Alex Bui                         |
| 2023      | Graduate Student Researcher, Dept. of Epidemiology. PI: Dr. Roch Nianogo                               |
| 2023      | Teaching Assistant Consultant, LS 495: Teaching in Life Science                                        |
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| 2022      | Graduate Student Researcher, Dept. of Epidemiology. PI: Dr. Roch Nianogo                               |
| 2021      | Teaching Assistant, EPI M403: Computer Management for Health Data                                      |
| 2020-2021 | Teaching Assistant, LS 7A: Cell and Molecular Biology                                                  |

### Awards

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|           |                                                              |
|-----------|--------------------------------------------------------------|
| 2020-2022 | University of California Los Angeles Dean's Leadership Grant |
|-----------|--------------------------------------------------------------|

|           |                                                      |
|-----------|------------------------------------------------------|
| 2018-2020 | University of California Santa Barbara Scholarship   |
| 2018-2020 | U.S. Federal Pell Grant                              |
| 2017-2020 | University of California Santa Barbara Dean's Honors |

### **Abstracts**

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|      |                                                                                 |
|------|---------------------------------------------------------------------------------|
| 2026 | Alzheimer's Association International Conference Poster Presenter               |
| 2026 | Society for Epidemiologic Research Annual Meeting Abstract and Poster Presenter |
| 2025 | Society for Epidemiologic Research Annual Meeting Abstract Presenter            |
| 2024 | Alzheimer's Association International Conference Poster Presenter               |
| 2024 | Society for Epidemiologic Research Mid-Year Meeting Virtual Poster Presenter    |
| 2023 | Turken Research Symposium Poster Presenter                                      |
| 2023 | NLM T15 Training Grant Conference Rapid Talk Presenter                          |
| 2021 | Turken Research Symposium Virtual Poster Presenter                              |

### **Peer-reviewed publications**

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|      |                                                                                                                                                                                                                                                                                                                           |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2026 | <b><u>Churchill, N. A.</u></b> , Barry, L., & Nianogo, R. A. Effects of Gilbert syndrome on cardiovascular disease risk reduction: a systematic review. <i>Egypt Heart J</i> 78, 25 (2026). <a href="https://doi.org/10.1186/s43044-026-00738-3">https://doi.org/10.1186/s43044-026-00738-3</a>                           |
| 2026 | <b><u>Churchill, N. A.</u></b> , , & Nianogo, R. A. Alzheimer's disease and related dementias state policies and mortality in the United States: A descriptive study. <i>J Alzheimers Dis.</i> 2026. In Press                                                                                                             |
| 2025 | Habib M, <b><u>Churchill N</u></b> , Nianogo RA (2025) Investigating the Role of Chronic Stress and Perceived Discrimination in Racial Disparities in Incident Dementia among US older Adults. <i>Soc Sci Med</i> 118192.                                                                                                 |
| 2024 | <b>Churchill N</b> , Barnes DE, Habib M, Nianogo RA. Forecasting the 20-Year Incidence of Dementia by Socioeconomic Status, Race/Ethnicity, and Region Based on Mid-Life Risk Factors in a U.S. Nationally Representative Sample. <i>J Alzheimers Dis.</i> 2024;99(4):1225-1234. doi: 10.3233/JAD-231133. PMID: 38788068. |

## **CHAPTER 1: INTRODUCTION**

### **SPECIFIC AIMS**

There were 7.2 million people 65 years and older living with dementia in the United States in 2025, and this number is expected to rise to 13 million in 2050.<sup>1,2</sup> The prevalence of dementia is higher in minoritized racial and ethnic subpopulations. For instance, Black individuals have the highest prevalence of all racial and ethnic groups, followed by Hispanic individuals.<sup>3</sup> Up to 40% of dementia cases can theoretically be prevented or delayed by targeting modifiable lifestyle risk factors, and studies have shown that specifically reducing the occurrence of depression has been associated with improving or maintaining cognitive reserve and reducing dementia risk.<sup>4,5</sup> Healthcare providers have turned to modifiable risk factors to ameliorate this disease's progression.<sup>4</sup> Among these, social support characteristics such as marriage, being in contact with family and children, and having a sense of community have been shown to have a positive impact on health and cognitive function.<sup>6–14</sup> *However, the mechanisms by which social support affects dementia, as well as the synergistic effect of multiple social support types, remained relatively unexplored.*

Social support is the tangible or intangible assistance and protection by others.<sup>15</sup> Social support can be particularly beneficial to Black populations since this group has strong social connections at older ages and usually gets informal care in times of need.<sup>16</sup> Studies have shown that increased social support is associated with a decreased risk of dementia.<sup>17,18</sup> The overarching goal of this study is to understand the mechanism through which social support affects dementia, as well as the potential synergistic effect of multiple social support types on dementia. The *specific aims* and hypotheses (*H*) are:

**1) To investigate the joint effects of positive spousal social support and closeness to spouse on dementia risk overall and by subgroups defined by race/ethnicity and sex/gender. Hypothesis 1 (H1): There is a synergistic effect between social support domains of positive spousal social support and closeness to spouse and dementia risk/cognitive decline. The joint effect will have a unique effect on each subpopulation.** We will use pooled logistic regression and parametric g-computation to analyze the Health and Retirement Study (HRS) data.

**2) To identify potential factors that can modify the effect of friendship social support on the risk of dementia and estimate subgroup heterogeneous effects across these factors in the overall and racial/ethnic subgroups. H2: Individuals with characteristics such as higher socioeconomic status (SES), less financial strain, less stress, and no depression will have the smallest risk for developing dementia. The average treatment effect will differ across racial and ethnic subpopulations due to different structural and social support stressors and facilitators.** Causal forests, a machine learning algorithm, will be used to analyze the HRS data.

**3) Examine the extent to which elevated depressive symptoms mediates the effects of positive social support from one's spouse on dementia risk and cognitive impairment, and evaluate if there is an interaction between this factor and social support for overall and within sex/gender subpopulations. H3: Depression will account for a substantial portion of the effect of social support on dementia risk and cognitive function, and there are interactions present between the mediator and social support. The mediated effect will differ between men and women.** We will use causal mediation analysis, pooled logistic regression, and the parametric g-computation, a causal inference method, applied to the nationally representative HRS.

**Impact:** Upon completion, researchers will understand the mechanisms underlying dementia and cognitive decline and identify alternative intervention targets to prevent its onset. In addition, the greatest impact of dementia prevention can be achieved by targeting resources to the group that will benefit most from interventions. Finally, the joint and sustained effects of multiple social support types could be used to reduce dementia incidence. These findings will assist policymakers in determining where to focus resources and efforts to mitigate dementia incidence, including lessening health disparities in cognitive health.

## INTRODUCTION

### *Prevalence of Dementia*

Dementia is a term used to represent a multitude of symptoms that can be caused by several neurodegenerative diseases.<sup>2</sup> The most common neuropathology among dementia cases is Alzheimer's disease (AD), which accounts for about 60-80% of dementia cases.<sup>2</sup> Additional dementia neuropathologies that are most prevalent in the U.S. include cerebrovascular disease, frontotemporal degeneration, hippocampal sclerosis, Lewy body disease, mixed pathologies, and Parkinson's disease. The prevalence of specific dementia causes varies by age. For instance, frontotemporal degeneration can account for 3% of dementia cases in individuals 65 or older, but up to 10% in those aged 65 or younger.<sup>19</sup> Most people have brain changes from multiple dementia causes called mixed pathologies.<sup>19</sup>

Dementia has several known risk factors that can increase one's chances of developing dementia later in life. The most important risk factors include age, genetics, and family history. Although dementia is not a normal part of aging, the increasing longevity of individuals in the U.S. will result in more dementia cases across the country. It should also be noted that recent advances in genetic research have identified 31 new genes that seem to affect the biological process of Alzheimer's disease, with *APOE-e4* remaining as the strongest genetic risk factor.<sup>19</sup> All of these risk factors are non-modifiable, but there are several modifiable risk factors that can also impact dementia risk. Up to 40% of dementia cases can be attributable to modifiable risk factors, and around 37% of dementia cases in 2022 could be found associated with 8 modifiable risk factors: hearing loss, diabetes, low education, current smoking, depression, physical inactivity, midlife hypertension, and midlife obesity.<sup>5,20</sup> The most common risk factors

associated with dementia were midlife obesity followed by physical inactivity and low education.<sup>20</sup> Not as common but still valuable, social and cognitive engagement by stimulating activity can potentially reduce the risk of dementia by building cognitive reserve. However, more research is required to link social and cognitive engagement to dementia risk.

There are at least 7.2 million Americans living with Alzheimer's dementia and this number is expected to rise to about 13 million by 2050.<sup>2</sup> In the U.S., 11% of people aged 65 and older, including 5.1% of people 65-74, 13.2% of people 75-84, and 33.4% of people 85 and older have Alzheimer's dementia.<sup>2</sup> The prevalence of Alzheimer's dementia also varies by state where Alaska has the lowest percentage at 8.8% and Maryland has the highest prevalence at 12.9%. The 10 counties with the highest dementia prevalence are in Texas, California, South Carolina, Georgia, Louisiana, Mississippi, Maryland, New York, Maryland again, and Florida, in increasing order.<sup>2</sup> Not only is dementia prevalent in the U.S., but it is deadly for older populations as well, solidifying the importance of effective treatments and interventions.

Alzheimer's dementia is the sixth leading cause of death among people aged 65 and older in 2022 and is the leading cause of disability and morbidity in older adults.<sup>2</sup> Among Americans aged 70, 61% of those with dementia are expected to die before they turn 80 years old, compared to 30% of people without dementia. The range of mortality rates for each state in the U.S. is broad, from 18.1% in New York to 57.4% in Mississippi. This death rate has increased 141% from 2000 to 2021 (17.6 to 36 per 100,000 people). The high prevalence and mortality of dementia are among the main reasons why research into what causes and how to delay the onset of this disease is so crucial.

## *Pathology of Alzheimer's Disease and Related Dementias*

The neuropathological changes that culminate in dementia begin decades before symptoms appear in the affected individual. Dementia is usually characterized by neuronal damage, but each ADRD has a more specific biological pathway. Alzheimer's disease entails the accumulation of protein inside and outside neurons in the brain that can lead to neuron death, brain damage, inflammation, and atrophy of the brain. Specifically, the beta-amyloid protein, produced from the breakdown of the amyloid precursor, can clump in the brain at high concentrations and disrupt normal cell functioning.<sup>21</sup> Another specific pathology of ADRD includes neurofibrillary tangles, which form from the accumulation of tau protein. Normally, tau would stabilize microtubules inside neurons by binding to them, but when in abnormally high concentrations, tau will detach from microtubules and attach to other tau molecules, creating tangles inside the neuron and therefore hindering synaptic communication between neurons by blocking the neuron's transport system.<sup>21</sup> Another common cause of dementia is frontotemporal degeneration, where the temporal and frontal lobes of the brain shrink due to nerve cells dying in those areas. Lewy body disease is characterized by abnormal protein aggregations in neurons of the cortex, leading to dementia. Parkinson's disease is a common cause of dementia where aggregation of protein occurs deep in the brain in an area called the substantia nigra, causing nerve cell degeneration of cells that produce dopamine.<sup>19</sup> Thus, multiple neuropathologies contribute to dementia. An important step in dementia research is to determine an effective way to protect the brain to reduce dementia incidence. One way to approach this goal is to focus on marginalized and high-risk groups in intervention research.

## *Health Disparities in Dementia*

The risk of dementia varies significantly by race and ethnicity, even with issues of small sample sizes for historically marginalized groups. Non-Hispanic (NH) Black and Hispanic individuals tend to have a higher risk and a higher prevalence than NH White individuals for developing dementia.<sup>20,22</sup> This is likely due to the historical and continued marginalization of Black and Hispanic people in the U.S., creating disparities in life experiences, socioeconomic indicators, and health conditions between Black and Hispanic and White populations in their later stages of life. Discrimination has been shown to play a key role in these disparities<sup>23</sup>.

However, it is important to note that these marginalized communities that face the struggles that come with structural racism also have some protective factors built into their community engagement. Some cultures encourage families and friends to interact more with extended family and friends, even without blood ties, to foster a sense of community.<sup>24</sup> A way to address these health disparities is by treating all the affected groups for their symptoms and implementing interventions that are subpopulation-specific to each racial and cultural group to delay the onset of disease symptoms. Racial and ethnic health disparities represent one dimension of a broader disparity burden observed in dementia research and outcomes. Beyond race and ethnicity, sex and gender also shape dementia outcomes in distinct ways.

Although there are more women than men living with dementia, the mechanism for this sex-based disparity is intricate.<sup>25</sup> Biologically, women have been found to have more beta amyloid and tau in the brain and more mixed AD cerebrovascular pathology when compared to men.<sup>26</sup> In addition, women experience differences in psychological stress responses, inflammation, genetic background, and vascular disorders that increase the risk and progression of dementia's most common form, Alzheimer's disease.<sup>27</sup> Women could have a higher risk of

dementia due to having lower income and education, and higher rates of unemployment, depression, and sleep disorders.<sup>27</sup> These sex/gender disparities demonstrate the complexities that accompany cognitive decline and dementia.

### *Social Interaction and Social Support*

Social interaction can have positive effects on one's general health, and it also may help prevent dementia.<sup>28</sup> In fact, low social participation was listed as one of 12 risk factors that account for slightly less than half of dementia risk worldwide.<sup>5</sup> Participation in social interactions with family and peers is a natural part of human life and is usually conducted daily. Social support goes further than a mutually cordial relationship with a stranger.

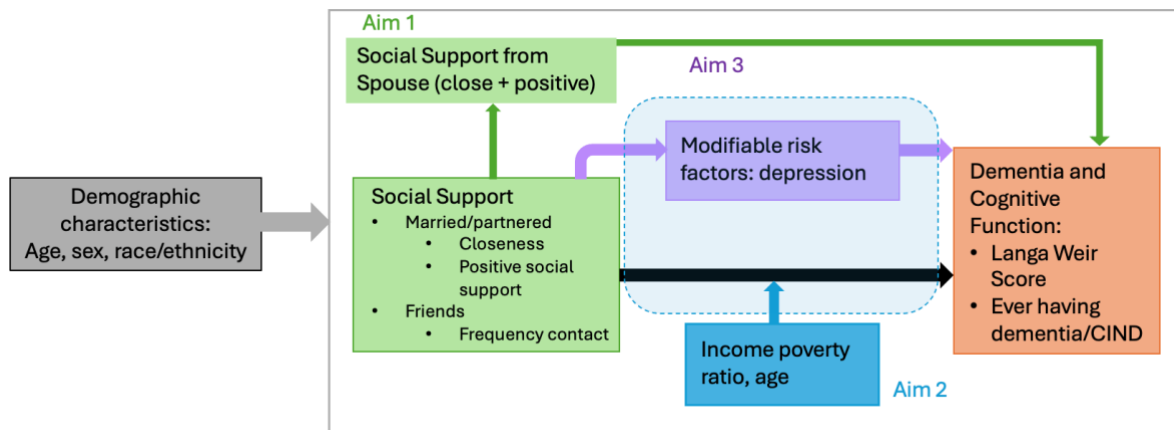
Spouses and friendships are relationships that go further than social interactions with strangers. Being married is associated with lower risk of developing dementia when compared to cohabitating, being divorced/separated, widowed, or never married.<sup>29</sup> Furthermore, having a higher level of perceived support in a marriage resulted in higher self-rated health and fewer functional limitations.<sup>30</sup> Establishing a relationship with a spouse that focuses on social support can benefit health overall and encourage the daily social interactions that also benefit health and disease risk. Interacting with friends in mid-life, compared to only family, has also been found to lower the likelihood of developing a dementia diagnosis later in life.<sup>31</sup> These interactions with friends were also found to improve cognitive performance, therefore further protecting against dementia.<sup>31</sup> Spousal and friendship social support are therefore more valuable than just social interactions alone, and should be considered when discussing potential interventions for dementia mitigation.

## *Interventions and Barriers*

Although there has been a recent approval of several new dementia medications that show promise in clinical trials, risk reduction using modifiable risk factors remains an important strategy to mitigate the expected rise in dementia cases.<sup>32</sup> Many clinical trials for Alzheimer's disease treatments have failed to decrease the disease's progression.<sup>33</sup> Interventions targeting modifiable risk factors earlier in life can delay the onset of symptoms and decrease the risk of developing dementia. For instance, active engagement in cognitive activities, higher educational attainment, frequent social contact with friends, a healthy relationship with a spouse/partner, participation in community cultural activities, regulating stress, and maintaining a normal BMI in midlife are all associated with reduced risk of dementia.<sup>4</sup> Despite the effectiveness of these interventions, there have yet to be race/ethnicity-specific interventions created to target a certain subpopulation's risk factors and unique characteristics.

## INNOVATION

This dissertation is innovative because it investigates two types of social support and how they individually and jointly affect dementia and cognitive functioning. It also uses a nationally representative dataset to accurately determine the effect of the chosen social support types on the United States population. The definition of spousal social support is unique as it uses both binary variables and indices to create a score for overall spousal social support. For friendship social support, both quantitative values, such as the number of friends, and qualitative values, such as the quality of friendships, are used to determine the overall support from friends. This study, unlike others, employs causal modeling methods, including g-computation, and novel techniques such as machine learning with causal forests.



**Figure. 1: Conceptual Diagram**

**Table 1: Summary Table for Aims of Dissertation**

| <b>Aim</b>                                                                                                                                                                                                          | <b>Gap</b>                                                                        | <b>Novelty</b>                                                                                       | <b>Exposure</b>                                                                  | <b>Outcome</b>                       | <b>Mediator/<br/>Moderator</b> | <b>Data</b> | <b>Method</b>                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------|--------------------------------|-------------|-------------------------------------------------------------------------------------|
| Examine the joint effects overall and stratified by race/ethnicity and sex/gender                                                                                                                                   | No generalizable results on joint effects of social support types on dementia     | Definitions of social support may better capture the true social support levels                      | Spousal social support (positive spousal social support and closeness to spouse) | Dementia risk and cognitive function | NA                             | HRS         | Pooled logistic regression                                                          |
| Identify potential factors that can modify the effect of friendship social support on the risk of dementia and estimate subgroup heterogenous effects across these factors overall and stratified by race/ethnicity | No literature on modification in friendship's effect on dementia                  | Uses newer machine learning techniques with the application of causality                             | Social support through contact with friends                                      | Dementia risk and cognitive function | SES, age                       | HRS         | Causal forest                                                                       |
| Examine the mediated effects and potential interactions between mediators overall and stratified by sex/gender                                                                                                      | Elevated depressive symptoms as mediators for spousal social support and dementia | Looks at spousal social support with elevated depressive symptoms that is known mediator of dementia | Spousal social support (positive spousal social support)                         | Dementia risk and cognitive function | Elevated depressive symptoms   | HRS         | Causal mediation analysis, parametric g-computation, and pooled logistic regression |

## ***CHAPTER 2: AIM 1: Investigating the Joint Effect of Positive Spousal Social Support and Closeness on Dementia Risk Among Older U.S. Adults***

### **INTRODUCTION**

Dementia is a major public health problem that burdens the U.S. healthcare system and can be a devastating diagnosis for patients and their family members. As there is currently no cure for dementia, identifying modifiable risk factors that can help reduce disease risk or delay its onset of disease is critical.<sup>19</sup> A vast body of literature has identified protective associations between social engagement and support with cognitive impairment and dementia incidence.

Social support can buffer the effects of stress by improving a person's ability to cope with challenges.<sup>34</sup> Individuals maintain more positive social relationships as they age and members of a social network pass away.<sup>35</sup> With these network changes and life transitions, individuals often come to rely most heavily on their spouse for frequent interaction and support.<sup>36</sup> Married individuals tend to exhibit better health outcomes than unmarried individuals, likely because of social support and more combined resources.<sup>37</sup> For those who are married or partnered, the spousal relationship can be a central source of social engagement and support.<sup>36</sup> Several studies have found not only consistent associations between marital quality and having better overall health, but marital quality can also predict poorer health outcomes.<sup>38</sup> Prior literature also reveals how marital conflicts were correlated to a decrease in the body's ability to heal wounds, and higher marital satisfaction was associated with lower blood pressure, lower stress, and less depression.<sup>39,40</sup> However, the associations between spousal support and other aspects of spousal relationship quality and dementia risk have seldom been explored. Additionally, how these associations vary by sex/gender and race and ethnicity remains elusive.

Dementia risk and social support structures vary significantly across racial, ethnic, and sex/gender groups, reflecting persistent and intersecting disparities. For instance, Non-Hispanic (NH) Black and Hispanic individuals exhibit disproportionately elevated rates of dementia prevalence and underdiagnosis relative to their Non-Hispanic (NH) White counterparts.<sup>2</sup> Additionally, more women than men are living with dementia, which may be partly attributed to their longer life expectancy.<sup>41</sup> Some race/ethnic subpopulations, such as Black individuals, have been reported to have strong social connections at older ages and get informal care in times of need.<sup>16</sup> Men benefited from co-residing family members and being married, whereas women benefited from community engagement and large social networks when focusing on dementia risk.<sup>7,42</sup> Also, women are more likely to rely on others in their social networks for support, and men are more likely to rely on their spouse as their main source of support.<sup>43,44</sup> This is due to men potentially having fewer social contacts outside of marriage than women do.<sup>44</sup> However, the ways these mechanisms may differ between married men and women or individuals of different racial/ethnic backgrounds remain insufficiently understood.

Although some studies found positive associations between various definitions of spousal social support and dementia, comprehensive research shows mixed findings. We wish to examine two potential definitions of spousal social support to determine whether the type of spousal social support affects the risk of dementia. In this study, we investigate the joint effects of positive spousal social support and closeness to spouse on dementia risk overall and by subgroups defined by race/ethnicity and sex/gender. We hypothesize that there is a synergistic effect between our selected social support definitions and dementia risk/cognitive decline. We also suspect the joint effect will be larger in minority racial/ethnic groups and for men compared to their counterparts.

## METHODS

### *Data source*

We used data from the Health and Retirement Study (HRS), a longitudinal study collected biennially that includes a representative sample of 20,000 people in the U.S. aged 50 or older and their spouses.<sup>45–47</sup> The study collects data on income, occupation, assets, pension plans, health insurance, disability, physical health and functioning, and cognitive functioning, as well as genomic, biomarker, and psychosocial data.<sup>46</sup> We used the data from the RAND longitudinal core interviews and leave-behind questionnaires from 2006 to 2020. The core dataset included information on respondents and their spouses' demographics and cognition. The leave-behind questionnaire was administered on a random 50% subsample of participants in the 2006 sample, collected every 4 years, and on the other 50% in the 2008 sample.<sup>48</sup> This questionnaire focused on topics related to well-being, lifestyle, social relationships, personality, work, and self-related beliefs.<sup>48</sup>

In particular, from the original 2006–2008 HRS data merged with the leave-behind questionnaires ( $N=13,064$ ), participants were excluded if they had dementia or cognitive impairment without dementia at analytic baseline ( $N=3,605$ ), were aged less than 50+ ( $N=290$ ), were not married/partnered ( $N=2,738$ ), or had missing values on questions related to positive spousal social support or closeness to spouse ( $N=528$ ) leaving an analytical sample size of 5,903 individuals (**Figure 1**).

### *Exposures*

We examined the joint effect that positive social support and closeness to a spouse have on dementia risk and defined these social support variables as follows:

**Positive social support** was based on three questions: “How much do they really understand the way you feel about things?”, “How much can you rely on them if you have a serious problem”, and “How much can you open up to them if you need to talk about your worries,” where each answer was reverse-coded so the questions were interpreted in the same direction where smaller numbers referred to less support. These questions were asked for spouses, friends, other family members, and children, but we focus on the relationship with the spouse. The four response options ranging from “not at all” to “a lot.” We averaged these three questions to get one response between 1 and 4 for the positive social support variable for a spousal relationship. We defined people with a score of 4 as very supported by a spouse and compared them with all scores lower than 4, as this has been used in other studies investigating social support.<sup>49</sup>

**Closeness to spouse** was based on the question: “How close is your relationship with your partner or spouse?”, with four response options ranging from “not at all close” to “very close.” We categorized responses as the very close vs. lower levels of closeness. This comparison is recommended by another study that examined social support in a similar dataset.<sup>49</sup>

### *Outcome*

The cognitive outcomes were defined using the Langa-Weir classification score.<sup>50</sup> We used the 27-point scale, which includes questions such as the serial sevens subtraction test, the immediate and delayed recall test, and the counting backwards test.<sup>50</sup> For the 27-point scale and based on the ADAMS, 12-27 was considered normal, 7-11 was cognitively impaired, not demented (CIND), and 0-6 was having dementia for respondents, whereas proxies had an 11-point scale with thresholds of 0-2, 3-5, and 6-11 for each respective group.<sup>50,51</sup> The proxy 11-

point scale included proxy assessment of memory, independent activities of daily living (IADL) limitations, and interviewer assessment of cognitive impairment.<sup>50</sup>

This score was used to identify the first wave at which a dementia/CIND diagnosis was recognized. This was used with follow-up time and censoring to create an event indicator variable, which identifies if the dementia/CIND event occurred in the interval or not.<sup>52</sup>

### *Covariates*

The potential confounders for the social support-dementia relationship based on the DAG are sex (male, female), age (years), race and ethnicity (NH White, NH Black, Hispanic), depression at baseline using the Center for Epidemiologic Studies Depression (CESD) scale (0-8), education (continuous), chronic disease number (0-8), ongoing chronic stress (continuous), and personality traits (openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism). We also included high physical activity ( $\text{MET} \geq 35$  vs.  $\text{MET} < 35$ ), financial strain (the income-poverty ratio with the individual difficulty of fulfilling monthly financial needs variables), and income-poverty ratio (continuous) as variables closely associated with the outcome of dementia or cognitive impairment to increase the precision of our estimates. (**Figure 2**). All covariates were measured at baseline.

### *Statistical analysis*

We estimated the joint effect of positive spousal social support and closeness to one's spouse on dementia and cognitive impairment risk using a pooled logistic regression model with an interaction term. The output, including the interaction term, was used to quantify whether the joint effect was larger or smaller than the sum of the separate effects on the additive scale by calculating the relative excess risk due to interaction (RERI) or attributable proportion (AP) or

on the multiplicative scale. We also accounted for censoring by applying inverse probability censoring weights to each observation. In the models, we included positive spousal support and closeness to spouse, their interaction, and a quadratic term for time to allow for flexible estimation, potential confounders, including sex, age, race, and ethnicity, depression, chronic disease count, education, ongoing chronic stress, and personality traits. We also included covariates associated with our outcome, including high physical activity, financial strain, and the income poverty ratio.

We used g-computation methods to predict survival probabilities at each person-time observation under four counterfactual scenarios—both exposures present, both absent, positive support only, and closeness only—and to estimate the cumulative incidence for all participants. Then we estimated the average survival using the cross-product Kaplan-Meier method and risk at each time point. Those risks were used to create risk difference and risk ratio contrasts, which were summarized as averages across the 14-year follow-up period and at its end. We reported these estimates to convey the effects of positive social support and closeness across the entire time period. We estimated standard errors and confidence intervals using bootstrap resampling and also calculated P-values for the interaction terms.<sup>53</sup> The discrete-time risks were used to make risk difference and risk ratio contrasts by year to plot on the cumulative risk across the 14 year follow up period. To account for missingness in our sample, multiple imputation by chained equations was implemented via miceRanger.<sup>54</sup> These steps were repeated for the stratified analyses for racial/ethnic subgroups and sex/gender groups. For the analyses, we used R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) via RStudio's Integrated Development Environment for R (Posit Software, PBC, Boston, MA).

We also estimated the effect of positive spousal support and closeness to spouse on dementia risk using the Expert model outcome in a sensitivity analysis. These results can be found in the supplemental materials.

## RESULTS

### *Sample characteristics*

The participants in this study had an average baseline age of 66 and contained more women than men. The population was majority NH White (86%) and had about 6.1% Hispanic and 5.8% NH Black individuals. Respondents who were completely retired (44%), engaged in low physical activity (71%), and did not experience financial strain (45%) were the most common in this sample. Forty percent of respondents reported the highest possible level of positive social support from their spouse (very supported). In contrast, 60% reported the highest level of closeness to their spouse (very close). Thirty-seven percent of respondents reported feeling both very supported and very close to their spouse (**Table 1**). Stratified descriptive statistics are available in the supplemental materials.

### *Separate and Joint Effects at the End of Follow-up: Risk Ratios and Risk Differences*

Reporting the highest level positive support from a spouse was associated with a lower risk of dementia (RR: 0.87, 95% CI: 0.71, 1.06), and reporting the highest level of closeness with one's spouse was associated with a higher risk of dementia (RR: 1.07, 95% CI: 1.01, 1.14) when compared to lower levels of support or closeness respectively. A similar pattern was found on the risk difference scale, where reporting being very supported by a spouse resulted in 6.25 fewer cases of dementia (RD: -6.25, 95% CI: -14.68, 2.18), and reporting being very close with a spouse resulted in 3.55 more cases of dementia (RD: 3.55, 95% CI: 0.56, 6.55).

Similar to the overall population, reporting among highest positive support from a spouse was associated with a lower risk of dementia (RR: 0.85, 95% CI: 0.67, 1.08) for White individuals, and reporting highest closeness with a spouse in the same group was associated with a greater risk of dementia (RR: 1.08, 95% CI: 0.98, 1.18) when compared to all lower levels of support or closeness respectively. There were 6.55 fewer dementia cases among White individuals who reported higher levels of positive support from a spouse when compared to all other lower levels (RD: -6.55, 95% CI: -15.85, 2.75), and 3.45 more cases when people reported higher closeness compared to lower levels (RD: 3.45, 95% CI: -0.93, 7.84). Among the Black participants, reporting having the highest support from a spouse was associated with a greater risk of dementia (RR: 1.17, 95% CI: 0.60, 2.28) and 12.37 more dementia cases when compared to lower levels of support (RD: 12.37, 95% CI: -23.88, 48.62). In the same group, reporting being very close with their spouse was associated with a moderately greater risk of dementia (RR: 1.08, 95% CI: 0.81, 1.44) and 4.9 more cases of dementia compared to lower levels of closeness (RD: 4.90, 95% CI: -11.92, 21.72). For Hispanic people, reporting high levels of positive social support was associated with a lower risk of dementia (RR: 0.85, 95% CI: 0.71, 1.06) and 13.91 fewer dementia cases than lower levels (RD: -13.91, 95% CI: -44.22, 16.41). The results for high levels of closeness among Hispanics were inconclusive. Among men, reporting high levels of positive social support was associated with a lower risk of dementia (RR: 0.82, 95% CI: 0.62, 1.08) and 8.77 fewer dementia cases than lower levels (RD: -8.77, 95% CI: -19.94, 2.40). When observing high closeness among men, the risk of dementia was higher (RR: 1.07, 95% CI: 0.94, 1.21), and 3.27 more cases occurred when compared to less closeness (RD: 3.27, 95% CI: -3.25, 9.79). For women, reporting high levels of positive social support was associated with a lower risk of dementia (RR: 0.90, 95% CI: 0.65, 1.24) and 4.25 fewer dementia

cases than lower levels (RD: -13.91, 95% CI: -17.16, 8.65). When observing high closeness among women, the same pattern appeared as men, where the risk of dementia was higher (RR: 1.08, 95% CI: 0.97, 1.20) and 3.58 more cases occurred when compared to less closeness (RD: 3.58, 95% CI: -1.56, 8.72) (**Table 2-5**).

The joint effects in the overall population were inconclusive for the fully adjusted model on both the risk difference and risk ratio scales. Our sensitivity analysis demonstrated similar results using the Expert model on both the risk difference and risk ratio scales.

For the racial/ethnic subpopulation, the joint effects among White individuals were inconclusive. For Black and Hispanic individuals, we observed lower risks of dementia from both being very supported and close with their spouse (RR: 0.81, 95% CI: 0.57, 1.16; RR: 0.95, 95% CI: 0.72, 1.26) and fewer dementia cases occurred when comparing to less supported and close individuals (RD: -10.53, 95% CI: -27.79, 6.72; RD: -2.57, 95% CI: -17.75, 12.61). Among men, reporting both positive social support from and closeness with their spouse was associated with a greater risk of dementia (RR: 1.06, 95% CI: 0.94, 1.19), and more dementia cases were observed when compared to individuals with less close relationships with their spouse (RD: 2.81, 95%CI: -3.15, 8.78). Conversely, among women, reporting both positive social support from and closeness with their spouse was associated with a lower risk of dementia (RR: 0.93, 95% CI: 0.84, 1.02) and fewer dementia cases than less supported individuals (RD: -3.35, 95% CI: -7.75, 1.04). The sensitivity analysis demonstrated similar results across the Hispanic, male, and female subpopulations, but inconclusive results for the Black subpopulation, likely due to small sample sizes in this population, since the Expert model requires all participants to be 70+.

All survival curves reflected the same direction of association as the risk ratios. (**eFigure 1-6**)

*Individual and Joint Effect on Average: Risk Ratios and Risk Differences*

The results were generally similar when estimating association with dementia risk averaged across the study period, with a few minor deviations. The effect of high positive support on the average risk of dementia in the overall population was inconclusive on both the risk difference and risk ratio scales. The same inconclusive results were found for all racial and ethnic subgroups when observing the effect of high positive support on the average risk of dementia.

All survival curves reflected the same direction of association as the risk ratios. (**Table 2-5. & eFigure 1-6.**)

## **DISCUSSION**

This research examined the joint effects of positive spousal social support and closeness to spouse on dementia risk overall and by race/ethnicity and sex/gender. Overall, reporting having the highest positive spousal social support was associated with lower dementia risk, and reporting having the highest closeness was associated with higher dementia risk. There was no variation by sex/gender or race/ethnicity. In the overall population, the joint effects of high positive spousal social support and closeness were highly imprecise, and thus, the results were inconclusive. For men, reporting having both high positive spousal social support and closeness was associated with a higher dementia risk. This was contrary to the results for women, as having both high positive spousal social support and closeness was associated with a lower dementia risk. Our results suggested nuanced insights into aspects of the spousal relationship

with dementia risk, including by sex/gender. The interaction analysis revealed that closeness to and positive social support from a spouse partially counteracted each other in terms of dementia risk. The opposing directions of these exposures could be explained by possible measurement error in the wording of survey questions used to capture spousal support exposure.

Traditionally, when dementia symptoms begin to appear, such as cognitive impairment, the presence and support from a spouse can positively affect the impaired spouse's health and well-being.<sup>55</sup> Spousal caregiving in the context of dementia-related cognitive decline is a well-studied phenomenon.<sup>56</sup> Findings of a higher dementia risk associated with high spousal support were unexpected and contrasted with prior literature on the protective associations between social support (not specific to support from spouses) and dementia risk. This counterintuitive finding could be driven by reverse causation, in which greater spousal closeness reflects caregiving dynamics in the context of early cognitive decline.

A potential mechanism that may explain the reverse causation observed in our analysis is the activation of social ties when a spouse observes their partner cognitively struggling, but no diagnosis is given. Certain chronic diseases have been found to lead to expansion or strengthening of social networks.<sup>57</sup> This would be expected in dementia, given the challenges that occur in accurately identifying and verifying the disease. The network of friends, family, and community, or the individual experiencing cognitive decline, could be motivated to activate their ties, especially close ties with spouses, for support and resources, and older adults may even expand their social networks to maintain their well-being.<sup>57</sup> Our study is in line with the hypothesis that social support has a duality in dementia risk due to the community-focused aspect of dementia diagnosis.

The results for men and women for the joint effect of having both high positive spousal social support and closeness made contrasting conclusions for dementia risk, with men having a higher risk and women having a lower risk. This is contrary to our expectations and demonstrates the complexity of social support for men versus women. A potential mechanism for the differing results between men and women is how connection patterns can differ between genders. With regards to mental health in general, females have been found to socialize to obtain support, while men have societal pressures of impassiveness and emotional limitation that make them more likely to internalize distress.<sup>58</sup> Also, women have been found to value emotional support given from their spouse more than their male counterparts, and how often they receive it will reflect how they feel positively about their marriage.<sup>59</sup> However, according to the American Psychological Association's stress survey in 2023, women were more likely to report family responsibilities and relationships as key stressors than men, and more likely to cancel social plans that could lead to more support.<sup>60</sup> The contradiction between women seeking support in relationships and relationships being a point of stress reveals the complexity social support can have within gender subgroups. Our results strengthen the idea that women who receive more support from their spouse have a lower risk of dementia.<sup>61</sup>

Current research on spousal social support and dementia is mixed, with some studies stating a protective effect and others stating no effect. However, some former and recent research shows the duality of social support on dementia risk due to reverse causation. A study examining social connectedness found that preclinical dementia symptoms could lead to stronger family relationships and lower social isolation.<sup>62</sup> Our results are in line with this conclusion but extend the existing literature by examining how a spousal relationship can impact dementia recognition. When targeting people with early dementia and their spouses, it was found that stresses

associated with caregiving and mood changes present in dementia symptoms could contribute to a decline in satisfaction with family relationships in later life.<sup>63,64</sup> This could explain how high support and closeness could be associated with higher dementia risk in our results, because symptoms can appear before dementia diagnosis, and the effects these symptoms have on their spouse and the individual can degrade the quality of support over time. Also, a delay between symptoms and diagnosis is frequently observed.<sup>65</sup> Finally, a study observing dementia diagnosis between unmarried and married individuals found that unmarried individuals had a delayed diagnosis—likely due to no immediate person recognizing preclinical symptoms—and found married individuals had more recognition of dementia from their partners.<sup>66</sup>

This study was not without limitations. First, we had small sample sizes for some higher-risk groups, such as Hispanic and NH Black individuals. These samples were further reduced when the analytic sample was restricted to married and partnered individuals, which accounts for the wider confidence intervals and the correspondingly inconclusive findings for these populations. Second, by restricting our analytic sample to married and partnered individuals, we may introduce selection bias. Although this restriction was necessary given that spousal support is only applicable within the context of a partnership, marital status itself is associated with dementia-related outcomes, and our study, by design, excluded individuals already living with dementia/CIND.<sup>67</sup> Inverse probability weighting was not a viable corrective strategy in this instance, as constructing an inverse probability of marriage weight would assume married/partnered status across the sample, thereby compromising the interpretability of the findings.

Additionally, HRS participants were older and likely susceptible to differential loss to follow-up by death or debilitating negative outcomes from comorbidities. This was addressed

through the application of IPCW, which accounts for censoring patterns inherent to this older study population. Third, the definition of positive social support from a spouse and of closeness to a spouse may not have captured the intended effect of social support since both survey questions were based on individuals' perceptions, and the definition of "close" may have different meanings to various individuals. Lastly, the Langa Weir score has been found to have lower classification accuracy in older adults compared to other scores.<sup>68</sup>

## **CONCLUSION**

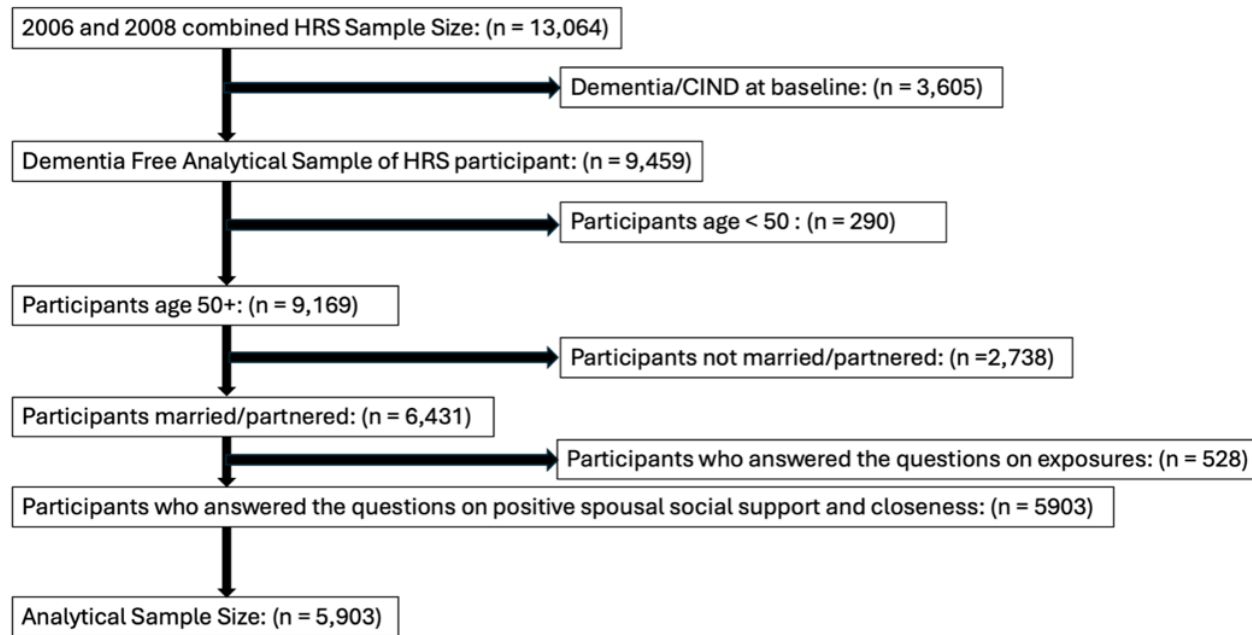
The role that spousal social support plays in dementia risk may be more nuanced and complex than previously thought. Social support appears to serve a dual role by reducing the risk of ADRD onset and promoting earlier identification of ADRD cases. The finding of increased risk of dementia among those reporting higher closeness could reflect reverse causation or possible information bias through the failure to capture the intended characteristic. Future research should examine social support and dementia risk across various stages of the life course to see if the same dual effects are observed. These future studies should also address additional sources of bias (e.g., marital selection) and evaluate potential mechanisms to interrogate the plausibility of observed associations.

## TABLES AND FIGURES

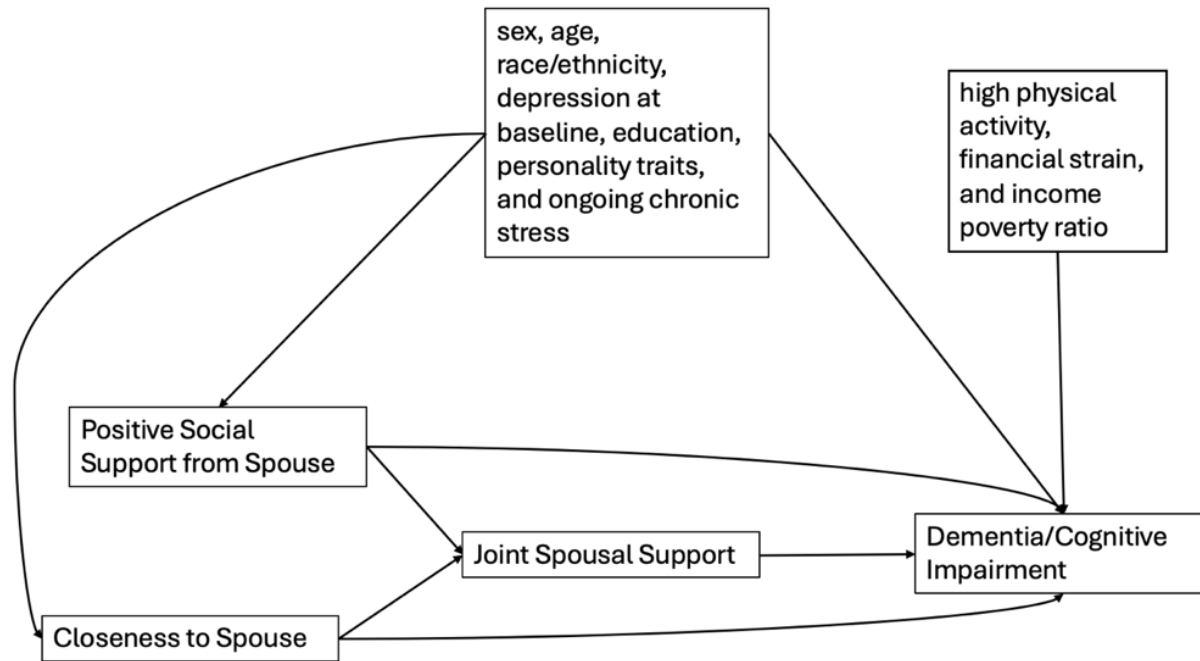
**Table 1.** Participant characteristics in the Health and Retirement Study (HRS) analytical sample of Married/Partnered Individuals in 2006-2020 (n = 5,903)

| <b>Characteristic</b>                                       | <b>N = 5,903</b>    |
|-------------------------------------------------------------|---------------------|
| <b>Age (Years)</b>                                          |                     |
| Mean (Min, Max)                                             | 66 (50, 95)         |
| <b>Male, n (%)</b>                                          |                     |
| Female                                                      | 3,133 (53%)         |
| Male                                                        | 2,770 (47%)         |
| <b>Race/Ethnicity (4 categories), n (%)</b>                 |                     |
| Hispanic                                                    | 363 (6.1%)          |
| Non-Hispanic Black                                          | 344 (5.8%)          |
| Non-Hispanic White                                          | 5,090 (86%)         |
| Other                                                       | 106 (1.8%)          |
| <b>Positive Support from Spouse (very supported), n (%)</b> |                     |
| High Positive Support                                       | 2,386 (40%)         |
| Low Positive Support                                        | 3,517 (60%)         |
| <b>Closeness to Spouse (very close), n (%)</b>              |                     |
| High Closeness                                              | 3,530 (60%)         |
| Low Closeness                                               | 2,373 (40%)         |
| <b>Joint Social Support from Spouse, n (%)</b>              |                     |
| High Support                                                | 2,157 (37%)         |
| Low Support                                                 | 3,746 (63%)         |
| <b>Participant Years of Education</b>                       |                     |
| Mean (Min, Max)                                             | 13.43 (0.00, 17.00) |
| <b>Income Poverty Ratio</b>                                 |                     |
| Mean (Min, Max)                                             | 6.6 (0.0, 680.0)    |
| <b>Retirement Status (3 categories), n (%)</b>              |                     |
| Completely retired                                          | 2,613 (44%)         |
| Not applicable                                              | 485 (8.2%)          |
| Not retired                                                 | 1,996 (34%)         |

| <b>Table 1.</b> Participant characteristics in the Health and Retirement Study (HRS)<br>analytical sample of Married/Partnered Individuals in 2006-2020 (n = 5,903) |                   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| <b>Characteristic</b>                                                                                                                                               | <b>N = 5,903</b>  |
| Partly retired                                                                                                                                                      | 806 (14%)         |
| <b>Chronic Disease Number</b>                                                                                                                                       |                   |
| Mean (Min, Max)                                                                                                                                                     | 1.79 (0.00, 7.00) |
| <b>CESD/Depression Score</b>                                                                                                                                        |                   |
| Mean (Min, Max)                                                                                                                                                     | 0.96 (0.00, 8.00) |
| <b>Openness to Experience Index</b>                                                                                                                                 |                   |
| Mean (Min, Max)                                                                                                                                                     | 2.99 (1.14, 4.00) |
| <b>Conscientiousness Index</b>                                                                                                                                      |                   |
| Mean (Min, Max)                                                                                                                                                     | 3.41 (1.20, 4.00) |
| <b>Extraversion Index</b>                                                                                                                                           |                   |
| Mean (Min, Max)                                                                                                                                                     | 3.23 (1.20, 4.00) |
| <b>Agreeableness Index</b>                                                                                                                                          |                   |
| Mean (Min, Max)                                                                                                                                                     | 3.54 (1.60, 4.00) |
| <b>Neuroticism Index</b>                                                                                                                                            |                   |
| Mean (Min, Max)                                                                                                                                                     | 2.02 (1.00, 4.00) |
| <b>High Physical Activity, n (%)</b>                                                                                                                                |                   |
| High Physical Activity                                                                                                                                              | 1,728 (29%)       |
| Low Physical Activity                                                                                                                                               | 4,175 (71%)       |
| <b>Married/Partnered, n (%)</b>                                                                                                                                     |                   |
| Married/Partnered                                                                                                                                                   | 5,903 (100%)      |
| <b>Financial Strain, n (%)</b>                                                                                                                                      |                   |
| Not at all difficult                                                                                                                                                | 2,607 (45%)       |
| Not very difficult                                                                                                                                                  | 1,942 (33%)       |
| Somewhat difficult                                                                                                                                                  | 1,017 (17%)       |
| Very difficult                                                                                                                                                      | 211 (3.6%)        |
| Completely difficult                                                                                                                                                | 51 (0.9%)         |
| <b>Chronic Stress Scale</b>                                                                                                                                         |                   |
| Mean (Min, Max)                                                                                                                                                     | 11.7 (2.0, 32.0)  |



**Figure 1.** Flow Diagram for Analytic Sample using Health and Retirement Study (HRS) core and leave behind questionnaires



**Figure 2.** Directed acyclic graph for joint effects of positive spousal social support and closeness to spouse on dementia and CIND

| <b>Table 2.</b> Average Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, Overall Population, N=5,903, HRS, 2006-2020 |                                        |                         |                                        |                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|-------------------------|----------------------------------------|-------------------------|
|                                                                                                                                                                                       | Age Adjusted <sup>1</sup>              |                         | Fully Adjusted <sup>2</sup>            |                         |
|                                                                                                                                                                                       | Risk difference, RD (per 100) (95% CI) | Risk ratio, RR (95% CI) | Risk difference, RD (per 100) (95% CI) | Risk ratio, RR (95% CI) |
| Positive Spousal Support                                                                                                                                                              | 0.04 (-7.88, 7.96)                     | 1.08 (0.85, 1.36)       | 0.15 (-7.36, 7.65)                     | 1.08 (0.86, 1.36)       |
| Closeness with Spouse                                                                                                                                                                 | 2.87 (0.14, 5.60)                      | 1.09 (0.99, 1.20)       | 3.04 (0.20, 5.89)                      | 1.10 (1.00, 1.22)       |
| Joint effect                                                                                                                                                                          | -0.93 (-3.81, 1.95)                    | 0.99 (0.90, 1.09)       | 1.12 (-1.87, 4.10)                     | 1.06 (0.96, 1.17)       |

model 1: adjusted for age  
model 2: adjusted for sex, age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio  
P-value for interaction = 0.15

**Table 3.** End of Follow-up Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, Overall Population, N=5,903, HRS, 2006-2020

|                          | Age Adjusted1                          |                         | Fully Adjusted2                        |                         |
|--------------------------|----------------------------------------|-------------------------|----------------------------------------|-------------------------|
|                          | Risk difference, RD (per 100) (95% CI) | Risk ratio, RR (95% CI) | Risk difference, RD (per 100) (95% CI) | Risk ratio, RR (95% CI) |
| Positive Spousal Support | -6.63 ( -15.45, 2.18)                  | 0.86 (0.70, 1.06)       | -6.25 (-14.68, 2.18)                   | 0.87 (0.71, 1.06)       |
| Closeness with Spouse    | 3.33 (0.54, 6.12)                      | 1.07 (1.01, 1.13)       | 3.55 (0.56, 6.55)                      | 1.07 (1.01, 1.14)       |
| Joint effect             | -2.22 (-5.62, 1.18)                    | 0.96 (0.89, 1.03)       | 0.40 (-3.26, 4.07)                     | 1.01 (0.93, 1.09)       |

model 1: adjusted for age  
model 2: adjusted for sex, age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio  
P-value for interaction = 0.78

**Table 4a.** Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, NH White Population, N=5,090, HRS, 2006-2020

|                          | Average <sup>1</sup>                   |                         | End <sup>2</sup>                       |                         |
|--------------------------|----------------------------------------|-------------------------|----------------------------------------|-------------------------|
|                          | Risk difference, RD (per 100) (95% CI) | Risk ratio, RR (95% CI) | Risk difference, RD (per 100) (95% CI) | Risk ratio, RR (95% CI) |
| Positive Spousal Support | -0.72 (-9.29, 7.86)                    | 1.03 (0.78, 1.37)       | -6.55 (-15.85, 2.75)                   | 0.85 (0.67, 1.08)       |
| Closeness with Spouse    | 2.56 ( -1.06, 6.18)                    | 1.07 (0.95, 1.21)       | 3.45 (-0.93,7.84)                      | 1.08 (0.98, 1.18)       |
| Joint effect             | 1.12 ( -2.19, 4.44)                    | 1.04 (0.93, 1.17)       | 1.14 (-2.78, 5.06)                     | 1.03 (0.94, 1.12)       |

model 1: average of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio

model 2: end of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio  
P-value for interaction for Average = 0.45  
P-value for interaction for End = 0.70

**Table 4b.** Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, NH Black Population, N=344, HRS, 2006-2020

|                          | Average <sup>1</sup>                      |                            | End <sup>2</sup>                          |                            |
|--------------------------|-------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                          | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support | 16.64 ( -13.97, 47.25)                    | 0.63 (0.00, 971.39)        | 12.37 (-23.88, 48.62)                     | 1.17 (0.60, 2.28)          |
| Closeness with Spouse    | 6.52 ( -6.43, 19.47)                      | 1.30 (0.83, 2.03)          | 4.90 (-11.92, 21.72)                      | 1.08 (0.81, 1.44)          |
| Joint effect             | -7.81 ( -22.26, 6.63)                     | 0.83 (0.37, 1.85)          | -10.53 (-27.79, 6.72)                     | 0.81(0.57, 1.16)           |

model 1: average of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio  
model 2: end of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio  
P-value for interaction for Average = 0.98  
P-value for interaction for End = 0.97

**Table 4c.** Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, Hispanic Population, N=363, HRS, 2006-2020

|                          | Average <sup>1</sup>                      |                            | End <sup>2</sup>                          |                            |
|--------------------------|-------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                          | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support | -5.43 (-34.62, 23.76)                     | 0.40 (0.00, 318.01)        | -13.91 (-44.22, 16.41)                    | 0.71 (0.34, 1.51)          |
| Closeness with Spouse    | -2.15 (-14.56, 10.25)                     | 0.82 (0.45, 1.50)          | -0.67 (-17.94, 16.61)                     | 0.98 (0.71, 1.35)          |
| Joint effect             | 2.81 (-10.26, 15.88)                      | 1.19 (0.79, 1.79)          | -2.57 (-17.75, 12.61)                     | 0.95 (0.72, 1.26)          |

model 1: average of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio

model 2: end of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio  
P-value for interaction for Average = 0.72  
P-value for interaction for End = 0.76

**Table 5a.** Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, Male Population, N=2,770, HRS, 2006-2020

|                          | Average <sup>1</sup>                      |                            | End <sup>2</sup>                          |                            |
|--------------------------|-------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                          | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support | -2.83 (-12.49, 6.83)                      | 0.96 (0.71, 1.31)          | -8.77 ( -19.94, 2.40)                     | 0.82 (0.62, 1.08)          |
| Closeness with Spouse    | 1.22 ( -3.81, 6.26)                       | 1.03 (0.89, 1.19)          | 3.27 (-3.25, 9.79)                        | 1.07 (0.94, 1.21)          |
| Joint effect             | 3.07 ( -1.76, 7.89)                       | 1.10 (0.96, 1.27)          | 2.81 ( -3.15, 8.78)                       | 1.06 (0.94, 1.19)          |

model 1: average of follow up and adjusted for age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio

model 2: end of follow up and adjusted for age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio

P-value for interaction for Average = 0.78

P-value for interaction for End = 0.38

**Table 5b.** Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, Female Population, N=3,133, HRS, 2006-2020

|                          | Average <sup>1</sup>                         |                            | End <sup>2</sup>                          |                            |
|--------------------------|----------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                          | Risk difference,<br>RD (per 100)<br>(95% CI) | Risk ratio, RR<br>(95% CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support | 1.81 (-9.10, 12.72)                          | 1.14 (0.79, 1.65)          | -4.25 (-17.16, 8.65)                      | 0.90 (0.65, 1.24)          |
| Closeness with Spouse    | 3.73 ( -0.23, 7.69)                          | 1.14 (0.98, 1.32)          | 3.58 (-1.56, 8.72)                        | 1.08 (0.97, 1.20)          |
| Joint effect             | -2.49 ( -6.21, 1.22)                         | 0.92 (0.79, 1.08)          | -3.35 (-7.75, 1.04)                       | 0.93 (0.84, 1.02)          |

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model 1: average of follow up and adjusted for age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio  
model 2: end of follow up and adjusted for age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio  
P-value for interaction for Average = 0.06  
P-value for interaction for End = 0.58

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## APPENDIX

### *Covariate details*

Personality traits were defined using five indexes: openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism. These variables make up the “Big 5” personality traits, and the scales are based on the Midlife Development in the U.S. and the International Personality Item Pool.<sup>69</sup> These items were scored from 1 to 4 and reverse-coded, with 1 indicating “not at all” and 4 indicating “a lot”.<sup>69</sup> Chronic stress was captured with an 8-item scale on a 4-point Likert scale (1 = “No, didn’t happen”, 4 = “Yes, very upsetting”) using the following questions: ongoing health problems (in yourself); ongoing physical or emotional problems (in spouse or child); ongoing problems with alcohol or drug use in family member; ongoing difficulties at work; ongoing financial strain; ongoing housing problems; ongoing problems in a close relationship; and helping at least one sick, limited, or frail family member or friend on a regular basis.

### *Stratified Table 1*

There are some notable differences in racial and ethnic characteristics. White participants were older (66) and reported more positive social support and greater closeness to their spouse (42% and 61%, respectively) than their non-white counterparts. Hispanic individuals had the lowest years of education participation (10.7), the highest number of not retired individuals (44%), the lowest chronic disease number (1.53), but the highest levels of depression (1.51). Black and Hispanic individuals had substantially lower

income poverty ratio scores and higher chronic stress levels than their white counterparts. Black participants had more chronic diseases, the lowest levels of high physical activity, the highest percentage of current smokers, but the lowest percentage of high-risk drinking behaviors, than the other two racial/ethnic groups. Black individuals also had lower levels of high spousal social support from their spouse when compared to Hispanic and White participants. (**eTable 1**).

The differences between male and female characteristics in this sample included age, positive social support from a spouse, closeness to a spouse, retirement, depression, exercise, smoking habits, drinking habits, and stress. Females were younger, had less positive social support and closeness to their spouse, had higher levels of depression, partook less often in smoking and risky alcohol behaviors, and experienced more stress than men. Men were more likely to be retired and exercise at a higher level (**eTable 2**).

| <b>eTable 1. Descriptive Statistics by Race and Ethnicity</b> |                             |                                           |                                             |
|---------------------------------------------------------------|-----------------------------|-------------------------------------------|---------------------------------------------|
| <b>Characteristic</b>                                         | <b>Hispanic<br/>N = 363</b> | <b>Non-Hispanic<br/>Black<br/>N = 344</b> | <b>Non-Hispanic<br/>White<br/>N = 5,090</b> |
| <b>Age (Years)</b>                                            |                             |                                           |                                             |
| Mean (Min, Max)                                               | 63 (50, 86)                 | 64 (50, 86)                               | 66 (50, 95)                                 |
| <b>Male, n (%)</b>                                            |                             |                                           |                                             |
| Female                                                        | 191 (53%)                   | 192 (56%)                                 | 2,700 (53%)                                 |
| Male                                                          | 172 (47%)                   | 152 (44%)                                 | 2,390 (47%)                                 |
| <b>Positive Support from Spouse (very supported), n (%)</b>   |                             |                                           |                                             |
| High Positive Support                                         | 122 (34%)                   | 97 (28%)                                  | 2,129 (42%)                                 |
| Low Positive Support                                          | 241 (66%)                   | 247 (72%)                                 | 2,961 (58%)                                 |
| <b>Closeness to Spouse (very close), n (%)</b>                |                             |                                           |                                             |

**eTable 1.** Descriptive Statistics by Race and Ethnicity

| <b>Characteristic</b>                          | <b>Hispanic<br/>N = 363</b> | <b>Non-Hispanic<br/>Black<br/>N = 344</b> | <b>Non-Hispanic<br/>White<br/>N = 5,090</b> |
|------------------------------------------------|-----------------------------|-------------------------------------------|---------------------------------------------|
| High Closeness                                 | 172 (47%)                   | 175 (51%)                                 | 3,121 (61%)                                 |
| Low Closeness                                  | 191 (53%)                   | 169 (49%)                                 | 1,969 (39%)                                 |
| <b>Participant Years of Education</b>          |                             |                                           |                                             |
| Mean (Min, Max)                                | 10.70 (0.00, 17.00)         | 13.04 (1.00, 17.00)                       | 13.64 (0.00, 17.00)                         |
| <b>Income Poverty Ratio</b>                    |                             |                                           |                                             |
| Mean (Min, Max)                                | 4.1 (0.0, 32.5)             | 4.7 (0.0, 52.4)                           | 6.9 (0.0, 680.0)                            |
| <b>Retirement Status (3 categories), n (%)</b> |                             |                                           |                                             |
| Completely retired                             | 119 (33%)                   | 142 (41%)                                 | 2,317 (46%)                                 |
| Not applicable                                 | 54 (15%)                    | 21 (6.1%)                                 | 406 (8.0%)                                  |
| Not retired                                    | 160 (44%)                   | 127 (37%)                                 | 1,653 (32%)                                 |
| Partly retired                                 | 30 (8.3%)                   | 54 (16%)                                  | 711 (14%)                                   |
| <b>Chronic Disease Number</b>                  |                             |                                           |                                             |
| Mean (Min, Max)                                | 1.53 (0.00, 6.00)           | 2.05 (0.00, 6.00)                         | 1.80 (0.00, 7.00)                           |
| <b>CESD/Depression Score</b>                   |                             |                                           |                                             |
| Mean (Min, Max)                                | 1.51 (0.00, 8.00)           | 1.06 (0.00, 8.00)                         | 0.91 (0.00, 8.00)                           |
| <b>Openness to Experience Index</b>            |                             |                                           |                                             |
| Mean (Min, Max)                                | 2.87 (1.29, 4.00)           | 3.05 (1.25, 4.00)                         | 2.99 (1.14, 4.00)                           |
| <b>Conscientiousness Index</b>                 |                             |                                           |                                             |
| Mean (Min, Max)                                | 3.35 (2.00, 4.00)           | 3.40 (1.40, 4.00)                         | 3.42 (1.20, 4.00)                           |
| <b>Extraversion Index</b>                      |                             |                                           |                                             |
| Mean (Min, Max)                                | 3.20 (1.60, 4.00)           | 3.33 (1.60, 4.00)                         | 3.22 (1.20, 4.00)                           |
| <b>Agreeableness Index</b>                     |                             |                                           |                                             |
| Mean (Min, Max)                                | 3.50 (2.00, 4.00)           | 3.60 (1.60, 4.00)                         | 3.54 (1.60, 4.00)                           |
| <b>Neuroticism Index</b>                       |                             |                                           |                                             |
| Mean (Min, Max)                                | 2.26 (1.00, 4.00)           | 1.88 (1.00, 4.00)                         | 2.01 (1.00, 4.00)                           |
| <b>High Physical Activity, n (%)</b>           |                             |                                           |                                             |
| High Physical Activity                         | 100 (28%)                   | 73 (21%)                                  | 1,522 (30%)                                 |
| Low Physical Activity                          | 263 (72%)                   | 271 (79%)                                 | 3,568 (70%)                                 |
| <b>Married/Partnered, n (%)</b>                |                             |                                           |                                             |

**eTable 1.** Descriptive Statistics by Race and Ethnicity

| <b>Characteristic</b>                                      | <b>Hispanic<br/>N = 363</b> | <b>Non-Hispanic<br/>Black<br/>N = 344</b> | <b>Non-Hispanic<br/>White<br/>N = 5,090</b> |
|------------------------------------------------------------|-----------------------------|-------------------------------------------|---------------------------------------------|
| Married/Partnered                                          | 363 (100%)                  | 344 (100%)                                | 5,090 (100%)                                |
| <b>Financial Strain, n (%)</b>                             |                             |                                           |                                             |
| Not at all difficult                                       | 88 (25%)                    | 88 (26%)                                  | 2,396 (48%)                                 |
| Not very difficult                                         | 137 (39%)                   | 127 (38%)                                 | 1,639 (33%)                                 |
| Somewhat difficult                                         | 95 (27%)                    | 98 (29%)                                  | 804 (16%)                                   |
| Very difficult                                             | 24 (6.8%)                   | 19 (5.6%)                                 | 161 (3.2%)                                  |
| Completely difficult                                       | 7 (2.0%)                    | 6 (1.8%)                                  | 35 (0.7%)                                   |
| <b>Chronic Stress Scale</b>                                |                             |                                           |                                             |
| Mean (Min, Max)                                            | 12.1 (5.0, 22.0)            | 12.0 (7.0, 26.0)                          | 11.6 (2.0, 32.0)                            |
| <b>Ever having dementia/cind after<br/>baseline, n (%)</b> | 133 (37%)                   | 127 (37%)                                 | 1,202 (24%)                                 |

**eTable 2.** Descriptive Statistics by Sex/Gender

| <b>Characteristic</b>                                       | <b>Female<br/>N = 3,133</b> | <b>Male<br/>N = 2,770</b> |
|-------------------------------------------------------------|-----------------------------|---------------------------|
| <b>Age (Years)</b>                                          |                             |                           |
| Mean (Min, Max)                                             | 65 (50, 91)                 | 67 (50, 95)               |
| <b>Race/Ethnicity (4 categories), n (%)</b>                 |                             |                           |
| Hispanic                                                    | 191 (6.1%)                  | 172 (6.2%)                |
| Non-Hispanic Black                                          | 192 (6.1%)                  | 152 (5.5%)                |
| Non-Hispanic White                                          | 2,700 (86%)                 | 2,390 (86%)               |
| Other                                                       | 50 (1.6%)                   | 56 (2.0%)                 |
| <b>Positive Support from Spouse (very supported), n (%)</b> |                             |                           |
| High Positive Support                                       | 1,054 (34%)                 | 1,332 (48%)               |
| Low Positive Support                                        | 2,079 (66%)                 | 1,438 (52%)               |
| <b>Closeness to Spouse (very close), n (%)</b>              |                             |                           |
| High Closeness                                              | 1,719 (55%)                 | 1,811 (65%)               |

**eTable 2.** Descriptive Statistics by Sex/Gender

| <b>Characteristic</b>                          | <b>Female</b><br>N = 3,133 | <b>Male</b><br>N = 2,770 |
|------------------------------------------------|----------------------------|--------------------------|
| Low Closeness                                  | 1,414 (45%)                | 959 (35%)                |
| <b>Participant Years of Education</b>          |                            |                          |
| Mean (Min, Max)                                | 13.23 (0.00, 17.00)        | 13.65 (0.00, 17.00)      |
| <b>Income Poverty Ratio</b>                    |                            |                          |
| Mean (Min, Max)                                | 6.4 (0.0, 127.3)           | 6.9 (0.0, 680.0)         |
| <b>Retirement Status (3 categories), n (%)</b> |                            |                          |
| Completely retired                             | 1,293 (41%)                | 1,320 (48%)              |
| Not applicable                                 | 416 (13%)                  | 69 (2.5%)                |
| Not retired                                    | 1,077 (34%)                | 919 (33%)                |
| Partly retired                                 | 346 (11%)                  | 460 (17%)                |
| <b>Chronic Disease Number</b>                  |                            |                          |
| Mean (Min, Max)                                | 1.75 (0.00, 7.00)          | 1.84 (0.00, 7.00)        |
| <b>CESD/Depression Score</b>                   |                            |                          |
| Mean (Min, Max)                                | 1.07 (0.00, 8.00)          | 0.83 (0.00, 8.00)        |
| <b>Openness to Experience Index</b>            |                            |                          |
| Mean (Min, Max)                                | 2.98 (1.25, 4.00)          | 3.00 (1.14, 4.00)        |
| <b>Conscientiousness Index</b>                 |                            |                          |
| Mean (Min, Max)                                | 3.47 (1.40, 4.00)          | 3.35 (1.20, 4.00)        |
| <b>Extraversion Index</b>                      |                            |                          |
| Mean (Min, Max)                                | 3.27 (1.20, 4.00)          | 3.18 (1.20, 4.00)        |
| <b>Agreeableness Index</b>                     |                            |                          |
| Mean (Min, Max)                                | 3.66 (1.60, 4.00)          | 3.41 (1.60, 4.00)        |
| <b>Neuroticism Index</b>                       |                            |                          |
| Mean (Min, Max)                                | 2.09 (1.00, 4.00)          | 1.95 (1.00, 4.00)        |
| <b>High Physical Activity, n (%)</b>           |                            |                          |
| High Physical Activity                         | 823 (26%)                  | 905 (33%)                |
| Low Physical Activity                          | 2,310 (74%)                | 1,865 (67%)              |
| <b>Married/Partnered, n (%)</b>                |                            |                          |
| Married/Partnered                              | 3,133 (100%)               | 2,770 (100%)             |
| <b>Financial Strain, n (%)</b>                 |                            |                          |

| <b>eTable 2. Descriptive Statistics by Sex/Gender</b>  |                            |                          |
|--------------------------------------------------------|----------------------------|--------------------------|
| <b>Characteristic</b>                                  | <b>Female</b><br>N = 3,133 | <b>Male</b><br>N = 2,770 |
| Not at all difficult                                   | 1,345 (44%)                | 1,262 (46%)              |
| Not very difficult                                     | 1,027 (33%)                | 915 (33%)                |
| Somewhat difficult                                     | 565 (18%)                  | 452 (16%)                |
| Very difficult                                         | 121 (3.9%)                 | 90 (3.3%)                |
| Completely difficult                                   | 30 (1.0%)                  | 21 (0.8%)                |
| <b>Chronic Stress Scale</b>                            |                            |                          |
| Mean (Min, Max)                                        | 12.0 (2.0, 32.0)           | 11.3 (2.0, 26.0)         |
| <b>Ever having dementia/CIND after baseline, n (%)</b> | 721 (23%)                  | 767 (28%)                |

### *Interactive Terms*

A purely additive interaction between closeness and positive support from spouse at the end of follow up was observed for the all populations given the p-values. (**eTable 3.**) A purely additive interaction between closeness and positive support from spouse at the average of follow up was observed for the Overall, White, Black, Hispanic, and male populations given the p-values. The female population exhibited, on average, an antagonistic effect of closeness and positive support from the spouse on average. (**eTable 4.**)

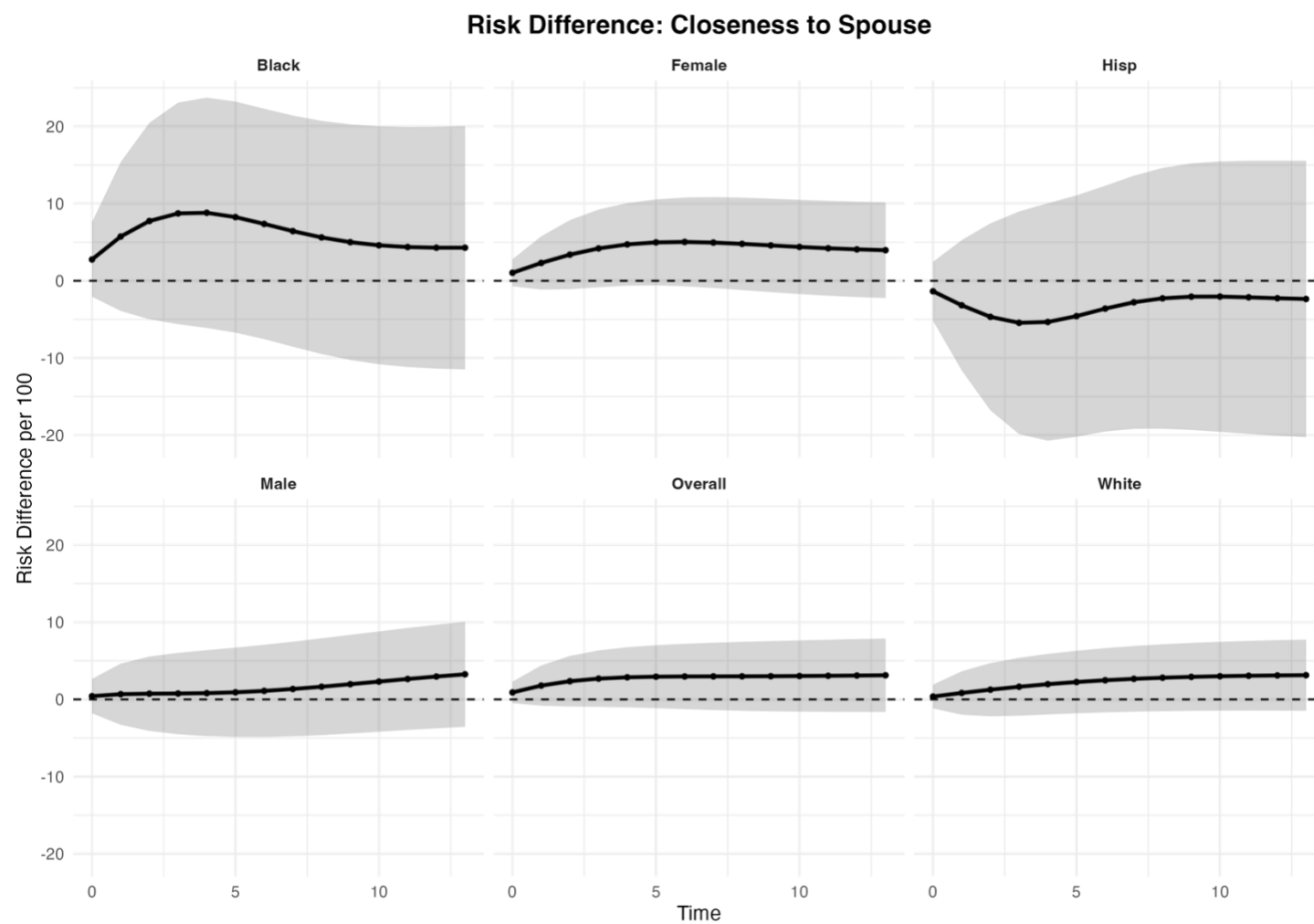
| <b>eTable 3. Relative Excess Risk due to Interaction (RERI) or Attributable Proportion (AP) for Subgroups for End Time</b> |                        |                 |                |
|----------------------------------------------------------------------------------------------------------------------------|------------------------|-----------------|----------------|
| <b>Subgroup</b>                                                                                                            | <b>RERI/AP for End</b> | <b>Estimate</b> | <b>P-value</b> |
| Overall                                                                                                                    | RERI (end)             | 0.03            | 0.78           |
|                                                                                                                            | AP (end)               | 0.03            | 0.78           |
| NH White                                                                                                                   | RERI (end)             | 0.06            | 0.70           |
|                                                                                                                            | AP (end)               | 0.06            | 0.70           |

|          |            |       |      |
|----------|------------|-------|------|
| NH Black | RERI (end) | 0.09  | 0.97 |
|          | AP (end)   | 0.11  | 0.97 |
| Hispanic | RERI (end) | 0.13  | 0.76 |
|          | AP (end)   | 0.13  | 0.76 |
| Male     | RERI (end) | 0.15  | 0.38 |
|          | AP (end)   | 0.14  | 0.38 |
| Female   | RERI (end) | -0.12 | 0.58 |
|          | AP (end)   | -0.12 | 0.58 |

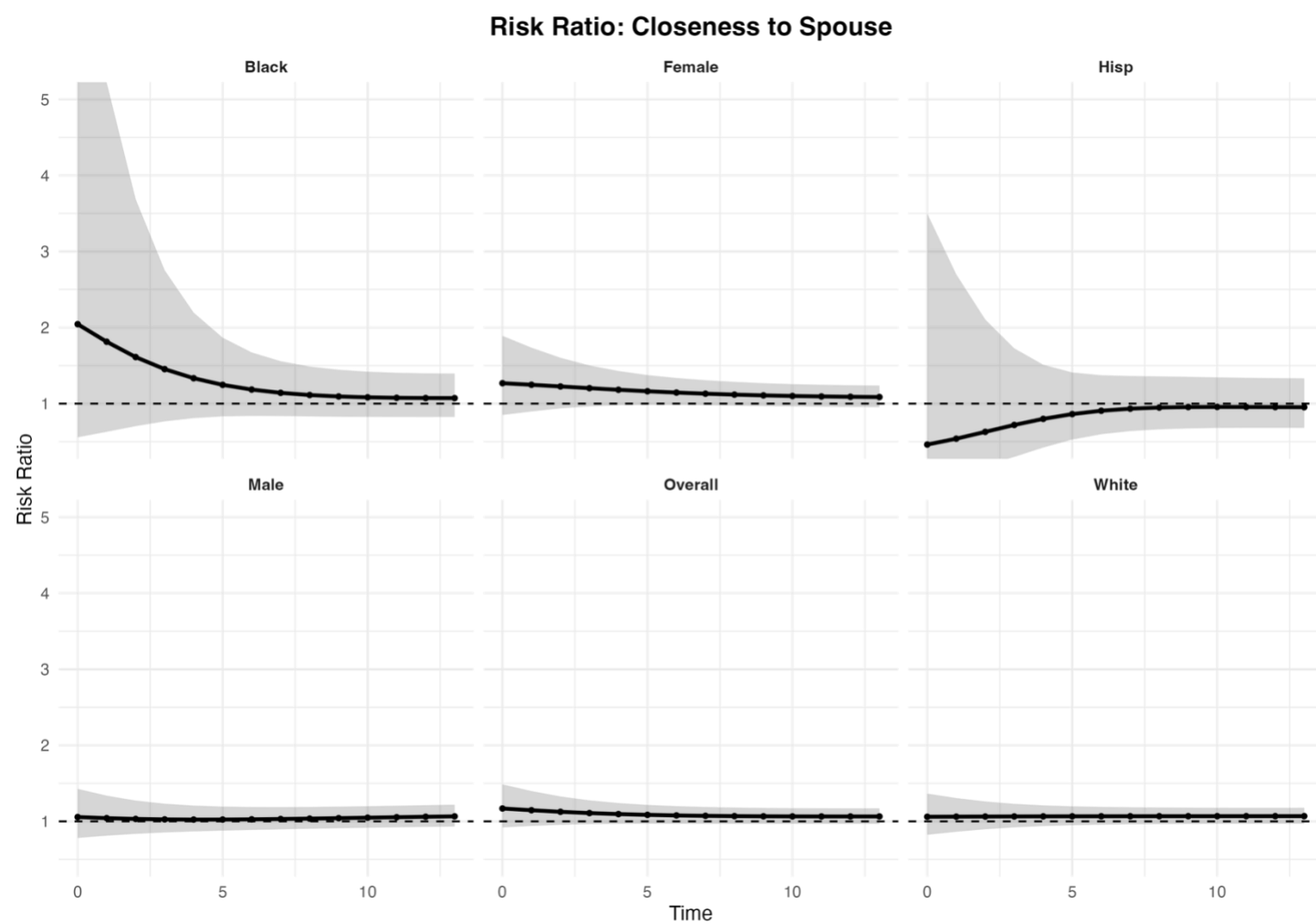
**eTable 4.** Relative Excess Risk due to Interaction (RERI) or Attributable Proportion (AP) for Subgroups for Average Time

| Subgroup | Interaction Term for |          | P-value |
|----------|----------------------|----------|---------|
|          | Average              | Estimate |         |
| Overall  | RERI (average)       | -0.18    | 0.15    |
|          | AP (average)         | -0.17    | 0.15    |
| NH White | RERI (average)       | -0.14    | 0.45    |
|          | AP (average)         | -0.14    | 0.45    |
| NH Black | RERI (average)       | 0.08     | 0.98    |
|          | AP (average)         | 0.09     | 0.98    |
| Hispanic | RERI (average)       | 0.50     | 0.72    |
|          | AP (average)         | 0.41     | 0.72    |
| Male     | RERI (average)       | 0.06     | 0.78    |
|          | AP (average)         | 0.05     | 0.78    |
| Female   | RERI (average)       | -0.49    | 0.06*   |
|          | AP (average)         | -0.51    | 0.06*   |

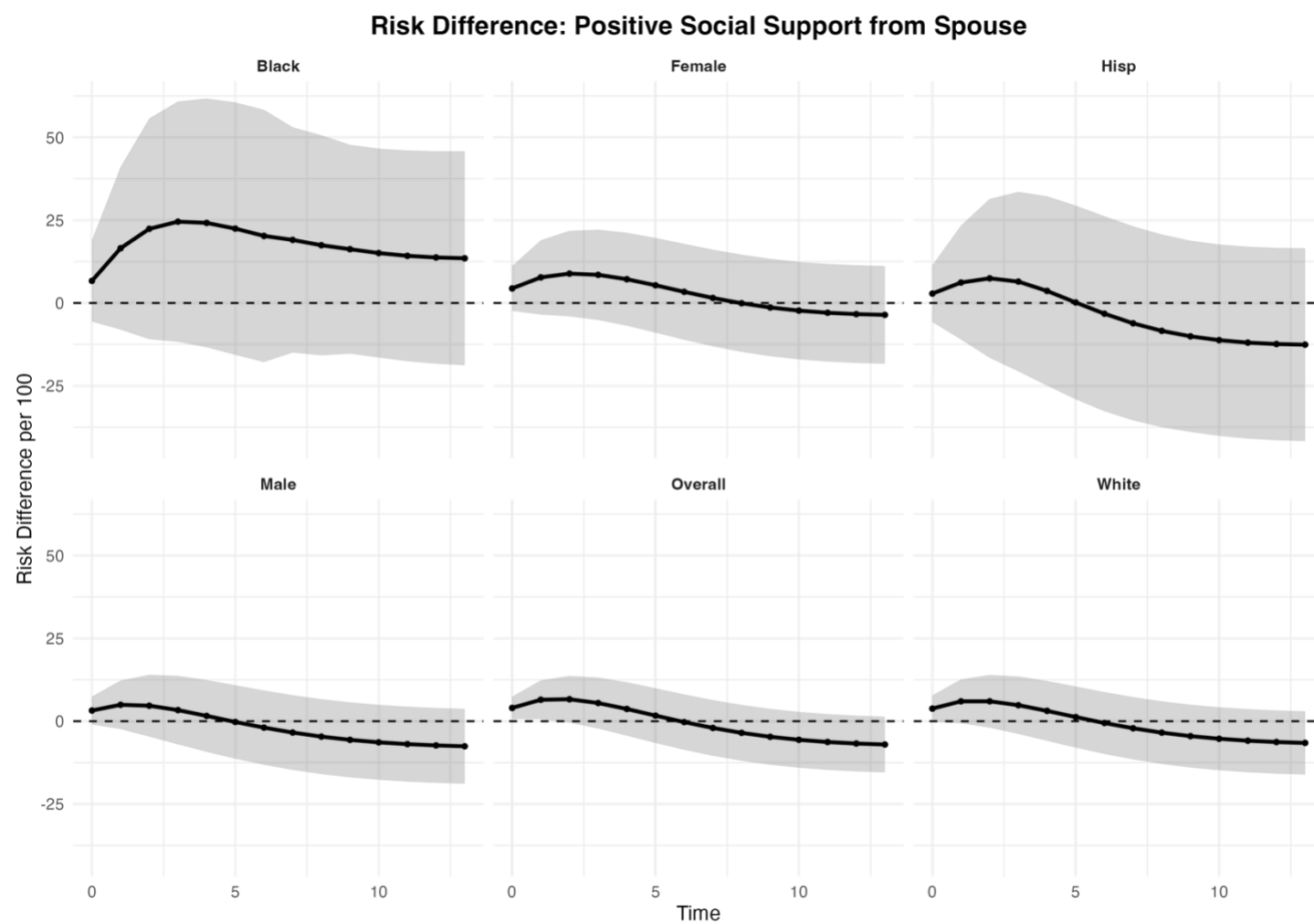
\*p-value < 0.1 indicating more than additive interaction



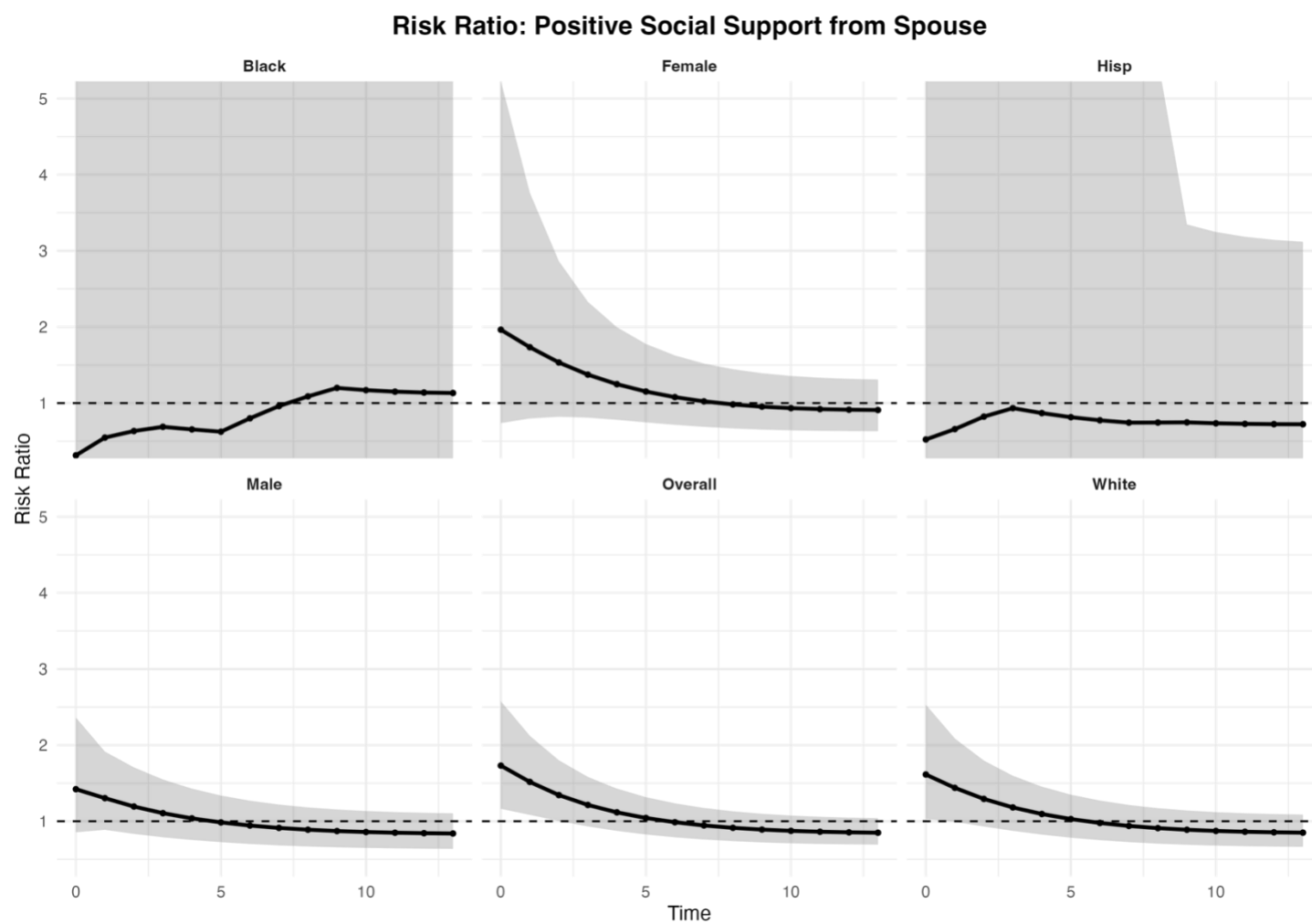
**eFigure 1.** Time Discrete Curves for Risk Differences for Closeness to Spouse



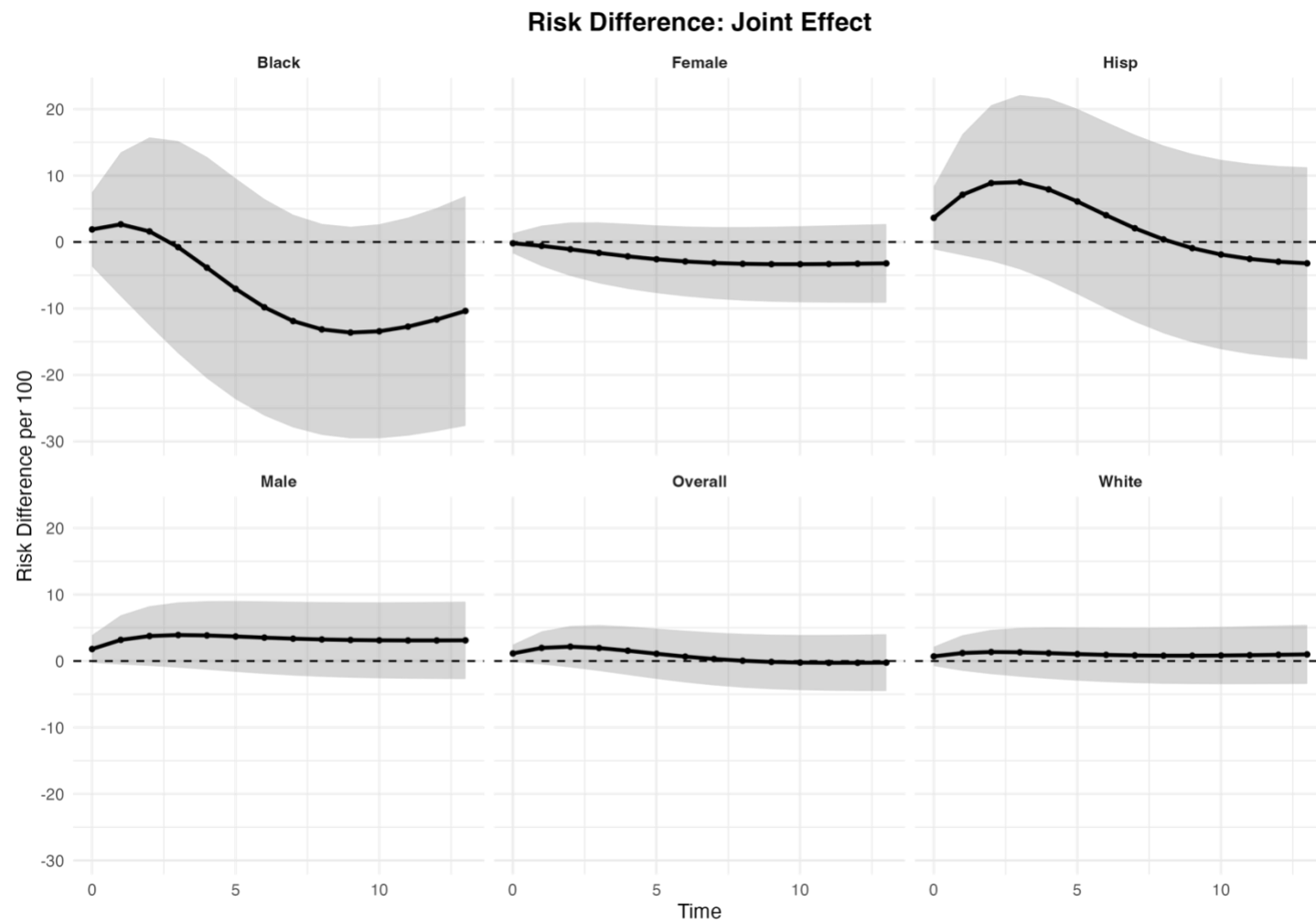
**eFigure 2.** Time Discrete Curves for Risk Ratios for Closeness to Spouse



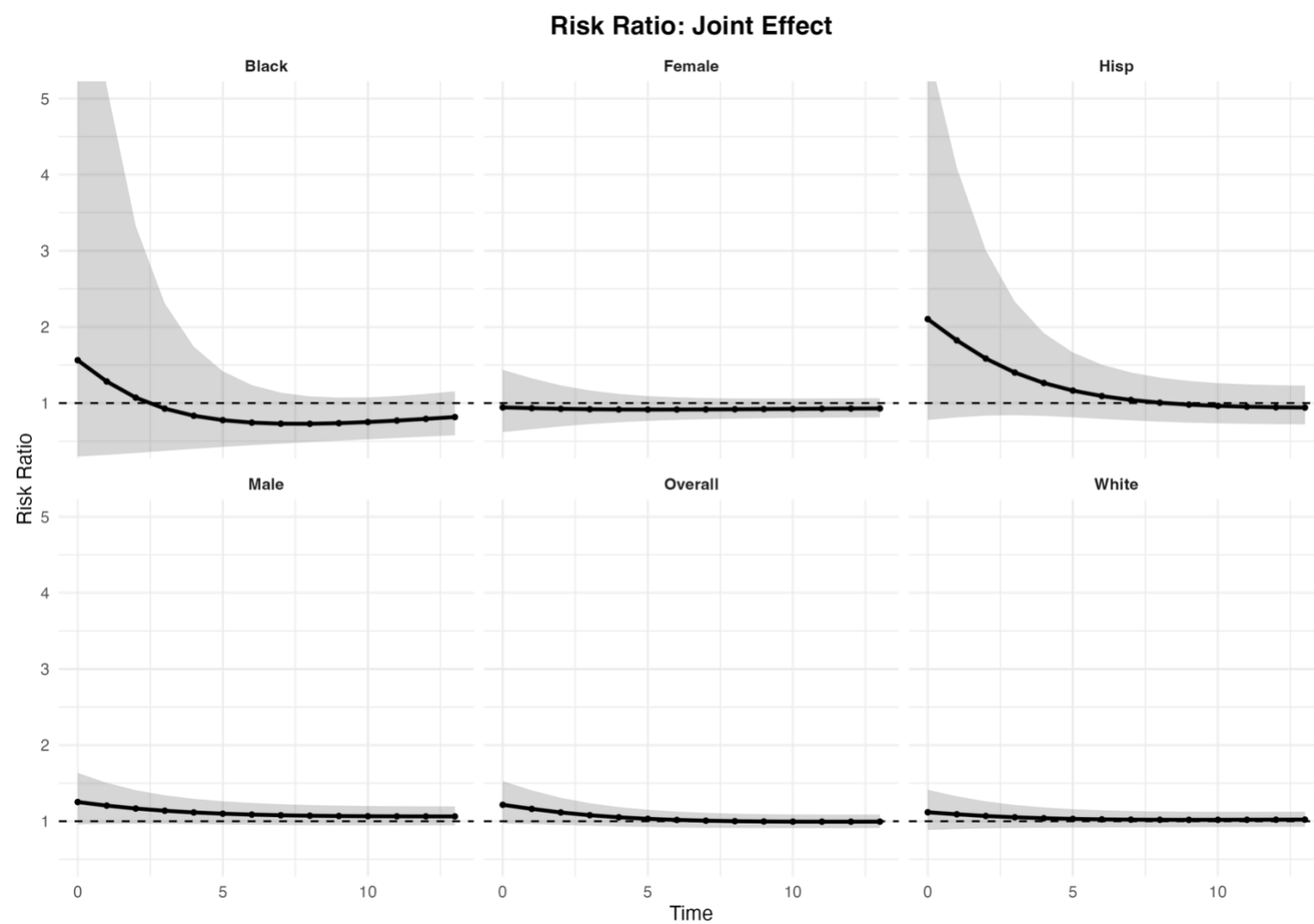
**eFigure 3.** Time Discrete Curves for Risk Differences for Positive Social Support from a Spouse



**eFigure 4.** Time Discrete Curves for Risk Ratios for Positive Social Support from a Spouse



**eFigure 5.** Time Discrete Curves for Risk Differences for Joint Effect between Positive Social Support from Spouse and Closeness to Spouse



**eFigure 6.** Time Discrete Curves for Risk Ratios for Joint Effect of Positive Social Support from Spouse and Closeness to Spouse on Dementia Risk

**eTable 5.** Average Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse using Expert Model, Overall Population, HRS, 2006-2020

|                          | Age Adjusted <sup>1</sup>                 |                            | Fully Adjusted <sup>2</sup>               |                            |
|--------------------------|-------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                          | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support | -1.93 (-11.58, 7.73)                      | 0.96 (0.80, 1.15)          | -0.39 (-10.03, 9.26)                      | 0.99 (0.83, 1.19)          |
| Closeness with Spouse    | -2.71 (-6.18, 0.76)                       | 0.95 (0.89, 1.02)          | -2.91 (-6.71, 0.89)                       | 0.95 (0.88, 1.02)          |
| Joint effect             | -2.47 (-6.19, 1.25)                       | 0.96 (0.90, 1.02)          | -0.13 (-4.48, 4.21)                       | 1.00 (0.92, 1.08)          |

model 1: adjusted for age  
model 2: adjusted for sex, age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio

**eTable 6.** End of Follow-up Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse using Expert Model, Overall Population, HRS, 2006-2020

|                          | Age Adjusted <sup>1</sup>                 |                            | Fully Adjusted <sup>2</sup>               |                            |
|--------------------------|-------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                          | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support | -3.83 ( -14.52, 6.85)                     | 0.94 (0.79, 1.12)          | -2.32 (-12.76, 8.13)                      | 0.96 (0.81, 1.14)          |
| Closeness with Spouse    | -2.46 (-6.59, 1.67)                       | 0.96 (0.90, 1.03)          | -2.72 (-7.20, 1.76)                       | 0.96 (0.89, 1.03)          |
| Joint effect             | -2.51 (-7.38, 2.36)                       | 0.96 (0.89, 1.04)          | -0.11 (-5.37, 5.15)                       | 1.00 (0.92, 1.08)          |

model 1: adjusted for age  
model 2: adjusted for sex, age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio

**eTable 7a.** Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, NH White Population, HRS, 2006-2020

|                          | Average <sup>1</sup>                      |                            | End <sup>2</sup>                          |                            |
|--------------------------|-------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                          | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support | -0.59 (-14.02, 12.84)                     | 0.97 (0.76, 1.25)          | -3.23 (-17.72, 11.26)                     | 0.95 (0.75, 1.20)          |

|                                                                                                                                                                                                            |                      |                   |                     |                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-------------------|---------------------|-------------------|
| Closeness with Spouse                                                                                                                                                                                      | -2.94 ( -8.63, 2.76) | 0.95 (0.85, 1.06) | -2.97 (-9.26, 3.33) | 0.95 (0.87, 1.05) |
| Joint effect                                                                                                                                                                                               | 0.37 ( -5.55, 6.29)  | 1.01 (0.91, 1.13) | 0.73 (-5.67, 7.13)  | 1.01 (0.92, 1.11) |
| model 1: average of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio |                      |                   |                     |                   |
| model 2: end of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio     |                      |                   |                     |                   |

**eTable 7b.** Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, NH Black Population, HRS, 2006-2020

|                                                                                                                                                                                                            | Average <sup>1</sup>                      |                            | End <sup>2</sup>                          |                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                                                                                                                                                                                                            | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR (95%<br>CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support                                                                                                                                                                                   | 5.07 (-26.43, 36.57)                      | 0.14 (0.00, 1363.53)       | 11.05 (-26.50, 48.61)                     | 1.14 (0.67, 1.95)          |
| Closeness with Spouse                                                                                                                                                                                      | 3.71 ( -17.34, 24.77)                     | 1.10 (0.72, 1.68)          | -1.34 (-27.78, 25.11)                     | 0.98 (0.66, 1.47)          |
| Joint effect                                                                                                                                                                                               | 5.98 ( -17.41, 29.36)                     | 1.16 (0.72, 1.88)          | -0.85 (-26.55, 24.84)                     | 0.99 (0.68, 1.46)          |
| model 1: average of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio |                                           |                            |                                           |                            |
| model 2: end of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio     |                                           |                            |                                           |                            |

**eTable 7c.** Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, Hispanic Population, HRS, 2006-2020

|                                                                                                                                                                                                            | Average <sup>1</sup>                      |                            | End <sup>2</sup>                          |                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                                                                                                                                                                                                            | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support                                                                                                                                                                                   | -15.45 (-53.50, 22.59)                    | 0.15 (0.00, 339.91)        | -7.85 (-61.75, 46.06)                     | 0.58 (0.01, 38.38)         |
| Closeness with Spouse                                                                                                                                                                                      | -21.35 ( -51.69, 8.99)                    | 0.18 (0.00, 199.24)        | -17.30 (-57.23, 22.64)                    | 0.50 (0.01, 37.71)         |
| Joint effect                                                                                                                                                                                               | -9.70 ( -38.91, 19.51)                    | 0.69 (0.25, 1.94)          | -6.21 (-40.42, 28.01)                     | 0.87 (0.46, 1.65)          |
| model 1: average of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio |                                           |                            |                                           |                            |
| model 2: end of follow up and adjusted for sex, age, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio     |                                           |                            |                                           |                            |

**eTable 8a.** Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, Male Population, HRS, 2006-2020

|                                                                                                                                                                                                                       | Average <sup>1</sup>                      |                            | End <sup>2</sup>                          |                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                                                                                                                                                                                                                       | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support                                                                                                                                                                                              | -5.42 (-20.02, 9.19)                      | 0.87 (0.65, 1.18)          | -6.83 (-23.50, 9.83)                      | 0.89 (0.66, 1.19)          |
| Closeness with Spouse                                                                                                                                                                                                 | -6.24 ( -11.95, -0.54)                    | 0.88 (0.79, 0.98)          | -3.96 (-10.92, 3.01)                      | 0.94 (0.84, 1.05)          |
| Joint effect                                                                                                                                                                                                          | 2.05 ( -4.98, 9.08)                       | 1.04 (0.92, 1.18)          | 3.47 (-4.03, 10.97)                       | 1.06 (0.94, 1.19)          |
| model 1: average of follow up and adjusted for age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio |                                           |                            |                                           |                            |
| model 2: end of follow up and adjusted for age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio     |                                           |                            |                                           |                            |

**eTable 8b.** Individual and Joint effects for the Association between Positive Spousal Social Support and Closeness to Spouse, Female Population, HRS, 2006-2020

|                                                                                                                                                                                                                       | Average <sup>1</sup>                      |                            | End <sup>2</sup>                          |                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|----------------------------|-------------------------------------------|----------------------------|
|                                                                                                                                                                                                                       | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) | Risk difference, RD<br>(per 100) (95% CI) | Risk ratio, RR<br>(95% CI) |
| Positive Spousal Support                                                                                                                                                                                              | 6.93 (-10.35, 24.21)                      | 1.12 (0.82, 1.55)          | 6.58 (-10.39, 23.54)                      | 1.09 (0.86, 1.39)          |
| Closeness with Spouse                                                                                                                                                                                                 | 0.26 ( -6.86, 7.39)                       | 1.01 (0.88, 1.15)          | -1.03 (-8.61, 6.56)                       | 0.98 (0.88, 1.11)          |
| Joint effect                                                                                                                                                                                                          | -5.19 ( -11.81, 1.44)                     | 0.90 (0.79, 1.03)          | -5.82 (-13.08, 1.45)                      | 0.91 (0.81, 1.02)          |
| model 1: average of follow up and adjusted for age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio |                                           |                            |                                           |                            |
| model 2: end of follow up and adjusted for age, race/ethnicity, depression at baseline, education, personality traits, high physical activity, financial strain, ongoing chronic stress, and income poverty ratio     |                                           |                            |                                           |                            |

### ***CHAPTER 3: AIM 2: Heterogeneous Treatment Effects of Contact with Friends on Dementia in a National Dataset***

#### **INTRODUCTION**

In 2025, there were 7.2 million people living with dementia in the United States and this number is expected to rise to 13 million by 2050.<sup>2</sup> Alzheimer's disease and related dementias (ADRD) are the sixth leading cause of death in 2022 and are the leading cause of disability and morbidity in older adults.<sup>70</sup> The prevalence and risk of dementia is higher in minoritized racial and ethnic populations such as Black and Hispanic individuals but these groups remain under represented in Alzheimer's disease research so mechanisms for this higher risk remain elusive.<sup>19,71,72</sup>

Despite the recent approval of several new dementia medications, healthcare providers turn to modifiable risk factors to delay disease progression.<sup>4,32</sup> Social modifiable risk factors including marriage, being in contact with family and children, and having a sense of community have been shown to have a positive impact on overall health and cognitive function.<sup>6–14</sup> Studies have shown that higher social support is associated with a lower risk of dementia.<sup>17,18</sup> Specifically, interacting with friends in mid-life, compared to only family, has been found to lower the likelihood of developing a dementia diagnosis later in life. This is possibly due to these individuals having a higher cognitive reserve from being mentally challenged by friends.<sup>73</sup> Unfortunately, social support is not equally distributed among racial/ethnic populations. Black and Hispanic individuals reported higher levels of social isolation and loneliness in the 2022 Behavioral Risk Factor Surveillance System.<sup>74</sup> Given the potential impact of interacting with

friends on dementia, we must identify target groups for social interventions and tailor them to individual characteristics.

The objective of this study is to identify potential factors that can modify the effect of friendship social support on the risk of dementia and to estimate heterogeneous effects across subgroups characterized by these factors in the overall and racial/ethnic subgroups.

## **METHODS**

### *Study population and data sources*

This research utilized the Health and Retirement Study (HRS), where people over 50 years old and their spouses were interviewed biennially until death.<sup>45,47</sup> The data collected for this study included the HRS core and the leave-behind questionnaire, combining the 2006 and 2008 cohorts. The leave behind questionnaire began in 2006 and includes items used for social support measures.

From the combined 2006 and 2008 HRS sample ( $n = 13,064$ ), participants were excluded if they were under 50 years old ( $n = 249$ ), had dementia at baseline ( $n = 506$ ), or had missing values for the contact with friends question ( $n = 2,186$ ). We conducted single imputation using missForest to address missingness in covariates ( $n = 6,639$ ). We employed the missForest function given its demonstrated effectiveness for imputing missing values in causal forest and other random forest analyses.<sup>75</sup> This method uses random forests to mimic multiple imputation by averaging over regression trees and excels with missingness in mixed-type data.<sup>75,76</sup>

We obtained an analytical sample of 10,309 participants.

## *Variables*

### *Exposure: Frequency of contact with friends*

The exposure was defined using the friend contact index was measured at baseline (2006 or 2008). Friend contact was averaged over 3 sub-questions: “On average, how often do you do each of the following? a) Meet up (include both arranged and chance meetings), b) Speak on the phone, c) Write or email”. The response options were: “less than once a year”, “once or twice a year”, “every few months”, “once or twice a month”, “once or twice a week”, or “three or more times a week”. We aimed to see the difference between having more interactions with friends and the rest of the sample. We therefore defined exposure as a binary cut-off: having contact with friends once a week or more versus less than once a week.

### *Outcome: Langa-Weir score*

The outcome was defined using the Langa-Weir classification score for cognitive outcomes of normal, cognitively impaired but not demented (CIND), and having dementia.<sup>50</sup> We used a 27-point scale administered to all HRS respondents, which included questions such as the serial sevens subtraction test, the immediate and delayed recall test, and the counting backward test.<sup>50</sup> A proxy 11-point scale included proxy assessment of memory, independent activities of daily living (IADL) limitations, and interviewer assessment of cognitive impairment.<sup>50</sup> For the 27-point scale and based on the Aging, Demographics, and Memory Study (ADAMS), 12-27 was considered normal, 7-11 was CIND, and 0-6 was having dementia for respondents, whereas proxies had an 11-point scale with thresholds of 0-2, 3-5, and 6-11 for each respective group.<sup>50,51</sup> We included both respondents and proxy interviews in our sample. We also grouped together CIND and normal outcomes into a category of not having dementia in order to have a binary outcome of having dementia or not.

## Covariates

We selected covariates from baseline that could be identified as potential confounders and/or effect modifiers of the effect of contact with friends and dementia risk. The covariates included in the causal forest analysis were the following: age (years), self-reported chronic disease count (0-8; hypertension, diabetes mellitus, cancer, coronary heart disease, congestive heart failure, stroke/cerebrovascular disease, arthritis), depression at baseline using the Center for Epidemiologic Studies Depression (CESD) scale (0-8), income-poverty ratio (continuous), sex (male, female), education (continuous), personality traits (openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism), high physical activity ( $\text{MET} \geq 35$ ,  $\text{MET} < 35$ ), high risk alcohol consumption (yes, no), marital status (married, not married), ongoing chronic stress (continuous), financial strain using income-poverty ratio with the individual difficulty of fulfilling monthly financial needs variables, smoking status (former or current, never), race and ethnicity (NH White, NH Black, Hispanic), and retirement status (complete retired, not retired).

## *Statistical analysis*

Knowledge of how treatment effects vary by subgroups (i.e., heterogeneous treatment effects [HTE]) ensure resources are properly used to implement intervention strategies that will maximize benefit while minimizing harm.<sup>77-79</sup> Identification of HTEs in social and behavioral research can increase effectiveness of interventions by reducing cost, improving outcomes, and reducing disparities within subgroups of an overall population.<sup>79,80</sup> There are various methods to estimate HTEs, including stratification and the use of interaction terms.<sup>81</sup> The new innovative methods to determine HTEs include machine learning techniques such as causal forest, Bayesian

causal forest, and g-computation based methods such as the generalized HTE approach.<sup>82,83</sup> In the current study, we will use causal forests to estimate HTEs because this method uses nonlinear relationships between variables and honest estimation.

We used causal forests to estimate heterogeneous treatment effects of contact with friends on dementia risk. Causal forests are an ensemble of causal trees that optimize the detection of heterogeneity to estimate individual or subgroup-specific treatment effects.<sup>77,78,84,85</sup> Causal trees are grown on random subsamples of the training data and can be combined with propensity score weighting to estimate the average treatment effect. This is a machine learning technique that can predict individual treatment effects based on the individuals' characteristics; it also extends random forests/regression tree algorithms by enabling improved characterization of treatment-effect heterogeneity across a broader range of individual covariates.<sup>86</sup> We used causal forest modeling to estimate the treatment effect for each individual, conditional on the covariates included in the model of contact with friends on the dementia risk.

After preparing the data, we conducted our analysis using the following steps:

1. We used propensity score matching (PSM) to remove confounding. For more details on PSM, see the article by Lee et al.<sup>87</sup> Causal forests require the exposure to be unconfounded by the covariates in the covariate set.<sup>88</sup> We used the following variables in the match set: chronic disease number, depression (CESD score), sex, marital status, identification as Non-Hispanic Black, identification as Hispanic, age, socioeconomic status, years of education, openness, extraversion, neuroticism, conscientiousness, agreeableness, and high physical activity. After matching, we used

- a love plot to confirm that the covariates were balanced across both groups (**eFigure. 1**).
2. We split our data into a training and testing subset (50:50) where none of the training data points were in the testing dataset.
  3. We then constructed the causal forest model using 2000 trees. We also tuned all parameters to estimate the importance of each covariate included using 10 folds cross-fitting within the *grf* function since this has been found to be an efficient form of data-splitting.<sup>86</sup>
  4. After the most important variables were identified, the average treatment effect was calculated using augmented inverse probability weighting (AIPW) and the 95% confidence interval was calculated from the estimated standard error. The standard error was calculated using bootstrapping. We used the AIPW method because it is applicable to binary exposures, it allows for flexible covariate adjustment in observational studies, and provides standard errors for ATEs using k-fold cross-fitting.<sup>89</sup>
  5. We selected the most important variables with an importance value greater than 0.1 then we compared predicted individual treatment effects within strata of the variables with high importance. We also plotted the individual treatment effects on the frequency of each occurrence and ranked the conditional average treatment effects (CATE).

6. We selected subgroups that were most representative of the treatment effect heterogeneity identified by the forest. This was done by first identifying tree split on the most important variables across the forest. Then, from these trees, we identified the tree with the greatest variance in ITEs and plotted it as a classification and regression tree (CART) plot.
7. The CATEs were calculated for the important variables. Then we selected cut points for subgroup analyses based on the two important variables using an untargeted and a targeted method to determine the value of each variable that yields the CART plot.
8. Finally, we estimated ATEs sub-grouped by race and ethnicity to observe health disparities and identify potential shifts in the direction of the ATEs.

All analyses were conducted using the Integrated Development Environment for R, RStudio 2024.12.1+563 (Posit Software, Boston, MA, 2024).

## RESULTS

### *Sample characteristics*

Participants at baseline (2006 or 2008) had an average age of 68 years (range: 50 – 99), and the majority were women (59%), Non-Hispanic (NH) White (80%), completely retired (50%), and married (65%). Hispanics made up 7.5% of the sample and 11% were Black. Our sample included 18% of people who interacted with friends once a week or more frequently and an average level of education of 12.8 years. Participants had, on average, 2 chronic diseases on average. The majority of the sample (76%) participated in low levels of physical activity (MET-hours/week < 35). (**Table 1**)

### *Distribution of CATEs*

Our analysis compared the dementia risk for contact with friends weekly or more versus contact that was less than once a week. After plotting the distribution of CATEs (**Fig. 1**), we found the distribution resembled a unimodal distribution with a center around a risk difference of -0.01. The majority of the risk difference values were found on the negative portion of the graph. The graph of the ranked CATEs (**eFigure. 2**) demonstrated similar findings to **Figure 1**. The results of decomposing the CATEs by variable, while marginalizing over others, estimated protective effects of friendship contact is stronger for people with these characteristics: higher age, lower income-to-poverty ratio, greater openness, and lower education. (**eFigure. 3**).

### *Important variables*

The variables of importance that exceeded the 0.1 threshold were age and the income-poverty ratio, both on continuous scales, for the overall HRS sample. Openness, education, and ongoing chronic stress were just under the threshold (**Fig. 2**)

### *Subgroup CATEs (Risk difference scale)*

We identified four subgroups within the overall analytic sample defined by age and income-poverty ratio (IPR) and used the untargeted method to select cut points of having an income-poverty ratio below 2.42 (defined as low IPR) using an *rpart* model. Using the targeted-cut-point strategy, we selected the threshold of 75 years for age because **eFigure 3** in the supplement materials showed a change in slope that began at around 75 years. The CATEs were reported as risk differences per 1000 individuals. The CATEs results demonstrated protective effects across subgroups of age and IPR but the confidence intervals were compatible with both protective and harmful effects. (**Fig. 3**).

### *Average Treatment Effects (Risk difference scale)*

The average treatment effects for the overall HRS sample and the NH White stratified subsample were -9.58 (95% CI: -28.02, 8.87) and -11.35 (95% CI: -31.76, 9.06) respectively. The ATEs for NH Black and Hispanic stratified samples were -1.12 (95% CI: -74.66, 72.43) and -1.34 (95% CI: -11.07, 8.39) respectively. (**Table 2**)

## **DISCUSSION**

The objective of this research was to estimate heterogeneous treatment effects from the frequency of contact with friends on the risk of dementia and identify differences in racial/ethnic subgroups. Our results suggest a moderate protective effect for dementia risk in the overall population among people who had contact with friends once a week or more when compared to less frequent contact. Given our causal assumptions, a risk difference ranging from fewer dementia cases to slightly more cases is compatible with a negative association with our data. Among NH White participants, the protective effect remained and the confidence interval ranged from fewer dementia cases to slightly more cases. Both NH Black and Hispanic individuals showed an inconclusive effect, with confidence intervals that were compatible with both fewer and more cases of dementia equally. These findings are supported by the literature and cultural dynamics could explain the disparities.

Our study extends and supports prior studies on contact with friends and their effect on dementia risk. Other studies have found that higher contact with friends alone and friend/family result in a lower risk of cognitive decline/dementia.<sup>73,90,91</sup> Some biological mechanisms for this protective effect have been suggested where white matter lesion volume increase and smaller volumes in the temporal lobe, occipital lobe, cingulum, hippocampus, and amygdala were

associated with lower frequency of social contact.<sup>92</sup> Our study's results are in line with the conclusion that higher contact with friends is associated with reduced dementia risk. However, our analyses extend beyond prior work by employing nonparametric machine learning methods that, while underutilized in epidemiological research, offer robust intrinsic mechanisms for controlling confounding and preventing overfitting.<sup>93</sup> Also, by accounting for multiple covariates, we were able to better explain the variation in dementia risk compared to traditional regression techniques. This method also allowed us to avoid confirmation bias from multiple testing, which when using interaction and stratification in regression analyses.<sup>94</sup> Unlike the previously conducted studies, we stratified our results and found differences in racial/ethnic subgroups.

The null findings in the NH Black and Hispanic populations could be partially explained by the tendencies of this subpopulation to value their relationships with their family more than their friends because of how they have built their culture in the U.S.<sup>95</sup> NH Black people specifically distinguish their friends from other family members in a way that could result in some closer friends being considered family through fictive kin.<sup>95</sup> This could explain how the NH Black individuals in the sample had lower contact with friends when compared to other racial/ethnic groups and no effect shown for dementia risk. Similarly, Hispanic individuals usually invoke the cultural value of familism which emphasizes respecting, supporting, and referencing the family unit.<sup>96</sup> Furthermore, NH White individuals are more likely to encourage individualism over familism and less likely than their non-white counterparts to live with or get support from extended or immediate family.<sup>97-99</sup> These differences in cultural dynamics could explain how having more contact with friends would be more beneficial for NH White individuals than their non-white counterparts.

Age and income poverty ratio were expected to be important indicators of dementia risk due to their known effect as risk factors.<sup>100,101</sup> Although having contact with friends once a week had the least benefit for those who were older and had a higher income poverty ratio, the highest benefit was observed among younger people with a higher income poverty ratio. Nevertheless, individuals in lower socioeconomic groups across all age ranges would gain substantial protection against dementia risk through increased friend contact, as both older and younger adults demonstrated comparable benefits. Interventions targeting both age groups could maximize impact, given that a larger proportion of the population falls into the low-income category.

Our research was not without limitations. First, the definition of contact with friends captures a large portion of social support by friends but does not capture the full definition of social support from friends, such as quality of the friendship. Second, the machine learning method was not designed to infer causality from variable selection and the selected variables may merely be surrogates for more complex physiological processes.<sup>102</sup> The available data does not allow us to explain the physiological mechanisms underlying the relationships, but it can demonstrate consistency in past findings.<sup>102</sup> The method of causal forests also assumes independent censoring after covariates were controlled for in the forest analysis.<sup>103</sup> Accessing HTEs with time to event outcomes is challenging as most methods assume complete observation but survival data violates this assumption due to right-censoring.<sup>104</sup> We attempted to conduct the analysis using causal survival forest but were informed that the assumption that probabilities do not go lower than a value 0.05 was violated and this method will be expected to give unreliable estimates. Another limitation concerns the relatively small sample sizes for Non-Hispanic Black and Hispanic populations, which may have resulted in wide confidence intervals and reduced our ability to

draw definitive conclusions. Although propensity score matching mitigated observed confounding in our analysis, this methodological approach further reduced sample size and statistical precision, contributing as well to the wide confidence intervals observed throughout our findings. Propensity score matching may demonstrate balance for our overall dataset but when stratifying by race and ethnicity the balance in the covariates may be lost. Our population also may also not reflect the target population after matching. A notable methodological concern is that causal forest analyses may yield variable results due to various data splits causing various honest trees to be created.<sup>105</sup> We improved reproducibility by using seeds and a large number of trees. Causal forests can find heterogeneous treatment effects even with unstable individual trees. Lastly, the causal forest method can identify subgroups using an intuitive heuristic, but no standard statistical approach does not yet exist to determine representative subgroups for the high benefit groups. Future studies should aim to compare average and subgroup treatment effects using the relative scale rather than just the absolute scale.<sup>106</sup>

## CONCLUSIONS

Having contact with friends once a week or more frequently appears protective against dementia risk for the overall U.S. population. Targeted interventions for Non-Hispanic White individuals should emphasize friend-based contact strategies. However, different interventions may be necessary for NH Black and Hispanic individuals due to cultural variations in social network conceptualization. Additionally, policy interventions should prioritize enhancing resource access and utilization among individuals of lower socioeconomic status, irrespective of age. Future studies should use causal forest methods to identify subgroups that benefit most from social interventions for dementia risk across datasets and continue focusing on modifiable risk factors for mitigating dementia onset.

## TABLES AND FIGURES

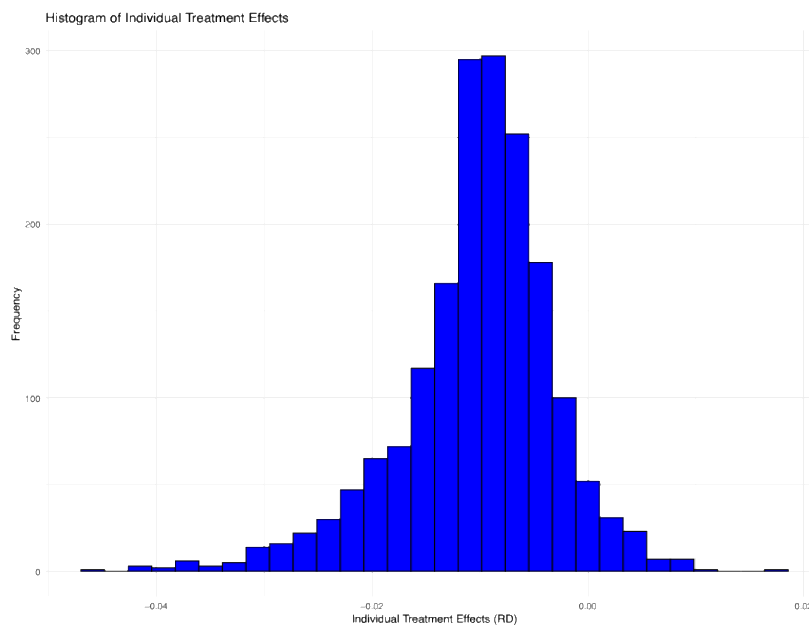
| <b>Table 1.</b> Descriptive characteristics of the analytical sample at baseline (2006 or 2008) |                     |
|-------------------------------------------------------------------------------------------------|---------------------|
| <b>Characteristic</b>                                                                           | <b>N = 10,309</b>   |
| <b>Age (Years)</b>                                                                              |                     |
| Mean (Min, Max)                                                                                 | 68 (50, 99)         |
| <b>Male, n (%)</b>                                                                              | 4,188 (41%)         |
| <b>Race and Ethnicity (4 categories), n (%)</b>                                                 |                     |
| Non-Hispanic White                                                                              | 8,241 (80%)         |
| Non-Hispanic Black                                                                              | 1,104 (11%)         |
| Other                                                                                           | 193 (1.9%)          |
| Hispanic                                                                                        | 769 (7.5%)          |
| <b>High Contact with Friends, n (%)</b>                                                         | 1,813 (18%)         |
| <b>Participant Years of Education</b>                                                           |                     |
| Mean (Min, Max)                                                                                 | 12.83 (0.00, 17.00) |
| <b>Income Poverty Ratio</b>                                                                     |                     |
| Mean (Min, Max)                                                                                 | 5.4 (0.0, 680.0)    |
| <b>Retirement Status, n (%)</b>                                                                 |                     |
| Not retired                                                                                     | 2,843 (28%)         |
| Completely retired                                                                              | 5,166 (50%)         |
| Partly retired                                                                                  | 1,285 (12%)         |
| Not applicable                                                                                  | 1,008 (9.8%)        |
| <b>Chronic Disease Number</b>                                                                   |                     |
| Mean (Min, Max)                                                                                 | 2.01 (0.00, 8.00)   |
| <b>CESD/Depression Score</b>                                                                    |                     |
| Mean (Min, Max)                                                                                 | 1.29 (0.00, 8.00)   |
| <b>Openness to Experience Index</b>                                                             |                     |
| Mean (Min, Max)                                                                                 | 2.95 (1.00, 4.00)   |
| <b>Conscientiousness Index</b>                                                                  |                     |
| Mean (Min, Max)                                                                                 | 3.37 (1.00, 4.00)   |
| <b>Extraversion Index</b>                                                                       |                     |
| Mean (Min, Max)                                                                                 | 3.23 (1.00, 4.00)   |
| <b>Agreeableness Index</b>                                                                      |                     |
| Mean (Min, Max)                                                                                 | 3.55 (1.00, 4.00)   |
| <b>Neuroticism Index</b>                                                                        |                     |
| Mean (Min, Max)                                                                                 | 2.03 (1.00, 4.00)   |
| <b>High Physical Activity (<math>\geq</math> MET 35), n (%)</b>                                 | 2,518 (24%)         |
| <b>Smoking Status, n (%)</b>                                                                    |                     |
| Current                                                                                         | 1,240 (12%)         |
| Former                                                                                          | 4,514 (44%)         |
| Never                                                                                           | 4,485 (44%)         |
| <b>Risky Alcohol Consumption, n (%)</b>                                                         | 632 (6.1%)          |
| <b>Married (binary), n (%)</b>                                                                  | 6,717 (65%)         |
| <b>Financial Strain Index, n (%)</b>                                                            |                     |
| Not at all difficult                                                                            | 4,272 (42%)         |
| Not very difficult                                                                              | 3,110 (31%)         |

| <b>Table 1.</b> Descriptive characteristics of the analytical sample at baseline (2006 or 2008) |                   |
|-------------------------------------------------------------------------------------------------|-------------------|
| <b>Characteristic</b>                                                                           | <b>N = 10,309</b> |
| Somewhat difficult                                                                              | 2,061 (20%)       |
| Very difficult                                                                                  | 506 (5.0%)        |
| Completely difficult                                                                            | 166 (1.6%)        |
| <b>Chronic Stress Scale</b>                                                                     |                   |
| Mean (Min, Max)                                                                                 | 11.7 (1.0, 32.0)  |

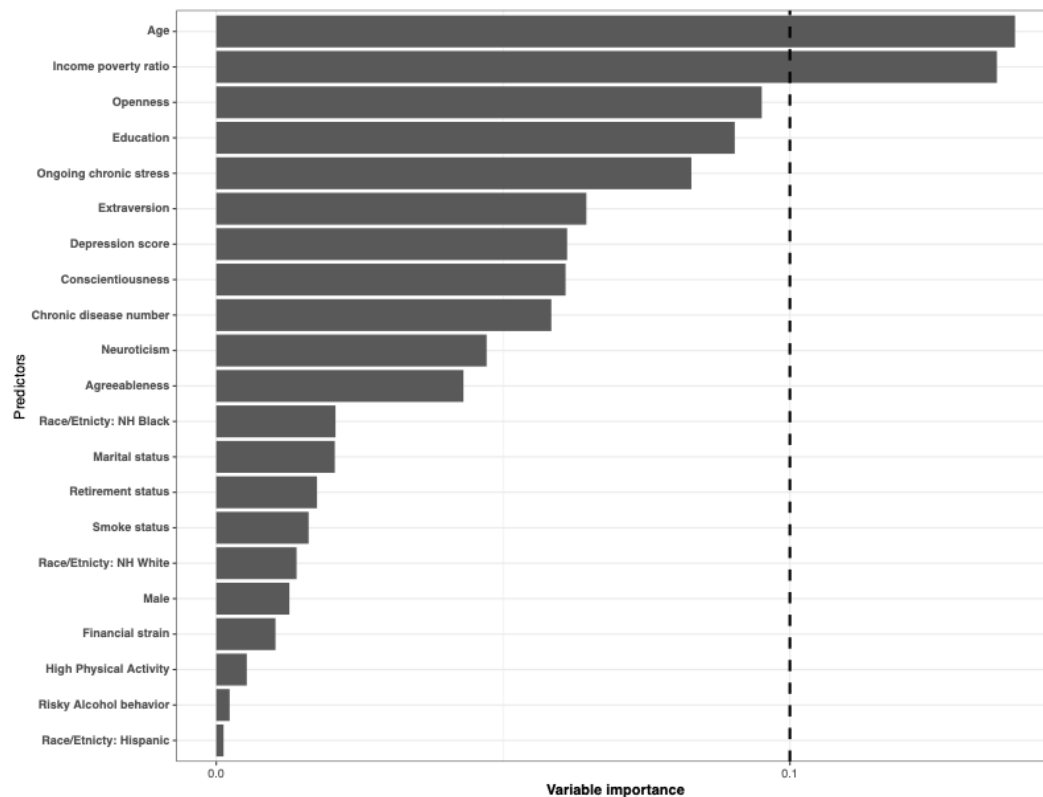
**Table 2.** Average Treatment Effect (in terms of risk difference per 1,000 individuals) for the Overall and Stratified Race/Ethnicity HRS Population

| <b>Group</b>       | <b>Average Treatment Effect</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>P-value from Difference in Difference</b> |
|--------------------|---------------------------------|---------------------|---------------------|----------------------------------------------|
| Overall            | -9.58                           | -28.02              | 8.87                |                                              |
| Non-Hispanic White | -11.35                          | -31.76              | 9.06                |                                              |
| Non-Hispanic Black | -1.12                           | -74.66              | 72.43               | 0.79                                         |
| Hispanic           | -1.34                           | -11.07              | 8.39                | 0.39                                         |

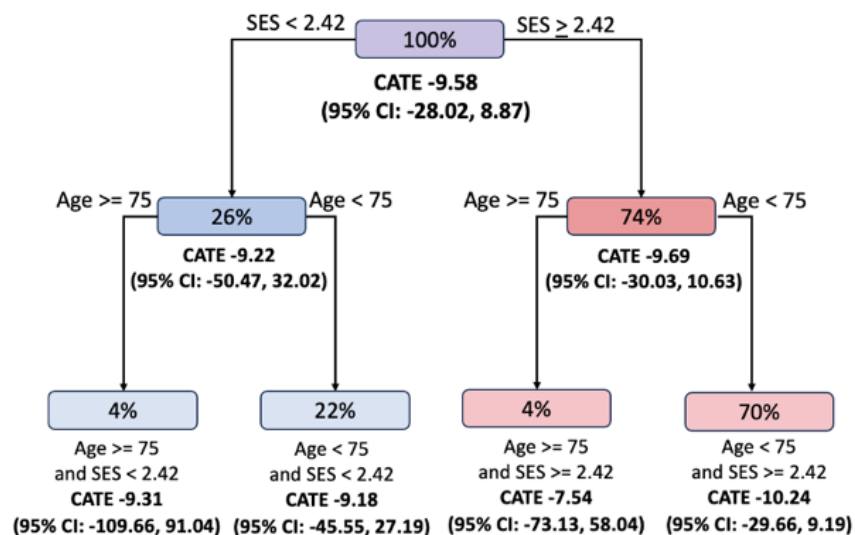
\*reference group was Non-Hispanic White



**Figure 1.** Distribution of CATEs as risk differences (RD)



**Figure 2.** Important variables for Overall Population in the Health and Retirement Study (HRS) analytical sample



**Figure 3.** CART plot for Overall Population in the Health and Retirement Study (HRS) analytical sample

## APPENDIX

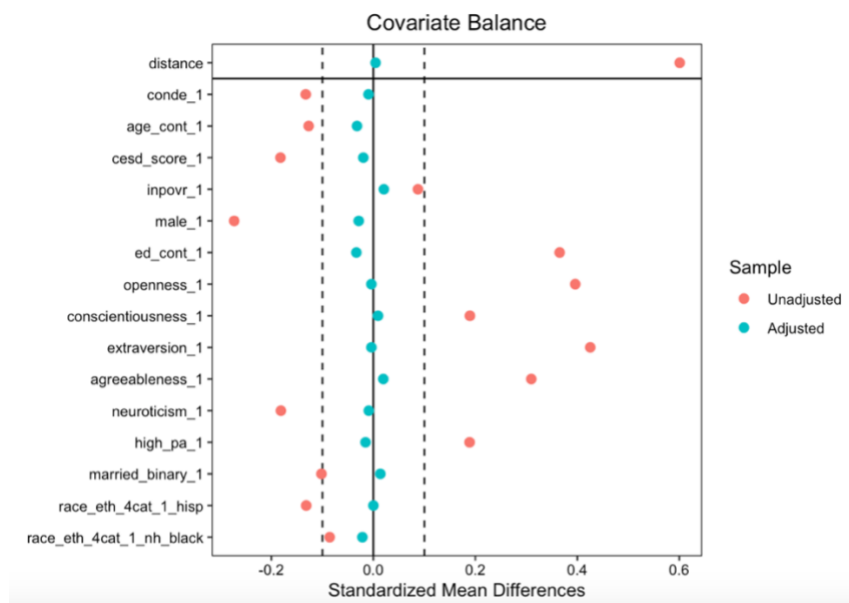
### *Covariate details*

Personality traits were defined using five separate indexes: openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism. These variables make up the “Big 5” personality traits, and the scales are based on the Midlife Development in the U.S. and the International Personality Item Pool.<sup>69</sup> These items were scored from 1 to 4 and were reverse-coded, with 1 indicating “not at all” and 4 indicating “a lot”.<sup>69</sup> Chronic stress was captured with an 8-item scale on a 4-point Likert scale (1 = “No, didn’t happen”, 4 = “Yes, very upsetting”) using the following questions: ongoing health problems (in yourself); ongoing physical or emotional problems (with spouse or child); ongoing problems with alcohol or drug use in family member; ongoing difficulties at work; ongoing financial strain; ongoing housing problems; ongoing problems in a close relationship; and helping at least one sick, limited, or frail family member or friend on a regular basis. Financial strain was measured using the annual income-poverty ratio, with variables on the difficulty of fulfilling monthly financial needs, resulting in a 5-category measure of self-reported difficulties in fulfilling monthly financial needs (ranging from 'not at all difficult' to 'completely difficult'). The number of chronic diseases ranged from 0 to 8, representing a sum of having any or multiple of the following diseases: high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, psychiatric problems, and arthritis.<sup>69</sup> Physical activity in this study was measured using the metabolic equivalent of task (MET) score, which describes the amount of energy consumed relative to resting.<sup>107–109</sup> This score was calculated by taking the frequency of activity at each intensity level per week and multiplying it by the average energy expenditure of each activity.<sup>108–110</sup> Low physical activity was defined as < 35 MET-hours/week, and high physical activity was defined as  $\geq$  35 MET-

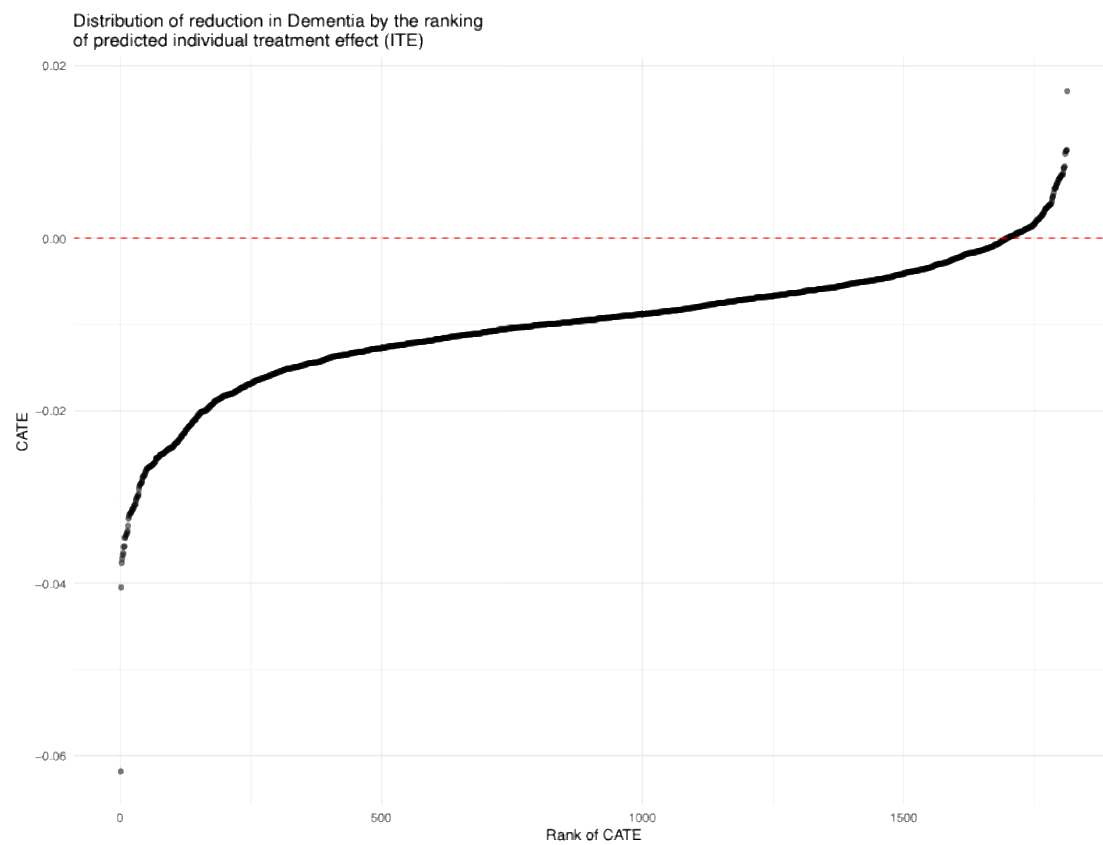
hours/week.<sup>110</sup> For alcohol consumption, a binary variable was created documenting heavy consumption (Yes/No), which was defined as 28 drinks in one week for men and 14 drinks in one week for women.<sup>111</sup>

### *Stratified Table 1*

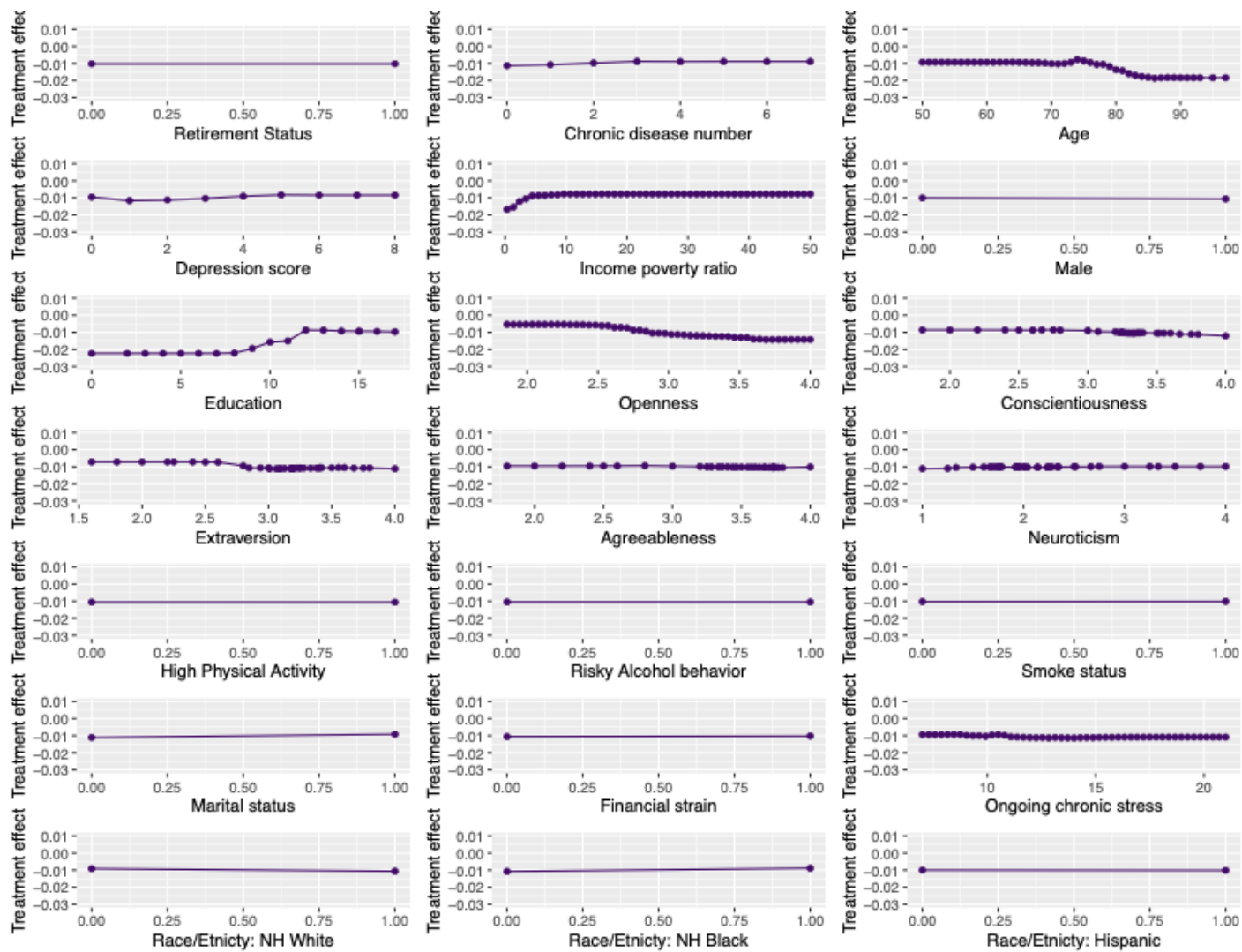
There were some notable differences in lifestyle risk factors across race/ethnicity. Hispanic participants had less contact with their friends once a week or more, less education, more participants who were not retired, higher average depression, and more financial strain when compared to the other two groups. NH White participants had the most contact with their friends every few months or more, a higher average income poverty ratio, higher physical activity, and fewer people struggling with financial strain when compared to the other two racial/ethnic groups. NH Black individuals had a higher average disease count, more people classified as less physically active, and fewer married people when compared to Hispanics and NH Whites. Personality traits were generally the same for all categories across race/ethnic groups, except that neuroticism was much higher for Hispanics. (**eTable 2**)



**eFigure. 1.** Covariate balance after Propensity Score Matching



**eFigure. 2.** Rank of Conditional Average Treatment Effects (CATEs)



**eFigure. 3.** CATE for Covariates in the Causal Forest Model

**eTable 1.** Descriptive Statistics Stratified by Contact with Friends

| <b>Characteristic</b>                           | <b>High Contact with Friends<br/>(once a week+)<br/>N = 1,877</b> | <b>Low Contact with<br/>Friends (&lt; a week)<br/>N = 8,681</b> |
|-------------------------------------------------|-------------------------------------------------------------------|-----------------------------------------------------------------|
| <b>Age (Years)</b>                              |                                                                   |                                                                 |
| Mean (Min, Max)                                 | 67 (31, 95)                                                       | 68 (26, 99)                                                     |
| <b>Male, n (%)</b>                              | 561 (30%)                                                         | 3,672 (42%)                                                     |
| <b>Race and Ethnicity (4 categories), n (%)</b> |                                                                   |                                                                 |
| Non-Hispanic White                              | 1,578 (84%)                                                       | 6,829 (79%)                                                     |
| Non-Hispanic Black                              | 166 (8.8%)                                                        | 966 (11%)                                                       |
| Other                                           | 29 (1.5%)                                                         | 178 (2.1%)                                                      |
| Hispanic                                        | 104 (5.5%)                                                        | 706 (8.1%)                                                      |
| <b>Positive Spousal Social Support, n (%)</b>   | 1,079 (87%)                                                       | 5,259 (85%)                                                     |
| <b>Contact with Other Family Members, n (%)</b> | 1,077 (61%)                                                       | 4,787 (58%)                                                     |
| <b>Participant Years of Education</b>           |                                                                   |                                                                 |
| Mean (Min, Max)                                 | 13.62 (0.00, 17.00)                                               | 12.66 (0.00, 17.00)                                             |
| <b>Income Poverty Ratio</b>                     |                                                                   |                                                                 |
| Mean (Min, Max)                                 | 6.7 (0.0, 680.0)                                                  | 5.2 (0.0, 556.6)                                                |
| <b>Retirement Status, n (%)</b>                 |                                                                   |                                                                 |
| Not retired                                     | 597 (32%)                                                         | 2,463 (28%)                                                     |
| Completely retired                              | 859 (46%)                                                         | 4,313 (50%)                                                     |
| Partly retired                                  | 246 (13%)                                                         | 1,046 (12%)                                                     |
| Not applicable                                  | 174 (9.3%)                                                        | 853 (9.8%)                                                      |
| <b>Chronic Disease Number</b>                   |                                                                   |                                                                 |
| Mean (Min, Max)                                 | 1.83 (0.00, 7.00)                                                 | 2.01 (0.00, 8.00)                                               |
| <b>CESD/Depression Score</b>                    |                                                                   |                                                                 |
| Mean (Min, Max)                                 | 1.06 (0.00, 8.00)                                                 | 1.35 (0.00, 8.00)                                               |
| <b>Openness to Experience Index</b>             |                                                                   |                                                                 |

**eTable 1.** Descriptive Statistics Stratified by Contact with Friends

| <b>Characteristic</b>                                                    | <b>High Contact with Friends<br/>(once a week+)<br/>N = 1,877</b> | <b>Low Contact with<br/>Friends (&lt; a week)<br/>N = 8,681</b> |
|--------------------------------------------------------------------------|-------------------------------------------------------------------|-----------------------------------------------------------------|
| Mean (Min, Max)                                                          | 3.13 (1.00, 4.00)                                                 | 2.92 (1.00, 4.00)                                               |
| <b>Conscientiousness Index</b>                                           |                                                                   |                                                                 |
| Mean (Min, Max)                                                          | 3.44 (1.60, 4.00)                                                 | 3.36 (1.00, 4.00)                                               |
| <b>Extraversion Index</b>                                                |                                                                   |                                                                 |
| Mean (Min, Max)                                                          | 3.40 (1.60, 4.00)                                                 | 3.19 (1.00, 4.00)                                               |
| <b>Agreeableness Index</b>                                               |                                                                   |                                                                 |
| Mean (Min, Max)                                                          | 3.66 (2.00, 4.00)                                                 | 3.53 (1.00, 4.00)                                               |
| <b>Neuroticism Index</b>                                                 |                                                                   |                                                                 |
| Mean (Min, Max)                                                          | 1.95 (1.00, 4.00)                                                 | 2.06 (1.00, 4.00)                                               |
| <b>High Physical Activity (<math>\geq</math> MET 35), n (%)</b>          | 593 (32%)                                                         | 1,994 (23%)                                                     |
| <b>Smoking Status, n (%)</b>                                             |                                                                   |                                                                 |
| Current                                                                  | 190 (10%)                                                         | 1,128 (13%)                                                     |
| Former                                                                   | 816 (44%)                                                         | 3,766 (44%)                                                     |
| Never                                                                    | 857 (46%)                                                         | 3,729 (43%)                                                     |
| <b>Risky Alcohol Consumption, n (%)</b>                                  | 123 (6.6%)                                                        | 547 (6.3%)                                                      |
| <b>Married (binary), n (%)</b>                                           | 1,157 (62%)                                                       | 5,751 (66%)                                                     |
| <b>Financial Strain Index, n (%)</b>                                     |                                                                   |                                                                 |
| Not at all difficult                                                     | 849 (46%)                                                         | 3,481 (41%)                                                     |
| Not very difficult                                                       | 551 (30%)                                                         | 2,636 (31%)                                                     |
| Somewhat difficult                                                       | 326 (18%)                                                         | 1,811 (21%)                                                     |
| Very difficult                                                           | 91 (4.9%)                                                         | 440 (5.2%)                                                      |
| Completely difficult                                                     | 26 (1.4%)                                                         | 151 (1.8%)                                                      |
| <b>Chronic Stress Scale</b>                                              |                                                                   |                                                                 |
| Mean (Min, Max)                                                          | 11.5 (2.0, 32.0)                                                  | 11.8 (1.0, 31.0)                                                |
| <b>Cognition Classification Based on<br/>Lange and Weir Score, n (%)</b> |                                                                   |                                                                 |
| Normal                                                                   | 1,169 (81%)                                                       | 4,486 (74%)                                                     |
| CIND                                                                     | 201 (14%)                                                         | 1,128 (19%)                                                     |

**eTable 1.** Descriptive Statistics Stratified by Contact with Friends

| <b>Characteristic</b> | <b>High Contact with Friends<br/>(once a week+)</b> | <b>Low Contact with<br/>Friends (&lt; a week)</b> |
|-----------------------|-----------------------------------------------------|---------------------------------------------------|
|                       | N = 1,877                                           | N = 8,681                                         |
| Demented              | 65 (4.5%)                                           | 455 (7.5%)                                        |

**eTable 2.** Descriptive Statistics Stratified by Race and Ethnicity

| <b>Characteristic</b>                                      | <b>Non-Hispanic White<br/>N = 8,241</b> | <b>Non-Hispanic Black<br/>N = 1,104</b> | <b>Hispanic<br/>N = 769</b> |
|------------------------------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------|
| <b>Age (Years)</b>                                         |                                         |                                         |                             |
| Mean (Min, Max)                                            | 69 (50, 99)                             | 67 (50, 96)                             | 65 (50, 95)                 |
| <b>Male, n (%)</b>                                         | 3,429 (42%)                             | 383 (35%)                               | 297 (39%)                   |
| <b>Contact with Friends Once a Week<br/>or More, n (%)</b> | 1,539 (19%)                             | 158 (14%)                               | 92 (12%)                    |
| <b>Friend Contact Index</b>                                |                                         |                                         |                             |
| Mean (Min, Max)                                            | 3.84 (1.00, 6.00)                       | 3.68 (1.00, 6.00)                       | 3.38 (1.00, 6.00)           |
| <b>Participant Years of Education</b>                      |                                         |                                         |                             |
| Mean (Min, Max)                                            | 13.22 (0.00, 17.00)                     | 12.10 (0.00, 17.00)                     | 9.54 (0.00, 17.00)          |
| <b>Income Poverty Ratio</b>                                |                                         |                                         |                             |
| Mean (Min, Max)                                            | 5.9 (0.0, 680.0)                        | 3.3 (0.0, 52.4)                         | 3.2 (0.0, 32.5)             |
| <b>Retirement Status, n (%)</b>                            |                                         |                                         |                             |
| Not retired                                                | 2,190 (27%)                             | 317 (29%)                               | 261 (34%)                   |
| Completely retired                                         | 4,256 (52%)                             | 538 (49%)                               | 291 (38%)                   |
| Partly retired                                             | 1,041 (13%)                             | 158 (14%)                               | 60 (7.8%)                   |
| Not applicable                                             | 748 (9.1%)                              | 91 (8.2%)                               | 156 (20%)                   |
| <b>Chronic Disease Number</b>                              |                                         |                                         |                             |
| Mean (Min, Max)                                            | 2.00 (0.00, 8.00)                       | 2.25 (0.00, 7.00)                       | 1.78 (0.00, 6.00)           |
| <b>CESD/Depression Score</b>                               |                                         |                                         |                             |
| Mean (Min, Max)                                            | 1.18 (0.00, 8.00)                       | 1.55 (0.00, 8.00)                       | 2.02 (0.00, 8.00)           |
| <b>Openness to Experience Index</b>                        |                                         |                                         |                             |
| Mean (Min, Max)                                            | 2.96 (1.00, 4.00)                       | 2.97 (1.14, 4.00)                       | 2.85 (1.00, 4.00)           |
| <b>Conscientiousness Index</b>                             |                                         |                                         |                             |

**eTable 2.** Descriptive Statistics Stratified by Race and Ethnicity

| <b>Characteristic</b>                                                    | <b>Non-Hispanic White</b><br>N = 8,241 | <b>Non-Hispanic Black</b><br>N = 1,104 | <b>Hispanic</b><br>N = 769 |
|--------------------------------------------------------------------------|----------------------------------------|----------------------------------------|----------------------------|
| Mean (Min, Max)                                                          | 3.39 (1.00, 4.00)                      | 3.32 (1.40, 4.00)                      | 3.32 (1.80, 4.00)          |
| <b>Extraversion Index</b>                                                |                                        |                                        |                            |
| Mean (Min, Max)                                                          | 3.22 (1.00, 4.00)                      | 3.31 (1.40, 4.00)                      | 3.21 (1.60, 4.00)          |
| <b>Agreeableness Index</b>                                               |                                        |                                        |                            |
| Mean (Min, Max)                                                          | 3.56 (1.00, 4.00)                      | 3.55 (1.60, 4.00)                      | 3.53 (1.80, 4.00)          |
| <b>Neuroticism Index</b>                                                 |                                        |                                        |                            |
| Mean (Min, Max)                                                          | 2.03 (1.00, 4.00)                      | 1.94 (1.00, 4.00)                      | 2.26 (1.00, 4.00)          |
| <b>High Physical Activity (<math>\geq</math> MET 35),<br/>n (%)</b>      | 2,115 (26%)                            | 189 (17%)                              | 166 (22%)                  |
| <b>Smoking Status, n (%)</b>                                             |                                        |                                        |                            |
| Current                                                                  | 946 (12%)                              | 178 (16%)                              | 86 (11%)                   |
| Former                                                                   | 3,672 (45%)                            | 457 (42%)                              | 318 (42%)                  |
| Never                                                                    | 3,572 (44%)                            | 462 (42%)                              | 354 (47%)                  |
| <b>Risky Alcohol Consumption, n (%)</b>                                  | 512 (6.2%)                             | 55 (5.0%)                              | 50 (6.5%)                  |
| <b>Married (binary), n (%)</b>                                           | 5,595 (68%)                            | 496 (45%)                              | 498 (65%)                  |
| <b>Financial Strain Index, n (%)</b>                                     |                                        |                                        |                            |
| Not at all difficult                                                     | 3,758 (46%)                            | 263 (25%)                              | 184 (25%)                  |
| Not very difficult                                                       | 2,504 (31%)                            | 309 (29%)                              | 234 (32%)                  |
| Somewhat difficult                                                       | 1,428 (18%)                            | 371 (35%)                              | 227 (31%)                  |
| Very difficult                                                           | 334 (4.1%)                             | 93 (8.7%)                              | 59 (8.0%)                  |
| Completely difficult                                                     | 98 (1.2%)                              | 29 (2.7%)                              | 33 (4.5%)                  |
| <b>Chronic Stress Scale</b>                                              |                                        |                                        |                            |
| Mean (Min, Max)                                                          | 11.6 (2.0, 32.0)                       | 12.2 (1.0, 28.0)                       | 12.0 (1.0, 27.0)           |
| <b>Cognition Classification Based on<br/>Lange and Weir Score, n (%)</b> |                                        |                                        |                            |
| Normal                                                                   | 4,538 (79%)                            | 458 (57%)                              | 355 (61%)                  |
| CIND                                                                     | 875 (15%)                              | 235 (29%)                              | 167 (29%)                  |
| Demented                                                                 | 335 (5.8%)                             | 114 (14%)                              | 61 (10%)                   |

**eTable 3.** Overall Subgroup CATEs

| <b>Population</b>                  | <b>Subgroup Conditional Average<br/>Treatment Effect Risk Difference<br/>per 1000 (95% Confidence<br/>Interval)</b> | <b>P-value from<br/>Difference in<br/>Difference</b> |
|------------------------------------|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| CATE for less than 75              | -10.00 (-27.13, 7.13)                                                                                               | 0.95                                                 |
| CATE for 75 or older               | -8.19 (-63.57, 47.20)                                                                                               |                                                      |
| CATE for low SES                   | -9.22 (-50.47, 32.02)                                                                                               | 0.98                                                 |
| CATE for high SES                  | -9.70 (-30.03, 10.63)                                                                                               |                                                      |
| CATE for less than 75 and high SES | -10.24 (-29.66, 9.19)                                                                                               | 0.99                                                 |
| CATE for 75 or older and high SES  | -7.54 (-73.13, 58.04)                                                                                               |                                                      |
| CATE for 75 or older and low SES   | -9.31 (-109.66, 91.04)                                                                                              | 0.94                                                 |
| CATE for less than 75 and low SES  | -9.18 (-45.55, 27.19)                                                                                               |                                                      |

## ***CHAPTER 4: AIM 3: Investigating the Mediating Role of Depression in the Effect of Positive Spousal Social Support on Dementia and Cognitive Impairment***

### **INTRODUCTION**

In 2025, there were about 7.2 million people living with dementia in the United States and this number is expected to rise to 13 million in 2050.<sup>2</sup> It is estimated that up to 40% of dementia cases could be prevented or delayed by targeting 12 modifiable risk factors including education, physical activity, social contact, depression, and obesity.<sup>5,112</sup> In the absence of a definitive cure for dementia, healthcare providers have focused on modifiable risk factors to ameliorate dementia's progression.<sup>4</sup> However, the mechanism for how modifiable risk factors, such as depression, change dementia risk remains under-researched.

Although late-life depression often accompanies dementia, depression and dementia are bidirectionally associated and treatment of depression has been found to potentially have positive effects on dementia risk.<sup>113–115</sup> People with a depression diagnosis are more likely to develop dementia, even when the timing of the depression diagnosis was in the early, mid, or later part of an individual's life.<sup>116,117</sup> The challenges that arise with depression can have a downstream effect on chronic disease risk, including dementia. Nevertheless, understanding the extent to which depression plays a role in any potential causal pathway between social support and dementia remains an area of active research.

We examined the extent to which elevated depressive symptoms mediated the effects of positive spousal social support on dementia and cognitive impairment risk and evaluated if these effects varied by sex/gender subpopulations. We hypothesized that elevated depressive symptoms would account for a substantial portion of the effect of positive social support from a

spouse on dementia and cognitive impairment risk and expected there to be interactions present between elevated depressive symptoms and social support. We hypothesize that the mediated effect will be different in women than in men.

## **METHODS**

### *Data source*

We used data from the Health and Retirement Study (HRS), a survey that includes a representative sample of 20,000 people aged 50 or older in the U.S. and their spouses.<sup>45–47</sup> The questionnaires used in this study include the core survey, which collected demographic characteristics, and the leave-behind survey, which collected information on social relationships, personality, and lifestyle behaviors.<sup>48</sup> Data were collected from 2006, when the leave-behind questionnaire began, to 2020 from participants who participated in the 2006 and 2008 cohorts.

In particular, to construct the analytic sample, we excluded at baseline, prevalent cases of dementia or cognitive impairment without dementia ( $N = 3,605$ ), along with participants who were aged less than 50 ( $N = 290$ ), were not married/partnered ( $N = 2,696$ ), or had missing values on questions related to positive spousal social support from one's spouse ( $N = 497$ ), leaving an analytical sample size of 5,934 individuals. **(Figure 1)**

### *Exposure: Spousal Positive Social Support*

Positive social support from a spouse was based on three questions: “How much do they really understand the way you feel about things?”; “How much can you rely on them if you have a serious problem?”; and “How much can you open up to them if you need to talk about your worries?” The four response options range from “not at all” to “a lot”. We averaged responses to these three questions to obtain a score ranging from 1 to 4, with higher scores representing more

positive social support. As in other studies, participants with a score of 4 were categorized as very supported by a spouse, and those with lower scores were categorized as not supported.<sup>49</sup>

The exposure variable was measured at analytic baseline (t0).

#### *Outcome: Dementia/CIND Incidence*

Our outcome of interest was incident dementia or cognitive impairment without dementia (CIND). We used the 27-point Langa-Weir classification score to assess respondents' cognitive outcomes: normal (12-27), CIND (7-11), and having dementia (0-6).<sup>50</sup> For individuals who were unable to complete the score or survey without assistance, the proxy 11-point scale was used, where 0-2, 3-5, and 6-11 for each respective group.<sup>50,51</sup> The outcome variable was measured as a time to event outcome.

#### *Potential Mediator: Elevated depressive symptoms*

Depression served as the mediator of interest in the present analysis. This variable was collected two years after baseline, and its baseline value was adjusted for in the analysis. Depression at baseline was defined using the Center for Epidemiologic Studies Depression (CESD) scale, which has a 0 to 8 range, with 6 negative and 2 positive indicators.<sup>69</sup> This scale is a summary measure of how the participants were feeling much of the time over the past week and focuses on feeling depressed, activities were efforts, restless sleep, happiness, loneliness, sadness, enjoyment of life, and feeling unmotivated.<sup>69</sup> We used the binary cut-off of 5 as an indicator of elevated depression symptoms, as this has been used in other studies using the HRS dataset.<sup>118</sup> We also used this cut off because a more conservative cut off has been suggested for older adults.<sup>118,119</sup> The mediator variable was measured at the first follow-up time, 2010 or 2012 (t1).

### *Potential Confounders*

Based on the directed acyclic graph (DAG), we selected the following potential confounders for the social support-dementia relationship: sex (male, female), age (years), race and ethnicity (NH White, NH Black, Hispanic), depression at baseline using the Center for Epidemiologic Studies Depression (CESD) scale ( $\geq 5$ ), education (continuous), and income-poverty ratio at baseline (continuous). We also conducted a sensitivity analysis with the same previously listed potential confounders, adding the number of chronic diseases (0-7). These covariate variables were measured at analytic baseline (t0). **(Figure 2)**

### *Statistical analysis*

We used g-computation in our causal survival mediation analysis to estimate the indirect and direct effects of spousal social support on dementia via depression symptoms and pathways not involving depression. We used a 2-way decomposition of the total effect (TE) into the total indirect effect (TIE) and the pure direct effect (PDE), also known as the natural indirect effect and natural direct effect, respectively.<sup>120</sup> This decomposition best fits our research question as we were interested in the extent to which positive spousal social support affects dementia/CIND risk through depression alone, accounting for interactions between social support and depression (TIE), and the extent to which positive social support from a spouse affects dementia/CIND risk in ways other than through depression alone (PDE).<sup>120</sup> The PDE compares the potential outcomes of incident dementia/CIND under high and low positive spousal support when the mediator (elevated depressive symptoms) is set to the level it would be if positive social support was low ( $E[Y_{xM_{x^*}} - Y_{x^*M_{x^*}}]$ ).<sup>53</sup> The TIE compares the potential outcomes of incident dementia/CIND under elevated depressive symptoms being set to what would occur if people

had high compared to low positive spousal support and the outcome is set to the value it would be under high positive spousal support ( $E[Y_{xM_x} - Y_{xM_{x^*}}]$ ).<sup>53</sup>

Additionally, we also calculated the pure indirect effect (PIE) and the controlled direct effect among individuals without the mediator (CDE) in order to look at interactions in the effect decompositions. Interactions between the exposure and mediator can account for some of the impact on the outcome in both the indirect and direct pathways. As an alternative to the TIE, the PIE examines the extent to which positive social support from a spouse affects dementia risk only through depression, without interactions between social support and depression ( $E[Y_{x^*M_x} - Y_{x^*M_{x^*}}]$ ).<sup>120</sup> The CDE examines the direct effect of positive spousal social support on dementia/CIND risk while fixing depression at a value of no depressive symptoms for the entire study population ( $E[Y_{xm^*} - Y_{x^*m^*}]$ ).<sup>120</sup> We included these additional measures to compare the indirect effects where interactions are present versus not and calculate the portion eliminated, which requires both the TE and the CDE.

Our analysis required the following causal assumptions: positivity, consistency, conditional exchangeability, no model misspecification, and no other sources of bias.<sup>120,121</sup> Positivity means that every value of exposure has a non-zero probability for each participant in the dataset.<sup>122</sup> Consistency indicates a clear definition for the exposure and assumes an individual's potential outcome when exposed to their observed exposure is their observed outcome.<sup>122,123</sup> In causal mediation analysis, conditional exchangeability refers to the absence of uncontrolled confounding between: exposure and mediator; exposure and outcome; and mediator and outcome.<sup>121</sup> We also assumed the exposure did not cause an additional mediator (besides depression) that would act as a confounder of the mediator-outcome relationship. We further

assumed that no other unaddressed sources of bias, such as selection or information bias, existed. Finally, we assumed no model misspecification and conditionally independent censoring for our data analysis.

The steps for g-computation include the following: i) create expectations of the exposure, mediator, and covariates guided by our DAG; ii) generate a model for the mediator by regressing the mediator on the other covariates and exposure and obtain regression coefficients, accounting for censoring (drop out or death) using inverse probability of censoring weights (IPCW); the IPCW to create a pseudo-population uses distribution of measured covariates and potential predictors of loss to follow-up including age, sex, education, baseline depression, race and ethnicity, income poverty ratio, and chronic disease number to imitate the total population before censoring<sup>124</sup>; iii) regress the outcome on the mediator, exposure, and other covariates and record the regression coefficients; iv) predict the potential mediators using the regression coefficients from the mediator model by simulating a new intervention variable, potential mediator variable, and covariates distributions that follows observed variables; v) simulate the exposure that follows the observed prevalence; vi) predict the potential outcomes using the regression coefficients from the outcome model by simulating a new intervention variable, potential mediator variable, and covariates distributions that follows observed variables; vii) obtain the TIE, PDE, and CDE with the entire sample set to not have elevated depressive symptoms, PIE, and TE using the sum (for the RD) or product (for the RR) of PDE and TIE; viii) Use bootstrap techniques to obtain the confidence intervals.<sup>120</sup> The following variables were included in IPCW formula was used to obtain our weights: sex/gender, age, depression at baseline, years of education, race/ethnicity, income poverty ratio, and number of chronic diseases.

We included a product term for the mediator and exposure in our analyses to examine if there is also an interaction present between elevated depressive symptoms and positive spousal social support. The portion eliminated was calculated as the difference between the TE and the CDE, while the proportion mediated was derived as the quotient of each indirect effect relative to the total effect. We stratified all analyses by sex/gender to find unique mechanisms for how social support affects dementia/CIND risk for each sex/gender subpopulation.

To model dementia/CIND as a time-to-event outcome, we used causal survival analysis, including pooled logistic regression with our exposure, outcome, mediator, interaction terms between the exposure and potential confounders, and a quadratic term for time. This method not only allowed us to properly model time when estimating our risk differences and risk ratios but also does not require a proportional hazard assumption.<sup>125,126</sup> All analyses were conducted using RStudio 4.5.1 (Posit Software, PBC, Boston, MA). We used *miceRanger* to impute any missing values in our data and calculated inverse probability censoring weights (IPCW) to account for attrition in our sample.

## RESULTS

### *Sample characteristics*

The participants in this study had an average baseline age of 66 years. The majority of the sample identified as Non-Hispanic (NH) White, female, completely retired, with no financial strain. About 6.2% of individuals identified as Hispanic, and 5.8% who identified as Non-Hispanic Black. About 40% of the sample were exposed to the highest level of spousal social support. Other characteristics include an average education of about 13 years, 1.79 chronic diseases, and an income poverty ratio of 6.6. The income poverty ratio compared the ratio of

household income to the poverty threshold, so a value above 1 demonstrates economic stability.<sup>127</sup> **(Table 1)**

Some sex-specific differences included women having an average baseline age of 65, which was older than the average baseline age for men (67). Women also had a lower percentage of high social support from a spouse than men (34% vs 48%), less education (13.23 vs 13.65 years), more depression (1.08), less high physical activity (26%), more ongoing chronic stress (12), less risky alcohol users (3.6%), and more never smokers (54%), than their male counterparts. **(eTable 1)**

*Total effect between positive spousal social support and time-to-dementia/CIND*

Among married/partnered individuals, there were 2.5 (RD = -2.5, 95%CI: -5.8, 0.8) fewer cases of dementia/CIND per 100 individuals at the end of the 14-year period among people with high positive spousal social support when compared to those with low positive spousal social support after adjusting for potential confounders. Among married/partnered men, the results for the total effect were inconclusive, with an RD of 0.1 (95%CI: -3.8, 4.0). For women, there were 3.7 (RD = -3.7, 95%CI: -8.8, 1.4) fewer cases of dementia/CIND per 100 individuals more cases of dementia/CIND per 100 individuals at the end of the 14 year follow-up, among women with high positive spousal social support, when compared to those with low positive spousal social support. These effects are mostly consistent with a protective effect of positive spousal support across the overall and female populations; however, given the imprecision of the estimates, one cannot rule out a null or detrimental effect of high positive social support on dementia/CIND risk. For the male population, this result is mostly compatible with a null effect of positive spousal support; given the imprecision of the estimates, one cannot rule out either detrimental or

protective effects of high positive social support on dementia/CIND risk. The average effects over the 14 years of follow-up were similar to the end-of-follow-up effects for each population.

**(Table 2 and 3)**

The total effect on the risk ratio scale for the overall population was inconclusive on average but end-of-follow-up effects for the overall populations and both effects for the male and female subgroup populations reflected the similar conclusions to the risk difference results.

**(eTable 3 and 4)** All results were similar for the model that included ongoing stress as a potential confounder for both scales. **(eTable 5-8)**

*Indirect effects via elevated depressive symptoms, portion eliminated, and portion mediated*

In particular, the total indirect effect of high positive spousal social support on dementia/CIND risk was mediated by elevated depressive symptoms and did not vary by sex/gender. Specifically, had all participants received high spousal support and their depressive symptoms reflected levels consistent with high spousal support, the number of dementia/CIND cases at the end of the 14-year follow-up period would have been 1.1 fewer (RD = -1.1, 95% CI: -2.1, -0.1) compared to a scenario in which all participants received high spousal support but their depressive symptoms reflected levels consistent with low spousal support. This effect was similar across groups when examining the average effect over the 14-year period, but continued not to vary by sex/gender (RD = -0.9, 95%CI (-1.7, 0)).

The corresponding percent mediated was 40% at the end of follow-up for the overall population, suggesting that the potential effect of high positive spousal support could be enhanced by depressive symptoms. **(Table 2 and 3)** The pure indirect effect yielded a comparatively smaller estimate, attributable to the exclusion of any interaction between high

spousal support and depressive symptoms on dementia/CIND risk, under assumptions of no unmeasured confounding and correct model specification. Therefore, the interaction between high positive spousal support and depressive symptoms accounts for the difference between the total indirect effect and the pure indirect effect. **(Table 2 and 3)**

All results were similar on the risk ratio scale and for the model that included ongoing stress as a potential confounder for both scales. **(eTable 3-8)**

*Direct effects between positive spousal social support and time-to-dementia/CIND*

The pure direct effect of high positive spousal social support on dementia/CIND risk at the end of follow-up suggested that a portion (RD = -1.6, 95%CI (-5.1, 1.9)) of the total effect was not operating through elevated depressive symptoms, though the estimates were imprecise. The pure direct effect on average for high positive spousal social support on dementia/CIND risk suggested little to no portion (RD = -0.2, 95%CI (-3.0, 2.7)) of the total effect was not operating through elevated depressive symptoms. These effects varied by sex/gender: the male subgroup of married/partnered individuals had a pure direct effect of RD = 1.2 (95% CI: -2.9, 5.2), whereas the female subgroup had a pure direct effect of RD = -2.6 (95% CI: -8.0, 2.8). The effects, on average, yielded similar conclusions, except that the pure direct effect was overall inconclusive.

The effect of high positive spousal social support on dementia/CIND risk, had all individuals not been exposed to depressive symptoms (i.e., CDE), was 2.5 fewer (RD = -2.5, 95%CI: -5.8, 0.8) cases at the end of follow-up, compared to the low positive support individuals. Among married/partnered men, the effect of high positive spousal social support on dementia/CIND risk was inconclusive, had all individuals not been exposed to depressive symptoms (RD = 0.6, 95%CI: -3.7, 4.8) at the end of follow-up. Among married/partnered

women, the effect of high positive spousal social support on dementia/CIND risk had all individuals not been exposed to depressive symptoms was 3.9 fewer cases (RD = -3.8, 95%CI: -8.8, 1.2) when compared to the low positive support individuals. The effects for the overall and female groups, on average, yielded similar conclusions. Among married/partnered men, the effect of high positive spousal social support on dementia/CIND risk had all individuals not been exposed to depressive symptoms was 2 more cases (RD = 2.0, 95%CI: -1.2, 5.2) on average when compared to the low positive support individuals. These effects are mostly compatible with a protective effect of positive spousal support across the overall and female populations; however, given the imprecision of the estimates, one cannot rule out a null or detrimental effect of high positive social support on dementia/CIND risk. For the male population, this result is mostly compatible with a null effect of positive spousal support; however, given the imprecision of the estimates, one cannot rule out a detrimental and protective effect of high positive social support on dementia/CIND risk. **(Tables 2 and 3)** The interaction present between positive spousal support and elevated depressive symptoms contributed to the difference seen when comparing CDE to PDE.

All results were similar on the risk ratio scale and for the model that included ongoing stress as a potential confounder for both scales. **(eTable 3-8)**

#### *Discrete time effects*

Our results demonstrated that the effect of positive social support from one's spouse on dementia/CIND risk varied by time and sex/gender. Overall, both the pure and total effects demonstrated detrimental associations in the early follow-up period, crossing the null at approximately 5 years, after which the combined protective contributions of the pure direct and

total indirect effects yielded a moderately protective total effect. **(Figure 4)** For men, the pure and total effect approached the null without ever crossing from detrimental effects into protective effects. **(Figure 5)** It is possible that, with a longer time frame, the pure and total effects could become protective, given current trajectories. Among women, the pure direct, total indirect, and total effects were uniformly protective throughout the 14-year follow-up period. However, the corresponding estimates were statistically compatible with predominantly protective and some detrimental effects, precluding definitive conclusions regarding the direction of association. **(Figure 6)**

## **DISCUSSION**

This study investigated the role of elevated depressive symptoms in the relationship between positive social support from one's spouse and time to incident dementia/CIND among married and partnered individuals. Additionally, we observed the mediated effects did not vary by sex/gender. Our results suggest that positive social support had a moderately protective effect on incidence dementia/CIND and some mediated occurred through elevated depressive symptoms in both the overall population and female subpopulation, although results were imprecise. Also, under the hypothetical scenario in which all participants had no depressive symptoms, positive social support had a slightly larger protective effect on dementia/CIND risk for the overall and sex/gender populations. In the male subpopulation, the total effect of positive spousal support on incident dementia/CIND was null, including effects that were equally protective and harmful. The indirect effect was consistently protective when both interactions between positive social support and elevated depressive symptoms were absent and present for all three groups.

The mechanism of how positive social support from one's spouse affects dementia/CIND risk remains elusive in the current literature. Our findings were crucial in uncovering this gap in the current social support research. Khondoker et al. examined the differential effects of positive and negative social support interactions across multiple key relationships on dementia risk.<sup>128</sup> Using the English Longitudinal Study of Ageing, they found that negative social support from spouse, children, and other immediate family was associated with an increased dementia risk. Although the findings for positive spousal social support were reported as null, the results suggest a hazard ratio of 0.83 (95% CI 0.67 to 1.04) for positive spousal support on dementia risk. The confidence interval was also compatible with moderately protective to minimally harmful effects on dementia risk, suggesting a moderate protective association, given the data and statistical assumptions. This finding aligns with our results, which show that positive spousal support has a moderately protective effect on dementia risk. Our study advances the current literature by not only identifying this protective effect among women and in the overall sample, but also by revealing that elevated depressive symptoms partially explains how this protection operates — that is, spousal support may reduce dementia risk in part by buffering against depression.

Several studies have explored depression as a mediator in the relationship between social factors and cognitive outcomes. A cross-sectional study conducted in China identified a mediating role of depression (47%) on the association between social support from multiple sources of the social network and global cognition.<sup>129</sup> Additionally, two longitudinal studies from China reported comparable findings, demonstrating that depression mediated the relationships between social activities and cognitive impairment (indirect effect = 0.023), and between loneliness and incident dementia, respectively (36%).<sup>130,131</sup> These findings are

consistent with these conclusions, as our observed indirect effect appeared to be a comparable magnitude, and our percent mediated was lower than the combined effect of multiple social support sources, as anticipated (overall percent mediated at 14-year follow-up = 40%).

The effects of marriage on depressive symptoms have been seen to vary by gender, where men have protection against depression from marriage and married women have higher depression rates than unmarried men and women respectively.<sup>132,133</sup> However, our null finding for the total effect in men, may be due to the indirect and direct effects being in opposite directions rather than discounting the presence of an indirect or direct effect.<sup>134</sup> The effect of positive spousal support on dementia/CIND for men accounts for a large portion of the total effect, and both effects are observed to increase dementia/CIND risk. This could be explained by reverse causation and activation of social ties when an individual starts exhibiting cognitive decline.<sup>57</sup>

The protective effect of depression suggests identifying depression among those with positive social support from their spouse may result in fewer dementia cases. This may allow an individual to treat their depressive symptoms, thereby reducing dementia risk, and limits the chances of the depressive symptoms being mistaken for dementia symptoms. Alternatively, depression may not be a straightforward mediator but rather one pathway among several competing mechanisms. This kind of inconsistent mediation can also arise when the outcome is influenced by suppressor effects — where controlling for depression actually reveals a stronger or differently-directed relationship between spousal support and dementia than exists in the other models not concerned with mediation.<sup>135,136</sup> These competing pathways suggest that the relationship between spousal support and dementia is not simply protective across all channels,

but is instead shaped by the interplay of emotional, behavioral, and relational factors that future research should disentangle.

Depression and dementia are the most common neuropsychiatric disorders in the older adult population.<sup>137</sup> These disorders may present concurrently or as discrete clinical entities among older adults. Depression can increase the risk of dementia/CIND, potentially due to mechanisms in the cerebrovascular pathology and neuroinflammation, and is prevalently listed as one of the top behavioral and psychological symptoms of dementia.<sup>113,138</sup> As a symptom of dementia, depression can accelerate cognitive and functional decline in elderly populations.<sup>138</sup> Given the complex, close relationship between depression and dementia, it is unsurprising that we discovered an indirect pathway between social support and dementia/CIND risk through depression. While the efficacy of antidepressants in treating depression and dementia simultaneously remains unclear, addressing depression proactively as patients age may nonetheless be a worthwhile clinical strategy, given its potential to reduce the long-term risk of dementia development.

The clinical manifestation and distribution of depression differ substantially between male and female populations.<sup>139–142</sup> For example, women are more likely to develop dementia than men.<sup>142</sup> However, our results showed depression mediates the pathway between positive social support and dementia/CIND risk, as seen by all TIEs demonstrating protective effects, despite the gender differences in social support perception and depression prevalence, symptomatology, and risk. Despite this, there should be a focus on treating aging women for depression, as this could potentially decrease the risk of later development of dementia in women, particularly because they are at greater risk for both diseases. These complex gender differences require further explanation to reveal the mechanisms for these effects.

Our study is not without limitations. First, we used the CES-D score for elevated depressive symptoms at one time point for interpretability and temporality. Still, by doing so, we assume that each individual's depression symptoms will remain consistent throughout the follow-up period. Second, our sample size was significantly reduced due to filtering requirements, so married/partnered individuals were the only participants in our study, potentially explaining the imprecision of our findings. Our selection of married/partnered-only participants could also introduce selection bias as seen in our DAG, since being married or partnered was required to answer the spousal support question and be included in this study. Marital status is associated with outcomes of dementia<sup>29</sup> (**eFigure 1**). In addition, changes in marital status are possible in the follow-up period, and these changes could reflect shifts in their positive social support from their spouse. The incidence of dementia/CIND outcomes was lower in our study due to our smaller sample; a longer study period and a larger married/partnered population, where more participants reach the higher risk years for developing dementia, might yield a stronger effect. Lastly, the Langa Weir score has been shown to have lower classification accuracy in older adults than other scores.<sup>68</sup> Future studies should investigate time-varying depression symptoms as a mediator and use other validated dementia algorithms to explore the mediated effect elevated depressive symptoms has on positive social support from one's spouse on dementia/CIND risk.

## CONCLUSION

Positive social support from a spouse had a moderately protective effect on dementia risk, and elevated depressive symptoms accounted for some of this impact. However, the confidence intervals included both large protective and small harmful effects. Depression mediated the association between the positive spousal support from a spouse and dementia/CIND. The

mediated effects did not vary by sex/gender. Treating depressive symptoms could potentially represent an alternative intervention target for reducing dementia risk. The positive effect from positive social support from a spouse on dementia and cognitive impairment risk can be partially explained by depressive symptoms. Future research should examine additional theoretical mechanisms — including social strain — alongside social support, employing larger samples and extended longitudinal designs to assess these relationships more rigorously.

## TABLES AND FIGURES

| <b>Table 1. Descriptive Statistics for Overall Health and Retirement Study Population, N=5,934, HRS, 2006-2020</b> |                     |
|--------------------------------------------------------------------------------------------------------------------|---------------------|
| <b>Characteristic</b>                                                                                              | <b>N = 5,934</b>    |
| <b>Age (Years)</b>                                                                                                 |                     |
| Mean (Min, Max)                                                                                                    | 66 (50, 95)         |
| <b>Male, n (%)</b>                                                                                                 |                     |
| Female                                                                                                             | 3,148 (53%)         |
| Male                                                                                                               | 2,786 (47%)         |
| <b>Race/Ethnicity (4 categories), n (%)</b>                                                                        |                     |
| Hispanic                                                                                                           | 369 (6.2%)          |
| Non-Hispanic Black                                                                                                 | 346 (5.8%)          |
| Non-Hispanic White                                                                                                 | 5,112 (86%)         |
| Other                                                                                                              | 107 (1.8%)          |
| <b>Positive Spousal Social Support, n (%)</b>                                                                      |                     |
| High Social Support                                                                                                | 2,395 (40%)         |
| Low Social Support                                                                                                 | 3,539 (60%)         |
| <b>Participant Years of Education</b>                                                                              |                     |
| Mean (Min, Max)                                                                                                    | 13.42 (0.00, 17.00) |
| <b>Income Poverty Ratio</b>                                                                                        |                     |
| Mean (Min, Max)                                                                                                    | 6.6 (0.0, 680.0)    |
| <b>Retirement Status (3 categories), n (%)</b>                                                                     |                     |
| Completely retired                                                                                                 | 2,628 (44%)         |
| Not applicable                                                                                                     | 491 (8.3%)          |
| Not retired                                                                                                        | 2,001 (34%)         |
| Partly retired                                                                                                     | 811 (14%)           |
| <b>Chronic Disease Number</b>                                                                                      |                     |
| Mean (Min, Max)                                                                                                    | 1.79 (0.00, 7.00)   |
| <b>CESD/Depression Score</b>                                                                                       |                     |
| Mean (Min, Max)                                                                                                    | 0.96 (0.00, 8.00)   |
| <b>Openness to Experience Index</b>                                                                                |                     |
| Mean (Min, Max)                                                                                                    | 2.99 (1.14, 4.00)   |

| <b>Table 1.</b> Descriptive Statistics for Overall Health and Retirement Study Population, N=5,934, HRS, 2006-2020 |                   |
|--------------------------------------------------------------------------------------------------------------------|-------------------|
| <b>Characteristic</b>                                                                                              | <b>N = 5,934</b>  |
| <b>Conscientiousness Index</b>                                                                                     |                   |
| Mean (Min, Max)                                                                                                    | 3.41 (1.20, 4.00) |
| <b>Extraversion Index</b>                                                                                          |                   |
| Mean (Min, Max)                                                                                                    | 3.23 (1.20, 4.00) |
| <b>Agreeableness Index</b>                                                                                         |                   |
| Mean (Min, Max)                                                                                                    | 3.54 (1.60, 4.00) |
| <b>Neuroticism Index</b>                                                                                           |                   |
| Mean (Min, Max)                                                                                                    | 2.02 (1.00, 4.00) |
| <b>High Physical Activity, n (%)</b>                                                                               |                   |
| High Physical Activity                                                                                             | 1,735 (29%)       |
| Low Physical Activity                                                                                              | 4,199 (71%)       |
| <b>Smoking Status (3 categories), n (%)</b>                                                                        |                   |
| Current                                                                                                            | 590 (10%)         |
| Former                                                                                                             | 2,665 (45%)       |
| Never                                                                                                              | 2,633 (45%)       |
| <b>Risky Alcohol Use, n (%)</b>                                                                                    |                   |
| High Risky Alcohol Use                                                                                             | 406 (6.8%)        |
| Low Risky Alcohol Use                                                                                              | 5,523 (93%)       |
| <b>Married/Partnered, n (%)</b>                                                                                    |                   |
| Married or Partnered                                                                                               | 5,934 (100%)      |
| <b>Financial Strain, n (%)</b>                                                                                     |                   |
| Not at all difficult                                                                                               | 2,620 (45%)       |
| Not very difficult                                                                                                 | 1,951 (33%)       |
| Somewhat difficult                                                                                                 | 1,022 (17%)       |
| Very difficult                                                                                                     | 214 (3.7%)        |
| Completely difficult                                                                                               | 51 (0.9%)         |
| <b>Chronic Stress Scale</b>                                                                                        |                   |
| Mean (Min, Max)                                                                                                    | 11.7 (2.0, 32.0)  |
| <b>Depression Score in Second Wave, n (%)</b>                                                                      |                   |
| Depressed                                                                                                          | 307 (5.8%)        |
| Not Depressed                                                                                                      | 4,948 (94%)       |

**Table 1.** Descriptive Statistics for Overall Health and Retirement Study Population, N=5,934, HRS, 2006-2020

| Characteristic                                     | N = 5,934   |
|----------------------------------------------------|-------------|
| Ever having dementia or CIND after baseline, n (%) | 1,499 (25%) |

**Table 2.** Risk differences for the average association between positive spousal social support and dementia mediated through depression, N=5,934, HRS, 2006-2020

| Population | Total Effect <sup>1</sup> | Pure Direct Effect (PDE) <sup>1</sup> | Total Indirect Effect (TIE) <sup>1</sup> | Pure Indirect Effect (PIE) <sup>1</sup> | Controlled Direct Effect (CDE) <sup>2</sup> | Proportion Eliminated (PE) <sup>3</sup> | % Mediated TIE <sup>4</sup> | % Mediated PIE <sup>5</sup> |
|------------|---------------------------|---------------------------------------|------------------------------------------|-----------------------------------------|---------------------------------------------|-----------------------------------------|-----------------------------|-----------------------------|
|            | RD (95% CI) per 100       | RD (95% CI) per 100                   | RD (95% CI) per 100                      | RD (95% CI) per 100                     | RD (95% CI) per 100                         |                                         |                             |                             |
| Overall    | -1.0 (-3.7, 1.6)          | -0.2 (-3.0, 2.7)                      | -0.9 (-1.7, 0)                           | -0.5 (-0.8, -0.2)                       | -0.9 (-3.6, 1.8)                            | 0.13%                                   | 84%                         | 48%                         |
| Men        | 1.6 (-1.4, 4.6)           | 2.5 (-0.6, 5.7)                       | -0.9 (-1.8, 0)                           | -0.6 (-1.1, -0.1)                       | 2.0 (-1.2, 5.2)                             | -0.23%                                  | -56%                        | -38%                        |
| Women      | -3.0 (-7.0, 1.0)          | -2.1 (-6.3, 2.0)                      | -0.9 (-2.0, 0.3)                         | -0.5 (-0.9, 0)                          | -3.0 (-7.1, 1.0)                            | -0.01%                                  | 29%                         | 15%                         |

<sup>1</sup>Model a: Adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio. Bootstrapping was performed to estimate 95% confidence interval.

<sup>2</sup>Controlled direct effect where the mediator is set to 0

<sup>3</sup>Proportion eliminated calculated by total effect - controlled direct effect divided by the total effect and therefore, depends on both total effect and controlled direct effect.

<sup>4</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and total indirect effect.

<sup>5</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and pure indirect effect.

**Table 3.** Risk differences for the end of follow up association between positive spousal social support and dementia mediated through depression, N=5,934, HRS, 2006-2020

| Population | Total Effect <sup>1</sup> | Pure Direct Effect (PDE) <sup>1</sup> | Total Indirect Effect (TIE) <sup>1</sup> | Pure Indirect Effect (PIE) <sup>1</sup> | Controlled Direct Effect (CDE) <sup>2</sup> | Proportion Eliminated (PE) <sup>3</sup> | % Mediated TIE <sup>4</sup> | % Mediated PIE <sup>5</sup> |
|------------|---------------------------|---------------------------------------|------------------------------------------|-----------------------------------------|---------------------------------------------|-----------------------------------------|-----------------------------|-----------------------------|
|            | RD (95% CI) per 100       | RD (95% CI) per 100                   | RD (95% CI) per 100                      | RD (95% CI) per 100                     | RD (95% CI) per 100                         |                                         |                             |                             |
| Overall    | -2.5 (-5.8, 0.8)          | -1.6 (-5.1, 1.9)                      | -1.1 (-2.1, -0.1)                        | -0.6 (-1.0, -0.2)                       | -2.5 (-5.8, 0.8)                            | 0.07%                                   | 40%                         | 23%                         |
| Men        | 0.1 (-3.8, 4.0)           | 1.2 (-2.9, 5.2)                       | -1.1 (-2.1, 0)                           | -0.8 (-1.4, -0.1)                       | 0.6 (-3.7, 4.8)                             | -4.60%                                  | —                           | —                           |

|       |                  |                  |                  |                |                  |        |     |     |
|-------|------------------|------------------|------------------|----------------|------------------|--------|-----|-----|
| Women | -3.7 (-8.8, 1.4) | -2.6 (-8.0, 2.8) | -1.2 (-2.7, 0.4) | -0.6 (-1.1, 0) | -3.8 (-8.8, 1.2) | -0.02% | 31% | 16% |
|-------|------------------|------------------|------------------|----------------|------------------|--------|-----|-----|

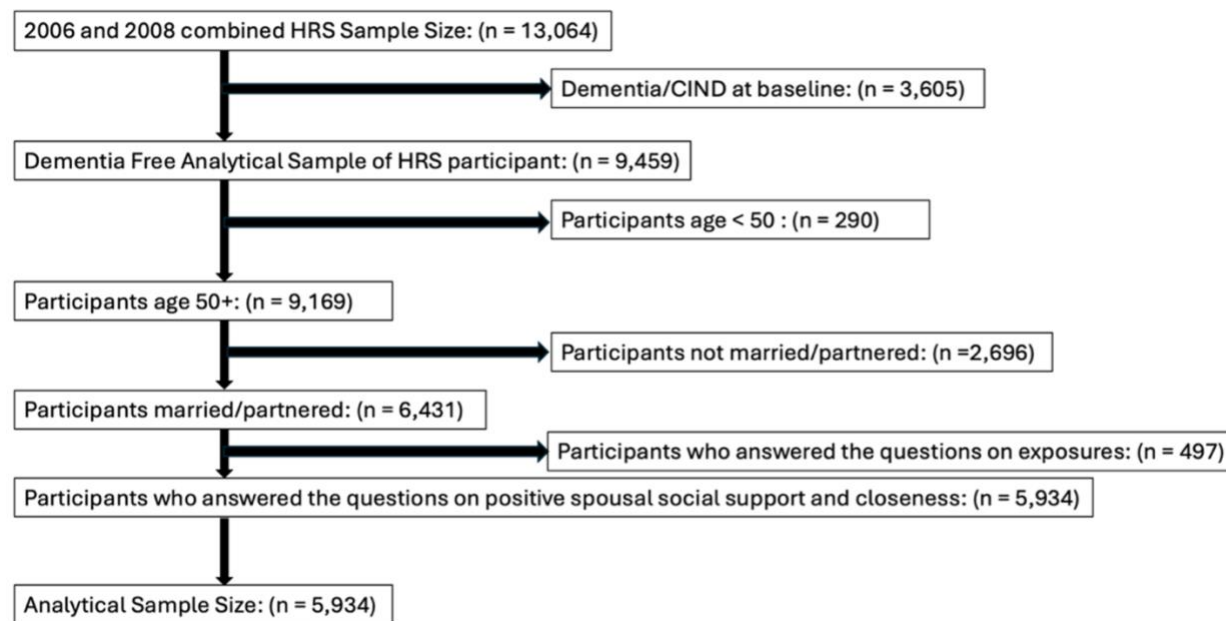
<sup>1</sup>Model a: Adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio. Bootstrapping was performed to estimate 95% confidence interval.

<sup>2</sup>Controlled direct effect where the mediator is set to 0

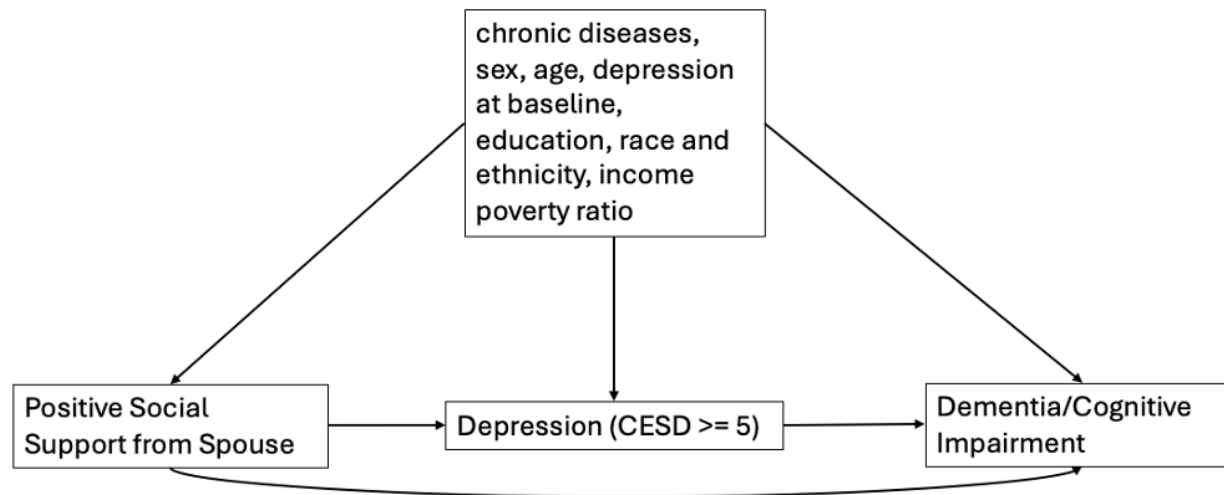
<sup>3</sup>Portion eliminated calculated by total effect - controlled direct effect and therefore, depends on both total effect and controlled direct effect.

<sup>4</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and total indirect effect. For the male subgroup, we did not calculate the percent mediated because the total effect was null and results in a large percent mediated that is > 100%.

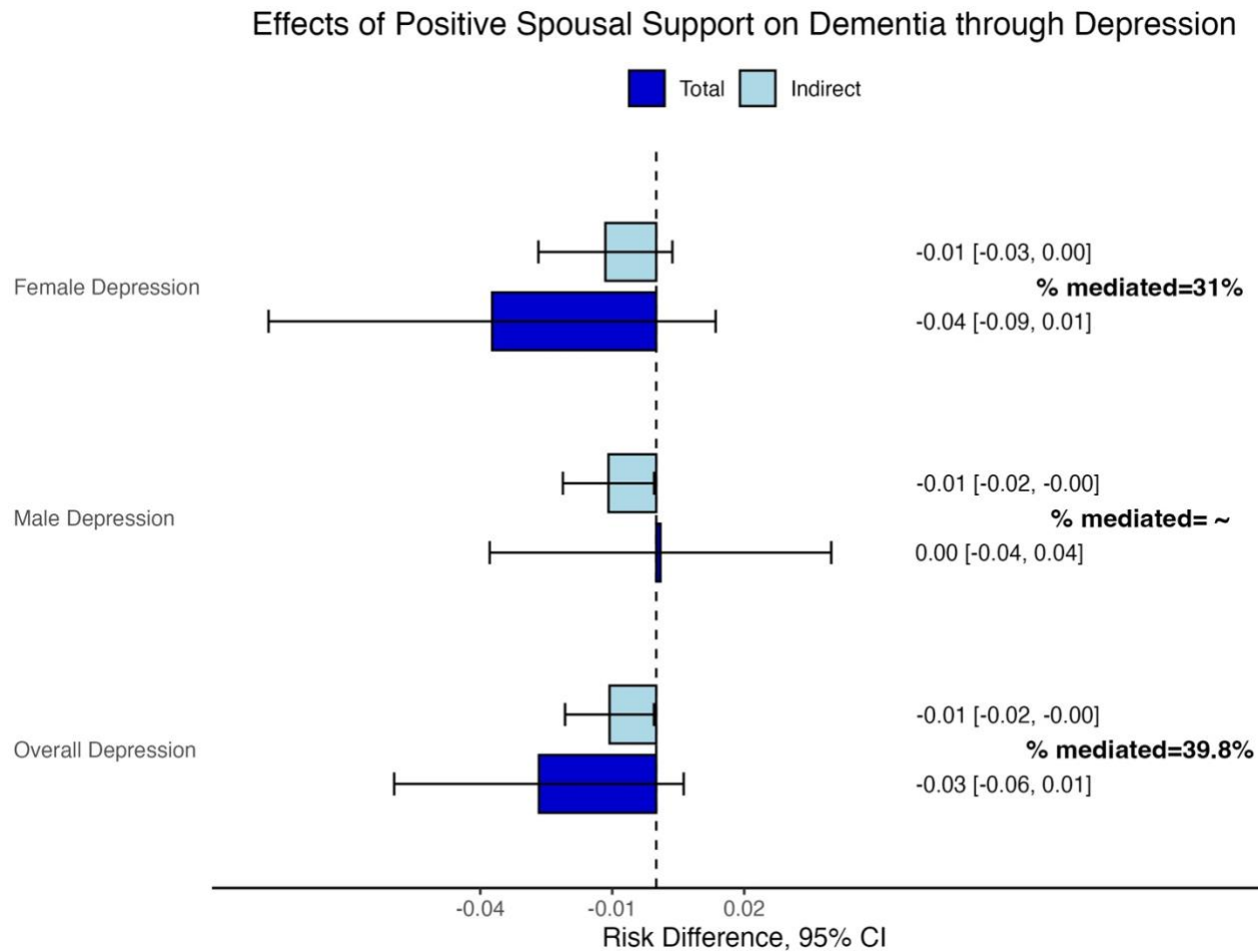
<sup>5</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and pure indirect effect. For the male subgroup, we did not calculate the percent mediated because the total effect was null and results in a large percent mediated that is > 100%.



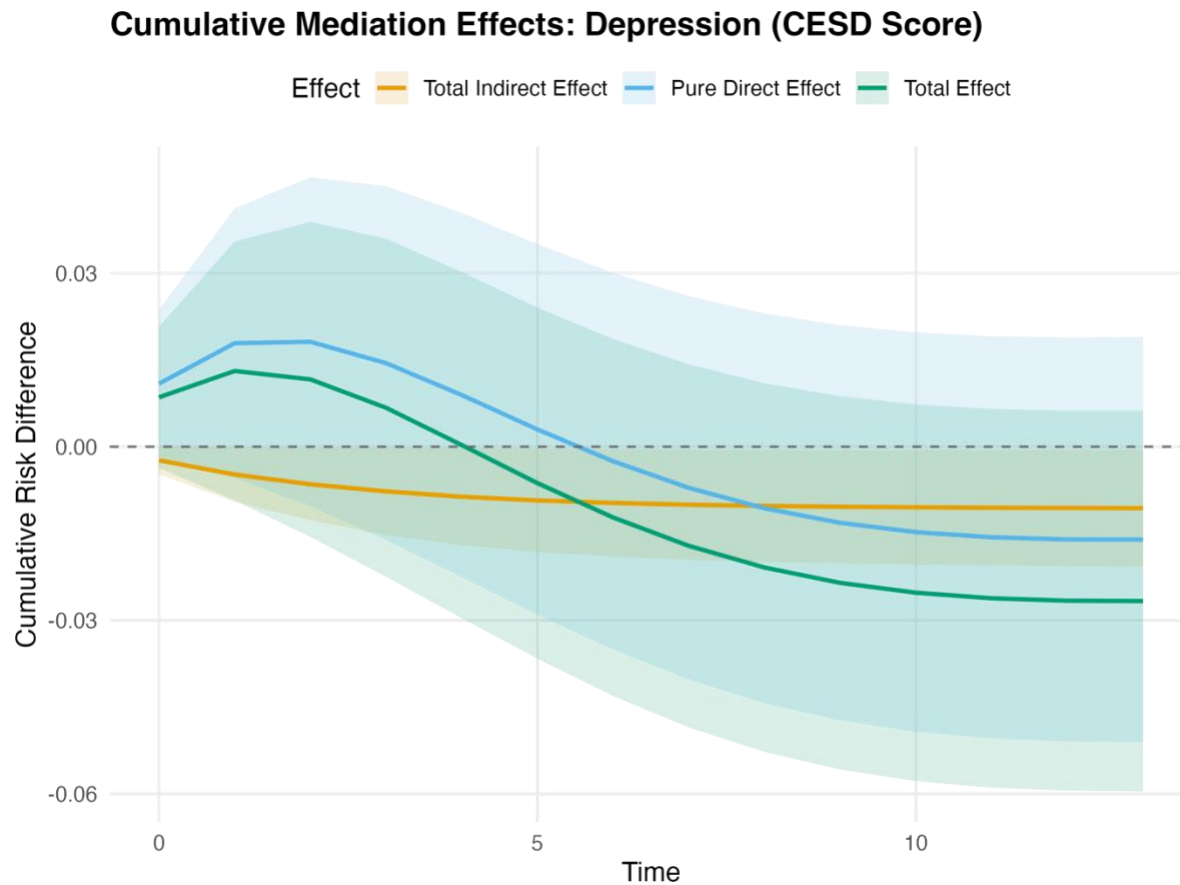
**Figure 1.** Flow diagram for Health and Retirement Study (HRS) sample, inclusion/exclusion criteria, and analytical sample



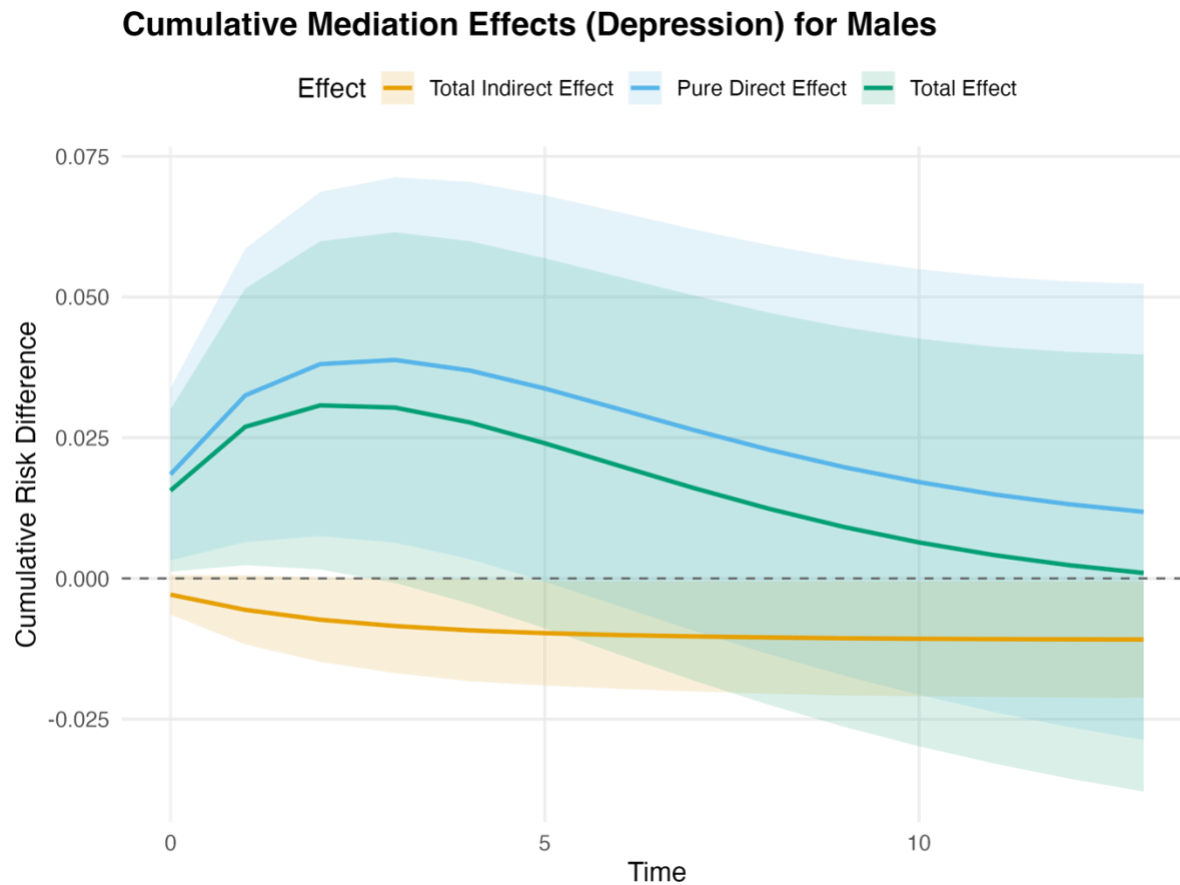
**Figure 2.** Directed acyclic graph (DAG) for study



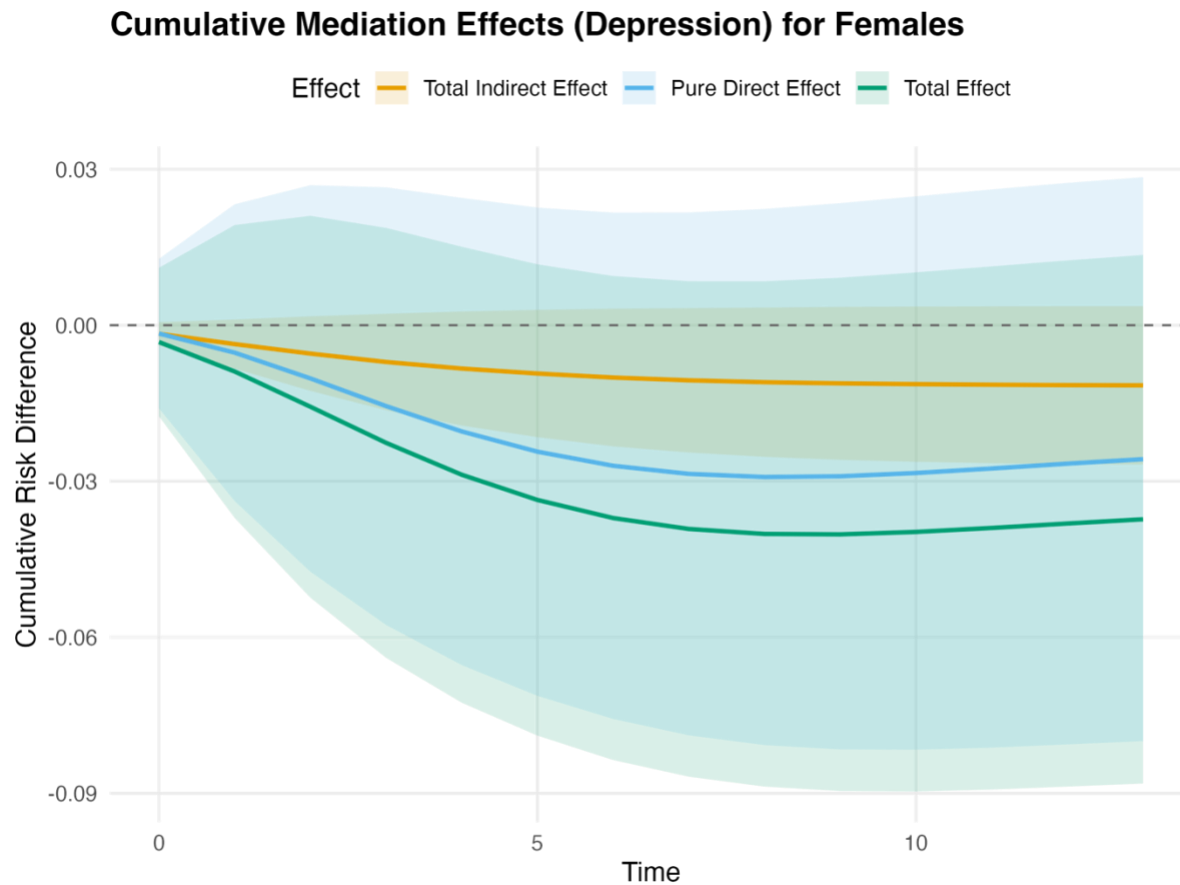
**Figure 3.** An overview of the study on positive spousal social support on dementia/CIND through depression in Risk Differences. TE, total effect; TIE, total indirect effect; and the portion mediated using the TIE and TE for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio



**Figure 4.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the overall population over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio



**Figure 5.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the male population over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio



**Figure 6.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the female population over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio

## APPENDIX

| <b>eTable 1.</b> Descriptive Statistics for Overall Health and Retirement Study Population Stratified by Sex/Gender, N=5,934, HRS, 2006-2020 |                             |                           |
|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|---------------------------|
| <b>Characteristic</b>                                                                                                                        | <b>Female<br/>N = 3,148</b> | <b>Male<br/>N = 2,786</b> |
| <b>Age (Years)</b>                                                                                                                           |                             |                           |
| Mean (Min, Max)                                                                                                                              | 65 (50, 91)                 | 67 (50, 95)               |
| <b>Race/Ethnicity (4 categories), n (%)</b>                                                                                                  |                             |                           |
| Hispanic                                                                                                                                     | 195 (6.2%)                  | 174 (6.2%)                |
| Non-Hispanic Black                                                                                                                           | 192 (6.1%)                  | 154 (5.5%)                |
| Non-Hispanic White                                                                                                                           | 2,710 (86%)                 | 2,402 (86%)               |
| Other                                                                                                                                        | 51 (1.6%)                   | 56 (2.0%)                 |
| <b>Positive Spousal Social Support, n (%)</b>                                                                                                |                             |                           |
| High Social Support                                                                                                                          | 1,058 (34%)                 | 1,337 (48%)               |
| Low Social Support                                                                                                                           | 2,090 (66%)                 | 1,449 (52%)               |
| <b>Participant Years of Education</b>                                                                                                        |                             |                           |
| Mean (Min, Max)                                                                                                                              | 13.23 (0.00, 17.00)         | 13.65 (0.00, 17.00)       |
| <b>Income Poverty Ratio</b>                                                                                                                  |                             |                           |
| Mean (Min, Max)                                                                                                                              | 6.3 (0.0, 127.3)            | 6.8 (0.0, 680.0)          |
| <b>Retirement Status (3 categories), n (%)</b>                                                                                               |                             |                           |
| Completely retired                                                                                                                           | 1,301 (41%)                 | 1,327 (48%)               |
| Not applicable                                                                                                                               | 419 (13%)                   | 72 (2.6%)                 |
| Not retired                                                                                                                                  | 1,080 (34%)                 | 921 (33%)                 |
| Partly retired                                                                                                                               | 347 (11%)                   | 464 (17%)                 |
| <b>Chronic Disease Number</b>                                                                                                                |                             |                           |
| Mean (Min, Max)                                                                                                                              | 1.75 (0.00, 7.00)           | 1.84 (0.00, 7.00)         |
| <b>CESD/Depression Score</b>                                                                                                                 |                             |                           |
| Mean (Min, Max)                                                                                                                              | 1.08 (0.00, 8.00)           | 0.82 (0.00, 8.00)         |
| <b>Openness to Experience Index</b>                                                                                                          |                             |                           |
| Mean (Min, Max)                                                                                                                              | 2.98 (1.25, 4.00)           | 3.00 (1.14, 4.00)         |
| <b>Conscientiousness Index</b>                                                                                                               |                             |                           |
| Mean (Min, Max)                                                                                                                              | 3.47 (1.40, 4.00)           | 3.35 (1.20, 4.00)         |

**eTable 1.** Descriptive Statistics for Overall Health and Retirement Study Population Stratified by Sex/Gender, N=5,934, HRS, 2006-2020

| <b>Characteristic</b>                         | <b>Female<br/>N = 3,148</b> | <b>Male<br/>N = 2,786</b> |
|-----------------------------------------------|-----------------------------|---------------------------|
| <b>Extraversion Index</b>                     |                             |                           |
| Mean (Min, Max)                               | 3.27 (1.20, 4.00)           | 3.17 (1.20, 4.00)         |
| <b>Agreeableness Index</b>                    |                             |                           |
| Mean (Min, Max)                               | 3.66 (1.60, 4.00)           | 3.41 (1.60, 4.00)         |
| <b>Neuroticism Index</b>                      |                             |                           |
| Mean (Min, Max)                               | 2.09 (1.00, 4.00)           | 1.95 (1.00, 4.00)         |
| <b>High Physical Activity, n (%)</b>          |                             |                           |
| High Physical Activity                        | 826 (26%)                   | 909 (33%)                 |
| Low Physical Activity                         | 2,322 (74%)                 | 1,877 (67%)               |
| <b>Smoking Status (3 categories), n (%)</b>   |                             |                           |
| Current                                       | 300 (9.6%)                  | 290 (10%)                 |
| Former                                        | 1,126 (36%)                 | 1,539 (56%)               |
| Never                                         | 1,698 (54%)                 | 935 (34%)                 |
| <b>Risky Alcohol Use, n (%)</b>               |                             |                           |
| High Risky Alcohol Use                        | 114 (3.6%)                  | 292 (10%)                 |
| Low Risky Alcohol Use                         | 3,033 (96%)                 | 2,490 (90%)               |
| <b>Married/Partnered, n (%)</b>               |                             |                           |
| Married or Partnered                          | 3,148 (100%)                | 2,786 (100%)              |
| <b>Financial Strain, n (%)</b>                |                             |                           |
| Not at all difficult                          | 1,351 (44%)                 | 1,269 (46%)               |
| Not very difficult                            | 1,032 (33%)                 | 919 (33%)                 |
| Somewhat difficult                            | 566 (18%)                   | 456 (17%)                 |
| Very difficult                                | 123 (4.0%)                  | 91 (3.3%)                 |
| Completely difficult                          | 30 (1.0%)                   | 21 (0.8%)                 |
| <b>Chronic Stress Scale</b>                   |                             |                           |
| Mean (Min, Max)                               | 12.0 (2.0, 32.0)            | 11.4 (2.0, 26.0)          |
| <b>Depression Score in Second Wave, n (%)</b> |                             |                           |
| Depressed                                     | 198 (6.9%)                  | 109 (4.5%)                |
| Not Depressed                                 | 2,652 (93%)                 | 2,296 (95%)               |

**eTable 1.** Descriptive Statistics for Overall Health and Retirement Study Population Stratified by Sex/Gender, N=5,934, HRS, 2006-2020

| <b>Characteristic</b>                                     | <b>Female</b><br>N = 3,148 | <b>Male</b><br>N = 2,786 |
|-----------------------------------------------------------|----------------------------|--------------------------|
| <b>Income Poverty Ratio in Second Wave, n (%)</b>         |                            |                          |
| Above poverty line                                        | 2,755 (96%)                | 2,360 (97%)              |
| At or below poverty line                                  | 108 (3.8%)                 | 76 (3.1%)                |
| <b>Ever having dementia or CIND after baseline, n (%)</b> | 724 (23%)                  | 775 (28%)                |

**eTable 2.** Descriptive Statistics for Overall Health and Retirement Study Population Stratified by Positive Spousal Social Support, N=5,934, HRS, 2006-2020

| <b>Characteristic</b>                          | <b>High Social Support</b><br>N = 2,395 | <b>Low Social Support</b><br>N = 3,539 |
|------------------------------------------------|-----------------------------------------|----------------------------------------|
| <b>Age (Years)</b>                             |                                         |                                        |
| Mean (Min, Max)                                | 66 (50, 93)                             | 66 (50, 95)                            |
| <b>Male, n (%)</b>                             |                                         |                                        |
| Female                                         | 1,058 (44%)                             | 2,090 (59%)                            |
| Male                                           | 1,337 (56%)                             | 1,449 (41%)                            |
| <b>Race/Ethnicity (4 categories), n (%)</b>    |                                         |                                        |
| Hispanic                                       | 125 (5.2%)                              | 244 (6.9%)                             |
| Non-Hispanic Black                             | 97 (4.1%)                               | 249 (7.0%)                             |
| Non-Hispanic White                             | 2,135 (89%)                             | 2,977 (84%)                            |
| Other                                          | 38 (1.6%)                               | 69 (1.9%)                              |
| <b>Participant Years of Education</b>          |                                         |                                        |
| Mean (Min, Max)                                | 13.69 (2.00, 17.00)                     | 13.25 (0.00, 17.00)                    |
| <b>Income Poverty Ratio</b>                    |                                         |                                        |
| Mean (Min, Max)                                | 7.3 (0.0, 680.0)                        | 6.1 (0.0, 129.5)                       |
| <b>Retirement Status (3 categories), n (%)</b> |                                         |                                        |
| Completely retired                             | 1,119 (47%)                             | 1,509 (43%)                            |
| Not applicable                                 | 186 (7.8%)                              | 305 (8.6%)                             |
| Not retired                                    | 763 (32%)                               | 1,238 (35%)                            |
| Partly retired                                 | 325 (14%)                               | 486 (14%)                              |

**eTable 2.** Descriptive Statistics for Overall Health and Retirement Study Population Stratified by Positive Spousal Social Support, N=5,934, HRS, 2006-2020

| Characteristic                              | High Social Support<br>N = 2,395 | Low Social Support<br>N = 3,539 |
|---------------------------------------------|----------------------------------|---------------------------------|
| <b>Chronic Disease Number</b>               |                                  |                                 |
| Mean (Min, Max)                             | 1.74 (0.00, 7.00)                | 1.83 (0.00, 7.00)               |
| <b>CESD/Depression Score</b>                |                                  |                                 |
| Mean (Min, Max)                             | 0.65 (0.00, 8.00)                | 1.17 (0.00, 8.00)               |
| <b>Openness to Experience Index</b>         |                                  |                                 |
| Mean (Min, Max)                             | 3.09 (1.43, 4.00)                | 2.92 (1.14, 4.00)               |
| <b>Conscientiousness Index</b>              |                                  |                                 |
| Mean (Min, Max)                             | 3.49 (2.00, 4.00)                | 3.36 (1.20, 4.00)               |
| <b>Extraversion Index</b>                   |                                  |                                 |
| Mean (Min, Max)                             | 3.33 (1.40, 4.00)                | 3.16 (1.20, 4.00)               |
| <b>Agreeableness Index</b>                  |                                  |                                 |
| Mean (Min, Max)                             | 3.60 (1.60, 4.00)                | 3.50 (1.60, 4.00)               |
| <b>Neuroticism Index</b>                    |                                  |                                 |
| Mean (Min, Max)                             | 1.89 (1.00, 4.00)                | 2.11 (1.00, 4.00)               |
| <b>High Physical Activity, n (%)</b>        |                                  |                                 |
| High Physical Activity                      | 779 (33%)                        | 956 (27%)                       |
| Low Physical Activity                       | 1,616 (67%)                      | 2,583 (73%)                     |
| <b>Smoking Status (3 categories), n (%)</b> |                                  |                                 |
| Current                                     | 208 (8.7%)                       | 382 (11%)                       |
| Former                                      | 1,122 (47%)                      | 1,543 (44%)                     |
| Never                                       | 1,048 (44%)                      | 1,585 (45%)                     |
| <b>Risky Alcohol Use, n (%)</b>             |                                  |                                 |
| High Risky Alcohol Use                      | 174 (7.3%)                       | 232 (6.6%)                      |
| Low Risky Alcohol Use                       | 2,217 (93%)                      | 3,306 (93%)                     |
| <b>Married/Partnered, n (%)</b>             |                                  |                                 |
| Married or Partnered                        | 2,395 (100%)                     | 3,539 (100%)                    |
| <b>Financial Strain, n (%)</b>              |                                  |                                 |
| Not at all difficult                        | 1,253 (53%)                      | 1,367 (39%)                     |
| Not very difficult                          | 733 (31%)                        | 1,218 (35%)                     |

**eTable 2.** Descriptive Statistics for Overall Health and Retirement Study Population Stratified by Positive Spousal Social Support, N=5,934, HRS, 2006-2020

| Characteristic                                            | High Social Support<br>N = 2,395 | Low Social Support<br>N = 3,539 |
|-----------------------------------------------------------|----------------------------------|---------------------------------|
| Somewhat difficult                                        | 319 (13%)                        | 703 (20%)                       |
| Very difficult                                            | 56 (2.4%)                        | 158 (4.5%)                      |
| Completely difficult                                      | 12 (0.5%)                        | 39 (1.1%)                       |
| <b>Chronic Stress Scale</b>                               |                                  |                                 |
| Mean (Min, Max)                                           | 10.9 (3.0, 25.0)                 | 12.2 (2.0, 32.0)                |
| <b>Depression Score in Second Wave, n (%)</b>             |                                  |                                 |
| Depressed                                                 | 70 (3.3%)                        | 237 (7.5%)                      |
| Not Depressed                                             | 2,044 (97%)                      | 2,904 (92%)                     |
| <b>Ever having dementia or CIND after baseline, n (%)</b> | 580 (24%)                        | 919 (26%)                       |

**eTable 3.** Risk ratios for the average association between positive spousal social support and dementia mediated through depression, N=5,934, HRS, 2006-2020

| Population | Total Effect <sup>1</sup><br>RR (95% CI) | Pure Direct<br>Effect (PDE) <sup>1</sup><br>RR (95% CI) | Total Indirect<br>Effect (TIE) <sup>1</sup><br>RR (95% CI) | Pure Indirect<br>Effect (PIE) <sup>1</sup><br>RR (95% CI) | Controlled<br>Direct Effect<br>(CDE) <sup>2</sup><br>RR (95% CI) | Proportion<br>Eliminated<br>(PE) <sup>3</sup> | % Mediated<br>TIE <sup>4</sup> | % Mediated<br>PIE <sup>5</sup> |
|------------|------------------------------------------|---------------------------------------------------------|------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------|-----------------------------------------------|--------------------------------|--------------------------------|
| Overall    | 1.00 (0.91, 1.09)                        | 1.02 (0.93, 1.12)                                       | 0.97 (0.95, 1.00)                                          | 0.98 (0.98, 0.99)                                         | 1.00 (0.91, 1.09)                                                | -0.37%                                        | —                              | —                              |
| Men        | 1.07 (0.98, 1.16)                        | 1.09 (1.00, 1.19)                                       | 0.98 (0.95, 1.00)                                          | 0.98 (0.97, 1.00)                                         | 1.08 (0.98, 1.18)                                                | -1.10%                                        | -36%                           | -27%                           |
| Women      | 0.91 (0.76, 1.05)                        | 0.94 (0.79, 1.09)                                       | 0.97 (0.93, 1.01)                                          | 0.98 (0.97, 1.00)                                         | 0.91 (0.75, 1.06)                                                | 0.45%                                         | 33%                            | 16%                            |

<sup>1</sup>Model a: Adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio. Bootstrapping was performed to estimate 95% confidence interval.

<sup>2</sup>Controlled direct effect where the mediator is set to 0

<sup>3</sup>Portion eliminated calculated by total effect - controlled direct effect and therefore, depends on both total effect and controlled direct effect.

<sup>4</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and total indirect effect.

<sup>5</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and pure indirect effect.

**eTable 4.** Risk ratios for the end of follow up association between positive spousal social support and dementia mediated through depression, N=5,934, HRS, 2006-2020

| Population | Total Effect <sup>1</sup> | Pure Direct Effect (PDE) <sup>1</sup> | Total Indirect Effect (TIE) <sup>1</sup> | Pure Indirect Effect (PIE) <sup>1</sup> | Controlled Direct Effect (CDE) <sup>2</sup> | Proportion Eliminated (PE) <sup>3</sup> | % Mediated TIE <sup>4</sup> | % Mediated PIE <sup>5</sup> |
|------------|---------------------------|---------------------------------------|------------------------------------------|-----------------------------------------|---------------------------------------------|-----------------------------------------|-----------------------------|-----------------------------|
|            | RR (95% CI)               | RR (95% CI)                           | RR (95% CI)                              | RR (95% CI)                             | RR (95% CI)                                 |                                         |                             |                             |
| Overall    | 0.95 (0.88, 1.01)         | 0.97 (0.9, 1.04)                      | 0.98 (0.96, 1.00)                        | 0.99 (0.98, 1.00)                       | 0.95 (0.88, 1.02)                           | -0.24%                                  | 41%                         | 23%                         |
| Men        | 1.00 (0.93, 1.08)         | 1.02 (0.94, 1.10)                     | 0.98 (0.96, 1.00)                        | 0.99 (0.97, 1.00)                       | 1.01 (0.93, 1.10)                           | -0.97%                                  | —                           | —                           |
| Women      | 0.92 (0.82, 1.03)         | 0.95 (0.83, 1.06)                     | 0.97 (0.94, 1.01)                        | 0.99 (0.98, 1.00)                       | 0.92 (0.81, 1.03)                           | 0.42%                                   | 32%                         | 15%                         |

<sup>1</sup>Model a: Adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio. Bootstrapping was performed to estimate 95% confidence interval.

<sup>2</sup>Controlled direct effect where the mediator is set to 0

<sup>3</sup>Portion eliminated calculated by total effect - controlled direct effect and therefore, depends on both total effect and controlled direct effect.

<sup>4</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and total indirect effect. For the male subgroup, we did not calculate the percent mediated because the total effect was null and results in a large percent mediated that is > 100%.

<sup>5</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and pure indirect effect. For the male subgroup, we did not calculate the percent mediated because the total effect was null and results in a large percent mediated that is > 100%.

**eTable 5.** Risk differences for the average association between positive spousal social support and dementia mediated through depression, N=5,934, HRS, 2006-2020

| Population | Total Effect <sup>1</sup> | Pure Direct Effect (PDE) <sup>1</sup> | Total Indirect Effect (TIE) <sup>1</sup> | Pure Indirect Effect (PIE) <sup>1</sup> | Controlled Direct Effect (CDE) <sup>2</sup> | Proportion Eliminated (PE) <sup>3</sup> | % Mediated TIE <sup>4</sup> | % Mediated PIE <sup>5</sup> |
|------------|---------------------------|---------------------------------------|------------------------------------------|-----------------------------------------|---------------------------------------------|-----------------------------------------|-----------------------------|-----------------------------|
|            | RD (95% CI) per 100       | RD (95% CI) per 100                   | RD (95% CI) per 100                      | RD (95% CI) per 100                     | RD (95% CI) per 100                         |                                         |                             |                             |
| Overall    | -0.5 (-3.2, 2.2)          | 0.1 (-2.7, 2.9)                       | -0.6 (-1.3, 0.1)                         | -0.3 (-0.6, -0.1)                       | -0.6 (-3.2, 2.1)                            | -0.16%                                  | 114%                        | 64%                         |
| Men        | 2.6 (-0.4, 5.6)           | 3.1 (0, 6.1)                          | -0.5 (-1.1, 0.1)                         | -0.3 (-0.7, 0.1)                        | 2.7 (-0.5, 5.9)                             | -0.03%                                  | -18%                        | -13%                        |
| Women      | -2.9 (-7.1, 1.3)          | -2.2 (-6.5, 2.1)                      | -0.7 (-1.7, 0.3)                         | -0.3 (-0.7, 0)                          | -3.1 (-7.3, 1.1)                            | -0.06%                                  | 24%                         | 12%                         |

<sup>1</sup>Model b: Adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, SES using the income poverty ratio, and ongoing chronic stress. Bootstrapping was performed to estimate 95% confidence interval.

<sup>2</sup>Controlled direct effect where the mediator is set to 0

<sup>3</sup>Portion eliminated calculated by total effect - controlled direct effect and therefore, depends on both total effect and controlled direct effect.

<sup>4</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and total indirect effect.

<sup>5</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and pure indirect effect.

**eTable 6.** Risk differences for the end of follow up association between positive spousal social support and dementia mediated through depression, N=5,934, HRS, 2006-2020

| Population | Total Effect <sup>1</sup> | Pure Direct Effect (PDE) <sup>1</sup> | Total Indirect Effect (TIE) <sup>1</sup> | Pure Indirect Effect (PIE) <sup>1</sup> | Controlled Direct Effect (CDE) <sup>2</sup> | Proportion Eliminated (PE) <sup>3</sup> | % Mediated TIE <sup>4</sup> | % Mediated PIE <sup>5</sup> |
|------------|---------------------------|---------------------------------------|------------------------------------------|-----------------------------------------|---------------------------------------------|-----------------------------------------|-----------------------------|-----------------------------|
|            | RD (95% CI) per 100       | RD (95% CI) per 100                   | RD (95% CI) per 100                      | RD (95% CI) per 100                     | RD (95% CI) per 100                         |                                         |                             |                             |
| Overall    | -2.0 (-5.2, 1.3)          | -1.3 (-4.7, 2.2)                      | -0.7 (-1.5, 0.1)                         | -0.4 (-0.7, -0.1)                       | -2.0 (-5.3, 1.2)                            | -0.05%                                  | 36%                         | 20%                         |
| Men        | 1.3 (-2.7, 5.3)           | 1.9 (-2.2, 5.9)                       | -0.4 (-0.8, 0.1)                         | -0.4 (-0.8, 0.1)                        | 1.4 (-2.8, 5.7)                             | -0.09%                                  | -41%                        | -29%                        |
| Women      | -3.6 (-9.0, 1.8)          | -2.7 (-8.3, 2.9)                      | -0.9 (-2.2, 0.4)                         | -0.4 (-0.9, 0)                          | -3.8 (-9.1, 1.4)                            | -0.07%                                  | 25%                         | 12%                         |

<sup>1</sup>Model b: Adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, SES using the income poverty ratio, and ongoing chronic stress. Bootstrapping was performed to estimate 95% confidence interval.

<sup>2</sup>Controlled direct effect where the mediator is set to 0

<sup>3</sup>Portion eliminated calculated by total effect - controlled direct effect and therefore, depends on both total effect and controlled direct effect.

<sup>4</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and total indirect effect.

<sup>5</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and pure indirect effect.

**eTable 7.** Risk ratios for the average association between positive spousal social support and dementia mediated through depression, N=5,934, HRS, 2006-2020

| Population | Total Effect <sup>1</sup> | Pure Direct Effect (PDE) <sup>1</sup> | Total Indirect Effect (TIE) <sup>1</sup> | Pure Indirect Effect (PIE) <sup>1</sup> | Controlled Direct Effect (CDE) <sup>2</sup> | Proportion Eliminated (PE) <sup>3</sup> | % Mediated TIE <sup>4</sup> | % Mediated PIE <sup>5</sup> |
|------------|---------------------------|---------------------------------------|------------------------------------------|-----------------------------------------|---------------------------------------------|-----------------------------------------|-----------------------------|-----------------------------|
|            | RR (95% CI)               | RR (95% CI)                           | RR (95% CI)                              | RR (95% CI)                             | RR (95% CI)                                 |                                         |                             |                             |
| Overall    | 1.01 (0.92, 1.10)         | 1.03 (0.94, 1.13)                     | 0.98 (0.96, 1.00)                        | 0.99 (0.98, 1.00)                       | 1.01 (0.92, 1.10)                           | 0.26%                                   | -143%                       | -82%                        |
| Men        | 1.10 (1.00, 1.19)         | 1.11 (1.01, 1.21)                     | 0.99 (0.97, 1.00)                        | 0.99 (0.98, 1.00)                       | 1.10 (1.00, 1.21)                           | -0.39%                                  | -13%                        | -10%                        |

Women 0.91 (0.76, 1.06) 0.93 (0.78, 1.09) 0.97 (0.94, 1.01) 0.99 (0.98, 1.00) 0.92 (0.74, 1.06) 1.11% 27% 13%

<sup>1</sup>Model b: Adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, SES using the income poverty ratio, and ongoing chronic stress. Bootstrapping was performed to estimate 95% confidence interval.

<sup>2</sup>Controlled direct effect where the mediator is set to 0

<sup>3</sup>Portion eliminated calculated by total effect - controlled direct effect and therefore, depends on both total effect and controlled direct effect.

<sup>4</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and total indirect effect.

<sup>5</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and pure indirect effect.

**eTable 8.** Risk ratios for the end of follow up association between positive spousal social support and dementia mediated through depression, N=5,934, HRS, 2006-2020

| Population | Total Effect <sup>1</sup> | Pure Direct Effect (PDE) <sup>1</sup> | Total Indirect Effect (TIE) <sup>1</sup> | Pure Indirect Effect (PIE) <sup>1</sup> | Controlled Direct Effect (CDE) <sup>2</sup> | Proportion Eliminated (PE) <sup>3</sup> | % Mediated TIE <sup>4</sup> | % Mediated PIE <sup>5</sup> |
|------------|---------------------------|---------------------------------------|------------------------------------------|-----------------------------------------|---------------------------------------------|-----------------------------------------|-----------------------------|-----------------------------|
|            | RR (95% CI)               | RR (95% CI)                           | RR (95% CI)                              | RR (95% CI)                             | RR (95% CI)                                 |                                         |                             |                             |
| Overall    | 0.96 (0.90, 1.03)         | 0.97 (0.91, 1.04)                     | 0.98 (0.96, 1.00)                        | 0.99 (0.98, 1.00)                       | 0.96 (0.89, 1.02)                           | 0.29%                                   | 36%                         | 20%                         |
| Men        | 1.03 (0.95, 1.11)         | 1.04 (0.96, 1.12)                     | 0.99 (0.98, 1.00)                        | 0.99 (0.98, 1.00)                       | 1.03 (0.94, 1.12)                           | -0.30%                                  | -38%                        | -28%                        |
| Women      | 0.92 (0.81, 1.04)         | 0.94 (0.83, 1.06)                     | 0.98 (0.95, 1.01)                        | 0.99 (0.98, 1.00)                       | 0.92 (0.80, 1.03)                           | 0.93%                                   | 26%                         | 12%                         |

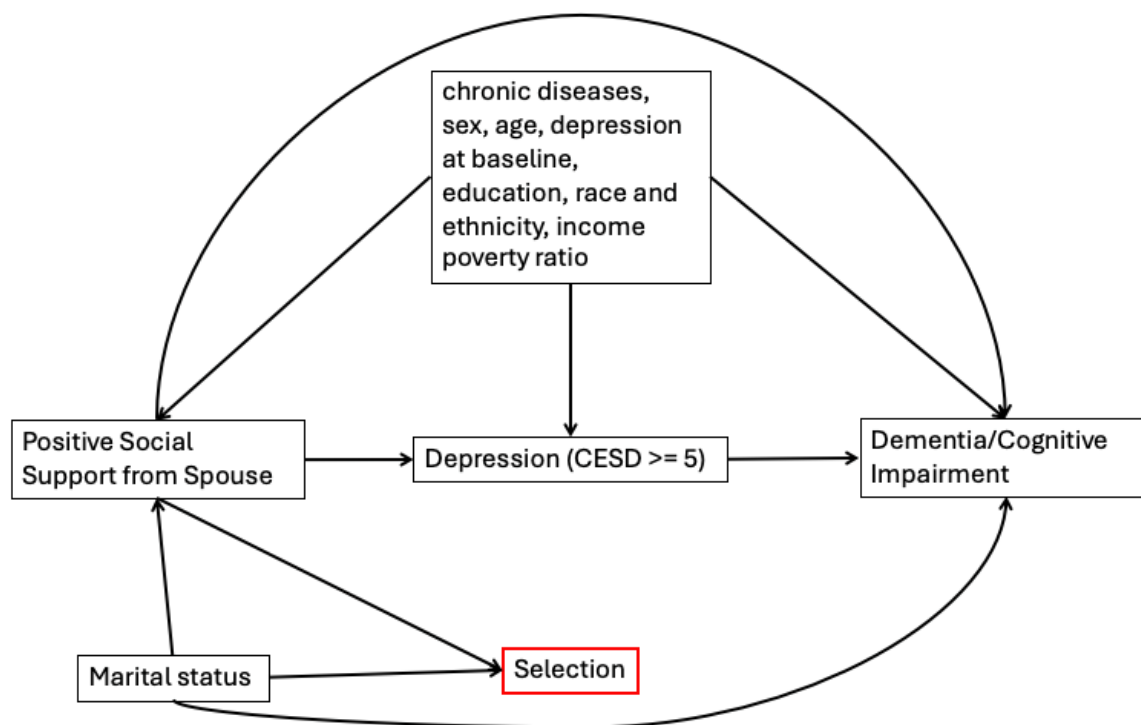
<sup>1</sup>Model b: Adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, SES using the income poverty ratio, and ongoing chronic stress. Bootstrapping was performed to estimate 95% confidence interval.

<sup>2</sup>Controlled direct effect where the mediator is set to 0

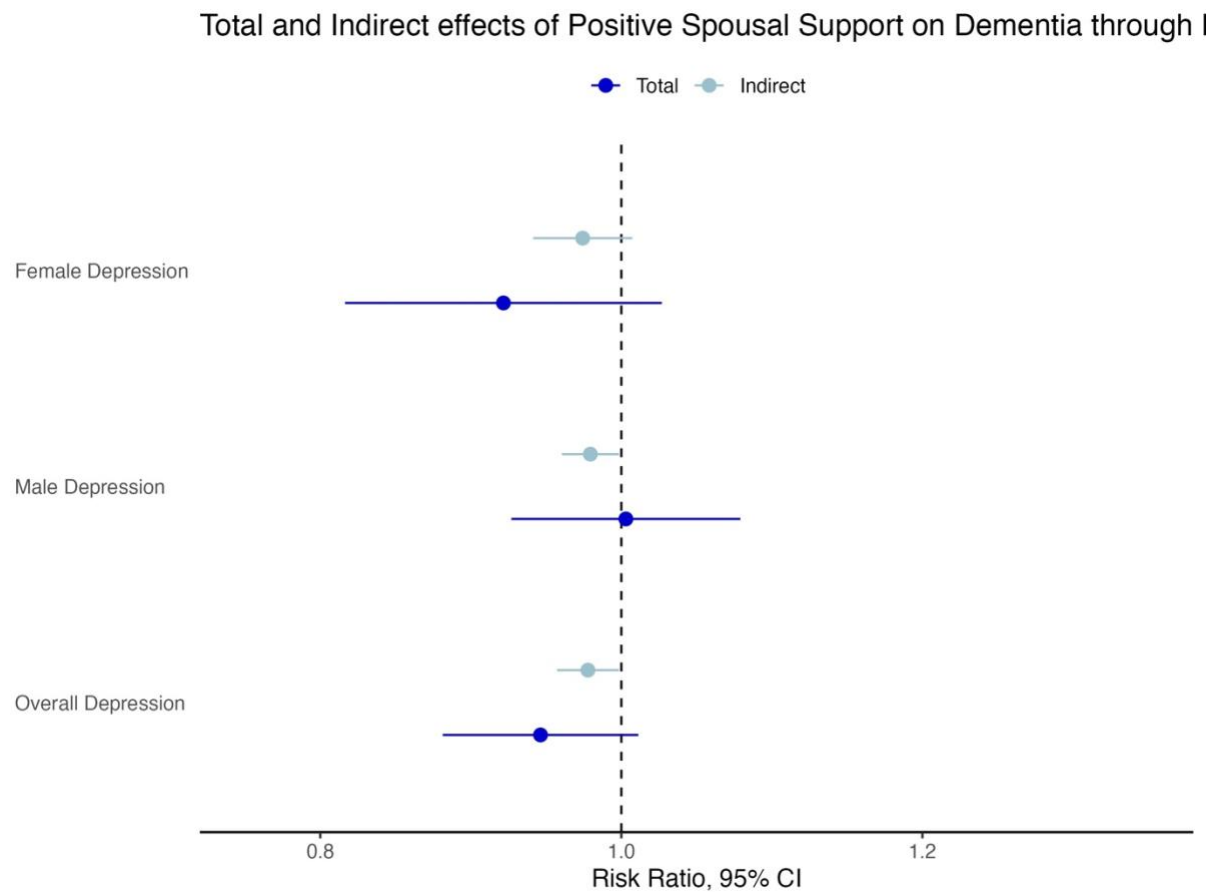
<sup>3</sup>Portion eliminated calculated by total effect - controlled direct effect and therefore, depends on both total effect and controlled direct effect.

<sup>4</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and total indirect effect.

<sup>5</sup>% Mediated was calculated by indirect effect/total effect, and therefore, depends on both total effect and pure indirect effect.

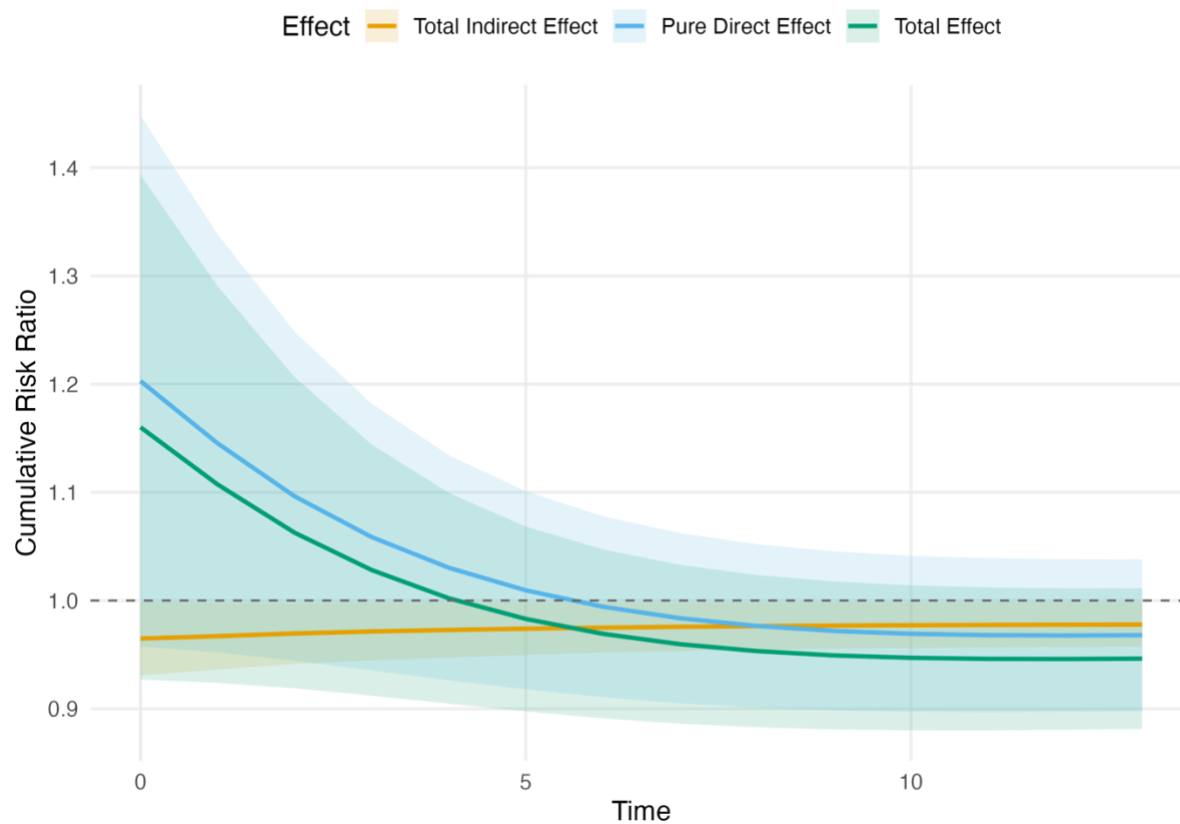


**eFigure 1.** Directed acyclic graph depicting the source of selection bias from selecting on marital status in the eligibility criteria



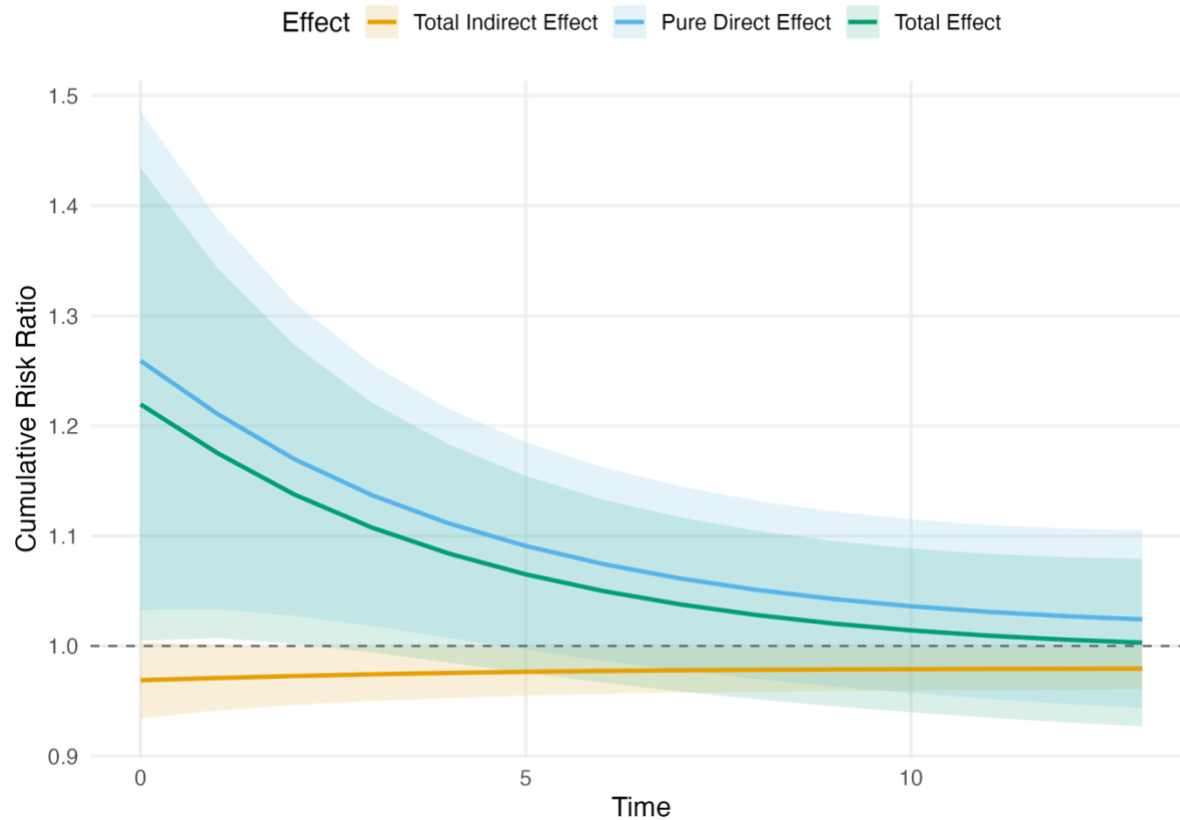
**eFigure 2.** An overview of the study on positive spousal social support on dementia/CIND through depression in Risk Ratios. TE, total effect; TIE, total indirect effect; and the portion mediated using the TIE and TE for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio

### Cumulative Mediation Effects: Depression (CESD Score)



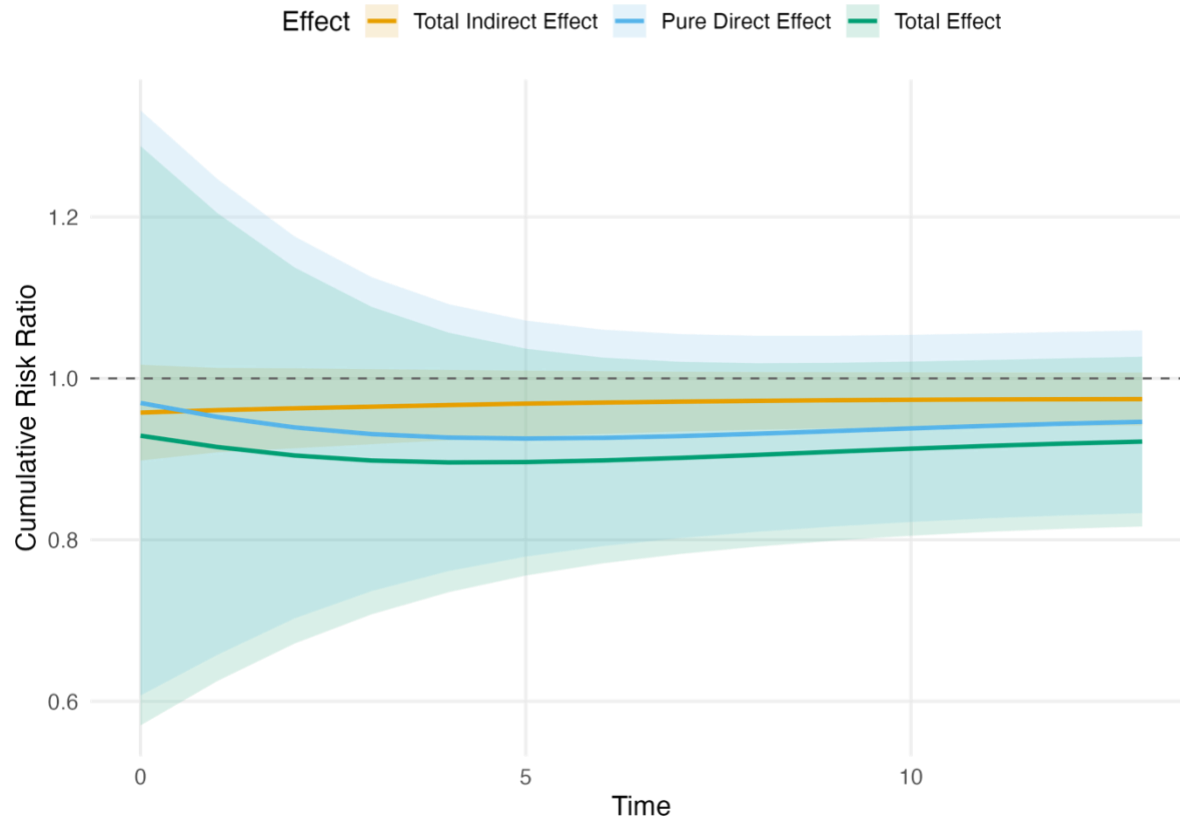
**eFigure 3.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the overall population over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio

### Cumulative Mediation Effects (Depression) for Males

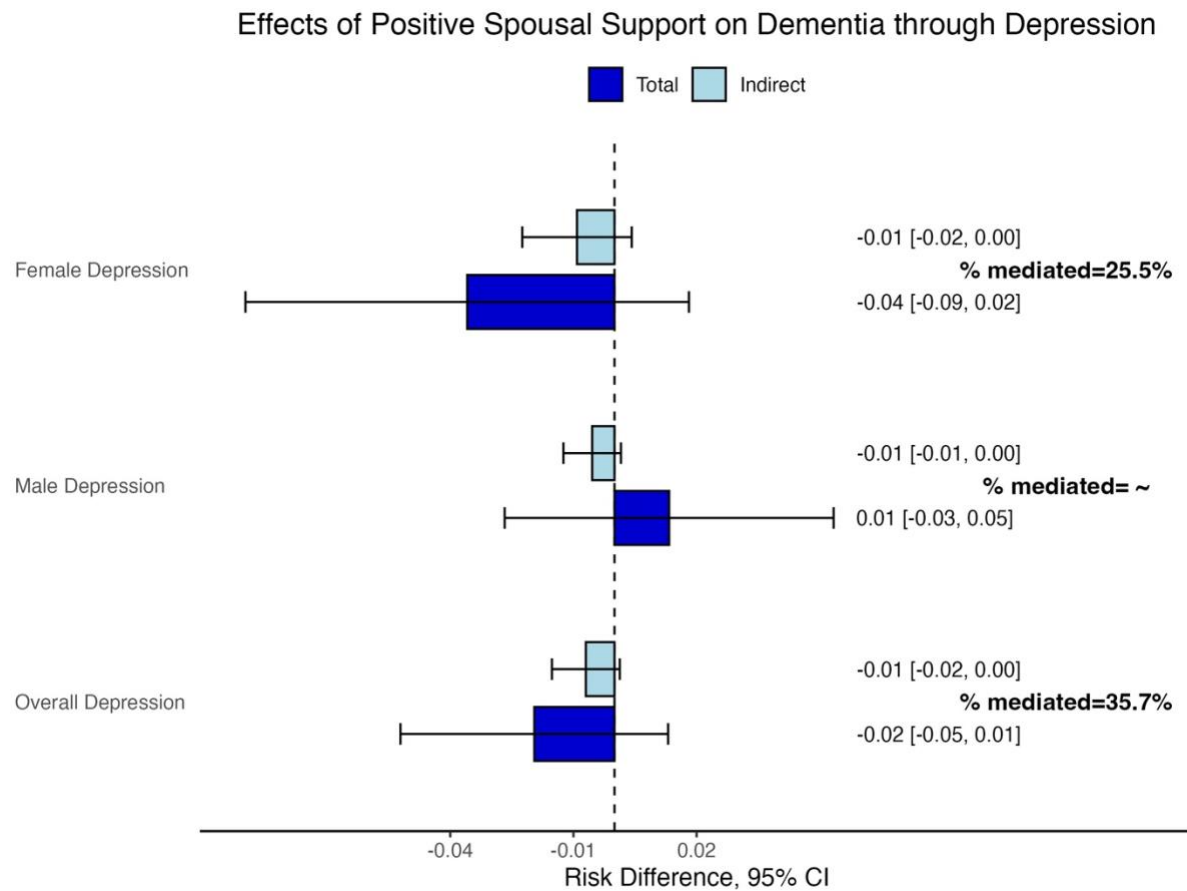


**eFigure 4.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the male population over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio

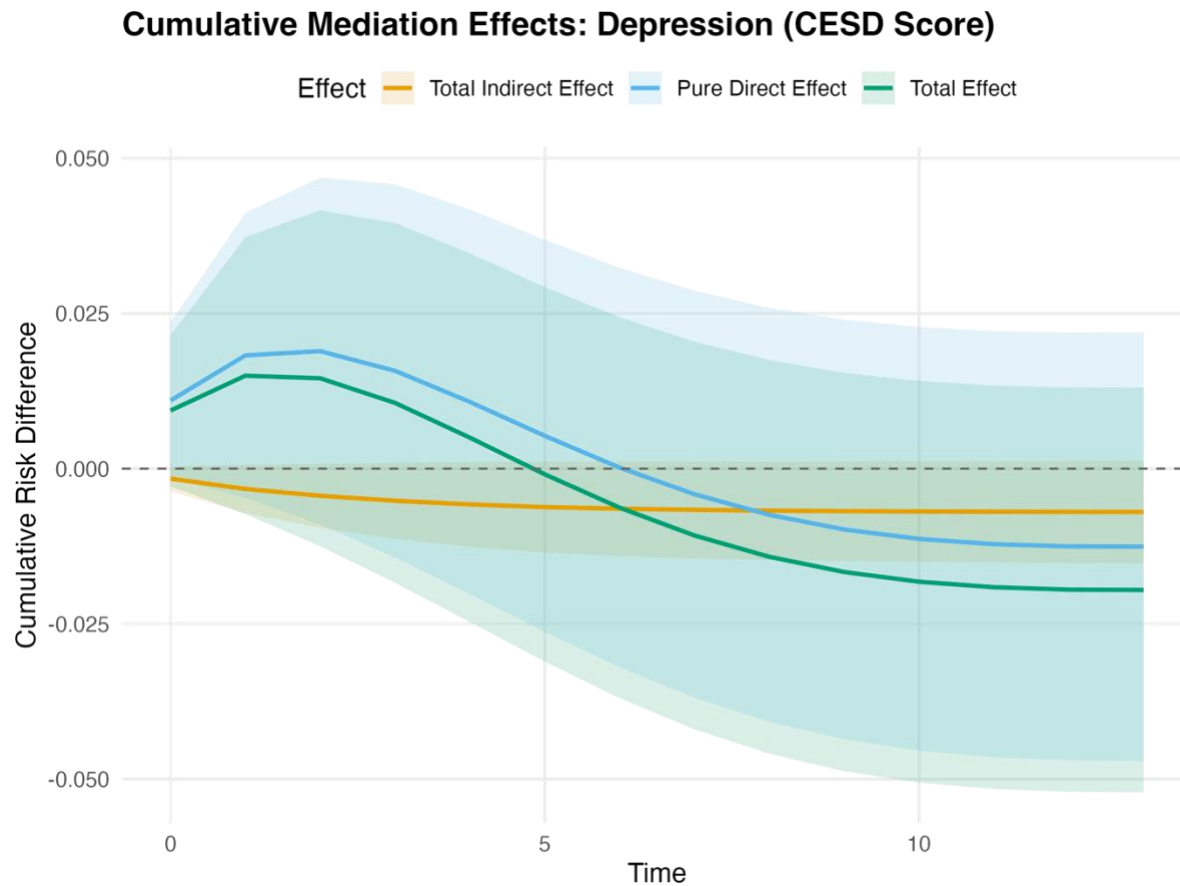
### Cumulative Mediation Effects (Depression) for Females



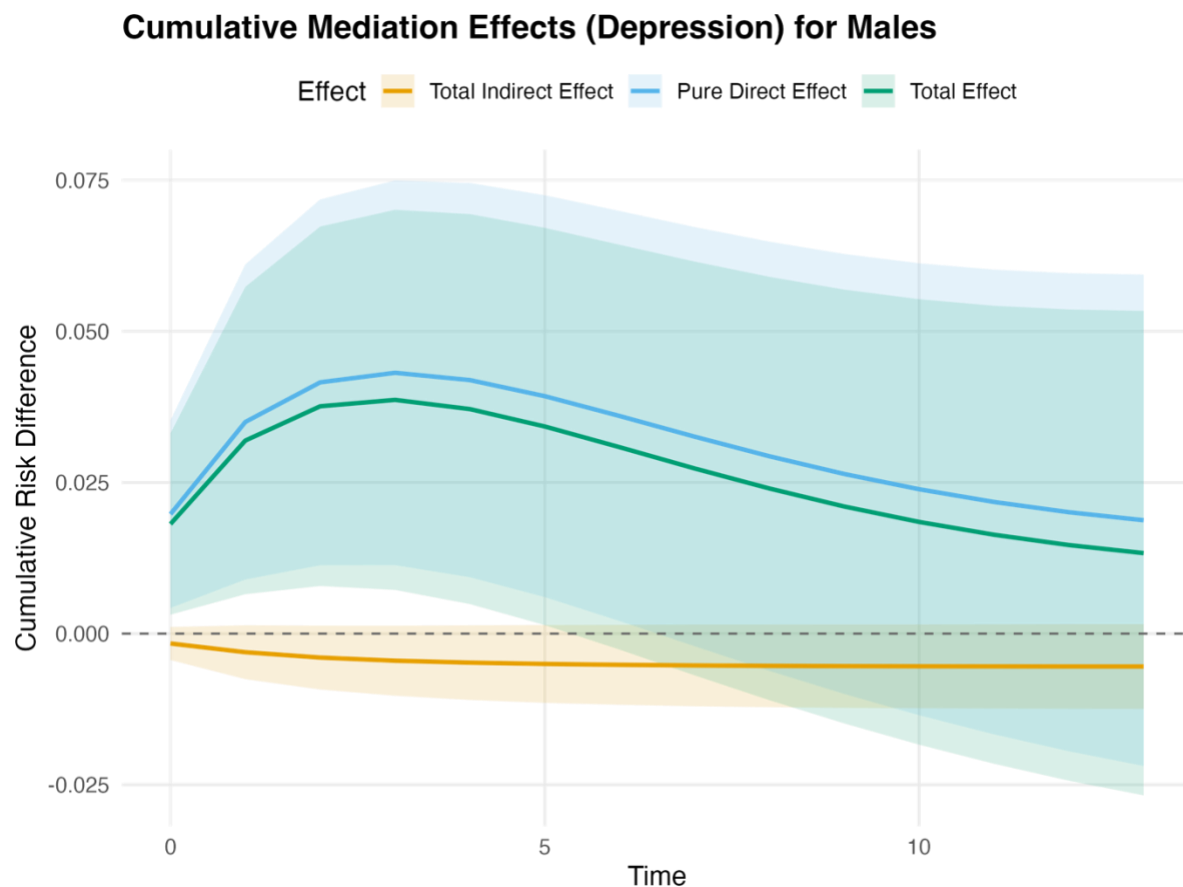
**eFigure 5.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the female population over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, and SES using the income poverty ratio



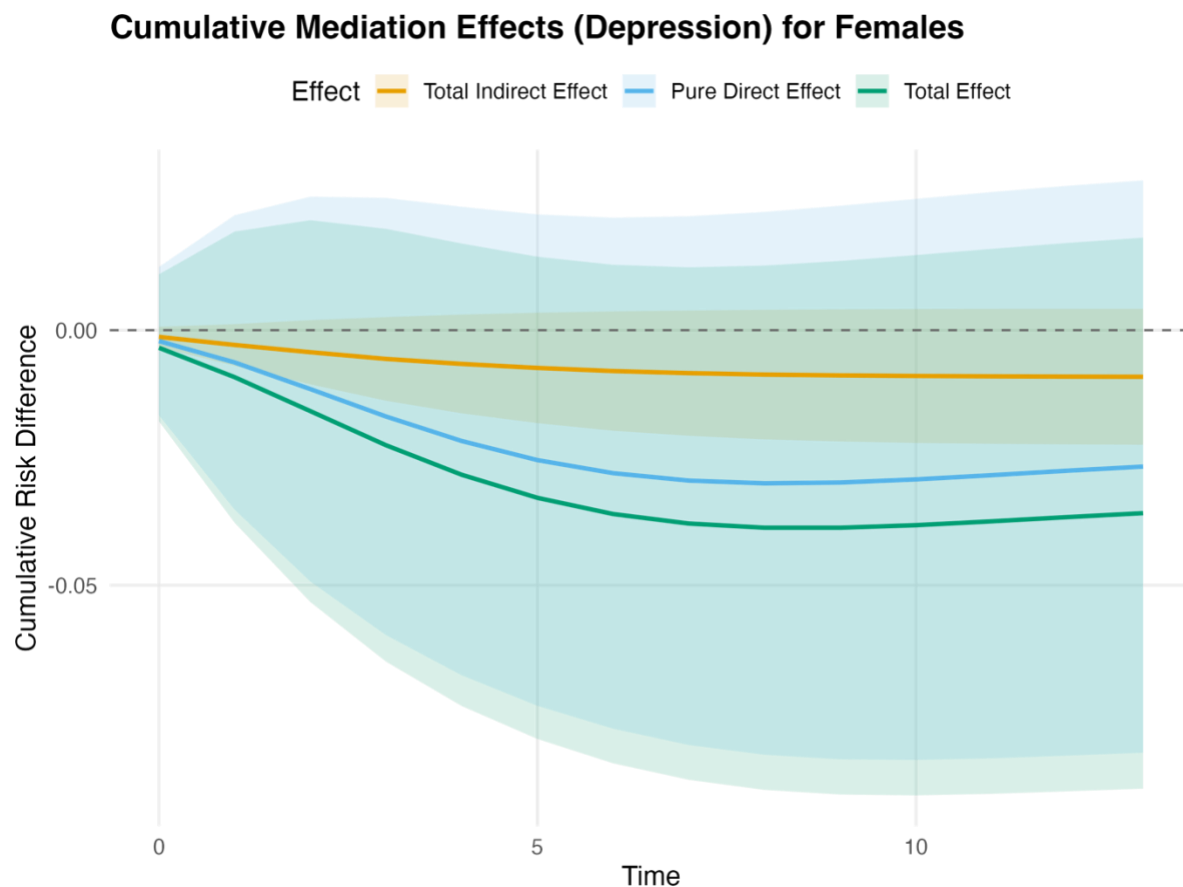
**eFigure 6.** Risk differences for the effects of positive spousal social support on dementia/CIND overall and mediated by depression. TE, total effect; TIE, total indirect effect; and the portion mediated using the TIE and TE for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, chronic stress, and SES using the income poverty ratio



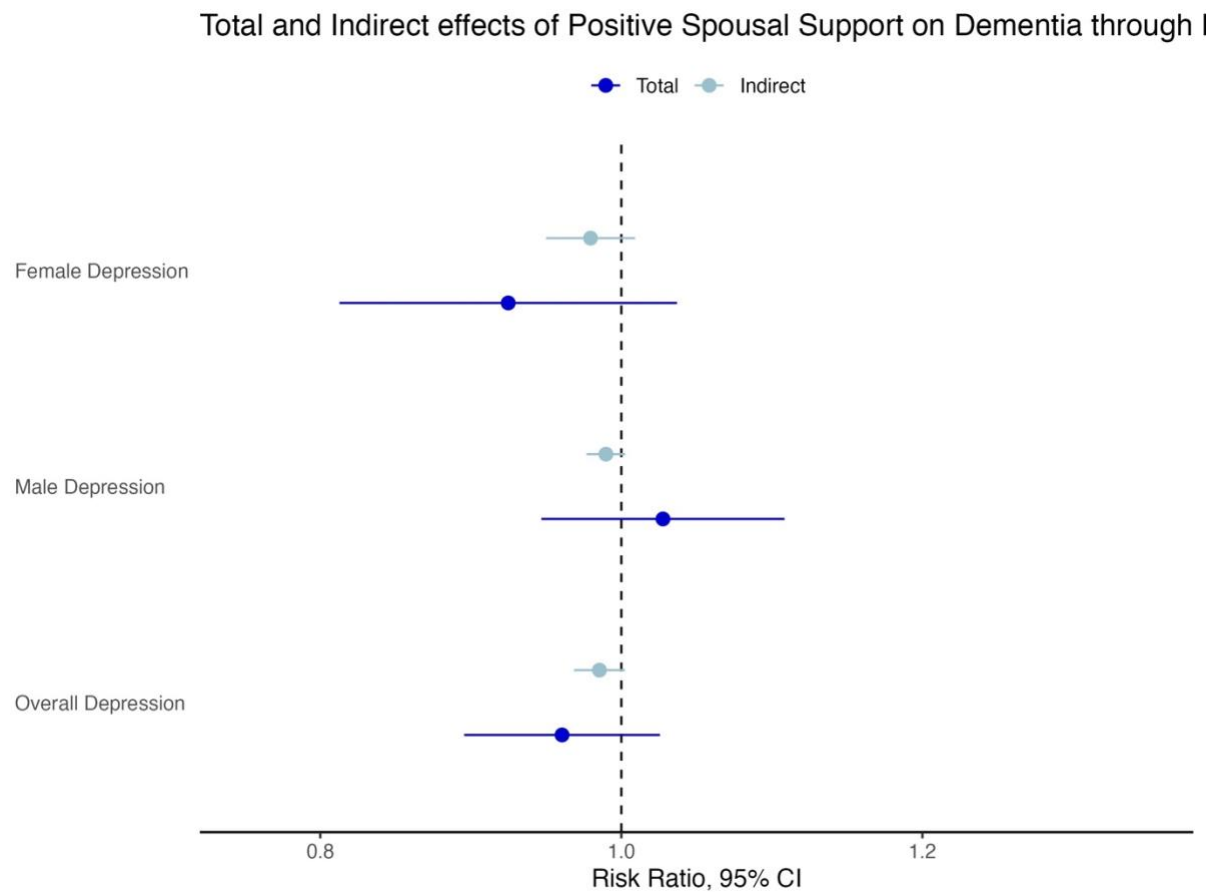
**eFigure 7.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the overall study sample over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, chronic stress, and SES using the income poverty ratio



**eFigure 8.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the male study sample over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, chronic stress, and SES using the income poverty ratio

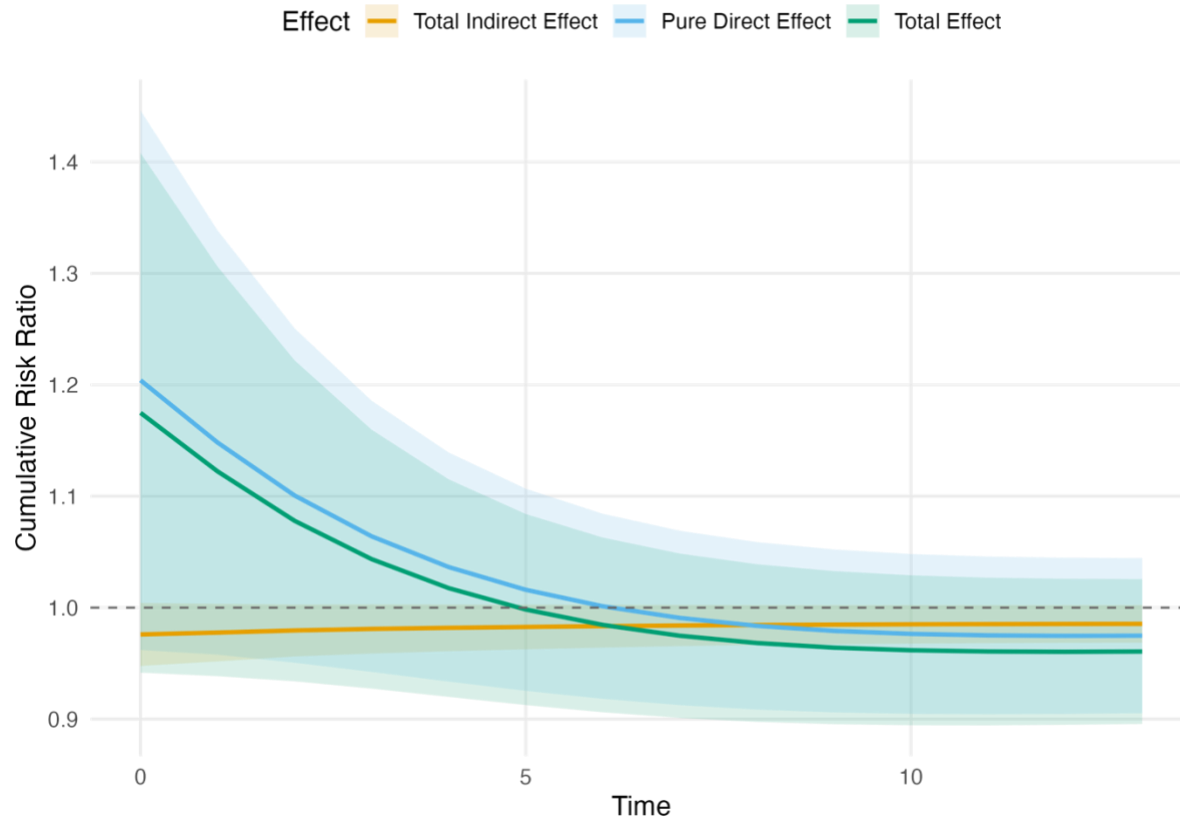


**eFigure 9.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the female study sample over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, chronic stress, and SES using the income poverty ratio



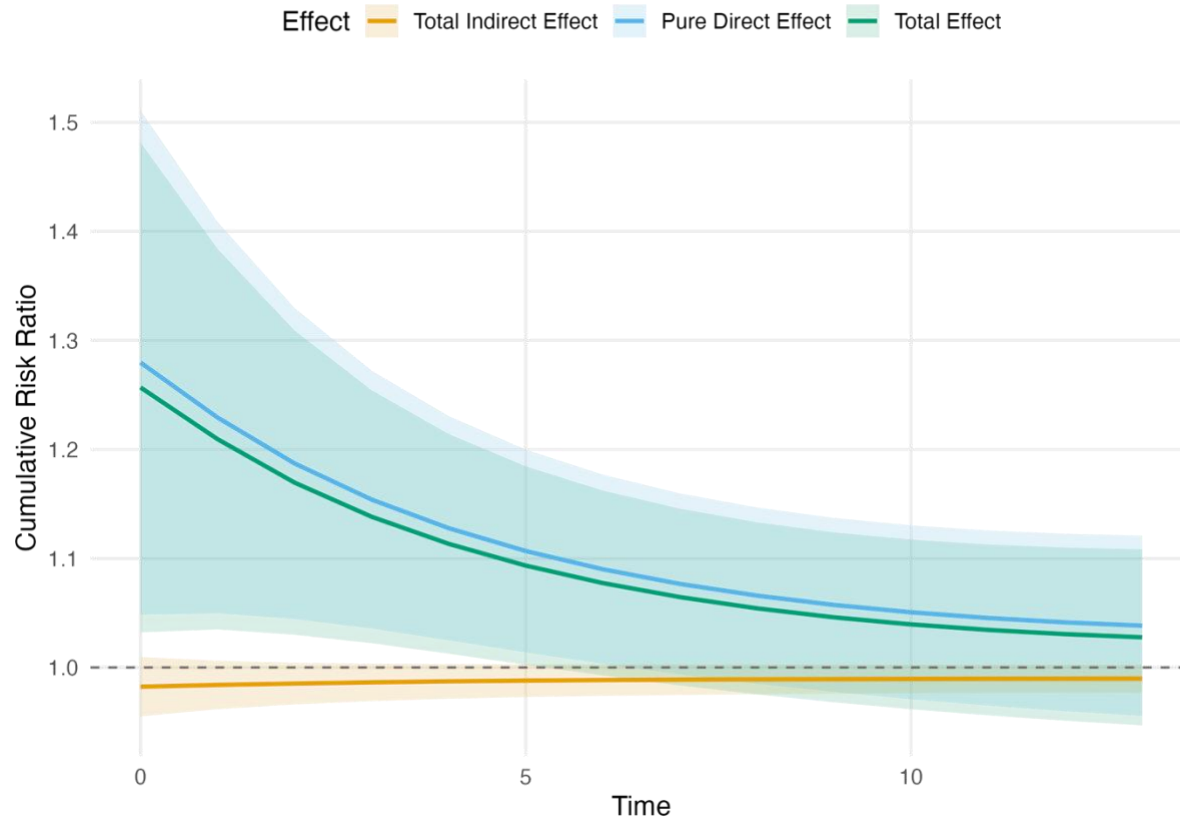
**eFigure 10.** An overview of the study on positive spousal social support on dementia/CIND through depression in Risk Ratios. TE, total effect; TIE, total indirect effect; and the portion mediated using the TIE and TE for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, chronic stress, and SES using the income poverty ratio

### Cumulative Mediation Effects: Depression (CESD Score)



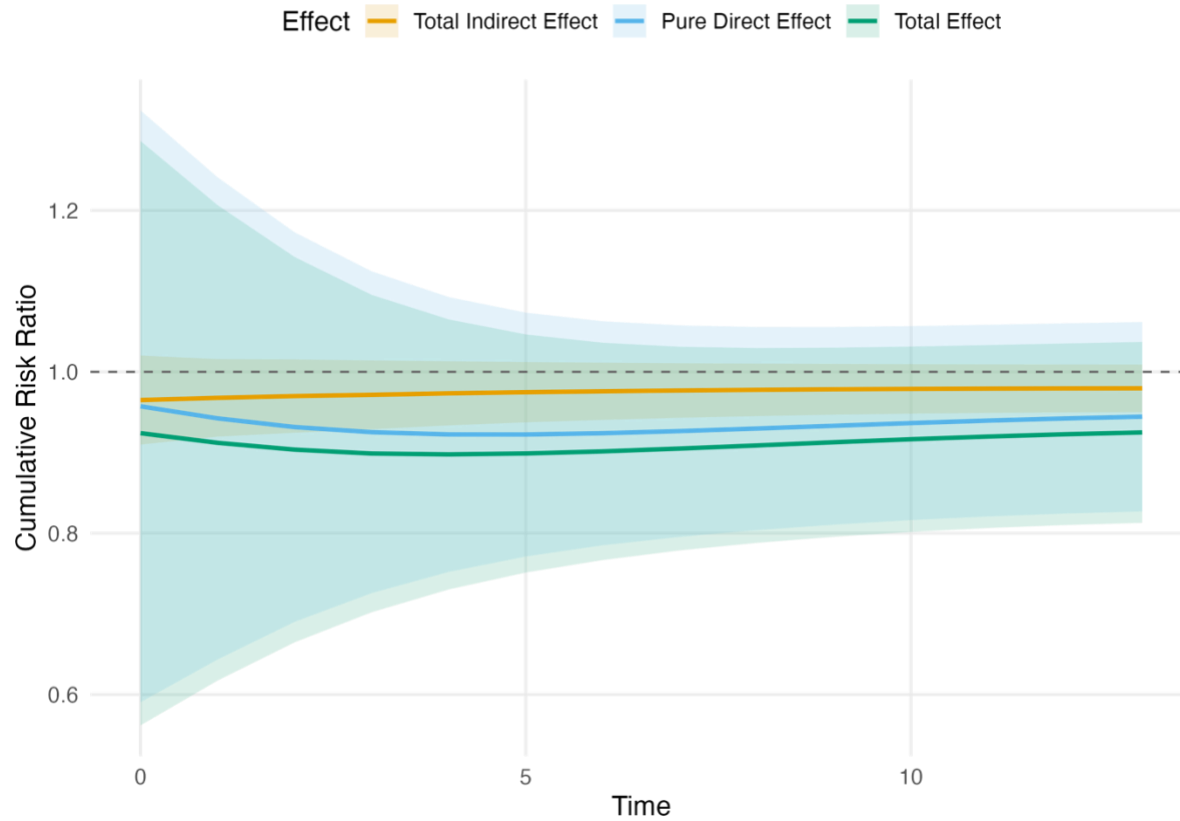
**eFigure 11.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the female study sample over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, chronic stress, and SES using the income poverty ratio

### Cumulative Mediation Effects (Depression) for Males



**eFigure 12.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the female study sample over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, chronic stress, and SES using the income poverty ratio

### Cumulative Mediation Effects (Depression) for Females



**eFigure 13.** Total effect, pure direct effect, and total indirect effect of positive spousal social support on dementia/CIND risk, with depression as mediator in the female study sample over time for model that adjusted for number of chronic diseases, sex, age, depression at baseline, education, race and ethnicity, chronic stress, and SES using the income poverty ratio

## ***CHAPTER 5: OVERALL CONCLUSION***

Social support appeared to play a complex, dual role in dementia risk. While contact with friends demonstrated a protective effect for the overall and White populations, findings for Black and Hispanic populations remained inconclusive, suggesting that other forms of social connection warrant further investigation in these groups. The joint influence of positive spousal support and marital closeness yielded mixed results as well — inconclusive for the overall population but associated with higher dementia/CIND risk among men and reduced risk among women. The surprising finding that closeness to a spouse may elevate dementia/CIND risk raised questions about reverse causation or potential information bias introduced by survey question framing. Depression emerged as a mediator for the relationship between positive social support and dementia/CIND risk, with the direction of both total and direct effects varying by sex and gender. The indirect effect demonstrated consistent protection across all groups and, therefore, treating depression remained a broadly recommended strategy for reducing dementia risk across all groups. Together, these findings highlight the intricate ways in which social factors shape dementia risk and underscore the need for more representative samples. In particular, expanding participation among Black and Hispanic individuals is essential to overcoming the small-sample-size limitations that currently hinder the identification of mechanisms within specific racial and ethnic subgroups. Future research should explore the nuanced social mechanisms that govern how support from a partner is both given and experienced, and how it affects long-term cognitive health, and whether quality, in addition to frequent interactions with friends, can affect dementia risk.

More data need to be collected on a longitudinal basis in order to increase sample sizes and power in social support studies using observational data. Although the sample size of the

general HRS was large in the beginning, this number shrinks as restrictions are implemented from an eligibility criterion. For example, the sample size in my projects decreased substantially after applying the married/partnered inclusion criterion. This criterion was necessary because all participants were required to have a defined level of spousal support, which required that they be married or in a partnered relationship. In spousal support research, we require larger cohorts of married individuals who have their marital status among other characteristics longitudinally followed. Additionally, there is a need for large data sets to be collected for longer follow-up times. Chronic diseases such as dementia, which may begin up to 20 years prior to the onset of clinical symptoms and have a higher risk among individuals aged 65 and older, require older study populations and longer follow-up periods to accurately capture disease incidence.<sup>2</sup> There is a crucial need for more data in social support research but additionally, how social support is measured requires improvement as well.

Social factors are currently measured using questions focused on self-perceived support from various individuals of a social network. However, some questions may not capture the intended exposure because of how an individual grew up, how they define words related to support, and how they think support should be given. For spousal support, the addition of interviews between couples with case-based scenarios targeting areas of stress, excitement, and one selective area for individuals to choose, could better capture a person's true social support from their spouse and relationship quality. These interviews would need to be conducted by a psychologist who can record and analyze the interaction and give a score that encompasses the targeted support and later incorporated with survey questions to create complex but more accurate depictions of social support from one's spouse. Furthermore, for targeting social support from friends, researchers could ask more specific questions about one's inner circle of friends

including, “What are the qualities of the seven friends you interact with most?”, “Does your inner circle only include quality friends or some toxic ones?”, and “What are the 3 qualities of the friends you interact with most often?”. Interview topics could be designed to target specific types of social support, such as emotional, informational, or appraisal support. Also, these new methods for collection social support variables should be implemented in studies whose primary focus is social support. By using datasets that explicitly prioritize social support as a key variable, researchers could tease apart the complex relationships between social support and dementia and cognition. This could also allow for pooling between datasets, provided that all datasets employ a standardized method for collecting social support data. These methodological enhancements in data collection and increases in sample size are essential for strengthening research on social support and may facilitate future investigations into the complex mechanisms between social support and dementia risk.

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