THE EFFECTS OF FASTING REGIMENS IN VULNERABLE POPULATIONS

By

STEPHANIE A. LEE

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2019
To my daughters Sophia and Jula who went on this journey with me and provided endless inspiration, support, and unconditional love, even if they didn’t realize it.
ACKNOWLEDGMENTS

I would first like to thank my daughters who agreed to move across country away from friends and family to let me pursue my dream of earning a PhD. I also thank my mentor, Dr. Mark Hart, for his assistance and guidance over the last four years and in the completion of this dissertation. I would also like to thank the members of my supervisory committee, Dr. Kimberly Sibille, Dr. Mike Moorhouse, and especially Dr. Steve Anton who has given me numerous opportunities and brought me on as a member of the Institute on Aging team. I am very privileged to have been able to surround myself with such brilliant minds and am forever grateful for the mentorship and guidance provided to me by my committee. I would like to thank the faculty within the Social and Behavioral Sciences program and other members of the College of Public Health and Health Professions who have supported me, especially Christy Ewing. I would like to thank other UF mentors including Dr. Troy Donahoo, Dr. Volker Mai, Dr. Ron Shorr, and Dr. Arch Mainous III who each left a lasting impression on me. I would also like to thank Dr. Tony Thomas for encouraging me to pursue a PhD and providing constant hometown support from the very beginning of my academic career.

I would also like to dearly thank the Jack Kent Cooke Foundation for the extensive social and financial support throughout my undergraduate and graduate education. I would have not reached this accomplishment without the JKCF family. Lastly, I would also like to thank my friends and fellow doctoral students, Dr. Nichole Stetten, Dr. Lindsey King, Dr. Jarrett Brunny and Brittney Dixon, for the constant social support through the process.
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>4</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>7</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>8</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>9</td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>1 INTRODUCTION</td>
<td>10</td>
</tr>
<tr>
<td>Vulnerable Populations</td>
<td>11</td>
</tr>
<tr>
<td>Older Adults</td>
<td>11</td>
</tr>
<tr>
<td>Chronic Health Conditions</td>
<td>12</td>
</tr>
<tr>
<td>Role of Inflammation</td>
<td>13</td>
</tr>
<tr>
<td>Intermittent Fasting</td>
<td>15</td>
</tr>
<tr>
<td>Theoretical Perspective</td>
<td>16</td>
</tr>
<tr>
<td>Social Cognitive Theory</td>
<td>17</td>
</tr>
<tr>
<td>Biopsychosocial Model</td>
<td>18</td>
</tr>
<tr>
<td>Purpose of Studies</td>
<td>19</td>
</tr>
<tr>
<td>Specific Aims</td>
<td>19</td>
</tr>
<tr>
<td>Specific Aim 1</td>
<td>19</td>
</tr>
<tr>
<td>Specific Aim 2</td>
<td>19</td>
</tr>
<tr>
<td>Specific Aim 3</td>
<td>19</td>
</tr>
<tr>
<td>2 FASTING REGIMENS TO COMBAT SYMPTOMS OF AUTOIMMUNE DISEASE: A SCOPING REVIEW</td>
<td>21</td>
</tr>
<tr>
<td>Methods</td>
<td>23</td>
</tr>
<tr>
<td>Research Question</td>
<td>24</td>
</tr>
<tr>
<td>Identification of Relevant Studies</td>
<td>24</td>
</tr>
<tr>
<td>Results</td>
<td>24</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>25</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>25</td>
</tr>
<tr>
<td>Systemic Lupus Erythematousus (SLE)</td>
<td>26</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>26</td>
</tr>
<tr>
<td>Mixed Connective Tissue Disease</td>
<td>26</td>
</tr>
<tr>
<td>Discussion</td>
<td>27</td>
</tr>
<tr>
<td>Limitations and Future Directions</td>
<td>28</td>
</tr>
<tr>
<td>Conclusion</td>
<td>29</td>
</tr>
</tbody>
</table>
3 TIME RESTRICTED FEEDING AND INFLAMMATION IN OLDER ADULTS ..........34

Methods .................................................................................................................................36
  Outcomes .............................................................................................................................37
Results.....................................................................................................................................38
Discussion ................................................................................................................................38
Conclusion ...............................................................................................................................40

4 DETERMINANTS OF ADHERENCE IN TIME RESTRICTED FEEDING IN OLDER ADULTS: LESSONS FROM A PILOT STUDY .................................................................43

Methods ..................................................................................................................................44
  Intervention ............................................................................................................................45
  Outcomes ..............................................................................................................................46
Results.....................................................................................................................................47
  Biological Factors ..............................................................................................................48
  Psychological Factors ..........................................................................................................48
  Socio-Environmental Factors .............................................................................................49
Discussion ...............................................................................................................................50
Conclusion ...............................................................................................................................52

5 SUMMARY AND IMPLICATIONS .......................................................................................54

Scoping Review .......................................................................................................................56
Inflammation and Older Adults ............................................................................................57
Lessons Learned from a Pilot Trial .......................................................................................59
Discussion ...............................................................................................................................61
Limitations ..............................................................................................................................63
Future Research .....................................................................................................................63

LIST OF REFERENCES ..........................................................................................................65

BIOGRAPHICAL SKETCH ......................................................................................................80
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>Terms and definitions of fasting described in this review.</td>
<td>30</td>
</tr>
<tr>
<td>2-2</td>
<td>Fasting studies included in review.</td>
<td>31</td>
</tr>
<tr>
<td>3-1</td>
<td>Baseline and Follow-Up Values on Study Measures.</td>
<td>42</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>1-1</td>
<td>Bandura’s Triadic Reciprocal Determinism</td>
<td>20</td>
</tr>
<tr>
<td>1-2</td>
<td>Biopsychosocial Model</td>
<td>20</td>
</tr>
<tr>
<td>2-1</td>
<td>Study selection</td>
<td>33</td>
</tr>
</tbody>
</table>
Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

THE EFFECTS OF FASTING REGIMENS IN VULNERABLE POPULATIONS

By

Stephanie A. Lee

August 2019

Chair: Mark Hart
Major: Public Health

The primary objective of this dissertation is to address the public health challenge regarding the prevalence and seriousness of chronic conditions in vulnerable populations by evaluating the utility of a dietary health strategies. This will be done by assessing how dietary fasting patterns affect two specific vulnerable populations through literature review, implementation of a pilot study, and assessment of clinical and behavioral outcomes. Three specific aims will guide this dissertation. First, to conduct a scoping review to analyze how fasting regimens are defined and operationalized and what outcome measures were utilized and evaluated in the context of adults with autoimmune disease. Second, to evaluate the effects of a time restricted feeding pattern in overweight, older adults on inflammatory biomarkers C-reactive protein, interleukin-6 and ferritin. Third, to assess challenges to adherence in a four-week pilot study using a time restricted feeding regimen in older adults, and to assess advantages, disadvantages and challenges to application of a fasting regimen and evaluate the lessons learned from a pilot study through weekly participant interviews. This dissertation will add to the scientific community to advance knowledge in the area of complementary and integrative health in aging and chronically ill populations to support future research.
CHAPTER 1
INTRODUCTION

In recent times people have begun to look for simplistic methods to improve overall health and well-being. Healthy People 2020 outlines a comprehensive set of goals aimed at improving the Nation’s health and reducing health disparities. An ambitious, yet achievable objective of improving the quality and years of healthy life is a key focus and included as one of the four overarching goals for advancing public health (Hesse et al, 2014). This initiative also includes promoting health related quality of life and well-being, healthy development, and health behaviors across all life stages (https://www.healthypeople.gov).

There has been a steady decline in America’s health which has been described in the public health literature for decades (Muennig et al., 2018). This deterioration has long been hypothesized to contribute to a variety of biopsychosocial factors that are not mutually exclusive (Lehman et al, 2017). These factors influence a person’s perceived need for health care, ability to attend to health concerns, and capacity to obtain a level of health literacy needed to sustain or improve general health and well-being (King et al., 2009).

Vulnerable populations, such as older adults and those with chronic health conditions, often have unnecessarily inadequate healthcare with disparate health outcomes compared to groups who may have greater socioeconomic status, health literacy or access to healthcare and the ability to circumvent poor health outcomes (Waisel, 2013). Alternative, complementary, and cost-effective strategies to approach disparities faced could offer longstanding positive impact on quality of life, health outcomes, and finances for these individuals. Promising interventions with opportunities and implications to collectively address biopsychosocial factors and offer simplistic yet impactful lifestyle modifications can have important bearings on health (Thornton et al., 2016).
Vulnerable Populations

Older Adults

The variability in the capacity to obtain, process, and understand basic health information needed to make suitable health decisions must be considered and modified appropriately for whom it is intended (Kindig et al., 2004). For instance, older adults (age 65 and older) are the fastest growing population in the United States and will account for nearly a quarter of the total population in the upcoming years (Colby & Ortman, 2017). Age-related challenges and factors contributing to overall health and well-being for this population are public health issues needing attention. Health literacy skills in older adults aged 65 and older are disproportionately low compared to younger age groups. It is estimated that 29 percent have below basic skills, 68 percent have basic to intermediate skills, and only three percent are proficient in health literacy skills (Kutner et al., 2006; Chesser et al., 2016). This is determined by comprehension and ability to use health information to take action on health behaviors. A few examples of health literacy in this context include: following directions, reading nutritional labels, and interacting with professionals in health care settings (Speros, 2009). This is partly due to the natural aging process triggering a decline in working memory (Salthouse, 2010) and cognitive and physical functioning (Spirduso et al., 2005). Psychosocial factors such as socioeconomic status, social isolation, and depression have also been associated with poor lifestyle choices (Cutilli, 2007) and consequently, negative health outcomes (Ussher et al., 2010). The absence of health-related knowledge may serve as a barrier to engaging in healthy behaviors, preventative services, and acute and chronic disease management (Chesser et al., 2016).

Older adults can learn skills in late life and have great potential to absorb and apply health-related information but may just take longer to comprehend and put into action compared to younger adults (Kail & Kavanaugh, 2018). Many older adults also stay engaged and
productive, continuing to work or volunteer and take part in social networks and exercise
regimens. Behavioral support and interventions to increase self-efficacy, health literacy, and
outcome expectations are critical for sustaining self-management in this population
(Grembowski et al., 1993). Most health promotion efforts have not been designed to reach the
most disadvantaged older adults; investments in younger populations are essential to the health
of all, however, additional investments in secondary and tertiary prevention efforts with older-
age populations are crucial (Cesari et al., 2016; Beard & Bloom, 2015). As the implications of
population aging become clear, public health professionals are beginning to identify places
where public health intersects with aging. Public health initiatives should include the
development and testing of population- and systems-level interventions that have the potential to
better manage chronic disease and disability that plagues a large percentage of older adults
(Chatterji et al., 2015; Chihuri et al., 2016), and consequently improve quality of life.

**Chronic Health Conditions**

Another notable vulnerable population is individuals with chronic health conditions,
specifically, autoimmune disease (AD), which occurs in over 50 million Americans and is
rapidly increasing (AARDA, 2011). AD is one of the top ten causes of death in women under the
age of 65, the second highest cause of chronic illness, and the top cause of morbidity in women
in the United States (Walsh & Rau, 2000).

Autoimmunity is the activation of an immune response against the body’s own healthy
cells and tissues, allowing the body to attack itself rather than foreign invaders such as bacteria
and viruses (Rich & Chaplin, 2019). In essence, an AD is where tissue damage is caused by the
immunologic reaction of the organism against its own tissues (Rose, 2008). In comparison,
autoimmunity refers to the presence of antibodies that react with self-antigens and does not
necessarily imply that the self-reactivity has pathogenic consequences (Firestein et al., 2016).
Autoimmunity is present in all individuals; however, AD occurs only in individuals where the breakdown of one or more of the basic mechanisms regulating immune tolerance results in self-reactivity thereby causing tissue damage (Rosenblum et al., 2015; Firestein et al., 2016). Although individuals can have genetic predisposition to AD, susceptibility to onset can be increased by environmental factors (Marrack et al., 2001), affecting the overall reactivity and quality of the cells of the immune system.

The etiology of AD is poorly understood and a public health burden at levels comparable to heart disease and cancer (Barouki et al., 2012). Allopathic treatments, such as anti-inflammatory drug therapy, are available for over 100 different types of autoimmune diseases (Rosenblum et al., 2012). Symptoms of AD can sometimes go into remission; however, frequent flare-ups are common creating a decreased quality of life for those affected (Basu & Banik, 2017). Currently, there is no curative care for AD, thereby creating a chronic illness that often has poor clinical and self-perceived outcomes. A severe lack of awareness amongst the general public and medical practitioners in addition to a lack of coordinated care and standardized diagnostic tests, results in an elevation of expenses which thus contributes a significant portion of the rising cost of healthcare in the U.S. (Bates et al., 2014; AARDA, 2011). Addressing the pressing concerns surrounding AD should be a major priority for not only reducing healthcare spending but improving this population’s quality of life.

**Role of Inflammation**

Inflammation is part of the body’s natural defense mechanism, signaling the immune system to remove harmful stimuli and begin the healing process. Generally, there are two types of inflammation, acute and chronic. Acute inflammation is a short-term response with localized effects, meaning it is allocated to the site where trauma or injury occurs. It is relieved after a relatively short duration lasting from minutes to days. Conversely, chronic inflammation begins
with a cellular response, but stays active regardless of any immediate threat to the body. Chronic inflammation can have whole body effects, as it produces a continuous low-level of inflammation lasting from months to years which can contribute to the development of disease (Anft, 2016). Additionally, chronic inflammation prompts the immune system to eventually attack healthy tissue and organs (Kolaczkowska & Kubes, 2013), causing deleterious health concerns.

Low grade chronic inflammation plays a role in many disease conditions such as AD (Lalani et al., 1997), heart disease (Wirtz, 2017), Alzheimer’s disease (Heppner et al., 2015), psychiatric diseases (Slavich & Irwin, 2014), and cancer (Crusz & Balkwill, 2015, Deng et al., 2016, Beatty et al., 2017). The substantial morbidity caused by low grade chorinic inflammation contributes to early mortality making it a significant public health issue for the medical community (Slavich, 2015). Current treatments to prevent or control chronic inflammation includes non-steroidal anti-inflammatory drugs (Johnsen & Meyers, 2015), corticosteroids (Torres et al., 2015), herbal supplements (Ambriz-Pérez et al., 2016), and dietary modification (Oddy et al., 2018, Sleiman et al, 2015). Evidence indicates nutritional and pharmaceutical based interventions are effective in significantly reducing chronic low-grade inflammation as indicated by recognized biomarkers of systemic inflammation (Custodero et al., 2018). Importantly, dietary pattern is the greatest contributor to chronic inflammation. (Bootz & Neri, 2016). For example, diets high in red meat, dairy products, and refined grains and sugars are associated with elevated C-reactive protein (CRP) and interleukin (IL)-6, two well known markers of chronic inflammation (Accardi & Caruso, 2018).

Genetics, lifestyle behaviors, and environmental factors that stimulate chronic inflammation or disrupt the body’s protective mechanisms against an inflammatory response
may increase the risk of premature aging and associated disorders (Franceschi et al., 2007). Inflammatory conditions (e.g. rheumatoid arthritis) are not currently well-managed (Firestein & McInnes, 2017) and thus, more effective, practical, and therapeutic agents are necessary. Acute inflammation can be a beneficial and effective defense mechanism against infection and injury, however, when a chronic state develops it can be destructive to health. Clinical and behavioral interventions to reduce chronic inflammation are a top scientific and public health priority.

**Intermittent Fasting**

In recent years, intermittent fasting (IF) has gained popularity in both the scientific community and through media outlets to combat poor health indicators such as excess adiposity and obesity (Anton et al., 2018; Varady et al., 2013), cardiovascular risk factors (Mattson et al., 2017), and elevated inflammatory biomarkers (Rothschild et al., 2014). Various IF regimens exist, offering choices for individuals to best meet their preference and needs. For example, IF consists of abstaining from caloric intake for 12 continuous hours or longer, compared to alternate day fasting, where days are alternated between no calorie intake, and unrestricted intake (Longo & Panda, 2016; Varady, 2011). Another popular IF regimen is time restricted feeding, where eating times are designated to a window of usually eight or less continuous hours every day (Longo & Panda, 2016).

IF regimens do not limit types of foods consumed or require calorie counting. Instead, the timing of eating is the primary focus. Thus, this health practice offers a basic protocol and an inexpensive regimen that does not change what an individual eats, but rather when they eat. However, there are a few occasional concerns described about IF, such as reports of elevated hunger and associated discomfort during fasting times (Wegman et al., 2015). Social obligations and interpersonal relationships could be negatively affected, limiting social support (Varady et al., 2016). There are also some populations who are not recommended to adopt restricted eating
patterns, such as pregnant women, insulin dependant individuals (Wei et al., 2017), and those with a history of eating disorders (Barthels et al., 2018). Additionally, there is a need for studies to evaluate specific challenges to adhering to IF and understand participant’s perceived benefits and barriers over time when adopting this lifestyle (Anton et al., 2018). This eating pattern is a paradigm shift from the traditional, and perhaps socially constructed thought, that three meals plus snacks is required for complete daily nutritional intake (Mattson et al., 2014). Studies are needed to further evaluate health outcomes, assess disadvantaged and vulnerable populations, and develop best strategies for dissemination and implementation of proper practice. Further clinical research is needed before IF is a recommended health intervention in clinical settings.

Success in any dietary regimen often depends on behavioral health factors such as intention, motivation, and willingness paired with confidence and support for long term adherence and true lifestyle change (Moreira et al., 2011). Application of social and behavioral theories to inform and guide interventions to best meet the needs of an individual or population should be utilized.

**Theoretical Perspective**

The most successful public health programs, initiatives, and studies are based on understanding health behaviors and the environment in which they occur (Glanz & Bishop, 2010). Interventions to modify health behavior should be designed with guidance from relevant theories of behavior change with the capacity to implement them accordingly. A large body of evidence suggests when interventions are informed by social and behavioral theories, the outcome is more effective than interventions that lack theoretical guidance (Davis et al., 2015). In clinical settings, strategies to change health behavior have traditionally focused on individual level factors related to knowledge, personal beliefs, and individual skill (Glanz et al., 2015). However, consideration of biological, psychological, environmental, and social factors could
remove limitations and offer a broad perspective on current behavior and suggest appropriate modifications to achieve the best outcome in an intervention (Davis et al., 2015). Two theoretical models, social cognitive theory and the biopsychosocial model incorporate constructs relating to the individual and their surroundings and are described in detail in the following sections.

**Social Cognitive Theory**

Social cognitive theory is an interpersonal level theory that emphasizes the interaction between people and their personal factors, their behavior, and their environments as a triadic and dynamic model of causation (Bandura, 1989). The interaction between the three factors is demonstrated by the construct called Reciprocal Determinism, illustrating the strong influence each factor has on the others. Figure 1-1.

Social cognitive theory is found extensively in health behavior literature, being used to predict and elicit behavior change in various settings and populations (McAuley et al., 2013; Saksvig et al., 2005). Key constructs of the theory include self-efficacy, outcome expectations, self-regulation, and perceived barriers of a behavior (Bandura, 2004). These constructs are known to explain current health behaviors and predict outcomes based on how the three factors (personal, behavioral, and environmental) can be modified, including dietary patterns (Doerksen & McAuley, 2014; Bandura, 2004).

Although social cognitive theory accounts for influential factors often ignored in seminal public health theories and has a solid reputation in social and behavioral research, there are limitations to the model. First, it minimizes emotional response and valid arguments exist explaining that emotions can have a large impact on behavior (Thomas et al., 2018). Second, it does not account for biological differences and hormonal responses. Genetic differences can lead to disparities between cognition and behavior (Vukasovic & Bratko, 2015), and hormones are known to influence the decision-making process and consequently, behavior (Nijhout & Laub,
Third, there is natural maturation in people and behavior tends to change throughout the lifespan, regardless of environmental factors (Bleidorn & Hopwood, 2018). Lastly, social cognitive theory does not consider psychological factors such as personality disorders, depression, and self-esteem issue (Dickinson & Perez, 2018).

**Biopsychosocial Model**

The biopsychosocial model is a theoretical framework that incorporates biological, psychological, and sociocultural factors in an approach to understand the intricate variabilities and specific differences and evolutions in human behavior (George & Engel, 1980; Adler, 2009). Figure 2-2. “Bio” refers to biological factors such as physical health, genetic make-up, physical functioning status, and other physiological influences (George & Engel, 1980). “Psycho” refers to psychological factors such as behavioral, mental, and thought processes, emotional and internal perspectives, and coping skills (Tramonti et al., 2019). “Social” refers to social factors that influence the health of an individual such as economic status, life roles, family dynamic, and social network (Wood et al., 2015).

The multilayered interaction in the biopsychosocial model between genetic constraints, growth trajectories, and life contexts is in contrast to the traditional reductionist model of medicine that suggests the disease process can be explained by pathogens, developmental abnormality, or injury (Wade & Halligan, 2017). The biopsychosocial model counters the biomedical mindset and takes burden of treatment, recovery, and good health out of medial expert’s hands and shares responsibility with the individual. This model, which has dominated research and theory in the health psychology field, can help push theory, practice, and policy in a direction that captures real-world, lived experiences (Lehman et al., 2017).

However, the biopsychosocial model does have limitations to consider. First, critics argue that the model is merely a concept of the ‘mind-body connection’ which addresses philosophical
arguments rather than empirical exploration and clinical application (Rosenbaum & White, 2016). Additionally, mental illness is highly complex, social issues are too variable, and biological considerations can be too intricate for some to interpret thoroughly enough to consider as a key role in health behavior interventions and outcomes (Ghaemi, 2009). Finally, the biopsychosocial model is highly generic, creating individual interpretation and application when less vague theories exist as alternatives (Ghaemi, 2009).

**Purpose of Studies**

The primary objectives of the following studies are to address a public health challenge through evaluation of how fasting regimens effect two specific vulnerable populations through literature review, implementation of a pilot study, and assessment of clinical and behavioral outcomes. This dissertation will add to the scientific community by exploring the effects of fasting regimens on both individuals with AD and separately, overweight older adults to advance knowledge in this area. The following specific aims will guide this dissertation:

**Specific Aims**

**Specific Aim 1**

To conduct a scoping review to analyze how fasting regimens are defined and operationalized and what outcome measures were utilized and evaluated in the context of adults with autoimmune disease.

**Specific Aim 2**

To evaluate the effects of a time restricted feeding pattern in healthy, older adults on inflammatory biomarkers C-reactive protein, interleukin-6 and ferritin.

**Specific Aim 3**

To assess challenges to adherence of an intermittent fasting regimen in older adults and evaluate the lessons learned from a pilot study through weekly participant interviews.
Figure 1-1. Bandura’s Triadic Determinism

Figure 1-2. Biopsychosocial Model
CHAPTER 2
FASTING REGIMENS TO COMBAT SYMPTOMS OF AUTOIMMUNE DISEASE: A SCOPING REVIEW

In the United States, 50 million Americans are affected by autoimmune disease (AD), the prevalence of the condition has increased over the last several decades (Lerner et al., 2015). An AD is a condition in which the immune system mistakenly attacks healthy cells and tissues and contributes toward a chronic inflammatory state that often requires life-long disease management (Manzel et al., 2013). Genetic factors have been indicated as clearly predisposing individuals toward the development of inflammatory autoimmune diseases (Sawcer et al., 2011; Cotsapas et al., 2013). However, twin studies (Bogdanos et al., 2013) suggest environmental factors, such as diet, are important contributors of the disease. Although the association between diet and chronic disease was proposed over 50 years ago (Varady & Hellerstein, 2008; Cahill, 2005), the exact role dietary influence has on disease symptoms is not well understood (Manzel et al., 2014). There are indications that some autoimmune conditions are influenced by reducing intake of inflammatory foods (Mijac et al, 2010), and there is growing interest in diet modification as a complementary therapeutic measure to the allopathic standard of care (Schwartz & Leweling, 2005). Specifically, fasting has earned a reputation as a promising dietary approach to combat various health conditions (Anton et al, 2013; Varady, 2011; Harvie et al, 2013) and has gained interest from the scientific community.

Fasting regimens are comprised of various dietary intake plans that cycle between a period of fasting and non-fasting over a defined period (Mattson et al, 2016). For example, alternate day fasting (ADF) interchanges complete caloric restriction with ad libitum intake every-other day; a modified version of this, ADMF, allows for up to 25 percent of baseline calorie intake on the fasting days. Subtotal fasting (SF) has been documented as continuous caloric restriction with minimal intake (under 500 kcal) from only vegetable juices and broths.
Fasting mimicking diets (FMDs) are a bit different and new in the literature. This fasting plan consists of specific nutritional intake for a predetermined number of consecutive days designed to mimic the effects of true fasting by tricking the body into entering fasting mode (Choi et al., 2016). Lastly, most prominent in animal studies, time restricted feeding (TRF) is limiting caloric intake to specific time periods of the day, usually between a 6 to 12-hour window.

The arguments for the benefits of fasting in humans is still in foundational stages (Horne et al., 2015) and the majority of research thus far has been done in animal models. Reducing caloric intake without malnutrition is known to have beneficial effects in mammals and invertebrates including extending the lifespan, delaying the physiological signs of aging, and reducing the likelihood of various ailments (Sprott, 1997; Frame et al., 1998; Masoro, 1993; Hargraves et al., 2005). Studies evaluating the efficacy of fasting on AD in animal models have been promising.

Wei et al. (2016) found that periodic three-day cycles of an FMD regimen were effective in improving demyelination (damage to the myelin sheath of neurons) and symptoms in experimental autoimmune encephalomyelitis (EAE), which is the animal model for multiple sclerosis (MS). Amid the results, the FMD cycles suppressed autoimmunity in all mice, and reversed disease progression at onset of symptoms in a portion of the mice. Importantly, findings were encouraging in that indications suggest it is safe, feasible, and possibly effective in treating humans with MS. Another study by Jahromi et al., (2016) tested an ADF regimen on EAE in mice. They found that fasting, especially during the early phase of disease, alleviated EAE by suppressing pro-inflammatory and increasing anti-inflammatory cytokines. Further, fasting
enhanced spinal cord myelination and was noted and there were no unfavorable effects from ADF on the disease state in the mice.

In humans, a prominent area typically investigated in fasting regimens is change in body composition in overweight and obese adults (Anton et al., 2017; Varady et al., 2011). Recent studies have demonstrated that fasting is achievable and can contribute toward a reduction of cardiovascular disease, (Rothschild et al., 2014; Mattson et al., 2017), rheumatic disease (Michalsen, 2013), and decrease inflammation biomarkers (Kacimi et al., 2012; Aksungar et al., 2007). Fasting regimens have gained popularity in recent years and has shown promise as a possible new approach to promote the reduction of inflammation, a significant contributing factor in AD (Malinowski et al., 2019). The purpose of this review is to gain a better understanding of the current evidence on the different fasting regimens as therapeutic modalities to treat symptoms related specifically to AD in humans. Definitions of the terms used to describe various forms of fasting regimens are shown in Table 2-1.

**Methods**

A scoping review was conducted to examine the evidence supporting dietary fasting regimens among adults with AD. This methodology was selected to examine the amount of existing research rather than a systematic review which includes a formal quality assessment (Levac et al, 2010). Standard protocol for scoping reviews was followed and had broadly defined research questions, included all study types, developed inclusion and exclusion criteria post hoc at study selection stage, and lastly a chart was created to summarize key findings (Arskey et al., 2005; Colquhoun et al., 2014). Comprehensive and structured searches using five search engines were completed to maximize recall and decrease bias. As a result of differing fasting regimens, dissimilar comparison groups (or lack thereof), and varied study designs and intervention durations, these studies cannot be combined (Patterson et al., 2015).
Research Question

This scoping review aimed to answer the following question: (1) What is the current evidence using fasting as a therapeutic dietary regimen to combat symptoms of autoimmune disease in humans?

Identification of Relevant Studies

The comprehensive search utilized the following online databases: PubMed, PsychInfo, Cinhal, EbscoHost and Google Scholar. Searches using combinations of search terms related to fasting (eg, fasting regimen, intermittent fasting, periodic fasting, time restricted feeding, dietary restriction, restricted nutrition) and AD (eg, autoimmune disease, autoimmunity). Filters were used for “humans” to eliminate animal studies.

The preliminary search yielded 71 journal articles. Duplicate articles were removed to produce a total of 13 articles for further review. Articles were then reviewed for relevancy based on inclusion and exclusion criteria. Inclusion criteria included: (1) publication in a peer-reviewed academic journal, (2) a dietary intervention with a fasting regimen, (3) human research with an autoimmune condition (4) written in English language, and timeframe of all studies up to 2018. Exclusion criteria included: (1) animal studies. A total of 11 studies meet inclusion criteria however two did not having a full text available. Thus, nine articles were included in this review. Figure 2-1 shows the screening process.

Results

The nine relevant studies focused on the following conditions: multiple sclerosis (MS) (n=2), rheumatoid arthritis (RA) (n=6), systemic lupus erythematosus (SLE) (n=2), fibromyalgia (FM) (n=2), and mixed connective tissue disease (n=1). Two of the studies included study arms with different diseases, which accounts for the higher number stated above than total in the
review. Author and study design, participant type, fasting regimen, duration of study and results pertinent to this review are shown in Table2-2.

There was a relatively even spread across the approximate 35-year timeline. A majority of the studies were completed internationally; Norway (n=1), Iran (n=1), Sweden (n=2), Switzerland (n=1), Germany (n=2) and United States (n=2). Combined, there was a total of 307 individuals evaluated in the studies. All participants were adults who had a clinically diagnosed autoimmune disorder. Due to the limited number of studies available, there were no exclusions on the type of study design for this review.

**Multiple Sclerosis**

Two studies were found that evaluated MS in adult participants each with a different fasting regimen. Choi et al., 2016 utilized a seven-day FMD cycle followed by six months of Mediterranean diet and found a clinically meaningful increase in quality of life and decrease in the expanded disability status scale (EDSS). The regimen was deemed feasible and safe for the MS population with 100% compliance rates. Saadatnia et al., 2009 evaluated participants through TRF during Ramadan. No significant changes in EDSS or disease status were found, however, no unfavorable effects on symptom load were reported and was proposed as safe for individuals with MS to possibly participate in Ramadan fasting.

**Rheumatoid Arthritis**

Six studies were found that evaluated RA in adult participants. Four consisted of total fasting regimens and two with subtotal fasting regimens. Nearly all studies were reported as medically supervised in an in-patient setting, with some not specifying where treatment took place. Fasting periods ranged from four days to three weeks of continuous fasting. All six studies reported improvements in disease status based on participant self-report such as decreased pain and joint stiffness. Transient side effects such as headache, weakness, mild discomfort and poor
sleep were reported in two of the studies. Thus, though limited, the research on fasting specific to RA is encouraging regarding possible treatment for alleviation of disease symptoms.

**Systemic Lupus Erythematosus (SLE)**

Two studies were found that evaluated fasting in participants with SLE. A case report by Fuhrman et al., 2002 used a medically supervised total fast for two weeks. The participant self-reported being free of SLE symptoms post fast and experiencing mild nausea during the fast. Additionally, weight loss (Fuhrman et al., 2002) and a decrease in blood pressure were noted. Goharifar et al., 2015 evaluated participants through TRF during Ramadan and found no change in self-reported disease activity or health related quality of life (HRQoL). However, there were no negative side effects reported by the participants suggesting that individuals with SLE may be able to safely participate in the fasting associated with Ramadan. As the current review is limited to two studies for SLE, findings encourage further research.

**Fibromyalgia**

Two studies were found that evaluated fasting in participants with FM. A case report by Fuhrman et al., 2002 used a medically supervised total fast for one week with the participant reporting to be symptom free (e.g. no fatigue or muscle pain) post fast and at follow-up. Michalsen et al., 2005 implemented an eight-day subtotal fast with participants. Following the intervention, participants reported reduced symptoms such as pain, fatigue, and stiffness when compared with baseline. However, no significant clinical improvements in intestinal flora or sIgA levels were found. As noted in the other conditions, research specific to fasting in FM are scarce but with the two described are sufficient to encourage future investigations.

**Mixed Connective Tissue Disease**

In regard to MCTD, one case report by was found evaluating a two week medically supervised total fast in participants with MCTD. The participant self-reported as symptom free
immediately following the fast and at one month follow up. Minor discomfort was reported in the first few days. No other studies were found for this disease.

**Discussion**

The goal of this review was to evaluate current evidence which used fasting as a therapeutic regimen to combat symptoms of AD in humans. Few studies were found and only five different ADs were studied, however, promising outcomes from self-report measures suggest fasting should be further evaluated as a possible treatment for symptoms of AD.

This investigation revealed a limited amount of existing studies spanning over nearly four decades. There are over 100 types of ADs, however, this review shows only a handful have looked at fasting as a treatment option with most outcomes being self-report measures. Self-reports have shown to be reasonably accurate for chronic conditions and can provide useful estimates to determine the burden of the disease and guide clinical management of disease symptoms (Martín et al., 2000). Specifically, HRQoL is gaining worldwide acceptance as a central approach to healthcare interventions (Fletcher et al., 1995).

The majority of the studies do suggest that fasting is safe, well tolerated, and has a positive impact on self-reported symptoms (most showing long term) in these participants. No major side effects were reported, only transient complaints including headache, nausea, lightheadedness and fatigue. Fasting regimens in the selected studies were all continuous with most classified as either a total fasting regimen (not including any caloric intake), or a subtotal fast (allowing some caloric intake from fruit and vegetable juices) and lacked in other methods. All studies represent a single bout of fasting; long-term or repeated types of fasting regimens should be evaluated in the future. Symptoms from disease activity improved in nearly all studies, including joint stiffness, fatigue, and overall pain. There were no negative effects on any diseases
in any of the studies. Adherence was near perfect in the studies that reported it, however, these were in medically supervised in-patient settings.

The growing importance of self-reported HRQoL is recognized by healthcare providers and policymakers with increasing use of HRQoL to measure the effects of chronic illness in patients to understand how an illness interferes with a person's day-to-day life (Ghosh et al., 2010). Nevertheless, quality of life is highly individual, and measures are not a substitute for clinical outcomes associated with disease but rather an adjunct to them: for example, rheumatologists do not treat RA with antirheumatic drugs solely on the basis of HRQoL scores (Higginson & Carr 2001).

**Limitations and Future Directions**

There were many limitations to this review. First, fasting regimens in the selected studies are all continuous with some classified as subtotal fasts allowing some caloric intake, and not true fasting regimens. Second, most studies were done in medically supervised in-patient settings. Third, all studies represent a single term of fasting and most did not have a control group. Fourth, there were few quantitative measures supporting the findings. However, safety and feasibility were the primary outcomes for many of these studies. Lastly, the search was conducted by one researcher and general terms were used for this scoping review and did not include specific AD conditions. It is possible that more studies could have been identified if individual ADs were searched. Despite the many limitations, these studies, along with findings from animal studies, do offer a foundational framework to support future human randomized trials. With millions of individuals suffering from AD, it is crucial to research the potential effectiveness of fasting as a supplemental intervention that is essentially cost-free and easy to implement with approval of a health care provider.
Although the studies in this review do not provide sufficient evidence to promote any specific fasting regimen in those that suffer from symptoms of AD, it is important to note the subjective improvements that were reported by the participants in most of the studies. Precision medicine for individuals with AD has attracted much attention in the medical community; revising diagnosis and treatments of AD toward personalized medicine could be the revolutionary next step for having more effective and safer therapeutic options (Tavalkopour, 2017).

**Conclusion**

The findings from the review of fasting interventions in ADs, although preliminary with many focused on feasibility, are encouraging in that adverse experiences are minimal and transient with most studies suggesting the interventions were tolerable. Moreover, many of the fasting-based interventions described were associated with positive self-reported outcomes and no detrimental outcomes in any studies relating to disease activity and symptom load. The findings should be interpreted cautiously, as there were many limitations in the review. Future studies should examine the effects of fasting patterns using larger samples of individuals and more types of ADs over longer time periods to better understand the effects of this intervention in this vulnerable population.
Table 2-1. Terms and definitions of fasting described in this review.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent fasting (IF)</td>
<td>Prolonged time periods (e.g., 16–48 h) with little or no caloric intake, and intervening periods of ad libitum food intake, on a recurring basis.</td>
</tr>
<tr>
<td>Fasting mimicking diet (FMD)</td>
<td>Severe caloric restriction for 3-5 consecutive days a month, with specific nutritional intake designed to mimic the effects of true fasting.</td>
</tr>
<tr>
<td>Alternate day fasting (ADF)</td>
<td>Complete caloric restriction with ad libitum intake every-other day.</td>
</tr>
<tr>
<td>Time restricted feeding (TRF)</td>
<td>Limiting caloric intake to specific time periods of the day, usually between a 12 to 18-hour window.</td>
</tr>
<tr>
<td>Subtotal/Periodic fasting</td>
<td>Singular intervention of continuous fasting with limited caloric intake up to 500 kcal usually from fruit and vegetable juices.</td>
</tr>
<tr>
<td>Total fasting</td>
<td>Complete caloric restriction for extended periods limited to water intake.</td>
</tr>
<tr>
<td>Study and Design</td>
<td>Participants</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Choi et al. (2016) Randomized 3 arm pilot</td>
<td>20 MS patients</td>
</tr>
<tr>
<td>Fuhrman et al., (2002) Case studies</td>
<td>6 total patients; 3 RA, 1 SLE, 1 FM, 1 mixed connective tissue disease</td>
</tr>
<tr>
<td>Goharifar et al., (2015) Case control pilot study</td>
<td>40 SLE patients</td>
</tr>
<tr>
<td>Hafstrom et al., (1988) Crossover</td>
<td>14 RA patients</td>
</tr>
<tr>
<td>Kjeldsen-Kragh et al., (1991) Randomized single-blind controlled trial</td>
<td>27 RA patients</td>
</tr>
<tr>
<td>Kroker et al., (1984) Multicenter observational study</td>
<td>43 RA patients</td>
</tr>
<tr>
<td>Michalsen et al., (2005) Controlled non-randomized study</td>
<td>51 patients; 16 RA, 35 FM</td>
</tr>
</tbody>
</table>
Table 2-2. Continued

<table>
<thead>
<tr>
<th>Study and Design</th>
<th>Participants</th>
<th>Fasting Regimen</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saadatnia et al., (2009)</td>
<td>80 MS patients</td>
<td>TRF Ramadan fasting</td>
<td>6 months</td>
<td>No significant changes in EDSS or disease relapse between groups, fasting had no unfavorable effects on MS symptoms and deemed safe for MS patients.</td>
</tr>
<tr>
<td>Prospective cohort study with matched controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skoldstam et al., (1979)</td>
<td>26 RA patients</td>
<td>7-10 subtotal fasting days (tea, juice up to 200 kcal)</td>
<td>10 weeks</td>
<td>Fasting patients had ↓ pain, stiffness and analgesic consumption compared to controls.</td>
</tr>
<tr>
<td>Randomized trial with controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p< 0.05; **p< 0.01; ***p< 0.001.

HRQoL, health related quality of life; TRF, time restricted feeding; RA, rheumatoid arthritis; MS, multiple sclerosis; FM, fibromyalgia; SLE, systemic lupus erythematosus; EDSS, expanded disability status scale.
Figure 2-1. Study selection
CHAPTER 3
TIME RESTRICTED FEEDING AND INFLAMMATION IN OLDER ADULTS

Americans are living longer and the number of older adults age 65 and older is substantially higher than ever before (NCHS, 2018, Statistics, 2000). Physical decline is a complex process that results from a combination of environmental, genetic, and epigenetic factors. Low-grade chronic inflammation is a common condition in aged individuals and has been termed ‘inflammaging’ (Franceschi et al., 2000; Xia et al., 2016) and can accelerate senescence (biological aging) and worsen many age-related diseases (Nasi et al., 2016). This is of particular interest with older adults due to the added concern of immunosenescence, the natural aging of the immune system, a known contributor to inflammation (Aw et al., 2007).

Growing evidence suggests systemic inflammation, partially characterized by high plasma C-reactive protein (CRP) and Interleukin (IL)-6 in the blood, (Sanders et al., 2013, Singh & Newman 2011) are independent risk factors for reduced muscle function, disability, impaired mobility, and slow walking speed, all of which are major concerns in older adults (Manini et al., 2017, Cesari et al., 2009). Also of concern is the implication that ongoing inflammaging increases ferritin levels and may mask underlying iron deficiency in the older population. Ferritin is a well-known inflammatory marker; however, it is unclear if it reflects or causes inflammation, or whether it is involved in an inflammatory cycle presenting a paradox when interpreting in clinical assessment (Kell & Pretorius, 2014; Cankurtaran et al., 2012). Chronic inflammation plays a role in many disease conditions causing substantial morbidity, subsequently contributing to early mortality, making chronic inflammation an urgent public health issue.

Standard treatments to minimize chronic inflammation include: non-steroidal anti-inflammatory drugs (Johnsen & Meyers, 2015), corticosteroids (Torres et al., 2015), herbal supplements (Ambriz-Pérez et al., 2016), and omitting inflammation-inducing foods from diet.
(Oddy et al., 2018, Sleiman et al., 2015). In a recent meta-analysis of the literature, Custodero et al., 2018 found that nutritional and pharmaceutical compounds such as probiotics, ARBs, and omega-3 can significantly reduce established biomarkers of inflammation in middle-age and older adults. However, although pharmacological interventions may be clinically beneficial, they are not without side effects. Common side effects include: gastrointestinal distress and cardiovascular complications (Pilotto et al., 2010), as well as the additional financial burden associated with their use, reducing the practicality of these interventions. Therefore, further exploration of lifestyle interventions such as dietary and eating pattern modifications is needed to offer a feasible alternative to limiting inflammation in older adults.

Various dietary factors have been reported to reduce levels of inflammation in the body, including increased intake of whole grains, olive oils, fruits, nuts, and green leafy vegetables (Shah et al., 2016; Sleiman et al., 2015), and limiting intake of red and processed meats, dairy, fried and processed foods (Ozawa, 2017). A caveat specifically in older adults, are factors influencing adherence such as low health literacy (Kutner et al., 2006), and socioeconomic constraints (Burgess et al, 2017). Alternatively, intermittent fasting is an umbrella term for a variety of eating patterns that cycle between periods of fasting and non-fasting and is known to also reduce markers of inflammation (Varady et al., 2013; Arumugam et al., 2010; Johnson et al., 2007), and does not limit types of foods or require calorie counting. Thus, this eating pattern offers a basic protocol and an inexpensive regimen that does not change what individuals eat, but rather when they eat it, which may be promising for older adults. However, no types of intermittent fasting regimens have been tested in the older adult population until recently. Anton et al., 2019 was the first to look at the safety and feasibility of a short-term time restricted feeding pattern in overweight, sedentary older adults. This current paper evaluates the effects of
a time restricted feeding (TRF) pattern on three standard measures of inflammation, CRP, IL-6, and serum ferritin in participants in the Time to Eat pilot study.

Methods

As described in more detail in Anton et al., 2019, ten overweight, sedentary older adults with mild to moderate functional limitations were recruited. Key inclusion criteria were as follows: overweight (BMI between 25 and 40 kg/m², inclusive), age 65 y and older, physical activity level at <30 min/week of structured exercise, difficulty walking ¼ mile or climbing stairs, not currently fasting >12 hours per day, weight stable for one month prior to the study (<5 lb weight loss) and not actively trying or intending to lose weight, and not taking any medications that would affect study protocol or outcomes.

A 4-week clinical pilot trial was employed to test the study objectives. All participants were instructed to abstain from any energy intake during the fasting window (~16h) and consume ad libitum during the eating window with no restrictions on type or quantity of foods consumed. Fasting time periods were chosen by the participant and they were instructed to fast for approximately 16 continuous hours per day. Participants were encouraged to drink plenty of water. Only zero-calorie items such as black coffee, unsweetened tea, diet soda, and sugar free gum were permitted during fasting periods. An animated instruction sheet was sent home with participants to illustrate these guidelines.

Participants were called by the trial interventionist at the end of each week using a semi-structured interview. The interview questions inquired about daily activities, changes to normal routine, and changes overall health. The daily time log was reviewed for each day of that week and support and guidance were provided for any challenges faced due to the intervention. To promote adherence, the protocol was reviewed and any reported changes to physical function or
health were documented in the adverse event log. Participants were provided with a food diary and instructed to record the time of first and final calorie intake each day.

Baseline and follow-up visits were at the University of Florida’s Institute on Aging Clinical Translational Research Facility. During these two visits, labs collected (1) 5.0mL tube of blood from participants in a fasted state.

Outcomes

Fasting blood samples were collected into serum separation tubes at baseline (week 1) and post-treatment (week 4). Serum assays of CRP, IL-6 and ferritin were given ample clotting time then centrifuged at 1600 x g for 15 minutes at 4°C and immediately stored at -80°C. Samples were thawed on ice just prior to analysis. Assays were performed at the Metabolism and Translational Science Core of the Institute on Aging at the University of Florida in duplicate using Enzyme-linked Immunosorbent Assays (ELISA) according to the instructions of the manufacturers (cat# DCRP00, R&D Systems, Minneapolis, MN, USA; cat# HS600C, R&D Systems, Minneapolis, MN, USA; cat# 25-FERHU-E01, ALPCO, Inc., Salem NH, USA). The average intra-assay CV was <6% for CRP, <4% for IL-6, and <10% for ferritin. Inter-assay CV was <7 % for CRP, <11% for IL-6, and <15% for ferritin.

Statistical Methods

Power analysis and sample size estimates for pilot studies are inherently difficult because by intent, a pilot study is meant to include a smaller sample than a fully powered study. Effect size was calculated to highlight the size of any differences observed using Cohen’s $d$ since the p-value is often impractical in a study this small (Kim & Bang, 2016). Effect size calculations are independent of sample size, and in accordance with convention, effect sizes were classified as small (−0.2), moderate (−0.5) and large (−0.8) (Cohen, 1992).
Analysis included paired sample two-tailed t-tests with $\alpha=0.05$. The means and standard deviations of variables were computed at baseline and follow-up; responses with missing values were not included in the analyses. The outcomes of interest were change from baseline to week four on the following inflammatory measures: (a) CRP, (b) IL-6, (c) ferritin. Data was analyzed using SPSS software (version 25).

**Results**

Nine of the 10 participants who commenced the study completed the entire protocol (mean age = 77.1 y; 6 women, 3 men). One participant was not able to be contacted during the intervention and did not provide post-treatment data thus was considered non-compliant. There were no significant changes in CRP, IL-6, or serum ferritin or relevant effect size differences confirmed with Wilcoxon Signed-rank non-parametric testing. Ferritin did have a statistical trend and increased slightly ($p < .075$) with this short term TRF regimen. The values on all outcome measures at baseline and follow-up are summarized in Table 3-1.

**Discussion**

There was no significant change in CRP, IL-6, or ferritin, however, ferritin did have a statistical trend with a slight increase in value.

Most observational studies and clinical trials have used CRP as a marker of inflammation because it is relatively stable and easy to measure (Musunuru et al., 2008). Consumption of healthy diets rich in fruits and vegetables have also been associated with significantly lower CRP levels. Thus, dietary patterns may influence the risk of diseases through the effects of CRP, with substantial evidence for an inverse relationship between adherence to anti-inflammatory eating patterns (e.g. Mediterranean diet) and CRP (Minihane et al., 2015). This has, however, only been shown after three months or more of dietary change (Neale et al., 2016).
IL-6 is often related to inflammatory and pathological situations, however, it is also a factor that contributes decisively in the normal function of the brain (Ruderman et al., 2006). Thus, IL-6 is involved in the control of body weight, food intake and energy expenditure (Eerta et al., 2012). The results from IL-6 in this study are not surprising, as this marker generally only decreases with at least a 5% weight loss (Heggen et al., 2014). Although significant weight loss of 2.6 kg was reported in this four-week trial (Anton et al., 2019), it was an average of 3% of total body weight, and possibly one explanation as to why this inflammatory marker was not altered.

Previous studies have shown short-term (2 day) fasting to decrease levels of ferritin in women (Wojciak, 2014), and a tendency for ferritin to drop progressively over a four week period in young males during Ramadan (Maughan et al., 2008), however changes were generally small and values remained within the normal range. Conversely, there was a slight increase in our study population. Ferritin has been shown to rise during periods of acute malnourishment in young women, due to iron storing as intravascular volume thereby decreasing the number of red blood cells (Kennedy et al., 2004). Additionally, slight elevation in ferritin has been found in older adults at risk for malnutrition (Ülger et al., 2010). Future TRF studies should include a nutritional assessment and closely evaluate ferritin in older adults to consider onset of nutritional deficiencies. However, in most clinical cases, ferritin is less than diagnostic and further work-up is often indicated, as the inflammatory response alters iron regulation due to ferritin being an acute phase reactant (Sharif et al., 2018; Weiss, 2005).

This study did have notable limitations. First, the small sample size and short duration of the intervention limits the generalizability of the results and may have limited our ability to detect statistical significance. For this reason, effect sizes using Cohen’s $d$ for all outcome
measures were done since this statistic is independent of sample size. Most notably, the primary aim for this pilot study was for safety and feasibility, therefore, the inclusion criteria did not require clinically elevated inflammatory markers for enrollment. There are currently no clinical thresholds for cytokines, including IL-6, however it is proposed that an IL-6 level of greater than 2.5 pg/mL is considered high (Akbaraly et al., 2013; Wyczalkowska-Tomasik et al., 2016). In our present group of participants, the average IL-6 level was slightly above this limit, however, the TRF regimen had no effect on this biomarker. The participants also had CRP levels within the average to moderate risk range of 1.0–3.0 mg/L according to recommendations by the American Heart Association and the CDC (Lopez-Candales, et al., 2017). Lastly, normal ferritin levels generally range from 12 to 300 ng/mL for males and 12 to 150 ng/mL for females (Schreiber et al., 2018). Participants in this study started in a low-normal range at baseline.

To our knowledge, this is the first study to examine the effects of a time restricted eating pattern on inflammatory markers in older adults (ages 65 and older). There are also a few notable strengths in this study. First, adherence rates were high at 84%, increasing accuracy in the lab work. This may be attributed to weekly phone calls to check on compliance and assist them in problem-solving any intervention-related challenges. Second, during these calls, adverse events were assessed and resolved. Lastly, we conducted an exit interview to obtain the participant perspective on what challenges and what changes, if any, they would recommend to the intervention in future trials.

**Conclusion**

The inflammation related findings from the Time to Eat pilot study suggest that a short term TRF regimen in overweight, sedentary older adults does not significantly change levels of inflammation and should be further studied in older adults. Follow up studies should recruit older
adults with clinically elevated levels of inflammation at start. Utilizing minimum inflammatory concentrations that are both associated with elevated disease risk and prevalence in sedentary populations will increase the clinical significance and applicability of the research question (Thompson et al., 2008). Additionally, future studies should also examine the effects of a TRF eating pattern using larger samples of older adults over longer time periods and incorporate a nutritional assessment to better understand the effects TRF has on inflammation. Anti-inflammatory benefits may take time to exert its effect and may continue to have an effect after it is withdrawn.
### Table 3-1. Baseline and Follow-Up Values on Study Measures

<table>
<thead>
<tr>
<th>Study Measures</th>
<th>Baseline $M$ (SD)</th>
<th>Follow-up $M$ (SD)</th>
<th>Cohen’s $d$ (Effect Size)</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammation Biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>1.76 (1.0)</td>
<td>1.68 (0.7)</td>
<td>.09</td>
<td>.395</td>
</tr>
<tr>
<td>Interleukin-6 (pg/ml)</td>
<td>3.44 (2.2)</td>
<td>3.44 (1.4)</td>
<td>.00</td>
<td>.271</td>
</tr>
<tr>
<td>Serum ferritin (ng/ml)</td>
<td>26.07 (16.5)</td>
<td>27.05 (19.8)</td>
<td>.05</td>
<td>.075</td>
</tr>
</tbody>
</table>
CHAPTER 4
DETERMINANTS OF ADHERENCE IN TIME RESTRICTED FEEDING IN OLDER ADULTS: LESSONS FROM A PILOT STUDY

The variability in the capacity to obtain, process, and understand health information needed to implement beneficial lifestyle modifications must be considered and modified appropriately for the intended population (Kindig et al., 2004). Researchers have increased focus attention on behavioral interventions in older adults defined as age 65 year and older (Sahyoun et al., 2014). This interest has come about due to demographic changes; people are now living longer, and consequently the older population is increasing rapidly and medical expenditure is rising with later life onset of several metabolic and chronic diseases (NCHS, 2018, Statistics, 2000).

There is growing interest in the effects of modifiable factors such as diet in older adults to address age-related diseases (Bloom et al., 2018). Specifically, one dietary pattern of interest in older adults is intermittent fasting (IF), as studies indicate loss of fat mass with retention of lean mass in this eating pattern (Klempel et al., 2013; Anton et al., 2017). This is particularly important for older adults, as loss of muscle mass is associated with aging (sarcopenia) (Buford et al., 2010). IF describes a variety of eating patterns in which no or few calories are consumed for varying time periods. Forms of IF have shown to have beneficial effects in in overweight adults (Anton et al., 2017) however, the effects of IF are not well understood in older adults aged 65 and older. A few of the beneficial effects of IF include improvements in lipid profiles (Rooth & Carlstrom, 1970), symptoms of autoimmunity (Choi et al., 2016; Michalsen et al., 2005) and cardiometabolic risk factors (Rothschild et al., 2014) in addition to weight loss without loss of lean mass and metabolic improvements (Anton et al., 2018; Varady et al., 2011).

There are biological concerns due to age-related changes in older adults when considering a dietary regimen such as nutritional vulnerability (Starr et al., 2015) and self-
reported mild to moderate cognitive decline (Rabin et al., 2015). Additionally, psychosocial factors such as socioeconomic status, social isolation, and reduced health literacy have been associated with poor lifestyle choices in older adults (King et al., 2009; Cutilli, 2007) and consequently, negative health outcomes (Ussher et al., 2010). Older adults can, however, learn skills in late life and have great potential to absorb and apply health-related information but may just take longer to comprehend and put into action when compared to younger adults (Kail & Kavanaugh, 2018). Behavioral support in interventions to increase self-efficacy, health literacy, and outcome expectations is critical for success in lifestyle change and sustaining self-management for this population (Grembowski et al., 1993).

According to the biopsychosocial model, interactions between people's physical health and functioning (biology), mental health and personality (psychology), and sociocultural environment (social world) contribute to their health and ability to embrace an intervention (Tramonti et al., 2019; Adler, 2009). Research using a dynamic biopsychosocial perspective can help to isolate the best approach and format for IF interventions in older adults to optimize adherence when adopting this type of regimen (Lehman el al., 2017).

Methods

As described previously with more detailed information in Anton et al., 2019, ten overweight, sedentary older adults age 65 and older with mild to moderate functional limitations were recruited. Primary outcomes were to evaluate safety and feasibility in addition to secondary outcomes including changes in body weight, waist circumference, cognitive and physical function, health-related quality of life, and adverse events. The goal of this paper was to evaluate participant perspectives on the real-world advantages, disadvantages, and challenges to adopting a time restricted feeding (TRF) eating pattern through weekly phone interviews and an exit interview during the study.
**Intervention**

A 4-week TRF single-arm clinical pilot trial was employed to test the study objectives. All participants were asked to abstain from any energy intake during the targeted fasting window of 16 continuous hours and consume ad libitum during the eating window. Fasting times were chosen by the participant and did not have to be the same each day. The first week involved a gradual increase to a full 16-hour fasting period (Days 1-3 fast for 12-14 hours per day, Days 4-6 fast for 14-16 hours per day, Days 7-28 fast for 16 hours per day). Participants were encouraged to drink plenty of water during fasting times.

During the baseline visit, participants were provided with directions on the TRF protocol and were provided with a dietary log, which they were instructed to complete by recording the times in which they first consumed calories and when they stopped consuming calories. To assist them in following the intervention, they were also provided with an animated flyer which depicted food items that were allowed and not allowed during fasting windows. On the flyer, “Go Foods” were written in green (water, diet soda, unsweetened teas, sugar free gum, black coffee) and “No Foods” were written in red (anything with calories including coffee creamer, sweet teas, alcohol, snacks, drinks with calories). The aim of the colorful flyer was to assist in common misconceptions of what would constitute as caloric intake to ensure avoidance during fasting times.

Weekly phone calls were made by the trial interventionist to each participant to promote adherence, review the protocol, monitor for adverse events, and provide support and guidance for any challenges faced during the intervention. A semi-structured, open ended interview guide was used for the calls to inquire about daily activities, changes to normal routine, and changes overall health. The daily time log was reviewed for each day of that week and support and guidance were provided for any challenges faced due to the intervention. To promote adherence, the
protocol was reviewed and any reported changes to physical function or health were documented in the adverse event log. The call concluded with general questions from the participant and flexibility for casual conversation. Participant answers and comments were documented during the phone call.

Exit interviews were also conducted in-person by the interventionist on the last day of the intervention. This interview was the similar format as the weekly calls but included questions about interest and the likelihood of continuing the TRF eating pattern and allowed the participant to offer suggestions for future trials. Baseline and follow-up visits were at the University of Florida’s Institute on Aging Clinical Translational Research Facility.

Outcomes

Participant views on the perceived advantages, disadvantages, and challenges to adopting the TRF regimen were explored through qualitative analysis to better understand how older adults can successfully adapt to this eating pattern.

Analysis

A constant comparison coding process was used to categorize and compare interview data for analysis purposes (Anderson & Jack, 2015). A trained researcher (SL), open coded each interview and mapped data within the three primary constructs of the biopsychosocial model (biological, psychological, socio-environmental) to systematically consider biological, these three primary factors in their interactions in the TRF intervention.

Open coding was completed by hand instead of using data mining software, in order to take on the full context of the interviews. Positive and negative categories within each of the three primary themes and were documented.
Results
Nine of the 10 participants who commenced the study completed the entire protocol (mean age = 77.1 y; 6 women, 3 men). We were unable to reach one participant by phone during the study, and thus he was considered non-compliant, however, the exit interview was conducted post intervention. Four participants completed all three weekly phone calls with the interventionist, three participants completed two calls due to missed calls, one participant completed one call due to wrong number being provided, and two participants completed zero phone calls due to vacation and study withdrawal. All participants completed the exit interview. Nine participants fully completed the dietary log with no days missed. Based on participant’s self-report, adherence to the TRF regimen was 84% and significant weight loss averaging 2.6 kg was reported (Anton et al., 2019).

The biopsychosocial model biological, psychological, and sociocultural factors in an approach to understand variabilities and specific differences in human behavior (George & Engel, 1980; Adler, 2009). “Bio” refers to biological factors such as physical health, genetic make-up, physical functioning status, and other physiological influences (George & Engel, 1980). “Psycho” refers to psychological factors such as behavioral, mental, and thought processes, emotional and internal perspectives, and coping skills (Tramonti et al., 2019). “Social” refers to social factors that influence the health of an individual such as economic status, life roles, family dynamic, and social network (Wood et al., 2015). Analysis and interpretation of the interview data revealed the following barriers and enablers experienced by participants throughout the study in each of the three primary themes of the biopsychosocial model used in coding.
**Biological Factors**

Most participants expressed that a 16 hour fast was easy to adjust to and not too drastic of a difference from normal eating patterns. After the first few days of fasting, uncomfortable hunger was not reported by any participant. Although caloric intake was not monitored, all but one participant felt they were consuming the same number of calories or more as before the intervention as indicated by self-report. Few sides effects were reported during phone interviews including transient headaches which dissipated with increased water intake, and dizziness in one participant which subsided with a small snack. Increased energy was reported by some participants, with greater self-reported activity levels in yardwork and light exercise.

Preexisting physical conditions including knee and back pain were outside of the exclusion criteria and required medical treatment during the study in two participants. These were identified during weekly phone calls and unknown during enrollment. Such treatments included biweekly epidurals for walking difficulty, and weekly cold laser therapy for hip and knee pain.

**Psychological Factors**

Most participants had positive attitudes on the phone calls throughout the study and reported feeling eager, motivated and excited; many had heard of IF regimens and were anxious to experience a form of this eating pattern. Directions to the study intervention were explained in-person at baseline and participants were sent home with an animated instruction sheet for reference, yet phone calls revealed most (7 out of 10) were continuously unclear about the protocol and goals of this study. First, over half of the participants did not fully understand that foods with calories were not to be consumed during fasting times. For instance, during weekly phone calls some participants stated they ate snacks in the evening before bed and did not record this in the eating window. Additionally, since there was no space on the dietary log to
specifically document this, some presumed any food consumed during fasting times did not have to be accounted for. Furthermore, low-calorie foods were often confused with no-calorie foods, and not recorded even after the interventionist reiterated that any food item with calories must be documented and participants were instructed to refer to the animated flyer provided for reference.

Second, participant’s reported weight loss early in the trial as motivation for adherence, however, there was confusion that TRF was being examined solely for weight loss. The interventionist did explain that other health outcomes would be evaluated, but some participants only associated TRF with weight loss. Due to this, some participants felt small or low-calorie snacks would not alter the protocol. Lastly, two participants actively tried to lose weight during the study by further adjusting their eating patterns by limiting carbohydrates and adopting a ketogenic eating pattern in addition to adopting the TRF regimen.

**Socio-Environmental Factors**

Participants stated that support from close family members was pivotal in maintaining the TRF regimen. Although not enrolled in the trial, spouses of the participants altered their eating pattern to mimic the fasting regimen and eat with their partner. Participants reported eating roughly the same amount of food as before the study.

One obstacle to TRF for a couple of participants was vacationing during the study, which made it difficult to follow the eating pattern and complete scheduled weekly phone calls with the interventionist. Additionally, it was noted by several participants in the exit interview that they would not want to restrict their diet in the future during holidays or vacations.

Some participants had weekly social events that included food; the timing of these events did not coincide with their eating window, creating an awkwardness amongst peers and making the social event less enjoyable. Additionally, work schedule changes interfered with the timing
of meals and there was difficulty in adjusting the eating window despite suggestions from the interventionist. Regular doctor appointments for the participant or their spouse requiring long commutes also created extended fasting times beyond the 14-18 hour goal for a few individuals.

**Discussion**

There are three prominent lessons learned to consider for design of future TRF regimens in overweight, sedentary, older adults from this pilot trial. First, to consider the level of comprehension of the eating pattern and guidelines of participants. Second, to apply motivational techniques to aid in adherence to the fasting regimen. Third, to offer adaptation skills to slowly incorporate lifestyle change prior to the start of the intervention.

To address comprehension, clear and complete understanding of the defined fasting regimen and guidelines for the intervention is essential for compliance. Specifically, the ability to identify foods with calories that are to be avoided during fasting times, and proper reporting of intake times. Weekly interaction is suggested to reiterate and reinforce behavioral guidelines for both diet and self-report measures in the initial phase of the intervention (Hartman et al., 2016). In addition, regular contact is needed to offer behavior modification strategies and monitor for adverse events as needed. Health literacy in older adults is notoriously low from natural cognitive decline (Fernandez et al., 2016), and regimen complexity was the largest factor influencing adherence. These suggested additional measures should be taken to supplement comprehension of a fasting regimen in older adults.

To aid in motivation to adhere to a TRF regimen, sharing potential outcomes outside of weight loss with participants could be beneficial. Possible outcomes such as increased mobility, quality of life, and cognitive function could bolster perceived benefits, increasing the likelihood of engaging in a longstanding behavior change and improved adherence to the regimen (McMorrow et al., 2016). Restricted feeding, even outside of caloric restriction, is commonly
associated with weight-loss, however, it is not a strong motivator for adherence to long-term lifestyle change (Burgess et al., 2017; Montesi et al., 2016). Explaining alternative reasons to participants for diet modification outside of the normal affiliation of weight loss could be valuable.

Adapting to change in everyday behaviors, such as eating, are challenging to adopt due to routine behavior (Kurz et al., 2015). Teaching skills to modify and/or break eating habits, such as late-night snacking, from daily routine before starting a TRF intervention could be effective. Successful habit change interventions involve disrupting the socio-environmental factors that cue habitual behavior (Verplanken & Wood, 2006). Pressures from work, long commutes, vacations, and influence from social engagements all act as barriers to change (Burgess et al., 2017; Venditti et al, 2014; Leone et al., 2013). Increasing health knowledge through group training to enforce shared learning in combination with social support from friends and immediate family members is advocated for successful integration of comprehension, motivation, and adaptation to the lifestyle change (Polan & Taylor, 2019).

Consideration of biological, psychological, and socio-environmental factors could remove limitations and offer a broad perspective on current behavior and suggest appropriate modifications to achieve the best outcome in an intervention (Davis et al., 2015). Ultimately, success in any lifestyle modification depends on factors such as intention, motivation, and willingness paired with confidence and support for long term adherence and possible beneficial health outcomes (Moreira et al., 2011). Application of social and behavioral theories to inform and guide interventions to best meet the needs of an individual or population should be utilized.

Barriers to behavior change should be openly discussed within the initial phases and at regular intervals throughout any intervention (McMorrow et al., 2016). A strength to this study
was the personalized attention given to participants to discuss individual problems that may have improved overall adherence. Weekly phone calls were also crucial in this trial for regimen adherence and adverse event monitoring. Ensuring that difficulties are being appropriately addressed regularly at a personalized level would supplement adherence in future older adult TRF trials (Burgess et al., 2017). Additionally, a more detailed food diary highlighting no-calorie consumption during fasting periods and offering a space for tracking non-adherent intake is recommended.

There were limitations to this study, including problems contacting participants via telephone. Additionally, only one coder was used for analysis and triangulation was not used to cross check data. Response bias is also a possible limitation in this study as participants may have only reported what they thought the interventionist wanted to hear in the interviews, or second guess what the interventionist was asking and altered their answers. Lastly, by nature, people tend to remember negative events more than positive events. Since there was only one call completed per week, it is possible that some information was forgotten during the phone call and more negative than positive events were relayed. More research needs to be conducted on a diverse group and address identified factors in this study that impeded or promoted adherence to TRF guidelines in older adults.

**Conclusion**

Most participants enjoyed the simplicity of a timed eating regimen and stated willingness to continue this eating pattern with slight modification such as decreased daily fasting times or a weekly ‘cheat’ day. Comprehension of the fasting regimen and guidelines were low, indicating more participant contact is needed. Additionally, baseline group instruction on the protocol with continued weekly in-person group sessions may benefit understanding from social support. Motivation to follow protocol was strongly guided by weight loss, as most participants thought
this was a weight loss study. Adaptation to TRF has challenges due to vacations and social events, however spousal encouragement was a supportive factor. Applying dietary regimens in older adults should consider such factors; by identifying determinants of adherence to dietary regimens, study outcomes and support for older adults in adopting lifestyle change in future studies can be optimized.

The findings of this study illustrate the usefulness of adopting a biopsychosocial model to explore specific factors that influence adherence to dietary regimens in older adults. The contribution of the model to better understand the impact of biopsychosocial factors on health interventions stimulates greater interest of a more holistic approach to clinical research. It is apparent that the individual does not function on his or her own but is affected by various determinants of health.
There are many possible ways to define vulnerable populations in the context of health research. Definitions often include the following: those who have chronic health conditions or are disabled, ethnic or racial minorities, children, the economically disadvantaged, elderly, and the underinsured to name a few (Browne et al., 2016). The numbers of vulnerable populations are increasing, particularly as the population ages. The 65-and-older age group’s share of the total population will rise to nearly 24 percent from 15 percent in the upcoming years (Colby & Ortman, 2017). Additionally, the number of individuals with chronic medical conditions is projected to rise from 141 million Americans in 2014 to 171 million by 2030 (Prince et al., 2015). Chronic diseases are significantly more prevalent among low-income and other disadvantaged populations (Kim et al., 2016), a public health crisis warranting the need for inexpensive and feasible preventative and therapeutic interventions to better the health of these underprivileged individuals.

Growing evidence shows chronic disease is initiated and accelerated by systemic chronic inflammation (Coussens & Werb, 2002; Hunter, 2016). Although this understanding might not lead to a cohesive theory of chronic disease, the crucial role of inflammatory processes must be considered in chronic disease research (Hunter, 2016). Inflammation is a normal component of human body defense mechanisms; however, elevated continuous chronic inflammation is a concern and instigator in a range of chronic diseases, particularly autoimmunity (Minihane et al., 2015). Treatment and therapy of chronic disease is largely focused on blocking the inflammatory process (Hunter, 2012). Nutritional intake, and perhaps the timing of such, can influence inflammatory processes and help reduce risk for chronic diseases and calm immune response due to autoimmunity (Anaya et al., 2016).
Diet is modifiable lifestyle risk factor for various health outcomes, however there is often poor long-term adherence, concerns from regimen complexity, and socioeconomic disparities to health that prohibit ideal outcomes (Riekert et al, 2013; Mirowsky, 2017). Additionally, people often confuse diet as a change in eating pattern for health purposes with an attempt to solely reduce weight. It is uncontentious that dietary habits have an impact almost every disease and health issue (Marques-Vidal et al., 2018), with older adults considered the most vulnerable for poor nutritional health (Sharkey, 2008). Strategies that consider the diverse human population and encompass a nutritional approach easily adoptable regardless of economic or health literacy state could be effective for addressing public health concerns and promote better health and wellbeing with lower health care costs (Segal & Opie, 2015). For those reasons, fasting regimens are potential eating patterns to evaluate for health outcomes, as its focus is on the timing of eating and not specifically the content itself.

Fasting regimens incorporate many different variations of eating patterns that typically have prolonged time periods with little to no caloric intake without starvation or causing malnutrition. There is not one clear or universal fasting regimen that has shown to benefit health in any population, especially those that are vulnerable. This dissertation focused on two specific vulnerable populations, older adults and individuals with autoimmunity, a chronic disease. The primary objectives of this dissertation were to first, review the literature to examine what types of fasting regimens have been done in adults with any autoimmune disease and organize the outcomes of the studies. Second, to initiate a pilot trial in overweight, sedentary older adults using a TRF regimen for four weeks to determine if inflammatory biomarkers were affected. Third, to assess challenges participants may have faced during the TRF intervention through
weekly phone calls and an in-person interview to gather information on application of TRF in a real-world setting directly from the participant.

**Scoping Review**

A scoping review was done to examine the literature on fasting regimens to therapeutically treat symptoms of autoimmunity in humans. Standard protocol for scoping reviews was followed and had broadly defined research questions, included all study types, developed inclusion and exclusion criteria post hoc at study selection stage, and lastly a chart was created to summarize key findings (Arskey et al., 2005; Colquhoun et al., 2014). Comprehensive and structured searches of the literature to maximize recall and decrease bias were done using seven search engines.

This investigation revealed a limited amount of existing studies despite spanning over four decades. Although there are over 100 types of autoimmune disorders, this review shows that only a handful have looked at fasting regimens as a treatment modality for symptoms from autoimmunity. Additionally, although the inclusion criteria were broad, only nine studies were relevant. These studies included multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, and fibromyalgia. The majority of the studies do suggest that fasting is safe, well tolerated, and has a positive impact on self-reported symptoms (most showing long term) in these participants. No major side effects were reported, only transient complaints including headache, nausea, lightheadedness and fatigue. Fasting regimens in the selected studies were all continuous with most classified as either a total fasting regimen (not including any caloric intake), or a subtotal fast (allowing some caloric intake from fruit and vegetable juices) and lacked in other methods. All studies represent a single term of fasting; long-term or repeated types of fasting regimens should be evaluated in the future.
Symptoms from disease activity improved in nearly all studies, including joint stiffness, fatigue, and overall pain. Although subjective, this is valuable for a population that will live with a life-long condition which affects quality of life. There were no negative effects on any diseases in any of the studies. Adherence was near perfect in the studies that reported it, however, these were in medically supervised in-patient settings.

There were few quantitative measures supporting any significance in the findings, however, weight and blood pressure decreased in the reporting studies. Despite the many limitations, these studies do offer a foundational framework to support future human randomized trials. Millions of individuals suffer from autoimmunity and accompanying symptoms; it is crucial to determine if fasting regimens can be effective as a complementary treatment to standard of care. Fasting regimens are also relatively cost-free and easy to implement with approval and guidance of a health care provider.

**Inflammation and Older Adults**

To our knowledge, this is the first study to examine the effects of a time restricted eating pattern on inflammatory markers in overweight, older adults (ages 65 and older). Low grade chronic inflammation is a modifiable risk factor and identifying feasible interventions to prevent increased threat for disability, impaired mobility, slower walking speed, and an array of deleterious health outcomes in older adults is crucial.

This study found that there were no significant changes in CRP, IL-6, or ferritin. Noticeably, from a less conservative viewpoint, it is valuable to know inflammation measured by serum ferritin did have a statistical trend and increased slightly ($p < .075$) with this short term TRF regimen. Numerous studies have argued that in situations involving factors such as small samples or samples with low statistical power, there are sound reasons to consider adopting a larger alpha (Schumm, 2010). Ferritin is jointly used clinically as a marker for inflammation and
for iron deficiency in older adults. Serum ferritin assay is the best single blood test for the diagnosis of iron deficiency (Choi et al., 2005), yet the interpretation in older adults is complicated sometimes due to ferritin naturally increasing with age. Iron deficiency anemia in older age has undesirable health outcomes, including increased susceptibility to falling and depression (Fairweather-Tait et al., 2014), therefore, monitoring ferritin in older adults during a fasting regimen could prevent iron deficiency from developing.

The study participants had low-normal ferritin levels at baseline. As ferritin is an acute phase reactant, the increase found in our study suggests future fasting regimen trials should monitor ferritin as an inflammatory marker. The participants in this trial remained in the low-normal range and were neither close to iron deficiency (low ferritin) nor represented an inflammatory state (high ferritin). Future trials implementing a fasting regimen should consider enrolling participants with elevated inflammatory markers at baseline to better understand the effects TRF could have on chronic inflammation. Additionally, low grade chronic inflammation is asymptomatic, therefore, monitoring trends over time using inflammatory biomarkers in the older population is suggested due to ‘inflammaging’ (Calder et al., 2017).

Most observational studies and clinical trials have used CRP as a marker of inflammation because it is relatively stable and easy to measure (Musunuru et al., 2008). Dietary patterns may influence the risk of diseases through the effects of CRP, with substantial evidence for an inverse relationship between adherence to anti-inflammatory eating patterns and CRP. However, this has only been shown after three months or more of dietary change (Neale et al., 2016). This was a pilot study and lasted just four weeks, which suggests longer trials are needed for CRP to be accurately evaluated in a TRF regimen.
The non-significant results from IL-6 are not surprising, as this marker generally only decreases with at least a 5% weight loss (Heggen et al., 2014). Although significant weight loss of 2.6 kg was reported in this four-week trial (Anton et al., 2019), it was an average of 3% of total body weight, and possibly one explanation as to why this inflammatory marker was not altered.

**Lessons Learned from a Pilot Trial**

The goal of this chapter was to gain valuable insight directly from participants on the real-world advantages, disadvantages, and challenges from adopting a TRF fasting regimen. As this was the first study to evaluate TRF in older adults, the results can support trial design in future studies. Baseline visit included in-person directions on the TRF protocol and participants were sent home with a dietary log to record first and last caloric intake, as well as an animated flyer to depict food items that were allowed and not allowed during fasting windows.

On the flyer, “Go Foods” were written in green (water, diet soda, unsweetened teas, sugarfree gum, black coffee) and “No Foods” were written in red (anything with calories including coffee creamer, sweet teas, alcohol, snacks, drinks with calories). The aim of the colorful flyer was to assist in common misconceptions of what would constitute as caloric intake to ensure avoidance during fasting times.

Weekly phone calls were made by the trial interventionist to each participant to check on adherence by going over intake times for each day that week, assist them in problem-solving any challenges they were experiencing, and monitor for adverse events. A semi-structured interview guide was used in the calls and included open-ended questions and flexibility for casual conversation. This allowed for participants to talk freely about aspects that could have otherwise been overlooked yet affected by the regimen such as, spousal support, social events, and snacking that participants did not realize was breaking protocol. Additionally, the conversations
revealed pre-existing medical conditions unknown at enrollment including weekly cold-laser therapy for hip and knee pain and bi-weekly epidurals for back pain and trouble walking that could have affected some of the other outcomes of the study. The phone calls were enjoyed by the participants and valuable in obtaining descriptive information for future trials. Exit interviews were also conducted by the interventionist which further elaborated on the weekly phone guide and asked about future adoption of TRF. Most participants said they would continue, but would not adhere during vacations, holidays, or family celebrations.

Comprehension of the fasting regimen was low with seven participants continuously misunderstanding fasting guidelines, specifically that foods with calories were not to be consumed during fasting times. Motivation to follow protocol was strongly guided by weight loss, as most participants thought this was a weight loss study. Adaptation to TRF has challenges due to vacations, doctor appointments, long commutes, and social events, however spousal encouragement was the most supportive factor. Participants stated that support from close family members was pivotal in maintaining the TRF regimen.

There were limitations, mostly including problems contacting participants via telephone. Response bias is also a possible limitation in this study as participants may have only reported what they thought the interventionist wanted to hear in the interviews, or second guess what the interventionist was asking and altered their answers. Lastly, by nature, people tend to remember negative events more than positive events. Since there was only one call completed per week, it is possible that some information was forgotten during the phone call and more negative than positive events were relayed.
The three most prominent lessons learned from this TRF pilot trial in overweight, sedentary older adults were comprehension of the eating pattern and guidelines, motivational factors to adhere to the fasting regimen, and adapting to the new lifestyle.

Clear and complete understanding of the defined fasting regimen and guidelines for the intervention is essential for compliance. Weekly interaction is suggested to reiterate and reinforce behavioral guidelines for both diet and self-report measures in the initial phase of the intervention (Hartman et al., 2016). In addition, regular contact is needed to offer behavior modification strategies and monitor for adverse events as needed. Health literacy in older adults is notoriously low from natural cognitive decline (Fernandez et al., 2016), and additional measures should be taken to supplement comprehension of a fasting regimen and provide support in implementing the lifestyle as there were many concerns in this pilot.

Overall Findings

This dissertation provided a first step in associating vulnerable populations with fasting regimens and will add to the literature with the study findings. No studies have looked at fasting to reduce chronic inflammation in autoimmune diseased populations as a therapeutic modality to treat related symptoms. The positive findings from the scoping review offer a foundation to support future pilot trials on fasting regimens as a complementary treatment to autoimmune related symptoms through self-report measures and inflammatory biomarkers.

Inflammation findings were not significant, although serum ferritin did have a statistical trend, and should be evaluated periodically over longer time frames to be used to demonstrate the value of TRF as a possible way to treat chronic inflammation in older adults. Participants should also be enrolled with elevated levels of inflammation at baseline. Descriptive analysis of TRF can support adherence and design of larger trials in older adults from the participant’s perspective in a real-world setting. Long term adherence and health outcomes are unknown.
Linking autoimmune disorders, inflammation, and participant views for best design to a fasting intervention could possibly help vulnerable populations as a complementary treatment to standard of care that is feasible and inexpensive. Health is impacted by multiple psychological, behavioral, social, and cultural factors, it is important to address this from bench to bedside to achieve social and behavioral change.

Most participants enjoyed the simplicity of a timed eating regimen and stated willingness to continue this eating pattern with slight modification such as decreased fasting times or a weekly ‘cheat’ day. Individuals with autoimmunity might have different views since chronic health conditions affect quality of life and can motivate individuals to adhere to an intervention.

Innovative ways to assist in comprehension to fasting regimens in older adults would be beneficial. This could include increasing phone calls per week, providing more detailed food diaries, or including spouses or close family members at baseline so the protocol is explained to and heard by more than one individual.

It is apparent that the individual does not function on his or her own but is affected by various determinants of health. Although around for centuries, fasting has quickly be associated with “fad diets”; with further studies to evaluate the potential to benefit health outcomes outside of weight loss this can be deterred. Human research has been extremely limited for fasting interventions, with only five different autoimmune diseases being evaluated for symptom relief using fasting regimens in the literature and this being the first study applying TRF in older adults. The possible approach to manage or prevent chronic and age-related symptoms through various complementary therapies, particularly dietary lifestyle modifications, apart from traditional pharmacological interventions is warranted.
Consideration of biological, psychological, environmental, and social factors could remove limitations and offer a broad perspective on current behavior and suggest appropriate modifications to achieve the best outcome in an intervention (Davis et al., 2015). Ultimately, success in any lifestyle modification depends on factors such as intention, motivation, and willingness paired with confidence and support for long term adherence and possible beneficial health outcomes (Moreira et al., 2011). Application of social and behavioral theories to inform and guide interventions to best meet the needs of an individual or population should be utilized.

**Limitations**

To elaborate previous limitation in this text: this dissertation had many limitations, notably, small samples in all of the studies. This is due to the limited research available on fasting regimens specifically in people with autoimmunity. Additionally, pilot studies are inherently small, with not knowing the feasibility, acceptability, and safety of modifying diet in older adults and individuals with chronic health conditions. The Time to Eat trial was short, which may have restricted findings in inflammation. Lastly, it was unknown that older adults would have issues in following protocol and the interviews were valuable to aid in follow-up studies.

**Future Research**

With millions of individuals suffering from symptoms of autoimmune diseases, and the older adult population steadily increasing, it is crucial to research the possible effectiveness of fasting as a complementary therapy that is relatively cost-free and easy to implement with initial guidance. The information from the scoping review and Time to Eat pilot study are valuable for early phase research in the translational cycle. Future studies should be done to progress through the stages to test for clinically meaningful effects measured in ideal designs, understand if it is
effective in real world settings, and finally to conduct dissemination and implementation studies before any fasting regimen is widely recommended and used in public health initiatives.
LIST OF REFERENCES


Kell, D. B., & Pretorius, E. (2014). Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. *Metallomics, 6*(4), 748-773.


74


Varady, K. A. (2011). Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss?. *Obesity reviews, 12*(7), e593-e601.


BIOGRAPHICAL SKETCH

Stephanie Lee is an alumnus of Valparaiso University where she obtained a Bachelor of Science in psychology with a minor in human biology. She is an active scholar for the prestigious Jack Kent Cooke Foundation where she has received awards for her undergraduate as well as graduate studies.

Stephanie pursued her PhD in Public Health with co-concentrations in social and behavioral sciences and clinical and translational science and will graduate in August 2019. Her research interests include understanding dietary influence on disease susceptibility and as therapeutic intervention, autoimmune disorders, chronic inflammation, and improving health related quality of life for people with chronic illness. Stephanie is training at the Institute on Aging where she assists with ongoing clinical trials. Complementary and integrative health are the core of her research passions, as well as bringing community awareness to social determinants of health.