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Personal Hardiness as an Unexamined Component of the Healthy Volunteer Effect

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This is to certify that the doctoral dissertation by

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Abstract

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by

Angelique Blann

MPH, Drexel University, 2009

BS, The College of New Jersey, 2007

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Clinical trials are the standard for approving medicines for public use. To conduct trials, researchers depend on a declining number of volunteers. The healthy volunteer effect, a phenomenon in which participants demonstrate better outcomes than their peers, limits the generalizability of trial outcomes. The healthy volunteer effect does not fully explain the outcome difference between volunteers and nonvolunteers. The purpose of this cross-sectional quantitative study was to examine personal hardiness as an unexplored component of the healthy volunteer effect and determine whether personal hardiness is associated with willingness to participate. Hardiness was a personality construct that represented resilience to stress. The hardiness model for performance and health enhancement served as the theoretical framework for this study. Data were collected through a single-administration electronic questionnaire with 208 U.S.-based adults. Ordinal regression was used to assess the relationship between hardiness and willingness. A statistically significant association was found between high hardiness and willingness ($p < .001$), and high hardiness increased the odds of being more willing to participate by four times. An association between hardiness and willingness may provide participants with more accurate risk/benefit assessments and allow researchers to quantify and adjust for bias due to hardiness. Results could influence future study designs, result in more careful participant considerations, and impact how trial outcomes are interpreted and applied to the public. Implications for positive social change include quantifying and adjusting for hardiness as a standard practice in clinical trials, which could maximize the effectiveness of new treatments and provide insight into real-world efficacy.

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Dedication

This work is dedicated to M.C.H and Q.C.H. You are and will always be my greatest accomplishment.

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Chapter 1: Introduction to the Study

I examined the relationship between personal hardiness and willingness to participate and assessed whether personal hardiness contributes to a type of selection bias in research known as the healthy volunteer effect. Contrary to its name, the healthy volunteer effect does not describe differences between healthy and sick patients but refers to a type of nonresponse bias in which individuals who participate or volunteer for research differ from nonparticipants in that participants are "healthier" in comparison (Delgado-Rodriguez, 2004). Clinical research relies on the participation of a declining percentage of the general population who volunteer for trials (English et al., 2010; Thomson et al., 2005; Unger et al., 2016). Selection bias due to the healthy volunteer effect is a known issue in clinical research (Czwikla et al., 2022; Pinsky et al., 2007; Struijk et al., 2015; Vehmas & Oksa, 2015).

Despite efforts to limit its effects, researchers performing retrospective analyses on clinical trials continue to highlight the differences between participants and nonparticipants (Czwikla et al., 2022; Froom et al., 1999; Hara et al., 2002; Lindsted et al., 1996; Thomson et al., 2005; Vehmas & Oksa, 2015) and its bias effects on research outcomes and conclusions (Bonovas et al., 2007; Church et al., 1993; Croswell et al., 2010; Elston, 2021b; Jordan et al., 2013; Kjellman et al., 2009; Krauss, 2018; Melton et al., 1993; Vehmas & Oksa, 2015). A component of the healthy volunteer effect that fully explains the differences between participants and nonparticipants remains unsubstantiated (Boniface et al., 2017; Foy et al., 2011; Jensen et al., 2022; Mölenberg et al., 2021; Peppercorn et al., 2004). As trial participation rates decline and research becomes

increasingly complicated and costly (Bentley et al., 2019; Collier, 2009; Moore et al., 2020), it is essential that the research being conducted is meaningful to the public and has the external validity necessary to support drug approvals and evaluations.

In the current study, I assessed whether personal hardiness, a personality construct that results in resiliency in the face of illness, was associated with willingness to participate in a trial. An association between personality and willingness could explain the healthy volunteer effect components that are not yet understood. In addressing this gap, researchers could quantify and address the lack of outcome generalizability. Clinical trials provide information on the safety and efficacy of drugs and procedures before they are approved and marketed to the public. If the applicability of trial outcomes is routinely biased by the personality constructs of trial participants, identifying a potential association between willingness and the internal characteristics of participants could be beneficial to the clinical research industry. In this chapter, I provide background information on the state of clinical research, the healthy volunteer effect, the current gap in understanding of the effect, and the impact that gap has on the generalizability of trial outcomes. I outline the study's purpose; detail the research questions and hypotheses; and explain the assumptions, limitations, and significance.

Background of the Problem

Clinical trials are cornerstones of drug development. According to the World Health Organization (2020), a "clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes" (para. 1). These health-related

interventions extend beyond drug approvals, and include medical procedures, devices, behavioral programs, and other health-care measures. Clinical trials are integral in developing and approving novel approaches in many health-related categories (National Library of Medicine, 2019). The information gathered from clinical trials allows for a greater understanding of a treatment or intervention's efficacy and safety and the risk-benefit profile in its application to the population. As drug research has grown increasingly complex, so has the importance, and by extension, the difficulty, of conducting clinical research (Karampatakis et al., 2021; Sine et al., 2021).

Clinical researchers are under pressure to rapidly execute an increasing number of clinical trials (Tufts Center for the Study of Drug Development [TCSDD], 2021). Since 2001, the total research and development pipeline size across major pharmaceutical companies has increased by 170%, reaching a peak of over 16,000 drugs in development in 2019 (Lloyd, 2019). Despite the plethora of drug candidates, successful drug development, progressing from discovery to market, is at an all-time low (Dowden & Munro, 2019). Because clinical trial recruitment relies on the willingness of volunteers, one of the most significant burdens is not the enormous cost and time commitment a clinical trial requires but the lack of participants. Between 2005 and 2011, 20% of cancer clinical trials failed to complete enrollment (Fogel, 2018). Researchers suggested that trial outcomes face selection bias because clinical trial volunteers are not representative of their peers in the general population and that this bias is compounded by low participation in clinical trials (Czwikla et al., 2022; Fogel, 2018; Khera et al., 2015; Murthy et al., 2004). For clinical trials testing new medications, studies found that

participation of a greater number of patients with a higher likelihood for successful outcome potentially skews the trial results (Elting et al., 2006; Markovic et al., 2017; Richiardi et al., 2002; Tang et al., 2022; Thomson et al., 2005). The healthy volunteer effect does not fully explain the differences in outcomes observed among clinical trial participants.

Researchers have established relationships between the healthy volunteer effect and several potential external contributors (Ackerman et al., 2019, 2021; Burke et al., 2007; Delgado-Rodriguez, 2004; Pinsky et al., 2012; Stuart & Rhodes, 2017; Vineis, 1998). A gap in the literature exists because the observed difference in outcomes between participants and the general population is not fully explained by the healthy volunteer effect or any factor explored to date (Czwikla et al., 2022; Fry et al., 2017; Khera et al., 2015). The absence of a comprehensive explanation for the healthy volunteer effect from factors external to the participant has generated support for research on the internal characteristics of the clinical participants as a contributor (Hillyer et al., 2019; Sun et al., 2017). Researchers had not examined whether participant personality characteristics are associated with willingness to participate, which represented a gap in the field of clinical research.

Problem Statement

The healthy volunteer effect has limited the generalizability of clinical trials, a phenomenon in which clinical trial participants manifest significantly better outcomes relative to their illness state than the general population (Froom et al., 1999). Although the healthy volunteer effect has been well documented, previous research has been

sporadic and has yet to identify what variables determine the effect (Czwikla et al., 2018; Pinsky et al., 2007; Vineis, 1998; Zheng et al., 2020). Researchers have attributed the healthy volunteer effect to either the constant monitoring and intensive care clinical trial participants receive or to an expression of the Hawthorne effect, a research bias in which participants modify their behavior in response to being observed (Abraham et al., 2018; Adair, 1984; Burke et al., 2007; Delgado-Rodriguez, 2004; Elston, 2021a; McCambridge et al., 2014; McCarney et al., 2007). Both variables have received some support in the literature; however, neither has explained the healthy volunteer effect. Moreover, the effects of these variables have been studied only among specific trial populations and never among trial participants in general (Abraham et al., 2018; Ederer et al., 1993; McCarney et al., 2007; Thomson et al., 2005). Because previous investigations have not substantiated influences external to trial participants, part of the healthy volunteer effect may be attributable to internal factors such as trial participants' behaviors or biopsychosocial characteristics.

Researchers examining participant characteristics have determined that clinical trial participants are healthier than their general population counterparts. However, it is not clear whether clinical trial participants would present better outcomes than equally healthy (or ill) clinical trial nonparticipants (Foy et al., 2011; Krauss, 2018). Due to clinical trial protocols requirements such as inclusion and exclusion criteria, trial participants have fewer comorbidities than their peers in the general population who suffer from the same illness (Foy et al., 2011; Fry et al., 2017; Unger, Hershman, et al., 2019). The lack of generalizability in clinical trials is a current and ongoing concern in

clinical research (Averitt et al., 2020; Malmivaara, 2019). Researchers acknowledged the difference between participants and nonparticipants and recognized the issue this creates for external validity, but very few randomized studies assessed or adjusted for generalizability (He et al., 2020). He et al. (2020) found that among a sample of 187 recently published trials, less than 40% conducted generalizability assessments on their trial outcomes. Of those that conducted assessments, less than 30% reported positive results. He et al. highlighted how the lack of generalizability and the approval of medicines based on outcomes from participants who differ from real-world nonparticipants represent a safety risk to patients. Krumholz (2021) concluded that the biased selection of trial participants limits the generalizability of trial results. Krumholz noted that additional data from real-world patients was required across therapeutic areas to understand intervention outcomes. The lack of generalizability and the differences between participants and nonparticipants is a systemic issue in clinical research (Czwikla et al., 2022).

Although the difference between participants and the general population has been acknowledged and accepted, the differences between participants and nonparticipants (i.e., individuals who meet the same criteria and are eligible to participate in a trial but do not) are less understood. Because nonparticipants would be eligible for participation if willing, they should have similar comorbidities as participants. The nonresponse of these individuals should not skew the outcomes of a trial, but previous research has demonstrated that nonresponse bias (healthy volunteer effect) exists (Elston, 2021b; Fry et al., 2017). Clinical trials depend on the public's willingness to participate, and

researchers have concentrated on capturing differences in willingness, defined as altruism, among trial participants (Kemeny et al., 2003; Lindsted et al., 1996; Olsen et al., 2020; Schutta & Burnett, 2000; Struijk et al., 2015; Stunkel & Grady, 2011; Truong et al., 2011; Verheggen et al., 1998; Weller et al., 2020). These investigations, predicated on a limited conceptualization of willingness, have not established a link between participant willingness and the demonstrated superior trial outcomes. In addition, these studies have not determined whether participant willingness is related to higher health status (Ginossar et al., 2022; Jordan et al., 2013; Scott et al., 2011). Further, research has yet to determine whether willing clinical trial participants possess characteristics that distinguish them from equally healthy (or ill) individuals who refuse to participate (Krauss, 2018).

In the current study, I examined willingness as part of a larger psychological construct not yet evaluated for its potential to better characterize a unique psychological and physical characteristic of clinical trial participants: personal hardiness. Personal hardiness is a personality construct that encompasses self-determination, a sense of personal control, the ability to become deeply committed to life activities, and a perception of challenges as growth opportunities (Bowsher & Keep, 1995; Kobasa, 1979; Maddi, 2013). Hardy individuals have the capacity to cope positively with stressful situations and exhibit better health in the face of adversity (Maddi, 1999a; 1999b). Hardy individuals are predisposed to take actions to manage their lives. This myriad of characteristics not only has the potential to explain previously uninvestigated components of the healthy volunteer effect but also has implications related to the divide between clinical trial participants and nonparticipants.

Purpose of the Study

In this quantitative study, I assessed the association between personal hardiness and willingness to participate in a clinical trial. I also examined the relationship between health status, health behaviors, social support, and willingness, and I assessed the moderation of any association by personal hardiness. This investigation addressed gaps in the healthy volunteer effect by examining the extent to which personal hardiness was associated with individuals who were more willing to participate in clinical.

Research Questions and Hypotheses

In this study, I examined whether personal hardiness explained differences between clinical trial volunteers and nonvolunteers that are not adequately accounted for in the healthy volunteer effect. I addressed the following research questions:

Research Question 1: Is there any association between personal hardiness and an individual's willingness to participate in a clinical trial?

$H_0$1: There is no statistically significant association between personal hardiness and an individual's willingness to participate in a clinical trial.

H_a1: There is a statistically significant association between personal hardiness and an individual's willingness to participate in a clinical trial.

Research Question 2: Is there any association between positive health behaviors and an individual's willingness to participate in a clinical trial?

$H_0$2: There is no statistically significant association between positive health behaviors and an individual's willingness to participate in a clinical trial.

H_a2: There is a statistically significant association between positive health behavior and an individual's willingness to participate in a clinical trial.

Research Question 3: Is there any association between social support measures and an individual's willingness to participate in a clinical trial?

$H_0 3$: There is no statistically significant association between social support measures and an individual's willingness to participate in a clinical trial.

$H_a 3$: There is a statistically significant association between social support measures and an individual's willingness to participate in a clinical trial.

Research Question 4: Is there any association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial moderated by personal hardiness?

$H_0 4$: There is no statistically significant moderation by personal hardiness in the association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial.

$H_a 4$: There is statistically significant moderation by personal hardiness in the association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial.

Theoretical Framework

In this study, I used the hardiness model for performance and health enhancement as the theoretical framework. Developed by Drs. Salvatore Maddi and Suzanne Kobasa, the concept of hardiness was refined throughout the mid-1970s as researchers sought to understand why stressful circumstances appeared debilitating to certain individuals but

created a positive stimulus in others (Maddi, 2006, 2013). Maddi and Kobasa's foundational analysis of stress in male business executives demonstrated that personality types or attitudes were associated with reduced illnesses and better physical and mental outlook (Kobasa, 1979; Kobasa et al., 1981; Kobasa, Maddi, & Kahn, 1982; Maddi & Kobasa, 1986). The traditional social and clinical psychological models that addressed the role of stress in physical and mental disorders focused on how behavior or social environment functioned to either increase susceptibility or decrease resistance to illness (Wiebe, 2020; Wiebe & Williams, 1992). Research by Maddi and Kobasa evolved to focus on stress resistance as a protective health factor. They defined hardiness as an intrinsic demonstration of strength that is best observed through a definable display of specified perspectives and coping mechanisms that help to facilitate protection from stress (Maddi, 2013). Three attitudes (challenge, commitment, and control) define hardiness (Maddi et al., 2009). These attitudes enable individuals to perceive stressful situations as growth opportunities and react accordingly (Maddi, 2006). Researchers established the relationship of all three attitudes to measures of personal hardiness and demonstrated that the absence of any of these attitudes diminishes measurable hardiness levels (Maddi, 2013).

The hardiness model of performance and health enhancement serves as the framework for defining the relationship between hardy attitudes and behaviors and health behaviors and outcomes. The hardiness model has been widely used to describe the mechanisms by which personal characteristics influence an individual's response to stress and illness (Abdollahi et al., 2019; Arshi et al., 2021; Bahrami et al., 2018; Baldassini

Rodriguez et al., 2022; Dewi et al., 2020; James, 2021; Luceño-Moreno et al., 2020; Nakamura & Tsuchiya, 2020; Ndlovu & Ferreira, 2019; Pandey & Shrivastava, 2017; Robinson, 2013; Sadeghpour et al., 2021; Samoilov & Aleshicheva, 2022; Sandvik et al., 2020; Soderstrom et al., 2000). I applied the hardiness model of performance and health enhancement to examine the potential relationship between personal hardiness and willingness to participate in a clinical trial. In Chapter 2, I discuss the theoretical framework and the conceptual framework for hardiness and the healthy volunteer effect in further detail.

Nature of the Study

I used a quantitative design to investigate the relationship between personal hardiness and willingness to participate as a potential pathway for unexplored components of the healthy volunteer effect. A quantitative cross-sectional approach was appropriate for this study because the hardiness among those more willing to participate was compared to the hardiness among those less willing or more unwilling at a single point in time. Previous researchers compared participants and nonparticipants using similar methods (Ellis et al., 2001; Moorcraft et al., 2016; Sun et al., 2017).

For the current study, the outcome variable was the willingness to participate in a clinical trial, which was measured as an ordinal variable and assessed on a 5-point scale. The predictor variable was personal hardiness, which was measured as a categorical variable. Other predictor variables, which included health status, positive health behaviors, and level of social support, were measured as categorical. The Hardiness Resilience Gauge (HRG) was used to measure hardiness (see Bartone et al., 2022). Social

support was measured using the Multidimensional Scale of Perceived Social Support (MSPSS; Zimet et al., 1988). Health status, positive heath behaviors, and demographic variables such as gender, marital status, and income level were measured using the 2020 Behavioral Risk Factor Surveillance Survey (BRFSS; National Center for Chronic Disease Prevention and Health Promotion, 2014). Participants were U.S.-based adults, and data were collected through a single administration electronic questionnaire using an online survey platform for recruitment. Ordinal logistic regression and regression with moderation were used for analysis.

Definitions

Clinical trial: A mechanism employed by researchers to assess new drugs, devices, and medical interventions (American Cancer Society, 2020). Clinical trials use volunteers who agree to participate in research. Before new treatments are approved for marketing and use, clinical trials are conducted to assess the safety and efficacy of treatment. Clinical trials are also conducted on previously approved drugs (American Cancer Society, 2020).

Hawthorne effect: A type of research bias in which a participant's awareness of an experiment causes a modification in behavior (Elston, 2021a). The effect may also be referred to as an observer effect because participants change their behavior in response to being observed by a researcher.

Health behavior: A combination of positive and negative behaviors that contribute to an individual's health status. Health behaviors include the following:

smoking, alcohol consumption, and exercise (Wiebe & McCallum, 1986). Health behavior was a covariate in the current study.

Health status: The perceived state of an individual's health, including physical, mental, and illness status (Wiebe & McCallum, 1986). Health status was a covariate in the current study.

Healthy volunteer effect: A type of selection bias subclassified as nonresponse bias. The healthy volunteer effect results when the participants in a study differ from the nonparticipants, and the participants are healthier than the general population they should represent (Delgado-Rodriguez, 2004).

Personal hardiness: A personality construct that describes a pattern of health-enhancing behavior and attitudes that facilitate an increased resistance to illness. Hardy individuals display qualities of control, commitment, and action in responding to life events and circumstances (Maddi, 2006). Personal hardiness was the independent variable in the current study.

Social support: The perceived support that people assess from those associated with them. Social support is the degree of believed care, love, value, and assistance people can anticipate from those close to them in times of crisis or stress (Ganellen & Blaney, 1984). Social support was a covariate in the current study.

Socioeconomic Status (SES): The economic and sociological currency an individual possesses that influences access to specific health resources. SES is categorized by three factors: education level, income, and occupational status (Institute of Medicine (US) Committee on Assessing Interactions Among Social, 2006).

Willingness to participate: A self-reported measure indicating whether an individual is more or less likely to be willing to participate in a trial. Clinical trials depend on participation from volunteers. Only a small percentage of the population participates in trials despite their eligibility (Jiang & Hong, 2021). Willingness to participate was the dependent variable in the current study.

Assumptions

The assumptions included in this study were assertions that I made regarding the healthy volunteer effect, personal hardiness, and clinical trial volunteers. My first assumption was that I would recruit enough participants willing to complete my questionnaire. Although I examined willingness to participate, I assumed I would identify individuals willing and unwilling to participate in my study. Cross-sectional study designs are efficient and effective for conducting research; however, cross-sectional surveys are subject to information and reporting bias (Sedgwick, 2015). Despite this, I assumed that participants would be truthful in their responses to my questionnaire. I did not actively observe participants, but I assumed I would not experience bias from the Hawthorne effect, and participants would not modify their responses because they were participants (see Elston, 2021a; McCambridge et al., 2014). Lastly, I assumed that willingness to participate in a hypothetical clinical trial could provide insight into the willingness to participate in an actual clinical trial and lead to insight into the healthy volunteer effect. These assumptions were necessary for this research to be conducted efficiently and cost-effectively. These assumptions were also necessary to assess the

relationship between hardiness and willingness to participate. Lastly, these assumptions allowed the results to be generalized beyond the study population.

Scope and Delimitations

I examined the association between hardiness and willingness to participate in a clinical trial, an association that may be used to understand unexplored components of the healthy volunteer effect. The hardiness model of health and performance enhancement provided a framework for how hardiness works in concert with health status, health behavior, and social support (see Maddi, 2006, 2013). In addition to examining hardiness, I assessed associations between health status, heath behaviors, and social support, and willingness to participate in a clinical trial. I also examined any moderation of those associations by personal hardiness. All participants were 18 years of age or older. I included only U.S.-based adults. My focus on U.S.-based adults potentially limited the generalizability of the study outcomes to ex-U.S. trial participants.

Limitations

The study design was cross-sectional and relied on self-reported survey data. Information bias from the participants, which is a potential bias in research that requires self-reported data (Sedgwick, 2015), was a limitation in my study. I was limited in participant follow-up and excluded from relevant data, such as actual trial participation and retention, because the research relies on willingness to participate in clinical trials unassociated with my study. In addition, the study was also limited by assuming that individuals have access to clinical trials or are patients under the care of a physician who participates in clinical trials. As such, I could not examine the influence of personal

hardiness in patients without access or means to participate in a clinical trial despite willingness. An additional limitation was that those unwilling to participate in a clinical trial who demonstrate a low degree of personal hardiness may also have declined participation in the current study. I was limited to analyzing those unwilling to participate in a clinical but who demonstrated enough personal hardiness to participate in this study.

Self-reporting bias may have limited the internal validity of this study. Self-reporting bias is a challenge in cross-sectional survey research. To address this limitation, I instructed participants that there were no right or wrong answers to the survey questions. In addition, I assessed willingness to participate in a trial on a 5-point scale. Using a 5-point scale to measure willingness allowed me to observe participants who were not definitively willing or unwilling to participate in a trial. A 5-point scale allowed for the nuances of willingness and avoided forcing participants to make a binary choice. Because hardiness worked in conjunction with health behaviors, health status, and social support, I explored associations between those predictors and willingness to participate. I did not account for other potential confounders such as neuroticism or altruism, which potentially limited the study's internal validity (see Funk, 1992; Kowalski & Schermer, 2019). There are several measurement scales for personal hardiness (Kowalski & Schermer, 2019). I measured hardiness through the HRG, which, despite adequate reported reliability and validity, is a recent scale (see Bartone et al., 2022). There is no standard measurement for hardiness and therefore construct validity was a potential concern.

Significance

Clinical trials are essential to developing and approving new medications, medical devices, products, and techniques (National Library of Medicine, 2019). Data from clinical trials inform regulatory bodies, physicians, and the public about the risks and benefits of a given drug, intervention, or procedure (National Library of Medicine, 2019). Most countries require clinical trials before drugs can secure official approval for marketing and use (Food and Drug Administration, 2017). Clinical trials are also a key criterion for the clinical acceptability of new medical treatments (National Library of Medicine, 2019). The number of clinical trials has increased rapidly and the complexity of the regulatory environment and the expense of conducting trials has increased simultaneously (Gresham et al., 2020). Furthermore, industry and academic sponsors and clinical investigators are under pressure to complete trials and reach conclusions more rapidly (DiMasi, 2002; Eichler & Sweeney, 2018; Wouters et al., 2020). The TCSDD (2021), an independent nonprofit research organization that seeks to improve pharmaceutical development, noted a 44% increase in the median number of required clinical procedures for Phase II and Phase III trials since 2009.

The healthy volunteer effect impacts the process and the outcome of clinical trials (Harrison et al., 2019; Leening et al., 2014; Lindsted et al., 1996; Struijk et al., 2015; Weller et al., 2020). Poor patient recruitment is one of the most frequently cited reasons for the discontinuation or failure of randomized clinical trials (Briel et al., 2021). Assessing a potential relationship between the willingness to volunteer and the personal predisposition that motivates a volunteer could improve public health practice by better

informing the recruitment campaigns designed to increase the number of clinical trial participants. Researchers attempting to increase trial enrollment have focused on trial awareness and education (Olsen et al., 2020). If barriers in trial participation are also related to individual personality constructs, assessing those associations could influence how researchers address issues of trial enrollment.

The healthy volunteer effect is a long-standing concern because it can potentially bias study outcomes (Delgado-Rodriguez, 2004; Elston, 2021b; Fry et al., 2017; Lindsted et al., 1996) by providing results only for best-case patients (Czwikla et al., 2018; Garrison et al., 2007; Tlimat et al., 2020). If the protective health behaviors associated with personal hardiness make an independent contribution to the healthy volunteer effect, defining this relationship could generate positive social change. Through this study, I addressed a gap in the literature by examining whether hardiness is associated with willingness to participate in a trial, which could help explain factors in the healthy volunteer that are not currently defined or measured. If an association between hardiness and willingness exists, the hardiness of trial participants could be quantified, and trial outcomes could be adjusted for hardiness in the general population.

Quantifying and adjusting for hardiness may maximize the effectiveness of new treatments or provide insight into real-world efficacy. Trial participants who demonstrate a higher degree of personal hardiness may engage in lifestyle choices that maximize their outcomes beyond the efficacy of the experimental medication or treatment. Testing and quantifying the contribution of those choices to optimal outcomes could contribute to estimating the generalizability of a trial outcome. If trial outcomes are linked to an

inherent level of personal hardiness, then optimal outcomes may be less likely to transfer beyond the trial population. Personal hardiness as an unexplored component of the healthy volunteer effect could clarify the extent to which positive clinical trial outcomes are reproducible for the population. This could generate positive change for individual trial participants and the public, researchers, and the broader clinical research industry by addressing the issues of outcome generalizability and providing a mechanism by which that generalizability could be quantified and proactively addressed.

Summary

In Chapter 1, I introduced clinical trial participation, the role of the healthy volunteer effect, and the potential contribution of personal hardiness. I outlined the research questions, purpose, theoretical framework, nature of the study, and significance of this research. I detailed the definitions of key terms, assumptions made in this study, scope and delimitations, limitations, and the approaches used to limit the influence of limitations on the validity of this research. Chapter 2 includes an extensive review of the current literature relevant to clinical trial participation, the healthy volunteer effect, and personal hardiness. The next chapter also provides additional detail and background on the theoretical and conceptual frameworks that served as this study's basis.

Chapter 2: Literature Review

Clinical research and drug development rely on the availability of volunteers willing to participate in clinical trials. Although a definitive number is difficult to establish, only 2%–3% of the population in the United States participates in clinical studies (Jiang & Hong, 2021). The differences between volunteers for clinical trials and the general population amplifies the consequences of low participation (Jiang & Hong, 2021). Researchers have determined that the outcomes of clinical trials are biased toward best-case patients because most individuals who volunteer for clinical trials manifest significantly better outcomes relative to their illness state than the general population (Froom et al., 1999; Fry et al., 2017; Garrison et al., 2007; Markovic et al., 2017; Tlimat et al., 2020). The healthy volunteer effect offers a potential explanation for the observed difference but does not account for it.

This chapter details my literature search strategy and the theoretical framework's origins, applications, and appropriateness. I also review the previous research on personal hardiness, the healthy volunteer effect, and clinical trial participation. I outline the conceptual model I used to examine my research questions from the literature presented. Finally, I summarize the key points from this chapter and present transition material as a prelude to Chapter 3.

Literature Search Strategy

I conducted an extensive literature review using Google Scholar as the principal source for peer-reviewed journal articles. I also accessed proprietary and publicly available databases including EBSCOhost (CINAHL Plus, EBSCO ebooks, ERIC,

PsycINFO, and Science Full-Text Select), APA PsycNet, EMBASE, JSTOR, MEDLINE Plus, PubMed, and SCOPUS. I used the following key terms for this literature review: *hardiness*, *stress and health*, *illness*, *social support*, *personality*, *resilience*, *optimism*, *coping*, *hardy*, *Personal Views Survey*, *Dispensational Resilience Scale*, *Hardiness Resilience Scale*, *Multidimensional Scale of Perceived Social Support*, *health performance*, *hardiness* and *illness*, *hardiness* and *health behavior*, *constitutional strength*, *hardy attitudes*, *healthy volunteer effect*, *selection bias*, *volunteer*, and *non-responder bias*. I used these search terms individually and in combinations to identify articles of interest. I did not limit this literature review to any specified period. Foundational research for the healthy volunteer effect began in the mid-1960s and extended to the present. Seminal literature for personal hardiness theory started in the late 1970s and early 1980s. Current research has focused on the application of hardiness.

Theoretical Foundation

The theoretical foundation of my investigation was Maddi and Kobasa's hardiness model for performance and health enhancement (Maddi, 2013). Maddi and Kobasa conceived of personal hardiness as a method to explain how and why individuals respond differently to stress (Maddi, 2013). Traditional social and clinical psychological models examining the role of stress in physical and mental disorders have focused on how a person's behavior or social environment functions to increase susceptibility or decrease resistance to illness (Wiebe & Williams, 1992). As researchers began to focus on the converse relationship (stress resistance as a protective health factor), the construct of

personal hardiness evolved and became the predominant paradigm for such investigations (Maddi, 2013).

Hardy individuals are resilient when facing challenging situations. They achieve this resiliency by exercising a well-developed sense of personal control, mustering the ability to become deeply committed to activities that address the challenges at hand, and perceiving these challenges as growth opportunities rather than threats and losses (Kobasa, 1979). The hardiness model of performance and health enhancement is a unified framework for describing the relationship between hardy attitudes and strategies and their influence on health behaviors and outcomes. This model originated in psychological resiliency research that examined the factors that distinguish individuals capable of coping with stress from those incapable.

Two pivotal studies by Dohrenwend and Dohrenwend (1974) and Gunderson and Rahe (1974) found that stressful life events precipitated illness and disease. A curious aspect of the research on stressful life events and illness was the lack of uniformity in the observed effects. Although associations were determined, these researchers observed that certain factors appeared to mitigate the stress-illness relationship in some individuals. Both studies suggested that personality characteristics may be a conditioner for the buffering effects and recommended that personality as a consideration for future research.

Kobasa (1979) proposed hardiness or the hardy personality construct as a mediator between stress and adverse health outcomes. Kobasa's initial study examined the differing personality structures of highly stressed individuals who remained healthy and individuals with similar high-stress levels who became ill. Using a population of

high-level business executives, Kobasa found that people who experienced high stress without falling ill expressed different personality traits than those who experienced illness under the same stressful conditions. Kobasa termed the personality structure observed in high-stress low-illness individuals as hardiness. In examining the specifics of this personality construct, Kobasa identified that hardy individuals demonstrate three general characteristics: "(1) the belief that they can control or influence the events of their experience, (2) an ability to feel deeply involved or committed to the activities in their lives, and (3) the anticipation of change as an exciting challenge to further development" (p. 3).

Kobasa's pivotal study confirmed that stress was associated with illness (Kobasa et al., 1981). Kobasa also observed that some individuals appeared to have mediators against stress and found that hardiness explained the differences between those who became ill due to stress and those who did not. Furthermore, Kobasa proposed the three characteristics of hardiness: control, commitment, and challenge. Kobasa theorized that the "components should be regarded not as mutually exclusive aspects of hardiness, but rather as inextricably intertwined aspects that bear a considerable resemblance to each other" (Kobasa et al., 1981, p. 369).

Researchers also focused on investigating and validating the hardiness concept, its components, and its role as a buffer to illness in the face of stress. Later prospective and longitudinal studies demonstrated that hardiness was valid as a mediator between stress and illness (Hull et al., 1987; Kobasa et al., 1981, 1983, 1985). Although the consensus of most researchers was that hardiness existed, further research was necessary to determine

whether hardiness was an artifact for other psychological characteristics or physical factors such as exercise (Kobasa et al., 1985; Kobasa, Maddi, & Puccetti, 1982), constitutional predisposition (Kobasa et al., 1981), social support and resources (Ganellen & Blaney, 1984; Kobasa et al., 1985; Kobasa & Puccetti, 1983), Type A personality (Kobasa et al., 1983; Nowack, 1989), and optimism (Maddi, 1999b; Scheier & Carver, 1985).

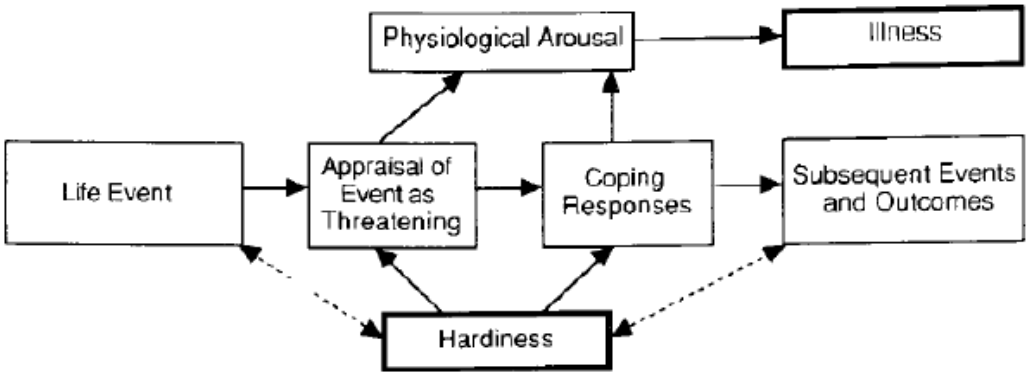
Prospective stress–illness analyses have consistently established hardiness as a significant resistance resource to stress and illness (Bartone, 1989; Kobasa et al., 1981; Kobasa, Maddi, & Puccetti, 1982; Kobasa & Puccetti, 1983; Wiebe & McCallum, 1986). In a 1982 analysis of hardiness and stress, Kobasa, Maddi, and Kahn noted that unlike stress, hardiness is not time bound and remains a consistent personality aspect that provides the most noticeable benefit during times of stress. These studies also indicated that the effect of hardiness was entirely separate or only partially accounted for by other psychological and physical factors (Kobasa et al., 1981, 1983; Kobasa & Puccetti, 1983). For example, Kobasa and Puccetti (1983) observed the joint effectiveness of personal hardiness and social resources. Kobasa and Puccetti confirmed that hardiness was a personality factor and was present in all demographics. Kobasa and Puccetti also observed that the most significant protective stress–illness effect was in individuals with high hardiness and high social resources. Individuals with high hardiness and low social support had some resistance, and those with low hardiness and high social support had the least protection.

In later studies, researchers differentiated hardiness and social support (Ganellen & Blaney, 1984; Kobasa et al., 1985). They also determined that although social support was related and could complement personal hardiness, hardiness protected the stress–illness relationship (Ganellen & Blaney, 1984; Kobasa et al., 1985). Wiebe and McCallum (1986) proposed a causal pathway for the relationship between hardiness, stress, and illness. Wiebe and McCallum found that illness is not an inevitable consequence of stress in all people. Additionally, Wiebe and McCallum determined that stress and hardiness are independent and that hardiness has direct and indirect effects on stress, working directly through resistance to illness and providing indirect impact through health behaviors.

Hardiness does not change the effect of stress on illness but directly mediates. (Wiebe, 1991, 2020; Wiebe & McCallum, 1986; Wiebe & Williams, 1992). Hardiness indirectly affects stress and illness through its influences on health practices (Wiebe, 2020; Wiebe & McCallum, 1986). As shown in Figure 1, with the addition of threat appraisal (Allred & Smith, 1989) and coping responses (Manning et al., 1988; Nowack, 1989; Parelkar et al., 2013; Scheier & Carver, 1985; Williams et al., 1992), the basic conceptual model for the relationship between hardiness, stress, and health was established.

Figure 1

Conceptual Model of the Relationship Between Hardiness, Stress, and Health



Note. Copyright Wiebe, 1992, p. 240.

Literature Review Related to Key Variables and Concepts

Components of Hardiness

In their initial hardiness studies, Kobasa and Maddi proposed elements that compose a hardy personality (Kobasa, 1979; Kobasa et al., 1981; Maddi, 1999a, 1999b). The foundation of the hardiness conceptualization is that all individuals face stressful situations (Maddi, 2006). To successfully navigate a life in which they face inherently stressful situations, people must possess existential courage. When faced with a stressor, people use existential courage to view stress (consciously or unconsciously) as a potential growth opportunity because a component of their personalities recognizes that avoidance, anger, or neglect are ineffective ways to process stressors (Maddi, 2006). When viewed from this perspective, hardiness as a concept is “an operationalization of existential

courage" (Maddi, 2006, p. 162) providing the specific "attitudes and strategies that work to facilitate resilience under stress" (Maddi, 2013, p. 7).

Three attitudes or the three Cs (challenge, commitment, and control) define hardiness (Kowalski & Schermer, 2019; Maddi, 2006). These attitudes and the strategies they influence are the underlying factors that endow an individual with the skills (courage, motivation, and fortitude) to view stressful situations as opportunities for growth (Maddi, 2006). An individual may demonstrate more strength in one attitude, but a deficiency in one of the three attitudes will not yield a personally hardy individual (Maddi, 2013). The belief that as much learning comes from failure as success personifies the first C of challenge (Maddi, 2013). Those with a strong challenge see stress as inherent to life and believe a stressful situation can be an advantage (Maddi, 2013). Commitment is the attitude that emphasizes engagement under stress (Maddi, 2013). Those possessing commitment do not see the benefit of avoidance and disconnection, understanding that full participation and involvement in a situation, despite the stress, is the best way to cope (Maddi, 2013). Lastly, people with the attitude of control believe that individuals can influence stress. They fight against thoughts of incapacitation and weakness, choosing instead to use stress to their advantage (Maddi, 2013). Researchers have cataloged the importance of all three components, demonstrating how the absence of one or more attitudes, even with the strong influence of the other attitudes, does not make a hardy individual (Hull et al., 1987; Kowalski & Schermer, 2019; Maddi, 2013; Wiebe, 2020).

Hardiness and Health

The theory of hardiness has generated rich literature (Abdollahi et al., 2019; Dewi et al., 2020; Sandvik et al., 2020; Wiebe, 2020). The initial Kobasa studies (1979, 1981) focused on the effects of stress, illness, and hardiness on male business executives. However, later research demonstrated the application of hardiness across demographics such as the level of education, gender, and SES (Kobasa & Puccetti, 1983). As hardiness research progressed, a subset of work began focusing not on how hardiness mediated individuals from experiencing illness but expanded to investigate how hardiness buffered the response to illness (Bigbee, 1985; Hannah, 1988; Nagy & Nix, 1989). For instance, in a 1988 study examining hardiness in women with rheumatoid arthritis, Okun et al. found that patients who ranked higher in personal hardiness coped significantly better with their disease despite experiencing the same functional limitations as the less hardy cohort. Although hardiness did not influence objective physician-performed disease assessments, hardier individuals underrated their disease and symptoms on self-reported health questionnaires. The study also indicated that biological differences correlated to hardiness. Okun et al. found that components of hardiness, such as control, were significantly associated with increased T cell circulation and better perception of health.

In additional work, researchers found an association between hardiness and increased coping among cancer patients (Abdollahi et al., 2019; Bahrami et al., 2018; Dewi et al., 2020), individuals with diabetes (Arshi et al., 2021; DeNisco, 2011; Livingstone et al., 2011), older adults with low appetite (Engel et al., 2011; Walker-Clarke et al., 2022), individuals with chronic pain (Dorado et al., 2018; West et al.,

2012), and individuals with sports injuries (Nakamura & Tsuchiya, 2020; Wadey et al., 2012; Williams et al., 2020). According to the Okun et al. (1988) study, the relationship between hardiness and health was not limited to people's coping and perception of their health or illness. Dolbier et al. (2001) investigated the differences in immune responses between high- and low-hardy individuals. Using blood samples, Dolbier et al. induced cellular immune responses to determine whether there were differences between high-hardy individuals and their low-hardy counterparts. In every antigen exposure, samples from high-hardy individuals demonstrated a greater response and proliferation rate in their immune response.

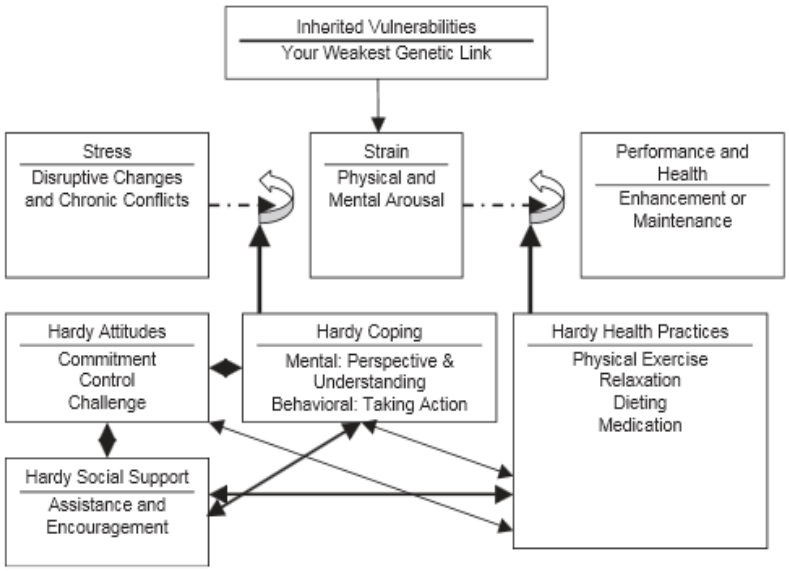
More recent studies replicated the neuroimmunological effects of hardiness (Pandey & Shrivastava, 2017; Reichmann & Holzer, 2016; Sandvik et al., 2013, 2020). Researchers also established the effect of hardiness on treatment-seeking behaviors (Bahrami et al., 2018; Tlimat et al., 2020; Tromp et al., 2004). Tromp et al. (2004) found a significant correlation between the time patients delayed treatment for head and neck cancer and hardiness. Patients who waited more than three months to seek medical care after experiencing known head and neck cancer symptoms were less hardy (Tromp et al., 2004). Tromp observed that less hardy head and neck cancer patients also demonstrated less active coping skills and less social support. In more recent studies in breast and lung cancer patients, researchers reached similar conclusions and observed that the healthy volunteer effect limited the generalizability of trial outcomes, and those trial participants demonstrated a high level of hardiness and coping ability (Bahrami et al., 2018; Tlimat et al., 2020).

Hardiness Model of Performance and Health Enhancement

Given the associations between hardiness and health, Salvatore Maddi and Susan Kobasa developed the hardiness model for performance and health enhancement in 1984 (Maddi, 2013). As Maddi (2013) noted, resilience is the ability of people to thrive and persevere in the face of stress and hardiness provides a method for explaining components of that resilience despite illness. Stress and how an individual handles and processes stress can play an intrinsic role in health (Antonovsky, 1979; Kobasa, 1979; Kowalski & Schermer, 2019; Wenzel et al., 2008; Wiebe & McCallum, 1986). As shown in Figure 2, the hardiness model of performance and health enhancement provides a unified paradigm for understanding how the implementation of hardy attitudes and strategies can influence performance and health (Maddi, 2006).

Figure 2

Hardiness Model for Performance and Health Enhancement.



Note. Copyright Maddi, 2006.

Critiques of Hardiness

Hardiness has been the subject of many critical reviews and analyses. Initial hardiness research lacked methodological grounding (Tartasky, 1993) or a validated measurement scale (Funk & Houston, 1987). In their critical analysis of hardiness, Funk and Houston (1987) questioned the generalizability of hardiness research due to the lack of uniformity in hardiness measurements or statistics. In a later review, Funk (1992) noted the growing consensus around 2nd and 3rd-generation hardiness scales, such as the Personal Views Survey and the Dispositional Resilience Scale; however, the overall applicability of hardiness research had yet to be determined. In 1995, Florian et al. validated the conceptual model of hardiness, stress, and illness among combat soldiers and addressed many flaws referenced by Funk's research.

Several aspects of personality and psychology potentially influence health outcomes. Through critiques of these pathways, researchers have studied personality aspects, including neuroticism, rumination, mindfulness, and worry, to explore confounding and correlation with hardiness (Aspinwall & Tedeschi, 2010; Kowalski & Schermer, 2019). Kowalski & Schermer (2019) found that hardiness acted separately from other personality constructs and better described the relationship between personality and mental health.

Use of Hardiness in the Current Study

The hardiness research summarized above validates my current exploration of hardiness as a potential component of the healthy volunteer effect. Researchers used the hardiness model for performance and health enhancement to examine groups of people facing similar health stresses but achieving different outcomes (Abdollahi et al., 2019; Arshi et al., 2021; Bahrami et al., 2018; Baldassini Rodriguez et al., 2022; Dewi et al., 2020; James, 2021; Luceño-Moreno et al., 2020; Nakamura & Tsuchiya, 2020; Ndlovu & Ferreira, 2019; Robinson, 2013; Sadeghpour et al., 2021; Samoilov & Aleshicheva, 2022; Sandvik et al., 2020; Weiss, 2002).

Clinical Research and Research Volunteer

Clinical trials provide the foundation for developing, manufacturing, and selling new medications. Clinical trials answer two fundamental questions about a potential drug or health intervention, (a) does it work (is it better than the standard of care, does it cause less severe side effects than the standard of care, and does it meet an unmet medical need?) and (b) do the benefits outweigh the risks? Clinical trials follow rigorous

protocols and are highly regulated. In most countries, a clinical trial has assessed any medication or medical procedure prescribed by physicians. Clinicaltrials.gov, a registry and results database of publicly and privately sponsored clinical studies conducted with human participation, listed approximately 420,000 clinical trials representing 220 countries (National Library of Medicine, 2022).

Drug development through the planning and execution of a clinical trial is a lengthy and costly endeavor (Eichler & Sweeney, 2018; English et al., 2010; Gresham et al., 2020). Although the exact cost of developing a new drug is difficult to determine, reviews of published data estimate the cost from $314 million to $2.8 billion per drug from discovery to market, depending on the therapeutic area (Wouters et al., 2020). A sizable portion of development costs are accrued in late-stage testing during phase II and phase III clinical trials, which are larger studies involving hundreds or thousands of volunteers (Arrowsmith, 2011; Gresham et al., 2020; van Norman, 2019). Due to the cost and commitment needed to progress a drug into Phase II and III testing, researchers have expressed concern that approximately half of clinical drug failures occur during phase II testing (DiMasi, 2001; van Norman, 2019). A 2019 Forbes article highlighted that much of what influences the pricing and availability of medication is the research cost from experimental medicines that fail in human testing (Fleming, 2019; Harper, 2013, 2017). Researchers at the American Cancer Society found that although it takes on average six years of testing before a drug is ready for use in human clinical trials, the most rate-limiting step in the availability of new medications is the time it takes to complete clinical trials (American Cancer Society, 2020).

Drug development has become increasingly complex. Results from an analysis by the TCSDD (2021) indicated that the rise in the complexity of trial protocols has led to increased pressure and workload for investigative sites and study participants that lengthened trial durations. The rising complexity also made trial recruitment more difficult. Other researchers observed a correlation between the increasing costs and drug development delays with the trial enrollment challenges (Bentley et al., 2019; Eichler & Sweeney, 2018; Lamberti et al., 2021; Martin et al., 2017; Sine et al., 2021). Researchers have estimated that most clinical trials fail to achieve their initial enrollment target dates, with approximately 10%-30% of trial sites never enrolling a patient (Lamberti et al., 2021; Stempel, 2017).

Researchers have focused on understanding why patients do not volunteer for clinical studies (Elston, 2021b; Guerra et al., 2022; Lara et al., 2001; Mills et al., 2006; Murthy et al., 2004; Ross et al., 1999; Unger, Vaidya, et al., 2019). Although previous research established some of the reasons why patients do or do not volunteer for trials (Mattson et al., 1985; Schutta & Burnett, 2000), the disparity between patients who are eligible, and report being interested and those who participate is large (CISCRP, 2021). Beyond the study-driven considerations (e.g., time for participation and costs), defining the relationship between personality and biopsychosocial differences between trial participants and nonparticipants is essential. As clinical trials become more complex and trial participation rates decline, testing whether differences in trial participants could potentially influence research outcomes is necessary.

Healthy Volunteer Effect

The healthy volunteer effect is a type of nonresponse selection bias (Delgado-Rodriguez, 2004; Struijk et al., 2015). This phenomenon occurs when individuals participating in a clinical trial or study are systemically different from nonparticipants (Struijk et al., 2015). Researchers have focused considerable attention on the volunteer subject and whether and how volunteerism biases study results (Bell, 1961; Burr et al., 2016; Edgerton et al., 1947; Fisher et al., 2018; Lasagna & von Felsinger, 1954; Locke, 1954; Olsen et al., 2020; Richards, 1960; Wallin, 1949; Wei et al., 2018). In their pivotal examination of the volunteer subject, Rosnow and Rosenthal (1965) recognized the growing concern over what they termed "the volunteer problem". Rosenthal cited the desire to extend the generalizability of their work and the barrier of nonrepresentation among volunteers participating in research studies.

Researchers acknowledged the potential selection bias inherent in the use of volunteers. Rosnow and Rosenthal (1965) were the first to define the characteristics of volunteers and nonvolunteers. Whether research participation was through mail questionnaires or in-person psychological experiments, Rosenthal observed systemic differences between volunteers and nonvolunteers. Volunteers demonstrated consistent characteristics. They displayed greater intellectual abilities and tended to be more social and younger. Rosenthal concluded that in many psychological experiments, significant differences exist between volunteers and nonvolunteers. Although these differences introduced the potential for bias in their violation of random sampling, the effect of this bias on research outcomes could not be determined. Rosenthal's results aligned with an

earlier assessment that found measurable differences (education, age, and religious inclinations) between participants and nonparticipants that introduced unmeasurable sampling bias in research studies that relied on volunteers (Wallin, 1949).

Impact of the Healthy Volunteer Effect on Research Outcomes

Subsequent studies on research volunteers clarified the healthy volunteer effect and determined the effects that participation had on research outcomes. Those studies focused on the effects on odds ratios (Austin et al., 1981; Schieve et al., 2018), statistical inference (Ackerman et al., 2021; Jones, 1996; Stuart & Rhodes, 2017), and relative risk (Kreiger & Nishri, 1997; Tabár et al., 2019). Researchers found inconsistent results when measuring the healthy volunteer effect on study outcomes (Schieve et al., 2018; Stuart & Rhodes, 2017; Tabár et al., 2019). Most authors concluded that differences between participants and nonparticipants could lead to a misestimation of risk factors, and that the generalization of research depended on a thorough assessment of nonrespondents to define the effect of the bias (Boniface et al., 2017; Fry et al., 2017; Jensen et al., 2022; Mölenberg et al., 2021; Schieve et al., 2018). Study results continued to confirm fundamental differences among trial participants and nonparticipants, with participants tending to be younger, better educated, and demonstrating overall better health than nonparticipants (Callahan et al., 2007; Croswell et al., 2010; Ederer et al., 1993; Guerra et al., 2022; Ludmir et al., 2019; van Heuvelen et al., 2005). In a study examining personality assessments among volunteers in a Phase I clinical central nervous system drug trial, Ball et al. (1993) showed that participants performed differently than the general population on the Eysenck Personality Questionnaire (EPQ). Ball et al. (1993)

found that participants demonstrated a higher willingness to take risks and more openness to new experiences. In a 2018 study, Wei et al. confirmed that trial volunteers performed differently from nonvolunteers on the EPQ and other personality assessments.

Studies on the healthy volunteer effect observed the impact on study outcomes in numerous ways. Ball et al.'s (1993) assessment of Phase I study subjects found that healthy individuals seeking participation in clinical trials may affect the reporting of side effects. Realo et al. (2018) indicated that subjects' personality was associated with their reporting of adverse drug reactions. In their research, Rosnow and Rosenthal (1966) found that volunteers are more likely to provide data that confirm what they perceive as the study's research goals. Participants and nonparticipants also show differences in health status (Boniface et al., 2017; Melton et al., 1993; Schieve et al., 2018). Using health records, Melton et al. (1993) analyzed nonresponders in a study of diabetic complications and determined that although the diabetes assessments were similar across participants and nonparticipants, nonparticipants showed a significant increase in non-diabetes risk factors.

Researchers proposed the healthy volunteer effect to explain the unexpected differences in mortality rates observed in trials (O'Keeffe et al., 2018; Struijk et al., 2015; Zheng et al., 2020). When estimating the appropriate duration of prevention trials, researchers found that death rates among control groups were routinely lower than expected due to the healthy volunteer effect (Church et al., 1993; Struijk et al., 2015; Zheng et al., 2020). In a retrospective analysis of a population-based prostate cancer screening study, Kjellman et al. (2009) observed the benefits of the initial screening but

found differences in overall survival and risk of death from other causes between participants and nonparticipants. Similar results were observed in assessments of lung cancer studies (Hestbech et al., 2011; O'Keeffe et al., 2018; Richiardi et al., 2002; Tang et al., 2022; Tlimat et al., 2020; Vehmas & Oksa, 2015) and breast cancer studies (Ellis et al., 2001; Paci & Alexander, 1997; Tabár et al., 2019) where the healthy volunteer effect led to an overestimation of benefits from intervention or screening and an underestimation of disease mortality. Retrospective analyses uncovered systemic errors or incorrect conclusions due to the healthy volunteer effect. For example, across several epidemiological and randomized clinical trials, Bonovas et al. (2007) concluded that statins prevented hematological malignancies. When this association was not clearly observed in the general population, Bonovas et al. suggested that the studies were subject to selection bias because of the healthy volunteer effect.

The observation of the healthy volunteer effect in randomized clinical trials is a significant finding because it does not question the internal validity of the participants (as all randomized groups have volunteered for participation) but questions the applicability of results to the general population (nonvolunteers). Similar outcomes were found in the Physicians' Health Research Group's testing of low-dose aspirin and decreased cardiovascular mortality. In this study, the significant reduction of low-dose aspirin on the risk of myocardial infarction was not detected because the cardiovascular mortality rate among the study participants was 15% of that observed in the general population ("Steering Committee of the Physicians' Health Study Research Group," 1989). The healthy volunteer effect made the impact of aspirin use impossible to confirm due to the

rate of events among participants, which was so low that it would have required 11 years from the study's initial completion date to achieve the required number of events ("Steering Committee of the Physicians' Health Study Research Group," 1989). Researchers identified statistical calculation errors due to the healthy volunteer effect in cardiovascular studies (Burr et al., 2016; Criqui et al., 1979; Leening et al., 2014), blood sampling trials (Jordan et al., 2013), and hypertensive interventions (Burke et al., 2007; Gorelick & Sorond, 2020).

A field of research focused on assessing trials and interventions for the healthy volunteer effect has emerged. Pinsky et al. (2007; 2012) found evidence of the healthy volunteer effect in an assessment of oncology prevention and screening trials. Volunteers in oncology trials were healthier and had a lower mortality rate than the general population. These results addressed findings from a 1996 study exploring the external validity of the Adventist Health Study results. Lindsted et al. (1996) observed the healthy volunteer effect when they found that the relative risk for all causes of death was higher among nonresponders than responders. Lindsted et al. attributed other differences in participants to the healthy volunteer effect. Participants in clinical trials demonstrate greater health awareness and, importantly, compliance with treatment. A study investigating healthy volunteer bias in dental research found that participants in a periodontitis study were more likely to utilize other health services, had lower surgery rates, and demonstrated differences in the effectiveness of treatment (del Aguila et al., 2004). In a cross-sectional examination of smokers participating in a dietary intervention trial, Thomson et al. (2005) found that participants had healthier dietary habits than those

who did not participate. The healthier behaviors of participating smokers counteracted the effects of their smoking (Thomson et al., 2005).

Researchers confirmed that participants and nonparticipants differ in indeterminate ways, and an adequate explanation for these differences had yet to be provided (Burr et al., 2016; Froom et al., 1999; Krauss, 2018; Olsen et al., 2020). In a 1999 study on the healthy volunteer effect among industrial workers, Froom et al. found that regardless of trial and intervention type, study volunteers were in better health than nonvolunteers despite their primary illness. The healthy volunteer effect had become an umbrella term for unexplained differences among trial participants. Researchers had explored numerous possible explanations for the differences, including the inclusion and exclusion criteria of study protocols and physicians targeting their trial recruitment to healthier individuals (Ederer et al., 1993; Elston, 2021b; Hillyer et al., 2019). None of these explanations fully account for the observed differences in trial participants and attempts to adjust for the healthy volunteer effect statistically have not been successful (Ackerman et al., 2019, 2021; Foy et al., 2011; Stuart & Rhodes, 2017). In a 2011 analysis, Foy et al. created a model for adjusting disease status-related eligibility criteria in cancer mortality prediction models used in clinical trials. Foy et al. hypothesized that volunteers are healthier than nonvolunteers due to enrollment criteria, which explained why data from clinical trials differed from the general population. They designed a model that successfully adjusted for eligibility-related criteria but found that despite this adjustment, the model still did not fully account for the observed differences in trial outcomes. Foy et al. determined that there were unexplained components of health

behaviors that the model could not account for and attributed those additional factors to the healthy volunteer effect. More recent statistical modeling attempts, including advanced analytics and artificial intelligence algorithms, failed to fully adjust for the differences in trial outcomes between participants and the general population (Ackerman et al., 2019, 2021; Stuart & Rhodes, 2017).

Conceptual Framework

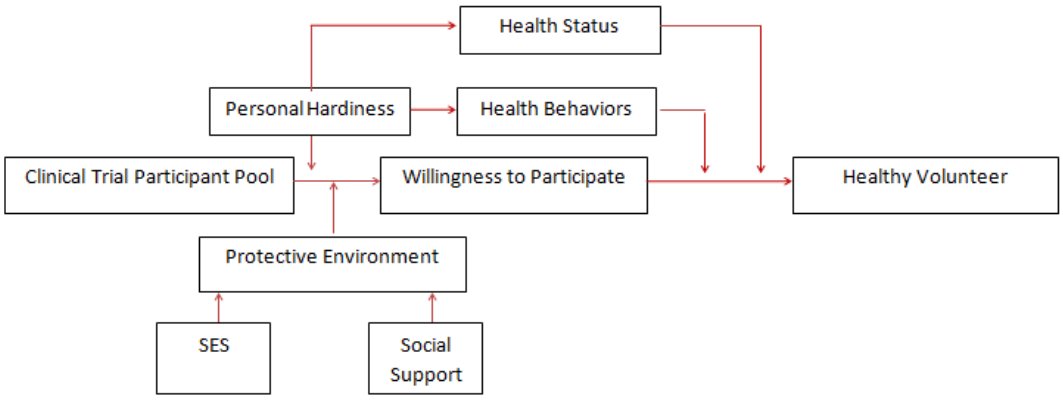
I used the hardiness model for performance and health enhancement as the theoretical framework for this study investigating the association between personal hardiness and willingness to participate in a trial as an unexplored of the healthy volunteer effect. Over the past 45 years, the model has been validated and applied in various situations and circumstances (Abdollahi et al., 2019; Baldassini Rodriguez et al., 2022; Luceño-Moreno et al., 2020; Maddi, 2006; Sadeghpour et al., 2021; Wiebe & Williams, 1992). Researchers used the model to describe differences in health care and health promotion behaviors (Abdollahi et al., 2019; Samoilov & Aleshicheva, 2022; Wiebe & McCallum, 1986). In this context, with modifications of specific inputs, the model served as an appropriate framework for understanding the effects of hardiness on a clinical trial participant's willingness to volunteer.

The hardiness model for performance and health enhancement was applied to a conceptual model for personal hardiness and the healthy volunteer effect. When applying the model to clinical trial participants, stress was the illness state precipitating the offer to enroll in a clinical trial. The willingness to participate in the clinical trial or effectively manage stressful circumstances reflected the model's hardy coping component. The

model further indicated that hardy individuals seek and maintain high-quality social support. These model components are consistent with research findings that healthy volunteers are culled from higher SES and have robust social and emotional support systems (Czwikla et al., 2022; Ellis et al., 2001; Fry et al., 2017; Jordan et al., 2013; Khera et al., 2015; Lindsted et al., 1996; Pinsky et al., 2007). The model also included a link between hardy coping and the adoption and maintenance of positive health behaviors, a variable of interest in this investigation. Finally, the model linked hardy attitudes and hardy coping to health status or outcomes through their interactive relationships with social support and health behavior variables. The conceptual model included personal hardiness as a personality component that leads to a greater willingness to participate among clinical trial volunteers. Personal hardiness influenced health status and behaviors. These components, coupled with the protective environmental factors associated with personal hardiness (increased SES and increased social support), comprised previously undetermined factors in the healthy volunteer effect. Figure 3 shows the proposed model.

Figure 3

Proposed Model for Hardiness and the Healthy Volunteer



Summary

Previous researchers established the unexplored differences between participants in clinical trials and nonparticipants. As drug development becomes more costly and complex, the need for trial participants becomes critical because it has a greater impact on the timely development of new medications. Current understanding of the healthy volunteer effect in clinical trials and its established influence on trial outcomes account for only a portion of the observed differences between participants and nonparticipants.

I proposed that individuals more willing to participate in a clinical trial demonstrate a higher degree of personal hardiness than those unwilling. In turn, hardiness makes participants more likely to participate and to express behaviors that may influence trial outcomes and lead to less generalizable results. In Chapter 3, I include details on the research methods, research questions, and hypotheses.

Chapter 3: Research Method

This chapter explains the quantitative methods I used in this research to examine the relationship between personal hardiness and willingness to participate in a clinical trial. I discuss the research design and rationale, study methodology for data collection and analysis, and threats to study validity. Approval from the Walden University Institutional Review Board (IRB) was granted before I collected any study data. This study was a nonexperimental examination of individuals offered the opportunity to participate in a hypothetical, unrelated, interventional clinical trial. I assessed individuals willing and unwilling to participate in the clinical trial for their personal hardiness, health status and behaviors, and perceived social support. I assessed differences in personal hardiness between those willing and unwilling to participate in a clinical trial and determined whether there was a statistically significant association between personal hardiness and willingness to participate.

Research Design and Rationale

I examined the association between personal hardiness and willingness to participate. The independent variable was personal hardiness, and the dependent variable was willingness to participate in a trial. Health status, behavior, and social support were covariates. Personal hardiness was assessed as a moderator on any association between the covariates and the outcome variable.

I used a cross-sectional design to examine personal hardiness among those willing and unwilling to participate in a clinical trial. I administered a single electronic questionnaire to gather data from participants. The research design was similar to that

used by Ellis et al. (2001), which focused on randomized clinical oncology trials and examined women's attitudes and motivations toward breast cancer clinical trial participation. The Ellis et al. study was a cross-sectional survey that assessed how willingness to participate in a clinical trial differed among groups of women and their characteristics, such as anxiety and depression levels. I used the Ellis et al. study as the basis for examining the attitudes and motivations in clinical trial participation through a cross-sectional survey.

There were differences between the Ellis et al. (2001) approach and that used in the current study. Ellis et al. studied participation in a hypothetical clinical trial and emphasized the physician's role in a patient's decision to participate in a trial. In the current study, I did not examine the interaction between physician and patient and the physician's role in the patient's decision to participate in a trial. In addition, Ellis et al. selected participants facing a health crisis. In contrast, the clinical trial in the current study was purely hypothetical. Recent researchers have employed similar designs to assess the difference between participants and nonparticipants (Ginossar et al., 2022; Moorcraft et al., 2016; Sebatta et al., 2020).

Methodology

Population

The intended participants for this study were U.S.-based adults 18 years of age or older. All participants were required to provide informed consent to this study, and only participants who met the inclusion criteria were eligible to participate. Because it was impossible to survey all U.S.-based adults, I used a sampling strategy that allowed for an

appropriate representation of the intended population. I used an electronic survey tool to obtain a representative sample of participants.

Sampling and Sampling Procedures

The minimum sample size for this study was 146 participants. I continued to survey participants until I achieved a minimum sample size of 73 participants willing to participate in a trial and at least 146 total participants. There are approximately 300 million U.S. adults (U.S. Census Bureau, 2022). Researchers estimated that fewer than 5% of eligible U.S. adults participate in interventional research (Unger, Vaidya, et al., 2019). Assuming a 95% confidence interval and a 5% margin of error, I calculated the minimum sample size as 73 participants willing to participate in a clinical trial. I conducted a power analysis in G*Power 3.1.9.7 for a one-tailed test with an alpha of 0.05, a sample size of 146, low association from covariates (R^2 other X = 0.04), and a moderate effect size (H_0 = 0.15 and H_1 = 0.4). I calculated the achieved power to be greater than 95% (1-β = 0.96). The electronic survey tool I used required a minimum of 100 responses to ensure census-based age and gender balance. Figure 4 shows the sample size formula.

Figure 4

Sample Size Calculation

$$n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2}$$

z= z score which for 95% confidence equals 1.96
ε= margin of error (0.05)
n= US adult population
$\hat{p}$ = proportion of population

Procedures for Recruitment, Participation, and Data Collection

I used an electronic survey tool to recruit participants and collect data. I deployed surveys electronically through Momentive's SurveyMonkey Target Audience feature. SurveyMonkey Audience is a paid service that allows a survey to be deployed to a target audience. SurveyMonkey, a company that provides internet-based survey tools, compiles panels of participants to participate in surveys where they are a demographic match. For researchers seeking participants from the United States, there are two sources for participants: SurveyMonkey Contribute and SurveyMonkey Rewards. Panelists in SurveyMonkey Contribute participate in surveys for charity and sweepstake chances. Participants in the SurveyMonkey Rewards are granted credits for each survey they complete. Credits are redeemable for charity or gift cards. Participants in each panel are volunteers and provide demographic information such as race, gender, occupation, and location. In the current study, I leveraged the Target Audience feature to sample participants who were U.S. based and over 18 years of age. Participants provided implied consent by continuing with the survey. Participants were allowed to exit the electronic survey at any time. SurveyMonkey Target Audience was contracted for 150 completed

surveys. I planned to conduct additional surveys in increments of 50 as needed until the minimum of 73 participants responded that they were willing to participate and the minimum of 146 total participants was reached.

Instrumentation and Operationalization of Constructs

I assessed personal hardiness using the HRG. I measured social support through the MSPSS. I assessed health status and behaviors using respective sections from the 2020 BRFSS questionnaire. I informed participants that participation in the study questionnaire was unrelated to their decision to participate or not participate in a clinical trial. I also informed participants that their participation was voluntary, and they were not offered compensation. I provided each potential participant with an informed consent, the selected BRFSS questions, and the HRG and MSPSS questionnaires. I collected demographic information, including age, race, marital status, education, and income, using the BRFSS questionnaire. Contact information (names, addresses, and phone numbers) was not part of the data collection.

Description of Instruments and Validation Studies

HRG

The HRG is a 28-item questionnaire used to calculate an overall personal hardiness score. The HRG evolved from the Dispositional Resilience Scale (DRS-15) (Bartone et al., 2022). Developed in 1995, the DRS-15 has undergone several transformations from the original 50-item scale developed to calculate the hardiness of city bus workers (Bartone, 1989, 2007, 2013). In identifying limitations in the DRS-15, Bartone et al. (2022) sought to improve the reliability and validity of the underlying

hardiness constructs of Commitment, Challenge, and Control. Bartone et al. combined 15 questions from the DRS-15 with 21 newly developed items. The most recent HRG consisted of 28 items, with the subscales of Challenge and Commitment containing 10 items each and the remaining eight measurements for Control. The HRG has a reported Cronbach's alpha coefficient $\alpha = .93$ for total hardiness and high reliability for each hardiness subscale: Challenge (0.85), Control (0.84), and Commitment (0.89; Bartone et al., 2022). The HRG is proprietary, and access is available through MHS Assessments. MHS Assessments does not share HRG scoring keys and algorithms but provides scored data sets through a web-based portal.

MSPSS

The MSPSS is a 12-item questionnaire developed as a self-reported measurement of perceived social support (Zimet et al., 1988). The MSPSS builds on the existing social support scales and addresses a previously missing component, the perception of social support. The MSPSS assesses social support through three sources: Friends, Family, and Significant Others (Zimet et al., 1988). Research has confirmed the MSPSS's validity and reliability. The Family, Friends, and Significant Other subscales have reported Cronbach's alpha coefficients between .81 and .98, with the full scale ranging from .84 to .92 (Zimet et al., 1990). The MSPSS questions and scoring are in the public domain and free to use. There is no established scoring convention, although results are often calculated as a total mean score (Zimet et al., 1990). I defined low perceived social support as a mean score between 12 and 35, medium perceived support as 36–60, and high perceived support as 61–84 (see Zimet et al., 1988).

BRFSS

The BRFSS is the world's largest ongoing health survey system (National Center for Chronic Disease Prevention and Health Promotion, 2014). Established in 1984, the BRFSS provides uniform questions on health-related risk behaviors and chronic health conditions. The BRFSS consists of a fixed core set of health and health behavior questions, a rotating set of core questions, and optional modules for specific U.S. states and health conditions. I included four BRFSS questions: one for health status and three for health behaviors. Health status is categorical and measures general health on a 5-point scale ranging from excellent to poor. Health behaviors include smoking, alcohol consumption, and exercise:

- Do you smoke cigarettes? (Every day, Some days, Not at all, Don't know/Not sure, Refused)
- During the past 30 days, how many alcoholic drinks per week did you have, include any alcoholic beverage such as beer, wine, a malt beverage, or liquor? (Number of drinks per week)
- During the past month, other than your regular job, did you participate in any physical activity or exercises such as running, calisthenics, golf, gardening or walking for exercise? (Yes, No, Don't know/Not Sure, Refused)

Alcohol consumption was categorized as low-risk drinking for females who report consuming fewer than seven alcoholic beverages and males who report consuming fewer than 14 alcoholic beverages. High-risk drinking was defined as seven or more alcoholic beverages for females and 14 or more for males. The BRFSS has been studied for

reliability and validity and has high reliability and validity for understanding general health, chronic conditions, and mental and physical health (Lara et al., 2001; Pierannunzi et al., 2016).

Willingness to Participate

The Center for Information and Study on Clinical Research Participation is a nonprofit organization whose core mission is to understand and influence public perception of clinical research. Biannually, CISCRP publishes a global study on public and patient clinical research views (CISCRP, 2013). I used the CISCRP's "willingness to participate" question to determine participant willingness:

- In general, how willing would you be to participate in a clinical research study (Very willing, Somewhat willing, Somewhat unwilling, Not willing, Not sure)?

I measured those very willing and somewhat willing as willing to participate, and those somewhat unwilling and not willing were measured as unwilling to participate. Table 1 shows the operationalization of constructs.

Table 1

Operationalization of Constructs

Variable	Definition	Measured/manipulated	Variable score
Age	Participant age in years	Survey	Years
Race	Participant race	Survey	White, Black, American Indian/Native Alaskan, Asian, Other
Marital status	Participant marital status	Survey	Married, divorced, widowed, separated, never married or member of unmarried couple
Education level	Highest level of education completed by the participant	Survey	Never attended school, elementary, some high school, HS grad, some college, college grad
Annual income	Participant household income from all sources	Survey	>$25K, >$35K, >$50K, >$75K, $75K+
Willingness to participate	Participant willingness to participate in a clinical research study	Survey using CISCRP's willingness to participate question (CISCRP, 2013)	Very willing, somewhat willing, somewhat unwilling, unwilling, not sure
Health status	Perceived state of participant's health	Survey using BRFSS 2020 questionnaire (National Center for Chronic Disease Prevention and Health Promotion, 2014)	Excellent, very good, good, fair, poor
Health behavior	Combination of positive and negative behaviors, which includes smoking, alcohol use and exercise	Survey using BRFSS 2020 questionnaire (National Center for Chronic Disease Prevention and Health Promotion, 2014)	Smoking: Every day, Some days, Not at all Alcohol: # of drinks per week. Categorized as low or high-risk drinking based on # and participant gender Exercise: Yes, No
Personal hardiness	Key characteristics that enhance or undermine stress resilience or adaptability	Survey using the HRG (Bartone et al., 2022)	Scored through MHS Assessments
Social support	Participant's perception of support from friends and family	MSPSS (Zimet et al., 1988)	Low = 12–35, Medium = 36–60 High = 61–84

Data Analysis Plan

This study addressed the following research questions:

Research Question 1: Is there any association between personal hardiness and an individual's willingness to participate in a clinical trial?

$H_0$1: There is no statistically significant association between personal hardiness and an individual's willingness to participate in a clinical trial.

H_a1: There is a statistically significant association between personal hardiness and an individual's willingness to participate in a clinical trial.

Research Question 2: Is there any association between positive health behaviors and an individual's willingness to participate in a clinical trial?

$H_0$2: There is no statistically significant association between positive health behaviors and an individual's willingness to participate in a clinical trial.

H_a2: There is a statistically significant association between positive health behavior and an individual's willingness to participate in a clinical trial.

Research Question 3: Is there any association between social support measures and an individual's willingness to participate in a clinical trial?

$H_0$3: There is no statistically significant association between social support measures and an individual's willingness to participate in a clinical trial.

H_a3: There is a statistically significant association between social support measures and an individual's willingness to participate in a clinical trial.

Research Question 4: Is there any association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial moderated by personal hardiness?

$H_0$4: There is no statistically significant moderation by personal hardiness in the association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial.

H_a4: There is statistically significant moderation by personal hardiness in the association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial.

I used descriptive statistics, including frequencies, to categorize the research participants. All descriptive variables were reported as frequencies, including gender, race, marital status, education level, and income. I reported the mean and standard deviation for age. The independent variable was personal hardiness. The dependent variable was willingness to participate in a clinical trial. Predictors of interest included health status, health-related behaviors, and social support. Logistic regression was used to assess the research hypotheses. The logistic regressions assessed for (a) any association between personal hardiness and willingness, (b) any association between health behaviors and willingness, and (c) any association between social support and willingness. I performed a regression analysis to determine if any significant association between health status, health-related behaviors, or social support variables and willingness were moderated by personal hardiness. The regression with moderation model included significant variables as covariates to address confounding.

All analyses were performed using the Statistical Package for Social Sciences (SPSS, version 27). A threshold of $p < 0.05$ indicated significance. Results were interpreted as odds ratios and significant moderation from personal hardiness was reported.

Threats to Validity

Potential threats to this study's internal validity included instrumentation and selection bias. As participants were recruited through an electronic survey tool, there was a risk that participants were not representative of the general U.S. adult population who could potentially volunteer for a trial. All panelists who are U.S.-based adults 18 years of age or older were allowed to participate. These criteria ensured that the study's participants were as representative as possible.

There are no standard measurements for personal hardiness. Previous hardiness research measured hardiness using the Personal Views Survey (PVS III-R) developed by Dr. Salvatore Maddi (Maddi et al., 2009). Through the Hardiness Institute, Dr. Maddi provided permission personally to utilize the PVS III-R. Upon his death, the Hardiness Institute no longer grants permission to utilize the PVS III-R for student research. The HRG is a recent hardiness measurement scale (Bartone et al., 2022). The HRG, which was developed in 2022, has sufficient reliability and validity and was based on the DRS-15, a hardiness measure that has been used for over 25 years (Bartone, 2007, 2013). The HRG, at 28-items, is a longer survey compared to the PVS III-R, which consists of 18 questions, and hardiness research has highlighted the risk in lengthy surveys (Bartone et

al., 2022). There was a threat to internal validity due to study instrumentation. The lack of a standard hardiness scale was a potential source of construct validity.

Regarding external validity, clinical trials recruit patients from across the globe. Although I included U.S.-based adults in this study, there is a risk that results are less generalizable to all potential clinical trial participants. Most trial participants are U.S.-based, and the risk to external validity is minimal (CISCRP, 2021; Lamberti et al., 2021). An additional threat to external validity for cross-sectional surveys is self-responder bias (Sedgwick, 2015). Participants were potentially less honest in self-assessing their hardiness and willingness to participate in a trial. Self-responder bias is often amplified when the researcher observes participants (Sedgwick, 2015). By administering the survey electronically, self-responder bias was minimized.

Ethical Procedures

Participation was voluntary. I did not collect any identifiable information, and the confidentiality of participants was maintained. Because data were collected through an electronically administered questionnaire, there was no risk that responses could be connected to specific participants. Approval from the Walden University IRB (10-21-22-0250384) was obtained before data collection began. MHS assessments own the HRG, and scored datasets were only available through their proprietary portal. All data, including scored HRG datasets, were stored securely on a password-protected file on a personal computer.

Summary

In summary, this chapter explains the methodology for this quantitative study examining the association between personal hardiness and willingness to participate in a trial. This chapter provides a detailed overview of the study design, study participants, sample size calculation, instruments, data collection, and data analysis plan. Results from this current study are discussed in Chapter 4.

Chapter 4: Results

In this quantitative study, I assessed personal hardiness among those willing and unwilling to participate in a clinical trial. I sought to determine (a) the association between personal hardiness and willingness to participate, (b) the association between positive health behaviors and social support and willingness to participate, and (c) whether personal hardiness moderates the association, if any, between health status, positive health behaviors, and social support and willingness to participate in a clinical trial. I administered a questionnaire to collect data from participants regarding their hardiness, health status, health behaviors, social support, and willingness to participate in a clinical trial. I measured personal hardiness utilizing the HRG (see Bartone et al., 2022). I measured social support through the MSPSS (see Zimet et al., 1988). I measured health status and behaviors using the 2020 BRFSS (see Pierannunzi et al., 2016).

I used a cross-sectional design to determine whether participants were willing or unwilling to participate in a clinical trial, their level of personal hardiness, their health status, their positive health behaviors, and their social support. I also collected additional demographic information including gender, age, race, marital status, level of education, and income. I used ordinal logistic regression to analyze (a) the association between personal hardiness and willingness to participate in a trial, (b) the association between health behaviors and willingness to participate in a trial, and (c) the association between social support and willingness to participate in a trial. Moderation analyses were used to determine whether the effect of an independent variable on a dependent variable was equal across all levels of a moderator, or second independent variable. Moderation or

interaction analyses were used to determine whether the presence of a moderator alters the relationship, if any, between variables. I performed a regression analysis with moderation to determine whether any association between health status, health behaviors, social support, and willingness to participate was moderated by personal hardiness.

In this chapter, I detail the results of my study, including an overview of the research questions, the purpose of the study, and data collection methods. For each research question, I discuss the results and present whether I failed to reject the null hypothesis or rejected the null hypothesis in favor of the alternative hypothesis.

Research Question 1: Is there any association between personal hardiness and an individual's willingness to participate in a clinical trial?

$H_0$1: There is no statistically significant association between personal hardiness and an individual's willingness to participate in a clinical trial.

H_a1: There is a statistically significant association between personal hardiness and an individual's willingness to participate in a clinical trial.

Research Question 2: Is there any association between positive health behaviors and an individual's willingness to participate in a clinical trial?

$H_0$2: There is no statistically significant association between positive health behaviors and an individual's willingness to participate in a clinical trial.

H_a2: There is a statistically significant association between positive health behavior and an individual's willingness to participate in a clinical trial.

Research Question 3: Is there any association between social support measures and an individual's willingness to participate in a clinical trial?

$H_0$3: There is no statistically significant association between social support measures and an individual's willingness to participate in a clinical trial.

H_a3: There is a statistically significant association between social support measures and an individual's willingness to participate in a clinical trial.

Research Question 4: Is there any association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial moderated by personal hardiness?

$H_0$4: There is no statistically significant moderation by personal hardiness in the association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial.

H_a4: There is statistically significant moderation by personal hardiness in the association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial.

Data Collection

I used a single administration questionnaire to collect data for this study. Before administering any surveys, I obtained approval from the Walden University IRB. Following receipt of IRB approval, I deployed surveys electronically through Momentive's SurveyMonkey using the Target Audience service. SurveyMonkey Audience is a paid service that allows a survey to be deployed to a target demographic of interest. SurveyMonkey is a company that provides internet-based survey tools. The SurveyMonkey Target Audience feature organizes panels of participants to participate in surveys where they are a demographic match. I used the Target Audience feature to

sample participants who were U.S. based and over 18 years of age. I contracted SurveyMonkey Target Audience for 150 completed surveys. I planned to deploy additional surveys in increments of 50 until a minimum of 73 participants responded that they were willing or somewhat willing to participate, and the minimum of 146 total participants was reached. Data collection began on October 21, 2022 and concluded on October 22, 2022. I collected a total of 209 responses. After review, 208 responses were included in the analysis because one survey was incomplete. Although I contracted SurveyMonkey for 150 responses, they collected 209 responses based on their estimated completion rate. The completion rate was higher than SurveyMonkey estimated, and an additional 58 responses were provided above the contracted number. Because 165 participants reported they were willing or somewhat willing to participate, I did not deploy additional surveys and concluded the data collection after the initial round of deployment.

MHS Assessments own the HRG and scored data sets are only available through their proprietary portal, Talent Assessment Portal-TAP. Hardiness scores were generated through Talent Assessment Portal-TAP from October 22, 2022, through October 31, 2022. I stored completed surveys, including calculated hardiness scores, on a password-protected file for analysis.

Review of Survey Responses

Demographics

All study participants ($N = 208$) were U.S.-based adults over the age of 18 years. The median participant age was 41 years ($SD = 15.2$), and most participants were 18–44

years (57.7%, *n* = 120). There were 109 respondents who identified as female (52.4%), 96 respondents identified as male (46.2%), and three participants identified as other (1.4%). Most participants were White (69.7%, *n* = 145), reported being married (52.4%, *n* = 109), and had a college degree (52.9%, *n* = 110). Regarding income, most participants, 34.6% (*n* = 72), reported making equal to or more than $75,000 per year. Table 2 provides the participant demographic characteristics.

Table 2

Descriptive Statistics for Demographic Variables

Variable	%	*n*
Age (in years)		
18–44	57.7	120
45–64	29.8	62
64–74	10.6	22
75 and older	1.9	4
Gender		
Male	46.2	96
Female	52.4	109
Other	1.4	3
Race		
White	69.7	145
Black	9.1	19
America Indian or Alaska Native	1.4	3
Asian	14.4	30
Other	3.4	7
Don't know/not sure/ refuse to answer	1.9	4
Marital status		
Married	52.4	109
Divorced	12.0	25
Widowed	2.9	6
Separated	2.4	5
Never married or member of unmarried couple	29.3	61
Refuse to answer	1.0	2
Education		
Elementary (Grade 1 through 8)	1.9	4
Some high school (Grade 9 through 11)	4.8	10
High school graduate (Grade 12 or GED)	18.3	38
Some college or technical school	21.6	45
College graduate	52.9	110
Refused	0.5	1
Income		
Less than $25,000	16.8	35
Less than $35,000	10.1	21
Less than $50,000	18.3	38
Less than $75,000	16.3	34
$75,000 or more	34.6	72
Don't know	3.8	8

Note. $N = 208$.

Health Status and Positive Health Behaviors

With regards to health status, 18.3% (*n* = 38) of participants reported excellent health, 36.5% (*n* = 76) self-reported having very good health, 31.3% (*n* = 65) reported having good health, 11.5% (*n* = 24) reported fair health, and 1.9% (*n* = 4) rated their health as poor. Most participants (77.4%, *n* = 161) reported that they performed some form of physical activity in the last 30 days. When asked about their smoking habits, most respondents reported being nonsmokers, with 69.2% (*n* = 144) stating they do not smoke at all.

Participants also reported their drinking habits. On a per week basis, participants reported having 0 to 50 (*SD* = 7.85) alcoholic drinks. For female participants, consuming fewer than seven alcoholic beverages per week was defined as low-risk, and consuming seven or more as high-risk. For participants who identified as male, low-risk drinking was defined as having fewer than 14 beverages and high-risk as consuming 14 or more per week. The majority of female and male participants were categorized as low-risk drinkers. Table 3 provides data on participant health status and behaviors responses.

Table 3

Descriptive Statistics for Health Status and Behaviors

Variable	%	*n*
Health status		
Excellent	18.3	38
Very good	36.5	76
Good	31.3	65
Fair	11.5	24
Poor	1.9	4
Don't know/not sure/refused	0.5	1
Exercise in last 30 days		
Yes	77.4	161
No	20.2	42
Don't know/not sure	2.4	5
Smoking		
Not at all	69.2	144
Some days	11.1	23
Every day	13.5	28
Don't know/not sure	3.4	7
Refused	2.9	6
Alcohol risk (female)		
Low risk	89.0	97
High risk	11.0	12
Alcohol risk (male)		
Low risk	87.5	84
High risk	12.5	12

Note. $N = 208$

Social Support

Social support was measured using the MSPSS (see Zimet et al., 1988). Standard MSPSS scoring rates are from 1 to 7, where 1 = *very strongly disagree* and 7 = *very strongly agree*. A total perceived social support score was calculated by totaling the 12 MSPSS measures. I used standard MSPSS categories in which scores of 12 through 35 were defined as low perceived support, 36 through 60 as medium perceived support, and

61 through 84 as high perceived support. Most participants (65.9%, *n* = 137) had high perceived support. Table 4 details participants' perceived social support.

Table 4

Descriptive Statistics for Perceived Social Support

Response	%	*n*
High perceived support	65.9	137
Medium perceived support	29.8	62
Low perceived support	4.3	9

Note. $N = 208$.

Willingness to Participate

Willingness to participate in a trial was measured on a 5-point Likert scale, from *very willing* to *not willing*, and included a *not sure* option. Participants were asked "In general, how willing would you be to participate in a clinical research study (trial)?" Most participants (40.9%, *n* = 85) reported being very willing or somewhat willing, 38.0% (*n* = 79) to participate in a clinical study. Table 5 details participants' responses for willingness to participate.

Table 5

Descriptive Statistics for Willingness to Participate

Response	%	*n*
Very willing	40.9	85
Somewhat willing	38.0	79
Somewhat unwilling	9.1	19
Not willing	3.4	7
Not sure	8.7	18

Note. $N = 208$

Hardiness

I measured hardiness using the HRG. HRG scoring is proprietary and only available through an access-restricted platform owned by MHS Assessments. Scores are

reported as a total hardiness score and available for Challenge, Control, and Commitment subscales. Each participant received a raw total hardiness score and a standard score. Standard scores were adjusted to enable comparison of HRG scores across a normalized population. The norm HRG group provided a benchmark for creating a normal curve for HRG scores. Per the HRG manual, scores can be reported as low, medium, or high, where high represents a score above 110, medium represents scores between 90 and 110, and low scores are below 90. Participants in the current study ranged in hardiness from 50 to 135 *(M* = 97.7, *SD* = 16.6). Table 6 provides participant responses for hardiness.

Table 6

Descriptive Statistics for Hardiness by Rank

Response	%	*n*
High hardiness	24.0%	50
Medium hardiness	42.3%	88
Low hardiness	33.7%	70

Note. N = 208

Research Questions

Personal Hardiness and Willingness to Participate

I assessed the association between personal hardiness and willingness to participate in a clinical trial.

Research Question 1: Is there any association between personal hardiness and an individual's willingness to participate in a clinical trial?

$H_0$1: There is no statistically significant association between personal hardiness and an individual's willingness to participate in a clinical trial.

H_a1: There is a statistically significant association between personal hardiness and an individual's willingness to participate in a clinical trial.

Hardiness was ranked as high, medium, or low, and I defined willingness to participate as *very willing, somewhat willing, somewhat unwilling, not willing*, and *not sure.* I conducted a regression analysis to assess the relationship between hardiness and willingness, where willingness was the dependent ordinal variable, and personal hardiness was an independent variable. As the response variable, willingness to participate was treated as ordinal and had an assumed natural order descending from *very willing* to *not sure*, where the distance between levels was unknown. An ordinal logistic regression (OLR) is an extension of logistic regression that assesses the association between an ordinal dependent variable and one or more independent variables. Four assumptions are required to confirm whether ordinal logistic regression is an appropriate test. Assumption 1 required that the dependent variable be ordinal. Willingness to participate, as the dependent variable, was measured on an ordinal level, ranging from *very willing* to *not sure*. Assumption 2 stated that the independent variable or variables must be continuous, ordinal, or categorical. The independent variable in this study is hardiness which was measured categorically. Assumption 3 required that the independent variables be not highly correlated. I conducted a series of collinearity diagnostics and determined that there was no multicollinearity between the independent variables for hardiness, social support, and health behaviors. Assumption 4 required proportional odds or that the independent variable has the same effect on each interval of the dependent variable. The model fitting showed that the final model significantly improved the fit of

the data, LR $\chi^2(2) = 14.9$, $p < .001$. In addition, the goodness-of-fit test rejected the null hypothesis and concluded that the model fit was good for both Pearson, $\chi^2(6, N = 208) = 5.4$, $p = .49$, and Deviance, $\chi^2(6, N = 208) = 4.67$, $p = .59$.

The independent variable, hardiness, contributed to the model at the high hardiness level, $\beta = 1.39$, $SE = .37$, $Wald = 14.42$, $p < .001$ High hardiness participants were more likely to be more willing to participate in a trial, Exp_β = 4.01, 95% CI [1.96, 8.21], compared to the reference level, low hardiness. For high hardiness participants, the odds of being more willing to participate in a trial was four times that of low hardiness participants. Table 7 details the regression results for hardiness and willingness.

Table 7

Regression Results for Willingness to Participate and Hardiness

						95% CI for Exp_β	
Response	β	*SE*	*Wald*	Sig	Exp_β	Lower	Upper
High hardiness	1.39	.37	14.42	.000	4.01	1.96	8..21
Medium hardiness	.48	.29	2.67	.102	1.62	.91	2.90

Note. Low hardiness is the reference variable.

Positive Health Behaviors and Willingness to Participate

I assessed the association between positive health behaviors and willingness to participate in a clinical trial.

Research Question 2: Is there any association between positive health behaviors and an individual's willingness to participate in a clinical trial?

$H_0$2: There is no statistically significant association between positive health behaviors and an individual's willingness to participate in a clinical trial.

H_a2: There is a statistically significant association between positive health behavior and an individual's willingness to participate in a clinical trial.

Participants responded to three questions related to positive health behaviors. I treated the independent variable, SMOKE, as an ordinal variable, with responses ranging from *not at all* to *every day*. The independent variable, EXERANY, was treated as a nominal variable, with responses of Yes and No. I asked participants how many alcoholic beverages they consumed per week. Responses were recoded to indicate low or high-risk drinking depending on gender. The independent variables, @DRINKRISKFEMALE and @DRINKRISKMALE, defined high or low risk drinking. I conducted a regression analysis to assess the relationship between positive health behaviors, smoking, and exercise, where having not smoked at all and having exercised at least once in the last 30 days were considered positive health behaviors, and willingness to participate in a clinical trial, where willingness was the dependent, ordinal variable. I defined low risk drinking as a positive health behavior. Because drinking risk was specific to gender, a separate regression analysis was performed for each gender. As the response variable, willingness to participate was treated as ordinal and had an assumed natural order descending from *very willing* to *not sure*, where the distance between levels was unknown. As with hardiness, an ordinal logistic regression analysis was conducted to assess the association between smoking, exercise, and willingness. The independent variables were assessed a priori to confirm there was no violation of the no multicollinearity assumption. The model fitting showed that the final model did significantly improve the fit of the data, LR $\chi^2(3) = 18.06$, $p < .001$. In addition, the

goodness-of-fit test failed to reject the null hypothesis and confirmed that the model fit was good for Deviance, $\chi^2(17, N = 191) = 23.34$, $p = .139$. The null hypothesis was rejected for Pearson, $\chi^2(17, N = 191) = 31.41$, $p = .018$.

The independent variables, SMOKE and EXERANY, contributed to the model. For SMOKE, the model was significant for those who reported not smoking at all, β = -1.25, *SE* = .44, *Wald* = 8.00, $p = .005$, and for those who reported smoking some days, β = -1.49, *SE* = .57, *Wald* = 6.90, $p = .009$, where smoking every day was the reference category. Not smoking at all was associated with less willingness to participate, Exp_β = .29, 95% CI [.12, .68] compared to the reference level, smoking every day. Smoking some days was also associated with less willingness to participate, Exp_β = .22, 95% CI [.07, .68] compared to the reference level, smoking every day. Participants who did not smoke at all were 3.5 times less likely to be willing to participate compared to those who reported smoking every day. Participants who smoked some days were 4.5 times less likely to be willing to participate compared to those who reported smoking every day. Not smoking at all was associated with lower odds of willingness. For EXERANY, the model was significant for those who reported exercising at least once in the last 30 days, β = .99 *SE* = .36, *Wald* = 8.18, $p = .004$. The estimated odds ratio indicated a relationship between exercise, any exercise in the last 30 days, and willingness, Exp_β = 2.69, 95% CI [1.37, .5.31] compared to the reference level, not exercising at all. Participants who exercised at least once in the last 30 days were 2.6 times more likely to be more willing to participate compared to those who did not exercise.

To assess the association between willingness and drinking risk by gender, I recoded the dependent variable willingness into separate variables for males, WILLMALE, and females, WILLFEMALE. The independent variables, @DRINKRISKFEMALE and @DRINKRISKMALE, defined high or low-risk drinking. An ordinal logistic regression analysis was conducted to assess the association between drinking risk and willingness. Both @DRINKRISKFEMALE and @DRINKRISKMALE were assessed a priori to confirm there was no violation of the no multicollinearity assumption. The model fitting showed that the final model did not significantly improve the fit of the data for @DRINKRISKMALE, LR $\chi^2(1) = 7.1$, $p = .69$ or for @DRINKRISKFEMALE, LR $\chi^2(1) = 7.65$, $p = .32$. As such neither regression returned results for goodness-of-fit. For @DRINKRISKFEMALE and @ DRINKRISKMALE, the association between high-risk drinking and willingness were not statistically significant. Table 8 details the regression results for health behaviors and willingness.

Table 8

Regression Results for Willingness to Participate and Health Behaviors

						95% CI for Exp_β	
Variable	β	*SE*	*Wald*	Sig	Exp_β	Lower	Upper
Smoking Not at all	-1.25	.44	8.03	.005	.29	.12	.68
Smoking Some days	-1.49	.57	6.90	.009	.22	.07	.68
Exercised At least once in 30 days	.99	.35	8.16	.004	2.69	1.37	5.31
High-risk drinking female	.64	.65	.96	.327	1.89	.53	6.84
High-risk drinking male	-.32	.80	.16	.692	.73	.15	3.51

Note. Smoking every day, not exercising in the last 30 days, and low risk drinking are the reference variables.

Social Support and Willingness to Participate

I assessed the association between social support and willingness to participate in a clinical trial.

Research Question 3: Is there any association between social support measures and an individual's willingness to participate in a clinical trial?

$H_0$3: There is no statistically significant association between social support measures and an individual's willingness to participate in a clinical trial.

H_a3: There is a statistically significant association between social support measures and an individual's willingness to participate in a clinical trial.

I measured participant social support using the MSPSS (see Zimet et al., 1988). I defined low perceived social support as a mean score between 12-35, medium perceived support as 36-60, and high perceived support as 61-84. The independent variable, SOCIALSUPPORTRANK, was treated as an ordinal variable with ranked low, medium,

and high responses. I conducted a regression analysis to assess the relationship between social support and willingness, where willingness was the dependent, ordinal variable. As the response variable, willingness to participate was treated as ordinal and had an assumed natural order descending from *very willing* to *not sure,* where the distance between levels was unknown. An ordinal logistic regression analysis was conducted to assess the association between social support and willingness. The independent variable was assessed a priori to confirm no violation of the no multicollinearity assumption. The model fitting showed that the final model did not significantly improve the fit of the data, LR $\chi^2(2) = 2.67$, $p = .264$. Regarding the goodness-of-fit test, the analysis failed to reject the null hypothesis for both Pearson, $\chi^2(6, N = 208) = 3.43$, $p = .754$ and Deviance, $\chi^2(16, N = 208) = 3.58$, $p = .734$. The independent variable, SOCIALSUPPORT RANK, did not contribute to the model in a statistically significantly way. Table 9 details the regression results for social support and willingness.

Table 9

Regression Results for Willingness to Participate and Social Support

						95% CI for Exp_β	
Variable	β	*SE*	*Wald*	Sig	Exp_β	Lower	Upper
High social support	.81	.63	1.67	.197	2.25	.66	7.68
Medium social support	.46	.65	.51	.474	1.59	.45	5.67

Note. Low social support is the reference variable.

Moderation by Personal Hardiness

I assessed whether any statistically significant association found between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial was moderated by personal hardiness.

Research Question 4: Is there any association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial moderated by personal hardiness?

$H_0$4: There is no statistically significant moderation by personal hardiness in the association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial.

H_a4: There is statistically significant moderation by personal hardiness in the association between health status, health-related behaviors, and social support variables and an individual's willingness to participate in a clinical trial.

Because social support was not associated with willingness in a statistically significant manner, I conducted a regression with moderation using general health, exercise, and smoking as the independent variables, willingness as the dependent variable, and hardiness as a moderator. General health, GENHEALTH, was treated as an ordinal variable with values ranging from *excellent* to *poor*. Smoking was recoded to the variable SMOKERECODE and treated as an ordinal variable with values from *not at all* to *every day*. Exercise in the last 30 days, recoded as EXERANYRECODE, was treated as a nominal variable, with responses of Yes and No. As the response variable, willingness to participate was treated as ordinal and had an assumed natural order descending from *very willing* to *not sure*, where the distance between levels was unknown. Hardiness was ranked as high, medium, or low. I created interaction terms for hardiness and health, hardiness and smoking, and hardiness and exercise.

I conducted a regression analysis to assess the association between smoking, general health, exercise, and willingness to participate in a clinical trial, and any moderation of those associations by personal by hardiness. The independent variables were assessed a priori to confirm no violation of the no multicollinearity assumption. The model fitting showed that the final model significantly improved the fit of the data, LR $\chi^2(18) = 183.42$, $p < .001$. In addition, the goodness-of-fit test failed to reject the null hypothesis and confirmed that the model fit was good for Deviance, $\chi^2(111.52, N = 114) = 23.34$, $p = .548$. The null hypothesis was rejected for Pearson, $\chi^2(215.99, N = 114) = 31.41$, $p = .000$.

Hardiness and the interaction between hardiness and health were significant predictors for willingness to participate and smoking and exercise status were not. High hardiness was associated with higher odds of being more willing to participate in a trial, the $\beta = 1.33$ $SE = .39$, $Wald = 13.02$, $p < .001$. High hardiness and excellent general health significantly increased the odds of being more willing to participate, the $\beta = 90.23$, $SE = 5.04$, $Wald = 320.11$, $p < .001$. I also found statistically significant moderation by hardiness, at the high hardiness level, for very good and good general health levels. Table 10 details the regression results for general health, hardiness, and willingness and interaction with hardiness.

Table 10

Regression Results for Willingness to Participate, General Health, Hardiness, and Hardiness and Health Interaction

Variable	β	*SE*	*Wald*	Sig
High hardiness	1.33	.39	13.02	.000
Medium hardiness	.43	.30	2.03	.154
High hardiness X Excellent health interaction	90.28	5.04	320.11	.000
High hardiness X very good health interaction	65.91	3.40	375.72	.000
High hardiness X good health interaction	43.84	2.56	293.70	.000
High hardiness X Exercise at least once interaction	2.42	1.34	3.28	.070
High hardiness X smoking not at all interaction	-1.14	.71	2.56	.110

Note. Low hardiness, poor health, no exercise in the last 30 days, and smoking every day are reference variables.

Summary

I rejected the null hypothesis for Research Question 1 and demonstrated an association between hardiness and willingness to participate. For Research Question 2, which examined positive health behaviors, I partially rejected the null hypothesis in favor of the alternative hypothesis. I did not find an association between drinking risk and willingness. Although I did demonstrate an association between smoking and willingness, the positive behavior, not smoking at all, and smoking some days were associated with a decrease in willingness not an increase in likelihood of being willing. The positive health behavior of exercising at least once in the last 30 days was associated with increased willingness. I failed to reject the null hypothesis in favor of the alternative hypothesis for Research Question 3, as no significant association between social support and willingness was observed. Lastly, I partially rejected the null hypothesis for Research Question 4 as

moderation by hardiness was observed in the association between general health and willingness to participate, however, I did not find moderation for smoking or exercise by hardiness. I discuss the findings of this research in Chapter 5.

Chapter 5: Discussion, Conclusions, and Recommendations

In this quantitative cross-sectional study, I examined the association between hardiness and willingness to participate in a clinical trial to determine whether hardiness is an unexplored component of the healthy volunteer effect. From October to November 2022, I collected and analyzed data to address four research questions and hypotheses. I deployed a single-administration electronic survey to a representative sample of U.S.-based adults. I measured personal hardiness using the HRG and social support using the MSPSS. Health behaviors and demographics were collected using the 2020 BRFSS questionnaire, and I assessed willingness to participate using language from the CISCRP willingness to participate questionnaire. I analyzed the data using ordinal regression analyses in SPSS to test (a) the association between personal hardiness and willingness to participate, (b) the association between positive health behaviors and willingness to participate, (c) social support and willingness to participate, and (d) whether personal hardiness moderates the association, if any, between health status, positive health behaviors, and social support and willingness to participate in a clinical trial.

I found a statistically significant association between personal hardiness and willingness to participate, where individuals with higher hardiness were more likely to be willing to participate in a clinical trial. I also determined that positive health behavior of exercise (having exercised at least once in the last 30 days) was significantly associated with an increased willingness to participate. I did not observe a significant association between social support and willingness or drinking risk and willingness. Regarding smoking, smoking was associated with increased willingness. However, the association

was the inverse and not smoking at all and smoking some days was associated with being less willing to participate. I also determined that the association between general health and willingness, where excellent health was associated with an increase in willingness, was moderated by personal hardiness.

Interpretation of Findings

I sought to examine unexplored components of the healthy volunteer effect, a phenomenon in which clinical trial participants demonstrate better outcomes than their peers who do not participate. The healthy volunteer effect leads to bias in clinical trials, their outcome, and interpretation (Callahan et al., 2007; Croswell et al., 2010; Ederer et al., 1993; Guerra et al., 2022; Ludmir et al., 2019). The healthy volunteer effect, as currently understood, does not fully explain the outcome difference between volunteers and nonvolunteers. Researchers have established that there are unexplored differences between participants and nonparticipants in clinical trials. Current understanding of the healthy volunteer effect in clinical trials and its established influence on trial outcomes accounts for only some differences between participants and nonparticipants (Burr et al., 2016; Froom et al., 1999; Krauss, 2018; Olsen et al., 2020).

I assessed the association between hardiness and willingness to determine whether individuals more willing to participate in a clinical trial would differ in their personal hardiness from those unwilling. An association between hardiness and willingness could explain why trial participants who are generally better educated, have higher income, are healthier, and are potentially hardier would express behaviors that may influence trial outcomes and lead to less generalizable results. In this study, I confirmed previous

research that found differences between individuals willing and unwilling to participate in a trial. As an extension of the field, I determined that hardiness was associated with willingness and that the relationship between excellent health and willingness was moderated by personal hardiness. Although previous research had established the relationship between hardiness, health, and coping in the face of stress and illness (Maddi, 2013), the association between personal hardiness and willingness had never been examined.

I used the hardiness model for performance and health enhancement as the theoretical framework for this study. The hardiness model of performance and health enhancement provides a unified paradigm for understanding how implementing hardy attitudes and strategies can influence performance and health (Maddi, 2006). The model was an appropriate framework for examining the association between hardiness and a potential clinical trial participant's willingness to volunteer. In this study, I applied the hardiness model for performance and health enhancement to a conceptual model for personal hardiness and the healthy volunteer effect. I considered personal hardiness a personality component that leads to a greater willingness to participate among clinical trial volunteers. Personal hardiness influences health status and behaviors and, coupled with the protective environmental factors associated with personal hardiness (increased SES and increased social support), comprises previously undetermined factors in the healthy volunteer effect. I found an association between hardiness and willingness and an association between excellent health and willingness that was moderated by hardiness, in alignment with the conceptual framework. Individuals more likely to be willing to

participate in a trial were hardier, in better health, and more likely to exercise when compared to individuals who were less likely to be willing to participate.

I considered smoking as a health behavior in this study, where not smoking at all was defined as a positive health behavior. In contradiction to my hypothesis, I found that not smoking at all and smoking some days was associated with a decrease in willingness, not an increase. Smoking is a unique health behavior. Although smoking is associated with comorbidities and negative health effects, there are also associations between smoking and personality (Hakulinen et al., 2015; Kang, 2022; Munafò et al., 2007; Zvolensky et al., 2015). Researchers have found that individuals often smoke as a coping mechanism in response to stressful situations (Firat et al., 2022). Although researchers have found that nonsmokers are more resilient than smokers, smoking is highly correlated with increased neuroticism and smokers demonstrate higher levels of extraversion and are generally more open to new experiences than nonsmokers (Carlucci & McCuaig Edge, 2022; Choi et al., 2017). Personal hardiness, as a personality construct, works in concert with increased coping and positive health behaviors. As a result, hardiness protects against illness and leads to better outcomes in the face of stress (Maddi, 2013). The association between smoking and willingness that I found in this study could be explained if smoking was considered as a coping mechanism instead of a health behavior. If smoking also acts as a coping mechanism, an association between smoking and less willingness (i.e., less coping in the face of stress and illness) could be a consideration. In addition, the relationship between smoking and other personality traits

such as neuroticism may be confounding and require controls that were not included in the current study.

Limitations of the Study

There were limitations to this study. Because I relied on self-reported survey data, self-reporting bias from participants was possible. This may limit the study's internal validity. Previous research indicated that only an estimated 5% of people in the United States participate in trials (Unger, Vaidya, et al., 2019). I designed this study to address an anticipated low response rate from those willing to participate in a trial. In contrast to expectations, most participants in this study indicated they would be very or somewhat willing to participate in a trial. Researchers have found that more individuals report being willing to participate in a trial in a hypothetical setting than would be willing to participate in a real-world setting (Lamberti et al., 2021). This was also a limitation to this study's external validity. Lastly, although I included known hardiness covariates and confounders in this study, such as health behaviors, health status, and social support, I did not account for other potential confounders such as neuroticism or altruism (see Funk, 1992; Kowalski & Schermer, 2019). I did not account for these cofounders in this study's analyses, which could limit the study's internal validity.

Recommendations

Through this study's findings, I established an association between willingness to participate and personal hardiness. I found that personal hardiness moderated an association between willingness and excellent health. Because I only examined participation in a hypothetical clinical trial, I recommend that additional research be

conducted that addresses these associations in potential clinical trial participants who are actively facing a participation decision. In addition, given the relatively small sample of the current study, I recommend repeating this research in a larger, multinational population. I also found conflicting associations with regard to positive health behaviors, in particular smoking. I recommend that subsequent research include a broader set of positive health behaviors and personality factors to better control for confounding.

Implications

Clinical trials, the cornerstones of drug development, depend on volunteers willing to participate. The number of individuals willing to participate represents a small percentage of the eligible populations, and researchers have determined that participants are different from nonparticipants in a way that biases trial results and limits their generalizability (Jensen et al., 2022; Mölenberg et al., 2021; Schieve et al., 2018). The healthy volunteer effect, a phenomenon in which clinical trial participants manifest significantly better outcomes relative to their illness state than the general population, has been used to explain the limited generalizability of clinical trials (Froom et al., 1999). Although the healthy volunteer effect has been well documented, previous research had not fully identified what variables determine the effect (Czwikla et al., 2018; Pinsky et al., 2007; Zheng et al., 2020). In the current study, I found that personal hardiness, a personality construct that describes a pattern of health-enhancing behaviors and attitudes that facilitates an increased resistance to illness, is associated with increased odds of being willing to participate in a clinical trial. Establishing an association between the

protective health behaviors associated with personal hardiness and willingness provides insight into hardiness as an unexplored component of the healthy volunteer effect.

Defining this relationship and the unexplained components of the healthy volunteer effect may generate positive social change. In this study, I addressed a gap in the literature by determining that hardiness is associated with willingness to participate in a trial and is a potential explanation for factors in the healthy volunteer effect that had not been defined or measured. Because an association between hardiness and willingness exists, the hardiness of trial participants could be quantified, and trial outcomes could be adjusted for hardiness in the general population. Quantifying and adjusting for hardiness as a standard practice in clinical trials could maximize the effectiveness of new treatments and provide insight into real-world efficacy. Quantifying the hardiness of trial participants compared to nonparticipants could assist in determining whether trial outcomes could be linked to an inherent level of personal hardiness and optimal outcomes that are less likely to transfer beyond the trial population. Personal hardiness as an unexplored component of the healthy volunteer effect clarifies the extent to which positive clinical trial outcomes are reproducible for the population. This may generate positive change for individual trial participants and the public, researchers, and the broader clinical research industry by addressing the issues of outcome generalizability and providing a mechanism by which that generalizability could be quantified and proactively addressed.

Conclusions

In this study, I examined the association between personal hardiness and willingness to participate in a clinical trial. I also examined the relationship between health status, health behaviors, social support, and willingness and assessed the moderation of any association by personal hardiness. The results addressed gaps in the healthy volunteer effect by indicating the extent to which personal hardiness was associated with individuals who were more willing to participate in clinical trials. This study's results align with previous research on personal hardiness and willingness to participate in a clinical trial and address a research gap by establishing an association between hardiness and willingness. I found conflicting associations between willingness and health behaviors with known relationships to personality, such as smoking. Additional research with a larger, global population should be conducted and include an expanded set of health behaviors and controls for behaviors closely related to personality. In addition, this research should be replicated in a real-world decision setting. Clinical trials are essential for developing new medicines, and in a postpandemic world, trials continue to drive innovations in medicines and health care. Understanding whether and why trial outcomes are not generalizable is essential. In the current study, I established an association between hardiness and willingness that could explain the lack of generalizability.

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Appendix: Permission to use HRG

RE: Use of Hardiness Resilience Gauge For Dissertation Research CRM:0129000555

Wed 7/6/2022 4:37 PM

Hello Angelique,
Thank you for returning the completed Research Discount forms.
MHS is pleased to approve you for the research discount on the HRG for use in your discount titled “Examining Personal Hardiness as an Unexplored Component of the Healthy Volunteer Effect.”
You will have access to the HRG research Scored Data Set Reports until July 7, 2023.
The current research price is $8.00 for each HRG Scored Data Set Report. Please note that this price is for 2022 and may increase in 2023.
We have set you up with a Talent Assessment Portal – TAP. You should have received an email today with instructions on how to access the TAP.
If you need help with the TAP, you can call our Client Service Team, Monday to Friday 8am to 6pm EST.
Once you are set up with this TAP, you will be able to begin administering the HRG to your participants prior to making any purchases.
However, before you can score, you will have to ensure that you have the appropriate number of tokens.
The TAP uses Tokens and each Token is valued at $1.00. You will have to purchase 8 Tokens for each HRG administration that you would like to score.
For instance, if you have 100 completed HRG to score, you will need to purchase 800 Tokens.
You will be able to purchase your Tokens directly in your TAP with a credit card.
Please let me know if you have any questions.