

BELIEFS ABOUT THE IMPACT OF EXCESS BODY WEIGHT ON
BIOPSYCHOSOCIAL FUNCTIONING IN MULTIPLE
SCLEROSIS PATIENTS

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By

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ABSTRACT

Background: Recent research indicates that obesity may exacerbate certain symptoms of Multiple Sclerosis (MS). Nevertheless, little research has examined patients' perceptions of how obesity may impact their MS symptoms. If MS patients are unaware of the relationship between obesity and MS symptoms, they may be less motivated and/or adherent to health behaviors that could reduce their symptoms.

Aims: (1) To determine whether functional differences exist between healthy weight and overweight/obese MS patients; (2) To examine patient beliefs about the impact of health behaviors on MS; (3) To explore MS patient beliefs regarding the impact of weight on symptom severity ; and (4) To explore the amount of exercise patients with MS would be willing to engage in to reduce their MS symptoms.

Methods: 81 MS patients completed neuropsychiatric tests and questionnaires. Height, weight, and waist circumference were measured to calculate body mass index (BMI) and waist-to-height ratio (WTHR). Participants completed novel measures designed to assess their beliefs regarding how weight gain or loss may impact their MS symptoms, and their willingness to exercise for symptom improvement.

Results: There was a significant association between WTHR and depression. There was no association between WTHR and the composite measures of cognition, physical function, or a singular measure of anxiety. As a whole, patients endorsed the belief that

excess body weight contributes to worse MS symptoms and progression. Patients reported logical increases in exercise willingness as the percentage of hypothetical improvement increased. Patients with higher current symptom severity reported increased willingness to exercise for higher levels of symptom improvement relative to patients with lower current symptom severity.

Discussion: This was the first study to examine patient beliefs about the impact of weight on disease symptoms and how much patients are willing to exercise to improve their symptoms. Results showed that patients with MS believe that excess body weight negatively influences disease symptoms. Furthermore, patients reported increased willingness to exercise as the percentage of proposed symptom improvement increases. This suggests that providing patients with information on the amount of improvement to expect from exercise and dietary interventions may enhance motivation for health behavior change.

APPROVAL PAGE

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CHAPTER 1

REVIEW OF THE LITERATURE

Historically, medicine relied upon biological explanations of disease(Deep, 1999), which assume that pathology is due to a specific etiology, such as a virus or bacteria. Clinicians and researchers were challenged in the late 1970s to incorporate environmental, social, and behavioral factors into their conceptualization of disease(Engel, 1977). Since that time, the biological model of disease has shifted toward a more integrated approach, often referred to as the biopsychosocial model(Engel, 2012). This shift has opened the door for greater exploration of the multi-factorial causes of disease. In particular, scientific understanding of idiopathic diseases has improved as greater efforts are made to examine epigenetic factors that incite disease as well as social or environmental factors that exacerbate disease activity(Engel, 2012).

Multiple sclerosis (MS) is the most common neurodegenerative illness among young adults(Steinman, 2009), yet, it is an enigmatic condition. Many of the risk factors for the disease are known, but researchers cannot accurately predict its progression(Ascherio, 2013; Ascherio & Munger, 2007a, 2007b, 2010; Ascherio et al., 2014; Munger, Chitnis, & Ascherio, 2009). Recent research has highlighted a potential link between obesity and increased risk for MS or worsened disease course and symptoms via the hormone leptin(Matarese, Carrieri, Montella, De Rosa, & La Cava, 2010; Matarese, Procaccini, & De Rosa, 2008). Examination of the impact of obesity on disability in MS may illuminate important behavioral factors that can be addressed to improve physical, emotional, and cognitive symptoms among MS patients. Moreover, a better understanding of how patients

perceive obesity contributing to their symptoms may be useful when developing diet and exercise interventions that require ongoing adherence.

The following literature review will first serve as an introduction to the etiology, symptoms, and patient beliefs of MS. Next, we will examine obesity and discuss research linking MS and obesity via immunoregulatory and hormonal mechanisms.

Multiple Sclerosis

MS is an autoimmune/neurological disease that attacks portions of the central nervous system (CNS) leading to inflammation and destruction of the myelin sheath on neurons(Sospedra & Martin, 2005). Damage to the myelin sheath disrupts communication within the brain, and between the brain and the rest of the body(Corthals, 2011). Symptoms caused by this disruption are variable and can include: tingling, numbness, weakness, and problems with coordination, balance, vision, speech, memory, cognitive processing, decision making, mood stability, and lack of energy. At least 400,000 individuals in the United States alone have MS, and more than 2.5 million people are believed to have MS worldwide(Braley & Chervin, 2010).

Disease Characteristics

Obesity as a potential risk factor for developing MS

Children who are overweight prior to the age of 20 have a two-fold increased risk of developing MS in comparison to their healthy weight counterparts(Langer-Gould, Brara, Beaber, & Koebnick, 2013; Munger et al., 2013). Risk of MS has been shown to increase by 1.61-1.95 fold for 7-13 year old girls who are \geq 95th percentile of BMI when compared to those below the 85th percentile(Munger et al., 2013). Research in the US and Europe has indicated that obesity in late adolescence/early adulthood may be especially dangerous as an

obese weight status at age 18 is associated with a 71 percent increased risk of MS(Munger et al., 2009). Some research indicates that the link between obesity and increased risk of MS may be especially pronounced in females(Hedström, Olsson, & Alfredsson, 2012; Munger et al., 2009). Females typically have a higher percentage of body fat than males(Blaak, 2001) and thus, increased weight, along with hormonal differences between men and women, may account for differential prevalence rates among genders(Sospedra & Martin, 2005). This is further supported by studies which show that MS disease activity wanes during pregnancy, but worsens during a woman's menstrual cycle, following pregnancy, and when estradiol levels are high but progesterone levels are low(Wingerchuk & Rodriguez, 2006; Zorgdrager & De Keyser, 1997, 2002).

Gender Differences

Women are diagnosed with MS at rates two to four times higher than men, depending upon the region of the world in which they live. Current estimates show that in northern latitudes as many as 4.55 women are affected for every man. In Canada the ratio of women-to-men afflicted with MS is 3.2:1, some areas of Europe have ratios as high as 3.77:1, and the overall worldwide ratio was 2.6:1 in the year 2000(Alonso & Hernán, 2008; Boström, Stawiarz, & Landtblom, 2013; Ramagopalan et al., 2010; Trojano et al., 2012). Researchers speculate that women who live in extreme latitudes are less frequently exposed to the sun and that their cosmetic makeup with UV protection further prevents exposure to sunlight and consequently decreases vitamin D levels(Corthals, 2011).

Potential Environmental Contributors to MS

A strong inverse relationship has been shown between sunlight exposure and the incidence of MS ($r = -.80$)(Acheson, Bachrach, & Wright, 1960). Researchers believe that

sunlight and therefore vitamin D, exerts protective effects on individuals at risk for MS(Ascherio, 2013). Supporting this assertion, the hormonal form of vitamin D₃, 1,25-dihydroxyvitamin D₃, can prevent the mouse model of MS known as experimental autoimmune encephalomyelitis (EAE)(Hayes, Cantorna, & DeLuca, 1997). The hormonal form of vitamin D₃ is believed to possess immunoregulatory effects that protect against MS and may reduce MS symptoms following vitamin D supplementation(Correale, Ysrraelit, & Gaitán, 2009).

The geographical based incidence of MS may also be explained by factors besides vitamin D. Countries located further from the equator are predominantly more wealthy and westernized and possess drastically different lifestyles than other under-developed countries(Cantorna, 2008). Differences in hygiene and dietary standards between westernized and undeveloped countries may contribute to increased risk of MS. An ongoing case-control study of environmental factors associated with pediatric MS found that pediatric MS patients consumed lower daily levels of fiber, iron, and dairy relative to controls(Pakpoor et al., 2016). Furthermore, low iron intake was significantly associated with an increased risk for MS(Pakpoor et al., 2016). However, groups did not differ in their daily consumption of sodium, fats, proteins, carbohydrates, sugars, fruits and vegetables(McDonald et al., 2016; Pakpoor et al., 2016). Indeed, the relationship between food intake and immune function and risk for MS warrants further study.

The hygiene hypothesis is an alternate explanation of the geographical incidence of MS. It suggests that natural, uninhibited exposure to disease is protective and allows for proper immune response development(Sotgiu, Angius, Embry, Rosati, & Musumeci, 2008). Individuals who live in westernized societies (i.e. many of which are located further from the

equator) are not exposed to the kinds of infections and diseases that those in under-developed societies are(Cantorna, 2008). Increased cleanliness, sanitation, and vaccinations may prevent the body from learning how to appropriately regulate immune function. This hypothesis has been supported by studies which demonstrate that animals exposed to worm infections are not susceptible to EAE and that societies experience an upsurge in MS following increased sanitation and eradication of diseases, such as malaria(Cantorna, 2008; Sotgiu et al., 2008).

Significant differences in diet are also found between Western and developing countries. The western diet is packed with foods that are scarcely eaten in developing countries. High levels of sugar, processed carbohydrates, animal fat, red meat, and fried food combined with low fiber and vegetable intake characterize the western diet(Riccio & Rossano, 2015). Long term dietary habits have been shown to significantly affect cellular function and gut microbiota(Riccio & Rossano, 2015). The gut contains between 70 and 80 percent of the body's immune cells and is considered to be the largest immune organ in the body(Vighi, Marcucci, Sensi, Di Cara, & Frati, 2008). Recently, gut system microbiota have been shown to influence extraintestinal biological and immunological functions such as human nutrition, metabolism, and immune-system function(Chassaing & Gewirtz, 2014; Chassaing et al., 2015; Riccio & Rossano, 2015; Vighi et al., 2008). Dietary factors may induce catabolism or anabolism by altering cell metabolism through interaction with transcription factors, enzymes, and nuclear receptors(Desvergne, Michalik, & Wahli, 2006). This may prompt unnecessary degradation or production of proinflammatory cytokines and could possibly mediate disease activity(Chassaing et al., 2015; Desvergne et al., 2006). In addition, research has shown that gut microbiota affect neurological inflammation in EAE by

altering the pro-inflammatory and anti-inflammatory immune response(Y. K. Lee, Menezes, Umesaki, & Mazmanian, 2011). Although diet is unlikely the sole causative factor of MS, it may be an important component that helps to explain, at least in part, the vast geographical differences in incidence.

Diagnosis and Treatment of MS

Patients are typically diagnosed with MS following acute episodes of neurological dysfunction that may be characterized by numbness, tingling, balance problems, dizziness, poor bladder control, spasticity, optic neuritis and/or blurred vision(Confavreux, Vukusic, Moreau, & Adeleine, 2000). MS symptoms may indicate any of several conditions. Clinicians must rule out other potential conditions prior to making a diagnosis of MS since there is *no single test* that will confirm a diagnosis of MS.

Currently, the McDonald criteria for MS are held as the gold-standard guidelines for confirmation of MS(Polman et al., 2011). According to these standards, clinicians must obtain objective evidence of lesions in the central nervous system (CNS) that are disseminated in time and space. Dissemination in time requires that patients experience at least two attacks (episodes of neurological dysfunction that last a minimum of 24 hours), that are at least 30 days apart so that distinct neurological events can be confirmed. Dissemination in space requires that patients express at least two lesions in two separate areas of the CNS. Magnetic resonance imaging (MRI) is used to detect lesions, but cerebrospinal fluid (CSF) and visual evoked potentials are also examined to help support a diagnosis in cases where the clinical or MRI data are inconclusive. MS is most typically diagnosed in patients aged 20-50, with an average age of onset at 34(McFarlin & McFarland, 1982a, 1982b). The majority of patients (≥ 80 percent) are initially diagnosed with a relapsing-remitting subtype of MS

(RRMS), which is characterized by recurrent periods of disease activity followed by a return to normal or nearly normal functioning(Confavreux et al., 2000). MS is a progressive disease and most patients who have RRMS eventually develop a secondary progressive course(Confavreux et al., 2000). Secondary progressive MS (SPMS) is characterized by insidious decline in neurologic function. Patients may still experience exacerbations with some remittance; however gradual decline replaces the stability seen in RRMS between relapses. MS patients can typically expect to experience greater disability the longer they have the disease. In addition, while men are diagnosed less often than women overall, they are more likely to be diagnosed with primary progressive MS (PPMS)(Miller & Leary, 2007). PPMS is a more aggressive MS subtype that is characterized by unremitting neurological and physical decline.

Though there is no cure for MS, pharmacotherapies are available that slow disease progression, reduce exacerbation severity, decrease the formation of new brain lesions, and reduce exacerbation frequency. Several FDA approved injection-based and oral medications are currently available for the treatment of RRMS(Corboy, Goodin, & Frohman, 2003). Symptom-specific medications are also available, and are effectively used to help patients manage the disease on a day-to-day basis and improve quality of life. Finally, psychotherapy, physical therapy, and occupational therapy are frequently used to treat resulting emotional, physical, and cognitive difficulties (Solari et al., 1999; Steultjens et al., 2003; van Kessel et al., 2008).

Physical Functioning in MS

MS patients endure a wide array of physical symptoms. Damage to the brain's grey matter, myelin and axons in different areas of the brain produces a variety of symptoms

throughout the body that range from mildly annoying to severely debilitating. These symptoms are often associated with neurologic disease processes, but are also commonly found among patients with obesity. It is possible that the common MS symptoms described below are exacerbated by the comorbid presence of obesity(Matarese et al., 2008).

Mobility

Mobility is often problematic for MS patients due to symptoms which impede the body's ability to move fluidly, safely, and effectively. Spasticity, unstable balance, and muscle weakness commonly interfere with walking, exercise, employment, and daily living activities(Hobart, Riazi, Lamping, Fitzpatrick, & Thompson, 2003; Martin et al., 2006; Messier, 2008; Messier et al., 1994; Rizzo, Hadjimichael, Preiningerova, & Vollmer, 2004).

Spasticity

MS patients experience spasticity which includes muscle spasms, feelings of stiffness or tightness, and difficulty initiating and/or controlling muscle movement(Rizzo et al., 2004). Spasticity most often occurs in the legs and manifests in two forms: flexor spasticity and extensor spasticity. Flexor spasticity involves the hamstrings and hip flexors and is characterized by bent knees and hips that are difficult to straighten. Extensor spasticity involves the quadriceps and adductors and is characterized by straight hips and knees and legs that remain extremely close together and may cross over at the ankles. Spasticity occurs due to imbalanced inhibitory and excitatory neuro-muscular input leading to hyperactivity in the muscles. 67 percent of MS patients experience minimal to moderate spasticity while 13 percent report severe spasticity(Rizzo et al., 2004). At least one-third of MS patients report that they must modify or remove certain daily activities due to their spasticity(Rizzo et al., 2004).

Balance

Poor balance and gait dysfunction in MS patients is evidenced during the gait cycle in temporal-spatial gait parameters of velocity, cadence, double limb support, and stride length(Hobart et al., 2003). MS patients walk at reduced speeds, with shorter stride length and increased double limb support compared to patients without MS(Martin et al., 2006). These aberrations in movement are considered to be indicators of instability. In particular, these temporal-spatial gait parameters have been associated with worse balance(Winter, Patla, & Frank, 1990). Other indicators of malfunction include knee and ankle kinematics, and aberrant tibialis anterior and medial gastrocnemius activity. Restricted ankle range of motion that is not attributable to reduced walking speed has been found in MS patients. Additionally, MS patients show aberrations in timing and amplitude of tibialis anterior and medial gastrocnemius throughout the duration of a stride(Martin et al., 2006). This combination of factors is a marker of compromised walking stability that hinders general mobility among MS patients. Mobility loss can be one of the most disabling symptoms of MS. Reduced mobility is related to loss of independence, loss of employment, increased need for caregivers, and reduced quality of life(Dunn, 2010). Decreased mobility may also exacerbate other symptoms associated with MS such as bowel/bladder problems, edema, numbness and tingling, muscle tightness/weakness, and decreased heart and lung function(Motl, 2014).

Weakness

Many MS patients experience muscle weakness. Complaints of a foot dragging or the feeling that one's arms or legs feel "heavy" are common in MS. Weakness may be due to deconditioning from mobility impairments related to pain, fatigue, gait problems, poor

balance, or reduced muscle activity(Dalgas, Stenager, & Ingemann-Hansen, 2008). Weakness may also result from neurological degradation caused by disease activity. Damage to nerve fibers may impede the communication of neuroelectrical signals from the brain to the muscle and decrease strength. Clinicians and researchers highlight continued movement and exercise as a preventative mechanism for maintained muscular strength, with the understanding that reduced physical activity may lead to increased weakness, pain, and movement difficulty(Dalgas & Stenager, 2012; Dalgas et al., 2008).

Fatigue

Fatigue has been labeled the most common and most debilitating symptom of MS(Induruwa, Constantinescu, & Gran, 2012). It has been defined as “a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with activities of daily living(Kos, Kerckhofs, Nagels, D'hooghe, & Ilsbroukx, 2008).” Fatigue may be primary (i.e. caused by disease activity) or secondary (i.e. stemming from conditions related to the disease such as sleep disturbance, pain, spasms, etc.). Up to 90 percent of MS patients report problems with fatigue(Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Vucic, Burke, & Kiernan, 2010) which results in significant cost to patient productivity, employment, activities of daily living and overall quality of life(Bralely & Chervin, 2010). Because fatigue is considered the most “debilitating” component of MS, it warrants more in-depth exploration. Controllable factors, such as carrying excess body weight, may be linked to added fatigue in MS and require more study. MS clinicians/researchers discuss two forms of fatigue, cognitive and physical, separately.

Cognitive Fatigue

Cognitive fatigue is defined as a “psychobiological state caused by prolonged periods of demanding cognitive activity (Marcora, Staiano, & Manning, 2009).” It has been positively associated with destruction of neural tissue. MRI and PET studies have shown that grey matter pathology of the cerebral cortex and deep structures (e.g. thalamus; caudate of basal ganglia) is associated with increased fatigue in MS⁶¹. Atrophy of the parietal cortex has also been associated with fatigue (Pellicano et al., 2010). Damage to axons results in reduced connectivity among neurons in the central nervous system. The ratio of N-acetylaspartate (NAA) to creatine is used as a proxy for axonal damage. Findings from proton magnetic resonance spectroscopy indicate that lower levels of NAA in proportion to creatine is associated with greater fatigue in MS patients (De Stefano et al., 2001; Tartaglia et al., 2004). These results support the theory that patients with axonal damage must recruit additional neural pathways and cortical areas to complete tasks. This increased expenditure of neuronal energy is believed to underlie the experience of cognitive fatigue and excessive effort required to complete activities (Induruwa et al., 2012).

Aberrations in neural activity within the frontal lobes, thalamus, and basal ganglia have also been postulated to underlie cognitive fatigue (Chaudhuri & Behan, 2000). fMRI studies have shown increased activation in basal ganglia, frontal areas including superior, medial, middle and inferior regions, parietal regions (precuneus and cuneus), thalamus, cingulate motor area, and anterior cingulate (DeLuca, Genova, Hillary, & Wylie, 2008). This increased activation is believed to indicate the need for increased effort in the presence of fatigue. Conversely, other studies have found significant deactivations in regions associated with movement and motor planning/execution (Filippi et al., 2002). Importantly for this

project, research has indicated that the experience of cognitive fatigue intensifies both the perception of physical fatigue as well as reduced physical performance. Patients with cognitive fatigue experience exhaustion from exercise sooner and report greater effort output compared to patients who are not cognitively fatigued (Marcora et al., 2009). This suggests a crucial relationship between cognitive and physical fatigue may exist, such that the experience of one increases the likelihood of the other and may create a cycle that perpetuates sedentary and unhealthy behaviors.

Physical Fatigue

Pro-inflammatory cytokines (e.g. Interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), and interleukin 1, 6, and 10) are believed to contribute to physical fatigue in MS. MS patients display higher levels of IFN- γ , TNF- α , and interleukin-6 than non-fatigued MS patients (Braley & Chervin, 2010; Induruwa et al., 2012). The endocrine system may play a role in MS-related fatigue. Increased reactivity of the hypothalamo-pituitary-adrenal (HPA) axis, higher levels of adrenocorticotrophic hormone (ACTH) and lower levels of dehydroepiandrosterone (DHEA) have been demonstrated in MS patients with fatigue when compared to those without fatigue (Gottschalk et al., 2005; Téllez et al., 2006). MS patients often report feeling less fatigue while on corticosteroids. Corticosteroids mimic hormones and reduce inflammation when given in high doses. Researchers believe that the hormonal mechanism of action by corticosteroids further supports a potential endocrine role in the development of fatigue (Braley & Chervin, 2010).

Emotional Functioning in MS

MS patients experience depression and anxiety at higher rates than in the general population and even compared to patients with other chronic conditions (Siegert &

Abernethy, 2005). The lifetime prevalence for depression in MS is 50 percent, with a point prevalence of 20 percent(Siegert & Abernethy, 2005). Most patients with MS develop depression and anxiety after the onset of their disease, which suggests that biosocial factors of MS may be causal to the development of psychological problems(Feinstein, Magalhaes, Richard, Audet, & Moore, 2014; Ron & Logsdail, 1989).

Depression and anxiety have been shown to increase both morbidity and mortality among MS patients. Comorbid anxiety and depression have been associated with greater somatic complaints, social difficulties, decreased quality of life, and increased thoughts of suicide(Brown et al., 2009; Feinstein et al., 2014). Research on suicide indicates that the proportion of suicides among MS patients is higher (in one study up to 7.5 times higher(Sadovnick, Eisen, Ebers, & Paty, 1991)) than in the age-matched general population(Siegert & Abernethy, 2005). Another study with the Danish National Registry of Cause of Death found that 25 percent more MS patients died by suicide over a 32 year period than would be expected for an age adjusted group of that size(Stenager et al., 1992).

Genetic, immunologic, biochemical, and psychosocial factors are known contributors to psychiatric difficulties in MS, but recent research indicates that neurological and structural changes due to MS account for the most variance (42 percent) in MS depression(Feinstein et al., 2014). MRI studies have shown that hypointense lesions in superior frontal and superior parietal regions, along with atrophy in the frontal lobes and enlarged third and lateral ventricles are related to the development of depression in MS(Bakshi, Czarnecki, et al., 2000). Another study found that hyperintense lesions in medial inferior frontal regions along with atrophy in dominant anterior temporal areas was associated with depression in

MS(Feinstein et al., 2004). These findings highlight the importance of brain atrophy in the pathogenesis of MS-related depression.

Hyperactivation in the HPA axis in combination with high levels of cortisol, ACTH, DHEA-sulfate have also been linked to depression in MS(Fassbender et al., 1998).

Dysfunction in the immune system has been recently theorized to underscore depression in MS. Increased circulating levels of proinflammatory cytokines (TNF, IL-1, IL-6) activate the HPA axis and can cause the high levels of ACTH and DHEA-sulfate described above(Gold & Irwin, 2009; Sukoff Rizzo et al., 2012). Researchers speculate that proinflammatory cytokines cause depression by reducing levels of serotonin released into the synapse(Kim et al., 2007). This reduction in serotonergic function may also disrupt noradrenergic and serotonergic systems that antidepressants are designed to modulate(Craddock & Thomas, 2006).

Antidepressant medications are frequently used to treat depression in MS and research has shown their effects to be approximately equivalent to those seen in the general population with depression(Feinstein et al., 2014; Feinstein, O'Connor, Gray, & Feinstein, 1999). Another treatment, cognitive behavioral therapy, has been shown to improve depression and anxiety among MS patients when used in isolation or in combination with psychotropic medications(Feinstein et al., 2014). Research on exercise for the treatment of depression and anxiety in MS is currently being conducted and may provide benefits that extend beyond neuropsychiatric improvement into the domains of quality of life, physical health, and cognitive function(Padgett & Kasser, 2013)

Cognitive Functioning in MS

Cognitive impairment afflicts between 40 and 60 percent of MS patients(Feinstein et al., 2014). Increasing cognitive impairment is associated with disease progression such that patients in later stages of the disease (SPMS versus RRMS) typically experience the most severe cognitive dysfunction. Commonly observed cognitive difficulties include problems with memory, processing speed, attention, executive control, and impulsivity(Riccitelli et al., 2011; Tinnefeld et al., 2005). These cognitive difficulties are, in turn, associated with impairment in one's ability to maintain employment, complete everyday tasks, sustain meaningful relationships, and plan effectively for future events(Chiaravalloti & DeLuca, 2008)

Processing speed

Up to 50 percent of MS patients experience reduced information processing speed(DeLuca, Chelune, Tulskey, Lengenfelder, & Chiaravalloti, 2004). Impairment is common on tasks like the symbol digit modalities test and paced auditory serial addition task (PASAT)(Paul, Beatty, Schneider, Blanco, & Hames, 1998). However, when time to process information is removed, RRMS patients show accurate performance on tasks that assess learning and memory(DeLuca et al., 2004; Demaree, DeLuca, Gaudino, & Diamond, 1999). This indicates that the basic ability to process, encode, and manipulate information is still intact among most RRMS patients. For this reason, information processing speed is frequently considered the primary cognitive deficit in RRMS. Eventually, information processing deficits reach a critical level in which other abilities (e.g. working memory) are impaired beyond what can be explained by deficient processing speed(Chiaravalloti & DeLuca, 2008; DeLuca et al., 2004; Demaree et al., 1999).

Memory

Impaired memory is one of the most cited cognitive complaints among MS patients with 40 to 65 percent reporting some form of memory impairment (Chiaravalloti & DeLuca, 2008). Memory includes the ability to acquire, retain, and retrieve information (Thornton & Raz, 1997). MS patients can have a problem with acquisition and effective encoding of information, but are often able to retrieve information as effectively as patients without MS (DeLuca, Barbieri-Berger, & Johnson, 1994). In addition to working memory difficulties, MS patients may display other varied forms of memory impairment. Research has found impairment in immediate and delayed recall, episodic, verbal and spatial memory among different samples of MS patients (Andrade et al., 1999; Arnett & Strober, 2011; Brissart, Morele, Baumann, & Debouverie, 2012). Research has demonstrated that the varied patterns of neurological atrophy, particularly in grey matter, partially accounts for differential memory impairments seen in MS patients (Benedict et al., 2006; Benedict, Ramasamy, Munschauer, Weinstock-Guttman, & Zivadinov, 2009).

Executive Function

Nearly 25 percent of MS patients experience problems with organization, planning, working memory and abstract reasoning (Chiaravalloti & DeLuca, 2008; Foong et al., 1997; Thornton & Raz, 1997). These abilities are commonly known by the broad term, “executive functions”. MS patients can demonstrate deficits in verbal fluency, cognitive estimation, spatial working memory, spatial span, strategic abilities and the Stroop task (Arnett et al., 1997; Foong et al., 1997). Some research has linked executive function disability to deterioration of the frontal lobe (Foong et al., 1997) and axonal deterioration (Foong et al.,

1999), although the exact location of atrophy in relationship to specific executive function deficits has not yet been determined (Foong et al., 1997).

Beliefs about Multiple Sclerosis

Patients define and attribute symptoms differently to their disease and frequently have diverse beliefs about the cause, severity, and progression of disease (Jopson & Moss-Morris, 2003). These attributions are known as *illness representations* and include five core dimensions of identity, cause, consequences, timeline, and cure/control (Jopson & Moss-Morris, 2003). Studies have indicated that how patients process their disease (cognitively and emotionally) impacts their coping strategies and reported physical, emotional, and social disability. These findings have been replicated among numerous patient populations (Chaboyer, Lee, Wallis, Gillespie, & Jones, 2010; Norcini Pala & Steca, 2015; Quiles Marcos, Terol Cantero, Romero Escobar, & Pagán Acosta, 2007; Rozema, Völlink, & Lechner, 2009; Vollmann, Scharloo, Langguth, Kalkouskaya, & Salewski, 2013; Ziarko, Mojs, Piasecki, & Samborski, 2014), including patients with MS when controlling for disease severity (Jopson & Moss-Morris, 2003). Patient beliefs about MS may directly impact engagement in health behaviors and therefore possess special importance, because some behavioral choices (e.g. diet and exercise) may directly or indirectly impact disease progression, cognition, emotion, and physical ability by increasing neuroinflammation, altering brain insulin, and increasing weight (Parrott & Greenwood, 2007).

MS patients experience levels of obesity that are at least as high as those in the general population (Pilutti, Dlugonski, Pula, & Motl, 2012; Slawta et al., 2003). Research estimates that approximately two-thirds of adults in the general population are overweight or

obese(Carmona, 2003). There is overlap between symptoms and underlying proinflammatory processes that may link worsened disease activity in MS with obesity.

Obesity

The prevalence of overweight and obesity in the United States has risen at such an alarming rate that obesity is now considered an epidemic(Carmona, 2003). Nearly two-thirds of adults in the US were overweight or obese in 2007, based on body mass index (BMI), and three-fourths were predicted to meet criteria for overweight or obesity in 2015(Y. Wang & Beydoun, 2007). BMI is a ratio of weight to height used to classify weight status. The World Health Organization (WHO) defines obesity as a condition of excess body fat to the point that health is impaired("Obesity: preventing and managing the global epidemic. Report of a WHO consultation," 2000).

Obesity is a problem of significant global and economic impact. Obese patients cost an estimated 30 to 42 percent more per capita in direct medical expenditures per year than their healthy weight counterparts(Calle, Rodriguez, Walker-Thurmond, & Thun, 2003; Shamseddeen, Getty, Hamdallah, & Ali, 2011). \$147 billion was spent on medical expenditures associated with obesity in 2008(Finkelstein, Trogon, Cohen, & Dietz, 2009). This accounted for nearly 10 percent of total medical expenditures that year. It has also been estimated that indirect economic costs associated with obesity amount to at least 4.3 billion dollars annually(Cawley, Rizzo, & Haas, 2007; Shamseddeen et al., 2011). These indirect costs are typically associated with physical, emotional, and cognitive disability that translates into work absenteeism, loss of productivity, and lost wages. By 2030, it is predicated that overweight and obesity will account for 15.8 to 17.6 percent of total health care costs. This amounts to annual spending between \$860 billion and \$956 billion(Y. Wang, Beydoun,

Liang, Caballero, & Kumanyika, 2008). The harmful impact of obesity at both an individual and global level is related to decrements in physical, emotional, and cognitive function.

Recent research has revealed the devastating impact that excess weight can have on all forms of health(Carmona, 2003).

Environmental Contributions to Obesity

When energy intake supersedes energy expenditure for an extended period of time, the human body accumulates excess weight. This basic “energy imbalance” accounts for the majority of obesity in westernized countries. Importantly, obesity has increased at rates far higher than can be accounted for by genetics alone(Wilding, 2012). In rare instances, genetic and biological syndromes, such as Prader Willi, Bardet Biedl, and Alstrom, lead to obesity(Péruisse et al., 2005). This rarity indicates that social/psychological factors may play an important role in the upsurge of obesity rates over the past few decades. Some of these environmental factors include increased consumption of processed foods, decreased activity levels, endocrine disruptors, use of air conditioning and heat leading to less variability in body temperature, and sleep debt. Commonly used medications, such as psychotropic medications, diabetic treatments, antihypertensives, steroid hormones and contraceptives, antihistamines, and protease inhibitors may also increase the likelihood for obesity(Wright & Aronne, 2012). Although the essential basis of the development of obesity is simple, the varied social-environmental effects are difficult to tackle effectively at both the individual and population level.

Diagnosis and Treatment of Overweight and Obesity

BMI is a ratio of weight to height that is used to clinically classify weight status. BMI has been strongly associated with negative weight-related health outcomes related to

cardiometabolic conditions. BMI values of 25 kg/m² and 30 kg/m² have been designated as the respective cutoff points for overweight and obesity. These cutoffs are founded on recommendations of the National Heart, Lung, and Blood Institutes and North American Association for the Study of Obesity expert committee("Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults," 1998).

Waist-to-height-ratio (WTHR) has also been indicated as a practical and accurate method of overweight and obesity assessment. It uses cutoffs of .40 for low body weight and .57 for severe central obesity(Peng et al., 2013). A general cutoff of .50 for women and .53 for men has been supported as a demarcation between healthy weight and overweight; a ratio of .54 in women and .58 in men indicates obesity (Ashwell & Hsieh, 2005). WTHR has been shown to be superior to BMI in diagnosing obesity, and identifying risk for cardiovascular disease, type II diabetes and metabolic malfunction(Ashwell, Gunn, & Gibson, 2012; Ashwell & Hsieh, 2005; Ashwell, Mayhew, Richardson, & Rickayzen, 2014; C. M. Lee, Huxley, Wildman, & Woodward, 2008; Rodea-Montero, Evia-Viscarra, & Apolinar-Jiménez, 2014). It is particularly sensitive to early signs of health risks when compared to BMI and other measurements of obesity(Ashwell & Hsieh, 2005).

Despite the "basic" energy imbalance that leads to obesity, there is no simple, effective treatment. Advice to exercise more and eat less typically is unsuccessful in the long-term, as few individuals are able to maintain an appropriate balance between diet and exercise(van Dale & Saris, 1989). Numerous prescription and over-the-counter treatments for obesity have been developed, but most are ineffective in the absence of diet and

exercise(Glenny, O'Meara, Melville, Sheldon, & Wilson, 1997; MacLaughlin et al., 2010). Thus, many may act as a boost rather than a cure by suppressing appetite or interfering with the body's ability to store fat, calories, and vitamins. Bariatric surgery is touted as the most effective form of weight loss(Bougoulia, Triantos, & Koliakos, 2006). Roux-en-Y, laparoscopic adjustable gastric banding (LAGB), and gastric sleeve are common procedures that reduce stomach volume and induce weight loss via caloric restriction(Buchwald et al., 2004). Despite success achieved in the first few years following bariatric surgery, many patients (up to 40 percent) cannot maintain the weight loss at seven-to-ten years post-operation(Suter, Calmes, Paroz, & Giusti, 2006). Clinicians continue to highlight the need for multi-faceted obesity treatments including support for diet, exercise, hunger reduction (medicinal or surgical), and psychotherapy to cope with the issues behind emotional eating. Below we outline symptoms of obesity that may overlap with MS.

Physical Functioning in Obesity

Decreased physical functioning and impaired mobility are among the most notable negative consequences of obesity. Overweight and obese patients are at a higher risk for serious and/or life-threatening health problems including: type II diabetes and metabolic syndromes, hypertension, heart disease, stroke, certain types of cancer, gout, sleep apnea, obesity hypoventilation syndrome, asthma, gallbladder problems, osteoarthritis, stress fractures, reproductive problems, and numerous autoimmune diseases(Kopelman, 2007). Excess fat obscures the internal organs and prohibits early detection of risk factors for conditions like cancer, heart disease, and reproductive problems. It also places surplus strain on the bones and muscles of the body which increases the probability that patients will experience pain, injury, and fractures. Breathing problems and circulatory problems are

common among obese patients(Kopelman, 2007). Added pressure and burden on the lungs and circulatory system forces their bodies to work harder when performing autonomic functions. Many patients also experience decreased mobility and increased fatigue due to the added strain of excess weight and fat(Jadelis, Miller, Ettinger, & Messier, 2001; Messier, 2008).

Mobility

Many obese persons experience problems related to mobility(Messier, 2008). There is a strong-positive relationship between obesity and functional impairment, such that as obesity and body fat increase, associated functional impairment mirrors this increase(Messier, 2008). Patients with high levels of body fat are nearly 200 times more likely to experience self-reported mobility-related disability than patients with the lowest levels of body fat (Ettinger et al., 1994). One mechanism by which obesity hinders mobility is osteoarthritis (OA). OA occurs when protective cartilage at the ends of bones is worn down from added weight induced pressure and bones no longer have protective cushioning to separate one another. OA of the knee has been specifically linked to mechanical complications caused by obesity(Messier et al., 1994). Patients with a BMI of 30kg/m² are 6.8 times more likely to develop OA of the knee than healthy weight individuals(Messier, 2008).

Weakness

Muscle weakness contributes to decreased balance and increased risk for falls that lead to injury and hospitalization(Rubenstein, 2006). Obese individuals show significant muscle weakness when compared to their healthy weight counterparts, which may arise from reduced physical activity combined with added strain due to excess body mass. Knee strength

has been compared in obese and healthy weight mid-to older adults. In healthy weight male and female patients, knee strength was 12 percent more of overall individual body weight than in obese patients(Miyatake et al., 2000). Other studies have found strong inverse relationships between obesity and balance such that increased BMI is associated with decreased balance¹³¹ and this effect is likely more pronounced in women(Kejonen, Kauranen, & Vanharanta, 2003).

Balance

Obese patients have been shown to change their gait to improve stability and reduce pressure on knees and joints(Messier, 2008). Stride length and knee extensor torque is reduced in obese patients such that patients with greater BMIs have shorter strides(Messier, 2008). Higher BMI is also associated with increased use of hamstrings to support the knees. This is in contrast to healthy weight patients who primarily use the quadriceps to support their knees. In addition, changes in the feet can increase the risk for injury and discomfort. Obese patients have been shown to walk with their toes pointed outward up to 276 percent more than normal weight patients(Messier et al., 1994). This form of abduction is indicative of a greater bodily emphasis on balance which is necessary with less stability(Chodera & Levell, 1973). Additionally, obese patients exhibit increased rear foot motion (e.g. more pronation range of motion, faster pronation and greater touchdown angle)(Messier, 2008) than normal weight individuals. Foot adjustments commonly made by obese patients have been linked to a five-fold increased risk of heel pain and/or plantar fasciitis(Riddle, Pulisic, Pidcoe, & Johnson, 2003). Overall, greater force is exerted by obese patients which leads to increased strain and injury(Kappus et al., 2015; Messier, 2008).

Fatigue

Controversy surrounds the relationship between fatigue and sleepiness in obesity. Some researchers have argued that they are fundamentally different, while others have argued that they are the same or on the same continuum. In 2005, researchers differentiated fatigue from sleepiness by defining fatigue as a tiredness that does not include greater sleep propensity (Vgontzas, Bixler, & Chrousos, 2006; Vgontzas, Bixler, Chrousos, & Pejovic, 2008). Chronic insomnia, elderly sleep disturbance, and psychogenic hypersomnia are considered to be conditions associated with fatigue while sleep apnea, narcolepsy, and sleep deprivation are conditions associated with increased sleepiness. Obesity research has not differentiated between sleepiness and fatigue historically, and it may be difficult to fully disentangle the two since patients often experience multiple health complications that are associated with fatigue and increased sleep propensity.

Obese patients experience sleep disorders at rates far higher than seen in the general population. In particular, 50 percent of obese patients have obstructive sleep apnea (OSA) and obesity increases the risk for OSA by 50 percent (Lurie, 2011; Romero-Corral, Caples, Lopez-Jimenez, & Somers, 2010). Patients with OSA may experience symptoms that could be interpreted as fatigue, but increased sleep propensity is the differentiating factor (Vgontzas et al., 2006).

Fatigue is believed to originate in obese patients via mechanisms consistent with MS fatigue. In some studies, obese patients with fatigue have demonstrated HPA hyperactivation (Duclos et al., 2001; Mårin et al., 1992; Pasquali et al., 1993), as seen in MS patients. However, researchers propose a more complex model to explain fatigue versus sleepiness in obese patients. They suggest that elevation of proinflammatory cytokines (IL-6)

in conjunction with HPA hyperactivation and depression leads to fatigue among obese patients(Vgontzas et al., 2006). Conversely, they suggest that proinflammatory cytokines (IL-6) in conjunction with HPA hypoactivation and lack of depression lead to sleepiness. Hyperactivation of the HPA axis in conjunction with proinflammatory cytokines is also believed to underlie fatigue in MS(Gottschalk et al., 2005; Téllez et al., 2006; Vgontzas et al., 2006). Given the similar proposed underpinnings, it is likely that obesity combined with MS could produce worse fatigue than experienced by patients who have only one of the two conditions.

Emotional Functioning in Obesity

Like MS patients, overweight and obese patients experience higher rates of mental health problems than those in the general population. Obesity has been associated with an 82 percent increased odds of having depression and 40 percent increased odds of having anxiety(Gariepy, Nitka, & Schmitz, 2010) (Onyike, Crum, Lee, Lyketsos, & Eaton, 2003). Depression and anxiety have been consistently shown to impair productivity and social/relational and physical functioning within the general population(Judd et al., 2000; Klerman, 1989; Klerman & Weissman, 1992). Obesity has also been shown to reduce quality of life by inhibiting functional abilities and impairing physical health(Markowitz, Friedman, & Arent, 2008). Obese patients with comorbid psychological conditions may experience greater overall disability related to social and physical functioning than obese patients without depression or anxiety(Markowitz et al., 2008). The exact relationship between psychological distress and obesity has not yet been disentangled, but researchers propose a bi-directional relationship between the two such that each one may perpetuate and exacerbate the other(Markowitz et al., 2008)

Obesity as a risk factor/cause for depression

Some studies have demonstrated a positive relationship between obesity and depression indicating that more severe obesity is associated with increased depression incidence (Roberts, Deleger, Strawbridge, & Kaplan, 2003; Roberts, Kaplan, Shema, & Strawbridge, 2000). One study found that 15.5 percent of obese patients were depressed in comparison with 7.4 percent of normal weight patients (Roberts et al., 2000). Another study showed obesity predicted depression one year following assessment (odds ratio= 1.73) (Roberts et al., 2003). The same study found that obesity also predicted unhappiness, pessimism, low positive affect, and life dissatisfaction at five years following the baseline interview. Obesity may increase one's risk for depression and negative affect via physical and psychosocial mechanisms.

Functional impairment, chronic disease, and pain are byproducts of obesity and have been demonstrated to reduce health-related quality of life (HRQOL) (Kolotkin, Meter, & Williams, 2001; Wells et al., 1989). Reduced HRQOL may lead to poorer self-rated health in which patients may believe that efforts toward health are futile and subsequently relinquish their efforts and succumb to depression (Markowitz et al., 2008). MS patients have also been shown to experience higher rates of depression in instances where QOL is reduced (Benito-León, Morales, & Rivera-Navarro, 2002).

Stereotypes characterize obese individuals as incompetent, ugly, and lazy (Carr & Friedman, 2005). These implicit and explicit judgments are damaging to self-esteem and increase social acceptance of cruelty and discrimination in educational, employment, health, and social institutions (Carr & Friedman, 2005; Puhl & Brownell, 2003). Weight-based ostracism based may be linked to the high prevalence of body image dissatisfaction among

obese/overweight individuals(Friedman & Brownell, 1995). Many report multiple failed diet attempts to attain a socially-acceptable body image(Markowitz et al., 2008) These two components together may lead to a circular loop of depression and reinforcement of poor self-esteem and feelings of failure.

Depression as a risk factor for obesity

Physiological and psychosocial pathways may link depression to obesity. As with MS, dysregulated HPA(De Bellis, Gold, Geraciotti, Listwak, & Kling, 1993), sustained elevations in cortisol(Lupien et al., 1998; Lupien et al., 1999), and increased proinflammatory cytokines (TNF, IL-1, IL-6, interferon- γ)(Kenis & Maes, 2002; Kubera, Maes, Kenis, Kim, & Lasoń, 2005) may be pathogenic to depression in obesity(Kern et al., 2011). Dysregulation of these systems has been shown to promote weight gain and may explain the physiological mechanisms that link depression to obesity(Greene & Wing, 1994). Some evidence indicates that depression is linked to future obesity via dysregulated eating, reduced self-efficacy, and poor social support. Depressed individuals may not possess adequate life coping strategies and some turn to large quantities of food (i.e. binge) to regulate mood in the context of emotional upset(Markowitz et al., 2008). Self-efficacy to control weight and eating may quickly disintegrate when patients experience overwhelming feelings and the sense that they've "lost control." A lack of social support may only exacerbate feelings of failure and reduced self-efficacy to cope with life and manage weight(Bishop, 2002). The exact directionality between obesity and depression is not fully understood. Models that exist suggest that each confers risk for the other and may create a cycle in which depression and obesity are maintained. Moreover, these mechanisms may interact with the biosocial factors that link MS with an increased incidence of depression.

Obesity may expose MS patients to further physiological disruption and social stigma that result in the development of depression.

Cognitive Functioning in Obesity

Excess weight contributes to an increased risk for stroke and decreased risk of full recovery following a stroke or brain trauma(Weitbrecht & Kirchhoff, 1995). However, risks for cognitive decline among the obese are not just related to stroke; recent research indicates that structural, hormonal, and biochemical changes may lead to poorer cognitive performance among the obese.

Diffuse atrophy(Benedict et al., 2006; Benedict et al., 2009) in MS has been associated with worse cognitive performance and the effects of brain atrophy on cognitive function are also seen among the obese. Enlarged orbitofrontal white matter, reductions in focal gray matter volume in the frontal lobes, and axonal/myelin abnormalities of the frontal lobes have been observed in overweight and/or obese young adults(Pannacciulli et al., 2006). The frontal lobes are particularly susceptible to age-related declines in functioning(Bruce-Keller, Keller, & Morrison, 2009). Morphological changes of the frontal lobes among overweight/obese patients are likely due to neuron loss and may indicate premature aging. Deficits in processing speed(Yim et al., 2012), memory, learning, and executive functioning have been demonstrated by obese/overweight individuals in comparison to healthy weight individuals(Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003, 2005; Gunstad et al., 2007; Waldstein & Katzel, 2006), and these functions have been well-associated with functioning in the frontal lobes (Dodds, Morein-Zamir, & Robbins, 2011; du Boisgueheneuc et al., 2006; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). Morphological changes resultant

from obesity may underscore the link between obesity and poor cognitive performance relative to healthy weight individuals.

Poorer cognitive function in obese patients may also be due to metabolic syndrome(Farr et al., 2008), high cholesterol, and chronic hyperglycemia(Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004; Morley, 2004). Strong evidence exists for the role of triglycerides in cognitive deterioration. Triglycerides ultimately break down into free fatty acids which can bind to specialized receptors in the brain (ex. GPR40)(Ma et al., 2008). This signals a cascade of inflammation and astrocytic and microglial activity which can disrupt cognition by reducing long-term potentiation in the hippocampus and impairing leptin transport at the blood brain barrier which subsequently triggers leptin resistance(Banks et al., 2004; Farr et al., 2008; Patil & Chan, 2005). Leptin is widely distributed throughout the brain and is involved in the regulation of neuronal excitability, control of appetite and energy(Elmqvist, Bjørbaek, Ahima, Flier, & Saper, 1998; Fei et al., 1997; Harvey, 2007). Dysregulated leptin can influence microglial inflammatory cascades that lead to oxidative stress and inflammation of the brain linked to cognitive decline(Bruce-Keller et al., 2009). Rodent studies have shown that signals of oxidative stress in the brain are reduced when triglyceride levels are lowered with medication thus highlighting the link between higher levels of triglycerides and inflammatory processes in the central nervous system.

Excess endogenous corticosterone and other glucocorticoids are found in obese and diabetic patients(Dallman et al., 2006). These glucocorticoids bind to receptors that regulate sugar metabolism and thereby decrease immune function and increase sugar production and levels in the blood. Increased blood sugar is associated with advanced glycation end products that can impair neurogenesis in the hippocampus, synaptic plasticity and cognitive

function(Stranahan, Arumugam, et al., 2008; Stranahan, Lee, et al., 2008). Indeed, the cognitive detriment associated with obesity may be due to complex interplay between physiologic, immunologic, and homeostatic mechanisms and these may negatively interact with MS and create further decline in functioning.

Beliefs about obesity

Overweight and obese patients have been shown to underestimate their weight status as determined by BMI(Irani & Abell, 2007; Johnson-Taylor, Fisher, Hubbard, Starke-Reed, & Eggers, 2008). Men have historically been more likely than women to underestimate their overweight or obesity status(Paeratakul, White, Williamson, Ryan, & Bray, 2002). However, as rates of obesity continue to climb, women have decreased in accurate categorization of themselves as healthy weight, overweight, or obese(Gillum & Sempos, 2005). Parents also demonstrate poor awareness of overweight/obesity in their children; nearly 90 percent of parents with overweight children underestimate their child's weight status significantly (Baughcum, Chamberlin, Deeks, Powers, & Whitaker, 2000; Carnell, Edwards, Croker, Boniface, & Wardle, 2005; Etelson, Brand, Patrick, & Shirali, 2003). Poor awareness of weight status is further compounded by poor understanding of health risks associated with obesity. Nearly a quarter of individuals in the US believe that one can be "significantly overweight" and still healthy(T. Thompson et al., 2013). Furthermore, the majority of individuals do not recognize a connection between obesity and health complications beyond heart disease and diabetes(T. Thompson et al., 2013). Fewer than one in five individuals in the US recognize a connection between obesity and high blood pressure, arthritis/joint problems, high cholesterol, mental health issues, stroke, cancer, and death. Reduced

awareness of overweight/obesity status may partially underlie failure to take precaution against health risks associated with obesity(Fleary & Ettiene, 2014).

Beyond basic miscalculation of weight status and complications associated with excess weight, patients may also differ in underlying beliefs about the etiology of obesity. Research has demonstrated that patients who believe their weight is out of their control (i.e. inherited) are more apt to report themselves as overweight, and report reduced health than patients who believe that weight is within their control (i.e. behavioral and due to poor diet/lack of exercise)(Fleary & Ettiene, 2014). Patients who believe weight is out of their control report higher weight and worse health; however, they also report less exercise and lower consumption of fruits and vegetables(C. Wang & Coups, 2010). This may indicate an attribution style that promotes acceptance of one's weight, but hinders taking action that may affect or improve weight. No research has been conducted examining MS patients' perceptions of obesity, which is one aim of the present study.

Physiological Relationship between Obesity and MS

The prevalence of obesity in the general population is of epidemic proportions. If obesity exacerbates or contributes to the development of MS it must be addressed in research and practice. Recent evidence indicates that there may be a link between leptin and the pathogenesis and/or exacerbation of MS(Matarese et al., 2008).

Leptin is necessary for healthy development of neural and glial cells, but can trigger a cascade of negative effects when at improper levels(Matarese et al., 2010; Matarese et al., 2008). It is a hormone that is derived from adipocytes in proportion to the amount of adipose tissue. Serum leptin levels are positively associated with BMI, weight, and body fat percentage among obese patients(Al Maskari & Alnaqdy, 2006). Thus, patients with higher

weight and body fat also have higher levels of leptin. When leptin is present in high levels, such as with leptin resistance seen in obesity, IFN - γ and IgG2a are produced and T_{reg} cell production is down-regulated producing significant inflammatory cascades.

Rates of obesity and overweight in the MS population are nearly equivalent or higher than in the general population(Matarese et al., 2010; Matarese et al., 2008). One-quarter of MS patients were obese and one-third were overweight in 2008 and those numbers are estimated to be higher today(R. Marrie et al., 2009). Moreover, RRMS patients exhibit higher levels of leptin and lower levels of T_{reg} cells than matched individuals without MS(Matarese et al., 2010; Matarese et al., 2008). Considering that both obese and MS patients individually have higher leptin levels, it can be reasoned that those with both MS and obesity are likely at a higher risk for inflammatory cascades signaled by excess leptin. Indeed, leptin and/or obesity may be an important pathogenic link to MS(Matarese et al., 2010; Matarese et al., 2008). This is further underscored by research indicating that obesity during adolescence, prior to age 20, results in a two-fold increased risk for developing MS(Langer-Gould et al., 2013; Munger et al., 2013; Munger et al., 2009). Research has indicated that this effect may be especially pronounced in females. Because women have higher leptin levels than men, it may partially account for the increased prevalence of MS among women(Matarese et al., 2008).

Conversely, deficient leptin levels have been linked to impaired immune function and increased risk for infection. However, leptin deficiency also acts as a protective mechanism against the mouse model of MS (experimental autoimmune encephalomyelitis (EAE)(Matarese et al., 2008). This may be due in part to the inverse relationship between leptin and T_{reg} cells. Increased T_{reg} cell count is associated with improved disease course in

EAE mice. These concurrent effects increase/allow inflammation related to exacerbation of MS. Research linking leptin to MS is relatively new and is not a fully inclusive explanation of pathogenesis. However, the existing research suggests that obesity may compound physical, emotional, and cognitive difficulties in MS patients via leptin-initiated inflammatory cascades.

Research of Weight Related MS Function

There is a relative dearth of research linking obesity and increased MS severity. A few studies have examined factors associated with obesity among MS patients. Research has shown that obesity and related comorbidities (e.g. hypertension, hyperlipidemia, and heart disease) are related to increased lesion burden and brain atrophy(Kappus et al., 2015). It is possible that neural inflammation and destruction are responsible in part for increased symptoms experienced by overweight/obese patients. In particular, MS patients with higher risk for cardiovascular disease had more lesions and increased brain atrophy(Kappus et al., 2015; Weiland et al., 2015). The added physical burden from excess weight may be responsible for worse outcomes by impairing physical function and enhancing negative psychosocial experiences.

Physical function in overweight/obese MS patients

Obesity may play a role in the deterioration of physical function above and beyond that caused by MS. Two studies have examined differences in mobility among healthy weight and overweight/obese MS patients(R. A. Marrie et al., 2010; Pilutti et al., 2012). The first study examined mobility outcomes in patients enrolled in the North American Research Committee on Multiple Sclerosis Registry (NARCOMS). They found that patients who reported one risk factor associated with cardiovascular disease (e.g. hypertension,

hypercholesterolemia) experienced a 51 percent increased risk of early ambulatory disability and those with two or more risk factors for cardiovascular disease experienced more than 200 percent increased risk for early ambulatory disability (R. A. Marrie et al., 2010). However, another study examined extensive mobility outcomes among 168 individuals with varying MS subtypes (approximately 80 percent RRMS). They found no association between BMI group (healthy weight, overweight, obese) on measures of mobility including the timed 25 foot walk, 6 minute walk, oxygen cost of walking, spatiotemporal gait parameters, and self-reported walking impairment (Pilutti et al., 2012). This study included well-validated and reliable mobility measures, but the relatively small sample of SPMS and PPMS within this study may have obscured the effect of obesity on mobility function. Examination of the effect of obesity on mobility among other subtypes of MS could indicate that the effects of obesity on mobility are delayed and only become apparent as disease course worsens.

Other studies have examined the relationship between obesity and disability in MS. In one, self-reported obesity at baseline was associated with higher disability as measured by Patient Determined Disease Steps (PDDS) at 12 months but not at 24 months. Another study grouped patients into categories of mild, moderate, and severe disability based on self-reported PDDS and did not find significant differences in self-reported BMI among groups (R. Marrie et al., 2009). However, studies that assessed BMI and disability (EDSS) objectively found that BMI was associated with higher levels of disability, but not for risk of relapse (Tettey et al., 2014). Obesity has also been examined as a correlate of fatigue in MS. Higher BMI and poorer self-reported dietary habits were associated with increased physical fatigue measured with the Fatigue Severity Scale (FSS) (Weiland et al., 2015). However,

another study found no association between BMI and general, physical, or mental fatigue after adjusting for age(Trojan et al., 2007).

The above studies paint a complicated picture of the impact of weight on physical function. In the present study, we sought to improve upon the methodology of prior studies by objectively measuring BMI and adding an additional measure of waist-to-height ratio. Well-validated measures of mobility were used and an additional measure of balance was included. Common measures of mobility only measure speed, but balance data provides information regarding an individual's general stability and core strength: two factors that are needed to perform everyday activities efficiently and without injury. Fatigue was assessed with a multi-dimensional measure of fatigue that has been specifically validated with MS patients.

Emotional function in overweight/obese MS patients

Increased incidence of depression in overweight/obese individuals has been well-documented and this relationship extends to the MS population(Cambil-Martín et al., 2014; Taylor et al., 2014). In one study, MS patients who met criteria for obesity had significantly increased odds of experiencing depression (OR= 2.18; adjusted OR= 1.47) and those with the least healthy diets (i.e. lowest quartile), on the dietary habits questionnaire, also experienced increased risk of depression (OR=4.86; adjusted OR= 2.73)(Taylor et al., 2014). The relationship between poor diet and depression was described by the authors as “dose-dependent” such that as diet worsens, the incidence of depression increases. In another study, overweight patients reported higher levels of depression than healthy weight patients(Cambil-Martín et al., 2014). Research has primarily focused on the relationship

between obesity and depression; therefore, this study will examine the relationship between both depression and anxiety and obesity.

Cognitive function in overweight/obese MS patients

Despite the known effects of obesity on cognition, no known studies examining cognitive function in healthy weight and overweight/obese MS patients were found for this literature review. The current study will fill in this gap by assessing the relationship between weight status and memory, processing speed, and executive function (verbal fluency).

MS patient beliefs about weight and disease progression

MS patients exhibit levels of obesity as high as or higher than that found in the general population (Slawta et al., 2003). It is important to determine what MS patients know and believe about the impact of weight on MS symptoms and progression given that a strong association may exist (Matarese et al., 2010; Matarese et al., 2008). No known studies have examined how MS patients believe their functional abilities are affected by current weight and/or future weight gain or weight loss. MS patients who do not see a connection between MS symptom expression and weight may be less likely to engage in health behaviors related to weight maintenance and may be more likely to be overweight or obese. It is possible that overweight/obese patients discount the effect of excess weight on symptoms and progression and therefore express less motivation to change obesogenic behaviors. Patients who do not see a connection between weight status and worsened MS symptoms may need greater benefits for smaller behavior change and may also require additional resources. By understanding patient knowledge and beliefs about weight, MS, and their interaction with one another, it may be possible to help clinicians develop targeted interventions to strengthen motivation and commitment to maintain healthy weight behaviors among MS patients.

Summary and Significance

A link between leptin and the development/exacerbation of MS has been proposed (Matarese et al., 2008). Higher levels of leptin induce inflammation that feeds into the cycle of neuronal destruction in MS. Both MS and obese patients exhibit higher levels of leptin than their healthy weight or non-diseased counterparts. The close overlap in the inflammatory and symptomatic profiles of obesity and MS highlights the possibility that they may be related (Matarese et al., 2010; Matarese et al., 2008). The research that has examined differences in cognition, physical ability and emotional health among healthy weight and overweight/obese MS patients has shown inconsistent results and can be methodologically improved. Additionally, it is currently unknown how healthy weight and overweight/obese patients think about the impact of weight on their disease symptoms and progression. Patients who do not believe weight negatively impacts their MS may be unmotivated to engage in health behaviors that could possibly improve MS symptoms and quality of life. Such patients may place more value on the costs of weight maintenance behaviors, like exercise, and therefore require greater rewards to participate in exercise. Gaining an understanding of how patients think obesity interacts with MS and how patients analyze costs and benefits of health behaviors may enable clinicians to develop targeted interventions to help MS patients gain motivation to lose excess weight and maintain healthy dietary and exercise habits. Thus, it may be possible to reduce symptoms in MS patients by supporting healthy weight loss and weight maintenance interventions.

Specific Aims and Hypotheses

The aims of this study were to investigate the association between obesity and MS symptoms and disability.

- 1) Examine the relationship between obesity and cognitive/physical/emotional functioning among healthy weight and overweight/obese MS patients. It was hypothesized that excess body weight would be associated with poorer cognitive performance on measures of processing speed, memory, and executive function than healthy weight patients. It was also hypothesized that excess body weight would be associated with worse physical functioning on measures of disability, mobility, balance and physical fatigue. Finally, excess body weight was hypothesized to be associated with greater depression, and anxiety.
- 2) Examine MS patient beliefs about the impact of excess weight on MS symptoms and disease progression, and determine reasons for and barriers to implementation of health behaviors among healthy weight and overweight/obese MS patients. It was hypothesized that excess body weight would be associated with reduced belief in one's ability to affect their weight and illness and reduced belief that weight has an impact on MS symptoms. Excess body weight was also expected to be associated with increased barriers to exercise and eating a healthy diet.
- 3) Explore MS patient beliefs about the impact of weight gain or loss on MS related symptom severity and fatigue severity. It was hypothesized that MS patients would perceive an association between body weight and symptom severity and that patients would predict the worst symptom severity for the most obese silhouettes.

- 4) Explore MS patient willingness to engage in exercise for hypothetical symptom improvement on the EWT. It was hypothesized that patients would report increased willingness to exercise for longer periods of time in exchange for higher percentages of symptom improvement.

CHAPTER 2

METHODOLOGY

Participants

Eighty-one patients with Multiple Sclerosis (MS) with either Relapsing Remitting (RRMS) or Secondary Progressive (SPMS) were recruited from a large specialty clinic in the Kansas City metropolitan area and by advertisements sent out to the community in the MS Society Newsletter. Eligible patients were required to have a confirmed diagnosis of MS and: (a) no movement impairments that would inhibit them from walking up to 25 feet; (b) no sensory impairments that might interfere significantly with cognitive testing; (c) no developmental history of learning disability or attention-deficit/hyperactivity disorder; (d) no neurologic condition other than MS that could substantially affect cognition (ex. no history of stroke or brain surgery); (e) no relapse and/or corticosteroid use within four weeks of assessment; (f) no history of alcohol or substance abuse disorder; (g) absence of severe physical/neurological impairment that would make testing insurmountable; (h) not have a BMI significantly below weight (i.e. below 17).

Procedure

Research personnel advertised via an MS newsletter and approached potential participants at an MS specialty clinic. Personnel described the study to potential participants who expressed interest and screened them at that time to determine eligibility. Following eligibility screening, the researcher set up a time to meet with the participant for a two hour testing session. When participants arrived for the session, the study was explained and participants were given time to review and sign the informed consent document. A study ID number was assigned to each participant so that names and other identifying information

would not be connected with study obtained data. A master key that contains participant identifying information attached with study ID number was maintained throughout the duration of the study in the event that a participant asked for their data to be removed. This key was stored separately from de-identified data in a separate, locked filing cabinet and was only be accessible to the principal investigator and study coordinator. At the conclusion of the study, this key was destroyed.

The two hour testing sessions were conducted in a quiet and private testing room. During the testing session, participants filled out demographic information and self-report questionnaires. They completed physical and neuropsychological cognitive testing. Participants' height, weight, and waist circumference were recorded following testing. Payment of \$40 was mailed to participants within a month of study completion.

Materials and Measures

Demographic

Demographic information was obtained at the beginning of the study from participants. This included age, date of birth, sex, ethnicity, education attained, household income, and number of individuals in their home. Patients also completed forms that assessed disease duration, disability, severity, and medication use.

Anthropometric

Body Mass Index

Participants were instructed to take off their shoes for weight and height to be recorded. A Befour MX805 Measurement Station and Column Scale was used for height and weight measurement. BMI was then calculated with the Center for Disease Control's calculator. It is calculated as $(\text{weight in pounds} \times 703) / \text{height in inches}^2$.

Waist Circumference

Researchers measured waist circumference at the thinnest portion of the waist between the iliac crest and the bottom portion of the ribs with a tape measure. Participants were asked to breathe out during the measurement to ensure reliability of measurement procedures. This process was repeated three times and the average circumference was calculated for each patient and then divided by height in inches to calculate waist to height ratio (Ashwell et al., 2012; Ashwell & Hsieh, 2005; Ashwell et al., 2014; Bosnar-Puretić, Basić-Kes, Jurasić, Zavoreo, & Demarin, 2009; Hara, Saitou, Iwata, Okada, & Harada, 2002; C. M. Lee et al., 2008; Rodea-Montero et al., 2014). Research assistants were trained to measure waist circumference by the study coordinator and tested to ensure accuracy.

Physical

Mobility

The *25-Foot Walk* is a functional test of mobility designed to assess gait speed. It includes two trials during which patients are instructed to walk as quickly as possible for 25 feet. The two trials are averaged for a final score. It has been validated for use with many patient populations including MS patients as a part of the Multiple Sclerosis Functional Composite (Bethoux & Bennett, 2011; Fischer, Rudick, Cutter, & Reingold, 1999). This procedure was completed by participants during the testing session.

Balance

The *SWAY Balance Mobile Application* (SWAY Medical, Tulsa, OK, USA) is an application that can be installed on an apple touch screen device. Users perform a series of five stance conditions for 10 seconds each with open eyes. It uses output from triaxial accelerometers during the stances to generate a stability score for movement in the anterior/

posterior and medial/lateral plane. Preliminary research has indicated that the SWAY balance software exhibits concurrent validity with validated balance measures including the Biodex Balance System SD and BESS (Jeremy A. Patterson, Amick, Pandya, Hakansson, & Jorgensen, 2014; J. A. Patterson, Amick, Thummar, & Rogers, 2014). This procedure was completed by participants during the testing session.

Fatigue

The *Modified Fatigue Impact Scale (MFIS)* (Fisk et al., 1994; Ritvo, 1997) is a 21-item inventory that has demonstrated good internal reliability in patients with MS (cronbach's alpha = .81-.85). Patients completed the full version MFIS as well as a shorter five-item version (MFIS-5) during a different activity. The 21-item version can be used to calculate subscale scores for physical, cognitive, and psychosocial fatigue (Fisk et al., 1994). The MFIS-5 has demonstrated good reliability (cronbach's alpha = .80) (Ritvo, 1997). Participants rate five-items on a five-point scale that assess the impact of fatigue during the past 4 weeks.

Stroke Risk Factors

The *Stroke Risk Scorecard* is an eight item self-report questionnaire that assesses factors associated with risk for stroke including blood pressure, atrial fibrillation, smoking, diabetes, physical activity, weight and family history of stroke. The Stroke Risk Scorecard was developed by the National Stroke Association to be used as a self-screener and scored using the total of the items (Association, 2015). The Stroke Risk Scorecard includes items that have been reliably shown to be related to risk for stroke and heart attack (Go et al., 2014; Mozaffarian et al., 2015). We chose to include the Stroke Risk Scorecard in our analyses

because the items it assesses are associated with poor health behaviors and obesity(Kopelman, 2007).

Emotion

Depression and Anxiety

The *Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983)* The HADS is a self-report scale that assesses depression and anxiety with a total of 14 items. Patients are asked to answer statements (e.g. “I feel restless and have to be on the move”) on a scale that ranges from zero to three. It has demonstrated good validity and high internal consistency and test-retest reliability(Bjelland, Dahl, Haug, & Neckelmann, 2002).

Cognition

Processing Speed

The *Symbol Digit Modalities Test (SDMT)(Benedict et al., 2012; Smith, 1982)* assesses speed of information processing, visuoperceptual processing, and attention by requiring participants to say numbers that corresponds with symbols according to a key. Correct responses within a 90 second time period are measured for the variable of interest. Research has shown that the SDMT has strong test-retest reliability ($r > .80$)(Benedict et al., 2012). The SDMT is commonly used to assess cognitive dysfunction in MS patients (Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007).

Verbal Memory

The *Rey Auditory Verbal Learning Test (AVLT)(Lezak, 1995)* assesses verbal memory during five learning trials and one delayed recall trial. During this task, participants learn and are subsequently asked to recall a list of words. The dependent variables of interest are

correct responses during the delay recall trial. Validity for the Rey AVLT has been found for patients with MS(Geffen, Butterworth, & Geffen, 1994; Ryan & Geisser, 1986).

Executive Function

The *Controlled Oral Word Association Test (COWAT)*(Ruff, Light, Parker, & Levin, 1996) has been designed to assess verbal fluency by requiring patients to spontaneously produce words orally that begin with a specific letter of the alphabet. The test includes three trials and patients are forbidden from saying proper nouns (e.g. names and numbers) and the same word with a different ending (e.g “eat” and “eating”). Patients are given 60 seconds for each of three trials. Research has shown that the COWAT is sensitive to brain dysfunction and displays high reliability (cronbach’s alpha= .83) and test-retest reliability ($r = .74$)(Ruff et al., 1996) as well as validity with MS patients(Gromisch et al., 2016).

Beliefs about weight, MS, and their interaction

Barriers to Weight Maintenance

A 25 item survey was modified for use in this study. The original survey has been validated among women and shown to express good internal reliability (Cronbach’s alpha .68-.83)(Andajani-Sutjahjo, Ball, Warren, Inglis, & Crawford, 2004). Barriers used in this survey have been well-documented in other studies assessing barriers to physical activity and healthy eating(Andajani-Sutjahjo et al., 2004).

MS Specific Health Beliefs

For the purpose of this study, we developed 8 questions specifically pertaining to beliefs about the impact of weight on MS symptoms and progression. Analyses following the study revealed that this questionnaire exhibits high reliability (Cronbach’s alpha= .94). Participants rated 8 items on a 6 point Likert scale with response options ranging from

strongly agree to strongly disagree. Items developed for this study include: 1. I believe that eating a healthy diet will improve my MS; 2. I believe that exercising consistently will improve my MS; 3. I believe that eating healthy may slow the progression of my MS; 4. I believe that exercising may slow the progression of my MS; 5. I experience fewer symptoms (or my symptoms improve) when I eat healthy; 6. I experience fewer symptoms (or my symptoms improve) when I exercise on a consistent basis; 7. I believe that maintaining a healthy weight will slow the progression of my MS; 8. I believe that maintaining a healthy weight may improve my MS symptoms.

Dieting Beliefs

The *Dieting Beliefs Scale* (Stotland & Zuroff, 1990) is a 16-item measure that assesses individual's beliefs that they can affect or control weight (i.e. weight locus of control (WLOC)) and includes one internal and two external factors related to internal and external locus of control. Items are scored on a likert type scale with options ranging from 1 (i.e. "not at all descriptive of my beliefs") to 6 (i.e. "very descriptive of my beliefs.") It has demonstrated acceptable internal consistency (Cronbach's alpha = .69) and test-retest reliability (.81). Higher scores indicate a paradigm consistent with an internal locus of control.

Beliefs about the impact of weight change on symptom severity and fatigue

Body Size and Symptoms Task (BSS)

We used the Figure Rating Scales to create a novel paradigm called the Body Size and Symptoms (BSS) task (See Appendices A and B) (A. Stunkard, 2000; A. J. Stunkard, Sørensen, & Schulsinger, 1983). The Figure Rating Scales consist of nine female and nine male silhouettes of increasing body mass. They have demonstrated good reliability and

validity and BMI norms for each figural stimuli have been determined (Bulik et al., 2001; A. Stunkard, 2000). The BSS uses the Figure Rating Scales to assess patient predicted symptom severity at silhouettes of varying increasing and decreasing weight. Participants were asked to estimate symptom severity on a scale from “0” to “6” for several symptoms (e.g. physical and cognitive fatigue, pain, balance, walking speed, sleep quality, memory, processing speed, sexual function, depression, anxiety, severity of exacerbations and number of yearly exacerbations) at silhouettes of varying weight status (e.g. underweight (silhouette 1), healthy weight (silhouette 4), and obese (silhouette 9). Patients also completed this activity for the Modified Fatigue Impact Scale (MFIS).

Willingness to Exercise for Symptom Improvement

Exercise Willingness Task (EWT) (See Appendix 3).

This novel task was designed to assess the extent to which patients are willing to endure inconvenience (i.e. time spent exercising) to hypothetically improve MS symptoms immediately and at a delayed time point of five years. Patients were asked to rate the amount of time they would be willing to allocate to exercise to receive varying percentages of symptom improvement for different symptoms (e.g. if you knew your cognitive fatigue would improve by 50% immediately, how many minutes of exercise would you be willing to do per day?). See Appendix II for items used in this study.

Statistical Analyses

Data were entered into IBM Statistical Package for the Social Sciences version 24.0 and reliability was checked by other research team members to ensure accuracy. Group differences in demographic data (age, education, gender, disease, subtype, disease duration) were examined with correlations, T- tests, and Chi-Square tests.

The first aim of this study was to examine the impact of excess body weight (per BMI guidelines and WTHR guidelines) on measures of cognition, physical function, and emotional distress. To reduce familywise error, Z-score composite variables were created for cognitive and physical measures. Partial correlations were used to examine the associations between WTHR, BMI and composite measures of cognitive and physical function as well as measures of emotional function and stroke risk while controlling for the impact of age. Follow-up Partial correlations were used to examine significant associations with specific measures from which composite variables were created.

The second aim was to examine patient beliefs about the impact of weight on MS symptoms and progression. Partial correlations were used to examine associations between BMI, and WTHR on measures of dieting beliefs, MS specific health beliefs and barriers to diet and exercise while controlling for the effect of age.

The third aim was to explore patient beliefs about the impact of excess body weight on symptom severity using the Body Size and Symptoms (BSS) task. Mixed-factor Analysis of Variance (ANOVA) statistics were used to examine within subject symptom severity rating at silhouettes 1, 4, and 9 for both general symptoms (ex. cognitive fatigue, physical fatigue) and MFIS with current symptom severity (higher or lower symptoms) as the between subjects variable. In the event that homogeneity of variance was violated, nonparametric statistics were used to evaluate within subject and between group differences.

The fourth aim was to explore MS patients' willingness to exercise to achieve increasing percentages of symptom improvement using the Exercise Willingness Task (EWT). Mixed-factor ANOVAs were used to examine within subject willingness to exercise to achieve improvement at increasing percentages of improvement. Current symptom

severity (lower vs. higher symptoms) was used as the between subjects factor. In the event that homogeneity of variance was violated, nonparametric statistics were used to evaluate within subject and between group differences.

Power Analysis An a priori power analysis was conducted with G*Power to determine necessary sample size. It indicated that with the significance criterion set at $\alpha = .05$ for small-medium effects (.15) and power of $\beta = .8$, a sample size of 78 is sufficient.

Previous studies have found effect sizes ranging from small to large when examining the impact of weight on mobility in MS (Pilutti et al., 2012). Other studies have found similar and larger effect sizes when comparing obese and healthy weight individuals on measures of cognition (effect size = .13- .55) (Kuo et al., 2006; Vancampfort et al., 2014), fatigue (Resnick, Carter, Aloia, & Phillips, 2006), and depression (effect size = .237) (Yim et al., 2012) indicating that this study is reasonably powered.

CHAPTER 3

RESULTS

Descriptive Statistics

The sample included 81 patients with MS, 64 of whom were female (79.0 %). In this sample, the average BMI was $28.69 \pm 7.13 \text{ kg/m}^2$ and the average waist to height ratio was $.54 \pm .10$ inches. Table 1 displays demographic characteristics of the sample.

Table 1
Descriptive characteristics of the sample

	MS Patients <i>n (%) or Mean (SD)</i>
Gender	
Female	64 (79%)
Male	17 (21%)
Race	
Caucasian	67 (82.7%)
African American	7 (8.6%)
Hispanic/Latino	6 (7.4%)
Asian/Pacific Islander	1 (1.2%)
Age (years)	48.01 (11.68)
Education (years)	14.68 (2.74)
MS subtype	
Relapsing Remitting	76 (93.8%)
Secondary Progressive	5 (6.2%)
Duration of Diagnosis (years)	12.25 (9.03)
PDDS	1.98 (1.79)
WTHR	.54 (.10)
BMI	28.69 (7.13)

Note. PDDS = Patient Determined Disease Steps; WTHR = Waist to Height Ratio; BMI =

Body Mass Index

Impact of Overweight and Obesity

Table 2 shows Spearman correlations between WTHR, BMI and demographic variables. WTHR was significantly associated with age, but not education, disease diagnosis duration, gender, ethnicity or subtype. As a result, age was entered as a covariate into the analyses where WTHR was used as a continuous variable. T-tests and Chi-Square tests were used to examine differences between healthy weight and overweight/obese groups on demographic variables. Categorical WTHR was not associated with any demographic variables. Therefore, no demographic covariates were included in mixed-factor ANOVAs.

Table 2

Spearman correlations between WTHR, BMI and demographic variables

	Age	Education	Disease Duration	Subtype	Gender	Race
WTHR	.240**	-0.111	0.082	0.037	0.046	-0.125
BMI	0.075	-0.048	-0.030	-0.083	0.044	-0.120

Note:

** Correlation is significant at the 0.01 level (2-tailed).

Table 3

Descriptive statistics for healthy weight and overweight/obese MS Patients based on categorical WTHR

Variable	MS Healthy Weight n=41		MS Overweight/Obese n=40		<i>t</i> (df)	<i>P</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
Age (years)	46.24	12.06	49.83	11.13	-1.39 (79)	.169
Education (years)	14.90	3.35	14.45	1.96	.745 (64.88) ^a	.459
Diagnosis duration (years)	12.17	10.33	12.33	7.60	-.076 (79)	.939
Body Mass Index (BMI)	23.84	3.41	33.66	6.50	-8.49 (58.63) ^a	.000
Waist-to-height ratio (WTHR)	.458	.040	.621	.073	-12.43 (59.93) ^a	.000
					<i>X</i> ² (df)	<i>P</i>
Subtype	RRMS (N=38)		RRMS (N=38)		.428 (79)	.670
	SPMS (N=3)		SPMS (N=2)			
Gender	Female = 29		Female = 35		3.433 (1)	.064
	Male = 12		Male = 5			
Ethnicity	White= 33		White= 34		2.955(3)	.399
	Black=5		Black=2			
	Hispanic/Latino=2		Hispanic/Latino=4			
	Asian Pacific Islander=1		Asian Pacific Islander=0			

Note. ^a Equal variances not assumed.

RRMS = Relapsing Remitting MS; SPMS = Secondary Progressive MS

Association between overweight/obesity and cognition, physical function, depression, anxiety, and stroke risk factors (Aim 1)

Partial correlations were conducted in SPSS with age as a covariate to examine the relationship between excess body weight and cognitive function, physical function, and emotional function. Z-score composite variables of cognitive measures (SDMT, COWAT, RAVLT delay, MFIS cognitive subscale) and physical measures (Sway Balance Total, Average 25 foot walk, PDDS, MFIS physical fatigue subscale) were created. Depression and anxiety scores were entered in separately. There was a significant relationship between WTHR, BMI and depression such that those with a higher WTHR and BMI reported more depression. However, no significant correlations were found between WTHR, BMI and the cognitive composite, physical composite, or anxiety. We also included patients' total score on the Stroke Risk survey because it assesses a range of health behaviors and health conditions associated with obesity (e.g. blood pressure, regularity of heartbeat, cholesterol, exercise, family history of stroke, diabetes, tobacco use, body weight)(Kopelman, 2007). Research has demonstrated that such cerebrovascular and cardiovascular risk factors are associated with increased lesion load, brain atrophy and adverse mobility functioning(Kappus et al., 2015). Higher WTHR and BMI were both associated with increased stroke risk. More stroke risk factors were associated with worse physical function and depression.

Table 4

Partial correlations of WTHR and BMI with cognitive, physical, and emotional function controlling for age

	WTHR	BMI	Stroke Risk	Cognitive	Physical	Depression	Anxiety
WTHR	1.000	.870**	.587**	-.071	.157	.323**	.114
BMI	.870**	1.000	.510**	.075	.061	.241*	.098
Stroke Risk	.587**	.510**	1.000	-.035	.353**	.540**	.184
Cognitive	-.071	.075	-.035	1.000	-.379**	-.213	-.093
Physical	.157	.061	.353**	-.379**	1.000	.423**	.120
Depression	.323**	.241*	.540**	-.213	.423**	1.000	.543**
Anxiety	.114	.098	.184	-.093	.120	.543**	1.000

Note: Partial Correlations used to control for age

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Follow-up correlations: Association between stroke risk factors and physical functioning

In our initial analysis, a higher risk for stroke was associated with worse physical function ($r = .540$; $p < .01$). Follow-up correlations with individual items from the physical composite revealed that a higher stroke risk score was associated with worse balance, more disability, and more physical fatigue (Table 5). We also conducted exploratory partial correlations to examine which stroke risk factors were most strongly related to the physical function composite and individual indices of physical function (Table 6). Heartbeat irregularity was associated with increased physical fatigue. Worse diabetes (i.e. blood sugar level) was associated with worse balance and more disability (PDDS). Worse cholesterol was

associated with worse balance. Less exercise was associated with more physical fatigue, and a family history of stroke was associated with increased physical fatigue.

Table 5
Partial correlations of stroke risk factors with measures of balance, walking speed, disability, and physical fatigue controlling for age

	Stroke Risk	WTHR	BMI	Physical Composite	Sway Total Balance	Average Walk	PDDS	MFIS Physical Fatigue
Stroke Risk	1.000	.593**	.515**	.363**	-.356**	.085	.304**	.455**
WTHR	.593**	1.000	.871**	.178	-.151	.031	.159	.247*
BMI	.515**	.871**	1.000	.076	-.084	-.024	.053	.139
Physical Composite	.363**	.178	.076	1.000	-.876**	.730**	.914**	.801**
Sway Total Balance	-.356**	-.151	-.084	-.876**	1.000	-.531**	-.783**	-.600**
Average Walk	.085	.031	-.024	.730**	-.531**	1.000	.555**	.347**
PDDS	.304**	.159	.053	.914**	-.783**	.555**	1.000	.700**
MFIS Physical Fatigue	.455**	.247*	.139	.801**	-.600**	.347**	.700**	1.000

Note:

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Table 6

Partial correlations of individual stroke risk factors with physical function measures of balance, walking speed, disability, and physical fatigue controlling for age

	Physical Composite	Balance	Average Walk	PDDS Disability	Physical Fatigue
Stroke Risk Total	.363**	-.356**	.085	.304**	.455**
Blood Pressure	.164	-.175	.148	.090	.132
Heart Beat Irregularity	.184	-.188	.020	.103	.295**
Diabetes	.164	-.226*	.004	.236*	.081
Cholesterol	.169	-.265*	-.030	.162	.166
Lack of Exercise	.185	-.097	.075	.169	.270*
Weight	.139	-.130	-.004	.163	.171
Stroke in family	.176	-.181	.006	.128	.267*

Note:

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Association between overweight/obesity and MS specific health beliefs, dieting beliefs, and barriers to diet and exercise (Aim 2)

To examine the relationship between excess body weight and barriers to diet and exercise, dieting beliefs scale (WLOC), and beliefs about the impact of health behaviors on MS symptoms and progression (MS Specific Health Beliefs), partial correlations were conducted in SPSS with age as a covariate. Higher WTHR and BMI were associated with increased barriers to diet and exercise. However, no significant correlations were found between WTHR, BMI and weight locus of control and MS specific health beliefs. Those with higher risk scores for stroke endorsed less belief that health behaviors could improve MS symptoms and progression ($r=-.379$; $p<.01$. See Table 7).

Table 7

Partial Correlations of WTHR and BMI with barriers, dieting beliefs, and MS specific health beliefs controlling for age

	WTHR	BMI	Stroke Risk	Dieting Beliefs	MS Health Beliefs	Barriers Exercise	Barriers Diet
WTHR	1.000	.871**	.604**	-.075	-.135	.328**	.331**
BMI	.871**	1.000	.527**	-.080	-.048	.303**	.327**
Stroke Risk	.604**	.527**	1.000	-.171	-.379**	.194	.160
Dieting Beliefs	-.075	-.080	-.171	1.000	.095	-.164	-.154
MS Health Beliefs	-.135	-.048	-.379**	.095	1.000	-.131	.043
Barriers Exercise	.328**	.303**	.194	-.164	-.131	1.000	.621**
Barriers Healthy Diet	.331**	.327**	.160	-.154	.043	.621**	1.000

Note:

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Beliefs about the impact of weight on symptom severity (Aim 3)

For the Body Size and Symptoms task (BSS), participants were asked to rate the hypothetical severity of several symptoms on a Likert-type scale that ranged from zero (no issues) to six (severe problems) for three different body silhouettes (body 1= underweight, body 4= healthy weight, body 9= obese) (Appendix 1).

Preliminary analyses showed that current symptom expression, not participant weight status, was significantly related to symptom rating on the BSS. Therefore, mixed-factor

repeated measures ANOVAs using current symptoms as the between subjects factor were used to explore within-subject and between-group differences in predicted symptom severity for the modified fatigue impact scale short-form (MFIS) and other symptoms (e.g. mental fatigue, cognitive fatigue, walking speed, balance, anxiety, depression, and memory) at body silhouettes 1, 4, and 9. Examination of histograms and frequency statistics were used to create two equal categorical groups. The mixed-factor ANOVAs revealed significant main effects for the MFIS and each symptom on rated symptom severity at each body silhouette. This indicates that participants predicted each symptom would significantly change based on body weight gain or loss. Mean symptom ratings indicated that participants predicted the worst severity at an obese body weight (silhouette 9) and the best severity at a healthy body weight (silhouette 4). There were significant interactions between group membership (lower vs. higher current symptoms) and rating of the various silhouettes for MFIS, physical fatigue, walking speed, balance, anxiety, and depression, but not memory or mental fatigue. These interactions revealed that those with higher current symptoms predicted higher symptom severity for all silhouettes relative to participants who had fewer current symptoms. The magnitude of the different ratings between groups was greatest for silhouettes 1 and 4 (Figures 1-8) and reduced for silhouette 9 for symptoms with significant interactions. Table 8 shows means and standard deviations of symptom ratings at each silhouette. Tables 9-10 show within and between subject ANOVA statistics which demonstrate significant between-group differences for every symptom. Follow-up t-tests were conducted to determine where group differences existed (Table 11). These analyses indicated that overall patients with higher current symptoms reported higher symptom severity at silhouettes 1, 4, and 9, than patients with lower current symptoms. However, there were no group differences on ratings

of walking speed, anxiety, and MFIS fatigue severity for silhouette 9. Pairwise comparisons showed significant differences in symptom ratings between all silhouettes for each symptom such that the ratings for silhouette 1 were significantly different than silhouette 4 and 9, and ratings for silhouette 4 were significantly different than silhouette 9.

Table 8 *Mean predicted symptom severity at various body silhouettes*

Measure		<i>M</i>	<i>SD</i>
	Silhouette 1 (Underweight)	9.66	5.35
MFIS	Silhouette 4 (Healthy Weight)	7.92	4.64
	Silhouette 9 (Obese)	16.22	2.90
	Silhouette 1 (Underweight)	3.09	1.94
Mental Fatigue	Silhouette 4 (Healthy Weight)	2.30	1.50
	Silhouette 9 (Obese)	4.15	1.73
	Silhouette 1 (Underweight)	2.98	2.02
Physical Fatigue	Silhouette 4 (Healthy Weight)	2.25	1.48
	Silhouette 9 (Obese)	5.37	.941
	Silhouette 1 (Underweight)	2.20	1.89
Walking Speed	Silhouette 4 (Healthy Weight)	2.02	1.62
	Silhouette 9 (Obese)	5.16	1.18
	Silhouette 1 (Underweight)	2.32	1.92
Balance	Silhouette 4 (Healthy Weight)	2.17	1.65
	Silhouette 9 (Obese)	4.78	1.43
	Silhouette 1 (Underweight)	2.35	1.99
Anxiety	Silhouette 4 (Healthy Weight)	1.63	1.61
	Silhouette 9 (Obese)	4.23	1.91
	Silhouette 1 (Underweight)	2.33	2.04
Depression	Silhouette 4 (Healthy Weight)	1.75	1.68
	Silhouette 9 (Obese)	4.67	1.70
	Silhouette 1 (Underweight)	2.57	1.73
Memory	Silhouette 4 (Healthy Weight)	2.32	1.66
	Silhouette 9 (Obese)	3.38	1.74

Table 9

Main effect of body silhouette on rating of MS symptom severity among patients with low and high current symptom severity

Measure	Within Subjects Main Effect		Within Subjects Interaction Main Effect*Group	
	<i>F(df)</i>	<i>P</i>	<i>F(df)</i>	<i>P</i>
MFIS	157.67 (1.90,149.89)	.000	12.45 (1.90,149.89)	.000
Mental Fatigue	51.03 (2,79)	.000	.014 (2,79)	.986
Physical Fatigue	133.77 (1.76, 136.99)	.000	.377 (1.76, 136.99)	.031
Walking Speed	177.64 (2, 79)	.000	9.70 (2, 79)	.000
Balance	136.62 (1.92, 151.49)	.000	3.44 (1.92, 151.49)	.036
Anxiety	88.14 (1.91, 264.37)	.000	5.65 (1.91, 264.37)	.005
Depression	93.57 (1.91, 150.98)	.000	3.61 (1.91, 150.98)	.031
Memory	20.64 (2,79)	.000	1.06 (2,79)	.349

Note: MFIS= Modified Fatigue Impact Scale

Table 10

Between subject effects of body silhouette on symptom severity rating among patients with low and high current symptom severity

Measure	Between Group ANOVA Current Symptom	
	<i>F(df)</i>	<i>P</i>
MFIS	41.70 (1, 79)	.000
Mental Fatigue	51.25 (1, 79)	.000
Physical Fatigue	24.56 (1, 79)	.000
Walking Speed	36.77 (1, 79)	.000
Balance	44.06 (1, 79)	.000
Anxiety	19.64 (1, 79)	.000
Depression	29.57 (1, 79)	.000
Memory	31.16 (1, 79)	.000

Table 11

Differences in symptom severity rating across silhouettes among patients with low and high current symptom severity

	Silhouette 1		Silhouette 4		Silhouette 9	
	<i>t (df)</i>	<i>p</i>	<i>t (df)</i>	<i>p</i>	<i>t (df)</i>	<i>p</i>
Mental Fatigue	-4.83 (79)	.000	-6.67 (79)	.000	-5.29 (59.1) ^a	.000
Physical Fatigue	-2.6 (78)	.011	-5.82 (78)	.000	-2.57 (67.07) ^a	.012
Walking Speed	-5.06 (79)	.000	-6.16 (79)	.000	-1.74 (75.75) ^a	.086
Balance	-4.94 (79)	.000	-6.56 (79)	.000	-3.38 (56.05) ^a	.001
Memory	-4.84 (79)	.000	-5.14 (45.64) ^a	.000	-3.69 (79)	.000
Depression	-3.6 (79)	.001	-6.57 (79)	.000	-2.2 (79)	.031
Anxiety	-2.64 (79)	.01	-7.71 (54.24) ^a	.000	-1.81 (79)	.074
MFIS Fatigue	-4.89 (79)	.000	-7.13 (79)	.000	-1.86 (79)	.067

Note: a = Equal variances not assumed.

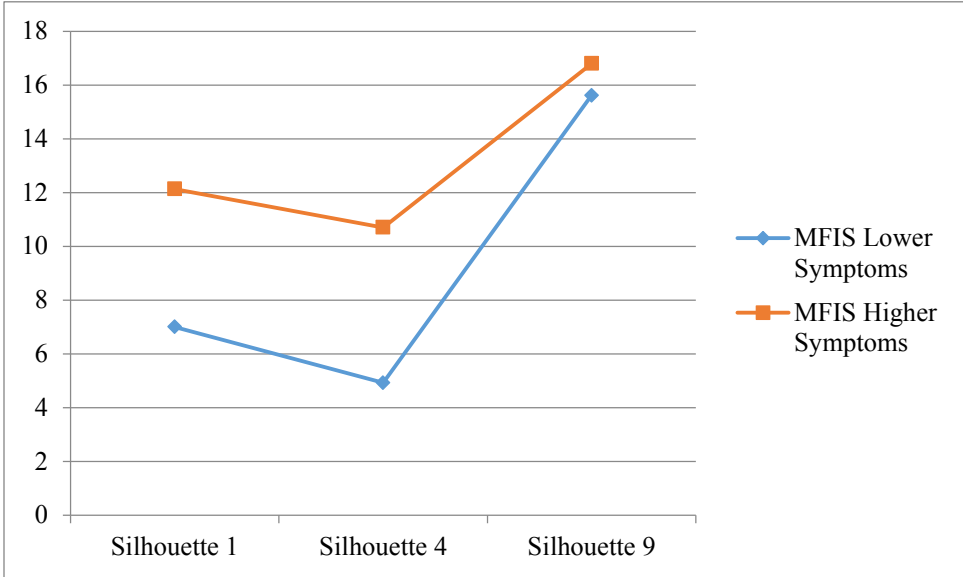


Figure 1. Mean ratings of fatigue at silhouettes 1, 4, and 9 among patients with low and high current fatigue

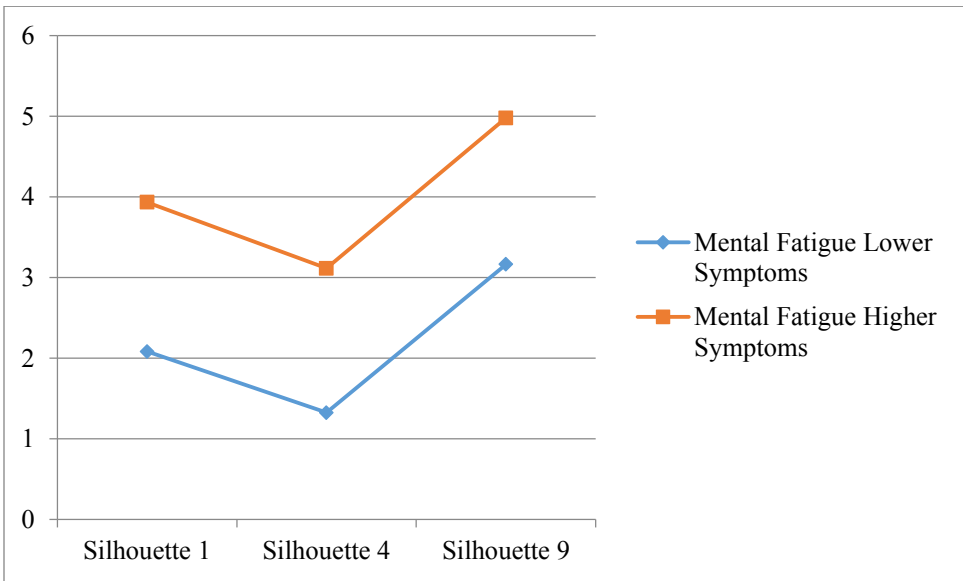


Figure 2. Mean ratings of mental fatigue at silhouettes 1, 4, and 9 among patients with low and high current mental fatigue

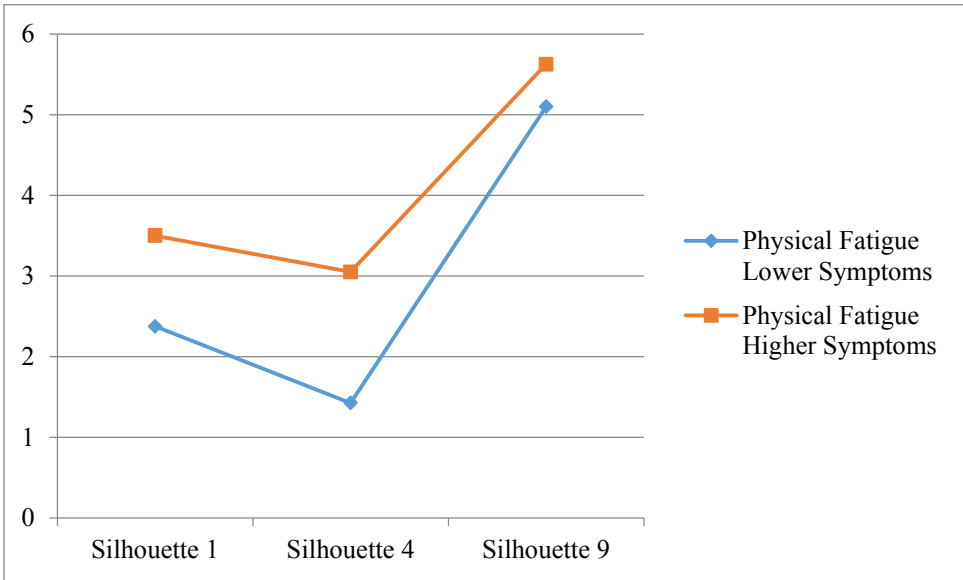


Figure 3. Mean ratings of physical fatigue at silhouettes 1, 4, and 9 among patients with low and high current physical fatigue

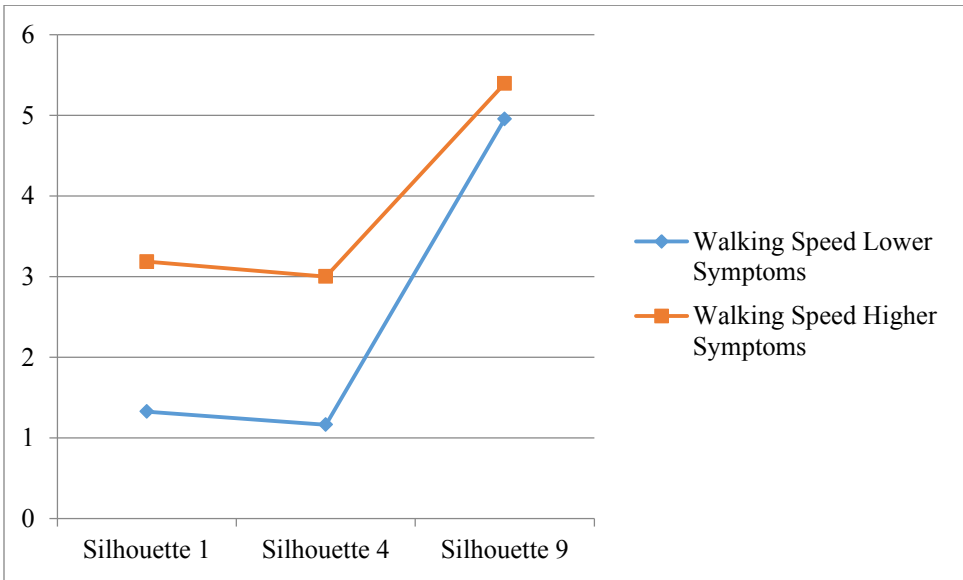


Figure 4. Mean ratings of walking speed impairment at silhouettes 1, 4, and 9 among patients with low and high current walking impairment

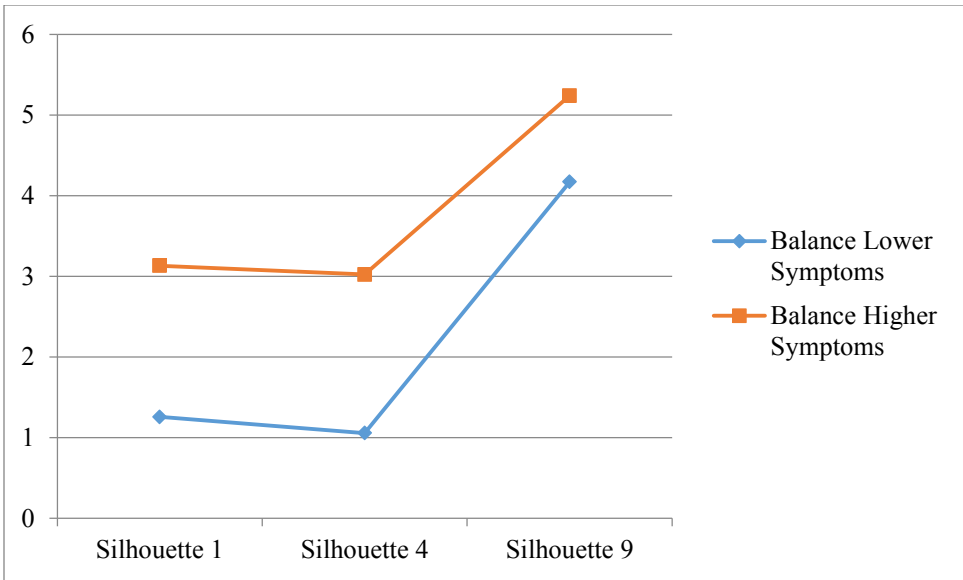


Figure 5. Mean ratings of balance impairment at silhouettes 1, 4, and 9 among patients with low and high current problems with balance

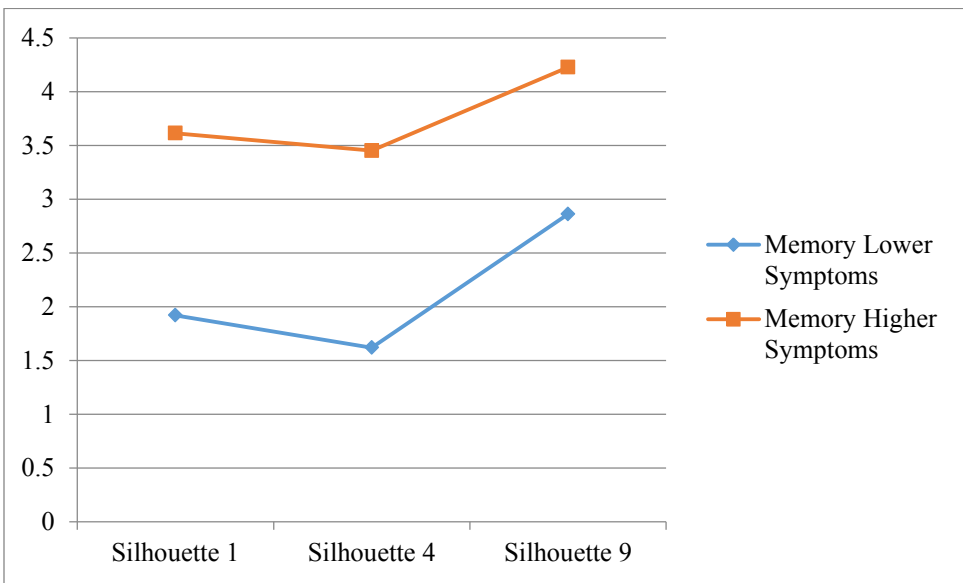


Figure 6. Mean ratings of memory impairment at silhouettes 1, 4, and 9 among patients with low and high current memory impairment

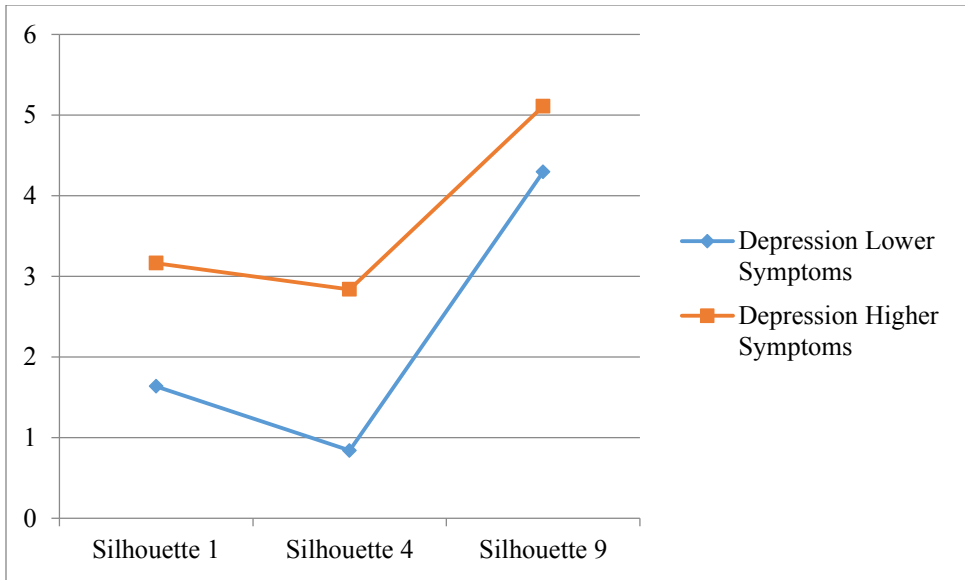


Figure 7. Mean ratings of depression at silhouettes 1, 4, and 9 among patients with low and high current depression

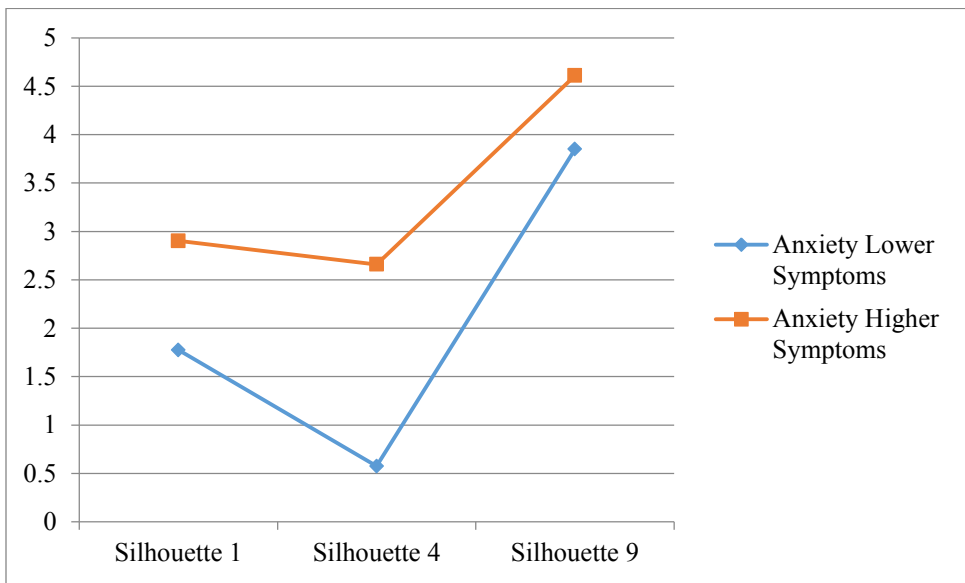


Figure 8. Mean ratings of anxiety at silhouettes 1, 4, and 9 among patients with low and high current anxiety

Impact of overweight/obesity on willingness to exercise for multiple sclerosis symptom improvement (Aim 4)

For the Exercise Willingness Task (EWT), participants were asked to provide the number of minutes of exercise they would be willing to do in order to achieve a hypothetical percentage (5%- 99%) of improvement in several symptoms common to MS (mental fatigue, physical fatigue, walking speed, balance, mood, memory, and overall quality of life) (Appendix C).

A principal components analysis was conducted to determine potential factors for the various symptoms contained within the EWT. The PCA revealed that the questionnaire is unitary and that the items have good validity. Therefore, we opted to average the minutes patients reported willing to exercise for each symptom (mental fatigue, physical fatigue, walking speed, balance, mood, memory) at each percentage of improvement (5%, 10%, 25%, 34%, 50%, 66%, 75%, 90%, 99%).

Two mixed-factor ANOVAs were performed to examine willingness to engage in exercise for a hypothetical percentage of symptom improvement at two time points: immediate and delayed. The average number of minutes an individual was willing to exercise to achieve a specific percentage of improvement (5%-99%) was entered into the analysis. Preliminary analyses showed that current symptom severity, but not weight, was related to exercise willingness. Therefore, current symptom severity was used as the between subjects factor in the analysis. Current symptom severity was calculated as the average of current symptom severity ratings. Examination of histograms and frequency statistics were used to create two equal categorical groups.

Immediate and Delayed Results

See Tables 12-14 for average reported minutes of exercise at each exercise percentage and Mixed-Factor ANOVA results. There was a significant main effect of minutes of exercise across percentage of improvement for both immediate and delayed symptom improvement. This indicated that willingness to exercise to improve symptoms increased as the percentage of benefit increased. There were significant differences between groups (higher and lower symptom severity) in willingness to exercise. Follow-up *t*-tests were conducted to examine differences in exercise willingness between patients with low and high current symptoms (Table 15). Additionally, there were significant interactions in exercise willingness based on group membership. These showed that patients with higher levels of symptom severity reported greater willingness to exercise overall, and, as percentage of improvement increased, group differences in exercise willingness broadened (Figures 9-10). Pairwise comparisons showed significant differences in between all amounts of exercise willingness at each level of hypothetical improvement.

Table 12

Means and standard deviations of exercise willingness to improve symptoms immediately and in 5 years among MS patients

Percentage of Improvement	Immediate		Delayed	
	M	SD	M	SD
5%	10.6313	24.56719	9.8203	16.27977
10%	14.9547	32.71548	12.8031	18.86754
25%	21.1578	35.36351	18.6359	23.90630
34%	26.8766	41.55916	21.8938	26.03822
50%	33.4750	44.51778	28.8141	34.59899
66%	39.3266	47.97595	31.9438	36.37868
75%	46.8938	52.83401	38.9859	44.08333
90%	53.1906	55.47951	44.4188	48.36530
99%	59.7031	63.96918	50.9453	54.55469

Table 13

Mixed-factor ANOVA within-subject effects of exercise willingness to improve symptoms among patients with low and high current symptom severity

Measure	Within Subjects Main Effect		Interaction Main Effect*Group	
	<i>F(df)</i>	<i>P</i>	<i>F(df)</i>	<i>P</i>
Immediate Symptom Improvement	88.20 (1.64,12 4.29)	.000	3.36 (1.64,124. 29)	.047
Delayed Symptom Improvement	103.47 (1.49, 114.97)	.000	581 (1.49, 114.97)	.008

Table 14

Mixed-factor ANOVA between subjects effects of exercise willingness to improve symptoms among patients with low and high current symptom severity

Measure	Between Group ANOVA Current Symptom	
	<i>F(df)</i>	<i>P</i>
Immediate Improvement	6.20 (1, 76)	.015
Delayed Improvement	7.64 (1, 77)	.007

Table 15

T-tests to examine differences in exercise willingness at various hypothetical levels of improvement among patients with low and high current symptom severity

Improvement Percentage	Immediate		Delayed	
	<i>t (df)</i>	<i>p</i>	<i>t (df)</i>	<i>p</i>
5%	-2.07 (66.06)*	.042	-2.02 (66.94)*	.047
10%	-2.13 (77)	.036	-2.11 (77)	.038
25%	-1.67 (77)	.099	-2.01 (77)	.048
34%	-2.01 (77)	.048	-2.13 (77)	.036
50%	-2.02 (77)	.047	-2.25 (77)	.027
66%	-2.27 (77)	.026	-2.16 (77)	.034
75%	-2.29 (77)	.025	-3.01 (77)	.004
90%	-2.07 (77)	.042	-2.94 (77)	.005
99%	-2.12 (77)	.037	-3.09 (59.52)*	.003

Note: *= equal variances not assumed

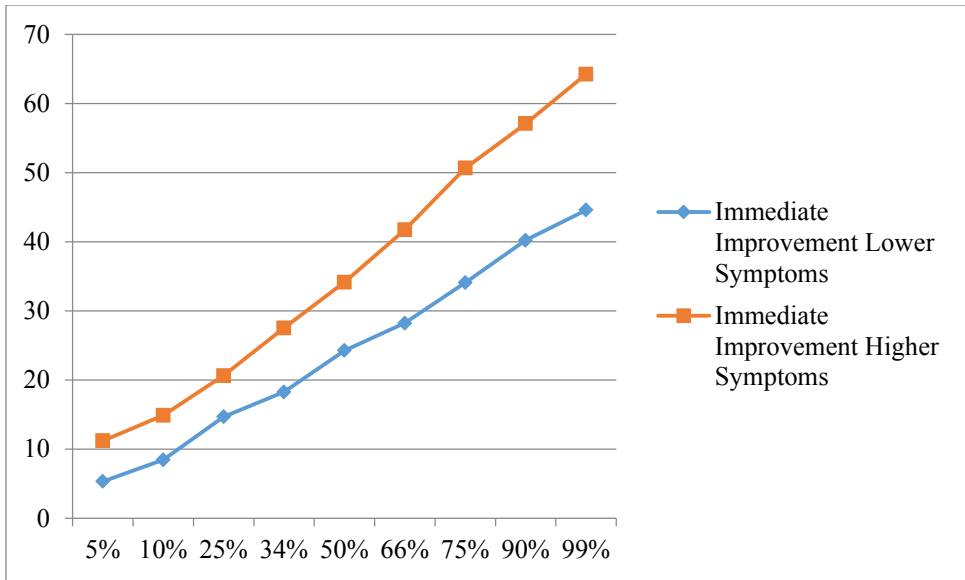


Figure 9. Number of minutes patients with low and high current symptoms reported willing to exercise to improve symptoms immediately

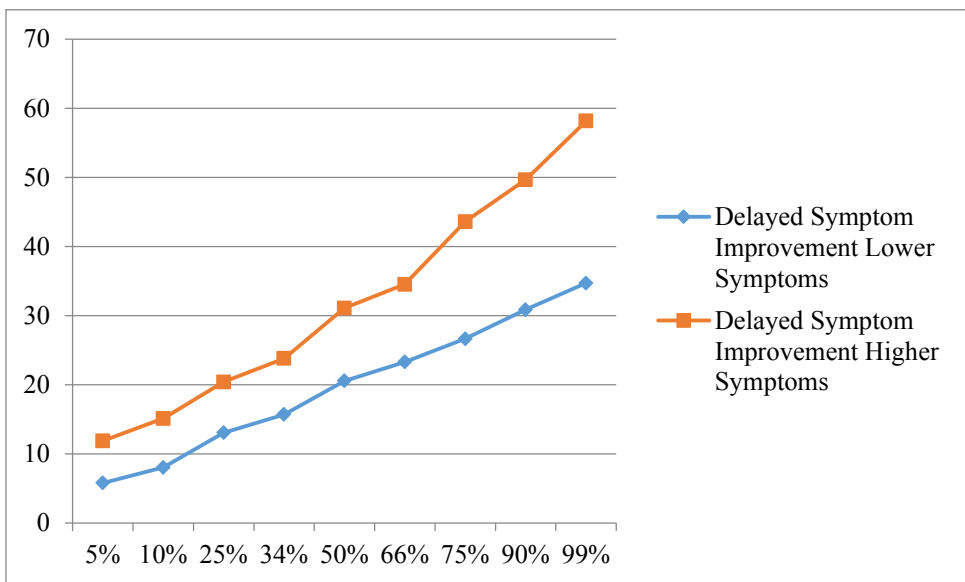


Figure 10. Number of minutes patients with low and high current symptoms reported willing to exercise to improve symptoms in 5 years

CHAPTER 5

DISCUSSION

Importance

High rates of obesity lead to increased risk for several life-threatening health conditions including type II diabetes and metabolic syndromes, hypertension, heart disease, stroke, certain types of cancer, gout, sleep apnea, obesity hypoventilation syndrome, asthma, gallbladder problems, osteoarthritis, stress fractures, reproductive problems, and numerous autoimmune diseases(Kopelman, 2007). Rates of obesity among patients with MS have been shown to be as high or higher than the general population (Matarese et al., 2010; Munger et al., 2009) and some researchers speculate that there is a link between higher levels of leptin and cascades of increased inflammation and eventual neuronal destruction in MS(Matarese et al., 2010; Matarese et al., 2008).

Both MS and obesity are individually linked to debilitating symptoms and their negative effects together may be exponential in furthering MS disease progression(Matarese et al., 2010; Matarese et al., 2008). Therefore, research on the perceived and objective impact of obesity on MS symptoms and progression is warranted. Studies that have examined objective functional differences between healthy weight and overweight MS patients show inconsistent results. Some studies have shown that obesity is related to increased lesion load(Kappus et al., 2015), risk of ambulatory disability(R. A. Marrie et al., 2010), fatigue(Weiland et al., 2015) and depression(Cambil-Martín et al., 2014; Taylor et al., 2014), while others have shown no differences in physical function and ambulatory mobility (Pilutti et al., 2012) or fatigue(Trojan et al., 2007). No research has examined the association between obesity and cognitive function among patients with MS. Furthermore, there is a lack

of knowledge surrounding patient beliefs about the impact of weight on MS symptoms. To date, no research has examined MS patient beliefs about how weight gain/loss impacts symptom severity or how MS patients make hypothetical cost-benefit health behavior decisions. By understanding how patients think weight impacts MS symptoms and their willingness to endure a cost (e.g. exercise) to receive a benefit (e.g. symptom reduction), we may be able to develop individualized interventions that increase motivation to improve health behaviors that lead to reduced symptoms and improved quality of life.

The purpose of this study was to determine if healthy weight and overweight/obese patients with MS differ in cognitive, physical, and emotional function, and beliefs about health and barriers to diet and exercise. We also sought to examine patient beliefs about the negative impact of weight gain on symptom severity, and to explore patient willingness to exercise for hypothetical symptom improvement.

Impact of obesity on physical, emotional, and cognitive function (Aim 1)

We hypothesized that having a healthy weight would be associated with better performance on measures of physical, emotional, and cognitive function. Age was entered into the analyses as a covariate. Consistent with our hypotheses, lower WTHR and lower BMI were both associated with lower levels of depression. Contrary to our hypotheses, excess body weight was not associated with cognition, physical function or anxiety. In contrast, a higher number of stroke risk factors was associated with poorer physical functioning ($r = .353$; $p < .01$) and higher levels of depression in MS ($r = .540$; $p < .01$).

Surprisingly, excess body weight was not associated with physical functioning. However, an increased number of stroke risk factors was associated with worse balance ($r = -.356$; $p < .01$), increased disability ($r = .304$; $p < .01$), and higher levels of physical fatigue ($r =$

.455; $p < .01$). This may indicate that it is not carrying excess weight per se, that negatively impacts physical functioning, but instead the combination of several health factors and behavioral choices associated with obesity. Research shows conflicting data on the impact of body weight on physical function. It is possible that certain cardiovascular and cerebrovascular consequences mediate the impact of weight on overall physical function. As noted above, several studies have found conflicting results when examining the relationship between obesity and physical functioning in MS patients. These conflicting findings may be due in part to the presence or absence of stroke risk factors in disparate study samples (R. A. Marrie et al., 2015) as past research has demonstrated worse lesion load and risk for ambulatory disability with increasing cardiovascular risk factors (Kappus et al., 2015). Future studies should examine which combination of factors (ex. blood pressure, heart beat regularity, diabetes, cholesterol, exercise,) account for the heterogeneous relationship between body weight and physical functioning. These factors may be especially important when discussing the impact of obesity on physical function in patients with MS, as prior research shows that MS patients have higher rates of vascular comorbidities than the general population (R. A. Marrie et al., 2015).

We examined follow-up partial correlations using age as a covariate to examine which individual stroke risk factors were related to variables of physical function. Heartbeat irregularity was associated with increased physical fatigue ($r = .295$; $p < .01$). Diabetes (i.e. blood sugar level) was associated with worse balance ($r = -.226$; $p < .05$) and more disability (PDDS) ($r = .236$; $p < .05$). Elevated cholesterol was associated with worse balance ($r = -.265$; $p < .01$). Less exercise was associated with more physical fatigue ($r = .270$; $p < .05$), and a family history of stroke was associated with increased physical fatigue ($r = .267$; $p < .05$).

These results are consistent with past research that shows clustering of negative health conditions among patients with chronic disease (Bernstein, Wajda, & Blanchard, 2005; Vogeli et al., 2007). That is, the more negative health conditions a person has, the more likely they are to develop health problems. For example, consistent with our study, research has demonstrated that diabetes is associated with poorer physical function. Processes associated with poorly regulated blood sugar, such as neuropathy, cardiorespiratory capacity, or sub-clinical cardiovascular disease, also contribute to worse disability and a higher risk for falling due to negative effects of unregulated blood sugar on cardiorespiratory capacity, balance, dizziness, general weakness, muscle cramps and blurred vision (Gregg et al., 2000; Najafi, Bharara, Talal, & Armstrong, 2012; Ryerson et al., 2003). Such processes may also set the stage for other chronic health conditions and research has shown that multiple chronic conditions can, at times, interact and cause synergistic functional impairment (Fultz, Ofstedal, Herzog, & Wallace, 2003). Patients with MS may be especially prone to developing other chronic conditions because of the inflammatory nature of the disease (Bernstein et al., 2005). Taken together, the results of our study, along with past research, highlight an important role for educational intervention among patients with multiple negative health conditions. Patients may not realize the interaction that several negative health behaviors and/or conditions may have with one another and may benefit from interventions that target risk factors for multiple chronic conditions. Physical activity, diabetes, and cholesterol can be addressed through behavioral intervention. Diabetes management may be especially important for patients with MS because of its relationship to physical and motor dysfunction which is also precipitated by the MS disease process. A healthy diet designed to manage and lower cholesterol is also consistent with nutrition guidelines for MS patients that recommend a diet low in saturated

fats (i.e. proinflammatory fats)(Zhang, Willett, Hernán, Olek, & Ascherio, 2000). Previous research has also demonstrated positive effects of exercise on cardiovascular and cerebrovascular risk factors, inflammation, and MS fatigue(Fulcher & White, 1997; Latimer-Cheung, Pilutti, et al., 2013; McCullagh, Fitzgerald, Murphy, & Cooke, 2008; Nicklas, You, & Pahor, 2005). Patients whose treatments target underlying risk factors for other chronic diseases and comorbid conditions may experience improved long-term outcomes relative to those whose treatments only consider MS.

Higher levels of depression and anxiety exist in both MS and obese persons relative to the general population(Jones et al., 2012; Siegert & Abernethy, 2005). However, some research indicates that obese patients experience higher lifetime levels of depression than anxiety(Zhao et al., 2009). Other research has found depression to be more highly associated with worse health behaviors than anxiety(Bonnet et al., 2005). Our study found that depression, but not anxiety, was associated with excess body weight in MS. Depression may compound the negative effects of fatigue and physical disability by further reducing motivation and energy to engage in health behaviors that have the capacity to maintain a healthy and stable body weight(Bakshi, Shaikh, et al., 2000; Kroencke, Lynch, & Denney, 2000). That there is a strong relationship between depression and fatigue such that those with higher levels of depression experience higher levels of fatigue (Bakshi, Shaikh, et al., 2000). Interventions to help patients cope with psychological aspects of chronic disease may have beneficial implications for both depression and MS fatigue.

Our study did not find significant associations between excess body weight and cognitive function. Some past research has indicated that there is an association between increased BMI and reduced cognitive function(Gunstad et al., 2007). Cognitive problems

caused by obesity may be relatively small compared to those caused by MS and thus, a very large sample size would be needed to detect an effect. It is also plausible that differences in cognitive function due to obesity may be unmasked at a later point in disease progression with greater disability. Specifically, the impact of obesity on cognitive function may not yet be detectable as we included patients who primarily had a diagnosis of RRMS and generally lower levels of disability (PDDS ≤ 5). The effect of obesity on these capabilities may compound over time and may be best studied in patients with greater disability and progressive forms of MS. It is also possible that a much larger sample of extreme obesity may provide greater power to detect differences between groups.

Impact of obesity on MS specific health beliefs, dieting beliefs, and barriers to healthy diet and exercise (Aim 2)

We hypothesized that excess body weight would be associated with increased barriers to exercise and a healthy diet and also reduced belief in one's ability to positively impact their MS and control body weight (Dieting Beliefs Scale). When controlling for age, excess body weight was associated with increased barriers to exercise and eating a healthy diet. However, there were no significant associations between excess body weight and belief in one's ability to control his/her weight or MS specific health beliefs. Our results indicated that both healthy weight and overweight/obese MS patients hold similar beliefs about weight and weight loss that reflect an internal locus of control. Likewise, participants perceived an association between health behaviors (i.e. eating healthy and exercise) and the potential for improvement in MS symptoms and progression. These results are promising and indicate that MS patients endorse the belief that weight can be managed by the individual and that health behaviors can be used to positively impact MS. A higher WTHR was associated with a

larger number of barriers to diet and exercise. Previous research has shown a relationship between higher BMI and increased barriers to health behaviors (Sharifi, Mahdavi, & Ebrahimi-Mameghani, 2013). Interventions which aim to reduce barriers to exercise and healthy eating may be imperative to facilitate health behavior change among patients who are overweight and have MS, as these two conditions often carry increased barriers to health behaviors. For example, patients may benefit from programs that emphasize small amounts of progress over sweeping changes (i.e. “5 minutes is better than zero minutes”) and that teach them ways to exercise from home. Simple exercises that don’t require expensive equipment or complex motor coordination may be especially suited to patients with MS. Dietary interventions that teach strategies to reduce fatigue while cooking could be paramount to improving patient dietary habits. For example, patients may benefit from learning simple recipes that can be prepared throughout the day, recipes that can be prepared and frozen in advance, grocery delivery services, or from modifications to kitchen work spaces (i.e. lowered tables, kitchen tools that require less strength and force). Importantly, interventions should strive to balance the disability of the individual while also promoting active engagement in health improvement.

Explore patient beliefs about the impact of weight on MS symptoms and fatigue

(Aim 3)

We sought to explore perceived associations between various body weights and symptom severity, including MFIS fatigue using the BSS task. Current symptom severity was used as the between subjects factor. On the BSS task, MS patients predicted that symptoms would significantly change based on weight gain or loss. Mean symptom ratings indicated that)participants predicted the worst severity at an obese body weight (silhouette 9)

and the best severity at a healthy body weight (silhouette 4). There were significant interactions based on group membership (low and high symptom severity) and ratings for the 3 silhouettes on symptoms of MFIS fatigue, physical fatigue, walking speed, balance, anxiety, and depression. Examination of these interactions generally showed that those with higher current symptom severity perceived higher symptom severity at the different silhouettes relative to patients with lower current symptom severity; the magnitude of this difference was greatest for silhouettes 1 and 4. It may be that patients with worse current symptoms have less hope that symptoms could be improved through weight loss which may reduce motivation to increase health behaviors.

These results confirm that MS patients perceive a link between weight gain/loss and change in symptom severity. However, these results do not illuminate reasons why many MS patients maintain an unhealthy weight if they also believe that obesity is related to worse MS symptoms. Interaction analyses showed that patients with higher current symptoms hypothesized less symptom improvement with weight loss than patients with lower current symptoms. This illuminates a need for research on the specific gains that patients can expect in symptom improvement if they lose various percentages of excess body weight. The ability to provide patients with reasonable expectations would be highly valuable in the development of tailored weight loss programs. Patients may also benefit from interventions which emphasize the link between weight, diet, exercise, and inflammation. Such future research with this added information may be used to harness and strengthen the perceived association between weight and worsened MS symptoms to subsequently produce changes in health behaviors that may result in improved outcomes during the disease course.

Explore predicted willingness to engage in exercise for a hypothetical symptom improvement (Aim 4)

We also sought to explore MS patient willingness to endure a cost (exercise) to achieve a hypothetical gain (symptom improvement) using the EWT. As expected, MS patients reported significantly increased willingness to exercise for a longer period of time as the hypothetical percentage of symptom improvement increased. This was consistent for both immediate and delayed improvements. The analysis of exercise to achieve immediate improvement revealed a significant interaction between group (higher versus lower current symptoms) and reported minutes of exercise at various percentages. Specifically, we found that patients with higher symptoms reported greater minutes of exercise willingness relative to patients with lower current symptoms and this difference increased as the percentage of hypothetical improvement increased. Future studies that target improving motivation for health behavior change when symptoms are less severe may improve patient outcomes as their disease progresses.

Exercise can improve hypertension, insulin resistance, glucose intolerance and high density lipoprotein levels (P. D. Thompson, 2003). Prevention and improvement of comorbidities such as diabetes, hypertension, hyperlipidemia, cardiovascular disease and cerebrovascular disease may require extra attention within the MS population due to the specific physical, cognitive, and psychological complications associated with MS. In addition to general comorbidities, past research has demonstrated that autoimmune diseases carry an increased risk of vascular disease that cannot be explained fully by traditional risk factors. Researchers speculate that inflammatory processes are risk factors in and of themselves for vascular comorbidities which result in several negative health outcomes (R.

A. Marrie et al., 2015). Furthermore, MS patients, even in the earlier stages of disease, have been shown to exercise less, use more tobacco, and be more overweight than the general population (R. A. Marrie et al., 2015). This indicates that patients with MS may have additional behavioral and physiological hurdles standing in the way of optimal health. Future methods which help patients engage in preventative strategies, especially during the early disease process, may be tantamount to improving long-term progression and symptom expression.

No previous studies have examined MS patient willingness to exercise (or engage in health behaviors) to achieve health benefits. We found that patients' reasoning followed a logical progression such that patients were willing to exercise more as the amount of benefit increased. These results are promising as they indicate that patients are able to engage in planning health behavior interventions in a meaningful and logical way. Patients may be especially motivated by real-world data on the amount of improvement that can be reasonably expected from exercise interventions. This is similar to how patients make cost-benefit decisions about medications. For example, patients often want to know how much medication will lead to improvement and what side effects to expect before making a decision to begin taking medication. This information is readily available for many medications, but little, if any, information regarding the amount of clinically significant improvement that will result from weight loss interventions or exercise is provided to patients (Latimer-Cheung, Pilutti, et al., 2013). More often, patients are told that they will likely see gains in functional abilities, strength, mobility, etc (Latimer-Cheung, Martin Ginis, et al., 2013; Latimer-Cheung, Pilutti, et al., 2013). This lack of specificity may reduce motivation or belief that exercise may be an important component of symptom improvement.

Future studies should garner data on the average amount of symptom improvement patients experience with different types and amounts of exercise. By understanding what kind and how much improvement patients require to maintain motivation for exercise, researchers may be better able to design tailored interventions and provide patients with reasonable and achievable expectations for improvement. This kind of shared decision making may help patients make decisions about what types and what amounts of exercise they would be willing to do for typical benefits experienced by patients with similar health problems. Such future studies may increase patient adherence to interventions and long-term health behaviors.

Although the preliminary results were promising and participants' answers followed a logical progression, it is unclear to what extent these results would hold in a real-life scenario. Previous research indicates that follow-through on intention for health behaviors is poor as a high proportion of individuals are poorly compliant to medications, weight loss regimens, smoking cessation, and other forms of health behavior change (Haynes, McDonald, & Garg, 2002). Even with the known benefits of exercise, most individuals do not meet the guidelines for minimal physical activity and often significantly overestimate the number of minutes of exercise they actually complete (Messer, 2012) (Dyrstad, Hansen, Holme, & Anderssen, 2014). Therefore, it can be reasoned that patients in this study overestimated the true number of minutes they could feasibly exercise on a consistent basis (Gomersall, Norton, Maher, English, & Olds, 2015). Patients may benefit from two types of information: (1) Information on how much exercise others of a similar health status are able to reliably complete on average, and (2) Information on the actual amount of exercise and health behavior change needed for specific amounts of symptom improvement. This may be used to

provide patients with realistic expectations and aid them in developing achievable goals that will result in measurable improvements in symptom severity.

Furthermore, many participants reported this task to be cognitively taxing which may have reduced motivation to consider each symptom and percent-improvement item individually. Future studies should determine which symptoms patients would like to improve most and use this to customize interventions that optimize the potential for adherence. Despite these limitations, results of this task indicate that patients may be willing, or even enthusiastic, to participate in the planning of their own health behavior interventions when given quantitative information about possible associated health outcomes.

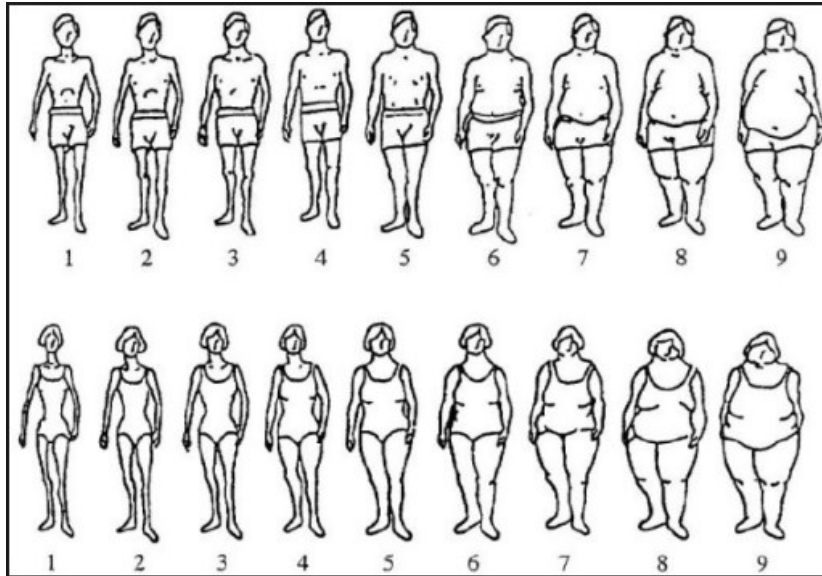
Conclusions

This was the first study to examine MS patient beliefs about the impact of excess body weight on disease symptoms and patient willingness to engage in exercise to experience proposed improvements in MS symptoms. Our results indicated that there is an association between depression and higher levels of obesity in MS. In addition, patients with more stroke risk factors exhibited poorer physical functioning. The BSS task showed that patients do perceive a link between their body weight and the severity of their symptoms. Furthermore, on the EWT patients reported increased willingness to exercise as the level of proposed benefit increased.

The results of this study highlight that patients with MS perceive an association between their weight and symptom severity; also, patients are willing to consider enduring health behavior costs that result in MS symptom improvement. Notably, current rated symptom severity emerged in our analyses as an important moderator of body silhouette symptom rating (those with the worst current symptoms expected less improvement in

symptoms at a healthy weight or low body weight) and willingness to exercise for proposed benefit (those with the worst current symptoms reported greater willingness to exercise and this increased alongside the percentage of hypothetical improvement). This shows that those with the worst current symptoms may expect less benefit with weight loss, but also express greater willingness to exercise when high levels of benefit are sure. This reveals a need for future research that objectively examines clinically significant changes in symptom expression, symptom severity, disease progression, and lesion load following weight gain or loss. Future studies may capitalize on these results by providing patients with data on what gains to expect for various health interventions. Interventions that provide this information may improve adherence by supporting patients in making logical decisions about the amount of health behavior change they are willing to endure to receive symptom improvement. Such tailored treatments may serve as a preventative strategy used to mitigate unnecessary physical, cognitive, and emotional decline associated with excess body weight. Capitalizing on prevention earlier in the disease course, when patients are most capable, is likely paramount to improving long-term outcomes for MS patients.

Appendix A
Body Size and Symptoms Task



Please write down what you think your symptoms would be if you were at body silhouettes 1, 4, and 9.

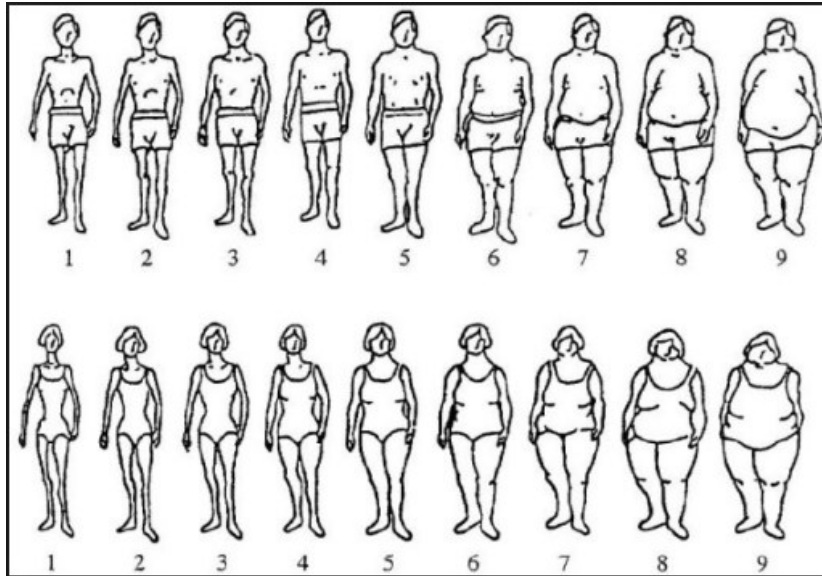
No issues	Slight Problems			Moderate Problems	Severe Problems	
0	1	2	3	4	5	6

	You at body silhouette #1	You at body silhouette #4	You at body silhouette #9
Mental Fatigue			
Physical Fatigue			
Pain			
Balance			
Walking Speed			
Sleep Quality			
Memory			
Thinking Speed			
Depression			
Anxiety			
Disease Progression Speed			

Appendix B

Body Size and Symptoms Task- Fatigue

Please fill out the following questionnaire based on how you believe you would feel at each of the listed body silhouettes. Starting with "silhouette 1" go down the column and fill in the number that you believe would correspond with how you'd feel if you were at each specified silhouette.



Never	Rarely	Sometimes	Often	Almost Always
0	1	2	3	4

	Silhouette #1	Silhouette #4	Silhouette #9
I would have reduced alertness			
I would be limited in my ability to do things away from home			
I would have trouble maintaining physical effort for long periods			
I would be less able to complete tasks that require physical effort			
I would have trouble concentrating			

Appendix C
 Exercise Willingness Task

Sometimes it is hard to do things that are healthy for our bodies. It may seem like exercise and eating healthy don't provide us with noticeable improvement in health. For this activity, let's pretend that you know exercising will improve your MS symptoms by a certain percent. Please **write down the number of extra minutes** (beyond what you already do) **you'd be willing to engage in strenuous exercise** (the kind that makes your heart beat fast and makes you feel out of breath) EACH DAY to receive symptom reduction.

We will do this exercise **2 times**. On the first you will write down the minutes you'd be willing to exercise strenuously to improve your symptoms IMMEDIATELY. The next two will surround what you're willing to do to achieve symptom improvement in 5 years without any *current* improvement.

Strenuous exercise includes things that make your heart beat faster and make you feel out of breath. This could be things like running, climbing the stairs, weight lifting, hiking a mountain, using a cardio machine at the gym.

Remember, try to imagine what it would feel like to have improvement in these areas of your life. You're not being asked to add up the exercise per day for each symptom. Try to think of them separately.

***Imagine what it would feel like to keep your heart rate up the entire time you're exercising for this activity.

Here's an example:

	33% improvement in symptoms	66% improvement in symptoms	90% improvement in symptoms	100% improvement in symptoms
Fatigue	10	15	30	60
Walking Speed	5	10	15	20
Balance	5	15	20	30
Mood	0	5	8	20
Weakness	10	25	40	55

Write down the additional number of minutes you'd be willing to spend in strenuous exercise each day to achieve the hypothetical improvement in your symptoms IMMEDIATELY (alternate form: IN 5 YEARS).

	Percent Symptom Improvement								
	<5%	10%	25%	34%	50%	66%	75%	90%	>99%
Mental Fatigue									
Physical Fatigue									
Walking Speed									
Balance									
Mood									
Memory									

References

- Acheson, E. D., Bachrach, C. A., & Wright, F. M. (1960). Some comments on the relationship of the distribution of multiple sclerosis to latitude, solar radiation, and other variables. *Acta Psychiatrica Scandinavica. Supplementum*, 35(147), 132-147.
- Al Maskari, M. Y., & Alnaqdy, A. A. (2006). Correlation between Serum Leptin Levels, Body Mass Index and Obesity in Omanis. *Sultan Qaboos University Medical Journal*, 6(2), 27-31.
- Alonso, A., & Hernán, M. A. (2008). Temporal trends in the incidence of multiple sclerosis: A systematic review. *Neurology*, 71(2), 129-135. doi:10.1212/01.wnl.0000316802.35974.34
- Andajani-Sutjahjo, S., Ball, K., Warren, N., Inglis, V., & Crawford, D. (2004). Perceived personal, social and environmental barriers to weight maintenance among young women: A community survey. *The International Journal of Behavioral Nutrition and Physical Activity*, 1(1), 15. doi:10.1186/1479-5868-1-15
- Andrade, V. M., Bueno, O. F., Oliveira, M. G., Oliveira, A. S., Oliveira, E. M., & Miranda, M. C. (1999). Cognitive profile of patients with relapsing remitting multiple sclerosis. *Arquivos de Neuro-Psiquiatria*, 57(3B), 775-783.
- Arnett, P. A., Rao, S. M., Grafman, J., Bernardin, L., Luchetta, T., Binder, J. R., & Lobeck, L. (1997). Executive functions in multiple sclerosis: An analysis of temporal ordering, semantic encoding, and planning abilities. *Neuropsychology*, 11(4), 535-544.
- Arnett, P. A., & Strober, L. B. (2011). Cognitive and neurobehavioral features in multiple sclerosis. *Expert Review of Neurotherapeutics*, 11(3), 411-424. doi:10.1586/ern.11.12
- Ascherio, A. (2013). Environmental factors in multiple sclerosis. *Expert Review of Neurotherapeutics*, 13(12 Suppl), 3-9. doi:10.1586/14737175.2013.865866
- Ascherio, A., & Munger, K. L. (2007a). Environmental risk factors for multiple sclerosis. Part I: The role of infection. *Annals of Neurology*, 61(4), 288-299. doi:10.1002/ana.21117
- Ascherio, A., & Munger, K. L. (2007b). Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. *Annals of Neurology*, 61(6), 504-513. doi:10.1002/ana.21141
- Ascherio, A., & Munger, K. L. (2010). Epstein-barr virus infection and multiple sclerosis: A review. *Journal of Neuroimmune Pharmacology*, 5(3), 271-277. doi:10.1007/s11481-010-9201-3
- Ascherio, A., Munger, K. L., White, R., Köchert, K., Simon, K. C., Polman, C. H., . . . Pohl, C. (2014). Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA Neurol*, 71(3), 306-314. doi:10.1001/jamaneurol.2013.5993
- Ashwell, M., Gunn, P., & Gibson, S. (2012). Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obesity Reviews*, 13(3), 275-286. doi:10.1111/j.1467-789X.2011.00952.x
- Ashwell, M., & Hsieh, S. D. (2005). Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. *International Journal of Food Sciences and Nutrition*, 56(5), 303-307. doi:10.1080/09637480500195066
- Ashwell, M., Mayhew, L., Richardson, J., & Rickayzen, B. (2014). Waist-to-height ratio is more predictive of years of life lost than body mass index. *PloS One*, 9(9), e103483. doi:10.1371/journal.pone.0103483
- Association, N. S. (2015). Stroke Risk Scorecard. In.
- Bakshi, R., Czarnecki, D., Shaikh, Z. A., Priore, R. L., Janardhan, V., Kaliszky, Z., & Kinkel, P. R. (2000). Brain MRI lesions and atrophy are related to depression in multiple sclerosis. *Neuroreport*, 11(6), 1153-1158.
- Bakshi, R., Shaikh, Z. A., Miletich, R. S., Czarnecki, D., Dmochowski, J., Henschel, K., . . . Kinkel, P. R. (2000). Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Multiple Sclerosis*, 6(3), 181-185. doi:10.1177/135245850000600308
- Banks, W. A., Coon, A. B., Robinson, S. M., Moinuddin, A., Shultz, J. M., Nakaoke, R., & Morley, J. E. (2004). Triglycerides induce leptin resistance at the blood-brain barrier. *Diabetes*, 53(5), 1253-1260.

- Baughcum, A. E., Chamberlin, L. A., Deeks, C. M., Powers, S. W., & Whitaker, R. C. (2000). Maternal perceptions of overweight preschool children. *Pediatrics*, *106*(6), 1380-1386.
- Benedict, R. H., Bruce, J. M., Dwyer, M. G., Abdelrahman, N., Hussein, S., Weinstock-Guttman, B., . . . Zivadinov, R. (2006). Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. *Archives of Neurology*, *63*(9), 1301-1306.
doi:10.1001/archneur.63.9.1301
- Benedict, R. H., Ramasamy, D., Munschauer, F., Weinstock-Guttman, B., & Zivadinov, R. (2009). Memory impairment in multiple sclerosis: Correlation with deep grey matter and mesial temporal atrophy. *Journal of Neurology, Neurosurgery and Psychiatry*, *80*(2), 201-206.
doi:10.1136/jnnp.2008.148403
- Benedict, R. H., Smerbeck, A., Parikh, R., Rodgers, J., Cadavid, D., & Erlanger, D. (2012). Reliability and equivalence of alternate forms for the Symbol Digit Modalities Test: Implications for multiple sclerosis clinical trials. *Multiple Sclerosis*, *18*(9), 1320-1325.
doi:10.1177/1352458511435717
- Benito-León, J., Morales, J. M., & Rivera-Navarro, J. (2002). Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients. *European Journal of Neurology*, *9*(5), 497-502.
- Bernstein, C. N., Wajda, A., & Blanchard, J. F. (2005). The clustering of other chronic inflammatory diseases in inflammatory bowel disease: A population-based study. *Gastroenterology*, *129*(3), 827-836. doi:10.1053/j.gastro.2005.06.021
- Bethoux, F., & Bennett, S. (2011). Evaluating walking in patients with multiple sclerosis: Which assessment tools are useful in clinical practice? *Int J MS Care*, *13*(1), 4-14.
doi:10.7224/1537-2073-13.1.4
- Bishop, K. L. (2002). Longitudinal predictors of weight fluctuation in men and women. *Dissertation abstracts international*, *64*, 1892-2046.
- Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Journal of Psychosomatic Research*, *52*(2), 69-77.
- Blaak, E. (2001). Gender differences in fat metabolism. *Current Opinion in Clinical Nutrition and Metabolic Care*, *4*(6), 499-502.
- Bonnet, F., Irving, K., Terra, J. L., Nony, P., Berthezène, F., & Moulin, P. (2005). Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. *Atherosclerosis*, *178*(2), 339-344. doi:10.1016/j.atherosclerosis.2004.08.035
- Bosnar-Puretić, M., Basić-Kes, V., Jursić, M. J., Zavoreo, I., & Demarin, V. (2009). The association of obesity and cerebrovascular disease in young adults: A pilot study. *Acta Clinica Croatica*, *48*(3), 295-298.
- Boström, I., Stawiarz, L., & Landtblom, A. M. (2013). Sex ratio of multiple sclerosis in the National Swedish MS Register (SMSreg). *Multiple Sclerosis*, *19*(1), 46-52.
doi:10.1177/1352458512446169
- Bougoulia, M., Triantos, A., & Koliakos, G. (2006). Effect of weight loss with or without orlistat treatment on adipocytokines, inflammation, and oxidative markers in obese women. *Hormones (Athens)*, *5*(4), 259-269.
- Braley, T. J., & Chervin, R. D. (2010). Fatigue in multiple sclerosis: Mechanisms, evaluation, and treatment. *Sleep*, *33*(8), 1061-1067.
- Brissart, H., Morele, E., Baumann, C., & Debouverie, M. (2012). Verbal episodic memory in 426 multiple sclerosis patients: Impairment in encoding, retrieval or both? *Neurological Sciences*, *33*(5), 1117-1123. doi:10.1007/s10072-011-0915-7
- Brown, R. F., Valpiani, E. M., Tennant, C. C., Dunn, S. M., Sharrock, M., Hodgkinson, S., & Pollard, J. D. (2009). Longitudinal assessment of anxiety, depression, and fatigue in people with multiple sclerosis. *Psychology and Psychotherapy*, *82*(Pt 1), 41-56.
doi:10.1348/147608308X345614

- Bruce-Keller, A. J., Keller, J. N., & Morrison, C. D. (2009). Obesity and vulnerability of the CNS. *Biochimica et Biophysica Acta*, 1792(5), 395-400. doi:10.1016/j.bbadis.2008.10.004
- Buchwald, H., Avidor, Y., Braunwald, E., Jensen, M. D., Pories, W., Fahrenbach, K., & Schoelles, K. (2004). Bariatric surgery: A systematic review and meta-analysis. *JAMA*, 292(14), 1724-1737. doi:10.1001/jama.292.14.1724
- Bulik, C. M., Wade, T. D., Heath, A. C., Martin, N. G., Stunkard, A. J., & Eaves, L. J. (2001). Relating body mass index to figural stimuli: Population-based normative data for Caucasians. *International Journal of Obesity and Related Metabolic Disorders*, 25(10), 1517-1524. doi:10.1038/sj.ijo.0801742
- Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *New England Journal of Medicine*, 348(17), 1625-1638. doi:10.1056/NEJMoa021423
- Cambil-Martín, J., Galiano-Castillo, N., Muñoz-Hellín, E., Díaz-Rodríguez, L., Laguarda-Val, S., Fernández-de-Las-Peñas, C., & Arroyo-Morales, M. (2014). Influence of body mass index on psychological and functional outcomes in patients with multiple sclerosis: A cross-sectional study. *Nutritional Neuroscience*. doi:10.1179/1476830514Y.0000000156
- Cantorna, M. T. (2008). Vitamin D and multiple sclerosis: An update. *Nutrition Reviews*, 66(10 Suppl 2), S135-138. doi:10.1111/j.1753-4887.2008.00097.x
- Carmona, R. H. (2003). *The obesity crisis in America*. Washington, DC.
- Carnell, S., Edwards, C., Croker, H., Boniface, D., & Wardle, J. (2005). Parental perceptions of overweight in 3-5 y olds. *International Journal of Obesity (2005)*, 29(4), 353-355. doi:10.1038/sj.ijo.0802889
- Carr, D., & Friedman, M. A. (2005). Is obesity stigmatizing? Body weight, perceived discrimination, and psychological well-being in the United States. *Journal of Health and Social Behavior*, 46(3), 244-259.
- Cawley, J., Rizzo, J. A., & Haas, K. (2007). Occupation-specific absenteeism costs associated with obesity and morbid obesity. *Journal of Occupational and Environmental Medicine*, 49(12), 1317-1324. doi:10.1097/JOM.0b013e31815b56a0
- Chaboyer, W., Lee, B. O., Wallis, M., Gillespie, B., & Jones, C. (2010). Illness representations predict health-related quality of life 6 months after hospital discharge in individuals with injury: A predictive survey. *Journal of Advanced Nursing*, 66(12), 2743-2750. doi:10.1111/j.1365-2648.2010.05431.x
- Chassaing, B., & Gewirtz, A. T. (2014). Gut microbiota, low-grade inflammation, and metabolic syndrome. *Toxicologic Pathology*, 42(1), 49-53. doi:10.1177/0192623313508481
- Chassaing, B., Koren, O., Goodrich, J. K., Poole, A. C., Srinivasan, S., Ley, R. E., & Gewirtz, A. T. (2015). Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature*, 519(7541), 92-96. doi:10.1038/nature14232
- Chaudhuri, A., & Behan, P. O. (2000). Fatigue and basal ganglia. *Journal of the Neurological Sciences*, 179(S 1-2), 34-42.
- Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet Neurology*, 7(12), 1139-1151. doi:10.1016/S1474-4422(08)70259-X
- Chodera, J., & Levell, R. (1973). *Footprint patterns during walking*. Baltimore, MD: University Park Press.
- Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. (1998). *American Journal of Clinical Nutrition*, 68(4), 899-917.
- Confavreux, C., Vukusic, S., Moreau, T., & Adeleine, P. (2000). Relapses and progression of disability in multiple sclerosis. *New England Journal of Medicine*, 343(20), 1430-1438. doi:10.1056/NEJM200011163432001
- Corboy, J. R., Goodin, D. S., & Frohman, E. M. (2003). Disease-modifying therapies for multiple sclerosis. *Current Treatment Options in Neurology*, 5(1), 35-54.

- Correale, J., Ysraelit, M. C., & Gaitán, M. I. (2009). Immunomodulatory effects of Vitamin D in multiple sclerosis. *Brain*, *132*(Pt 5), 1146-1160. doi:10.1093/brain/awp033
- Corthals, A. P. (2011). Multiple sclerosis is not a disease of the immune system. *Quarterly Review of Biology*, *86*(4), 287-321.
- Craddock, D., & Thomas, A. (2006). Cytokines and late-life depression. *Essent Psychopharmacol*, *7*(1), 42-52.
- Dalgas, U., & Stenager, E. (2012). Exercise and disease progression in multiple sclerosis: Can exercise slow down the progression of multiple sclerosis? *Therapeutic Advances in Neurological Disorders*, *5*(2), 81-95. doi:10.1177/1756285611430719
- Dalgas, U., Stenager, E., & Ingemann-Hansen, T. (2008). Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. *Multiple Sclerosis*, *14*(1), 35-53. doi:10.1177/1352458507079445
- Dallman, M. F., Pecoraro, N. C., La Fleur, S. E., Warne, J. P., Ginsberg, A. B., Akana, S. F., . . . Bell, M. E. (2006). Glucocorticoids, chronic stress, and obesity. *Progress in Brain Research*, *153*, 75-105. doi:10.1016/S0079-6123(06)53004-3
- De Bellis, M. D., Gold, P. W., Geraciotti, T. D., Listwak, S. J., & Kling, M. A. (1993). Association of fluoxetine treatment with reductions in CSF concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. *American Journal of Psychiatry*, *150*(4), 656-657.
- De Stefano, N., Narayanan, S., Francis, G. S., Arnaoutelis, R., Tartaglia, M. C., Antel, J. P., . . . Arnold, D. L. (2001). Evidence of axonal damage in the early stages of multiple sclerosis and its relevance to disability. *Archives of Neurology*, *58*(1), 65-70.
- Deep, P. (1999). Biological and biopsychosocial models of health and disease in dentistry. *Journal of the Canadian Dental Association. Journal de L'Association Dentaire Canadienne*, *65*(9), 496-497.
- DeLuca, J., Barbieri-Berger, S., & Johnson, S. K. (1994). The nature of memory impairments in multiple sclerosis: Acquisition versus retrieval. *Journal of Clinical and Experimental Neuropsychology*, *16*(2), 183-189. doi:10.1080/01688639408402629
- DeLuca, J., Chelune, G. J., Tulskey, D. S., Lengenfelder, J., & Chiaravalloti, N. D. (2004). Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *Journal of Clinical and Experimental Neuropsychology*, *26*(4), 550-562. doi:10.1080/13803390490496641
- DeLuca, J., Genova, H. M., Hillary, F. G., & Wylie, G. (2008). Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI. *Journal of the Neurological Sciences*, *270*(1-2), 28-39. doi:10.1016/j.jns.2008.01.018
- Demaree, H. A., DeLuca, J., Gaudino, E. A., & Diamond, B. J. (1999). Speed of information processing as a key deficit in multiple sclerosis: Implications for rehabilitation. *Journal of Neurology, Neurosurgery and Psychiatry*, *67*(5), 661-663.
- Desvergne, B., Michalik, L., & Wahli, W. (2006). Transcriptional regulation of metabolism. *Physiological Reviews*, *86*(2), 465-514. doi:10.1152/physrev.00025.2005
- Dodds, C. M., Morein-Zamir, S., & Robbins, T. W. (2011). Dissociating inhibition, attention, and response control in the frontoparietal network using functional magnetic resonance imaging. *Cerebral Cortex*, *21*(5), 1155-1165. doi:10.1093/cercor/bhq187
- du Boisgueheneuc, F., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., . . . Dubois, B. (2006). Functions of the left superior frontal gyrus in humans: A lesion study. *Brain*, *129*(Pt 12), 3315-3328. doi:10.1093/brain/awl244
- Duclos, M., Gatta, B., Corcuff, J. B., Rashedi, M., Pehourcq, F., & Roger, P. (2001). Fat distribution in obese women is associated with subtle alterations of the hypothalamic-pituitary-adrenal axis activity and sensitivity to glucocorticoids. *Clinical Endocrinology*, *55*(4), 447-454.

- Dunn, J. (2010). Impact of mobility impairment on the burden of caregiving in individuals with multiple sclerosis. *Expert Review of Pharmacoeconomics & Outcomes Research*, 10(4), 433-440. doi:10.1586/erp.10.34
- Dyrstad, S. M., Hansen, B. H., Holme, I. M., & Anderssen, S. A. (2014). Comparison of self-reported versus accelerometer-measured physical activity. *Medicine and Science in Sports and Exercise*, 46(1), 99-106. doi:10.1249/MSS.0b013e3182a0595f
- Elias, M. F., Elias, P. K., Sullivan, L. M., Wolf, P. A., & D'Agostino, R. B. (2003). Lower cognitive function in the presence of obesity and hypertension: The Framingham heart study. *International Journal of Obesity and Related Metabolic Disorders*, 27(2), 260-268. doi:10.1038/sj.ijo.802225
- Elias, M. F., Elias, P. K., Sullivan, L. M., Wolf, P. A., & D'Agostino, R. B. (2005). Obesity, diabetes and cognitive deficit: The Framingham Heart Study. *Neurobiology of Aging*, 26 Suppl 1, 11-16. doi:10.1016/j.neurobiolaging.2005.08.019
- Elmqvist, J. K., Bjørbaek, C., Ahima, R. S., Flier, J. S., & Saper, C. B. (1998). Distributions of leptin receptor mRNA isoforms in the rat brain. *Journal of Comparative Neurology*, 395(4), 535-547.
- Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science*, 196(4286), 129-136.
- Engel, G. L. (2012). The need for a new medical model: A challenge for biomedicine. *Psychodyn Psychiatry*, 40(3), 377-396. doi:10.1521/pdps.2012.40.3.377
- Etelson, D., Brand, D. A., Patrick, P. A., & Shirali, A. (2003). Childhood obesity: Do parents recognize this health risk? *Obesity Research*, 11(11), 1362-1368. doi:10.1038/oby.2003.184
- Ettinger, W. H., Fried, L. P., Harris, T., Shemanski, L., Schulz, R., & Robbins, J. (1994). Self-reported causes of physical disability in older people: The Cardiovascular Health Study. CHS Collaborative Research Group. *Journal of the American Geriatrics Society*, 42(10), 1035-1044.
- Farr, S. A., Yamada, K. A., Butterfield, D. A., Abdul, H. M., Xu, L., Miller, N. E., . . . Morley, J. E. (2008). Obesity and hypertriglyceridemia produce cognitive impairment. *Endocrinology*, 149(5), 2628-2636. doi:10.1210/en.2007-1722
- Fassbender, K., Schmidt, R., Mössner, R., Kischka, U., Kühnen, J., Schwartz, A., & Hennerici, M. (1998). Mood disorders and dysfunction of the hypothalamic-pituitary-adrenal axis in multiple sclerosis: Association with cerebral inflammation. *Archives of Neurology*, 55(1), 66-72.
- Fei, H., Okano, H. J., Li, C., Lee, G. H., Zhao, C., Darnell, R., & Friedman, J. M. (1997). Anatomic localization of alternatively spliced leptin receptors (Ob-R) in mouse brain and other tissues. *Proceedings of the National Academy of Sciences of the United States of America*, 94(13), 7001-7005.
- Feinstein, A., Magalhaes, S., Richard, J. F., Audet, B., & Moore, C. (2014). The link between multiple sclerosis and depression. *Nature Reviews: Neurology*, 10(9), 507-517. doi:10.1038/nrneurol.2014.139
- Feinstein, A., O'Connor, P., Gray, T., & Feinstein, K. (1999). The effects of anxiety on psychiatric morbidity in patients with multiple sclerosis. *Multiple Sclerosis*, 5(5), 323-326.
- Feinstein, A., Roy, P., Lobaugh, N., Feinstein, K., O'Connor, P., & Black, S. (2004). Structural brain abnormalities in multiple sclerosis patients with major depression. *Neurology*, 62(4), 586-590.
- Filippi, M., Rocca, M. A., Colombo, B., Falini, A., Codella, M., Scotti, G., & Comi, G. (2002). Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis. *Neuroimage*, 15(3), 559-567. doi:10.1006/nimg.2001.1011
- Finkelstein, E. A., Trogon, J. G., Cohen, J. W., & Dietz, W. (2009). Annual medical spending attributable to obesity: Payer-and service-specific estimates. *Health Affairs*, 28(5), w822-831. doi:10.1377/hlthaff.28.5.w822

- Fischer, J. S., Rudick, R. A., Cutter, G. R., & Reingold, S. C. (1999). The Multiple Sclerosis Functional Composite Measure (MSFC): An integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Multiple Sclerosis*, 5(4), 244-250.
- Fisk, J. D., Pontefract, A., Ritvo, P. G., Archibald, C. J., & Murray, T. J. (1994). The impact of fatigue on patients with multiple sclerosis. *Canadian Journal of Neurological Sciences*, 21, 9-14.
- Fleary, S., & Ettiene, R. (2014). Inherited or behavior? What causal beliefs about obesity are associated with weight perceptions and decisions to lose weight in a US sample? *International Scholarly Research Notices*. doi:10.1155/2014/632940
- Foong, J., Rozewicz, L., Davie, C. A., Thompson, A. J., Miller, D. H., & Ron, M. A. (1999). Correlates of executive function in multiple sclerosis: The use of magnetic resonance spectroscopy as an index of focal pathology. *Journal of Neuropsychiatry and Clinical Neurosciences*, 11(1), 45-50.
- Foong, J., Rozewicz, L., Quaghebeur, G., Davie, C. A., Kartsounis, L. D., Thompson, A. J., . . . Ron, M. A. (1997). Executive function in multiple sclerosis. The role of frontal lobe pathology. *Brain*, 120 (Pt 1), 15-26.
- Friedman, M. A., & Brownell, K. D. (1995). Psychological correlates of obesity: Moving to the next research generation. *Psychological Bulletin*, 117(1), 3-20.
- Fulcher, K. Y., & White, P. D. (1997). Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ*, 314(7095), 1647-1652.
- Fultz, N. H., Ofstedal, M. B., Herzog, A. R., & Wallace, R. B. (2003). Additive and interactive effects of comorbid physical and mental conditions on functional health. *Journal of Aging and Health*, 15(3), 465-481. doi:10.1177/0898264303253502
- Garipey, G., Nitka, D., & Schmitz, M. (2010). The association between obesity and anxiety disorders in the population: A systematic review and meta-analysis. *International Journal of Obesity*, 34, 407-419.
- Geffen, G. M., Butterworth, P., & Geffen, L. B. (1994). Test-retest reliability of a new form of the auditory verbal learning test (AVLT). *Archives of Clinical Neuropsychology*, 9(4), 303-316.
- Gillum, R. F., & Sempos, C. T. (2005). Ethnic variation in validity of classification of overweight and obesity using self-reported weight and height in American women and men: The Third National Health and Nutrition Examination Survey. *Nutrition Journal*, 4, 27. doi:10.1186/1475-2891-4-27
- Glenny, A. M., O'Meara, S., Melville, A., Sheldon, T. A., & Wilson, C. (1997). The treatment and prevention of obesity: A systematic review of the literature. *International Journal of Obesity and Related Metabolic Disorders*, 21(9), 715-737.
- Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Blaha, M. J., . . . Subcommittee, A. H. A. S. C. a. S. S. (2014). Heart disease and stroke statistics-2014 update: A report from the American Heart Association. *Circulation*, 129(3), e28-e292. doi:10.1161/01.cir.0000441139.02102.80
- Gold, S. M., & Irwin, M. R. (2009). Depression and immunity: Inflammation and depressive symptoms in multiple sclerosis. *Immunology and Allergy Clinics of North America*, 29(2), 309-320. doi:10.1016/j.iac.2009.02.008
- Gomersall, S. R., Norton, K., Maher, C., English, C., & Olds, T. S. (2015). In search of lost time: When people undertake a new exercise program, where does the time come from? A randomized controlled trial. *Journal of Science and Medicine in Sport*, 18(1), 43-48. doi:10.1016/j.jsams.2014.01.004
- Gottschalk, M., Kümpfel, T., Flachenecker, P., Uhr, M., Trenkwalder, C., Holsboer, F., & Weber, F. (2005). Fatigue and regulation of the hypothalamo-pituitary-adrenal axis in multiple sclerosis. *Archives of Neurology*, 62(2), 277-280. doi:10.1001/archneur.62.2.277
- Greeno, C. G., & Wing, R. R. (1994). Stress-induced eating. *Psychological Bulletin*, 115(3), 444-464.

- Gregg, E. W., Beckles, G. L., Williamson, D. F., Leveille, S. G., Langlois, J. A., Engelgau, M. M., & Narayan, K. M. (2000). Diabetes and physical disability among older U.S. adults. *Diabetes Care*, 23(9), 1272-1277.
- Gromisch, E. S., Zemon, V., Holtzer, R., Chiaravalloti, N. D., DeLuca, J., Beier, M., . . . Foley, F. W. (2016). Assessing the criterion validity of four highly abbreviated measures from the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). *Clinical Neuropsychologist*, 30(7), 1032-1049. doi:10.1080/13854046.2016.1189597
- Gunstad, J., Paul, R. H., Cohen, R. A., Tate, D. F., Spitznagel, M. B., & Gordon, E. (2007). Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Comprehensive Psychiatry*, 48(1), 57-61. doi:10.1016/j.comppsy.2006.05.001
- Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., & Owen, A. M. (2010). The role of the right inferior frontal gyrus: Inhibition and attentional control. *Neuroimage*, 50(3), 1313-1319. doi:10.1016/j.neuroimage.2009.12.109
- Hara, M., Saitou, E., Iwata, F., Okada, T., & Harada, K. (2002). Waist-to-height ratio is the best predictor of cardiovascular disease risk factors in Japanese schoolchildren. *J Atheroscler Thromb*, 9(3), 127-132.
- Harvey, J. (2007). Leptin regulation of neuronal excitability and cognitive function. *Current Opinion in Pharmacology*, 7(6), 643-647. doi:10.1016/j.coph.2007.10.006
- Hayes, C. E., Cantorna, M. T., & DeLuca, H. F. (1997). Vitamin D and multiple sclerosis. *Proceedings of the Society for Experimental Biology and Medicine*, 216(1), 21-27.
- Haynes, R. B., McDonald, H. P., & Garg, A. X. (2002). Helping patients follow prescribed treatment: Clinical applications. *JAMA*, 288(22), 2880-2883.
- Hedström, A. K., Olsson, T., & Alfredsson, L. (2012). High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. *Multiple Sclerosis*, 18(9), 1334-1336. doi:10.1177/1352458512436596
- Hobart, J. C., Riazi, A., Lamping, D. L., Fitzpatrick, R., & Thompson, A. J. (2003). Measuring the impact of MS on walking ability: The 12-Item MS Walking Scale (MSWS-12). *Neurology*, 60(1), 31-36.
- Induruwa, I., Constantinescu, C. S., & Gran, B. (2012). Fatigue in multiple sclerosis - a brief review. *Journal of the Neurological Sciences*, 323(1-2), 9-15. doi:10.1016/j.jns.2012.08.007
- Irani, J., & Abell, R. (2007). Awareness of body weight status among family medicine clinic patients. *Journal - Oklahoma State Medical Association*, 100(5), 139-143.
- Jadelis, K., Miller, M. E., Ettinger, W. H., & Messier, S. P. (2001). Strength, balance, and the modifying effects of obesity and knee pain: Results from the Observational Arthritis Study in Seniors (oasis). *Journal of the American Geriatrics Society*, 49(7), 884-891.
- Johnson-Taylor, W. L., Fisher, R. A., Hubbard, V. S., Starke-Reed, P., & Eggers, P. S. (2008). The change in weight perception of weight status among the overweight: Comparison of NHANES III (1988-1994) and 1999-2004 NHANES. *The International Journal of Behavioral Nutrition and Physical Activity*, 5, 9. doi:10.1186/1479-5868-5-9
- Jones, K. H., Ford, D. V., Jones, P. A., John, A., Middleton, R. M., Lockhart-Jones, H., . . . Noble, J. G. (2012). A large-scale study of anxiety and depression in people with multiple sclerosis: A survey via the web portal of the UK MS Register. *PloS One*, 7(7), e41910. doi:10.1371/journal.pone.0041910
- Jopson, N. M., & Moss-Morris, R. (2003). The role of illness severity and illness representations in adjusting to multiple sclerosis. *Journal of Psychosomatic Research*, 54(6), 503-511; discussion 513-504.
- Judd, L. L., Akiskal, H. S., Zeller, P. J., Paulus, M., Leon, A. C., Maser, J. D., . . . Keller, M. B. (2000). Psychosocial disability during the long-term course of unipolar major depressive disorder. *Archives of General Psychiatry*, 57(4), 375-380.
- Kanaya, A. M., Barrett-Connor, E., Gildengorin, G., & Yaffe, K. (2004). Change in cognitive function by glucose tolerance status in older adults: A 4-year prospective study of the Rancho

- Bernardo study cohort. *Archives of Internal Medicine*, 164(12), 1327-1333.
doi:10.1001/archinte.164.12.1327
- Kappus, N., Weinstock-Guttman, B., Hagemeyer, J., Kennedy, C., Melia, R., Carl, E., . . . Zivadinov, R. (2015). Cardiovascular risk factors are associated with increased lesion burden and brain atrophy in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*.
doi:10.1136/jnnp-2014-310051
- Kejonen, P., Kauranen, K., & Vanharanta, H. (2003). The relationship between anthropometric factors and body-balancing movements in postural balance. *Archives of Physical Medicine and Rehabilitation*, 84(1), 17-22. doi:10.1053/apmr.2003.50058
- Kenis, G., & Maes, M. (2002). Effects of antidepressants on the production of cytokines. *International Journal of Neuropsychopharmacology*, 5(4), 401-412.
doi:10.1017/S1461145702003164
- Kern, S., Schultheiss, T., Schneider, H., Schrepf, W., Reichmann, H., & Ziemssen, T. (2011). Circadian cortisol, depressive symptoms and neurological impairment in early multiple sclerosis. *Psychoneuroendocrinology*, 36(10), 1505-1512.
doi:10.1016/j.psyneuen.2011.04.004
- Kim, Y. K., Na, K. S., Shin, K. H., Jung, H. Y., Choi, S. H., & Kim, J. B. (2007). Cytokine imbalance in the pathophysiology of major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 31(5), 1044-1053.
doi:10.1016/j.pnpbp.2007.03.004
- Klerman, G. L. (1989). Depressive disorders: Further evidence for increased medical morbidity and impairment of social functioning. *Archives of General Psychiatry*, 46(9), 856-858.
- Klerman, G. L., & Weissman, M. M. (1992). The course, morbidity, and costs of depression. *Archives of General Psychiatry*, 49(10), 831-834.
- Kolotkin, R. L., Meter, K., & Williams, G. R. (2001). Quality of life and obesity. *Obesity Reviews*, 2(4), 219-229.
- Kopelman, P. (2007). Health risks associated with overweight and obesity. *Obesity Reviews*, 8 Suppl 1, 13-17. doi:10.1111/j.1467-789X.2007.00311.x
- Kos, D., Kerckhofs, E., Nagels, G., D'hooghe, M. B., & Ilsbrouckx, S. (2008). Origin of fatigue in multiple sclerosis: Review of the literature. *Neurorehabilitation and Neural Repair*, 22(1), 91-100. doi:10.1177/1545968306298934
- Kroencke, D. C., Lynch, S. G., & Denney, D. R. (2000). Fatigue in multiple sclerosis: Relationship to depression, disability, and disease pattern. *Multiple Sclerosis*, 6(2), 131-136.
doi:10.1177/135245850000600213
- Kubera, M., Maes, M., Kenis, G., Kim, Y. K., & Lasoń, W. (2005). Effects of serotonin and serotonergic agonists and antagonists on the production of tumor necrosis factor alpha and interleukin-6. *Psychiatry Research*, 134(3), 251-258. doi:10.1016/j.psychres.2004.01.014
- Kuo, H. K., Jones, R. N., Milberg, W. P., Tennstedt, S., Talbot, L., Morris, J. N., & Lipsitz, L. A. (2006). Cognitive function in normal-weight, overweight, and obese older adults: An analysis of the Advanced Cognitive Training for Independent and Vital Elderly cohort. *Journal of the American Geriatrics Society*, 54(1), 97-103. doi:10.1111/j.1532-5415.2005.00522.x
- Langer-Gould, A., Brara, S. M., Beaver, B. E., & Koebnick, C. (2013). Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. *Neurology*, 80(6), 548-552.
doi:10.1212/WNL.0b013e31828154f3
- Latimer-Cheung, A. E., Martin Ginis, K. A., Hicks, A. L., Motl, R. W., Pilutti, L. A., Duggan, M., . . . Smith, K. M. (2013). Development of evidence-informed physical activity guidelines for adults with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation*, 94(9), 1829-1836.e1827. doi:10.1016/j.apmr.2013.05.015
- Latimer-Cheung, A. E., Pilutti, L. A., Hicks, A. L., Martin Ginis, K. A., Fenuta, A. M., MacKibbin, K. A., & Motl, R. W. (2013). Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: A systematic review to

- inform guideline development. *Archives of Physical Medicine and Rehabilitation*, 94(9), 1800-1828.e1803. doi:10.1016/j.apmr.2013.04.020
- Lee, C. M., Huxley, R. R., Wildman, R. P., & Woodward, M. (2008). Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *Journal of Clinical Epidemiology*, 61(7), 646-653. doi:10.1016/j.jclinepi.2007.08.012
- Lee, Y. K., Menezes, J. S., Umesaki, Y., & Mazmanian, S. K. (2011). Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. *Proceedings of the National Academy of Sciences of the United States of America*, 108 Suppl 1, 4615-4622. doi:10.1073/pnas.1000082107
- Lezak, M. (1995). Neuropsychological assessment, third edition (3rd ed.). In. New York: Oxford University Press.
- Lupien, S. J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N. P., . . . Meaney, M. J. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience*, 1(1), 69-73. doi:10.1038/271
- Lupien, S. J., Nair, N. P., Brière, S., Maheu, F., Tu, M. T., Lemay, M., . . . Meaney, M. J. (1999). Increased cortisol levels and impaired cognition in human aging: Implication for depression and dementia in later life. *Reviews in the Neurosciences*, 10(2), 117-139.
- Lurie, A. (2011). Obstructive sleep apnea in adults: Epidemiology, clinical presentation, and treatment options. *Advances in Cardiology*, 46, 1-42. doi:10.1159/000327660
- Ma, D., Lu, L., Boneva, N. B., Warashina, S., Kaplamadzhiev, D. B., Mori, Y., . . . Yamashima, T. (2008). Expression of free fatty acid receptor GPR40 in the neurogenic niche of adult monkey hippocampus. *Hippocampus*, 18(3), 326-333. doi:10.1002/hipo.20393
- MacLaughlin, H. L., Cook, S. A., Kariyawasam, D., Roseke, M., van Niekerk, M., & Macdougall, I. C. (2010). Nonrandomized trial of weight loss with orlistat, nutrition education, diet, and exercise in obese patients with CKD: 2-year follow-up. *American Journal of Kidney Diseases*, 55(1), 69-76. doi:10.1053/j.ajkd.2009.09.011
- Marcora, S. M., Staiano, W., & Manning, V. (2009). Mental fatigue impairs physical performance in humans. *J Appl Physiol (1985)*, 106(3), 857-864. doi:10.1152/jappphysiol.91324.2008
- Mårin, P., Darin, N., Amemiya, T., Andersson, B., Jern, S., & Björntorp, P. (1992). Cortisol secretion in relation to body fat distribution in obese premenopausal women. *Metabolism: Clinical and Experimental*, 41(8), 882-886.
- Markowitz, S., Friedman, M., & Arent, S. (2008). Understanding the relation between obesity and depression: Causal mechanisms and implications for treatment. *American Psychological Association*, 15(1).
- Marrie, R., Horwitz, R., Cutter, G., Tyry, T., Campagnolo, D., & Vollmer, T. (2009). High frequency of adverse health behaviors in multiple sclerosis. *Multiple Sclerosis*, 15(1), 105-113. doi:10.1177/1352458508096680
- Marrie, R. A., Reider, N., Cohen, J., Stuve, O., Trojano, M., Cutter, G., . . . Sorensen, P. S. (2015). A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. *Multiple Sclerosis*, 21(3), 318-331. doi:10.1177/1352458514564485
- Marrie, R. A., Rudick, R., Horwitz, R., Cutter, G., Tyry, T., Campagnolo, D., & Vollmer, T. (2010). Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. *Neurology*, 74(13), 1041-1047. doi:10.1212/WNL.0b013e3181d6b125
- Martin, C. L., Phillips, B. A., Kilpatrick, T. J., Butzkueven, H., Tubridy, N., McDonald, E., & Galea, M. P. (2006). Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. *Multiple Sclerosis*, 12(5), 620-628.
- Matarese, G., Carrieri, P. B., Montella, S., De Rosa, V., & La Cava, A. (2010). Leptin as a metabolic link to multiple sclerosis. *Nature Reviews: Neurology*, 6(8), 455-461. doi:10.1038/nrneurol.2010.89

- Matarese, G., Procaccini, C., & De Rosa, V. (2008). The intricate interface between immune and metabolic regulation: A role for leptin in the pathogenesis of multiple sclerosis? *Journal of Leukocyte Biology*, *84*(4), 893-899. doi:10.1189/jlb.0108022
- McCullagh, R., Fitzgerald, A. P., Murphy, R. P., & Cooke, G. (2008). Long-term benefits of exercising on quality of life and fatigue in multiple sclerosis patients with mild disability: A pilot study. *Clinical Rehabilitation*, *22*(3), 206-214. doi:10.1177/0269215507082283
- McDonald, J., Graves, J., Waldman, A., Lotze, T., Schreiner, T., Belman, A., . . . Waubant, E. (2016). A case-control study of dietary salt intake in pediatric-onset multiple sclerosis. *Mult Scler Relat Disord*, *6*, 87-92. doi:10.1016/j.msard.2016.02.011
- McFarlin, D. E., & McFarland, H. F. (1982a). Multiple sclerosis (first of two parts). *New England Journal of Medicine*, *307*(19), 1183-1188. doi:10.1056/NEJM198211043071905
- McFarlin, D. E., & McFarland, H. F. (1982b). Multiple sclerosis (second of two parts). *New England Journal of Medicine*, *307*(20), 1246-1251. doi:10.1056/NEJM19821113072005
- Messer, A. E. (2012). Americans fall short of federal exercise recommendations. *Penn State News*. Retrieved from
- Messier, S. P. (2008). Obesity and osteoarthritis: disease genesis and nonpharmacologic weight management. *Rheumatic Diseases Clinics of North America*, *34*(3), 713-729. doi:10.1016/j.rdc.2008.04.007
- Messier, S. P., Davies, A. B., Moore, D. T., Davis, S. E., Pack, R. J., & Kazmar, S. C. (1994). Severe obesity: Effects on foot mechanics during walking. *Foot and Ankle International*, *15*(1), 29-34.
- Miller, D. H., & Leary, S. M. (2007). Primary-progressive multiple sclerosis. *Lancet Neurology*, *6*(10), 903-912. doi:10.1016/S1474-4422(07)70243-0
- Miyatake, N., Fujii, M., Nishikawa, H., Wada, J., Shikata, K., Makino, H., & Kimura, I. (2000). Clinical evaluation of muscle strength in 20-79-years-old obese Japanese. *Diabetes Research and Clinical Practice*, *48*(1), 15-21.
- Morley, J. E. (2004). The metabolic syndrome and aging. *Journals of Gerontology. Series A: Biological Sciences and Medical Sciences*, *59*(2), 139-142.
- Motl, R. W. (2014). Benefits, safety, and prescription of exercise in persons with multiple sclerosis. *Expert Review of Neurotherapeutics*, *14*(12), 1429-1436. doi:10.1586/14737175.2014.983904
- Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., . . . Subcommittee, A. H. A. S. C. a. S. S. (2015). Heart disease and stroke statistics-2015 update: A report from the American Heart Association. *Circulation*, *131*(4), e29-322. doi:10.1161/CIR.0000000000000152
- Munger, K. L., Bentzen, J., Laursen, B., Stenager, E., Koch-Henriksen, N., Sørensen, T. I., & Baker, J. L. (2013). Childhood body mass index and multiple sclerosis risk: A long-term cohort study. *Multiple Sclerosis*, *19*(10), 1323-1329. doi:10.1177/1352458513483889
- Munger, K. L., Chitnis, T., & Ascherio, A. (2009). Body size and risk of MS in two cohorts of US women. *Neurology*, *73*(19), 1543-1550. doi:10.1212/WNL.0b013e3181c0d6e0
- Najafi, B., Bharara, M., Talal, K., & Armstrong, D. G. (2012). Advances in balance assessment and balance training for diabetes. *Diabetes Management*, *2*(4), 293-308.
- Nicklas, B. J., You, T., & Pahor, M. (2005). Behavioural treatments for chronic systemic inflammation: Effects of dietary weight loss and exercise training. *CMAJ: Canadian Medical Association Journal*, *172*(9), 1199-1209. doi:10.1503/cmaj.1040769
- Norcini Pala, A., & Steca, P. (2015). Illness perceptions and coping strategies among individuals diagnosed with HIV. *Journal of Behavioral Medicine*. doi:10.1007/s10865-015-9639-0
- Obesity: preventing and managing the global epidemic. Report of a WHO consultation. (2000). *World Health Organization Technical Report Series*, *894*, i-xii, 1-253.
- Onyike, C. U., Crum, R. M., Lee, H. B., Lyketsos, C. G., & Eaton, W. W. (2003). Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. *American Journal of Epidemiology*, *158*(12), 1139-1147.

- Padgett, P. K., & Kasser, S. L. (2013). Exercise for managing the symptoms of multiple sclerosis. *Physical Therapy, 93*(6), 723-728. doi:10.2522/ptj.20120178
- Paeratakul, S., White, M. A., Williamson, D. A., Ryan, D. H., & Bray, G. A. (2002). Sex, race/ethnicity, socioeconomic status, and BMI in relation to self-perception of overweight. *Obesity Research, 10*(5), 345-350. doi:10.1038/oby.2002.48
- Pakpoor, J., Seminatore, B., Graves, J., Schreiner, T., Waldman, A., Lotze, T., . . . Waubant, E. (2016). Dietary factors and risk of pediatric multiple sclerosis. *Neurology, 86*(16; Supplement S29.006).
- Pannacciulli, N., Del Parigi, A., Chen, K., Le, D. S., Reiman, E. M., & Tataranni, P. A. (2006). Brain abnormalities in human obesity: A voxel-based morphometric study. *Neuroimage, 31*(4), 1419-1425. doi:10.1016/j.neuroimage.2006.01.047
- Parmenter, B. A., Weinstock-Guttman, B., Garg, N., Munschauer, F., & Benedict, R. H. (2007). Screening for cognitive impairment in multiple sclerosis using the Symbol digit Modalities Test. *Multiple Sclerosis, 13*(1), 52-57.
- Parrott, M. D., & Greenwood, C. E. (2007). Dietary influences on cognitive function with aging: From high-fat diets to healthful eating. *Annals of the New York Academy of Sciences, 1114*, 389-397. doi:10.1196/annals.1396.028
- Pasquali, R., Cantobelli, S., Casimirri, F., Capelli, M., Bortoluzzi, L., Flaminia, R., . . . Barbara, L. (1993). The hypothalamic-pituitary-adrenal axis in obese women with different patterns of body fat distribution. *Journal of Clinical Endocrinology and Metabolism, 77*(2), 341-346. doi:10.1210/jcem.77.2.8393881
- Patil, S., & Chan, C. (2005). Palmitic and stearic fatty acids induce Alzheimer-like hyperphosphorylation of tau in primary rat cortical neurons. *Neuroscience Letters, 384*(3), 288-293. doi:10.1016/j.neulet.2005.05.003
- Patterson, J. A., Amick, R. Z., Pandya, P. D., Hakansson, N., & Jorgensen, M. J. (2014). Comparison of a mobile technology application with the balance error scoring system. *International Journal of Athletic Therapy and Training, 19*(3), 4-7. doi:10.1123/ijatt.2013-0094
- Patterson, J. A., Amick, R. Z., Thummar, T., & Rogers, M. E. (2014). Validation of measures from the smartphone sway balance application: A pilot study. *International Journal of Sports Physical Therapy, 9*(2), 135-139.
- Paul, R. H., Beatty, W. W., Schneider, R., Blanco, C., & Hames, K. (1998). Impairments of attention in individuals with multiple sclerosis. *Multiple Sclerosis, 4*(5), 433-439.
- Pellicano, C., Gallo, A., Li, X., Ikonomidou, V. N., Evangelou, I. E., Ohayon, J. M., . . . Bagnato, F. (2010). Relationship of cortical atrophy to fatigue in patients with multiple sclerosis. *Archives of Neurology, 67*(4), 447-453. doi:10.1001/archneurol.2010.48
- Peng, Y. G., Li, Y., Guo, M., Tian, Y., Li, X., Li, S. H., . . . Zhao, L. C. (2013). The optimal cut-off value of waist-to-height ratio for detecting severe central obesity and low body weight adult Chinese population. *Zhonghua Xin Xue Guan Bing Za Zhi, 41*(7), 607-610.
- Pérusse, L., Rankinen, T., Zuberi, A., Chagnon, Y. C., Weisnagel, S. J., Argyropoulos, G., . . . Bouchard, C. (2005). The human obesity gene map: The 2004 update. *Obesity Research, 13*(3), 381-490. doi:10.1038/oby.2005.50
- Pilutti, L. A., Dlugonski, D., Pula, J. H., & Motl, R. W. (2012). Weight status in persons with multiple sclerosis: Implications for mobility outcomes. *Journal of Obesity, 2012*, 868256. doi:10.1155/2012/868256
- Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., . . . Wolinsky, J. S. (2011). Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology, 69*(2), 292-302. doi:10.1002/ana.22366
- Puhl, R., & Brownell, K. D. (2003). Ways of coping with obesity stigma: Review and conceptual analysis. *Eat Behav, 4*(1), 53-78.

- Quiles Marcos, Y., Terol Cantero, M. C., Romero Escobar, C., & Pagán Acosta, G. (2007). Illness perception in eating disorders and psychosocial adaptation. *Eur Eat Disord Rev*, *15*(5), 373-384. doi:10.1002/erv.793
- Ramagopalan, S. V., Byrnes, J. K., Orton, S. M., Dyment, D. A., Guimond, C., Yee, I. M., . . . Sadovnick, A. D. (2010). Sex ratio of multiple sclerosis and clinical phenotype. *European Journal of Neurology*, *17*(4), 634-637. doi:10.1111/j.1468-1331.2009.02850.x
- Resnick, H. E., Carter, E. A., Aloia, M., & Phillips, B. (2006). Cross-sectional relationship of reported fatigue to obesity, diet, and physical activity: Results from the third national health and nutrition examination survey. *Journal of Clinical Sleep Medicine*, *2*(2), 163-169.
- Riccio, P., & Rossano, R. (2015). Nutrition facts in multiple sclerosis. *ASN Neuro*, *7*(1). doi:10.1177/1759091414568185
- Riccitelli, G., Rocca, M. A., Pagani, E., Rodegher, M. E., Rossi, P., Falini, A., . . . Filippi, M. (2011). Cognitive impairment in multiple sclerosis is associated to different patterns of gray matter atrophy according to clinical phenotype. *Human Brain Mapping*, *32*(10), 1535-1543. doi:10.1002/hbm.21125
- Riddle, D. L., Pulisic, M., Pidcoe, P., & Johnson, R. E. (2003). Risk factors for plantar fasciitis: A matched case-control study. *Journal of Bone and Joint Surgery (American Volume)*, *85-A*(5), 872-877.
- Ritvo, P. (1997). MSQLI Multiple Sclerosis Quality of Life Inventory: A user's manual. In t. C. o. M. S. c. H. S. R. Subcommittee (Ed.). New York, NY: National Multiple Sclerosis Society.
- Rizzo, M. A., Hadjimichael, O. C., Preiningerova, J., & Vollmer, T. L. (2004). Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Multiple Sclerosis*, *10*(5), 589-595.
- Roberts, R. E., Deleger, S., Strawbridge, W. J., & Kaplan, G. A. (2003). Prospective association between obesity and depression: Evidence from the Alameda County Study. *International Journal of Obesity and Related Metabolic Disorders*, *27*(4), 514-521. doi:10.1038/sj.ijo.0802204
- Roberts, R. E., Kaplan, G. A., Shema, S. J., & Strawbridge, W. J. (2000). Are the obese at greater risk for depression? *American Journal of Epidemiology*, *152*(2), 163-170.
- Rodea-Montero, E. R., Evia-Viscarra, M. L., & Apolinar-Jiménez, E. (2014). Waist-to-height ratio is a better anthropometric index than waist circumference and BMI in predicting metabolic syndrome among obese Mexican adolescents. *International Journal of Endocrinology*, *2014*, 195407. doi:10.1155/2014/195407
- Romero-Corral, A., Caples, S. M., Lopez-Jimenez, F., & Somers, V. K. (2010). Interactions between obesity and obstructive sleep apnea: Implications for treatment. *Chest*, *137*(3), 711-719. doi:10.1378/chest.09-0360
- Ron, M. A., & Logsdail, S. J. (1989). Psychiatric morbidity in multiple sclerosis: A clinical and MRI study. *Psychological Medicine*, *19*(4), 887-895.
- Rozema, H., Völlink, T., & Lechner, L. (2009). The role of illness representations in coping and health of patients treated for breast cancer. *Psycho-Oncology*, *18*(8), 849-857. doi:10.1002/pon.1488
- Rubenstein, L. Z. (2006). Falls in older people: Epidemiology, risk factors and strategies for prevention. *Age and Ageing*, *35 Suppl 2*, ii37-ii41. doi:10.1093/ageing/af1084
- Ruff, R. M., Light, R. H., Parker, S. B., & Levin, H. S. (1996). Benton Controlled Oral Word Association Test: Reliability and updated norms. *Archives of Clinical Neuropsychology*, *11*(4), 329-338.
- Ryan, J. J., & Geisser, M. E. (1986). Validity and diagnostic accuracy of an alternate form of the Rey Auditory Verbal Learning Test. *Archives of Clinical Neuropsychology*, *1*(3), 209-217.
- Ryerson, B., Tierney, E. F., Thompson, T. J., Engelgau, M. M., Wang, J., Gregg, E. W., & Geiss, L. S. (2003). Excess physical limitations among adults with diabetes in the U.S. population, 1997-1999. *Diabetes Care*, *26*(1), 206-210.

- Sadovnick, A. D., Eisen, K., Ebers, G. C., & Paty, D. W. (1991). Cause of death in patients attending multiple sclerosis clinics. *Neurology*, *41*(8), 1193-1196.
- Shamseddeen, H., Getty, J. Z., Hamdallah, I. N., & Ali, M. R. (2011). Epidemiology and economic impact of obesity and type 2 diabetes. *Surgical Clinics of North America*, *91*(6), 1163-1172, vii. doi:10.1016/j.suc.2011.08.001
- Sharifi, N., Mahdavi, R., & Ebrahimi-Mameghani, M. (2013). Perceived barriers to weight loss programs for overweight or obese women. *Health Promot Perspect*, *3*(1), 11-22. doi:10.5681/hpp.2013.002
- Siegert, R. J., & Abernethy, D. A. (2005). Depression in multiple sclerosis: A review. *Journal of Neurology, Neurosurgery and Psychiatry*, *76*(4), 469-475. doi:10.1136/jnnp.2004.054635
- Slawta, J. N., Wilcox, A. R., McCubbin, J. A., Nalle, D. J., Fox, S. D., & Anderson, G. (2003). Health behaviors, body composition, and coronary heart disease risk in women with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation*, *84*(12), 1823-1830.
- Smith, A. (1982). Symbol Digit Modalities Test (SDMT) Manual (Revised). In. Los Angeles: Western Psychological Services.
- Solari, A., Filippini, G., Gasco, P., Colla, L., Salmaggi, A., La Mantia, L., . . . Mendozzi, L. (1999). Physical rehabilitation has a positive effect on disability in multiple sclerosis patients. *Neurology*, *52*(1), 57-62.
- Sospedra, M., & Martin, R. (2005). Immunology of multiple sclerosis. *Annual Review of Immunology*, *23*, 683-747. doi:10.1146/annurev.immunol.23.021704.115707
- Sotgiu, S., Angius, A., Embry, A., Rosati, G., & Musumeci, S. (2008). Hygiene hypothesis: Innate immunity, malaria and multiple sclerosis. *Medical Hypotheses*, *70*(4), 819-825. doi:10.1016/j.mehy.2006.10.069
- Steinman, L. (2009). A molecular trio in relapse and remission in multiple sclerosis. *Nature Reviews: Immunology*, *9*(6), 440-447. doi:10.1038/nri2548
- Stenager, E. N., Stenager, E., Koch-Henriksen, N., Brønnum-Hansen, H., Hyllested, K., Jensen, K., & Bille-Brahe, U. (1992). Suicide and multiple sclerosis: An epidemiological investigation. *Journal of Neurology, Neurosurgery and Psychiatry*, *55*(7), 542-545.
- Steultjens, E. M., Dekker, J., Bouter, L. M., Cardol, M., Van de Nes, J. C., & Van den Ende, C. H. (2003). Occupational therapy for multiple sclerosis. *Cochrane Database Syst Rev*(3), CD003608. doi:10.1002/14651858.CD003608
- Stotland, S., & Zuroff, D. C. (1990). A new measure of weight locus of control: The Dieting Beliefs Scale. *Journal of Personality Assessment*, *54*(1-2), 191-203. doi:10.1080/00223891.1990.9673986
- Stranahan, A. M., Arumugam, T. V., Cutler, R. G., Lee, K., Egan, J. M., & Mattson, M. P. (2008). Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. *Nature Neuroscience*, *11*(3), 309-317. doi:10.1038/nn2055
- Stranahan, A. M., Lee, K., Pistell, P. J., Nelson, C. M., Readal, N., Miller, M. G., . . . Mattson, M. P. (2008). Accelerated cognitive aging in diabetic rats is prevented by lowering corticosterone levels. *Neurobiology of Learning and Memory*, *90*(2), 479-483. doi:10.1016/j.nlm.2008.05.005
- Stunkard, A. (2000). Old and new scales for the assessment of body image. *Perceptual and Motor Skills*, *90*(3 Pt 1), 930. doi:10.2466/pms.2000.90.3.930
- Stunkard, A. J., Sørensen, T., & Schulsinger, F. (1983). Use of the Danish Adoption Register for the study of obesity and thinness. *Research Publications - Association for Research in Nervous and Mental Disease*, *60*, 115-120.
- Sukoff Rizzo, S. J., Neal, S. J., Hughes, Z. A., Beyna, M., Rosenzweig-Lipson, S., Moss, S. J., & Brandon, N. J. (2012). Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes. *Transl Psychiatry*, *2*, e199. doi:10.1038/tp.2012.120

- Suter, M., Calmes, J. M., Paroz, A., & Giusti, V. (2006). A 10-year experience with laparoscopic gastric banding for morbid obesity: High long-term complication and failure rates. *Obesity Surgery, 16*(7), 829-835. doi:10.1381/096089206777822359
- Tartaglia, M. C., Narayanan, S., Francis, S. J., Santos, A. C., De Stefano, N., Lapierre, Y., & Arnold, D. L. (2004). The relationship between diffuse axonal damage and fatigue in multiple sclerosis. *Archives of Neurology, 61*(2), 201-207. doi:10.1001/archneur.61.2.201
- Taylor, K. L., Hadgkiss, E. J., Jelinek, G. A., Weiland, T. J., Pereira, N. G., Marck, C. H., & van der Meer, D. M. (2014). Lifestyle factors, demographics and medications associated with depression risk in an international sample of people with multiple sclerosis. *BMC Psychiatry, 14*(1), 327. doi:10.1186/s12888-014-0327-3
- Télliez, N., Comabella, M., Julià, E., Río, J., Tintoré, M., Brieva, L., . . . Montalban, X. (2006). Fatigue in progressive multiple sclerosis is associated with low levels of dehydroepiandrosterone. *Multiple Sclerosis, 12*(4), 487-494.
- Tettey, P., Simpson, S., Taylor, B., Blizzard, L., Ponsonby, A. L., Dwyer, T., . . . van der Mei, I. (2014). Adverse lipid profile is not associated with relapse risk in MS: Results from an observational cohort study. *Journal of the Neurological Sciences, 340*(1-2), 230-232. doi:10.1016/j.jns.2014.02.038
- Thompson, P. D. (2003). Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. *Arteriosclerosis, Thrombosis, and Vascular Biology, 23*(8), 1319-1321. doi:10.1161/01.ATV.0000087143.33998.F2
- Thompson, T., Benz, J., Agiesta, J., Brewer, K., Bye, L., Reimer, R., & Junius, D. (2013). *Obesity in the United States: public perceptions*. Retrieved from <http://www.apnorc.org/PDFs/Obesity/AP-NORC-Obesity-Research-Highlights.pdf>
- Thornton, A. E., & Raz, N. (1997). Memory impairment in multiple sclerosis: A quantitative review. *Neuropsychology, 11*(3), 357-366.
- Tinnefeld, M., Treitz, F. H., Haase, C. G., Wilhelm, H., Daum, I., & Faustmann, P. M. (2005). Attention and memory dysfunctions in mild multiple sclerosis. *European Archives of Psychiatry and Clinical Neuroscience, 255*(5), 319-326. doi:10.1007/s00406-005-0565-y
- Trojan, D. A., Arnold, D., Collet, J. P., Shapiro, S., Bar-Or, A., Robinson, A., . . . Da Costa, D. (2007). Fatigue in multiple sclerosis: Association with disease-related, behavioural and psychosocial factors. *Multiple Sclerosis, 13*(8), 985-995. doi:10.1177/1352458507077175
- Trojano, M., Lucchese, G., Graziano, G., Taylor, B. V., Simpson, S., Jr., Lepore, V., . . . Oreja-Guevara, C. (2012). Geographical variations in sex ratio trends over time in multiple sclerosis. *PloS One, 7*(10), 1-9. doi:10.1371/journal.pone.0048078
- van Dale, D., & Saris, W. H. (1989). Repetitive weight loss and weight regain: Effects on weight reduction, resting metabolic rate, and lipolytic activity before and after exercise and/or diet treatment. *American Journal of Clinical Nutrition, 49*(3), 409-416.
- van Kessel, K., Moss-Morris, R., Willoughby, E., Chalder, T., Johnson, M. H., & Robinson, E. (2008). A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosomatic Medicine, 70*(2), 205-213. doi:10.1097/PSY.0b013e3181643065
- Vancampfort, D., De Herdt, A., Vanderlinden, J., Lannoo, M., Soundy, A., Pieters, G., . . . Probst, M. (2014). Health related quality of life, physical fitness and physical activity participation in treatment-seeking obese persons with and without binge eating disorder. *Psychiatry Research, 216*(1), 97-102. doi:10.1016/j.psychres.2014.01.015
- Vgontzas, A. N., Bixler, E. O., & Chrousos, G. P. (2006). Obesity-related sleepiness and fatigue: The role of the stress system and cytokines. *Annals of the New York Academy of Sciences, 1083*, 329-344. doi:10.1196/annals.1367.023
- Vgontzas, A. N., Bixler, E. O., Chrousos, G. P., & Pejovic, S. (2008). Obesity and sleep disturbances: Meaningful sub-typing of obesity. *Archives of Physiology and Biochemistry, 114*(4), 224-236. doi:10.1080/13813450802521507

- Vighi, G., Marcucci, F., Sensi, L., Di Cara, G., & Frati, F. (2008). Allergy and the gastrointestinal system. *Clinical and Experimental Immunology*, *153 Suppl 1*, 3-6. doi:10.1111/j.1365-2249.2008.03713.x
- Vogeli, C., Shields, A. E., Lee, T. A., Gibson, T. B., Marder, W. D., Weiss, K. B., & Blumenthal, D. (2007). Multiple chronic conditions: Prevalence, health consequences, and implications for quality, care management, and costs. *Journal of General Internal Medicine*, *22 Suppl 3*, 391-395. doi:10.1007/s11606-007-0322-1
- Vollmann, M., Scharloo, M., Langguth, B., Kalkouskaya, N., & Salewski, C. (2013). Illness representations as mediators of the relationship between dispositional optimism and depression in patients with chronic tinnitus: A cross-sectional study. *Psychology & Health*, *29*(1), 81-93. doi:10.1080/08870446.2013.828294
- Vucic, S., Burke, D., & Kiernan, M. C. (2010). Fatigue in multiple sclerosis: Mechanisms and management. *Clinical Neurophysiology*, *121*(6), 809-817. doi:10.1016/j.clinph.2009.12.013
- Waldstein, S. R., & Katzel, L. I. (2006). Interactive relations of central versus total obesity and blood pressure to cognitive function. *International Journal of Obesity (2005)*, *30*(1), 201-207. doi:10.1038/sj.ijo.0803114
- Wang, C., & Coups, E. J. (2010). Causal beliefs about obesity and associated health behaviors: Results from a population-based survey. *The International Journal of Behavioral Nutrition and Physical Activity*, *7*, 19. doi:10.1186/1479-5868-7-19
- Wang, Y., & Beydoun, M. A. (2007). The obesity epidemic in the United States-gender, age, socioeconomic, racial/ethnic, and geographic characteristics: A systematic review and meta-regression analysis. *Epidemiologic Reviews*, *29*, 6-28. doi:10.1093/epirev/mxm007
- Wang, Y., Beydoun, M. A., Liang, L., Caballero, B., & Kumanyika, S. K. (2008). Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. *Obesity (Silver Spring)*, *16*(10), 2323-2330. doi:10.1038/oby.2008.351
- Weiland, T. J., Jelinek, G. A., Marck, C. H., Hadgkiss, E. J., van der Meer, D. M., Pereira, N. G., & Taylor, K. L. (2015). Clinically significant fatigue: Prevalence and associated factors in an international sample of adults with multiple sclerosis recruited via the internet. *PloS One*, *10*(2), e0115541. doi:10.1371/journal.pone.0115541
- Weitbrecht, W. U., & Kirchoff, D. (1995). Long-term prognosis of cerebral infarct in comparison with a normal population. *Versicherungsmedizin*, *47*(2), 46-49.
- Wells, K. B., Stewart, A., Hays, R. D., Burnam, M. A., Rogers, W., Daniels, M., . . . Ware, J. (1989). The functioning and well-being of depressed patients: Results from the Medical Outcomes Study. *JAMA*, *262*(7), 914-919.
- Wilding, J. (2012). Are the causes of obesity primarily environmental? Yes. *BMJ*, *345*, e5843.
- Wingerchuk, D. M., & Rodriguez, M. (2006). Premenstrual multiple sclerosis pseudoexacerbations: Role of body temperature and prevention with aspirin. *Archives of Neurology*, *63*(7), 1005-1008. doi:10.1001/archneur.63.7.1005
- Winter, D. A., Patla, A. E., & Frank, J. S. (1990). Assessment of balance control in humans. *Medical Progress Through Technology*, *16*(1-2), 31-51.
- Wright, S. M., & Aronne, L. J. (2012). Causes of obesity. *Abdominal Imaging*, *37*(5), 730-732. doi:10.1007/s00261-012-9862-x
- Yim, C. Y., Soczynska, J. K., Kennedy, S. H., Woldeyohannes, H. O., Brietzke, E., & McIntyre, R. S. (2012). The effect of overweight/obesity on cognitive function in euthymic individuals with bipolar disorder. *European Psychiatry*, *27*(3), 223-228. doi:10.1016/j.eurpsy.2011.02.004
- Zhang, S. M., Willett, W. C., Hernán, M. A., Olek, M. J., & Ascherio, A. (2000). Dietary fat in relation to risk of multiple sclerosis among two large cohorts of women. *American Journal of Epidemiology*, *152*(11), 1056-1064.
- Zhao, G., Ford, E. S., Dhingra, S., Li, C., Strine, T. W., & Mokdad, A. H. (2009). Depression and anxiety among US adults: Associations with body mass index. *International Journal of Obesity (2005)*, *33*(2), 257-266. doi:10.1038/ijo.2008.268

- Ziarko, M., Mojs, E., Piasecki, B., & Samborski, W. (2014). The mediating role of dysfunctional coping in the relationship between beliefs about the disease and the level of depression in patients with rheumatoid arthritis. *ScientificWorldJournal*, 2014, 585063. doi:10.1155/2014/585063
- Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, 67(6), 361-370.
- Zorgdrager, A., & De Keyser, J. (1997). Menstrually related worsening of symptoms in multiple sclerosis. *Journal of the Neurological Sciences*, 149(1), 95-97.
- Zorgdrager, A., & De Keyser, J. (2002). The premenstrual period and exacerbations in multiple sclerosis. *European Neurology*, 48(4), 204-206. doi:66166

VITA

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