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The Association Between Dietary Flavonoid Intake and Chronic Obstructive Pulmonary Disease, Systemic Inflammation, and Comorbidity Burden

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This is to certify that the doctoral dissertation by

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Abstract

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by

Tennador A. Sanderson

MBA, Rosemont College, 2009

BS, Thomas Jefferson University (formerly Philadelphia University), 2004

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in the United States. Dietary habits may have an impact on COPD through anti-inflammatory mechanisms. For this cross-sectional secondary data analysis study, the advanced model of the epidemiology triangle was used as a guide to assess the association between total daily flavonoid intake and COPD diagnosis, COPD severity, systemic inflammation, and comorbidity burden. Data from over 5,100 male and female participants aged 30 and older were obtained from the 2007-2010 National Health and Nutrition Examination Survey. The prevalence of COPD was 5.2% according to spirometry data. Multiple logistic regression analysis showed that a 1% increase in total daily flavonoid intake resulted in a 5.9% decrease (95% CI [0.940, 0.943]) in the odds of having COPD after controlling for age, BMI, dietary fiber intake, education level, gender, race/ethnicity, and smoking status. After controlling for the same variables, multiple linear regression analyses showed that a 1% increase in total daily flavonoid intake among those with COPD resulted in a .00001 (95% CI [.001, .002], $p < .001$) increase in the percentage of the predicted FEV_1 and a 0.076% decrease in C-reactive protein (95% CI [-.078, -.074], $p < .001$). A one-way ANOVA showed that total daily flavonoid intake was significantly ($p < .001$) different for each comorbidity burden level, and those with 2 or 3 comorbid diseases had significantly ($p < .001$) lower flavonoid intake than those with 1 or no comorbid diseases. These findings expand the knowledge of this topic and may effect positive social change by informing public health policies and interventions that aim to reduce COPD prevalence, morbidity, and mortality.

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Chapter 1: Introduction to the Study

Chronic obstructive pulmonary disease (COPD) is a major public health concern, given its severe impact on morbidity and mortality in the United States and around the world. Ranked as the third leading cause of death in the United States, COPD is responsible for millions of hospitalizations each year (American Lung Association [ALA], 2014; Centers for Disease Control and Prevention [CDC], 2012a). Worldwide, COPD is likely to rank as the fifth leading cause of disease burden and the third leading cause of mortality by 2020 (Vestbo et al., 2013).

As with many chronic diseases, individual behavior, including dietary habits, can influence COPD. Both healthy and unhealthy dietary habits appear to affect COPD. Healthy diets appear to decrease the risk of COPD, COPD severity, and comorbidity, while unhealthy diets seem to have the opposite effect (Annesi-Maesano & Roche, 2014; Mekary, 2015; Okubo et al., 2014; Root, Houser, Anderson, & Dawson, 2014; Shaheen et al., 2010; Varraso, Fung, Hu, Willett, & Camargo, 2007). Despite an apparent relationship between diet and COPD, it is unclear which specific components of a diet are the causative agents for these effects. Polyphenolic compounds known as flavonoids are a potential candidate responsible for the observed decreased risk of COPD attributed to diets high in fruits and vegetables (Celik & Topcu, 2006; Tabak, Arts, Smit, Heederik, & Kromhout, 2001). However, more research is needed in this area to elucidate this potential relationship between increased dietary intake of flavonoids and decreased COPD risk. Results from such research could be used by public health advocates to

develop interventions aimed towards reducing the disease burden of COPD, which would have positive implications for social change.

This chapter includes an overview of the key components in this study. The introduction to the study includes a background review, the research problem, the study purpose, and the research questions. Additional facets of the study development, design, and impact presented in this chapter include the theoretical framework, nature of the study, definitions, assumptions, scope and delimitations, limitations, and significance.

Background

COPD disease is characterized as a progressive decrease in key measures of lung function, such as maximum expiratory flow and forced expiratory volume in the first second (FEV_1), and includes an enhanced inflammatory response (Zhou et al., 2014). A diagnosis of COPD occurs most accurately using spirometry and assessing results related to forced vital capacity (FVC) and FEV_1. Specifically, COPD involves having a ratio of FEV_1 / FVC < 0.70 (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2015). As COPD progresses, increases in disease severity include incremental increases in airflow limitation. Increases in airflow limitation decrease the FEV_1 that an individual can produce. The four stages of COPD severity reflect the percentage of the predicted normal FEV_1 (FEV_1% predicted). FEV_1% predicted values that are less than or equal to 80% indicate mild COPD or Stage I, values of 50–79% indicate moderate COPD or Stage II, values of 30–49% indicate severe COPD or Stage III, and values less than 30% indicate very severe COPD or Stage IV (GOLD, 2015).

A sustained inflammatory response to tissue damage caused by repetitive inhalation of pollutants, such as cigarette smoke, ultimately drives COPD. During this process, cellular lung damage triggers the recruitment of inflammatory cells, which in turn signal the release of cytokines (Rovina, Koutsoukou, & Koulouris, 2013). Eventually, the release of more cytokines causes more tissue damage, which ultimately sustains a cycle of inflammation and cellular damage even after exposure to noxious particles and gases has ended (Lago et al., 2014; Rovina et al., 2013; Simpson et al., 2013; Tuder & Petrache, 2012; Zuo et al., 2014). The clinical manifestations of COPD include chronic bronchitis and emphysema. Chronic bronchitis involves inflammation and remodeling within the large bronchial airways, and emphysema involves the distal airways and the loss of surface area and elasticity due to inflammatory processes, which limit gas exchange (Rovina et al., 2013; Tuder & Petrache, 2012).

Beyond acute local inflammation within the lungs, research has indicated that an association may exist between COPD and systemic inflammation. In fact, an association does exist between COPD and increased serum levels of circulating inflammatory mediators such as C-reactive protein (CRP), interleukins 6 (IL-6) and 8 (IL-8), tumor necrosis factor-alpha (TNF-α), and fibrinogen (Agustí et al., 2012). Furthermore, an association exists between these inflammatory mediators and an increased risk of major comorbidities, such as hypertension, cardiovascular disease, ischemic heart disease, myocardial infarction, heart failure, diabetes, lung cancer, and pneumonia (Miller et al., 2013; Thomsen, Dahl, Lange, Vestbo, & Nordestgaard, 2012). An association also exists between an increased accumulation of comorbidities and poor health outcomes, such as

increased mortality among people with COPD (Miller et al., 2013). Therefore, systemic inflammation has serious implications for compounded morbidity and mortality risk among COPD patients.

Tobacco smoke is the predominant cause of COPD, and other causes can include prolonged exposure to air pollutants and alpha-1 antitrypsin (A1AT) deficiency (National Heart, Lung, and Blood Institute, 2013). A1AT is a circulating antiprotease produced by the liver that acts to protect lung tissue from damage associated with inflammation; a deficiency in the production of A1AT, caused by a rare genetic condition, can induce COPD (Caroll, 2014). The absence of functional A1AT ultimately leaves the lungs vulnerable to an insufficient inhibition of serine protease activity and repetitive uncontrolled proteolytic attack, which leads to alveolar destruction among those less than 40 years old, regardless of environmental exposures, such as tobacco smoke (Olfert, Malek, Eagan, Wagner, & Wagner, 2014).

Researchers have linked body mass index (BMI) to the onset and progression of COPD. For example, an association exists between a low BMI and a greater risk of COPD (Beiko, Paoletti, Strange, & Kumbhare, 2015; Zhou et al., 2013). An association also exists between lower BMI and greater severity of COPD (Mitra et al., 2013; Vanfleteren et al., 2013). Researchers still do not have a strong understanding of the primary underlying mechanism or cause for this association, but the association between BMI and COPD is likely due to losses in muscle mass from restricted physical activity and cachexia resulting from the limitations of a compromised respiratory system (Baarends, Schols, Mostert, & Wouters, 1997; Emtner, Hallin, Arnardottir, & Janson,

2015; Engelen, Schols, Does, & Wouters, 2000; Remels, Gosker, Langen, & Schols, 2013).

Like BMI, an association also exists between diet and COPD; however, the association with diet appears to be more than just a physiological response to the onset and progression of COPD. Ample evidence supports the premise that diet might affect COPD outcomes. For example, results from prospective studies have indicated that an association exists between a healthy diet rich in fruits and vegetables and a reduced risk of COPD (Mekary, 2015; Varraso, Willett, & Camargo, 2010). Researchers have also found an association between healthy diets and a reduced risk of a range of chronic comorbid diseases, including those linked to chronic systemic inflammation (Boeing et al., 2012; Chiuve et al., 2012; Li et al., 2014). Conversely, unhealthy diets rich in processed and cured meats are associated with increased COPD severity, decreased pulmonary lung function, and hospital readmission for COPD (De Batlle, Mendez, et al., 2012; Mekary, 2015; Okubo et al., 2014; Root et al., 2014; Varraso & Camargo, 2014).

Although researchers have linked dietary habits with COPD and its associated severity, systemic inflammation, and comorbidity, literature regarding the identification of a specific dietary constituent or component responsible for this observed effect is lacking. Some researchers have pointed to potential associations with select compounds, such as fiber and antioxidant micronutrients (Annesi-Maesano & Roche, 2014; Fonseca Wald, Borst, Gosker, & Schols, 2014). In fact, researchers have found that diets high in fiber intake have a protective effect against systemic inflammation (Esmaillzadeh & Azadbakht, 2012; Grooms, Ommerborn, Pham, Djousse, & Clark, 2013). Furthermore,

dietary fiber intake is associated with reduced COPD risk, better lung function, and fewer COPD symptoms (Butler, Koh, Lee, Yu, & London, 2004; Kan, Stevens, Heiss, Rose, & London, 2008; Van den Borst et al., 2012). The associations observed between dietary fiber and COPD are consistent with associations between fruit and vegetable intake and COPD. These similarities could arise because fruits and vegetables are sources of fiber, and there may be some overlapping or shared nutrients among these dietary components (Bentley et al., 2012; Boeing et al., 2012). However, there is no definitive consensus regarding any one nutrient or class of nutrients that fully explains the association between diet and COPD, although the class of dietary compounds known as flavonoids may be partly responsible for the protective effects observed between diet and COPD outcomes. These polyphenolic compounds are cytoprotective and exist in many dietary plants, including fruits and vegetables.

The anti-inflammatory properties of flavonoids are attributed to their ability to attenuate inflammatory response by inhibiting the recruitment of inflammatory mediators, such as TNF-α, matrix-metalloproteinases 9, IL-8, and others (Kim et al., 2015; Li et al., 2012). Researchers of multiple in vitro studies have pointed to specific mechanisms that may account for this effect (Esposito, Chen, Grace, Komarnytsky, & Lila, 2014; Ferlazzo, Visalli, Smeriglio, Cirmi, & Enrico, 2015; Flores et al., 2012; Ganesan et al., 2010; Kim et al., 2011; Li et al., 2012; Lixuan et al., 2010; Weseler et al., 2009). Likewise, animal studies have also shown benefits associated with increased dietary flavonoid intake, including a reduced risk of COPD outcomes (Bao et al., 2013; Ganesan et al., 2010; Guan et al., 2012; Huang, Zhong, & Wu, 2015; Yang, Luo, et al., 2012).

Cross-sectional studies in humans involving Turkish and Dutch participants have also shown that dietary intake of flavonoids are positively associated with lung function and inversely associated with COPD symptoms, including coughing and breathlessness (Celik & Topcu, 2006; Tabak et al., 2001). However, researchers have conducted very few human studies examining the potential relationship between dietary flavonoid intake and COPD outcomes. Of the studies conducted in this regard, most have involved the participants from only one country, gender, or age group, while COPD outcome variables from large-scale studies have only included measures of lung function and COPD symptoms (Butland, Fehily, & Elwood, 2000; Butler et al., 2004; Garcia-Larsen, Amigo, Bustos, Bakolis, & Rona, 2015; Landberg et al., 2011; Tabak et al., 2001). Researchers have not yet explored the potential relationship between dietary flavonoid intake and COPD, COPD severity, systemic inflammation, and comorbidity using a large national sample of the U.S. population aged 30 years and older. In this study, I addressed this gap in the literature while also reinforcing findings noted in existing research.

Problem Statement

Few interventions are available to target the underlying factors contributing to the pathogenesis and pathophysiology of COPD. Anti-inflammatory treatments for COPD are limited, and health care providers treat many patients with inhaled corticosteroids (ICSs) or oral corticosteroids (Barnes, 2013). However, some COPD patients respond poorly to ICSs or oral corticosteroids, even at high doses (Barnes, 2013). Inhaled corticosteroids do not have a significant effect on the prevalence, progression, or mortality of COPD, despite minor reductions in COPD exacerbations (Li et al., 2012;

Yang, Clarke, Sim, & Fong, 2012). Specifically, ICSs do not reduce systematic inflammation, inflammatory cell counts, or inflammatory mediators in COPD patients (Singanayagam, Chalmers, Akram, & Hill, 2011). Therefore, I sought to explore alternative public health interventions to curtail the prevalence, progression, and morbidity of COPD.

Diet affects the risk of COPD and COPD outcomes. Flavonoids may have at least a partial role in this effect due to their anti-inflammatory properties (Celik & Topcu, 2006; Kim et al., 2015; Li et al., 2012; Tabak et al., 2001). Increased dietary intake of flavonoids may play a protective role in the development and progression of COPD and may represent a viable therapeutic option for COPD patients. However, researchers do not fully understand, and must further elucidate, the relationship between flavonoids and COPD in humans. Determining if an association exists between flavonoid intake and COPD diagnosis, COPD severity, systemic inflammation, or comorbidity burden would represent a major step forward in that regard.

Purpose of the Study

The purpose of this quantitative study was to explore the possible relationship between dietary flavonoid intake and COPD outcomes, systemic inflammation, and comorbidity among adults aged 30 years and older in the United States. The independent variable was total daily flavonoid intake, and the dependent variables were COPD diagnosis, FEV_1% predicted, CRP serum level, and comorbidity burden. The CRP level and the number of comorbidities were suitable dependent variables because they are measures of systemic inflammation that served as indicators of COPD morbidity (Agustí

et al., 2012; Miller et al., 2013). In particular, comorbidities related to systemic inflammation among those with COPD include cardiovascular disease, hypertension, and type 2 diabetes (Miller et al., 2013). Covariates included age, gender, race or ethnicity, smoking status, education level, annual income group, BMI, and dietary fiber intake, as research has indicated that these are associated with the independent variable and study outcomes, and they might have confounded results (ALA, 2014; Beiko et al., 2015; Eisner et al., 2009; Fonseca Wald et al., 2014; Hooper et al., 2012; Marott & Lange, 2013; Pistelli et al., 2012; Sebastian, Enns, Goldman, Steinfeldt, & Moshfegh, 2016; Zhou et al., 2013). This exploration of flavonoid intake and the development and progression of COPD using a nationally representative sample was necessary to gain a better understanding of the relationship between flavonoid intake and COPD in the United States.

Research Questions and Hypotheses

Research Question 1 (RQ1): What is the relationship between total daily flavonoid intake and COPD among adults?

$H_0$1: There is no statistically significant association between total daily flavonoid intake and spirometry-diagnosed COPD among adult participants of the 2007–2010 National Health and Nutrition Examination Survey (NHANES) after adjusting for relevant confounders.

$H_1$1: There is a statistically significant association between total daily flavonoid intake and spirometry-diagnosed COPD among adult participants of the 2007–2010 NHANES after adjusting for relevant confounders.

Research Question 2 (RQ2): What is the relationship between total daily flavonoid intake and COPD severity among adults?

$H_0$2: There is no statistically significant association between total daily flavonoid intake and FEV_1% predicted among adult participants of the 2007–2010 NHANES after adjusting for relevant confounders.

$H_1$2: There is a statistically significant association between total daily flavonoid intake and FEV_1% predicted among adult participants of the 2007–2010 NHANES, after adjusting for relevant confounders.

Research Question 3 (RQ3): What is the relationship between total daily flavonoid intake and systemic inflammation among adults with COPD?

$H_0$3: There is no statistically significant association between total daily flavonoid intake and the CRP serum levels among adult participants of the 2007–2010 NHANES with COPD after adjusting for relevant confounders.

$H_1$3: There is a statistically significant association between total daily flavonoid intake and the CRP serum levels among adult participants of the 2007–2010 NHANES with COPD after adjusting for relevant confounders.

Research Question 4 (RQ4): What is the relationship between total daily flavonoid intake and comorbidity burden among adults with COPD?

$H_0$4: There is no statistically significant association between total daily flavonoid intake and comorbidity burden among adult participants of the 2007–2010 NHANES with COPD after adjusting for relevant confounders.

$H_1$4: There is a statistically significant association between total daily flavonoid intake and comorbidity burden among adult participants of the 2007–2010 NHANES with COPD after adjusting for relevant confounders.

Theoretical Framework

The advanced model of the epidemiology triangle served as the theoretical foundation and framework for this research study. The advanced model of the epidemiology triangle includes three key components that influence the occurrence of disease over time: causative factors, the group or population and their characteristics, and the environment and behavior (Merrill, 2009). The advanced model of the epidemiology triangle serves to encourage researchers to look beyond just causative factors, and to include other elements such as the environmental and behavioral factors that may work synergistically to bring about the occurrence of disease (Merrill, 2009). The environmental and behavioral components of the model in this study consisted of available food choices and dietary behavior. Applying this model to the current study supported the theoretical premise that changes in dietary behavior may affect the occurrence of COPD. The research questions and associated variables of this study aligned with the advanced model of the epidemiology triangle to facilitate my exploration of a potential relationship between flavonoid intake and COPD. For example, causative factors of the model were the variable for smoking status, and the population's characteristics included socioeconomic and demographic variables, such as age, annual income group, education, gender, and race or ethnicity. Additionally, the variables for dietary fiber intake and total daily flavonoid intake indirectly represented the

environmental component of the model, as the environment often influences the availability of certain foods and dietary habits (Blitstein, Snider, & Evans, 2012; Gustafson, Christian, Lewis, Moore, & Jilcott, 2013; Swinburn et al., 2011). The research questions for this study were suitable for determining the relationship between these variables because they related to key components of the model. The study variables and research questions were suitable given the theory that changes in key components of the advanced model of the epidemiology triangle affect disease outcomes. Detailed information regarding this theoretical framework appears in Chapter 2.

Nature of the Study

In this study, I used a quantitative methodology and a cross-sectional approach. Quantitative research is suitable for assessing differences in prevalence and frequency of outcomes among groups, which was a key focus in this study as I attempted to address the research questions. Therefore, nationally representative retrospective data from publicly available datasets were suitable for determining if a relationship or an association exists between flavonoid intake and COPD outcomes. This quantitative analysis helped to determine if flavonoids might play a role in the development of COPD, COPD severity, systemic inflammation, and comorbidity.

Definitions

Body mass index (BMI): Body mass index provides a measure of nutritional status and body fat of an individual (National Heart, Lung, and Blood Institute [NHLBI], 2012). Values for BMI can serve as a guide to determine if people are underweight, normal weight, overweight, or obese. Calculating BMI involves using an individual's weight in

kilograms and dividing that value by their height in meters squared (NHLBI, 2012). In this study, I included the BMI values obtained for participants in the 2007–2010 NHANES.

Cardiovascular disease: Cardiovascular disease is a term used to encapsulate several diseases and problems with the heart, blood vessels, and arteries often related to the process of atherosclerosis, which includes the build-up of plaque within arterial walls (ALA, 2014). Cardiovascular disease typically manifests as an occurrence of a heart attack or stroke (ALA, 2014). Many people with cardiovascular disease have not yet experienced an occurrence of a heart attack or stroke but are at increased risk for such an outcome. In this study, a self-reported physician diagnosis of an occurrence of stroke, heart attack, or congestive heart failure determined the presence of cardiovascular disease.

Chronic obstructive pulmonary disease (COPD): Chronic obstructive pulmonary disease is a progressive disease that consists of airflow obstruction with an FEV_1 / FVC ratio of < 70% that is not fully reversible (Drummond, Buist, Crapo, Wise, & Rennard, 2014; Morrow et al., 2015). In the United States, the term COPD includes chronic bronchitis and emphysema, with most people diagnosed with COPD having both conditions (NHLBI, 2013). The presence of COPD among participants within the current study was determined using spirometry values. Those having a postbronchodilator FEV_1 / FVC ratio of < 70% were confirmed as having COPD.

Comorbidity: Comorbidity, also referred to as multimorbidity, refers to a person having more than one disease during a specific period (Valderas, Starfield, Sibbald,

Salisbury, & Roland, 2009). In most cases, comorbid diseases are long-term chronic conditions (Valderas et al., 2009). The comorbid diseases of interest in this study were cardiovascular disease, type 2 diabetes, and hypertension. Participants' self-reported physician diagnosis determined the presence of each of these comorbid diseases.

C-reactive protein (CRP): C-reactive protein is a protein produced in the liver as a response to inflammation within the body (MedlinePlus, 2015). C-reactive protein is a measure of systemic inflammation because circulating levels of this protein increase in the presence of inflammation. Values for CRP came from a laboratory analysis of blood samples from participants of the 2007–2010 NHANES. These CRP values were suitable for assessing systemic inflammation among participants in the study.

Diabetes: Diabetes is a condition that entails having too much glucose present in the blood, which can cause nerve damage, blood vessel damage, and complications such as heart disease, stroke, blindness, and kidney disease (National Institutes of Health [NIH], 2014). There are two types of diabetes, often referred to as type 1 and type 2. Type 1 diabetes is as an inability to produce enough insulin to allow glucose to disseminate to cells within the body, while type 2 diabetes refers to insulin resistance by fat, muscle, and liver cells that can no longer use insulin (NIH, 2014). For this study, references to diabetes denote type 2 diabetes. Participant self-reported data determined the presence of diabetes.

Dietary fiber: Dietary fiber refers to the undigested components of carbohydrates derived from plant-based foods, such as fruits, vegetables, grains, beans, and nuts (Hoy & Goldman, 2014). Dietary fiber provides bulk in an individual's diet and contributes to the

feeling of satiety, which promotes gastrointestinal function, assists in managing weight, and reduces risk of chronic diseases (Hoy & Goldman, 2014). The measurement of dietary fiber intake for the foods and proportions consumed by participants of the 2007–2010 NHANES was in grams, as determined by responses to 24-hour dietary recalls. The current study included the values obtained for dietary fiber intake during the 2007–2010 NHANES.

Flavonoids: Flavonoids are a diverse and ubiquitous group of polyphenolic metabolites found primarily in plant-based foods (Kozlowska & Szostak-Wegierek, 2014). The major sources of dietary flavonoids are fruit, vegetables, nuts, and beverages such as tea (Corcoran, McKay, & Blumberg, 2012). Furthermore, flavonoids have antioxidant and anti-inflammatory properties (Kozlowska & Szostak-Wegierek, 2014). The flavonoid content values for foods reported in the 2007–2010 NHANES 24-hour dietary recalls came from the U.S. Department of Agriculture (USDA), which maintains a publicly available database of flavonoid content, and these values were suitable for use in the current study. Additional information appears in Chapter 3.

Hypertension: Another common term for hypertension is high blood pressure. Hypertension or high blood pressure is a disease characterized as having a systolic blood pressure of at least 140 mm/Hg with a diastolic blood pressure of at least 90 mm/Hg (AHA, 2015). Hypertension increases the risk for adverse cardiac events due to vascular weakness, vascular scarring, and increased possibility of blood clots, plaque build-up, tissue and organ damage, and strain on the circulatory system (AHA, 2015). Self-reporting indicated the presence of hypertension among participants for the current study.

Spirometry: Spirometry is a diagnostic test using a device called a spirometer that measures the amount of air an individual can exhale forcibly based on measures of FEV and FVC. The FEV_1 / FVC spirometry value for an individual without obstructive disease is a ratio of ≥ 70%, and those with obstructive disease have a ratio of < 70% (GOLD, 2015). FEV_1 values are indicative COPD severity, with severity increasing as FEV_1 decreases. Additional information appears in Chapter 3.

Total energy intake: Total energy intake refers to the total amount of calories consumed by an individual in a day (Evans, Jacques, Dallal, Sacheck, & Must, 2015). Responses to two 24-hour dietary recalls served to indicate total energy intake for the foods and proportions consumed by participants of the 2007–2010 NHANES. An average of the values obtained from each 24-hour dietary recall provided an estimate of total energy intake for participants in the current study.

Assumptions

In this secondary analysis of data from the NHANES, I assumed that all data came from a sample that was representative of adults in the United States. I also assumed that the collection of all study data, such as self-reports, CRP, spirometry values, and anthropometric values, involved using established guidelines and lacked measurement error. Further, I assumed that the average of two 24-hour dietary recalls, obtained as a part of the NHANES, was representative of a study participant's typical dietary intake. It was not possible to rule out the chance that study participants may have altered their dietary habits in previous years, which may have had an impact on observed effects within the study. However, research has shown the use of multiple 24-hour dietary recalls

to be an acceptable method to determine average dietary patterns (Carroll et al., 2012; Freedman et al., 2011; Schatzkin et al., 2003). Further details appear in Chapter 3.

Scope and Delimitations

The scope of this study entailed obtaining information related to the association between total daily flavonoid intake and COPD among a representative sample of U.S. adults aged 30 and older. The scope included secondary data from the 2007–2010 NHANES that I used to examine potential associations between flavonoid intake and COPD diagnosis, severity, systemic inflammation, and comorbidity. Potential confounders included age, annual income group, BMI, dietary fiber intake, education level, gender, race or ethnicity, and smoking status. I excluded individuals from the study who were missing spirometry measures and those who answered affirmatively to having asthma. Other participants were excluded from additional analyses related to COPD severity, systemic inflammation, and comorbidity burden if they had missing data, self-reported responses of unknown, or refused to answer a question. A power calculation analysis for the study sample size appears in Chapter 3. A final boundary for the scope of this study was the statistical analyses I performed. Identifying the statistical analyses for this study a priori ensured that I could achieve my aims in this study without deviating from the intended scope.

Limitations

This study was subject to several limitations related to secondary data analysis and study design. The first limitation was my use of secondary data from a previously collected survey. Because the use of previously collected data does not allow an

opportunity to check the accuracy of the data, there may have been an increased likelihood of statistical error during secondary data analysis. However, CDC researchers have refined and validated the NHANES data collection methods and techniques over the course of decades (CDC, 2015a). Using data from an identifiable and reputable source such as the CDC minimized the chance for errors in data collection and subsequent statistical errors during analysis. Another key limitation of this study was the lack of long-term dietary information due to limitations of the 24-hour dietary recall instrument and the cross-sectional nature of the study design. It remains unknown whether dietary intake reported in the 24-hour dietary recall is reflective of dietary habits prior to the onset of COPD or if dietary changes took place after diagnosis, potentially even due to the diagnosis. However, the lack of long-term dietary data is an acceptable limitation because researchers have shown that long-term dietary habits are consistent with findings from 24-hour dietary recalls (Bertoia et al., 2015). Another limitation of the study was the lack of data for other measures of systemic inflammation in the NHANES, such as IL-6, IL-8, and TNF-α. However, the use of CRP is an acceptable measure of systemic inflammation among those with COPD (Baldrick et al., 2012). Finally, the cross-sectional design of this study limited my ability to establish causality between the independent variable and the dependent variables. However, this was an acceptable limitation because my aim was to pursue an understanding of potential associations between variables rather than to establish causation.

Significance of the Study

Researchers have not conducted studies in the United States using a nationally representative population to assess the potential relationship between total dietary flavonoid intake and COPD, COPD severity, systemic inflammation, and comorbidity. Results from this study add to the current literature regarding this topic and provide further evidence of an association between diet and COPD. The results of this study have the potential to reinforce broader recommendations for maintaining a healthy diet high in fruits and vegetables, which supports a healthy lifestyle overall.

There are numerous health benefits associated with the consumption of fruits and vegetables through anti-inflammatory and antioxidant interactions. For example, evidence indicates that diets high in fruits and vegetables are associated with a decreased risk of cancer, coronary heart disease, hypertension, stroke, dementia, certain eye diseases, and osteoporosis (Boeing et al., 2012). Americans fail to eat the amounts of fruits and vegetables necessary to maintain good health (Slavin & Lloyd, 2012). Therefore, the results obtained from this study support previous research related to the consumption of greater quantities of fruits and vegetables. Given the lack of anti-inflammatory treatments addressing the underlying systemic inflammatory processes of COPD, the results of this research study have implications for managing flavonoid intake among COPD patients. Results from this study have additional implications for managing patients with other inflammatory-based diseases.

Summary

The increasing prevalence of COPD and associated morbidity and mortality represents a significant public health concern. The literature has indicated that diet might affect COPD; however, researchers do not understand the underlying cause of the effect. Micronutrients within certain foods may be responsible for the associations observed between diet and COPD. Given their anti-inflammatory and antioxidant properties, flavonoids were a viable target for further research to elucidate the relationship between diet and COPD, and my primary aim in this study was to determine the relationship between total daily flavonoid intake and COPD.

The variables in this study aligned with the advanced model of the epidemiology triangle, which I used to assess the relationship between causative factors, the group or population and its characteristics, and environmental and behavioral components. For example, the environmental and behavioral components in this study were represented by the independent variable, total daily flavonoid intake. The study design included a cross-sectional approach and a quantitative research methodology to analyze secondary data from the 2007–2010 NHANES. The scope of the study included examining potential associations between total daily flavonoid intake and COPD outcomes among a nationally representative sample of adults aged 30 years and older in the United States.

The design of this study included several key assumptions and specific limitations; however, despite the limitations, the study contributes to the literature surrounding this topic. Key assumptions for this study included the expectation that data collected in the NHANES came from a nationally representative population, were

collected following accepted guidelines, and were free of measurement error. The limitations of the study did not inhibit my analysis of data or my ability to draw conclusions from the results, as the scope and design of the study minimized the impact of study limitations. The outcome of this study expands the current knowledge and understanding of the role that flavonoids may play in the development and progression of chronic diseases, such as COPD. Furthermore, the study results could influence policy decisions related to public health interventions, which may effect positive social change.

Chapter 2 includes an overview of the literature search strategy and the theoretical framework for this study, and a review of the relevant literature related to flavonoid intake and COPD. Chapter 3 includes an outline of the research methodology, inclusive of the study variables and planned statistical procedures. Chapter 4 contains an in-depth review of the dataset preparation and statistical results from this study. Finally, the dissertation concludes with Chapter 5, which contains a discussion of relevant study findings, recommendations for future research, and implications for social change.

Chapter 2: Literature Review

Introduction

COPD is a progressive disease consisting of emphysema, which involves damage to alveoli over time, and chronic bronchitis, which involves inflammation of the airways manifested by a long-term cough with mucus (Medline, 2014). COPD is characterized by a persistent and progressive reduction or obstruction in airflow due to prolonged and repetitive exposure to noxious gases or particles (NHLBI, 2013). Ultimately, exposure to these noxious gases or particles results in loss of airway and alveoli elasticity, destruction of the walls between alveoli, and overproduction of mucus within the airways (NHLBI, 2013). COPD is also associated with a heightened chronic inflammatory response in the airways, exacerbation of symptoms, and development of comorbidities contributing to the level of severity within patients (GOLD, 2015). Common symptoms associated with COPD include dyspnea, chronic cough, and mucus production (Wheaton, Cunningham, Ford, & Craft, 2015). These symptoms are consistent with an inflammatory response and are consistent with the understanding that COPD is an inflammatory-based lung disease (Augusti et al., 2012).

Oxidative stress and the persistent inflammation of the airways is one of the primary mechanisms involved in the pathophysiology of COPD (Augusti et al., 2012). Anti-inflammatory treatments for COPD are limited, and many patients are often treated with an ICS or oral corticosteroids; however, most COPD patients respond very poorly to these treatments (Barnes, 2013; Yang et al., 2012). Specifically, ICSs do not reduce systematic inflammation, inflammatory cell counts, or inflammatory mediator levels in

COPD patients (Singanayagam, Chalmers, Akram, & Hill, 2011). Therefore, alternative interventions are needed to provide anti-inflammatory relief in the management of COPD. There is a growing body of research indicating that dietary habits may influence the prevalence and severity of COPD through anti-inflammatory mechanisms. For instance, a higher intake of fruit and vegetables is associated with a decrease risk of COPD and improve lung function (Keranis et al., 2010; Boeing et al., 2012). There has been some speculation that flavonoids may be responsible for these beneficial outcomes related to COPD.

Flavonoids are polyphenolic compounds known to have anti-inflammatory and anti-oxidant properties, and are abundant in fruits, vegetables, and nuts (Lago et al., 2014). Researchers of in vitro studies have pointed to several mechanisms related to molecular signaling pathways that reduce the accumulation of inflammatory cells and the gene and protein expression of inflammatory mediators (Flores et al., 2012; Kim et al., 2011; Li et al., 2012). Researchers conducting animal studies have demonstrated that some flavonoids, such as apple polyphenol and liqueritin apioside derived from licorice, reduced cigarette-induced lung inflammation and reversed oxidative stress in the lungs (Bao et al., 2013; Guan et al., 2012). Researchers of animal studies have also demonstrated the ability of flavonoids to inhibit the activation of inflammation-regulatory transcription factors in the expression of inflammation-mediating genes (Kim et al., 2015). Results from studies with humans are supportive of findings from in vitro and animal studies (Celik & Topcu, 2006; Tabak et al., 2001; Siedlinski, Boer, Smit, Postma, & Boezen, 2012). Specifically, researchers have found that human dietary flavonoid

intake has a positive association with lung function in the general population and also is associated with a decreased occurrence of COPD and COPD symptoms (Celik & Topcu, 2006; Tabak et al., 2001; Siedlinski, Boer, Smit, Postma, & Boezen, 2012). However, no studies have been conducted in the United States using a nationally representative population to test this association.

My aim in this research was to explore the potential associations between dietary flavonoid intake and COPD in the U.S. population. Such a large-scale study of flavonoid intake should help to elucidate the role of these compounds in the health of the nation with regard to COPD. Furthermore, this study may also have implications for further understanding the impact that dietary flavonoid intake may have on other inflammatory-based diseases, such as cardiovascular disease, diabetes, and hypertension.

In this chapter, I present the literature search strategy, theoretical framework, and literature findings relevant to this study. The literature search strategy section of the chapter provides a description of the research databases, key search terms, and techniques I used to identify relevant literature. The theoretical framework section of the chapter highlights the application of the advanced model of the epidemiology triangle and how it informed my understanding of the potential relationship between variables in this study. The literature review section includes a discussion that highlights the existing gaps in the scientific understanding of the association between flavonoids and COPD.

Literature Search Strategy

I obtained the literature I summarize in this chapter from systematic searches for peer reviewed articles in PubMed, Google Scholar, and the CINAHL and MEDLINE

databases, which I accessed via the Walden University Library. Key search terms were selected to target articles relating to the independent and dependent variables. Search terms included *COPD GOLD, COPD cost, COPD NHANES, COPD burden, COPD comorbidity, COPD prevalence, COPD flavonoids, diet COPD, fruits vegetables COPD, polyphenols COPD, flavonoids emphysema, flavonoids bronchitis, flavonoids inflammation COPD, flavonoids antioxidant COPD, flavonoids respiratory disease, flavonoids pulmonary, flavonoids lung, flavonoids lung function, flavonoids NHANES,* and *flavonoids airways.* I conducted multiple searches using various combinations of these search terms. The initial search was restricted to English-language articles published between 2012 and 2016 that reported results from studies exploring COPD and flavonoid intake in the U.S. population. The scope of the initial search was then expanded to include results reported from studies using populations foreign to the United States, because I found that seminal research on this topic was conducted outside of the United States.

After organizing the studies I found in the database searchers, I first examining human experimental and observational studies. Next, I reviewed in vitro studies of potential molecular mechanisms to support a biological basis for a potential association between flavonoid intake and COPD. Finally, I reviewed animal studies in the same regard. Full-text copies of the articles selected for this review were obtained directly from the publishing journal's website or the Walden University Library.

I identified additional articles by reviewing the list of references cited by authors of the articles from the initial searches, and by using Google Scholar's option to review

"related articles." Of these additional articles, only those articles that appeared relevant to the topic or seminal to the body of literature were included for review and synthesis. Full-text copies of these articles were obtained as previously described.

Theoretical Framework

The advanced model of the epidemiology triangle includes three primary components that directly influence the occurrence of disease (Merrill, 2009). These components include causative factors, the group or population and its characteristics, and various facets of the environment, such as behavior, culture, physiological factors, and ecological elements (Merrill, 2009). The model posits that these components interact over time to determine the occurrence of chronic disease. As it relates to this study, causative factors in the occurrence of COPD included cigarette smoke, long-term environmental exposure to lung irritants, and A1AT deficiency. The study participants represented the group or population implicated in the occurrence of COPD, and the environment consisted of dietary behavior in the consumption of foods containing flavonoids, such as fruits and vegetables. The combination of these components over time can be used to describe the impact of flavonoid intake on the prevalence, severity, and morbidity of COPD. Theoretically, if the environmental component of the model was manipulated with regard to the quantity of flavonoid intake, then the occurrence of COPD may be impacted.

Researchers applying the advanced model of the epidemiology triangle, as it relates to diet and COPD, have consistently acknowledged that cigarette smoke is not the only contributor to risk of COPD. For example, in a study of dietary antioxidants and the

risk of COPD, researchers examined multiple factors that served as proxies for environmental components of the advanced epidemiologic triangle, such as income level, education, and body mass index (Joshi, Kim, & Lee, 2015). Results of this study indicated that each of these environmental components were significant risk factors for COPD, but the risk of COPD was reduced as antioxidant consumption increased (Joshi et al., 2015). The strength and utility of the theoretical model was evident in how it allowed Joshi et al. (2015) to recognize the importance of examining multiple factors of the environment and how these environmental factors interacted with dietary antioxidants to impact the risk of COPD. Another strength of this model is that it allows researchers the flexibility to see how multiple components of the model interact to impact disease outcome. For example, results from researchers examining the relationship between causative factors, such as smoking, and environmental factors, like diet, have indicated that the combination of smoking and poor diet results in a higher risk of COPD as compared to individual factors alone (Bentley et al., 2012; Hanson, Root, Houser, Anderson, & Dawson, 2014; Rutten, Wouters, & Rennard, 2013). By linking causative factors and environmental factors, researchers could identify specific segments of the population most at risk for COPD, such as those who smoke and consume an unhealthy diet (Bentley et al., 2012; Hanson et al., 2014; Rutten et al., 2013). When examining the component of time in relation smoking duration and diet, researchers have found that those with longer smoking duration and diets low in fruits and vegetables have an increased risk of developing negative COPD outcomes (Bentley et al., 2012; Lange, Sparrow, Vokonas, & Litonjua, 2012). Ultimately, the greatest utility of this model is that

it allows for flexibility in the combination and pairing of the model's components to assess the risk of disease outcome. Therefore, I deemed this model appropriate to serve as the theoretical lens through which I designed this study and analyzed its results.

Literature Review Related to Key Variables/Concepts

COPD Burden

COPD is a major cause of illness and death in the United States. COPD is the sixth leading contributor to the total number of years lived with disability by people in the United States (Murray et al., 2013). COPD is also considered the primary contributor to mortality by chronic lower respiratory diseases and is ranked as the third leading cause of mortality in the United States, resulting in 134,676 deaths in 2010 (ALA, 2014; CDC, 2012a). COPD became the third leading cause of death in the United States in 2008, which was more than 10 years sooner than projected by the Global Burden of Disease Study (Miniño, Xu, & Kochanek, 2010; Lopez et al., 2006). Additionally, COPD is the only leading cause of death among the top five causes that showed an increasing rate between 2010 and 2011 (Hoyert & Xu, 2012). The increasing morbidity and mortality of COPD in the United States is reflected as an increasing economic burden. It is estimated that the annual COPD-attributable cost to the United States is $36 billion, with projections for increases reaching $49 billion by 2020 (Ford et al., 2015). Given the disease and economic burden of COPD, it is important to fully understand its prevalence.

Prevalence. The worldwide prevalence of COPD is not easily determined, given the lack of diagnostic testing and limited access to multiple regions and countries around the world. A leading estimate of COPD prevalence indicates that approximately 210

million people worldwide have COPD (Cruz, 2007). Most COPD-related deaths around the world are concentrated in low- and middle-income countries (World Health Organization [WHO], 2015). More than 3 million people died in 2012 due to COPD, which represents 6% of all deaths occurring around the world that year (WHO, 2015). Worldwide, COPD now affects men and women equally due to increased smoking among women in high-income countries and indoor pollution from the use of biomass fuel in low-income countries (WHO, 2015). Overall, the distribution of COPD in the global population, as it relates to age, gender, and exposure to noxious gases appears to be consistent with findings in the United States (Wheaton et al., 2015).

In 2013, an estimated 15.7 million Americans reported being told by a physician or another healthcare provider that they had COPD (Wheaton et al., 2015). It is estimated that an additional 24 million people are undiagnosed and living with COPD as of 2011 (ALA, 2014). According to self-reported diagnosis, the age-adjusted prevalence distribution is as low as 2.6% among individuals ages 18-36, and increases with each older age group to as high as 12.3% among those age 75 or greater (Wheaton et al., 2015). Prevalence estimates according to clinical diagnosis using spirometry testing were 14% overall for those aged 40-79 years, with higher prevalence rates among older age groups (Tilert, Dillon, Paulose-Ram, Hnizdo, & Doney, 2013). Given the linear distribution of prevalence across age groups, there appears to be a relationship between age and prevalence of COPD. Gender and smoking status also appear to be risk factors for COPD, as 2013 data from the Behavioral Risk Factor Surveillance System has indicated. For example, women have a higher prevalence of COPD than men at 6.6%

among women as compared to 5.4% among men (Wheaton et al., 2015). Additionally, COPD is found to be more common among those who are current smokers at 14.3% than among those who are former smokers or have never smoked at 7% and 2.8%, respectively (Wheaton et al., 2015). It is also important to note that 38% of adults with COPD are current smokers even though continued smoking contributes to increased mortality (Wheaton et al., 2015).

Economic impact. Given the significant prevalence of COPD in the United States, the corresponding economic impact is substantial. As with most chronic diseases, the economic burden is not limited to only direct costs, but also includes indirect costs. In 2010, the total estimated economic costs of COPD were $49.9 billion, with approximately $30 billion attributed to direct costs and $20 billion resulting from indirect costs (Boccia, Villari, & Ricciardi, 2015).

Indirect costs include those costs associated with the morbidity and mortality caused by COPD, which includes the disabling effects of COPD, such as low productivity and missed days from work. Approximately 13%-18% of people with COPD have limitations in their ability to work or the type of work they perform (Patel, Nagar, & Dalal, 2014). Overall, the workforce participation range for those with COPD is 56%-69%, as compared to 65%-77% for those without COPD (Patel et al., 2014). For those with COPD who can work, they are limited in the number of working days they can contribute due to the limitations of their illness. For example, the number of restricted activity days for those with COPD ranged from 27 to 63 days annually (Patel et al., 2014). Additionally, the number of sick days per year ranged from 1.3 to 19.4, and the

number of bed confinement days was estimated to range from 13 to 32 days per year (Patel et al., 2014). Overall, COPD represents a significant burden for employers and employees due to lost productivity and loss of income, respectively (Patel et al., 2014). In 1990, COPD was ranked as the twelfth leading cause of disability-adjusted life years (DALY) lost, accounting for 2.1% of all DAYLs worldwide (GOLD, 2015). Given the recent increase in prevalence, COPD is projected to become the seventh most prominent cause of DALYs lost worldwide in 2030 (GOLD, 2015). While indirect costs pose a considerable impact on the U.S. economy, it is the smallest contributor to the overall economic costs for COPD.

Direct costs for COPD include those health care costs related to diagnosis, treatment, prevention, and rehabilitation in the form of physician services, hospitalizations, medications, and home healthcare. Of the overall direct costs for COPD in the United States, $13.2 billion are associated with hospital care, $5.5 billion result from physician services, $5.8 billion are associated with prescription drugs, $1.3 billion are associated with home healthcare, and $3.7 billion result from nursing home care (Blanchette, Dalal, & Mapel, 2012). There is a significant correlation between direct costs and severity of COPD, including the number of comorbid diseases associated with COPD (Emre et al., 2014; GOLD, 2015; Lazic et al., 2012; Vestbo et al., 2013). According to GOLD guidelines, COPD is divided into four stages of increasing severity (Vestbo et al., 2013). COPD Stages I, II, III, and IV correspond to a disease severity of mild, moderate, severe, and very severe, respectively (Vestbo et al., 2013). The total direct costs incurred for COPD increases as the stage of severity increases among COPD

patients. For example, Stage I patients incur the lowest direct annual cost of $1681, Stage II patients incur $5,037 in annual direct costs, and Stage III patients incur $10,812 in direct annual costs (Guarascio, et al., 2013). The economic burden of COPD will continue to increase as new diagnoses are made and the disease advances among those who already have the disease.

Leading Causes

COPD is primarily caused by exposure to tobacco smoke, which includes primary and second-hand smoke (NHLBI, 2013). Additionally, smoking is the cause of 80% of all deaths from COPD (Warren, Alberg, Kraft, & Cummings, 2014). Approximately 18 of every 100 people in the United States smoke cigarettes, and this proportion represents approximately 42.1 million people in the United States (Jamal et al., 2014). Cigarette smoke causes airway inflammation and oxidative stress (GOLD, 2015). Airway inflammation is a key characteristic of COPD and specifically involves neutrophilic airway inflammation (Simpson et al., 2013). As exposure to cigarette smoke through primary or second-hand smoke accumulates, it contributes to chronic inflammation and oxidative stress within the lungs, which are processes central to the pathogenesis of COPD (GOLD, 2015). The inflammation and oxidative stress initiated by exposure to cigarette smoke in the lungs is characterized as persistent and not fully reversible even after smoking cessation is initiated (Simpson et al., 2013; Zuo et al., 2014). With cigarette smoke established as the primary risk factor for developing COPD, it is important to note that approximately 25% to 33% of COPD patients are non-smokers

(Zeng & Zhong, 2012). Therefore, other causes of COPD must be considered aside from just smoking.

Other causes of COPD include chronic exposure to noxious gases and pollutants, such as occupational dusts and gases and indoor pollution originating from the combustion of biomass fuel for cooking and heating (GOLD, 2015). Occupational exposures linked to the development of COPD include coal mine dust, breathable silica, agricultural dusts, metal fumes, specific flavoring chemicals, and second-hand smoke (Minov et al., 2014; Rose, 2013). Additionally, researchers conducting cross-sectional and longitudinal studies have demonstrated that occupational exposure to gases, dust, and fumes among those who have never smoked is independently and significantly associated with an increased risk of COPD (Hagstad et al., 2015;Torén, & Järvholm, 2014). During occupational exposure to dusts and chemicals, pro-inflammatory mediators, such as macrophages, are activated and subsequently stimulate other pro-inflammatory factors, such as nitric oxide, reactive oxygen species, and TNF-α (Gasparotto et al., 2013). With repetitive and prolonged exposure to dust and chemicals, the combination of inflammation and oxidative stress seems to be the contributing factor in the pathogenesis of COPD (Gasparotto et al., 2013). Ultimately, prolonged occupational exposure to noxious gases and dust limit lung function, obstruct airways, and lead to respiratory complications and diseases, including COPD (GOLD, 2015).

Exposure to indoor pollution resulting from the use of biomass fuel was also found to be significantly associated with the development of COPD, particularly among women living in low to middle-income countries (Cheng et al., 2015; Da Silva et al.,

2012; Diette et al., 2012; WHO, 2015). Fuels for combustion, such as firewood, charcoal, crop residues, and animal dung constitute biomass fuels (Cheng et al., 2015). The burning of biomass for fuel produces smoke containing fine particulate matter (PM) of less than 2.5 μm in aerodynamic diameter (Da Silva et al., 2012). Exposure to biomass smoke (BMS) is significantly associated with an amplified prevalence of respiratory symptoms, reductions in pulmonary function, and onset of COPD (Da Silva et al., 2012). Furthermore, these effects are significantly correlated with the length and intensity of the exposure to BMS (Da Silva et al., 2012). Ultimately, BMS contributes to the pathogenesis of COPD by instigating an increase in acute inflammation and oxidative stress within the lungs while also increasing overall systemic inflammation (Silva, Oyarzun, & Olloquequi, 2015). As such, women exposed to BMS have higher alveolar levels of leukocytes and macrophages along with higher saliva and mucus levels of interleukin (IL)-6, IL-8, and TNF-α than women who do not utilize biomass as fuel (Banerjee, Mondal, Das, & Ray, 2012; Mondal, Bhattacharya, & Ray, 2011).

Another important factor in the development of COPD is a rare genetic deficiency known as A1AT deficiency (NHLBI, 2013). A1AT is the only known genetic disorder that leads to COPD (Bhattacharjee, 2013). A1AT is considered a rare disorder, as it affects 1 in 1,500 to 3,500 people of European descent, and is uncommon among people with Asian ancestry (NIH, 2015). A1AT is a circulating antiprotease produced by the liver and acts to protect lung tissue from damage associated with inflammation (Caroll, 2014). Low levels of A1AT in serum and lungs characterize deficiency in the production of this antiprotease, with a high risk for the development of emphysema approximately

between ages 30 and 59 (Bhattacharjee, 2013). A1AT deficiency ultimately causes an elastase imbalance through an inability to fully inhibit neutrophil elastase, which contributes to the development of severe COPD conditions, such as emphysema (Bhattacharjee, 2013). For example, in response to cigarette smoke, neutrophil elastase attack the alveolar wall matrix along with other proteases, which results in the release of elastin fragments and chemo-attractants, causing oxidative stress that intensifies inflammation and lung damage in emphysema (Bhattacharjee, 2013; Hoenderdos & Condliffe, 2013; Zuou et al., 2014). Therefore, as with the other causes of COPD, A1AT also contributes to underlying chronic inflammation and oxidative stress that brings about the onset of COPD.

Effects of Diet on COPD

Researchers have identified diet and nutrition as significant factors in the prevention, development, and progression of a wide array of chronic diseases, including hypertension, congestive heart disease, stroke, and cancer (Boeing et al., 2012; Chiuve et al., 2012; Li et al., 2014). Therefore, although exposure to tobacco smoke, air pollution, and genetic disorders are primary risk factors for COPD, it is important to explore the role that diet plays in the development and progression of this disease. In general, the literature demonstrates that diets high in fruit, vegetables, whole-meal cereals, and fish are associated with a reduced risk of COPD, while diets rich in cured and red meats, refined grains, and desserts are associated with an increased risk of COPD (Mekary, 2015; Okubo et al., 2014; Root et al., 2014; Shaheen et al., 2010; Varraso et al., 2007).

An overall healthy diet has a positive effect on lung function in terms of airflow rate and lung capacity, as measured by FEV_1 and FVC, respectively. For example, findings from a prospective cohort study of 15,567 Americans indicated that a healthy diet, according to the overall healthy eating index 2005 (HEI-2005), was positively associated with FEV_1/ FVC ratio at visit 1 ($\beta = .101$) and visit 2 ($\beta = .140$) between quintiles of the HEI-2005 (Root et al., 2014). These findings are meaningful because each quintile decrease in HEI-2005 corresponded to the approximate equivalent of three years of decline in FEV_1/ FVC found with age. The HEI-2005 is an index developed by the USDA to assess compliance with the 2005 Dietary Guidelines for Americans, which emphasizes an ideal healthy diet and provides standard scoring that measures compliance with each HEI-2005 dietary component (Guenther et al., 2006). The dietary components of the HEI-2005 included total fruit, vegetables, grains, whole fruit, and other items, such as legumes, beans, meats, oils, alcoholic beverages, and saturated fat (Guenther et al., 2006). When examining the component HEI-2005 scores, Root et al. (2014) found that several dietary constituents were positively associated with lung function, such as, animal protein ($\beta = .132$ and .093) and dietary fiber ($\beta = .129$). Likewise, in a prospective cohort study of 73,228 female nurses and 47,026 male health professionals in the United States, researchers found that a higher Alternate Healthy Eating Index 2010 (AHEI-2010) score was inversely associated with risk of COPD, which provided further evidence of the positive effects of a healthy diet (Mekary, 2015). Higher AHEI-2010 scores are indicative of diets high in grains, polyunsaturated fatty acids, nuts, long chain omega-3 fats, and limited consumption of red meat, and processed meat (Mekary, 2015). A higher AHEI-

2010 score was associated with lower risk of COPD (RR = 0.67, 95% CI [0.53-0.85]) when comparing the top and bottom quintiles (Mekary, 2015). The AHEI-2010 was an update to the HEI-2005 to align with the 2010 Dietary Guidelines for Americans. Updates made in the AHEI-2010 included the replacement of dark green and orange vegetables and legumes with greens and beans (Guenther et al., 2013). Additionally, fatty acids replaced oils and saturated fats while refined grains replaced total grains. Also, seafood and plant proteins were added to reflect subgroup choices for proteins (Guenther et al., 2013). Despite minor changes in the HEI from 2005 to 2010, results from the studies mentioned above indicate that a healthier diet is associated with better COPD outcomes (Roote et al., 2014; Mekary, 2015).

A healthy diet is typically characterized as having a high intake of fruits, vegetables, and whole grains while maintaining a low intake of processed meats (Mekary, 2015). However, it is important to note that the dietary intake of animal protein is associated with some health benefits relevant to COPD. In fact, animal protein was found by Root et al. (2014) to be positively associated with lung function, but the reference to animal protein in the study by Root et al. did not include processed meats and is consistent with findings by Mekary (2015). This distinction between animal protein and processed meats is noteworthy because other researchers demonstrated that diets high in processed meats have negative associations with a lung function (Okubo et al., 2014; Varraso, & Camargo, 2014). For example, a cross-sectional analysis of 1551 males and 1391 females from the United Kingdom demonstrated that diets high in processed meat consumption showed a high correlation with lower FEV_1 in men and women (Okubo et

al., 2014). However, this finding was more pronounced among men, with the difference in FEV_1 between the first and fifth quintile of consumption at -170 mL (95% CI [−250, −80]; Okubo et al., 2014). Also, increased intake of cured meats among those with COPD impacts the rate of COPD-related hospitalizations (De Batlle, Mendez et al., 2012). For instance, researchers who conducted a prospective cohort study in Spain found that after adjusting for age, FEV_1, and total caloric intake, a high intake of cured meat was associated with an increased risk (adjusted HR 2.02, 95% CI 1.31–3.12, $p = 0.001$) of hospital readmission for COPD (De Batlle, Mendez et al., 2012).

Of the many components that make up a healthy diet, fiber intake seems to have generated the most interest among researchers. Fiber is negatively associated with COPD outcome and lung function (Lyden et al., 2015; Varraso et al., 2010). For example, researchers who conducted a prospective case-control study of 111,580 U.S. women and men found that total fiber intake was negatively associated with a risk (RR = 0.67, 95% CI [0.50-0.90], $p = 0.03$) of new COPD diagnosis for those with the highest intake of fiber versus those with the lowest intake (Varraso et al., 2010). Likewise, researchers who conducted a cross-sectional study using data from 1,929 participants in the 2009-2010 NHANES dataset found that after adjusting for age, BMI, height, and smoking status, subjects in the highest quartile of fiber intake had values for FEV_1 of 212 mL and FVC of 291 mL higher than the lowest quartile of fiber intake (Lyden et al., 2015). These results show that dietary fiber was associated with lung function in this study, which may have implications for the development and progression of COPD. However, this study was limited by the cross-sectional nature of the design and the reliance on participant

memory for reporting dietary intake and frequency patterns (Lyden et al., 2015). A systematic review conducted to assess the relationship between dietary fiber and COPD was supportive of the findings by Varasso et al. (2010) and Lyden et al. (2015). However, the review incorporated only nine articles, of which four reported on dietary fiber and five reported on fatty acids (Fonseca Wald et al., 2014). Based on these articles, the researchers ultimately concluded that greater intake of dietary fiber was consistently found to be associated with a reduced risk of COPD, healthier lung function, and attenuated respiratory symptoms (Fonseca Wald et al., 2014).

Several studies with contrary results must also be considered. For example, researchers who conducted a prospective Korean study of 325 COPD patients and 6,781 at risk participants found that dietary fiber intake was not significantly associated with COPD risk as a function of overall daily nutrients intake among men and women (Joshi et al., 2015). However, this study was limited by using a simplified clinical definition of COPD instead of a clinical diagnosis, which may have resulted in non-differential misclassification of COPD cases versus non-cases (Joshi et al., 2015). Additionally, dietary intake relied on participant recall of food frequency and portion, which could have resulted in biased responses (Joshi et al., 2015). Researchers conducted a Japanese case-control study of 278 COPD patients and 340 controls to assess the potential relationship between intake of fruit and vegetables and risk of COPD (Hirayama et al., 2009). Despite finding high levels of insoluble fiber and total dietary fiber intake in this population, researchers found no significant association linking dietary fiber intake and risk of COPD (Hirayama et al., 2009). However, tt is important to note that this study

also relied on participant recall of past dietary patterns and proportions, which could be subject to recall bias. Additionally, the researchers admitted that their study was also subject to selection bias, as participation in the study was voluntary (Hirayama et al., 2009).

Given the findings regarding fiber intake and COPD, it is of interest to explore specific sources of fiber that have a significant association with COPD. Fruits and vegetables are the main sources of soluble and insoluble fiber and are found to have a strong association with a reduced risk of COPD (Bentley et al., 2012; Boeing et al., 2012). For example, while the study by Hirayama et al. (2009) did not identify a significant association between total dietary fiber intake and reduced risk of COPD, a trend was identified linking higher total daily vegetable intake with COPD risk (p_{trend} = 0.037). The prevalence of dyspnea, a common symptom of COPD, was also found to be lower among individuals with higher vegetable consumption (OR = 0.49, 95% CI [0.27-0.88]; Hirayama, 2009). A prospective randomized controlled study of 120 participants with COPD was conducted to determine if a diet high in fruits and vegetables impacted lung function decline over 3 years (Keranis et al., 2010). Significantly lower FEV_1 (p = 0.03) was found among participants assigned to the high fruit and vegetable diet intervention as compared to participants assigned to the control group (Keranis et al., 2010). Moreover, participants in the intervention group exhibited a significant lower average annual risk of COPD exacerbation as compared to participants in the control group (Keranis e al., 2010). When examining specific components of a healthy diet, it becomes apparent that certain components may be more strongly related to COPD risk

than others. Researchers studying the association between fruits and vegetables and COPD have focused on specific micronutrients found in fruits and vegetables (Baldrick et al., 2012; Hanson et al., 2013; Joshi et al., 2015; Rezaeetalab & Dalili, 2014). The micronutrients found in fruits and vegetables like antioxidants, such as vitamins A, C, D, E, and others, are speculated to be responsible for the positive associations observed between pulmonary function and COPD exacerbation (Keranis et al., 2010; Hirayama et al., 2009). Furthermore, researchers have demonstrated that vitamin A, C, D, and E are all independently associated with COPD (Annesi-Maesano & Roche, 2014; Hanson et al., 2013).

Researchers assessing biomarkers in humans have indicated that a relationship may exist between antioxidants and COPD outcome and severity (Lin, Wu, Chen, Hseih, & Yeh, 2010; Pirabbasi et al., 2012). For instance, researchers who conducted a case-control study of 34 COPD patients and 43 controls in Taiwan demonstrated that plasma levels of vitamin antioxidants and total carotenoids were lower among those with COPD as compared to those without (Lin et al., 2010). Similar findings were observed in a cross-sectional study that explored the association between antioxidants, oxidative stress status, and lung function in 149 male COPD subjects in Malaysia (Pirabbasi et al., 2012). Serum vitamin C was below 0.4mg/dl in 86% of participants. Total antioxidant capacity was significantly (p = <0.05) lower among those with very severe COPD as compared to those with less severe stages of the disease (Pirabbasi et al., 2012). Additionally, low levels of vitamin A (p=0.012) and vitamin C (p = 0.007) were observed among those who were undernourished (Pirabbasi et al., 2012). Also, FVC percent predicted and

consumption of β-carotene were significant predictors ($R^2 = 0.104$, $p = 0.002$) of total antioxidant capacity (Pirabbasi et al., 2012).

Antioxidants may be protective against declines in lung function and risk of COPD, given their ability to attenuate oxidative stress caused by chronic inflammation within the lungs (Domej, Oettl, & Renner, 2014; Fischer, Voynow, & Ghio, 2015; Hanson et al., 2013; Rezaeetalab & Dalili, 2014). For example, post hoc analysis of a randomized double-blind placebo-controlled study involving 38,597 female participants throughout a 10-year follow-up period revealed a 10% reduced risk of COPD (HR = 0.90, 95% CI [0.81-0.99], $p = 0.029$) among those randomized to the vitamin E intervention as compared to placebo (Agler, Kurth, Gaziano, Buring, & Cassano, 2011). Likewise, researchers who conducted a prospective Korean study of 325 COPD patients and 6,781 at risk subjects found a negative association between risk of COPD and dietary intake of antioxidant vitamins when comparing the first quintile of intake to the fifth quintile (Joshi et al., 2015). The vitamins found to have significant negative association with COPD included vitamins C and E, especially among males (Joshi et al., 2015). Findings from this study also showed a significant positive association between intake of vitamin C and FEV_1 ($p = 0.04$) and FVC ($p = 0.03$; Joshi et al., 2015). Furthermore, a positive association was also observed between vitamin E intake and FEV_1 ($p = 0.03$) and FVC ($p = 0.04$; Joshi et al., 2015).

Comparable findings regarding the protective association of micronutrients have also been observed among smokers. For example, researchers who conducted a prospective cohort study of 1,443 adults in the United States found that higher intake of

vitamin C and fruit and vegetables among smokers resulted in an 8 mL ($p < 0.0001$) and 24 mL ($p = 0.003$) slower degree of annual deterioration in FEV_1, respectively (Bentley et al., 2012). Researchers who conducted a prospective cohort study found that vitamin D may also reduce the rate of decline in FEV_1 (Lange et al., 2012). Longitudinal analysis from this study revealed that rates of decline in FEV_1 were significantly higher ($p = 0.023$) among those with vitamin D deficiency when compared to those who had sufficient levels of vitamin D (Lange et al., 2012). Furthermore, a cross-sectional analysis of 626 male veterans from Massachusetts showed that lung function, measured by FEV1, FVC, and FEV1/FVC, was significantly ($p \leq 0.0002$) lower among those who were vitamin D deficient (Lange et al., 2012). Analogous results were reported by researchers who conducted a cross-sectional population-based study of 1002 women in the United States to determine if an association exists between serum carotenoids and reduced lung function in older women (Semba et al., 2012). Findings showed that higher serum α- and β-carotene concentrations were positively associated with FEV_1 ($p < 0.05$) and FVC ($p < 0.05$), respectively (Semba et al., 2012). Additionally, total serum carotenoids were also significantly associated with FEV_1 ($p = 0.08$) and FVC ($p = 0.06$; Semba et al., 2012).

Many of the antioxidant-associated health benefits reported in the literature are attributed to the ability of these micronutrients to attenuate oxidative stress within the lungs (Domej et al., 2013; Hanson et al., 2013; Rezaeetalab & Dalili, 2014). Oxidative stress has a direct relationship with COPD through various mechanisms; however, the foremost mechanism is the amplified expression of pro-inflammatory genes that perpetuate long-lasting inflammation (Domej et al., 2013). Because chronic inflammation

is the central component in the pathogenesis of COPD, it is of interest to also explore the impact of diet on inflammation.

Diet and inflammation. Diet has been implicated as a modulator of systemic inflammation. For example, dietary fiber may explain some of the variations in the distribution of systemic inflammation among those identifying as Hispanic, African American, and non-Hispanic White (Young & Hopkins, 2014; Young & Hopkins, 2013a). This explanation is relevant to COPD because prospective research has demonstrated that between 50% and 70% of people who develop COPD and lung cancer have elevated systemic inflammation (Young & Hopkins, 2013b). Because Hispanic people have the highest intake of fiber while exhibiting the lowest rates of COPD, the association of fiber intake and systemic inflammation may hold some significance in assessing COPD risk (Young & Hopkins, 2013a).

Researchers conducting cross-sectional studies have provided supporting information that demonstrates a significant association between higher levels of fiber intake and lower systemic inflammation (Esmaillzadeh & Azadbakht, 2012; Grooms et al., 2013). For example, researchers examining data from the 1999-2010 NHANES found that high fiber intake among the highest quintile, as compared with the lowest, was associated with lower systemic inflammation, obesity, and metabolic syndrome (Grooms et al., 2013). These associations remained significant after adjusting for confounding variables (Grooms et al., 2013). The strongest significant association (risk ratio = 0.66, 95% CI [0.61-0.72] was found between high fiber consumption and lower systemic inflammation (Grooms et al., 2013). Likewise, in an Iranian cross-sectional study of 486

women, researchers found that high intake of fiber consisting of lentils, peas, chickpeas, various beans, and chickling vetch was inversely associated with serum concentrations of inflammatory biomarkers (Esmaillzadeh & Azadbakht, 2012). The researchers measured the consumption of the aforementioned foods, as these represent the main sources of fiber in the Iranian population (Esmaillzadeh & Azadbakht, 2012). Results from adjusted analyses indicated that the percentage difference found between the lowest and highest tertile was −39.2% ($p < 0.001$) for CRP, −15.9% ($p = 0.04$) for TNF-α, and −39.5% ($p < 0.01$) for IL-6 (Esmaillzadeh & Azadbakht, 2012).

Researchers have reported contradictory results when assessing the association between increasing fruit and vegetable intake and measures of oxidative stress and COPD-related inflammation (Baldrick et al., 2012). In a randomized controlled trial involving 454 UK participants, Baldrick et al. (2012) found no significant changes in systemic inflammation, measured by CRP, or systemic oxidative stress, measured by 8-isoprostane, among those who received a 12-week intervention requiring intake of five or more servings of fruits and vegetables each day (Baldrick et al., 2012). However, this study was limited by a short intervention period, which prohibits generalizing results beyond short-term fruits and vegetables intake. Furthermore, the short intervention period may be responsible for yielding results that conflict with the findings of Keranis et al. (2010), as they utilized a 3-year intervention in their study.

Fiber and antioxidants are the dietary constituents most widely implicated in the literature as having an associated with COPD (Fonseca Wald et al., 2014). The focus on these dietary components might be partially explained by the interrelatedness of fruit and

vegetables as good sources of fiber and antioxidant micronutrients (Annesi-Maesano & Roche, 2014). Overall, the beneficial effects of the foods found in a healthy diet may be attributable to more specific micronutrients, such as antioxidants in the form of vitamin A, C, D, and E (Hanson et al., 2013; Rezaeetalab & Dalili, 2014). In addition to these micronutrients, flavonoids have been proposed as one of the most potent compounds that may be responsible for the beneficial associations between diet and COPD (Lago et al., 2012).

Flavonoids

Flavonoids are polyphenolic compounds that are ubiquitous in plant-based foods and are primarily abundant in fruits, vegetables, and teas (Birt & Jeffery, 2013). There are more than 5,000 unique flavonoid compounds, and they have been categorized into six major subclasses: Flavones, flavonols, flavan-3-ols (flavanols), flavanones, anthocyanidins, and isoflavones (Corcoran et al., 2012). All flavonoids share the same fifteen carbon skeleton C_6–C_3–C_6 chemical structure, with different substitutions that make up the various subclasses (Rodgriguea-Mateos et al., 2012). Figure 1 shows the basic three-ring chemical structure consisting of two benzene rings (A and B) that are linked by a third ring (C), which is a heterocyclic pyran ring (Kumar & Pandey, 2013a). The subgroups of flavonoids vary according to the level of oxidation and pattern of C ring substitutions, while specific compounds within a subgroup differ in the pattern of the A and B ring substitutions (Middelton Jr., 1998). The activities of various flavonoids are structure dependent with regard to their specific subgroup, the degree of hydroxylation, conjugations, and degree of polymerization (Kumar & Pandey, 2013a). Some flavonoids,

such as flavones and flavonols, occur naturally as aglycones; however, the majority of flavonoids are found stored within plants as glycosides (Corcoran et al., 2012).

Flavonoids that occur as glycosides are characterized as being bound to one or more sugar molecules of the plants in which they are stored, and they are more stable than the flavonoids occurring as non-sugar aglycones (Corcoran et al., 2012). However, aglycones can be easily absorbed by the small intestine while flavonoid glycosides often require hydrolysis to convert into flavonoid aglycones before being absorbed in the small intestine (Corcoran et al., 2012; Kumar & Pandey, 2013a; Németh et al., 2003). After absorption takes place, the flavonoids are then conjugated in the liver or metabolized into smaller phenolic compounds. Given the liver conjugation reactions, no free flavonoid aglycones are found in plasma or urine, with the exception of catechins (Hollman, 2004).

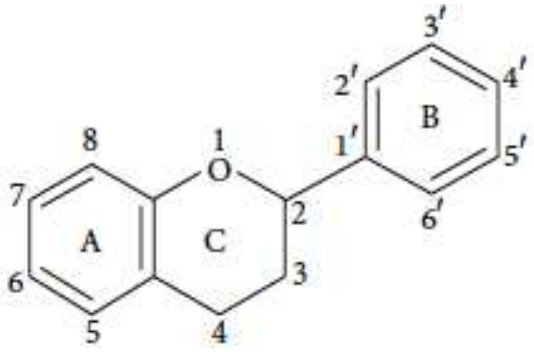

Figure 1. Basic flavonoid structure. Adapted from "Chemistry and biological activities of flavonoids: An overview," by S. Kumar and A. Pandey, 2013, *The Scientific World Journal, 2013* (pp. 2). Copyright 2013 by Shashank Kumar and Abhay K. Pandey. Reproduced with permission.

The bioavailability of flavonoids has been noted as poor, with only less than 10% of the consumed flavonoids found to reach peak concentrations in circulation at nanomolar or low micromolar range within a few hours (Corcoran et al., 2012). The flavonoid subgroups that appear to have the most bioavailability are isoflavones, while

flavan-3-ols and anthocyanidins are the most poorly absorbed (Barnes et al., 2011; Kumar & Pandey, 2013a; Manach, Williamson, Morand, Scalbert, & Remesy, 2005). However, it is important to note that the bioavailability of flavonoids is not fully understood and further studies are needed to understand the factors that influence the process in vivo. Bioavailability can be influenced by various factors, including the presence of fiber, macronutrients, micronutrients, gastrointestinal transit time, gut microbiota, sugar moiety of flavonoid glycosides, dimerization, and food matrix (Corcora et al., 2012; Kumar & Pandey, 2013a). For example, if enzymes found in the small intestine do not hydrolyze flavonoids bound to dietary fiber, then their bioavailability may be extended and later degraded by colonic microbiota (Perez-Jimenez et al., 2009). Additionally, the homogenization and processing of some foods have been found to enhance bioavailability of flavonoids. For example, the flavonone naringenin is better absorbed from tomato-based products instead of fresh fruit (Porrini & Riso, 2008). Furthermore, the flavonoid content from green tea is absorbed rapidly after ingestion, as indicated by a significant rise in the level of plasma antioxidant status (Benzie, Szeto, Strain, & Tomlinson, 1999). Also, plasma concentrations of catechins have been found to reach levels of 637.1 μg/L ($p < 0.001$) following a meal with wine, fruit, and vegetables (Ruidavets et al., 2000). Such findings provide an indication that dietary intake of flavonoids can lead to increased serum levels of these compounds to a point at where they can execute a wide range of pharmacological effects. For instance, flavonoids have been documented to mediate antioxidant effects, chelate metals, and induce protective enzyme systems (Kumar & Pandey, 2013a). Additionally, flavonoids have been reported

to exhibit anti-proliferative, anti-tumor, anti-inflammatory, and pro-apoptic properties (Buer, Imin, & Djordjevic, 2010).

Dietary intake of flavonoids. Understanding the dietary flavonoid intake of individuals in different settings is also key to further understanding the health effects of flavonoids. Several studies were conducted to estimate dietary flavonoid intake for various populations. For example, the mean flavonoid intake in South Korea was estimated to be 107 ± 1.47 mg/d among 11, 474 healthy adults aged 19 years older, with women having a significantly higher intake than men (Kim, Park, Chang, & Kwon, 2015). In another study, researchers estimated the Brazilian population to have a mean flavonoid intake of 138.92 mg/day (Correa, Tureck, Locateli, Peralta, & Koehnlein, 2015). In an Australian study of 79 participants aged 60 to greater than 80 years old, researchers found the mean dietary intake of flavonoids to be 638 mg/day (Kent, Charlton, Russell, Mitchell, & Flood, 2015). Finally, researchers conducted a study of flavonoid intake among approximately 30,000 Europeans from 14 countries aged 18 to 64 years and estimated their mean flavonoid intake to be 428 ± 49 mg/day (Vogiatzoglou et al., 2015). Although, it is important to note there is considerable variation in mean flavonoid intake among individual European countries assessed in this study. For instance, the UK, Ireland, and Germany are among the lowest consumers of flavonoids among European countries (Vogiatzoglou et al., 2015). In fact, the average flavonoid intake in the UK and Ireland was assessed in a separate study by researchers who estimated flavonoid intake to be 182 mg/day and 177 mg/day, respectively (Beking & Vieira, 2011). Similarly, the mean flavonoid intake in Germany was found to be 181

mg/day, but this finding was greatly skewed, as the researchers noted the median was found to be 60-fold less at 3 mg/day (Vogiatzoglou et al., 2015). Ultimately, Vogiatzoglou et al. (2015) noted that their data was skewed because approximately half the population in Germany was found to consume negligible amounts of flavonoids.

Beyond providing insight into the mean intake of dietary flavonoids among various populations within different countries, the results from the aforementioned studies also provide insight into demographic associations and leading sources of dietary flavonoids. For example, researchers found that gender is associated with flavonoid intake in some countries (Correa et al., 2015; Kim, Park, et al., 2015). Researchers reported that women consume greater quantities of flavonoids than men in South Korea, while men were found to have greater flavonoid intake than women in Brazil (Correa et al., 2015; Kim, Park, et al., 2015). Therefore, gender may be a significant factor to be considered when estimating flavonoid intake within any population. Also, dietary flavonoids appear to come from very different food sources in each of these countries. While South Koreans, Brazilians, Europeans, and Australians all obtain flavonoids from fruits and vegetables, the leading flavonoid food sources, such as kimchi, legumes, apples, oranges, and bananas, appear to vary based on availability within each country (Correa et al., 2015; Kent et al., 2015; Kim, Park, et al., 2015; Vogiatzoglou et al., 2015; Zamora-Ros et al., 2010; Zujko, Witkowska, Waśkiewicz, & Mirończuk-Chodakowska, 2015). Among the Australian and European studies, tea was found to be the leading source of flavonoid intake in these countries (Kent et al., 2015; Vogiatzoglou et al., 2015; Zujko et al., 2015). Specifically, black tea accounted for 89% of flavonoid intake among

Australians (Kent et al., 2015). While South Koreans and Brazilians also consumed tea, but they did so to a lesser extent than Australians and Europeans. South Koreans and Brazilians obtain most of their flavonoid intake from other sources, such fruits and vegetables (Correa et al., 2015; Kim, Park, et al., 2015). Therefore, a lower intake of tea may partially explain the low flavonoid intake levels among South Koreans and Brazilians.

Researchers have conducted several studies to assess flavonoid intake within the U.S. population with varying results for different time periods. For instance, results from an early study utilizing 24-hour dietary recall from the NHANES 1999-2002 and the 2003 USDA Database for the Flavonoid Content of Select Food (DFCSF) indicated that the average flavonoid intake was 189.7 mg/day, with flavanols accounting for 83.5% of all flavonoids consumed (Chun, Chung, & Song, 2007). Results from a later study conducted to estimate the intake of flavonoids utilizing 24-hour dietary recall from NHANES 1988-1994 and the 2011 USDA DFCSF showed that average flavonoid intake among Americans was 344.83 ± 9.13 mg/day (Bai, Wang, & Ren, 2014). However, researchers who conducted a more recent study using the 2014 USDA DFCSF and data from NHANES 1999-2002 and 2007-2010 estimated that the average daily flavonoid intake of the U.S. population was 201.9 mg/day and 200.1 mg/day, respectively (Kim, Vance, & Chun, 2015). Despite changes in the estimated flavonoid intake within the U.S. from the aforementioned studies, the leading food sources contributing to flavonoid intake remained consistent across studies. In the US, tea was identified as the leading

contributor followed by wine, citrus juice, citrus fruits, and vegetables (Bai et al., 2014; Chun et al., 2007; Kim, Vance, & Chun, 2015).

The proportional distribution of flavonoid intake across key demographic factors remained relatively constant across the 1988-1994, 1999-2002, and 2007-2010 NHANES populations. However, given the relevance of the findings from the 2007-2010 NHANES population to the current study, it is important to highlight the average daily flavonoid intake across gender, age, and race (Kim, Vance, & Chun, 2015). As such, men were found to have a slightly higher mean daily flavonoid intake (206.7 mg/day) than women (194.1 mg/day) in the 2007-2010 NHANES (Kim, Vance, & Chun, 2015). Additionally, mean daily flavonoid intake was highest among those aged 51-70 followed in descending order by those aged 31-50 years, 70 years and older, and 19-30 years (Kim, Vance, & Chun, 2015). Also, there are sharp contrasts in the estimated intake of daily flavonoid intake by race among participants in 2007-2010 NHANES (Kim, Vance, & Chun, 2015). Specifically, the mean daily energy-adjusted flavonoid intake for Whites, Blacks, Mexican-Americans, and Other are 218.6 mg/day, 157.6 mg/day, 123.5 mg/day, and 185.2 mg/day, respectively (Kim, Vance, & Chun, 2015). Taken together, these findings indicate that age, gender, and race are be important demographic factors to consider when assessing mean daily flavonoid intake among participants in the 2007-2010 NHANES.

Health benefits. Flavonoids are believed to promote good health through their high antioxidant capacity, as demonstrated in vitro and in vivo (Kumar, Mishra, & Pandey, 2013; Kumar & Pandey, 2013b). Flavonoids have been found to provide a wide variety of protective health effects across a broad range of chronic disease states related

to cardiovascular systems, neurology, urology, gastroenterology, metabolic disorders, and immunology among others (Andriantsitohaina et al., 2012; Can & Ozkay, 2012; Cote, Caillet, Doyon, Sylvain, & Lacroix, 2010; Hariprasath, Raman, & Nanjian, 2012; Nicolle, Souard, Faure, & Boumendjel, 2011; Peluso, Miglio, Morabito, Ioannone, & Serafini, 2015). These protective benefits are believed to result from antioxidant activity and the build-up of protective enzymes brought about through the mechanism of enzyme induction that follows flavonoid consumption (Hoensch &Oertel, 2015; Kumar & Pandey, 2013a).

Reducing oxidative stress is a significant underlying mechanism contributing to protective effects of flavonoids against cardiovascular disease, which may also have implications for COPD (Kim et al., 2011; Kumar, Kant, Maurya, & Rizvi, 2012). Specifically, Kim et al. (2011) found that several flavonoids, such as epicatechin, avicularin, and quercitrin, derived from *Lindera erythrocarpa* protect cardiac muscle cells against cell death related to oxidative stress. Furthermore, in a study of hypertensive patients, researchers demonstrated that (-) epicatechin was found to have a significant ($p < 0.001$) protective effect against oxidative stress, which was induced by tert-butyl hydroperoxide on isolated erythrocytes (Kumar et al., 2012). The overall effect observed in this study was noted to be dose-dependent by the researchers (Kumar et al., 2012). Antioxidant properties of flavonoids also protect against the damaging effects of hyperglycemia while improving glucose metabolism (Nicolle et al., 2011; Qi, Liu, Su, & Yu, 2011; Tang et al., 2011; Zheng et al., 2011). For example, researchers conducting animal studies have demonstrated that flavonoid extracts from leaves of *Boldoa*

purpurascens and *Phoenix dactylifera* have produced anti-hyperglycemic activity in rats with alloxan-induced diabetes (Gonzalez Mosquera et al., 2013; Michael, Salib, & Eskander, 2013). Flavonoids also exhibit biochemical actions indicating anti-inflammatory effects and the ability to influence the immune system (Peluso et al., 2015). The anti-inflammatory actions of flavonoids are suggested to result from several mechanisms of action, such as the inhibition of eicosanoid generating enzymes, the reduced production of pro-inflammatory molecules, and the modulation of pro-inflammatory gene expression, which attenuates the inflammatory response (Garcia-Lafuente, Guillamon, Villares, Rostagno, & Martinez, 2009). Flavanol-rich lychee fruit extract (FRLFE) supplementation, as part of a clinical trial, was found to be potentially protective against inflammation and tissue damage during extreme physical training (Nishizawa et al., 2011). The changes in serum IL-6 levels between pre-training and mid-training among young healthy male athletes were found to be significantly lower in the FRLFE group compared to placebo (Nishizawa et al., 2011). Furthermore, results indicated that changes in transforming growth factor-β levels prior to training and after training were significantly greater among those in the FRLFE group compared to placebo (Nishizawa et al., 2011). In an animal study conducted to investigate the effect of icariin on the expression of Toll-like receptor 9, researchers found that icariin-induced the expression of Toll-like receptor 9 and its mRNA in murine macrophages (Li et al., 2011). Toll-like receptor 9 plays a pivotal role in the regulation of the innate immune response (Li et al., 2011). Additional findings from this study also showed that several systemic

immune response molecules, such as myeloid differentiation factor 88, TNF-α, and IL-6, were significantly modulated as a response to icariin stimulation (Li et al., 2011).

These findings have implications for patients with COPD because major comorbid diseases associated with COPD are thought to result from increased systemic inflammation (Agusti & Faner, 2012; Divo et al., 2012; Smith & Wrobel, 2014). For example, cardiovascular disease, hypertension, and type-2 diabetes are the most common comorbidities associated with systemic inflammation among those with COPD (Miller et al., 2013). Flavonoids appear to reduce the risk of these and many other chronic diseases by attenuating various underlying inflammatory mechanisms and processes. For example, in an animal study using rats that were susceptible to stroke and spontaneous hypertension, researchers demonstrated that flavonoids could suppress age-related increases in blood pressure, decrease thrombotic tendency, and increase the production of NO metabolites in urine (Ikemura, Sasaki, Giddings, & Yamamoto, 2012). Also, flavonoids have been found to inhibit neuroinflammatory processes that contribute to the development of degenerative neurological disorders, such as Parkinson's and Alzheimer's disease (Spencer, Vafeiadou, Williams, & Vauzour, 2012). For instance, methylalpinumisoflavone isolated from *Cudrania tricuspidata* was found to suppresses LPS-induced microglial activation and production of pro-inflammatory mediators by attenuating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling and by phosphorylation of mitogen-activated protein kinases (Lim, Hwang, Hwang, & Park, 2012). These findings are clinically significant because chronic brain

inflammation is ascribed to prolonged activation of microglial cells, which induce degenerative neurological events (Lim et al., 2012).

The anti-inflammatory health benefits of flavonoids also extend to the genitourinary and gastrointestinal tracts. Researchers have reported that flavonoids have a positive effect on patients with prostatitis, urinary tract infections, and other similar events possibly through a reduction in inflammation (Cote et al., 2010; Katz, 2002; Theoharides, 2007). For example, a review of the flavonoids present in cranberries and cranberry juice has found anthocyanins, flavonols, the flavanols, proanthocyanidins, and phenolic acid derivatives work in a synergistic way to reduce inflammation and prevent bacterial infection within the urinary tract (Cote et al., 2010). The gastrointestinal benefits of flavonoids have been found to include the inhibition of gastric ulcers, intestinal inflammation, and inflammatory activity in human adenocarcinoma gastric cells (Hariprasath et al., 2012; Park, Ji, & Sung, 2012; Bulgari et al., 2012). In fact, researchers who conducted an animal study in mice found that dietary Kaempferol restricts inflammation of colitis in mice (Park et al., 2012). This finding is clinically significant because the reduction of inflammation is a key component in ulcerative colitis therapy (Park et al., 2012). Additionally, flavonoids demonstrated anti-inflammatory effects in human adenocarcinoma gastric cells during an in vitro study to determine if the anti-inflammatory effects of chamomile infusion at the gastric level could be attributed to the inhibition of metalloproteinase-9 and elastase (Bulgari et al., 2012). Ultimately, results from this study indicated that the flavonoid-7-glycosides might account for the observed anti-inflammatory action of the chamomile infusion (Bulgari et al., 2012). Given these

and other findings related to the aforementioned comorbid diseases, increased flavonoid intake might potentially reduce the comorbidity burden associated with COPD.

Flavonoids and COPD. Taken together, the health benefits of flavonoids appear to cover a broad gamut of disease states. Ultimately, it seems that many of these benefits are driven by the antioxidant and anti-inflammatory properties of flavonoids, as inflammation appears to be at the center of many chronic diseases, such as arteriosclerosis, obesity, diabetes, cancer, and others as described above (Garcia-Lafuente et al., 2009). COPD is also considered to be an inflammatory-based disease. In fact, chronic inflammatory and immune responses are established in the literature as leading contributors in the development and progression of COPD (Rovina et al., 2013). For example, COPD may be associated with systemic inflammation, given observed increases in levels of systemic inflammatory mediators among those with COPD (Augusti et al., 2012). These biomarkers include white blood cells, CRP, IL-6, IL-8, TNF-α, and fibrinogen (Augusti et al., 2012). In the short-term, these inflammatory mediators facilitate the resolution of cell injury; however, if the cellular injury is repetitive or sustained, more inflammatory mediators are recruited, which cause added tissue damage and perpetuates the inflammation (Lago et al., 2014). Given the pathology of COPD, the antioxidant and anti-inflammatory structure activity of flavonoids has been purported to influence the development and progression of the disease (Lago et al., 2014).

In vitro research. Many researchers conducting in vitro studies have explored the relationship between specific flavonoids and inflammatory cellular and molecular actions related to COPD. Researchers conducting in vitro research have documented the ability

of specific flavonoids or groups of flavonoids to inhibit or regulate the release of pro-inflammatory enzymes, proteins, and genes in the cells of rodents and humans (Esposito et al., 2014; Ferlazzo, et al., 2015; Flores et al., 2012; Ganesan et al., 2010; Lixuan et al., 2010; Weseler et al., 2009). For instance, researchers who conducted a study with four flavone C-glycosides from the neotropical blueberry, *anthopterus wardii,* found a dose-dependent relationship with anti-inflammatory activity against IL-8 and with inhibiting matrix metalloproteinase (MMP)-1 expression in the small airway epithelial cells of humans (Flores et al., 2012). This finding is noteworthy because IL-8, like other cytokines, is a circulating inflammatory mediator associated with COPD-related inflammation and MMP-1, which are key contributors in the pathology of COPD (Flores et al., 2012). The inhibition of MMP-1 in human small airway epithelial cells is particularly significant because excess MMPs produced by inflamed epithelial cells in the lungs ultimately degrade the alveolar walls and lead to the development of emphysema (Lago et al., 2014). In an earlier study testing the impact of the flavonoid quercetin on cell cultures of murine alveolar macrophages, researchers found that quercetin also decreased the expression and activity of MMP-9 and MMP-12 by increasing expressions of the type III protein deacetylase Sirt-1 (Ganesan et al., 2010). Sirt-1 is a negative regulator of MMP transcription (Ganesan et al., 2010). This finding demonstrates that different subgroups of flavonoids exhibit similar cytoprotective and anti-inflammatory properties in vitro.

In addition to inhibiting the expression of IL-8 and MMPs, research has also found that flavonoids can attenuate the expression of a much broader range of cytokines

associated with COPD progression and inflammation. For example, baicalin, a flavone obtained from the root of *Scutellaria baicalensis Georgi,* has exhibited the cytoprotective properties of flavonoids through documented in vitro inhibition of a range of cytokines (Li et al., 2012; Lixuan et al., 2010). In a study investigating the relationship between baicalin and COPD inflammation and mechanisms of anti-inflammatory effect, researchers noted that baicalin inhibited the pro-inflammatory expression of TNF-α, IL-6, IL-8, MMP-9, and NF-κB (Lixuan et al., 2010). In a later study investigating the effect of baicalin on respiratory inflammation of human lung adenocarcinoma epithelial cells, researchers also found that baicalin attenuates cigarette smoke-induced inflammation by reducing inflammatory cells and diminishing production of TNF-α, IL-8, and MMP-9 (Li et al., 2012). Furthermore, in an in vitro study of wild low bush blueberries, researchers found that polyphenol-rich, anthocyanin-rich, and proanthocyanidins-rich fractions of this blueberry's crude extract were effective in suppressing interleukin 1 Beta (IL-1β), cyclooxygenase-2, and nitric oxide synthase in murine RAW 264.7 macrophage cells (Esposito et al., 2014). These findings demonstrate the capability of flavonoids to regulate the expression of pro-inflammatory genes and enzymes. These findings are significant because macrophages typically activate pro-inflammatory genes, such as IL-1β, cyclooxygenase-2, and nitric oxide synthase, to up-regulate cytokine production in response to damage or infection (Esposito et al., 2014). Furthermore, researchers conducting a separate study showed that the flavonoids fisetin and tricetin, inhibitors of the nuclear enzyme poly(ADP-ribose) polymerase-1, could diminish lipopolysaccharide (LPS) induced increases in concentrations of TNFα and IL-6 in vitro using blood samples

from 10 male patients with COPD (Weseler et al., 2009). The authors attributed the attenuation of cytokine release to the poly(ADP-ribose) polymerase-1 inhibiting properties of fisetin and tricetin, which further demonstrates the range of pathways through which flavonoids can potentially disrupt the perpetual cycle of inflammation associated with the onset and progression of COPD.

Flavonoids appear to further impact the pathophysiology of COPD through other mechanisms, such as the reduction of oxidative stress through free radical scavenging activity (Ferlazzo et al., Zhong et al., 2014). Specifically, researchers have demonstrated that the free radical scavenging activity of flavonoids can minimize the intracellular oxidative damage caused by reactive oxygen species, which are associated with inflammatory diseases, such as COPD (Ferlazzo et al., Zhong et al., 2014). For example, researchers who conducted an in vitro study to examine the effect of flavonoids from bergamot and orange juices on hydrogen peroxide-induced oxidative stress in human lung epithelial cells found that these flavonoids demonstrated antioxidant activities that may help reduce the damage caused by oxidative stress in the pathology of COPD (Ferlazzo et al., 2015). Specific results indicated that both juice extracts reduced the production of reactive oxygen species and membrane lipid peroxidation, which improved mitochondrial functionality and prevented DNA-oxidative damage in the A549 cells (Ferlazzo et al., 2015).

Animal research. Animal studies have been conducted to reproduce the in vitro research described previously. Several in vivo animal studies have been conducted involving the administration of quercetin to mice and rats with acute lung inflammation

and acute lung injury (ALI) similar to that of COPD. Quercetin was found to suppress inflammation, oxidative stress, and mucus production and demonstrates overall therapeutic potential in the prevention of the disease (Ganesan et al., 2010; Huang et al., 2015; Yang, Luo et al., 2012). Quercetin also suppressed inflammation, mucus cell hyperplasia, oxidative stress, epidermal growth factor receptor (EGFR) phosphorylation, and NF-κB signal pathway activation in a study to examine the protective effect of quercetin against cigarette smoke-induced mucin expression and inflammation in rats (Yang, Luo et al., 2012). These findings demonstrate that quercetin can attenuate mucus production and airway inflammation, which is consistent with the findings of other in vivo animal studies involving flavonoids (Lee et al., 2015; Xie, Dong, Wu, Yan, & Xie, 2009). For example, an earlier study was conducted to investigate the effects of licorice flavonoids (LF) derived from the roots of *Glycyrrhiza uralensis* on lung inflammation in mice (Xie, Dong, Wu, Yan, & Xie, 2009). LF at doses of 3 mg/kg, 10 mg/kg, and 30 mg/kg significantly decreased the production of inflammatory response cells in bronchoalveolar lavage fluid (BALF), such as neutrophils, macrophages, and lymphocytes (Xie et al., 2009). Additionally, LF was found to reduce neutrophil-mediated oxidative injury by significantly increasing superoxide dismutase activity, which is the body's primary antioxidant defense, while also significantly decreasing lung myeloperoxidase activity (Xie et al., 2009). Likewise, similar results were obtained from a study that explored the effect that casticin, a flavonoid extracted from *Vitex Fructus*, on cigarette smoke-induced acute lung inflammation in mice (Lee et al., 2015). Findings indicated that casticin significantly inhibits the amount of total cells, neutrophils,

macrophages, and lymphocytes while reducing the amount of pro-inflammatory cytokines and chemokines in BALF (Lee et al., 2015). Researchers conducting in vivo animal studies have shown that Quercetin can ameliorate LPS-induced ALI through suppression of inflammation and oxidative stress (Huang et al., 2015). For instance, in a study conducted to assess the effects of quercetin on LPS-induced ALI in rats, researchers found that quercetin significantly ($p < 0.05$) counteracted the four to five-fold rise in BALF levels of TNFα and IL-6 found in controls (Huang et al., 2015). Additionally, quercetin also significantly ($p < 0.05$) suppressed oxidative stress by increasing activities of superoxide dismutase, catalase, and glutathione peroxidase in the lungs of LPS-treated rats (Huang et al., 2015). Given these results, the researchers have asserted that quercetin might have therapeutic potential in the prevention of ALI, which has implications for COPD.

Additional animal studies provide evidence that other flavonoids, in addition to quercetin, are also able to protect against LPS-induced ALI in vivo (Chen et al., 2013; Guan et al., 2012). For instance, researchers who conducted a study to investigate the therapeutic effects and mechanisms of *Mosla scabra* flavonoids (MF) on LPS-induced ALI in mice found that MF was protective against oxidative stress by lowering myeloperoxidase activity and total protein concentrations in the BALF (Chen et al., 2013). Furthermore, was found to MF exhibit a protective effect against inflammation by reducing serum levels of NO, TNF-α, IL-1β and IL-6 in ALI model using mice (Chen et al., 2013). Comparable findings were identified in separate study exploring the beneficial effects of liqueritin apioside (LA), a main flavonoid component from *Glycyrrhiza*

uralensis, against lung epithelial cell injury in mice caused by cigarette smoke. Results from this study demonstrated that LA at doses of 3 mg/kg, 10 mg/kg, and 30 mg/kg inhibited pulmonary neutrophil and macrophage inflammation in a dose-dependent manner (Guan et al., 2012). Additionally, LA was found to reduce the pulmonary release of TGF- β and TNF-α, attenuate myeloperoxidase activity, and enhance superoxide dismutase activity (Guan et al., 2012). These results indicate that LA, like MF and quercetin, may protect against ALI related to COPD.

In addition to effectively attenuating ALI and airway inflammation in vivo, researchers have also demonstrated that flavonoids have the potential to disrupt the progression of emphysema and chronic bronchitis in animal studies. For instance, in a study assessing the ability of quercetin to prevent the progression of emphysema in elastase/LPS-treated mice, researchers reported that quercetin effectively decreased lung inflammation, goblet cell metaplasia, mRNA expression of pro-inflammatory cytokines, the expression of MMP9 and MMP12, and levels of thiobarbituric acid reactive substances (Ganesan et al., 2010). The decrease in thiobarbituric acid reactive substances is significant because it is a measure of lipid peroxidation caused by oxidative stress (Ganesan et al., 2010). In this study, researchers reported that quercetin prevented the progression of emphysema in elastase/LPS-treated mice. A reduction in the progression of emphysema in mice during this study was marked by reduced oxidative stress and inflammation within the lungs. Additional markers of the attenuated progression of emphysema within mice during the study also included a reduction in the expression of MMP9 and MMP12. Similar findings were observed in studies assessing flavonoids

derived from *Baccharis retusa*, such as 5,6,7-Trihydroxy-4′-Methoxy-Flavanone (5,6,7-FLA) and sakuranetin, in mice with emphysema (Pinheiro et al., 2012; Taguchi et al., 2015). Findings from one study indicate that this flavanone significantly ($p < 0.001$) attenuated the total cells, macrophages, and lymphocytes in BALF while also significantly ($p < 0.001$) reducing collagen and elastic fibers contents in mice with emphysema as compared to controls not treated with 5,6,7-FLA (Pinheiro et al., 2012). Findings from a separate but similar study involving mice with emphysema indicated that sakuranetin also reduced the alveolar enlargement, collagen and elastic fiber deposition, and number of MMP9 and MMP12 cells (Taguchi et al., 2015). Additionally, findings from this study also indicated that administration of sakuranetin decreased inflammation and levels of TNF-α, IL-1β, and macrophage colony-stimulating factor in the BALF (Taguchi et al., 2015). These findings related to inflammation are consistent with findings from similar studies that have investigated other flavonoids, such as Baicalin and flavonoids derived from *Broussonetia papyrifera* (Ko, Oh, Jin, Son, & Kim, 2013; Lixuan et al., 2010). Baicalin was found to inhibit the pro-inflammatory effects of cigarette smoke exposure-induced COPD in rats by attenuating the release of IL-8, IL-6, and TNF-α (Lixuan et al., 2010). Additionally, a novel phytoformula containing *Broussonetia papyrifera* and *Lonicera japonica* was found to inhibit production of TNF-α, interferon gamma, and IL-1β in mice with LPS-induced inflammation (Ko et al., 2013). Furthermore, among mice with LPS-induced chronic bronchitis, *Broussonetia papyrifera* and *Lonicera japonica* significantly inhibited cell recruitment in BALF and reduced lung injury based on histological observation (Ko et al., 2013). Taken together,

the results from the studies described above demonstrate the ability of flavonoids to counteract lung remodeling, oxidative stress, and inflammation in vivo. These in vivo results also support the premise that flavonoids have a potential to interrupt the development and progression of COPD.

Human research. While interest in the therapeutic benefits of flavonoids is growing, human studies examining the potential association between dietary flavonoid intake and the development of COPD are lacking. However, the researchers that have conducted studies in humans suggest a potential relationship exists between flavonoid intake and COPD. A Turkish case-control study involving 40 male smokers diagnosed with COPD (Group-I) and 36 healthy male smokers without COPD (Group-II) was conducted to investigate whether nutritional risk factors were inversely associated with the development of COPD in male smokers (Celik & Topcu, 2006). The researchers noted that significant differences were observed between Group-I and Ggroup-II for the intake of black tea and fruits and vegetables (Celik & Topcu, 2006). Additionally, significant differences were also observed between Group-I and Group-II for breakfast habits and eating salty dietary constituents (Celik & Topcu, 2006). Also, the area under the receiver-operating characteristic (ROC) curve for black tea (0.898, 95% CI [0.819–0.977]) and fruits and vegetables (0.833, 95% CI [0.727–0.938]) offered a significant degree of precision in distinguishing between the COPD group and the control group ($p <$ 0:001; Celik & Topcu, 2006). While flavonoid content in black tea and vegetables-fruits consumption was not directly measured, these foods were noted as having high concentrations of flavonoids (Celik & Topcu, 2006). The researchers suggested that the

high concentration of flavonoids may have been responsible for protecting male smokers in their study from developing COPD (Celik & Topcu, 2006).

Researchers have also conducted several studies to assess the association of specific flavonoid intake and lung function, systemic inflammation, and symptoms related to COPD. Researchers who conducted the earliest cross-sectional studies found significant associations between flavonoids and COPD symptoms and lung function (Butland et al., 2000; Tabak et al., 2001). In a Dutch study of 13,651 adults aged 20 to 59 years old, researchers found that increased consumption of catechins, flavonols, and flavones was associated with improved lung function, as measured by FEV_1, and COPD symptoms, such as cough, phlegm production, and breathlessness (Tabak et al., 2001). A food frequency questionnaire was used to measure dietary intake of catechins, flavonols, and flavones among study participants. The estimated intake of these flavonoids was found to be 58 mg/day (SD = 46), with tea and apples identified as the main flavonoid food sources (Tabak et al., 2001). High dietary intake of these flavonoids was found to be beneficial against COPD symptoms and lung function measures. For example, dietary intake of catechins, flavonols, and flavones was found to have a protective significant associated with FEV_1, chronic cough, and dyspnea (Tabak et al., 2001). Additionally, intake of catechins was independently associated with FEV_1 ($\beta_{Q5\text{-}Q1}$ = 130 ml, 95% CI [101-159]) and all COPD symptoms ($OR_{Q5\text{-}Q1}$ = 0.74, 95% CI [0.58-0.94]) after researchers adjusted for potential confounding variables and the intake of flavonols and flavones. Flavonol and flavone intake was only independently associated with cough (Tabak et al., 2001). Similar results were later found by researchers who conducted a

cohort study of 63,257 Chinese men and women aged 45 to 74 years old to assess dietary factors impacting chronic respiratory symptoms, such as cough and phlegm (Butler et al., 2004). Results showed that consumption of soy isoflavones significantly reduced new onset of cough and phlegm (OR = 0.67, p_{trend} = 0.001, 95% CI [0.53 – 0.86]; Butler et al., 2004). A cross-sectional study using a prospective cohort of 2,512 Welshmen aged 45 to 59 years old also yielded similar results related to lung function and the consumption of apples (Butland et al., 2000). Higher apple intake, consisting of five or more apples per week, was positively and significantly associated with FEV_1 (Butland et al., 2000). Furthermore, the association between high apple intake and FEV_1 was independent of other variables, such as consumption of vitamin E and vitamin C (Butland et al., 2000). The authors attributed this effect to the high quercetin content of apples, although quercetin content was not directly measured in this study (Butland et al., 2000).

An association may also exist between flavonoid intake and measures of systemic inflammation. Researchers conducted a cross-sectional study of 2,115 women aged 43 to 70 years to examine the relationship between intake of the six primary flavonoid subgroups and biomarkers of inflammation and endothelial dysfunction (Landberg et al., 2011). Flavonoid intake was measured using a food frequency questionnaire, and inflammatory biomarkers were assessed using blood sample measurements of several biomarkers for inflammation, including CRP, IL-6, and IL-18 (Landberg et al., 2011). Multivariate-adjusted results indicated that mean plasma IL-8 levels were lower among participants grouped in the highest intake quintile for flavones, flavanones, and total flavonoids compared to participants grouped in the lowest intake quintiles (Landberg et

al., 2011). The difference in mean plasma IL-8 concentrations between the highest and lowest intake quintiles for each of the aforementioned flavonoid categories were "9% (Q1: 264 ng/L, Q5: 241 ng/L, $p_{trend} = 0.019$), 11% (Q1: 273 ng/L, Q5: 244 ng/L, $p_{trend} = 0.011$), and 8% (Q1: 276 ng/L, Q5: 55 ng/L, $p_{trend} = 0.034$), respectively," according to Landberg et al. (2011, p. 618). Overall, the results of this study demonstrated that various subgroups of flavonoids are associated with smaller amounts of systemic inflammatory biomarkers, which may have an effect on the chronic inflammation present in COPD.

A relationship between dietary flavonoid intake and lung function has also been suggested, which may implications for COPD because declining lung function is a key characteristic of the disease. For instance, researchers conducted a cross-sectional study to assess the relationship between ventilator function and antioxidant components of 1,232 Chileans aged 22-28 years found positive associations between lung function and flavonoid intake (Garcia-Larsen et al., 2015). Results indicated that total intake of catechins was positively correlated with FVC (regression coefficient of the highest versus lowest quintile of intake [RC_{Q5-Q1}] = 0.07, 95% CI [0.01-0.15], $p_{trend} = 0.006$; Garcia-Larsen et al., 2015). Additionally, total fruit intake was significantly associated with FVC ($RC_{Q5-Q1} = 0.08$, 95% CI [0.003-0.15], $p_{trend} = 0.02$; Garcia-Larsen et al., 2015). Furthermore, intake of omega 3 fatty acids was also found to be associated with higher FEV_1 ($RC_{Q5-Q1} = 0.08$; 95% CI [0.01-0.15]; $p_{trend} = 0.02$) and with FVC ($RC_{Q5-Q1} = 0.08$, 95% CI [0.001-0.16], $p_{trend} = 0.04$; Garcia-Larsen et al., 2015). The authors concluded that dietary constituents, such as fresh fruits, flavonoids, and omega 3 fatty acids might support and help to maintain overall lung function. Researchers reported similar results

when examining the association of curry intake and pulmonary function among 2,478 Chinese adult smokers and non-smokers aged 55 and older (Ng, Niti, Yap, & Tan, 2012). Positive associations were present between curcumins, the flavonoids present in curry, and lung function (Ng et al., 2012). Consuming curry at least once per month was significantly associated with better FEV_1 (b = 0.045 ± 60.018, $p = 0.011$) and FEV_1/FVC (b = 1.146 ± 0.52, $p = 0.029$) in multivariate analysis (Ng et al., 2012). Additionally, increasing levels of curry intake were found to be associated with higher mean adjusted FEV_1 ($p_{linear\ trend} = 0.001$) and FEV_1/FVC ($p_{linear\ trend} = 0.048$; Ng et al., 2012). Also, significant effect modifications were identified for interaction between curry and smoking for FEV_1 ($p = 0.028$) and FEV_1/FVC ($p = 0.05$; Ng. et al., 2012). Significant differences between FEV_1 were also observed between curry consumption and non-consumption among both current and former smokers (Ng. et al., 2012). In fact, consuming curry was associated with a 9.2% and 10.3% higher adjusted mean FEV_1 among current smokers and past smokers, respectively (Ng. et al., 2012). Similar findings were reported by researchers who conducted a longitudinal study examining the association of flavonoid intake and age-related lung function decline among 839 participants from the Veterans Affairs Normative Aging Study (Mehta et al., 2016). In particular, Mehta et al. (2016) reported a slower decline in FEV_1 by 22.5 mL/year (95% CI: 10.8, 34.2) for those who consumed two servings or more of anthocyanin-rich blueberries each week as compared to those who consumed less. Similarly, a slower decline in FVC by 37.9 mL/year was observed among those who consumed two servings or more of anthocyanin-rich blueberries weekly as compared to those who consumed less

(Mehta et al., 2016). Ultimately, the findings from Garcia et al. (2015), Ng. et al. (2012), and Mehta et al. are supportive of the findings noted in the earlier study by Tabak et al. (2001) regarding the association between flavonoid intake and lung function.

Overall, findings from the in vitro, animal, and human studies reviewed above appear to provide support for the premise that a potential relationship may exist between dietary flavonoid intake and the development and progression of COPD. In particular, findings from human studies have demonstrated significant associations between dietary flavonoid intake and lung function, systemic inflammation, and COPD. Additionally, results from the in vitro and animal studies seem to provide support for the biological basis that a relationship may be present between dietary flavonoid intake and COPD outcomes.

Measurement Tools

An accurate accounting of the types and quantity of food consumed is necessary to determine the relationship between diet and flavonoids. Additionally, and equally as important, a reliable source of data is necessary to estimate the total flavonoid content of the individual foods within a given diet. The combination of these two sources of data enables the assessment of flavonoid intake. However, the measurement tools for these data can vary, and some tools have limitations that must be considered.

Dietary intake. Several measurement tools are available to measure dietary intake. Some of the more standard tools include 24-hour food recalls, food frequency questionnaires (FFQ), food screeners, and food record diaries covering multiple days. Each tool has specific strengths and limitations that are ideal under certain conditions and

when using specific study designs. For example, the 24-hour food recall allows for collection of detailed and quantified intake data, utilization among low-literacy populations, increased precision through multiple administrations, and utilization in large-scale cross-sectional studies (Castell, Serra-Majem, & Ribas-Barbara, 2015; Illner et al., 2012; Kirkpatrick et al., 2014). However, the limitations of this tool include the need for well-trained interviewers, multiple administrations to capture typical intake of foods, reliance on participant recall, and increased risk of random error (Castell et al., 2015; Illner et al., 2012; Kirkpatrick et al., 2014). Also, if the 24-hour food recall is not administered at various times throughout the year, it may not account for foods that are eaten infrequently (Castell et al., 2015).

Alternatively, the FFQ has strengths that include low administration costs, the ability to estimate individual intake in one administration, and the ability to capture dietary information for longer periods (Illner et al., 2012; Kirkpatrick et al., 2014; National Cancer Institute [NCI], n.d.). Because the FFQ captures dietary intake for longer periods, such as up to 1 month or 1 year, the FFQ may account for episodic or seasonal variations in dietary intake (Illner et al., 2012; Kirkpatrick et al., 2014). The FFQ is often used in retrospective case-control studies because it is a cost-effective method, typically involving one-time self-administration, for capturing past dietary intake data (Kirkpatrick et al., 2014; NCI, n.d). However, the FFQ is limited to a finite pre-specified food items list, which may not accurately represent all foods that an individual may have consumed, and this limitation can be a source of systemic measurement error (Illner et al., 2012; Kirkpatrick et al., 2014; NCI, n.d). Furthermore, the results captured by the FFQ are

prone to recall bias (Illner et al., 2012; Kirkpatrick et al., 2014; NCI, n.d). Other limitations of FFQs include lack of dietary details and limited quantification of portion sizes in some cases (Illner et al., 2012; Kirkpatrick et al., 2014; NCI, n.d.). Given these limitations, the use of an FFQ to describe the dietary intake of a population in cross-sectional studies is not recommended (NCI, n.d).

Food screeners are more limited in scope than FFQs because screeners are developed to collect data on very specific dietary components or behaviors. As a result, food screeners have more weaknesses than the FFQ. Given the limited pre-specified food items list of food screeners, they are not ideal for estimating typical dietary intake (Kirkpatrick et al., 2014; NCI, n.d.). However, food screeners can be used in cross-sectional studies and retrospective case-control studies when the dietary scope, study resources, and study duration are limited (Kirkpatrick et al., 2014; NCI, n.d.). In contrast, the strengths of the food diary record seem to surpass those of the 24-hour recall and FFQ. The strengths of the food record diary include the ability to encompass a longer intake time frame than the 24-hour recall, obtain quantified and detailed intake data, and provide a real-time accounting of intake (Illner et al., 2012; Kirkpatrick et al., 2014). However, the food record diary is limited by high respondent and responder burden, reliance on participant literacy, decreased compliance over time, altered eating habits due to reactivity, and potential selection bias due to exclusion of participants with low literacy (Illner et al., 2012; Kirkpatrick et al., 2014; NCI, n.d.).

Of these various dietary measurement tools, the 24-hour food recall appears to be the most widely utilized in studies purposed with capturing quantified and detailed data

on flavonoid intake, particularly for the U.S. population (Bai et al., 2014; Chun et al., 2007; Chun, Lee, Wang, Vance, & Song, 2012; Kim, Vance, & Chun, 2015). The choice to utilize a 24-hour food recall as the primary instrument in these studies appears to be based on the accuracy of this instrument in providing precise portion quantities, which is essential to determining the flavonoid content of reported food items (Bai et al., 2014; Chun et al., 2007; Chun, Lee, Wang, Vance, & Song, 2012; Kim, Vance, & Chun, 2015). One study used an FFQ instead of the 24-hour food recall to successfully estimate flavonoid intake at midlife in relation to healthy aging (Samieri, Sun, Townsend, Rimm, & Grodstein, 2014). However, the FFQ utilized in this study contained a component for standard portion size, which allowed researchers to estimate the quantity of flavonoid content for foods listed on the FFQ (Samieri et al., 2014).

It is recognized that a single 24-hour dietary recall may not adequately capture typical micronutrient intake. Micronutrient intake can fluctuate due to certain factors, like the day of the week and cultural beliefs, which can impact the intake of certain foods (Chun & Davis, 2012; Chun et al., 2007; Ma et al., 2009). Utilizing multiple 24-hour recalls when reporting nutrient intake can improve the measurement tool's ability to reflect typical nutrient intake in relation to health outcomes (Beydoun et al., 2015; Ma et al., 2009). Among studies utilizing the 24-hour food recall to assess the flavonoid intake of Americans, researchers have obtained mean values from two non-consecutive 24-hour food recalls obtained from the NHANES (Bai et al., 2014; Chun et al., 2007; Chun, Lee, Wang, Vance, & Song, 2012; Kim, Vance, & Chun, 2015). Researchers averaged results from the two 24-hour food recalls within the NHANES datasets to account for typical

intake patterns to improve the limitation of using a single 24 hour food recall administration (Bai et al., 2014; Chun et al., 2007; Chun, Lee, Wang, Vance, & Song, 2012; Kim, Vance, & Chun, 2015). Overall, it appears that accurately estimating typical flavonoid intake necessitates utilizing more than one 24-hour dietary recall, and the dietary components of the 2007-2010 NHANES includes two 24-hour dietary recalls. However, it is acknowledged that two 24-hour dietary recalls cannot fully account for within-individual variations in typical dietary intake, which is a known limitation given the cross-sectional design of this current study.

NHANES. Several large-scale population-based health surveys that address nutrition and health outcomes are publicly available. For example, questions related to the diagnosis of COPD are found within National Health Interview Survey, the Behavioral Risk Factor Surveillance System, and the NHANES. However, the dietary collection tools along with other health outcome and diagnostic components make the NHANES datasets ideal for conducting comprehensive secondary analyses. For example, the NHANES is particularly relevant, as it collects information related to COPD diagnosis, spirometric diagnostic testing, comorbid chronic diseases, and biological laboratory testing (CDC, 2015a). In fact, studies have utilized spirometry values and self-report of physician diagnosis obtained from the medical conditions and examination components of the NHANES to successfully estimate COPD prevalence for the United States (Doney, Hnizdo, & Halldin, 2014; Telert et al., 2013). Furthermore, researchers have also utilized medical conditions component of the NHANES to identify and

determine if relationships exist between COPD and other comorbid diseases (Putcha, Puhan, Hansel, Drummond, & Boyd, 2013; Schnell et al., 2012).

The NHANES has long attempted to provide nationally representative data since it began in the early 1960s as a series of surveys focused on various population groups and health topics (CDC, 2015a). As of 1999, the survey has changed to become a continuous program conducted every 2 years to allow for increased flexibility with survey changes and adaptations to meet emerging needs (CDC, 2015a). While earlier versions of NHANES were limited in the ability to provide accurate estimates of certain measures, such as dietary intake, more recent changes in the NHANES measurement protocols have improved upon attempts at obtaining more accurate measures. For example, the improvements to measurement protocols for dietary intake include the using two days of recall, obtaining recall on weekends in addition to weekdays, utilizing the multi-pass approach, providing enhanced training to survey administrators, and improving quality controls (Archer, Hand, & Blair, 2013; McDowell, Briefel, Buzzard, Gardner, & Warren, 1989). Additionally, each version of the NHANES now involves approximately 5,000 participants from various counties across the United States, of which 15 counties remain the same each year (CDC, 2015a). The validity and reliability of the data collected in the NHANES are enhanced due to various internal quality checks and supplemental guidelines on how to interpret and analyze the collected survey data (CDC, 2015a). The process of participant selection, administration of surveys and questionnaires, diagnostic testing, and use guidelines are well documented and continuously reviewed by government and private experts (CDC, 2015a).

Flavonoid databases. There are very few resources available to aid in the determination of flavonoid content in a wide variety of foods for all six flavonoid subclasses. The USDA provides the most complete sources for flavonoid content in a broad spectrum of foods. For example, the USDA Database for Flavonoid Content of Select Foods (DFCSF), Release 3.2, contains flavonoid content for 506 food items (USDA, 2015). However, the USDA DFCSF only provides flavonoid content for five subclasses of flavonoids, which include flavonols, flavones, flavanones, flavan-3-ols, and anthocyanidins. The USDA maintains a separate database for the sixth flavonoid subclass known as isoflavones. The USDA Database for Isoflavone Content of Select Foods (DICSF), Release 2.1, contains the data on the isoflavone content of 560 food items (USDA, 2015). The expansion of the DFCSF and DICSF formed the basis for the Expanded Flavonoid Database for the Assessment of Dietary Intakes (FDB-EXP), Release 1.1, which has flavonoid content data for 2,926 food items. The flavonoid content profiles for the food items in the FDB-EXP were generated by applying the analytical values for the flavonoids identified for the 506 food items in the DFCSF and the flavonoids identified for the 560 food items in the DICSF (USDA, 2015). Together these databases provide the basis for the most comprehensive information on flavonoid content of foods currently available (USDA, 2015). Only data generated by acceptable analytical procedures resulting in good separation of flavonoid compounds are included in the USDA flavonoid databases to ensure quality reporting for specific flavonoid compounds (USDA, 2015). As such, the USDA flavonoid databases have been widely used in several large-scale studies within the United States and other countries, such as

Australia, Germany, the UK, and Ireland to quantify the flavonoid content of specific foods (Bai et al., 2014; Beking & Vieira, 2011; Chun et al., 2007; Chun et al., 2012; Filiberto et al., 2013; Kent et al., 2015; Kim, Vance, & Chun, 2015; McCullough et al., 2012; Samieri et al., 2014; Vogiatzoglou et al., 2013).

As the most comprehensive source for flavonoid content of select foods, the USDA flavonoid databases have enabled researchers to make more accurate estimates of flavonoid intake (Chun et al., 2012). For example, studies utilizing other sources to quantify flavonoid content of select foods prior the release of the DFCSF have reported lower estimates of flavonoid intake due lack of complete data for all flavonoid subclasses (Chun et al., 2012). For example, estimates of flavonoid intake using food tables from the Department of Nutrition at Harvard School of Public Health for postmenopausal women and middle-aged and older women were 24.6 mg/day and 21.2 mg/day, respectively (Lin et al., 2007; Sesso, Gaziano, Liu, & Buring, 2003). The food tables provided only flavonol and flavone content for several foods based on data initially produced in the Netherlands, but updated to include American foods (Sesso et al., 2003). Ultimately, the estimates of flavonoid intake by the aforementioned studies were likely underreported because only two subclasses of flavonoids, flavonols and flavones, were included due to the limitations of the flavonoid measurement tools that were used. These estimates were approximately ten times less than a more accurate estimate of 268 mg/day for men and women of similar age calculated using the DFCSF and DICSF, which included a broader and more comprehensive range of flavonoid subclasses (McCullough et al., 2012). Therefore, it is apparent that utilizing a current and comprehensive source for flavonoid

content in foods is essential to calculating accurate estimates of flavonoid intake, and the DFCSF and DICSF are appropriate sources in this regard.

Summary and Conclusions

COPD represents a significant disease burden and a major public health concern within the United States and around the world. In addition to the individual toll that COPD can take on those with the disease, this condition also has economic disadvantages manifested as losses in productivity and increases in medical expenditures. A wide range of research indicates that overall diet and the intake of specific foods can affect the onset and progression of COPD. However, it is still uncertain what specific dietary components and mechanisms of action are responsible for these effects. Research has suggested that there may be a relationship between high flavonoid intake and COPD outcomes. Furthermore, many of the foods found to have significant associations with COPD are noted to contain a high quantity of flavonoids, which adds further support to the suggested relationship between flavonoids and COPD. In general, no studies have been conducted that directly examined the potential relationship between dietary intake of flavonoids and COPD diagnosis, COPD severity, systemic inflammation, and comorbidity burden within the U.S. population.

The NHANES and USDA flavonoid databases presented a novel opportunity to address this gap in the literature. The data from the NHANES allows for an accurate assessment of diet, COPD diagnosis and severity, systemic inflammation, and associated comorbidities within the general population. The combination of the NHANES data with that of the USDA flavonoid databases enabled the quantification of flavonoid intake as it

relates to specific COPD outcomes. Therefore, my aim with this study was to examine the potential relationship between total daily flavonoid intake and COPD. The design and methodological approach that I used in this study are described in the following chapter.

Chapter 3: Research Method

Introduction

This chapter includes a review of the study design and rationale I used to explore the potential effects of dietary flavonoid intake on the diagnosis, severity, and comorbidity of COPD among a sample of the U.S. population aged 30 years and older. I also present the methodology for this study, including a description of the population and sampling procedures used in the 2007-2010 NHANES. Furthermore, the methods for dietary and COPD data collection are reviewed, and the operationalization of variables are discussed in this chapter. Similarly, I describe the methodology for determining flavonoid content of selected foods using the USDA flavonoid databases, and provide a comprehensive explanation of the data analyses and statistical procedures employed to test the study hypotheses. Finally, I discuss the ethical considerations in this research study.

Research Design and Rationale

This was a quantitative, cross-sectional study using data from the 2007-2008 and 2009-2010 iterations of NHANES in conjunction with expanded flavonoid data from the USDA's DFCSF, Release 3.2 (September 2015, Slightly revised November 2015) and DICSF, Release 2.1 to test the association between dietary flavonoid intake and COPD. I selected these NHANES datasets because they provide comprehensive data using a large-scale sample of participants who are representative of the population of the United States. Also, these specific iterations of the NHANES are the most current surveys that include laboratory testing and reporting of CRP, which was a key variable in the assessment of

systemic inflammation for this study. The USDA's flavonoid databases were the most robust databases available for the flavonoid content of foods. The use of these flavonoid databases and the NHANES dataset together allowed for the appropriate assessment of the research questions for this study.

Cohort, case-control, and cross-sectional non-interventional study designs are all appropriate for use when the units of observation are individuals, and the research questions are designed to identify associations with health outcomes rather than establish causation (Szklo & Nieto, 2014). I selected a cross-sectional design for this study because this design is well aligned with the quantitative nature of the research questions. Cohort and case-control studies require multiple measurements for study outcomes over a long period of time and significant resources, which are prohibitive constraints for a large population-based study (Szklo & Nieto, 2014). In contrast, cross-sectional study designs only require data to be captured at one point in time and also provide the opportunity to assess exposure and outcome associations (Szklo & Nieto, 2014). However, it is not possible to identify temporal relationships and trends or establish causation when using a cross-sectional study design. Despite these limitations, a cross-sectional design was the most appropriate for this study based on feasibility, logistics, and efficiency, as compared to other viable non-experimental designs.

Methodology

Population

The subjects included in this study were participants in the 2007-2010 NHANES, and their data were obtained from the publicly available 2007-2010 NHANES datasets

(CDC, 2015b; CDC, 2015c). The 2007-2010 year range encapsulates two distinct NHANES datasets, those from 2007-2008 and 2009-2010. The sample size for the 2007-2008 NHANES was 10,149, and the sample size for the 2009-2010 NHANES was 10,537. Taken together, the total sample size for the 2007-2010 NHANES was 20,686. The NHANES aims to include a sample population that is representative of the non-institutionalized U.S. population. Therefore, the NHANES includes participants ranging in age from less than 1 year old to 80 years or older from various races and ethnicities (CDC, 2015b; CDC, 2015c). In this cross-sectional analysis, the sample population excluded participants aged 29 years and younger, as COPD is a progressive disease with symptoms manifesting later in life. While the majority of COPD cases are diagnosed at 40 years and older, the inclusion of participants 30-39 years old in the current study was relevant because COPD is found among younger patients within this age range (Wheaton et al., 2015).

Sampling Procedures

The 2007-2010 NHANES used a complex probability sampling design consisting of multiple stages to select study participants who are reflective of the non-institutionalized, civilian population of the United States (CDC, 2013b). The NHANES sampling procedures consisted of a four-stage process starting with the selection of primary sampling units (PSUs), which included individual counties or clusters of adjoining counties. The PSUs were segmented into smaller area groupings of households from which a sample was randomly drawn (CDC, 2013). One or more individuals from these households were selected at random to participate. During this process certain

demographic groups, such as those identifying as Hispanic, non-Hispanic Black, low-income White, and people aged 80 years and older were oversampled to provide dependable and precise estimates of health status indicators that assist with public health measures of relevance for these subgroups (CDC, 2013b). Therefore, each participant was assigned a sample weight to produce unbiased national estimates. This complex sampling strategy was well validated, justified, and documented for all iterations of the NHANES, including the 2007-2010 iterations (CDC, 2013b).

I included as many participants from the 2007-2010 NHANES datasets as possible to ensure an appropriate sample size. Participants were included in this study if they performed spirometry testing to determine the presence of COPD, had responded negatively to having a diagnosis of asthma, and had complete dietary data to assess flavonoid intake. Participants without acceptable measures for FEV_1 and FVC and CRP measurements were excluded from the severity analyses and systemic inflammation analyses, respectively. Those patients without an affirmative or negative response when providing a self-report of cardiovascular disease, diabetes, and hypertension were excluded from the comorbidity analysis. In Chapter 4 I provide further details regarding the composition of the final study sample, given the application of exclusion criteria.

Data collection. The data from the 2007-2010 NHANES, as in other iterations of this national survey, were collected from participants through interviews, diagnostic testing, and medical health examinations. Interviews were conducted in participants' homes by trained interviewers who administered all questionnaires for the household interview component, which included screener, family, and sample person interview

questionnaires (CDC, 2015a). The screener questionnaire was used to determine household eligibility and the relationships between all household residents. The family questionnaire was used to obtain family and household-level demographic information. The sample person questionnaire was used to obtain self-reported individual-level information on various health outcomes and behaviors, such as oral health, physical activity, and medical conditions (CDC, 2015a). Following completion of the household interview, study participants were asked to visit a mobile examination center (MEC). During the visit to the MEC, interviewers administered a 24-hour dietary recall questionnaire. Interviewers also administered additional questionnaires to collect data on more sensitive topics, such as reproductive health, drug use, and depression (CDC, 2015a). Data collected throughout the interview process was obtained using a mostly electronic system that incorporated technology, such as touch-screen computers, a computer-assisted personal interview (CAPI) system, a computer-assisted self-interview system, and electronic questionnaires. All diagnostic testing and medical health examinations took up to 4 hours for each participant and were conducted in the MECs, which allowed for a standardized environment for all participants (CDC, 2015a). The MEC staff consisted of trained and certified physicians, dietary interviewers, medical technologists, phlebotomists, two interviewers, and computer managers (CDC, 2015a). The MECs had automated collection procedures with diagnostic components being recorded directly into the study database.

All NHANES staff were trained in obtaining informed consent for all aspects of the survey and associated examinations, and in maintaining the privacy and

confidentiality of participants (CDC, 2015a). The 2007-2010 NHANES data files were made available for free public access on the CDC website. Because the data collected during the NHANES were intended for public use and participants provided consent for future use of their data, additional permission to use the data was not necessary. Therefore, I downloaded the data files for this study from CDC website for analysis following receipt of Walden University's IRB approval.

Constructing weights. To ensure that the sum of the weights matched the survey population, I had to weight the combined sampling data from the 2007-2008 and 2009-2010 NHANES datasets. The weights that I used in this cross-sectional analysis included the 2-year examination weight with the variable name WTMEC2YR, and the 4-year examination weight with the variable name WTMEC4YR. The WTMEC2YR variable was included in the 2007-2010 NHANES datasets, and was used to construct the 4-year weight using the following formula: If SDDSRVYR in (5,6), then WTMEC4YR = 1/2 * WTMEC2YR (CDC, 2013a). The term SDDSRVYR represents the survey cycle variable, with the value of 5 representing 2007-2008 and the value of 6 representing 2009-2010 (CDC, 2013a).

Power analysis. The sample size for this study was calculated using G*Power 3.1 (Faul, Erdfelder, & Buchner, 2007). To address the research questions in this study, multivariate analyses using multiple linear and logistic regression were required. These statistical procedures would require sufficient sample sizes to achieve 80% statistical probability of rejecting a false null hypothesis. In the absence of other studies with analyses directly matching this study, I made an approximation of the anticipated effect

size for changes in CRP and FEV_1% predicted based on effect sizes found in the literature. The effect size for CRP in this study was based on the change in CRP predicted by total fruit intake ($\beta = -0.100$) in a study exploring the association between dietary constituents and serum CRP (Corley, Kyle, Starr, McNeill, & Deary, 2015)). Therefore, the sample size calculation using G*Power 3.1 included an effect size of 0.100 mg/dL change in CRP, alpha of .05, power of 80%, and nine predictors. The resulting sample size estimate for multiple linear regression analysis involving CRP was 166 participants. I estimated the effect size for FEV_1% predicted based on the effect sizes found in a study by Schünemann et al. (2002) assessing the association between FEV_1% predicted and lutein/zeaxanthin ($\beta = 0.997$), vitamin C ($\beta = 1.04$), and vitamin E ($\beta = 1.601$). Therefore, the sample size calculation using G*Power 3.1 was based on an estimated effect size of 1% change in the FEV_1% predicted, an alpha of .05, power of 80%, and nine predictors. The resulting sample size estimate for multiple linear regression analysis involving FEV_1% predicted was 26 participants. Taken together, the total sample size needed to accommodate multiple linear regression for CRP and FEV_1% predicted was estimated to be 166.

Using G*Power 3.1, the calculation for logistic regression, based on a two-tailed test with an alpha of .05, power of 80%, and an odds ratio of 0.7-1.3, yielded a sample size ranging between 395 and 721. I selected this 30% range to account for both positive and negative effects of increased flavonoid intake between participants with COPD and those without. Additionally, 30% appears to be a moderate indicator of likely effect, as similar odds ratios of were observed in studies of flavonoid intake and outcomes, such as

COPD-related symptoms and various cancers (Fink et al., 2007; Tabak et al., 2001; Woo & Kim, 2013). Therefore, to accommodate multiple logistic regression analysis, the overall sample size required for this study was 721.

Instrumentation

The overall data collection instruments researchers used to obtain data for this study included survey questionnaires and diagnostic equipment. I obtained data from the 2007-2010 NHANES datasets that were related to the variables of interest my study including medical, dietary, demographic, and health outcome assessments. Trained health technicians obtained this information from participants during interviews, examinations, and laboratory sample collections.

Dietary Measurement

During the 2007-2010 NHANES, CDC interviewers obtained a 24-hour food recall from participants at two different time points. The food recalls were used by CDC interviewers to collect data on the individual foods and portion sizes consumed by each participant within the previous 24-hour period. To more accurately reflect daily flavonoid intake for this study, I averaged the dietary data derived from the two non-consecutive 24-hour food recalls obtained during the 2007-2010 NHANES. The first 24-hour food recall was obtained from participants through an in-person interview conducted while visiting a MEC. The second 24-hour food recall was obtained three to 10 days later by phone interview. All 24-hour dietary recalls were administered by trained dietary interviewers who were guided by an automated dietary interview program designed to aid in executing the multiple-pass method. The multiple-pass method is designed to enhance

the accuracy of short-term dietary habits elicited from participants (Raper, Perloff, Ingwersen, Steinfeldt, & Anand, 2004; Steinfeldt, Anand, & Murayi, 2013). The USDA's computer-based automated multi-pass method (AMPM) program was used to prompt the interviewers to ask participants standardized questions about the foods and beverages that each participant consumed in the past 24-hours (CDC, 2015b; CDC, 2015c). The validity of the USDA's AMPM has been confirmed by researchers in several studies to improve estimates of total energy and nutrient intake (Blanton, Moshfegh, Baer, & Kretsch, 2006; Moshfegh et al., 2008; Rhodes et al., 2013).

This USDA's AMPM involves five steps that ensure participants are provided with structured and unstructured opportunities to report the foods they consume. During administration of the 24-hour recall, the first step of the AMPM required each participant to provide a quick list of foods and beverages consumed within the past 24 hours. During the second step, the interviewer probed each participant for foods they may have forgotten to report during the first step. The interviewer probed for forgotten foods by bringing common food categories to each participant's attention, such as non-alcoholic beverages, savory snacks, fruits, vegetables, and cheeses (CDC, 2015b; CDC, 2015c). The third step required the interviewer to ask each participant to identify the time and occasion that each food was consumed. Next, the interviewer placed all participant-reported foods into chronological order and grouped those foods by eating occasion. During the fourth step, the interviewer asked each participant to provide detailed information regarding each reported food item, such as the amount consumed, where it was obtained, and where it was consumed (CDC, 2015b; CDC, 2015c). Additionally, the

interviewer reviewed each eating occasion and the duration of time between each eating occasion with participants to help them identify additional foods that may have been forgotten. The fifth step entailed a final probe by the interviewer to aid the participant in recalling additional foods. The final probe involved encouraging participants to recall other occasions where food may have been consumed or small amounts of foods that might have been viewed as insignificant (CDC, 2015b; CDC, 2015c). The interviewers recorded all participants' responses directly into the AMPM computer program. The interviewers provided all participants with identical measuring guides to aid them in accurately reporting the quantity of the foods and beverages they consumed. The measuring guides included three-dimensional tools, such as bowls, spoons, and cartons, and two-dimensional tools, such as pictures of chicken pieces and shapes (CDC, 2015b; CDC, 2015c). The duration of each dietary interview ranged between 15 and 30 minutes, depending on the amount and types of foods reported by the participants (CDC, 2015b; CDC, 2015c). At the end of each participant's 24-hour dietary recall interview at the MEC, the interviewer provided each participant with a set of measurement guides to take with them for use during the subsequent telephone interview. The interviewer conducted the telephone interview using the AMPM dietary interview program and by following the same procedures as the initial MEC interview (CDC, 2015b; CDC, 2015c).

Demographics and Diseases

CDC interviewers collected data regarding the demographics and diagnosis of COPD, cardiovascular disease, diabetes, and hypertension from study participants during the conduct of the 2007-2010 NHANES using standard questionnaires. The

demographics data were collected using the Demographics Questionnaire (DMQ). The Medical Conditions Questionnaire (MCQ) was used to collect data on self-reported diagnosis of COPD and cardiovascular disease. Data on self-reported diagnoses for diabetes and hypertension were collected using the Diabetes Questionnaire (DIQ) and Blood Pressure and Cholesterol Questionnaire (BPQ), respectively. The DMQ, MCQ, DIQ, and BPQ, were designated as in-home questionnaires. These questionnaires were administered to participants using standard modes of administration. The standard method of administration involved the use of portable CAPI systems, which contained electronic versions of the DMQ, MCQ, and BPQ. While present in participants' homes, trained interviewers asked all questions using the CAPI system. Interviewers read the questions provided by the CAPI system to each participant. All participants' responses were recorded directly into the CAPI system by the interviewers. Quality assurance and control were maintained through the CAPI system because the system is programmed to perform consistency checks, which reduces data entry errors (CDC, 2015a). Furthermore, onscreen help menus provided interviewers with assistance in providing standardized definitions of key terms to participants (CDC, 2015a).

Medical Examinations

Examination data, including spirometry values, height and weight measurements, and blood samples were collected from study participants by trained health technicians in the MECs. The spirometry testing procedures used in NHANES were performed according to recommendations from the American Thoracic Society recommendations (CDC, 2015a; Miller et al., 2005). The spirometry testing procedures entailed coaching,

ensuring adequate duration of expiratory maneuvers, and ensuring acceptability of testing. Prior to initiating a spirometry test, the spirometry technician coached participants on how to perform the expiratory maneuvers by describing the actions participants would need to take. These actions included taking a deep breath to fill the lungs with air, placing the mouthpiece of the spirometer in the mouth, sealing the lips around the mouthpiece, and blasting air out as hard and fast as possible until prompted by the technician to stop (CDC, 2015a). Expiratory maneuvers performed by participants during spirometry testing were considered acceptable if they were free of hesitation or false starts when blowing into the mouthpiece (CDC, 2015a). Additional acceptability criteria for expiratory maneuvers included no coughing during the first second, no mouthpiece obstruction, an extrapolated volume of < 150 ml or 5% of the FVC, a visible plateau toward the end of the volume-time spirogram, and duration of 6 seconds (CDC, 2015a). Participants were asked to repeat the expiratory maneuver if it was found to be unacceptable by the technicians, with a maximum of eight attempts allowed. To ensure the quality of spirometry administration and performance the respiratory division of the National Institute for Occupational Safety and Health (NIOSH) acted as the training consultant for spirometry technicians during the NHANES. Furthermore, the quality control division at NIOSH reviewed all spirometry data, and spirometry equipment was regularly calibrated by trained technicians and confirmed by supervisors (CDC, 2015a).

Trained NHANES examiners calculated BMI using height and weight measurements obtained from participants. The examiners received their training from expert anthropometrists. All body measurements were collected in a standardized manner

by an examiner who was assisted by a recorder. The standardized process for obtaining a participant's weight involved providing disrobing instructions to participant, positioning them on a digital scale, and entering their weight result directly into a computer integrated survey information system. Examiners instructed participants to disrobe, with the exception of their undergarments, and change into a standard exam gown. The standard gown consisted of a disposable shirt, pants, and slippers (CDC, 2015a). The examiner instructed the participants to step onto the center of a digital scale platform with their hands at their sides and facing the examiner (CDC, 2015a). All participants were expected to use the same digital scale type and model provided in the MEC. The digital scale could only provide accurate weight measurements up to a maximum of 440 pounds (CDC, 2015a). If a participant weighed greater than 440 pounds, then two portable digital scales were used to weigh the participant (CDC, 2015a). In this instance, the examiner provided the same instructions; however, the examiner would instruct the participant to place one foot on each scale. All weight measurements obtained by the examiner, regardless of the number of scales used, were entered into the computer-based survey information system (CDC, 2015a).

The standard process used by NHANES examiners to obtaining a height measurement for each participant included positioning the participant on a standometer, adjusting the standometer head piece, and recording the height result. The examiners instructed each participant to stand on the standometer platform with their arms at their sides and heels together with toes apart (CDC, 2015a). Additionally, the examiner ensured that each participant was positioned with his or her back and head against the

backboard of the standometer (CDC, 2015a). With the participant in place, the examiners lowered the headpiece along the measurement column until it rested on the top of the participant's head. The examiners would then recorded the height value into the computer-based survey information system. As an added measure to minimize variability, all measurement examination rooms within the MECs were designed to be identical. Also, all equipment used to collect body measurements were calibrated regularly by technicians and confirmed by supervisors. Trained health technicians obtained blood sample collections from participants while they visited the MEC in order to obtain CRP data. All blood samples obtained from participants were processed, stored, and shipped to the University of Washington in Seattle, WA using quality control and assurance procedures that meet the requirements of 1988 Clinical Laboratory Improvement Act (CDC, 2015a).

Operationalization of Study Variables

Independent Variable

The independent variable for this study was total daily flavonoid intake, measured as the total amount of flavonoids consumed per day. I calculated the total flavonoid intake of each study participant by averaging the flavonoid content of the foods reported in two non-consecutive 24-hour dietary recalls by participants of the 2007-2010 NHANES. For this study, the total daily flavonoid intake was measured as a continuous interval variable. Adjusting flavonoid intake by total energy intake in regression models yields more accurate results when conducting epidemiologic analysis related to disease outcomes (Willett, Howe, & Kushi. 1997). Nutrient intake among people tends to be

correlated with their overall caloric intake (Willett & Stamphfer, 1986). By adjusting for total energy intake, flavonoid intake can be interpreted as a function of dietary composition and constituency rather than that of total caloric intake. Therefore, I adjusted all values for total flavonoid intake used for regression analysis in this study for total energy intake using the residual method (Willett & Stamphfer, 1986). Total energy intake was defined as the total daily caloric intake for all participants measured in kilocalories (kcal). The residual method entailed calculating the total energy-adjusted flavonoid intake values as the residual values obtained from a logistic regression model with total energy intake and total flavonoid intake as the independent and dependent variables, respectively.

I obtained the flavonoid values of foods reported by each participant in this study from the USDA Flavonoid Intake Data Files (FIDFs), which corresponds to the dietary component of the 2007-2010 NHANES (USDA, 2016). The USDA compiled the FIDFs by applying expanded analytical flavonoid values from the DFCSF, Release 3.2 and DICSF, Release 2.1 to the self-reported 24-hour dietary recall information from the 2007-2010 NHANES (Sebastian, Enns, Goldman, Steinfeldt, Martin, & Moshfegh, 2016). The DFCSF, Release 3.2 and DICSF, Release 2.1 were the most recent versions of the flavonoid databases with expanded analytical values that were the most comprehensive source of flavonoid data available at the time of the present study. The expanded USDA flavonoid databases provide the flavonoid content for 2,926 specific foods and identify those foods using a nutrient databank (NDB) number (USDA, 2016). The USDA used the Food and Nutrient Database for Dietary Studies (FNDDS) revision 4.1 and 5.0 to link the

codes from the USDA flavonoid databases and the 24-hour dietary recalls for the 2007-2008 and 2009-2010 NHANES iterations, respectively (Sebastian, Enns, Goldman, Steinfeldt, Martin, & Moshfegh, 2016). The USDA took this approach because the food codes from the NHANES 24-hour dietary recalls and NDB numbers referenced in the USDA flavonoid databases differ. The USDA FNDDS was used because it contains a translation table linking the food codes from the NHANES with the corresponding NDB numbers referenced in the USDA flavonoid databases (USDA, 2014). Each revision of the FNDDS corresponds directly to the dietary intake component of a specific iteration of the NHANES (USDA, 2014). Specifically, the FNDDS revision 4.1 corresponds to the 2007-2008 NHANES and the FNDDS revision 5.0 corresponds to the 2009-2010 NHANES. Ultimately, the FIDFs provided the total daily flavonoid intake for each 24-hour dietary recall for each participant who reported dietary data in the 2007-2010 NHANES. The combination of the FIDFs and the NHANES datasets enabled the calculation of average total daily flavonoid intake for this study.

Dependent Variables

The dependent variables for these analyses include COPD, FEV_1% predicted, CRP, and Comorbidity burden. These variables represent COPD diagnosis, COPD severity, systemic inflammation, and the accumulation of inflammation-related comorbid diseases. Table 1 provides a description of the measurement characteristics of these variables.

Table 1

Dependent Variable Characteristics

Variable name	Level of measurement
Comorbidity burden	Ordinal
COPD	Dichotomous
FEV1% predicted	Interval
CRP	Interval

COPD Diagnosis. To minimize misclassification error due to potential recall bias, I decided that the diagnosis of COPD would be defined by spirometry measurements instead of participant self-reporting. Therefore, I defined the diagnosis of COPD for this study as having a post-bronchodilator FEV_1/FVC ratio of < 70%, according to GOLD (2015) guidelines. Participants with a pre-bronchodilator or post-bronchodilator FEV_1/FVC ratio of ≥70% were noted as not having COPD.

COPD Severity. I defined COPD severity as the FEV_1% percentage of the predicted normal FEV_1 using individual post-bronchodilator spirometry results obtained in the 2007-2010 NHANES, converted from milliliters to liters. FEV_1% predicted values were used in this study as an indicator of COPD severity because there are gradual declines in FEV_1 among COPD patients prior to reaching the threshold for inclusion in each COPD severity stage, as specified by the GOLD criteria (Lange et al., 2015; Tantucci & Modina, 2012). Therefore, FEV_1% predicted values were treated as continuous interval measurements for all relevant analyses instead of being categorized into stages of severity. As such, the statistical precision for addressing RQ2 increased by accounting for incremental changes in FEV_1% predicted.

Systemic inflammation. I used serum CRP values as a measure of systemic inflammation among the COPD population. In this regard, CRP served as an indicator for the mechanism of action between flavonoid intake and COPD. CRP values were obtained from laboratory testing of blood samples obtained from participants in the 2007-2010 NHANES. The lower limit of detectability for serum CRP was 0.02 ng/mL. Any test results that were obtained below this detectable limit were assigned a notional value, which was reported as the detection limit divided by the square root of two (CDC, 2015b; CDC, 2015c). By dividing the limit of detection by the square root of two, laboratory technicians were able to provide an estimate of the undetectable value, which lies between zero and the detectible limit (Hornung & Reeed, 1990). Assigning a notional value for CRP results below the detectable limit avoided the need to assign a zero value or omit these data points. If undetectable data points are assigned a zero value or omitted, then the mean for CRP concentrations can be skewed too high. Therefore, to improve the accuracy of the overall results for the sample population, the NHANES technicians applied the notional value to CRP results below the detectable limit (CDC, 2015b; CDC, 2015c; Hornung & Reeed, 1990). In general, the normal range for adult serum CRP level is < 10 mg/L, with results above this threshold indicating a serious acute infection or trauma (Pearson et al., 2003; Shivappa et al., 2014). For the purposes of the current study, CRP was analyzed as a continuous interval variable.

Comorbidity. I defined the comorbidity burden of participants in the 2007-2010 NHANES with COPD as the number of concurrent self-reports of cardiovascular disease, diabetes, and hypertension. The determination of whether or not participants had

cardiovascular disease was made based on responses to three questions found within the NHANES. The first question asked, "Has a doctor or other health professional ever told you that you had a stroke?" The second question asked, "Has a doctor or other health professional ever told you that you had a heart attack?" The third question asked, "Has a doctor or other health professional ever told you that you had congestive heart failure?" Participants who responded positively to at least one of these questions were noted as having cardiovascular disease. Participants who responded negatively to all three questions were noted as not having cardiovascular disease. The self-report of diabetes was based on the affirmative or negative response to the NHANES interview question that asked, "Have you ever been told by a doctor or other health professional that you had diabetes or sugar diabetes?" Likewise, the self-report of hypertension was determined based on an affirmative or negative response to the NHANES interview question that asked, "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?" I created a comorbid disease burden score specifically for this study by summing the number of systemic inflammation-related comorbid diseases for each participant in the COPD population.

Covariates

Covariates recognized as potential confounders according to research findings included age, annual income group, BMI, dietary fiber intake, education level, gender, race/ethnicity, and smoking status (ALA, 2014; Beiko et al., 2015; Eisner et al., 2009; Fonseca Wald et al., 2014; Hooper et al., 2012; Marott & Lange, 2013; Pistelli et al.

2012; Sebastian, Enns, Goldman, Steinfeldt, & Moshfegh, 2016; Zhou et al., 2013). Table 2 provides a description of the characteristics of these variables.

Table 2

Covariate Characteristics

Variable name	Level of measurement
Age	Interval
Annual income group	Nominal
BMI	Interval
Dietary fiber intake	Interval
Education level	Nominal
Gender	Nominal, Dichotomous
Race/ethnicity	Nominal
Smoking status	Nominal

The variable for age was defined by NHANES researchers as the age of a participant at screening during the 2007-2010 NHANES and consisted of age values ranging from 30 to 80. The age value of 80 represents participants who were ≥ 80 years old at the time of screening. The individual age of participants who were ≥ 80 years old was not reported in the 2007-2010 NHANES, as this would introduce an identification disclosure risk (CDC, 2015b; CDC, 2015c). Annual income group was defined as self-reported annual household income reported categorically because these data were collected as such in the 2007-2010 NHANES. Therefore, annual income group consisted of reported income that corresponded to one of 15 income categories that consist of $0-$4,999, $5,000-$9,999, $10,000-$14,999, $15,000-$19,999, under $20,000, over $20,000, $20,000-$24,999, $25,000-$34,999, $35,000-$44,999, $45,000-$54,999, $55,000-$64,999, $65,000-$74,999, $75,000-$99,999, and $100,000 and over. BMI was calculated in units of kg/m^2 based on the height and weight measurements for all

participants. Dietary fiber intake was defined by NHANES researchers as the dietary fiber intake for all participants measured in grams per day. I adjusted all values for dietary fiber used for regression analyses in this study for total energy intake using the residual method (Willett & Stamphfer, 1986). Total energy intake was defined by NHANES researchers as the total daily caloric intake for all participants measured in kilocalories (kcal).

NHANES researchers defined education level as the highest grade or level of school a participant reported based on their response to the NHANES survey question that asked, "What is the highest grade or level of school you have completed or the highest degree you have received?" The categories for education level included "less than 9^{th} grade," "9^{th}-11^{th} grades," "high school grad/GED or equivalent," "some college or AA degree," and "college graduate or above." Gender had a binary value and was defined as either "male" or "female."

NHANES researchers defined race/ethnicity as participants reporting themselves to be Mexican American, other Hispanic, non-Hispanic White, Non-Hispanic Black, or other race/multiracial. Variables for race and ethnicity were not provided separately within the NHANES dataset. Instead, only one variable for combined race and ethnicity was made available within the NHANES datasets based on participants' self-reported race and ethnicity. Participants who identified themselves as "Mexican American" were categorized as such regardless of their other racial identities (CDC, 2015b; CDC, 2015c). Participants who otherwise identified themselves as "Hispanic" ethnicity were categorized as "other Hispanic" (CDC, 2015b; CDC, 2015c). All other non-Hispanic

people were categorized according to their self-identified races, which included "non-Hispanic White," "Non-Hispanic Black," or "other race/multiracial" (CDC, 2015b; CDC, 2015c). For this study, the categories of "Mexican American" and "other Hispanic" were combined into a single category labeled as "Mexican or Hispanic" to align with the racial categories used to determine FEV_1% predicted values (Hankison et al., 1999).

I created three categories for smoking status, which include "nonsmoker," "current smoker," and "former smoker." Participants were assigned to a smoking status category based on their responses to two survey questions. The first question asked, "Have you smoked at least 100 cigarettes in your entire life?" The second question asked, "Do you now smoke cigarettes?" I defined nonsmokers as participants who smoked fewer than 100 cigarettes throughout their lifetime. Current smokers were defined as those participants who have smoked at least 100 cigarettes in their lifetime and currently smoke every day or some days. Former smokers were defined as those participants who smoked at least 100 cigarettes throughout their lifetime and did not currently smoke at all.

Statistical Analysis

I performed all analyses for this study using the statistical package for social sciences (SPSS) version 21. I extracted and organized the data used in this study appropriately to create a complete dataset that included all variables required for analysis. Subsequently, I assessed the final dataset to ensure that all assumptions were met for each statistical procedure utilized to test the study hypotheses. These assumptions are discussed in more detail in Chapter 4.

Dataset preparation

The initial step in preparing the dataset required me to the download and extraction of the data files for all relevant variables from the 2007-2010 NHANES. I generated frequencies for all variables in the study to ensure the correct number of records was successfully obtained for each variable. The data for all study variables were reviewed to identify values that required recoding, such as those indicating a participant refused to answer a question, had missing data, did not know the answer. All values indicating a participant refused to answer the question or didn't know the answer were recoded as missing data. To confirm that the appropriate values were recoded, I generated frequencies again for all variables and compared them to the original NHANES data codebook to ensure the final record counts were accurate.

Data preparation for the independent variable, total daily flavonoid intake, initially entailed downloading the FIDFs from the USDA website. The FIDFs included a separate file for each 24-hour recall and I imported both files into SPSS. Next, I used SPSS to compute the mean of two total daily flavonoid intake observations from both 24-hour dietary recalls. Subsequently, I adjusted the average total daily flavonoid intake values to account for total energy intake using the residual method (Willett & Stamphfer, 1986). Adjustment for total energy intake involved performing a linear regression with total energy intake as the independent variable and the average total daily flavonoid intake as the dependent variable. I saved the residual values from this linear regression in SPSS as the new energy-adjusted total daily flavonoid intake values. The residuals had a mean of zero and contain negative values. Therefore, I added a constant to the residuals

to removed negative values and a natural log transformation was performed to improve normality in accordance with the residual method (Willett & Stamphfer, 1986).

Likewise, I created the dietary fiber intake variable in SPSS by averaging the dietary fiber intakes from both 24-hour dietary recalls. Subsequently, I adjusted the average dietary fiber intake values for total dietary intake using the residual method. Specifically, a linear regression was performed using total energy intake as the independent variable and dietary fiber intake as the dependent variable. I saved the residuals from this regression in SPSS as the energy-adjusted dietary fiber intake values. As with total daily flavonoid intake, I added a constant to the residuals to removed negative values. Subsequently, I performed a natural log transformation of the residual values to improve normality of the distribution.

I created the dependent study variable, COPD, in SPSS by coding the FEV_1/FVC ratio values to reflect a diagnosis of COPD or not, according to the spirometric definition provided earlier. The dichotomous COPD variable was coded as "0" to indicate that a participant did not have COPD and "1" to indicate a participant had COPD. Upon creation of the new variable, I generated frequencies to ensure the correct number of records was available.

I combined three separate dichotomous variables to create the dependent variable for comorbidity burden. These three variables include cardiovascular disease, diabetes, and hypertension. Using SPSS, I summed the values for all three self-reported diseases to create a composite score for comorbidity burden for each participant. The composite score consisted of values ranging from "0" to "3." Each score corresponded to the

number of comorbid diseases a participant had. A value of "0" indicate no comorbid disease was reported while a value of "1" indicates only one comorbid disease was reported. Likewise, a value of "2" indicates two comorbid diseases were reported and a value of "3" indicates all three comorbid diseases were reported. I categorized and labeled the composite scores as comorbidity burden level categories in SPSS. Scores of "0" and "1" were labeled as comorbidity burden "Level 0" and "Level 1" in SPSS, respectively. Those participants with a score of "3" were combined into the same category as those with a score of "2" because there were very few participants with scores of "3". Therefore, the final combined category was labeled as comorbidity burden "Level 2 and 3" in SPSS.

I computed the dependent variable for COPD severity, FEV_1% predicted, by exporting all relevant variables for all patients with COPD from SPSS into an Excel spreadsheet. The variables included gender, age, race, height, and post-bronchodilator FEV_1. These characteristics were used to identify the FEV_1 for a person with comparable characteristics who does not have COPD. I calculated the FEV_1% predicted value by dividing the FEV_1 value by the predicted normal FEV_1 reference value for a person of similar age, gender, race, and height (Hankinson, Odencrantz, & Fedan, 1999). The normal FEV_1 reference values used as the denominator in COPD severity calculations were established using spirometric testing results from healthy participants in the NHANES 1988-1994 (Hankinson et al., 1999). I imported the FEV_1% predicted values into SPSS from Excel as the new continuous variable labeled FEV_1% predicted.

Descriptive Analysis

I provide a summary and review of the data in Chapter 4 using descriptive statistics to characterize the sample population. I generated frequencies for all categorical variables, including annual income group, cardiovascular disease, COPD, diabetes, education, gender, hypertension, race/ethnicity, and smoking status. I also generated measures of central tendency and dispersion for all continuous variables, including age, FEV_1% predicted, CRP, dietary fiber intake, and total daily flavonoid intake. These descriptive statistics serve to describe the basic features of the data in this study. I evaluated the symmetry of the distributions for continuous data to determine if they were normally distributed. Variables that failed to meet assumptions of normality for a given statistical procedure are discussed in further detail in Chapter 4.

Bivariate Analysis

I conducted bivariate analyses to test for associations between all individual variables. These bivariate analyses enabled the assessment of potential associations between variables that may impact statistical analyses. The outcome of these bivariate analyses determined which variables were relevant potential confounding variables to be included in multivariate analyses. Specifically, only those potential confounding variables found to have a statistically significant association with both the independent and dependent variables, defined as having a *p*-value of $< .15$, were included in multivariate analyses. Table 3 shows all bivariate statistical tests used to analyze possible associations between the dependent variables and potential confounding variables.

Likewise, Table 4 shows all bivariate statistical tests used to analyze possible associations between the independent variable and potential confounders.

Table 3

Statistical Tests for Dependent and Potentially Confounding Variables

Dependent variable		Comparison variable		
Name	Level of measurement	Name	Level of measurement	Statistical test
COPD	Dichotomous	Age	Interval	Independent *t* test
		Annual income group	Nominal	Chi-square
		BMI	Nominal	Chi-square
		Education level	Nominal	Chi-square
		Dietary fiber intake	Interval	Independent *t* test
		Gender	Dichotomous	Chi-square
		Race/ethnicity	Nominal	Chi-square
		Smoking status	Nominal	Chi-square
FEV_1% predicted	Interval	Age	Interval	Pearson correlation
		Annual income group	Nominal	One-way ANOVA
		BMI	Interval	Pearson correlation
		Dietary fiber intake	Interval	Pearson correlation
		Education level	Nominal	One-way ANOVA
		Gender	Dichotomous	Independent *t* test
		Race/ethnicity	Nominal	One-way ANOVA
		Smoking status	Nominal	One-way ANOVA
Comorbidity burden	Ordinal	Age	Interval	Spearman correlation
		Annual income group	Nominal	Chi-square
		BMI	Interval	Spearman correlation
		Dietary fiber intake	Interval	Spearman correlation
		Education level	Nominal	Chi-square
		Gender	Dichotomous	Chi-square
		Race/ethnicity	Nominal	Chi-square
		Smoking status	Nominal	Chi-square
CRP	Interval	Age	Interval	Pearson correlation
		Annual income group	Nominal	One-way ANOVA
		BMI	Interval	Pearson correlation
		Dietary fiber intake	Interval	Pearson correlation
		Education level	Nominal	One-way ANOVA
		Gender	Dichotomous	Independent *t* test
		Race/ethnicity	Nominal	One-way ANOVA
		Smoking status	Nominal	One-way ANOVA

Table 4

Statistical Tests for Independent and Potentially Confounding Variables

Variable		Comparison variable		
Name	Level of measurement	Name	Level of measurement	Statistical test
Flavonoid intake	Interval	Age	Interval	Pearson correlation
		Annual income group	Nominal	One-way ANOVA
		BMI	Interval	Pearson correlation
		Dietary fiber intake	Interval	Pearson correlation
		Education level	Nominal	One-way ANOVA
		Gender	Dichotomous	Independent *t* test
		Race/ethnicity	Nominal	One-way ANOVA
		Smoking status	Nominal	One-way ANOVA

Analysis of Research Questions and Hypotheses

The statistical analyses utilized to test the hypotheses associated with the study research questions are described below. Study analyses were restricted to only those participants from whom spirometry values and two dietary recalls were obtained. Study procedures were selected according to the level of measurement for each of the variables included.

The first study research question and associated null and alternative hypotheses for this study included:

RQ1. What is the relationship between total daily flavonoid intake and COPD among adults?

$H_0$1**:** There is no statistically significant association between total daily flavonoid intake and spirometry-diagnosed COPD among adult participants of the 2007–2010 NHANES, after adjusting for relevant confounders.

$H_1$1**:** There is a statistically significant association between total daily flavonoid intake and spirometry-diagnosed COPD among adult participants of the 2007–2010 NHANES, after adjusting for relevant confounders.

Two logistic regression models were used to test the null hypothesis for this research question. The first model consisted of a simple unadjusted logistic regression analysis between total daily flavonoid intake and COPD. The second model entailed utilizing a multiple logistic regression with total daily flavonoid intake and all relevant confounders as covariate predictors of COPD. Relevant confounding variables selected for inclusion in multivariate analysis were identified using bivariate analyses. Results from the multivariate analyses were interpreted according to *p*-values, odds ratios, and corresponding confidence intervals.

The second study research question and associated null and alternative hypotheses for this study included:

RQ2. What is the relationship between total daily flavonoid intake and COPD severity among adults?

$H_0$2: There is no statistically significant association between total daily flavonoid intake and FEV_1% predicted among adult participants of the 2007–2010 NHANES, after adjusting for relevant confounders.

$H_1$2: There is a statistically significant association between total daily flavonoid intake and FEV_1% predicted among adult participants of the 2007–2010 NHANES, after adjusting for relevant confounders.

Two linear regression models were used to test the null hypothesis for this research question. The first model consisted of a simple linear regression to analyze the potential association between total daily flavonoid intake and FEV_1% predicted. The second model consisted of a multivariate linear regression that included total daily flavonoid intake as the independent variable and all relevant confounders as covariate predictors of FEV_1% predicted. Relevant confounding variables selected for inclusion in multivariate analysis were identified using bivariate analyses. Results from the multivariate analyses were interpreted according to *p*-values, odds ratios, and corresponding confidence intervals.

The third study research question and test hypotheses that were explored in this study included:

RQ3. What is the relationship between total daily flavonoid intake and Systemic inflammation among adults with COPD?

$H_0$3: There is no statistically significant association between total daily flavonoid intake and the CRP serum levels among adult participants of the 2007–2010 NHANES with COPD, after adjusting for relevant confounders.

$H_1$3**:** There is a statistically significant association between total daily flavonoid intake and the CRP serum levels among adult participants of the 2007–2010 NHANES with COPD, after adjusting for relevant confounders.

Two linear regression models were utilized to test the null hypothesis for this research question. The first model consisted of a simple linear regression with total daily flavonoid intake and CRP. The second model consisted of a multiple linear regression

that included total daily flavonoid intake and all relevant confounders as covariate predictors of CRP. Relevant confounding variables selected for inclusion in multivariate analysis were identified using bivariate analyses. Results from the multivariate analyses were interpreted according to β-values, *p*-values, and corresponding confidence intervals.

The fourth study research question and test hypotheses that were explored in this study included:

RQ4. What is the relationship between total daily flavonoid intake and comorbidity burden among adults with COPD?

$H_0$4: There is no statistically significant association between total daily flavonoid intake and comorbidity burden among adult participants of the 2007–2010 NHANES with COPD, after adjusting for relevant confounders.

$H_1$4: There is a statistically significant association between total daily flavonoid intake and comorbidity burden among adult participants of the 2007–2010 NHANES with COPD, after adjusting for relevant confounders.

I planned to use two ordinal logistic regression models to test the null hypothesis for this research question. The first model entailed utilizing a simple ordinal logistic regression to test the association of the total daily flavonoid intake and comorbidity burden. The second model consisted of utilizing a multiple ordinal logistic regression with total daily flavonoid intake as the independent variable along with all relevant confounders as covariates predictors of comorbidity burden. Relevant confounding variables selected for inclusion in multivariate analysis were identified using bivariate analyses. Results from the multivariate analyses were to be interpreted according to β-values, *p*-values, and

corresponding confidence intervals. However, due to sample size limitations among the subset of participants who had COPD, the use of logistic regression was not possible as compared with RQ1. The scope of RQ1 included all participants in analysis dataset. However, the scope of RQ4 was limited to testing the association between total daily flavonoid intake and comorbidity burden only among the subset of participants with a COPD diagnosis. As such, there were an insufficient number of participants with COPD to achieve the desired statistical power to detect an odds ratio of 0.7-1.3, as described earlier. Therefore, I treated the variable for comorbidity burden as a nominal variable and tested the null hypothesis for this research question using a one-way ANOVA to explore the association with total daily flavonoid intake. Although a one-way ANOVA would not provide information on the predictive relationship between total daily flavonoid intake and comorbidity burden, this statistical procedure did provide insight into the differences in total daily flavonoid intake across different comorbidity burden levels. Specifically, I performed the one-way ANOVA to determine whether any statistically significant differences were present between the total daily flavonoid intake means for each comorbidity burden group (Level 0, Level 1, and Level 2 and 3). The one-way ANOVA is an omnibus test and cannot indicate which group means are significantly different from each other. Therefore, I performed a Games-Howell post hoc analysis to identify the specific comorbidity burden level groups with significantly different means for total daily flavonoid intake.

Threats to Validity

The most significant threat to validity for this study was the limitation of the 24-hour dietary recall to provide long-term dietary habits for each participant. While the 24-hour dietary recall provides only short-term information, multiple administrations of 24-hour dietary recalls are able to provide more accurate estimates of long-term dietary habits as compared to the FFQ (Carroll et al., 2012; Freedman, Schatzkin, Midthune, & Kipnis, 2011; Schatzkin et al., 2003; Shim, Oh, & Kim, 2014). Therefore, a key assumption for this study was that the participants' current diet was reflective of long-term dietary habits for fruit and vegetable intake spanning several decades. This assumption was supported by a study analyzing the changes in intake of fruits and vegetables and weight change among U.S. men and women participating in three prospective cohort studies who were followed for up to 24 years (Bertoia et al., 2015). Among 289,916 participants aged 25-75 the intake of fruits and vegetables from 1986 to 2010 remained relatively constant with minor changes exceeding no more than 0.1 and 0.2 servings per day of fruit and vegetables, respectively (Bertoia et al., 2015). Therefore, it was anticipated that the reported dietary intake based on the average of two 24-hour dietary recalls was sufficient to estimate long-term dietary habits with regard to fruit and vegetable intake.

Another limitation linked to the use of the 24-hour recall for this study was the limited ability to fully account for day-to-day or seasonal variation in dietary intake for each participant. In particular, data obtained from a single 24-hour recall cannot fully account for individual variations, and intake is usually shown to have a lower distribution

slope, as participants with true low intakes may report higher intake and the inverse may apply for those with true high intakes (Ramachandran, 2006). Statistical methods, such as the Iowa State University (ISU) adjustment procedure and the ISU food (ISUF) method, have been proposed to estimate the usual intake distribution from multiple 24-hour recalls (Guenther, Kott, & Carriquiry, 1997; Nusser, Carriquiry, Dodd, & Fuller, 1996; Nusser, Fuller, W. A., & Guenther, 1995). The basic aim of these methods is to estimate usual intake distribution for a group by partitioning total variation present in 24-hour recall data into within-person and between-person components and estimating usual intake distribution by accounting for within-person variation. However, estimates of usual individual intake derived from only two 24-hour recalls can be unreliable when using the ISU and ISUF statistical methods (Carriquiry, 2003; Dodd et al., 2006). For example, using aforementioned methods with only two 24-hour recalls would yield three possible consumption probabilities consisting of zero, one-half, and one, which would not provide a smooth distribution of expected intake probabilities (Dodd et al., 2006). Also, while the intermediary values calculated using these statistical procedures are derived from the means of each individual, the intermediary values are not appropriate estimates of usual individual intake (Dodd et al., 2006). Specifically, the intermediary values are solely used for describing the distribution of usual intake for the overall sample (Dodd et al., 2006). Therefore, the ISU and ISUF statistical methods were not appropriate for this study. This study required measures of food items reported by each individual in order to determine flavonoid intake for each participant. As such, using the average of the dietary information from two 24-hour recalls for each individual in this study was considered to

be the most practical approach. However, it is acknowledged that utilizing data from two 24-hour recalls from the 2007-2010 NHANES cannot fully account for the within-individual variation for dietary intake.

Another potential threat to validity was recall bias because the data for key variables, such as total daily flavonoid intake and comorbid diseases, were reliant upon participant self-report. However, recall bias among participants was minimized for the independent variable given the short 24-hour period for recall, which is found to produce data that are far more accurate than long-term recall periods (Carroll et al., 2012; Freedman et al., 2011). Also, recall bias was further minimized through the use of two non-consecutive 24-hour dietary recalls, which has been demonstrated to improve recall accuracy exceeding that which is achieved by the FFQ (Carroll et al., 2012; Freedman et al., 2011; Schatzkin et al., 2003). Recall bias related to participant self-reporting of comorbid diseases was expected to be minimal and with no impact to study results. Specifically, research has demonstrated that self-reporting diagnoses of COPD, cardiovascular disease, diabetes, and hypertension have proven to be accurate reflections of true diagnoses as confirmed by medical records (Barr, Herbstman, Speizer, & Camargo, 2002; Okura, Urban, Mahoney, Jacobsen, & Rodeheffer, 2004; Schneider, Pankow, Heiss, & Selvin, 2012; Van der Heyden, De Bacquer, Tafforeau, & Van Herck, 2014). Therefore, recall bias was not anticipated to contribute to misclassification of comorbid diseases.

Temporal bias can also pose a threat to validity in cross-sectional studies. Temporal bias occurs when researchers incorrectly infer the sequence of occurrence for

an exposure versus an outcome (Szklo & Nieto, 2014). A major limitation of cross-sectional studies is the inability to establish causation, given the measurement of data at only one point in time (Szklo & Nieto, 2014). In this study, it was not be possible to determine if flavonoid intake caused COPD outcomes or if COPD outcomes caused changes in flavonoid intake. Therefore, the aim of this study was to identify any potential associations between independent and dependent variables rather than demonstrating causation through temporal inferences.

Another threat to validity was the selection of a study sample that was not representative of the population of interest. The external validity of a study is threatened if the characteristics of the subjects included in the study are not reflective of the population being investigated (Frankfort-Nachmias & Nachmias, 2008). Specifically, a study lacking a representative sample will produce results that are specific only to the study sample and cannot be generalized to the broader population. As described earlier, the sample for this study was obtained using a complex, multistage, probability-sampling design to ensure it was representative of the national population of the United States (CDC, 2013b). Based on the sampling design for this study, the results were expected to be generalizable to the U.S. population. To ensure that this assumption held true, the demographics of the final study sample were compared to the broader U.S. population. The results of this assessment are provided in Chapter 4.

Ethical Considerations

There were no ethical concerns related to participant recruitment and data collection for this study. The NHANES datasets are freely available for public access, as

personal identifiers have been removed, and it is not possible to identify a participant by combining various parts of the data. Furthermore, the CDC adheres to all data privacy and confidentiality laws for the storage and protection of NHANES participant data. Such laws include the Public Health Service Act (42 USC 242k) and Section 308(d) of that law (42 USC 242m), the Privacy Act of 1974 (5 USC 552A), and the Confidential Information Protection and Statistical Efficiency Act (PL 107-347; CDC, 2015a). This study did not require the use of confidential or private participant data, and no additional sources were used in combination with NHANES data that could identify a specific participant.

To further ensure the ethical conduct of this study, this research did not proceed before review and approval by the Walden University Institutional Review Board. The data used in this study will be maintained for at least 5 years following completion of the study. To ensure the security of the study data, all data files were stored in a password-protected online cloud-based storage server.

Summary and Conclusions

A cross-sectional study design supported the examination of associations between flavonoid intake and COPD-related outcomes. I used dietary, socioeconomic, demographic, and diagnostic data from the 2007-2010 NHANES and flavonoid data from the USDA to assess the previously mentioned associations among study participants from these iterations of the NHANES. The data collection instruments and methods of administration used in the collection of data during the 2007-2010 NHANES minimized potential threats to validity.

In Chapter 4, I provide an overview of the study results. I will also characterize the study population and data using descriptive statistics. Additionally, I will describe the statistical analyses conducted to address each the hypotheses for each research question and present the relevant findings.

Chapter 4: Results

The purpose of this study was to explore the potential association between total daily flavonoid intake and COPD, COPD severity, systemic inflammation, and comorbidity burden among U.S. adults aged 30 years and older. This chapter includes the results from the statistical analyses of data from the 2007–2010 NHANES and the USDA Flavonoid Databases that I used to address the study research questions. As such, the chapter includes a description of the methods I used to create the final study dataset, the rationale for the manipulations and modifications I made to the data, an overview of descriptive statistics for study cases, and a review of findings from bivariate analyses and multivariate analyses. This chapter ends with a summary of statistical results related to each research question.

The initial study design included participant self-reported diagnosis of COPD and COPD severity categorized into stages according to the GOLD criteria. However, I changed the study design to include a spirometry diagnosis of COPD to classify participants as having COPD or not, because diagnostic measures are more reliable than participant recall. Additionally, COPD severity changed from a categorical measure of the percentage of the predicted FEV_1 value (FEV_1% predicted) to a continuous measure of FEV_1% predicted. Given the modifications to the operational definition of the study variable for COPD and COPD severity, it was necessary to slightly update the research questions and associated hypotheses accordingly. The research questions and hypotheses for the statistical analyses for this study were as follows:

RQ1: What is the relationship between total daily flavonoid intake and COPD among adults?

$H_0$1: There is no statistically significant association between total daily flavonoid intake and spirometry-diagnosed COPD among adult participants of the 2007–2010 NHANES after adjusting for relevant confounders.

$H_1$1: There is a statistically significant association between total daily flavonoid intake and spirometry-diagnosed COPD among adult participants of the 2007–2010 NHANES after adjusting for relevant confounders.

RQ2: What is the relationship between total daily flavonoid intake and COPD severity among adults?

$H_0$2: There is no statistically significant association between total daily flavonoid intake and FEV_1 percent predicted among adult participants of the 2007–2010 NHANES after adjusting for relevant confounders.

$H_1$2: There is a statistically significant association between total daily flavonoid intake and FEV_1 percent predicted among adult participants of the 2007–2010 NHANES after adjusting for relevant confounders.

RQ3: What is the relationship between total daily flavonoid intake and systemic inflammation among adults with COPD?

$H_0$3: There is no statistically significant association between total daily flavonoid intake and the CRP serum levels among adult participants of the 2007–2010 NHANES with COPD after adjusting for relevant confounders.

$H_1$3: There is a statistically significant association between total daily flavonoid intake and the CRP serum levels among adult participants of the 2007–2010 NHANES with COPD after adjusting for relevant confounders.

RQ4: What is the relationship between total daily flavonoid intake and comorbidity burden among adults with COPD?

H_Ω4: There is no statistically significant association between total daily flavonoid intake and comorbidity burden among adult participants of the 2007–2010 NHANES with COPD after adjusting for relevant confounders.

$H_1$4: There is a statistically significant association between total daily flavonoid intake and comorbidity burden among adult participants of the 2007–2010 NHANES with COPD after adjusting for relevant confounders.

Dataset Preparation

This study received approval from the Walden University IRB (#10-04-16-0370817) prior to the collection of any data for analysis. Following IRB approval, I he downloaded and compiled datasets from the 2007-2010 NHANES. Obtaining the flavonoid intake data involved downloading the publicly available USDA FIDFs for the dietary component of the 2007–2010 NHANES (USDA, 2016). Analysts at the USDA compiled these intake files using the methods outlined in Chapter 3, which entailed applying the flavonoid values found in the flavonoid databases to the participant self-reported 24-hour dietary recall information from the 2007–2010 NHANES. The flavonoid intake data from the USDA FIDFs and the prepared 2007–2010 NHANES dataset formed a complete dataset for the study, as described in Chapter 3.

The initial combined 2007-2010 NHANES study dataset included 20,686 participants, which consisted of 10,149 from the 2007-2008 NHANES dataset and 10,537 from the 2009-2010 NHANES dataset. As shown in Figure 2, my removal of cases according to the exclusion criteria for this study reduced the study sample size to 5,172 to address RQ1. The sample was further restricted to 5.2% of participants (n = 270) who had a spirometry-confirmed diagnosis of COPD to address RQ2, RQ3, and RQ4.

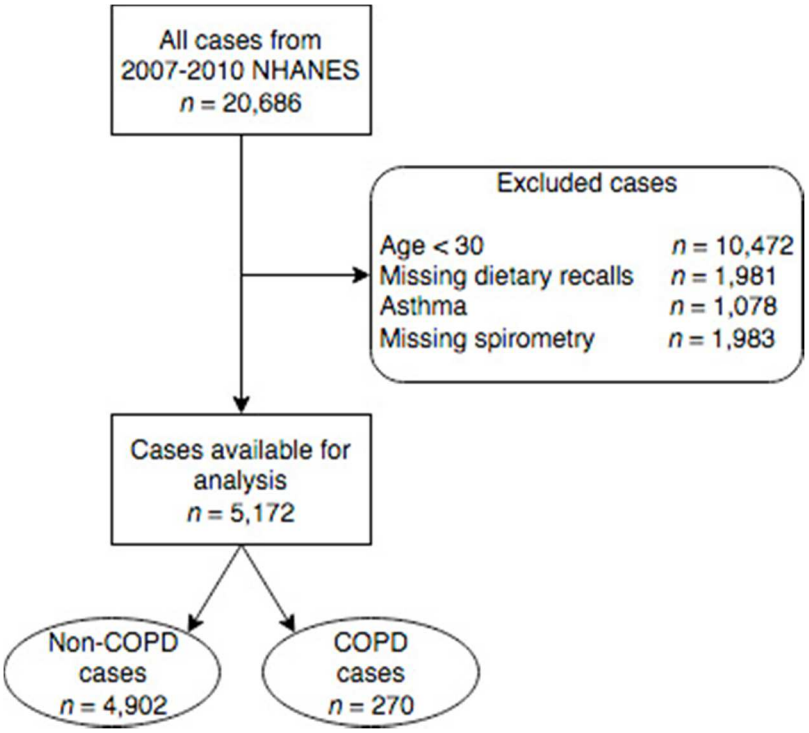

Figure 2. Cases available for analysis after applying exclusion criteria.

Adjustments to Study Data

I made several adjustments to the dataset after it was downloaded and reviewed. These changes included redefining COPD diagnosis, transforming the CRP variable, and removing annual income from study analyses. These adjustments were necessary to

minimize potential misclassification, meet statistical assumptions, and address missing data.

For this study, I initially defined the diagnosis of COPD as a self-reporting of COPD by participants. However, the diagnosis of COPD based on diagnostic measures, such as spirometry, is more accurate than self-reported data because self-reported diagnoses often result in underreporting COPD (Murgia et al., 2014; Rycroft, Heyes, Lanza, & Becker, 2012). A cross-tabulation of the study dataset with participant self-reported COPD against COPD diagnoses based on spirometry showed that 169 participants incorrectly self-reported that they had COPD when they did not, and 251 participants incorrectly self-reported that they did not have COPD when they did. Therefore, I changed the definition of COPD diagnosis for this study from participant self-reporting of COPD diagnosis to spirometry-diagnosed COPD to strengthen the internal validity of the study. The diagnosis of COPD in this study was based on pre- and post-bronchodilator spirometry values obtained during the 2007–2010 NHANES. Therefore, participants must have performed spirometry in order to be included in this study. Participants were classified as having COPD based on post-bronchodilator FEV_1/FVC ratio values according to the GOLD criteria, as described in Chapter 3.

The data for the CRP variable were right-skewed with steep kurtosis and did not meet the assumption of normality to address RQ3. The skewness and kurtosis values for the CRP variable were 6.25 and 46.11, respectively. Therefore, I performed a natural log transformation of the CRP variable to improve normality prior to performing linear regression analysis for RQ3. Following the natural log transformation, the normality of

the data for CRP improved considerably, with the new values for skewness and kurtosis reflected as 0.536 and 0.341, respectively.

I used a missing values analysis to assess the quantity and nature of missing values among the 5,172 cases in the dataset, which led to a determination that the variable for annual income had the highest frequency of missing data, which affected 190 cases. Because it is well documented that those with high income often do not report their annual income (Hurst & Pugsley, 2014; Moore & Welniak, 2000; Turrell, 2000), this variable could have been a source of error when conducting study analyses. My final decision was to remove the annual income group variable from the study analyses. The removal of annual income group likely did not limit the ability to incorporate the measure of socioeconomic status in multivariate analyses because the variable for education level served as a surrogate measure for annual income.

Descriptive Characteristics

I conducted univariate analyses to generate descriptive statistics for all participants in the study sample. The 4-year MEC sample weight was applied to the means and percentages for continuous and categorical variables, respectively. Most participants in this study were females (n = 2,646) and consisted of 50.9% of the study sample, while males accounted for 49.1% (n = 2,526). The average age of all participants was 49.9 (SD = 12.4) years old. Those identifying as non-Hispanic White were the largest racial segment of the study population and accounted for 72.2% (n = 2,494), followed by those identifying as Mexican or Hispanic at 12.9% (n = 1,551). Most participants were nonsmokers and accounted for 56.4% (n = 2, 863) of this group. Former smokers

consisted of 26.2% (n = 1,228) of participants, and current smokers accounted for 17.4% (n = 973).

To assess if the study sample was representative of the general non-institutionalized U.S. population, I compared the demographic proportions for the study sample against published data from the U.S. Census Bureau. While it was not possible to conduct statistical comparisons, the study sample appeared to reflect the general civilian non-institutionalized U.S. population. For example, among the general civilian non-institutionalized U.S. population, 72.4%, 12.6%, 16.3%, and 9.1%, of people identify themselves as non-Hispanic White, non-Hispanic Black, Hispanic, and other races or multiracial, respectively (U.S. Census Bureau, 2011). These proportions aligned well with those of the participants in this study, with the exception of those who identified as Hispanic and other races or multiracial. People identified as Hispanic and other races or multiracial appeared to be slightly underrepresented by approximately 4%in this study, compared to the general U.S. population. The proportion of males and females in this study was also was similar to that of the U.S. non-institutionalized civilian population, which consisted of 49.2% males and 50.8% females (U.S. Census Bureau, 2011). Likewise, the proportion of current smokers in this study was similar to that of the general U.S. population, which is 19.3% (CDC, 2012b). Within the general U.S. non-institutionalized population, the percentage of people who have attained the educational level of less than 9^{th} grade, 9^{th}-11^{th} grade, high school grad/GED or equivalent, some college or AA degree, and college graduate or above is 5.2%, 7.6%, 31.2%, 26%, and 29.9%, respectively (U.S. Census Bureau, 2011). In this study, those achieving an

education level of 9th-11th grade were overrepresented by 3.6%, while those with an education level of high school grad/GED or equivalent were underrepresented by approximately 8%. Despite slight discrepancies in education level, the proportional distributions in this study align with that of the broader U.S. population. Likewise, as shown in Table 5, the demographic parameters for the group of participants without COPD closely resembled that of the overall sample population.

The group of participants with a spirometry-confirmed diagnosis of COPD consisted of 270 participants, which reflected a prevalence of 5.2%. The COPD prevalence among participants in this study was representative of the national COPD prevalence because 5% of U.S. adults are reported to have a diagnosis of COPD (CDC, 2016). The majority of the participants with COPD were males (70.7%, $n = 200$), and females accounted for 29.3% ($n = 70$). The average age of participants in the COPD group was 58.6 ($SD = 10.7$) years old. Nonsmokers made up the minority of participants in the COPD subset at 24.8% ($n = 59$), while former smokers and current smokers accounted for the majority at 40.2% ($n = 108$) and 35.1% ($n = 103$), respectively. Table 5 includes more detailed information on the distribution of demographic variables for the COPD group.

Table 5

Demographic Data for Study Sample

Variable	All $N = 5,172$	Participant groups: Non-COPD $n = 4,902$	Participant groups: COPD $n = 270$	*p*-value
Age (years)				
Mean ± SD	49.9 ±12.4	49.4 ±12.3	58.6 ±10.7	< .001
Min-max	30-79	30-79	30-79	
BMI				
Mean ± SD	29.1 ±6.4	29.2 ±6.5	27.1 ±4.8	< .001
Min-max	13.2-81.3	14.2-81.3	13.2-46.2	
Education level (frequency [%])				< .001
Less than 9th grade	613 (5.7)	593 (5.8)	20 (3.6)	
9-11th grade	786 (11.2)	741 (11.2)	45 (11.9)	
High school grad/GED or equivalent	1174 (23)	1094 (22.6)	80 (30.2)	
Some college or AA degree	1400 (28.6)	1326 (28.6)	74 (28.7)	
College graduate or above	1192 (31.4)	1141 (31.8)	51 (25.7)	
Gender (frequency [%])				< .001
Male	2526 (49.1)	2325 (47.8)	200 (70.7)	
Female	2646 (50.9)	2576 (52.2)	70 (29.3)	
Race/Ethnicity (frequency [%])				< .001
Non-Hispanic White	2494 (72.2)	2300 (71.3)	194 (87.4)	
Non-Hispanic Black	944 (10)	905 (10.2)	39 (5.9)	
Mexican or Hispanic	1551 (12.9)	1521 (13.5)	30 (2.9)	
Other race or multiracial	183 (4.9)	176 (4.9)	7 (3.8)	
Smoking status (frequency [%])				< .001
Nonsmoker	2863 (56.4)	2804 (58.2)	59 (24.8)	
Former smoker	1336 (26.2)	1228 (25.4)	108 (40.2)	
Current smoker	973 (17.4)	870 (16.4)	103 (35.1)	

Note. Totals will vary due to missing data for some variables.

To illustrate the dietary distribution for the sample, descriptive statistics for total daily flavonoid intake and dietary fiber intake are shown in Table 6 for all participants and among those with and without COPD. Table 6 includes weighted mean intake values, standard deviation, and minimum and maximum values to demonstrate the full scope of dietary variance for all cases and among those with and without COPD. The mean daily flavonoid and dietary fiber intake for all participants in the study sample was 249.3 mg/day and 17.6 g/day, respectively. Among participants with COPD, the mean daily flavonoid and dietary fiber intake was 238.1 mg/day and 17.9 g/day. The data shown in Table 6 indicate that the flavonoid and dietary fiber intake among participants diagnosed with COPD differed significantly from participants who did not have COPD.

Table 6

Total Daily Flavonoid and Dietary Fiber Intake Data

		Participant groups		
Variable	All (N = 5,172)	Non-COPD (n =4,902)	COPD (n = 270)	p-value
Flavonoid intake (mg)				
Mean ± SD	249.3 ± 393.8	249.9 ± 395.2	238.1 ± 369.7	< .001
Min-max	.08-4938.60	.08-4938.60	1.0-4321.86	
Dietary fiber intake (g)				
Mean ± SD	17.6 ± 8.7	17.6 ± 8.7	17.9 ± 9.1	< .001
Min-max	.40-73.8	.40-73.8	2.3-64.2	

The main health outcome variables I assessed among participants with COPD included FEV_1% predicted, CRP, and comorbidity burden. Therefore, descriptive statistics were generated to assess the distribution of these data within the COPD group. Table 7 shows frequencies and weighted percentages for comorbidity burden and values for measures of distribution for FEV_1% predicted and CRP. As shown in Table 7, the

majority of participants (61.9%) in the COPD group had no comorbid diseases of interest in this study, while the rest of the participants (38.1%) in the COPD group had at least one comorbid disease.

Table 7

Comorbidity Burden, CRP, and FEV1% Predicted Data

Variable	All (N = 5,172)	Participant groups: Non-COPD (n =4,902)	Participant groups: COPD (n = 270)	p-value
Comorbidity burden (frequency [%])				< .001
Level 0	3,158 (65.5%)	3,003 (65.7%)	155 (61.9%)	
Level 1	1,437 (26.6%)	1,358 (26.4%)	79 (29.4%)	
Level 2-3	577 (7.9%)	541 (7.9%)	36 (8.6%)	
CRP (mg/dL)				
Mean ± SD	.36 ± .69	.36 ± .69	.35 ± .77	< .001
Min-max	.01-18.01	.01-18.01	.01-6.73	
FEV_1% predicted				
Mean ± SD	.90 ± .15	.94 ± .12	.87 ± .16	< .001
Min-max	.30-1.29	.5-1.29	.30-1.29	

Descriptive statistics were generated to further explore the distribution of demographic parameters across comorbidity burden levels within the COPD group. As seen in Table 8, the average age of participants within each comorbidity burden level is higher for groups with a greater number of comorbid diseases. Specifically, the mean age among participants in comorbidity burden Level 0, Level 1, and Level 2-3 was found to be 55.4, 61.5, and 71.1 years old, respectively. Additional details regarding the distribution of other demographic parameters across comorbidity burden levels are shown in Table 8. Results related to the statistical significance of associations between each outcome variable and demographic parameters are presented in a review of bivariate analyses in the following section below.

Table 8

Demographic Data Across Comorbidity Burden Levels

Variable	Comorbidity burden levels			Spearman *r*	χ2 (df)	*p*-value
	Level 0 (*n* = 155)	Level 1 (*n* = 79)	Level 2-3 (*n* = 36)			
Age (years)						
Mean ± SD	55.4 ±9.2	61.5 ±11.1	71.1 ±5.1	.418		< .001
Min-max	30-79	33-79	59-79			
BMI						
Mean ± SD	26.3 ±4.5	28.0 ±4.7	28.4 ±4.7	.201		< .001
Min-max	13.2-40.8	18.2-45.2	20.4-42.6			
Dietary fiber intake (g)						
Mean ± SD	18.22 ±9.6	17.9 ±8.4	15.9 ±7.7	-.054		< .001
Min-max	2.3-64.2	2.6-41.1	2.4-33.1			
Education level (frequency [%])					1647662.10 (8)	< .001
Less than 9th grade	11 (2.8)	4 (3.6)	4 (8.3)			
9-11th grade	22 (8.3)	14 (15.0)	8 (26.5)			
High school grad/GED or equivalent	47 (33.7)	24 (24.5)	9 (28.3)			
Some college or AA degree	46 (30.7)	20 (27.1)	6 (15.1)			
College graduate or above	29 (24.6)	17 (29.8)	4 (21.8)			
Gender (frequency [%])					140662.86 (2)	< .001
Male	118 (73.5)	55 (65.1)	24 (74.5)			
Female	37 (26.5)	24 (34.9)	7 (25.5)			
Race/Ethnicity (frequency [%])					1557001.70 (6)	< .001
Non-Hispanic White	112 (87.6)	57 (88.8)	23 (82.8)			
Non-Hispanic Black	18 (4.8)	14 (7.0)	5 (7.5)			
Mexican or Hispanic	21 (3.4)	6 (1.8)	2 (2.7)			
Other race or multiracial	4 (4.2)	2 (2.4)	1 (7.0)			
Smoking status (frequency [%])					1415077.50 (4)	< .001
Nonsmoker	33 (23.8)	18 (27.7)	7 (24.5)			
Former smoker	54 (37.1)	37 (43.7)	15 (49.5)			
Current smoker	68 (39.1)	24 (28.6)	9 (26.1)			

Note. Level 0 = no comorbid diseases, Level 1 = one comorbid disease, Level 2-3 = two or three comorbid diseases. Totals will vary due to missing data for some variables.

Bivariate Analyses

I performed bivariate analyses between all potential confounding variables and each dependent variable for the study. I also performed bivariate analyses between all potential confounding variables and the independent variable for the study. As noted in Chapter 3, these bivariate analyses helped to determine if any potential confounding variables were significantly associated with both the independent and the dependent variables. All bivariate analyses involved using the 4-year MEC exam weight variable for the 2007-2010 NHANES dataset.

Bivariate statistical procedures included chi-square tests, independent *t* tests, one-way ANOVAs, Pearson correlations, and Spearman correlations. The assumptions for bivariate statistical analysis included random sampling from the population and independence of scores on variables between cases (Green & Salkind, 2011). Additional assumptions for chi-square included no expected empty cells, and independent *t* tests and ANOVAs also require normal distribution of data and homogeneity of variance (Green & Salkind, 2011). Results indicated variances might be unequal, which violated Levene's tests for homogeneity. However, Levene's test is sensitive to large sample sizes and identifies inconsequential differences in variances, and these statistical procedures show robustness even when the assumption is violated (Field, 2013; Green & Salkind, 2011; Lumley, Diehr, Emerson, & Chen, 2002). Therefore, I determined that proceeding with bivariate statistical procedures was acceptable.

Assessment of Potential Confounding Variables

I assessed all potential confounding variables to determine if they were significantly associated with the independent variable (flavonoid intake) and the dependent variables (COPD, comorbidity burden, CRP and FEV_1% predicted). I assessed associations between the potential confounding variables and COPD first. Next, I performed chi-square tests to assess the association between potential confounding categorical variables and COPD. All potential confounding categorical variables were significantly ($p < .001$) associated with COPD. I performed independent samples *t*-tests to determine the association between potential confounding continuous variables and COPD. The mean differences between participants with COPD and those without COPD were statistically significant ($p < .001$) for all potential confounding continuous variables. The details of these findings are presented in Table 5 and Table 6.

Next, I assessed the association between FEV_1% predicted and potential confounding variables using one-way ANOVAs and an independent samples *t*-test. One-way ANOVAs were suitable to test the association between FEV1% predicted and potential confounding nominal variables with three or more categories. As shown in Table 9, results from the one-way ANOVAs indicated that education level, race/ethnicity, and smoking status were significantly ($p < .001$) associated with FEV_1% predicted. Additionally, results of the independent samples *t*-test indicated that gender was also significantly ($p < .001$) associated with FEV_1% predicted.

Table 9

FEV_1% Predicted and Potential Confounding Variables

Potential confounding variable	Pearson *r*	Mean (SD)	Welch's *F* (*df1, df2*)	*t*-test value (*df*)	*p*-value
Age	-.079				< .001
BMI	-.043				< .001
Dietary fiber intake	.164				< .001
Education level			94450.17 (4, 2263483)		< .001
Less than 9th grade		.90 (.14)			
9-11th grade		.87 (.19)			
High school grad/GED or equivalent		.88 (.16)			
Some college or AA degree		.90 (.15)			
College graduate or above		.94 (.12)			
Gender				157.51 (8483173)	< .001
Male		.90 (.15)			
Female		.89 (.14)			
Race/ethnicity			69515.30 (3, 975017)		< .001
Non-Hispanic White		.90 (.15)			
Non-Hispanic Black		.87 (.15)			
Mexican or Hispanic		.95 (.14)			
Other race or multiracial		.98 (.15)			
Smoking status			537640.08 (2, 6391513)		< .001
Nonsmoker		.95 (.11)			
Former smoker		.90 (.15)			
Current smoker		.84 (.16)			

Note. $N = 1572$.

I assessed the association between CRP and potential confounding variables using Pearson correlation tests, one-way ANOVAs, and an independent samples *t*-test. As shown in Table 10, results of the one-way ANOVAs indicated education level, race/ethnicity, and smoking status were significantly ($p < .001$) associated with CRP. Pearson correlation tests served to determine the association between potential confounding continuous variables and CRP. As seen in Table 10, results from the Pearson correlations indicated that age, BMI, and dietary fiber intake were significantly

($p < .001$) associated with CRP. Likewise, results from the independent samples *t*-test indicated that gender was significantly ($p < .001$) associated with CRP as well.

Table 10

CRP and Potential Confounding Variables

Potential confounding variable	Pearson *r*	Mean (SD)	Welch's *F* (*df1, df2*)	*t*-test value (*df*)	*p*-value
Age	-.004				< .001
BMI	.270				< .001
Dietary fiber intake	-.102				< .001
Education level			166761.18 (4, 25922321)		< .001
Less than 9th grade		.47 (.81)			
9-11th grade		.45 (.91)			
High school grad/GED or equivalent		.38 (.71)			
Some college or AA degree		.37 (.68)			
College graduate or above		.29 (.56)			
Gender				816.05 (96771400)	< .001
Male		.30 (.69)			
Female		.42 (.69)			
Race/ethnicity			172719.89 (3, 13746286)		< .001
Non-Hispanic White		.33 (.63)			
Non-Hispanic Black		.55 (.99)			
Mexican or Hispanic		.40 (.71)			
Other race or multiracial		.27 (.70)			
Smoking status			88497.75 (2, 36642223)		< .001
Nonsmoker		.34 (.62)			
Former smoker		.37 (.70)			
Current smoker		.43 (.87)			

Note. $N = 1572$.

Spearman correlation tests served to determine the association between potential confounding continuous variables and comorbidity burden. As seen in Table 8, results from the Spearman correlation tests indicated that age, BMI, and dietary fiber intake were significantly ($p < .001$) associated with comorbidity burden. I used chi-square tests to determine if a significant association was present between comorbidity burden and gender, education level, race/ethnicity, and smoking status. As shown in Table 8, results indicated that these variables were also significantly associated with comorbidity burden.

I assessed the association between total daily flavonoid intake and potential confounding variables using Pearson correlation tests, one-way ANOVAs, and an independent samples *t*-test. As shown in Table 11, education level, race/ethnicity, and smoking status were significantly ($p < .001$) associated with total daily flavonoid intake. Pearson correlation tests served to determine the association between potential confounding continuous variables and total daily flavonoid intake. As seen in Table 11, age, BMI, and dietary fiber intake were also significantly ($p < .001$) associated with total daily flavonoid intake. Additionally, results from the independent samples *t*-test indicated that gender was significantly ($p < .001$) associated with total daily flavonoid intake as well.

The results from all bivariate statistical procedures related to potential confounding variables indicated that all potential confounding variables were significantly associated with the independent variable and all dependent variables. The associations were statistically significant below the threshold of $p < .15$ for inclusion of

the confounding variables in multivariate analyses for hypothesis testing. Therefore, the confounding variables qualified for inclusion in multivariate analyses.

Table 11

Flavonoid Intake and Potentially Confounding Variables

Potential confounding variable	Pearson *r*	Mean (SD)	Welch's *F* (*df1, df2*)	*t*-test value (*df*)	*p*-value
Age	.027				< .001
BMI	-.026				< .001
Dietary fiber intake	.097				< .001
Education level			512678.71 (4, 30369183)		< .001
Less than 9th grade		128.0 (234.1)			
9-11th grade		224.2 (412.9)			
High school grad/GED or equivalent		217.8 (362.1)			
Some college or AA degree		256.4 (409.8)			
College graduate or above		297.6 (410.2)			
Gender				158.77 (97480558)	< .001
Male		242.9 (416.3)			
Female		255.4 (370.8)			
Race/ethnicity			984577.40 (3, 16216058)		< .001
Non-Hispanic White		268.6 (417.6)			
Non-Hispanic Black		187.2 (294.4)			
Mexican or Hispanic		143.5 (235.5)			
Other race or multiracial		369.1 (464.1)			
Smoking status			28550.53 (2, 39731233)		< .001
Nonsmoker		253.8 (378.1)			
Former smoker		234.8 (341.1)			
Current smoker		256.3 (502.1)			

Note. $N = 1572$.

Multivariate Analyses

Before proceeding with multivariate testing, I assessed total daily flavonoid intake and all confounding variables for collinearity using linear regression testing. The intent of the regression was to assess the collinearity statistics for tolerance and variance inflation factors (VIFs) for each variable. The utility of tolerance and VIF can be described using R_i^2, which is used to represent the proportion of variance for the *i*th independent variable in relation to the other independent variables (Belsley, Kuh, & Welsch, 2005; O'Brien, 2007). As such, the tolerance for each independent variable is determined by subtracting one from the proportion of variance shared with the other independent variables and is represented mathematically as 1-R_i^2. The resulting tolerance value is the proportion of variance for each independent variable that is unrelated to the other independent variables (Belsley et al., 2005; O'Brien, 2007). VIF is represented as 1/(1-R_i^2) because it is the reciprocal of tolerance (Belsley et al., 2005; O'Brien, 2007). Therefore, VIF is an indicator of the degree to which the estimated variance would be for the *i*th regression coefficient if the proportion of variance for the *i*th independent variable associated with the other independent variables was equal to zero (Belsley et al., 2005; O'Brien, 2007). More specifically, VIF indicates the inflation in the standard error of a given beta weight for a particular predictor variable that is attributable to collinearity. Taken together, tolerance and VIF provide a reasonable indication of collinearity among independent variables, with values greater than 10 for VIF or lower than .01 for tolerance indicating unacceptable degrees of collinearity (Belsley, 1991; Belsley et al., 2005; O'Brien, 2007; Hair, Anderson, Tatham, & Black, 1995; Tabachnick & Fidell, 2001). As shown in Table

12, all variables were below the threshold of concern for collinearity, with values greater than .01 for tolerance and less than 10 for VIF. Therefore, I included all predictor variables in the planned multivariate analyses, which included linear regression and logistic regression. All multivariate analyses included the 4-year MEC exam weight variable for the 2007-2010 NHANES dataset.

Table 12

Collinearity Statistics

Variable	Tolerance	VIF
BMI	.938	1.066
Dietary fiber intake	.859	1.165
Education level		
9-11th grade	.335	2.981
High school grad/GED or equivalent	.214	4.677
Some college or AA degree	.186	5.372
College graduate or above	.166	6.039
Total daily flavonoid intake	.946	1.057
Gender	.952	1.051
Race/ethnicity		
Non-Hispanic Black	.920	1.087
Mexican or Hispanic	.787	1.270
Other race or multiracial	.961	1.041
Smoking status		
Former smoker	.899	1.112
Current smoker	.799	1.252

Note. VIF = variance inflation factor.

RQ1 Results

Testing the null hypothesis for RQ1 involved running two logistic regression models to assess the potential relationship between total daily flavonoid intake and an outcome of COPD. Model 1 consisted of conducting a simple logistic regression to investigate if total daily flavonoid intake was a significant predictor of COPD. This model explained little of the variance in COPD (Nagelkerke $R^2 = .0003$), but correctly

classified 94.5% of cases. Total daily flavonoid intake was a statistically significant ($p <$ .001) predictor of COPD in the logistic regression analysis. Results presented in Table 13 indicate that for every 1% increase in total daily flavonoid intake, there was a 7.1% decrease (Exp [β] = 0.929, 95% CI [0.928, 0.930]) in the odds of having COPD.

Table 13

Logistic Regressions for Total Flavonoid Intake and COPD

Model and predictors	χ^2 (*df*)	R^2	β *(SE)*	OR (95% CI)	*p*-value
Model 1	107320.35 (8)	.0003			< .001
Total flavonoid intake			-.074 (.001)	.929 (.928, .93)	<.001
Model 2	342302.12 (8)	.2276			
Total flavonoid intake			-.061 (.001)	.941 (.940, .943)	<.001
Age			.072 (< .001)	1.075 (1.075, 1.075)	<.001
BMI			-.071 (< .001)	.931 (.930, .931)	<.001
Dietary fiber intake			.188 (.002)	1.207 (1.202, 1.211)	<.001
Education level					
Less than 9th grade			Ref.		
9-11th grade			.441 (.003)	1.554 (1.545, 1.562)	<.001
High school grad/GED or equivalent			.749 (.003)	2.116 (2.105, 2.127)	<.001
Some college or AA degree			536 (.003).	1.710 (1.701, .719)	<.001
College graduate or above			.335 (.003)	1.398 (1.390, 1.405)	<.001
Gender					
Female			Ref.		
Male			1.027 (.001)	2.794 (2.788, 2.80)	<.001
Race/ethnicity					
Non-Hispanic White			Ref.		
Non-Hispanic Black			-.712 (.002)	.491 (.489, .493)	<.001
Mexican or Hispanic			-1.287 (.003)	.276 (.275, .278)	<.001
Other Race or multiracial			-.248 (.002)	.781 (.777, .784)	<.001
Smoking status					
Nonsmoker			Ref.		
Former smoker			.949 (.001)	2.584 (2.578, 2.590)	<.001
Current smoker			1.925(.001)	6.855 (6.837, 6.873)	<.001

Note. $N = 270$.

Model 2 consisted of conducting a multiple logistic regression to control for confounding variables. Therefore, Model 2 was adjusted for potential confounding variables as previously described. The Hosmer-Lemeshow goodness-of-fit was significant ($p < .05$), which indicated that the model fit may not be ideal and the

interpretation should include some degree of caution. Results presented in Table 13 show that total daily flavonoid intake and all confounding predictor variables were statistically significant ($p < .001$) predictors of COPD. While controlling for all confounding variables in the logistic regression model, a 1% increase in total daily flavonoid intake resulted in a 5.9% decrease (Exp [β] = 0.941, 95% CI [0.940, 0.943]) in the odds of having COPD. Based on the results of both logistic regression models, the null hypothesis for RQ1 was rejected.

RQ2 Results

Analysis involved generating two linear regression models to investigate RQ2. Model 1 consisted of conducting a simple linear regression to investigate the potential relationship between total daily flavonoid intake and FEV_1% predicted. As shown in Table 14, total daily flavonoid intake was significantly associated with COPD severity (β = .013, 95% CI [.013, .013], $p < .001$), such that for every 1% increase in total daily flavonoid intake, the FEV_1% predicted increased by .00013. However, the model explained little of the variability (R^2 = .002).

Model 2 involved conducting a multiple linear regression to control for confounding variables. Therefore, Model 2 was adjusted for potential confounding variables as previously described. Results presented in Table 14 show that total daily flavonoid intake and all confounding predictor variables were statistically significant ($p <$ .001) predictors of FEV_1% predicted. The regression coefficient (β = .001, 95% CI [.001, .002], $p < .001$) associated with total daily flavonoid intake suggests that FEV_1% predicted increases by .00001 for every 1% increase in total daily flavonoid intake. While

statistically significant, this regression coefficient was lower than that found in Model 1, which indicates a reduction in the utility of total daily flavonoid intake as a predictor of FEV1% predicted. Based on the results of both linear regression models, the null hypothesis for RQ2 was rejected.

Table 14

Linear Regressions for Total Flavonoid Intake and FEV1% Predicted

Model and predictors	R^2	*B (SE)*	95% CI	*p*-value
Model 1	.002			
Total flavonoid intake		.013 (< .001)	.013, .013	< .001
Model 2	.214			
Total flavonoid intake		.001 (< .001)	.001, .002	< .001
Age		.0003 (< .001)	.0003, .0003	< .001
BMI		-.002 (< .001)	-.002, -.002	< .001
Dietary fiber intake		.087 (< .001)	.086, .087	< .001
Education level				
Less than 9th Grade		Ref.		
9-11th Grade		-.011 (< .001)	-.012, -.010	< .001
High school grad/GED or equivalent		.007 (< .001)	.006, .007	< .001
Some college or AA degree		.044 (< .001)	.043, .044	< .001
College graduate or above		.064 (< .001)	.043, .044	< .001
Gender				
Female		Ref.		
Male		.047 (< .001)	.047, .047	< .001
Race/ethnicity				
Non-Hispanic White		Ref.		
Non-Hispanic Black		-.003 (< .001)	-.004, -.003	< .001
Mexican or Hispanic		.024 (< .001)	.024, .025	< .001
Other race or multiracial		.024 (< .001)	.023, .025	< .001
Smoking status				
Nonsmoker		Ref.		
Former smoker		-.068 (< .001)	-.068, -.068	< .001
Current smoker		-.125 (< .001)	-.126, -.125	< .001

Note. $N = 270$.

RQ3 Results

Analysis also involved generating two linear regression models to investigate RQ3. Model 1 consisted of conducting a simple linear regression to investigate the

potential relationship between total daily flavonoid intake and CRP. Results presented in Table 15 show that total daily flavonoid intake was statistically significant (β = .036, 95% CI [.034, .038], p < .001) and indicated that a 1% increase in total daily flavonoid intake results in a 0.036% increase in CRP. However, the model explained little of the variability (R^2 = .0003).

Table 15

Linear Regressions for Total Flavonoid Intake and CRP

Model and predictors	R^2	*B (SE)*	95% CI	*p*-value
Model 1	.0003			
Total flavonoid intake		.036 (.001)	.034, .038	< .001
Model 2	.186			
Total flavonoid intake		-.076 (.001)	-.078, -.074	< .001
Age		.012 (< .001)	.012, .012	< .001
BMI		.085 (< .001	.085, .085	< .001
Dietary fiber intake		-.042 (.002)	-.046, -.039	< .001
Education level				
Less than 9th grade		Ref.		
9-11th grade		-.178 (.003)	-.183, -.172	< .001
High school grad/GED or equivalent		-.626 (.003)	-.631, -.621	< .001
Some college or AA degree		-.600 (.003)	-.605, -.594	< .001
College graduate or above		-.568 (.003)	-.574, -.563	< .001
Gender				
Female		Ref.		
Male		-.256 (.001)	-.258, -.254	< .001
Race/ethnicity				
Non-Hispanic White		Ref.		
Non-Hispanic Black		.225 (.002)	.221, .229	< .001
Mexican or Hispanic		.106 (.003)	.101, .111	< .001
Other race or multiracial		-.299 (.002)	-.304, -.294	< .001
Smoking status				
Nonsmoker		Ref.		
Former smoker		.147 (.001)	.144, .149	< .001
Current smoker		.526 (.001)	.523, .529	< .001

Note. N = 270.

Model 2 consisted of conducting a multiple linear regression to control for confounding variables. Therefore, Model 2 was adjusted for potential confounding

variables as previously described. Results presented in Table 15 show that total daily flavonoid intake and all confounding predictor variables were statistically significant ($p <$ .001) predictors of CRP. The regression coefficient (β = -.076, 95% CI [-.078, -.074], $p <$ .001) associated with total daily flavonoid intake suggests a 1% increase in total daily flavonoid intake results in a 0.076% decrease in CRP. Also, by adjusting for the confounding variables, the direction of the association between total daily flavonoid intake and CRP changed from positive to negative. Based on the results of both linear regression models, the null hypothesis for RQ2 was rejected.

RQ4 Results

Investigating RQ4 involved performing a one-way ANOVA to determine if differences in total daily flavonoid intake were significant among participants in the COPD subset with different levels of comorbidity burden. Levene's test for equality of variances indicated a violation of the assumption of homogeneity of variances ($p < .05$). Results from the one-way ANOVA indicated that total daily flavonoid intake was statistically significantly different for different levels of comorbidity burden, Welch's $F(2, 1348601.11) = 55509.04$, $p < .001$. Figure 3 shows the differences in mean flavonoid intake for the comorbidity burden Level 0 group (M = 201.7, SD = 308.5), Level 1 group (M = 332.1, SD = 483.9), and Level 2 and 3 group (M = 179.3, SD = 243).

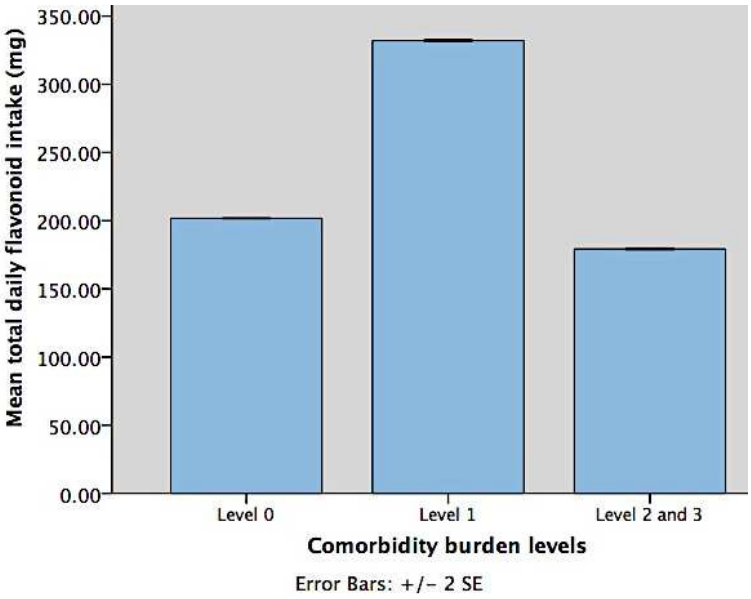

Figure 3. Flavonoid intake across comorbidity burden levels.

A Games-Howell post hoc analysis was suitable to explore the nature of the differences in total daily flavonoid intake between comorbidity burden levels. As seen in Table 16, results from the Games-Howell post hoc analysis revealed that the mean differences between each of the comorbidity burden levels were statistically significant ($p < .001$). Specifically, there was an increase in total daily flavonoid intake from the comorbidity burden Level 0 group to the Level 1 group. Additionally, a decrease in total daily flavonoid intake occurred from the comorbidity burden Level 0 group to the Level 2 and 3 group. A decrease in total daily flavonoid intake also occurred from the comorbidity burden Level 1 group to the Level 2 and 3 group. Taken together, the results of the one-way ANOVA and associated post hoc analysis indicated that the group means were significantly ($p < .001$) different and, therefore, the null hypothesis for RQ4 was rejected.

Table 16

Total Flavonoid Intake Between Comorbidity Burden Levels

Comorbidity burden levels	Mean difference	*SE*	95% CI	*p*-value
Level 0 and Level 1	130.31	.42	129.35, 131.30	< .001
Level 0 and Level 2-3	-22.43	.39	-23.34, -21.52	< .001
Level 1 and Level 2-3	-152.76	.52	-153.97, -151.54	< .001

Note. $N = 270$.

Summary

This chapter included the results from the secondary analysis of data from the 2007–2010 NHANES and USDA flavonoid databases. Preparation of the data for analysis resulted in several modifications and adjustments, which included revisions to the study inclusion criteria, key study variables, and planned statistical procedures used to test RQ4. Bivariate analyses indicated that all potentially confounding variables were true confounders, as they were each statistically significantly ($p < .001$) associated with total flavonoid intake and each dependent variable. Subsequently, I evaluated all confounding variables for collinearity. Results of collinearity testing revealed that all confounding variables were suitable for inclusion in multivariate analysis as covariates.

The results from the multivariate analyses addressed RQ1, RQ2, and RQ3, and the result from a one-way ANOVA addressed RQ4. Results from the logistic regressions addressing RQ1 indicated that total flavonoid intake was a statistically significant predictor of COPD. Results from the linear regressions used to address RQ2 and RQ3 indicated that total flavonoid intake was a significant ($p < .001$) predictor of FEV_1% predicted and CRP, respectively. Results from the one-way ANOVA used to address RQ4 showed a significant ($p < .001$) difference in total daily flavonoid intake for

different levels of comorbidity burden among participants with COPD. Based on these results, I rejected the null hypothesis for all research questions.

In Chapter 5, I provide an interpretation and comparison of the results from this study with those of other studies. I also include a review of the strengths and limitations of the current study, as well as recommendations for future research. Furthermore, the next chapter contains a discussion of the results of the study as they relate to influencing positive social change. Finally, I conclude Chapter 5 with a brief overview of the study findings.

Chapter 5: Discussions, Conclusions, and Recommendations

The purpose of this cross-sectional secondary analysis of the 2007-2010 NHANES dataset was to explore the potential association between total daily flavonoid intake and COPD, COPD severity, CRP, and comorbidity among U.S adults aged 30 years and older. These analyses indicated that total daily flavonoid intake was a significant predictor of COPD. Also, I determined that total daily flavonoid intake was a significant predictor of FEV_1% predicted and CRP. The inclusion of confounding variables in multiple regression models was critical in identifying the true effect of total daily flavonoid intake on the dependent variables. In fact, results varied substantially between simple and multiple regression models. Also, total daily flavonoid intake was significantly associated with comorbidity burden level among participants in this study. This chapter includes an interpretation of these findings to further address each research question. Additionally, I review study limitations, offer recommendations for future research, discuss implications for social change, and provide conclusions.

Interpretation of the Findings

Flavonoid Intake and COPD

My exploration of the relationship between total daily flavonoid intake and COPD in this study expanded upon the findings of other researchers. In this study, I examined total flavonoid intake, which was measured as the sum of six flavonoid subclasses, and spirometry-confirmed COPD diagnosis. Researchers who previously studied the association between flavonoid intake and COPD were restricted in the ability to use direct measures for flavonoids and COPD in a single study. Some researchers who

measured flavonoid content directly were limited to assessments of lung function and symptoms of COPD, while other researchers who directly measured COPD diagnosis were restricted to indirect surrogate assessments of flavonoid content (Butland et al., 2000; Celik & Topcu, 2006; Tabak et al., 2001). Despite these limitations, the authors of previous studies consistently demonstrated that higher intake of flavonoids or foods high in flavonoid content was associated with not having COPD or with having favorable measures of lung function and decreased COPD symptoms (Butland et al., 2000; Celik & Topcu, 2006; Tabak et al., 2001). The results from my study support these findings by demonstrating that a statistically significant relationship is present between flavonoid intake and COPD. Specifically, results from the bivariate analysis in the present study indicated that those without COPD had a significantly higher average total daily flavonoid intake of 11.80 mg/day ($p < .001$) than those who had COPD.

When examining the unadjusted simple logistic regression analysis of total daily flavonoid intake and COPD, I found that total daily flavonoid intake was a statistically significant ($p < .001$) predictor of COPD. When the regression model was adjusted to control for confounding variables, I found that total daily flavonoid intake remained a statistically significant ($p < .001$) predictor of COPD despite a slight reduction in the odds ratio from 7.1% to 5.9%. As such, I found that higher total daily flavonoid intake was significantly associated with lower odds of having COPD. Other researchers have also reported inverse associations between flavonoids or foods high in flavonoid content and COPD or COPD symptoms (Celik & Topcu, 2006; Tabak et al., 2001). For example, catechin, flavonol, and flavone intake is inversely associated with the odds of developing

chronic cough ($OR_{Q5\text{-}Q1} = 0.80$) and dyspnea ($OR_{Q5\text{-}Q1} = 0.74$), which are common symptoms of COPD (Tabak et al., 2001). Also, the intake of flavonoid-rich beverages and foods, such as black tea, fruits, and vegetables is significantly lower among male smokers with COPD compared to healthy male smokers without COPD (Celik & Topcu, 2006). As previously mentioned, this is the first study to directly explore the relationship between total daily flavonoid intake and COPD, as diagnosed by spirometry, in a large sample of adult males and females within the United States. Therefore, results from the RQ1 analyses have served to further the understanding of this association.

Flavonoid Intake and COPD Severity

My examination of the association between total daily flavonoid intake and COPD severity, as measured by FEV_1% predicted, showed a weak but significant positive correlation between total daily flavonoid intake and FEV_1% predicted. This result aligns with findings from other researchers who reported positive associations between flavonoids or foods with high flavonoid content and measures of lung function (Butland et al., 2000; Tabak et al., 2001). For example, higher intake of catechins, flavonols, flavones, and apples, which are known to have high levels of the flavonoid quercetin, are associated with higher FEV_1 (Butland et al., 2000; Tabak et al., 2001). However, these observations are derived from examining only a few flavonoid subclasses or surrogate measures of flavonoid intake and no direct assessment of FEV_1% predicted. This is the first study to directly explore the correlation between total daily flavonoid intake and FEV_1% predicted in a COPD population and serves to address this gap in the literature.

I also found total daily flavonoid intake to be a significant ($p < .001$) predictor of FEV_1% predicted in both simple and adjusted regression models. However, the regression coefficient ($\beta = .001$) from the multivariate model reflected a nearly zero effect. Specifically, a 1% increase in total daily flavonoid intake resulted in only a 0.00001 increase in FEV_1% predicted. Other antioxidant vitamins have also been found to be significant predictors of FEV_1% predicted, with effect sizes larger than that found in this study (Ochs-Balcom et al., 2006; Schünemann et al., 2001; Schünemann et al., 2002). For example, lutein/zeaxanthin, vitamin C, and vitamin E are all significant predictors of FEV_1% predicted, with linear regression coefficients of approximately 1.00 or greater (Ochs-Balcom et al., 2006; Schünemann et al., 2001; Schünemann et al., 2002). Additionally, beta-cryptoxanthin, beta-carotene, and lycopene are also significant predictors of FEV_1% predicted, with linear regression coefficients of 5.16, 5.10, 6.33, and 4.28, respectively (Ochs-Balcom et al., 2006). As such, total daily flavonoid intake may not be a meaningful predictor of FEV_1% predicted. Nevertheless, despite the minimal effect size observed in this study for total flavonoid intake as a predictor of FEV_1% predicted, this result still serves to address the gap in the literature regarding this topic.

Flavonoid Intake and Systemic Inflammation

Results from this study showed a significant negative correlation between total daily flavonoid intake and CRP. Furthermore, I found total daily flavonoid intake to be a significant ($p < .001$) predictor of CRP. The absolute magnitude of the effect size for total daily flavonoid intake increased considerably in the adjusted regression model ($\beta = -0.076$) compared to the unadjusted model ($\beta = 0.036$). The association between total daily

flavonoid intake and systemic inflammation, as measured by CRP, within a COPD population is understudied. However, this finding from my study aligns well with observations reported by other researchers (Chun, Chung, Claycombe, & Song, 2008; Corely et al., 2015; Landberg et al. 2011). For instance, a negative linear trend in serum CRP concentrations has been identified between tertiles of flavonoid intake (Chun et al., 2008). Likewise, higher intake of flavonoid rich-foods like grapefruit, total fruit, and apples is significantly associated with lower levels of serum CRP (Corely et al, 2015; Landberg et al., 2011). Furthermore, relatively large effect sizes have been reported for apples ($\beta = -0.456$) and total fruit ($\beta = -0.100$) as significant predictors of CRP (Corely et al., 2015). However, the magnitude of this effect may reflect the combined effect of other favorable compounds found in fruits, such as vitamin A, vitamin C, and fiber, but further studies are needed to confirm this assertion (Corely et al., 2015). Given these nuances, the effect size for the association between total daily flavonoid intake and CRP in the present study appears to be a more accurate measure of this relationship compared to surrogate measures using apples and total fruit.

In contrast with previous findings, individual flavonoid sub-classes (Catechins, Flavanones, Flavones, Flavonols, and, Proanthocyanidins) have also been reported as non-significant predictors of CRP, but within a non-COPD population (Corley et al., 2015). This conflicting finding is attributed to variations in estimates of flavonoid intake derived from the use of a UK flavonoid database (Kyle & Duthrie, 2006) having flavonoid values for only 386 food items (Corely et al., 2015). Therefore, it is possible that intake of these five flavonoid subclasses may have been underestimated. In contrast,

I used the USDA flavonoid database, which is the most comprehensive source of flavonoid values for over 2,900 food items (USDA, 2016). Therefore, this study may offer a more precise estimate of the relationship between total daily flavonoid intake and CRP, particularly among those with COPD.

Other significant predictors of CRP include total fiber, insoluble fiber, total polyunsaturated fatty acids (PUFAs), and omega-6 PUFAs (Muka et al., 2015; Villaseñor et al., 2011). The effect sizes reported by researchers (Muka et al., 2015; Villaseñor et al., 2011) for total fiber ($\beta = -0.029$), insoluble fiber ($\beta = -0.039$), PUFAs ($\beta = -0.03$), and omega-6 PUFAs ($\beta = -0.03$) were relatively small compared to the effect size I found in my study for total daily flavonoid intake ($\beta = -0.076$). As such, total daily flavonoid intake may be a stronger predictor of COPD than fiber or PUFAs. However, the reported effects of fiber and PUFAs on CRP were observed within a non-COPD population that included either female cancer patients (Villaseñor et al., 2011) or Dutch nationals aged 55 years or older (Muka et al., 2015). Nevertheless, these findings in the literature (Muka et al., 2015; Villaseñor et al., 2011) align with the results of my study in supporting the premise that diet is associated with CRP. Ultimately, my study serves to clarify the relationship between total daily flavonoid intake and CRP among Americans with COPD. Given the limited research on this topic, further studies are needed to replicate and confirm these findings from my study.

Flavonoid Intake and Comorbidity Burden

Comorbidity among those with COPD is a common occurrence, with most COPD patients having at least one comorbid disease (Dal Negro, Bonadiman, & Turco, 2015;

Divo et al., 2012; Putcha et al., 2013). However, comorbid diseases occurring in those with COPD are posited to be an extension of the systemic inflammatory nature of COPD (Agusti & Faner, 2012; Divo et al., 2012; Smith & Wrobel, 2014). Therefore, I performed analyses for RQ4 to explore the relationship between total daily flavonoid intake and comorbidity burden consisting of an accumulation of cardiovascular disease, diabetes, and hypertension. Through these analyses, I found that the total daily flavonoid intake was significantly ($p < .001$) different for each comorbidity burden group. Furthermore, I found the mean flavonoid intake for the comorbidity burden Level 0 group to be significantly ($p < .001$) lower than that of the comorbidity burden Level 1 group. While this finding was unexpected, it may be reflective of dietary changes made after receiving counseling for self-care following diagnosis of any one of the comorbid diseases included in the current study. Current counseling recommendations for managing cardiovascular disease, diabetes, and hypertension call for increased dietary intake of fruits and vegetables as a core self-care component (American Association of Diabetes Educators, 2009; Eckel et al., 2014; Evert et al., 2013; Weber et al., 2014). However, given the cross-sectional study design used in these analyses, identifying the direction of association between total daily flavonoid intake and the accumulation of comorbid diseases is not within the scope of this study. Longitudinal studies are recommended to further elucidate the nature of the association identified in this study.

I also found that the mean flavonoid intake for those with two or three comorbid diseases was significantly ($p < .001$) lower than those with one or no comorbid disease. This particular discovery is consistent with previous findings by other researchers who

show higher fruit and vegetable intake is significantly associated with a lower risk of multimorbidity (Ruel et al., 2014; Wikström, Lindström, Harald, Peltonen, & Laatikainen, 2015). In fact, those having less than three to five servings of fruit and vegetables each week are more likely (HR = 1.75, 95% CI [1.16 – 2.66]) to develop two or more comorbid diseases within a 10-year period compared to those with higher fruit and vegetable intake (Wikström et al., 2015). As previously mentioned, this study is the first to examine the relationship between total daily flavonoid intake and the comorbidity burden of cardiovascular disease, diabetes, and hypertension among Americans with COPD. Therefore, the results from this study support previous work and broaden the literature with respect to populations with COPD. However, additional studies with larger samples of COPD participants are needed to further explore the relationship between total daily flavonoid intake and comorbidity burden using multivariate analysis.

Theoretical Framework

I used the advanced model of the epidemiology triangle as a guide to explore the relationship between total daily flavonoid intake and COPD, COPD severity, systemic inflammation, and comorbidity burden. The advanced model of the epidemiology triangle places emphasis on the interaction between multiple causative factors, the group or population and their characteristics, and the environment over time to bring about the onset of chronic diseases (Merrill, 2009). Using this theoretical framework as a guide, I carefully selected all study variables based on their relevance to the components of the model. Specifically, the variable for smoking status represented a causative factor, and the population's characteristics were represented by socioeconomic and demographic

variables. Additionally, the environmental component of the model was represented indirectly by dietary fiber intake and total daily flavonoid intake. The advanced model of the epidemiology triangle was proven effective in my study because I found all covariates, which represented key components of the theoretical framework, to be statistically significant predictors during multivariate analyses. Furthermore, the inclusion of these variables increased the predictive utility of each multiple regression model considerably from nearly zero percent to 23%, 21.4%, and 18.6% for RQ1, RQ2, and RQ3, respectively. Ultimately, the advanced model of the epidemiology triangle proved effective in guiding my design and execution of this study and served to elucidate the relationships between total daily flavonoid intake and COPD, COPD severity measured by FEV_1% predicted, CRP, and comorbidity burden.

Limitations of the Study

This research was subject to several limitations that have some bearing on the interpretation of study results. The primary limitation of this study was the lack of long-term dietary information due to limitations of the 24-hour dietary recall instrument and the cross-sectional nature of the study design. Specifically, it is uncertain if dietary intake reported in the 24-hour dietary recall is reflective of dietary habits prior to the onset of COPD or if dietary changes were initiated after diagnosis. Therefore, I could not identify temporal relationships or make causal inferences because the study design was limited to observational identification of associations between variables of interest at a cross-section in time. However, it is plausible that flavonoid intake could be responsible for the variability in the dependent variables of the study because long-term dietary habits have

been found to be consistent with findings from the 24-hour dietary recalls (Bertoia et al., 2015). Ultimately, the results of this study should be interpreted with caution, given the aforementioned limitation.

Another limitation of this study was the lack of data for other measures of systemic inflammation, such as interleukins 6 (IL-6) and 8 (IL-8), and tumor necrosis factor-alpha (TNF-α) to more fully address RQ3. However, CRP has been well established as an acceptable measure of systemic inflammation among those with COPD (Baldrick et al., 2012). Furthermore, CRP can be used as a surrogate measure for IL-6 because CRP is induced in the body by IL-6 through the involvement of mechanisms related to NF-κB (Agrawal, Samols, & Kushner, 2003; Maehira, Miyagi, & Eguchi, 2003). However, regardless of this relationship, additional measures of systemic inflammation could not be directly assessed due to limitations of the available data within the 2007-2010 NHANES dataset. Therefore, the results of this study only serve to elucidate the relationship between total daily flavonoid intake and one measure of systemic inflammation. Furthermore, given this limitation, it was not possible to conclusively assert that there is a relationship between total daily flavonoid intake and systemic inflammation.

Sample size in the COPD subgroup was also a limitation of the study with regard to fully addressing RQ4. As mentioned, it was not possible to perform logistic regression to explore the relationship between total daily flavonoid intake and comorbidity burden due to the small sample size of the COPD subgroup. Therefore, my investigation of the relationship between total daily flavonoid intake and comorbidity burden was limited to

bivariate analysis. The small sample size resulted in an insufficient number of participants who had three comorbid diseases. Therefore, I combined participants with three comorbid diseases into the same group as those who had two comorbid diseases. By combining these participants into the same group, it was not possible to assess associations with flavonoid intake among those with three comorbid diseases in relation to participants with other comorbidity burden levels. Although I found statistically significant differences in mean total daily flavonoid intake between the comorbidity burden level groups, it is unclear if a predictive relationship exists between these two variables. The inability to perform multivariate analyses restricted my further examination of the relationship between total daily flavonoid intake and comorbidity burden.

While the USDA flavonoid databases are a robust source of flavonoid content, several limitations related to the composition of the flavonoid data within the database should be acknowledged. For instance, analytical values were not determined for all foods in the database. Instead, researchers at the USDA imputed flavonoid values for approximately 24% of the values in the database using flavonoid data from foods that were similar in botanical origin (USDA, 2016). Therefore, the volume of analytical values within the USDA flavonoid database was limited, and may affect the precision of the flavonoid content of some foods within the database. Also, USDA researchers assigned a zero value for isoflavone content in some foods for which a non-zero isoflavone value was available. Zero values were assigned only when the isoflavones in a food item was attributable to an ingredient that may or may not be present in a food type.

For example, USDA researchers noted that two different brands of hot dogs have the same FNDDS code, but one brand may include isoflavone ingredients, like soy, and the other brand does not (USDA, 2016). Therefore, all food items within a given food type, such as hot dogs, that met this criterion were assigned a zero isoflavone value. Taken together, the limitations attributed to the compilation of the USDA flavonoid database may have resulted in an underestimation of total daily flavonoid intake in the present study.

Another limitation of this study was that I did not account for variations in the bioavailability of flavonoid intake attributable to interactions with other food components. The absorption of flavonoids can be affected by food matrix components, such as dietary fat, fiber, and protein (Lesser, Cermak, & Wolffram, 2014; Mullen et al., 2009; Ortega, Reguant, Romero, Macià, & Motilva, 2009; Probert, Emmett, & Heaton, 1995). Dietary fat may enhance the digestibility and absorption of flavonoids within the small intestine (Lesser et al., 2014; Ortega et al., 2009). This effect is attributed to physiological interactions between dietary fat and flavonoids that result in prolonged transit time within digestive tract (Rao, Lu, & Schulze-Delrieu, 1996). Dietary fiber also impacts the duration of transit time for flavonoids in the gut, with insoluble fiber decreasing transit time and soluble fiber increasing transit time (Probert et al., 1995). As such, a reduction in transit time within the digestive tract is thought to be associated with a lower bioavailability of flavonoids, as observed with various pharmaceuticals (Kimura & Higaki, 2002). Furthermore, fermentable fibers, such as inulin and fructo-oligosaccharides, act as prebiotics in animals and humans by increasing the microbiota

fermentation of flavonoids, which enhances the bioavailability of flavonoid aglycones and metabolites (Larkin, Price, & Astheimer, 2007; Piazza et al., 2007; Tamura, Nakagawa, Tsushida, Hirayama, & Itoth, 2007; Uehara et al., 2001). Proteins, on the other hand, such as those found in milk, appear to reduce the bioavailability of flavonoids (Mullen et al., 2009; Roowi, Mullen, Edwards, & Crozier, 2009; Serafini et al., 2009). For instance, consuming cocoa with milk results in reduced plasma concentrations of the flavan-3-ols by 25% and increased urine concentration of the same by 50% compared with consuming cocoa with water (Mullen et al., 2009). Similar findings were observed for blueberries consumed with and without milk and when orange juice was consumed with and without yogurt (Roowi et al., 2009; Serafini et al., 2009). These effects are suggested to reflect flavonoid-protein interactions that form bonds and complexes, which inhibit the uptake of flavonoids in the digestive tract and reduce bioavailability (Upri-Sarda et al., 2010). Despite these food matrix effects on flavonoid bioavailability, the assessment of individual flavonoid sub-classes and food matrix composition in relation to COPD outcomes were beyond the scope of this study. As such, it may be of interest to explore the impact of individual flavonoid subclasses on COPD outcomes in future studies, as some flavonoid sub-classes offer more bioavailability than others.

Recommendations for Further Research

Results obtained from this study support assertions found in the literature that diet is associated with COPD outcomes. This study adds to the body of knowledge about the relationship between total daily flavonoid intake and COPD, COPD severity as measured by FEV_1% predicted, systemic inflammation as measured by CRP, and comorbidity

burden consisting of cardiovascular disease, diabetes, and hypertension. However, due to the limitations noted above, further research in this area is warranted.

Given the significant associations between total daily flavonoid intake and COPD outcomes of interest in this study, I recommend the use of prospective longitudinal study designs for future research to determine temporal relationships between variables. Ideally, dietary intake should be monitored and recorded multiple times each year over approximately 20 years or longer before diagnosis of COPD. Such a study would increase the likelihood of potentially identifying a temporal relationship between total daily flavonoid intake and odds of having COPD. In parallel, a similar design should be utilized with an observational period beginning at the time of COPD diagnosis and lasting for 10 to 20 years or longer. This additional recommendation targets identification of a potentially temporal relationship between flavonoid intake and COPD severity, systemic inflammation, or comorbidity burden among those with COPD. In addition to multiple collections of dietary data each year, measurements for spirometry and serum biomarkers for systemic inflammation should also be collected at similar time points along with medical records to identify the onset of comorbid diseases. Ample participants with COPD must be enrolled in future studies to overcome the sample size limitations noted in this study. For instance, if this study is replicated, I recommended that three or more NHANES datasets be combined to create a larger sample size with an increased number of participants with COPD. As previously mentioned, the associations between total daily flavonoid intake and COPD outcomes are understudied, and further research involving those with COPD is warranted.

Alternative study design recommendations for future research would entail utilization of a case-control or retrospective cohort research methodology. Use of these research design methods would improve the ability to make temporal assessments regarding total daily flavonoid intake and COPD outcomes. Furthermore, utilization of these alternative study design methodologies for future research may be more cost-effective and less time consuming compared to the longitudinal study design proposed earlier.

Future research should also incorporate more extensive flavonoid content data for an even greater number of foods. Such an approach would serve to increase the precision of flavonoid estimates for the study population. While the USDA flavonoid databases are the most comprehensive source of flavonoid content data, they are not exhaustive. Therefore, future research should entail combining the USDA flavonoid databases with other flavonoid data sources to expand flavonoid content information beyond what was available in the present study. The European BioActive Substances in Food Information System (eBASIS) database may serve as a viable adjunct to the USDA flavonoid databases because it has been successfully utilized to provide flavonoid content for other research studies (Euorpean Food Information Resource, 2015; Pounis et al., 2015; Samieri et al., 2014). Future versions of the USDA flavonoid databases and the eBASIS database may provide increased flavonoid content to provide more accurate estimates of flavonoid intake for an even greater number of foods. Therefore, future research should include the use of the most current version of these or other available databases and to combine them when possible.

A final recommendation for future research is to further examine the effect of individual flavonoid subclasses on COPD, COPD severity, systemic inflammation, and comorbidity. Individual flavonoid subclasses offer greater bioavailability than others, which reflect variations in the ability of each subclass to enact antioxidant and anti-inflammatory properties throughout the body. Isoflavones seem to have the most bioavailability after being consumed, while flavan-3-ols and anthocyanidins are the most poorly absorbed (Barnes et al., 2011; Kumar & Pandey, 2013a; Manach, Williamson, Morand, Scalbert, & Remesy, 2005). As such, I recommended that considerations for the effects of dietary composition on the bioavailability of flavonoids are incorporated in future research. As described above, some dietary constituents increase the bioavailability of flavonoids while others reduce bioavailability. Therefore, it would be of interest to examine the potential relationship between each flavonoid subclass and COPD, COPD severity, systemic inflammation, and comorbidity burden to accounting for variations in bioavailability of each flavonoid subclass. Furthermore, it is recommended to stratify the study population by high and low intake of dietary fat, soluble and insoluble fiber, and proteins to account for potential effects on flavonoid bioavailability. Taken together, these recommendations are provided to further expand the understanding of the relationship between flavonoid intake and COPD, which can serve to inform public health policy and effect positive social change.

Implications for Social Change

The results obtained from this study offer some implications for social change by potentially improving population-based health outcomes. The literature indicates that a

healthy diet high in fruits and vegetables plays a substantial role in the development of a wide range of chronic diseases, including COPD (Boeing et al., 2012; Chiuve et al., 2012; Li et al., 2014; Mekary, 2015). However, most Americans consume insufficient servings of fruits and vegetables to meet recommendations for maintaining a healthy diet (Slavin & Lloyd**,** 2012). Findings from this study show that higher intake of dietary flavonoids may have a substantial effect on COPD, systemic inflammation, and the accumulation of multiple comorbid diseases. These results can be used by public health advocates to inform public health policy and support recommendations and national goals for nutrition, such as the Healthy People 2020 objectives that call for greater fruit and vegetable intake (Healthy People, 2017). Also, it is likely that maintaining a healthy diet is also indicative of other positive lifestyle behaviors that improve overall health, such as abstaining from smoking or smoking cessation. Smoking is associated with several poor health outcomes in addition to COPD, such as lung cancer, heart disease, and stroke (Thun et al., 2013). In this study, I found that smoking status was the strongest predictor of COPD, COPD severity, and systemic inflammation, with non-smokers having more favorable outcomes than current and former smokers. Therefore, another implication for social change derived from the results of this study is the added scientific support for current initiatives that target smoking cessation and reductions in second-hand smoke exposure.

COPD is the third leading cause of death within the United States and is responsible for millions of hospitalizations annually (ALA, 2014; CDC, 2012a). Therefore, COPD is a major public health concern within the United States that requires

evidence-based interventions informed by scientific research to reduce the mortality and morbidity associated with this disease. Ultimately, the results from this study have implications for effecting social change in this regard. Findings from this study can serve to inform public health policies that may help to reduce the morbidity and mortality of COPD and other comorbid diseases within the United States.

Conclusions

The results of this study further elucidated the relationship between dietary flavonoid intake and COPD among a broad sample of the US population. Results from multivariate regression analyses indicated that greater total daily flavonoid intake was associated with a reduced likelihood of COPD, a slight increase in FEV_1% predicted, and decreased serum CRP concentrations. The relationship between total daily flavonoid intake and FEV_1% predicted was very small, and not practically significant, given the small magnitude of change in FEV_1% predicted that was observed in this study. Results from a one-way ANOVA indicated that statistically significant differences in mean total daily flavonoid intake were present between all comorbidity burden level groups. These results showed that the mean total daily flavonoid intake among those with two or three comorbid diseases was lower than among those with one comorbid disease or none. The findings from the present study have implications for promoting healthy dietary behavior and an overall healthy lifestyle among people in the United States. Subsequently, changes in dietary behavior and lifestyle choices can ultimately help to reduce the morbidity and mortality associated with COPD and other chronic diseases.

While this study has further elucidated the relationship between dietary flavonoid intake and FEV_1% predicted, CRP, and comorbidity burden outcomes, identifying temporal relationships or causation outside the scope of this study because I used a cross-sectional study design. Therefore, further research is recommended using prospective longitudinal study designs to fully explore the associations identified in this study and potentially identify temporal relationships and establish causation. Taken together, the results from this study, along with those of prior and future studies, can serve to inform public health policy and effect positive social change with regard to reducing the morbidity and mortality of COPD and potentially other chronic diseases.

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