PREDICTORS OF WOUND HEALING IN LOWER EXTREMITY WOUNDS

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JEREMY SETH HONAKER

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We hereby approve the thesis/dissertation of

Jeremy Seth Honaker
Candidate for the degree of Doctor of Philosophy*.

Committee Chair
Dr. Elizabeth Madigan
Committee Member
Dr. Diana Morris
Committee Member
Dr. Andrew Reimer
Committee Member
Dr. Kevin Cooper
Date of Defense
3/14/2017

*We also certify that written approval has been obtained for any proprietary material contained therein.
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Abstract

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The purpose of the study is to evaluate the temporal development of symptom onset and severity and to determine relationships between delayed wound healing (wound total surface area), symptoms (depressive symptoms [DS], pain, sleep disturbance [SD]), and health related quality of life (HRQoL) in older adults undergoing Mohs micrographic surgery [MMS] of lower extremity non melanoma skin cancer (NMSC) healing by secondary intention. This is a prospective exploratory study of patients undergoing MMS for NMSC in a single academic dermatological surgery clinic. Subjects were enrolled on the day of surgery and followed weekly for 4 weeks, except 4 subjects were followed weekly until healed. Descriptive statistics and T-tests were used to explore differences between those with and without wound expansion at week 1 among these variables: demographics, co-morbidities, laboratory values, and NIH PROMIS DS, pain, SD, and HRQoL surveys. Logistic regression was performed between the variables and the wound expansion group to determine predictors of wound healing. An analysis revealed that subjects undergoing MMS for NMSC generally have good HRQoL, and symptom
measures and HRQoL consistently improve by week 4 postoperatively. There was no significant relationships noted between demographics, co-morbidities, laboratory values, symptom measures, HRQoL, and wound total surface area. A trend was noted with the 14 subjects with 5 experiencing wound expansion greater than -15% expansion and 9 were without expansion at week 1. No significant differences were noted between demographics, co-morbidities, laboratory values, symptom measures, or health related quality of life with those with and without wound expansion, except for age. Age was significantly different with the wound expansion group averaging 12 years older ($p = 0.02$). Of the 4 subjects followed until healed, 2 subject's wounds expanded and required 10-12 weeks to heal compared to 6-8 weeks in 2 subjects without wound expansion. Logistic regression revealed a trending toward significance ($p=.08$) with age. The likelihood for experiencing wound expansion increases by 24% for every increase in year ($OR = 1.24 \ CI 95\% 0.97-1.58$). In conclusion, this preliminary report reveals that older adults may be more likely to have wound expansion, which may result in delayed wound healing.
Chapter 1

Microbiome Psychological Stress Health Related Quality of Life Middle Range Theory

Older adults who experience post-operative wound complications, and subsequently develop a chronic leg wound, experience impaired health related quality of life (HRQoL). Over 200,000 older adults require surgical correction of non-melanoma skin cancers (NMSC) of the leg occur each year (Rogers, Weinstock, Feldman, & Coldiron, 2015; Solus, Murphy, & Kraft, 2015; Pearson, King, & Boyd, 1999; Gallagher et al., 1990). Surgical correction of NMSC of the leg carries the highest rates (17%) of postoperative complications in comparison to other NMSC body locations (0.72%) (Honaker, Bordeaux, & Tuttle, 2015; Stankiewicz, Coyer, Webster, & Osborne, 2015; Dixon, Dixon, Askew, & Wilkinson, 2006). Subsequently, older adults who experience postoperative complications may develop a chronic non-healing surgical leg wound. People who live with chronic non-healing leg wounds experience increased psychological stress as a result of increased financial burden (greater than $27,500 to heal a wound), symptom severity (e.g., wound pain), and treatment burden (e.g., frequent wound dressing changes), all of which impair HRQoL (Greenhalgh, 2015; Mekkes, Loots, Van Der Wal, & Bos, 2003; Briggs & Flemming, 2007; Franks & Moffatt, 2006). In a meta-analysis, Walburn et al. (2009) demonstrated that increased psychological stress accounted for 42% of the variance in delayed wound healing. People who experience higher levels of psychological stress are 3.5 times more likely to have delayed wound healing (Bosch, Engeland, Cacioppo, & Marucha, 2007) and 3.7 times more likely to develop postoperative wound infection (Doering, Moser, Lemankiewicz, Luper, & Khan, 2005) generating decreased worse or prolonged of impaired HRQoL (Kuhns et al., 2015).
Furthermore, individuals with chronic leg wounds experience multiple psychological stressors (depressive symptoms, fatigue, pain, sleep disturbance)(Edwards et al., 2014). Yet, the temporal development of particular psychological stressors, and the influence on subsequent manifestation of other psychological stressors has not been determined in either the acute or chronic leg wound populations. As there are multiple influential variables, and potential temporal influences on additional psychological stressor development, identifying the complex interactions between an individual’s adaptive response to psychological stressors and the emergence of additional psychological stressors would aid in further understanding the dynamic nature of psychological stressors on wound infection, delayed healing, and HRQoL. (Wilson & Cleary, 1995).

The aim of this paper is to present the Microbiome Psychological Stress (MPS) HRQoL middle range theory. A theory derivation and synthesis was performed by translocating components of Ferran et al. adaptation of Wilson & Cleary’s HRQoL model(Ferrans, Zerwic, Wilbur, & Larson, 2005) to the complexity science paradigm(Zimmerman, Lindberg, & Plsek, 1998). Components were then substructed to the MPS HRQoL middle range theory. The MPS HRQoL middle range theory was created to provide a framework for understanding the phenomenon of interest: psychological stress induced wound infection with delayed healing, and associated impaired HRQoL in people undergoing dermatologic surgery for lower leg NMSC. The MPS HRQoL middle range theory can be used to guide future clinical and research initiatives by identifying influential variables (e.g., individual characteristics, symptoms)
that may contribute to the development of wound infection with delayed healing, and impaired HRQoL.

**Health Related Quality of Life Model**

Wilson & Cleary’s HRQoL model explores the influence of characteristics of individuals and their environment, as well as the influential and inter-relationships of biophysiological variables, symptom status, functional status, and general health perception on overall quality of life and patient outcomes (Wilson & Cleary, 1995). In 1995, Wilson & Cleary noted that the current medical model, which emphasized biological and reductionistic philosophies to explain illness, was insufficient to account for all the dimensions associated with illness (Wilson & Cleary, 1995). Therefore, the medical model was merged with the social science paradigm, which focused upon the measurement of complex behaviors and feelings that reflects dimensions of functionality and overall well-being. In contrast to the medical model’s use of experimental designs to determine causation, social science employed a combination of qualitative and quantitative research methodologies to determine the complex influence of social structures and institutions influence on individuals (Sousa & Kwok, 2006). Through the use of multiple data methods, Wilson & Cleary believed that additional dimensions of health could be measured and used as endpoints to determine the effects of pharmacologic and non-pharmacologic interventions, in clinical trials and comparative effective research, on HRQoL (Wilson & Cleary, 1995). As a result, more effective interventions could be designed that will improve disease and overall HRQoL.

Ferran et al adaptation of Wilson & Cleary’s HRQoL model (Ferrans et al., 2005) is being used to characterize the current phenomenon of interest. The adapted model
includes 7 constructs: individual characteristics, environmental characteristics, biological function, symptoms, functional status, general health perception and HRQoL. An identified weakness of Wilson & Cleary (1995) HRQoL model was addressed by applying McLeroy’s ecological model (McLeroy, Bibeau, Steckler, & Glanz, 1988) to assist in defining the potential influences of the individual and environmental characteristics on the remaining constructs of HRQoL. Ferran et al. (2005) added causal pathways between individual and environmental characteristics and the biological function construct, incorporated nonmedical factors throughout individual and environmental characteristics, and established explicit definitions of individual and environmental characteristics (Ferrans et al., 2005).

The HRQoL model is composed of assumptions and propositions. Assumptions proposed by the HRQoL model are: 1) individual’s change their aspirations and expectations as circumstances change, and 2) an individual’s experience, interpretation, and evaluation of symptoms results in the assignment of tolerance thresholds (Ferrans et al., 2005). Propositions proposed by the HRQoL conceptual model are: 1) individual and environmental characteristics have direct causal pathways to each of the five constructs represented in the HRQoL model, 2) sleep disturbance and depressive symptoms have a bidirectional relationship, 3) individual characteristics (e.g., personal behaviors) influence vulnerability and resilience to health/disease, 4) HRQoL may be effected by cultural, spiritual, economic, and political factors, which falls outside of the purview of healthcare providers, and 5) direct causal relationship exist between biological function, symptoms, functional status, health perception, which then influences HRQoL (Wilson & Cleary, 1995). While the HRQoL model includes direct causal relationships amongst the
constructs, bidirectional relationships may exist between construct concepts (Wilson & Cleary, 1995). For example, subjects who experience elevated levels of wound pain may experience decreased occupational functional status. In contrast, decreased occupational status as a result of wound pain can result in increased depressive symptoms (Hareendran et al., 2005). The use of the assumptions and propositions of the HRQoL model aids in determining potential variables that influence HRQoL, but there are some challenges with using the HRQoL model in research studies.

The propositions in the HRQoL model do not occur consistently across all individual scenarios and are therefore context driven (Ferrans et al., 2005). For example, an older adult with osteoarthritis learns to maximize physical, social, and role functional status by employing new body mechanics or mobility assist devices, which subsequently improves their HRQoL. The older adult’s HRQoL improves as a result of improved functional status despite no improvement of the underlying altered biological function (joint erosion). Thus, improvement in biological function did not have a direct causal influence on improving HRQoL. Therefore, HRQoL is dynamic in nature with individual perceptions changing overtime, even without changes in biological function, symptom status, or functional status (Ferrans et al., 2005).

Additionally, the relationship that exists between biological function and symptoms is also context driven (Wilson & Cleary, 1995). A return to homeostasis of abnormal biological function does not always result in improvement of experienced symptoms. For example, critical colonization (increased bacterial load, decreased bacterial diversity) of a lower extremity wound represents a state of disequilibrium between the host and the microbiome (Tuttle, 2015). Critical colonization results in
increased wound pain as a result of local structural damage. The structural damage occurs due to a combination of bacterial exo/endotoxins effects on cell membrane damage and the interaction of the host innate/adaptive defense mechanisms with the bacteria (Leaper et al., 2012). As a result of these interactions, there is a burst of inflammatory mediators (e.g., prostaglandins, bradykinins, cytokines) and reactive oxygen species that further produces structural damage and activation of local nerve pathways (Woo & Sibbald, 2008). Interventions used to mitigate critical colonization influence on wound pain may not result in the resolution of biological dysfunction. For example, patients who have an infected venous leg ulcer receive antibiotics for a suspected infection. Following correction of critical colonization, the patient continues to experience wound pain although other biological markers of inflammation have decreased. As some symptoms are multi-factorial, not all interventions that target biophysiological variable will result in the improvement in patient reported symptoms. Additionally, the impact of biological function on functional status is theorized to be mediated by symptom status. Yet, there may be clinical conditions that effect functional status, but there are no biophysiological or symptom variables to measure.

Another challenge with using the HRQoL model is accounting for the non-linear relationships that exist between variables as a result of inter-individual variability. An individual’s HRQoL is influenced by both individual (e.g., personal preferences, cognitive appraisal) and environmental characteristics (e.g., culture, residence), as well as biological functions, perceived symptoms, functional status, and health perception (Ferrans et al., 2005). The complex linear and non-linear interaction of these factors results in the production of a very individualized perspective regarding personal
HRQoL. Therefore, controlling for confounding variables that influence HRQoL is difficult.

**Complexity Theory**

Complexity theory is a theoretical understanding that is more congruent with explaining contextual relationships between construct concepts/variables and inter-individual variability of outcomes in the HRQoL model. The HRQoL model is based upon the medical model, which approaches conducting science from a reductionistic perspective. Reductionism proposes that objects or phenomenon (e.g., system) can be explained by understanding the role and function of the individual parts (sub-systems), and that relationships that occur within the individual parts are linear. As a result, the observed phenomenon and particular outcome can be reliably predicted (Zimmerman et al., 1998; Higgins, 2002). In contrast to reductionism, complexity theory approaches objects or phenomenon by viewing the individual parts as complex adaptive systems. Complexity theory proposes that the whole (phenomenon, object) is more than and different from the sum of the individual parts. Random unpredictable self-organized patterns develop at unique times and places. The random and unpredictable patterns develop as a result of unpredictable interactions within or between the individual parts (Zimmerman et al., 1998; Higgins, 2002). When evaluating interactions, complexity theory approaches the phenomenon from a non-linear perspective, which indicates that the magnitude of the input does not equal a proportional output (curvilinear) (Zimmerman et al., 1998; Higgins, 2002; Clancy, 2004). In contrast to the experimental methods used to evaluate interactions in reductionism/medical model, complex theory requires observation using a combination of quantitative and qualitative approaches to assist in
determining interactions or reality, which is more consistent with Ferran’s adaptation of the Wilson & Cleary’s HRQoL model. Yet a working flaw of both Ferran et al. (2005) and Wilson & Cleary’s HRQoL model is that neither authors’ incorporate the assumptions explicit to complexity theory to account for the inconsistent relationships and inter-individual variability.

The key assumptions of complexity theory establishes the basis by which we understand how systems behave and outcomes occur. First, complexity theory views systems as a diverse set of symbiotic and independent agents (e.g., molecule, person, organization) capable of changing in response to shifts within independent agents or other systems (Zimmerman et al., 1998). Independent agents are governed by a set of internalized rules (e.g., chemical reactions, instincts) that support unpredictable behavior and adaptation in response to changes in other independent agents or systems (J. P. Higgins, 2002; Plsek & Greenhalgh, 2001). Second, the inter-relationships between the independent agents are as important as the agents themselves. Within complexity theory, the diversity of independent agents produces a state of paradox and tension as a result of non-linear and bidirectional relationships. By producing paradox and tension, an environment of complexity or perpetual novelty and innovation is fostered. For example, the effects of competition amongst independent agents could result in the emergence of dominant players or create environments for individual agents to self-organize into new innovative behaviors or patterns that produce unexpected outcomes, rather good or bad. In contrast, systems that lack tension or paradox result in high certainty and agreement, which does not allow for novelty and adaptation, which may lead to eventual system collapse (Wilson & Holt, 2001). Furthermore, the actions or reactions of one independent
agent can lead to unpredictable outcomes. The unpredictable outcomes are further
perpetuated by the number of networks that independent agents interact with. For
example, immunoglobulins are produced by the immune system to identify and neutralize
foreign antigens (e.g., bacteria). The antigen binding site of the immunoglobulin is
composed of a variable region on the heavy and light chains. The heavy and light chains
have 11,000 and 320 different combinations respectively, which results in the production
of $3.5 \times 10^6$ possible antigen specificities. As a result of having so many specificities for
foreign antigens, our body is capable of adapting to the new pathogens (Decker, n.d.).

Third, independent agents mutually co-evolve within the larger system that they
are a part of and are dependent upon each other. For example, long term immunity to
pathogens is reliant upon B cell exposure to pathogenic antigens so that antibodies can be
produced. The B cells retain memory of the previous exposures to particular antigens and
are capable of producing a more robust immune response upon second exposure (Higgins,
2002). If antigen presenting cells are unable to phagocytize pathogens due to the
production of a biofilm (symbiotic development of a protective extracellular polymeric
substance that encases a bacterial community) for presentation to B cells, specific
immunoglobulins for the pathogen will not be produced (Dowd et al., 2008). The B cells,
in addition to other adaptive immune cells (e.g., T cells), evolve together within the
human host (larger complex adaptive system) and are reliant upon each other (T cell
antigen presentation to B cells). Fourth, complexity theory assume that complex systems
yearn for order and stability and adapt to changing environments in order to preserve the
agents or systems. The unpredictable nature of independent agents allows for diversity,
which is necessary to sustain complex adaptive systems. Diversity produces novelty or
information that leads to new ways to adapt (Clancy, 2004). Finally, complex adaptive systems are drawn to attractors (Zimmerman et al., 1998). Attractors are a type of random unpredictable pattern or behavior that develop at unique times and places as a result of unpredictable interactions. The unpredictable interactions can lead to the development of unpredictable states, which results in the emergence of a new form of order (structure, processes) or self-organization. The new form of order or self-organization allows independent agents or the larger complex adaptive system to adapt to changes in the environment (Zimmerman et al., 1998; Clancy, 2004; Plsek & Greenhalgh, 2001).

Complexity theory will be applied to HRQoL model to inform the propositional statements and structure of the model. As a result, a greater understanding of how diverse independent agents interact within a system adapt (i.e., self-organize) can be ascertained. As the HRQoL model integrates medical and social science models, there is an integration of multiple diverse independent agents that are within (e.g., biophysiological, personal values) and outside (e.g., environmental characteristics, sociocultural) an individual to influence unpredictably unpredictable patterns of behavior. As a result of numerous independent agents existing within the HRQoL, there is state of greater tension. The increased tension between independent agents could result in a more attenuated HRQoL, especially as interactions are non-linear with a small input resulting in a large change in HRQoL. Therefore, predicting HRQoL in an individual is complex and challenging. Yet, complexity theory proposes that instead of fixing one particular independent agent (e.g., symptom status) to improve HRQoL, the focus should be upon nurturing the system toward a direction through attractors. The identification of independent agents that are associated with a particular attractor would allow for the
development of complex care plans to assist independent agents to self-organize toward a
positive pattern could aid an individual to maximize perceived HRQoL. Through the
application of complexity theory to the HRQoL model, a new theoretical approach will
be created to aid in understanding the phenomenon of interest.

**HRQoL Complexity Theory and MPS HRQoL Middle Range Theory**

The HRQoL complexity theory was created to explore the variables that influence
psychological stress and wound related outcomes (i.e., wound bacterial bioburden,
delayed wound healing, wound infection symptoms, impaired functional status [physical,
mental, social], altered general health perception, poorer HRQoL) in patients with
surgical leg wounds. Consistent with the HRQoL model, individual and environmental
characteristics influence an individual’s vulnerability or resistance to the development of
abnormal biological functions (delayed wound healing, wound infection), symptoms,
functional status and perception of HRQoL. Furthermore, biological function variables
and symptoms may have direct and indirect effects on functional status, general health
perception, and HRQoL model (Ferrans et al., 2005). An individual with a chronic
surgical leg wound utilizes psychological processing (cognitive appraisal) to evaluate the
threat of a stressor, which evokes an emotional response that causes biological function
changes (hypothalamic pituitary axis activation). In the presence of multiple
stressors (e.g., wound pain, soiled clothing from excess wound drainage), or a few
significant stressors (e.g., significant other death), maladaptive biophysiological changes
can culminate in host environmental alterations leading to an increased susceptibility to
delayed wound healing, wound infection symptoms, and poorer functional status, worse
general health perception, and reduced HRQoL (Holmes, Plichta, Gamelli, & Radek,
The application of complexity theory using complex adaptive systems approach would suggest that interactions amongst environmental characteristics (e.g., interpersonal support, community factors) and other independent agents (psychosocial development, personal behaviors) have the ability to influence an individual’s self-efficacy and subsequent response to stressors leading to changes in the host environment. As a result, new patterns (i.e., attractors) of physical, social, or mental function occur as a result of the multiple individual and environmental characteristics working in synchrony to reestablish biological function (e.g., homeostasis), reduce symptom status, and subsequently reestablish HRQoL.

**Conceptual Definitions and Measurements**

The 7 constructs of the HRQoL model are used to determine concepts relevant to the phenomenon of interest, psychological stress related wound outcomes. Individual characteristic concepts included are demographics, personal behaviors, biological factors, and psychological factors. Personal behaviors (e.g., sleep, smoking) and psychological factors (e.g., affective response) represent independent predictor variables (IPV) within the theory, while demographic and biological factors are considered influential variables. These concepts were incorporated to explore the influence, and potential consequents (e.g., depressive symptoms, wound infection) of personal behaviors and the individual’s appraisal process to determine their ability to overcome or be overwhelmed by particular stressors. Environmental characteristic concepts included are the physical and social interpersonal and community factors, of which both are considered influential variables. These concepts have the ability directly influence individual characteristics, and have
both direct and indirect effects on biological function, symptoms, functional status, general health perception, and HRQoL (Ferrans et al., 2005).

Biological function concepts included are bacterial bioburden, wound healing, ankle brachial index (ABI), and clinical-etiologic-anatomy-pathophysiology (CEAP) classification of lower-extremity chronic venous disorders. Bacterial bioburden and wound healing will serve as IPV and dependent outcome variables (DOV) with direct and indirect effects on symptoms, functional status, general health perception, and HRQoL. ABI and CEAP are considered influential variables as underlying vascular impairment may predispose individuals to delayed wound healing and infection (Sibbald et al., 2011). Alterations in bacterial bioburden lead to host environmental changes (i.e., wound infection) through physiological stress responses, which promote commensal or pathogenic bacteria activity that can lead to the development of wound infection symptoms (Holmes, Plichta, Gamelli, & Radek, 2015). Symptom concepts represented within the theory are sleep disturbance, reactive depression, pain, and wound infection symptoms. Sleep disturbance, reactive depression, and pain function as IPV and DOV as the inter-relationships are complex and share bi-directional relationships. The individual’s psychological response to the aforementioned symptoms leads to activation of physiological stress pathways resulting changes allowing for altered bacterial bioburden, and the subsequent development of wound infection symptoms. Within the theory, wound infection symptoms will function as an IPV with functional status, general health perception, and HRQoL, and as a DOV with bacterial bioburden, wound healing, pain, depressive symptoms, sleep disturbance, and individual characteristics.
Functional status concepts included are psychological, role, social, and physical function. Psychological, role, social, and physical function act as IPV in direct and indirect pathways with general health perception and HRQoL, and DOV with individual characteristics, biological function, and symptom concepts. An individual’s appraisal of type and severity of symptoms results in poorer social and physical function, which causes downstream poorer general health perception and HRQoL (Ferrans et al., 2005; Wachholz, Masuda, Nascimento, Taira, & Cleto, 2014; Hareendran et al., 2005). The general health perceptions concept used in the theory is general health perception, which acts as IPV with HRQoL and DOV with individual characteristics, environmental characteristics, biologic function, symptoms, and functional status concepts. The overall quality of life concept used within the theory is HRQoL, which is the DOV with the 6 other constructs within the theory. In the following sections, conceptual and operational definitions, substracted from the 7 constructs, will be presented (Ferrans et al., 2005). Additionally, propositional statements that link the concepts will be presented.

**Individual Characteristics**

The individual characteristics construct is defined as the attributes that make an individual unique and distinct from the group (“Individual,” 2016; “Characteristics,” 2016) The construct is composed of multiple concepts (i.e., attributes), which are demographics (age, sex, ethnicity), developmental stage (e.g., Erikson’s stages of psychosocial development), personal behaviors, biological factors (family history), and psychological factors (cognitive appraisal, affective response). For the theory, demographics, personal behaviors, biological, and psychological factors will represent the construct. Demographic variables age, gender, and race, and biological factor
variables skin color, family medical history, genetic linked disease, have causal pathways with biologic function (Ferrans et al., 2005). For example, older people undergoing surgery have an increased risk of experiencing a wound infection due to normative age changes (e.g., altered keratinocyte motility (Gould et al., 2015), reduced neutrophil activity (Brubaker, Rendon, Ramirez, Choudhry, & Kovacs, 2013), impaired lymphatic drainage (Greenhalgh, 2015)), and multiple underlying co-morbidities (e.g., diabetes, vascular disease) (Stankiewicz et al., 2015). Furthermore, there are many variables that influence NMSC development: individuals with increasing age and lightly pigmented skin (e.g., Caucasian) experience more NMSC than darker pigmented individuals (Rogers et al., 2015). Regarding gender and biological factors influence on biological function, NMSC tend to occur more commonly in men, yet NMSC of the lower extremity tend to occur more often in females as a result of epigenetic changes with increased cytokeratin 15 (Solus et al., 2015).

The psychological processes concept is composed of the variables affective response (e.g., fear), cognitive appraisal (e.g., attitudes towards health/disease), and motivation (e.g., self-determination). These variables influence an individual's interpretation of events and stressors, and subsequently influence or are influenced by personal behaviors (e.g., alcohol, sleep habits, exercise) (Ferrans et al., 2005). To the detriment of those with high levels of perceived stress or increased helplessness, patients often adopt health damaging behaviors such as reduced exercise, deficient nutritional intake, increased alcohol intake, or reduced sleep (Holmes et al., 2015). Additionally, individuals with poor sleep habits, and who subsequently experience sleep disturbance,
may experience more negative affective response to stressful events (Linder, Jansen, Ekholm, & Ekholm, 2014).

Perceived stress will be used to operationalize the psychological processes concept. Perceived stress is the cognitive appraisal of emotional or mental strain that is a result of straining or adverse circumstances (“Stress,” 2016; Taylor, 2015). Examples of stress are disfigurement, social isolation, pain, loss (e.g., status), traumatic life events, and alterations in the environment (e.g., social support)(Taylor, 2015; Jones, Robinson, Barr, & Carlisle, 2008). An individual’s response to perceived stress (e.g., cognitive rationale, emotional levels) determines stressor severity. The subsequent development of adaptive or maladaptive responses occurs as a result of perceived helplessness or self-efficacy. Furthermore, the duration and frequency of the perceived stress has been associated with various stress related pathology, such as immunosuppression and increased morbidity (e.g., cardiovascular disease) (Buysse, 2004; Lutgendorf & Costanzo, 2003; Koschwanez & Broadbent, 2011). When viewing the combined influence of the independent agents demographic, biological factors, psychological process, and personal behaviors, there are a multitude of potential downstream non-linear influences leading to the alteration in biological functions, intensifying perceived symptoms, worsening functional status, and producing poorer overall general health perception and HRQoL (Wilson & Cleary, 1995; Ferrans et al., 2005; Zimmerman et al., 1998). For example, repeated exposure to a stressor may result in a complex interaction of independent agents that allow an individual to develop behaviors that improve perceived predictability leading to the subsequent development of perceived control (Koolhaas et al., 2011).
Environmental Characteristics

Environmental characteristics are defined as those social and/or physical systems that reside within the individuals living space (Ferrans et al., 2005; “Environment,” 2016). The concepts of environmental characteristics are interpersonal factors (social support systems), institutional factors (education, healthcare access), community factors (institutions, social networks), and public policy (Ferrans et al., 2005). The concepts represent the varying levels of physical and social environmental systems that have the potential for influencing individual characteristics, biological function, symptoms, functional status, general health perception, and HRQoL. For example, spouses or significant others (interpersonal factors) can positively or negatively influence the individual’s adherence with attending scheduled healthcare appointments or the prescribed treatment plan (Ferrans et al., 2005). Therefore, the interpersonal factors have the ability to directly impact individual characteristics (e.g., psychological processes), and indirectly the concepts of biological function, symptoms, functional status, general health perception, and HRQoL. In addition to spouses or significant others, an individual’s culture or heritage (community factors) may influence whom they approach for healthcare and whether or not they will seek out healthcare when symptoms are noted or functional status is impaired (Ferrans et al., 2005). In contrast to social systems, physical systems such as homes, working environments, and public buildings can contribute positively or negatively to biological function, symptom manifestation, functional status, general health perception, and HRQoL. For example, an individual working as a coal miner is exposed to environmental contaminants that lead to the development of coal worker’s pneumoconiosis. As a result, the individual subsequently
develops symptoms of chronic obstructive pulmonary disease that can lead to impaired ability to work due to shortness of breath.

**Biological Function**

Biological function variables measure the functional status of cells, organs, and organ systems (Ferrans et al., 2005). A complex interaction occurs between cellular processes within adjacent, distal organs, or organ systems that produce subsequent changes in the host biophysiological environment that may produce symptoms immediately or following failure of compensatory mechanisms after years of dysfunction (Wilson & Cleary, 1995). Biological function concepts included within the theory are physiologic stress, wound healing, microbiome, and vascular status. Physiologic stress response has been proposed as a pathway that directly influences disease (delayed wound healing, wound infection), which may result in the development of wound infection symptoms (pain, wound odor/drainage) that results in decreased functional status, general health perception, and HRQoL.

Physiologic stress is the production of stress hormones (e.g., cortisol, epinephrine) as a result of higher order (infralimbic region of prefrontal cortex) cognitive processing (e.g., perceived predictability/control) in response to perceived stressors (Koolhaas et al., 2011). The two systems primarily involved in the physiologic response include the hypothalamic pituitary axis (i.e., cortisol) and autonomic nervous system (e.g., norepinephrine). Perceived uncontrollability leads to a delay in recovery (i.e., cortisol levels are delayed in returning to homeostasis) following stressor exposure (Koolhaas et al., 2011). Persistent perceived uncontrollability can result in chronic stress, which has been associated with persistently elevated cortisol levels (Walburn, Vedhara, Hankins,
The elevation of this biomarker has been associated with increasing the risk of infection through decreasing antimicrobial peptide (i.e., cathelicidin, β-defensin) production, and hyperglycemia induced promotion of bacterial metabolism and inhibition of neutrophilic activity. Elevated cortisol has also been associated with delayed wound healing through decreased keratinocyte proliferation, fibroblast activity, and increased skin barrier permeability (Jozic, Stojadinovic, Kirsner, & Tomic-Canic, 2014). In addition, the cumulative influence of persistent autonomic nervous system stimulation (e.g., catecholamines) may work to dampen the immune response and alter the host microenvironment to be conducive for bacterial proliferation. The downstream autonomic nervous system stimulation effects include increased iron availability for bacterial replication (e.g., Staphylococcus aureus), promotion of Pseudomonas aurginosa biofilm production by increasing attachment sites on host tissue, and neutrophil chemotaxis inhibition. Cholinergic stimulation has been shown to amplify bacterial pathogenecity (potential for developing infection) by decreasing antimicrobial peptides and increasing skin barrier permeability (Holmes et al., 2015). As a result of the aforementioned host environment physiologic changes, bacteria within the microbiome can become pathogenic.

Microbiome is defined as the collective community of micro-organisms within a particular environment (“Microbiome,” 2016). Bacteria have two roles: 1) commensal role that promotes the innate immune response (e.g., Staphylococcus epidermidis interacts with host immune cells to increase anti-microbial peptides) 2) pathogen role that overwhelms the host immune response (e.g., Pseudomonas aurginosa and methicillin resistant Staphylococcus aureus collaborate to enhance pathogenecity). The development
of the microbial community is a result of both individual characteristics (e.g., age, co-
morbidities, immune response) and environmental characteristics (e.g., habitat,
hygiene)(Holmes et al., 2015). The host physiologic environment, along with the immune
system, are determinants of the skin microbiome acting as commensal or pathologic
organisms(Grice et al., 2010). Our skin, and its components, oppose infection
development through the interaction of the host cell's (e.g., keratinocytes, dendritic cells)
toll like receptors with pathogen associated molecular patterns (e.g., LPS,
peptidoglycan)(Holmes et al., 2015;Chehoud et al., 2013). As a result of pathogenic
bacterial causing wound infection, delayed wound healing occurs.

Wound healing is an orchestrated cascade of biophysiological processes that leads
to the regeneration (partial thickness wounds) or repair (full thickness wounds) of tissue
following trauma or injury(Sibbald et al., 2011;Gould et al., 2015). Wounds that fail to
progress through the stages of wound healing (hemostasis, inflammation, proliferation,
maturity) develop into chronic wounds. Factors that lead to the development of
delayed wound healing or chronic wounds are repeated trauma, malnutrition, vascular
disease, persistent inflammation, necrotic tissue, hyperglycemia, psychological stress,
and wound infection(Gould et al., 2015). In regards to wound infection, psychological
processes (perceived stress) and symptoms (depressive symptoms) have been associated
with increased wound infection risk(Holmes et al., 2015;Doering, Moser, Lemankiewicz,
Luper, & Khan, 2005). Psychological stress induced elevation of norepinephrine was
shown to increase expression of bacterial surface adhesion molecules, which supports
biofilm production(Holmes et al., 2015). In addition, psychological stressed mice were
shown to have a 2-5 log fold increase in Staphylococcus aureus in wounds, and 85.4% of
mice had counts predictive of infection at 7 days after stress dosing, which resulted in delayed wound healing (Gouin & Kiecolt-Glaser, 2012).

An additional biological function concept that influences delayed wound healing and wound infection is altered vascular status. Altered vascular status is the anatomical and physiological changes in arteries, capillaries, and veins that results in over or under perfusion of tissue (Sibbald et al., 2011; Lavery et al., 2006). Peripheral arterial disease and chronic venous insufficiency represent unique local anatomical and physiological changes in the vasculature of the lower extremities that leads to adverse tissue functioning by impeding the delivery of oxygen, key nutrients, and innate/adaptive immune cells. As a result, the host’s defense mechanism could be diminished, resulting in impaired control of bacterial bioburden, which can lead to an increased risk of wound infection development (Lavery et al., 2006; Sibbald et al., 2003).

**Symptoms**

Symptom status is a complex phenomenon that is defined as a patient’s perception of psychological, cognitive, or physical experiences, which are perceived with varying levels of effect upon the individual. The influence of symptom severity on functional status, general health perception, and overall quality of life may be influenced by demographics, socio-cultural factors, patient characteristics (personality, expectations), or relationships (e.g., physician-patient relationship) (Wilson & Cleary, 1995). Symptom concepts included within the theory are reactive depression, sleep disturbance, pain, and wound infection symptoms. Within the context of the HRQoL model, the combination of experienced symptoms (e.g., pain) and increased perceived stress resulted in increased symptom intensity, self-reported negative mood (e.g., reactive depression), and greater
disruption of social and physical functioning, general health perception, and HRQoL (Ferrans et al., 2005). For example, patients with more severe depressive symptoms following surgery were 3.7 times more likely to develop wound infection, and were more likely to report poorer self-recovery and HRQoL scores (Doering et al., 2005).

Reactive depression (non-melancholia) is the development of despondent feelings and dejection in response to a stressful external event (Taylor, 2012; Parker, Fletcher, & Hadzi-Pavlovic, 2012). Depression is a disorder of affect (i.e., short term observable state) and mood (i.e., persistent internal state). A neurobiological view would encompass depression as a peripheral and subjective experience that drives the other phenomenon noted (e.g., negative mood, poor concentration, lack of motivation). Individuals with lower stress threshold may respond to stress with either psychological or emotional responses when perception of stress is less severe (Paykel, 2008; Stojadinovic, Gordon, Lebrun, & Tomic-Canic, 2012). Additionally, maladaptive processes may influence phenomenon associated with depression such as altered immune system and sleep disturbance (Paykel, 2008). Even mild mood alterations in adults >72 may lead to impaired immune responses through elevated cortisol and catecholamines (Holmes et al., 2015; Lutgendorf & Costanzo, 2003). For example, proposed downstream influences of depressive symptoms on the host immune response include decreased IL-2 mediated natural killer cell activity, and poorer T cell response to mitogens (Lutgendorf & Costanzo, 2003).

Common individual characteristics associated with depression in older adults include: more common in women, multiple co-morbidities, and socioeconomic stressors (e.g., institutionalization, losses) (Buysse, 2004). Additional individual, environmental and biological factors with a predisposition to depressive symptoms.
include familial links, early childhood adversity, and prenatal viral infection induced cerebral damage, respectively (Garcia-Toro & Aguirre, 2007). In addition to individual, environmental, and biological factors, other symptoms have also been shown to share complex inter-relationships with depression. For example, depressive symptoms and sleep disturbance have been shown to have a bi-directional relationship in that both variables were shown to predict the other variables development (Sivertsen et al., 2012).

Sleep disturbance is the patient’s perception of alterations in sleep patterns or behaviors within a natural setting, and a reported impairment in daytime function (Irwin, 2015). Sleep disturbance is associated with individual characteristics age, gender, co-morbidities, and environmental characteristics socioeconomic status. Older adults experience earlier sleep hours, insomnia, sleep disorder prevalence (e.g., sleep apnea, restless leg), sleepiness, and daytime napping with 20-40% reporting at least one symptom of insomnia (Buysse, 2004). In addition, women have 20-50% more insomnia than men (Buysse, 2004) While age has been associated with sleep disturbance, co-morbidities were found to lessen the significance of the relationship. This suggests that increasing numbers of co-morbidities confounds the relationship between older adults and sleep disturbance. Another confounder of sleep disturbance is socioeconomic status, which has been shown to share an inverse relationship with reported sleep disturbance (Buysse, 2004).

In evaluating the complex relationship that sleep disturbance shares with psychological processes, depression and sleep disturbance were noted to share a positive relationship with pain (Upton & Andrews, 2013; Jones, Barr, Robinson, & Carlisle, 2006) and 58% of individuals with chronic leg wounds indicated that pain caused their sleep
disturbance (Linder et al., 2014; Upton & Andrews, 2013). During sleep, cortisol, norepinephrine, and epinephrine levels drop. Similar to depressive symptoms, sleep disturbance has been shown to stimulate the hypothalamic pituitary axis and autonomic nervous pathways (Irwin, 2015). The primary influence of sleep disturbance has been on the host adaptive immune response through the following mechanisms decreased T cell (CD 3, 4, & 8) production and circulation, decreased monocyte production/circulation, and decreased cytokines (interferon gamma, IL-10). Furthermore, mice exposed to sleep disturbance and crowding stress had a significant reduction in anti-microbial peptides (i.e., cathelicidin) and exhibited a more severe infection response when injected with group A streptococci. The influence of stress on anti-microbial peptides were eliminated when a glucocorticoid antagonist was administered, suggesting glucocorticoids as a potential mechanism (Gouin & Kiecolt-Glaser, 2012). This highlights the potential contribution of sleep disturbances influence on increasing host susceptibility to infection. The aforementioned findings suggest that there is a complex relationship that exists between individual characteristics (psychological processes, personal behaviors), and symptoms sleep disturbance and wound infection.

The conceptual definition for wound infection is a development of a disease state as a result of microorganisms (“Infect,” 2016). Studies exploring psychological processes, health behaviors, and biological factors influences on wound infection have centered on measuring bacteria through traditional culturing methods, and not wound infection symptoms (Gardner, Hillis, Heilmann, Segre, & Grice, 2013; Davies et al., 2007; Tuttle, 2015). This focus is due to the low sensitivity and specificity of wound infection symptoms with actual wound infection. A meta-analysis of fifteen studies identified that
increasing pain in a chronic wound may indicate infection, and the remaining symptoms are not helpful in diagnosing infection (Reddy, Gill, Wu, Kalkar, & Rochon, 2012). However, a combination of symptoms have been correlated with better predictability of critical colonization (subclinical wound infection) or deep wound infection (Gardner, Hillis, & Frantz, 2009; Woo & Sibbald, 2009). Wound infection symptoms are a manifestation of inflammation mediated by the adaptive and innate immune systems. Adaptive and innate immune cells instigate the inflammatory response in response to antigens or due to autoimmunity (Irwin, 2015). Additionally, chronic wounds are commonly stuck in the inflammatory phase resulting in an occasional misinterpretation of clinical findings leading to misdiagnosis of wounds that are not infected (Gardner et al., 2009; Woo & Sibbald, 2009).

**Functional Status**

Functional status represents the measurement of an individual’s capacity to perform and adapt in order to complete particular tasks (i.e., social, role, physical, psychological). There is a complex interaction of individual characteristics (personality, motivation), environmental characteristics (social support, physical barriers), biological functions (joint erosion), and symptoms (fatigue, pain) that results in an individual’s ability to adapt and maintain a particular level of function or fail and experience decreased function. Functional status concepts included within the theory are physical, role, social and psychological (Wilson & Cleary, 1995). Individuals who develop postoperative leg wound complications are at an increased risk of experiencing decreased physical, social, role, and psychological function as a result of developing a chronic
wound (Hareendran et al., 2005; Franks, Moffatt, Doherty, Smithdale, & Martin, 2006; Honaker, Bordeaux, & Tuttle, 2016).

There have been a number of biological function (e.g., vascular status) and symptoms (wound infection) found to influence functional status domains. The wound characteristics of wound exudate, leg edema, and wound odor have been found to have associations with impaired physical function (i.e., mobility), participation in social activities, and an alteration in fulfilling roles (Persoon et al., 2004). Furthermore, wound odor was noted to impair psychological function as wound odor greatly impacted social interaction, social isolation, and ADLs due to psychological distress (e.g., fear, anxiety, depression) from altered body image (i.e., embarrassment from wound odor or drainage) (Jones et al., 2008; Herber, Schnepp, & Rieger, 2007). Hareendran et al. (2005) identified that 47.2% of patients reported unable to participate in hobbies or inability to enjoy swimming, gardening, or hiking because of the ulcer; and 97.2% of VLU patients report an impairment in overall function (Hareendran et al., 2005). While biological function and symptom concepts unique to chronic leg wounds have found to influence functional status, older age may account for these effects. Renner et al. (2009) demonstrated that increasing age was associated with increasing dependency, decreased social activities, and socially withdrawn behavior in individuals with chronic leg wounds. As physical problems, daily handicaps, and social problems are common with increasing with age, and chronic leg wounds occur commonly in older adults, perhaps age may mediate the influence of chronic leg wound biological function and symptom variables influence on functional status (Renner, Gebhardt, Simon, & Seikowski, 2009).

HRQoL
Overall quality of life is a reflection of an individual’s satisfaction with life and is influenced by the patient's perception of the impact of illness or medical therapies, required to treat disease, on their health, well-being, and overall functional status (Wilson & Cleary, 1995; González-Consuegra & Verdú, 2011). Concepts that comprise the overall quality of life construct are psychological and spiritual, health and functioning, social, family, and socioeconomic. The overall quality of life concept included in the theory is health and functioning (i.e., HRQoL), which is a composite of physical, mental, role and social health. There is a complex interplay of individual characteristics, environmental characteristics, biological function, symptoms, functional status, and general health perception that results in direct and indirect influences on HRQoL. For example, older adults with chronic non-healing leg wounds (biological function) experience worse HRQoL as a result of increased pain (symptoms) (Gould et al., 2015; González-Consuegra & Verdú, 2011; Salomé, Blanes, & Ferreira, 2014). In response to increased pain, individuals may begin to experience sleep disturbance and minimize daily activities (physical, role function) that exacerbate the wound pain (Herber et al., 2007). As the patient continues to live with wound pain and is unable to fulfill family and work responsibilities. The individual becomes overwhelmed as his/her attempts to adapt fail, which leads to the development of reactive depression (Ferrans et al., 2005). The reactive depression then worsens perceived symptoms (e.g., sleep disturbance, pain) (Franks & Moffatt, 2006; Franks et al., 2006; Herber et al., 2007). The longer the chronic leg wound persists, the individual may continue to suffer impairments in psychological, physical, social, and role functioning due to maladaptive behaviors to cope with symptoms experienced, which results in poorer general health perception and quality of life.
At other times, HRQoL may not be influenced by living with a chronic leg wound. Renner et al., identified that HRQoL was no different between patients who had an active or healed chronic leg wounds (Renner et al., 2009). Franks et al. (2006) identified that HRQoL was noted to improve during active treatment, but the initial improvements in HRQOL (i.e. energy level) at 24 weeks were not sustained at the 48 week mark. These findings highlights the issues of other factors effecting HRQoL, and may be effected by deteriorating biological functions associated with aging or some other factor (i.e. underlying ulcer etiology, smaller wounds, minimal wound pain)(Franks et al., 2006). Additional linkages noted between the theory’s domains and poorer HRQoL are biological function (larger wounds) are associated with individual characteristics (emotion) symptoms (pain), and functional status (social isolation).

**Theoretical Assumptions**

The HRQoL Complexity Theory and MPS HRQoL Middle Range Theory has several key theoretical assumptions:

- Humans are complex systems that yearn for order and stability and adapt to changing environments in order to foster homeostasis within and amongst independent agents and systems.

- Individual characteristics, environmental characteristics, biological function, symptoms, functional status, and general health perception are complex systems composed of numerous independent agents that share membership or are interconnected with other independent agents within one or multiple systems.

- Health perception and HRQoL is highly individualized.
• Life events can change or modify independent agents (motivation, expectation) within the individual characteristics system that results in changes in perceived HRQoL.

• Sleep is a restorative process

• An individual's positive or negative reaction to stress involves both individual characteristics (psychological processes), environmental characteristics (social support), and biological function (physiological stress response).

• Depression is the emergence of dysfunctional behavior in response to independent interactions with changes in the system (an individual’s psychological response to a stressor).

• Biological functions are unique to every individual.

• Need assumptions regarding the host immune system

• Need assumptions for microbiome

**Propositional Statements**

• HRQoL has great inter-individual variability and is influenced by a complex interplay of interactions that occur between individual characteristics, environmental characteristics, biological function, symptoms, functional status, and general health perception.

• There are dominant causal associations between complex systems individual characteristics, environmental characteristics, biological function, symptoms, functional status, general health perception, and overall quality of life.

• Individual characteristics (demographics, psychosocial/cognitive development, personal behaviors, biological, psychological processes) and environmental
characteristics (interpersonal, institutional, community, public policy) directly influence biological function, symptoms, functional status, general health perception, and overall quality of life.

- Interactions between independent agents (e.g., personal behaviors) within the Individual characteristics with other systems results in patterns or behaviors that produce vulnerability or resilience to health/disease within the larger complex system.

- Sleep is a restorative process that influences other independent agents within individual characteristics and biological function that produces self-organized behavior that decreases vulnerability/resistance to disease.

- Individual characteristics age, gender, and comorbidities influence non-melanoma skin cancer development (biological function)

- Individual characteristics beliefs, preferences, knowledge, affective response are associated with adaptive or maladaptive responses to perceived stress.

- Perceived stress (psychological processes) is associated with individual characteristics age, gender, co-morbidities, smoking, alcohol use, sleep, pain, and depressive symptoms.

- Environmental characteristics (significant other, spouse, culture, and community residence) influence individual characteristics (psychological processes, personal behaviors), symptoms (pain, reactive depression, sleep disturbance), and well as functional status (physical, role, social, psychological).

- Perceived stress may or may not result in activation of the HPA axis.
• Persistent activation of the HPA activation is associated with decreased host immune system function.

• Wound healing is influenced by individual characteristics age, gender, comorbidities and other biological functions (physiological stress, bacterial bioburden, vascular status).

• Age, co-morbidities, medical treatments, sleep disturbance, and depressive symptoms influence the microbiome

• Physiologic stress, vascular status, and wound healing are associated with bacterial bioburden.

• Chronic perceived stress, and subsequently persistently elevated physiological stress, is associated with changes in the host immune system that causes physiological changes that foster changes in microbiome activity.

• Alteration in microbiome activity produces wound infection symptoms

• Wound infection symptoms are associated with changes in functional status and indirectly influence general health perception and overall quality of life.

• Perceived stress and depressive symptoms influence wound infection symptoms.

• A consequent of elevated perceived stress is depression.

• Sleep disturbance and depressive symptoms have a bi-directional relationship.

• Perceived stress and depressive symptoms influence HPA axis activity.

• Perceived stress and sleep disturbance influences wound infection symptoms.

• Individual characteristics (age, gender, personal behaviors, beliefs, knowledge), environmental characteristics (community residence, significant other) and
symptoms (wound infection symptoms, pain, reactive depression, sleep disturbance) influence physical, social, role, and psychological function.

- Individual characteristics (age, gender, personal behaviors, beliefs, knowledge), environmental characteristics (community residence, significant other) and symptoms (wound infection symptoms, pain, reactive depression, sleep disturbance), and functional status (physical, social, role, psychological) influence general health perception.

- Individual and environmental characteristics influence biological function, symptoms, functional status, general health perception, and overall quality of life.

- There is a direct causal pathway between biological function, symptoms, functional status, general health perception, and overall quality of life.

- The complex interaction of individual characteristics (beliefs/values, previous experiences, interpretation of symptoms) results in the emergence of tolerance thresholds of stressors or symptoms.

- Pharmacologic and non-pharmacologic interventions have the capacity of influencing multiple independent agents within biological function, symptoms, functional status, and general health perception complex systems to produce patterns or behaviors that foster or negate overall quality of life.

- Biological functions can influence individual characteristics health behaviors, psychological processes, and other biological functions (physiological processes).

- The development of depression results in changes in other systems (biological function, symptom, functional status).
• The symbiotic relationship between the microbiome and humans is maintained by the host immune system.

• Alterations in the host immune system influences independent agents within the microbiome, which can lead to the emergence of wound infection.

Reduced Propositions

• Individual characteristics age, gender, and comorbidities influence non-melanoma skin cancer development (biological function)

• Individual characteristics beliefs, preferences, knowledge, affective response are associated with adaptive or maladaptive responses to perceived stress.

• Perceived stress (psychological processes) is associated with individual characteristics age, gender, co-morbidities, smoking, alcohol use, sleep, pain, and depressive symptoms.

• Environmental characteristics (significant other, spouse, culture, and community residence) influence individual characteristics (psychological processes, personal behaviors), symptoms (pain, reactive depression, sleep disturbance), and well as functional status (physical, role, social, psychological).

• Perceived stress and depressive symptoms influence HPA axis activity.

• Wound healing is influenced by individual characteristics age, gender, comorbidities and other biological functions (physiological stress, bacterial bioburden, vascular status).

• Age, co-morbidities, medical treatments, sleep disturbance, depressive symptoms, physiologic stress, vascular status, and wound healing are associated with alterations in the microbiome.
• Chronic perceived stress, and subsequently persistently elevated physiological stress, is associated with changes in the host immune system that causes physiological changes that foster changes in microbiome activity, which results in wound infection symptom development.

• Perceived stress, depressive symptoms, and sleep disturbance influence wound infection symptoms.

• A consequent of elevated perceived stress is depression.

• Sleep disturbance and depressive symptoms have a bi-directional relationship.

• Individual characteristics (age, gender, personal behaviors, beliefs, knowledge), environmental characteristics (community residence, significant other) and symptoms (wound infection symptoms, pain, reactive depression, sleep disturbance) influence physical, social, role, and psychological function.

• Individual characteristics (age, gender, personal behaviors, beliefs, knowledge), environmental characteristics (community residence, significant other) and symptoms (wound infection symptoms, pain, reactive depression, sleep disturbance), and functional status (physical, social, role, psychological) influence general health perception.

• Individual and environmental characteristics influence biological function, symptoms, functional status, general health perception, and overall quality of life.

• There is a direct causal pathway between biological function, symptoms, functional status, general health perception, and overall quality of life.

Figure 2 highlights the reduced propositions, and represents a framework for identifying, explaining, and discussing the relationship between the IPV individual
characteristics (perceived stress, demographics), biological functions (physiological stress, wound healing, microbiome, vascular status), symptoms (reactive depression, sleep disturbance, pain, wound infection), functional status (physical, social, role, psychological), general health perception, and overall quality of life (HRQoL). The framework is consistent with Ferran’s adaptation of Wilson & Cleary’s HRQoL model. The literature served as the means for determining existing propositions.

Conclusion

The addition of complexity theory’s complex adaptive systems to Ferran’s HRQoL of model provides a new perspective on how to approach complex health problems, including HRQoL. There are multiple independent agents that work in unison to produce an individual’s perceived satisfaction with life. By applying the theoretical assumptions of how independent agents interact and co-evolve within the larger system, scientists can develop new scientific approaches that would aid in studying how independent agents within the system self-organize to re-establish order when chaos occurs. By understanding the interconnectedness of independent agents within a system, and the subsequent patterns that develop as a result of interactions, scientists are more capable of discerning new approaches to influencing system behavior. Furthermore, understanding inconsistent patterns and behaviors that emerge following interaction of particular independent agents may provide scientists with new insights into why there is great inter-individual variability when it comes to functional status, general health perception, and HRQoL. The identification of particular patterns that emerge as a result of independent agents may allow for the development of complex care plans to nurture
independent agents to self-organize toward a particular behavior or pattern that would support order, and subsequently maximize perceived HRQoL.
Chapter 2

The Influence of Psychological Stressors on Surgical Outcomes in Older Adults with Below the Knee Non-melanoma Skin Cancer: An Integrated Literature Review

Background and Significance

Chronic lower extremity wounds can be life-threatening for older adults and may present an increased risk of cellulitis, osteomyelitis, limb loss, or sepsis, any of which are associated with death. (Meagher, Corkery, Concannon, & Kavanagh, 2014; Davies et al., 2007; Gardner, Frantz, & Doebbeling, 2001) Surgical lower extremity wounds that fail to progress through the stages of wound healing in a timely manner progress to become chronic wounds and may require months or years to heal (Sibbald et al., 2011). Non-melanoma skin cancer (NMSC) removal is a common indication for lower extremity surgery in older adults. NMSC is the most common malignancy occurring in older adults with greater than 5 million occurrences each year (Rogers et al., 2015). Of these NMSC, more than 200,000 adults, 65 years or older, undergo lower extremity dermatologic surgery (Mohs micrographic surgery [MMS]) to remove the malignancy (Gallagher et al., 1990; Rogers et al., 2015; Pearson et al., 1999; Solus et al., 2015). Surgical correction of lower extremity NMSC has a higher rate (17%) (Honaker et al., 2015) of postoperative complications (e.g., wound infection, delayed wound healing) in comparison to other body locations (0.72%) (Alam et al., 2013) in older adults. Therefore, older adults who undergo surgical correction of NMSC have a higher risk of their surgical wound transitioning from an acute to chronic wound if they experience postoperative complications.
Variables suggested to increase older adults risk of experiencing postsurgical complications, such as delayed wound healing and wound infection, are normative age changes (e.g., altered keratinocyte motility(Gould et al., 2015), reduced neutrophil activity(Brubaker et al., 2013), impaired lymphatic drainage(Greenhalgh, 2015)), multiple comorbidities (e.g., diabetes, vascular disease)(Stankiewicz et al., 2015), and psychological stressors (e.g., depressive symptoms(Doering et al., 2005), sleep disturbance(Aberg et al., 2007;Alessi & Vitiello, 2015), pain(Greenhalgh, 2015)). Older adults who develop chronic surgical leg wounds due to post-operative complications experience additional psychological stressors such as increased financial burden ($27,500 or more per patient to heal), increased symptom severity (e.g., wound pain), and treatment burden (e.g., wound care, clinic visits)(Greenhalgh, 2015;Mekkes et al., 2003) all of which have been associated with poorer HRQoL in chronic leg wounds(Briggs & Flemming, 2007;Franks & Moffatt, 2006). The added psychological stressors present additional barriers to healing the chronic surgical leg wound(Walburn et al., 2009). As a result, people undergoing dermatologic surgery for NMSC, who experience wound infection or delayed wound healing, may experience poorer health related quality of life (HRQoL). Identifying the mechanism by which preoperative and postoperative psychological stressors (e.g., psychological stress) are associated with postoperative complications, and subsequently poorer HRQoL in people undergoing dermatologic surgery for NMSC of the lower extremity, would aid in developing precision care plans for this high volume population.

The mechanism(s) by which psychological stressors cause postoperative complications (e.g., delayed wound healing(Walburn et al., 2009), wound
infection (Doering et al., 2005; Cohen, Doyle, Alper, Janicki-Deverts, & Turner, 2009)) in acute surgical wounds, both of which may result in a chronic surgical wound, has not been studied. Alterations in bacterial bioburden (increased bacterial load, decreased diversity, pathogenicity) has been shown to be associated with delayed wound healing (Tuttle et al., 2011) and increased wound infection symptoms (pain, wound size, peri-wound skin edema) in human chronic wounds (Sprockett, Ammons, & Tuttle, 2015). The proposed hypothesis is that older adults with one or more psychological stressors will have increased bacterial bioburden, postoperative complications, and poorer HRQoL.

**Purpose and Significance**

The purpose of this integrated literature review is to critique and synthesize information regarding 1) psychological stressors on infection development and delayed wound healing, 2) the influence of psychological stressors on bacterial bioburden, 3) common changes in the surgical wound microbiome, 4) and predictors of surgical outcomes and HRQoL in older adults undergoing dermatologic surgery for the removal of lower extremity. Findings reviewed in this manuscript will evidence regarding the role of psychological stress and other variables (e.g., co-morbidities, health behaviors) in the development of postoperative complications and poorer HRQoL in older adults undergoing surgical correction of a lower extremity NMSC. In the interest of reducing the burden of cost on the healthcare system, and the burden of disease on people who have lower extremity NMSC, if psychological stress has an influence on altering the surgical wound bacterial bioburden resulting in wound infection, and delaying wound healing, timely identification and treatment is paramount. This topic is of particular interest to nursing, and advanced practice nurses, as they are point of care providers for
many of these patients. Furthermore, nurses and advanced practice nurses can directly impact patient outcomes by ensuring timely identification and implementation of interventions to stabilize surgical wound bacterial bioburden and/or improve the patient’s response to stressors that may produce poorer HRQoL and wound outcomes (Kelechi & Bonham, 2008).

Methods

The HRQoL conceptual model was used to develop conceptual linkages, and variables of interest, between psychological stress, bacterial bioburden, wound infection, wound healing, and health related quality of life. The model explores the influence of characteristics of the individual and their environment, as well as the inter-relational and influential relationships of bio-physiological variables, symptom status, functional status, and general health perception on overall quality of life and patient outcomes (e.g., response to medical therapy) (Wilson & Cleary, 1995). The HRQoL conceptual model suggests a direct causal relationship between biophysiological variables (bacterial bioburden) and symptom status (depressive symptoms, sleep disturbance, wound infection symptoms), which then influences HRQoL.

The literature review was completed by JH, the principal investigator, by searching the following search repositories: PubMed, Cochrane Database, Science Direct, and CINAHL. The following search terms were matched in various combinations to identify potential articles of interest from the year 2000 to 2016: older adult, geriatric, bacterial bioburden, microbiome, wound infection, wound healing, dermatologic surgery, mohs micrographic surgery, surgical wound, chronic surgical wound, leg, lower extremity, non-melanoma skin cancer, complications, postoperative complications,
wound complications, psychological stress, depression, depressive symptoms, sleep disturbance, pain, anxiety, outcomes, quality of life, and health related quality of life. Subsequently, abstracts were reviewed by JH for content that was pertinent to the subject of this integrated literature review.

For the purposes of this review, studies were included in the review if they were written in English, the majority (i.e., >50%) of the study population were people with NMSC, and were original qualitative, quantitative, or meta-analysis research articles published in peer reviewed journals. Furthermore, full articles were selected for review if the abstract contained information regarding 1) Psychological stress (depressive symptoms, sleep disturbance, pain, anxiety, stress), wound healing, and/or wound infection in acute wounds or chronic surgical wounds, 2) Psychological stress and bacterial bioburden/microbiome, 3) Postoperative dermatologic surgery outcomes/postoperative complications in lower extremity NMSC, 4) Surgical wound and bacterial bioburden/microbiome, and 5) HRQoL in people undergoing dermatologic surgery for NMSC located in all locations and/or lower extremities. Articles were further excluded upon full review if the articles were case series or unpublished data (e.g. conference abstracts, dissertations). Additional articles were retrieved following the review of manuscript bibliographies, author publications, and recommended manuscripts shared on PubMed and Science Direct websites. The authors were not contacted for further information regarding their respective study.

Following a review of the literature, a total of forty four manuscripts from five disciplines (nursing, medicine, psychology, dentistry, biology), across eight different countries (America, France, England, New Zealand, Germany, Australia, Spain, Sweden)
met the inclusion criteria. After critiquing the manuscripts, seven were excluded, as they did not match up with this literature review’s inclusion criteria or were removed due to severe methodological flaws resulting in a total of thirty seven manuscripts. The distribution of designs is as follows: one mixed methods, twenty three observational, four quasi-experimental, eight experimental, and one meta-analysis. Emerging themes following a synthesis of the literature were formulated within the context of the HRQoL model. In the following sections, findings (i.e. six themes) from the literature will be synthesized so as to present a current state of the science regarding symptom clusters, wound healing, and HRQoL for patient’s undergoing surgery for NMSC.

**Results**

**Theme 1: Psychological Stressors**

There are multiple permutations for measuring psychological stress in the literature. Psychological stress is defined as a negative emotional state whereby the individual is aware of emotional or mental strain that is a result of straining or adverse circumstances (“Stress,” 2016; Taylor, 2015). Within the literature, psychological stress is measured as pessimism (Walburn et al., 2009; Maple et al., 2015), emotional distress (Kiecolt-Glaser et al., 2005), depressive symptoms (Bosch, Engeland, Cacioppo, & Marucha, 2007; Doering et al., 2005), anxiety (Walburn et al., 2009), loneliness (Bosch et al., 2007; Ebrecht et al., 2004), perceived stress (Ebrecht et al., 2004; Maple et al., 2015; Broadbent, Petrie, Alley, & Booth, 2003; Broadbent et al., 2012), pain (Walburn et al., 2009; McGuire et al., 2006), and sleep disturbance (Bosch et al., 2007; Mostaghimi, 2008; Aberg et al., 2007; Radek et al., 2010). Conceptually, the measures of psychological stress could be further categorized into specific stressors (pain, sleep disturbance,
lonesickness, marital interaction, surgery), states (emotional distress, depressive symptoms, anxiety, perceived stress), and personality traits (pessimism, negative affect) (Koolhaas et al., 2011). While the aforementioned measures represent psychological stress, they are measuring unique aspects of psychological stress and therefore the results presented in psychological stressor empirical studies should be interpreted accordingly to the concept(s) of psychological stress being evaluated. Of the fourteen studies that evaluated psychological stress, three studies (Walburn et al., 2009; Maple et al., 2015; Ebrecht et al., 2004) measured three dimensions of psychological stress (specific stressors, states, traits), nine studies (Kiecolt-Glaser et al., 2005; Doering et al., 2005; Broadbent et al., 2012; McGuire et al., 2006; Broadbent, Petrie, Alley, & Booth, 2003; Bosch et al., 2007; Koschwanez et al., 2015; Chen et al., 2015; Shah & Coates, 2006) measured two dimensions (specific stressor, state), and two studies (Mostaghimi, 2008; Landis & Whitney, 1997) measured one dimension (specific stressor). Personality traits were only studied in 2 studies. As personality traits have been suggested to moderate the negative effects of stress (Maple et al., 2015), the majority of the studies (85%) do not provide information regarding the potential moderating effect of personality traits on wound outcomes. Specific stressors and states were the most commonly studied dimensions of psychological stressors within the context of wound outcomes. The specific stressors, states, and traits identified in the literature, and their subsequent temporal inter-relationships, will be presented below.

**Theme 2: Psychological Stressors and Wound Outcomes**

The inter-relationship and temporal development of specific stressors or states, in the context of wound outcomes, has not been determined. Of the studies that measured
different specific stressors and/or states, all studies were exploratory observational studies. Regarding inter-relationships of specific stressors or states, people with higher depressive symptoms report more sleep disturbance and increased daytime drowsiness (Bosch et al., 2007), higher perceived stress is associated with greater emotional distress (Ebrecht et al., 2004), and higher perceived stress is associated with less optimism and conscientiousness (Maple et al., 2015). Regarding temporal development of specific stressors and/or states, preoperative ($r^2=0.23$) and postoperative anxiety ($r^2=0.03$) predicted increased postoperative pain and accounted for 23% of the variance of increased postoperative pain (Broadbent et al., 2003; Chen et al., 2015). Preoperative depressive symptoms ($r^2=0.46$) and pre-existing pain ($r^2=0.52$) was shown to predict persistent postoperative pain (McGuire et al., 2006). However, this finding may be confounded as McGuire et al. (2006) did not control for preoperative pain when analyzing the effect of depressive symptoms on persistent pain. Furthermore, depressive symptoms were not found to predict increased acute pain (McGuire et al., 2006). No further analyses were reported regarding the potential inter-relationships or temporal development of specific stressors and/or states. In the following paragraph, we will highlight the potential individual and combined influences of specific stressors, states, and traits on wound healing.

People who experience psychological stressors have delayed wound healing. A meta-analysis of 12 studies, with a cumulative sample size of 582 subjects experiencing various types of stressors (e.g., depressive symptoms, perceived stress) and wounding (punch biopsy, tape stripping, clinical wounds), demonstrated that psychological stress accounts for 42% of the variance in delayed wound healing with a range of 22 to
51% (Walburn et al., 2009). To account for potential overestimation of effect size, as a result of publication bias and differing wound types, Walburn et al. (2009) demonstrated that there was no significant influence of the heterogeneity of the studies on the overall effect size via funnel plot analysis (Walburn et al., 2009). Further evaluation of human subject psychological stress wound healing studies (Kiecolt-Glaser et al., 2005; Bosch et al., 2007; Doering et al., 2005; Ebrecht et al., 2004; Broadbent et al., 2003; McGuire et al., 2006; Bosch et al., 2007) included in the meta-analysis (Walburn et al., 2009) that also matched inclusion criteria, showed that people with depressive symptoms are 3.5 times more likely to experience delayed wound healing (Bosch et al., 2007), and are 3.7 times (95% CI 1.15-12.0) more likely to develop postoperative infection even with controlling for age, diabetes, and obesity at 6 weeks after surgery (Doering et al., 2005). Additionally, those people who are considered to have more hostile relationships required one additional day to heal (HR = 0.60) in comparison to those with lower hostile relationships (Kiecolt-Glaser et al., 2005), higher perceived stress was strongly correlated with speed of wound healing ($r^2 = 0.35$) (Ebrecht et al., 2004), and those averaging <4/10 pain in the 4 weeks following surgery healed in 21 days in comparison to those ≥4/10 pain healed at 28 days (McGuire et al., 2006). While psychological stressors (i.e. depressive symptoms, pain, perceived stress) have been shown to cause delayed wound healing, the clinical significance of the results varies from 1-7 days longer to heal is confounded by the wound type (partial thickness [blister wound] versus full thickness [punch wound] healing). Therefore when comparing the rate of healing between the blister and punch wound studies, analysis of the Kiecolt-Glaser et al. (2005) and McGuire et al. (2006) studies revealed that wounds healed 60% and 25% slower, respectively, in
comparison to their respective case controls. Therefore, when attempting to apply the clinical significance of psychological stress on wound healing in lower extremity NMSC wounds healing by secondary intention, people experiencing higher levels of psychological stress may experience 25-60% decrease in time to wound healing.

Since the publication of the 2009 meta-analysis by Walburn et al. (2009), additional studies (Maple et al., 2015; Broadbent et al., 2012; Koschwanez et al., 2015) have presented mixed results. Maple et al. (2014) showed that higher levels of perceived stress, lower levels of optimism ($r^2=0.1$), and conscientiousness ($r^2=0.03$) predicted delayed wound healing in living kidney donor (Maple et al., 2015). However, the effect of perceived stress and conscientiousness on tissue edema/wound width were not considered clinically significant as perceived stress accounted for 0.1% of the variance, and conscientiousness had a power of 36%. The use of tissue edema and wound width, as measured by ultrasound, as a surrogate marker likely influenced the results in the study. Furthermore, the study used surgically closed wounds whereas previous studies included in Walburn et al. (2009) meta-analysis included only open wound wounds. Therefore, the findings presented in the Maple et al. study support that psychological stress causes delayed wound healing, but failed to reach the effect size ($r^2=0.42$) presented by Walburn et al. (2009) due to using a different measure of wound healing (i.e., ultrasound) and different kinds of wounds. Interestingly, when exploring an interaction effect of perceived stress, optimism, and conscientiousness, conscientiousness remained as the predictor of wound healing (Maple et al., 2015). Similarly, through the use of a stress reduction intervention (relaxation and guided imagery) intended to increase conscientiousness, Broadbent et al. (2012) found that a stress reduction intervention was
associated with an increase of 9 points in hydroxyproline (a surrogate marker of collagen deposition) in those who received the intervention ($r^2=0.2$). The authors proposed that those with increased conscientiousness, as a result of guided imagery and muscle relaxation, may have had an increase in positive affect, which may have moderated or mediated the effects of perceived stress on hydroxyproline (Broadbent et al., 2012).

Furthermore, Broadbent et al., (2012) showed that perceived stress was not associated with their surrogate marker for wound healing, but this finding was likely influenced by their intervention and therefore does not contradict the findings presented by Walburn et al., (2009) regarding the influence of psychological stress on wound healing.

Koschwanez et al. (2015) performed a secondary analysis of two experimental studies (N=41) looking at the influence of a stress reduction intervention on wound healing. The authors identified that subjects with high stress/decrease wound healing were noted to have a significant decrease in human leukocyte antigen ($r^2=0.17$), a surrogate marker of immune cell activation, and langerhan cells ($r^2=0.34$), but not macrophages. While the authors used staining to identify cells and human leukocyte antigens in the tissue of the subjects, the findings are not specific as the type of human leukocyte antigens are not specified. Further study with transcriptomics is necessary to further elucidate the potential influence of psychological stress on the immune cells required to orchestrate wound healing and protect against infection.

Psychological stress impairs wound healing by influencing the cutaneous immune system via increased activation of the hypothalamic pituitary axis (HPA) and/or autonomic nervous system. In animal studies, exposure to a combination of crowding and sleep disturbance was used to elicit a psychological stress response. Consistently across
the four studies (Aberg et al., 2007; Rojas, Padgett, Sheridan, & Marucha, 2002; Martin-Ezquerra et al., 2011) that evaluated the role of psychological stress on wound healing/wound infection, glucocorticoids were elevated in the group receiving the psychological stress intervention. When RU486, a glucocorticoid receptor blocker, was administered in conjunction with the psychological stressor group, mice were noted to have an improvement in wound healing (Aberg et al., 2007; Rojas et al., 2002; Martin-Ezquerra et al., 2011). While animal studies have produced very consistent results in demonstrating the association between psychological stress and elevated glucocorticoids, human studies have presented mixed findings. The lack of translation from animals to humans may be a result of bench science conditions not being reproducible in humans.

In studies of humans, Ebrecht et al. (2004) demonstrated that glucocorticoid levels were elevated in the higher stress group the day after wounding, and the higher stress group was associated with delayed (< 1.5 mm healing over a 14 day period) wound healing ($r^2=0.35$) (Ebrecht et al., 2004). In contrast, Bosch et al. (2007) did not find an association between elevated glucocorticoid levels and higher depressive symptoms or delayed wound healing. The non-significant associations may have been confounded by sampling or storage error due to the samples being collected by patients in the field, where as Ebrecht at al. (2004) stored the samples in a -20°C refrigerator (Bosch et al., 2007). Additionally, other physiologic responses of stress (e.g., parasympathetic) (Radek et al., 2010) were not measured in the study, and may have revealed additionally pathophysiologic mechanisms for elucidating the findings that higher psychological stress predicted delayed wound healing (Bosch et al., 2007).
In addition to psychological stress being associated with increased glucocorticoid levels, pro-inflammatory cytokines (IL-1, IL-6, TNF-α, MMP-9) required to aid in the wound healing process are decreased. Kiecolt-Glaser et al. (2005) showed that serum levels of IL-6 and TNF-α were not impacted by either social support or marital conflict. Yet, IL-1, IL-6, and TNF-α levels in wound blister fluid were significantly and clinically different in social support (increased) and marital conflict (decreased) (Kiecolt-Glaser et al., 2005). Furthermore, psychological stress accounted for 17% and 12% of the variance in lower IL-1 and MMP-9 levels, respectively (Broadbent et al., 2003). While both studies showed that decreased pro-inflammatory cytokines at the wound site are associated with increased psychological stress, neither author attempted to elucidate the potential mechanism by which the cytokines are decreased. As norepinephrine and cortisol have been shown to influence levels of other cytokines (e.g., MMP-2), perhaps these two distinct physiologic pathways may influence the decrease in cutaneous pro-inflammatory cytokine signaling.

Another cutaneous pathophysiologic mechanism by which increased psychological stress has been found to influence wound healing is through anti-microbial peptides. In animal studies, psychological stress (crowding conditions and insomnia) has been shown to increase serum corticosteroid levels and increase the prevalence of opportunistic organisms in acute wounds (Rojas et al., 2002). The potential mechanism by which psychological stress influences the microbiome is through nicotinic anticholinergic receptor and corticosteroid mediated decrease in antimicrobial peptides (cathelicidin, beta defensin, catestatin) (Aberg et al., 2007; Radek et al., 2010; Martin-Ezquerra et al., 2011). The aforementioned findings are further supported as anti-microbial peptides increase
when RU486 (corticosteroid receptor blocker)(Aberg et al., 2007; Rojas et al.,
2002; Martin-Ezquerra et al., 2011) or alpha bungarotxin (nicotinic cholinergic receptor
blocker)(Radek et al., 2010) are administered. While Aberg et al. (2007), Radek et
al. (2010), Rojas et al. (2002), and Martin-Esquerra (2011) showed consistent findings,
animal studies may or may not translate to humans. Future studies are needed to evaluate
the role of psychological stress on the wound microbiome and wound infection. While
there is mounting evidence for the influence of psychological stress on delayed wound
healing and wound infection, not all psychological stressors have the same impact.

While psychological stress has been shown to be associated with delayed wound
healing, the potential mediating or moderating influence of lifestyle behaviors, co-
morbidities, or socioeconomic status have not been determined. Consistently across
studies (Walburn et al., 2009; Maple et al., 2015; Kiecolt-Glaser et al., 2005; Ebrecht et al.,
2004; Broadbent et al., 2003; Bosch et al., 2007) that reported controlling for potential
confounding variables smoking, exercise, diet, alcohol consumption, body mass index,
diabetes, medications, gender, ethnicity, and age were not found to attenuate the
association between psychological stress and delayed wound healing. However, the
studies that reported on potential confounding variables may not have had a large enough
sampling of the aforementioned variables to determine true confounding effect. For
example, two studies excluded smokers from their study (Ebrecht et al., 2004; Kiecolt-
Glaser & Glaser, 2002), and the remaining studies had a smoker population of 4-14
subjects each. Furthermore, people who were considered unhealthy or who had diabetes
were excluded two studies (Ebrecht et al., 2004; Bosch et al., 2007) further complicating
the ability to determine the role of potential confounding variables on psychological stress and delayed wound healing.

Another confounding variable of interest is age. The role of psychological stress on delayed wound healing in older adults has not been determined. The average age of human subjects in the nine psychological stress wound healing studies were 45.5, with a mean age range of 20 to 78. The four (Doering et al., 2005; Broadbent et al., 2003; Broadbent et al., 2012; Koschwanez et al., 2015) studies with age mean > 50 years old are inconclusive. Koschwanez et al. (2015) experimental study consisted of two groups who both performed a writing intervention that subsequently showed no difference in wound healing time. Neither higher depressive symptoms nor perceived stress were found to be associated with delayed wound healing (Koschwanez et al., 2015). The nonsignificant finding may have be as a result of both groups participating in a writing intervention. Broadbent et al. (2005) and Broadbent et al. (2012) studies both used surrogate wound healing markers (hydroxyproline, IL-1, IL-6, TNF-α) to show that wound healing was delayed as a result of decreased inflammatory cytokines (Broadbent et al., 2012; Broadbent et al., 2003). Yet, no specific information was provided regarding the wound healing time of the two different wound types (wound blister, surgically closed wound). Furthermore, Doering et al. (2005) reported that patients with higher levels of psychological stress had a higher probability (3.7) of developing wound infection and wound healing problems at postoperative week 6 (Doering et al., 2005). Once again, the wounds were surgically closed wounds and no specific details were given regarding wound healing. Walburn et al. (2009) identified similar issues in their meta-analysis.
citing that one of the limitations of their study was a lack of evidence to determine the
effect on confounding variables on their study results.

While there is much still to learn about potential moderator or mediators of
psychological stress influence on wound healing, some evidence points to certain
psychological stressors not influencing delayed wound healing. Psychological stressors
loneliness and sleep disturbance are not associated with delayed wound healing.
Loneliness were not associated with delayed wound healing (Ebrecht et al., 2004; Bosch et al., 2007). Even with using the same instrument (UCLA Loneliness scale), similar findings were found in the young adult population (college students, university employees). Perhaps, exploring loneliness in an older adult population (people with NMSC) would present different results as older adults may have increased difficulty with transportation/mobility. Consistently across animal (Mostaghimi, 2008; Landis & Whitney, 1997) and human (Ebrecht et al., 2004; McGuire et al., 2006; Bosch et al., 2007; Broadbent et al., 2015; McGuire et al., 2006) studies, sleep disturbance has not been associated with delayed wound healing. However, animal studies (Aberg et al., 2007; Radek et al., 2010; Rojas et al., 2002; Martin-Ezquerra et al., 2011) have shown that sleep disturbance as a psychological stressor is capable of increasing the severity of a wound infection. While neither loneliness nor sleep disturbance is associated with delayed wound healing in animal or human studies, sleep disturbance may assist with explaining increased wound infection severity.

**Theme 3: Psychological Stressors and the Microbiome**

Psychological stressors are associated with increased wound infection severity.

Doering et al. (2005) is the only human study that demonstrated that psychological stress
increased the probability of wounds developing wound infection (Doering et al., 2005). Yet, there are animal studies to support the findings presented by Doering et al. (2005). Rojas et al. (2002) demonstrated that 85% of psychologically stressed mice developed wound infections, using the $10^5$ criterion, compared to 27% of the controls following inoculation with Group G Streptococci. Interestingly, 75% of the psychological stress mice contained significantly increased numbers of opportunistic infections compared to 11% of the control group. When psychological stressed mice’s glucocorticoid receptors were blocked (RU486), there was a 1 log decrease in opportunistic organisms versus those who received vehicle (Rojas et al., 2002). The significant reduction of opportunistic organisms as a result of glucocorticoid blockade highlights the influence supported by Aberg et al. (2007), which showed that HPA axis has direct inhibitory effects on aspects of the innate immune (anti-microbial peptides) (Aberg et al., 2007).

Aberg et al. (2007) further showed that psychologically stressed mice with elevated hypothalamic pituitary axis activity (elevated glucocorticoids), inoculated with group A Streptococci, developed abscesses 50% larger than controls at 4 days after inoculation. (Aberg et al., 2007) In contrast to the HPA activity increased wound infection severity, Radek et al. (2010) demonstrated that psychological stressed mice have significant increases in nicotinic acetylcholine receptor activity. Activation of the nicotinic acetylcholine receptor resulted in significant decreases in anti-microbial peptides cathelicidin, beta defensin, and catestatin, and resulted in an 81% and 67% increase in wound necrosis for mice groups injected with methicillin resistant staphylococcus aureus or group A Streptococci, respectively. Following nicotinic acetylcholine receptor blockade, the wound size decreased 50% in compared to those
mice who received vehicle. A weakness of the aforementioned studies are they are unable to fully categorize what is actually happening in the wound microbiome. Colony forming units (CFU) characterization of wound bacteria are heavily biased towards non-facultative bacteria (Brugger et al., 2012). Yet, for the purposes of the aforementioned studies, the CFU were used to characterize common pathogens, of which CFU works well for. However, understanding the context of what is happening in the bacterial community structure (bacterial load/diversity) has gained increased interest recently as a result of next generation sequencing increased capacity of fully characterizing bacterial bioburden.

No studies have been conducted exploring the influence of psychological stress on the cutaneous or wound bacterial bioburden using next generation sequencing. Psychological stress has been shown to alter bacterial diversity in the gut microbiome. A short term (2 hour social disruption) stressor was noted to influence unique bacterial community clusters, but no difference in species abundance or richness of the gut microbiome (Galley et al., 2014). The social disruption group had significant decreases in relative and absolute abundance of *lactobacillus* spp., but not other species types (*Parabacteroides, Bacteroides-Prevotella-Porphyromonas*) (Galley et al., 2014). Of particular interest is that psychological stress reduces lactobacillus spp., a common organism known to produce anti-inflammatory effects on the intestine. A similar effect on cutaneous commensal bacteria may produce a potential targeted probiotic therapy for individuals with psychological stress. Voigt et al. (2014) also identified that mice with altered circadian rhythm (i.e., sleep disturbance) and diet (high fat/carbohydrate) resulted in decreased lactobacilli and increased *Ruminococcus*, a bacteria known for pro-
inflammatory effects on the intestine (Voigt et al., 2014). Furthermore, beta bacterial diversity (species abundance/richness) was significantly lower in the circadian rhythm plus diet group compared to the control group (Voigt et al., 2014). As demonstrated by Galley et al. (2014) and Voigt et. al (2014), psychological stress has the potential for altering the gut bacterial bioburden. Prior to testing the effect of psychological stress on the cutaneous/wound bacterial bioburden, identifying the common bacterial bioburden signatures of surgical wounds is warranted.

**Theme 4: Surgical Wound Bacterial Bioburden**

The surgical wound bacterial bioburden of below the knee dermatologic surgery patients has not been determined using next generation sequencing. Using traditional culturing methods (i.e., CFU), Saleh et al. (2011) showed the most commonly occurring bacteria of facial dermatologic surgical wounds were commensals *Propionibacterium acnes* and *Staphylococcus aureus* (Saleh, Sonesson, Persson, Riesbeck, & Schmidtchen, 2011). A bacterial load of $\geq 10^5$ was shown to be associated with wound infection symptoms (pain, increased drainage, induration, erythema), loss of surgical graft/flap, and necrosis in dermatological procedures involving the face (Saleh et al., 2011). Furthermore, preoperative and intraoperative bacterial load were not predictive of postoperative complications. Bacterial load was not shown to be associated with smoking, diabetes, gender, or ulceration of lesion. There was insufficient information to determine the effect size or power of the study, but the study was likely underpowered due to having a sample of 18 subjects. As the study focused on facial surgical wounds only, the identification of *Propionibacterium acnes* and *Staphylococcus aureus* as the primary bacteria are not surprising due to the involvement of the sebaceous zone (Grice et
al., 2009). Yet, next generation sequencing’s increased sensitivity and specificity has resulted in superior characterization of the bacterial community structure, and not just restricted to bacteria that can be cultured in the laboratory (SanMiguel & Grice, 2015).

Using next generation sequencing to characterize perioperative coronary artery bypass graft surgical wound changes, Romano-Bertrand et al. (2015) revealed that six phylum, with 147 different species, compose the bacterial community structure of the chest. The most common genera, as determined by prevalence in subjects, are *Staphylococcus, Propionibacterium, Sphigomonas, Corynebacterium, Paracoccus, Streptococcus, Anaerococcus,* and *Acinetobacter* (Romano-Bertrand et al., 2014). To detect changes through the perioperative period, the bacteria were grouped at the phylum level with *Actinobacteria* (e.g., *Corynebacterium, Propionibacterium*), *Firmicutes* (e.g., *Staphylococcus, Anaerococcus*) and *Proteobacteria* (e.g. *Acinetobacter, Paracoccus*) being the most common. Following the application of antiseptic, *Proteobacteria* increased substantially and *Firmicutes* decreased. The alpha diversity (bacterial community richness/abundance) of the surgical site increased significantly from pre-operation thoracic samples (29 species) to post-operative scar site samples (61 species) with the dominant phylum being *Firmicutes* (39%), *Proteobacteria* (33%), and *Actinobacteria* (23%). The greatest limitation of the study was the author’s failure to include demographics of the population and any associated post-operative complications. Studying the bacterial community structure perioperative changes alone is informative, but only provides a one dimensional evaluation as the inter-individual changes are not considered. Yet the information supports that the bacterial community structure, common to sebaceous regions (e.g., *Propionibacterium, Staphylococcus, Corynebacterium*) (Grice
et al., 2009), change in response to antiseptic application, contaminate the surgical wound environment despite antisepsis, and following surgical closure the surgical site has increased diversity. Although Romano-Bertrand et al. (2015) reported great inter-individual surgical wound bacterial community structure signatures, they identified common bacteria in the surgical wound environment. While similar location specific bacteria exist in chronic surgical wounds, the community structures are different from acute surgical wounds.

The chronic surgical wound microbiome is composed of commensal (Staphylococcus, Corynebacterium, Propionibacterium) and anaerobic (Fingoldia, Prevotella, Peptoniphilus, Anaerococcus) bacteria. Using next generation sequencing, Wolcott et al. (2015) performed a retrospective analysis of 2,963 subjects with four distinct wound etiologies, which are diabetic foot ulcer, pressure ulcer, non-healing surgical wound, and venous leg ulcer. Over 20 dominant bacteria genera were identified with the most common non-healing surgical wound bacterial community structure, as determined by relative abundance, consist of Staphylococcus, Pseudomonas, Corynebacterium, Streptococcus, Enterococcus, and Fingoldia (Wolcott et al., 2015). Interestingly, four out of the top ten genera were strict anaerobic (Wolcott et al., 2015). Yet, Wolcott et al. (2009) presented similar findings that anaerobic bacteria make up the largest percentage of bacterial community structure (Wolcott, Gontcharova, Sun, Zischakau, & Dowd, 2009). The two dominant genera noted to occur most commonly amongst all wound types are Staphylococcus and, Pseudomonas (Wolcott et al., 2015). On average, non-healing surgical wounds have a composite of 2-5 genus that make up the majority of the bacterial community structure, with the remaining bacteria representing
1% of the sample. No particular bacterial community structure was correlated with age, gender, wound type, or diabetes. Yet, the aforementioned results presented by Wolcott et al. must be approached with caution despite being a large sample size. A potential methodological flaw may have occurred as a result of using universal primers (28F, 519R), which have been shown to have >10% non-coverage rates resulting in under representation of particular genus, and furthermore skew the actual relative abundance composition of the bacterial community(Mao, Zhou, Chen, & Quan, 2012). Another limitation of the study is that the authors did not report on the anatomical distribution of the chronic wounds. Yet, the findings from Wolcott et al. (2015) suggest that there is a specific bacterial community structure unique to all chronic wounds. Determining the role that bacterial bioburden plays in contributing to particular post-operative complications in below the knee dermatologic surgery patients is needed.

**Theme 5: Lower Leg NMSC Postoperative Complications**

Lower leg dermatologic surgeries experience the highest location specific complications in dermatologic surgery. The overall postoperative complication for dermatologic surgery ranges from 0.72% to 6%.(Alam et al., 2013; Amici et al., 2005) The most common postoperative complications for all sites were hemorrhage/hematoma (0.1-3%), syncope (2%), infection (0.3-1.3%), partial/full graft or flap failure (0.1-1.7%), and wound dehiscence (0.73%)(Alam et al., 2013; Amici et al., 2005; Bordeaux et al., 2011). Specific to legs, the postoperative complication rate is 17 to 53.4%. The most common complications reported are hematoma (20.5%), infection (3.3-16%), delayed wound healing (4.3%-26%), hypergranulation tissue (3%), and hypertrophic scar (1.4%)(Honaker et al., 2015; Stankiewicz et al., 2015; Audrain, Bray, & De Berker,
2015; Dixon et al., 2006). While dermatologic surgery of other locations are associated with lower postoperative complication rates, legs present unique challenges as they experience higher complication rates (Bordeaux et al., 2011). Identifying modifiable factors is essential for reducing postoperative dermatologic surgery complications in the older adult population.

The predictors of postoperative dermatologic surgery complications are surgical closure type, post-operative wound size, and surgical location. People undergoing surgical closure with surgical grafts, flaps, or primary closure are 7.58 to 9, 6.7 to 11.93, and 5.8 times, respectively, more likely to experience postoperative hemorrhage/hematoma (Amici et al., 2005; Bordeaux et al., 2011). Amici et al. (2005) et al reported that people who experienced postoperative hemorrhage/hematoma were 7.59 times more likely to develop wound infection (Amici et al., 2005). Furthermore, people undergoing surgical closure via graft/flap closure are 2.5-5.9 times more likely to develop postoperative wound infection (Amici et al., 2005; Dixon et al., 2006). Stankiewicz et al. (2015) reported that 66.5% of split thickness skin grafts failed, and postoperative hematoma predicted surgical graft failure (Stankiewicz et al., 2015). As surgical graft and flap closure procedures are associated with increased risk of hemorrhage/hematoma that may further beget additional postoperative complications (e.g. infection), perhaps patients who receive anti-coagulation for other disease processes are at an increased risk for postoperative complication. Bordeaux et al. (2011) showed that patients taking clopidogrel and warfarin and undergoing dermatologic surgery are 40 times more likely to develop postoperative hemorrhage (Bordeaux et al., 2011). In addition to surgery type, and
postoperative hemorrhage/hematoma, another risk factor associated with increased risk of experiencing postoperative complication is wound size.

Surgical grafts or flaps are frequently used to close larger surgical wounds to aid in the healing process and for cosmetic purposes (Alam et al., 2013; Audrain et al., 2015). Yet, Honaker et al. (2016) showed that wound size was the only predictor of postoperative complications (for every 1 cm² increase in size, the odds of having complication increased 7.7%) in dermatologic surgery of the leg when controlling for gender, age, surgical type, and co-morbidities (Honaker et al., 2015). Unfortunately, five (Alam et al., 2013; Stankiewicz et al., 2015; Amici et al., 2005; Bordeaux et al., 2011; Dixon, Dixon, & Dixon, 2009) of the eight studies exploring postoperative complications in dermatologic surgery did not account for or report postoperative wound size (total surface area) in their analysis, which is a large limitation of those studies. Of the studies evaluating wound size, Dixon et al. (2006) study showed wounds larger than 11 mm² in diameter had an incidence of 11.6% infections in contrast to 2.2% in those with wounds <11 mm² (Dixon et al., 2006). In contrast, wounds in Audrain et al. (2015) study were on average 52 cm², but only 16% of the patients developed postoperative complications (i.e., infection) (Audrain et al., 2015). Results presented by the study are confounded as 66% of the patients received prophylactic antibiotics. While not exploring the influence of wound size on postoperative outcomes, Joo et al. (2014) identified no difference in complications between the two groups (primary closure, secondary intention healing), which is likely explained by both groups having nearly equivalent wounds sizes (5.2 versus 6.4 cm²) (Joo et al., 2015). No studies were identified to evaluate the combined role of anticoagulants and wound size on postoperative complications. Further
complicating the identification of key independent predictor variables versus moderators/moderators of postoperative complications is surgical location.

Bordeaux et al. (2011), Amici et al. (2005), Dixon et al. (2006), and Dixon et al. (2009) identified that lower leg surgical wounds were 3.88 to 4.28 times more likely to develop wound infection. The most common areas for infection were the genitals (10-14%), legs (3.3-16%), and face/scalp (0.78-3.3%)(Alam et al., 2013; Stankiewicz et al., 2015; Bordeaux et al., 2011; Dixon et al., 2006). Wound infections were often reported 6.3 days after surgery, and were primarily reported as cellulitis with abscesses being the second most common complication (Amici et al., 2005; Dixon et al., 2006). Dermatologic surgical wounds of the leg were also found to predict surgical site failure rate of surgical grafts, but no effect size could be determined (Stankiewicz et al., 2015). Dermatologic surgical leg wounds were also associated with more pain (mean score of 5/10) compared to other locations on the body (mean score 2.75/10) (Chen et al., 2015). Unfortunately, Chen et al. (2015) did not evaluate the influence of postoperative pain on postoperative complications. As noted previously, McGuire et al. (2006) showed that patients with higher pain scores were associated with delayed wound healing. Furthermore, delayed wound healing can be complicated in lower leg surgical wounds due to low ankle brachial index values, a marker of lower leg tissue perfusion (Mätzke, Franckena, Albäck, Railo, & Lepäntalo, 2003). Only one (Audrain et al., 2015) of the nine studies controlled for lower leg tissue perfusion, and that study was confounded by prophylactic antibiotic administration. In order to determine the true effect of lower leg surgical wounds on postoperative complications, tissue perfusion must be accounted for. While surgical type,
wound size, and surgical location have been shown to predict postoperative complications, there is insufficient evidence to exclude other factors.

There is insufficient evidence linking age, immunosuppressants, diabetes, smoking, and malnutrition as predictors of postoperative complications in people undergoing dermatologic surgery for NMSC. Stankiewicz et al. (2015) identified that increasing age was predictive of developing complications. However, the effect size was small ($r^2=0.06$), and was underpowered (70%). Dixon et al. (2009) identified that persons >66 years of age were 1.02 times more likely (95% CI 1.01-1.03) to develop postoperative wound infection. As the clinical significance of the aforementioned studies are small to insignificant, the effect of older age on postoperative complications requires further study. In addition to age, immunosuppressant medications may increase the risk of postoperative wound infection. One study (Amici et al., 2005) showed that people taking immunosuppressant medications were 5.4 times more likely to develop wound infection. However, immunosuppressants have not been reported in other studies indicating further study is needed.

Another factor known to suppress the immune system, and influence wound healing, is diabetes (Sibbald et al., 2011). Dixon et al. (2009) showed that people with diabetes were 1.7 (95% CI 1.05-2.65) times more likely to develop postoperative wound infections after controlling for surgery type, age, gender, surgical location, anticoagulant medication, and smoking status. However, Stankiewicz et al. (2015) did not find any relationship between diabetes and postoperative complications. Complicating the findings presented on diabetes is data regarding severity of disease. Neither study presented laboratory data (e.g., hemoglobin A1c) regarding the severity of disease.
Furthermore, the findings presented by Dixon et al. (2009) suggest wound infection incidence was only increased by 2.4% in comparison to the non-diabetes group. Therefore, further study is required to delineate the influence of diabetes on postoperative complications. Of the studies exploring postoperative complications in people with NMSC, only Amal et al. (2013) reported that twice as many postoperative complications occurred in those reporting a history of smoking, but no further data was provided. A combination of insufficient sample size (2-20%) and data regarding severity of smoking status may account for the differences. Another factor considered to have insufficient evidence to influence postoperative complications is malnutrition. One study accounted for nutritional status, but found that the subjects did not have signs of malnutrition (Stankiewicz et al., 2015). As the authors did not have any subjects with malnutrition, the evidence is inconclusive regarding the effect of malnutrition on postoperative complications. However, the impact of impaired nutrition versus malnutrition has not been established. An additional challenge in studying postoperative complications in NMSC patients is they are generally healthy older adults (mean age 66.3) with the majority having ≤ 2 co-morbidities and HRQoL (Bertenthal, Sahay, Sen, & Chren, 2007; Steinbauer et al., 2011).

**Theme 6: HRQoL in older adults with NMSC**

Older adults diagnosed with NMSC have a normal distribution of HRQoL and experience minimal changes in HRQoL. The majority (66-69%) of older adults who have NMSC have HRQoL scores that are average or better than population means (Shah & Coates, 2006; Chen et al., 2007; Steinbauer et al., 2011). Of those older adults with a NMSC, 31% reported no effect of the NMSC on their life, and 31% reported moderated
to severe impairment (Steinbauer et al., 2011). However, the HRQoL values reported by Steinbauer et al. (2011) did not take into consideration pre-NMSC diagnosis HRQoL. Then breaking down the HRQoL into themes, people, on average, report slight impairment. Those who reported moderate to severe HRQoL primarily involved NMSC involvement of the face (78%) and leg (33%) (Steinbauer et al., 2011). Using the Skindex, a dermatology specific HRQoL measure with a score range from 0-100 (100 = worse HRQoL), older adults on average had an average improvement of 12 points following surgical correction when accounting for age, marital status, gender, race, socioeconomic status, mental health status, educational level, and co-morbidity index (Chen et al., 2007).

Preoperative HRQoL scores, comorbidities, and mental status predict worse postoperative HRQoL scores. The single greatest predictor of postoperative HRQoL scores was preoperative HRQoL scores. For every 10 point change in preoperative Skindex HRQoL scores, postoperative Skindex scores changed by 5 points. Better preoperative HRQoL scores were correlated with lower Charlson Comorbidity Index scores (less comorbidities), socioeconomic status (> $30,000), educational level (graduate degree), and SF-12 physical health (≥46) and mental health (≥50) component scores (Chen et al., 2007). People with NMSC who had SF-12 mental health component scores of <44, and higher co-morbidity scores were noted to have worse pre and postoperative HRQoL scores. The mental health status and the Charlson Comorbidity Index were predictive of postoperative HRQoL, but had minimal clinical significance. A 10 point changes in mental health status and a one point change in the Charlson Comorbitiy index resulted in changes of 3 points and 1 point changes, respectively, in postoperative Skindex HRQoL scores (Chen et al., 2007). To reach clinically meaningful
changes, a 10 point change in the Skindex score is required (Chen et al., 2007). While not considered to be predictive of postoperative HRQoL, preoperative HRQoL were worse in those whose wounds were \( \geq 12 \text{ mm}^2 \) (Chen et al., 2007). No other studies were found that explored predictors of HRQoL in NMSC patients. The greatest limitation of the study is that the findings can only be generalized to the Caucasian male veteran population. When looking more specifically at the personal experience of people diagnosed with NMSC, patients who report lower HRQoL scores share a common theme of stress.

Common themes (e.g., treatment burden, emotional distress) that impair HRQoL in people are intertwined and worse HRQoL scores are reported by younger females. The most common theme reported to have impairment is emotions, followed by daily activities, leisure, and treatment (Chen T et al., 2007; Steinbauer et al., 2011). Almost two thirds (65%) of people report anxiety regarding their skin cancer spreading or reoccurring, which led to 59% avoiding midday daily or leisure activities due to potential sun exposure (Burdon-Jones, Thomas, & Baker, 2010). Additionally, 21% of people with NMSC report worries about postoperative bleeding, non-healing wounds, and permanent scarring/disfigurement (Burdon-Jones et al., 2010). Furthermore, female patients reported worse HRQoL scores in comparison to males when NMSC were located on the face, and required complex reconstructions (Burdon-Jones et al., 2010; Rhee JS et al., 2006). While pain anxiety scores increased more in females than in males undergoing dermatologic surgery and for those with increasing tumor size \( (> 2 \text{ cm}^2) \), the pain anxiety scores were not correlated with surgical location, surgical closure type, or tumor type (Chen et al., 2015). Perhaps the increased worries regarding postoperative bleeding, non-healing
wounds, and permanent scarring/disfigurement may explain increased pain anxiety scores in females as reported by Chen et al. (2015).

Unfortunately, HRQoL has not been studied in the context of postoperative symptoms (e.g., pain) or complications in people diagnosed with NMSC. While Doering et al. (2005) did not measure HRQoL, patients with higher depressive symptoms reported poorer self-rated recovery and had higher incidence of wound infection. Therefore, people undergoing dermatologic surgery for NMSC who experience increased psychological stress may have worse postoperative HRQoL. While more research is needed to understand HRQoL in people diagnosed with NMSC, age, skin cancer type, or tumor size was found to predict pre or postoperative HRQoL (Chen et al., 2007).

Furthermore, the themes not found to be influenced by the diagnosis of NMSC is love life, occupational restrictions, or sports activities (Burdon-Jones et al., 2010).

**Gaps in the Literature**

The first limitation of the study is that 73% of the studies were quantitative studies without randomization. A limitation inherent to quantitative studies without randomization is the use of convenience sampling, which requires further caution when generalizing findings to the population. Another limitation of the study is the predominance of a heterogeneous group of wound locations used to study the role of psychological stress on wound outcomes and surgical wound microbiome changes, which may limit generalizability to dermatologic surgical leg wounds. A majority of the studies lacked a theoretical basis, and that became more evident as the measures utilized to assess psychological stress failed to adequately capture the three dimensions (specific stress, state, trait). As a result, the studies were limited in their capacity to define
potential relationships that existed between psychological stress and wound outcomes. Furthermore, the majority of dermatologic surgery studies exploring postoperative complications and HRQoL included all surgical locations, not just the leg. Only three of ten NMSC postoperative complications focused on the lower leg, and those studies had small sample sizes (<70). No studies were found synthesizing psychological stressors, bacterial bioburden, postoperative complications, and HRQoL in people with lower leg NMSC in a single study, which provides a more comprehensive perspective of potential relationships and outcomes.

**Summary and Future Directions**

While no information was found characterizing the depressive symptoms, sleep disturbance, or pain in older people undergoing dermatologic surgery for NMSC of the leg, the most common symptoms reported in chronic leg wound patients are pain (74-80%)(Upton & Andrews, 2013; Edwards et al., 2014), depressive symptoms (27-50%)(Jones et al., 2006) and sleep disturbance (69-80%)(Edwards et al., 2014; Upton & Andrews, 2013) with 64% experiencing 4 or more co-existing symptoms(Edwards et al., 2014). Depressive symptoms and sleep disturbance were noted to share a direct relationship with pain(Upton & Andrews, 2013; Jones et al., 2006), and 58% of older adult patients with chronic leg wounds indicated that pain caused their sleep disturbance(Upton & Andrews, 2013). Furthermore, depressive symptoms were identified to predict chronic persistent pain(McGuire et al., 2006). While the above associations have been identified in older adults with chronic leg wounds, the temporal nature of symptom development and the subsequent manifestation of additional symptoms have not been determined in either acute or chronic leg wound populations. In
addition to the temporal nature of symptoms development, a paucity of literature exists regarding the role of the three dimensions (specific stressor, state, trait) of psychological stress and wound outcomes. We hypothesize that optimism may or may not mediate or moderate the individuals response to stressors, which therefore would mitigate or instigate the poorer outcomes seen in people with higher levels of psychological stress. Furthermore, there is insufficient evidence regarding the role of psychological stress on wound outcomes in older adults. The studies that incorporated older adults limited our ability to determine any potential influence. Due to the normative age changes associated with older adults, we hypothesize that older adults who experience higher levels of psychological stress may experience more severe wound infections or delayed wound healing in comparison to younger adults.

The influence of psychological stress on the microbiome in humans has not been determined. Until more recently, the effects of psychological stress were considered to be only related to circulating stress hormones. However, Stojadinovic et al. (2012) identified that keratinocytes produced localized glucocorticoids in response to tissue injury and IL-1β (Stojadinovic, Gordon, Lebrun, & Tomic-Canic, 2012). Yet, the findings have only be performed in animal models, which do not directly translate to humans. Future studies that measure levels of cathelicidin, beta defensin, and catestatin in human wound exudate is needed to aid in confirming bench science findings. We hypothesize that increased psychological stress results in localized immunosuppression of particular innate immune system mechanisms (e.g., antimicrobial peptides) used to maintain a state of eubiosis with commensal bacteria. Yet, other mechanisms may be implicated in psychological stress, but have yet to be identified.
A dearth of literature has explored the role of bacterial community structures in human health and disease. Bacteria have been implicated in severe disease processes (i.e., sepsis) that result in death. The identification of key commensal bacteria that promote or inhibit inflammatory mechanisms may result in the development of new interventions for the prevention or treatment of wound critical colonization and/or infection. Another question to be determined is the role of functionally equivalent pathogens in the development of disease. Functional equivalent pathogen are commonly occurring bacteria clusters in a particular environment, and may provide an indirect characterization of bacteria community members associated with biofilm (i.e., symbiotic development of a protective extracellular polymeric substance that encases a bacterial community) development (Dowd et al., 2008). Perhaps under certain circumstances (e.g., psychological stress, peripheral vascular disease), particular commensal bacteria work in synchrony with other members of the bacterial community structure to develop a biofilm, which can lead to disease (e.g., delay wound healing). In contrast, identifying conditions where host states (e.g., optimism) contribute to symbiotic bacterial community signatures may add in the identification of health and disease signatures for which targeted therapeutics can be employed to correct dysbiosis in surgical or chronic wounds.

The reason that dermatologic surgical leg wounds experience more postoperative complications has not been determined. Future exploratory studies must take into account the following variables: surgical closure type, tissue perfusion (i.e., ankle brachial index), anti-coagulants, diabetes severity (i.e., elevated hemoglobin A1c), postoperative wound size, postoperative symptoms (e.g., anxiety, pain), medications (antibiotics, immunosuppressants), smoking, nutritional status, and age. Furthermore,
identifying modifiable predictors (anti-coagulants, immunosuppressants, psychological stress) on specific wound infection and delayed wound healing in dermatologic surgical leg wounds is warranted to aid in reducing potential postoperative burden in older adults. In addition to modifiable predictors, the identification of non-modifiable predictors (surgical closure type, postoperative wound size) would aid the dermatologic surgeon to provide precision medical care by providing prophylactic antibiotics to regulate the bacterial community structure or initiate advanced wound care dressings (e.g., collagen) to nurture faster wound healing in older adults. While NMSC primarily occur in older adults, people as young as 29 years old develop NMSC (Amici et al., 2005). A study comparing psychological stress and lower leg wound outcomes in both populations would aid in discerning age effects on postoperative outcomes.

A paucity of literature exists characterizing HRQoL in patients diagnosed with NMSC. No studies were found exploring the impact of postoperative complications on HRQoL. As Chen et al. (2007) identified that preoperative HRQoL scores predicted worse HRQoL in patients undergoing dermatologic surgery for NMSC, the question remains whether or not HRQoL could be used to predict poorer outcomes in patients undergoing dermatologic surgery. As HRQoL captures physical and mental health domains, and may be influenced by the number of comorbidities, perhaps the measure of HRQoL may have utility as a screening tool for determining at risk individuals. Ultimately, the question remains rather or not psychological stress contributes to the development of chronic surgical wounds as a result of delayed wound healing, and subsequently HRQoL is impaired in older adults who have dermatologic surgical leg wounds.
Chapter 3 Methods, Results, and Discussion

Predictors of Delayed Healing in Lower Extremity Surgical Wounds in Older Adults

Background

Nonmelanoma skin cancer (NMSC) is the most common malignancy occurring in the United States with greater than 5 million cases each year. The population most affected by NMSC are those 65 or older (Rogers et al., 2015). While NMSC frequently occur on the face, neck, and upper trunk as a result of chronic sun exposure, more than 200,000 NMSC occur on the lower extremity each year (Rogers et al., 2015; Solus et al., 2015; Pearson et al., 1999; Gallagher et al., 1990). Surgical correction (Mohs micrographic surgery [MMS]) of lower extremity NMSC is associated with a higher rate of complication (17%) (Honaker et al., 2015) compared to other surgical locations for MMS (0.72%) (Alam et al., 2013). Furthermore, persons undergoing lower extremity MMS for NMSC are 4.28 times more likely to develop a postoperative infection (Bordeaux et al., 2011). Known predictors of complication rates in lower extremity NMSC are postoperative hematoma, wound size (7.7% increase in odds for every 1 cm² increase in wound size), and increasing age (older adults) (Honaker et al., 2015; Stankiewicz et al., 2015).

Normative age changes that occur in older adults may predispose them to increased risk of postoperative complications (e.g., wound infection, delayed wound healing). Normal integumentary and immune physiological changes in older adults are altered keratinocyte motility, (Gould et al., 2015) reduced neutrophil activity, (Brubaker et al., 2013) impaired lymphatic drainage (Greenhalgh, 2015), and multiple underlying comorbidities (e.g., diabetes, vascular disease) (Stankiewicz et al., 2015). In addition to normative age changes, there is evidence that other kinds of symptoms (depressive
symptoms (Doering et al., 2005), sleep disturbance (Aberg et al., 2007; Alessi & Vitiello, 2011), pain (Greenhalgh, 2015) may influence postoperative complications (e.g., wound infection, delayed wound healing). Recent evidence has shown that bacterial bioburden (bacterial load, diversity, pathogenicity) in postoperative surgical wounds in conjunction with increasing age, co-morbidities, and underlying symptoms may influence the development of wound infection development and/or delayed wound healing (Stankiewicz et al., 2015; Doering et al., 2005). These factors, alone and in combination, are hypothesized to negatively influence the health-related quality of life (Edwards et al., 2014; Kuhns et al., 2015).

Depressive symptoms, sleep disturbance, and pain share complex interrelationships and have been associated with altered bacterial bioburden (increased bacterial load, decreased bacterial diversity), delayed wound healing, and poorer HRQoL. A review of the literature revealed no information on the incidence of depressive symptoms, sleep disturbance, and pain, or their influence on postoperative complications in older people undergoing dermatologic surgery for NMSC of the leg. Depressive symptoms are associated with an increased risk of wound infection and delayed wound healing in surgical patients (Doering et al., 2005; Bosch et al., 2007; Scheier et al., 1999), share a direct relationship with sleep disturbance and pain (Upton & Andrews, 2013; Jones et al., 2006) and predict chronic persistent pain (McGuire et al., 2006). Although the aforementioned relationships have been identified between depressive symptoms, sleep disturbance, and pain, the temporal nature of symptom development, and the subsequent influence on wound characteristics and bacterial bioburden has not been studied.
Sleep disturbance has not been associated with delayed wound healing (Landis & Whitney, 1997). However, sleep disturbance has been associated with an increased risk of developing wound infection (Aberg et al., 2007) and has been shown to influence pain and HRQoL scores (Raymond, Ancoli-Israel, & Choinière, 2004; Franks & Moffatt, 2006). Furthermore, alterations in circadian rhythm, a form of sleep disturbance, has been demonstrated to change intestinal bacterial communities in humans, (Voigt et al., 2014) suggesting that symptoms (e.g., sleep disturbance, depression) may increase a person’s susceptibility to developing a post-surgical wound infection.

Pain has been associated with increased bacterial bioburden (Sprockett et al., 2015) and delayed wound healing (McGuire et al., 2006). Tuttle et al. (2015) demonstrated that increased wound pain was associated with increased bacterial load and diversity (Sprockett et al., 2015). The identification of factors (e.g., depressive symptoms, pain) that influence the development of wound infection or delayed wound healing in surgical wounds would aid in the development of targeted interventions that would support timely wound healing and avoid the subsequent sequelae (Gardner et al., 2001) (e.g., sepsis, amputation) of non-healing wounds.

**Conceptual model**

Ferran et al. adaptation of Wilson & Cleary’s HRQoL model (Ferrans et al., 2005) is being used to characterize the current phenomenon of interest. In 1995, Wilson & Cleary noted that the current medical model, which emphasized biological and reductionistic philosophies to explain illness, was insufficient to account for all the dimensions associated with illness (Wilson & Cleary, 1995). Therefore, the medical model was merged with the social science paradigm, which focused upon the
measurement of complex behaviors and feelings that reflects dimensions of functionality and overall well-being.

The adapted model includes 7 constructs: individual characteristics, environmental characteristics, biological function, symptoms, functional status, general health perception and HRQoL. An identified weakness of Wilson & Cleary HRQoL model was addressed by applying McLeroy’s ecological model (McLeroy et al., 1988) to assist in defining the potential influences of the individual and environmental characteristics on the remaining constructs of HRQoL. Ferran et al. (2005) added causal pathways between individual and environmental characteristics and the biological function construct, incorporated nonmedical factors throughout individual and environmental characteristics, and established explicit definitions of individual and environmental characteristics (Ferrans et al., 2005). See figure 2 for the proposed concepts and their respective relationships.

**Specific Aims**

As there is a lack of literature that has explored the influence and temporal nature of depressive symptoms, sleep disturbance, and pain on alterations in wound healing and HRQoL, the goal of the study is to improve our understanding of the relationships between wound characteristics, patient characteristics (e.g., demographics, co-morbidities) and the presence of other symptoms such as pain, depressive symptoms and sleep disturbance in order to develop novel interventions to improve HRQoL in older adults. Therefore, the specific aims for this study are to: 1) Determine the temporal nature of symptom development and influence on subsequent symptom severity; and 2) Determine associations between wound characteristics (wound total surface area and
infection), patient characteristics, symptoms (depressive symptoms, pain, sleep disturbance), and HRQoL.

**Research Design and Methods**

A longitudinal prospective study was conducted following approval from the University Hospitals of Cleveland Institutional Review Board (UH IRB# 05-11-30). The study was conducted at the University Hospitals of Cleveland Outpatient Dermatologic Surgery Clinics from February 2016 to February 2017. Subjects were enrolled from the outpatient surgery clinics of one dermatologic surgeon where the primary surgical approach of the dermatologic surgeons was MMS. MMS is the primary surgical approach of the dermatologic outpatient surgery clinics. While there are patients who undergo traditional surgical excision, those patients traditionally underwent primary closure in comparison to secondary intention healing, surgical graft or flap for those undergoing MMS.

**Subjects**

A convenience sample of 14 subjects undergoing Mohs micrographic surgery for below the knee NMSC were followed weekly from week 0 (T1), the day of surgery, through week 4 (T2). A subsample of the convenience sample was followed weekly until healed. The inclusion criteria for the study was: 1) ≥ 50 years of age, 2) diagnosis of basal/squamous cell carcinoma located below the knee and above the malleoli, 3) patients are not undergoing a surgical closure procedure (e.g., surgical graft/flap) of the surgical wound, and 4) Mini-Cog score of ≥2. The determination of underlying cognitive impairment was necessary to ensure the subject’s capacity to accurately complete the symptom measures. Subjects were excluded from the study if: 1) surgical wound
undergoing surgical closure procedure (i.e., primary closure, surgical graft/flap), 2) peripheral arterial disease (ankle-brachial index (ABI) of <0.80), and 3) antibiotic or immunosuppressant therapy use in the 2 weeks prior to enrollment.

**Measures**

**Cognitive Impairment**

The Mini-Cog is a very brief instrument used to screen for cognitive impairment. The instrument consists of a clock drawing test and a 3-word recall. Patients receive a point for each word recalled. Word recall scores range from 0 to 3. The clock drawing test (CDT) is completed by drawing a circle, appropriately drawing the numbers of a clock face in the circle, and placing the hour and minute hand at 11:10 in the correct position. Patients with 1 to 3 recalled words, plus a correct CDT, were considered a negative for cognitive impairment (Borson, Scanlan, Brush, Vitaliano, & Dokmak, 2000; Borson, Scanlan, Chen, & Ganguli, 2003). The specificity and sensitivity for detecting mild cognitive impairment is 78-87.9% and 39-84%, respectively (Lin et al., 2013). Interrater reliability of the test is $K=0.80$ (Trongsakul, Lambert, Clark, Wongpakaran, & Cross, 2015).

**Vascular Status**

For vascular status, the ankle brachial index and the Clinical Etiology Anatomy Pathophysiology (CEAP) venous disease classification system were used. Ankle brachial index provides an indirect measure of lower extremity tissue perfusion. The screening test is completed by taking the ankle systolic blood pressure (SBP), by using a doppler ultrasound device, and dividing it by the highest brachial systolic blood pressure. Construct validity was shown with 90% of peripheral arterial disease patients with an
abnormal ABI (Nam et al., 2010). Variability in ABI, resulting in false negative results, can occur in those who have hypertension (e.g., untreated, white coat syndrome), non-compressible vessels, or the proximity of the stenotic vessel in proximity to the placement of the doppler ultrasound (i.e., downstream occlusion would not be detected) (Nam et al., 2010; Caruana, Bradbury, & Adam, 2005). Populations noted to have higher false negative results include patients with diabetes (i.e., 4.4 times more likely), stenosis below the tibial trifurcation (3.4 times more likely), and those >60 years old (3 times more likely) resulting in an ABI sensitivity of 36 to 61% (Nam et al., 2010). Without the above variables, sensitivity of 90% has been reported when comparing ABI to angiography results in patients with peripheral arterial disease (Aboyans et al., 2012). For reliability, inter-rater produces less variability issues than does the biological variants noted between patients. Test-retest reliability in past studies was 0.56 with a variation of +/- 0.15 (Mätzke, Franckena, Albäck, Railo, & Lepäntalo, 2003). The CEAP provides a marker for underlying venous insufficiency. There are seven clinical classes: 0 no disease; 1 signs of telangiectasias or reticular veins; 2 varicose veins; 3 edema without skin changes; 4 skin changes that are associated with venous disease; 5 skin changes with healed ulcers; and 6 skin changes with active ulceration (Eklöf et al., 2004). Subjects who were noted to have a CEAP category of 2 or higher used personal compression stockings or use temporary compression therapy products (i.e., tubigrip).

**Patient Reported Outcome Measure Information System**

The National Institutes of Health Patient Reported Outcomes Measurement Information System (NIH PROMIS) was selected to represent the empirical indicators for the pain, depressive symptoms, sleep disturbance, and HRQoL (Cella et al., 2010). Each
item bank is composed of questions, with response scoring from 1 to 5 (1 = not at all, to 5 = very much); the questions, referencing the particular symptoms experienced within the last 7 days (Cella et al., 2010; Khanna et al., 2012). The PROMIS instruments used to operationalize empirical indicators in the study are depression, sleep disturbance, pain interference, and global health short form. Depression, sleep disturbance, and pain interference results range from 0 to 100, with 100 representing a poorer symptom experience. The cutoff scores for the depression item bank are <56 is nonclinical, 56 to 58.9 is mild/moderate, and ≥ 59 is major depressive symptoms (Pilkonis et al., 2014). The sleep disturbance item bank score of > 60 was correlated with a matching score of PSQI >5 indicating disturbed sleep (r=0.80) (Ananthakrishnan, Long, Martin, Sandler, & Kappelman, 2013). For the study, a score of > 60 will indicate sleep disturbance. HRQoL will be measured by the global health short form, which is a 10 item questionnaire. Using Revicki’s methods for determining responsiveness and minimally important differences for patient reported outcomes, patient responses will be converted into a EuroQoL composite HRQoL score (Revicki et al., 2009). Scores range from -0.109 to 1, with higher scores indicating a higher quality of life (Revicki et al., 2009). Alpha reliability of the aforementioned PROMIS measures range from α=0.74 to 0.96 (Cella et al., 2010; Khanna et al., 2012; Pilkonis et al., 2014; Ananthakrishnan et al., 2013; Revicki et al., 2009). Construct, convergent, and discriminant validity for the PROMIS measures have been reported in the literature (Cella et al., 2010; Khanna et al., 2012; Pilkonis et al., 2014; Ananthakrishnan et al., 2013; Revicki et al., 2009).

Wound Characteristics
Wound healing is operationalized by the Wound Bed Score. The Wound Bed Score is an instrument developed to measure wound bed status and the peri-wound skin condition (Falanga, Saap, & Ozonoff, 2006). The items in the instrument are healing wound edges, peri-wound dermatitis, peri-wound fibrosis, black eschar, granulation tissue depth, peri-wound callous, edema, exudate amount, wound bed moisture, pink wound bed, and ulcer duration. The range for each item is from 0 to 2, with 2 representing the best score. Each item score is added together for the total wound bed score with a range of 0 (worst score) to 18 (best score). An increase in the total score of a wound was associated with a 22.8% increase in odds of healing (Falanga et al., 2006). No reliability or validity tests were reported. See Appendix A for the Wound Bed Score instrument.

Wound infection will be measured by the NERDS, which is an acronym that stands for Non-healing wound (i.e., wounds that are not 20-40% smaller in 4 weeks), Exudative wound (i.e., >50% of dressing stained with exudate), Red bleeding wound (i.e., wound bed tissue bleeds easily with light palpation), Debris (i.e., slough, eschar, or discolored granulation tissue in wound bed), and Smell (i.e., foul odor). The NERDS instrument was used to determine wound infection. Each item (e.g., Exudative wound) is scored as 1 (present) or 0 (absent). Total score ranges from 0 to 5. NERDS has a sensitivity of 73.3% and 80.5% specificity for identifying wound infection when collating any 3 of the above categories with a positive finding (i.e., positive= foul smell noted) (Woo & Sibbald, 2009). Construct validity of the instrument was performed by comparing semi-quantitative bacteriology reports of wounds against the NERDS categories (Woo & Sibbald, 2009). No reliability studies have been reported (Woo &
For the study, a NERDS score of $\geq 3$ indicates the presence of a wound infection.

The ulcer size was measured using the Wound Zoom™, a noncontact wound imaging, documentation, and measurement device. The device is able to determine wound total surface area in cm$^2$ by using 2 laser beams to correct for image scale and anatomical irregularity. To determine Nonhealing in the NERDS instrument, the percentage change was calculated by comparing initial wound surface area to subsequent wound surface area measurements at weeks 1 through 4. Delayed wound healing will be defined as the failure to reach > 30% reduction in wound TSA by week 4 (Margolis, Berlin, & Strom, 1999).

**Procedures**

The subjects were approached for study consideration upon notification from the dermatologic surgeon that the subject had chosen not to have a surgical closure procedure (e.g., primary closure, graft). Upon fulfilling the requirements for enrollment (e.g., Mini-cog $>2$, ABI score $>0.8$), the subjects were enrolled upon the day of surgery (T1). The PI (JH) collected and stored the following data in University Hospitals (UH) REDCap (Research Electronic Data Capture Application) database under the participant's unique study ID: demographic variables, zip code, employment, family history, comorbidities, mobility status, medication (e.g., antibiotics, antidepressants), physical exam variables (e.g., BMI, vital signs, CEAP, wound pain 0-10 scale), and wound characteristics. Additionally, the subjects completed the NIH PROMIS electronic surveys through UH REDCap system. Prior to dressing application, the noncontact wound imaging, documentation, and measurement device was used to photograph the wound.
Subjects followed a standardized wound dressing protocol, which was determined by wound exudate amount. For minimal to small amounts of drainage, moisture-providing dressings (e.g., petroleum-based gauze) were used. Wounds with moderate to large amounts of drainage used absorptive dressing (e.g., hydrofiber) in combination with a gauze wrap to secure the dressing on the leg. Patients were instructed to perform dressing changes daily using sterile normal saline to cleanse the wound prior to dressing reapplication.

At weeks 1 through 4, the wound dressings were removed by the PI and cleansed with 0.9% sterile normal saline in preparation to assess the wound and collect wound and intact skin swab specimens. Additionally, ulcer size, wound bed score, NERDS score, and calf and ankle measurements were measured and entered into the UH REDCap. At week 4 (T2), final data were collected: final wound and intact skin swab specimens, physical exam variables, wound characteristic variables, ulcer size (via wound imaging device), and NIH PROMIS item banks (e.g., depression, pain interference).

Statistical Analysis

Data were analyzed using IBM SPSS v. 24.0 (IBM Corp., Armonk, NY). Descriptive statistics (i.e., mean, standard error, and confidence intervals) were used to describe demographics, co-morbidities, T1 laboratory values, wound characteristics, and symptom measures of the MMS surgery population. Data were reviewed for skewness and kurtosis. Following an evaluation of the demographic and clinical characteristics, a trend of wound expansion at week 1 was noted in 50% of the sample. Subsequently, the sample was divided into two groups based upon wound expansion, which was defined as ≥ -15% increase in wound size between enrollment and week 1.
For wound characteristics, absolute wound total surface area change (delta) and wound total surface area percentage change were calculated. The absolute total surface area delta was determined by calculating the change between enrollment and week 1, week 1 and 2, week 2 and 3, and week 3 and 4. The wound total surface area percentage change was calculated by taking the difference between the weekly wound total surface area subtracting from the baseline wound total surface area and dividing by the baseline wound total surface. The value was then multiplied by 100 to provide a percentage score. The Kraemer & Thiemann method was used to determine the absolute wound total surface area delta slope to allow for comparison of slopes between both groups. The Kraemer and Thiemann method provides a means for determining effect size and power of longitudinal data using absolute delta values over time (Kraemer & Thiemann, 1989).

For specific aim 1, the Pearson correlation test was used to examine the linear relationship between symptom measurements at T1 and T2. For specific aim 2, the baseline data measurements (e.g., laboratory variables, HRQoL, depressive symptoms, sleep disturbance) were used to determine potential longitudinal associations with wound total surface area. Pearson correlation tests were used to examine linear relationships between wound characteristics, demographics, laboratory variables, symptom measures, and HRQoL. To evaluate the differences between subject’s demographics, co-morbidities, laboratory variables, wound characteristics, and symptoms measures, Student’s independent t-test and Chi square tests were used. Next, the independent predictor variables found to be significantly different were incorporated into a logistic regression analysis to determine the effects of the various demographics, co-morbidities, wound characteristics, wound absolute wound TSA delta slope, and symptom measures.
alone and in combination. Therefore, the best fitting model that characterizes predictors of delayed wound healing would be determined. Assumptions for all statistical tests (i.e., Pearson’s correlation, Student’s independent t-test, Chi square, logistic regression) were undertaken (Fields, 2012).

Results

Fourteen subjects were enrolled with 4 of these subjects being followed until the wounds were healed. The population was predominately Caucasian female (n=10/14) with an average age of 72.4. The skin cancer location was between the bilateral pre-tibial crest and malleolus areas with 64% of lower extremity skin cancers involving the left leg. Squamous cell carcinoma was the pre-dominant (71%, n=10/14) skin cancer type diagnosed in the population. When looking at skin cancer type by gender, squamous cell carcinoma was exclusive in females and basal cell carcinoma was exclusive in males.

After applying the wound expansion filter of ≥15% increase in wound TSA at week 1, there were 9 subjects in the non-wound expansion group and 5 in the wound expansion group. When evaluating the demographic, co-morbidity, and laboratory variables (See Table 1) there were no significant differences noted between those with and without wound expansion, except for age. Subjects were on average 12 years older in the wound expansion (M = 78.4) group in comparison to the non-wound expansion (M = 66.4) group (t= 2.58, p=0.02). When comparing total co-morbidities, the groups were similar with 2.6 and 2.4 comorbid conditions in those with and without wound expansion, respectively. No significant differences were noted between those with or without venous disease based upon CEAP classification. However, 50% of the population was noted to have a CEAP category of ≥4 indicating chronic skin changes consistent with venous
disease. Although most of the patient population had venous disease, the subjects experienced $\leq 0.5$ cm or $\leq 1$ cm change in ankle and calf measurements from baseline, respectively.

The symptom measurement surveys (See Table 2) revealed that subjects undergoing surgery considered themselves physically and mentally healthy with no clinically relevant pain interference, depressive symptoms, or sleep disturbance. On average, subjects reported global physical and mental health values that were higher than the population mean, which represents better perceived health. The EuroQoL score also revealed that, on average, the subjects considered themselves to have good HRQoL. Additionally, the pain interference, sleep disturbance, and depressive symptoms survey data did not reach thresholds that represent clinically relevant disease. When evaluating for differences between those with and without wound expansion, no significant differences were noted in any of the symptom measures.

For specific aim 1, there were no temporal relationships connected with symptom development or severity amongst the sleep disturbance, pain interference, depressive symptoms, and HRQoL measures. A common trend noted was that depressive symptoms, pain interference, sleep disturbance, and HRQoL measure (global physical health, global mental health, EuroQoL) scores were consistently improved at T2. When exploring Pearson correlations to determine the relationships that exist between symptom measures at T1 and T2, EuroQoL was significantly associated with global physical ($r=0.86; p=0.006$) and mental ($r=0.79; p=0.003$) health scores at T1 and T2; global mental health T1 was trending toward significance with an inverse correlation with sleep disturbance at T1 ($r=-0.607; p=0.08$), but not sleep disturbance T2; EuroQoL T1 shared a significant
correlations with depressive symptoms T1 (r=-0.71; p=0.03), but not depressive symptoms T2. Sleep disturbance, depressive symptoms, and pain interference did not share any significant correlations with either T1 or T2 symptom measure data. For specific aim 2 data see Tables 4-7. At T1, an inverse relationship was noted between EuroQoL T1 and wound TSA T1 (r=-0.87, p=0.002), suggesting that patients with smaller wounds had higher quality of life. No significant relationships or trends were noted between symptom measures, laboratory data, and the primary outcome measure (wound total surface area T2).

Wound characteristics were not found to predict those who develop wound expansion at week 1. The postoperative wounds were generally small (<5 cm²) and shallow (<3 mm). The wound pain trend revealed that pain was higher at week 1 and then continued to subsequently decrease each following week. There were no significant differences noted between both groups in regards to wound pain at week 1 and 2 (weeks with highest reported pain). The wound expansion group reported wound pain as 3.2/10 in comparison to 1.8/10 in the non-wound expansion group at week 1. At week 2, the mean reported pain values were 2 and 1.1 for those with and without wound expansion, respectively. In regards to wound complications, 3 subjects (wound expansion = 1; non-wound expansion = 2) experienced delayed wound healing. No subjects experienced wound infections in either group as determined by NERDS scores. Fibrinous slough >25% was noted in 1 subject in the wound expansion group in contrast to 2 in the non-wound expansion group. When comparing wound characteristics, there were no significant differences between those with or without wound expansion at T1 or T2 (see Table 3), except for the wound absolute TSA delta slope. The wound expansion had a
significantly higher change (UNSTDβ = 0.70) in comparison to the non-wound expansion group (UNSTDβ=0.13) with a mean difference of 0.57 (t=2.25; p=.04 r2=0.42), which suggests that the wound expansion group requires a longer time to heal (see Appendix B for wound absolute TSA delta slope graphs for those with and without wound expansion). This is supported based upon those subjects followed longitudinally until healed (n=4) whereby 2 subjects experienced wound expansion at week 1 and 2 subjects did not have wound expansion at week 1. For those in the wound expansion group, healing time was 10 and 12 weeks in comparison to 6 and 8 weeks for the non-wound expansion group. Furthermore, when graphing the slope of the wound TSA percentage change for those with and without wound expansion at week 1, the wound expansion group slope appears to expand at the week 1. By week 4, both group slopes appear to converge (See Appendix C).

To better elucidate potential independent predictor variables that predict those with and without wound expansion, we conducted a series of Chi square and Student’s independent t-test of independent predictor variables. The analyses revealed that wound absolute TSA delta slope and age reached significance. These variables were then included into a logistic regression while controlling for wound TSA at week 0. Of the independent predictor variables, age was trending toward significance (-2 log likelihood = 11.88; Nagelkerke R= 0.50; UNSTDβ=0.21; SE=0.122; OR = 1.24 CI .97-1.58; p=0.08), which suggests that the likelihood for experiencing wound expansion increases by 24% for every increase in year.

Discussion
People undergoing Mohs micrographic surgery for lower extremity NMSC report good HRQoL. No literature was found describing the HRQoL in people undergoing MMS for below the knee NMSC. However, when looking at HRQoL of individuals undergoing MMS at other body locations, the majority (66-69%) of older adults reported average or better than population means with the worst HRQoL reported in those with facial NMSC (Shah & Coates, 2006; Chen et al., 2007; Steinbauer et al., 2011). Common themes reported in those with facial NMSC and poorer HRQoL are emotional distress due to concern regarding spreading of cancer, disfigurement/scarring, and surgical complications (non-healing wounds, postoperative bleeding) (Steinbauer et al., 2011; Burdon-Jones et al., 2010). The lower extremity may be considered a less cosmetic area, and often subjects healing by secondary intention often produce excellent scar outcomes compared to primary closure (Joo et al., 2015). Furthermore, lower extremity SCC are generally characterized with a better prognostic outcome due to the majority being well differentiated without perivascular or perineural invasion (Solus et al., 2015). As lower extremity NMSC carry a better prognostic outcome and lower cosmetic concern, people with lower extremity SCC may have better HRQoL compared to those with NMSC at other locations. In addition, Chen et al. (2007) noted that less comorbidities, socioeconomic status >$30,000, graduate level degrees, and physical/mental health values that are higher than the population mean predicted better preoperative HRQoL scores. Our study was underpowered to evaluate predictors of better preoperative HRQoL. However, similar findings were found in our study group with our population experiencing physical (50.8) and mental (53.7) health values are higher than the population mean, 78% of the population annual income >$60,000, and the average co-
morbidities was 2.5. Furthermore, the reported symptoms (depressive symptoms, sleep disturbance, pain interference) did not reach clinical relevance thresholds at T1, which indicates that subjects perceived minimal to no symptoms. As a result, the population likely had a better HRQoL. As supported by Ferran’s et al.’s (2005) adaptation of Wilson & Cleary HRQoL model, individual characteristics (socioeconomic status, comorbidities), symptoms (depressive symptoms, sleep disturbance, pain interference), and general health perception (physical/mental health) positively influenced HRQoL in this study sample.

People undergoing MMS for lower extremity NMSC experience an improvement in HRQoL following surgery. Additionally, subjects reported improved depressive symptoms, sleep disturbance, and pain interference 4 weeks after surgery. Measuring of HRQoL and symptoms at T2 revealed a general decrease in severity of symptoms and an improvement in HRQoL. As a result of not having an increase in the severity of symptoms from T1 to T2 in any of our population, our ability to answer specific aim 1 (temporal development of symptoms onset and severity) was limited. Consistent with findings from this study, Chen et al. (2007) noted that older adults experienced an improvement in HRQoL following surgical correction of the NMSC, even after controlling for socioeconomic status, age, mental health status, educational level, and comorbidity index. Additionally, Chen et al. (2007) noted that preoperative scores predicted worse scores in people undergoing dermatologic surgery for NMSC. However, findings from our study are unable to support the predictive nature of preoperative HRQoL as the consistent trend was overall improvement in HRQoL at T2. The consistent improvement in symptom measures and HRQoL may be due to the subject’s experiencing minimal
postoperative wound pain, completing the treatment for the lower extremity NMSC, or delayed wound healing does not worsen HRQoL. By postoperative week 2, those with and without wound expansion reported wound pain of 2.1 and 1 respectively, which indicates minimal pain. People with chronic venous leg ulcers often report more severe pain, which has been shown to have a direct relationship with depressive symptoms and sleep disturbance symptom severity (Upton & Andrews, 2013; Jones et al., 2006). However, pain in acute wounds may be different. As a result of decreased postoperative wound pain associated with lower extremity acute wounds, people undergoing MMS for lower extremity NMSC may be more likely to report no worsening of depressive symptoms, sleep disturbance, pain interference, or HRQoL. Consistent with the adapted HRQoL model, people with lower pain symptoms have a more positive HRQoL (Ferrans et al., 2005; Wilson & Cleary, 1995).

The improvement in postoperative HRQoL may also be due to reduced emotional distress as a result of completing therapy. MMS is a very effective surgical treatment option for NMSC with a cure rate >99%, and is completed on an outpatient basis (Alam et al., 2013). As a result, people undergoing MMS, people can have confidence that the skin cancer was completely removed upon the completion of their surgery. HRQoL T1 scores likely reflect emotional distress associated with a diagnosis of skin cancer and undergoing surgery. HRQoL at T2 may reflect that people are relieved the cancer is gone, or that they did not experience any complications with the procedure. The overall complication rate of MMS is 0.72% (Alam et al., 2013). The literature has highlighted a range of complication rates for people undergoing MMS for lower extremity NMSC ranging from 17 to 53.4%. The most common complications reported for lower extremity
NMSC are hematoma (20.5%), delayed wound healing (4.3%-26%), infection (3.3-16%), hypergranulation tissue (3%), and hypertrophic scar (1.4%)(Honaker et al., 2015; Stankiewicz et al., 2015; Audrain et al., 2015; Dixon et al., 2006). As 21.4% (3/14) of our population experienced complications (i.e., delayed wound healing), perhaps people did not appraise delayed wound healing as emotionally distressing at 1 month. As a result, the subjects consistently reported an improvement in HRQoL. No literature was identified exploring the HRQoL in people who experience postoperative complications status post MMS for NMSC. While there were no findings identified in literature, perhaps patients who experience wound infections or postoperative hematoma may experience worse HRQoL. Consistent with the adapted HRQoL model, individual characteristics (cognitive appraisal, affective response), lower symptom severity (depressive symptoms, sleep disturbance, pain interference), and positive general health perception have a positive influence on HRQoL in this study sample.

Symptom measures and HRQoL were not found to predict wound expansion or delayed wound healing in acute wounds. Findings from this study may in part be due to the subjects being generally healthy with an average of 2.5 co-morbidities and the absence of diabetes, post-operative complications, clinically relevant depressive symptoms or alterations in global mental health, and minimal post-operative wound pain. In contrast, people with chronic wounds on average have 8 co-morbidities(Gould et al., 2015), report severe symptoms (16-48% with moderate to severe pain(Edwards et al., 2014), 27-50% depressive symptoms(Jones et al., 2006), 69-80% sleep disturbance(Edwards et al., 2014; Upton & Andrews, 2013)), and experience 4 or more co-existing symptoms(Edwards et al., 2014). Additionally, people with chronic wounds
report poorer HRQoL (Edwards et al., 2014). Furthermore, the ability to detect the influence of symptoms on wound healing requires that you have individuals with severe symptoms. As none of the study sample reached clinical relevant thresholds, we were unable to detect influence in this population. As previous studies (Kiecolt-Glaser et al., 2005; Bosch et al., 2007; Doering et al., 2005; Ebrecht et al., 2004; Broadbent et al., 2003; McGuire et al., 2006; Bosch et al., 2007) evaluating psychological stress and delayed wound healing have primarily focused on acute wounds in various populations, perhaps people undergoing MMS for NMSC is associated with less stress in comparison to other cancers or surgical procedures. Therefore, people status post MMS for lower extremity NMSC may be less likely to experience severe symptoms that will result in delayed wound healing.

As wound healing could conceptually fall within the biological function construct of the adapted HRQoL model, the model would support that symptom measures and HRQoL did not predict delayed wound healing in this study population. Based upon the adapted model, the biological function subsequently influences symptoms, functional status, general health perception, and HRQoL. An alteration in biological function (delayed wound healing) was not found to influence symptom severity and subsequently HRQoL in the study population. As previously discussed, the subjects in our study experienced minimal wound pain. Wilson & Cleary (1995) point out that biological function and symptoms may share inconsistent relationships (Wilson & Cleary, 1995). For example, delayed wound healing noted with acute lower extremity wounds may not experience worse symptom severity (e.g., depressive symptoms, pain). As a result, the subjects did not experience increased symptom severity, which subsequently had a
positive influence on HRQoL. However, the replication of this study with a different population (e.g., chronic wounds) may reveal a more inconsistent relationship between biological function and symptom severity, or symptom severity and wound healing may have a bi-directional relationship based upon the population. For example, people with higher depressive symptoms or psychological stress may experience delayed wound healing. Findings from this study support the Wilson & Cleary’s statement that biological function and symptom severity may share inconsistent relationships, and may be related to the type and severity of symptoms experienced and the type and severity of altered biological function.

Older adults who are greater than 70 years old are more likely to experience slower wound healing. Age was the only predictor of wound expansion in the logistic regression analysis that was trending toward significance. When exploring the differences between those ≥ 70 and <70 years old, 75% (6/8) of the subjects in the study who were ≥ 70 experienced delayed wound healing (non-wound expansion group = 2) or wound expansion (wound expansion = 4) at week 1. In contrast, 17% (1/6) of those <70 years old experienced wound expansion at week 1, but no delayed wound healing. As noted from observing a subsample until healed, those with wound expansion resulted in a clinical difference in wound healing time of an additional 2-4 weeks to completely heal compared to those without wound expansion. However, all patients attained healing. Delayed wound healing in older adults has been described in various situations including dehiscence (Karamanos, Osgood, Siddiqui, & Rubinfeld, 2015), split thickness skin graft failure (Henderson, Fancourt, Gilkison, Kyle, & Mosquera, 2009; Dixon et al., 2009), and primary closure (Stankiewicz et al., 2015). Findings from animal studies, and a few
human studies, reinforce that older adults experience a temporal delay in wound healing by 20-60% in comparison to younger skin and there are physiologic changes that occur throughout the stages of wound healing that contribute to the delay (Gould et al., 2015). These findings are further supported by Ferran et al.’s (2005) adaptation of Wilson & Cleary’s HRQoL model in that individual characteristics (age) influence biological function (delayed wound healing).

**Limitations**

Findings from this study may be limited by study location, sample size, using global mental health and depressive symptoms to measure psychological stress, and using a population with low symptom severity to determine the effects of symptom severity on delayed wound healing. The results from this study represent the population of a single outpatient dermatologic surgery clinic. Therefore, the findings from this study may not be generalizable to the larger population. Furthermore, the surgical outcomes for the population may be a result of the surgeon’s skill and experience. As a result, people undergoing MMS at this single outpatient dermatologic surgery clinic may have less post-operative complications (e.g., hematoma, infection) as a result of the surgeon’s skill.

While the Kraemer & Thiemann method (Kraemer & Thiemann, 1989) allowed us to determine a strong effect size given our longitudinal data, the ability to discern potential relationships in this population is limited due to having a small sample size (n=14). While the population data were normally distributed, as we continue to enroll additional subjects, the patterns may completely change and findings presented could be disproven. Therefore, continued enrollment is necessary to continue to evaluate the role of age on wound expansion at week 1 and delayed wound healing. The authors operationalized
psychological stress by using the NIH PROMIS global health form and depressive symptoms surveys. In the past, a majority of studies have used the perceived stress scale to measure psychological stress and the subsequent influence on wound healing. As the perceived stress scale measures helplessness and self-efficacy (Cohen, Kamarck, & Mermelstein, 1983), the use of the scale may have assisted with elucidating additional dimensions of the patient’s perceptions and ability to cope and deal with the current stressor. Additionally, measuring personality traits (pessimism, negative effect) could have added an additional psychological dimension not measured in this study. As personality traits have been suggested to moderate the negative effects of stress (Maple et al., 2015), the measuring of such traits, for example, may have identified that subjects in our study primarily had a positive affect. Therefore, the subjects would be expected to have lower depressive symptoms.

Another limitation of the study involves the lower extremity NMSC population in our study. Their subsequent low symptom severity precluded our ability to determine the influence of psychological stress on wound healing. Conducting a study using a different population of lower extremity NMSC with associated higher co-morbidities, symptom severity, and poorer prognosis may reveal different relationships between symptoms, HRQoL, and wound healing.

Additional limitations to our study, specific to the use of symptom measures, is testing and history or concurrent events (Higgins & Straub, 2006). The reported symptoms at T2 could have been influenced by the subject’s familiarity with the survey measure. While reducing testing influence can be improved by limiting the number of times the survey is completed, and by increasing the time frame between each time the
surveys are completed, results can still be influenced. In our study, this is less likely as a consistent trend was noted in the whole population. In regards to history or concurrent events, no events were identified that would have caused a consistent trend with improved HRQoL scores.

**Recommendations for Future Research**

As age was the only variable found to predict wound expansion at week 1, future studies could evaluate pro-inflammatory cytokine (matrix metalloproteinase, interleukin 1) values and immune cell activity during the first week postoperatively to determine potential mechanisms contributing to the temporal delay in wound healing. Additionally, the application of oxidized reduced cellulose dressings (i.e., Promogran) on wounds introduces synthetic collagen, a substance required to promote granulation tissue deposition, into wounds and have been noted to bind matrix metalloproteinases (Cullen, Smith, McCulloch, Silcock, & Morrison, 2002). As a result, cytokines associated with promoting pro-inflammatory environment are reduced and the potential for increased granulation tissue may occur. Furthermore, the exploration of changes in the microbiome in those with and without wound expansion at week 1 may highlight unique patterns that may guide future development of interventions. The development of a randomized clinical trial with the use of the specialty dressing during the first postoperative week may prevent the wounds from experiencing wound expansion and encourages a more timely wound healing trajectory for older patients. Another future study could involve replicating this study in the venous leg ulcer population, and add measurement of the perceived stress scale and personality traits. Replication of findings in chronic wounds is
warranted as most studies of psychological stress influence on wound healing has been in the human or animal acute wound models.

**Conclusion**

This preliminary report reveals that older adults may be more likely to have wound expansion, which may result in delayed wound healing. While our findings were not able to identify the influence of symptoms (depressive symptoms, sleep disturbance, pain) on wound healing, future research in other populations may identify a potential influence. As older adults ≥ 70 years old are more likely to experience wound expansion during the first postoperative week, dermatologic surgeons should consider implementing interventions (e.g., compression stockings, collagen matrix dressings) to promote wound healing during the first postoperative week. Future research is needed to help identify particular mechanisms in human studies so that clinical trials can be developed to determine effective interventions to assist with the temporal delay in wound healing in older adults.
Chapter 4
Dissertation Overview

My dissertation topic is the “Predictors of alterations in lower extremity wound healing”. In preparation for my dissertation, I conducted a systematic review (Chapter 2) of the literature focused upon concepts influencing wound complications following surgical removal of lower leg non-melanoma skin cancer in older adults. As a result of the systematic review, I was able to discern particular themes that highlighted the state of the science.

Six themes were identified following my systematic review. First, psychological stress has various permutations that can be categorized into stressors, states, and personality traits, but 85% of studies reviewing psychological stressors and wound outcomes did not measure the three categories. The majority of the studies measured state and stressors. Second, psychological stress is associated with delayed wound healing but the inter-relationship and temporal development of specific stressors or states and the influence of personality traits on wound healing outcomes in older adults has not been determined. Third, psychological stress has been shown to increase cortisol levels and autonomic nervous system activation in mouse models, which results in the reduction of anti-microbial peptide production leading to dysbiosis within the wound microbiome. Fourth, next generation sequencing of acute and chronic surgical wound microbiome signatures have revealed compositions of both aerobic and anaerobic bacteria and are greatly influenced by inter-individual variability, location, and use of anti-septics/biotics. Fifth, predictors of post-operative dermatologic surgery complications are larger post-operative wound size, surgical closure type (surgical flap/graft), and location (lower extremity, genitals). However, there was insufficient evidence to determine the effect of
age, immunosuppressants, diabetes, smoking, and malnutrition as predictors of postoperative complications. Sixth, older adults diagnosed with NMSC have a normal distribution of HRQoL and experience minimal changes in HRQoL, yet lower preoperative HRQoL scores, more comorbidities, and worse mental status predict worse postoperative HRQoL scores.

Following a review of the literature, my phenomenon of interest evolved to: psychological stress induced wound infection, delayed healing, and impaired HRQoL in people undergoing dermatologic surgery for lower leg NMSC. Next, I set out to identify a theoretical framework that would guide me in determining conceptual definitions, assumptions, and propositions regarding my phenomenon of interest. I selected the Ferran et al. adaptation of Wilson & Cleary’s HRQoL conceptual model. The Ferran et al. model was an improvement over Wilson & Cleary’s HRQoL model by adding McLeroy’s ecological model to assist with explicitly defining the potential influences of the individual and environmental characteristics on the remaining constructs (biological function, symptoms, functional status, health perception, HRQoL). Furthermore, the model added causal pathways between individual and environmental characteristics and the biological function construct, which was previously absent in the Wilson & Cleary model. As my phenomenon of interest is focused on the influence of psychological stress on bacterial bioburden, delayed wound healing, and HRQoL, I wanted to use a model that accounted for the influence of individual characteristics and environment on biological function concepts.

After further evaluating Ferran et al. model propositions in context of my phenomenon of interest, the systematic review revealed potential bi-directional
relationships and great inter-individual variability in bacterial bioburden and HRQoL values. The Ferran et al. HRQoL model uses reductionism to guide the propositional statements that exist between the constructs/concepts. Reductionism proposes that individual parts within constructs have linear relationships, and are therefore predictable. To better explain the bi-directional and variability noted in my systematic review, I explored additional theoretical understandings that would aid in explaining contextual relationships between construct concepts/variables and inter-individual variability of outcomes in bacterial bioburden and HRQoL. Following a review of the literature, I chose to apply complexity science’s assumptions and propositions to assist in explaining contextual relationships between construct concepts/variables as a result of inter-individual variability. Complexity science proposes that inter-individual variability, which is a form of unpredictability, occurs as relationships are curvilinear. Upon determining that complexity science would best support my ability to understand the contextual relationships within the HRQoL model, I set out to perform a derivation of both the Ferran et al. HRQoL model and complexity science. Upon completion, I then synthesized the derived components into the HRQoL Complexity Theory model, from which the psychological stress wound outcome middle range theory was created (Chapter 1).

The creation of my theoretical framework and performing a systematic review of the literature resulted in the identification and development of knowledge that is seemingly disparate from my planned dissertation, which is linear in nature. In addition to not using the HRQoL complexity theoretical model for my initial dissertation study, identified biological function and individual characteristic concepts in the systematic
review were not used due to funding limitations and patient burden, respectively. Biological function variables like cortisol, cathelicidin, beta defensin, cytokines, and potential other unstudied variables (bacterial metabolomics), require funding to support laboratory processing and analysis. I currently have funding to conduct only microbiome analysis. While microbiome samples will be collected throughout the study and analyzed in one batch, that data will be used during the second phase of the larger study evaluating predictors of lower extremity wound healing. Regarding psychological stress, I have selected to begin my program of research by evaluating stressor and state. The stressors are surgery, sleep disturbance, wound infection symptoms, delay wound healing and the states are depressive symptoms and anxiety. For the purpose of my dissertation (chapter III), the focus was exploring predictors of wound healing in older adults healing by secondary intention following mohs micrographic surgery for lower extremity non-melanoma skin cancer.

Following a preliminary analysis of data collected, a consistent trend was noted that the subject’s reported symptom measures and HRQoL surveys consistently improved 4 weeks after surgery. As a result of the consistent improvement in symptom measures and HRQoL from T1 (enrollment) to T2 (postoperative week 4), the ability to answer specific aim 1 (determine the temporal nature of symptom development and influence on subsequent symptom severity) was limited. The noted trend was consistent with findings in the literature. The consistent improvement in symptom measures and HRQoL may be due to the subject’s clearance of skin cancer, minimal postoperative wound pain, or that delayed wound healing is not appraised as an experience that worsens HRQoL. As supported by Ferran et al. HRQoL model, individual characteristics (cognitive appraisal,
affective response), lower symptom severity (depressive symptoms, sleep disturbance, pain interference), and positive general health perception have a positive influence on HRQoL in this study sample.

For specific aim 2, wound characteristics, patient characteristics, symptoms, and HRQoL were not found to predict wound healing in the lower extremity non-melanoma skin cancer population. While literature has supported that psychological stress can result in delayed wound healing, the findings in our study may be based upon the population, the relatively low stress associated with the diagnosis and surgical procedure, or the general absence of postoperative complications. As the population was generally healthy and the symptom measures did not reach clinical relevant thresholds, we were unable to detect any influence in this population. As previous studies evaluating psychological stress and delayed wound healing have primarily focused on acute wounds in various populations, perhaps people undergoing MMS for NMSC is associated with less stress in comparison to other cancers or surgical procedures. Therefore, people status post MMS for lower extremity NMSC may be less likely to experience severe symptoms that will result in delayed wound healing. As pointed out by Wilson & Cleary (2005), the biological function influences the symptoms, functional status, general health perception, and HRQoL constructs. However, biological function and symptoms may share inconsistent relationships. Findings from this study support the Wilson & Cleary’s statement that biological function and symptom severity may share inconsistent relationships, and may be related to the type and severity of symptoms experienced and the type and severity of altered biological function.
Older adults who are greater than 70 years old are more likely to experience slower wound healing. After controlling for other variables (wound depth week 0, wound total surface area week 0, and wound absolute delta slope), age was the only variable found to predict wound expansion at week 1. When exploring the differences between those ≥ 70 and <70 years old, 75% (6/8) of the subjects in the study who were ≥ 70 experienced delayed wound healing (non-wound expansion group = 2) or wound expansion (wound expansion = 4) at week 1. In contrast, 17% (1/6) of those <70 years old experienced wound expansion at week 1, but no delayed wound healing. Delayed wound healing in older adults has been described in various situations including dehiscence, split thickness skin graft failure, and primary closure. Findings from animal studies, and a few human studies, reinforce that older adults experience a temporal delay in wound healing by 20-60% in comparison to younger skin and there are physiologic changes that occur throughout the stages of wound healing that contribute to the delay. These findings are further supported by Ferran et al.’s (2005) adaptation of Wilson & Cleary’s HRQoL model in that individual characteristics (age) influence biological function (delayed wound healing).

Following completion of the study, the Microbiome Psychological Stress HRQoL middle range theory was adapted to reflect the study findings in the population (see figure 3). Based upon the study findings, individual characteristics (i.e., age) likely has a direct influence on biological variables (inflammatory cytokines, macrophages), which can subsequently influence the development of wound expansion. Findings from animal studies, and a few human studies, reinforce that older adults experience a temporal delay in wound healing by 20-60% in comparison to younger skin and there are physiologic
changes that occur throughout the stages of wound healing that contribute to the delay (Gould et al., 2015). The particular physiological changes may be due to increased type 1 macrophage activity, which promotes a more pro-inflammatory environment (Gould et al., 2015). As many patients had skin changes consistent with hemosiderin there is likely increased iron present in the tissue environment, which can promote increased type 1 macrophage activity (Sindrilaru et al., 2011). Further studies are warranted to determine the particular mechanisms of biological factors, including wound bacterial burden, involved with wound expansion in order that interventions can be developed so that older adults will not experience a delay in wound healing.

While psychological variables did not influence delayed wound healing in older adults undergoing MMS for NMSC, the middle range theory may be more applicable to patients with chronic wounds. The study did not have adequate variance in severity of symptoms. Therefore, the ability to detect an influence of symptom severity on wound outcomes was prohibited. As the patients in our study reported higher pain levels in the wound expansion group, a hypothesized adjustment to the model would be that wound expansion may influence pain symptoms. Higher pain levels may subsequently influence depressive symptoms and sleep disturbance. While unable to detect this influence in our population, patient’s with venous leg ulcers are known to experience depressive symptoms (27-50% (Jones et al., 2006)), sleep disturbance (69-80% (Edwards et al., 2014; Upton & Andrews, 2013)), moderate to severe pain (16-48% (Edwards et al., 2014)), and experience 4 or more co-existing symptoms (Edwards et al., 2014). Furthermore, with the increased severity of symptom(s), patients may have increased risk of developing a wound infection as a result of psychological stress (Aberg et al., 2007;
Rojas, Padgett, Sheridan, & Marucha, 2002; Martin-Ezquerra et al., 2011). While depressive symptoms, sleep disturbance, and pain were not found to influence wound outcomes, they may be still relevant in other populations who experience more severe symptoms. While the findings from the study did not support the Microbiome Psychological Stress HRQoL middle range theory in older adults undergoing MMS for NMSC, the middle range theory could be validated in the chronic wound population.

Consistent with Microbiome Psychological Stress HRQoL middle range theory, patients with lower reported severity of symptoms were found to have better HRQoL. Furthermore, older patients with smaller wounds were found to have better HRQoL. However, the ability to evaluate the influence of delayed wound healing and wound expansion on HRQoL was prohibited due to inadequate variance. Perhaps the application of Microbiome Psychological Stress HRQoL middle range theory in a chronic wound population wound provide adequate variance in HRQoL to aid in the detection of the effect of delayed wound healing on HRQoL. Therefore, the proposed adaptation of the model would suggest that age influences wound expansion, which may influence patients to experience higher levels of pain, and the potential development of other symptoms. As a result, wound expansion or delayed wound healing may indirectly influence HRQoL through the symptoms patients experience.

My dissertation serves as a beginning point for my program of research, which will be focusing on evaluating predictors of wound healing in older adults. While I did not apply the theoretical understanding of complexity theory to my current study, I plan to design a mixed methods study that will explore the lived experience of those with and without wound expansion at week 1 to determine any aspects of their lived experience.
By applying complexity theory to the Ferran et al. (2005) HRQoL model, I hope to ascertain themes that guide future studies.

The logical next step, in conjunction with a mixed methods study, would be to add the individual characteristic concept of personality traits. While there has been little research conducted on how personality traits influence on psychological stress, the data available suggest that optimism/pessimism may have a moderating effect. Additionally, with the identification that those who are greater than 70 years old are more likely to experience delayed wound healing or wound expansion at week 1, perhaps the microbiome analysis may reveal potential trends in the microbiome community that contribute to delayed wound healing. Furthermore, more mechanistic studies could be planned to further elaborate upon the temporal delay in wound healing that older adults experience. By identifying a potential mechanism, future clinical trials could be developed to test interventions during the first week to promote wound healing.

In conclusion, while I will not utilize all of the information determined through my systematic review and the creation of the HRQoL complexity theory model, my initial work has established a firm foundation that will guide my future program of research. Furthermore, the insight obtained through the systematic review, theory construction, and dissertation findings were essential to assist me in seeing the bigger picture regarding how to approach conducting scientific research from a linear and non-linear perspective. As a result, I am better prepared to take the knowledge obtained from my initial dissertation study and proceed forward with a theoretical framework and knowledge base to inform the future studies I conduct.
Appendix

Appendix A Wound Bed Score (Falanga et al., 2006)

<table>
<thead>
<tr>
<th>Wound Bed Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing Edges</td>
<td>None</td>
<td>25-75%</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Black Eschar</td>
<td>&gt;25% of surface area</td>
<td>25-75%</td>
<td>None</td>
</tr>
<tr>
<td>Greatest wound depth/gra-</td>
<td>Severly depressed or raised when compared to periwound skin</td>
<td>Moderate</td>
<td>Flushed or almost even</td>
</tr>
<tr>
<td>tulation tissue</td>
<td>None</td>
<td>25-75%</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Exudate amount</td>
<td>Severe</td>
<td>Moderate</td>
<td>None/Minimal</td>
</tr>
<tr>
<td>Edema</td>
<td>Severe</td>
<td>Moderate</td>
<td>None/Minimal</td>
</tr>
<tr>
<td>Periwound dermatitis</td>
<td>Severe</td>
<td>Moderate</td>
<td>None/Minimal</td>
</tr>
<tr>
<td>Pink wound bed</td>
<td>None</td>
<td>50-75%</td>
<td>&gt;75%</td>
</tr>
</tbody>
</table>

Appendix B Wound absolute total surface area delta slope for those with & without wound expansion at week 1

![Graph showing wound total surface area absolute delta for non-wound expansion over time]

- Patient 1: Age = 73, Pain_wk 1 = 2/10
- Patient 2: Age = 65, Pain_wk 1 = 3/10
- Patient 3: Age = 64, Pain_wk 1 = 2/10
- Patient 4: Age = 75, Pain_wk 1 = 2/10
- Patient 5: Age = 76, Pain_wk 1 = 3/10
Appendix C Wound total surface area absolute percentage delta with and without outliers

- Wound total surface area absolute delta with and without outliers
- Group
- Patient 1: Age=67, Pain_wk_1=1/10
- Patient 2: Age=79, Pain_wk_1=6/10
- Patient 3: Age=74, Pain_wk_1=1/10
- Patient 4: Age=83, Pain_wk_1=1/10
## Appendix D Tables

### Table 1 Demographic, Co-morbidities, Laboratory values, and Vascular info by group

<table>
<thead>
<tr>
<th>Column1</th>
<th>Wound Expansion</th>
<th>Non-Wound Expansion</th>
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<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Male</td>
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</tr>
<tr>
<td>Female</td>
<td>4</td>
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</tr>
<tr>
<td>Age Range</td>
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<tr>
<td>Age Mean</td>
<td>78.4</td>
<td>66.4</td>
<td>0.02</td>
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<tr>
<td><strong>Co-morbidities</strong></td>
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<tr>
<td>Basal cell carcinoma</td>
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<tr>
<td>Squamous cell carcinoma</td>
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<td>Diabetes</td>
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<td>Dyslipidemia</td>
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<td>5</td>
<td>0.31</td>
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<tr>
<td>Hypertension</td>
<td>4</td>
<td>3</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypothyroidism</td>
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<td>0.30</td>
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<tr>
<td>Angina</td>
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</tr>
<tr>
<td>Peripheral Vascular Disease</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>Hip/Knee replacement</td>
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<td>1.0</td>
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<tr>
<td>Chronic Kidney Disease</td>
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</tr>
<tr>
<td>Connective Tissue Disease</td>
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<tr>
<td>Disease/Autoimmune</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Body Mass Index</td>
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<td>Smoking</td>
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<tr>
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<td>Yes</td>
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<th>Alcohol</th>
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<tr>
<td>&gt;14 glasses a week</td>
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<td>0</td>
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<td>1-14 glasses a week</td>
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<td>7</td>
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<td>None</td>
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<th>Labs</th>
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<td>Hemoglobin A1c</td>
<td>5.2</td>
<td>5.5</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.8</td>
<td>14.45</td>
<td>0.30</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.3</td>
<td>4.45</td>
<td>0.84</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.76</td>
<td>0.94</td>
<td>0.30</td>
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<tr>
<td>Vitamin D</td>
<td>31.8</td>
<td>33.8</td>
<td>0.80</td>
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<tr>
<td>Cholesterol</td>
<td>186</td>
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<tr>
<td>HDL</td>
<td>82</td>
<td>60.5</td>
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<tr>
<td>LDL</td>
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<td>108</td>
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<td>Triglycerides</td>
<td>98</td>
<td>113.5</td>
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<td>Ace bandage</td>
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<td>Tubigrip</td>
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<tr>
<td>&lt;20 mmHg stocking</td>
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<td>0</td>
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</tr>
<tr>
<td>&gt;20 mmHg stocking</td>
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<td>Unna boot</td>
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<tr>
<td>No disease</td>
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<td>Telangectasia/reticular veins</td>
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<td>Varicose veins</td>
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<td>1</td>
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<tr>
<td>Edema without skin changes</td>
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<td>0</td>
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<tr>
<td>venous disease skin changes</td>
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<td>3</td>
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<tr>
<td>Skin change w/healed ulcer</td>
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</tr>
<tr>
<td>Active ulcer</td>
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<td>0</td>
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<table>
<thead>
<tr>
<th>Ankle Brachial Index*</th>
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<th>0.06</th>
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<tbody>
<tr>
<td></td>
<td>1.29</td>
<td>1.05</td>
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Table 2 Symptom Measures

<table>
<thead>
<tr>
<th>Symptom Survey Results</th>
<th>Wound Expansion</th>
<th>Non-Wound Expansion</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td>n=2</td>
<td>n=6</td>
<td></td>
</tr>
<tr>
<td>Physical Global Health T1 (95% CI)</td>
<td>50.8 (50.8)</td>
<td>53.9 (48.7-59.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Physical Global Health T2 (95% CI)</td>
<td>52.5 (50.8-54.1)</td>
<td>55.2 (51.8-58.7)</td>
<td>0.40</td>
</tr>
<tr>
<td>Mental Global Health T1 (95% CI)</td>
<td>53.7 (48.6-58.8)</td>
<td>56.1 (50.3-61.9)</td>
<td>0.62</td>
</tr>
<tr>
<td>Mental Global Health T2 (95% CI)</td>
<td>54.3 (50.8-57.8)</td>
<td>56.1 (49.5-62.8)</td>
<td>0.80</td>
</tr>
<tr>
<td>EuroQoL T1 (95% CI)</td>
<td>0.79 (0.78-0.79)</td>
<td>0.79 (0.75-0.83)</td>
<td>0.90</td>
</tr>
<tr>
<td>EuroQoL T2 (95% CI)</td>
<td>0.79 (0.78-0.79)</td>
<td>0.81 (0.77-0.85)</td>
<td>0.41</td>
</tr>
<tr>
<td>PROMIS Pain T1 (95% CI)</td>
<td>46.75 (41.0-52.5)</td>
<td>50.6 (45.4-55.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>PROMIS Pain T2 (95% CI)</td>
<td>44.8 (41-48)</td>
<td>45.1 (42.2-49.9)</td>
<td>0.93</td>
</tr>
<tr>
<td>PROMIS Sleep Dist T1 (95% CI)</td>
<td>41.6 (33.1-51.1)</td>
<td>46.9 (39.1-54.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>PROMIS Sleep Dist T2 (95% CI)</td>
<td>38.4 (28.9-47.9)</td>
<td>44.1 (37.1-51.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>PROMIS Depress Sx T1 (95% CI)</td>
<td>50.5 (41.6-59.3)</td>
<td>46.2 (39.7-52.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>PROMIS Depress Sx T2 (95% CI)</td>
<td>50.3 (48.2-52.3)</td>
<td>44.4 (38.8-49.9)</td>
<td>0.24</td>
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</tbody>
</table>

Table 3 Wound Characteristics

<table>
<thead>
<tr>
<th>Wound Characteristics</th>
<th>Wound Expansion</th>
<th>Non-Wound Expansion</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=5</td>
<td>n=9</td>
<td></td>
</tr>
<tr>
<td>Wound Total Surface Area wk0 (95% CI)</td>
<td>4.3 cm² (1.2-9.8)</td>
<td>4.5 cm² (1.3-7.6)</td>
<td>0.93</td>
</tr>
<tr>
<td>Wound Total Surface Area/wk 4 cm² (95% CI)</td>
<td>2.1 cm² (0.9-5.1)</td>
<td>1.5 cm² (0.4-2.5)</td>
<td>0.60</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>-----</td>
</tr>
<tr>
<td>Wound depth wk0</td>
<td>2 mm</td>
<td>2.84 mm</td>
<td>0.25</td>
</tr>
<tr>
<td>Wound depth wk4</td>
<td>1 mm</td>
<td>1 mm</td>
<td>0.32</td>
</tr>
<tr>
<td>Wound Bed Score wk0 (95% CI)</td>
<td>10.8 (9.4-12.2)</td>
<td>10.7 (10.0-11.3)</td>
<td>0.80</td>
</tr>
<tr>
<td>Wound Bed Score wk4 (95% CI)</td>
<td>14.2 (12.4-16.0)</td>
<td>14.8 (13.6-15.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>Wound Absolute Percent delta change wk4</td>
<td>-54.5 (17.1-97.2)</td>
<td>-62.0 (41.6-82.4)</td>
<td>0.64</td>
</tr>
<tr>
<td>Wound Absolute Total Surface Area slope (95% CI)</td>
<td>.70 (-0.07 – 1.47)</td>
<td>.13 (-0.14 – 0.40)</td>
<td>0.44</td>
</tr>
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</table>

**Table 4 Correlations for symptom measures, health related quality of life, and wound total surface area T1 (DOV)**

<table>
<thead>
<tr>
<th>Symptom Survey</th>
<th>Pearson’s R</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=9</strong></td>
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<td></td>
</tr>
<tr>
<td>Physical Global Health T1</td>
<td>-0.59</td>
<td>0.09</td>
</tr>
<tr>
<td>Physical Global Health T2</td>
<td>-0.53</td>
<td>0.14</td>
</tr>
<tr>
<td>Mental Global Health T1</td>
<td>-0.67</td>
<td>0.05</td>
</tr>
<tr>
<td>Mental Global Health T2</td>
<td>-0.54</td>
<td>0.13</td>
</tr>
<tr>
<td>EuroQoL T1</td>
<td>-0.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EuroQoL T2</td>
<td>-0.52</td>
<td>0.20</td>
</tr>
<tr>
<td>PROMIS Pain T1</td>
<td>0.27</td>
<td>0.50</td>
</tr>
<tr>
<td>PROMIS Pain T2</td>
<td>0.49</td>
<td>0.20</td>
</tr>
<tr>
<td>PROMIS Sleep dist T1</td>
<td>0.67</td>
<td>0.05</td>
</tr>
<tr>
<td>PROMIS Sleep dist T2</td>
<td>0.57</td>
<td>0.11</td>
</tr>
<tr>
<td>PROMIS Depress Sx T1</td>
<td>0.61</td>
<td>0.80</td>
</tr>
<tr>
<td>PROMIS Depress Sx T2</td>
<td>0.06</td>
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**Table 5 Correlations for symptom measures, health related quality of life, and wound total surface area T2 (DOV)**
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<tr>
<td>Physical Global Health T1</td>
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</tr>
<tr>
<td>Physical Global Health T2</td>
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<tr>
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<td>Mental Global Health T2</td>
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<tr>
<td>EuroQoL T1</td>
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</tr>
<tr>
<td>EuroQoL T2</td>
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<td>0.90</td>
</tr>
<tr>
<td>PROMIS Pain T1</td>
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<td>PROMIS Depress Sx T2</td>
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Table 6 Correlations for demographics, wound characteristics, laboratory values, and wound total surface area T1 (DOV)

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Appendix E Figures

Figure 1. Ferran et al. Adapted Health Related Quality of Life Model

Figure 2. Microbiome Psychological Stress Health Related Quality of Life Middle Range Theory
Figure 3. Adapted Psychological Stress Health Related Quality of Life Middle Range Theory
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