ABSTRACT

Title of Dissertation: STAYING HEALTHY AFTER CANCER: THE HIDDEN INFLUENCE OF SOCIAL NETWORKS

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**Background:** Few rigorous empirical studies have used social network models to investigate changes to the relationships most important to cancer survivors and their effects on health. The objective of this dissertation was to longitudinally examine the associations between egocentric social network change over time and physical, physiological, and mental health among cancer survivors and older adults without a history of cancer.

**Method:** The National Social Life Health and Aging Project (NSHAP) (2004-2011) is a nationally representative cohort of older adults aged 57 and older. Physical functioning was measured with the Activities of Daily Living Scale and inflammation was measured by C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF). Depressive symptoms were measured with the 11-item version of the Centers for Epidemiologic Studies Depression (CES-D) Scale. Multiple logistic and linear regression and structural equation modeling were used to assess the relationships of interest.

**Results:** Older cancer survivors and older adults without cancer experienced similar social network changes over time. In the overall NSHAP sample, adding new network members was protective of functional decline [odds ratio (OR): 0.64, 95% confidence interval (CI): 0.41-0.99] and experiencing a change in the frequency of contact was positively associated with functional decline (OR: 1.92, 95% CI: 1.15- 3.20). CRP levels were significantly 26% lower among cancer survivors who added two network members compared to those who added no network members. Experiencing a change in the frequency of contact was associated with a 19% higher level of TNF-α. Social support was directly associated with depressive symptoms and did not vary by cancer status. No mediation effects between social support, inflammation, and depressive symptoms were observed in path models and latent variable models.

**Conclusion:** Together these results suggest that when new relationships form or when stable relationships remain strong over time, their effects on health are positive. Alternatively, negative health effects may emerge when relationships become weaker over time. This study provides significant and timely information to develop effective interventions to improve quality of life for cancer survivors and older adults.

# STAYING HEALTHY AFTER CANCER: THE HIDDEN INFLUENCE OF SOCIAL NETWORKS

by

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Dissertation submitted to the Faculty of the Graduate School of the
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## Dedication

This dissertation is dedicated to my family. Thank you for being my champions and for your unwavering faith in my perseverance. Without your emotional support and encouragement, none of this would have been a reality. This dissertation is as much yours as it is mine.

Acknowledgements

I would like to acknowledge the collective support and wisdom of my committee members. I thank each one of you for the precious time you spent helping and guiding me along the way. I would especially like to express gratitude to my advisor and mentor, Dr. Hongjie Liu. You have set an example for excellence in research, mentoring, and teaching.

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# Chapter 1: Introduction

## *Background and Rationale*

The World Health Organization describes being "healthy" as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity" (1). In this dissertation, I argue that these domains are interrelated and that changes in the social well-being domain can alter physical, physiological and mental health, especially for those who have already experienced a life-changing event, such as cancer.

Cancer is the second leading cause of death (2) and with advances in early detection and treatment, the life expectancy of cancer survivors has been greatly extended. While these advances should be noted as important public health achievements, over the next decade, the predicted number of cancer survivors living in the United States (U.S.) will approach 18-19 million (3–5) and the number of cancer survivors aged 65 and older will increase 42% during this time (6). Additionally, the number of individuals expected to live beyond five years after initial diagnosis will approach 11.9 million (a 37% increase) (4), posing new challenges to the aging survivor, the US healthcare system, and public health programs.

The definition of a cancer survivor varies. The Committee on Cancer Survivorship for the National Cancer Policy Board, Institute of Medicine, and the National Research Council of the National Academies classifies cancer survivors as those who live through their treatment, disease, or both, which includes a broad range of cancer experiences. For example, some cancers are no longer considered terminal and in most

cases, are completely curable (e.g., testicular cancer) (7). Some cancer survivors, such as those of lymphoma, live with cancer and receive ongoing or intermittent treatment, and many individuals diagnosed with common cancers often become long-term survivors, living past the five-year survival mark (e.g., breast, colon, prostate) (8).

The most common cancer diagnoses among all cancer survivors include breast cancer (22%), prostate cancer (20%), and colorectal cancer (9%), as well as gynecologic (8%) and hematologic (8%) cancers. The most common cancers among males are prostate (43%), colorectal (9%), and melanoma of the skin (7%), while among females the most common tumor sites are breast (41%), uterine corpus (8%), and colorectal (8%) (3). The median age at diagnosis for all cancer sites is 66, and the majority of the most common cancers appear among those aged 65 and older at the time of diagnosis. For example, 68.5% of lung cancer, 66.8% of colon cancer, and 59.6% of prostate cancer cases occur among those aged 65 and older. Exceptions to this pattern include breast cancer (median age at diagnosis: 61 years) and ovarian cancer (median age at diagnosis: 63 years) (5,6). Given that the majority of cancer patients will be diagnosed in old age, progress into old age during treatment, and/or survive into old age, the issues of aging must be addressed concurrently with cancer treatment and remission.

The hallmark signs of aging include a gradual decline in the physiologic reserve. Aging-related physiological changes include degeneration of the cardiovascular, musculoskeletal, neurologic, pulmonary, and renal systems (9,10). Because of the decline among these systems, older adults have different responses to cancer treatment and require closer monitoring of care (10). Cancer

treatment, including surgery, chemotherapy, and radiation therapy can have inadvertent effects and progress the decline of organ systems and tissues. Additionally, some anticancer drugs are taken for extended periods of time (7). Together, these complexities may contribute to or accelerate declines in immune functioning, physical functioning, and mental health. Because of the potential for aging-related complications, this dissertation will focus on older adults (aged 57 years and older, as defined by the National Social Life Health and Aging Project (NSHAP)) who reported and did not report a history of cancer to differentiate between aging- and cancer-related changes to health and the social environment.

Social networks may improve health and promote successful aging when they are adequate in terms of support and resources. Social network studies among cancer survivors have shown that social support can improve quality of life (8), and that more social support and larger social network sizes can reduce the risk of mortality by 25% and 20%, respectively (11). However, few studies have comprehensively measured the social networks of cancer survivors and the current literature has yet to explore the role of the changing social environment on functional decline, immune functioning and mental health among cancer survivors.

*Objectives and Research Questions*

To address the limitations of the current literature, we investigated multiple dimensions of health among cancer survivors and older adults without a history of cancer. Our objective was to explore the intrapersonal and interpersonal (social network) factors that contribute to a cancer survivors' health status including: (1) physical functioning, (2) immunologic functioning, and (3) mental health. The central hypothesis was that any change to the social network (either positive or negative) over time would impact the health status of cancer survivors. The rationale for completing this study was that identification of the interpersonal and intrapersonal factors that influence health status provides insight to develop comprehensive bio-behavioral interventions for this population.

To achieve these objectives we proposed the following three specific aims:

1. To observe social network change and physical health decline among cancer survivors over a five-year period.
2. To examine the association between social networks and inflammation over time.
3. To determine if inflammation mediates the relationship between social support and depressive symptoms over time.

All aims were addressed by conducting a secondary data analysis from the National Social Life, Health and Aging Project (NSHAP) (Wave 1 (W1): 2004-2005, Wave 2 (W2): 2010-2011). NSHAP is a large, nationally representative cohort of community dwelling older adults aged 57 and older. NSHAP provides rich data on egocentric social networks, as well as, cancer survivorship, biomeasures,

physical, and mental health (12). An egocentric social network focuses on an individual, "ego" and their local network of peers. NSHAP operationalizes egocentric social networks by asking survey participants to name five people with whom they discuss "*important matters*" with. Each participant then provides details about their relationship with each of their peers.

Aim 1 utilizes an egocentric social network analysis of cancer survivors and healthy older adults over a five-year period to determine if social network change is associated with physical disability. Lagged logistic regression models were used to test the associations between social network change and physical disability among cancer survivors and those without cancer.

Aims 2 and 3 utilized biomarker data collected in W1 and W2 to understand the role of social networks on the physiological and mental health profiles of cancer survivors. Markers of immune functioning that have been previously associated with angiogenesis (e.g., the formation of new blood vessels) and/or tumor progression were assessed (13–15). Aim 2 specifically tested whether network change predicted elevated inflammation in W2 using linear regression among cancer survivors and older adults. Aim 3 explored the intermediate pathways by which social support is hypothesized to influence depressive symptomatology. Direct and indirect paths between social support and depressive symptoms were evaluated, using inflammatory markers as the primary mediators of interest. Structural equation modeling was used to simultaneously evaluate these interrelationships.

Using an innovative social network methodology, the proposed study fills the research gaps by providing a broad profile of cancer survivors in late life. It is

significant because it pinpoints the extent to which social network factors can facilitate or deter successful aging after cancer. It also provides timely information to develop effective, blended biomedical and behavioral interventions to help cancer survivors navigate the intricacies of the healthcare system, adhere to screening regimens, and improve quality of life at the interpersonal level.

*Theoretical Framework*

Social network theory guided the conceptual framework for this dissertation. Social network theory insinuates that individuals are connected through the social relationships they create with others. Social networks are defined as a set of members linked by a particular behavior or social interaction (16). Relationships can influence a person's behaviors, ideas, emotions, and beliefs more than their individual characteristics, such as age, sex, and socioeconomic status (17). Therefore, close contacts and their attributes can have profound effects on health through social influence, norms, the perception of support, and the flow of information and resources (18). Understanding the social environment is fundamental to deciphering the mechanisms through which health status can be improved, damaged or stabilized. First, two types of social network studies will be described. Next, the terms used to describe networks and how they change over time will be presented, followed by the conceptual model for social networks as they pertain to cancer survival.

**Types of Social Network Studies**

Sociocentric networks encapsulate the whole network, where all group connections or community members are known and described. For example, Figure 1 depicts multiple generations from the Framingham Heart Study (19). In the illustration, each dot represents a person and each line connecting the dots represents two people who are tied to each other based on some attribute, such as, a family tie or a friend tie. Sociocentric networks provide a birds eye view, where one's position within the network can easily be identified. In Figure 1, Person A is located in the center of the network and Person B is located at the periphery. Exposure to infectious

agents or the spread of information to these individuals may be very different because of their network position. Sociocentric networks require that all network members are identified and interviewed, which can be expensive and cumbersome. For these reasons, sociocentric network studies are not feasible in large, nationally representative cohort studies because there would be a large proportion of people who are unconnected. Egocentric networks on the other hand, focus on an individual (ego) and his/her local network of close contacts (alters).

Visually, the egocentric 'local' network looks like a wheel, with ego in the center and alters on the rim of the wheel, connected to ego by spokes (Figure 2). The spokes represent the ties that ego has to his/her alters and represent specific attributes about their relationship, such as, how long they have known each other or how emotionally close they are. Egocentric network studies do not have the same measurement challenges that sociocentric studies face because they only require gathering information from ego, which can easily be collected with traditional data collection techniques, such as surveys. Therefore, egocentric network studies are more feasible, pragmatic, and less costly than sociocentric studies and for these reasons, are more commonly used (20).

Figure 1. Illustration of a sociocentric social network.

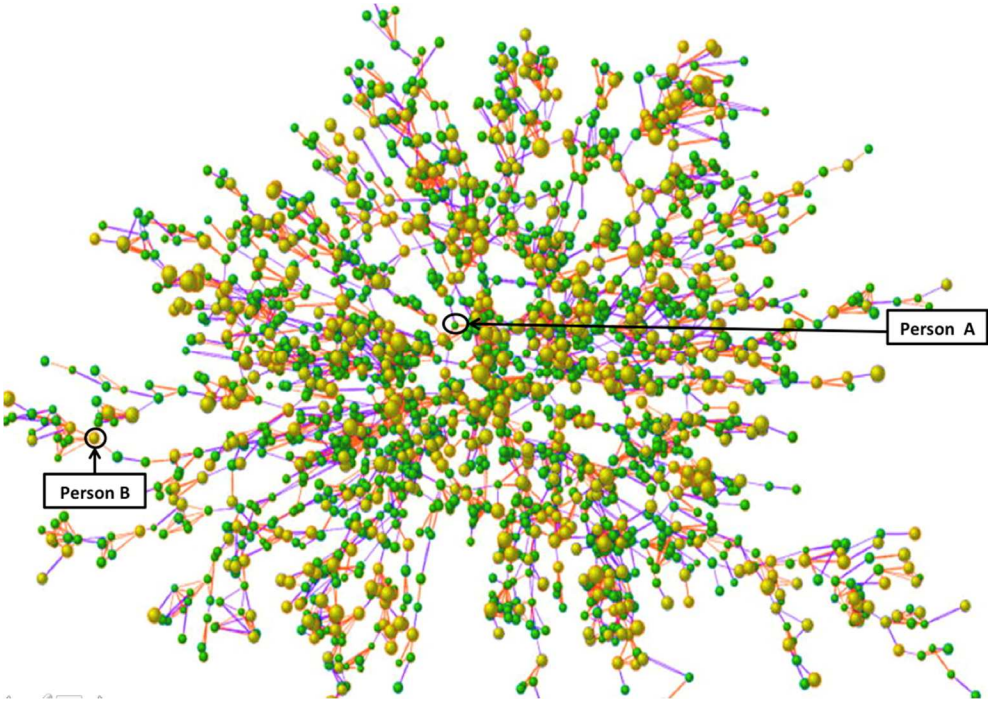
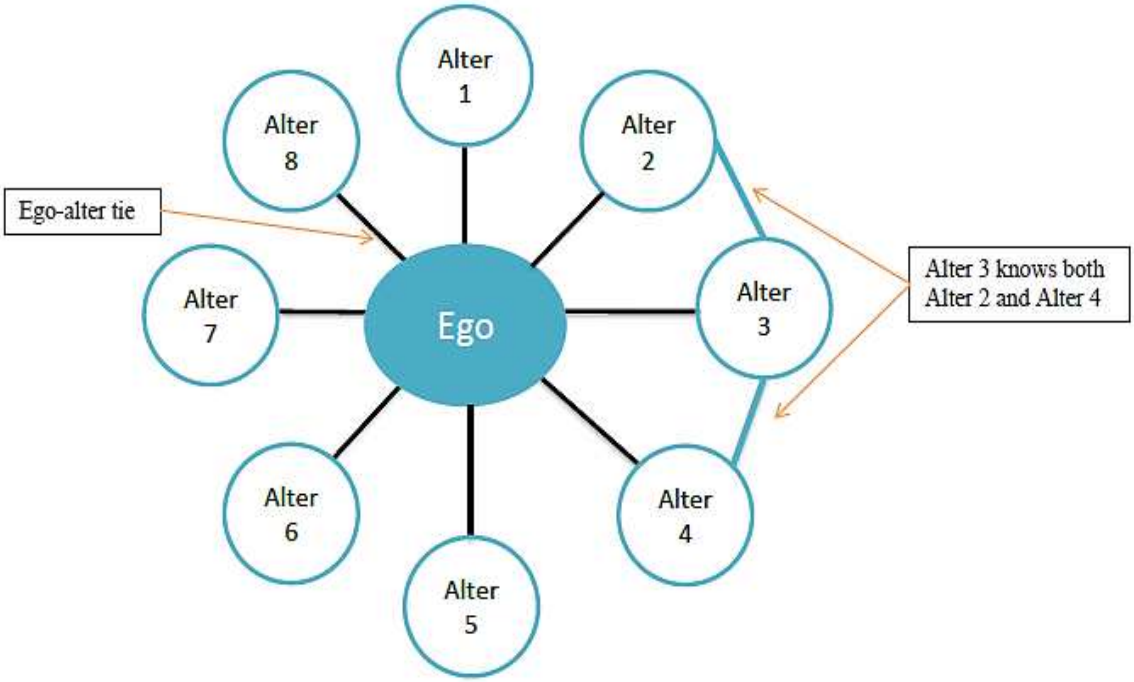



Illustration of a sociocentric network. Each dot represents a person and the lines between them indicate a tie, or attribute that links network members. All relationships between network members are known and described. Person A is located at the center of the network and Person B is located at the periphery of the network. Different structural positions in the network may expose individuals to different ideas, resources, and infectious agents.

Photo credit: Christakis, N. A., & Fowler, J. H. (2007). The spread of obesity in a large social network over 32 years. *New England Journal of Medicine*, 357(4), 370-379.

Figure 2. Illustration of an egocentric social network.




A single egocentric network includes an index person (ego) and his/her network members (alters) who share behaviors, ideas, and emotions and interact with ego. Each egocentric network is treated as its own distinct world.

The proposed study utilizes an egocentric social network approach from secondary data. Techniques used to measure social networks and describe social network change over time are outlined below.

## Social Network Measures

There are three distinct components that comprise of an egocentric social network: 1) network relations, 2) network structure, and 3) network functions.

### Network Relations

Network relations (or network composition) are the types of relationships that ego maintains with his/her alters and include social network range, closeness and the frequency of contact. Social network range is a measure of the different types of relations or diversity of ties that ego has, such as family, friends, coworkers, neighbors, etc. Other measures of network relations include measures of closeness and the frequency of contact. Together these measures indicate the strength of the relationship between ego and their alter. Theoretically, stronger relationships are more likely to exert influence over network members because of the assured availability of support. Weak ties are more effective at transmitting information, but less important in terms of behavior change and norms (21).

### Network Structure

The structure of ego's network is indicative of the availability, the type of resources, and information that could spread throughout the network. An example of network structure would be the visual representation of an ego network in Figure 2. Density and network size are two measures of network structure.

Network size

Network size is the most basic measure of network structure and is simply a count of the number of alters in ego's network.

Density

Density describes ego's embeddedness within the network. Network density is the proportion of ties who know each other relative to all potential ties in the network and ranges from 0 to 1 (16). The number of actual ties is the total number of alters who know each other. The number of potential ties is calculated as the proportion of [k(k−1)/2] pairs, where k is the total number of alters in ego's network (not including ego) and ego has at least two alters. For example, in Figure 2, Alter 3 knows Alter 2 and Alter 4, so the number of actual ties equals two. The number of potential ties is [(8(8-1))/2]=28. Therefore, the density of ego's network is 0.07 (2 actual ties /28 potential ties). A network density of 1 signifies that all alters in ego's network know each other, whereas a network density of 0 indicates no connections among alters. High network density is indicative of a close-knit social environment where ego is able to call upon his/her alters for uncoordinated, reliable support and access to resources. Structural holes are described as the "empty spaces in the social structure" and result from an *absence* of ties between ego's network members. For example, in Figure 2, alters 4 and 5 do not know each other and indicate a structural hole. In a network that is 100% densely connected there are no structural holes because all network members are acquainted with each other. Burt (1992) theorized that high network density leads to poor decision-making because ego is less likely to be exposed to new and diverse perspectives. In a less dense network, members are

unlikely to know each other and ego will receive new information first, giving him/her a strategic advantage to capitalize on new resources and make more informed decisions (22). Therefore, structural holes are important to health outcomes as they directly impact access to health information and resources. For example, a cancer survivor who has a highly dense network may have more alters to call on in a time of crisis, but may make poor decisions in terms of their treatment and care (20). Therefore, the situation in which network density is health promoting or deterring may be context specific.

### Network Functions

Network functions are the types of social support available to ego. There are four main types of social support: informational, appraisal, tangible and emotional (23). Informational support refers to the delivery of advice or information by network members. Appraisal refers to support in the decision making process, such as helping ego decide on a course of treatment. Tangible (or instrumental) support refers to the provision of assistance and aid by network members to help ego meet his daily needs, such as cooking, cleaning, providing rides to doctor's appointments, etc. Emotional support is related to the amount of love, care, and sympathy that ego receives from network members. Knowing whom ego receives support from, and the kind of support ego receives, is suggestive of how well resourced ego is. Numerous studies have shown the benefits of social support, as well as, reported detrimental health consequences when support is inadequate (23–25).

### Social Network Change Over Time

At any one time, the composition of a network is a function of the additions of new ties, loss of old ties, and ties that remain stable over time, as well as changes to

the distribution of network attributes as a whole. Network properties such as closeness and frequency of contact may change over time with respect to ego's position, including ego's participation in activities, situation (e.g., health, life stage, and work status), and surrounding circumstances (e.g., neighborhood change, natural and political events, and life events) (26). Network change can be characterized by: 1) changes to the overall network size; 2) network losses, additions, and persistent ties, and 3) changes to the attributes of personal networks over time (26–28).

1. Changes to the overall network structure:

Changes to the overall network size describes whether ego's network has expanded or contracted over time, and is simply the absolute difference in the network size at different time points.

2. Network losses, additions, and persistent ties:

Persistent or stable ties are defined as alters listed at the first time point that still exist at a later time point. Network losses are alters who were named at the first time point, but not in subsequent time points. Network additions consist of alters who were not named at the first time point, but were listed at later time points. The goal of measuring network persistence and turnover is to understand the factors that distinguish between ties that endure and those that do not. Network persistence and turnover may occur as a result of life changes or ego's circumstances, such as sickness, retirement, or bereavement (26). Network turnover should be considered *instead* of changes to the overall network size, because subtle network changes

become masked. For example, the overall network size may be the same at two time points (e.g., five friends are listed at time 1 and time 2) and, therefore, the network appears stable, but may have suffered from complete network turnover (e.g., ego lost five friends and gained five new friends between time 1 and time 2), which may have different health consequences.

3. Changes to the attributes of personal networks over time:

Changes to the characteristics of ties that last over time allows researchers to understand the why some relationships last long-term and others do not. Attributes such as, emotional closeness, the frequency of contact, social support, and their changes over time, can depict fluctuations in the availability of resources to ego and changes to the strength of ties over time.

## A Conceptual Framework for Social Networks

The conceptual framework includes the social ecological model and social network model (Figure 3). The social network model identifies interpersonal relationships and their interactions. The social ecological model integrates individual, interpersonal, and environmental determinants of behaviors to explain the dynamic nature of behavioral changes (29–31). One key component of the ecological perspective is the idea that an individual interacts with their social environment (32). The environment is defined as the social, cultural, economic, structural, and political space in which a variety of factors exogenous to the individual interact to either directly or indirectly improve or deteriorate quality of life for cancer survivors (33).

Environmental factors, such as socioeconomic position, may directly facilitate survival through access to treatment services and support for cancer survivors. For example, one review paper pointed out that the lowest SES group had an excess cancer death toll of 30–50% compared to that of the most affluent one (34).

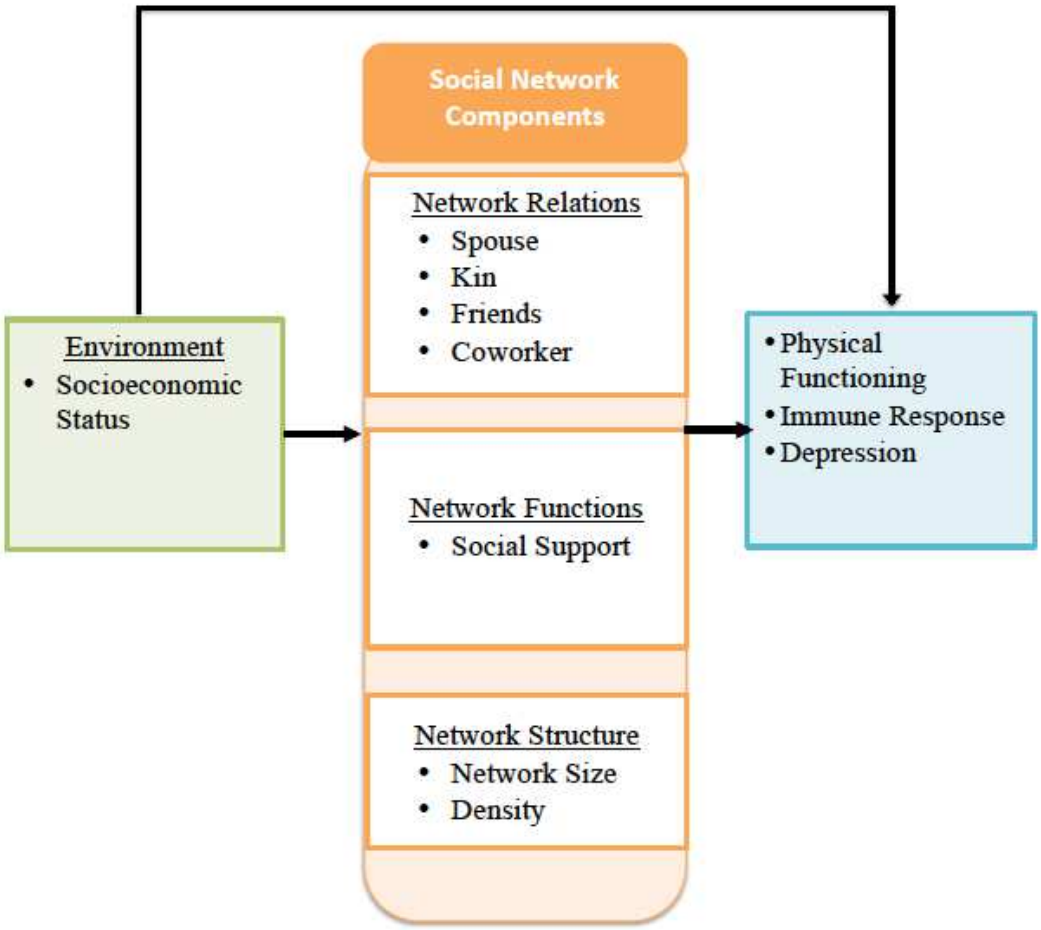
Social networks operate at the interpersonal group level, where perceived network 'norms or control' dictate what is considered acceptable behavior. Ideas, beliefs, opinions and emotions of the individual are considered a function of the network, and therefore, adoption or maintenance of norms depends on the actions or behaviors of the network (17,35–37). Norming is the validation and enforcement of beliefs, behaviors, and practices in social networks. Two types of social norms have been reported: subjective and descriptive. Subjective norms are defined as the beliefs of people important to the individual and the individual's motivation to comply with these beliefs (38,39). Subjective norms are perceptions of social pressure from significant others, such as network members. Descriptive norms are one's perceptions of other people's behaviors (40,41), which shape the way individual's behave. Subjective and descriptive norms may influence a cancer survivor's health behaviors and medical care decision-making during treatment and remission (42).

The influence of social support on network members may stem from consensus, as well as from coercion, depending on the type and sources of social support and the characteristics of the relationship in which it occurs among network peers (43). High social support has been shown to reduce cancer mortality risk by 25% and is associated with a lower risk of recurrence and longer survival (11). Moreover, social support can improve quality of life (33). However, the mechanisms

by which social support exerts direct and indirect effects on health outcomes has been of recent interest, despite several calls for more research (23,25).

In sum, social networks can have profound impacts on the life course by shaping norms, exerting influence on behavior, and spreading information, ideas and resources. Networks change over time as people enter and exit one's personal circle of close contacts. Analytic methods have been developed to describe egocentric network change over time, which is the central component of this dissertation.

Figure 3. Mechanisms by which social-behavioral factors influence physical, physiological and mental health



*Significance and Innovation*

**Significance**

Individuals are interconnected, and so is their health. Therefore, health choices are not solely the actions of the individual, but are influenced and spread interdependently among close contacts (18). Cancer survivors are more likely rate their quality of life (QOL) (33) and self-reported health worse than healthy controls (8,44). Some qualitative studies suggest that life after cancer can be extremely challenging- including experiencing treatment sequelae and reduced social support (45). Previous studies demonstrate that low social support and low social integration, or social embeddedness into society, are associated with adverse lifestyle choices (46), decreased immune functioning (47–49), physical decline (50), poorer quality of life (51), and mortality (11,52). However, there are several methodological issues with these two measures (23). First, social support, often cited as a type of network function, is only one component of a social network. A single measure of social support ignores the structural and relational network factors. Second, both measures do not capture the specific connections that individuals identify as most important to their social circle, nor do they indicate characteristics of those ties. For example, a close friend may provide more resources and support than a friend who is distant. Third, social networks are dynamic and interactions with network members, their motivations, and the resources they provide, may change after diagnosis, treatment, and beyond. The majority of studies only consider a cross-sectional view of the network at one point in time. Together, these limitations call for a more robust methodology to measure social networks over time.

Egocentric social networks describe the relationship between a cancer survivor (ego) and their closest contacts (alters). Together, egos, alters, and their ties to each other, constitute the personal network. Understanding how social networks change over time and their influence on health is critical to address the needs of the aging survivor. The contribution of the proposed research will capture egocentric social networks over a five-year period in a large cohort of cancer survivors and healthy older adults. *This contribution is significant because it elucidates the evolving social landscape that may facilitate poor health among aging cancer survivors over a five-year period.* Addressing multiple dimensions of one's personal social network could improve independence in daily living, management of comorbidities, and quality of life for aging cancer survivors.

**Innovation**

The status quo as it pertains to social network methodology has largely consisted of studies that utilize social support scales or the social network index. This has been the approach despite calls for methodological changes (23,25). The benefits of social support have been recognized since the pioneering work of the Alameda County Study (24) and continue to be demonstrated today. These seminal studies have consistently shown that socially isolated individuals cannot buffer stressors, which ultimately leads to negative health consequences, such as morbidity and mortality (23,53,54). *The proposed research in this application is innovative, in our opinion, because it represents a significant departure from the status quo by measuring egocentric social network turnover and its impact on successful aging among cancer survivors over time.* Understanding the network components that shape

resources, health behaviors, and access to information for aging cancer survivors could likely be transposable to other defining illnesses in late life.

## Chapter 2: Methods

### *Study Design*

This dissertation uses secondary date from the National Social Life, Health and Aging Project (NSHAP). NSHAP is a large, nationally representative cohort of older adults aged 57-85 years old. NSHAP provides rich data on social relationships, physical and mental health, and biomarker data. Wave 1 (W1) data were collected in 2005-2006 (n=3,005) and Wave (W2) (n=3,377) from 2010-2011 (12). Social networks may change as a result of a disease status. For example, one might not be able to participate in activities with network members because of limited mobility or illness. Therefore, a cohort study design is ideal because the longitudinal impact of social networks on health outcomes can be assessed and the results will not be subject to temporal ambiguity bias.

#### Sampling and Design

NSHAP is a complex multistage probability sample of older adults. The multiple stages of selection included: 1) two area stages, 2) a household stage, and 3) an individual selection stage. In the area stage, primary sampling units (PSUs) consisted of geographic areas (either counties or metropolitan areas) that were selected based on probabilities proportional to their sizes. In the household stage, households units were identified within census blocks with the probability of selection proportional to their size. Census blocks were selected from within the

PSUs. At the individual selection stage, NSHAP staff used a list of all housing units to select people for an interview. Only one individual from each household was eligible to be selected into the study.

The goal of sampling is to select individuals with equal probabilities of selection because it provides more precise estimates (e.g., smaller standard errors) (55). NSHAP had the predetermined goal of subsampling three age groups by gender, for a total of six subgroups, with the ultimate goal of equalizing their probabilities of selection within each subdomain. A priori power calculations determined that a sample size of 500 subjects in each subgroup (total of 3,000 participants) would be needed to perform subgroup analyses with adequate power. African Americans and Latinos were oversampled by 10 percent to ensure adequate representation. NSHAP provided weights, clustering and stratification variables to account for oversampling and the complex design.

A priori NSHAP assumed that 5% of individuals would be ineligible to participate in the study and the response rate would be 70%. Therefore, 4,400 people from the sampling frame with an equal probability of section from the six subdomains was required to generate 3,000 interviews (56). The final W1 sample was 3,005 participants, of whom 2,261 participated again in W2 (57). Participants were offered a $100.00 incentive to participate in W1 and were given a summary book of their anthropometrics and biomeasures after participation. In W2, participants were offered an additional $100.00, with up to a $300.00 increase, if they refused participation repeatedly.

**Biospecimen Collection Procedures**

Non-medical field interviewers were trained to collect biomeasures during the in-home interview. Interviewers were required to pass a certification on their last day of training to participate in data collection, as well as 'refresher' trainings throughout the data collection process. Cytokines were measured using serum plasma. Interviewers were responsible for collecting, storing, packing and shipping all biospecimens. NORC at the University of Chicago was responsible for quality control, which included tracking biospecimens from the in-home interview to their final laboratory destination, as well as biomarker quality (58). W2 biospecimen collection is outlined in O'Doherty et al.'s (2014) paper and a summary of the protocol measures related to C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF) are presented here (59).

The adherence rate for blood collection in W2 was 92.1%. Whole blood (250 µl) was collected by field interviewers by placing the respondent's finger over a Microtainer (BD Microtainer Tube with Dipotassium EDTA, Beadless additive BD Microgard closure, Catalog No. 365974; Becton Dickinson and Company). At the interviewer's field base, the Microtainer was shipped overnight to the University of Chicago, Flow Cytometry Facility. Plasma from unclotted whole blood was used to measure key analytes representing immune function. The unclotted blood was centrifuged and plasma was extracted and frozen (−80°C). A multiplex panel of 18 cytokines-chemokines were assayed in duplicate with Luminex technology (Luminex 100 device; BioRad, München, Germany) using the BioPlex Manager Software (Version 5, BioRad). Multiplex magnetic-bead antibody kits were used for cytokines-

chemokines (HCYTOMAG-60K-18; Millipore, Schwalbach, Germany). The coefficient of variation (CV) is the standard deviation divided by the mean and is often expressed as a percentage. The CV is a standardized measure that is used to compare the overall precision of estimates regardless of the magnitude of the analyte concentration. The median CV ranged from 7.2%-10.4% for all three biomarkers and were consider to be within acceptable range (typically less than 10-15%).

*Assessment of Potential Biases*

**Selection bias**

Selection bias occurs when the probability of being selected into the study/analytic sample is influenced by exposure or disease status. Attrition, a type of selection bias, is common in cohort studies of older adults because they have higher risks of illness and death. Older adults who dropped out or died may suffer from poorer overall health than those who remained in the study, thereby leading to selection bias. A total of 314 participants from W1 died prior to the W2 interview (173 men and 141 women), however none of these participants reported a history of cancer in W1. To prevent further attrition, NSHAP participants were offered $100.00 to participate in W2, with up to a $300.00 increase if they refused repeatedly, which retained an additional 161 participants (57).

Selection bias can also arise from missing data. For the first manuscript, the Activities of Daily Living (ADL) scale was completed by all NSHAP respondents in W2 and was missing for only one participant in W1. Less than 10 percent of the data were missing covariate information, so we included individuals with missing covariate information as dummy variables in the analysis. In manuscripts 2 and 3,

there were large amounts of missing data, as the majority of participants did not have data on all three inflammatory markers. To derive the analytic sample we enforced strict exclusion criteria to compare our results across the different inflammatory markers. However, we omitted approximately 67% of the NSHAP subjects who participated in both waves of data collection (1504/2261) and it is possible that selection bias was introduced, potentially compromising the internal validity and limiting the external validity of our study (See Model Specification, Manuscript 2 for results of the sensitivity analysis).

**Information bias**

Information bias arises when key variables are inaccurately measured or classified (e.g., measurement error). The consequences of information bias are a distortion of the measure of association. In addition to the potential information bias issues reported in the manuscript, there are several other potential measurement issues surrounding egocentric social networks. First, NSHAP's social network module was derived from a single name generator. Problems arise if the name generator does not reliably generate ego's list of alters or predict the full support network. Failure to accurately predict the full support network undermines the construct validity of a multidimensional definition of support. Therefore, the NSHAP network module would be strengthened by using multiple name generators to describe different aspects of ego's network (60). Second, fixed design networks limit ego to list a small number of alters (e.g., five alters). This could be a faulty assumption if a respondent's true network consists of more than five alters. Therefore, measurement error may be introduced into the design because individuals are forced to constrain their networks

to five people when in reality they are larger. Less motivated, ill, or fatigued participants may have been less willing to name more alters or participate in the network module. Additionally, ego may forget to include important alters in his personal network or they may have trouble recalling whether the corresponding alter in W2 was the same person named in W1. NSHAP identified 29 inconsistent cases where the ego could not recall whether the alter named in W2 was the same alter listed in W1. These alters were subsequently removed from the dataset by NSHAP (28). Recall bias in this case is unlikely to be dependent upon the outcomes, functional impairment, inflammation, and depression and therefore, non-differential misclassification would result, most likely biasing the results toward the null. Third, egos may not accurately report data about alters. For example, studies have shown that egos overestimate their frequency of contact with alters (61). Certain questions may elicit higher accuracy than others (such as, alters' gender and ethnicity). However, the objective is for ego to report perceptions about his relationships with alters, and therefore, ego's beliefs and opinions about their alters are of importance, not necessarily facts.

For manuscripts 2 and 3 we used three markers of inflammation: CRP, TNF-α, and VEGF. Despite NSHAP's attempt to regulate and ensure quality control measures, measurement issues arise when specimens are damaged during transport or shipping, or potential laboratory extraction problems occur. A NORC staff member mentioned that all initial plasma samples were over-diluted and had to be re-assayed. This means that individuals who submitted two blood samples were included in the inflammation dataset. Of those with assay data, NSHAP highlighted some questionable values in the

dataset that were either indeterminate or below threshold batches, or presented an uncertain value after quantification. To avoid introducing measurement error, we excluded participants with these values in the analysis. In our original proposal we were going to include interleukin-6 (IL-6), a pro-inflammatory cytokine that has been extensively studied in the literature. However, over 80% of the values in the dataset were demarcated as suspect and therefore were unusable. Given that 92% of individuals submitted an initial blood sample and that the reason for the measurement error in the outcome variables was assay-related, it is unlikely that differential misclassification resulted, because missing social network data could not be dependent upon a laboratory error. Therefore, any information bias introduced is likely non-differential and would attenuate the results towards the null.

**Confounding bias**

Confounders were identified from the literature and were tested in our analytic sample using the 10% change in effect estimate strategy (62,63). The goal is to determine whether the effect changes by more than 10 percent when individual covariates are removed from the model. If the effect changes by more than 10 percent from the crude (or minimally adjusted) effect then the variable is considered a confounder and should be retained in the model to control for systematic bias. The percent change formula is: [(crude effect-adjusted effect)/adjusted effect].

In manuscripts 2 and 3, TNF-α and VEGF were only collected during W2, which is problematic because we could not adjust for the baseline values of these variables. Inflammation at baseline may be associated with social networks because social

networks may change in response to pre-disease or morbidity. Additionally, TNF-α and VEGF at baseline are likely associated with their values at a later time point, since in our study we found that CRP at baseline was strongly associated with CRP at W2. Therefore, in order to ensure that network change predicts inflammation, the baseline values of inflammation should be controlled for. Since these data were not available for TNF-α and VEGF, it is possible that residual confounding (e.g., distortion leftover after controlling for confounding) may have occurred.

*Statistical Approaches to Test Hypotheses*

**Manuscript 1**

Univariate analysis was conducted to assess the distributions of all variables. Chi-squared tests and simple linear regression were used to determine if sociodemographic and social network variables differed by cancer survivor status. Simple linear regression was used instead of a T-test or ANOVA because SAS does not offer these options for complex survey designs. NSHAP is a multistage area probability sample and therefore, sampling weights must be used to get an unbiased estimate of the population. We used the survey procedures in SAS (e.g., surveymeans, surveyfreq, surveyreg, and surveylogistic) with the sampling weights, stratification and clustering statements to take into account the complex survey design. Sampling weights were used to ensure correct calculation of point estimates. NSHAP provides two sets of weights in their dataset: a baseweight and a weight that accounts for non-response by age and race. We used the weight adjusting for non-response in W1 as NSHAP recommended for assessing social network change (28).

The stratification and clustering statements were used to calculate the standard errors and their corresponding tests of statistical significance.

To test the hypothesis that social network change was associated with functional impairment in cancer survivors and adults without cancer, a series of lagged regression models were tested to determine which results most meaningfully captured social network change on functional impairment. Lagged linear and logistic regression models were conducted to assess whether social network change predicted ADL. Lagged regression is similar to ANCOVA, because the baseline values on the dependent variable are controlled. The difference is that lagged regression is not limited to using only categorical covariates, like ANCOVA. If functional impairments at baseline are not controlled for, an association between social network change and functional impairment might exist only because the impairments preceded social network change. Including $\beta_{Y1}Y_1$ as a covariate equates participants on their baseline values, which controls for any *initial* differences that may be present (64). The basic form of the lagged linear regression model is:

$$Y_2=\beta_0+ \beta_{Y1}Y_1+ \beta_1X_1 + e$$

First, lagged linear regression models using a log transformation of the ADL scale was considered (results shown in Appendix A). However, because approximately 70% of the sample reported no impairments we dichotomized the ADL scale as one or more impairments versus no impairments. We tested a log binomial model because the prevalence of disease was high (e.g., >10%) and the odds ratio tends to overestimate the relative risk when the disease is common. However, the log

binomial model would not converge and therefore, we present logistic regression models despite its known limitations.

**Manuscript 2**

The term "allostatic load" is an indicator of the body's 'wear and tear' and can be described as a count of the number of elevated biomeasures across the bodily system. Allostatic load is a comprehensive indicator of the accumulative burden of physiological dysreguation and has been shown to be associated with poor population-level health, including cognitive decline, heart disease, and mortality (65). Given some relatively new evidence that the burden of inflammation is associated with mortality in cancer survivors, we were initially interested in creating a summary index to test the collective burden of inflammation, since it has yet to be studied. We created the summary index by summing the total number of inflammatory markers that were "high." High inflammation was categorized as the top quartile for TNF-α and VEGF, and using the established cutoff value of 3-10 to indicate chronic inflammation for CRP (48,66).

To confirm that these three markers comprised of a single indicator of inflammation, a principle components analysis (PCA) with oblique rotation was conducted. PCA is a dimension reduction technique that can be used to determine if all three inflammatory markers load on a single component. In PCA, the first principal component is a linear combination of variables that explains the most variation. The second principal component is another linear combination of the variables and independently explains the remaining variation. We extracted three components that each explained the remaining variation not previously explained by the prior

components. All biomarkers loading heavily on the first principal component provides evidence that the inflammatory markers comprise of a single indicator. If the inflammatory markers load heavily on multiple components then this suggests that the index is of little use, and each marker should be considered separately. Scree plots (Figure 4), the percentage of the variance explained, eigenvalues, and the loading coefficients were used to evaluate the utility of an inflammatory index (Table 1).

The first component had an Eigenvalue greater than one and the scree plot showed that the largest drop in Eigenvalue occurred with the first component. However, the PCA indicated that the first component explained only 40.33% of the variance (unrotated) and generally, components that explain 75-85% of the variance should be extracted. Therefore, to achieve 75-85% of the variance explained, all three components would have to be extracted. This indicates that the inflammatory markers do not comprise of a single indicator and therefore, should be evaluated separately. To evaluate each inflammatory marker separately, we used each continuous (log-transformed) biomarker as the outcome variable in separate lagged linear regression models.

Figure 4. Scree Plot

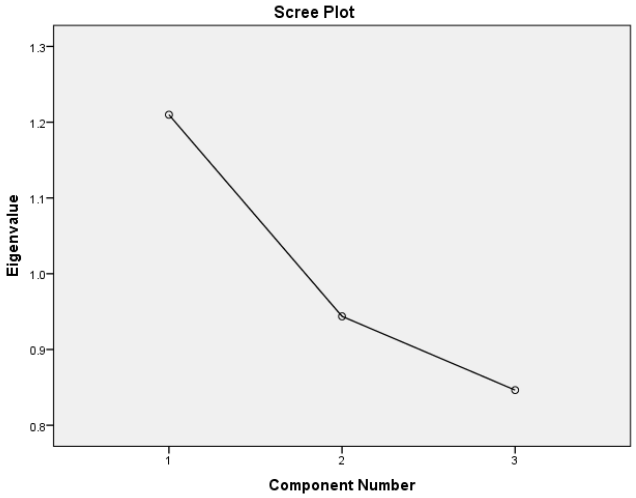


Table 1. PCA Results

**Total Variance Explained**

| | Initial Eigenvalues | | | Extraction Sums of Squared Loadings | | | Rotation Sums of Squared Loadings[a] |
|---|---|---|---|---|---|---|---|
| Component | Total | % of Variance | Cumulative % | Total | % of Variance | Cumulative % | Total |
| 1 | 1.21 | 40.33 | 40.328 | 1.21 | 40.33 | 40.33 | 1.01 |
| 2 | 0.94 | 31.46 | 71.787 | 0.94 | 31.46 | 71.79 | 1.03 |
| 3 | 0.85 | 28.21 | 100.000 | 0.85 | 28.21 | 100.00 | 1.03 |

Extraction Method: Principal Component Analysis.

a. When components are correlated, sums of squared loadings cannot be added to obtain a total variance.

### Manuscript 3

The statistical approaches for Manuscript 3 are described in detail in the Methods section of the manuscript.

*Assessment of Mediation and/or Interaction Effects*

### Subgroup Analysis

In each manuscript a subgroup analysis was conducted by stratifying each model by cancer survivor status. Stratification facilitated comparisons among cancer survivors and older adults without cancer to determine if the relationships between social network features and physical functioning, inflammation, and depressive symptoms varied across the two groups. It is thought that subpopulations might be unrelated to the sample design and therefore, the sample sizes for the subpopulations might actually be random variables. We used the "domain" statement within the survey procedure in SAS to include this variability into the variance estimation. For the structural equation model (SEM) we used a two-group design, which facilitated subgroup analyses.

### Manuscript 1

We tested interaction terms in the models to determine if the number of comorbidities, gender, and age modified the relationship between network losses, additions, and social support. All interaction terms were not statistically significant. Likelihood ratio tests indicated that the reduced model with no interaction terms fit significantly better than the full model with the interaction terms, and was considered our final model.

**Manuscript 2**

No additional mediation or moderation was tested.

**Manuscript 3**

Structural equation modeling was used to assess inflammatory mediators and is described in detail in Manuscript 3.

*Model Specification*

**Manuscript 1**

The Hierarchical Well Formulated Approach was used for variable selection and retention in models. In the hierarchical well-formulated approach, covariates are first selected based on the literature. Then, all of the covariates are added into the model and a priori interaction terms are tested. If an interaction exists, then testing for confounding becomes irrelevant because the lower order items are retained in the model regardless. Three models were considered using the Hierarchical Well Formulated Approach:

**Model 1:** a minimally adjusted model to determine the association between all independent variables and functional impairment in Wave 2, adjusted for functional impairment in Wave 1.

**Model 2:** a full model with all interaction terms and potential confounders.

**Model 3:** a reduced model removing the interaction terms that were not statistically significant ($p>0.05$) and confounding variables that failed to change the odds ratio by 10% or more.

**Manuscript 2**

Variables were selected for inclusion based on the literature. We estimated multiple linear regression models to determine if social network change from W1 to W2 predicted subsequent risk of inflammation in cancer survivors and those who never had cancer. For CRP we tested lagged models that included the baseline values of CRP. We first estimated reduced models that adjusted only for CRP at baseline. Next we estimated a full model with all potential confounding factors and then tested confounding using the 10% change in effect estimate strategy, eliminating any potential confounders that did not change the effect sizes by 10%. All potential confounders were retained in the models based on these criteria. Since we did not have the baseline values of VEGF and TNF-α, we tested multiple linear regression models and assessed confounding based on the 10% change rule. Similarly, all confounders were retained in the models. Two models were presented for each outcome variable: a model with cancer survivors and a model with older adults.

**Manuscript 3**

The objective of the third manuscript was to conduct a two group mediation model using structural equation modeling (SEM) to understand whether social support is directly or indirectly associated with depression among cancer survivors and older adults. By definition a mediator is a third variable that is on the causal pathway and is situated between the exposure and the outcome. Figure 5 represents a simple mediation model where the arrows indicate directionality and the paths are labeled a, b, and c to represent a specific relationship from one variable to another. The path *a*

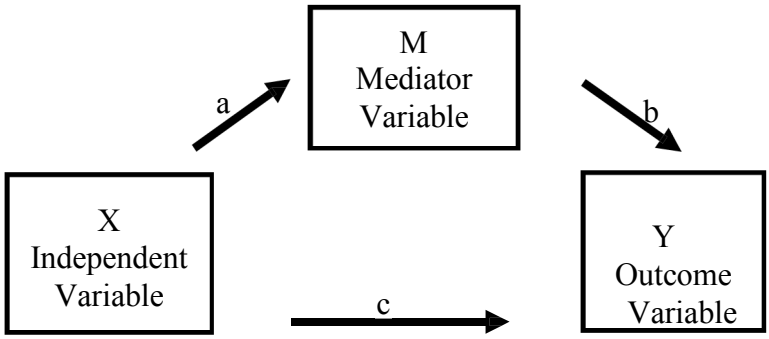
represents the relationship from X to the mediator M, the path *b* represents the path from M to Y, and the path *c* indicates the relationship from X to Y. Together, the *ab* path represents the indirect effect where the path from X to Y is mediated by M. The *c* path is the direct path from X to Y. Mediation effects can be completely, partially, or inconsistently mediated. Complete mediation occurs when the direct effect (path *c*) is zero and the indirect effect (path *ab*) is nonzero. Partial mediation occurs when the direct effect (path *c*) and the indirect effect (path *ab*) are the same sign. Inconsistent mediation occurs when the direct effect (path *c*) and the indirect effect (path *ab*) are nonzero and have opposite signs (67).

The SEM multi-group models would not converge due to the small sample size relative to the number of parameters in the model for the cancer survivor group. Therefore, group invariance was tested using a path model, which significantly reduced the number of parameters. The path model for both groups converged, but Mplus warned that the standard errors of the model parameter estimates "may not be trustworthy due to having more parameters than the number of clusters minus the number of strata with more than one cluster." SEM methods with complex survey designs are relatively new and understudied. Expert consultation (Laura Stapleton, EDMS Department, UMD, College Park) suggested a sensitivity analysis comparing the parameter estimates and standard errors with and without the complex survey design option (Appendix B). It was suggested that if the estimates and standard errors were similar (albeit an appropriate increase in the standard errors for the model that takes into account the complex survey design), then the complex survey design option should not be used. After conducting the sensitivity analysis, the parameter estimates

and standard errors were similar in the two models and analyses proceeded without the use of the complex survey design.

After conducting the constrained path analysis, the likelihood ratio test revealed that the cancer survivor group was not different from the older adult group (scaled $\chi^2$=66.81, *df*= 54, p=0.1132). Therefore, we conducted a latent variable model to determine if there was evidence of mediation in the overall sample using a more powerful modeling approach (68).

Figure 5. Simple Mediation Model



*Assessment of Model Assumptions*

**Manuscript 1**

Our outcome variable of interest (ADL) was a continuous scale. Therefore, we first checked the assumptions (e.g., independent observations, linearity, equal variance, and normality) of linear regression prior to conducting any analyses. Linearity was assessed with correlations and scatterplots. The Shapiro-Wilks test was used to determine whether our outcome variable, the ADL scale, was normally distributed. The Shapiro-Wilks test indicated a departure from normality ($p<0.0100$) and therefore log transformation was necessary. However, after transformation, the distribution was still skewed and it was noted that~70% of our sample had 0 or no impairments in their activities of daily living. Therefore, we created a binary variable to indicate 0=no impairments vs. 1=at least one impairment.

Pearson residuals with values of + or – 3 were used to detect outliers and Cook's distance was used to detect influential points. An observation was considered an outlier if: 1) if an influential point shifted the slope of the regression line, determined by a Cooks D value >1, or 2) or if extremeness is observed in the observations in the independent variables (e.g. leverage). Leverage points greater than the cut off of 0.026 (e.g., 2(k+1)/n]= [2(28+1)/2212]=0.026), where k= the number of predictors (including covariates) and n is the total sample size. Values for outliers and influential points for all variables were checked for implausible values. All values were deemed plausible (e.g., biologically plausible or within normal ranges) and were not removed from the dataset. Multicollinearity was checked with the variance inflation factor (VIF). VIF values over 10 are considered to be multicollinear. No variables reached

this level. There were no participants missing data on the ADL scale in W1 and only one subject was missing the outcome variable in W2. NSHAP participants missing data on categorical covariates were modeled as dummy variables and included in models to avoid losing incomplete cases (e.g., SAS automatically drops these cases).

**Manuscript 2**

The distribution of all variables was assessed with univariate statistics. The distributional assumptions for linear regression were also assessed (e.g., homoscedasticity (equal variance), independent observations, linearity, and normality). Normality was assessed with the Shapiro-Wilk Test. Despite log transformation to normalize the distributions of the biomarker variables, the Shapiro-Wilks Test was <0.05, which indicated that the data were not from a normally distributed population. Therefore, we decided to use natural log transformed outcome values, which is in accordance with other studies (47,66,69). Homoscedasticity was tested by plotting the residuals versus the predicted values.

Pearson residuals were used to assess outliers with absolute values of three. Influential points were assessed with Cook's distance (Cook's D) to determine if outliers changed the beta coefficients in the model. If an observation shifted the slope of the regression line, determined by a Cooks D value >1, then it was considered to be an influential point. If extremeness in any observations were observed in the independent variables (e.g. leverage) then they were considered outliers. No Cooks D values >1 were observed, although several outliers were identified for VEGF and TNF-α. We tested models that excluded the top and bottom 1% of extreme observations for these two outcomes. However, the results were the same and therefore, we retained

those observations in the dataset. Multicollinearity was tested using the variance inflation factor. VIF values over 10 are considered to be highly multicollinear. No variables met this criterion.

For Manuscript 2, a series of sensitivity analyses were conducted to determine if those missing the outcome variables were different from the analytic sample. Data missing on the outcome variables or social network variables resulted in a largely reduced sample size (see Figure 6 in Manuscript 2 for a description of the missing/excluded data). First, we compared participants who were missing biomarker data on key study variables to those with data on all three biomarkers. Those with missing data were significantly different in regards to the number of alters added to the network, smoking status and physical activity, compared to those who were retained in the analytic sample (Table 2a). Cancer survivors with missing data were significantly different in terms of educational status, where those with missing data reported significantly higher percentages of being college educated (Table 2b). It should be noted, however, that regardless of how similar the samples are selection bias is still possible and should not be ruled out. Second, we compared the models for CRP, TNF-α, and VEGF in our analytic sample (n=757) to a model with the full sample of each inflammatory marker, since subjects may have been missing one, two or all three biomarkers (Appendices C-E). The sensitivity analyses revealed that the magnitudes of the associations were similar between those with all three biomarkers compared to those with at least one biomarker; however some associations became statistically significant.

Table 2a. Sensitivity analysis comparing missing outcome data on key variables

| | Missing at least one biomarker | | Complete data for all three biomarkers | | |
|---|---|---|---|---|---|
| | n | % | n | % | p-value |
| Cancer survivor status | | | | | |
| Cancer survivor | 80 | 11.86 | 105 | 14.79 | 0.13 |
| Older adult without cancer history | 546 | 88.14 | 652 | 85.21 | |
| Lost Ties | | | | | 0.94 |
| Lost 0 alters | 97 | 14.59 | 122 | 15.06 | |
| Lost 1 alter | 176 | 28.04 | 208 | 26.31 | |
| Lost 2 alters | 159 | 27.33 | 206 | 27.48 | |
| Lost 3 or more alters | 194 | 30.03 | 221 | 31.15 | |
| Added Ties | | | | | |
| Add 0 alters | 151 | 24.96 | 146 | 18.23 | **0.01** |
| Add 1 alter | 145 | 24.21 | 219 | 29.17 | |
| Add 2 alters | 167 | 27.13 | 203 | 27.59 | |
| Add 3 or more alters | 163 | 23.70 | 189 | 25.01 | |
| Age | | | | | |
| 57-64 (Ref.) | 253 | 48.60 | 297 | 46.55 | 0.41 |
| 65-74 | 239 | 35.84 | 286 | 35.32 | |
| 75-85 | 134 | 15.56 | 174 | 18.13 | |
| Gender | | | | | |
| Male (Ref.) | 279 | 43.90 | 317 | 41.80 | 0.46 |
| Female | 347 | 56.10 | 440 | 58.20 | |
| Race | | | | | |
| White (Ref.) | 463 | 83.17 | 576 | 85.31 | 0.24 |
| Non white | 161 | 16.83 | 178 | 14.69 | |
| Marital Status | | | | | |
| Married/Cohabitating Partner | 419 | 72.15 | 498 | 72.17 | 0.99 |
| Not married | 207 | 27.85 | 259 | 27.83 | |
| Education | | | | | |
| Less than high school | 95 | 12.10 | 117 | 11.88 | 0.62 |
| High School Diploma or Equivalent | 152 | 24.01 | 194 | 25.81 | |
| Some college | 204 | 32.95 | 246 | 34.89 | |
| Bachelor's Degree or more | 175 | 30.94 | 200 | 27.42 | |
| Comorbidity Index (mean, SE) | 2.14 | 0.08 | 2.11 | 0.06 | 0.75 |
| BMI | | | | | |
| Underweight/ Normal (Ref.) | 150 | 26.19 | 185 | 24.29 | 0.58 |
| Overweight | 221 | 33.81 | 262 | 37.18 | |

| | | | | | |
|---|---|---|---|---|---|
| Obese | 227 | 40.00 | 274 | 38.53 | |
| Physical Activity | | | | | |
| Less than once a month | 404 | 63.66 | 529 | 70.49 | **0.04** |
| Exercise once a month to 1-2 times/week | 73 | 10.91 | 88 | 11.01 | |
| 3 or more times/week | 147 | 25.44 | 139 | 18.50 | |
| Smoking | | | | | |
| Nonsmoker | 561 | 90.81 | 656 | 85.95 | **0.03** |
| Smoker | 64 | 9.19 | 101 | 14.05 | |

*Bold indicates $p<0.05$

Table 2b. Sensitivity analysis comparing missing outcome data on key variables by cancer status

| | Cancer Survivor | | | | | Older adults | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Missing at least one biomarker (n=80) | | Complete data for all three biomarkers (n=105) | | p-value | Missing at least one biomarker (n=546) | | Complete data for all three biomarkers (n=652) | | p-value |
| | n | % | n | % | | n | % | n | % | |
| Lost Ties | | | | | | | | | | |
| Lost 0 alters | 10 | 11.4 | 12 | 11.8 | 0.81 | 87 | 15.0 | 110 | 15.6 | 0.84 |
| Lost 1 alter | 27 | 30.1 | 34 | 30.0 | | 149 | 27.8 | 174 | 25.7 | |
| Lost 2 alters | 17 | 24.5 | 27 | 30.4 | | 142 | 27.7 | 179 | 27.0 | |
| Lost 3 or more alters | 26 | 34.0 | 32 | 27.7 | | 168 | 29.5 | 189 | 31.7 | |
| Added Ties | | | | | | | | | | |
| Add 0 alters | 12 | 16.3 | 22 | 22.5 | 0.36 | 139 | 26.1 | 124 | 17.5 | **<0.01** |
| Add 1 alter | 26 | 34.0 | 31 | 28.1 | | 119 | 22.9 | 188 | 29.4 | |
| Add 2 alters | 14 | 14.6 | 27 | 23.5 | | 153 | 28.8 | 176 | 28.3 | |
| Add 3 or more alters | 28 | 35.0 | 25 | 25.9 | | 135 | 22.2 | 164 | 24.9 | |
| Age | | | | | | | | | | |
| 57-64 | 19 | 34.6 | 23 | 31.8 | 0.92 | 234 | 50.5 | 274 | 49.1 | 0.42 |
| 65-74 | 33 | 41.2 | 48 | 44.6 | | 206 | 35.1 | 238 | 33.7 | |
| 75-85 | 28 | 24.2 | 34 | 23.7 | | 106 | 14.4 | 140 | 17.2 | |
| Gender | | | | | | | | | | |
| Male | | | | | | | | | | |
| Female | 33 | 40.1 | 42 | 41.3 | 0.88 | 246 | 44.4 | 275 | 41.9 | 0.45 |
| Race | 47 | 59.9 | 63 | 58.7 | | 300 | 55.6 | 377 | 58.1 | |
| White | 69 | 93.6 | 88 | 88.6 | 0.24 | 394 | 81.8 | 488 | 84.7 | 0.09 |
| Non white | 11 | 6.4 | 17 | 11.4 | | 150 | 18.2 | 161 | 15.3 | |
| Marital Status | | | | | | | | | | |
| Married/Cohabitating Partner | 48 | 64.6 | 63 | 65.7 | 0.90 | 371 | 73.2 | 435 | 73.3 | 0.97 |
| Not married | 32 | 35.4 | 42 | 34.3 | | 175 | 26.8 | 217 | 26.7 | |
| Education | | | | | | | | | | |

| | Cancer Survivor | | | | | Older adults | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Missing at least one biomarker (n=80) | | Complete data for all three biomarkers (n=105) | | p-value | Missing at least one biomarker (n=546) | | Complete data for all three biomarkers (n=652) | | p-value |
| | n | % | n | % | | n | % | n | % | |
| Less than high school | 5 | 5.6 | 17 | 14.6 | **0.03** | 90 | 13.0 | 100 | 11.4 | 0.67 |
| High School Diploma or Equivalent | 16 | 16.6 | 24 | 28.0 | | 136 | 25.0 | 170 | 25.4 | |
| Some college | 37 | 47.7 | 38 | 38.0 | | 167 | 31.0 | 208 | 34.4 | |
| Bachelor's Degree or more | 22 | 30.1 | 26 | 19.5 | | 153 | 31.1 | 174 | 28.8 | |
| Comorbidity Index (mean, SE) | 2.1 | 0.1 | 2.3 | 0.2 | 0.35 | 2.2 | 0.1 | 2.1 | 0.1 | 0.43 |
| BMI | | | | | | | | | | |
| Underweight/ Normal | 21 | 29.6 | 23 | 24.2 | 0.24 | 129 | 25.7 | 162 | 24.3 | 0.83 |
| Overweight | 24 | 24.5 | 37 | 37.3 | | 197 | 35.1 | 225 | 37.2 | |
| Obese | 33 | 46.0 | 41 | 38.5 | | 194 | 39.2 | 233 | 38.5 | |
| Physical Activity | | | | | | | | | | |
| Less than once a month | 50 | 62.1 | 67 | 61.2 | 0.41 | 354 | 63.9 | 462 | 72.1 | **0.03** |
| Exercise once a month to 1-2 times/week | 6 | 5.6 | 11 | 11.1 | | 67 | 11.6 | 77 | 11.0 | |
| 3 or more times/week | 24 | 32.3 | 27 | 27.6 | | 123 | 24.5 | 112 | 16.9 | |
| Smoking | | | | | | | | | | |
| Nonsmoker | 73 | 91.2 | 95 | 89.8 | 0.79 | 488 | 90.8 | 561 | 85.3 | **0.02** |
| Smoker | 7 | 8.8 | 10 | 10.2 | | 57 | 9.2 | 91 | 14.7 | |

Bold indicates $p<0.05$

**Manuscript 3**

Similar to regression, bias arises in structural equation models if certain model assumptions are violated. Therefore, we first tested the distribution of all variables with univariate statistics. The distributional assumptions SEM include: independent observations, large sample size, a correctly specified model, and multivariate normal data (68). The inflammatory markers were highly skewed and also had high kurtosis (skewness>2 and kurtosis>10). High nonnormality can impact the findings so log transformation was performed to normalize the distributions of the biomarker variables. However, the Shapiro-Wilks Test was <0.05 after transformation, which indicated that the data were still not from a normally distributed population. Therefore, we decided to use the log transformed values and the robust Maximum Likelihood (e.g., "MLR option" in Mplus) for estimation. The MLR estimator was chosen over Maximum Likelihood because the MLR calculates the standard errors using the sandwich estimator, which is robust to non-normality and non-independence of observations. The MLR chi-square test statistic is asymptotically equivalent to the Yuan-Bentler T2* test statistic (70).

Similar to Manuscripts 1&2, Pearson residuals were used to assess outliers with absolute values of three. Influential points were assessed with Cook's distance (Cook's D) to determine if outliers changed the beta coefficients in the model. No Cooks D values >1 were observed, although (again) several outliers were identified for VEGF and TNF-α. We tested models that excluded the top and bottom 1% of extreme observations for these two outcomes. However, the results were the same and therefore, we retained those observations in the dataset. Multicollinearity was tested using the variance inflation factor. VIF values over 10 are considered to be highly multicollinear. No variables met this criterion and

therefore all variables were retained in the models.

To determine if the path model findings were impacted by the reduced sample size in the biomarkers, a sensitivity analysis was conducted by comparing our final path model to models with each biomarker separately, since the sample size for participants with at least one biomarker was larger. Participants missing data were compared to participants with data on all three biomarkers to determine if differences existed among key study variables. Modeling CRP, TNF- α, and VEGF separately with their full sample sizes yielded similar results to the path model with complete data on all three biomarkers (Appendices F-H). Participants with missing data on one or more biomarkers were compared to participants with data on all three biomarkers on key study variables. Participants with missing biomarker data were more likely to be non-white race/ethnicity ($p<0.01$), non-smokers ($p=0.01$), engage in frequent physical activity ($p<0.01$), have at least one functional impairment ($p<0.01$), and have lower median TNF-α levels ($p=0.02$) (Appendix I). Cancer survivors with missing data were more likely to be non-smokers ($p=0.03$), have lower TNF- α ($p=<0.01$) and higher CRP W2 values ($p=<0.01$) (Appendix J).

*Limitations*

There are several limitations to the work completed in this dissertation, including biases introduced from the study design and measures.

**Study Design:**

Despite using the strongest observational study design, the validity of cohort data can be affected by attrition and missing data, especially when the population of

interest is older adults. The consequence of attrition and missing data is selection bias. As previously mentioned, steps were taken by NSHAP to reduce selection bias, such as contacting individuals numerous times and providing varying levels of incentives to participate (71). The conditional response rate for W2 was high (89%), minimizing the introduction of selection bias via attrition between waves (57).

NSHAP previously quantified item-level missingness for the dataset and reported that missing data was associated with race/ethnicity, income level, education level, self-reported health, cognitive function, and marital status (72). However, these results did not take into account the large amount of missing data from the biospecimens collected in W2. The biospecimen data were missing because the first set of blood samples were overdiluted (laboratory error). Therefore, only the second set of blood samples were included in the dataset. Variation between interviewers encouraging two blood samples may have occurred, however we have no way to test this assumption.

**Cancer survivor population and measures**

NSHAP did not verify cancer diagnoses with a cancer registry and they also collected limited information related to prognostic factors. For example, clinical characteristics and treatment information were not collected and therefore, we may not be adequately describing some aspects of the cancer experience. The sample of cancer survivors in the NSHAP dataset may also be different than cancer survivors in other populations. For example, there were no deaths among cancer survivors between W1 and W2 and the mean number of years since initial diagnosis was 13.8, introducing potential selection bias into the sample. Additionally, cancer may go undiagnosed and untreated.

For example, 18% of colon and rectal cancers and 36% of prostate cancers were undiagnosed pre-mortem, as verified by autopsy reports (73,74). It is possible that some "cancer-free" older adults in our sample had undiagnosed cancer. If a large number of "cancer-free" individuals were undiagnosed, then the older adult group would look similar to the cancer survivor group, which would bias our results. Unfortunately, there is no way for us to discern who had undiagnosed cancer or preclinical disease in our sample and so we note this limitation here.

Additionally, only a small number of cancer survivors had complete data on all of the variables of interest. To conduct SEM with mediators in multiple groups, a sufficiently large sample size is needed relative to the number of parameters in the model. Because our model had many parameters relative to the size of the cancer survivor group, we experienced problems with convergence and were forced to conduct a path analysis instead.

**Limitations of social network measures**

Information bias arises when key variables are inaccurately measured or classified (e.g., measurement error) and result in a distortion of the measure of association. There are several measurement issues surrounding egocentric social networks. First, NSHAP's social network module is derived from a single name generator. If the name generator does not reliably produce ego's list of alters and predict the full support network, its use undermines the construct validity of the multidimensional definition of support. Therefore, the NSHAP's network module would be strengthened by using multiple name generators to describe different aspects of ego's network (60).

Second, fixed design networks force ego to list a small number of alters (e.g., five alters). This could be a faulty assumption if a respondent's true network consists of more than five alters. Therefore, measurement error may be introduced into the design because individuals are forced to constrain their networks to five people when in reality they are larger. Less motivated, ill, or fatigued participants may have been less willing to name more alters or participate in the network module. Additionally, ego may forget to include important alters in his/her personal network or have trouble recalling whether the corresponding alter in W2 was the same person named in W1. NSHAP identified 29 cases where respondents could not verify the linked alters in W1 and W2 and these alters were subsequently removed from the dataset (28). Recall bias in this case is unlikely to be dependent upon any of the outcomes (e.g., functional impairment, inflammation, and depressive symptoms). Therefore, any misclassification would likely be non-differential misclassification, biasing the results toward the null. Third, egos may not accurately report data about alters. For example, studies have shown that egos overestimate their frequency of contact with alters (61). Certain questions may elicit higher accuracy than others, such as alters' gender and ethnicity. However, the objective is for ego to report their perceptions about their relationships and ego's beliefs and opinions, not necessarily facts, are of importance. Fourth, participants were only allowed to name up to five alters and as a consequence, there may be ceiling effects. If the majority of older adults have more than five alters, then we have potentially underestimated the social network and its attributes and functions, such as the total amount of social support received from network members and bias the results.

**Limitations of functional impairment**

We had originally proposed to use two outcome measures of disability, a perceived measure (e.g., activities of daily living scale) and an objective measure (e.g., the timed up and go test). The timed up and go test was conducted on a subsample of the NSHAP participants. Unfortunately, only a small number of cancer survivors (n=36) were classified as having a disability by the timed up and go test and therefore, we could not use this measure. Thus, we present only perceived measures of disability (the Activities of Daily Living Scale). Individuals with low levels of social support may rate their impairments as more severe due to social isolation. Therefore, we cannot rule out differential misclassification. The direction of the bias would likely overestimate our results, since a higher proportion of individuals with disabilities would report low support. Additionally, since changes to functional status could have occurred at any time throughout the study period, we cannot pinpoint when during the five-year period functional decline started and therefore the social network at W2 may already reflect adjustment to restrictions in ADL.

**Limitations of inflammatory markers**

First, we could not control for VEGF and TNF-α at baseline and residual confounding may have impacted the findings. Although biomarker data at several time points are rarely available, longitudinal designs provide the proper the temporal sequence thereby improving the methodological deficiencies of cross-sectional studies. Second, inflammatory markers were only measured once during each wave and inter-assay variation may exist, although markers of inflammation have been shown to be stable over time (75,76). Third, we could not assess the cumulative burden of inflammation by

creating an index as others have done, despite our a priori hypothesis that these markers could be combined into a similar index. Our results suggested that these makers do not comprise of a single factor and have unique relationships with different social network components. Fourth, to describe the results across biomeasures we included only complete cases for all three outcome measures, which may have introduced selection bias into the analytic sample. However, sensitivity analyses suggested that the magnitude of the associations were similar, although statistical significance for some associations did not hold.

### Limitations of the 11-item CES-D

The 11-item Iowa short-form CES-D measures depressive symptoms, rather than a clinical diagnosis of depression. However, the CES-D is a commonly used scale in the epidemiologic literature and the 11-item Iowa short-form has been shown to be reliable and lose little precision compared with the 20-item CES-D (77).

### Limitations of covariates

Socioeconomic status was measured by a proxy, education, which likely has cohort effects, meaning that the level of education among the youngest old (e.g., 57-60 years) and the oldest old (e.g., 80-85) is likely very different. Education was chosen over income and wealth variables due to a large number of missing observations. Additionally, education is relatively stable over the life course, is more easily recalled than income, and is not confounded by retirement status. Therefore, this measure was chosen as an imperfect proxy of the socioeconomic experience. The modified Charlson Comorbidity Index is a crude estimate of the number and severity of comorbidities (78). Inaccuracies in

reporting may result if participants incorrectly recall their comorbidity status or do not understand the medical terms used in the questionnaire. Additionally, residual confounding may occur if the categories used to define comorbidity are not precise enough or if some comorbidities were not measured or included in the index. Smoking status was measured by self-report. Although cotinine data were available, they were missing for at least 75% of the sample. A previous paper documented that self-reported smoking and biomarker data were comparable in the NSHAP sample, with inconsistencies found in less than four percent of non-smokers (79).

Chapter 3: Manuscript 1

**Title:** Social network change and functional impairment in older adults with cancer over a five year period

*Abstract*

**Background:** Few studies have described how the social networks of cancer survivors change over time, and whether these changes are associated with quality of life. The objective of this study was to examine the relationship between egocentric social network change on functional impairment among a sample of cancer survivors and older adults without a cancer diagnosis.

**Method:** Data collected from the National Social Life, Health and Aging Project (NSHAP) were analyzed to assess the relationships of interest (2005-2006 and 2010-2011). Functional impairment was measured with the Activities of Daily Living Scale. Change in social networks was assessed by calculating the difference scores in closeness, frequency of contact, density, and social support between waves. Network turnover was defined as the number of alters who were lost or added to the network over time. Multivariable lagged logistic regression was used to assess the relationships between network change and functional impairment in cancer survivors compared with older adults without cancer.

**Results:** 29.4% of cancer survivors reported experiencing at least one functional impairment compared to 26.3% older adults (p=0.57). Both groups reported similar levels of losing or adding three or more network members over time. Participants who added two

new alters exhibited protective effects against the development of disability (OR: 0.64, 95% CI: 0.41-0.99) in the overall sample. Changes to the frequency of contact over time were associated with having at least one functional impairment among cancer survivors (OR: 1.92, 95% CI: 1.15- 3.20). No social network components were associated with disability in older adults.

**Conclusions:** Broad network interventions may be useful to identify older adults at risk for functional impairment, irrespective of cancer status. Future studies should consider using an egocentric network approach in large population-based cancer studies to assess long-term network changes.

*Background*

The Institute of Medicine defines cancer survivors as individuals who live through their cancer treatment, disease, or both (7). Over the next decade the number of cancer survivors living in the United States will approach 18 million individuals (3–5), with the majority of these survivors aged 65 and older (e.g., older adults) (6). The characteristic signs of aging include a gradual decline in functional capacity, including deterioration of the cardiovascular and musculoskeletal systems (9,10). The gradual decline of these systems may cause older adults to respond differently to cancer treatment (10) and endure post-treatment sequela, which may accelerate physical disability and mortality (80,81).

According to 2013 data from the Behavioral Risk Factor Surveillance System (BRFSS), 10.7% of cancer survivors reported having a mobility disability (e.g., walking or climbing up stairs) (82). Previous studies show that cancer survivors are more likely to self-report fair or poor health (11–13) and perceive their functional impairments worse than healthy controls (8,44). Cancer survivors living into old age are also more likely to have comorbidities, which may exacerbate physical deterioration (83–85) underscoring the need to design effective interventions to prevent or halt the progression of functional decline.

**Social networks, cancer survivorship, and aging.**

Adequate social network support may slow the progression of physical decline (86,87), while inadequate support may exacerbate disability (83). Social networks are the relationships or "ties" that people form with each other and attributes of those specific connections (16). Social networks can improve health by encouraging health behavior change and care utilization, and through tangible and emotional support (88). In studies of

older adults, network size (89) and interaction with network members (89–91) were associated with lower disability over time, while those who required more instrumental support (89,90) and emotional support (91) had the highest risk of disability *onset* over time (89,90). Studies among cancer survivors are somewhat inconsistent (33,92–96); yet, all of these studies assume that network properties are static and unwavering over time. Cross-sectional assessments cannot take into account the evolving nature of social networks and several longitudinal studies only measured social networks at baseline (87,90,97) and therefore, cannot account for individuals who may enter and exit the network over a given period of time. This is imperative because the degree of support received and the availability of network members may decline as the time from initial diagnosis and treatment increases. Cancer survivors report loneliness, social isolation, and significant declines in social network support after treatment (45,98,99), which may impact cancer-related disability and psychosocial well-being (98).

**Social network change.**

Little research has described social network change over time among cancer survivors (50,100). Therefore, it is relatively unknown whether these changes result in improved or deteriorated functional impairment and whether these changes are unique to the cancer survivor experience, or rather reflect the process of aging, in general. In fact we identified only one study that investigated network changes over time and their role on functional impairment. Michael et al., (2002) found that individuals with stable networks over a four-year period had slightly better physical functioning compared to those people whose networks changed (an increase or decrease), however these results did not approach statistical significance (50). Social networks were measured in Michael et al.

(2002)'s study by the level of social integration, which is a summary indicator of the number network connections and group affiliations (101). Social integration indices have been criticized because they cannot identify personally meaningful network members or describe specific attributes of each personal relationship. For example, qualities such as emotional closeness and the frequency of contact between specific network members cannot be distinguished and their influences on health cannot be determined.

**Egocentric social networks.**

Egocentric social network methods can explain the characteristics of specific relationships and how they evolve over time (26). An egocentric social network focuses on an individual, "ego" and their personal network of peers (alters). Egocentric social networks are typically described in terms of network relations, structure, and functions (16). Network relations (or network composition) are the types of relationships that ego maintains with his/her alters over time and their characteristics, such as consistent communication and emotional closeness. Network relations describe the strength of the tie between an ego and his/her alters. Relationships that are strengthened over time may yield protective qualities against functional decline because close contacts can be called upon for impromptu support. Network structure is indicative of the availability of resources that could spread throughout the network and is often measured by density or connections among alters. As described by Cornwell and Laumann (2015), losing network members (e.g., network losses) through death or conflict can disrupt the regular functioning of the network (100). Stress and diminished support may result from irregular network functioning, which may have negative impacts on health. The addition of new network members (e.g., network additions) may improve physical functioning by creating

additional sources of support, diversifying the types of relations one has, and improving self-esteem through the formation of new relationships. Equally, adding new network members could also disrupt normal network functioning and negatively impact functional decline (100); however these relationships have yet to be explored in cancer survivors. Network functions are often described as the type and amount of social support the ego receives from network members. Even subtle changes to the network may alter the consistency of support, which could have profound impacts on completing activities necessary for daily life. For example, network members may feel strained or perceive that support is no longer needed after initial cancer treatment ends (102), which may be particularly stressful for cancer survivors with functional limitations.

To date, no prior studies have investigated the social networks of cancer survivors using an egocentric network approach over time. To address this research gap, we conducted a secondary analysis of egocentric network data over a five-year follow-up period. Understanding how social networks evolve over time and their influence on physical decline is critical to adequately address the needs of the aging survivor. The objective of this study was twofold: 1) to compare the patterns of social network changes between cancer survivors and a similarly aged group without cancer; and 2) to investigate if changes to social networks are associated with perceived physical functioning over a five-year period.

## *Methods*

### Study Population

A secondary analysis of the National Social Life Health and Aging Project (NSHAP) was used to assess social network change on physical functioning. NSHAP is a

large, nationally representative cohort of community dwelling older adults aged 57-85 years old who provided data in two waves; wave 1 (W1) and wave 2 (W2) data were collected in 2005-2006 and 2010-2011, respectively (12). The study design and methods of recruitment and sampling have been well described elsewhere (12,57,103). Briefly, NSHAP is a complex multistage probability sample of older adults. Oversampling by age, race/ethnicity, and gender was conducted to ensure adequate representation of subgroups. The W1 sample contained 3,005 participants, of which 2,261 participated again in W2.

NSHAP participants who participated in both waves of data collection were included in the analytic sample. Participants were considered cancer survivors if they indicated on the NSHAP W1 questionnaire that they had been diagnosed with cancer. Participants who were diagnosed with cancer after W1 (n=148) were excluded because their social network at baseline would not reflect their cancer experience. Individuals with missing functional impairment data (n=1), or missing social network data (n=631) were excluded from the analysis, resulting in a final sample size of 1,481 men and women. This study was approved by the Institutional Review Board at University of Maryland, College Park.

### Measures

#### Functional Impairment

Disability is often measured as the incapacity to perform tasks required for autonomous living (100) and is predictive of future health complications and mortality (38). The Activities of Daily Living (ADL) scale is a 7-item instrument that asks respondents to self-report difficulties performing activities lasting three months or more: walking one block, walking across a room, dressing, bathing, eating, getting in or out of bed, and using the

toilet. Responses ranged from 0 (no difficulty) to 3 (difficulty). Scores were summed with higher scores indicating more severe impairments. The Cronbach's alpha for the scale in W1 was 0.84 and in W2 was 0.81. The distribution of impairments was skewed with over 70% of the sample indicating no functional impairments. Therefore, functional impairment was analyzed as a binary variable where 1= any impairment and 0= no impairments.

*Social Network Change.*

The NSHAP social network module has been previously described (27,28,104). Egocentric social network data were collected using the following name generator "*from time to time, most people discuss things that are important to them with others. For example, these may include good or bad things that happen to you, problems you are having, or important concerns you may have. Looking back over the last 12 months, who are the people with whom you most often discussed things that were important to you? (Prompt if do not know: This could be a person you tend to talk to about things that are important to you).*" The *"important matters"* question is a commonly used name generator that elicits strong ties from frequently contacted, enduring relationships (60,105). NSHAP was interested in documenting different types of relationships and recorded them in four different lists (Rosters A-D). Respondents were asked to name up to five core confidents in Roster A and record any other potentially important individuals in Rosters B-D. Close contacts named in Roster A were used in the analysis for purposes of reproducibility and to capture features of lasting relationships over time (100).

To distinguish between ties that were added, lost, or persisted between waves, NSHAP developed a computer assisted personal interviewing (CAPI) exercise to

distinguish network members. During the W2 interview, NSHAP respondents were first asked the *"important matters"* question, as done in W1. Interviewers then presented matches between the respondent's W1 and W2 alters and asked participants to verify that the linked matches were the same alters. If an alter was named in W1, but not in W2, participants were asked to provide the reason why the alter was not named. Social network change can be measured in three ways: 1) changes to the overall network structure, 2) network turnover, and 3) changes to the characteristics of ties that persist over time.

*Changes to the overall network structure.*

Density is the proportion of alters within ego's network who know each other and represents ego's embeddedness in the network. Density was calculated by dividing the total number of actual ties among alters by the number of potential ties. The number of potential ties is computed as the proportion of [k(k−1)/2] pairs, where k is the total number of alters in ego's network (not including ego) and ego has at least two alters. Density ranges from 0-1, where a network density of 1 signifies that all alters in ego's network know each other and a network density of 0 indicates no connections among alters. High network density is indicative of a cohesive social environment where the ego is able to call upon his/her alters for uncoordinated, reliable support and access to resources. Variations in network density over time were assessed by calculating density scores for each ego at both waves and taking the absolute difference from W1 to W2.

*Network turnover.*

Previous studies calculate overall network change as the absolute difference in network size (e.g., network size (W2) – network size (W1)). However, in agreement with

Cornwell and Laumann (2015) (100), we believe this approach is flawed because a net change of zero (e.g., Network size W2- Network size W1=0) or a "stable" network size over time can be achieved in multiple ways, including losing all alters and replacing them with entirely new alters (e.g., complete network turnover). Therefore, understanding subtle changes at the tie level between ego and each of their alters and their subsequent effects on disability should be considered. The CAPI matching exercise made it possible to distinguish between alters who were added, lost, or consistently named at both time points. To capture potential differences in the direction and magnitude of the associations of interest, we created categorical variables for the numbers of lost and added ties. Lost ties were defined as alters who were named in W1, but not in W2. Categories were created based on the distribution: 0=no lost alters (reference group), 1=1 lost alter, 2=2 lost alters, 3= 3 or more lost alters. Added ties were alters that were not named in W1 and were named for the first time in W2, and were coded in the same fashion as lost ties.

*Changes to the characteristics of persistent ties.*

Describing changes to the attributes of ties that persist over time at the *personal network* level can be used to understand why some ties endure and why others do not. NSHAP measured emotional closeness by the question *"How close do you feel is your relationship with [name]?"* Response options comprised of: 0="not very close," 1="somewhat close," 2=" very close," or 3="extremely close." Average difference scores were calculated to assess the mean change from W1 to W2.

The frequency of contact indicates how often ego interacts with their personal network. NSHAP asked each respondent to rate on an ordinal scale how often they talked to each alter, including via telephone and email. Responses ranged from 1= "once a year"

to 8= “every day.” Average difference scores were calculated to assess the mean change between W1 and W2. Participants were asked to report how often they could 1) open up to, and 2) rely on their spouse/partner, family, and friends (total of six questions). All responses were measured on a three-point scale ranging from 0= “hardly ever or never” to 2= “often.” The two social support questions were summed to calculate the total amount of support the ego received from each specific relation. Change was calculated as the absolute difference between W1 and W2.

*Covariates.*

Covariates were identified *a priori* from the literature and dummy variables were created for all categorical variables. Age was categorized as: 57-65, 65-75, 75-85 because older age groups may have different levels of risk for functional impairments (106). The youngest age group was used as the reference category. Body mass index (BMI, $kg/m^2$) was categorized based on established cut points (BMI <18.5=underweight, 18.5-24.9=normal, 25-29.9=overweight, >30=obese) (77). Underweight and normal categories were combined due to small sample size and were used as the reference group. Race was categorized as white (reference), black, and other based on the distribution of the sample. Additionally, we controlled for gender (male (reference) vs. female), education (high school education or less vs. some college or more (reference)), marital status (married/cohabitating partner (reference) vs. unmarried), and smoking (yes/no). To account for the influence of co-morbid conditions, a modified version of the Charlson Comorbidity Index was created with the available variables in the NSHAP W1 dataset (78,107). Individuals who reported having any of the following conditions were assigned one point for each condition: hypertension, heart attack/myocardial infarction, congestive

heart failure, stroke, any procedure for coronary artery disease, depression, diabetes, COPD/asthma, arthritis, Alzheimer's disease/dementia, urinary/stool incontinence, and other urinary problems. Scores of the 12 conditions were summed, for a total of 12 possible points.

*Prognostic factors.*

Participants who reported having a cancer diagnosis were asked, *"Sometimes, cancer will start in one place and spread to other parts of the body. Right now we are interested in knowing about primary cancer, or, in other words, where your cancer began. In which organ or part of your body did the cancer start?"* Participants self-reported primary cancers across 29 sites including: leukemia/lymphoma, breast cancer, colon cancer, prostate cancer, gynecological cancers (e.g., ovarian, uterine, cervical cancers), and other cancers (e.g., bladder, bone, brain, esophageal, kidney, liver, lung, mouth, stomach, throat, thyroid, other/not specified). The "other" category was created based on a small number of cases reported for each primary cancer site. Respondents self-reported when they were diagnosed with cancer, providing either their age at diagnosis or their date of diagnosis (month/year). A variable was constructed based on either response to calculate a consistent variable and is presented as the age at diagnosis in years. The time since diagnosis (in years) was constructed by subtracting the year of the W1 interview from the year of diagnosis.

**Statistical Analysis**

Means and proportions were used to describe the distributions of variables by cancer status (Table 3 and Table 4). Simple linear regression and chi-squared tests were used to test for differences between cancer survivors and older adults and continuous and

categorical variables, respectively. Although we could not adjust for the prognostic factors in order to make valid comparisons across the groups of cancer survivors and older adults, we described the heterogeneity in the cancer survivor group with social network and prognostic factors by primary cancer site (Table 5). Multicollinearity was assessed using the variance inflation factor. Lagged multiple logistic regression was used to assess whether social network change predicts functional impairment. Lagged regression is a common strategy to assess change over two time points by controlling for the baseline values of the dependent variable (e.g., ADL at W1) Effect modifiers were tested in regression models to determine if changes in the number of network losses and additions, and changes in social support varied by the number of comorbidities, gender, and age. Three models were evaluated using the hierarchical well-formulated approach (108): 1) a model adjusting only for functional impairment at baseline, 2) a full model including all covariates of interest and interaction terms, and 3) a reduced model that included a covariates. No interaction terms were significant and therefore, we present the reduced model. Testing for confounding was conducted by employing the 10 percent change in estimate strategy (62,63). All covariates changed the odds ratio by more than 10 percent and were retained in the models. To determine if network change impacted physical functioning differently for cancer survivors, stratified analyses by cancer survival status were conducted (Table 6). The complex survey design was taken into account using the survey procedures in SAS version 9.3 (SAS Inc., Cary, NC) and by utilizing the W1 survey weights adjusted for non-response (28).

*Results*

The final analytic sample included 1,481 participants (Table 3), of whom 13.8%

(n=201) indicated they had a cancer diagnosis. Overall, 26.7% of the sample reported impairments in their activities of daily living in W2, which is an increase from W1 (21.2%). There were no significant differences in functional impairment between cancer survivors and older adults (p=0.57). About half the sample were aged 57-64 years (47.7%) and female (57.6%) and the majority were white (83.8%), had some college or more (62.4%), were married (71.7%), overweight or obese (75.4%), and non-smokers (88.2%) in W1. Cancer survivors had a significantly higher proportion of older ($p<0.01$), unmarried (p=0.02) adults compared to older adults.

Overall, the majority of networks experienced some network turnover, with both cancer survivors and older adults reporting similar percentages of lost (p=0.74) and added (p=0.28) alters. Changes in the frequency of contact, closeness, density and social support received by spouses and friends declined slightly over time; however, the patterns of change were similar between the two groups (Table 4).

Within the cancer survivor group, approximately 98% (197/201) of W1 cancer survivors reported their primary cancer site and their age at diagnosis (Table 5). The majority of survivors reported having primary breast cancer (23.3%) or prostate cancer (19.5%). The mean age at diagnosis was 43.2 years (Standard Error (SE): 4.15 years) for gynecologic cancer, 61 years (SE: 2.06) for breast cancer, 65.4 years (SE: 3.23 years) for colon cancer, 64.9 years (SE: 1.79 years) for prostate cancer, 75.5 years (SE: 1.05 years) for blood cancers (e.g., leukemia/lymphoma), and 56.8 years (SE: 2.83 years) for other cancers. The time since diagnosis also varied by primary cancer site, with gynecologic survivors having the longest average time since diagnosis (mean: 23.6 years, SE: 2.02 years) and prostate cancer with the shortest (mean: 5.3 years, SE: 0.63 years).

Individuals with blood (39.5%), colon (31.65%), and other (36.6%) cancers reported the highest percentage of impairments. While the majority of cancer survivors lost and added alters over time, breast, blood, and colon cancer survivors reported a higher proportion of losing and adding three or more alters over time, indicating substantial network turnover. All cancer survivors showed declines in the average frequency of contact (except breast cancer) with their networks and emotional closeness (except breast and blood cancer).

Results from the multiple logistic regression are presented in Table 6. In the overall sample, adding two new alters to the network was associated with a lower odds of impairment (OR: 0.64, 95% CI: 0.41-0.99). Among cancer survivors, having more frequent contact was associated with a higher odds of impairment (OR: 1.92, 95% CI: 1.15- 3.20). Among older adults without a history of cancer, no social network components were associated with functional impairments, but being in the oldest age category (OR: 2.22, 95% CI: 1.45- 3.49), having a high school education or less (OR: 1.59, 95% CI: 1.12- 2.26), and reporting more comorbid conditions (OR: 1.47, 95% CI: 1.34- 1.62) were associated with a higher odds of functional limitations.

*Discussion*

The goal of this study was to describe the evolving social environment among cancer survivors and older adults and its impact on functional impairment. This is the first study, to our knowledge, to describe egocentric social network change over a five-year period among cancer survivors. Our study suggests that while the social networks of older adults with and without cancer are quite similar, there are a few distinct characteristics that could have profound impacts on physical health, and more broadly,

quality of life. First, increases in the frequency of contact were associated with disability among cancer survivors, controlling for functional impairments at baseline and other confounding factors. Second, in the overall sample, adding new relationships was protective of disability over time.

The proportion of functionally impaired older adults was similar in the two groups, and is consistent with estimates from other studies in older adults (109) and cancer survivors (110,111). The social networks between the two groups also displayed similar patterns of change, with a few key differences. Our study showed that more frequent contact over a five-year period was associated with a higher odds of having at least one functional impairment among cancer survivors, but not among older adults. More frequent contact over time may be associated with disability because close contacts may provide and coordinate care for the disabled. Cancer survivors may require more frequent contact than the general adult population because they may already rely on network members for ongoing or intermittent cancer treatment, in addition to assistance with daily activities. Therefore, an increase in the frequency of contact may signify a reduction in independence and an increased reliance on network members for help. The different types of contact may help distinguish between network members who offer more emotional versus tangible support. For example, providing more telephone contact may be beneficial to both parties because the strain of caregiving is eliminated, but emotional support can still be offered (50). Our study does not distinguish between face-to-face contact and remote forms of communication. Therefore, we cannot discern which contacts may be geographically close to the survivor to provide different types of support. Future studies should consider distinguishing the types of contact and support provided

by network members.

Our study indicates that both cancer survivors and individuals without cancer were both adding and losing a high proportion of alters over time, indicating that network turnover occurred. Among the cancer survivor sample, blood and colon cancer survivors reported high percentages of impairments and reported substantial network turnover. Adding two alters to the network was associated with lower disability over time in the overall sample, but did not reach statistical significance in the stratified analyses. However, the direction of the association is consistent across groups, indicating a potential protective effect when alters are added to the network. Similarly, in the cancer survivor group network losses showed a consistent positive direction, indicating a potential increased risk of functional impairment, however these results also did not reach statistical significance. Losing network members over time could impact functional impairment because it eliminates potential sources of tangible and emotional support required to sustain an independent lifestyle (89,112). Although different measures were used to evaluate social network connectedness, these results are consistent with Michael et al., (2002)'s study, indicating that changes in network integration were not associated with disability in cancer survivors (50). The relatively high and unchanged levels of emotional closeness, social support from family members, and the frequency of contact among lasting ties suggest that strong relationships were maintained for both cancer survivors and older adults. Therefore, the specific relationships lost over time may have been weaker ties less likely to provide help to the ego, and therefore making no impact on functional impairment.

To expand on this point, studies on aging suggest that older adults maintain a

close-knit network consisting of mainly familial ties that provide social support (113,114). Van Tilberg's four year longitudinal study in older Dutch adults showed that older adults preserved a strong circle of familial ties, and lost more friend ties over time (115). Keeping a close network may be one strategy to ameliorate some of the challenges of aging and cope with the transitions to come (116). While losing certain network members to death, conflict, or other reasons may be a stressful situation to endure, a wealth of literature suggests that the process of aging itself can help older adults become resilient to future stressors (116,117).

Cancer survivors may also become resilient to life challenges as they transition from their initial treatment phase to long-term survivors. First, cancer survivors are also aging, which may cause them to arrange their networks into similar patterns as their aging counterparts. Second, overcoming a major life event, such as cancer, may renew one's perspective on life, maintaining and perhaps deepening close relationships, while shedding inauthentic ones (116). Therefore, network change may not impact functional impairment because meaningful relationships are maintained and support and resources are relatively stable. The majority of cancer survivors in our sample were long-term survivors (e.g., surviving >5 years) and therefore, their social networks may reflect adjustment to these processes. Future studies should replicate these findings in large-scale epidemiologic studies.

Given the similarities between cancer survivors and older adults in terms of their social networks and functional impairments, broad interventions focusing on improving quality of life with comprehensive strategies to guide individuals with disabilities should be encouraged for older adults. Public health interventions focusing on the

family/caregiving level have been shown to have positive impacts on aging individuals with disabilities and improve access to resources (118). Additionally, artificial networks of online communities may be a convenient way for immobile adults to receive emotional support, although their efficacy has yet to be established (119).

The strengths of our study include utilizing egocentric network change over a five-year period from a large cohort of older adults with the ability to evaluate differences amongst cancer survivors and older adults. However, our study is not without limitations. First, there were a limited number of cancer survivors in the NSHAP sample and by cancer site. Prognostic features such as cancer stage and treatment information were not collected by NSHAP and therefore, it is possible that our sample of survivors includes cancer patients diagnosed at earlier stages with better prognosis. However, a separate analysis within the cancer survivor sample indicated that age since diagnosis, duration of survival, and primary cancer sites (except having gynecologic cancer) were not associated with functional impairment, further suggesting that functional impairments may reflect the process of aging, rather than a unique aspect of the cancer experience (Appendix K) (85,120,121).

Second, the measures of disability in our study were self-reported measures of ADL. Individuals with low levels of social support may rate their impairments as more severe due to social isolation. Therefore, we cannot rule out differential misclassification. The direction of the bias would likely overestimate our results, since a higher proportion of individuals with disabilities would report low support. Additionally, since changes to functional status could have occurred at any time throughout the study period, we cannot pinpoint when during the five-year period functional decline started and therefore the

social network at W2 may already reflect adjustment to restrictions in ADL.

Third, social network change may be an artifact due to a cap on the number of alters listed at each wave. In a post-hoc analysis of lost alters, the majority of egos cited that the reason their alter was not named in W2 was because the alter moved, died, or they lost touch for other reasons. Additionally, these estimates did not differ by cancer status or by impairment status (Appendix L). This suggests that network change over time is not due to the restricted number of network members listed on the network roster, and therefore, we are confident that any differences detected reflect actual changes in social networks over time. Lastly, disability is common in older adults and the prevalence was high in our sample (e.g., >20%). When a disease is common, the odds ratio tends to overestimate risk. We tried to estimate a log binomial model to calculate prevalence ratios; however, the model would not converge. Therefore, we used a logistic regression model and it is possible that the odds ratios reported in our study are an overestimate of the true measure of risk.

In conclusion, our results suggest that the social networks of cancer survivors and older adults have similar impacts on functional impairments, albeit a few subtle differences. These subtle changes may help practitioners identify older adults at risk for functional impairment and provide network strategies, such as increased network engagement, to stop the progression of functional decline. Recommendations for future research include the use of a personal network approach to describe the social networks of older adult cancer survivors and the use of health promoting aspects of social relationships to maintain good functional capacity in late life.

Table 3. Characteristics of cancer survivors and older adults

| | Overall (n=1481) | | Cancer survivor (n=201) | | Older adults (n=1280) | | |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | p-value[c] |
| Age (years) | | | | | | | |
| 57-64 | 592 | 47.7 | 49 | 33.4 | 543 | 50.0 | **<0.01** |
| 65-74 | 561 | 35.5 | 89 | 44.6 | 472 | 34.0 | |
| 75-85 | 328 | 16.8 | 63 | 22.0 | 265 | 16.0 | |
| Gender | | | | | | | |
| Male | 628 | 42.4 | 82 | 41.7 | 546 | 42.5 | 0.82 |
| Female | 853 | 57.6 | 119 | 58.3 | 734 | 57.5 | |
| Race | | | | | | | |
| White | 1099 | 83.8 | 167 | 89.5 | 932 | 82.9 | 0.07 |
| Black | 214 | 8.4 | 24 | 5.8 | 190 | 8.8 | |
| Hispanic/Other | 162 | 7.9 | 10 | 4.7 | 152 | 8.4 | |
| Education | | | | | | | |
| Less than high school | 235 | 12.1 | 23 | 10.6 | 212 | 12.4 | 0.16 |
| High School | 373 | 25.5 | 42 | 23.5 | 331 | 25.8 | |
| Some college | 477 | 33.6 | 82 | 41.4 | 395 | 32.3 | |
| Bachelor's degree or higher | 396 | 28.8 | 54 | 24.5 | 342 | 29.4 | |
| Married/cohabitating partner | | | | | | | |
| Yes | 970 | 71.7 | 120 | 65.1 | 850 | 72.8 | **0.02** |
| No | 511 | 28.3 | 81 | 34.9 | 430 | 27.2 | |
| Smoking | | | | | | | |
| Nonsmoker | 1303 | 88.2 | 183 | 90.4 | 1120 | 87.8 | 0.42 |
| Smoker | 177 | 11.8 | 18 | 9.6 | 159 | 12.2 | |

Table 3. Characteristics of cancer survivors and older adults

| | Overall (n=1481) | | Cancer survivor (n=201) | | Older adults (n=1280) | | |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | p-value[c] |
| BMI | | | | | | | |
| Underweight | 2 | 0.1 | 0 | 0.0 | 2 | 0.1 | 0.72[d] |
| Normal | 344 | 24.4 | 44 | 25.0 | 300 | 24.4 | |
| Overweight | 506 | 35.1 | 66 | 32.5 | 440 | 35.5 | |
| Obese | 556 | 40.3 | 81 | 42.4 | 475 | 40.0 | |
| Comorbidity Index (mean, SE[a]) | 2.14 | 0.05 | 2.20 | 0.14 | 2.13 | 0.05 | 0.65 |
| Functional Impairment W2 | | | | | | | |
| Impaired | 423 | 26.7 | 62 | 29.4 | 361 | 26.3 | 0.57 |
| Not impaired | 1058 | 73.3 | 139 | 70.6 | 919 | 73.7 | |
| Functional Impairment W1 | | | | | | | |
| Impaired | 340 | 21.2 | 47 | 22.6 | 293 | 21.0 | 0.75 |
| Not impaired | 1141 | 78.8 | 154 | 77.4 | 987 | 79.0 | |
| Lost alters between W1 and W2 | | | | | | | |
| No lost alters | 238 | 15.4 | 25 | 12.5 | 213 | 15.9 | 0.74 |
| Lost one alter | 414 | 27.2 | 65 | 29.4 | 349 | 26.8 | |
| Lost two alters | 388 | 27.2 | 47 | 26.7 | 341 | 27.2 | |
| Lost three or more alters | 441 | 30.3 | 64 | 31.4 | 377 | 30.1 | |
| Added alters between W1 and W2 | | | | | | | |
| No added alters | 319 | 21.5 | 38 | 21.5 | 281 | 21.5 | 0.28 |
| Added one alter | 391 | 27.0 | 61 | 29.6 | 330 | 26.5 | |

Table 3. Characteristics of cancer survivors and older adults

| | Overall (n=1481) | | Cancer survivor (n=201) | | Older adults (n=1280) | | |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | p-value[c] |
| Added two alters | 396 | 27.5 | 45 | 20.4 | 351 | 28.6 | |
| Added three or more alters | 375 | 24.1 | 57 | 28.5 | 318 | 23.4 | |

+Responses are weighted for non-response. *Bold indicates $p<0.05$

[a]Standard error of the mean

[b]Change is the absolute difference between W2 and W1

[c]p-value is testing the difference between cancer survivors and older adults with chi-squared or simple linear regression

[d]Body Mass Index; underweight/normal categories are combined in regression models

Table 4. Network characteristics among persistent ties among cancer survivors and older adults

| | Cancer survivors (n=201) | | | | | | Older adults (n=1280) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Wave 1 | | Wave 2 | | Change | | Wave 1 | | Wave 2 | | Change | | |
| | Mean | SE[a] | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE | p-value[b] |
| Mean frequency of contact | 7.08 | 0.07 | 6.95 | 0.07 | -0.13 | 0.06 | 7.05 | 0.04 | 6.99 | 0.04 | -0.06 | 0.03 | 0.22 |
| Mean closeness | 2.33 | 0.05 | 2.27 | 0.04 | -0.05 | 0.04 | 2.33 | 0.02 | 2.29 | 0.02 | -0.04 | 0.02 | 0.73 |
| Density | 0.80 | 0.05 | 0.74 | 0.04 | -0.05 | 0.07 | 0.81 | 0.02 | 0.75 | 0.01 | -0.06 | 0.02 | 0.96 |
| Social Support[c] | | | | | | | | | | | | | |
| Spouse | 2.37 | 0.12 | 2.12 | 0.15 | -0.25 | 0.11 | 2.64 | 0.06 | 2.38 | 0.06 | -0.26 | 0.04 | 0.97 |
| Family | 3.22 | 0.07 | 3.12 | 0.08 | -0.11 | 0.07 | 3.07 | 0.03 | 3.12 | 0.03 | 0.04 | 0.03 | 0.05 |
| Friends | 2.51 | 0.08 | 2.38 | 0.14 | -0.13 | 0.16 | 2.47 | 0.04 | 2.38 | 0.04 | -0.09 | 0.04 | 0.77 |

[a]Standard error of the mean

[b]p-value is testing the difference in network change between cancer survivors and older adults using simple linear regression

[c]Not an egocentric measure of support

Table 5. Clinical characteristics, disability, and social networks of cancer survivors by primary cancer site

| | Primary cancer site (n=197)[a] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Breast (n=48) | | Blood[b] (n=21) | | Colon (n=20) | | Prostate (n=40) | | Gynecologic[c] (n=35) | | Other[d] (n=33) | |
| | N | % | N | % | N | % | N | % | N | % | N | % |
| Functional Impairment W2 | | | | | | | | | | | | |
| No Impairment | 36 | 78.5 | 13 | 60.5 | 12 | 68.4 | 31 | 77.2 | 24 | 72.1 | 22 | 63.4 |
| Impairment | 12 | 21.5 | 8 | 39.5 | 8 | 31.7 | 9 | 22.9 | 11 | 27.9 | 11 | 36.6 |
| Time since diagnosis | | | | | | | | | | | | |
| <5 years | 7 | 28.8 | 1 | 21.5 | 3 | 35.7 | 6 | 33.7 | 2 | 6.6 | 5 | 29.8 |
| > 5 years | 15 | 71.2 | 2 | 78.5 | 6 | 64.3 | 12 | 66.3 | 18 | 93.4 | 11 | 70.2 |
| Network Turnover | | | | | | | | | | | | |
| # Alters Lost | | | | | | | | | | | | |
| No lost alters | 3 | 11.7 | 6 | 21.6 | 2 | 13.5 | 7 | 18.8 | 2 | 5.9 | 4 | 7.5 |
| Lost one alter | 11 | 17.3 | 6 | 25.9 | 7 | 33.6 | 11 | 25.3 | 14 | 34.7 | 14 | 40.9 |
| Lost two alters | 13 | 32.3 | 1 | 15.9 | 3 | 16.0 | 13 | 34.3 | 11 | 34.6 | 6 | 17.1 |
| Lost three or more alters | 21 | 38.7 | 8 | 36.7 | 8 | 36.8 | 9 | 21.5 | 8 | 24.9 | 9 | 34.5 |
| # Alters Added | | | | | | | | | | | | |
| No added alters | 8 | 14.5 | 3 | 20.9 | 4 | 15.7 | 11 | 31.0 | 5 | 22.1 | 7 | 24.4 |
| Added one alter | 13 | 24.3 | 6 | 20.4 | 0 | . | 17 | 42.3 | 12 | 35.1 | 13 | 38.1 |
| Added two alters | 8 | 16.4 | 5 | 17.0 | 7 | 38.2 | 6 | 15.1 | 12 | 27.6 | 6 | 15.8 |
| Added three or more alters | 19 | 44.8 | 7 | 41.7 | 9 | 46.1 | 6 | 11.6 | 6 | 15.1 | 7 | 21.8 |
| | Mean | SE[e] | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| Age at diagnosis | 61.0 | 2.1 | 75.5 | 1.1 | 65.4 | 3.2 | 64.9 | 1.8 | 43.2 | 4.2 | 56.8 | 2.8 |

Table 5. Clinical characteristics, disability, and social networks of cancer survivors by primary cancer site

| | Primary cancer site (n=197)[a] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Breast (n=48) | | Blood[b] (n=21) | | Colon (n=20) | | Prostate (n=40) | | Gynecologic[c] (n=35) | | Other[d] (n=33) | |
| | N | % | N | % | N | % | N | % | N | % | N | % |
| Length of survival | 9.9 | 0.9 | 9.4 | 2.5 | 9.7 | 1.7 | 5.3 | 0.6 | 23.6 | 2.0 | 16.0 | 5.0 |
| Change in closeness | 0.0 | 0.1 | 0.0 | 0.1 | -0.2 | 0.1 | -0.0 | 0.1 | -0.1 | 0.1 | -0.2 | 0.1 |
| Change in frequency of contact | 0.0 | 0.1 | -0.1 | 0.1 | -0.0 | 0.2 | -0.1 | 0.2 | -0.1 | 0.1 | -0.5 | 0.2 |
| Change in density | -0.1 | 0.1 | 0.0 | 0.19 | -0.1 | 0.1 | 0.0 | 0.1 | -0.1 | 0.1 | 0.0 | 0.3 |
| Change in social support | | | | | | | | | | | | |
| Spouse | -0.4 | 0.1 | -0.7 | 0.5 | -0.8 | 0.4 | -0.1 | 0.1 | 0.1 | 0.2 | -0.2 | 0.2 |
| Family | -0.1 | 0.3 | 0.1 | 0.3 | 0.0 | 0.2 | -0.1 | 0.2 | -0.2 | 0.2 | 0.1 | 0.1 |
| Friends | -0.2 | 0.4 | 0.1 | 0.4 | -0.1 | 0.2 | -0.2 | 0.2 | 0.1 | 0.2 | -0.5 | 0.2 |

[a]Data on primary cancer site was unavailable for 58 cancer survivors and are not included in the table

[b]Blood cancer includes leukemia/lymphoma

[c]Gynecologic cancers include cervical, ovarian, and uterine cancers

[d]Other cancers include bladder, bone, brain, esophageal, kidney, liver, lung, mouth, stomach, throat, thyroid, other (not specified)

[e]Standard Error

Table 6. Lagged logistic regression models for cancer survivors and non-cancer survivors for ADL outcome

| | Overall | Cancer Survivors | Older adults |
|---|---|---|---|
| | OR[b] (95% CI)[c] | OR (95% CI) | OR (95% CI) |
| Age (years) | | | |
| 57-64 (Ref.) | | | |
| 65-74 | 1.25( 0.85- 1.86) | 0.83( 0.26- 2.68) | 1.30( 0.87- 1.94) |
| 75-85 | **2.11( 1.42- 3.15)** | 1.66( 0.54- 5.10) | **2.22( 1.45- 3.39)** |
| Gender | | | |
| Male (Ref.) | | | |
| Female | 1.06( 0.73- 1.54) | 1.16( 0.44- 3.08) | 1.04( 0.70- 1.53) |
| Race | | | |
| White (Ref.) | | | |
| Black | 0.94( 0.64- 1.39) | 0.89( 0.32- 2.49) | 0.96( 0.64- 1.43) |
| Marital Status W1 | | | |
| Not married | 0.89( 0.62- 1.29) | 0.78( 0.32- 1.92) | 0.86( 0.57- 1.28) |
| Married (Ref.) | | | |
| Education | | | |
| High school education or less | **1.56( 1.12- 2.17)** | 1.71( 0.70- 4.17) | **1.59( 1.12- 2.26)** |
| More than a high school education (Ref.) | | | |
| BMI | | | |
| Underweight/Normal (Ref.) | | | |
| Overweight | 0.85( 0.56- 1.30) | 0.61( 0.20- 1.88) | 0.92( 0.61- 1.40) |
| Obese | 1.33( 0.89- 1.99) | 1.23( 0.41- 3.75) | 1.33( 0.89- 1.99) |
| Comorbidity Index | **1.41( 1.28- 1.55)** | **1.27( 0.92- 1.75)** | **1.47( 1.34- 1.62)** |
| Impairment W1 | **7.15( 4.95-10.34)** | **9.68( 3.66- 25.54)** | **6.81( 4.78- 9.71)** |
| Smoker | | | |
| Yes | | | |

| | | | |
|---|---|---|---|
| No (Ref.) | | | |
| Network turnover at the tie level | 1.04( 0.60- 1.81) | 0.55( 0.14- 2.23) | 1.19( 0.69- 2.05) |
| Lost Ties between W1 and W2 | | | |
| No Lost Alters (Ref.) | | | |
| Lost one alter | 1.47( 0.85- 2.54) | 1.57( 0.36- 6.76) | 1.46( 0.82- 2.60) |
| Lost two alters | 1.10( 0.62- 1.94) | 1.26( 0.26- 6.02) | 1.05( 0.57- 1.94) |
| Lost three or more alters | 1.77( 0.90- 3.48) | 4.32( 0.68-27.33) | 1.48( 0.73- 3.02) |
| Added Ties between W1 and W2 | | | |
| No added alters (Ref.) | | | |
| Added one alter | 0.67( 0.41- 1.09) | 0.39( 0.11- 1.39) | 0.75( 0.42- 1.33) |
| Added two alters | **0.64( 0.41- 1.00)** | 0.27( 0.07- 1.11) | 0.74( 0.45- 1.22) |
| Added three or more alters | 0.63( 0.37- 1.08) | 0.31( 0.08- 1.17) | 0.70( 0.39- 1.25) |
| Change in closeness | 0.82( 0.60- 1.12) | 0.69( 0.25- 1.91) | 0.84( 0.60- 1.17) |
| Change in frequency of contact | 1.16( 0.98- 1.37) | **1.92( 1.15- 3.20)** | 1.09( 0.91- 1.30) |
| Change in density | 1.02( 0.73- 1.41) | 0.63( 0.26- 1.51) | 1.09( 0.75- 1.58) |
| Change in social support | | | |
| Spouse | 1.05( 0.95- 1.16) | 1.15( 0.82- 1.61) | 1.05( 0.94- 1.17) |
| Family | 1.06( 0.94- 1.20) | 0.97( 0.65- 1.45) | 1.08( 0.96- 1.22) |
| Friends | 0.99( 0.87- 1.13) | 1.24( 0.90- 1.72) | 0.94( 0.83- 1.07) |

*Bold indicates $p<0.05$

[a]Odds ratio

[b]95% Confidence Interval

Chapter 4: Manuscript 2

**Title:** Egocentric social network change and immunologic functioning among cancer survivors

*Abstract*

**Background:** There is established evidence linking social networks to chronic diseases, including cancer survival. Studies suggest that network support may afford protective effects on cancer survival through biophysiologic pathways. However, no studies have explored the impact of specific relationships on inflammation using an egocentric social network framework. This study assessed the role of egocentric social network change over time and its association with several inflammatory markers.

**Method:** A secondary data analysis from the National Social Life, Health, and Aging Project (NSHAP) (2005-2011) was conducted to assess the relationship between egocentric social network change and inflammation among aging cancer survivors (n=105) and older adults without cancer (n=652). Tumor necrosis factor-alpha (TNF-α), Vascular Endothelial Growth Factor (VEGF), and C-Reactive Protein (CRP) were chosen as markers of inflammation based on previous studies and were measured with plasma. Multiple linear regression models were used to assess the relationship between network change and each inflammatory marker.

**Results:** Both cancer survivors and the older adults without cancer reported comparably high levels of network turnover, losing a greater proportion of network members over

time (cancer survivors: 27.7%, older adults: 31.7%) than adding new relationships (cancer survivors: 25.9%, older adults: 24.9%). CRP levels were significantly 26% lower among cancer survivors who added two network members compared to those who added no network members. Greater spousal support over time was associated with elevated CRP (exp(β): 1.19, 95% CI: 1.09, 1.30). Experiencing a change in the frequency of contact was associated with a 19% higher level of TNF-α. No associations were observed between network change and CRP, TNF- α or VEGF among the older adults without cancer.

**Conclusions:** The social environment may influence immune functioning for cancer survivors. Given the health relevance of chronic inflammation, interventions should consider the role of social networks for cancer survivors. Future research is warranted to fully understand the pathways by which social networks improve or deteriorate physiologic functioning to promote well-being in late life.

*Background*

Accumulating evidence supports a relationship between social connectedness and chronic diseases, including cancer (13,14,122). When social networks are adequate in terms of support and resources, they can improve cancer prognosis and survival (86). However, when they are inadequate, individuals are at risk for poorer health-related quality of life (92) and mortality (123,124). Understanding interpersonal relations within the social environment may elucidate the mechanisms that improve, damage, or stabilize health in late life. One pathway by which social networks may serve to improve cancer-related outcomes is by decreasing chronic inflammation (23,54).

Social networks are hypothesized to influence health through an intermediate process of altered physiological functioning (25). Responses to stressors, including negative social network interactions and social isolation, can induce an inflammatory response. Inflammation is largely driven by pro-inflammatory cytokines, which include tumor necrosis factor-alpha (TNF-α) and several interleukins (125). The primary function of pro-inflammatory cytokines is to mobilize an immune response to fight infection. However, under situations of chronic stress, hormones are continuously secreted, promoting chronic low-grade inflammation throughout the body and eventually lead to a breakdown of the immune system (e.g., immunosuppression). Previous studies emphasize that long-lasting, low-grade, systemic inflammation is an important physiological contributor to aging-related conditions, such as cancer (126).

The inflammatory response has been indicated in all stages of carcinogenesis, including initiation, promotion, progression, recurrence, and prognosis (13,14,127). Evidence from animal studies indicates that chronic stress can promote tumor growth and

angiogenesis (13,128). Human studies suggest that psychosocial stressors and cancer treatment may play a role in acute or sustained levels of elevated inflammation among cancer survivors (129). Immunosuppression can modify factors associated with the tumor microenvironment, creating an ideal atmosphere for tumor growth, progression, metastasis and angiogenesis to occur (13). Collectively, the accumulation of inflammation within the bodily system and inadequate network resources may put cancer survivors at a greater risk for inflammatory-related conditions and mortality (129,130).

Despite a call for more research to elucidate the biophysiological mechanisms in which social networks influence disease (23), studies suggesting a link between social networks and chronic inflammation in the general population have only begun to emerge (25,48,53,54,131–133), and studies centered on cancer survivors remain limited (125). The majority of studies in cancer survivor samples have demonstrated that greater social support is linked to improved immune functioning (69,134–139), albeit one study which showed no association (140). However, these studies focus on a limited number of pro-inflammatory cytokines, such as interleukin-6 (69,135) and C-reactive protein (CRP) (47) and other less studied markers, such as VEGF and TNF-α may be implicated. For example, VEGF is also a pro-inflammatory cytokine that promotes angiogenesis, a contributing factor to tumor growth and metastasis. Higher VEGF levels have been previously associated with metastatic disease and poorer survival (141). TNF-α is also a well-established pro-inflammatory cytokine that has been linked to chronic inflammatory diseases (14) and may have antitumor properties (142,143), including tumor regression and longer survival (144).

A small number of studies have laid the foundational framework to explicate the potential mechanisms by which network factors contribute to chronic inflammation in cancer survivors. However, these studies often use cross-sectional designs and small convenience samples of clinical populations. In addition, cancer is often diagnosed at older ages, and aging plays a significant role in the occurrence of low-grade inflammation, even in the absence of chronic disease (145). Therefore, using a similarly aged comparison group of older adults without cancer may be useful to discern if the relationship between social networks and inflammation is unique to the cancer survivor experience, or merely reflects the process of aging.

Finally, these studies use distinct measures of social networks, each with their own sets of methodological limitations. For example, social support studies fail to recognize the relational (e.g., emotional closeness and frequency of contact with network members) and structural components (e.g., connections among network members) of the network that contribute to health. The social network index (SNI) captures more network features (e.g., network size, the number of number of friends and family members, membership to organizations, and religious service attendance, etc.), but does not consider the impact of particular network connections and their effects on health. Moreover, social networks evolve in regards to one's life circumstances, such as retirement, bereavement, or illness (116). Such changes may cause a reshuffling of the network either in anticipation of, or in response to life events; possibly resulting in lost or weakened relationships or new friendships and strengthened relationships over time. This is significant because cancer survivors experience declines in social support over time,

which is associated with poorer psychosocial functioning (98) and possibly immune functioning (47,125).

Egocentric social networks can address the current limitations of the literature because they can: 1) be used in population based studies; 2) describe all social network properties (e.g., network relations, structure, and functions); and 3) explore the impact of specific relationships on inflammation and changes to those relationships over time. An egocentric social network focuses on an individual, "ego" and their network of close contacts (alters) (16). Network relations describe the strength of the tie between ego and their alters and are defined as the types of relationships that ego maintains over time and their characteristics, such as constant communication and closeness. Network structure describes potential resources that could spread throughout the network and is typically measured by the network size or density (e.g., connections among network members). Network functions are often described as the type and amount of social support ego receives from network members. Slight changes to the network could potentially shift or alter the consistency of support, forcing cancer survivors to compensate by finding new sources of support or adjust to the loss of support. Losing specific network members (e.g., network losses) through death or conflict may disrupt normal network functioning, especially if the individual was a prominent figure in the network. Evidence from the bereavement literature suggests that experiencing the loss of a loved one is associated with higher circulating inflammation (146,147), which may, in part, explain the increased risk of morbidity and mortality for a surviving spouse following the death of their significant other (146).

Relationships that are lost or weakened over time may induce an inflammatory

response for two reasons. First, the act of emotional distancing, bereavement, or geographical inaccessibility to network members may be perceived as a stressful event and induce a stress response. Second, contacts that are no longer physically available cannot be called upon for uncoordinated and reliable support. Conversely, adding new network members (e.g., network additions) may have positive impacts on immune functioning by creating additional sources of support, diversifying the types of relations one has, and improving self-esteem through the formation of new relationships. It is also possible that adding new network members could disrupt normal network functioning and thus negatively impact immune functioning (100); however these relationships have yet to be explored in cancer samples and the general population.

The objective of this study was to examine the role of social networks on inflammation using a robust egocentric social network methodology in a population-based sample of older adults. Specifically, we assessed the contribution of changes to the social environment and their impacts on immunologic functioning among cancer survivors compared to older adults without a cancer diagnosis.

## *Methods*

### Study Population

This study utilized data from the National Health, Social Life, and Aging Project (NSHAP). In Wave 1 (W1) (2005-2006), NSHAP collected data on a nationally representative sample of older adult Americans aged 57 to 85 years, obtained via multistage probability sampling. Data on socio-demographic variables were obtained through home interviews. Field interviewers administered questionnaires and also collected biospecimens. The biospecimen collection procedures have been previously

described (59). Briefly, in Wave 2 (W2) (2010-2011) VEGF, TNF-α, and CRP were collected. Interviewers were responsible for collecting, storing, packing and shipping all biospecimens. NORC at the University of Chicago was responsible for quality control, which included tracking biospecimens from the in-home interview to their final laboratory destination, as well as quality control (58,148). The adherence rate for blood collection in W2 was 92.1% (58).

There were 2,261 NSHAP participants who participated in both waves of data collection. Participants were considered cancer survivors if they self-reported a history of cancer (excluding skin cancers such as, melanoma, basal cell carcinoma, and squamous cell carcinoma) on the W1 questionnaire. The exclusion criteria and derivation of the analytic sample are presented in Figure 6. Participants were excluded from the analysis if they: 1) were newly diagnosed with cancer in W2 (n=148) because their social networks in W1 would not reflect their cancer experience; 2) had markers of acute inflammation (e.g., CRP values greater than 10), following the recommendation by the American Heart Association and Centers for Disease Control and Prevention (n=160) (149); 3) had missing social network data (n=541); or 4) had missing biospecimen data (n=626). The final analytic sample consisted of 757 participants, of whom 105 had reported a history of cancer in W1 (155 cancer survivors were eliminated due to the exclusion criteria). The study was considered exempt from formal review by the University of Maryland.

## Measures

### *Inflammatory biomeasures*

Plasma from unclotted whole blood was used to measure cytokines. NSHAP measured select biomarkers, including CRP, in W1 and expanded the panel of

biomeasures assayed in W2 to include more markers of immune functioning. Therefore, CRP was measured in both waves, while TNF-α and VEGF were only measured in W2. Indeterminate, below threshold batches, and out of range biomarker values were excluded. The coefficients of variation were considered within an acceptable range for all inflammatory markers (9.5% for CRP, 7.2% for TNF-α and 8.5% for VEGF). The term "allostatic load" is an indicator of the body's 'wear and tear' and can be described by elevated inflammatory biomarkers across the bodily system. Allostatic load is a comprehensive indicator of the accumulative burden of physiological dysregulation and has been shown to be associated with poor population-level health, including cognitive decline, heart disease, and mortality (65). Originally, our analytic objective was to construct a composite score of inflammatory biomarkers to provide a comprehensive assessment of the cumulative effects of social networks on inflammation, as done in previous research (47). However, each biomarker did not load heavily on a single factor in the principal components analyses, suggesting that these markers are distinct and should be analyzed separately. Therefore, we present each biomeasure as a separate outcome measure using their continuous form. Natural log transformation was performed on each continuous inflammatory marker to normalize their distributions.

***Social Network Change***

The NSHAP social network module has been described in detail (27,28,104). Respondents were asked to name up to five people with whom they discussed "*important matters*." To distinguish between ties that were added, lost, or persisted between waves, NSHAP developed a computer assisted personal interviewing (CAPI) exercise to distinguish network members. During the W2 interview, NSHAP respondents were first

asked the "*important matters*" question, as done in W1. Interviewers then presented the matches between the respondent's W1 and W2 alters and asked participants to verify the linked matches. In this way, network change can be characterized at the ego-alter tie level and attributes of those relationships can be observed over time. Social network change is often measured in three ways: 1) network turnover; 2) changes to the overall network structure; and 3) changes to the characteristics of ties that persist over time

***Network turnover***

The CAPI matching exercise made it possible to distinguish between alters who were added, lost, or consistently named at both time points (28,100). Lost ties were defined as alters who were named in W1, but not in W2. Added ties were categorized as alters named for the first time in W2, and stable ties were defined as alters named at both time points. To observe differences in the strength and direction of associations, we created categorical variables for the number of lost and added ties (none, 1, 2, or 3 or more), where "none" was used as the reference group.

***Changes to the overall network structure***

The structure of the ego's network is indicative of the availability of resources to the ego. Density was used to describe the network structure. Density is the proportion of people within ego's network who know each other and represents ego's embeddedness within the network. Density was assessed as an unweighted measure and was calculated by dividing the total number of actual ties among alters by the number of potential ties. The number of potential ties is computed as the proportion of $[k(k-1)/2]$ pairs, where k is the total number of alters in ego's network (not including ego) and ego has at least two alters. Density ranges from 0-1, where a network density of 1 signifies that all alters in

ego's network know each other and a network density of 0 indicates no connections among alters. High network density is indicative of a cohesive social environment where ego is able to call upon his/her alters for uncoordinated, reliable support and access to resources. Variations in network density over time were assessed by calculating density scores for each ego at both waves and taking the absolute change from W1 to W2.

***Changes to the characteristics of persistent ties***

Changes to the attributes of ties that last over time at the *personal network* level explain why some ties endure and why others do not. NSHAP measured emotional closeness to each alter by the question *"How close do you feel is your relationship with [name]?"* Response options comprised of: 0="not very close," 1="somewhat close," 2="very close," or 3="extremely close." Average difference scores were calculated by first computing the mean closeness for each ego at both waves, and then taking the absolute difference from the means.

The frequency of contact indicates how often ego interacts with their personal network. NSHAP asked each respondent to rate on an ordinal scale how often they talked to each alter, including via telephone and email. Responses ranged from 1= "once a year" to 8= "every day." Average difference scores were calculated to assess the mean change from W1 to W2.

Participants were asked to report how often they could 1) open up to, and 2) rely on their spouse/partner, family, and friends (total of six questions). All responses were measured on a three-point scale ranging from 0= "hardly ever or never" to 2= "often." The two social support questions were summed to calculate the total amount of support

ego received from each specific relation. Change was calculated as the absolute change from W1 to W2.

**Covariates**

Potential confounders were selected from the literature *a priori* and included: age (0=57-65 (reference), 1=65-75, 2=75-85), gender (0=male (reference) vs. 1=female), education (1=high school education or less vs. 0=some college or more (reference), marital status (0=married/cohabitating partner (reference) vs. 1=unmarried), race (0=non-Hispanic white (reference), 1=other), and smoking (1=smoker vs. 0=non-smoker (reference). Body Mass Index (BMI) was measured by trained NSHAP interviewers. BMI was calculated as [(weight (lbs.)/ height $(in)^2$)*703] and was categorized based on established cut points (BMI <18.5=underweight, 18.5-24.9=normal, 25-29.9=overweight, >30=obese) (77). The underweight and normal categories were combined due to small sample size and were used as the reference group. Individuals who indicated that they exercised less than once a month were considered 'low activity', while those who exercised more than once a month but less than twice a week were considered to have 'moderate activity', and those who exercised 3 or more times per week were categorized as 'frequent activity' (reference).

We controlled for comorbid conditions by creating a modified version of the Charlson Comorbidity Index. Individuals who reported having any of the following conditions in W1 were assigned one point for each condition: hypertension, heart condition (including: heart attack/myocardial infarction, congestive heart failure, stroke, or any procedure for coronary artery disease), depression, diabetes, COPD/asthma, arthritis, Alzheimer's disease or dementia, and sensorimotor conditions (e.g., urinary or

stool incontinence, or other urinary problems). Scores of the 12 conditions were summed, for a total of 12 possible points.

Some medications may induce or reduce an inflammatory response; therefore, we adjusted for hypertension medications and cardiovascular agents. For the CRP outcome we adjusted for baseline values of CRP. However, TNF-α and VEGF were not collected in W1 and therefore, we could not control for the baseline values of these variables.

**Statistical Analysis**

Medians and interquartile ranges for continuous variables and proportions for categorical variables were estimated by cancer survivor status in W1 (yes/no) (Table 7). Differences between groups were tested with simple linear regression and chi-square tests. Prognostic factors for cancer survivors by each biomarker are presented in Table 8 to describe the cancer survivor sample and were not included as covariates in the analysis because the older adults without cancer do not have the factors of interest. Social network characteristics among persistent ties are presented in Table 9 by cancer status. Multicollinearity was assessed using the variance inflation factor. All statistical tests were conducted with log-transformed values for each biomarker. CRP was modeled using lagged linear regression to assess change over two time points by controlling for the baselines values of CRP (64). TNF-α and VEGF were modeled using multiple linear regression. Potential confounders were selected from previous studies and were tested with the 10 percent change in estimate strategy (62,63). All covariates significantly changed the estimates and were retained in the models. To determine if network change impacted inflammation differently for cancer survivors, we stratified models by cancer survival status. Models are presented for cancer survivors and older adults without a

reported history of cancer for each dependent variable (Table 10, full table with covariates can be found in Appendix M). All results were back transformed to their original scales. The complex survey design was taken into account using the survey procedures in SAS version 9.3 (SAS Inc., Cary, NC) and by utilizing the W1 survey weights adjusted for non-response (28). (28). In order to compare the influence of social networks across the inflammatory markers, we included only participants in the analytic sample that had data on all three biomarkers. We conducted a sensitivity analysis to determine if the analytic sample was biased from excluding participants who had biomarker data, but not data on all three biomarkers (e.g., the full sample of each biomarker). The final multiple linear regression models were used to compare the full sample of each inflammatory marker to the sample with all three biomarkers. The results of the sensitivity analysis are presented in Appendices C-E.

*Results*

Approximately 15% of participants reported a history of cancer in W1 (n=105). In the overall study sample (n=757), the majority of participants were aged 57-64 (46.5%), female (58.2%), white (85.3%), married or co-habitating with a partner (72.2%), had a high school education or less (62.3%), were obese (38.5%), non-smokers (85.9%), and exercised less than once a month (70.5%). Cancer survivors and older adults who did not report a history of cancer were similar in terms of socio-demographics, with the exception of age (p=0.01). The median inflammatory measures for the overall sample were 1.82 for CRP in W2 (Interquartile Range (IQR): 0.95-3.41), 11.02 for TNF-α (IQR: 8.04-15.86), and 164.3 for VEGF (IQR: 102.4-4282.4). Biomarker values did not differ between groups and they were weakly correlated with each other (CRP with TNFA:

Pearson's r= 0.10, p=0.01; CRP with VEGF: Pearson's r= 0.09, p=0.01, TNFA with VEGF: Pearson's r= 0.19, p<0.01).

Both cancer survivors and older adults without cancer had comparably high levels of network turnover, losing a higher proportion of alters over time (cancer group: 27.7%; older adults: 31.7%) than adding new relationships (cancer group: 25.9%; older adults: 24.9%). Characteristics of persistent ties over both time points were also similar in both groups. For example, both cancer survivors and older adults reported high levels of network density and emotional closeness to their network members at both time points, experiencing only slight declines over time. Both groups also reported subtle declines in social support from friends.

CRP levels were significantly 26% lower among cancer survivors who added two network members compared to those who added no network members (exponentiated regression coefficient (exp) (β): 0.74, 95% CI: 0.56, 0.98). Experiencing a change in spousal support was positively associated with elevated CRP (exp (β): 1.19, 95% CI: 1.09, 1.30) in adjusted models. Experiencing a change in the frequency of contact was associated with a 19% higher level of TNF-α (exp (β): 1.19, 95% CI: 1.08, 1.30). No social network components were significantly associated with VEGF.

No social network components were significantly associated with CRP, TNF- α, or VEGF among older adults. The sensitivity analysis compared the final models with full samples for each biomarker to the participants with complete data on all three biomarkers. The estimates had comparable magnitudes, however there were some discrepancies in terms of statistical significance for some of the estimates. For example, in the full sample of TNF- α, losing two alters (exp (β): 1.57, 95% CI: 1.14, 2.15 vs. exp

(β): 1.33, 95% CI: 0.95, 1.87) was statistically significant in the full sample, but was not statistically significant among the sample with all three biomarkers among the cancer survivors. Additionally, for CRP, adding two alters (exp (β): 0.83, 95% CI: 0.62, 1.12 vs. exp (β): 0.74, 95% CI: 0.56, 0.98) and receiving social support from spouses (exp (β): 1.02, 95% CI: 0.92, 1.13 vs. exp (β): 1.19, 95% CI: 1.09, 1.30), were not statistically significant in the full sample of each individual biomarker, but became significant in the sample of participants with all three biomarkers among cancer survivors. No discrepancies in results were observed with VEGF.

*Discussion*

Persistent, low-grade inflammation is an important underlying factor that contributes to the development of chronic disease and mortality. The current study is the first, to our knowledge, to use a methodologically rigorous social network approach to understand the contribution of specific network members on inflammation over time using multiple biomarkers in a population based sample of older adult cancer survivors and a similarly aged group without a history of cancer. Our results indicate that changes to social networks contribute differentially to chronic low-grade inflammation, whereby, some aspects of social network change may beneficially reduce levels of CRP and increase TNF-α for cancer survivors, but has weak or no effect on inflammation in the general population of older adults. Further, the evolving social environment seems to play inconsistent roles across different inflammatory markers, suggesting that social networks contribute to these markers in unique ways.

Studies investigating the association between social networks and the inflammatory response are limited. Our study extends the current literature by

investigating egocentric network change over time. Adding new relationships to one's circle of close contacts was associated with lower levels of CRP and increasing contact with specific network members was associated with a stronger TNF-α response. Social networks may be advantageous after experiencing a life-altering event, like cancer. Cancer survivors may purposefully reorganize their networks in response to their cancer diagnosis by adding new sources of support, diversifying the network, strengthening existing relationships (100), and becoming resilient to interpersonal conflicts (116). Together these results demonstrate that social networks and their change over time are beneficial to physiological regulation for cancer survivors.

Both cancer survivors and older adults experienced similar changes to their social networks over time, yet the patterns of associations differed by cancer status and were inconsistent across the three inflammatory markers. The study by Glei et al. (2012), conducted among Taiwanese and American populations, also demonstrated weak and varying results across six markers of inflammation (interleukin-6, C-reactive protein (CRP), fibrinogen, and soluble forms of intercellular adhesion molecule 1, E-selectin, and IL-6 receptor) (134). In addition, the directions and magnitudes of the associations were different across groups, suggesting that social network change may be beneficial for cancer survivors, but have little effect on older adults. Given that both groups were similar in respect to the high and relatively unchanged amounts of support, closeness, and contact they received from stable network members, it is intriguing that such variation exists.

**Cancer survivors, network change, and inflammation**

Our findings are consistent with Marucha et al. (2005)'s pilot study, which demonstrated a link between social adjustment and TNF-α among 44 breast cancer

patients. Specifically, they showed that a change in social activities was associated with higher levels of TNF-α (139). Although this study was small and controlled for a limited number of confounding factors (e.g., TNF-α at baseline and cancer stage), it does shed light on the relationships of interest- mainly that the directions of the associations are consistent, providing confidence in our interpretation of these results. Interventions that focus on enhancing existing relationships and creating new sources of support may be important for cancer survivors. We did not observe any associations between social network change and VEGF. Although there has been little published on this relationship, our results are inconsistent with one small study of ovarian cancer survivors, which demonstrated that more social support perceived from friends and neighbors and less social distancing was inversely associated with VEGF (137).

Yang and colleagues' (2014) found that the social network index (SNI) was not associated with CRP, after adjusting for key confounding factors including age, sex, race, BMI and others. However, the SNI is an aggregate measure of overall integration into society and does not explain the impact on specific relationships over time, which may explain the inconsistencies in the results. Additionally, this study was cross-sectional and those with elevated CRP may have become less integrated into society because of latent morbidity. We found that experiencing more spousal support was associated with *higher* levels of CRP. Although counterintuitive to stress-buffering hypothesis, which posits that social support can buffer the negative effects of stressful situations, it is possible that increases in support specifically from spouses may signify the inception of health decline, as demarcated by higher levels of chronic, low-grade inflammation. It is also possible that our findings may be due to chance given our limited sample of cancer survivors. Future

research should replicate these findings in large population based studies of cancer survivors.

### Older adults, network change, and inflammation

We consistently observed no associations with network change across inflammatory markers among older adults without cancer. While prior population-based studies have also documented null associations between social networks and CRP in the general population (48,133,150–152), some studies have demonstrated that social integration is correlated with both lower (153) and higher levels of CRP (132,134). For example, Glei et al. (2012) found a positive association between the SNI and CRP in the Midlife Development in the United States (MIDUS) National Study (134) and Ford et al. (2006) documented a dose response relationship between the SNI and CRP, however this association was only observed in older adult men (132). Although the use of different social network measures makes it difficult to compare findings across studies, our results further add to the literature demonstrating that a no association exists between social network change and inflammation in the general population of older adults. Potential differences may also reflect our study sample, which was educated and relatively homogeneous in terms of race. Other pathways may better explain how social networks get "under the skin," such as psychosocial distress (25) or moderating factors, including race/ethnic differences (154). However, it is premature to draw conclusions, as VEGF and TNF-α markers have not been extensively studied in social network studies, despite evidence that they are important markers of longevity and physiological health in the general older adult population. For example, higher TNF-α concentrations have been implicated in several other chronic diseases, including Major Depressive Disorder (MDD)

(155), cardiovascular disease (156,157), and Alzheimer's disease (158). Future studies should consider investigating these markers to confirm the results presented here. Another possible explanation that cannot be ruled out is that high levels of inflammation at baseline drive the associations for VEGF and TNF-α and residual confounding may have impacted the findings. Despite this limitation, we did find strong associations among the cancer survivor group and little evidence of an association between network change and CRP among older adults, while controlling for baseline values of CRP. This further supports our conclusion that social relationships may have little impact on inflammation or operate through different mechanisms for older adults.

There are notable strengths to this study, including the use of multiple key inflammatory markers and a robust egocentric social network framework over two waves of data. Additionally, we used a large sample of older adults, facilitating comparisons between cancer survivors and older adults without a reported history of cancer. However, our study is not without limitations. First, to describe the results across biomeasures we restricted analyses to individuals with all three outcome measures, which may have introduced selection bias into the analytic sample. Sensitivity analyses demonstrated that those who were missing were healthier than those included in the analytic sample on factors such as smoking and physical activity, which are both associated with inflammatory levels (159,160). Therefore, the inclusion of unhealthier older adults may have overestimated the true associations. The results should be interpreted with caution, since the smaller sample size may have reduced the power to detect differences.

Second, we could not control for VEGF and TNF-α at baseline and residual confounding may have impacted the findings. Although biomarker data at several time

points are rarely available, longitudinal designs provide the proper the temporal sequence thereby improving the methodological deficiencies of cross-sectional studies. Third, inflammatory markers were only measured once during each wave and inter-assay variation may exist, although CRP has been shown to be stable over time (75,76). Fourth, the cancer survivor sample was small and heterogeneous in terms of primary cancer site, which may not be representative of cancer survivors in other populations. Fifth, we did not assess the cumulative burden of inflammation by creating an index as others have done, despite our a priori hypothesis that these markers could be combined into a similar index. Our results suggest that these makers do not comprise of a single factor and have unique relationships with different social network components. Sixth, we did not adjust for clinical characteristics in the cancer survivor group in order to make valid comparisons between groups, and the time since diagnosis and treatment type may impact physiologic functioning. However, other population-based studies on cancer survivor samples suggest that clinical characteristics are not associated with inflammation (66). Lastly, our subgroup analysis did not test for statistical interactions and therefore, any differences reported between groups are only suggestive and require confirmation by future research.

The social environment may be a key contributor to inflammation for survivors of cancer. Understanding the mechanisms whereby social situations differentially give rise to higher or lower inflammatory risk may shed light on strategies to improve survivorship, including therapeutic approaches that address the behavioral aspects of interpersonal relations. Interventions that facilitate and maintain network stability, support and resources for cancer survivors may be beneficial. Future studies should

consider the differential pathways in which the evolving social landscape contributes to inflammation and chronic disease among cancer survivors and the older adult population.

Figure 6. Description of the analytic sample (N=757)

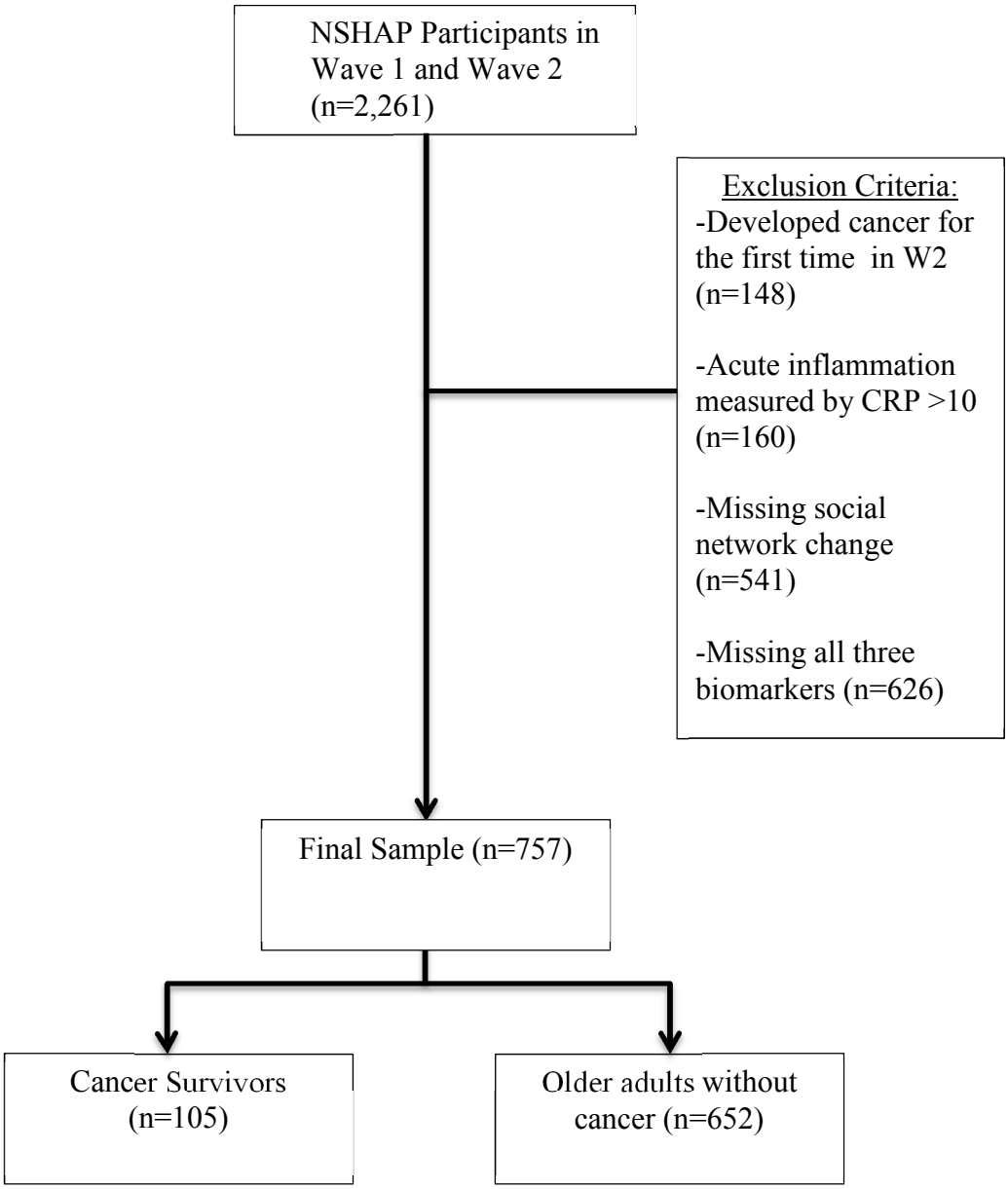


Table 7. Sociodemographic, social network factors and inflammation by cancer survivorship status

| | Overall (n=757) | | Cancer Survivor (n=105) | | Older adults (n=652) | | |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | p-value |
| Age (years) | | | | | | | |
| 57-64 (Ref.) | 297 | 46.5 | 23 | 31.8 | 274 | 49.1 | 0.01 |
| 65-74 | 286 | 35.3 | 48 | 44.6 | 238 | 33.7 | |
| 75-85 | 174 | 18.1 | 34 | 23.7 | 140 | 17.2 | |
| Gender | | | | | | | |
| Male (Ref.) | 317 | 41.8 | 42 | 41.3 | 275 | 41.9 | 0.91 |
| Female | 440 | 58.2 | 63 | 58.7 | 377 | 58.1 | |
| Race | | | | | | | |
| White (Ref.) | 576 | 85.3 | 88 | 88.6 | 488 | 84.7 | 0.33 |
| Non white | 178 | 14.7 | 17 | 11.4 | 161 | 15.3 | |
| Marital Status | | | | | | | |
| Married/cohabitating partner (Ref.) | 498 | 72.2 | 63 | 65.7 | 435 | 73.3 | 0.15 |
| Not married | 259 | 27.8 | 42 | 34.3 | 217 | 26.7 | |
| Education | | | | | | | |
| High school education or less | 446 | 62.3 | 64 | 57.4 | 382 | 63.1 | 0.35 |
| Some college or more (Ref.) | 311 | 37.7 | 41 | 42.6 | 270 | 36.9 | |
| Comorbidity Index (median, IQR[a, b]) | 757 | 2.00(1.00, 3.00) | 105 | 2.00(1.00, 3.00) | 652 | 2.00(1.00, 3.00) | 0.30 |
| BMI | | | | | | | |
| Underweight/ Normal (Ref.) | 185 | 24.3 | 23 | 24.2 | 162 | 24.3 | 0.99 |
| Overweight | 262 | 37.2 | 37 | 37.3 | 225 | 37.2 | |
| Obese | 274 | 38.5 | 41 | 38.5 | 233 | 38.5 | |

Table 7. Sociodemographic, social network factors and inflammation by cancer survivorship status

| | Overall (n=757) | | Cancer Survivor (n=105) | | Older adults (n=652) | | |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | p-value |
| Physical Activity | | | | | | | |
| Low activity | 529 | 70.5 | 67 | 61.2 | 462 | 72.1 | 0.08 |
| Moderate activity | 88 | 11.0 | 11 | 11.1 | 77 | 11.0 | |
| Frequent activity (Ref.) | 139 | 18.5 | 27 | 27.6 | 112 | 16.9 | |
| Smoking | | | | | | | |
| Nonsmoker (Ref.) | 656 | 85.9 | 95 | 89.8 | 561 | 85.3 | 0.21 |
| Smoker | 101 | 14.1 | 10 | 10.2 | 91 | 14.7 | |
| **Social network change** | | | | | | | |
| Network Turnover | | | | | | | |
| Lost Ties | | | | | | | |
| Lost 0 alters (Ref.) | 122 | 15.1 | 12 | 11.8 | 110 | 15.6 | 0.61 |
| Lost 1 alter | 208 | 26.3 | 34 | 30.0 | 174 | 25.7 | |
| Lost 2 alters | 206 | 27.5 | 27 | 30.4 | 179 | 27.0 | |
| Lost 3 or more alters | 221 | 31.2 | 32 | 27.7 | 189 | 31.7 | |
| Added Ties | | | | | | | |
| Added 0 alters (Ref.) | 146 | 18.2 | 22 | 22.5 | 124 | 17.5 | 0.70 |
| Added 1 alter | 219 | 29.2 | 31 | 28.1 | 188 | 29.4 | |
| Added 2 alters | 203 | 27.6 | 27 | 23.5 | 176 | 28.3 | |
| Added 3 or more alters | 189 | 25.0 | 25 | 25.9 | 164 | 24.9 | |
| **Inflammatory Markers**[b] | n | Median (IQR) | N | Median (IQR) | n | Median (IQR) | |
| TNF-α pg/mL | 757 | 11.0 (8.03,15.85) | 105 | 11.0 (8.40,16.62) | 652 | 11.0 (8.00,15.54) | 0.53[b] |
| VEGF pg/mL | 757 | 164.3 (102.4, | 105 | 153.1(106.7, | 652 | 164.3(101.3, | 0.55[b] |

Table 7. Sociodemographic, social network factors and inflammation by cancer survivorship status

| | Overall (n=757) | | Cancer Survivor (n=105) | | Older adults (n=652) | | |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | p-value |
| | | 282.4) | | 299.9) | | 278.6) | |
| CRP mg/L (W2) | 757 | 1.81 (0.95, 3.40) | 105 | 1.7 (0.90, 3.82) | 652 | 1.8 (0.95, 3.33) | 0.69[b] |
| CRP mg/L (W1) | 538 | 1.31 (0.52, 3.14) | 70 | 0.96(0.49, 1.94) | 468 | 1.34(0.56, 3.25) | 0.25[b] |

[a]Interquartile Range is denoted as the 25th-75th percentiles

[b]p-value is testing the association between log transformed values by cancer status to take the complex survey design into account

Table 8. Clinical characteristics of cancer survivors

| Clinical Characteristics | n | % |
|---|---|---|
| Age at diagnosis (mean, SE[a]) | 56 | 1.4 |
| Number of years since diagnosis[b] (mean, SE) | 13.8 | 2.1 |
| Time since diagnosis | | |
| < 5 years | 25 | 27.8 |
| > 5 years | 65 | 72.2 |
| Primary cancer site | | |
| Breast | 23 | 22.2 |
| Blood | 12 | 9.2 |
| Colon | 9 | 6.8 |
| Prostate | 21 | 20.3 |
| Gynecologic | 20 | 21.8 |
| Other[c] | 18 | 19.7 |
| Metastasis | | |
| Yes | 4 | 6.4 |
| No | 92 | 93.6 |

[a]Standard Error of the Mean

[b]Calculated as the number of years since the year of diagnosis to the Wave 2 interview

[c]Other includes bladder, bone, brain, esophageal, kidney, liver, lung, mouth, stomach, throat, thyroid, other/not specified

Table 9. Network characteristics among persistent ties

| | Overall (n=757) | | | | | | Cancer Survivors (n=105) | | | | | | Older Adults (n=652) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Wave 1 | | Wave 2 | | Change | | Wave 1 | | Wave 2 | | Change | | Wave 1 | | Wave 2 | | Change | | |
| | Mean | SE[a] | Mean | SE | Mean | SE | Mean | SE[c] | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE | p-value[b] |
| Mean frequency of contact[a] | 7.0 | 0.0 | 7.0 | 0.0 | 0.0 | 0.0 | 7.1 | 0.1 | 6.9 | 0.1 | -0.2 | 0.1 | 7.0 | 0.0 | 7.0 | 0.0 | 0.0 | 0.0 | 0.26 |
| Mean closeness[a] | 2.3 | 0.0 | 2.3 | 0.0 | -0.1 | 0.0 | 2.4 | 0.1 | 2.3 | 0.1 | -0.1 | 0.1 | 2.3 | 0.0 | 2.3 | 0.0 | -0.1 | 0.0 | 0.65 |
| Density[a] | 0.8 | 0.0 | 0.7 | 0.0 | -0.1 | 0.0 | 0.8 | 0.1 | 0.7 | 0.0 | -0.1 | 0.1 | 0.8 | 0.0 | 0.7 | 0.0 | -0.1 | 0.0 | 0.77 |
| Social Support[a] | | | | | | | | | | | | | | | | | | | |
| Spouse | 2.6 | 0.1 | 2.4 | 0.1 | -0.3 | 0.0 | 2.4 | 0.2 | 2.4 | 0.2 | 0.0 | 0.1 | 2.7 | 0.1 | 2.4 | 0.1 | -0.3 | 0.1 | 0.56 |
| Family | 3.1 | 0.0 | 3.1 | 0.0 | 0.0 | 0.0 | 3.3 | 0.1 | 3.2 | 0.1 | -0.1 | 0.1 | 3.0 | 0.1 | 3.1 | 0.1 | 0.1 | 0.0 | 0.13 |
| Friends | 2.4 | 0.0 | 2.3 | 0.1 | -0.1 | 0.1 | 2.5 | 0.1 | 2.3 | 0.2 | -0.3 | 0.2 | 2.4 | 0.1 | 2.4 | 0.1 | -0.1 | 0.1 | 0.79 |

[a]Standard error of the mean

[b]p-value is testing the difference in network change between cancer survivors and adults without cancer

Table 10. Adjusted associations between social network change and circulating markers of inflammation among cancer survivors and older adults without cancer (n=757)

| | CRP [a,b] | | TNF-α[a] | | VEGF[a] | |
|---|---|---|---|---|---|---|
| | Cancer Survivors (n=105) | Older Adults (n=652) | Cancer Survivors (n=105) | Older Adults (n=652) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β)[c] (95% CI)[d] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Network Turnover | | | | | | |
| Lost Ties (Ref. none) | | | | | | |
| Lost 1 alter | 1.30( 0.84, 2.02) | 1.02( 0.92, 1.12) | 0.87( 0.60, 1.26) | 1.03( 0.89, 1.19) | 0.99( 0.55, 1.79) | 1.09( 0.86, 1.37) |
| Lost 2 alters | 1.30( 0.81, 2.08) | 0.93( 0.81, 1.08) | 1.33( 0.95, 1.87) | 0.94( 0.81, 1.09) | 1.09( 0.61, 1.96) | 1.01( 0.74, 1.39) |
| Lost 3 or more alters | 1.20( 0.74, 1.94) | 0.94( 0.77, 1.14) | 0.78( 0.54, 1.11) | 0.91( 0.77, 1.08) | 1.33( 0.70, 2.52) | 0.87( 0.61, 1.25) |
| Added Ties (Ref. none) | | | | | | |
| Add 1 alter | 0.92( 0.68, 1.24) | 1.13( 1.01, 1.27) | 1.30( 0.93, 1.82) | 0.99( 0.85, 1.15) | 0.72( 0.41, 1.26) | 0.88( 0.71, 1.09) |
| Add 2 alters | **0.74( 0.56, 0.98)** | 0.98( 0.86, 1.13) | 1.03( 0.74, 1.43) | 1.04( 0.84, 1.28) | 0.94( 0.56, 1.60) | 0.93( 0.72, 1.21) |
| Add 3 or more alters | 0.78( 0.54, 1.12) | 1.06( 0.87, 1.29) | 1.28( 0.84, 1.93) | 1.15( 0.92, 1.43) | 0.64( 0.32, 1.25) | 1.04( 0.77, 1.40) |
| Change in closeness | 0.91( 0.79, 1.04) | 1.01( 0.95, 1.07) | 0.94( 0.74, 1.18) | 0.95( 0.84, 1.06) | 1.06( 0.76, 1.46) | 0.92( 0.81, 1.04) |
| Change in frequency of contact | 0.97( 0.85, 1.11) | 1.05( 0.99, 1.11) | **1.19( 1.08, 1.30)** | 1.06( 0.99, 1.13) | 1.04( 0.82, 1.31) | 1.07( 0.95, 1.21) |
| Change in density | 0.84( 0.66, 1.07) | 0.98( 0.87, 1.12) | 1.22( 0.95, 1.57) | 1.06( 0.94, 1.20) | 0.91( 0.60, 1.39) | 1.04( 0.82, 1.32) |
| Change in social support | | | | | | |
| Support from spouse | **1.19( 1.09, 1.30)** | 1.01( 0.98, 1.05) | 0.92( 0.81, 1.05) | 0.98( 0.93, 1.03) | 0.95( 0.79, 1.15) | 1.08( 0.99, 1.17) |
| Support from family | 0.96( 0.90, 1.03) | 1.01( 0.98, 1.04) | 1.00( 0.93, 1.08) | 1.01( 0.97, 1.06) | 1.04( 0.93, 1.18) | 1.00( 0.95, 1.06) |
| Support from friends | 0.98( 0.93, 1.03) | 0.98( 0.95, 1.02) | 1.02( 0.96, 1.10) | 1.01( 0.98, 1.05) | 0.94( 0.86, 1.04) | 1.01( 0.94, 1.07) |

*Bold indicates $p<0.05$

CRP: C-reactive Protein, TNF- α: Tumor necrosis factor- alpha, VEGF: Vascular endothelial growth factor

[a]Models are adjusted for age, gender, race, marital status, education, physical activity, BMI, number of comorbid conditions, smoking status, network size in W1, hypertension and cardiovascular medications in W1 and W2

[b]Model is additionally adjusted for CRP in W1

[c]Beta coefficients are exponentiated to transform results back to the original scale
[d]95% Confidence interval

Chapter 5: Manuscript 3

**Title:** Social support, inflammation, and depressive symptoms among cancer survivors and older adults: testing direct and mediation effects

*Abstract*

**Background:** There are two leading hypotheses that explain how social networks influence chronic diseases, such as depression. The "main effects hypothesis" describes a direct relationship between social support and depressive symptoms. The "stress-buffering hypothesis" posits that inadequate social support and life events increase the risk of disease outcomes. Insufficient social support is believed to be expressed through physiological changes (e.g., inflammation) that lead to the development of depression and other chronic conditions. The objective of this study was to empirically test these two leading hypotheses among cancer survivors and older adults without cancer and to explore the intermediate pathways between social support, chronic inflammation, and depressive symptoms.

**Method:** A secondary analysis of two waves of data (2005-2011) from the National Social Life, Health, and Aging Project (NSHAP) was used to test the hypotheses of interest (n=698). Depressive symptoms were measured with the 11-item Iowa version of the CES-D. Inflammation was measured by C-reactive protein (CRP), Tumor necrosis factor-alpha (TNF-α), and Vascular Endothelial Growth Factor (VEGF). Social support was assessed with six items measuring emotional and tangible support. Structural equation models were used to assess direct and indirect paths between social support, inflammation, and depressive symptoms.

**Results:** Cancer survivors and older adults without a history of cancer were similar in terms of their depressive symptoms, inflammatory levels and social support over time. A significant negative direct effect was observed between the total amount of social support in Wave 2 (W2) and depressive symptoms in W2 ($p=0.01$). No differences between cancer survivors and older adults without cancer were observed in path models and no indirect paths between social support, inflammation, and depressive symptoms were statistically significant in either group.

**Discussion:** The results support the main effects hypothesis, whereby social networks directly influence depressive symptoms. Clinicians should consider screening for social support to prevent or reduce depressive symptomatology.

*Background*

Cancer survivors are at risk for depressive symptoms in the United States. Approximately 14% of cancer survivors in 2010 self-reported current depression compared to 9% of those without a history of cancer (161). The prevalence of depression varies by primary cancer site with lung, gynecological, and hematological cancer survivors reporting the highest levels of depression at the time of cancer diagnosis (162). Variation in the prevalence estimates also exists between studies. For example, studies among breast cancer survivors report prevalence estimates ranging from 1% to as high as 56% (163). Despite this variation, the consistently high occurrence of depressive symptoms in this population underscores the need to understand the potential pathways that place cancer survivors at risk for poor mental health outcomes.

**Social Networks and Depression**

Two prominent frameworks, the "main effects hypothesis" and the "stress-buffering hypothesis," have emerged to describe how social support gets "under the skin" (164–166). The "main effects" hypothesis posits that social support directly contributes to health via the perception of help from peers and social influence on health behaviors, ideas, and emotions, irrespective of existing levels of support or experiencing a stressful life events, such as cancer (164,166). The perception of adequate social support from the network members may directly improve health outcomes, while inadequate support may lead to poor to health outcomes (7). Among cancer survivors, low social support is associated with higher depressive symptomatology (167,168) and is predictive of the development of depression (10–12). However, few studies have considered how alterations in social support from life events, such as cancer, directly impact psychosocial

well-being.

Disparities in social structures (e.g., policies, norms, etc.), interpersonal relations, including negative social interactions, and individual risk factors (e.g., economic position, demographics, etc.) are expressed through biological pathways. The "stress-buffering hypothesis" posits that socially supported individuals are safeguarded against physiological responses to acute and chronic stressors, ultimately protecting them from the development of disease downstream (164,165). Stressors activate the immune response in ways that elevate systemic levels of inflammation (e.g., pro-inflammatory cytokines such as, tumor necrosis factor-alpha (TNF-α)) (172). Instable or low social support over time may be perceived as a continuously stressful situation and may result in sustained levels of chronic, low-grade inflammation (165). Chronic inflammation can create an ideal tumor promoting environment (13,173) where tumor initiation, progression, angiogenesis, and metastasis can occur (13). This is especially important for cancer survivors, as deleterious physiological changes may lead to inequities in cancer recurrence (174). Moreover, inflammation is related to aging (175), the development of depressive symptoms, and atherosclerosis (172). Therefore, cancer survivors may be at an increased risk of inflammation-related comorbidities, including depression (155), compared to the general older adult population.

Previous studies have established a robust link between elevated inflammation and depression in both clinically depressed (176) and community samples (177). The relationship between inflammation and depression is bi-directional (178), as depressed individuals exhibit a larger inflammatory response to stressors (176,179) and medication-induced inflammation can result in the manifestation of depressive symptoms (177).

Previous studies provide mixed evidence for an association between immune functioning and social network components in the general adult population (25,54,131–134,180), and among cancer survivors (47,69,135–139). However, several studies demonstrate beneficial effects when social networks are adequate, and elevated levels of inflammation when they are inadequate. For example, an experimental study demonstrated that participants who perceived negative social situations with their partner, friends, and family had higher Interleukin-6 (IL-6) and TNF-α responses over time and demonstrated worse stress tolerance (181). In a longitudinal population-based study, Yang et al., (2014) observed that social strain was positively associated with C-reactive protein (CRP) and IL-6 and that social support was negatively associated with CRP and IL-6 (48). Glei et al. (2012) found that higher social support was associated with higher CRP (134) and Ford et al. (2006) showed that higher social network index scores were associated with elevated CRP in older men (aged >60) (132). Similarly, in a qualitative review of cancer survivors, Penwell and Larkin (2010) noted that the majority of studies (5/7) supported a positive association between social support and inflammation (125).

Collectively, the literature provides evidence for direct relationships between social support and inflammation, social networks and depressive symptoms, and depressive symptoms and inflammation. However, no studies have formally tested inflammation as an intermediate pathway. The objective of this study was to empirically test the main effects and stress-buffering model in a population of older adults, who either did or did not report a history of cancer (Figure 7). Specifically, our aims are threefold: 1) to assess the main effects hypothesis by directly testing the role of social support and depressive symptomatology; 2) to test the stress-buffering hypothesis by

assessing the relationship between social support and depressive symptoms; and 3) to investigate three markers of inflammation (TNF-α, CRP, and Vascular Endothelial Growth Factor (VEGF)) as potential intermediate pathways to elucidate the mechanisms by which social support influences depressive symptoms. Support for a main effects hypothesis would be indicated by no group differences between cancer survivors and older adults without cancer. More pronounced relationships between social support and depressive symptoms, as well as significant intermediate paths between social support, inflammation, and depressive symptoms among cancer survivors would provide evidence for the stress-buffering hypothesis.

*Methods*

**Study Population**

A sample of 2,261 older adults between the ages of 57-85 participated in two waves of data collection (Wave 1 (W1): 2005-2006, Wave 2 (W2): 2010-2011) by the National Social Life, Health, and Aging Project (NSHAP) (12,57). Cancer survivorship was defined by individuals who self-reported a diagnosis of cancer (excluding skin cancers such as, melanoma, basal cell carcinoma, and squamous cell carcinoma) on the W1 questionnaire. Participants who self-reported a history of cancer for the first time in W2 were excluded, since their social support networks would not reflect their cancer diagnosis in W1 (n=148). In accordance with the American Heart Association and the CDC guidelines, participants with CRP levels greater than 10 (an indication of acute infection) were excluded from the analysis because the present study is focused on chronic, low-grade inflammation (n=160) (149). We conducted a complete case analysis and excluded individuals with out of range biomarker data or who were missing at least

one inflammatory marker (n=1,226). Missing data on social support (n=1) and covariates (n=28) was also excluded. There was no missing data for depressive symptoms. Our final sample consisted of 698 individuals, of whom 90 reported a history of cancer.

## Measures

### Depressive symptoms

Depressive symptoms was measured during the W1 and W2 home interview and was assessed using the 11-item Iowa short-form version of the Center for Epidemiologic Studies Depression (CES-D) Scale (182). The Iowa version of the CES-D has been previously validated and shown to exhibit the same dimensions as the 20-item CES-D, while losing little precision (183). Each respondent was asked to report how often in the past week they felt depressed, like everything was an effort, sad, etc. All scale items are presented in Appendix N. Response options included 0= "rarely or none of the time", 1= "some of the time", 2= "occasionally", and 3= "most of the time." Two items 'felt happy' and 'enjoyed life' were reverse coded to be consistent with the other items. The Iowa short form does not diagnose clinical depression, but rather, is a scale of depressive symptomatology. For the path analysis, all items were summed with higher scores indicating higher levels of depressive symptoms. For the latent variable model each scale item was used to measure the underlying construct of depression. The Cronbach's alpha for the NSHAP sample was 0.80 in W1 and 0.79 in W2.

### Social Support

Social support questions were adapted from Schuster et al. (1990) (184). Participants were asked in each wave of data collection to report how often they could 1) open up to, and 2) rely on their spouse/partner, family, and friends, for a total of six

questions (Appendix N). Responses were measured on a three-point scale ranging from 0= "hardly ever or never" to 2= "often." The six social support questions were summed to calculate the total amount of support received, with higher scores indicating more perceived social support for path models. For the latent variable model each scale item was used to measure the underlying construct of social support.

Inflammation

Three inflammatory markers previously associated angiogenesis and tumor progression, were chosen to estimate chronic, low-grade inflammation: CRP, TNF-α, and VEGF (13,14). CRP was measured in both waves, while the other two biomarkers were only collected in W2 (58). Biospecimen collection, storage and processing have been previously described (58,59,148). The coefficients of variation were considered within an acceptable range for all inflammatory markers (9.5% for CRP, 7.2% for TNF-α and 8.5% for VEGF). All inflammatory markers were natural log transformed to normalize their distributions.

Covariates

Confounders were selected from the literature and were measured in W1: age (continuous), gender (0=male (reference) vs. 1=female), education (1=high school education or less vs. 0=some college or more (reference), marital status (0=married/cohabitating partner (reference) vs. 1=unmarried), race (0=non-Hispanic white (reference), 1=other), smoking (1=smoker vs. 0=non-smoker (reference), and CRP (continuous). Physical activity was classified as: low activity (e.g., exercise less than once a month), some activity (exercise at least once a month to less than twice a week), or frequent activity (exercise three or more times per week). Obesity was assessed with body mass index (BMI). Trained NSHAP interviewers objectively measured height and

weight. Body mass index was derived from measured height and weight and was calculated as [(weight (lbs)/ height $(in)^2$)*703] (77). Comorbid conditions were defined by a modified version of the Charlson Comorbidity Index (107). Individuals who reported any of the following conditions were assigned one point for each condition: hypertension, heart condition (including: heart attack/myocardial infarction, congestive heart failure, stroke, or any procedure for coronary artery disease), diabetes, COPD/asthma, arthritis, Alzheimer's disease or dementia, and sensorimotor conditions (e.g., urinary or stool incontinence, or other urinary problems). Scores of the 11 questions were summed, for a total of 11 possible points. Functional impairment was measured using the Activities of Daily Living Scale (77) (Appendix N). Scores were summed to represent higher levels of impairment in the path analysis. For the latent variable model each scale item was used to measure the underlying construct of physical disability.

**Statistical Analysis**

Means and standard deviations for continuous variables and proportions for categorical variables were calculated to compare cancer survivors to older adults without cancer on sociodemographic, social support, mediator, and outcome variables. Simple linear regression was conducted to test differences between continuous variables and cancer survivors and older adults. Chi-square tests were used to test for differences in the proportions of categorical variables for cancer survivors and older adults (Table 11). Pearson correlations were used to test preliminary correlations between depressive symptoms, social support, and inflammatory markers (Table 12).

Path analyses were used to test for group invariance because convergence problems were experienced with the latent variable model for the cancer group. First,

each group was tested separately to determine if the model fit well for both groups using Hu & Bentler (1999)'s criteria for satisfactory model fit: RMSEA ≤ 0.06, CFI ≥ 0.95, and SRMR ≤ 0.08 (185). Improvements in model fit often take many forms, but the present study only focused on adding a residual covariance if it was theoretically plausible and substantial enough that over-fitting (and possibly chance covariation) did not occur.

We additionally conducted a latent variable model with the total sample because latent models have the ability to parcel out measurement error (68). SEM testing proceeded in two phases: a measurement phase and a structural phase (68). In the measurement phase, we estimated the construct reliability using coefficient H (68), which was considered acceptable for all factors (Social Support W1= 0.95, Social support W2= 0.95, Functional Impairment W1= 0.85, Depressive symptoms W1= 0.81, Depressive symptoms W2= 0.80). In the initial measurement phase, a confirmatory factor analysis (CFA) model was imposed on the variance-covariance matrix in which all latent variables and standalone manifest variables were allowed to covary. This method ensures that any badness of fit in the model is the result of measurement model misspecification, rather than structural relations among the latent variables. Similar to the path model, the measurement model was evaluated to determine if improvements in model fit could be made. Modification indices were used to determine if meaningful improvements from residual covariances could be added to improve the initial model fit. Theoretically plausible modifications were made in a sequential fashion starting with the modification that would provide the largest drop in chi-square value. Once a modification was incorporated, the model was re-estimated and new modifications were reviewed. Direct and indirect effects were estimated for the structural model and are reported in Table 13.

SAS version 9.3 (SAS Inc., Cary, NC) was used to test distributional assumptions and calculate descriptive statistics and Mplus version 7 (Muthén & Muthén, Los Angeles, CA) was used to conduct SEM.

*Results*

A total of 698 NSHAP participants were included in the analytic sample, of whom 90 (13%) reported a history of cancer (Table 11). In the overall sample, the majority of participants were female (54.4%), white (84.7%), had a high school education or less (59.7%), were married or had a cohabitating partner (71.0%), were non-smokers (83.5%), sedentary (70.9%), and had no functional impairments (75.9%). The mean depressive symptoms score was similar in the overall sample across waves (4.8 in W1 vs. 4.8 in W2) and was similar across groups (W2 mean score cancer survivors= 4.9 vs. mean score for older adults= 4.8, $p=0.98$). Cancer survivors and older adults were comparable in terms of their socio-demographic characteristics, except in terms of age, where cancer survivors were significantly older (69.4 years vs. 66.7 years, $p<0.01$).

Correlations between social support, inflammation, and depressive symptoms are reported in Table 12. Depressive symptoms were moderately correlated across waves ($r=0.55$, $p<0.05$). Depressive symptoms in W2 was weakly correlated with social support in W1 ($r=-0.21$, $p<0.05$), social support in W2 ($r=-0.25$, $p<0.05$), CRP in W1 ($r=0.14$, $p<0.05$), CRP in W2 ($r=0.12$, $p<0.05$), and TNF-α in W2 ($r=0.13$, $p<0.05$). Social support in W2 was weakly, but positively correlated with TNF-α in W2 ($r=0.14$, $p<0.05$), CRP W1 ($r=0.10$, $p<0.05$), and CRP in W2 ($r=0.08$, $p<0.05$).

The hypothesized path model fit well for each group, albeit a low CFI for the cancer survivors (Cancer survivors: RMSEA= 0.05, CFI=0.93, SRMR=0.04; Older

adults: RMSEA=0.03, CFI=0.98, SRMR=0.02). No theoretically plausible misspecifications were identified for each group. Configural invariance was estimated by testing the model for both groups simultaneously. The model fit well and the modification indices did not indicate significant misspecification (RMSEA= 0.03, CFI=0.98, SRMR=0.02). More social support in W2 was directly associated with less depressive symptoms in W2 for older adults (estimate= -0.12, p<0.01). Social support in W1 was associated with VEGF in W2 among older adults (estimate=-0.10, p=0.04). TNF-α was positively associated with depressive symptoms among cancer survivors (estimate=0.18, p=0.02) (Figure 8).

Finally, path invariance was tested by constraining all paths to be equal across groups. The p-value was not statistically significant, indicating that a significant amount of badness of fit was not introduced into the model when constraining the parameters to be equal across groups (scaled $\chi^2$=66.81, *df*= 54, p=0.1132), indicating that these groups did not differ and was considered the final model. The final path model fit well (RMSEA= 0.03, CFI= 0.97, SRMR=0.03) and is presented in Figure 9. No mediation effects were observed between social support, inflammation and depression (Table 13). Social support in W2 was significantly associated with depressive symptoms (estimate= -0.11, p=0.01).

For the latent variable model, the initial measurement model fit well despite a low CFI, (RMSEA=0.03, CFI=0.92, SRMR=0.05) but the modification indices suggested three plausible modifications: a covariance between the indicator for social support "rely on spouse" and the CES-D indicator "felt lonely" in W1 and W2, and a covariance between the CES-D indicator "could not get going" and the functional impairment

indicator "getting dressed" in W1. After incorporating the final modifications we assessed the model fit. The model fit well (RMSEA ≤ 0.06 and SRMR ≤ 0.08), except in terms of the CFI (Appendix O). Next, items measured at two time points were constrained to be equal to each other. The scaled chi-square indicated that constraining the items to be equal across time points did not introduce a significant amount of badness of fit (scaled $\chi^2$=21.71, *df*= 15, p=0.1156) and was considered our final measurement model (RMSEA=0.03, CFI=0.92, and SRMR=0.05). The results of the measurement model for the factors and their corresponding indicators are presented in Appendices P-R.

Next, the hypothesized structural model was estimated using the modifications from the final measurement model. Specifically, hypothesized direct and indirect paths were modeled from social support in W1 and W2 to each inflammatory marker in W2, and depressive symptoms in W2. The final structural model fit well, except in terms of CFI (RMSEA=0.03, CFI=0.92, and SRMR=0.05) (Appendix S). The results of the latent variable model for the total sample were similar to the constrained path analysis, and supported a direct path from the factor social support in W2 to the factor depressive symptoms in W2 (estimate= -0.25, p=0.03) (Figure 10). No evidence of an indirect effect between social support, inflammation, and depressive symptoms was observed (Table 13).

*Discussion*

The current study is one of few to investigate intermediate inflammatory pathways using two social support frameworks. Our study provides support for a main effects hypothesis, whereby social support directly influences depressive symptoms, and provides little evidence for the stress buffering hypothesis.

Consistent with other studies that support a direct relationship between social support and depressive symptomatology (166,177), our study demonstrated that a constrained path model fit the data well, indicating no group differences between cancer survivors and older adults. Additionally, we observed an inverse relationship, meaning that higher total support was associated with lower depressive symptoms, while controlling for a number of known confounding factors, such as sociodemographic factors, smoking status, physical activity, functional impairment, and multiple comorbidities.

Although social science researchers hypothesize that chronic inflammation is a key pathway by which social support influences chronic disease outcomes, we found no empirical evidence for an intermediate link, whereby higher levels of social support lead to lower levels of chronic inflammation, which in turn leads to a lower occurrence of depressive symptoms. Moreover, these relationships were similar across groups, suggesting that social support directly influences depressive outcomes, regardless of facing a major stressful life experience, like cancer.

We only identified one study that tested inflammation as a mediator among cancer survivors. Hughes et al. (2014) showed that breast cancer patients with lower pre-treatment social support had higher IL-6 concentrations over time, and that higher levels of IL-6 predicted marginally larger increases in depressive symptoms (135). The differences in the results may be due to the use of clinical samples versus population based samples and the inflammatory measures used. Additionally, we simultaneously tested these interrelationships using robust a SEM framework. Support for a main effects model may suggest that interactions with network members directly influence emotional states (186,187) and that the perception of lower support is detrimental to psychosocial

functioning, regardless of experiencing a stressful event. In a meta-analysis, Mitchell and colleagues demonstrated that the pooled risk of depressive symptoms in long-term survivors was similar to their spouses, which may suggest transmission of depressive symptoms between partners (prevalence in cancer survivors= 26.7% versus 26.3%, RR=1.01 (95% CI: 0.86–1.20; p=0.88) through shared maladaptive behaviors or coping strategies, and/or lower resources that contribute to poor psychosocial outcomes (188).

However, not all stressful events are perceived equally and may be individual and context specific. Therefore, some cancer survivors may be more resilient to life stress (189). It should also be noted that socially supported individuals may be able to buffer stress by attenuating or preventing a stress response in the first place. The perception that others will help them and provide resources in times of need may prevent a situation from being interpreted as highly stressful (164); however we had no way of measuring perception of the stress response. Additionally, we only tested depressive symptoms as the main outcome and other chronic or acute diseases may show more pronounced relationships that support the stress-buffering hypothesis. For example, Kielcott-Glaser et al. (2005) showed that socially supportive interactions were associated with a stronger immune response and faster wound healing compared to those who reported conflict interactions (190).

Our results, in accordance with other studies, highlight that increased social support can reduce depressive symptomatology for cancer survivors and the older adult population, in general (177). Both groups may benefit from network interventions that enhance perceived feelings of emotional and tangible support. Providers should screen older adults and cancer survivors for adequate social support in order to prevent the

negative cascade of symptoms associated with depressive symptoms and other chronic diseases. Given the health relevance of inflammation and depressive symptoms, social support interventions may improve long-term health and quality of life.

The goal of this study was to empirically test two leading social network hypotheses over a five-year period using a two-group SEM framework with a large sample of older adults and multiple markers of inflammation. Despite these strengths, our study is not without limitations. First, the 11-item Iowa short-form CES-D measures depressive symptoms, rather than a clinical diagnosis of depression and some researchers have argued that this scale measures psychological distress, rather than depressive symptoms (191,192). Second, the results may be due to reverse causality, given that individuals with depressive symptoms may have higher levels of circulating inflammation (190). However, other studies support a unidirectional, rather than bidirectional relationship between social support, inflammation, and depressive symptoms (135). Third, TNF-α and VEGF were only measured in W2 and failure to control for these variables at baseline may have caused residual confounding. Fourth, our cancer survivor sample was small and the model (or portions of the model) may have been underpowered. Fifth, the cancer survivors and older adults were similar in terms of network support and depressive symptoms, which may be attributed to the time since cancer diagnosis, since the majority of cancer survivors had been diagnosed more than 10 years prior to the start of the NSHAP study. Therefore, a better proxy for stressful life events should be considered. Future large-scale studies should investigate the interrelationships among recent cancer survivors (e.g., < five years from diagnosis) to determine if differences exist. Finally, our analytic sample had large amounts of missing data due to assay-related problems with the inflammatory markers.

Sensitivity analyses demonstrated that those who were missing were healthier than those included in the analytic sample on factors such as smoking and physical activity, which are both associated with inflammatory levels (159,160). Therefore, the inclusion of unhealthier older adults in the analytic sample may have overestimated the true associations of interest. Future longitudinal studies with repeated biomarker measures are needed to verify our findings. Additionally, because of the strict exclusion criteria, our study may have limited generalizability outside of this population.

### Conclusion

In conclusion, our analysis supports a main effects hypothesis whereby social support is associated with lower levels of depressive symptoms, irrespective of life events. The results do not support an intermediate mechanism whereby inflammation mediated the relationship between social support and depressive symptoms. A better understanding of the physiological mechanisms underlying social influences on depressive symptomatology and cancer survival is needed to elucidate meaningful biomarkers for therapeutic agents, as well as psychosocial interventions to improve well-being in late life. Public health interventions should consider the direct benefits of enhancing network support for cancer survivors and older adults at risk for depressive symptoms.

Figure 7. Hypothesized relations between social support, inflammation, and depression

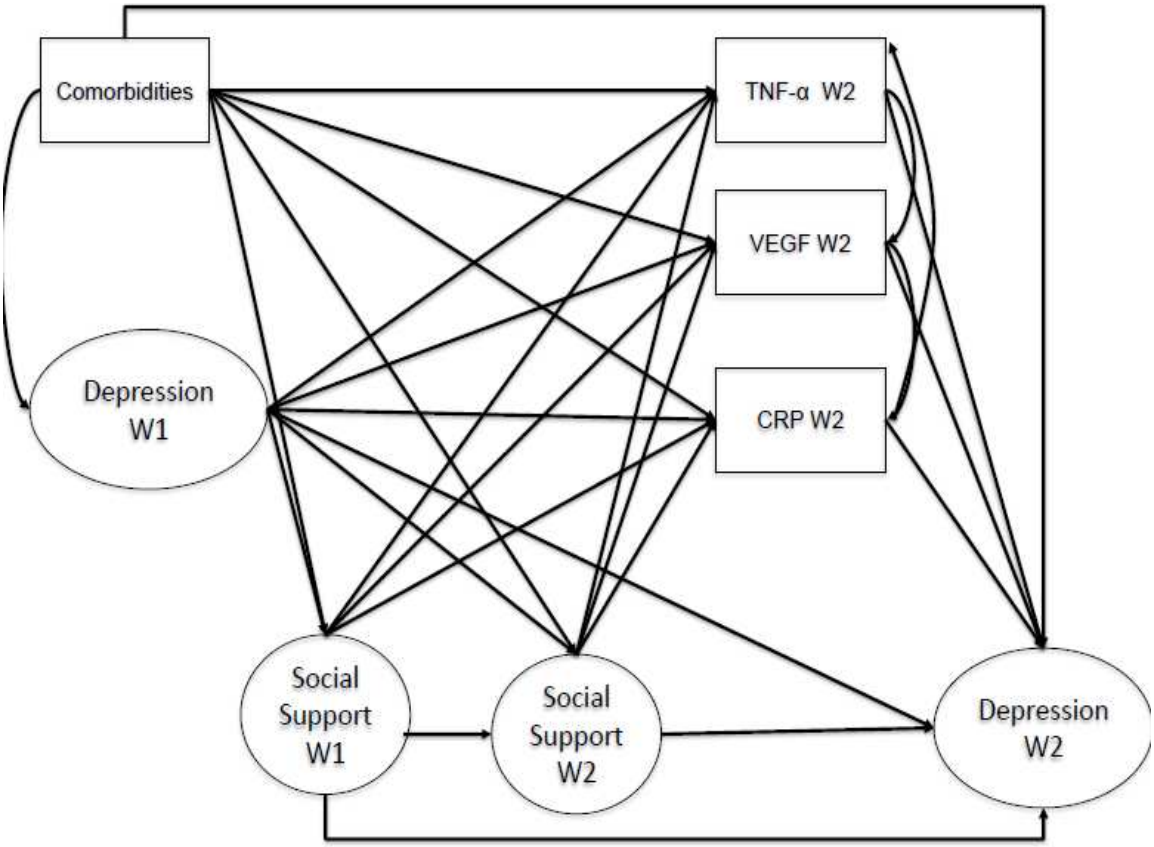


Table 11. Study sample characteristics by cancer survivorship status

| | Overall (n=698) | | Cancer Survivor (n=90) | | Older Adults (n=608) | | |
|---|---|---|---|---|---|---|---|
| | Mean or n | SE[a] or % | Mean or n | SE or % | Mean or n | SE or % | p-value[c] |
| Age | 67.1 | 0.3 | 69.4 | 0.6 | 66.7 | 0.3 | **<0.01** |
| Gender | | | | | | | |
| Male | 312 | 45.6 | 35 | 41.7 | 277 | 46.3 | 0.44 |
| Female | 386 | 54.4 | 55 | 58.3 | 331 | 53.7 | |
| Race | | | | | | | |
| White | 526 | 84.7 | 76 | 88.1 | 450 | 84.2 | 0.43 |
| Non white | 172 | 15.3 | 14 | 11.9 | 158 | 15.8 | |
| Education | | | | | | | |
| High school education or less | 394 | 59.7 | 55 | 62.1 | 339 | 59.3 | 0.66 |
| Some college or more | 304 | 40.3 | 35 | 37.9 | 269 | 40.7 | |
| Marital Status | | | | | | | |
| Married/Cohabitating Partner | 452 | 71.0 | 54 | 64.1 | 398 | 72.1 | 0.17 |
| Not married | 246 | 29.0 | 36 | 35.9 | 210 | 27.9 | |
| Smoking | | | | | | | |
| Nonsmoker | 593 | 83.5 | 78 | 84.2 | 515 | 83.4 | 0.86 |
| Smoker | 105 | 16.5 | 12 | 15.8 | 93 | 16.6 | |
| Comorbidity Index | 1.9 | 0.1 | 2.1 | 0.2 | 1.9 | 0.1 | 0.23 |
| BMI | 29.0 | 0.2 | 28.3 | 0.5 | 29.2 | 0.3 | 0.14 |
| Physical Activity | | | | | | | |
| Low activity | 484 | 70.9 | 61 | 68.7 | 423 | 71.2 | 0.77 |
| Moderate activity | 87 | 11.4 | 10 | 10.5 | 77 | 11.5 | |
| Frequent activity | 127 | 17.8 | 19 | 20.8 | 108 | 17.3 | |
| Functional Impairment | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No Impairment | 515 | 75.9 | 61 | 72.2 | 454 | 76.5 | 0.50 |
| At least one impairment | 183 | 24.1 | 29 | 27.8 | 154 | 23.5 | |
| Depression Wave 2 | 4.8 | 0.2 | 4.9 | 0.6 | 4.8 | 0.2 | 0.98 |
| Depression Wave 1 | 4.8 | 0.2 | 5.4 | 0.6 | 4.7 | 0.2 | 0.35 |
| Social Support W2 | 7.4 | 0.1 | 7.2 | 0.3 | 7.4 | 0.2 | 0.46 |
| Social Support W1 | 7.7 | 0.1 | 7.5 | 0.3 | 7.7 | 0.1 | 0.51 |
| Change in social support | -0.3 | 0.1 | -0.4 | 0.4 | -0.3 | 0.1 | 0.88 |
| Inflammatory Markers | Median | IQR[b] | Median | IQR | Median | IQR | |
| TNF-α pg/mL | 11.3 | 8.0-15.2 | 11.8 | 8.0-18.7 | 11.3 | 8.0-15.0 | 0.35[d] |
| VEGF pg/mL | 167.6 | 104.0-277.5 | 161.8 | 102.0-303.0 | 167.8 | 104.2-274.2 | 0.85[d] |
| CRP mg/L (W2) | 1.8 | 0.9-3.3 | 1.82 | 1.0-4.0 | 1.8 | 0.9-3.3 | 0.22[d] |
| CRP mg/L (W1) | 1.3 | 0.5-3.0 | 1.08 | 0.5-2.1 | 1.3 | 0.6-3.1 | 0.46[d] |

*Bold indicates $p<0.05$

[a]Standard Error

[b]Interquartile Range is the 25th-75th percentiles

[c]P-value is comparing the differences between cancer survivors and older adults

[d]Biomarkers were log transformed for p-value calculation

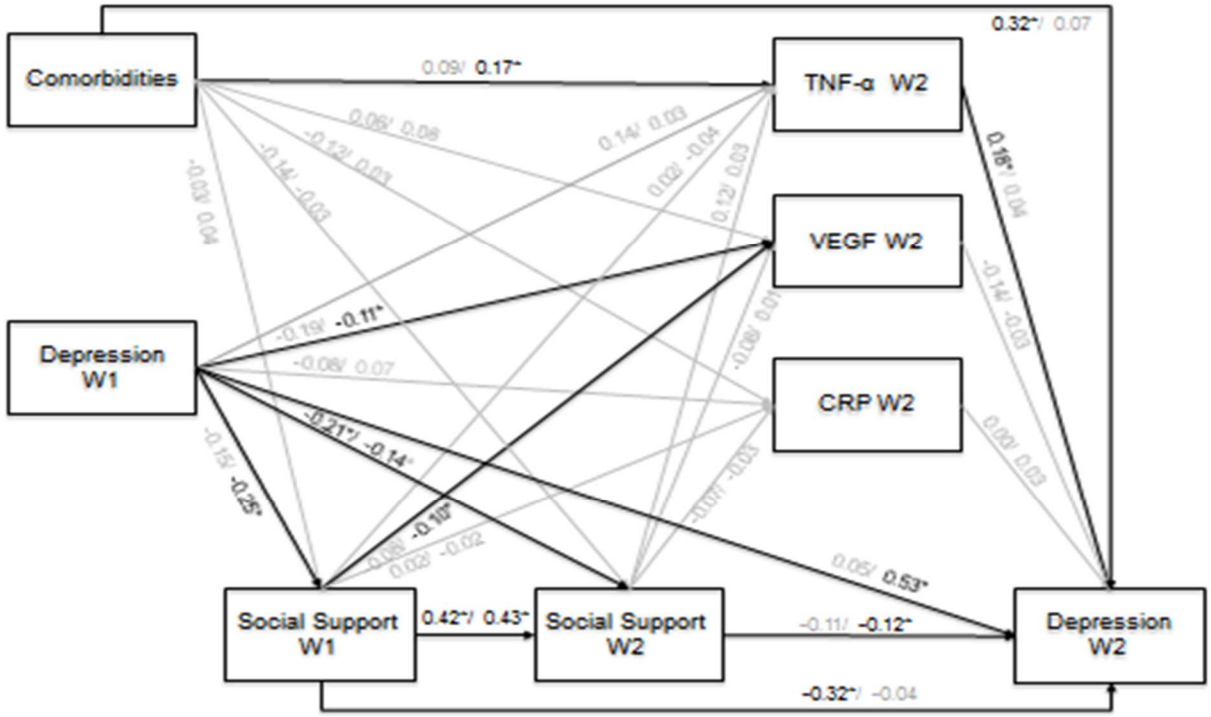
Table 12. Correlations among depressive symptoms and inflammation in Wave 2 (n=698)

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| 1. Depressive Symptoms W2 | - | | | | | | | |
| 2. Depressive Symptoms W1 | **0.55*** | - | | | | | | |
| 3. Social Support W2 | **-0.25*** | **-0.30*** | - | | | | | |
| 4. Social Support W1 | **-0.21*** | **-0.30*** | **0.61*** | - | | | | |
| 5. CRP W2 | **0.12*** | **0.08*** | **-0.10*** | -0.07 | - | | | |
| 6. CRP W1 | **0.14*** | **0.10*** | 0.00 | -0.01 | **0.51*** | - | | |
| 7. TNF-α | **0.13*** | **0.14*** | -0.05 | -0.06 | **0.09*** | **0.09*** | - | |
| 8. VEGF | 0.00 | -0.05 | -0.03 | **-0.08*** | **0.11*** | **0.09*** | **0.20*** | - |

*Bold indicates $p<0.05$

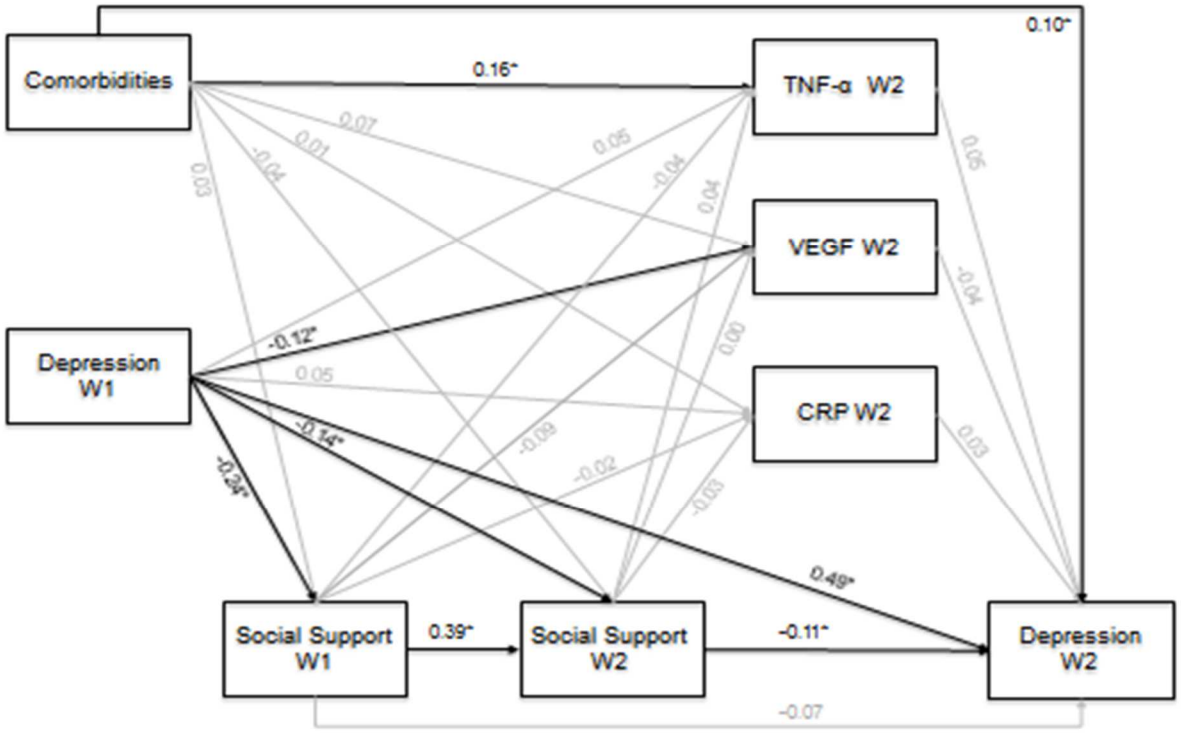
Note: Inflammatory markers are log transformed

Figure 8. Standardized results from the path analysis for cancer survivors and older adults prior to constraining paths to be equal




Final path model for cancer survivors and older adults. All parameters are free to vary across groups. Controlling for BMI, CRP, age, race, gender, education level, marital status, smoking status, physical activity, and functional impairment in Wave 1. Estimates are standardized and presented as cancer survivor/ older adults.
*denotes $p<0.05$

Figure 9. Standardized results from the path analysis for cancer survivors and older adults after constraining paths to be equal across



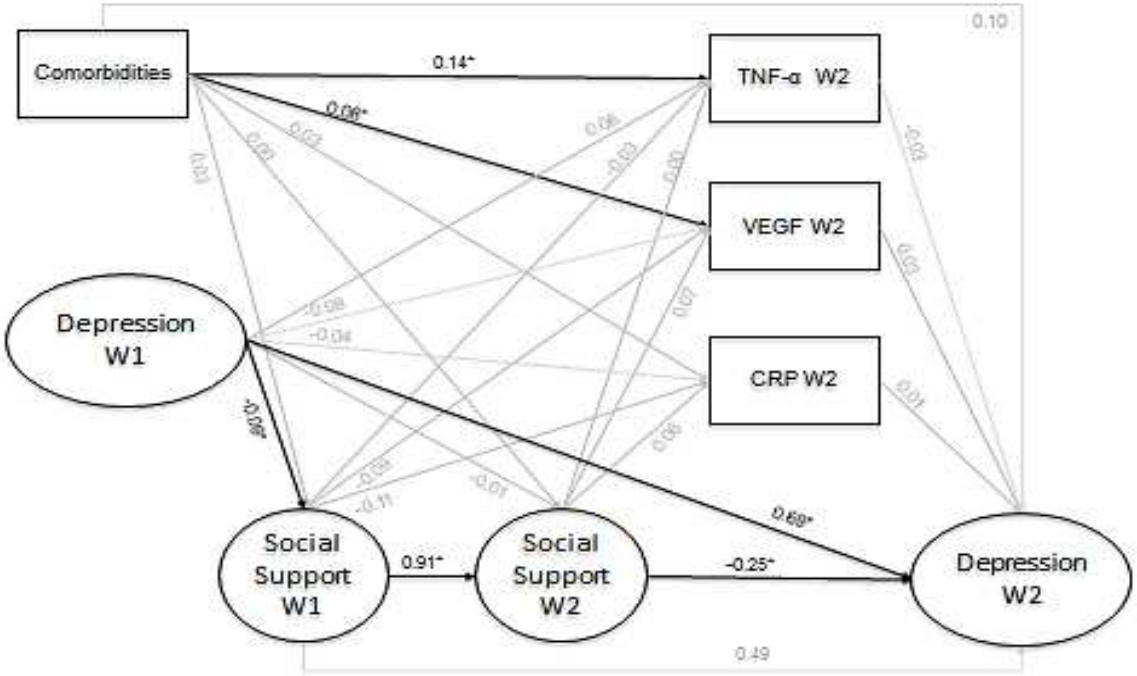

Final path model for cancer survivors and older adults. All paths are constrained to be equal across groups. Controlling for BMI, CRP, age, race, gender, education level, marital status, smoking status, physical activity, and functional impairment in Wave 1. Estimates are standardized.
*denotes $p<0.05$

Table 13. Standardized estimated direct and indirect effects for the path models

| | Unconstrained model | | | | Constrained Model | | Latent variable Model | |
|---|---|---|---|---|---|---|---|---|
| | Cancer Survivors | | Cancer free older adults | | | | | |
| | Estimate | p-value | Estimate | p-value | Estimate | p-value | Estimate | p-value |
| From Social Support W2 to Depression W2 | | | | | | | | |
| Total effect | -0.07 | 0.61 | **-0.12** | **<0.01** | **-0.11** | **0.01** | **-0.24** | **0.03** |
| Total indirect effect | 0.03 | 0.36 | 0.00 | 0.99 | 0.00 | 0.82 | 0.00 | 0.64 |
| Direct Effect | | | | | | | | |
| Social Support W2 → Depression W2 | -0.11 | 0.42 | **-0.12** | **<0.01** | **-0.11** | **0.01** | **-0.25** | **0.03** |
| Specific indirect effect | | | | | | | | |
| Social Support W2 → CRP W2 → Depression W2 | 0.00 | 0.99 | 0.00 | 0.66 | 0.00 | 0.58 | 0.00 | 0.82 |
| Social Support W2 → TNF-α → Depression W2 | 0.02 | 0.35 | 0.00 | 0.70 | 0.00 | 0.57 | 0.00 | 0.99 |
| Social Support W2 → VEGF → Depression W2 | 0.01 | 0.59 | 0.00 | 0.80 | 0.00 | 0.97 | 0.00 | 0.56 |

*Bold indicates p<0.05

Figure 10. Structural model depicting relationships between factors and observed variables




Controlling for BMI, CRP, age, race, gender, education level, marital status, smoking status, physical activity, and functional impairment in Wave 1. Estimates are standardized. Covariances and residuals are not depicted for simplicity.
*denotes $p<0.05$

# Chapter 6: Conclusions

## *Conclusion of the Findings*

The findings from this dissertation suggest that different social network components contribute differentially to health status for cancer survivors and older adults. For example, we observed that adding new network members was protective of functional decline in the overall NSHAP sample and was associated with lower levels of CRP among cancer survivors. Experiencing a change in the frequency of contact with network members was positively associated with functional decline and TNF-α in cancer survivors. We also observed that spousal support was associated with higher CRP levels among cancer survivors and the total amount of support was associated with lower levels of depression in the overall NSHAP sample. Together these results suggest that social networks may shape health in both positive and negative ways. For example, when new ties are integrated into one's circle of close contacts and network relations and functions remain strong over time, their effects on health are positive. Alternatively, negative health effects may emerge when relationships fade or become weaker over time.

## *Public Health Implications*

Cancer is the second leading cause of death in the United States (2). With the advent of screening and early diagnoses, more individuals are expected to survive cancer and return to healthy, productive lives (6). Understanding the central aspects of the social environment that shape metastasis and cancer-related comorbidities allows researchers to design interventions that pinpoint the social components that have the most impact on an individual's quality of life. Individuals are embedded within social structures through

which ideas, behaviors, information, and resources flow, suggesting that social networks may have important downstream effects stemming from health events and characteristics of disease. Health events and characteristics of disease may take many forms including, chronic diseases, health behaviors, or access to care and treatment (23). To date, interventions for cancer survivors have focused on psychosocial and behavioral factors to improve health at the individual level (193). A social network approach may complement current interventions and improve their effectiveness by creating a network structure that provides social support and emotional closeness, either artificially (e.g., cancer survivor groups in person or online communities) or by including close contacts into interventions to educate network members on the importance of sustained support over time. For example, a randomized clinical trial demonstrated improved social quality of life and coping for advanced cancer patients by focusing the intervention on the patient-caregiver dyad (194).

Improving the lives of cancer survivors may also positively impact their network's health. For example, returning to a productive, healthy life after cancer may improve the mental health of the cancer survivor's spouse by eliminating caregiving needs. Therefore, the cost benefit of social embeddedness on health is not solely to the individual, but rather, to the whole egocentric network. Health interventions should consider calculating the indirect benefits to network members to increase their cost-effectiveness, in addition to targeted individuals (18).

Finally, given the similarities between the cancer survivor group and the older adults in the NSHAP sample, social network interventions may be applicable and efficacious in both groups. Antonucci, Ajrouch, & Birditt (2014) suggest in the "Convoy

Model" that shared support and quality relationships are essential to healthy network functioning (195). Moving from a treatment focused framework to prevention could start with interventions for older adults (including cancer survivors) that focus on building a certain number of relationships with the goal of strengthening these relationships over time and creating connections between network members. Thereby creating a close-knit circle of connections, embeddedness within the social structure, and ultimately preventing social isolation. Gierveld, Tilburg, & Dykstra (2016) endorse educating older adults about the consequences of social isolation and loneliness, and creating an actionable plan as a necessary first step toward prevention (196).

*Limitations*

There limitations have been described in detail in Chapter 2. The main limitations of this work include the possibility of selection bias due to missing data in the biomarkers and social network components. The cancer survivor sample was small and relied on a self-reported history of cancer. A larger sample with verified cancer cases would improve the strength of these findings. The sample of cancer survivors in the NSHAP dataset may also be different than cancer survivors in other populations. For example, there were no deaths among cancer survivors between W1 and W2 and the mean number of years since initial diagnosis was 13.8, which indicates that these cancer survivors were relatively healthy and may have had better prognosis.

The main limitation of egocentric social network methods are the implementation of fixed designs, where networks force ego to list a small number of alters (e.g., five alters). If ego's network is larger the five then the network becomes misspecified.

Therefore, measurement error may be introduced into the design because individuals are forced to constrain their networks to five people when in reality they are larger.

Information bias is always a possibility with self-reported measures. For example, individuals with low levels of social support may rate their functional impairments or depressive symptoms more severe due to social isolation. Therefore, we cannot rule out differential misclassification. The direction of the bias would likely overestimate our results, since a higher proportion of individuals with disabilities or depressive symptoms would report low support.

*Future Directions*

The relationship between social networks and health has been of interest for over two decades, yet our understanding of the mechanisms in which the social landscape contributes to health has only begun to emerge. The joint contribution of the three manuscripts significantly impacts the fields of cancer survivorship, aging, public health, and sociology by utilizing a novel methodology to measure social networks and their changes over time. We are the first, to our knowledge, to utilize egocentric social network methods and theory to describe the social environment as it evolves over time in this population; thereby expanding the field beyond conventional methods, such as social support and deepening our understanding of the complex interplay between social network change and several health outcomes. As the number of cancer survivors continues to increase and remission is prolonged, timely information to develop bio-behavioral interventions to holistically address the challenges of life after cancer is required. Public health programs should consider exploring effective ways to incorporate social network approaches into interventions. Providers should consider screening for

social network support and resources to prevent social isolation. Future studies should address the limitations of this dissertation, including the small sample size of cancer survivors; unverified cancer diagnoses; consider analyzing breast cancer survivors' social networks separately due to organization level media campaigns to promote breast cancer awareness; and confirm the findings using population-based approaches.

Appendices

Appendix A. Lagged linear regression models for cancer survivors and non-cancer survivors for ADL outcome

| | Overall | Cancer Survivors | Adults without cancer |
|---|---|---|---|
| | Exp(β)[a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Age | | | |
| 57-64 (Ref.) | | | |
| 65-74 | 1.02( 0.94, 1.10) | 1.04( 0.82, 1.31) | 1.02( 0.95, 1.09) |
| 75-85 | **1.19( 1.07, 1.33)** | 1.07( 0.85, 1.34) | **1.23( 1.09, 1.38)** |
| BMI | | | |
| Underweight/Normal (Ref.) | | | |
| Overweight | 1.01( 0.95, 1.08) | 0.91( 0.73, 1.13) | 1.02( 0.96, 1.10) |
| Obese | 1.06( 0.99, 1.15) | 1.00( 0.75, 1.34) | 1.07( 0.99, 1.15) |
| Gender | | | |
| Male (Ref.) | | | |
| Female | 0.97( 0.90, 1.05) | 1.01( 0.84, 1.23) | 0.97( 0.90, 1.05) |
| Race | | | |
| White (Ref.) | | | |
| Other | 1.02( 0.94, 1.11) | 1.06( 0.82, 1.38) | 1.02( 0.94, 1.12) |
| Marital Status W1 | | | |
| Not married | 0.98( 0.91, 1.06) | 0.93( 0.75, 1.16) | 0.98( 0.90, 1.06) |
| Married (Ref.) | | | |
| Education | | | |
| High school education or less | **1.10( 1.01, 1.19)** | **1.26( 1.03, 1.53)** | 1.08( 1.00, 1.16) |

| | Overall | Cancer Survivors | Adults without cancer |
|---|---|---|---|
| | Exp(β)[a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) |
| More than a high school education (Ref.) | | | |
| Comorbidity Index | **1.07( 1.05, 1.10)** | 1.07( 0.99, 1.14) | **1.09( 1.06, 1.11)** |
| Impairment W1 (logged) | **1.96( 1.72, 2.23)** | **1.98( 1.50, 2.62)** | **1.91( 1.68, 2.16)** |
| Smoker | | | |
| Yes | 1.04( 0.88, 1.23) | 0.86( 0.66, 1.12) | 1.07( 0.90, 1.28) |
| No (Ref.) | | | |
| Lost Ties between W1 and W2 | | | |
| No Lost Alters between W1 and W2 (Ref.) | | | |
| Lost one alter | 1.06( 0.96, 1.17) | 1.16( 0.83, 1.61) | 1.04( 0.94, 1.16) |
| Lost two alters | 1.02( 0.93, 1.13) | 1.01( 0.75, 1.36) | 1.02( 0.92, 1.14) |
| Lost three or more alters | 1.13( 0.99, 1.30) | 1.27( 0.88, 1.81) | 1.11( 0.95, 1.29) |
| Added Ties between W1 and W2 | | | |
| No added alters between W1 and W2 (Ref.) | | | |
| Added one alter | **0.89( 0.82, 0.97)** | 0.86( 0.67, 1.10) | 0.92( 0.83, 1.01) |
| Added two alters | 0.92( 0.83, 1.01) | 0.81( 0.60, 1.09) | 0.94( 0.84, 1.06) |
| Added three or more alters | **0.88( 0.78, 0.98)** | 0.89( 0.65, 1.24) | **0.88( 0.78, 1.00)** |
| Change in closeness | 0.96( 0.90, 1.02) | 0.91( 0.72, 1.14) | 0.96( 0.89, 1.03) |

| | Overall | Cancer Survivors | Adults without cancer |
|---|---|---|---|
| | Exp(β)[a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Change in frequency of contact | 1.02( 0.99, 1.06) | 1.10( 1.00, 1.22) | 1.02( 0.99, 1.05) |
| Change in density | 0.99( 0.92, 1.06) | 0.96( 0.80, 1.15) | 0.99( 0.91, 1.07) |
| Change in social support | | | |
| Spouse | 1.00( 0.96, 1.04) | 0.98( 0.91, 1.05) | 1.00( 0.97, 1.04) |
| Family | 1.00( 0.98, 1.02) | 1.00( 0.93, 1.07) | 1.00( 0.98, 1.02) |
| Friends | 1.01( 0.98, 1.04) | 1.06( 0.99, 1.13) | 1.00( 0.96, 1.03) |

*Bold indicates $p<0.05$

[a]Beta coefficients are exponentiated to transform results back to the original scale

[b]95% Confidence Interval

Appendix B. Comparison of standardized estimates and standard errors with and without the complex survey design

| | No Complex Survey Design | | | | | | Complex Survey Design | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cancer Survivors | | | Older adults | | | Cancer Survivors | | | Older adults | | |
| | Estimate | SE | p-value | Estimate | SE | p-value | Estimate | SE | p-value | Estimate | SE | p-value |
| Social Support W1 | | | | | | | | | | | | |
| Depression W1 | -0.15 | 0.12 | 0.19 | -0.25 | 0.03 | <0.01 | 0.02 | 0.11 | 0.86 | -0.24 | 0.04 | <0.01 |
| Not married | 0.16 | 0.12 | 0.18 | 0.16 | 0.03 | <0.01 | 0.22 | 0.14 | 0.11 | 0.19 | 0.03 | <0.01 |
| Number of comorbidities | -0.52 | 0.11 | <0.01 | -0.57 | 0.03 | <0.01 | -0.57 | 0.13 | <0.01 | -0.57 | 0.03 | <0.01 |
| Social Support W2 | -0.03 | 0.12 | 0.79 | 0.04 | 0.04 | 0.29 | <0.01 | 0.12 | 0.98 | 0.02 | 0.06 | 0.77 |
| Social Support W1 | | | | | | | | | | | | |
| Depression W1 | 0.42 | 0.12 | <0.01 | 0.43 | 0.04 | <0.01 | 0.41 | 0.12 | <0.01 | 0.46 | 0.04 | <0.01 |
| BMI W1 | -0.21 | 0.09 | 0.02 | -0.14 | 0.04 | <0.01 | -0.24 | 0.09 | 0.01 | -0.17 | 0.05 | <0.01 |
| Age | 0.11 | 0.10 | 0.30 | -0.04 | 0.03 | 0.21 | 0.13 | 0.11 | 0.23 | -0.05 | 0.03 | 0.10 |
| Non-white | -0.29 | 0.08 | <0.01 | -0.16 | 0.03 | <0.01 | -0.31 | 0.08 | <0.01 | -0.18 | 0.04 | <0.01 |
| Female | -0.21 | 0.09 | 0.01 | -0.12 | 0.03 | <0.01 | -0.20 | 0.09 | 0.03 | -0.12 | 0.04 | <0.01 |
| Less high school education | -0.07 | 0.10 | 0.50 | <0.01 | 0.04 | 0.99 | -0.08 | 0.10 | 0.39 | -0.03 | 0.04 | 0.46 |
| Not married | -0.16 | 0.10 | 0.11 | -0.02 | 0.03 | 0.48 | -0.18 | 0.10 | 0.07 | -0.03 | 0.03 | 0.18 |
| Number of comorbidities | -0.07 | 0.11 | 0.53 | -0.18 | 0.04 | <0.01 | -0.06 | 0.12 | 0.65 | -0.16 | 0.05 | <0.01 |
| Sedentary | -0.14 | 0.10 | 0.19 | -0.03 | 0.03 | 0.35 | -0.21 | 0.12 | 0.09 | -0.02 | 0.03 | 0.61 |
| Some exercise | 0.16 | 0.10 | 0.09 | 0.04 | 0.03 | 0.24 | 0.20 | 0.10 | 0.05 | 0.04 | 0.03 | 0.27 |
| Smoker | 0.03 | 0.11 | 0.74 | -0.04 | 0.03 | 0.28 | 0.04 | 0.11 | 0.70 | -0.06 | 0.03 | 0.08 |
| Functional Impairment | 0.13 | 0.10 | 0.20 | -0.02 | 0.03 | 0.48 | 0.19 | 0.11 | 0.07 | 0.02 | 0.03 | 0.66 |
| CRP W2 | 0.18 | 0.10 | 0.07 | 0.04 | 0.04 | 0.28 | 0.20 | 0.12 | 0.08 | 0.10 | 0.05 | 0.04 |
| CRP W1 | | | | | | | | | | | | |
| Social Support W1 | 0.58 | 0.08 | <0.01 | 0.53 | 0.05 | <0.01 | 0.49 | 0.12 | <0.01 | 0.51 | 0.07 | <0.01 |
| Social Support W2 | 0.02 | 0.09 | 0.84 | -0.02 | 0.04 | 0.64 | <0.01 | 0.08 | 0.96 | -0.01 | 0.04 | 0.75 |

| | No Complex Survey Design | | | | | | Complex Survey Design | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cancer Survivors | | | Older adults | | | Cancer Survivors | | | Older adults | | |
| | Estimate | SE | p-value | Estimate | SE | p-value | Estimate | SE | p-value | Estimate | SE | p-value |
| Depression W1 | -0.07 | 0.10 | 0.48 | -0.03 | 0.04 | 0.54 | -0.11 | 0.10 | 0.28 | -0.10 | 0.06 | 0.09 |
| Age | -0.08 | 0.09 | 0.35 | 0.07 | 0.04 | 0.09 | -0.15 | 0.10 | 0.15 | 0.01 | 0.05 | 0.77 |
| Number of comorbidities | -0.12 | 0.10 | 0.25 | -0.01 | 0.04 | 0.81 | -0.24 | 0.12 | 0.04 | -0.01 | 0.04 | 0.81 |
| TNF-α | -0.12 | 0.09 | 0.17 | 0.03 | 0.04 | 0.47 | -0.05 | 0.13 | 0.68 | 0.02 | 0.04 | 0.62 |
| Social Support W1 | | | | | | | | | | | | |
| Social Support W2 | 0.02 | 0.11 | 0.87 | -0.04 | 0.05 | 0.42 | 0.05 | 0.12 | 0.67 | -0.02 | 0.05 | 0.64 |
| Depression W1 | 0.12 | 0.12 | 0.28 | 0.03 | 0.05 | 0.62 | 0.12 | 0.10 | 0.23 | 0.02 | 0.06 | 0.81 |
| Age | 0.14 | 0.10 | 0.18 | 0.03 | 0.04 | 0.39 | 0.27 | 0.14 | 0.06 | 0.07 | 0.04 | 0.13 |
| Number of comorbidities | 0.09 | 0.11 | 0.40 | 0.09 | 0.04 | 0.03 | -0.01 | 0.09 | 0.91 | 0.05 | 0.05 | 0.32 |
| VEGF | 0.09 | 0.12 | 0.46 | 0.17 | 0.04 | <0.01 | 0.12 | 0.15 | 0.39 | 0.19 | 0.04 | <0.01 |
| Social Support W1 | | | | | | | | | | | | |
| Social Support W2 | -0.08 | 0.12 | 0.52 | -0.10 | 0.05 | 0.04 | -0.13 | 0.11 | 0.26 | -0.09 | 0.07 | 0.16 |
| Depression W1 | -0.08 | 0.13 | 0.53 | 0.01 | 0.05 | 0.78 | -0.07 | 0.13 | 0.59 | 0.03 | 0.06 | 0.63 |
| Age | -0.19 | 0.13 | 0.15 | -0.11 | 0.05 | 0.03 | -0.29 | 0.14 | 0.04 | -0.06 | 0.04 | 0.17 |
| Number of comorbidities | -0.13 | 0.13 | 0.30 | 0.07 | 0.04 | 0.13 | -0.19 | 0.14 | 0.18 | 0.05 | 0.04 | 0.17 |
| Depression W2 | 0.06 | 0.11 | 0.58 | 0.08 | 0.04 | 0.06 | 0.14 | 0.12 | 0.25 | 0.08 | 0.04 | 0.03 |
| CRP W2 | | | | | | | | | | | | |
| TNF-α | <0.01 | 0.10 | 0.99 | 0.03 | 0.04 | 0.52 | 0.02 | 0.08 | 0.83 | 0.02 | 0.04 | 0.64 |
| VEGF | 0.18 | 0.08 | 0.02 | 0.04 | 0.04 | 0.33 | 0.23 | 0.08 | <0.01 | 0.02 | 0.05 | 0.73 |
| CRP W1 | -0.14 | 0.09 | 0.12 | -0.03 | 0.03 | 0.45 | -0.12 | 0.09 | 0.18 | <0.01 | 0.04 | 0.91 |
| Social Support W1 | -0.04 | 0.13 | 0.76 | 0.03 | 0.05 | 0.61 | 0.01 | 0.11 | 0.91 | 0.09 | 0.06 | 0.18 |
| Social Support W2 | -0.32 | 0.11 | <0.01 | -0.04 | 0.04 | 0.41 | -0.33 | 0.11 | <0.01 | 0.02 | 0.04 | 0.64 |
| Depression W1 | -0.11 | 0.13 | 0.42 | -0.12 | 0.04 | <0.01 | -0.07 | 0.13 | 0.59 | -0.11 | 0.05 | 0.02 |
| BMI W1 | 0.05 | 0.13 | 0.69 | 0.53 | 0.04 | <0.01 | 0.01 | 0.14 | 0.92 | 0.54 | 0.05 | <0.01 |

| | No Complex Survey Design | | | | | | Complex Survey Design | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cancer Survivors | | | Older adults | | | Cancer Survivors | | | Older adults | | |
| | Estimate | SE | p-value | Estimate | SE | p-value | Estimate | SE | p-value | Estimate | SE | p-value |
| Age | -0.20 | 0.11 | 0.06 | -0.04 | 0.03 | 0.28 | -0.29 | 0.09 | <0.01 | -0.04 | 0.04 | 0.26 |
| Non-white | -0.22 | 0.10 | 0.03 | 0.05 | 0.04 | 0.19 | -0.19 | 0.10 | 0.06 | 0.04 | 0.04 | 0.29 |
| Female | -0.19 | 0.08 | 0.01 | -0.02 | 0.04 | 0.67 | -0.16 | 0.08 | 0.06 | -0.03 | 0.04 | 0.49 |
| Less high school education | 0.04 | 0.09 | 0.65 | 0.02 | 0.04 | 0.57 | 0.06 | 0.09 | 0.49 | 0.02 | 0.04 | 0.62 |
| Not married | -0.05 | 0.10 | 0.59 | 0.02 | 0.04 | 0.50 | 0.01 | 0.11 | 0.94 | 0.01 | 0.04 | 0.73 |
| Number of comorbidities | -0.21 | 0.11 | 0.06 | -0.07 | 0.04 | 0.12 | -0.22 | 0.10 | 0.04 | -0.06 | 0.04 | 0.19 |
| Sedentary | 0.32 | 0.11 | <0.01 | 0.07 | 0.04 | 0.10 | 0.30 | 0.09 | <0.01 | 0.11 | 0.04 | 0.01 |
| Some exercise | -0.03 | 0.12 | 0.77 | 0.05 | 0.04 | 0.25 | 0.01 | 0.11 | 0.90 | 0.04 | 0.05 | 0.45 |
| Smoker | 0.03 | 0.11 | 0.82 | -0.01 | 0.03 | 0.77 | 0.03 | 0.08 | 0.71 | -0.01 | 0.03 | 0.69 |
| Functional Impairment | -0.02 | 0.12 | 0.87 | 0.01 | 0.04 | 0.86 | -0.05 | 0.12 | 0.65 | <0.01 | 0.04 | 0.99 |
| Covariances | 0.26 | 0.13 | 0.04 | -0.05 | 0.04 | 0.28 | 0.30 | 0.12 | 0.01 | -0.06 | 0.05 | 0.29 |
| VEGF with CRP W2 | | | | | | | | | | | | |
| VEGF with TNF-α | 0.07 | 0.12 | 0.56 | 0.05 | 0.04 | 0.27 | 0.08 | 0.13 | 0.51 | 0.07 | 0.05 | 0.12 |
| CRP W2 with TNF-α | 0.18 | 0.11 | 0.09 | 0.20 | 0.05 | <0.01 | 0.04 | 0.13 | 0.76 | 0.21 | 0.05 | <0.01 |

Appendix C. Sensitivity analysis for participants with only CRP data compared to participants who had data on all three biomeasures available

| | All CRP data included | | Participants with data on all 3 biomarkers | |
|---|---|---|---|---|
| | CRP (n=1263) | | CRP (n=757) | |
| | Cancer Survivors (n=175) | Older Adults (n=1088) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β) [a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Network Turnover | | | | |
| Lost Ties (Ref. lost 0 alters) | | | | |
| Lost 1 alter | 1.02( 0.74, 1.40) | 1.06( 0.96, 1.16) | 1.30( 0.84, 2.02) | 1.02( 0.92, 1.12) |
| Lost 2 alters | 1.14( 0.76, 1.69) | 0.99( 0.88, 1.11) | 1.30( 0.81, 2.08) | 0.93( 0.81, 1.08) |
| Lost 3 or more alters | 1.22( 0.86, 1.74) | 1.01( 0.86, 1.17) | 1.20( 0.74, 1.94) | 0.94( 0.77, 1.14) |
| Added Ties (Ref. add 0 alters) | | | | |
| Add 1 alter | 1.05( 0.83, 1.32) | 1.06( 0.96, 1.18) | 0.92( 0.68, 1.24) | 1.13( 1.01, 1.27) |
| Add 2 alters | 0.83( 0.62, 1.12) | 1.01( 0.91, 1.12) | **0.74( 0.56, 0.98)** | 0.98( 0.86, 1.13) |
| Add 3 or more alters | 0.81( 0.61, 1.08) | 1.01( 0.88, 1.16) | 0.78( 0.54, 1.12) | 1.06( 0.87, 1.29) |
| Change in closeness | 0.93( 0.81, 1.06) | 1.00( 0.96, 1.05) | 0.91( 0.79, 1.04) | 1.01( 0.95, 1.07) |
| Change in frequency of contact | 1.01( 0.87, 1.17) | 1.02( 0.98, 1.08) | 0.97( 0.85, 1.11) | 1.05( 0.99, 1.11) |
| Change in density | 0.85( 0.69, 1.03) | 0.96( 0.86, 1.08) | 0.84( 0.66, 1.07) | 0.98( 0.87, 1.12) |
| Change in social support | | | | |
| Support from spouse | 1.02( 0.92, 1.13) | 1.00( 0.97, 1.03) | **1.19( 1.09, 1.30)** | 1.01( 0.98, 1.05) |
| Support from family | 1.00( 0.93, 1.08) | 1.02( 0.99, 1.05) | 0.96( 0.90, 1.03) | 1.01( 0.98, 1.04) |
| Support from friends | 1.00( 0.94, 1.07) | 0.98( 0.96, 1.01) | 0.98( 0.93, 1.03) | 0.98( 0.95, 1.02) |
| Age (Ref. 57-64) | | | | |

| | All CRP data included | | Participants with data on all 3 biomarkers | |
|---|---|---|---|---|
| | CRP (n=1263) | | CRP (n=757) | |
| | Cancer Survivors (n=175) | Older Adults (n=1088) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β) [a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| 65-74 | 0.86( 0.71, 1.03) | 1.00( 0.93, 1.07) | 0.98( 0.81, 1.19) | 1.01( 0.92, 1.11) |
| 75-85 | 0.88( 0.70, 1.10) | 0.99( 0.89, 1.09) | 0.95( 0.75, 1.19) | 1.05( 0.93, 1.18) |
| Gender (Ref. male) | | | | |
| Female | 1.07( 0.87, 1.32) | 1.05( 0.98, 1.12) | 1.20( 0.91, 1.59) | 1.08( 0.99, 1.17) |
| Race (Ref. white) | | | | |
| Non-white | 1.09( 0.91, 1.30) | 0.98( 0.89, 1.08) | 1.13( 0.85, 1.49) | 1.06( 0.95, 1.18) |
| Marital Status (Ref. married) | | | | |
| Not married in W1 | 0.99( 0.83, 1.18) | 1.04( 0.97, 1.12) | 1.09( 0.84, 1.41) | 0.99( 0.90, 1.10) |
| Education (Ref. some college or more) | | | | |
| High school education or less | 1.16( 0.99, 1.36) | 1.03( 0.97, 1.10) | 1.19( 0.96, 1.47) | 1.02( 0.95, 1.10) |
| Physical Activity (Ref. Frequent activity) | | | | |
| Low activity | **0.68( 0.50, 0.94)** | 1.03( 0.91, 1.16) | 0.83( 0.58, 1.18) | 0.94( 0.81, 1.09) |
| Moderate activity | **0.85( 0.72, 0.99)** | 1.01( 0.93, 1.09) | **0.75( 0.64, 0.88)** | 1.00( 0.88, 1.13) |
| BMI (Ref. Underweight/ Normal) | | | | |
| Overweight | 1.08( 0.87, 1.35) | **1.13( 1.02, 1.25)** | 1.23( 0.87, 1.72) | **1.14( 1.01, 1.29)** |
| Obese | 1.16( 0.93, 1.43) | **1.32( 1.20, 1.46)** | 1.10( 0.84, 1.45) | **1.30( 1.13, 1.50)** |
| No. comorbid conditions | 1.05( 0.98, 1.13) | 1.02( 0.99, 1.04) | 0.99( 0.90, 1.08) | 1.00( 0.97, 1.04) |

| | All CRP data included | | Participants with data on all 3 biomarkers | |
|---|---|---|---|---|
| | CRP (n=1263) | | CRP (n=757) | |
| | Cancer Survivors (n=175) | Older Adults (n=1088) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β) [a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Smoking status (Ref. nonsmoker) | | | | |
| Smoker | 1.10( 0.72, 1.69) | 1.02( 0.91, 1.15) | 1.02( 0.65, 1.59) | 0.98( 0.87, 1.10) |
| CRP W1 (Ref. < 3) | | | | |
| < 3 | **1.90( 1.40, 2.57)** | **1.77( 1.56, 2.00)** | **1.87( 1.33, 2.62)** | **1.77( 1.53, 2.04)** |
| 3-10 | **3.10( 2.29, 4.21)** | **2.49( 2.07, 3.00)** | **3.26( 2.21, 4.79)** | **2.23( 1.89, 2.64)** |
| Medication Use | 1.09( 0.87, 1.36) | 0.97( 0.90, 1.03) | 1.26( 0.94, 1.69) | 0.94( 0.86, 1.02) |
| Hypertension W1 | 0.98( 0.83, 1.16) | 0.93( 0.86, 1.00) | 0.99( 0.80, 1.22) | 0.94( 0.85, 1.04) |
| Hypertension W2 | 0.93( 0.79, 1.11) | **1.10( 1.01, 1.20)** | 0.92( 0.73, 1.14) | 1.09( 0.97, 1.23) |
| Cardiovascular Drugs W1 | 1.10( 0.91, 1.35) | 0.94( 0.85, 1.04) | 1.05( 0.81, 1.37) | 0.93( 0.82, 1.05) |
| Cardiovascular Drugs W2 | 1.02( 0.74, 1.40) | 1.06( 0.96, 1.16) | 1.30( 0.84, 2.02) | 1.02( 0.92, 1.12) |

*Bold indicates p<0.05

[a]Beta coefficients are exponentiated to transform results back to the original scale

[b]95% Confidence Interval

Appendix D. Sensitivity analysis for participants with only TNF-α data compared to participants who had data on all three biomeasures available

| | All TNF-α data included | | Participants with data on all 3 biomarkers | |
|---|---|---|---|---|
| | TNF-α (n=968) | | TNF-α (n=757) | |
| | Cancer Survivors (n=126) | Older Adults (n=842) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β) [a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Network Turnover | | | | |
| Lost Ties (Ref. lost 0 alters) | | | | |
| Lost 1 alter | 1.03( 0.69, 1.53) | 1.05( 0.92, 1.19) | 0.87( 0.60, 1.26) | 1.03( 0.89, 1.19) |
| Lost 2 alters | **1.57( 1.14, 2.15)** | 0.97( 0.84, 1.12) | 1.33( 0.95, 1.87) | 0.94( 0.81, 1.09) |
| Lost 3 or more alters | 0.94( 0.67, 1.32) | 0.97( 0.83, 1.13) | 0.78( 0.54, 1.11) | 0.91( 0.77, 1.08) |
| Added Ties (Ref. add 0 alters) | | | | |
| Add 1 alter | 1.21( 0.89, 1.63) | 1.03( 0.90, 1.19) | 1.30( 0.93, 1.82) | 0.99( 0.85, 1.15) |
| Add 2 alters | 1.02( 0.75, 1.39) | 1.04( 0.89, 1.23) | 1.03( 0.74, 1.43) | 1.04( 0.84, 1.28) |
| Add 3 or more alters | 1.18( 0.81, 1.70) | 1.11( 0.92, 1.33) | 1.28( 0.84, 1.93) | 1.15( 0.92, 1.43) |
| Change in closeness | 0.97( 0.82, 1.16) | 0.94( 0.85, 1.04) | 0.94( 0.74, 1.18) | 0.95( 0.84, 1.06) |
| Change in frequency of contact | **1.13( 1.06, 1.21)** | **1.06( 1.01, 1.12)** | **1.19( 1.08, 1.30)** | 1.06( 0.99, 1.13) |
| Change in density | 1.18( 0.97, 1.44) | 1.01( 0.91, 1.12) | 1.22( 0.95, 1.57) | 1.06( 0.94, 1.20) |
| Change in social support | | | | |
| Support from spouse | 0.95( 0.87, 1.04) | 0.98( 0.94, 1.03) | 0.92( 0.81, 1.05) | 0.98( 0.93, 1.03) |
| Support from family | 0.99( 0.91, 1.08) | 1.00( 0.97, 1.04) | 1.00( 0.93, 1.08) | 1.01( 0.97, 1.06) |
| Support from friends | 0.99( 0.93, 1.05) | 1.03( 1.00, 1.06) | 1.02( 0.96, 1.10) | 1.01( 0.98, 1.05) |

| | All TNF-α data included | | Participants with data on all 3 biomarkers | |
|---|---|---|---|---|
| | TNF-α (n=968) | | TNF-α (n=757) | |
| | Cancer Survivors (n=126) | Older Adults (n=842) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β) [a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Age (Ref. 57-64) | | | | |
| 65-74 | 0.99( 0.76, 1.28) | 1.06( 0.97, 1.15) | 0.84( 0.64, 1.10) | 1.03( 0.94, 1.14) |
| 75-85 | 1.07( 0.82, 1.40) | 1.12( 0.95, 1.30) | 0.99( 0.77, 1.27) | 1.11( 0.94, 1.31) |
| Gender (Ref. male) | | | | |
| Female | 0.89( 0.74, 1.07) | 0.96( 0.88, 1.05) | **0.83( 0.70, 0.99)** | 0.94( 0.85, 1.04) |
| Race (Ref. white) | | | | |
| Non-white | 0.96( 0.81, 1.14) | 0.96( 0.87, 1.06) | 0.93( 0.75, 1.15) | 0.96( 0.86, 1.07) |
| Marital Status (Ref. married) | | | | |
| Not married in W1 | 0.90( 0.78, 1.04) | 1.03( 0.94, 1.13) | 0.98( 0.82, 1.17) | 1.05( 0.94, 1.18) |
| Education (Ref. some college or more) | | | | |
| High school education or less | 0.91( 0.75, 1.11) | 1.00( 0.93, 1.08) | 0.85( 0.70, 1.04) | 1.03( 0.94, 1.14) |
| Physical Activity (Ref. Frequent activity) | | | | |
| Low activity | 1.25( 0.96, 1.63) | 0.99( 0.82, 1.19) | 1.20( 0.87, 1.67) | 1.00( 0.81, 1.24) |
| Moderate activity | 0.82( 0.66, 1.02) | 1.07( 0.95, 1.22) | 0.85( 0.68, 1.08) | 1.11( 0.97, 1.27) |
| BMI (Ref. Underweight/ Normal) | | | | |
| Overweight | **0.73( 0.59, 0.90)** | 1.08( 0.96, 1.21) | 0.78( 0.59, 1.03) | 1.04( 0.89, 1.21) |

| | All TNF-α data included | | Participants with data on all 3 biomarkers | |
|---|---|---|---|---|
| | TNF-α (n=968) | | TNF-α (n=757) | |
| | Cancer Survivors (n=126) | Older Adults (n=842) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β) [a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Obese | 0.93( 0.70, 1.24) | **1.18( 1.04, 1.34)** | 0.92( 0.68, 1.24) | 1.12( 0.94, 1.34) |
| No. comorbid conditions | 1.04( 0.98, 1.10) | **1.04( 1.02, 1.07)** | **1.06( 1.00, 1.12)** | **1.05( 1.02, 1.08)** |
| Smoking status (Ref. nonsmoker) | | | | |
| Smoker | 1.12( 0.81, 1.56) | **1.16( 1.01, 1.34)** | 1.13( 0.82, 1.56) | **1.18( 1.02, 1.36)** |
| Medication Use | 0.94( 0.74, 1.21) | 1.00( 0.90, 1.11) | 0.95( 0.69, 1.32) | 1.01( 0.90, 1.14) |
| Hypertension W1 | 1.00( 0.78, 1.28) | 0.99( 0.90, 1.10) | 0.99( 0.75, 1.31) | 1.02( 0.90, 1.17) |
| Hypertension W2 | 1.03( 0.81, 1.30) | 1.00( 0.87, 1.16) | 1.06( 0.83, 1.37) | 0.97( 0.81, 1.15) |
| Cardiovascular Drugs W1 | 0.93( 0.67, 1.29) | 1.06( 0.93, 1.20) | 0.98( 0.71, 1.35) | 1.06( 0.90, 1.24) |
| Cardiovascular Drugs W2 | 1.03( 0.69, 1.53) | 1.05( 0.92, 1.19) | 0.87( 0.60, 1.26) | 1.03( 0.89, 1.19) |

*Bold indicates $p<0.05$

[a]Beta coefficients are exponentiated to transform results back to the original scale

[b]95% Confidence Interval

Appendix E. Sensitivity analysis for participants with only VEGF data compared to participants who had data on all three biomeasures available

| | All VEGF data included | | Participants with data on all 3 biomarkers | |
|---|---|---|---|---|
| | VEGF (n=863) | | VEGF (n=757) | |
| | Cancer Survivors (n=127) | Older Adults (n=736) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β)[a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Network Turnover | | | | |
| Lost Ties (Ref. lost 0 alters) | | | | |
| Lost 1 alter | 1.03( 0.69, 1.53) | 1.05( 0.92, 1.19) | 0.99( 0.55, 1.79) | 1.09( 0.86, 1.37) |
| Lost 2 alters | **1.57( 1.14, 2.15)** | 0.97( 0.84, 1.12) | 1.09( 0.61, 1.96) | 1.01( 0.74, 1.39) |
| Lost 3 or more alters | 0.94( 0.67, 1.32) | 0.97( 0.83, 1.13) | 1.33( 0.70, 2.52) | 0.87( 0.61, 1.25) |
| Added Ties (Ref. add 0 alters) | | | | |
| Add 1 alter | 1.21( 0.89, 1.63) | 1.03( 0.90, 1.19) | 0.72( 0.41, 1.26) | 0.88( 0.71, 1.09) |
| Add 2 alters | 1.02( 0.75, 1.39) | 1.04( 0.89, 1.23) | 0.94( 0.56, 1.60) | 0.93( 0.72, 1.21) |
| Add 3 or more alters | 1.18( 0.81, 1.70) | 1.11( 0.92, 1.33) | 0.64( 0.32, 1.25) | 1.04( 0.77, 1.40) |
| Change in closeness | 0.97( 0.82, 1.16) | 0.94( 0.85, 1.04) | 1.06( 0.76, 1.46) | 0.92( 0.81, 1.04) |
| Change in frequency of contact | **1.13( 1.06, 1.21)** | **1.06( 1.01, 1.12)** | 1.04( 0.82, 1.31) | 1.07( 0.95, 1.21) |
| Change in density | 1.18( 0.97, 1.44) | 1.01( 0.91, 1.12) | 0.91( 0.60, 1.39) | 1.04( 0.82, 1.32) |
| Change in social support | | | | |
| Support from spouse | 0.95( 0.87, 1.04) | 0.98( 0.94, 1.03) | 0.95( 0.79, 1.15) | 1.08( 0.99, 1.17) |
| Support from family | 0.99( 0.91, 1.08) | 1.00( 0.97, 1.04) | 1.04( 0.93, 1.18) | 1.00( 0.95, 1.06) |
| Support from friends | 0.99( 0.93, 1.05) | 1.03( 1.00, 1.06) | 0.94( 0.86, 1.04) | 1.01( 0.94, 1.07) |
| Age (Ref. 57-64) | | | | |

| | All VEGF data included | | Participants with data on all 3 biomarkers | |
|---|---|---|---|---|
| | VEGF (n=863) | | VEGF (n=757) | |
| | Cancer Survivors (n=127) | Older Adults (n=736) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β)[a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| 65-74 | 0.99( 0.76, 1.28) | 1.06( 0.97, 1.15) | 0.74( 0.47, 1.17) | 1.02( 0.82, 1.26) |
| 75-85 | 1.07( 0.82, 1.40) | 1.12( 0.95, 1.30) | 0.63( 0.36, 1.09) | 1.10( 0.86, 1.42) |
| Gender (Ref. male) | | | | |
| Female | 0.89( 0.74, 1.07) | 0.96( 0.88, 1.05) | 1.35( 0.81, 2.23) | **1.19( 1.03, 1.37)** |
| Race (Ref. white) | | | | |
| Non-white | 0.96( 0.81, 1.14) | 0.96( 0.87, 1.06) | 0.99( 0.59, 1.66) | 0.93( 0.76, 1.13) |
| Marital Status (Ref. married) | | | | |
| Not married in W1 | 0.90( 0.78, 1.04) | 1.03( 0.94, 1.13) | 0.86( 0.52, 1.40) | 0.94( 0.78, 1.14) |
| Education (Ref. some college or more) | | | | |
| High school education or less | 0.91( 0.75, 1.11) | 1.00( 0.93, 1.08) | 0.99( 0.69, 1.42) | 0.96( 0.79, 1.18) |
| Physical Activity (Ref. Frequent activity) | | | | |
| Low activity | 1.25( 0.96, 1.63) | 0.99( 0.82, 1.19) | 0.73( 0.42, 1.26) | 1.02( 0.80, 1.29) |
| Moderate activity | 0.82( 0.66, 1.02) | 1.07( 0.95, 1.22) | **1.55( 1.17, 2.06)** | 1.02( 0.85, 1.23) |
| BMI (Ref. Underweight/ Normal) | | | | |
| Overweight | **0.73( 0.59, 0.90)** | 1.08( 0.96, 1.21) | 1.05( 0.65, 1.71) | 0.92( 0.75, 1.12) |
| Obese | 0.93( 0.70, 1.24) | **1.18( 1.04, 1.34)** | 0.76( 0.45, 1.27) | 1.11( 0.90, 1.37) |
| No. comorbid conditions | 1.04( 0.98, 1.10) | **1.04( 1.02, 1.07)** | 1.06( 0.93, 1.20) | 0.99( 0.92, 1.05) |

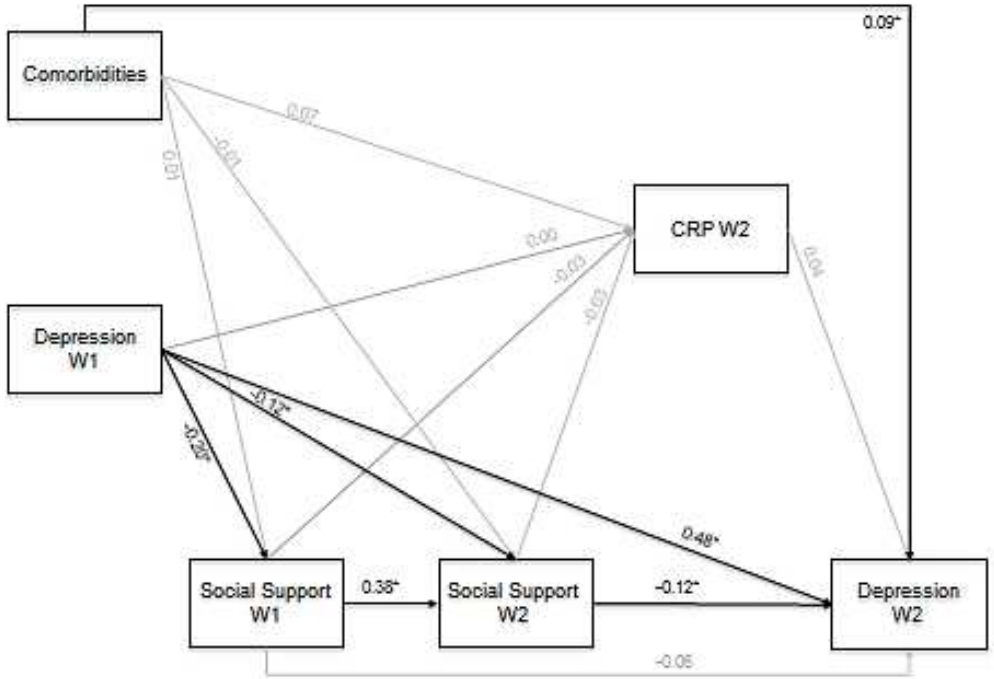
| | All VEGF data included | | Participants with data on all 3 biomarkers | |
|---|---|---|---|---|
| | VEGF (n=863) | | VEGF (n=757) | |
| | Cancer Survivors (n=127) | Older Adults (n=736) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β)[a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Smoking status (Ref. nonsmoker) | | | | |
| Smoker | 1.12( 0.81, 1.56) | **1.16( 1.01, 1.34)** | 1.08( 0.64, 1.84) | 1.15( 0.93, 1.43) |
| Medication Use | 0.94( 0.74, 1.21) | 1.00( 0.90, 1.11) | 0.87( 0.59, 1.30) | 1.11( 0.85, 1.45) |
| Hypertension W1 | 1.00( 0.78, 1.28) | 0.99( 0.90, 1.10) | 0.76( 0.48, 1.18) | 0.97( 0.79, 1.17) |
| Hypertension W2 | 1.03( 0.81, 1.30) | 1.00( 0.87, 1.16) | **2.16( 1.51, 3.09)** | 0.97( 0.77, 1.23) |
| Cardiovascular Drugs W1 | 0.93( 0.67, 1.29) | 1.06( 0.93, 1.20) | 0.69( 0.46, 1.04) | 1.08( 0.84, 1.38) |
| Cardiovascular Drugs W2 | 1.03( 0.69, 1.53) | 1.05( 0.92, 1.19) | 0.99( 0.55, 1.79) | 1.09( 0.86, 1.37) |

*Bold indicates $p<0.05$

[a]Beta coefficients are exponentiated to transform results back to the original scale

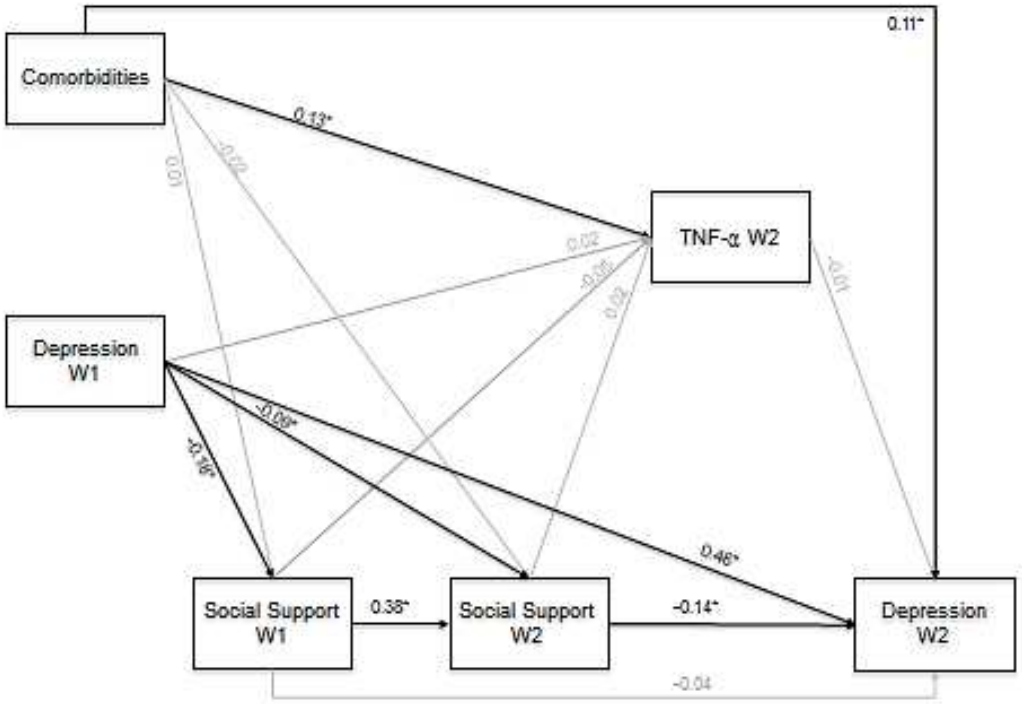
[b]95% Confidence Interval

Appendix F. Results using the full CRP W2 sample (n=1135)



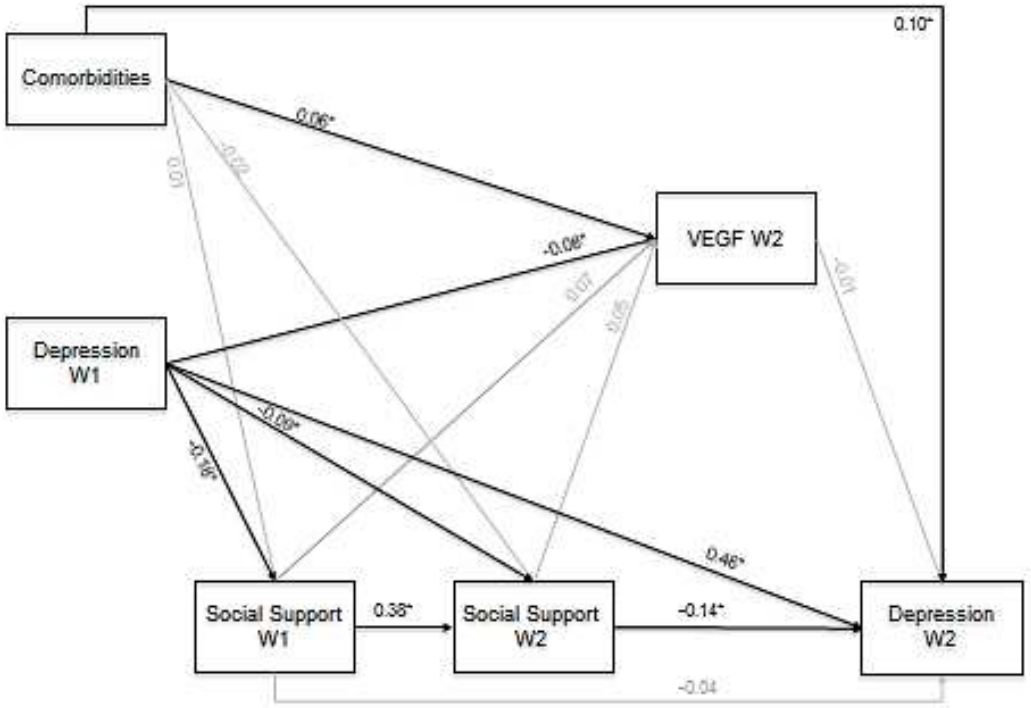

Controlling for BMI, CRP, age, race, gender, education level, marital status, smoking status, physical activity, and functional impairment in Wave 1. Estimates are standardized. Covariances and residuals are not depicted for simplicity.
*denotes $p<0.05$

Appendix G. Results using the full TNF-α W2 sample (n=1260)




Controlling for BMI, age, race, gender, education level, marital status, smoking status, physical activity, and functional impairment in Wave 1. Estimates are standardized. Covariances and residuals are not depicted for simplicity.
*denotes $p<0.05$

Appendix H. Results using the full VEGF W2 sample (n=1103)




Controlling for BMI, age, race, gender, education level, marital status, smoking status, physical activity, and functional impairment in Wave 1. Estimates are standardized. Covariances and residuals are not depicted for simplicity.
*denotes $p<0.05$

Appendix I. Sensitivity analysis comparing participants with missing data on at least one biomarker to those with complete biomarker data

| | Missing biomarker data (n=1226) | | Complete biomarker data (n=727) | | |
|---|---|---|---|---|---|
| | N | % | N | % | p-value |
| Cancer survivor status | | | | | |
| Older adults | 1079 | 88.2 | 636 | 86.7 | 0.34 |
| Cancer Survivor | 147 | 11.8 | 91 | 13.3 | |
| Age (Mean, SE[a]) | 66.9 | 0.3 | 67.1 | 0.3 | 0.46 |
| Gender | | | | | |
| Male | 604 | 48.6 | 323 | 45.5 | 0.28 |
| Female | 622 | 51.4 | 404 | 54.5 | |
| Race | | | | | |
| White | 841 | 79.6 | 546 | 84.8 | **<0.01** |
| Non white | 379 | 20.4 | 179 | 15.2 | |
| Education | | | | | |
| High school education or less | 681 | 59.7 | 406 | 59.1 | 0.83 |
| Some college or more | 545 | 40.3 | 321 | 40.9 | |
| Marital Status | | | | | |
| Married/Cohabitating Partner | 808 | 72.0 | 469 | 70.8 | 0.66 |
| Not married | 418 | 28.0 | 258 | 29.2 | |
| Smoking | | | | | |
| Nonsmoker | 1070 | 88.8 | 619 | 83.5 | **0.01** |
| Smoker | 155 | 11.2 | 108 | 16.5 | |
| Comorbidity Index (Mean, SE) | 1.9 | 0.0 | 1.9 | 0.1 | 0.50 |

| | | | | | |
|---|---|---|---|---|---|
| BMI (Mean, SE) | 29.3 | 0.3 | 29.0 | 0.2 | 0.55 |
| Physical Activity | | | | | |
| Low activity | 792 | 64.4 | 504 | 71.1 | **<0.01** |
| Moderate activity | 147 | 11.2 | 92 | 11.5 | |
| Frequent activity | 284 | 24.4 | 130 | 17.5 | |
| Functional Impairment | | | | | |
| No Impairment | 831 | 70.6 | 533 | 75.6 | **<0.01** |
| At least one impairment | 395 | 29.4 | 194 | 24.4 | |
| Depression Wave 2 (Mean, SE) | 4.8 | 0.4 | 4.8 | 0.2 | 0.72 |
| Depression Wave 1 (Mean, SE) | 5.2 | 0.4 | 4.8 | 0.1 | 0.60 |
| Social Support W2 (Mean, SE) | 7.5 | 0.1 | 7.4 | 0.1 | 0.63 |
| Social Support W1 (Mean, SE) | 7.6 | 0.1 | 7.7 | 0.1 | 0.60 |
| Inflammatory Markers[b] | Median | IQR[c] | Median | IQR | p-value |
| TNF-α (pg/mL) | 10.1 | 7.40-14.38 | 11.4 | 8.02-15.53 | **0.02** |
| VEGF (pg/mL) | 178.1 | 113.4-289.1 | 167.3 | 104.1-281.0 | 0.20 |
| CRP mg/L (W2) | 1.7 | 0.86- 3.30 | 1.8 | 0.92- 3.35 | 0.29 |
| CRP mg/L (W1) | 1.3 | 0.54- 2.72 | 1.3 | 0.57- 2.99 | 0.56 |

*Bold indicates $p<0.05$

[a]Standard Error

[b]Inflammatory markers are log transformed

[c]Interquartile range is defined as the $25^{th}$-$75^{th}$ percentiles

Appendix J. Sensitivity analysis comparing participants with missing data on at least one biomarker to those with complete biomarker data by cancer status

| | Cancer Survivor | | | | | Older Adults | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Missing biomarker data (n=156) | | Complete biomarker data (n=82) | | p-value | Missing biomarker data (n=1136) | | Complete biomarker data (n=579) | | p-value |
| | N | % | N | % | | N | % | N | % | |
| Age (Mean, SE[a]) | 69.3 | 0.6 | 69.0 | 0.7 | 0.81 | 66.7 | 0.3 | 66.6 | 0.4 | 0.95 |
| Gender | | | | | | | | | | |
| Male | 73 | 47.1 | 34 | 43.4 | 0.61 | 556 | 48.3 | 264 | 46.5 | 0.53 |
| Female | 83 | 52.9 | 48 | 56.6 | | 580 | 51.7 | 315 | 53.5 | |
| Race | | | | | | | | | | |
| White | 127 | 90.5 | 70 | 88.5 | 0.69 | 756 | 78.1 | 434 | 84.9 | **0.00** |
| Non white | 28 | 9.5 | 12 | 11.5 | | 373 | 21.9 | 145 | 15.1 | |
| Education | | | | | | | | | | |
| High school education or less | 99 | 63.4 | 52 | 63.7 | 0.97 | 611 | 58.6 | 325 | 59.5 | 0.75 |
| Some college or more | 57 | 36.6 | 30 | 36.3 | | 525 | 41.4 | 254 | 40.5 | |
| Marital Status | | | | | | | | | | |
| Married/Cohabitating Partner | 99 | 69.8 | 50 | 64.5 | 0.42 | 744 | 71.7 | 384 | 72.8 | 0.70 |
| Not married | 57 | 30.2 | 32 | 35.5 | | 392 | 28.3 | 195 | 27.2 | |
| Smoking | | | | | | | | | | |
| Nonsmoker | 143 | 92.4 | 70 | 83.3 | **0.03** | 985 | 88.1 | 491 | 83.6 | **0.05** |
| Smoker | 13 | 7.6 | 12 | 16.7 | | 150 | 11.9 | 88 | 16.4 | |
| Comorbidity Index (Mean, SE) | 2.1 | 0.1 | 2.1 | 0.2 | 0.86 | 1.9 | 0.1 | 1.9 | 0.1 | 0.51 |
| BMI (Mean, SE) | 29.6 | 0.8 | 28.1 | 0.5 | 0.10 | 29.3 | 0.2 | 29.1 | 0.2 | 0.77 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Physical Activity | | | | | | | | | | |
| Low activity | 87 | 55.7 | 58 | 69.9 | 0.17 | 746 | 65.8 | 405 | 71.4 | 0.12 |
| Moderate activity | 19 | 10.3 | 7 | 9.3 | | 143 | 11.7 | 70 | 11.2 | |
| Frequent activity | 50 | 33.9 | 17 | 20.8 | | 243 | 22.5 | 104 | 17.4 | |
| Functional Impairment | | | | | | | | | | |
| No Impairment | 99 | 67.0 | 60 | 75.6 | 0.17 | 769 | 70.7 | 436 | 76.8 | **0.01** |
| At least one impairment | 57 | 33.0 | 22 | 24.4 | | 367 | 29.3 | 143 | 23.2 | |
| Depression Wave 2 (Mean, SE) | 4.9 | 0.5 | 4.7 | 0.6 | 0.82 | 5.1 | 0.2 | 4.8 | 0.2 | 0.26 |
| Depression Wave 1 (Mean, SE) | 5.4 | 0.5 | 5.2 | 0.7 | 0.83 | 5.0 | 0.2 | 4.7 | 0.2 | 0.25 |
| Social Support W2 (Mean, SE) | 7.4 | 0.2 | 7.6 | 0.3 | 0.54 | 7.5 | 0.1 | 7.8 | 0.1 | 0.84 |
| Social Support W1 (Mean, SE) | 7.5 | 0.3 | 7.3 | 0.3 | 0.68 | 7.4 | 0.1 | 7.5 | 0.2 | 0.17 |
| Inflammatory Markers[b] | Median | IQR[c] | Median | IQR | p-value | Median | IQR[c] | Median | IQR | p-value |
| TNF-α (pg/mL) | 10.7 | 7.1-13.4 | 11.8 | 8.1-18.7 | **<0.01** | 10 | 7.4-15.6 | 11.3 | 8.0-15.1 | **0.03** |
| VEGF (pg/mL) | 171.1 | 134.9-278.9 | 160.7 | 102.0-303.0 | 0.29 | 180.9 | 106.9-291.6 | 167.8 | 104.2-274.2 | 0.38 |
| CRP mg/L (W2) | 1.9 | 1.2-3.9 | 1.8 | 1.0-4.0 | 0.72 | 1.7 | 0.9-3.3 | 1.8 | 0.9-3.2 | 0.77 |
| CRP mg/L (W1) | 2.2 | 0.6-4.1 | 1.0 | 0.5-2.1 | **<0.01** | 1.2 | 0.5-2.7 | 1.3 | 0.6-3.1 | 0.41 |

Bold indicates $p<0.05$

Appendix K. Lagged logistic regression predicting functional impairment and adjusting for prognostic factors among cancer survivors

| | OR[a] (95% CI)[b] |
|---|---|
| Age at diagnosis | 0.99( 0.83- 1.17) |
| Duration of Survival | 1.04( 0.88- 1.23) |
| Primary cancer site (Ref. breast cancer) | |
| Leukemia/Lymphoma | 0.76( 0.07- 8.74) |
| Colon | 0.76( 0.16- 3.53) |
| Prostate | 1.37( 0.17-10.78) |
| Gynecologic | **0.04( 0.00- 0.39)** |

*Bold indicates $p<0.05$

[a]Odds Ratio

[b]95% Confidence Interval

[c]Models adjusted for the number of lost alters, number of added alters, change in closeness, change in frequency of talking, change in density, age, BMI, gender, education, marital status, smoking, number of comorbidities, functional impairment in W1, network size in W1

Appendix L. Reasons alters were "lost" over time

| | Overall | | | | Cancer Survivor | | | | Cancer-free older adults | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Impairment | | No Impairment | | Impairment | | No Impairment | | Impairment | | No Impairment | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Respondent Moved | 60 | 5.1 | 132 | 5.2 | 4 | 2.4 | 14 | 4.7 | 56 | 5.5 | 118 | 5.3 |
| Alter moved | 180 | 15.3 | 392 | 15.4 | 28 | 16.6 | 46 | 15.3 | 152 | 15.0 | 346 | 15.5 |
| Respondent became ill or had a health problem | 17 | 1.4 | 20 | 0.8 | 1 | 0.6 | 3 | 1.0 | 16 | 1.6 | 17 | 0.8 |
| Alter became ill or had a health problem | 77 | 6.5 | 105 | 4.1 | 12 | 7.1 | 19 | 6.3 | 65 | 6.4 | 86 | 3.8 |
| Alter died | 233 | 19.7 | 465 | 18.3 | 35 | 20.7 | 58 | 19.3 | 198 | 19.6 | 407 | 18.2 |
| Other reason | 613 | 51.9 | 1426 | 56.1 | 89 | 52.7 | 161 | 53.5 | 524 | 51.8 | 1265 | 56.5 |

Appendix M. Results from full model presenting the associations for all covariates between social network change and inflammation among cancer survivors and older adults without cancer (n=757)

| | CRP | | TNF-α | | VEGF | |
|---|---|---|---|---|---|---|
| | Cancer Survivors (n=105) | Older Adults (n=652) | Cancer Survivors (n=105) | Older Adults (n=652) | Cancer Survivors (n=105) | Older Adults (n=652) |
| | Exp(β)[a] (95% CI)[b] | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) | Exp(β) (95% CI) |
| Network Turnover | | | | | | |
| Lost Ties (Ref. lost 0 alters) | | | | | | |
| Lost 1 alter | 1.30( 0.84, 2.02) | 1.02( 0.92, 1.12) | 0.87( 0.60, 1.26) | 1.03( 0.89, 1.19) | 0.99( 0.55, 1.79) | 1.09( 0.86, 1.37) |
| Lost 2 alters | 1.30( 0.81, 2.08) | 0.93( 0.81, 1.08) | 1.33( 0.95, 1.87) | 0.94( 0.81, 1.09) | 1.09( 0.61, 1.96) | 1.01( 0.74, 1.39) |
| Lost 3 or more alters | 1.20( 0.74, 1.94) | 0.94( 0.77, 1.14) | 0.78( 0.54, 1.11) | 0.91( 0.77, 1.08) | 1.33( 0.70, 2.52) | 0.87( 0.61, 1.25) |
| Added Ties (Ref. add 0 alters) | | | | | | |
| Add 1 alter | 0.92( 0.68, 1.24) | 1.13( 1.01, 1.27) | 1.30( 0.93, 1.82) | 0.99( 0.85, 1.15) | 0.72( 0.41, 1.26) | 0.88( 0.71, 1.09) |
| Add 2 alters | **0.74( 0.56, 0.98)** | 0.98( 0.86, 1.13) | 1.03( 0.74, 1.43) | 1.04( 0.84, 1.28) | 0.94( 0.56, 1.60) | 0.93( 0.72, 1.21) |
| Add 3 or more alters | 0.78( 0.54, 1.12) | 1.06( 0.87, 1.29) | 1.28( 0.84, 1.93) | 1.15( 0.92, 1.43) | 0.64( 0.32, 1.25) | 1.04( 0.77, 1.40) |
| Change in closeness | 0.91( 0.79, 1.04) | 1.01( 0.95, 1.07) | 0.94( 0.74, 1.18) | 0.95( 0.84, 1.06) | 1.06( 0.76, 1.46) | 0.92( 0.81, 1.04) |
| Change in frequency of contact | 0.97( 0.85, 1.11) | 1.05( 0.99, 1.11) | **1.19( 1.08, 1.30)** | 1.06( 0.99, 1.13) | 1.04( 0.82, 1.31) | 1.07( 0.95, 1.21) |
| Change in density | 0.84( 0.66, 1.07) | 0.98( 0.87, 1.12) | 1.22( 0.95, 1.57) | 1.06( 0.94, 1.20) | 0.91( 0.60, 1.39) | 1.04( 0.82, 1.32) |
| Change in social support | | | | | | |
| Support from spouse | **1.19( 1.09, 1.30)** | 1.01( 0.98, 1.05) | 0.92( 0.81, 1.05) | 0.98( 0.93, 1.03) | 0.95( 0.79, 1.15) | 1.08( 0.99, 1.17) |
| Support from family | 0.96( 0.90, 1.03) | 1.01( 0.98, 1.04) | 1.00( 0.93, 1.08) | 1.01( 0.97, 1.06) | 1.04( 0.93, 1.18) | 1.00( 0.95, 1.06) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Support from friends | 0.98( 0.93, 1.03) | 0.98( 0.95, 1.02) | 1.02( 0.96, 1.10) | 1.01( 0.98, 1.05) | 0.94( 0.86, 1.04) | 1.01( 0.94, 1.07) |
| Age (Ref 57-64) | | | | | | |
| 65-74 | 0.98( 0.81, 1.19) | 1.01( 0.92, 1.11) | 0.84( 0.64, 1.10) | 1.03( 0.94, 1.14) | 0.74( 0.47, 1.17) | 1.02( 0.82, 1.26) |
| 75-85 | 0.95( 0.75, 1.19) | 1.05( 0.93, 1.18) | 0.99( 0.77, 1.27) | 1.11( 0.94, 1.31) | 0.63( 0.36, 1.09) | 1.10( 0.86, 1.42) |
| Gender (Ref. male) | | | | | | |
| Female | 1.20( 0.91, 1.59) | 1.08( 0.99, 1.17) | **0.83( 0.70, 0.99)** | 0.94( 0.85, 1.04) | 1.35( 0.81, 2.23) | **1.19( 1.03, 1.37)** |
| Race (Ref. white) | | | | | | |
| Non-white | 1.13( 0.85, 1.49) | 1.06( 0.95, 1.18) | 0.93( 0.75, 1.15) | 0.96( 0.86, 1.07) | 0.99( 0.59, 1.66) | 0.93( 0.76, 1.13) |
| Marital Status (Ref. married) | | | | | | |
| Not married in W1 | 1.09( 0.84, 1.41) | 0.99( 0.90, 1.10) | 0.98( 0.82, 1.17) | 1.05( 0.94, 1.18) | 0.86( 0.52, 1.40) | 0.94( 0.78, 1.14) |
| Education (Ref. some college or more) | | | | | | |
| High school education or less | 1.19( 0.96, 1.47) | 1.02( 0.95, 1.10) | 0.85( 0.70, 1.04) | 1.03( 0.94, 1.14) | 0.99( 0.69, 1.42) | 0.96( 0.79, 1.18) |
| Physical Activity (Ref. frequent activity) | | | | | | |
| Low activity | 0.83( 0.58, 1.18) | 0.94( 0.81, 1.09) | 1.20( 0.87, 1.67) | 1.00( 0.81, 1.24) | 0.73( 0.42, 1.26) | 1.02( 0.80, 1.29) |
| Moderate activity | **0.75( 0.64, 0.88)** | 1.00( 0.88, 1.13) | 0.85( 0.68, 1.08) | 1.11( 0.97, 1.27) | **1.55( 1.17, 2.06)** | 1.02( 0.85, 1.23) |
| BMI (Ref. Underweight/ Normal) | | | | | | |
| Overweight | 1.23( 0.87, 1.72) | **1.14( 1.01, 1.29)** | 0.78( 0.59, 1.03) | 1.04( 0.89, 1.21) | 1.05( 0.65, 1.71) | 0.92( 0.75, 1.12) |
| Obese | 1.10( 0.84, 1.45) | **1.30( 1.13, 1.50)** | 0.92( 0.68, 1.24) | 1.12( 0.94, 1.34) | 0.76( 0.45, 1.27) | 1.11( 0.90, 1.37) |
| No. comorbid conditions | 0.99( 0.90, 1.08) | 1.00( 0.97, 1.04) | **1.06( 1.00, 1.12)** | **1.05( 1.02, 1.08)** | 1.06( 0.93, 1.20) | 0.99( 0.92, 1.05) |
| Smoking status (Ref. nonsmoker) | | | | | | |
| Smoker | 1.02( 0.65, 1.59) | 0.98( 0.87, 1.10) | 1.13( 0.82, 1.56) | **1.18( 1.02, 1.36)** | 1.08( 0.64, 1.84) | 1.15( 0.93, 1.43) |
| CRP W1 (Ref. < 3) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| < 3 | **1.87( 1.33, 2.62)** | **1.77( 1.53, 2.04)** | - | - | **-** | **-** |
| 3-10 | **3.26( 2.21, 4.79)** | **2.23( 1.89, 2.64)** | - | - | **-** | - |
| Medication Use | | | | | | |
| Hypertension W1 | 1.26( 0.94, 1.69) | 0.94( 0.86, 1.02) | 0.95( 0.69, 1.32) | 1.01( 0.90, 1.14) | 0.87( 0.59, 1.30) | 1.11( 0.85, 1.45) |
| Hypertension W2 | 0.99( 0.80, 1.22) | 0.94( 0.85, 1.04) | 0.99( 0.75, 1.31) | 1.02( 0.90, 1.17) | 0.76( 0.48, 1.18) | 0.97( 0.79, 1.17) |
| Cardiovascular Drugs W1 | 0.92( 0.73, 1.14) | 1.09( 0.97, 1.23) | 1.06( 0.83, 1.37) | 0.97( 0.81, 1.15) | **2.16( 1.51, 3.09)** | 0.97( 0.77, 1.23) |
| Cardiovascular Drugs W2 | 1.05( 0.81, 1.37) | 0.93( 0.82, 1.05) | 0.98( 0.71, 1.35) | 1.06( 0.90, 1.24) | 0.69( 0.46, 1.04) | 1.08( 0.84, 1.38) |

*Bold indicated $p<0.05$

[a]Beta coefficients are exponentiated to transform results back to the original scale

[b]95% Confidence interval

**Centers for Epidemiologic Depression Scale Items in W1 and W2**

Prompt: During the past week…

CESD-1 I did not feel like eating; my appetite was poor.
CESD-2 I felt depressed.
CESD-3 I felt that everything I did was an effort.
CESD-4 My sleep was restless.
CESD-5 I was happy.
CESD-6 I felt lonely.
CESD-7 People were unfriendly.
CESD-8 I enjoyed life.
CESD-9 I felt sad.
CESD-10 I felt that people disliked me.
CESD-11 I could not get "going."

**Social Support Scale Items in W1 and W2**

SS-1 How often can you open up to your spouse if you need to talk about your worries?
SS-2 How often can you rely on your spouse for help if you have a problem?
SS-3 How often can you open up to your family if you need to talk about your worries?
SS-4 How often can you rely on your family for help if you have a problem?
SS-5 How often can you open up to your friends if you need to talk about your worries?
SS-6 How often can you rely on your friends for help if you have a problem?

**Activities of Daily Living Scale Items in W1**

Prompt: Please look at the answer categories on the hand card and tell me how much difficulty you have with each activity. Exclude any difficulties that you expect to last less than three months.

FI-1 Walking across a room?
FI-2 Dressing, including putting on shoes and socks?
FI-3 Bathing or showering?
FI-4 Eating, such as cutting up your food?
FI-5 Getting in or out of bed?

FI-6 Using the toilet, including getting up and down?

Appendix O: Summary of measurement model modifications

| | Original Measurement Model | Mod. 1[2] | Mod. 2[3] | Mod. 3[4] | Constrained Model[5] |
|---|---|---|---|---|---|
| Estimated $\chi^2$ drop | NA | 19.68 | 13.13 | 14.56 | NA |
| $\chi^2$, $df$[1] | 1970.21, 976 | 1933.86, 975 | 1908.28, 974 | 1908.490, 973 | 1929.64, 988 |
| RMSEA | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 |
| CFI | 0.92 | 0.92 | 0.92 | 0.92 | 0.92 |
| SRMR | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |

[1]$\chi^2$ is not scaled. *df*= degrees of freedom

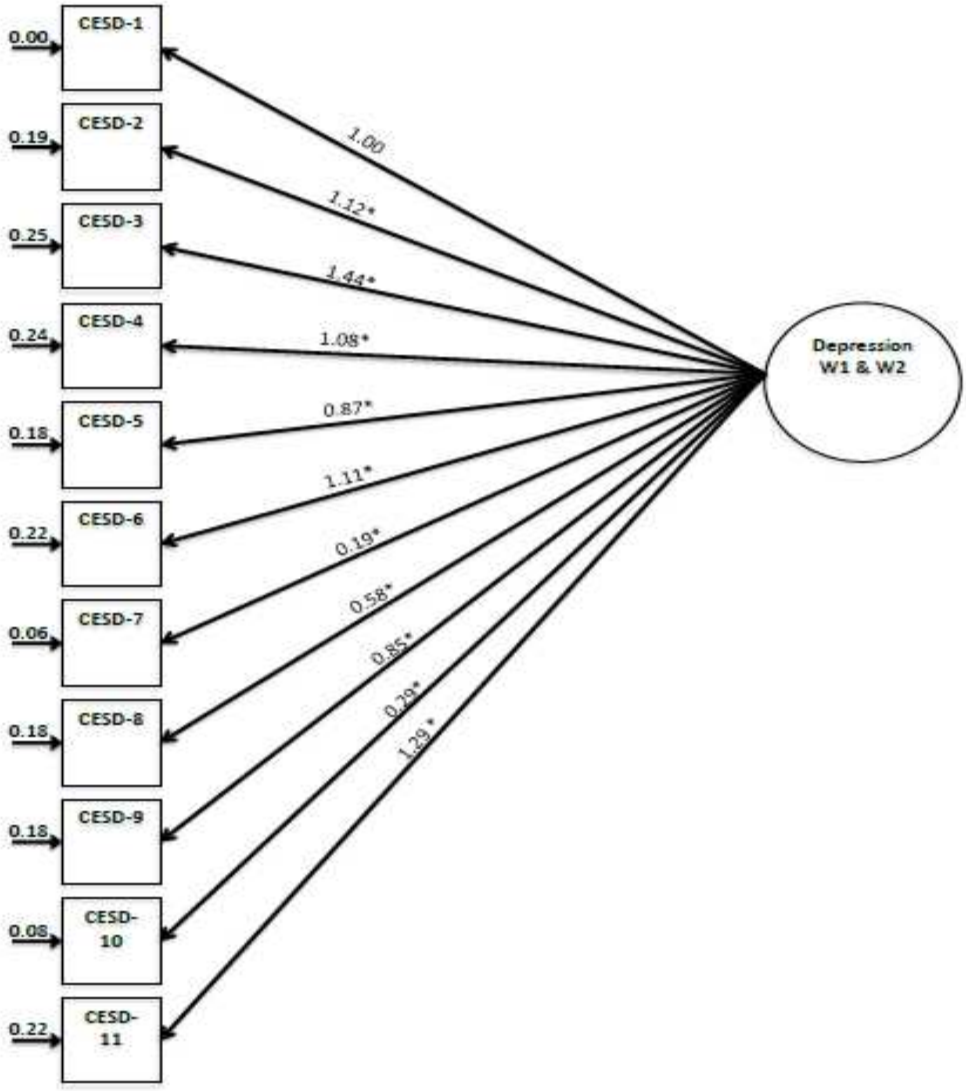
[2]Modification 1. Social support: rely on spouse with CES_D was lonely in W2

[3]Modification 2. CESD: not get going and Functional Impairment: dressing

[4]Modification 3. Social support: rely on spouse and CES-D: lonely W1

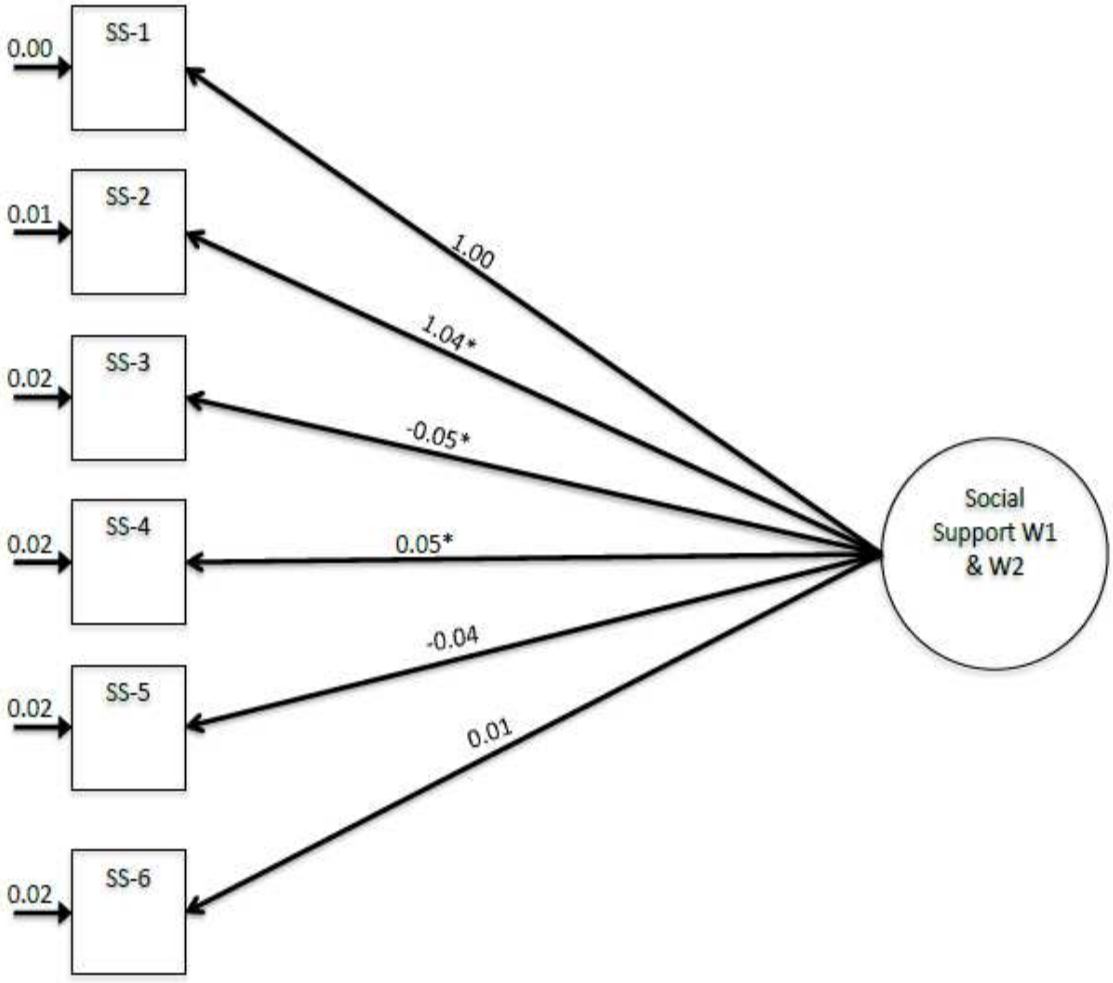
[5]The constrained model is the final measurement model where all paths with two time points were constrained to be equal to each other.

Appendix P. Final measurement model for latent variable depression in W1 and W2 and its indicators



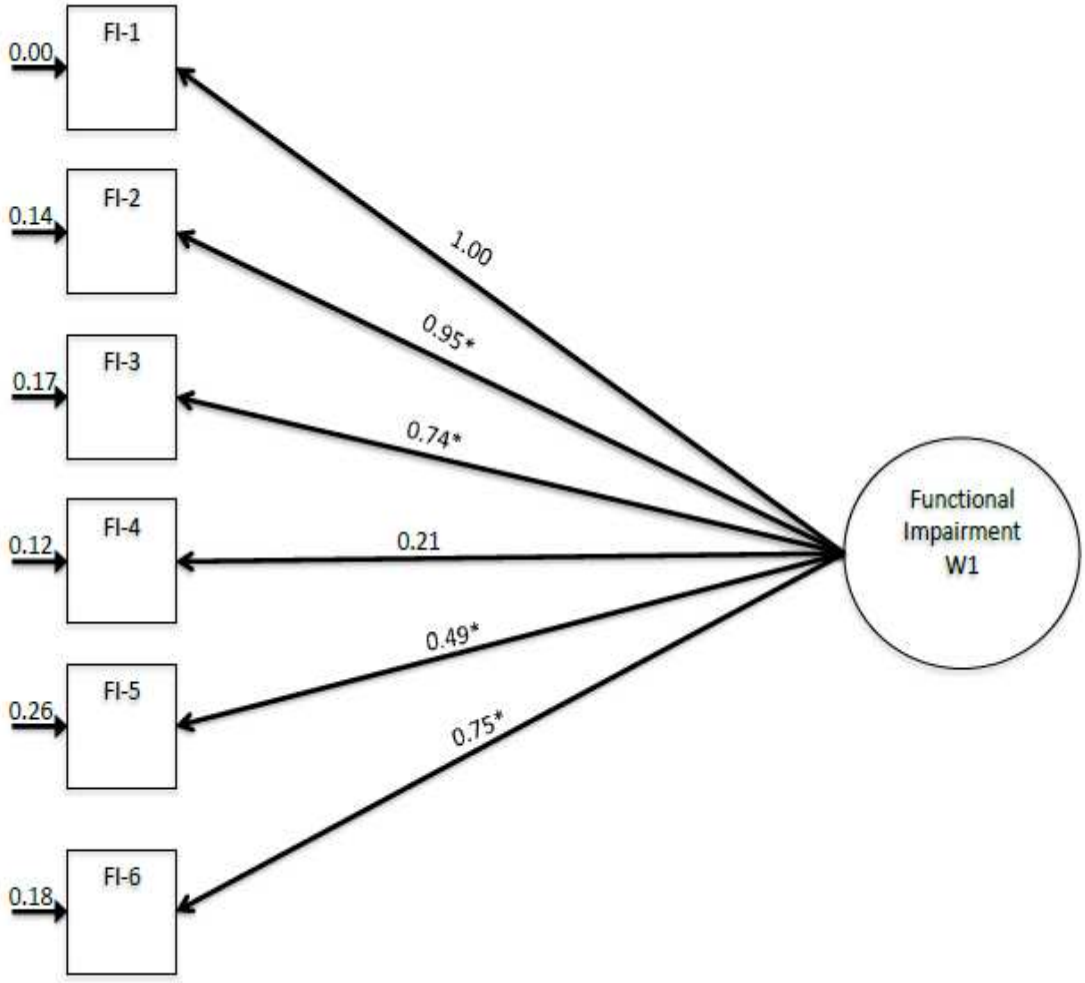

*indicates p<0.05. All estimates are unstandardized

Appendix Q. Final measurement model for latent variable Social Support in W1 and W2 and its indicators




*indicates p<0.05. All estimates are unstandardized

Appendix R. Final measurement model for latent variable Functional Impairment in W1 and its indicators




*indicates p<0.05. All estimates are unstandardized

Appendix S. Structural model with a summary of the modifications made

| Model Fit | Final Measurement Model | Structural Model | Suggested values for satisfactory model fit[1] |
|---|---|---|---|
| Chi Square, DF[2] | 1929.64, 988 | 1933.59, 981 | |
| RMSEA | 0.03 | 0.03 | $\leq 0.06$ |
| CFI | 0.92 | 0.92 | $\geq 0.95$ |
| SRMR | 0.05 | 0.05 | $\leq 0.08$ |

[1.] Hu and Bentler (1999)
[2.] Chi Squared value not scaled

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