ASSOCIATION BETWEEN METABOLIC SYNDROME AND DEPRESSION IN ADULTS WITH OSTEOARTHRITIS

by

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ABSTRACT

Approximately 7.1% of individuals are affected by depression in North America annually. Depression is a severe form of mental illness characterized by upset mood, loss of self-esteem, sadness, lack of interest in performing daily activities and lack of pleasure. Severe depression can lead to functional limitations and even mortality. Conversely, timely diagnosis can lead to early intervention and longevity.

Although prior research has documented that depression is a major public health problem, few studies have examined the association between metabolic syndrome and depression from a preventive perspective. Of the limited studies, there are unclear results pertaining to the direction of the relationship. In addition, there is a paucity of information on individuals living with chronic illnesses, such as osteoarthritis.

Moreover, meta-analyses conducted in the past utilized limited demographic characteristics of the participants. Also, nationally representative studies rarely have examined disparities in demographics (e.g., marital status, education) using a prospective research design. To our knowledge, no studies have considered social isolation while measuring depression among individuals with osteoarthritis. Such descriptive research can provide a foundation for future analytical studies. Therefore, the purpose of this study was to address the mentioned gaps in the literature by using nationally and publically available data to conduct a meta-analysis and use Generalizing Estimating Equations (GEE) to examine the association between metabolic syndrome and depression.

In order to conduct the meta-analysis, we searched various databases such as PsycINFO, MEDLINE Complete, CINAHL Complete, ScienceDirect, SportDiscuss, and JEWL from the year 1999-2019. Search criteria and keywords such as “Metabolic Syndrome”, “Syndrome x”, “insulin resistance syndrome”, “depression”, and a combination of these keywords after the equivalent-subject expander were used to identify potentially relevant terms. Using inclusion criteria, the initial search was narrowed down to thirteen articles. For the meta analysis, comprehensive meta-analysis (CMA) software was used. For the Generalizing Estimating Equations (GEE), data from the Osteoarthritis Initiative (OAI), an existing National Institute of Health (NIH) database, were used. Participants (N = 2643) had severe osteoarthritis or were at risk of developing it. The majority of included participants were White (85.9%) and women (57.3%) with an average age of 60 years.

Metabolic syndrome was measured using confirmatory factor analysis (CFA) of systolic blood pressure, diabetes, BMI, and waist circumference variables that were available in the OAI database. Depression was measured using the Center for Epidemiological Scale for depression (CES-D) from the OAI database. Data were measured at baseline, 24 months, 72 months, and at 96 months. Associations were adjusted for age, race, gender, education, marital status, social isolation, baseline depression, and time between visits. SPSS *(v25)* was utilized to conduct the GEE analysis.

Results from the meta-analysis indicate that there is a significant association between METS and depression. In total, 17 effect sizes were calculated from 13 studies. Statistical heterogeneity between studies was not significant (I2 = 38.71%, df = 16 and p=.053), indicating

that studies were compatible. Due to insignificant heterogeneity, a fixed-effect model was used. Individuals who live with METS are 1.14 times more likely to have depression when compared with individuals without METS. .

Results from the GEE analysis indicated that there is no significant association between METS and depression among individuals living with osteoarthritis across time (B = .285, p = .302). The overall model intercept was significant (B = 4.24, p = .000). Among other predictors, education, marital status, social isolation, baseline depression, and time (years) between the visits were found to be significantly associated with depression. When controlling all other significant predictors, positive associations with depression over time were found for marital status (B = .280, p = .017), baseline depression (B = .653, p = .000), and years (B = .333, p = .000). Negative associations with depression over time were found for education (B = -.206, p = .009) and social isolation (B = -.1.469, p = .000).

Results from both meta-analysis and GEE provide a foundation for future research and have practical implications for the treatment of depression. Clinicians should note the prevalence of depression and consider these issues in treatment, planning, and implementation.

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CHAPTER I: INTRODUCTION

Mental Health

Mental health is defined as a state of psychological well-being. It includes the ability to manage daily stresses and understand one's potential to contribute socially and economically to the community (World Health Organization [WHO], 2014). Positive mental health allows individuals to enjoy life and meaningful relationships with their friends, coworkers, and family (National Alliance of Mental Illness [NAMI], 2018). In contrast, mental illnesses are characterized by abnormal emotional reactions, such as atypical thoughts and defiant behaviors (WHO, 2018). These unusual and abnormal behaviors can interfere with the conventional functioning of the body and social interactions. When left untreated, mental illness can become a serious cause of morbidity and mortality. It can lead to various forms of physical and emotional disabilities including nutritional, respiratory, musculoskeletal diseases, and sexual dysfunction (Hert et al., 2011). Mental illness should be treated with the same urgency as other diseases. Unfortunately, stigma is a barrier to treatment (Kohn et al, 2013; Corrigan, 2016). Biological factors such as genetic make-up, changes in brain chemistry, lifestyle events (trauma and abuse), and family history are determinants of mental illness (NAMI, 2018).

Approximately $193.2 billion of earnings are lost annually due to mental illness (NAMI, 2018), with an additional $8 billion added due to pre-mature deaths (Kohn et al., 2003). The amount is expected to rise to $6 trillion by the year 2030 (WHO, 2014). In addition, mental illness is the third highest reason for hospitalization among adults and children (NAMI, 2018). When compared with statistics from 2001, approximately 40 million more people are currently living in the United States (CDC, 2018). This boom in population has resulted in a high

incidence of mental illness issues and deaths associated with it (Connolly, 2017). The cost of mental illness is expected to rise to $280.5 billion by the year 2020 (NAMI, 2018). Deductible costs for psychiatrist visits as well as the cost of diagnostics and psychotherapy are high, and limited prescribed medications are covered by insurance companies. Almost 50% of psychiatrists in North America do not accept insurance, which makes it even more difficult for insured people to pay high the cost of treatment (NAMI, 2018).

During a 12 month period, it is estimated that more than 45 million people in North America live with mental illness, and almost 20 million never receive treatment (WHO, 2016). Self-stigmatization occurs in patients living with depression and individuals believing that they are weak due to illness. Stigma may lead to feelings of shame and guilt and can prevent patients from sharing their symptoms with healthcare professionals. Indirectly, self-stigma can delay effective treatment and result in worse health outcomes (Corrigan, 2016). Furthermore, stigma leads to social distance, loneliness, fear, isolation, and rejection of depressed individuals from society as well as family (Corrigan, 2014; Pugh et al., 2015). This social isolation can result in delayed treatment, physical disability, and suicidal attempts among individuals who are living with depression (Corrigan et al, 2014). Delays in treatment can put individuals further at risk for developing co-morbidities, increasing the cost of treatment, worsening health outcomes, and leading to loss of income (Wolpert, 2001; Friedman, 2014; Sutin, 2014; Link et al., 1999).

If the cost of mental illness was covered by insurance companies, including the cost of prescribed medications and psychiatrist visits, more people would prefer to get treatment. Further, if confidentiality and privacy laws were strengthened, stigma and fear associated with mental illness could be reduced, making treatment for mental illness accessible and manageable.

History of Mental Illness in the United States

Historically, superstitions and supernatural powers were thought to be the causes of mental illness (Kohn et al., 2013; Corrigan et al., 2014; Stanley et al., 2016). In the late 1700s, mental illness was considered to be the result of ghostly power, demonic possession, or a result of the evil eye (Colman, 2016), a curse thought to be cast by someone's wicked glare. Stigma and cold-hearted treatment, such as being abandoned and disowned by society, have been associated with mental illness (Stanley et al., 2016). Individuals with mental illness were either forced to live in asylums or became homeless (Stanley et al., 2016; Bond, 2018; Colman, 2016; Tracy, 2018).

Living conditions in asylums were unhygienic with little food, no light, and no visitors (Stanley et al., 2016). Also, asylum patients were subjected to shock treatment and lobotomy in an attempt to treat their illnesses (Stanley et al., 2016; Tracy, 2018). Patient requests to return home were ignored by their families due to stigma associated with mental illness (Stanley et al., 2016; Bond, 2018; Colman, 2016; Tracy, 2018). Patients were left to die in asylums and jails that worsened their mental and physical conditions (Stanley et al., 2016).

Two major reforms developed during the 1800s (Stanley et al., 2016; Bond, 2018). The first humanitarian movement by Philip Pinel (1810) and second by William Tuke (1815) stated that mental illness could be treated with kindness, respect, and consideration (Stanley et al., 2016). Pinel and Tuke encouraged psychiatric teams to abandon traditional treatments for mental illness. Their reforms inspired medical practitioners to develop humanitarian treatments such as providing feasible, affordable, and timely treatment for mental illness (Stanley et al., 2016; Tracy, 2018). Tuke's and Pinel's reforms increased society's awareness of the positive association between mental and physical health. Both reformers educated society about how

eating healthy and improving physical surroundings would improve mental health and result in de-institutionalization (Stanley et al., 2016).

With the success of these two reforms, the US government funded 32 psychiatric hospitals and asylums in 1880 to protect society and people with mental illness (Stanley et al., 2016). Funding hospitals introduced the concept of improving the quality of life for individuals living with mental illness (Stanley et al., 2016). Treatment was focused on providing a 'normal life' back to individuals. A 'normal' life included having a positive attitude, self-acceptance, being able to live without physical or emotional abuse, being able to work and earn a living, eating healthy food, and drinking clean water. Funding for psychiatric hospitals resulted in the establishment of the Mental Health America (MHA) association, which further contributed to increased awareness.

In 1963, the US Community Mental Health Act (CMHA) was passed to provide treatment for mental illnesses in community settings. CMHA provided funds for the construction of community-based mental health centers to facilitate screening, early detection, diagnosis, and timely treatment (Sheffield, 2016; National Council for Behavioral Health, 2016). At this time psychopharmacology, psychoanalysis, psychosurgery, and electroconvulsive therapy were practiced along with the introduction of the non-sedative drug chlorpromazine, which allowed patients to return to normal daily activities.

Deinstitutionalization and community-oriented care followed as the quality of life for those living with mental illness became more of a priority (Leeman, 2014). In addition, MHA created the National Alliance for Research on Schizophrenia and Depression (NARSAD) in order to raise funds for mental illness research (MHA, 2018). Results from the MHA survey

indicated that few Americans were knowledgeable about mental illness (MHA, 2018). In an effort to increase mental health awareness, MHA launched various educational campaigns on depression, schizophrenia, and other mental illnesses. As an example, MHA produced a film *Only Human* to increase awareness about causes and treatment of mental illness (MHA, 2018). Individuals living with mental illness became more accepted by society, as stigma associated with mental illness was reduced (MHA, 2018).

The Mental Health Parity Act (1966) mandated health insurance companies bring more equity in covering the cost of mental illness as a part of overall health insurance (MHA, 2018). Clearly, mental illness and treatment have a vast history in America. Over time, society's perception of mental illness began to shift from being demonized towards legitimate medical diagnoses. Further research revealed that mental illness is a brain disorder, with brain scans reflecting metabolic differences for those living with mental illness (Sitek & Utter, 2016). Nevertheless, stigma is still a major barrier in the treatment of mental illness.

Types of mental illness

Five broad categories of mental illness are: (NAMI, 2018):

i. Anxiety disorders (panics and phobias)
ii. Mood disorders (depression and bipolar disorder)
iii. Psychotic disorders (schizophrenia, hallucinations, and delusions)
iv. Personality disorders (anti-social personality disorder, paranoid, and schizoid disorder)
v. Eating disorders (binge eating and anorexia nervosa).

Depression is the most common mood disorder in the United States, affecting approximately 16.2 million people (National Institute of Mental Health [NIMH], 2016). Of those affected by depression, approximately 10.3 million people develop severe impairment due to the disease (NIMH, 2016). Almost 36% of individuals relapse within 10 years of receiving treatment for depression (WHO, 2016). In addition, adults aged 45 years and older who become depressed or experience persistent depression over the course of one year are more likely to exhibit significant declines in cognitive and functional status compared to those who are never depressed (Pellegrino et al., 2013; Ganguli, 2009).

Patients may relapse due to some situations and behaviors that act as triggers (Burton, 2017). Some of these triggers include intake of drugs and/or alcohol, stressful life events, and conflict in relationships (Burton, 2017). Providing warnings for the triggers to individuals with mental illness can help in preventing the relapse, as individuals can be prepared to face them (Burton, 2017). There are early signs of relapse such as mood changes, irritability, lack of humor, inability to concentrate, and changes in eating or sleeping. Annual screenings of individuals with a history of mental illness can help in diagnosing symptoms of relapse, and timely treatment can be administered for better health outcomes (Burton, 2017; WHO, 2016).

Depression

Depression is characterized by mood changes such as loss of self-esteem, feeling guilty and/or sad, irritability, loss of concentration, and lack of pleasure in performing daily tasks (WHO, 2012). Due to its debilitating effects, depression should be treated with the same urgency as physical illness, according to the Centers for Disease Control and Prevention (CDC, 2010). Depression is the leading cause of disability in women and the second leading cause of disability in men (WHO, 2014), with women being twice as likely as men to live with depression (National

Center for Health Statistics, (NCHS), 2018). Often, those living with severe depression are dependent on relatives or friends for performing daily tasks (NCHS, 2018).

Hormonal factors, premenstrual changes, pregnancy, miscarriage, postpartum phase, pre-menopause, and menopause place women at a higher risk for depression than men. Symptoms of depression are often confused with signs of aging, resulting in under treatment of depression. The current study focused on adults aged 45 years and above, as they are at increased risk for developing depression. (Martin, 2016; Haggerty, 2016; Iliades, 2018).

When considering race and ethnicity, the prevalence of depression is highest in non-Hispanic blacks (9.2%), followed by Hispanics (8.2%) and Caucasians (7.9%), (NIMH, 2016). Lower household income, lack of education, unemployment, lack of access to healthcare due to limited insurance coverage, lack of transportation, and linguistic differences have been associated with higher rate of depression among ethnic minorities (Bailey et al., 2019; Budhwani et al., 2015; Brauser, 2013).

Depression ranges from mild to severe (National Institute of Mental Health, 2011). In mild to moderate cases, depression causes feelings of helplessness, anger, and shame. Severe cases can lead to suicide, with more than one million lives lost annually around the globe (WHO, 2012). Depression results in unnecessary hospitalization and increases the social and economic burden of disease on the nation (NAMI, 2011). In terms of treatment, medications and lifestyle modifications are appropriate for mild to moderate cases. However, severe cases may require electroconvulsive therapy, which triggers seizure in order to produce clinically favorable outcomes (Mayo Clinic, 2018).

Clearly, there is an urgent need in the public health sector to create strategies and interventions that can aid in reducing the incidence and prevalence rates of depression among adults aged 45 years and older. Preventative measures need to be strengthened and encouraged, including options to handle daily stresses, maintaining healthy sleeping and eating habits, accessing social support with friends and families, and annual screenings for mental disorders, which can help in reducing new cases of depression (MHA, 2018). With timely diagnosis of depression, treatment can occur (Beekman et al., 1995; MHA, 2018; Saxena et al., 2006). Those with low socioeconomic status, along with females and the elderly, are at notable risk for developing depression. Perceived low social status, cultural barriers (i.e cross-cultural communication), lack of contact with healthcare providers also act as an obstacles, placing individuals at risk for developing depression.

Antipsychotics and treatment of depression

Anti-depressants such as sertraline, citalopram, and fluoxetine are the most common medications prescribed to people living with depression (Martin, 2016). However, medications have many related side effects such as weight gain, increased lipid levels, and insulin resistance (Chokka et al., 2006). For example, one clinical trial demonstrated that patients taking anti-depressants had higher waist circumferences, increased triglycerides, and increased body mass index (BMI), (Eker et al., 2017). Study participants were also more likely to be lethargic, placing them at risk for sedentary behavior. Therefore, anti-depressants may put individuals at risk for developing one or more symptoms of metabolic syndrome.

Metabolic Syndrome

Metabolic syndrome (METS) is characterized by the presence of three or more of the following symptoms: hypertension, diabetes mellitus, hypercholesterolemia, gout, obesity (BMI

> 30), and high abdominal circumference (Stoppler, 2018). METS is positively associated with fatty liver, cirrhosis, kidney damage, dementia, cognitive impairment, and polycystic ovarian disease (Stoppler, 2018).

The definition used most commonly in clinical practice is the presence of three or more of the following: National Cholesterol Education Program-Adult Treatment Panel III [NCEP-ATP III] (2001),

i. Waist circumference: > 102 cm in men and > 88 cm in women
ii. Hypertension: > 130 mmHg systolic and > 85 mmHg diastolic blood pressure
iii. Fasting blood glucose: > 110 mg/dl
iv. Plasma triglycerides: > 150 mg/dl
v. High density cholesterol (HDL): < 40 mg/dl

History of metabolic syndrome

In the early 1900s, scientists noted that obesity, hypertension, cardiovascular diseases, diabetes, and increased levels of uric acid were found in the same patients (Paulescu, 1920). Some scientists also concluded that arterial hypertension was a pre-diabetic phase, with diet playing a major role in treating metabolic disorders (Vague et al., 1947; Maranon, 1927; Haragus, 1932). By 1947, it was apparent that abdominal obesity was commonly associated with cardiovascular diseases and diabetes (Vague et al., 1947). Results from additional studies indicated that high uric acid levels, diabetes, hypertension, and high triglyceride levels were all positively associated with cardiovascular disease and deaths due to myocardial infarction (Haller, 1977; Philips, 1977). A clinical study conducted for 12 weeks with six participants revealed an association between metabolic disorders and a low carbohydrate diet (Avogaro et al., 1967). The

six participants had reduced fasting glucose levels, blood pressure, cholesterol, and triglycerides when they were given a low carbohydrate and low-calorie diet for 12 weeks.

By the end of 1990, a cluster of metabolic disorders such as diabetes, insulin resistance, obesity, high lipid levels, and hypertension was commonly known as "Syndrome X" (Reaven G, 1988). Also, since insulin resistance was considered to be a precursor of the 'Syndrome X', metabolic syndrome was also known as insulin resistance disorder (Kahn et al., 2005). Studies further demonstrated that Syndrome X was often associated with a lack of physical activity and age. In 1998, the first criteria for Syndrome X were developed by the World Health Organization that included the presence of three or more of following: high blood pressure (> 140/90 mm of hg), high triglycerides (> 150 mg/dl), BMI > 30 kg/ m^2, and urinary albumin excretion > 20 μgm/mg. The definition was revised by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III, (ATP III) in 2001. These standardized criteria assisted researchers in conducting various studies on metabolic syndrome.

Physiology of Metabolic Syndrome and causes

METS is the result of various pathophysiological changes in the body due to altered metabolism, usually as the result of environmental, lifestyle, and genetic factors (Stoppler, 2018). Lifestyle factors include consuming a diet high in fats, carbohydrates, and sodium, but also low in fiber, vitamins and essential minerals (Gosadi, 2016). Low physical activity, a diet high in carbohydrates and fats, progressive weight gain, and lack of sleep are all associated with metabolic syndrome (Stoppler, 2018; Gosadi, 2016). Genetic factors include genes that can affect fat and glucose metabolism, such as the presence of genes that code for lipoprotein lipase, beta 3-adrenergic receptors, and skeletal muscle glycogen synthase (Groop, 2000). Individuals with a family history of diabetes, high blood pressure, and heart disease are at risk for developing

metabolic syndrome (Stoppler, 2018). Post-menopausal women, people who smoke, and those who consume high carbohydrate diets are at risk for developing metabolic syndrome as well.

Prevalence and Consequences of Metabolic Syndrome

METS is prevalent in 25% of adults worldwide (Mandal, 2018). Symptoms of metabolic syndrome are equally prevalent; high lipid levels are present in approximately 41.2% of the global population, followed by high blood pressure at 26.6% (Nolan et al., 2017). Abdominal obesity is prevalent in 23.65% of individuals worldwide, and high fasting glucose is seen in 15.4% of the global population (Nolan et al., 2017). The presence of one component (e.g. high blood pressure, abdominal obesity, high lipid levels) serves as a precursor for others which increases the burden of metabolic syndrome worldwide.

When compared to other countries, the prevalence of metabolic syndrome is highest in the United States, followed by Mexico. Thirty-two percent of people live with metabolic syndrome in the United States in any 12-month period, with approximately 85% of them concurrently living with diabetes type 2 (Stoppler, 2018). The prevalence of METS increased by 25.3% between 1999 and 2006. The prevalence increased to 33.5% by 2015 and has almost remained stable since then (Shin et al., 2018).

Specific populations are impacted by METS. Women are 33% more likely than men to develop metabolic syndrome, which may be related to the fact that they are more likely to be depressed and to be prescribed antipsychotics (Moore et al., 2017; Albert, 2015). Antipsychotics alter normal metabolism and result in high lipid levels, high fasting glucose, high blood pressure, and increased abdominal circumference, resulting in a higher risk for developing METS. Aging populations may further be at higher risk for developing metabolic syndrome due to lack of

physical activity, pain due to joint degeneration, and the presence of one or more chronic diseases such as cardiovascular diseases (Milanovic et al., 2013; Moore et al., 2017; Devers et al., 2016). Approximately 20% of people above 40 years of age, 35% above 50, and 45% above 60 years old will develop metabolic syndrome (Aguilar et al., 2015). The exact mechanism for increased risk of METS with aging is not known, although longevity genes such as living beyond 95 years of age can be associated with the development of the disease (Veronica & Esther, 2012).

There are also several social determinants that can serve as risk factors for METS. Those with less education and lower socioeconomic status are more likely to develop metabolic syndrome (Agular et al., 2015), which may be associated with reduced fruit and vegetable consumption, sedentary lifestyles, and lack of awareness about disease development (Moore et al, 2017). In the United States, METS is seen in Hispanics (35.4%), followed by non-Hispanic Whites (33.4%) and non-Hispanics Blacks (32.7%), (Aguilar et al., 2015), due to consuming a diet high in carbohydrates and saturated fats. Subsequently, sedentary lifestyles combined with unhealthy eating habits have resulted in an increased economic and social burden of METS in society. Due to the increased prevalence of METS over the last decade, it is now considered both epidemic and pandemic (Neil & Driscoll, 2015). As such, there is an urgent need to study health consequences associated with METS so that public health professionals can develop community-based interventions and stop the spread of this epidemic.

Metabolic Syndrome and Depression

Review of literature on metabolic syndrome and depression

Unhealthy eating behaviors and sedentary lifestyles are commonly seen in people living with depression (Robert & Rita, 2018). Sedentary lifestyles and poor eating habits tend to increase stress in the body, resulting in high cortisol levels and inflammation (Corell, 2015). Multiple studies have demonstrated a positive relationship between depression and METS, though medications for depression can add to issues as well. First and second-generation antipsychotics such as loxapine, fluphenazine, clozapine, and olanzapine are usually prescribed to treat depression but have many side effects, such as weight gain and dyslipidemia. These side effects can interfere in normal metabolic processes and can place individuals at risk for developing insulin resistance, obesity, and eventually METS (Corell, 2015).

McElory (2014) concluded that there is a symbiotic relationship between stress and METS, observing that stress can lead to METS, which further increased stress. Her seven-year observational study was conducted with 644 participants in an outpatient facility at Stanley Foundations Bipolar Treatment Outcomes Network. Additionally, obesity was positively associated with depression among women compared to men. Women who were unable to manage stress also had mood disorders and depression and thus were prescribed anti-depressants for treatment. The side effects of prescribed anti-depressants caused metabolic changes, like an increase in abdominal circumference, lipids, and fasting glucose. Additionally, participants developed hormonal imbalances. Women with a combination of altered metabolism and hormonal imbalances developed METS and were further stressed, while additional stress led to increased dosages of anti-depressants. McElroy (2014) also concluded that high waist circumference was associated with depression among both men and women.

In another study conducted in the United States, participants diagnosed with bipolar depression experienced increased components of METS when compared with people without depression (Aggarwal et al., 2016). Their study was conducted among individuals who were aged 50 years or younger. Depression was objectively measured using the Diagnostic and Statistical Manual –II (DSM-II) of Mental Illness criteria. Participants were also clinically evaluated for depression. Pearson's correlation coefficient was analyzed to study the association between METS and depression. However, this study had several limitations; firstly, due to small sample size, these findings could not be generalized to the normal population. Secondly, causality could not be established due to the cross-sectional research design. This study also revealed that METS prevalence was 24% in people with bipolar depression, compared to 26% of those with recurrent depression.

Prior studies have reported mixed results on the association between METS and depression. Akbaraly et al. (2011), studied the association between METS and depression among people aged 65-91 years and found no association among people aged 70 years and above. However, the study did find an association between for those between 65-70 years old. Also, the study did not report to what extent METS affected depression.

Similarly, Akbaraly (2009) discerned that obesity and the dyslipidemia components of METS were associated with depression in middle-aged civil servants from Great Britain. Limitations to the study included that depression was not measured with a clinically recognized scale and the study was conducted only among White Britains. Additionally, possible confounders were not controlled for, such as social support, education, socio-economic status, marital status, and alcohol. In contrast, a study conducted in Sweden did not demonstrate an association between metabolic syndrome and depression (Roos et al., 2007). Furthermore, according to Liaw et al.,

(2015), the association between METS and depression is mediated by the presence of insulin resistance. However, causality could not be established due to the cross-sectional nature of the study. It would be helpful to have a study including those individuals without insulin resistance due to multicollinearity between metabolic syndrome and insulin resistance. Chronic diseases such as osteoarthritis could be a factor as well.

Osteoarthritis (OA) is a chronic disease that has poor health outcomes (Parkinson et al, 2017). Individuals living with OA are at risk for developing sedentary behavior due to joint pain and inflammation (Xie et al, 2016). This sedentary behavior puts them at risk for developing METS that further deteriorates their health condition and recovery (Xie et al, 2016). Since OA does not have a cure, intervention strategies to delay the disease progression can help in maintaining the independence of the individuals living with it.

Metabolic syndrome and depression in osteoarthritis

Osteoarthritis is a degenerative disease that affects joints in the knees, hips, wrist, thumb, toes, and ankles (CDC, 2018). It is defined as an inflammatory condition in which slippery tissue between two joints is damaged and cartilage breaks down (National Institute of Health, 2016). For individuals affected by arthritis, bones rub against each other, resulting in pain, inflammation, and reduced mobility (CDC, 2018). Due to the degenerative and inflammatory nature of osteoarthritis, individuals are at risk for cardiovascular disease and sedentary behavior.

Sedentary behavior or lack of physical activity puts those living from arthritis at greater risk for developing metabolic syndrome. Xie et al. (2017), concluded that there was a positive correlation between the number of metabolic disorders and severity of osteoarthritis. This study also revealed that middle-aged people who live with osteoarthritis were five times more likely to

develop METS when compared with those without osteoarthritis. Overall, limited functional mobility puts individuals with osteoarthritis at a higher risk for developing METS (Xie et al., 2017).

Osteoarthritis is strongly and positively associated with the development of various components of METS, resulting in increased morbidity and mortality. There is also evidence that METS and osteoarthritis share common pathological processes in which joint inflammation is associated with adipose tissues (Pavelka, 2017). High pressure and mechanical load due to increased weight in obese individuals stimulate joint degeneration, inflammation, and friction between joint surfaces. This process triggers development of osteoarthritis at weight-bearing joints such as knees, hips, and ankles (Pavelka, 2017; Kluzek et al., 2015). Also, the presence of various types of mental illness such as depression and anxiety reduces the quality of life for adults living with osteoarthritis, and can even result in suicide (Sharma et al., 2016). Jung et al. (2018), revealed that people who live with osteoarthritis are twice as likely to feel depressed when compared with those who do not have osteoarthritis.

Severe depression among individuals living with osteoarthritis inhibits their normal functioning, as they live with a higher level of physical and mental stress. Therefore, it is very important to protect individuals who live with osteoarthritis from developing depression and suicidal thoughts. Holistic treatment approaches have been advised for people who live with osteoarthritis so that their quality of life can be improved (Jung et al., 2016; Myers, 2014). Treatments such as yoga, acupuncture, meditation, relaxation techniques, deep breathing exercises and therapeutic massages can help in relieving mental stress (Jung et al., 2014).

Few studies have examined the relationship between METS and depression in individuals with osteoarthritis. One clinical trial concluded that higher waist circumference was associated with increased pain, disability, and depression in individuals living with osteoarthritis (Li et al., 2016). However, the study did not examine the role of other components of metabolic syndrome such as hypertension, high fasting glucose, or altered lipids in causing depression among individuals living with osteoarthritis. Moreover, this study recruited a small sample from one institution in China and did not randomize study participants. All these factors limited the generalizability of the results to other races and geographical areas. Researchers advised that further studies be conducted with a more representative sample (Li et al., 2016; Xie et al., 2017; Kluzek et al., 2015). There is a need to conduct more studies to understand the relationship between METS and depression, especially in individuals living with osteoarthritis, so that better health outcomes can be achieved. Hence, the current study was conducted using data from the Osteoarthritis Initiative (OAI) database.

Gaps in the Literature

Various studies have clearly demonstrated the development of metabolic syndrome due to depression. Few studies have an association between METS and depression (Dunbar et al., 2008; Miettola et al., 2008; Liawh et al., 2015; Friends et al., 2013). However, these studies are cross-sectional and do not explain the causal relationship between METS and depression. Also, most of the studies were conducted with participants18-50 years of age (Liaw et al., 2015; Ford et al., 2008; Dunbar et al., 2008) or among children (Friends et al., 2013). Since METS increases with age, further research needs to be conducted with individuals aged 50 years and older.

Social determinants of metabolic syndrome and depression

Social determinants are defined as the social and environmental factors in which people live from birth to death (WHO, 2017). Social determinants such as health deficiencies in infancy and childhood, poverty, social exclusion, workplace stress, unemployment, health policies, and access to resources contribute to health outcomes (WHO, 2017; Wilkinson & Marmot, 2003). Social determinants impacting depression are socioeconomic status, employment, and marital status (Assari, 2017).

Social determinants and demographic factors impacting depression also include education, marriage, gender, and race (Liang et al., 2012). Assari (2017) concluded that in the United States, Whites with high household incomes, education, employment, and who were married were less likely to be depressed. Researchers indicated that high-income levels provided individuals with access to healthcare, while education increased their knowledge about preventative health checks. Also, employed individuals had a feeling of job security that helped them to manage their stressors more effectively (Assari, 2017; Liang et al., 2012).

Gender is a noted determinant of depression (Liang et al., 2012). Women were more likely to live with depression compared to men. In a study by Assari, (2017), it was concluded that white women with higher income levels were less likely to be depressed. Reasons listed were job satisfaction, ability to afford healthy foods, and positive sleep habits. Also, this study revealed that high-income African-American men were at risk for developing depression due to workplace stress, poor sleep habits, and lower levels of physical activity (Assari, 2017; Assari & Caldwell, 2018). Education played an important role in reducing depression among all races

when compared with those who were not educated, since it is associated with employment and healthier lifestyles (Assari, 2017; WHO, 2014).

Other determinants strongly associated with depression are low levels of social cohesion, negative life event and age. Individuals who were more socially isolated, had three or more negative life events, and were less educated were more likely to live with depression (Shittu et al., 2014). Perez et al (2017) concluded that social cohesion is inversely associated with depression. In their study, individuals who did not participate in parks, recreational events, and social gatherings in their community were more depressed than those who had higher social cohesion. Researchers also concluded that depression was prevalent in divorced, widowed, or separated couples compared to married couples, indicating that marriage was protective towards depression (Shittu et al., 2014). Older age was also found to be positively associated with depression as well (Shittu et al., 2014; Liang et al., 2012; WHO, 2014).

Similar to depression, social and demographic determinants of metabolic syndrome are socio-economic status, race, gender, lifestyle factors (i.e. smoking, low physical activity), and presence of chronic illness. For example, researchers concluded that individuals with lower income may not have access to buy healthy food, increasing likelihood of METS (Cai et al., 2012). Also, lower-income families may be more sedentary due to limited access to playgrounds and safe streets (Cai et al., 2012; Chang & Kim, 2017).

Studies have also demonstrated racial disparities in developing METS. For non-Hispanic Black individuals, lower cholesterol and triglycerides levels serve as a protective factor for METS, when compared with non-Hispanic White individuals and Hispanics (Gurka et al., 2014). Also, women were found to be at higher risk for developing METS when compared to men. In

women, hormonal regulation of fat in the body can result in obesity, high waist circumference, and other components of METS (Pradhan, 2013; Chang & Kim, 2017).

Prior studies have revealed that smoking, presence of diabetes, hypertension, and cardiovascular diseases are associated with metabolic syndrome (Cai et al., 2012; Marquezine et al., 2008; Al-Thani et al., 2016). In the past, studies have revealed overlapping social determinants for METS and depression. Gender, race, socio-economic level, and age are a few common social determinants associated with METS and depression (Shittu et al., 2014; Assari, 2017; Gurka et al., 2014; Pradhan, 2013). People with a lower income and who are not educated are at increased risk of developing depression and METS. Similarly, women, non-Hispanic Whites, and Hispanics are at risk of developing METS and depression. Additionally, aging puts individuals at risk of developing both METS and depression. In severe forms, both the diseases — METS and depression — can cause premature deaths and can worsen health outcomes, so it is very important to understand the underlying social determinants. In summary, public health professionals should develop strategies for women, individuals with lower socioeconomic status, and the elderly.

Purpose of Current Study

Few prior studies have examined the association between METS and depression and have yielded inconsistent results. Furthermore, depression was not measured with objective instruments in some studies (Aggarwal et al., 2016), limiting the reliability and validity of the findings. Given the high prevalence of metabolic syndrome globally, lack of generalizability is also a limitation to previous studies.

To the best of our knowledge, the current study was the first to conduct a longitudinal analysis, using OAI database, in order to study the association between METS and depression in adults living with osteoarthritis. In addition, prior studies conducted with the general population did not indicate a directional association between METS and depression. Therefore, the study has utilized a large sample size of approximately 4800 participants aged 45 years and older, so that a clear examination of the potential relationship between METS and depression could be conducted. Results from the current study can aid in addressing limitations of prior studies and provide direction for future research.

For the current study, we conducted a meta-analysis that highlighted strengths and limitations of previous studies. The last meta-analysis including longitudinal and cross-sectional studies was conducted in 2012 (Pan et al., 2012). The current study included data from January 1998 – 2018. Gheshlag et al. (2016), conducted a meta-analysis that included only case-control and cross-sectional studies and did not address causality. The current study included longitudinal studies that could show causality between METS and depression.

The priority population, those living with osteoarthritis, are at risk for developing various components of metabolic syndrome. Results from the current study can help clinical and other public health professionals plan future strategies for people with osteoarthritis. Strategies developed as a result of current study can aid in improving functional independence, health outcomes and quality of life of people with osteoarthritis, while simultaneously reducing the economic burden of osteoarthritis in society.

The current study was reported as two manuscripts. Two independent manuscripts address the extent to which metabolic syndrome can cause depression and how metabolic syndrome is

associated with depression. Chapter two (manuscript one) is a systematic review of existing literature on metabolic syndrome and depression among adults. Various bibliographic databases were searched to locate potential articles based on inclusion criteria. Comprehensive meta-analysis (CMA) software (*v*3) was used to analyze the articles.

Chapter three (Manuscript two) utilized data from an existing NIH, publicly funded Osteoarthritis Initiative (OAI) database. The database contains information on participants with severe clinically diagnosed arthritis or at risk of developing the disease. Since the Osteoarthritis Initiative is a prospective longitudinal study, the variables measuring metabolic syndrome and depression were studied at baseline, 24 months, 72 months and at 96 months. The Generalized Estimate Equations (GEE) method was used to respond to the research question. SPSS software (*v25*) was used for data analysis.

Research Questions

Research question 1

What is the association between metabolic syndrome and depression in the literature?

Research question 2

What effect does metabolic syndrome have on depression in people living with osteoarthritis, when controlling for age, gender, race, education, time, baseline depression, social isolation, and marital status?

Summary

The purpose of this dissertation was to describe and analyze the association between metabolic syndrome and depression in people with osteoarthritis. Study findings can lead to the

development of preventive strategies for those who are at risk for developing severe osteoarthritis while delaying or preventing the onset of metabolic syndrome.

REFERENCES

Akbaraly, T., Kivimaki, M., Brunner, E., Chandola, T., Marmot, M., Singh-Manoux, A., & Ferrie, J. (2009). Association between metabolic syndrome and depressive symptoms in middle-aged adults: results from the Whitehall II study. *Diabetes care, 32*(3), 499-504. Retrieved from http://care.diabetesjournals.org/content/diacare/suppl/2012/04/13/35.5.1171.DC1/DC112055SupplementaryData.pdf.

Akbaraly, T., Ancelin, M.L., Jaussent, I., Ritchie, C., Barberger, P., Dufouil, C., Kivimaki,M., Claudine,B., Ritchie, K. (2011). Metabolic syndrome and onset of depressive symptoms in the elderly. *Diabetes Care, 34*(4), 904–909. doi: 10.2337/dc10-1644

Al-Thani, M. H., Al-Thani, A. M., Cheema, S., Sheikh, J., Mamtani, R., Lowenfels, A. B., Chetachi, W., Almalki, B., Khalifa, S.,Bakri, A., Maisonneuve, P. (2016). Prevalence and determinants of metabolic syndrome in Qatar: Results from a National Health Survey. *BMJ Open, 6*(9), e009514. doi:10.1136/bmjopen-2015-009514.

Albert, P. R. (2015). Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience,40* (4). 219-221.

American Psychological Association (APA). (2018). By the numbers: The cost of treatment. Retrieved from http://www.apa.org/monitor/2017/03/numbers.aspx.

Avogaro, P., Crepaldi, G., Enzi, G., & Tiengo, A. (1967). Association of hyperlipemia, diabetes mellitus and middle-degree obesity (Associazione di iperlipemia, diabete mellito e

obesita' di medio grado). *Acta Diabetologica Latina*, (4), 572-90. doi:10.1007/BF01544100.

Avogaro, A., Fadini, G., Vigili de Kreutzenberg, S., & Tiengo, A. (2007). Coronary heart disease in diabetes. *International Congress Series- Amsterdam - Excerpta Medica Then Elsevier Science*, 1241-1247.

Assari, S. (2017). Social determinants of depression: The intersections of race, gender, and socioeconomic status. *Brain Sciences*, *7*(12), 156-168. doi:10.3390/brainsci7120156.

Beigh, S. & Jain, S. (2012). Prevalence of metabolic syndrome and gender differences. *Bioinformation*, *8*(13), 613-616.

Burton, N. (2012). Mental illness: Preventing a relapse [Blog post]. Retrieved from https://www.psychologytoday.com/us/blog/hide-and-seek/201210/mental-illness-preventing-relapse

Cai, H., Huang, J., Xu, G., Yang, Z., Liu, M., Mi, Y., Liu, W., Wang, H., & Qian, D. (2012). Prevalence and determinants of metabolic syndrome among women in chinese rural areas. *Plos One*, 7(5), e36936. doi:10.1371/journal.pone.0036936

Centers for Disease Control and Prevention (CDC). (2016). Depression in the U.S. Household Population, 2009-2012. Retrieved from https://www.cdc.gov/nchs/data/databriefs/db172.htm.

Centers for Disease Control and Prevention (CDC). (2017). National Center for Health Statistics. Retrieved from https://www.cdc.gov/nchs/fastats/depression.htm.

Corell, C. (2015). Metabolic syndrome in patients with mental illness: Challenges and solutions [Blog post]. Retrieved from https://www.psychcongress.com/article/metabolic-syndrome-patients-mental-illness-challenges-and-solutions.

Devers, M. C., Campbell, S., Jonathan, S., Zimmet, P., & Simmons, D. (2016). Influence of age on the prevalence and components of the metabolic syndrome and the association with cardiovascular disease. *Open Diabetes Research Care, 4. doi:10.1136/bmjdrc-2016-000195.*

Dix,S. (2015, November 12). Filling the gap in mental health research [Blog post]. Retrieved from https://www.pharmaceutical-journal.com/opinion/comment/filling-the-gap-in-mental-health-research/20200022.article?firstPass=false.

Dunbar, J., Reddy, P., Davis-Lameloise, N., Philpot, B., Laatikainen, T., Kilkkinen, A., & Lo, S. (2008). Depression: An important comorbidity with metabolic syndrome in a general population. *Diabetes Care, 31* (12), 2368-2373. doi: 10.2337/dc08-0175.

Friedman, M. (2014, May 13). The stigma of mental illness is making us sicker [Blog post]. Retrieved from https://www.psychologytoday.com/us/blog/brick-brick/201405/the-stigma-mental-illness-is-making-us-sicker.

Ganguli, M. (2009). Depression, cognitive impairment and dementia: Why should clinicians care about the web of causation?. *Indian Journal Of Psychiatry, 51* (1), S29-S34.

Gheshlagh, R. Parizad, N. & Sayehamiri, K. (2016). The relationship between depression and metabolic syndrome: Systematic Review and Meta-Analysis Study. *Iranian Red Crescent Medical Journal, 18*(6), e26523. doi: 10.5812/ircmj.26523.

Gluckman, D. and Hanson, A. (2004). The developmental origins of the metabolic syndrome. *Trends in Endocrinology and Metabolism, 15*(4), 183-187.

Gosadi, I. (2016). Assessment of the environmental and genetic factors influencing prevalence of metabolic syndrome in Saudi Arabia. *Saudi Medical Journal, 37*(1), 12-20. doi:10.15537/smj.2016.1.12675.

Groop, L. (2000). Genetics of the metabolic syndrome. *British Journal of Nutrition, 83*(1), S39-S48.

Haggerty, J. (2018, October 8). Risk Factors for Depression [Blog post]. Retrieved from https://psychcentral.com/lib/risk-factors-for-depression/

Haller, H. (1977). Epidemiology and associated risk factors of hyperlipoproteinemia. *Zeitschrift für sie Gesamte Innere Medizin und Ihre Grenzgebiete, 32*(8), 124-28.

Huang, S., Wang, W., Lin, L., Liou, T., Liao, C., & Lin, H. (2016). Association between psychiatric disorders and osteoarthritis: A nationwide longitudinal population-based study. *Medicine, 95*(26), e4016. doi: 10.1097/MD.0000000000004016.

Iliades, C. (2014, August 5). Facts About Depression: Who's at Risk? [Blog post]. Retrieved from https://www.everydayhealth.com/depression/facts-about-depression-whos-at-risk.aspx

Jung, J. H., Seok, H., Kim, J., Song, G. G., & Choi, S. J. (2018). Association between osteoarthritis and mental health in a Korean population: A nationwide study. *International Journal Of Rheumatic Diseases, 21*(3), 611-619. doi:10.1111/1756-185X.13098

Liang, Y., Gong, Y., Wen, X., Guan, C., Li, M., Yin, P., & Wang, Z. (2012). Social determinants of health and depression: A preliminary investigation from rural China. *Plos ONE, 7*(1), e30553. doi:10.1371/journal.pone.0030553.

Mandal, A. (2015). History of metabolic syndrome [Blog post]. Retrieved from https://www.news-medical.net/health/History-of-Metabolic-Syndrome.aspx.

Martin, B. (2016).What are the risk factors for depression? [Blog post]. Retrieved from https://psychcentral.com/lib/what-are-the-risk-factors-for-depression/

Marquezine, G. F., Oliveira, C. M., Pereira, A. C., Krieger, J. E., & Mill, J. G. (2008). Metabolic syndrome determinants in an urban population from Brazil: Social class and gender-specific interaction. *International Journal of Cardiology*, *129*(2), 259-265. doi: 10.1016/j.ijcard.2007.07.097

McElroy, S., & Keck, P. (2014). Metabolic syndrome in bipolar disorder: A review with a focus on bipolar depression. *Journal of Clinical Psychiatry, 75*(1), 46-61. doi: 10.4088/JCP.13r08634.

Milanović, Z., Pantelić, S., Trajković, N., Sporiš, G., Kostić, R., & James, N. (2013). Age-related decrease in physical activity and functional fitness among elderly men and women. *Clinical Interventions In Aging, 8,* 549-556.

Myers, L. (2014, August 8). The relationship between depression and arthritis [Blog post]. Retrieved from http://brainblogger.com/2014/08/08/the-relationship-between-depression-and-arthritis/

Milici, N. (2010). A short history of the metabolic syndrome definitions. *Proceedings- Romanian Academy series b chemistry life sciences and geosciences,* (1). 13-20.

Neil, S & Driscoll,L. (2015). Metabolic syndrome: A closer look at the growing epidemic and its associated pathologies. *Obesity Reviews, 16*(1), 1-12 doi:10.1111/obr.12229.

Nolan, P., Ranson, G., Stinear, J., Reading, S. & Dalleck, L. (2017). Prevalence of metabolic syndrome and metabolic syndrome components in young adults: A pooled analysis. *Preventive Medicine Reports*, 7, 211-215. doi:10.1016/j.pmedr.2017.07.004.

Kahn, R., Buse, J., Ferrannini, E., & Stern, M. (2005). The metabolic syndrome: time for a critical appraisal: Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*,*28*(9), 2289–2304.

Kluzek, S., Newton, L., & Arden, N. (2015). Is osteoarthritis a metabolic disorder? *British Medical Bulletin, 115*(1), 111-121. doi: 10.1093/bmb/ldv028.

Li, H., George, D, M., Jaarsma, R, L., & Mao, X. (2016). Metabolic syndrome and components exacerbate osteoarthritis symptoms of pain, depression and reduced knee function. *Annals of Translational Medicine, 4*(7), 133-142, doi: 10.21037/atm.2016.03.48.

Lima, S. (2014). Medical comorbidities and functioning in depression: A clinical perspective. *Medicographia, 36*, 464-469. Retrieved from https://www.medicographia.com/2015/06/medical-comorbidities-and-functioning-in-depression-a-clinical-perspective/.

Link, B. G., Phelan, J. C., Bresnahan, M., Stueve, A., & Pescosolido, B. A. (1999). Public conceptions of mental illness: Labels, causes, dangerousness, and social distance. *The American Journal Of Public Health, 89*(9), 1328-1333.

Pavelka, K. (2017).Osteoarthritis as part of metabolic syndrome? *Internal Medicine, 63*(10), 707-711.

Paulescu, N. (1920). An elementary treatise on human physiology, on the basis of the precis elementaire de physiologie. *Christian Advocate & Journal*, *18*(24), 1833-1865.

Pellegrino, L. D., Peters, M. E., Lyketsos, C. G., & Marano, C. M. (2013). Depression in cognitive impairment. *Current Psychiatry Reports, 15*(9), 384-390 doi:10.1007/s11920-013-0384-1

Phillips,B. (April 1977). Relationship between serum sex hormones and glucose, insulin and lipid abnormalities in men with myocardial infarction. *Proceedings of the National Academy of Sciences of the United States of America, 74(*4), 1729–33.

Reaven, M. (1997). Role of insulin resistance in human disease. *Diabetes*, (37), 1595-1607.

Rowan, K., McAlpine, D., & Blewett, L. (2013). Access and cost barriers to mental health care by insurance status, 1999 to 2010. *Health Affairs (Millwood), 32*(10), 1723-1730. *doi:* 10.1377/hlthaff.2013.0133

Saxena, S., Llopis, E., & Hosman, C. (2006). Prevention of mental and behavioural disorders: implications for policy and practice. *World Psychiatry, 5*(1), 5-14.

Sheffield,W. (2013, October 31). The community mental health act of 1963 [Blog post]. Retrieved from https://www.ymadvocacy.org/the-community-mental-health-act-of-1963/

Shittu, R., Baba A. I, Ganiyu F., Abdulraheem O. M., Louis O., & Abdullateef, S. (2014). Social determinants of depression: Social cohesion, negative life events, and depression among people living with HIV/Aids in Nigeria, West Africa. *International Journal Of MCH And AIDS, 2*(2), 174-181.

Sitek, K. (2016, April 1). Can computers use brain scans to diagnose psychiatric disorders? [Blog post]. Retrieved from http://sitn.hms.harvard.edu/flash/2016/can-computers-use-brain-scans-to-diagnose-psychiatric-disorders/

Stutin, A. (2014, May 6). Perceived age, weight discrimination worse for health than perceived racism, sexism [Blog post]. Retrieved from http://news.fsu.edu/news/health-medicine/2014/05/06/perceived-age-weight-discrimination-worse-for-health-than-perceived-racism-sexism/

Stopplet, M. (2018). Metabolic Syndrome [Blog post]. Retrieved from https://www.medicinenet.com/insulin_resistance/article.htm.

Tracy, N. (2018, September 16). The history of mental illness [Blog post]. Retrieved from https://www.healthyplace.com/other-info/mental-illness-overview/the-history-of-mental-illness

Veronica, G. & Esther, R. (2012). Aging, metabolic syndrome and the heart. *Aging and Disease, 3*(3). 269-279.

Wolpert, L. (2001). Stigma of depression – a personal view. *British Medical Bulletin, 57*(1), 221-224. doi: https://doi.org/10.1093/bmb/57.1.221. Retrieved from https://academic.oup.com/bmb/article/57/1/221/301582

WebMD. (2018). Can You Prevent Depression? [Blog post]. Retrieved from https://www.webmd.com/depression/understanding-depression-prevention#1

World Health Organization (WHO). (2014). Social determinants of health. Retrieved from http://apps.who.int/iris/bitstream/handle/10665/112828/9789241506809_eng.pdf;jsessionid=BFD940109A34CEA8F3A481803BB4EF0A?sequence=1

World Health Organization (WHO). (2015). Mental health. Retrieved from http://www.who.int/mental_health/management/en/.

World Health Organization (WHO). (2018). Depression. Retrieved from http://www.who.int/news-room/fact-sheets/detail/depression.

Xie, D., Wei, J., Zeng, C., Yang, T., Li, H., Wang, Y., Long, H., Wu, Z., Qian, Y., Li, K., & Lei, G. (2017). Association between metabolic syndrome and knee osteoarthritis: a cross-sectional study. *BMC Musculoskeletal Disorders*, 18, 533-539. doi: 10.1186/s12891-017-1890-9.

CHAPTER II: SYSTEMATIC REVIEW OF LITERATURE AND META-ANALYSIS

Introduction

History of Depression in the United States

In ancient times, depression was believed to be the result of some supernatural phenomena attached with superstition, demonic possession and the result of evil eyes (Stanley, 2016). There were stigmas, negative beliefs and practices associated with depression and other mental illnesses (Stanley, 2016). Individuals with depression and other forms of mental illness received shock treatment, skull drills and were sent to asylums. With the attached stigma, society believed that depression was due to disabling genes in the blood (Stanley, 2016). Societal stigma forced people with depression to live in confinement or jail.

Women with mental health issues were considered "unladylike" and were either sterilized or lobotomized (Leeman, 2014). While in asylums, patients were untreated or abused, as they were thought to be uncivilized. Also, due to stigma, families would not visit them and ignore their requests to come home (Stanley, 2016). Eventually, two major reforms contributed to the treatment of mental illness (Stanley, 2016). These two humanitarian efforts by Pinel (1840) and William Tuke (1850) indicated that depression and mental illness could be treated with kindness and consideration.

With the success of these two reforms, the hospital movement was launched by Dorothy Dix (1860). The US government then funded 32 hospitals to protect people with depression and mental illness. It also birthed the idea of treating those who can be treated and caring for those who cannot be treated in order to improve quality of life (Stanley, 2016). Creating psychiatric hospitals led the way for the development of Mental Health America (MHA) and the US

community Mental Health Act of 1963. Both had the mission of improving the lives of mentally ill people in the United States. Psychoanalysis, introduced by Sigmund Freud as a part of treating mental illnesses, began to gain great importance as well (Stanley, 2016). Psychopharmacology, psychoanalysis, psychosurgery and electroconvulsive therapy were practiced along with the introduction of the non-sedative drug chlorpromazine for depression (Stanley, 2016). Deinstitutionalization and community-oriented care followed as improving quality of life gained importance (Leeman, 2014).

During this time period, MHA created the National Research Institute for Schizophrenia and Depression to raise funds and support research on mental illness (MHA, 2018). In 1987, MHA launched exhibitions on the experiences of homeless people to show the human side of homelessness and created policies on depression treatment in rural areas (MHA, 2018). MHA also launched educational campaigns on depression and conducted surveys showing mental health illiteracy among the general public (MHA, 2018). Also, studies started to show biochemical indicators of depression, such as glucose metabolism (Baxter et al., 1989). Eventually, in 1996, MHA promoted the Mental Health parity act to increase health insurance coverage (MHA, 2018). Depression treatment and society's perceptions have a vast history, having moved from demonizing those affected to being understood as a body's natural reaction to various stressors and inability to cope with that stress.

More than 11 million people in North America aged 18 years and older live with depression, with almost 35% never receiving treatment (WHO, 2017). Depression affects a person's ability to perform basic and instrumental activities of daily living, such as daily hygiene, eating, financial management, driving a vehicle and managing medication. It is characterized by upset moods, loss of self-esteem and concentration, guilt, sadness, and irritability (WHO, 2017). In the

last decade, an approximately 18% increase in depression has resulted in $1 trillion loss in productivity (WHO, 2017). Due to the associated loss in productivity, depression has become one of the leading causes of disability and poor health outcomes (WHO, 2017). Untreated and severe depression can lead to suicide (WHO, 2017).

Multiple barriers interfere with obtaining treatment for depression. First, stigma serves as a barrier to the treatment of mental illness (Corrigan, 2016; Jezard, 2018; Subramanium et al., 2017; Xie et al., 2018). Patients living with depression may self-stigmatize if they believe that they are weak due to their illness. Self-stigmas along with societal stigma may lead to feelings of shame and guilt, preventing patients from sharing symptoms with healthcare professionals. Stigma can delay effective treatment, resulting in worse health outcomes (Jezard, 2018; Subramanium et al., 2017; Xie et al., 2018).

Other barriers include high insurance deductibles or lack of coverage from psychiatrists; almost 50 percent do not accept insurance in North America (WHO, 2016; Kamal, 2017). Still, approximately $187 billion is spent annually on depression treatment in North America and it is considered the sixth most costly health condition (Chiu et al., 2017). According to Chiu et al. (2017), individuals living with depression usually pay approximately $3210 - $4008 per year for treatment, compared to approximately $2629 - $2945 annually for other types of mental illness. Due to the high costs and lack of coverage associated with the treatment of depression, many individuals are not able to access care. Lower-income families in particular may not be able to afford medical visits or insurance. Lastly, fear of institutionalization may hinder treatment for mental illness (Connolly, 2017; Rowan et al., 2013). In part, due to these barriers, depression has become a new epidemic in North America. Public-health professionals need to study the barriers to treatment and the precursors of depression so that strategies can be developed in order to

reduce this growing epidemic (CDC, 2013; American Psychology Association, 2017; World Health Organization; 2018).

Prevention of depression is the best and first line of treatment preferred by healthcare professionals. Healthcare professionals advise annual screenings by psychiatrists, physical activity, and the promotion of positive thinking through community-based interventions (Kingstone et al., 2017; Niemi et al., 2016; Thomas, 2018). Positive thinking helps by releasing serotonin and balancing cortisol that results in a happy mood (Kingstone et al., 2017; Niemi et al., 2016; Thomas, 2018). Community-based interventions, such as psychoeducational counseling, yoga, depression-awareness programs and development of communication skills, have been shown to reduce depression (Kingstone et al., 2017; Niemi et al., 2016; Thomas, 2018). Of interest to practitioners, multiple studies have demonstrated an association between depression and metabolic syndrome (METS) (Aggarwal et al., 2016; Gheshlagh et al., 2016; Mcelory et al., 2014; Moore et al., 2017). The relationship between depression and METS is due in part to anti-depressants, which tend to increase body weight and lipid levels.

Metabolic Syndrome (METS)

Recently defined by the World Health Organization as a pandemic disease, METS can have various consequences such as kidney failure, fatty liver, dementia, cognitive impairment and polycystic ovarian disease (Stoppler, 2018). METS can be a result of sedentary behavior and dietary intake of foods high in saturated fats, impacting adults and children at increasing levels (Beigh & Jain, 2012). Stress, lack of motivation, lack of resources for purchasing healthy food, absence of health-club memberships and lack of education are additional factors contributing to METS (CDC, 2018; Ochel, 2015).

Various studies have shown that METS can be treated with simple lifestyle modifications, such as performing recommended levels of physical activity of 150 minutes per week and eating a healthy diet (Boggs, 2017; Bumgardner, 2019; Stoppler, 2018). People living with METS are advised to limit their sodium intake and monitor their blood pressure (Stoppler, 2018). Surgical interventions such as liposuction have not shown much improvement in treating METS (Stoppler, 2018).

METS is an escalating public-health issue globally, as it has been associated with various comorbidities like cardiovascular diseases, diabetes and stroke (Dang & Deswal, 2014). It is characterized by the presence of three or more of the following symptoms: hypertension, diabetes mellitus, hypercholesterolemia, gout, obesity (BMI>30) and high abdominal circumference (Stoppler, 2018). METS is prevalent in adults worldwide at 25% (Mandal, 2018). Symptoms of METS are equally prevalent. High lipid levels are present in approximately 41.2% of the global population, followed by high blood pressure at 26.6% (Nolan et al., 2017). Abdominal obesity is prevalent in 23.65% of individuals worldwide and high fasting glucose is seen in 15.4% of the global population (Nolan et al., 2017). The presence of one component, (i.e. high blood pressure, abdominal obesity, high lipid levels) serves as a precursor for others, which increases the burden of METS worldwide. In addition, studies have shown that the economic burden of METS is in trillions annually (Mahabaleshwarkar, 2019; Miller, 2015; Saklayen, 2018; Tremmel et al., 2017).

The prevalence of METS is highest in the United States followed by Mexico. In any twelve-month period, 32% of people in the United States are affected by METS, with approximately 85% of them living with diabetes type 2 (Stoppler, 2018). The prevalence increased to 34.3% by 2018 and has almost remained stable since then (Saklayen, 2018; Shin et al., 2018). Due to the

increased prevalence of METS over the last decade, it is now considered an epidemic and pandemic (Neil & Driscoll, 2015). There is definitely an urgent need to study health consequences associated with METS so that public-health professionals can develop community-based interventions and decrease the spread of this epidemic disorder.

History of METS

In the early 1900s, scientists noted that obesity, hypertension, cardiovascular diseases, diabetes and increased levels of uric acid were found in the same patients (Paulescu, 1920). Some scientists also concluded that arterial hypertension is a pre-diabetic phase, with diet playing a major role in treating metabolic disorders (vague et al., 1947; Maranon, 1927; Haragus, 1932). By 1947, it was apparent that abdominal obesity was commonly associated with cardiovascular diseases and diabetes (Vague et al., 1947). A clinical study conducted for 12 weeks with six participants revealed an association between metabolic disorders and diet (Avogaro et al., 1967). During the study, participants were given low carbohydrate and low calorie diets, resulting in lower fasting glucose levels. Results from other studies indicated that high uric acid levels, diabetes, hypertension and high triglyceride levels were all positively associated with cardiovascular disease and deaths due to myocardial infarction (Haller, 1977; Philips, 1977).

By the end of 1990, a cluster of metabolic disorders such as diabetes, insulin resistance, obesity, high lipid levels and hypertension were commonly known as ‘syndrome X’ (Reaven G, 1988). Also, since insulin resistance was considered to be a pre-cursor of METS or Syndrome X’, METS was also known as insulin resistance disorder (Kahn et al., 2005). Studies further demonstrated that Syndrome X was often associated with a lack of physical activity and advancing age. In 1998, the first criteria for Syndrome X were developed by the World Health

organization and revised by National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) in 2001. These standardized criteria assisted researchers in conducting various studies on METS.

Prevalence of METS and depression

As the annual prevalence of METS among U.S. adults is 34% and depression is prevalent in approximately 8.1% of Americans in a given two-week period (CDC, 2018), both METS and depression pose a public-health threat. METS is associated with dramatic increases in cardiovascular disease, type II diabetes and abdominal fat, while severe depression is associated with disability (Henriques, 2016; Lima, 2014; National Alliance on Mental Illness, 2018). Therefore, timely diagnosis and treatment of METS and depression will help public-health professionals in achieving better health outcomes.

Prior METS and Depression Studies

A study conducted in men aged 65-84 years demonstrated that obesity and METS were positively associated with depression (Miettola et al., 2008). However, this study was done only among white-collar men, thus limiting generalizability. Similarly, another cross-sectional study indicated that depression scores were high in METS patients when compared with the scores in non-METS patients but was not able to establish a temporal relationship between the two health conditions. Other study findings indicate that high waist circumference and low HDL are associated with high depression (Almeida et al., 2009; Chang et al., 2017; Dunbar et al., 2008; Miettola et al., 2008). Prior studies conducted have not been able to establish the clear association between METS and depression. Also, the results cannot be generalized to the population of United States as they were done within specific settings. These studies were conducted only among men aged 40 years or less, among diabetic patients or specific clinical

sites. Finally, not many prior studies used METS as a whole but have included individual components and their relationship with depression. Overall, prior studies demonstrate mixed statistical results, with few cross-sectional studies establishing a positive, but not causal, relationship between METS and depression (Dunbar et al., 2008; Friends et al., 2013; Liawh et al., 2015; Miettola et al., 2008). In addition, most studies were conducted with adults between 18-50 years of age (Dunbar et al., 2008; Ford et al., 2008; Liaw et al., 2015) or among children (Friends et al., 2013). Since studies have shown that METS increases with age, future studies should include individuals over 50 years of age. The current study addresses the age limitation of prior studies and includes individuals from an osteoarthritis (OA) initiative database.

One meta-analysis indicated a bi-directional association between METS and depression, but included articles with a high level of heterogeneity (Pan et al., 2012). Included articles were not similar in research design, covariates or sample size, which might have led to bias in the results. Another meta-analysis conducted by Gheshghal et al. (2016) included case-control as well as cross-sectional studies to analyze the association between METS and depression. Due to a small number of articles included in this study, the findings cannot be generalized (Gheshghal et al., 2016; Pan et al., 2012). Moreover, further research has been advised by both the researchers to meet the limitations of their studies. To our knowledge, further meta-analysis studies have not been conducted on the topic since 2012.

Chronic diseases such as osteoarthritis (OA) can exaberbate METS and depression. OA is a chronic disease that has poor health outcomes (Parkinson et al., 2017). Individuals living with OA are at risk for developing sedentary behavior due to joint pain and inflammation (Xie et al., 2016). This sedentary behavior puts them at risk for developing METS, futher deteriorating their health condition and recovery (Xie et al., 2016). Since OA does not have a cure, intervention

strategies to delay disease progression can help individuals living with it in maintaining independence. Studies have indicated that OA can result in sleep disturbances, severe pain, functional limitations, dependency on relatives and depression (Chang et al. 2017; Sharma et al., 2016; Xie et al., 2016).

In summary, prior studies have shown an increase in the prevalence of METS and depression in North America over the last decade, but prior meta-analysis studies do not consistently explain the relationship between the two variables. Further, some studies only show the relationship between depression and specific components of METS, such as obesity and waist circumference, instead of the entire METS profile. Hence, there is a need to further study the association between the overall presence of METS and depression. Therefore, the purpose of the current study is to conduct a systematic literature review and meta-analysis of all studies published between January 1999 and April 2019 that have analyzed the association between METS and depression. To our knowledge, there are no known programs that address METS and depression together. Current study findings can help health professionals in understanding the association between METS and depression so that future programs can be established. Due to several definitions of METS, the current study has included all articles that used METS as independent variables in predicting depression. Only studies that described METS as a predictor of depression were used.

Purpose

The purpose of the study was to conduct a systematic review and meta-analysis in order to explore the association between METS and depression.

Research design and methodology

Data source

We analyzed existing data on the association between METS and depression among adults and included studies with METS as a predictor for depression. Published articles were searched in PsycINFO, MEDLINE Complete, CINAHL Complete, ScienceDirect, SportDiscuss and Jewl databases. Key words such as 'Metabolic Syndrome', 'syndrome x', insulin resistance syndrome', 'depression' and a combination of these key words after the equivalent-subject expander were used to identify potentially relevant terms. The search was limited to studies with the title depression and/or METS, studies in English, studies published in peer-reviewed academic journals and studies conducted from January 1999 until April 2019.

Study selection

Two reviewers (GT and JF), independently reviewed articles and titles to remove duplicates and articles published in languages other than English. Articles were included for analysis if they met the following inclusion criteria:

A. Studies were peer-reviewed original studies and not abstracts or comments/letters;
B. Studies were conducted among adults above 18 years of age;
C. METS was an independent variable and depression a dependent variable; and
D. Studies were published in the English language.

The final studies were chosen by consensus of the reviewers. Studies were included that used all definitions for METS, such as those defined by World Health Organization (WHO), National Cholesterol Education Program(NCEP), Adult Treatment Panel III (ACT III) and International Diabetes Federation (IDF). Studies included all reliable and valid criteria for diagnosing

depression such as the Geriatric depression scale (GDS), Center for epidemiologic disease – depression (CES-D), and clinically diagnosable criteria by other organizations.

Data Extraction

The above-mentioned search criteria yielded 626 relevant studies. After removal of duplicates, there were 316 studies remaining. We reviewed the title and subject line of all three hundred and sixteen studies to identify potential candidates for inclusion.

Two studies were excluded because they were not published in English while 267 studies were excluded because they did not include both variables of interest (i.e., depression and METS). Further, two studies were excluded because they were non-human/animal studies. The remaining 45 studies were screened further for inclusion through examination of the abstract. Thirty-four of the studies were excluded because depression was not the dependent variable. An additional hand search, along with research library consultation, was used to identify three studies. Two studies from the previous meta-analysis were not reported because we were unable to access the articles to retrieve the data.

In total, 13 full-text studies met the criteria for meta-analysis. Information extracted included the name of the study, name of the first author, year of publication, journal title, sample size, mean age of the sample and participant information (i.e., demographics), and METS and depression measures. Data analysis methods and results were extracted. Mean age was included in the analysis as a moderator variable, which was expected to influence depression as an outcome variable. The primary outcome measure for each included study was depression. All the studies that had a standard criterion for depression were included.

Data synthesis

The data (i.e., reported results) were entered in comprehensive meta-analysis software (CMA) version 3 and the level of significance was set to .05. The software provides the option to obtain an odds ratio, coefficient of correlation, hedge's g, r square and various other measures to calculate effect size. After data entry was completed, CMA was used to conduct the meta-analysis.

Data were analyzed using a random-effects model to allow for study-level heterogeneity in the distribution of effect-size estimates. A moderator analysis was performed to determine if the effect size was influenced by the mean age of the sample. Parameter-estimates examination included the overall effect size with 95% confidence intervals, test of homogeneity of variance (Q) and the percentage of total variance across studies due to heterogeneity (I^2). I^2 indicates that the included studies in meta-analysis are different due to the type of participants, research design, study settings and variables used.

Results

Systematic review results

Using the designated search terms previously outlined, 626 relevant records were identified through database searches and author contacts. The breakdown of record identification can be seen in the PRISMA diagram in Figure A1. In total, 13 full-text studies were reviewed for potential relevance and inclusion after the rest was excluded using the systematic review criteria.

Overall results

Effect-size estimates for each study in predicting depression can be seen in Table A1 and the Forest plot (Figure A2). In total, 17 effect sizes were calculated from 13 studies. Statistical

heterogeneity between studies was not significant (I^2 = 38.71%, df = 16 and p=.053) indicating that studies were compatible. Due to insignificant heterogeneity, a fixed-effect model was used. Results of the fixed-effect meta-analysis showed that the overall OR was 1.14 (95% CI =1.09, 1.19, p=.000). This indicated that there is a significant association between METS and depression. Individuals who live with METS are 1.14 times more likely to have depression when compared with individuals without METS.

Moderator results

Moderator analysis was done by age. Statistical heterogeneity between studies was significant [Q(between) = 23.95, df = 14, and p=.046] indicating that studies had different mean ages. Q (between) indicates the impact of moderators used in the meta-analysis (Chang et al., 2017). Due to significant heterogeneity, a mixed-effect model was used. Results of the mixed-effect meta-analysis showed that the OR was 1.14 (95% CI =1.09, 1.19, p=.000). This indicated that age is a significant moderator in the association between METS and depression. Individuals who are between 41 to 69 years and live with METS are 1.14 times more likely to have depression, when compared with individuals who are above 69 years and have METS.

Discussion

Results from this study indicate that individuals with METS are more likely to have depression. METS is a metabolic disease that affects insulin homeostasis, disturbs blood glucose levels and interferes in C-reactive protein synthesis and mitochondrial respiration (Engelsen et al., 2012; George, 2018; Han & Lean, 2016). Mitochondrial respiration refers to the metabolic reaction that occurs in mitochondria and utilizes oxygen to release stored energy and distribute it in the body (Hoeks et al., 2012). All of these factors are associated with depressive moods (Anderson et al., 2013; Chamberlein, 2019). In addition, studies have shown that METS is

associated with vascular damage in neurological and cardiovascular organs (Feng et al., 2016). This damage can further lead to altered mood and depressive symptoms.

Studies have reported that individuals who are diagnosed with METS can have social stigma, body shame and the inability to have an active lifestyle (Tomiyama et al., 2018). Individuals with METS often have negative perceptions of their body weight and are at risk for developing depressive symptoms (Toich, 2017). Similarly, high body mass index and waist circumference can lead to low self-esteem and depression (Toich, 2017; Tomiyama et al., 2018). Based on prior studies, the pathogenesis and complex pathways for METS seem to be related to depression. However, more studies are needed to clarify the relationship between the development of METS and depression. The understanding of this relationship can help in preventing and treating both diseases so that individuals can live healthier lives.

Limitations

This meta-analysis has several limitations. First, the CMA software (lite software, version 3), does not have a feature called publication bias. The researchers are unable to determine if the meta analysis was biased due to bias that may have occurred within the individual studies. Second, the results in most of the included studies did not take into account demographics such as race, gender or socio-economic status. Most of the included studies reported overall results based on mean age as a covariate. Access to results based on demographics would have aided in moderator analysis and might have produced different results. Third, articles published in languages other than English were excluded. Fourth, few cohort and clinical trials were included in this meta-analysis due to lack of published data. More research is needed using these designs to have better understanding of the association between METS and depression.

However, this study has several strengths. First, data were extracted from studies that were unable to individually provide a clear picture on the association between METS and depression. The results from this study indicate a clear picture of association between both the variables of interest. Second, the sample size combined from all the included studies in this meta-analysis was approximately 1, 63,416 participants. Due to this large sample size, the results of this study are strong and can be generalized among various population groups from across different regions of the world. Third, the heterogeneity was not significant indicating that all the studies included in the analysis were compatible.

Conclusion and Future Direction

The results of this study support prior studies in establishing a significant association between METS and depression. Future studies can be conducted to understand how various components of METS are associated with depression. Presently, there is limited knowledge about this association. In addition, further information is needed on exactly how METS is associated with various levels of depression (i.e., mild, moderate and high). Since both diseases can lead to poor life expectancy and health outcomes, future methods for timely diagnosis can result in better treatment strategies.

On the clinical side, METS and depression are usually diagnosed separately, since few of the symptoms overlap. The diagnosis is based on the presence of the majority of symptoms that reflect either METS or depression (Chamberlein, 2019; WHO, 2017). Healthcare providers should be able to identify the symptoms of depression while they are treating individuals living with METS (WHO, 2017). Also, METS and depression are usually not diagnosed in a timely manner, as their symptoms are often confused with normal signs of aging (Chamberlein, 2019). Various strategies should be developed in healthcare practices so that individuals at risk for

developing METS can be diagnosed early and prevention strategies can be planned for successful treatment plans. In addition, once depression is clinically diagnosed with the comorbidity of METS, a holistic approach should be established so that individuals can be treated and be able to live healthy lives.

REFERENCES

Akbaraly, T., Kivimaki, M., Brunner, E., Chandola, T., Marmot, M., Singh-Manoux, A., & Ferrie, J. (2009). Association between metabolic syndrome and depressive symptoms in middle-aged adults: results from the Whitehall II study. *Diabetes care, 32*(3), 499-504.

Akbaraly, T., Ancelin, M.L., Jaussent, I., Ritchie, C., Barberger, P., Dufouil, C., Kivimaki, M., Claudine,B., & Ritchie, K. (2011). Metabolic syndrome and onset of depressive symptoms in the elderly. *Diabetes Care*, *34*(4), 904–909. doi: 10.2337/dc10-1644.

Almeida, O., Calver, J., Jamrozik, K., Hankey, G., & Flicker, L. (2009). Obesity and metabolic syndrome increase the risk of incident depression in older men: The health in men study. *American Journal of Geriatric Psychiatry*, (10), 889-898.

Agarwal, A., Agarwal, M., Garg,K., Kumar, P., Kumar, T & Srivastava,S. (2016). Metabolic syndrome and central obesity in depression: A cross-sectional study. *Indian Journal of Psychiatry, 58*(3), 281–286. doi: 10.4103/0019-5545.192021.

Baxter, L. R., Schwartz, J. M., Phelps, M. E., Mazziotta, J. C., Guze, B. H., Selin, C. E., & Sumida, R. M. (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry*, *46*(3), 243-250.

Block, A., Schipf, S., Van der Auwera, S., Hannemann, A., Nauck, M., & Grabe, H. J. (2016). Sex- and age-specific associations between major depressive disorder and metabolic syndrome in two general population samples in Germany. *Nordic Journal of Psychiatry*, *70*(8), 611–620.

Bakhtiari, A., Hashemi, M., Hosseini,S., Omidvar,S., Bijani, A., & Khairkhah, F. (2018). The relationship between depression and metabolic syndrome in the elderly population: The cohort aging study. *Iranian Journal of Psychiatry, 13*(4), 230 – 238.

Center for Disease Control and Prevention (CDC). (2018). Prevalence of depression among adults aged 20 and over: United States. Retrieved from https://www.cdc.gov/nchs/products/databriefs/db303.htm

Chang,H., Tien-Mu, H., Mei-Huei, L., Chih-Jung, Y., & Hao-Jan, Y. (2017). Metabolic syndrome and depression are not correlated: results from a community sample exploring the unique and common correlates for the two diseases. *Neuropsychiatry, 7*(2), 142. doi:10.4172/Neuropsychiatry.1000190

Chang, T., Lung,F., Yen,Y. (2016). Depressive symptoms, cognitive impairment, and metabolic syndrome in community-dwelling elderly in Southern Taiwan. *Psychogeriatrics, 15*(2), 109-115. doi: 10.1111/psyg.12080

Colman, D. (2016). Is it superstition or obsessive-compulsive disorder (OCD)? [Blog post]. Retrieved from https://medium.com/@danna310/is-it-superstition-or-obsessive-compulsive-disorder-ocd-5fa76a0d0d6

Connolly, D. (2017). High costs prevent people from seeking mental health services [Blog post]. Retrieved from http://thehill.com/blogs/pundits-blog/healthcare/320727-high-costs-prevent-people-from-seeking-mental-health-services

Dunbar, J. A., Reddy, P., Davis-Lameloise, N., Philpot, B., Laatikainen, T., Kilkkinen, A., & Janus, E. D. (2008). Depression: An important comorbidity with metabolic syndrome in a general population. *Diabetes Care, 31*(12), 2368-2373. doi:10.2337/dc08-0175.

Friend, A., Craig, L., & Turner, S. (2013). The prevalence of metabolic syndrome in children: A systematic review of the literature. *Metabolic Syndrome & Related Disorders, 11*(2), 71-80. doi:10.1089/met.2012.0122.

Ford, E., Li, C., & Sattar, N. (2008). Metabolic syndrome and incident diabetes: Current state of the evidence. *Diabetes care*, *31*(9), 1898-1904.

Gheshlagh, R. Parizad, N.& Sayehamiri, K. (2016). The relationship between depression and metabolic syndrome: Systematic review and meta-analysis study. *Iranian Red Crescent Medical Journal, 18*(6), e26523. doi: 10.5812/ircmj.26523.

Goldbacher, E. M., Bromberger, J., & Matthews, K. A. (2009). Lifetime history of major depression predicts the development of the metabolic syndrome in middle-aged women. *Psychosomatic Medicine –Washington, 71*(3), 266–272. doi:10.1097/PSY.0b013e318197a4d5.

Gurka, M. J., Lilly, C. L., Oliver, M. N., & DeBoer, M. D. (2014). An examination of sex and racial/ethnic differences in the metabolic syndrome among adults: A confirmatory factor analysis and a resulting continuous severity score. *Metabolism, 63*(2), 218-225. doi:10.1016/j.metabol.2013.10.006

Herniques, G. (2016). Anxiety and depression are symptoms, not diseases [Blog post]. Retrieved from https://www.psychologytoday.com/us/blog/theory-knowledge/201603/anxiety-and-depression-are-symptoms-not-diseases.

Hert, M., Correll, C., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Moller,H., Ndetei,D., Newcomer,J., Uuwakwe,R., & Leucht, A. (2011). Physical illness in patients with severe mental disorders. Prevalence, impact of medications and disparities in health care. *World Psychiatry, 10*(1), 52-77.

Kim, Y., & Kim, H.-Y. (2019). Association between depression and metabolic syndrome in Korean adults: Data from the 2014 and 2016 Korea National Health and Nutrition Examination Survey (KNHANES). *Asia-Pacific Journal of Public Health*, *31*(1), 18-29.

Ko, K., Han, M., Shin, C., Lee, H., Han, C., Kim, Y., Yoon, K., & Ko, H. (2019). Association of metabolic syndrome and its components with suicidal ideation and depression in adults: A nationally representative sample of the Korean population. *Journal of Affective Disorders*, (249), 319–326. Retrieved from https://doi-org.ezproxy.mtsu.edu/10.1016/j.jad.2019.02.049

Jeon, S., Lim, S., Shin, D., Ryu, S., Chang, Y., Kim, S., Oh, K., Shin, Y., & Kim,Y. (2019). Metabolic syndrome and incident depressive symptoms in young and middle-aged adults: A cohort study. *Journal of Affective Disorders*, (246), 643–651. Retrieved from https://doi-org.ezproxy.mtsu.edu/10.1016/j.jad.2018.12.073

Jezzard, A. (2018). Depression is the no. 1 cause of ill health and disability worldwide [Blog post]. Retreived from https://www.weforum.org/agenda/2018/05/depression-prevents-

many-of-us-from-leading-healthy-and-productive-lives-being-the-no-1-cause-of-ill-health-and-disability-worldwide/

Kingstone, T., Burroughs, H., Bartlam, B., Ray, M., Proctor, J., Shepherd, T., Bullock, P., & Graham, C. (2017). Developing a community-based psycho-social intervention with older people and third sector workers for anxiety and depression: A qualitative study. *BMC Family Practice, 18*(77). doi:10.1186/s12875-017-0648-7.

Kohn, R., Saxena, S., Levav, I. & Saraceno, B. (2003). The treatment gap in mental health care / Le défaut de traitement en santé mentale / La brecha terapéutica en la atención de salud mental. *Bulletin Of The World Health Organization, 82*(11), 858 - 866.

Lee, Y. (2013). Effect and Treatment of Chronic Pain in Inflammatory Arthritis. *Current Rheumatology Reports, 15*(1), 300-304. doi: 10.1007/s11926-012-0300-4

Liang, Y., Gong, Y., Wen, X., Guan, C., Li, M., Yin, P., & Wang, Z. (2012). Social determinants of health and depression: A preliminary investigation from rural china. *Plos ONE, 7*(1), e30553. doi:10.1371/journal.pone.0030553.

Liaw, F., Tung-Wei, K., Ju-Ting, H., Yi-Hsin, C., Wen, C., & Wei-Liang, C. (2015). Exploring the link between the components of metabolic syndrome and the risk of depression. *Biomed Research International, 2015*(1). doi:10.1155/2015/586251.

Lorenzo,C., Williams,K., Hunt,K., & Haffner,S. (2007). National cholesterol education program-adult treatment panel III, International Diabetes Federation, and World Health Organization Ddefinitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. (2007). *Diabetes care, 30*(1), 8-13.

McElroy, S., & Keck, P. (2014). Metabolic Syndrome in Bipolar Disorder: A review with a focus on bipolar depression. *Journal of ClinicalPpsychiatry, 75*(1), 46-61. doi: 10.4088/JCP.13r08634.

Miettola, J., Niskanen, L., Viinamaki, H., & Kumpusalo, E. (2008). Metabolic syndrome is associated with self-perceived depression. *Scandinavian Journal Of Primary Health Care,* (4), 203-210.

Moore, J. X., Chaudhary, N., & Akinyemiju, T. (2017). Metabolic syndrome prevalence by race/ethnicity and sex in the United States, national health and nutrition examination survey, 1988-2012. *Preventing Chronic Disease, 14*, 1-16. doi:10.5888/pcd14.160287.

National Institute of Mental Illness (NIMH). (2019). Depression. Retrieved from https://www.nimh.nih.gov/health/topics/depression/index.shtml.

Pan, A., Keum, N., Okereke, O., Sun, Q., Kivimaki, M., Rubin, R., & Hu, F. B. (2012). Bidirectional association between depression and metabolic syndrome: A systematic review and meta-analysis of epidemiological studies. *Diabetes Care*, *35*(5), 1171-1180. doi:10.2337/dc11-2055.

Parkinson, L., Waters, D. L., & FranckL. (2017). Systematic review of the impact of osteoarthritis on health outcomes. *Osteoarthritis Cartilage, 25*(11), 1751-1770. doi: 10.1016/j.joca.2017.07.008.

Pradhan, A. (2013). Sex differences in the metabolic syndrome: Implications for cardiovascular health in women. *Clinical Chemistry, 60*(1), 44-52. doi: 10.1373/clinchem.2013.202549.

Pyykkonen, A. J., Raikkonen, K., Tuomi, T., Eriksson, J. G., Groop, L., & Isomaa, B. (2012). Association between depressive symptoms and metabolic syndrome is not explained by antidepressant medication: Results from the PPP-Botnia Study. *Annals of Medicine - Helsinki*, *44*(3), 279-288.

Puenpatom, R., & Victor, T. (2009). Increased prevalence of metabolic syndrome in individuals with osteoarthritis: An analysis of NHANES III data. *Postgraduate Medicine, 121*(6), 9-20.

Ruas, L. G., Diniz, B. S., Firmo, J. O., Peixoto, S. V., Mambrini, J. V., Filho, A., Costa, M., & Castro, É. (2016). Components of the metabolic syndrome and depressive symptoms in community-dwelling older people: The Bambuí Cohort Aging Study. *Revista Brasileira de Psiquiatria*, *38*(3), 183–189.

Sharma, A., Kudesia, P., Shi, Q., & Gandhi, R. (2016). Anxiety and depression in patients with osteoarthritis: impact and management challenges. *Open Access Rheumatology : Research And Reviews*, 8, 103-113.

Stoppler, M. (2018). Insulin Resistance. Retrieved from https://www.medicinenet.com/insulin_resistance/article.htm

Subramanium, M., Abdin, E., Picco, L., Pang, S., Shafie, S., Vaigankar, A. J., Kwok, K. W., Verma, K., & Chong, A. S. (2017). Stigma towards people with mental disorders and its components – A perspective from multi-ethnic Singapore. *Epidemiology and Psychiatric Sciences, 26*(4), 371. doi: 10.1017/S2045796016000159

Takeuchi, T., Nakao, M., Nomura, K., Inoue, M., Tsurugano, S., Shinozaki, Y., & Yano, E. (2009). Association of the metabolic syndrome with depression and anxiety in Japanese men: A 1-year cohort study. *Diabetes Metabolism Research And Reviews*, *25*(8), 762-767.

Thomas, F. (2018). Can positive thinking really get you through a depressive episode? [Blog post]. Retrieved from https://metro.co.uk/2018/02/02/can-positive-thinking-really-get-you-through-a-depressive-episode-7278823/

Van,D., Giltay, E. J., Van Veen, T., Zitman, F. G., & Penninx, B. (2010). Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. *Acta Psychiatrica Scandinavica*, *122*(1), 30-39. doi: 10.1111/j.1600-0447.2010.01565.x.

Vogelzangs, N., Beekman, A. T. F., Boelhouwer, I. G., Bandinelli, S., Milaneschi, Y., Ferrucci, L., & Penninx, B. (2011). Metabolic Depression: A Chronic Depressive Subtype? Findings From the InCHIANTI Study of Older Persons. *Journal of Clinical Psychiatry*, *72*(5), 598-604. doi:10.4088/JCP.10m06559.

WebMD. (2018). Metabolic syndrome: growing health threat. Retrieved from https://www.webmd.com/heart/metabolic-syndrome/news/20050912/metabolic-syndrome-growing-health-threat#1.

Wilkinson, R. and Marmot, M. (2003). Social determinant of health: the solid facts. *Copenhagen*. Retrieved from http://www.euro.who.int/__data/assets/pdf_file/0005/98438/e81384.pdf

World Health Organization (WHO). (2012). Depression: let's talk. Retrieved from http://www.who.int/mental_health/management/depression/en/.

Xie, H., Wen, P. C., Long, Z., Xuan, S., & Jie, X. J. (2018). Relationship between activities of daily living and depression among older adults and the quality of life of family caregivers. *Frontiers of Nursing*, (2), 97. doi: 10.2478/fon-2018-0013.

APPENDIX A: PRISMA Diagram

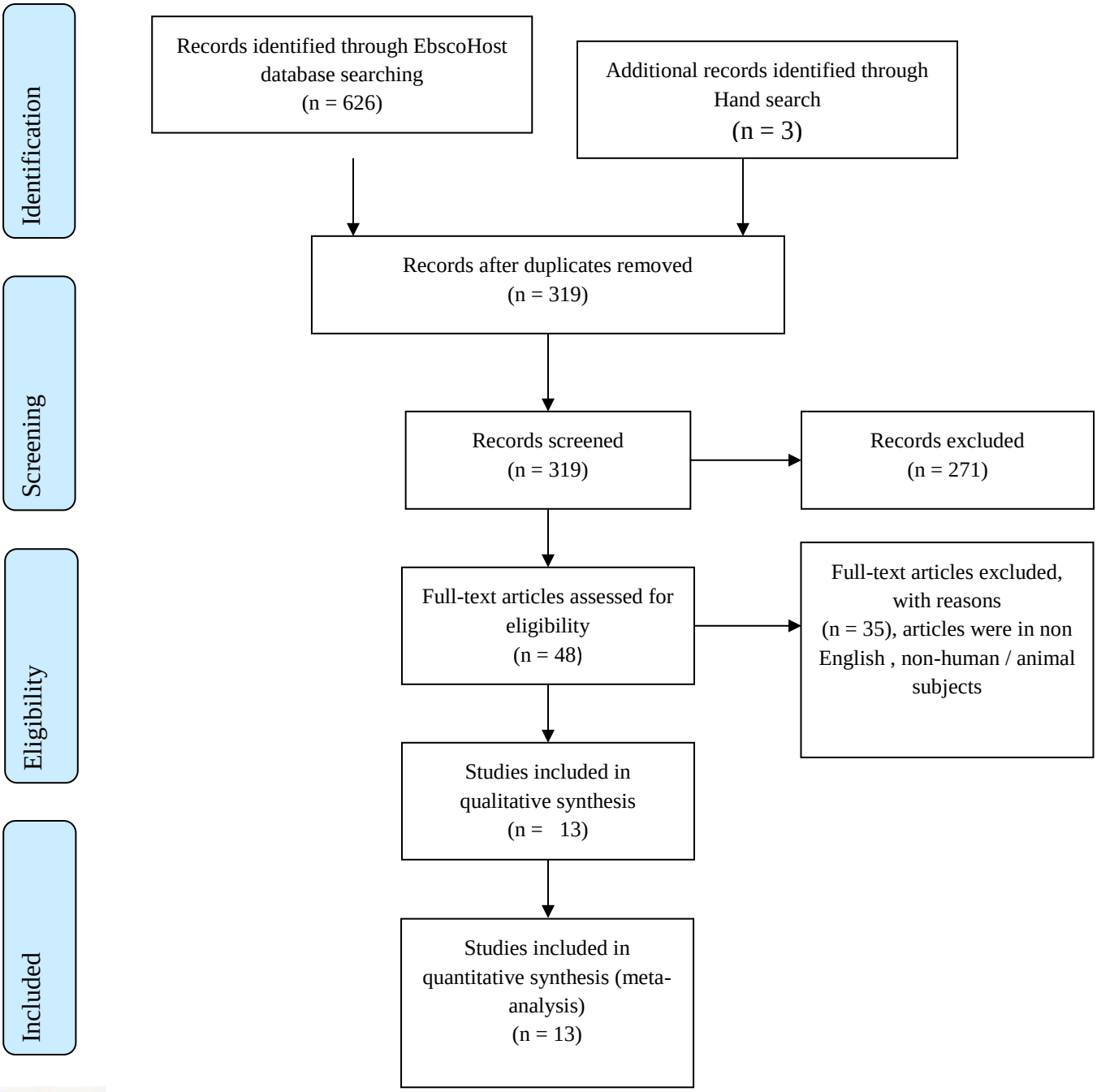

Figure A1. PRISMA 2009 Flow Diagram

Table A1. Study characteristics and overall results

Principal Author	Year	N	Age	MetS Component	OR	LL	UL
Jeon et al	2019	115,223	41.5	Fully adjusted model (model 2) 5 components	1.25	1.1	1.5
Ko et al	2019	9867	50.23	Mets with Depression	1.16	1	1.4
Kim Y & Kim HY	2019	10459	48.17	Mets with Depression	1.41	1.1	1.8
Bakhtiari et al	2018	1560	69.3	All Components Clustered	1.03	0.9	1.1
Ruas et al	2016	1469	69.3	All Components Clustered	1.25	0.7	2.1
				High fasting plasma glucose	0.94	0.8	1.2
				high blood pressure	0.94	0.8	1.2
				low HDL	1.17	1	1.5
				high triglycerides	1.47	1.2	1.8
				high waist circumference	1.19	0.9	1.5
Block et al	2016	4083	63	Mets with Depression at syndromal level			
				Males	1.53	1.1	2.2
				Females	1.14	0.8	1.6
Pyykkonen et al	2012	4967	46.1	Fully adjusted model	1.10	1.1	1.2
Akbaraly et al	2011	4446		Age Group			
			67.9	65-69.4	1.73	1	3
			71.1	69.4-72.8	1.18	0.7	2
			74.7	72.8-76.8	0.94	0.6	1.5
			79.9	76.8-91.1	0.89	0.6	1.4
Vogelzangs et al	2011	823	73.3		1.01	0.7	1.5
Van et al	2010	2981	41	All Components Clustered	2.21	1.1	4.6
				Mets with Depression controling for anti-depressent usage	2.18	1	4.6
Akbaraly et al	2009	5232	49.5	Model 2 (fully adjusted model)	1.38	1	1.9
Goldbachet et al	2009	429	45.6	Mets with Depression	1.66	1	3.8
Takeuchi et al	2009	956	42.7	Mets with Depression	2.14	1.1	4.2
TOTAL N		162,495					

META ANALYSIS

Model	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Jeon et al, 2019	1.250	1.100	1.420	3.421	0.001
	Ko et al, 2019	1.164	0.964	1.405	1.580	0.114
	Kim Y & Kim HY, 2019	1.410	1.125	1.768	2.980	0.003
	Bakhtiari et al, 2018	1.030	0.931	1.140	0.571	0.568
	Ruas et al, 2016	1.250	0.737	2.121	0.827	0.408
	Block et al-M, 2016	1.530	1.060	2.209	2.269	0.023
	Block et al- F, 2016	1.140	0.832	1.563	0.814	0.416
	Pyykkonen et al, 2012	1.100	1.025	1.180	2.661	0.008
	Akbaraly et al-67.9, 2011	1.730	1.017	2.942	2.023	0.043
	Akbaraly et al-71.1, 2011	1.180	0.703	1.980	0.627	0.531
	Akbaraly et al-74.7, 2011	0.940	0.576	1.535	-0.247	0.805
	Akbaraly et al-79.9, 2011	0.890	0.559	1.417	-0.491	0.623
	Vogelzangs et al, 2011	1.010	0.661	1.543	0.046	0.963
	Van et al, 2010	2.210	1.056	4.624	2.105	0.035
	Akbaraly et al, 2009	1.380	1.019	1.869	2.083	0.037
	Goldbacher et al, 2009	1.660	0.735	3.750	1.219	0.223
	Takeuchi et al, 2009	2.140	1.099	4.167	2.238	0.025
Fixed		1.140	1.089	1.194	5.562	0.000

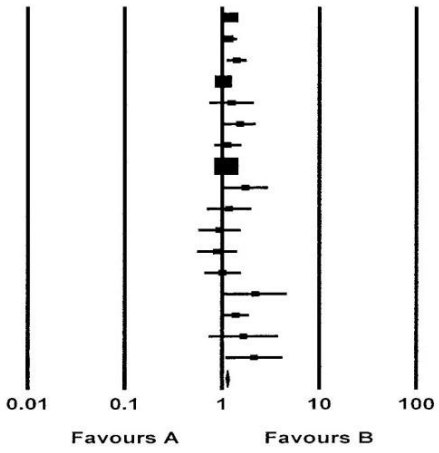

Figure A2. High resolution forest plot for fixed effects

META ANALYSIS

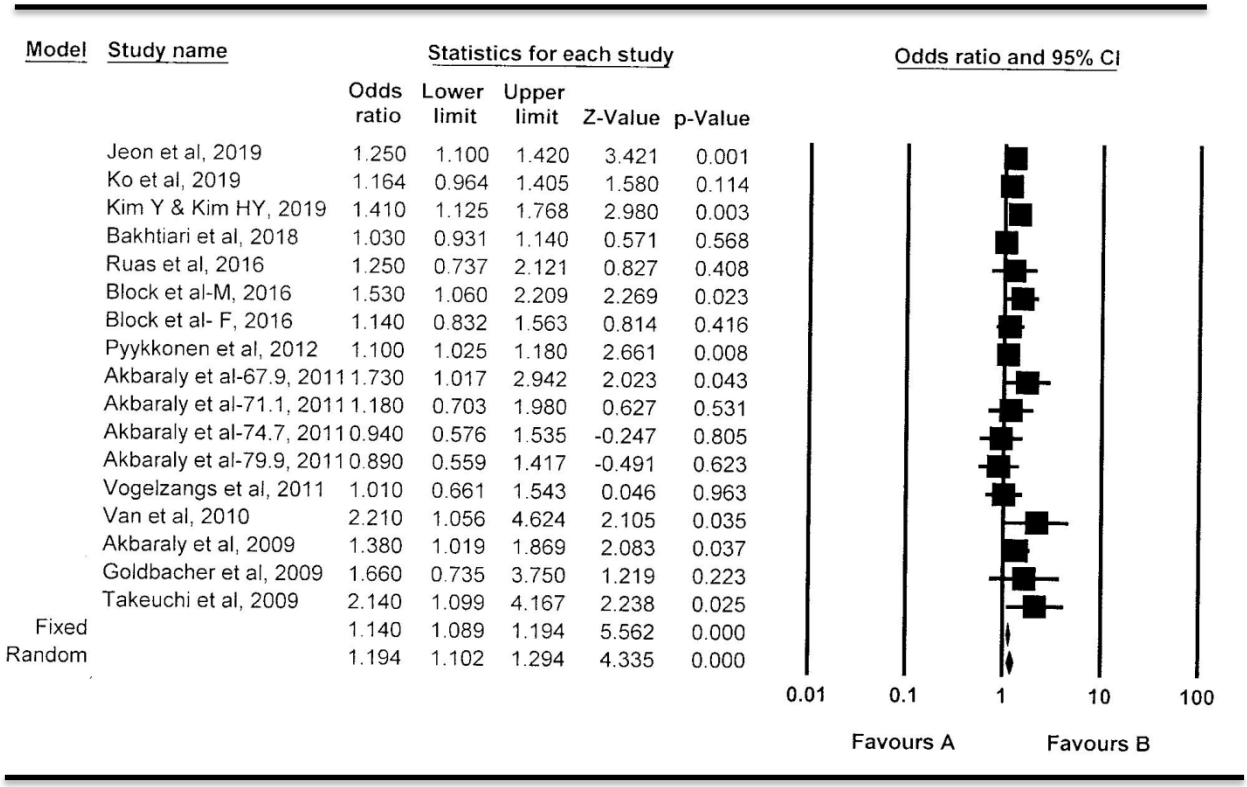

Figure A3. Fixed and random effects in meta-analysis: High resolution forest plot.

META ANALYSIS

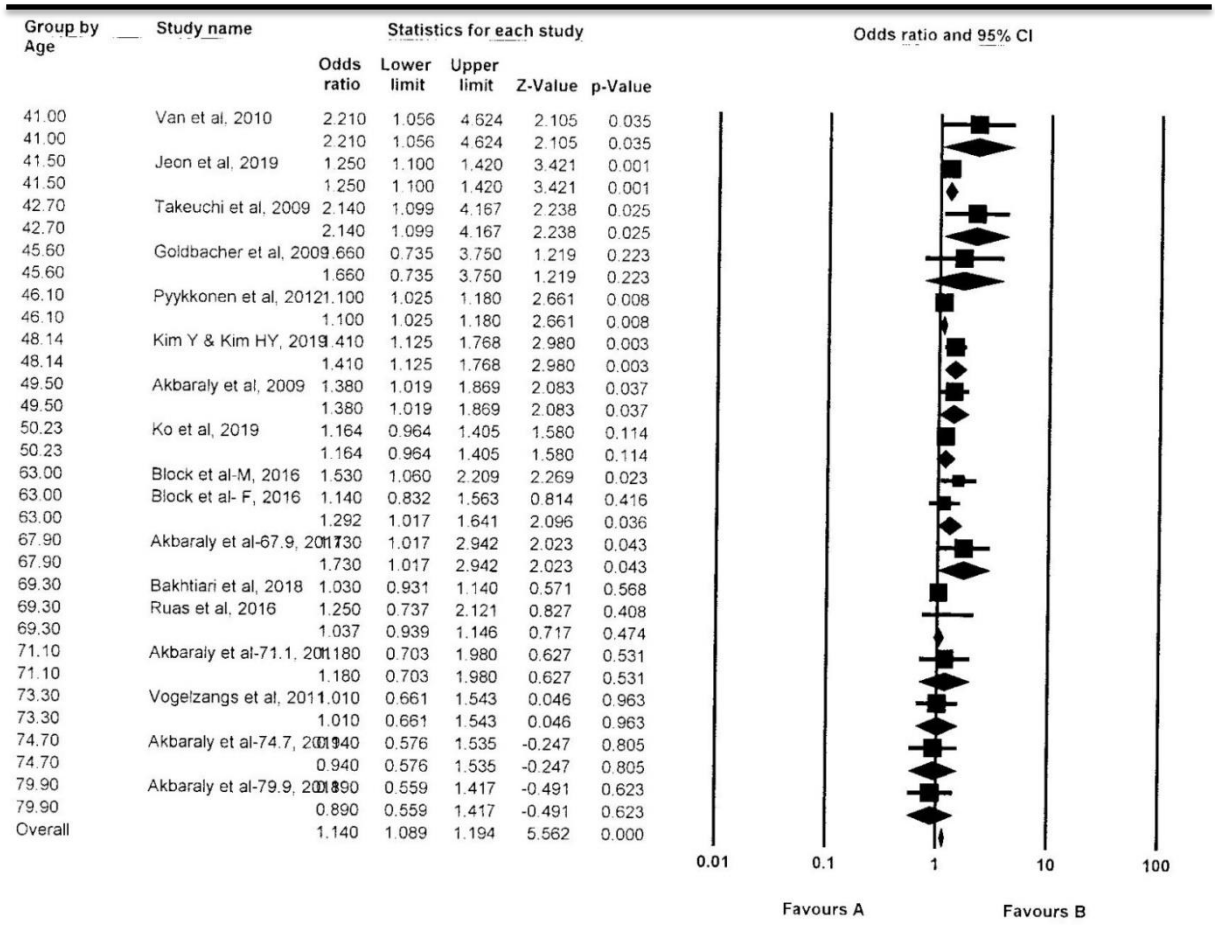

Figure A4. High resolution forest plot for mean age as moderator.

CHAPTER III: ASSOCIATION BETWEEN METABOLIC SYNDROME AND DEPRESSION AMONG ADULTS WITH OSTEOARTHRITIS

Introduction

What is osteoarthritis?

Osteoarthritis is a degenerative disease that affects joints in the knees, hips, wrist, thumb, toes and ankles (CDC, 2018). It is defined as an inflammatory condition in which slippery tissue between two joints is damaged and cartilage breaks down (National Institute of Health [NHIS], 2016). For individuals affected by arthritis, bones rub against each other, resulting in pain, inflammation, reduced mobility and sometimes a sedentary lifestyle (CDC, 2018). Studies have shown that one in four adults will develop symptomatic knee osteoarthritis (CDC, 2017; Arthritis Foundation, 2018). Among individuals who are over 60 years of age, 1 in every 12 will develop hand osteoarthritis (Arthritis Foundation, 2018; Lee, 2013).

Burden of Arthritis in North America

Osteoarthritis is a common form of arthritis that affects more than 30 million adults in North America (CDC, 2018), with women significantly impacted more than men (60% women and 40% men) (CDC, 2019). Among individuals affected by osteoarthritis, approximately 43.55% are unable to perform their activities of daily living (CDC, 2018). Therefore, individuals living with osteoarthritis become increasingly dependent on others for daily tasks. Arthritis can put individuals at risk for developing cardiovascular diseases, diabetes and obesity (CDC, 2018).

Due to limited physical activity associated with joint inflammation, individuals living with osteoarthritis are at risk for developing metabolic syndrome. The Centers for Disease Control and Prevention (CDC) predicts that 20% of the population by the year 2030 will include

people above 60 years of age. Approximately 86% of seniors will be either overweight or obese (CDC, 2003), further putting them at risk for developing other components of metabolic syndrome. Individuals who are overweight or obese are more likely to have worsening symptoms of arthritis, due to increased pressure on their joints.

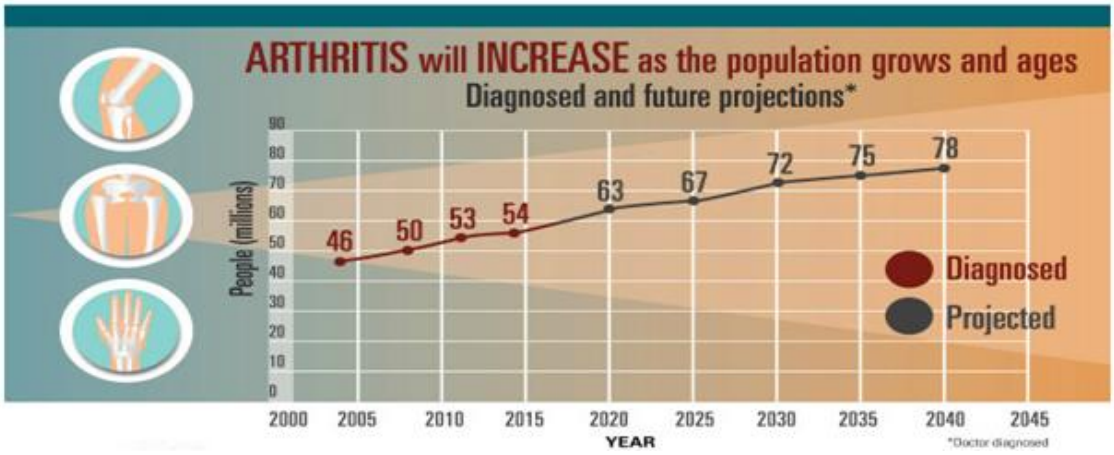

Figure B1. Estimated and Projected Number of Adults with Doctor-Diagnosed Arthritis in the United States [retrieved from national health interview survey (2015)].

There is no cure for osteoarthritis or strategies to stop its progression. Individuals with osteoarthritis are given only symptomatic treatment with medications and physical therapy to reduce joint pain and inflammation (CDC, 2018; Lee, 2013). Due to lack of permanent treatment options, individuals with osteoarthritis are often advised to undergo joint replacement surgeries. Lack of permanent treatment strategies and loss of mobility could lead to depression.

Osteoarthritis is considered to be a very costly health condition with approximately 16.5 billion dollars spent in treatment (CDC, 2018). Due to the high costs associated with treatment and progressive nature of osteoarthritis, it is imperative to understand the association of various

co-morbidities such as metabolic syndrome and depression in this priority population. By examining the association between metabolic syndrome and depression, more effective treatment strategies can potentially be developed.

Metabolic Syndrome and Arthritis

Metabolic syndrome METS) is characterized by clusters of health conditions. According to the National Cholesterol Education Program (NCEP)-Adult Treatment Panel III (ATP III), metabolic syndrome is defined as the presence of three or more of the following health conditions - hypertension > 130/85 mm hg, hyperlipidemia of >150 mm/dl, reduced high density lipoproteins (HDL) to <50 mm / dl, obesity and BMI > 30 and fasting blood glucose levels > 110 mm/dl.

Multiple studies include an analysis of the association between metabolic syndrome and osteoarthritis. Findings by Peunpatom & Victor (2009) indicate that 59% of respondents had METS and osteoarthritis, while 23% had METS without osteoarthritis. Another study conducted in Japan demonstrated that individuals above 45 years and who have one or more indicators of metabolic syndrome are at risk for developing osteoarthritis (Yoshimura et al., 2011).

In addition, Sowers et al. (2010) concluded that knee and joint pain is positively associated with presence of one or more risk factors for cardiovascular disease in obese women. Other studies have also indicated that osteoarthritis in obese individuals is not only seen in weight bearing joints, but also in non-weight bearing joints, as osteoarthritis alters metabolism and inflammatory reactions (Grotle et al., 2008; Viller et al., 2017). Prior studies show a strong association between osteoarthritis and metabolic syndrome.

Depression and osteoarthritis

Depression is characterized by upset mood, loss of self-esteem, feeling of guilty, sadness, lack of interest in performing daily activities, irritability, loss of concentration and lack of pleasure (WHO, 2012). It can alter and affect the ability to live a normal life and can interfere in performing basic and instrumental activities of daily living. Various studies have reported the prevalence of depression among individuals living with osteoarthritis (Swain et al., 2019; Louati et al., 2019; Sharma et al., 2016). Swain et al. (2019) noted that osteoarthritis is associated with 2.5% greater risk for developing depression (Swain et al., 2019). Another study indicated that depression effects one in every five individuals living with osteoarthritis (Rathbun et al., 2018).

However, the literature demonstrates some mixed results regarding depression among people living with osteoarthritis. Prior studies have revealed that certain factors, such as pain due to osteoarthritis, physical and functional limitations and less social contact are associated with depression (Upham et al., 2018; Sharma et al., 2016; Gandhi et al., 2015). Therefore, individuals living with osteoarthritis are at risk for developing depression due to the progressive and painful nature of the degenerative disease. Few studies have also demonstrated that depression can reduce the pain threshold and increase symptoms of osteoarthritis, resulting in poor health outcomes and reduced quality of life (Arthritis Foundation, 2018; Eustice, 2018; Lee, 2013). Further, osteoarthritis can limit functional capacity of an individual, making them further depressed due to high dependency on others for performing activities of daily living.

Additional information is needed about the association between metabolic syndrome and depression in adults living with osteoarthritis. To the best of our knowledge, the current study is the first prospective longitudinal study to analyze the association between metabolic syndrome and depression at various points in time among people living with osteoarthritis.

Purpose of the study

The purpose of the study was to examine the association between metabolic syndrome (METS) and depression among individuals living with osteoarthritis. The study was conducted using the Osteoarthritis Initiative (OAI) database, funded by Institute of Health (NIH). The OAI database is the product of a prospective cohort study collected from 4,796 participants who either had significant osteoarthritis or are at risk of developing significant osteoarthritis. The study created a public archive of data, biomarkers and joint images collected at baseline and every 12 months for follow-up visits. The study began in May 2004 and data was collected annually for 9 years. As osteoarthritis can lead to lower extremity pain and functional limitation, it is one of the major causes of disability among adults above 45 years of age (Neogi et al., 2015). Therefore, the OAI has developed a public domain research resource to facilitate scientific research on osteoarthritis.

There are both practical and theoretical reasons for analyzing adults above 45 years of age in this study. Adults aged 45 years and above are likely to live with one or two chronic illnesses that can lead to depression or other mental illness and functional impairment, due to burden of disease and pain (WHO, 2016). Functional impairment further increases the dependency of individuals and increases the economic burden of the chronic illness (CDC, 2017). In addition, we can gain an understanding of the impact of social isolation, baseline depression and demographics in predicting depression over time among people living with osteoarthritis. Results can broaden the treatment options among for individuals living with osteoarthritis. Appropriate lifestyle modifications such as ways to monitor blood glucose, blood pressure, blood cholesterol levels, and maintaining waist circumference can be advised along with medications to get successful treatment outcomes.

From a theoretical prospective, the study has included objectively measured criteria for metabolic syndrome and depression to better understand their association in people living with osteoarthritis. Moreover, we can better understand if reducing components of metabolic syndrome be helpful in reducing depression in adults with osteoarthritis.

Therefore the research question is what effect does metabolic syndrome have on depression over time among people living with osteoarthritis, when controlling for age, gender, education, baseline depression, time, race, social isolation and marital status? We hypothesize that individuals with metabolic syndrome will be positively related to the level of depression over time among individuals living with osteoarthritis.

Methods

Participants

The current study utilized data from the OAI database. OAI study recruitment was conducted from February 2004 to May 2006. Approximately, 1,992 men and 2,804 women (n= 4,796), aged 45-79 years who have or are at risk of developing symptomatic osteoarthritis were recruited. Participants response varied from no symptom for the disease to severe symptoms. About 74.2% individuals had osteoarthritis. Among the recruited participants, 75.8% were white and 24.2% were non-white.

OAI is a seven year project in which data is collected at baseline and every 12 months. The project began in May 2004 and initial enrolment was completed by 2011. For the current study, data was extracted at baseline, 24 months, 72 months and 96 months. The database contains various questionnaires based on variables associated with osteoarthritis. Variables include participant height, weight, and presence of diabetes, advisement to reduce cholesterol, BMI,

blood pressure, and depression using the Center for Epidemiologic Studies Depression Scale (CES-D). The variable list and database can be accessed online at https://oai.epiucsf.org/datarelease/DataClinical.asp.

Study Design

This study is a longitudinal prospective design that examined the association between baseline metabolic syndrome and repeated measures of depression. Four waves of OAI data were utilized by this current study: baseline, 24 months, 72 months and 96 months. Of the 4796 people that were enrolled in the OAI study, 3201 were included in this study due to missing data.

The dependent variable was depression represented by repeated measures of depression taken at baseline, 24 months, 72 months and 96 months. The predictor variable was METS, calculated using confirmatory factor analysis (CFA). METS was added as a latent variable in the CFA model. Observed variables added to measure METS were elevated systolic blood pressure (<120 mm/hg), elevated diastolic blood pressure (>80 mm/hg), diabetes, high waist circumference (>88 cm) and high BMI (>30). Associations were adjusted for age, sex, race, education, marital status and social isolation. The Institutional review Board of Middle Tennessee State University approved the research protocol to conduct this study (see Appendix A).

Measures

From 2004 – 2006, anthropometric measures such as age, height, weight, BMI, blood pressures were taken at the time of OAI study enrollment. Lifestyle characteristics such as depression scores were assessed. Follow – up assessments were conducted at approximately 24, 72 and 96 months.

Variables

CES-D depression score

The Center for Epidemiologic Studies Depression Scale (CES-D) is the screening tool for depression, and measures symptoms as defined by American Psychiatric Association's Diagnostic and Statistical Manual (Moon et al., 2017). The tool has a self-report set of 20 questions based on the symptoms of depression that occurred in the past week. The score range is 0 to 3 based on the answer option selected by the participants. Individuals with a score of 16 or higher are more likely to have symptoms of depression and are recommended to visit a healthcare provider. If more than 4 responses are missing, the questionnaire is not scored. Studies suggest that CES-D is a reliable and valid instrument. The CES-D is used among various populations including African Americans (Torres, 2012), Asian- Americans (Mackinnon et al., 1998), French & Greek Populations (Van et al., 2009), Latins (Reuland et al., 2009) and Japanese (Wada et al., 2007). The CES-D score was measured at baseline (visit 1) and then at subsequent follow-up visits.

Demographic Data

Demographic data includes age, gender, race, education, marital status and social isolation. The age of each participant is measured at baseline and at every visit. Gender was categorized as male and female, per OAI database. Race was characterized into White or Caucasians, Black or African-Americans, Other Non-White and Asians per the OAI database. It was recoded into two dummy variables- White or others; and Black. Education was a categorical variable described as: less than high school graduate, high school graduate, some college, college graduate, some college, graduate school and graduate degree, per the OAI database. It was dummy coded into high school or less, and college or graduate level. Marital status was categorized as married,

widowed, divorced, separated and never married, per the OAI database. It was dummy coded into married and single. Social isolation was measured by "How often have physical health/emotional problems interfered with social activities (visiting with friends), in the past 4 weeks"? The question was characterized into 5 categories in OAI database as: all of the time, most of the time, some of the time, a little of the time and none of the time. This variable was recoded and collapsed into two categories as 'mostly or highly socially isolated' and 'low social isolation'. Time was calculated from the first day of the enrollment and subsequent follow up visits.

Metabolic syndrome

METS was analyzed using CFA in SPSS-AMOS software (v25), based on guidelines for metabolic syndrome criteria given by the National cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III). The OAI database contains variables for systolic blood pressure, diastolic blood pressure, presence/absence of diabetes, BMI, and measures of waist circumference. There is no objective measure for cholesterol in the database. The remaining components of METS and depression (continuous scale) data is available at baseline, 24th month follow-up visit, 72 month follow up visit and 96th month follow up visit.

Threats to internal and external validity

The current study used data from over 108 months. Threats to internal validity were testing, instrumentation and statistical regression. Threats to external validity were reactive or interactive effects of testing. Participants might have reacted differently due to their baseline depression score. The database also contains missing data for race, education, marital status and social isolation variables which are threats to internal validity.

Statistical Analysis

We utilized SPSS and SPSS – AMOS software's (v25) for conducting the analysis. Confirmatory factor Analysis (CFA) and Generalized Estimating Equations (GEE) test were used for analyzing the data. In the CFA analysis, METS was the latent variable and systolic blood pressure (SYSBP), diastolic blood pressure (DIASBP), BMI, diabetes (DIAB), waist circumference (ABCIRC) > 88 cm were the observed variables. Error or residual variances: e1, e3, e4 and e5 were set to 1 and path coefficient between ABCIRC and METS was set to 1 to complete the model input graphics.

In the GEE analysis, the independent variable was metabolic syndrome and depression was the dependent variable. Data used in this study were at baseline, 24 months, 72 months and 96 months. Since this is a longitudinal study, first order autoregressive working correlation matrix was used to represent correlations among repeated measurements of depression among participants. A main effects model was selected in reporting the final analysis, as it had lower corrected Quasi Likelihood under Independence Model Criterion (QICC) compared to the interaction effects. Results were reported using standardized regression coefficients (B), standard errors (SE) and estimates of significance (p). The significance level was set at 0.05.

Results

CFA was used to analyze the variables that measured METS. Results helped in creating a METS variable that was used in the GEE analysis. GEE was used to analyze the association between METS and depression over time, when controlling for covariates.

CFA

Results from the final model of CFA can be seen in table B1. Results of CFA are reported in fit indices and help us in establishing if model is acceptable or not (Moss, 2016). A good model fit indices indicate that the results are reliable and consistent with the data (Kenny, 2015). In the study, an initial CFA model 1 included five latent variables: diabetes, systolic blood pressure, diastolic blood pressure, BMI, and waist circumference to measure METS. Model fit indices indicated an inadequate fit of variables in measuring METS. Chi square was 1286.61 and significant (p = .000). According to the literature, diastolic blood pressure is not a strong measurement for METS, so it was removed from the final CFA model to improve fit indices. The final CFA model included four variables: diabetes, systolic blood pressure, BMI and waist circumference. The model fit indices showed an excellent fit [χ 2 (2, N = 4,464) = 8.265, p = .016; RMSEA = .026, 90% CI = .010- .046; CFI = .999, TLI = .996, GFI = .999]. All paths were significant. Standardized regression coefficients and R2 for each path can be seen in the output graphics. The METS variable was created using the four significant variables with an excellent fit. Input and output graphics with standardized regression weights can be seen in figure B2 and B3 respectively.

Table B1. Model Fit Indices for measuring METS.

Model fit indices for METS									
					RMSEA				
Model	n	χ 2	df	RMSEA	C.I.	CFI	TLI	GFI	NFI
Model 1	4202	1286.609***	5	0.247	0.236-0.258	0.767	0.533	0.906	0.766
Final Model	4464	8.265	2	0.026	0.010-0.046	0.999	0.996	0.999	0.998

***p<.001

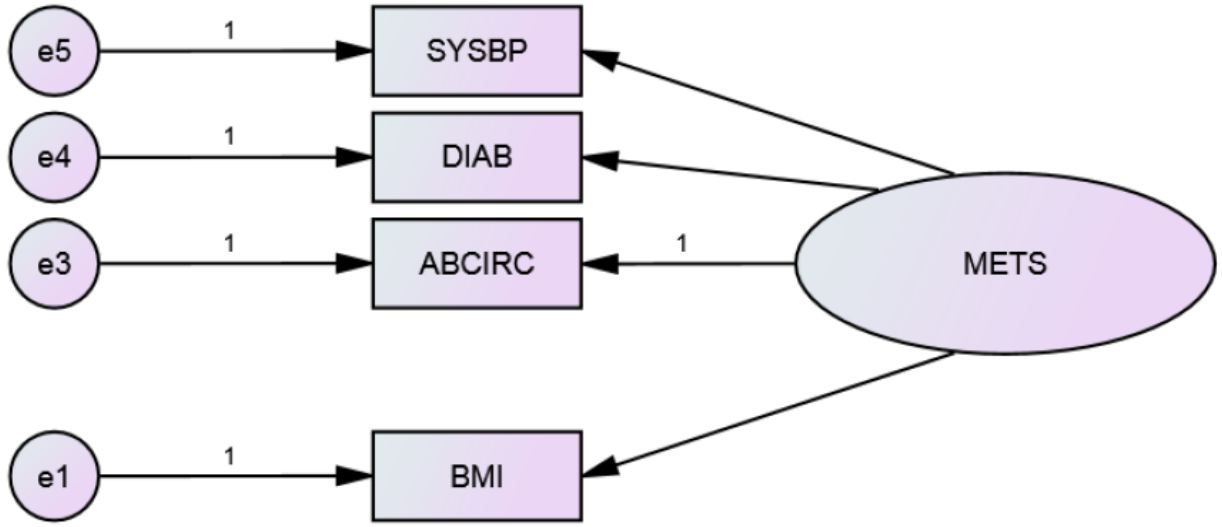

Figure B2. Input graphics in AMOS (SPSS), in measuring METS.

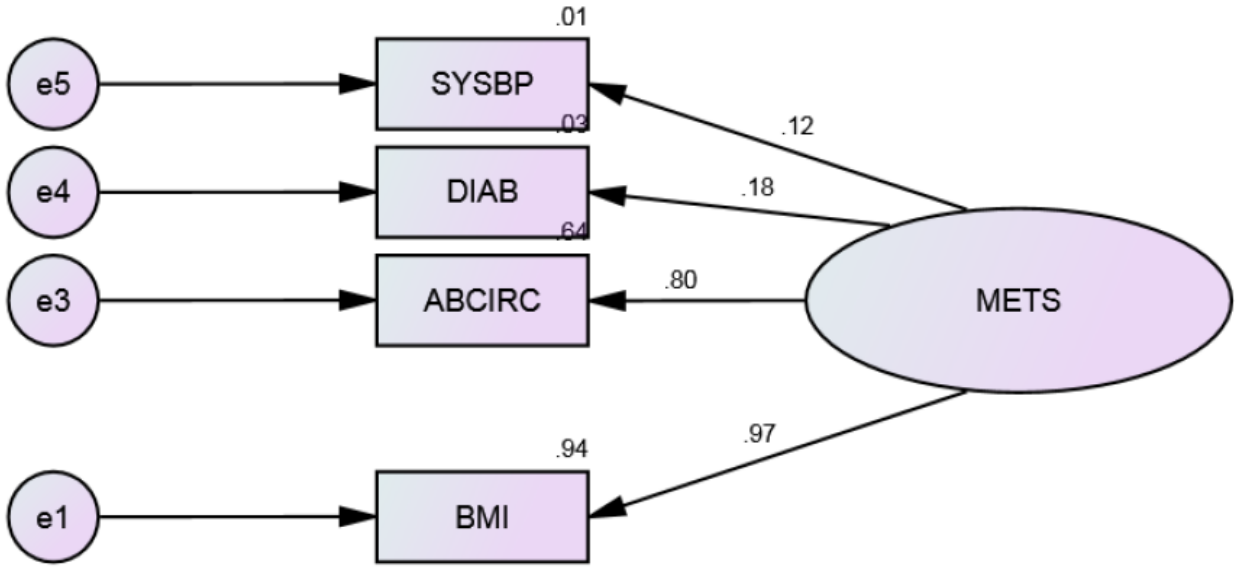

Figure B3. Output graphics and standardized estimates for measuring METS

GEE Results

GEE analysis included control variables such as age (baseline), gender (male/female), race (white or other/black), marital status (married /single), education (high school or less; and college or graduate level), social isolation (low social isolation/ mostly or highly socially isolated), time (years) and baseline depression in predicting future depression, over time. There were 4,796 participants enrolled in the OAI database. Approximately 2153 had missing data and were excluded from this study. Data from 2643 participants was used in this study. There was no multicollinearity among the predictor variables.

Demographic characteristics of participants can be seen in table B2. The majority of included participants were White or other Non-Whites (85.9%) and women (57.3%) with an average age of 60.36 years at the baseline. Table B3 shows descriptive statistics for repeated measures of depression for participants included in the study. The average depression score for the participants was 6.23. Depression scores increased to 6.59, over a period of 8 years. Table B4 shows working correlation matrix for depression, indicating low correlations among scores at 4 data points. Parameter estimates and standard error for the final model can be seen in table B5.

The overall model intercept was significant (B = 4.24, p = .000), meaning that among the study participants, white men who had METS and had a mean age of 60 years and depression score of 6.23, had a depression score of 7.30 over 8 years. CES-D scores can range from 0 – 60, with higher scores indicating more symptoms of depression (Henry et al., 2018). A cut off score of 16 or higher is considered high level of depression (Henry et al., 2018).

Table B2

Baseline characteristics of participants (N = 2643).

Variable		**Mean**	***SD***
Depression at baseline		6.23	6.42
Age		60.36	8.79
		n	**%**
Gender			
	Men	4,512	42.72
	Women	6,060	57.28
Race			
	White or others	9,083	85.92
	Blacks	1,489	14.08
Education			
	High school or less	5,989	56.58
	College or graduate level	4,583	43.42
Marital status			
	Married	7,371	69.78
	Single	3,201	30.32
Social Isolation			
	Low Social Isolation	820	7.84
	Mostly or highly socially isolated	9,752	92.16
METS			
	Yes	2,780	26.25
	No	7,792	73.75

Table B3

Characteristics of repeated measurements of depression for participants included in the study

	Measurement Time							
	Baseline		24 Months		72 Months		96 Months	
	M	SD	M	SD	M	SD	M	SD
Depression	6.00	6.424	5.82	6.446	6.52	7.023	6.59	7.087

Table B4

Working correlation matrix for depression

Time of measurement	Month 1	Month 2	Month 3	Month 4
Month 1	--	0.291	0.085	0.025
Month 2	0.291	--	0.291	0.085
Month 3	0.085	0.291	--	0.291
Month 4	0.025	0.085	0.291	--

Table B5

Summary of Generalizing Estimating Equations for variables predicting depression over time (N = 2643)

Variable		B	SE B	p
Main effects:				
Intercept		2.563**	0.4717	0.000
Depression at baseline		0.653**	0.0153	0.000
Age		0.005	0.0054	0.393
Time		.333	.0139	.000
Gender				
	Men	(reference)		
	Women	0.110	0.1031	0.284
Race				
	White or others	(reference)		
	Blacks	-0.050	0.2023	0.804
Education				
	High school or less	(reference)		
	College or graduate level	-0.237**	0.1015	0.020
Marital status				
	Married	(reference)		
	Single	0.281**	0.1225	0.022
Social isolation				
	Low Social isolation	(reference)		
	Mostly or highly socially isolated	-1.504**	0.3246	0.000
METS				
	Yes	(reference)		
	No	0.285	0.2743	0.298

**p < .05

METS

METS was not significantly associated with depression (B = .285, p = .302) across time. The results were adjusted for age, race, sex, education, marital status, baseline depression, social isolation and time between the visits

Additional Predictors

Among other predictors, education, marital status, social isolation, baseline depression and time (years) between the visits were found to be significantly associated with depression. When controlling all other significant predictors, positive associations with depression were found for marital status (B = .280, p = .017), baseline depression (B = .653, p = .000) and years (B = .333, p = .000). Negative associations with depression were found for education (B = -.206, p = .009) and social isolation (B = -.1.469, p = .000).

When controlling for all other variables, participants who had college or graduate level education were found to have significantly low depression scores (B = -.237, p = .020), when compared with those who had less than high school education. Similarly, participants who were single were found to have higher depression scores (B = .281, p = .022), compared with those who were married. Negative associations were found between social isolation and depression. Individuals who were mostly or highly socially isolated had lower depression scores (B = -1.504, p = .000), when compared with those who had low social isolation.

Among the continuous variables, depression at baseline was found to be a significant predictor of depression in the future (B = .653, p = .000). Likewise, time (years) was also found

to be positively associated with depression (B = .333, p = .000). Depression tends to increase over time.

The results of this study did not support the hypothesis. When controlling for age, gender, education, baseline depression, race, social isolation and marital status, individuals with metabolic syndrome did not have higher rates of depression over time.

Discussion

Current study findings indicate that METS is not associated with depression over time among participants of the Osteoarthritis Initiative Study (OAI). The relationship was independent of examined confounding variables. To the best of our knowledge, this is the first study to examine the association between METS and depression over time using generalizing estimating equations (GEE) among individuals who live with osteoarthritis.

Individuals with osteoarthritis usually have chronic pain, have to take more frequent medications and make more hospital visits (Mclntosh, 2014). In addition, they are at risk for developing 'cycle of osteoarthritis distress', in which they have either poor or disturbed sleep, joint inflammation and disability leading to depressive symptoms (Mclntosh, 2014). Various studies in the past have concluded that individuals with osteoarthritis are at high risk for developing depression due to various associated comorbidities as mentioned above (Upham, 2018; Gandhi et al., 2015; Sharma et al., 2016; Zelman, 2017). The presence of comorbid conditions can worsen the pain and further limit functional mobility, leading to depression (Calders & Ginckel, 2018).

Surprisingly, results from the current study indicate that METS is not a significant predictor of depression over time among individuals living with osteoarthritis. METS is a cluster of

various diseases, so its diagnosis can easily be missed or confused with normal physiological changes associated with osteoarthritis (Louati et al., 2019). More research needs to be conducted in this area and among the general population.

Findings indicate that marital status, education, social isolation, baseline depression and time are stronger predictors of depression over time among individuals living with osteoarthritis. This was not an experimental study, so future research should be conducted to explore the various effects of these variables in leading to depression among individuals living with osteoarthritis. Public health strategies should focus on all of the variables potentially associated with depression among individuals with osteoarthritis.

Limitations of the study

This study has various limitations. The OAI database included patients who have severe osteoarthritis or are at risk for developing symptomatic osteoarthritis. Depression scores can depend on variables such as pain, due to mild, moderate or severe osteoarthritis. There is a possibility that severe depression may be seen in individuals living with severe osteoarthritis, which could results in potential bias for the study. Researchers would not be able to differentiate if depression was due to intensity of osteoarthritis or due to METS. Secondly, there are various determinants of depression that are not environmental, such as hereditary and genetics. The OAI database does not have access to information on hereditary or genetic causes for depression. Thirdly, threat to internal validity such as instrumentation and history, is present in this longitudinal study. Also, multiple medications can reduce pain sensation or can alter cognition. The database does not does not include other health conditions associated with medications. Lastly, some of the variables such as age, race, height, weight, education status, weight were measured on a self-report scale, and participants may not have reported the variables correctly.

The study still has numerous strengths. METS was objectively measured by utilizing CFA. Also, results can be generalized among individuals living with OA, as the study included a large number of people who were either at risk for developing severe OA or were living with the disease. Most importantly, the study has data from a seven year longitudinal study which shows the depression disease trend over time.

Summary

The current study examined the association between metabolic syndrome and depression among adults with osteoarthritis. Due to the large sample size from the existing Osteoarthritis Initiative database, generalizability to the osteoarthritis population is enhanced. Results can help clinicians and public health professionals develop intervention strategies customized for individuals living with osteoarthritis, metabolic syndrome and depression. Ultimately, results from the current study can help in planning future studies and' lead to improved quality of life for those impacted by osteoarthritis and depression.

CHAPTER IV: PROJECT CONCLUSION

Globally, depression is a major cause of social and economic burden (Wei et al., 2016). In the United States, the cost of treating depression is expected to be approximately $210.5 billion by the year 2020 (Greenberg et al., 2015). Early diagnosis and timely treatment can lead to an increased likelihood of better long term care outcomes, as depression is highly treatable (Wei et al., 2016). It is estimated that depression is usually underdiagnosed, especially among older individuals, as the signs and symptoms of depression can naturally occur during the aging process (Patel et al., 2015; Zanni, 2011). In addition, there is a delay of 5 – 10 years in the onset of depressive symptoms that can lead to delayed treatment (Patel et al, 2015). Individuals who have received treatment for depression are at high risk for relapsing within five years, leading to increased social and economic burden (Greenberg et al, 2015; Zanni, 2011). Educating individuals to recognize the signs and causes of depression can contribute to timely interventions and positive health outcomes. Educated individuals living with depression are able to manage their lifestyle and medications to prevent relapse.

METS can be considered as a comorbid disease with depression. It is often the result of a sedentary lifestyle and unhealthy dietary intake, such as consuming food high in carbohydrates and fats (Stoppler, 2018). METS is associated with various other comorbidities such as diabetes, stroke, heart disease and kidney failure (Dang & Deswal, 2014). As METS can result in morbidity and early mortality, it is a major public health issue (Dang & Deswal, 2014). It is estimated that individuals with METS spend approximately 60% more on annual medical treatment when compared with those without METS (Mahabaleshwarkar et al., 2016). However, few studies have examined the potential association between METS and depression (Dunbar et

al., 2008; Friends et al., 2013; Liawh et al., 2015; Miettola et al., 2008). The studies have mixed results, and most were conducted with adults between 18-50 years of age (Dunbar et al., 2008; Ford et al., 2008; Liaw et al., 2015) or children (Friends et al., 2013). Since studies have shown that METS and depression increase with age, future studies should include individuals over 50 years of age. Also, due to the specifications of study design and research settings, past study results cannot be generalized across populations or settings.

Another potential comorbid condition with both depression and METS is osteoarthritis. Osteoarthritis is a degenerative joint disease associated with poor health outcomes, as it is a progressive disease with no cure (Sharma et al., 2016; Parkinson et al., 2017). Since individuals with joint damage have pain, stiffness, inflammation and lack of mobility, they are at higher risk for physical inactivity (Xie et al., 2016). The lack of physical activity can put them at greater risk for developing METS. Also, studies have concluded that individuals with osteoarthritis have sleep disturbances, anxiety, functional dependency on relatives and family and mood disturbances that places them at increased risk for developing depression (Chang et al. 2017; Sharma et al., 2016; Xie et al., 2016). Additional information is needed about the association between METS and depression among individuals living with osteoarthritis. Further information can aid public health providers in planning treatment strategies to reduce the progression of osteoarthritis, while delaying or treating METS and depression.

The main objective of this dissertation was to examine the association between METS and depression, and also how this association impacts individuals living with osteoarthritis. The purpose of the first study was to conduct a systematic review and meta-analysis in order to explore the association between METS and depression. A secondary goal was to determine if age moderates the association between METS and depression. The study utilized comprehensive

meta-analysis (CMA) software (v3) to conduct the analysis. Various databases were searched for data using specific search criteria. In total, 13 full text studies were included in the analysis. As hypothesized, there is a significant association between METS and depression. Further, moderator analysis was conducted using age as the moderator. Results indicated that age was a significant moderator in the association between METS and depression. Individuals who are between 41 to 69 years and live with METS are 1.14 times more likely to have depression, when compared to individuals who are above 69 years and have METS.

The purpose of the second study was to examine the association between METS and depression over time among individuals living with osteoarthritis. The study was conducted using seven years of data from the Osteoarthritis Initiative (OAI) database. The dependent variable was depression represented by repeated measures of depression taken at baseline, 24 months, 72 months and 96 months. METS was a derived variable and was calculated using confirmatory factor analysis (CFA). Observed METS variables in the database were hypertension, diabetes, high waist circumference and BMI. Generalizing Estimating Equations (GEE) was conducted to analyze the association between METS and depression among individuals living with osteoarthritis. Results did not support the hypothesis and indicated that there is no significant association between METS and depression over time. Also, among other predictors, education, marital status, social isolation, baseline depression and time (years) between the visits were found to be significantly associated with depression over time.

Future Directions

The contribution of this dissertation was to analyze the association between METS and depression. Results from the meta-analysis are similar to prior research findings, demonstrating a significant association between METS and depression in the general population. Study findings

can help public healthcare providers develop strategies focusing on early diagnosis and timely treatment of depression among individuals diagnosed with METS. Future studies can be conducted to examine how various components of METS are associated with levels of depression (i.e. mild, moderate or high). Results from the second study indicate that the association between METS and depression is not significant among individuals living with osteoarthritis. Although the results did not support the hypothesis, other predictors were found to be significantly associated with depression among the priority population. Future studies can be conducted on each of the significant predictors associated with depression in order to provide a deeper understanding of the association.

In summary, depression can be treated early if individuals are made aware of the various risk factors. Healthcare providers can also implement early screening to promote healthy outcomes. Future research can be oriented towards examining the role of healthy lifestyles (i.e. performing recommended levels of physical activity and healthy dietary intake) in METS, depression and osteoarthritis prevention. Interventions can then include various holistic approaches for all age groups as protection from chronic disease.

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REFERENCES

Arthritis Foundation. (2018). Osteoarthritis. Retrieved from https://www.arthritis.org/about-arthritis/types/osteoarthritis/.

Center for Disease Control and Prevention (CDC). (2003). Public health and aging: Trends in aging --- United States and worldwide. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5206a2.htm

Center for Disease Control and Prevention (CDC). (2010). A national public health agenda for osteoarthritis. Retrieved from https://www.cdc.gov/arthritis/docs/OAAgenda.pdf

Center for Disease Control and Prevention (CDC). (2018). Arthritis. Retrieved from https://www.cdc.gov/arthritis/index.htm

Eustice, C. (2018, August 3). Physical limitations – A consequence of arthritis [Blog post]. Retrieved from https://www.verywellhealth.com/physical-limitations-arthritis-189337

National Institute of Health (NIH). (2016). Osteoarthritis-in depth. Retrieved from https://www.niams.nih.gov/health-topics/osteoarthritis

National Institute of Health (NIH). (2001). National cholesterol education program-adult treatment panel III, detection, evaluation, and treatment of high blood cholesterol in adults. Retrieved from https://web.archive.org/web/20050530005143/http://www.nhlbi.nih.gov:80/guidelines/cholesterol/atp3full.pdf

Puenpatom, R., & Victor, T. (2009). Increased prevalence of metabolic syndrome in individuals with osteoarthritis: An analysis of NHANES III data. *Postgraduate medicine*, *121*(6), 9-20. doi: 10.3810/pgm.2009.11.2073. Retrieved From https://www.ncbi.nlm.nih.gov/pubmed/19940413.

Radloff, L. S. (1977). The CES-D scale: A self report depression scale for research in the general population. *Applied Psychological Measurements*, (1), 385-401.

World Health Organization (WHO). (2012). Depression: let's talk. Retrieved from http://www.who.int/mental_health/management/depression/en/ .

Yoshimura, N., Muraki, S., Oka, H., Tanaka, S., Kawaguchi, H., Nakamura, K., & Akune, T. (2012). Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: A 3-year follow-up of the ROAD study. *Osteoarthritis And Cartilage*, (20), 1217-1226. doi:10.1016/j.joca.2012.06.006.

APPENDICES

APPENDIX B: IRB APPROVAL

IRB

INSTITUTIONAL REVIEW BOARD
Office of Research Compliance,
010A Sam Ingram Building,
2269 Middle Tennessee Blvd
Murfreesboro, TN 37129

IRBN007 – EXEMPTION DETERMINATION NOTICE

Tuesday, May 22, 2018

Principal Investigator	**Garvita Thareja** (Student)
Faculty Advisor	Norman Weatherby
Co-Investigators	Chandra Story, Bethany Wrye and Janet Colson
Investigator Email(s)	*gt2g@mtmail.mtsu.edu; normal.weatherby@mtsu.edu*
Department	Health and Human Performance
Protocol Title	***Metabolic syndrome and depression: A prospective analysis from the osteoarthritis initiative***
Protocol ID	**18-1270**

Dear Investigator(s),

The above identified research proposal has been reviewed by the MTSU Institutional Review Board (IRB) through the **EXEMPT** review mechanism under 45 CFR 46.101(b)(2) within the research category *(4) Study involving existing data* A summary of the IRB action and other particulars in regard to this protocol application is tabulated as shown below:

IRB Action	EXEMPT from furhter IRB review***
Date of Approval	**5/22/2018** Date of Expiration NOT APPLICABLE
Sample Size	NOT APPLICABLE
Participant Pool	**NOT APPLICABLE**
Exceptions	Research on previously collected data through IRB-approval
Mandatory Restrictions	1. Participants must be 18 years or older 2. Informed consent must be obtained from the participants 3. Identifying information must not be collected
Restrictions	**1. Not permitted to enroll participants.** **2. The data may not be re-identified without IRB's written consent.**
Comments	NONE

***This exemption determination only allows above defined protocol from further IRB review such as continuing review. However, the following post-approval requirements still apply:

- Addition/removal of subject population should not be implemented without IRB approval
- Change in investigators must be notified and approved
- Modifications to procedures must be clearly articulated in an addendum request and the proposed changes must not be incorporated without an approval
- Be advised that the proposed change must comply within the requirements for exemption
- Changes to the research location must be approved – appropriate permission letter(s) from external institutions must accompany the addendum request form
- Changes to funding source must be notified via email (irb_submissions@mtsu.edu)
- The exemption does not expire as long as the protocol is in good standing
- Project completion must be reported via email (irb_submissions@mtsu.edu)
- Research-related injuries to the participants and other events must be reported within 48 hours of such events to compliance@mtsu.edu

Post-approval Protocol Amendments:

The current MTSU IRB policies allow the investigators to make the following types of changes to this protocol without the need to report to the Office of Compliance, as long as the proposed changes do not result in the cancellation of the protocols eligibility for exemption:

- Editorial and minor administrative revisions to the consent form or other study documents
- Increasing/decreasing the participant size

Only THREE procedural amendment requests will be entertained per year. This amendment restriction does not apply to minor changes such as language usage and addition/removal of research personnel.

Date	Amendment(s)	IRB Comments
NONE	NONE.	NONE

The investigator(s) indicated in this notification should read and abide by all applicable post-approval conditions imposed with this approval. Refer to the post-approval guidelines posted in the MTSU IRB's website. Any unanticipated harms to participants or adverse events must be reported to the Office of Compliance at (615) 494-8918 within 48 hours of the incident.

All of the research-related records, which include signed consent forms, current & past investigator information, training certificates, survey instruments and other documents related to the study, must be retained by the PI or the faculty advisor (if the PI is a student) at the sacure location mentioned in the protocol application. The data storage must be maintained for at least three (3) years after study completion. Subsequently, the researcher may destroy the data in a manner that maintains confidentiality and anonymity. IRB reserves the right to modify, change or cancel the terms of this letter without prior notice. Be advised that IRB also reserves the right to inspect or audit your records if needed.
Sincerely,

Institutional Review Board
Middle Tennessee State University

Quick Links:

Click here for a detailed list of the post-approval responsibilities. More information on exmpt procedures can be found here.