THE ASSOCIATION BETWEEN CAFFEINE INTAKE AND CARDIOVASCULAR MORTALITY: AN ANALYSIS OF THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) 1999-2014 DATABASE

by

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ABSTRACT

The Association between Caffeine Intake and Cardiovascular Mortality: An Analysis of the National Health and Nutrition Examination Survey (NHANES) 1999-2014 Database

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Sixty-four percent of adults in America drink coffee daily and 71% of caffeine intake comes from coffee in the United States (US) diet. Cardiovascular disease (CVD) is the number one cause of death in the US. The purpose of this study was to examine the association between caffeine intake and CVD mortality in a nationally representative sample of the US civilian non-institutionalized population. The association between caffeine intake and CVD mortality among 21,938 participants (age ranging from 20 to 85 years) in the NHANES 1999-2014 database was examined by multivariate Cox's proportional hazards regression model. Daily caffeine intake was assessed once at enrollment. Mortality data came from the 2015 Public-use Linked Mortality Files (LMF). A total of 2,206 deaths occurred, including 394 cases of CVD death. Compared with those with a caffeine intake of < 100 mg/day (1 cup/8 oz/240 ml of coffee contains about 100 mg caffeine), the hazard ratios (HRs) for CVD mortality were significantly lower in the participants with a caffeine intake of 100-200 mg/day (HR, 0.63; 95% CI, 0.45-0.88; $p = 0.008$), and those with a caffeine intake of > 200 mg/day (HR, 0.70; 95% CI, 0.53-0.94; $p = 0.02$), after

adjusting for age, race, gender, education, income, body mass index (BMI), smoking status, total daily intake of energy, carbohydrates, protein, and fat, and presence of diabetes, hypertension (HTN), CVD (excluding HTN), and cancer at enrollment. Higher caffeine intake (compared to < 100 mg/day as the reference group) was associated with lower CVD mortality. Further research is needed to figure out the mechanism of this inverse association. The current study cannot prove cause-effect relationship.

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Pursuing a Ph.D. degree in Nursing has been the most difficult decision I had to make, but also the most rewarding experience I have ever had. As I am working on the last chapter of this journey, I could not help but wonder how different my life would be if I had not started this program back in August 2016.

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CHAPTER 1

INTRODUCTION

The Americans consume 200 mg caffeine per person per day, and the United States (US) ranks number 11 among the countries with the highest caffeine consumption (Food and Agriculture Organization [FAO], 2015). Seventy-one percent of caffeine intake comes from coffee in the US diet (Frary et al., 2005). Coffee is one of the most consumed beverages in the US and around the world. According to the 2019 National Coffee Data Trends released by the National Coffee Association (NCA), 64% of adults in America drink coffee daily and the average coffee intake is 3.1 cups/day (containing about 310 mg caffeine; NCA, 2019). The global consumption of coffee was estimated to be 7 million tons per year (FAO, 2015). Coffee is a complex beverage containing more than 1,000 biologically active compounds, among which caffeine is the most studied component. Traditionally, people were recommended to reduce or avoid coffee, especially those with a history of cardiovascular disease (CVD), because it increases blood pressure (BP; Noordzij et al., 2005), total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (Cai et al., 2012; Jee et al., 2001). More recent studies have reported that coffee improves insulin sensitivity, reduces chronic inflammation and liver enzymes, and may be inversely associated with all-cause and some of the cause-specific mortality rates (Andersen et al., 2006; Arnlov et al., 2004; Jacobs et al., 2014; Koloverous et al., 2015; Loftfield, Shiels et al., 2015; Lopez-Garcia et al., 2006; Martini et al., 2016).

CVD usually includes coronary heart disease (CHD), heart failure (HF), stroke, and hypertension (HTN; Virani et al., 2020). In 2016, the prevalence of CVD in adults aged 20 years or older was 48% (121.5 million) and it increases with age in both men and women (Virani et al.,

2020). CVD is the major cause of death in the US. More people die from CVD each year than cancer and chronic lung disease combined (National Center for Health Statistics [NCHS], 2016). The age-adjusted mortality rate attributable to CVD was 258.2 per 100,000 populations in 2016 (Virani et al., 2020). The direct and indirect cost of CVD was estimated to be $351.2 billion in 2015 (Virani et al., 2020).

Most previous studies (Andersen et al., 2006; Freedman et al., 2012; Loftfield et al., 2018) categorized participants based on how many cups of coffee they drank daily. However, the cup size was not standardized and the caffeine content in each cup of coffee was different (Cano-Marquina et al., 2013). Few studies have examined the association between caffeine intake and CVD mortality. The purpose of this study was to examine the association between caffeine intake and CVD mortality by examining the National Health and Nutrition Examination Survey (NHANES) 1999-2014 database. This chapter will include the background and significance of this research problem. The theoretical framework utilized by this study will be described. The purpose of the research study and the research question will be presented.

Background and Significance

Over 70 countries produce coffee, but more than 50% comes from three countries: China, Angola, and Myanmar (FAO, 2015). The US imports about 30% of the world's coffee (Lundsbert, 1998). In 2012, total exports of 7 million tons of coffee accounted for a value of $24 billion (FAO, 2015). It was estimated that 2.25 billion cups of coffee were consumed worldwide per day, and this consumption continues to grow at a rate of 1.3% per year (FAO, 2015). Sixty-four percent of adults in America drink coffee daily (NCA, 2019), consuming over 400 million cups/day with the highest per capital coffee intake of any country (O'Keefe et al., 2013).

Seventy-one percent of caffeine intake comes from coffee in the US diet (Frary et al., 2005). Since coffee is consumed regularly over the life course, it is important to identify the benefits and risks associated with coffee intake.

CVD is a major health care problem affecting 121.5 million adults aged 20 years or older in the US (Virani et al., 2020). The prevalence of CVD excluding HTN is 9.0% (24.3 million adults) in 2016 (Virani et al., 2020). CVD accounted for 859,125 deaths in 2017, which was the number one cause of death in the US (Virani et al., 2020). In 2016, there were 72,128,000 physician office visits and 4,774,000 emergency department visits with a primary diagnosis of CVD (Virani et al., 2020). CVD costs the US $351.2 billion annually, and it was estimated to increase to $1.1 trillion in 2035 (Virani et al., 2020).

CVD is the leading global cause of death, claiming 17.92 million lives every year (Roth et al., 2017). In 2015, CVD was responsible for 32% of all deaths in the world (Institute for Health Metrics and Evaluation [IHME], 2016). Because of its significant burden, it is important to identify lifestyle factors to improve CVD mortality rates. The risk factors for CVD include diet, high systolic blood pressure (SBP), high body mass index (BMI), high total cholesterol level, high fasting plasma glucose level, tobacco smoking, and low levels of physical activity (Virani et al., 2020). In 2005, high BP was the single largest risk factor for CVD mortality in the US and accounted for an estimated 395,000 CVD deaths (45% of all CVD deaths; Virani et al., 2020).

There are more than 1,000 compounds in coffee, such as caffeine, phenolic compounds, and diterpenes (Cano-Marquina et al., 2013), among which caffeine is the most investigated component. Caffeine was reported to raise BP (Noordzij et al., 2005), increase arterial stiffness

and circulating norepinephrine, and decrease endothelial-dependent vasodilation (Riksen et al., 2009). This effect maybe acute and does not influence BP over the long-term (Winkelmayer et al., 2005), but it is still unclear. On the other hand, some other compounds in coffee have been associated with lower levels of inflammation, insulin resistance, and risk for diabetes (Lopez-Garcia et al., 2006; van Dam & Hu, 2005). The overall effect of coffee consumption is still under investigation. Because of its popularity, any benefits or risks of coffee intake will have a profound public health implication.

The NHANES is a periodic survey conducted by the NCHS of the Centers for Disease Control and Prevention (CDC). It is a national effort to assess the health and nutritional status of children and adults in the US (CDC, 2017). NHANES employed a stratified multistage probability sampling design to enable representation of the non-institutionalized civilian population of the US (CDC, 2017). Participants are randomly selected through a complex statistical process each year, and they complete personal structured interviews at home and then have physical examinations at the mobile examination centers (MEC; CDC, 2017). The physical examination includes medical, dental, height, weight, and laboratory tests. Three studies (Greenberg et al., 2007; Loomba et al., 2016; Tsujimoto et al., 2017) have been conducted to examine the association between coffee/caffeine intake and CVD mortality using the NHANES database, but the results have been conflicting. Greenberg et al. (2007) reported that there was an inverse association between caffeinated beverage intake and CVD mortality while the other two studies (Loomba et al., 2016; Tsujimoto et al., 2017) reported no association. Since there are limited and conflicting results regarding this association, further research is needed to assess if caffeine intake is associated with CVD mortality.

Theoretical Framework

The theoretical framework utilized in this dissertation is the middle-range theory of self-care of chronic illness developed by Riegel et al. (2012). It is an important theory because half of the adults in the US have at least one chronic illness (Ward et al., 2014). Self-care is very important for people with chronic illness because it leads to better clinical outcomes (Riegel et al., 2012). According to Riegel and Dickson (2008), self-care is defined as "a naturalistic decision-making process involving the choice of behaviors that maintain physiological stability (maintenance) and the response to symptoms when they occur (management)" (p. 190). The purpose of this theory is to clarify the elements of self-care, identify the relationships between the concepts, provide assumptions and propositions, and guide future nursing practice and research (Riegel et al., 2012). This theory is applicable to many chronic illnesses, such as diabetes (Fearon-Lynch et al., 2019), HTN (Dickson et al., 2017), and inflammatory bowel disease (Wickman et al., 2019).

Description of the Theory

Self-care is very important for people with chronic illness, but it is confusing in the literature (Riegel et al., 2012). Different researchers have been using different terms when discussing self-care behaviors, such as symptom monitoring, symptom management, self-monitoring, and self-management (Bennett et al., 2000; Carvalho, Bocchi, & Guimaraes, 2009; Creber et al., 2016; Riegel et al., 2012; Toukhsati et al., 2015). Under this circumstance, Riegel et al. (2012) developed this middle-range theory to discuss key concepts, assumptions, propositions, and outcomes. This theory also discussed the factors that affect self-care and provided implications for nursing practice and future research (Riegel et al., 2012). In 2008,

Riegel and Dickson developed the situation-specific theory of HF self-care, which provided the theoretical base for this middle-range theory (Riegel et al., 2012). Also, the theorists have conducted many research studies on self-care with HF patients in the US and Europe (Riegel et al., 2012).

Concepts

This theory has six key concepts: self-care maintenance, self-care monitoring, self-care management, decision making, reflection, and clinical outcomes (Riegel et al., 2012). Self-care maintenance are the activities patients perform to maintain health, enhance well-being, and improve physical and emotional health (Riegel et al., 2012). Healthy people use self-care to improve health, but for patients with chronic illness, self-care maintenance includes food choices (caffeine intake is part of the food choices), smoking cessation, exercise, stress reduction, weight management, and medication adherence (Riegel et al., 2012).

Self-care monitoring is defined as the assessment to see if there is any change in the manifestations (Riegel et al., 2012). For example, HF patients need to weigh themselves daily to see if there is any change; diabetes patients need to check their blood glucose level regularly (Riegel et al., 2012). If they can recognize the change in the manifestations, they are more likely to take self-care actions (Riegel et al., 2012).

Self-care management are the actions patients take when they notice a change in the manifestations (Riegel et al., 2012). When the patients notice a change, they need to be able to figure out the reason and decide the action (Riegel et al., 2012). For example, if HF patients recognize that they gained extra weight due to fluid retention, they can take a diuretic (Lewis et

al., 2014). If patients with diabetes recognize that their tremors are due to low blood glucose level, they can take a few crackers (Lewis et al., 2014).

Riegel et al. (2012) stressed the importance of decision making and reflection in the process of self-care. The theorists used naturalistic as opposed to cognitive decision making to describe how patients make decisions in real-world (Riegel et al., 2012). Usually, patients are rushed to make a decision without having enough information (Riegel et al., 2012).

Reflection is defined as the careful consideration of a past action (Oluwatoyin, 2015). The purpose of reflection is to learn from past events and develop better actions for the future (Oluwatoyin, 2015). Patients should reflect on an action to decide if they should implement it again next time (Riegel et al., 2012). In an ideal situation, patients make good decisions and reflect on them to guide the future self-care (Riegel et al., 2012).

Clinical outcomes are the results of patients after applying therapeutic interventions (Capuzzo & Moreno, 2010). Researchers are interested in different clinical outcomes, such as mortality rates, hospital readmission rates, and quality of life. Patients will have better clinical outcomes if they practice effective self-care (Riegel et al., 2012).

The Relationships between the Concepts

Assumptions. There are three assumptions in this middle-range theory (Dickson et al., 2011), and they can be summarized as follows:

1. General self-care differs from self-care for a certain illness.
2. To be able to make a decision, patients need to gather information, focus, reason logically, and compare options regarding benefits and risks.

3. Patients with multiple chronic illnesses may need to utilize a self-care strategy that conflicts the care for one of the illnesses. Literature suggested that self-care is very complicated for patients with multiple co-morbidities.

Propositions. This theory has seven propositions, which can be summarized as follows: Patients with different chronic illnesses use similar self-care strategies. Patients can learn the self-care process, and they need to reflect on their previous experience to improve self-care. Misconceptions can lead to ineffective self-care. Self-care management is more complicated than self-care maintenance. Patients with chronic illness need to perform self-care monitoring to notice a change, then they can perform self-care management. Evidence-based self-care strategies lead to better outcomes (Riegel et al., 2012). The following relationships between the concepts are identified from these propositions. Self-care maintenance, self-care monitoring, and self-care management are positively correlated with each other (Riegel et al., 2012; see Figure 1). According to Lee et al. (2015), self-care management increases when patients perform self-care monitoring. Self-care maintenance, self-care monitoring, and self-care management together are positively correlated with the clinical outcomes (Riegel et al., 2012). Consistent and effective self-care monitoring and management lead to better clinical outcomes, such as decreased hemoglobin A1c (HbA1c) level for a patient with diabetes (Ausili et al., 2017).

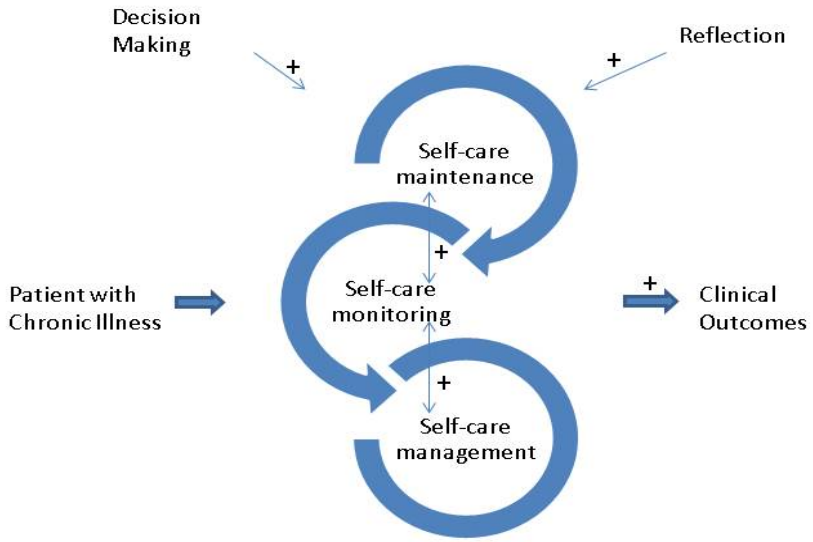
Decision making is positively correlated with self-care (Riegel et al., 2012; see Figure 1). The more patients practice decision making, the better they can perform self-care (Riegel et al., 2012). Research evidence is needed to support this relationship. Reflection is also positively correlated with self-care (Riegel et al., 2012). It was reported that guided reflection increased self-care maintenance and self-care management on HF patients (Sethares & Asselin, 2017).

Application to Current Study

This middle-range theory could serve as the theoretical framework for this dissertation because it includes the study variables in the model, and it provides hypothesis of the relationship between the study variables. This theory is applicable to people with chronic illness and well population (Riegel et al., 2012). The concepts of interest in this research study are self-care maintenance and clinical outcomes, in this case, CVD mortality rates. Self-care maintenance are the activities patients perform to maintain health (Riegel et al., 2012). Self-care maintenance includes food choices, exercise, coping with stress, taking medication as prescribed, and smoking cessation. The 2015-2020 US Dietary Guidelines suggested that moderate coffee consumption (three to five 8-oz cups/day or up to 400 mg/day of caffeine) can be a part of a healthy diet (US Department of Health and Human Services [DHHS] and Department of Agriculture [DOA], 2015). Operationally in this study, daily caffeine intake measured in mg/day is the self-care maintenance variable. Clinical outcome is defined as the result of patients after applying therapeutic interventions (Capuzzo & Moreno, 2010). Operationally in this study, CVD mortality rate is the clinical outcome variable. According to this theory, self-care is consisted of self-care maintenance, self-care monitoring, and self-care management; and self-care maintenance is correlated with the clinical outcome (Riegel et al., 2012). Operationally in this study, is there an association between daily caffeine intake and CVD mortality?

Figure 1

The Middle Range Theory of Self-care of Chronic Illness



Adapted from "A Middle-range Theory of Self-care of Chronic Illness," by B. Riegel, T. Jaarsma, and A. Strömberg, 2012, *Advances in Nursing Science, 35*(3), p.199 (http://doi.org/10.1097/ANS.0B013e318261b1ba)

Research Purpose

The purpose of this study was to examine the association between caffeine intake and CVD mortality in a nationally representative sample of the US civilian non-institutionalized population.

Research Question

The research question was: In a nationally representative sample of the US civilian non-institutionalized population, is there an association between caffeine intake and CVD mortality?

Summary

This chapter introduced the background and significance of the research problem. The theoretical framework utilized by this study was explained in detail. The research purpose and research question were presented.

CHAPTER 2

LITERATURE REVIEW

The Americans consume 200 mg caffeine per person per day, and US ranks number 11 among the countries with the highest caffeine consumption (FAO, 2015). Seventy-one percent of caffeine intake comes from coffee in the US diet (Frary et al., 2005). Coffee has long been one of the most consumed beverages worldwide, so even a slight health effect can have a profound public health implication. Caffeine is the most widely known component in coffee, although it can also be provided by tea, soda, energy drinks, and chocolate and cocoa-containing products (Drewnowski & Rehm, 2016). Recent epidemiology studies have yielded conflicting results, with some studies claiming an inverse association between coffee intake and CVD mortality (Ding et al., 2015; Freedman et al., 2012; Greenberg et al., 2007; Loftfield et al., 2018; Lopez-Garcia et al., 2008; Park et al., 2017), while others have found no effect (Loomba et al., 2016; A. T. Nordestgaard & Nordestgaard, 2016; Tsujimoto et al., 2017; Yamakawa et al., 2019). The purpose of this literature review was to identify what is known and not known about the association between coffee intake and CVD mortality.

CVD is the number one cause of death in the US for both men and women regardless of their ethnic groups (Virani et al., 2020). The age-adjusted mortality rate attributable to CVD was 258.2 per 100,000 populations in 2016 (Virani et al., 2020). More people die from CVD each year than cancer and chronic lung disease combined (NCHS, 2016). One of the American Heart Association's (AHA) 2020 Impact Goals is to reduce the CVD mortality rate by 20% (Lloyd-Jones et al., 2010), so it is important to identify lifestyle factors that may influence this crucial clinical outcome.

Data Sources and Search Strategy

Existing literature on the association between coffee intake and CVD mortality were retrieved by searching Ovid Medline, Pubmed, and Scopus with no restriction on publication dates. The keywords used include cardiovascular disease, heart disease, coffee, caffeine, mortality, and cause of death. The criteria for inclusion of articles for review were original research on adults that were peer reviewed and written in English. The initial search resulted in a total of 487 papers as of January 8, 2020. All papers were exported into EndNote and 127 duplicates were removed mechanically. The second step for article selection was based on a review of the published abstracts for its consistency with the inclusion criteria and resulted in the selection of 77 articles. Next, the full texts and the abstracts were reviewed again, and some articles were excluded due to the reasons listed in Figure 2. Finally, 30 studies were included in this literature review. Figure 2 presents a flowchart depicting the selection process.

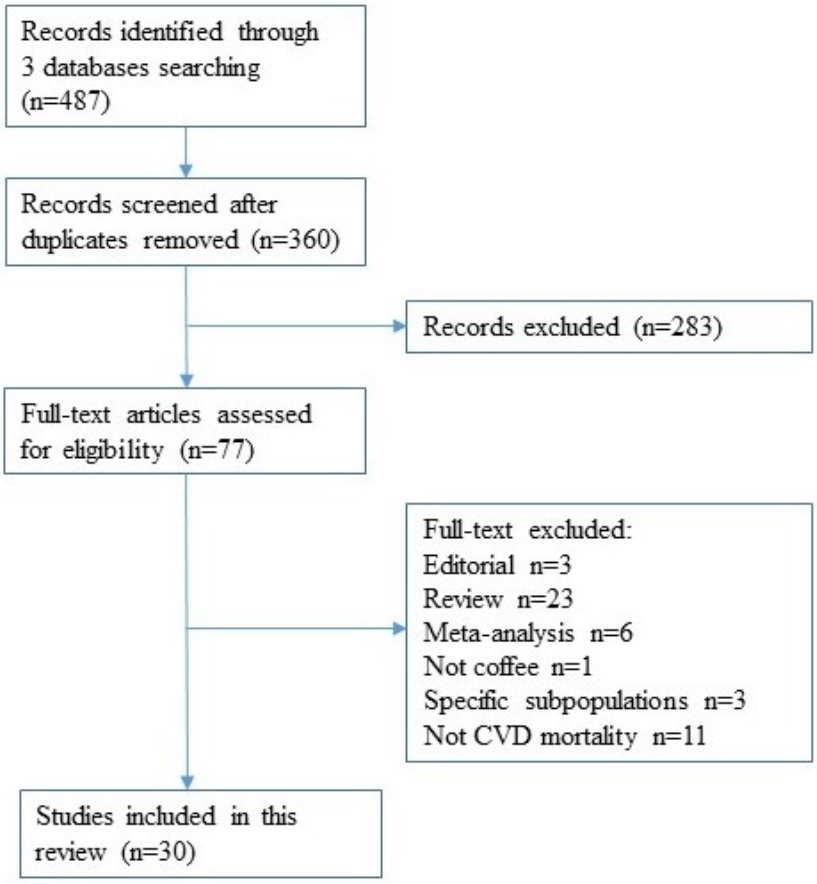
Coffee's Effects on Cardiovascular Disease

Coffee consumption worldwide has been growing at a rate of 1.3% per year since 1998 (FAO, 2015). It was thought to be a risk factor for CVD because coffee can increase BP (Noordzij et al., 2005), total cholesterol, LDL cholesterol, and triglycerides (Cai et al., 2012; Jee et al., 2001). However, coffee also has antioxidant and anti-mutagenic capacity, improves insulin sensitivity and vascular function, reduces chronic inflammation, and has positive effects on liver enzymes and endothelial function (Andersen et al., 2006; Arnlov et al., 2004; Jacobs et al., 2014; Koloverous et al., 2015; Loftfield, Shiels et al., 2015; Lopez-Garcia et al., 2006; Martini et al., 2016). Because of this more positive profile, the 2015-2020 US Dietary Guidelines suggested that moderate coffee consumption (three to five 8-oz cups/day or up to 400 mg/day of caffeine)

can be a part of a healthy diet (US DHHS and DOA, 2015). However, non-coffee drinkers are not encouraged to incorporate coffee into their eating patterns.

Figure 2

Flowchart of the Literature Search



Caffeine is by far the most studied component in coffee, and it is the main reason people tend to drink coffee habitually over the life course (Bhatti et al., 2013). The concentration of caffeine is highest in coffee compared to other dietary products (Cano-Marquina et al., 2013). A meta-analysis reported a slight increase in both SBP (1.22 mmHg) and diastolic pressure (0.49 mmHg) with an intake of 295-750 mg caffeine for up to 3 hours (Noordzij et al., 2005).

Traditionally, people are advised to avoid or reduce coffee intake especially those people who have CVD risk factors (Jick et al., 1973). More recent studies suggested that there was an inverse association between coffee intake and all-cause mortality (Abe et al., 2019; Ding et al., 2015; Freedman et al., 2012; Lopez-Garcia et al., 2008); however, the association between coffee intake and CVD mortality among previous studies have been highly variable (Freedman et al., 2012; Liu et al., 2013; Loomba et al., 2016).

Out of the 30 studies included in this literature review, 29 studies examined the association between coffee intake and CVD mortality; only one study examined the association between caffeine intake and CVD mortality. The purpose of this literature review was to identify what is known and not known about the association between coffee intake and CVD mortality. Information regarding the authors, publication year, study location, follow-up years, age, highest category of coffee intake, sample size, number of CVD deaths, covariates, and main findings were manually extracted for each of the 30 studies and presented in Table 1. Some studies have suggested an inverse association between coffee intake and CVD mortality (Andersen et al., 2006; Ding et al., 2015; Freedman et al., 2012; Greenberg et al., 2007; Loftfield et al., 2018; Lopez-Garcia et al., 2008; Park et al., 2017), while others have found no effect (Loomba et al., 2016; Tsujimoto et al., 2017; Yamakawa et al., 2019).

Some researchers suggested that the reason for the highly variable results from previous studies may be that different studies have been focusing on different age groups (Liu et al., 2013). However, the mean age of the Aerobics Center Longitudinal Study (Liu et al., 2013) is 43, which is not that different from the Scandinavian Women's Lifestyle and Health Cohort's 40 (Lof et al., 2015) or the Health Professionals Follow-up Study and Nurses' Health Study's 46 (Lopez-Garcia

et al., 2008). Most of the other studies did focus on older age groups. Liu et al. (2013) suggested that this inverse association between coffee intake and CVD mortality among older age groups was due to survival selection. However, Ding et al. (2015) reported that this inverse association was stronger among younger people.

Most of the studies that reported inverse association between coffee intake and CVD mortality have been conducted among white participants, but there are a few studies using other populations: such as Asians (Mineharu et al., 2011; Saito et al., 2015), Hispanics (Torres-Collado et al., 2019), non-whites (Park et al., 2017), even among patients with a history of myocardial infarction (MI; van Dongen et al., 2017). The researchers used participants from different countries: such as the United Kingdom (Loftield et al., 2018), Japan (Mineharu et al., 2011; Saito et al., 2015), US (Andersen et al., 2006; Ding et al., 2015; Freedman et al., 2012; Greenberg et al., 2007; Greenberg et al., 2008; Loftfield, Freedman et al., 2015; Lopez-Garcia et al., 2008; Park et al., 2017), Netherlands (van Dongen et al., 2017), Finland (Happonen et al., 2008), and Eastern European countries (Grosso et al., 2017). The Northern Manhattan Study (NOMAS; Gardener et al., 2013) reported a strong inverse association between coffee consumption and vascular-related mortality (stroke, MI, heart failure, pulmonary embolus, and cardiac arrhythmia) among Hispanics (but not among whites or blacks), which is the only study that reported a different association across ethnic groups.

The Health Professionals Follow-up Study and the Nurses' Health Study (Lopez-Garcia et al., 2008) examined 41,736 men and 86,214 women with no history of CVD or cancer at baseline. The hazard ratio (HR) of CVD mortality among men who drank 6 or more cups of coffee per day (137 mg caffeine per cup of coffee), as compared with men who drank less than 1

cup/month, was 0.56 (95% confidence interval [CI], 0.31-1.03; $p = 0.03$); and for women the HR was 0.81 (95% CI, 0.61-1.06; $p < 0.001$). Although it is worth mentioning that among the group of men who drank 6 or more cups/day, only 15 CVD deaths happened during the 18 years of follow-up, which may raise some concerns on the reliability of the results due to the small number of CVD events. Freedman and colleagues (2012) followed a cohort of 402,260 people for 14 years and found that men who drank 6 or more cups/day (researchers did not specify the cup size) had a 12% lower risk of CVD mortality compared to non-consumers whereas women in this category of consumption had a 28% lower risk. Loftfield et al. (2018) followed 498,134 participants over 10 years and found that people who drank 6-7 cups of coffee per day (researchers did not specify the cup size) had a 13% lower risk to die from CVD compared to non-coffee drinkers. A recent meta-analysis (Kim et al., 2019) pooled 40 studies with 3,852,651 participants and reported that the lowest HR was an intake of 2.5 cups of coffee per day for CVD mortality (HR, 0.83; 95% CI, 0.80-0.87; $p < 0.001$).

It is suggested that the association between coffee intake and CVD mortality is dose dependent (Crippa et al., 2014; Freedman et al., 2012; Greenberg et al., 2007; Grosso et al., 2017). For example, Grosso et al. (2017) found an inverse association between coffee intake and CVD mortality, but the effect disappeared when participants drank more than 4 cups of coffee per day. The hypothesis was that high intake of coffee might have an acute effect at the vascular level and it could increase the risk of MI among people at high CVD risk, which could increase CVD mortality rates (Greenberg et al., 2007). However, Freedman et al. (2012) reported an inverse association even among people who drank 6 or more cups of coffee per day. Although, there were fewer participants in that category with fewer CVD deaths, which might limit the

statistical power of that group (Lopez-Garcia et al., 2008). According to Freedman et al. (2012), the lowest risk group were people who drank two to four cups of coffee per day.

Some researchers have suggested a U-shaped (Andersen et al., 2006; Mineharu et al., 2011) or J-shaped (LeGrady et al., 1987; Mostofsky et al., 2012) association between coffee intake and CVD mortality. According to Andersen et al. (2006), the HRs for CVD mortality were 0.85 (95% CI, 0.68-1.06), 0.76 (95% CI, 0.64-0.91), 0.81 (95% CI, 0.66-0.99), and 0.87 (95% CI, 0.69-1.09) for people who drank < 1, 1-3, 4-5, and ≥ 6 cups (1 cup = 240 ml) of coffee per day respectively compared to non-coffee drinkers, suggesting a U-shaped association. Also, the association between coffee intake and CVD mortality appeared greater within the first few years of follow-up and then gradually attenuated (Happonen et al., 2008; Loftfield, Freedman et al., 2015; Torres-Collado et al., 2019). Torres-Collado et al. (2019) suggested that it was probably due to fewer participants at the end of the study period and some participants might reduce coffee consumption as they age, although Freedman et al. (2012) have found similar associations occurring in different categories of follow-up time (0 to < 4 years, 4 to < 9 years, and 9 to 14 years).

Caffeine and Other Bioactive Compounds

Among the studies that reported an inverse association between coffee intake and CVD mortality, researchers do not have a consensus whether this association is due to caffeine or other bioactive substances in coffee (Freedman et al., 2012; Greenberg et al., 2007; Loftfield et al., 2018; Loftfield, Freedman et al., 2015). Greenberg et al. (2007) found protective effect from caffeinated beverages but not from decaffeinated beverages, although the other three studies (Freedman et al., 2012; Loftfield et al., 2018; Loftfield, Freedman et al., 2015) observed similar

associations from caffeinated and decaffeinated coffee. Even decaffeinated coffee contains small amount of caffeine, with an 8-oz cup containing approximately 5-15 mg caffeine (McCusker et al., 2006). Tsujimoto et al. (2017) reported that people who drank no coffee or decaffeinated coffee only consume some caffeine, and their daily caffeine intake increased with higher decaffeinated coffee consumption. More research is needed to examine if caffeinated and decaffeinated coffee have different effects on CVD mortality.

There are up to 1,000 biologically active compounds in coffee, including caffeine, polyphenols, diterpenes, magnesium, trigonelline, quinides, lignans and so on (Cano-Marquina et al., 2013). Coffee is the number one source of antioxidants in the US diet (Halvorsen et al., 2006). In Norway, coffee provides more than 60% of total dietary antioxidants (A. Svilaas et al., 2004). The antioxidants in coffee have been found to improve glucose and lipid metabolism, reduce chronic inflammation and oxidative stress in the atherosclerotic process (Rebello & van Dam, 2013). This may counterbalance some of the harmful effects from caffeine, such as stimulating the release of epinephrine, inhibiting insulin activity, and increasing BP and homocysteine levels (Hartley et al., 2004). Forty percent of polyphenol (antioxidant) intake comes from coffee (Zamora-Ros et al., 2016). An average cup of brewed coffee includes 396 mg polyphenols with up to 100 mg chlorogenic acid, which was reported to improve glucose metabolism (Gardener et al., 2013). However, it is still unclear which component in coffee is responsible for this reported inverse association with CVD mortality.

Since HTN is the single largest risk factor for CVD mortality in the US and accounted for 45% of all CVD deaths in 2005 (Virani et al., 2020), understanding the effects of coffee/caffeine intake on BP is very important. Although regular caffeine intake increases BP, when ingested

through coffee, the pressure effect is small (Noordzij et al., 2005). This mainly affects naïve coffee drinkers not the habitual drinkers (Corti et al., 2002) and only for about 3 hours (Robertson et al., 1978). People develop tolerance to coffee after only 4-5 days of administration (Ammon et al., 1983; Robertson et al., 1981), although not all coffee drinkers develop this tolerance (Lovallo et al., 2004). Besides, the chlorogenic acids and potassium in coffee generally decrease BP (Kozuma et al., 2005). A recent systematic review suggested a neutral effect of coffee intake on BP among habitual drinkers (Steffen et al., 2012).

Preparation Methods and Coffee Additives

The different preparation methods of coffee may also have an effect, but most studies did not collect this information, so more research is needed to identify the preparation method that offers the most benefits. Some researchers suggested that ground coffee had stronger associations with CVD mortality than instant or decaffeinated coffee (Greenberg et al., 2007; Loftield et al., 2018), probably because there were lower amounts of bioactive compounds (including polyphenols) in instant coffee compared to ground coffee (Rodrigues & Bragagnolo, 2013).

It was believed that coffee additives (milk, cream, and sugar) might be a risk factor for CVD, but studies have found that the inverse association with CVD mortality is present for coffee with or without additives (Loftfield, Freedman et al., 2015; van Dongen et al., 2017). However, consumers should consider other health effects from the additives, such as added calories, fat, and sugar, especially for people with co-morbidities, such as diabetes.

Coffee Consumption and Genetic Variations

Researchers have identified some of the genes with roles in coffee metabolism. Some people are fast metabolizers while others are slow metabolizers. It was reported that common genetic polymorphisms predisposing people to faster coffee metabolism were associated with higher coffee intake (Taylor et al., 2018). However, Loftfield et al. (2018) found that these genetic polymorphisms did not modify the association between coffee intake and CVD mortality. For people with slower coffee metabolism, coffee increases the risk of HTN (Palatini et al., 2009) and MI (Cornelis et al., 2006), but for people with faster coffee metabolism, it decreases the risk of HTN (Palatini et al., 2009). Since HTN is the single largest risk factor for CVD mortality in the US (Virani et al., 2020), it is surprising that slower and faster coffee metabolizers had similar associations between coffee intake and CVD mortality. More research is needed to examine the effects of genetic variation in coffee metabolism on this association.

Different Effects of Coffee among Men and Women

Some studies have suggested a different effect of coffee intake on CVD mortality among men and women. Coffee intake has been associated with a decreased CVD mortality in women (Andersen et al., 2006; van den Brandt, 2018), but this effect is less pronounced in men (Gunter et al., 2017; Lopez-Garcia et al., 2008), or there is no significant association in men (Sado et al., 2019; Sugiyama et al., 2010). Abe et al. (2019) reported a dose-dependent response in women. Specifically, coffee was protective in the 1-2 cups per day group among women but became a CVD risk factor for those who drank more than 5 cups per day (Abe et al, 2019). This dose-dependent response was not found in men (Abe et al, 2019). In general, it seems like coffee

consumption benefits women more than men (Gunter et al., 2017; Lopez-Garcia et al., 2008); only one study reported opposite findings (Yamakawa et al., 2019).

Some of the possible explanations suggested are, in men, coffee intake increases BP by increasing peripheral vascular resistance, but in women, it increases stroke volume and cardiac output with no change in peripheral vascular resistance (Hartley et al., 2004; Pincomb et al., 1985). This difference may contribute to the observed different associations with CVD mortality between men and women. Lopez-Garcia et al. (2008) suggested that this different effect among men and women might be due to a difference in follow-up time, different distribution of causes of death, and different age ranges. Gunter et al. (2017) reported that, among women only, coffee drinkers had a higher level of high-density lipoprotein (HDL) cholesterol, and lower levels of C-reactive protein, lipoprotein (a), and HbA1c. These biomarkers have been associated with CVD (Lewis et al., 2014), which offers a possible explanation for the observed difference between men and women. Sisti et al. (2015) suggested that coffee changed estrogen metabolism. Yamakawa et al. (2019) suggested that women reported coffee intake less accurately than men.

Confounding Variables

Coffee Consumption and Smoking

It has been established that coffee consumption is associated with smoking (Freedman et al., 2012; Lopez-Garcia et al., 2008), but it is not clear how smoking status moderates the association between coffee intake and CVD mortality. Loftield et al. (2018) reported a stronger association among smokers than never-smokers, while other researchers reported a stronger association among never smokers or former smokers than current smokers (Ding et al., 2015;

Freedman et al., 2012; Grosso et al., 2017; Loftfield, Freedman et al., 2015). Nevertheless, smoking status should be controlled during data analysis because it is a potent CVD risk factor.

Other Confounding Variables

Characteristics of coffee drinkers could confound the association between coffee intake and CVD mortality. Some studies reported that coffee drinkers tend to have lower BMI (Andersen et al., 2006; Mineharu et al., 2011; Sugiyama et al., 2010; Tsujimoto et al., 2017), while others found the opposite (Greenberg et al., 2008; Loftfield, Freedman et al., 2015; van den Brandt, 2018). This is probably due to whether participants drink black coffee or add coffee additives, since a cup of specialty coffee (with cream and sugar) could provide 200 or more calories (Loftfield, Freedman et al., 2015). Coffee drinkers tend to have a higher daily intake of total energy (Andersen et al., 2006; Loftfield, Freedman et al., 2015; Sugiyama et al., 2010; Tsujimoto et al., 2017; van Dongen et al., 2017; Yamakawa et al., 2019), fat (Loftfield, Freedman et al., 2015; Tsujimoto et al., 2017), carbohydrates (Tsujimoto et al., 2017), and protein (Tsujimoto et al., 2017). Coffee drinkers tend to have a lower prevalence of diabetes (de Koning Gans et al., 2010; Happonen et al., 2008; Loftfield, Freedman et al., 2015; Mineharu et al., 2011; Saito et al., 2015; Tsujimoto et al., 2017; Yamakawa et al., 2019), and HTN (Grosso et al., 2016; Mineharu et al., 2011; Saito et al., 2015; Torres-Collado et al., 2019; Tsujimoto et al., 2017). Based on these findings from previous research, the confounding variables that were controlled in this study include age, gender, race, education, income, personal history of HTN, diabetes, CVD (excluding HTN), and cancer, smoking status, BMI, and total daily intake of energy, carbohydrates, fat, and protein.

Coffee's Effects on Non-cardiovascular Disease

Although the purpose of this review is to identify the association between coffee intake and CVD mortality, coffee's effects on some non-cardiovascular disease could influence CVD mortality rates. For example, 65-75% of people with diabetes die from CVD (Lewis et al., 2014), so the association between coffee intake and incidence of diabetes is of highly importance when discussing CVD mortality rates. It has been established that there is an inverse association between coffee consumption and the incidence of diabetes (Huxley et al., 2009) and serum biomarkers of inflammation (Lopez-Garcia et al., 2006). Besides, coffee intake was thought to be inversely associated with incidence of colorectal cancer (Woolcott et al., 2002), liver cancer (Inoue et al., 2009), Alzheimer's disease (Lindsay et al., 2002), and depression (Lucas et al., 2011). Previous studies also suggested an inverse association between coffee intake and mortality from respiratory disease (Freedman et al., 2012), infectious (Yamakawa et al., 2019), and digestive diseases (Gunter et al., 2017; Yamakawa et al., 2019).

The studies that reported no association between coffee intake and CVD mortality have been conducted among diverse populations, such as Americans (Liu et al., 2013; Loomba et al., 2016; Lopez-Garcia et al., 2011; Tsujimoto et al., 2017), Chinese (Odegaard et al., 2015), Croats (Jazbec et al., 2003), Dutch (de Koning Gans et al., 2010), and Swedish (Lof et al., 2015). The Aerobics Center Longitudinal Study reported no association between coffee consumption and CVD mortality but a positive association between heavy coffee consumption (> 28 cups per week) and all-cause mortality especially for people younger than 55 years (Liu et al., 2013). The Nurses' Health Study followed a cohort of 11,696 women with a history of CVD over 24 years and found no association between coffee consumption and CVD mortality (Lopez-Garcia et al.,

2011). In the Singapore Chinese Health study, 52,584 Chinese men and women with no history of CVD, diabetes, and cancer at baseline were followed for 18 years, and the HRs of CVD mortality for each category of coffee consumption did not reach statistical significance ($p = 0.28$; Odegaard et al., 2015).

There have been three studies, which examined the NHANES database looking for association between coffee/caffeine intake and CVD mortality (Greenberg et al., 2007; Loomba et al., 2016; Tsujimoto et al., 2017). Greenberg et al. (2007) examined NHANES I, which was conducted from 1971 to 1973; Loomba et al. (2016) examined NHANES III collected from 1988 to 1994, while Tsujimoto et al. (2017) examined NHANES for the period of 1999-2010. Greenberg et al. (2007) reported an inverse association between caffeinated beverages and CVD mortality while the other two studies reported no association. There are a few possible reasons that these studies have found conflicting results. First, Tsujimoto et al. (2017) divided the participants based on the caffeine intake into 4 groups (< 10, 10-99, 100-199, and ≥ 200 mg/day), while the other two studies divided the participants based on how many cups/servings of coffee/caffeinated beverages they consumed per day. The caffeine content in different servings of coffee is highly variable, which is why the current study is using daily caffeine intake instead of how many cups of coffee per day to categorize participants. Second, Loomba et al. (2016) only focused on coffee while the other two studies examined caffeine from other sources as well. Third, the mortality codes used in these three studies are different: Greenberg et al. (2007) used the International Classification of Diseases (ICD), Ninth Revision (ICD-9), although the categories covered was similar to Tsujimoto et al. (2017) that used ICD, Tenth Revision (ICD-10). Loomba et al. (2016), on the other hand, examined ischemia-related, heart failure-related,

and stroke-related mortality separately. Fourth, these three studies have examined different age groups: Loomba et al. (2016) focused on participants older than 45 years; Tsujimoto et al. (2017) examined people between 20 to 79 years of age, and the participants in Greenberg et al. (2007) aged 32-86 years. Finally, Greenberg et al. (2007) excluded participants with a self-reported history of CVD, while the other two studies did not exclude based on the participants' medical history. The sample size of these three studies ranges from 6,594 to 17,594, while the current study includes 21,938 participants. Out of the 30 studies included in this literature review, only one study (Tsujimoto et al., 2017) categorized participants according to the daily caffeine intake (mg/day) instead of how many cups of coffee consumed every day.

According to Greenberg et al. (2007), the HRs for CVD mortality were 1.00 (referent), 0.72 (95% CI, 0.52-0.99), 0.69 (95% CI, 0.52-0.92), and 0.53 (95% CI, 0.38-0.75) for < 0.5, 0.5-2, 2-4, and ≥ 4 servings/day of caffeinated beverages respectively (the estimated caffeine content in one serving of ground coffee was 159 mg, 83 mg for instant coffee, 42 mg for colas, and 36 mg for tea). Loomba et al. (2016) and Tsujimoto et al. (2017) found no association between coffee/caffeine intake and CVD mortality.

Summary

Because there is limited and conflicting evidence regarding the association between coffee/caffeine intake and CVD mortality especially the studies using the NHANES database, the purpose of this dissertation is to examine the association between caffeine intake and CVD mortality using the NHANES database from 1999 to 2014. The unique feature of this dissertation is that it includes the most recent data set from NHANES that also included linked mortality data.

Table 1

Characteristics of Studies Included in the Literature Review

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
Jazbec et al. (2003)	Croatia	1972-1999	1561M 1776F	35-59	> 2	254M 181F	Age, gender, smoking, DBP, stomach ulcer, feeling of well-being, region	No significant effects of coffee on CVD mortality
Andersen et al. (2006)	US	1986-2001	27312F	55-69	≥ 6	1411F	Age, smoking, intake of alcohol, BMI, waist-hip ratio, education, PA, use of estrogens, use of multivitamin supplements, energy intake, and intakes of whole and refined grain, red meat, fish, seafood,	Inverse association between coffee and CVD mortality

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
							total fruit and vegetables	
Greenberg et al. (2007)	US	1971-1984	6594	32-86	≥ 4	426	Age, gender, income, education, smoking, alcohol, PA, BMI, BP, diabetes, tea	Inverse association between caffeinated beverages and CVD mortality
Happonen et al. (2008)	Finland	1991-2005	311M 506F	70-94	≥ 7	344	Age, gender, BMI, smoking, calendar period, marital status, educational, previous occupational group, history of MI, presence of diabetes, cognitive impairment, physical disability	Inverse association between coffee and CVD mortality

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
Lopez-Garcia et al. (2008)	US	1980-2004	41736M 86214F		≥ 6	4417	Age, smoking, BMI, PA, alcohol, family history of MI, menopausal status, postmenopausal hormone replacement therapy (in women), multivitamin, energy intake, polyunsaturated, saturated, trans fat, glycemic load	Inverse association between coffee and CVD mortality
Greenberg et al. (2008)	US	1984-1996	1354	65-96	≥ 1	210	Age, gender, smoking, PA, alcohol, BMI, presence of CVD, marital status, BP, use of	Inverse association between coffee and CHD mortality

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
							antihypertensive	
Sugiyama et al. (2010)	Japan	1990-2001	18287M 19455F	40-64	≥ 3	426	Age, gender, BMI, smoking, alcohol, presence of HTN and diabetes, education, walking time, tea, rice, miso soup, meat, dairy products, fish, vegetables, fruits, energy	Inverse association between coffee and CVD mortality in women but not men
de Koning Gans et al. (2010)	Netherlands	1993-2006	37514		> 6	1950	Age, gender, education, PA, waist circumference, smoking, menopausal status, postmenopausal hormone replacement therapy (in	No significant effects of coffee on CVD mortality

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
							women), alcohol, tea, energy intake, saturated fat, fiber, vitamin C	
Mineharu et al. (2011)	Japan	1988-2003	76979	40-79	≥ 3	650	Age, BMI, smoking, alcohol, presence of HTN, diabetes, education, waking hours, PA, perceived mental stress, multivitamin use, fruits, vegetable, beans, meat, fish, energy intake	Inverse association between coffee and CVD mortality
Lopez-Garcia et	US	1980-2004	11697F		≥ 4	579	Age, smoking, BMI, PA, alcohol, family history of MI,	No significant effects of coffee on CVD

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
al. (2011)							menopausal status, postmenopausal hormone replacement therapy (in women), presence of HTN, hypercholesterolemia, diabetes, cancer, use of medications, energy intake, polyunsaturated, saturated, trans fat, glycemic load	mortality
Freedman et al. (2012)	US	1995-2008	229119M 173141F	50-71	≥ 6	8127	Age, gender, BMI, smoking, alcohol, race, education, health status, diabetes, marital status,	Inverse association between coffee and CVD mortality

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
							PA, energy intake, fruits, vegetables, red meat, white meat, saturate fat, and use of vitamin supplements, postmenopausal hormone	
Gardener et al. (2013)	US	1993-2012	2461	68	≥ 4	342	Age, gender, BMI, race, education, smoking, alcohol, energy, protein, carbohydrates, total fat, saturated fat, history of vascular risk factors, other non-water beverage consumption, coffee additives (milk, cream,	Inverse association between coffee and CVD mortality only in Hispanics

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
							nondairy creamer), tea	
Liu et al. (2013)	US	1971-2003	43727	20-87	> 28 cups/wk	804	Age, tea, PA, BMI, smoking, alcohol, presence of diabetes, HTN, hypercholesterolemia, and family history of CVD, fitness	No significant effects of coffee on CVD mortality
Odegaard et al. (2015)	Singapore	1993-2001	52584	45-74	≥ 2	3097	Age, gender, education, PA, sleep, BMI, presence of HTN, dietary pattern score, energy intake, tea, alcohol, soft drinks, juice	No significant effects of coffee on CVD mortality
Saito et al.	Japan	1990-	90914	40-69	≥ 5	1577	Age, gender, region, smoking,	Inverse association

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
(2015)		2011					alcohol, BMI, presence of HTN, diabetes, PA, tea, soda and juice, energy, fruit, vegetables, fish, meat, dairy products, rice, miso soup, job status	between coffee and CVD mortality
Loftfield, Freedman et al. (2015)	US	1993-2001	90317	55-74	≥ 4	1744	Age, gender, smoking, race, educational, marital status, employment status, presence of diabetes, BMI, supplemental vitamin, ibuprofen or aspirin use, menopausal hormone therapy, alcohol, energy intake,	Inverse association between coffee and CVD mortality

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
							red and processed meat, white meat, saturated fat, fruits, and vegetables	
Lof et al. (2015)	Sweden	1991-2010	49259F	30-49	> 5	158	BMI, education, smoking, alcohol, parity, and age at first birth	No significant effects of coffee on CVD mortality
Ding et al. (2015)	US	1984-2012	40557M 167944F	25-75	> 5	2587	Age, smoking, presence of HTN, hypercholesterolemia, BMI, PA, energy intake, sugar-sweetened beverage consumption, alcohol, menopausal, postmenopausal	Inverse association between coffee and CVD mortality

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
							hormone	
Loomba et al. (2016)	US	1988-2006	8608	≥ 45	≥ 6		Gender, race, total cholesterol, LDL, HDL	No significant effects of coffee on CVD mortality
Grosso et al. (2017)	Eastern Europe	2002-2011	13350M 15119F	45-69	> 4	914	Age, gender, smoking, BMI, educational, PA, alcohol (>12 g/d), presence of HTN, diabetes, hypercholesterolemia, CVD, cancer, family history of CVD, cancer, energy intake, vitamin supplement, menopausal status (in women)	Inverse association between coffee and CVD mortality

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
Park et al. (2017)	US	1993-2012	185855	45-75	≥ 4	21023	Age, gender, race, smoking, BMI, education, PA, alcohol, energy intake, fat, preexisting illness	Inverse association between coffee and CVD mortality
Gunter et al. (2017)	Europe	1992-2008	130662M 321081F	≥ 35	≥ 3	9106	Age, energy intake, BMI, PA, smoking, education, menopausal status, ever-use of contraceptive pill or menopausal hormone therapy, alcohol, red and processed meat, fruits, vegetables	Inverse association between coffee and CVD mortality in women only
van	Netherlands	2002-	4365	60-80	> 4	396	Age, gender, presence of	Inverse association

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
Dongen et al. (2017)		2013					diabetes, BMI, PA, education, smoking, alcohol, energy intake, tea, whole grains, red and processed meat, dairy, vegetables and fruits, chocolate, sugar-sweetened beverages	between coffee and CVD mortality
Tsujimoto et al. (2017)	US	1999-2010	17594	20-79	≥ 200 mg/day	303	Age, gender, race, education, smoking, BMI, presence of dyslipidemia, HTN, diabetes, CHD, HF, stroke, cancer, energy intake, carb, fat, protein	No association between caffeine intake and CVD mortality
van den	Netherlands	1986-	120852	55-69	≥ 6	1995M	Age, smoking, presence of	Inverse association

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
Brandt (2018)		1996				932F	HTN, diabetes, BMI, PA, education, alcohol, nuts, vegetables and fruit, tea, energy, use of nutritional supplements, postmenopausal hormone replacement therapy (in women)	between coffee and CVD mortality in women, positive association in men
Loftfield et al. (2018)	United Kingdom	2006-2016	498134	38-73	≥ 8	2833	Age, gender, smoking, race, alcohol, general health status, education, BMI, PA, tea	Inverse association between coffee and CVD mortality
Torres-Collado et	Spain	12 years	903	≥ 65	> 1	161	Age, gender, education, BMI, waist circumference, sleeping	Inverse association between coffee and

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
al. (2019)							time, smoking, presence of diabetes, high cholesterol, HTN, relative Mediterranean Diet, PA, leisure time	CVD mortality
Sado et al. (2019)	Japan	15 years	39685M 43124F	40-79	≥ 5	860	Age, presence of HTN, diabetes, stroke, heart disease, BMI, smoking, alcohol, type of job, type of insurance, consumption of rice, bread, meat, fish, egg, milk, green/ yellow vegetable, non-green and non-yellow vegetable, fruit,	Inverse association between coffee and CVD mortality in women

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
							miso soup, pickled vegetable, tea	
Abe et al. (2019)	Japan	17 years	144750M 168631F	> 40	≥ 5	7321	Age, region, smoking, alcohol, BMI, presence of diabetes, HTN, tea	Inverse association between coffee and CVD mortality in men. Dose-dependent response in women.
Yamakawa et al. (2019)	Japan	1992-2008	29079	≥ 35	≥ 4	1678	Age, gender, marital status, education, BMI, smoking, presence of diabetes, alcohol, PA, multivitamin, energy intake, vegetables and fruits,	Inverse association between coffee and CVD mortality in men, but not women

References	Country	Follow-up year	Sample size	Age at baseline	Highest category cups/day	No. of CVD deaths	Adjustment for covariates	Main findings
							red meat, tea	

BP: blood pressure; DBP: diastolic blood pressure; PA: physical activity; MI: myocardial infarction; HTN: hypertension; LDL: low-density lipoprotein; HDL: high density lipoprotein; CVD: cardiovascular disease; CHD: coronary heart disease; HF: heart failure; wk: week

CHAPTER 3

METHODS AND PROCEDURES

A cross-sectional study using NHANES 1999-2014 dataset was conducted to examine the association between caffeine intake and CVD mortality. The study variable is caffeine intake (mg/day), and the outcome variable is CVD mortality. The potential confounders are age, gender, race, education, income, personal history of HTN, diabetes, CVD (excluding HTN), and cancer at enrollment, smoking status, BMI, and total daily intake of energy, carbohydrates, fat, and protein. Conceptual and operational definitions of the study variables are included in this chapter. Statistical tests for data analysis are identified. Ethical considerations of the study are also presented.

Research Design

A cross-sectional descriptive correlational research design was used to examine the association between caffeine intake and CVD mortality. According to Grove et al. (2013, p. 225), the purpose of a descriptive correlational design is to analyze data to identify possible associations among study variables. This study was carried out using secondary analysis of existing data from NHANES collected from 1999 to 2014. The mortality data came from the 2015 Public-use Linked Mortality Files (LMF), which has been updated through December 31, 2015. Information gained from this study will help identify the benefits and risks of caffeine consumption and provide recommendations for dietary guidelines.

Sample

NHANES used a stratified multistage probability sampling design to enable representation of non-institutionalized civilian US population. In this study, NHANES 1999-

2014 database was used. The NHANES participants completed a structured interview at home and a physical examination at the MECs. Adults aged 20 years or older who responded to questionnaire items regarding caffeine consumption were included. Participants with missing information on any potential confounders were excluded. Mortality data were provided by the 2015 Public-use LMF, including mortality status and cause of death. The current study examined 21,938 NHANES participants aged 20 to 85 years.

Measurements

Demographic Data

The demographic variables include age, gender, and race, which are essential to describe the sample and determine the population for generalization of the findings (Grove et al., 2013). Other potential confounders include education, income, personal history of HTN, diabetes, CVD (excluding HTN), and cancer at enrollment, smoking status, BMI, and total daily intake of energy, carbohydrates, fat, and protein. These were obtained from NHANES questionnaires, interviews, and physical examinations. HTN is defined as either a previous diagnosis of HTN or intake of antihypertensive medications (CDC, 2015). Diabetes is defined as either a previous diagnosis of diabetes or an HbA1c level of ≥ 6.5% or intake of anti-diabetic medications or insulin. Cancer is defined as a previous diagnosis of cancer. CVD (excluding HTN) include coronary heart disease, heart failure, and stroke. Coronary heart disease is defined as a previous diagnosis of coronary heart disease, myocardial infarction, or angina pectoris (CDC, 2015). Heart failure is defined as a previous diagnosis of heart failure. Stroke is defined as a previous diagnosis of stroke. BMI is calculated as body weight in kilograms divided by height in meters squared.

Race was classified into four categories: black, Hispanic, white, and other. Education was classified into four categories: < high school, high school, some college, and postgraduate. Income was classified into six categories: < 15,000, 15,000-25,000, 25,000-35,000, 35,000-55,000, 55,000-75,000, and > 75,000 dollars/year (CDC, 2017). Smoking status was divided into two categories: smokers and non-smokers. BMI was classified into four categories: underweight (< 18.5 kg/m^2), normal (18.5-24.9), overweight (25-29.9), and obese (≥ 30; CDC, 2020). Daily intake of total energy was presented as kcal. Daily intake of carbohydrates, fat, and protein was presented as grams per 100 kcal.

Study Variables

The study variable is caffeine intake (mg/day), and the outcome variable is CVD mortality. For all the NHANES participants, a 24-hour dietary recall interview was collected in person during the examination in a private room at the MECs. The United States Department of Agriculture (USDA) and the US DHHS partnered to conduct the dietary interview, which was sent electronically from the field and imported into Survey Net (a computer-assisted food coding and data management system developed by the USDA; Raper et al., 2004). The participants were provided a standard set of measuring guides (measuring cups, spoons, and a ruler) and a food model booklet to help them report the volume and dimensions of the food items consumed during the 24-hour period before the interview (CDC, 2015). The USDA designed a dietary data collection instrument: The Automated Multiple-Pass Method (AMPM) to provide an efficient and accurate way to collect intake data for large-scale national surveys (Agricultural Research Service, 2019).

During the 2003-2014 cycles, the NHANES collected a second dietary interview by telephone 3 to 10 days after the first interview but not on the same day of the week to obtain a more complete picture of the dietary patterns. The mean of the nutritional information from both recalls during these cycles was used in this study. Caffeine intake in the 24-hour period was estimated by using the USDA food and nutrient databases for dietary studies (FNDDS) 5.0 (USDA, 2012) and available in the NHANES database. The USDA National Nutrient Database for Standard Reference provides the basis of nutrient values for foods and beverages (USDA, 2012). The sources of nutrient data for this database include data provided by the food companies and trade associations, USDA analytical contracts, and literature (USDA, 2012).

The mortality data came from the 2015 Public-use LMF, which is available for NHANES participants for the period of 1999-2014 and have been updated through December 31, 2015. NHANES used the International Classification of Diseases-10 for deaths occurred in or after 1999. In the 2015 Public-use LMF, the codes that are used for CVD mortality include I00-I09, I11, I13, and I20-I51. This dissertation will focus on all the CVD deaths except stroke deaths because stroke ranks fifth among all causes of death behind heart disease, cancer, chronic lower respiratory disease, and accidents (Virani et al., 2020), and the mortality rate for stroke is usually listed separately in statistic reports.

Data Collection

The NHANES data were collected during the structured interviews at home and the physical examinations at the MECs. The principal investigator (PI) extracted demographic data and study variables from the NHANES 1999-2014 database (PI was not involved in data collection). Caffeine intake in NHANES database was calculated including these sources: coffee,

tea, soda, energy drinks, chocolate, and cocoa-containing products (Drewnowski & Rehm, 2016). Considering each cup (8 oz/240 ml) of coffee contains 96 mg caffeine (US DHHS and DOA, 2015), the daily intake of caffeine was divided into three categories (< 100 mg/day, 100-200 mg/day, and > 200 mg/day). The outcome measure of this study was CVD mortality.

CVD mortality in this study included acute rheumatic fever (I00-I02), chronic rheumatic heart diseases (I05-I09), hypertensive heart disease (I11), hypertensive heart and chronic kidney disease (I13), ischemic heart diseases (I20-I25), pulmonary heart disease and disease of pulmonary circulation, acute pericarditis, endocarditis, valve, cardiomyopathy, cardiac arrest, atrial fibrillation, and heart failure (I30-I51; CDC, 2019; ICD-10, 2018). Death from stroke is not included in this study because it is listed separately in the Codebook for the 2015 Public-Use LMF.

Data Analysis

All data were entered into SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC) and checked for missing data, which was excluded from the analysis. Demographic data were presented as number and percentage for categorical variables or mean ± standard deviation (SD) for continuous variables. Multivariate Cox's proportional hazards regression was used to answer the research question by examining the association between caffeine intake and CVD mortality, controlling for potential confounders age, gender, race, education, income, smoking status, BMI, total daily intake of energy, carbohydrates, fat, and protein, and presence of HTN, diabetes, CVD (excluding HTN), and cancer at enrollment. The HRs and 95% CIs for CVD mortality in participants with a caffeine intake of 100-200 mg/day and > 200 mg/day were compared with those having a caffeine intake of < 100 mg/day (Tsujimoto et al., 2017). Because

of the scale difference in variables, the values of total energy were divided by 100; the values of carbohydrates, protein, and fat were divided by 10. Statistical tests were two-sided, and $p < 0.05$ was considered statistically significant for all tests.

Ethical Considerations

The NCHS Research Ethics Review Board reviewed and approved the NHANES protocols. All the NHANES participants provided written informed consent (CDC, 2017). The current study is a secondary analysis of the NHANES 1999-2014 database. The Office of Regulatory Services of the Institutional Review Board (IRB) of the University of Texas at Arlington (UTA) was consulted. Since the data were obtained from a public dataset that was de-identified, the PI was notified that she did not need UTA IRB approval for this dissertation (see Appendix). The PI stores the data in a locked university office, and all data will be destroyed 3 years after completion of the study. The benefits of the study include increased knowledge of the association between caffeine intake and CVD mortality, better understanding of benefits and risks of caffeine consumption, and providing recommendations for dietary guidelines. Because of the popularity of caffeine in the US and worldwide, this information will be valuable to the public to inform them the benefits and risks of incorporating caffeine into their diet.

Summary

This chapter introduced the research design of this study. The sampling and measurement methods were discussed in detail. It also described the data collection process and data analysis method. Ethical considerations were presented.

CHAPTER 4

FINDINGS

Characteristics of Participants by Caffeine Intake

Among the 21,938 participants, 9,499 (43.3%) had a caffeine intake of < 100 mg/day (1 cup/8 oz/240 ml of coffee contains about 100 mg caffeine), 5,090 (23.2%) had a caffeine intake of 100-200 mg/day, and 7,349 (33.5%) had a caffeine intake of > 200 mg/day. Caffeine intake included these sources: coffee, tea, soda, energy drinks, chocolate, and cocoa-containing products (Drewnowski & Rehm, 2016). Characteristics of all study participants stratified by daily caffeine intake are presented in Table 2.

Higher caffeine consumers were more likely to be older, female, white, smokers, have a higher BMI, a higher income, and a higher education level; they were more likely to have a higher daily intake of total energy, carbohydrates, protein, and fat; they were less likely to report a history of HTN and diabetes, more likely to report a history of CVD (excluding HTN) and cancer with *p* values < 0.05 across all categories (Table 2).

Table 2

*Characteristics of Participants Stratified by Daily Caffeine Intake**

Characteristics	Caffeine intake (mg/day)			*p* value^
	< 100	100-200	>200	
	N (%)	N (%)	N (%)	
Age				<.001
20-34	4959（28.7）	1732（22.3）	1426（15.7）	
35-50	4036（23.4）	1966（25.3）	2807（30.9）	

Characteristics	Caffeine intake (mg/day)			*p* value^
	< 100	100-200	>200	
	N (%)	N (%)	N (%)	
50+	8271（47.9）	4075（52.4）	4843（53.4）	
Gender				<.001
Male	9477 (54.9)	4009 (51.6)	3879 (42.7)	
Female	7789 (45.1)	3764 (48.4)	5197 (57.3)	
Race				<.001
White	6174 (35.8)	3967 (51.0)	6348 (69.9)	
Black	4960 (28.7)	1286 (16.5)	768 (8.5)	
Hispanic	4945 (28.6)	2002 (25.8)	1530 (16.9)	
Other	1187 (6.9)	518 (6.7)	430 (4.7)	
Education				<.001
< high school	5402 (31.3)	2043 (26.3)	1944 (21.4)	
High school	3826 (22.2)	1855 (23.9)	2276 (25.1)	
Some college	3336 (19.4)	1726 (22.3)	2150 (23.7)	
Postgraduate	4678 (27.1)	2138 (27.5)	2698 (29.8)	
Income (dollars/year)				<.001
<15000	4826 (29.7)	1865 (25.2)	1986 (22.7)	
15000-25000	2065 (12.7)	870 (11.8)	941 (10.8)	
25000-35000	2103 (12.9)	967 (13.1)	1026 (11.8)	
35000-55000	2713 (16.7)	1332 (18.0)	1611 (18.4)	

Characteristics	Caffeine intake (mg/day)			*p* value^
	< 100	100-200	>200	
	N (%)	N (%)	N (%)	
55000-75000	1609 (9.9)	762 (10.3)	1027 (11.8)	
>75000	2954 (18.1)	1600 (21.6)	2143 (24.5)	
BMI (kg/m^2)				<.001
<18.5	284 (1.7)	122 (1.6)	126 (1.4)	
18.5-24.9	4853 (28.7)	2166 (28.3)	2467 (27.5)	
25-29.9	5644 (33.4)	2658 (34.7)	3202 (35.7)	
≥30	6134 (36.2)	2706 (35.4)	3167 (35.4)	
Smoke				
Yes	6480 (37.6)	3762 (48.4)	5745 (63.3)	<.001
HTN				
Yes	6115 (35.9)	2726 (35.2)	3082 (34.1)	.01
CVD (excluding HTN)				
Yes	1372 (9.0)	612 (8.8)	753 (9.3)	<.001
Diabetes				
Yes	2088 (12.3)	913 (12.0)	983 (11.1)	<.001
Cancer				
Yes	1491 (8.7)	775 (10.0)	1007 (11.1)	<.001
Nutrition				
Energy (kcal)	1824±826	2121±901	2294±956	<.001

Characteristics	Caffeine intake (mg/day)			*p* value^
	< 100	100-200	>200	
	N (%)	N (%)	N (%)	
Carbohydrate (g)	238±110	266±121	279±131	<.001
Protein (g)	68±35	80±37	86±39	<.001
Fat (g)	67±34	78±37	87±40	<.001

*Data are presented as number (percentage) of participants for categorical variables or mean ± SD for continuous variables.
^*p* value was calculated with chi-square test for categorical variables and ANOVA F test for continuous variables.

The Prevalence of Chronic Illness among Study Participants

The prevalence of HTN, diabetes, CVD (excluding HTN), and cancer among the 21,938 participants are presented in Table 3. Among the study participants, 32.4% have HTN at enrollment. The prevalence of diabetes among the study participants is 10.5%. The prevalence of cancer and CVD (excluding HTN) are 7.7% and 9.1% respectively.

Table 3

The Prevalence of Chronic Illness among Study Participants

Chronic Illness	Prevalence
	N (%)
HTN	
Yes	11,919 (32.4%)
No	24,876 (67.6%)
Diabetes	

Chronic Illness	Prevalence N (%)
Yes	3,816 (10.5%)
No	32,472 (89.5%)
Cancer	
Yes	2,857 (7.7%)
No	34,079 (92.3%)
CVD (excluding HTN)	
Yes	2,737 (9.1%)
No	27,502 (90.9%)

Caffeine Intake and CVD Mortality

Table 4 shows the HRs and 95% CIs for the effects of caffeine consumption on CVD mortality adjusted for age, race, gender, education, income, BMI, smoking status, total daily intake of energy, carbohydrates, protein, and fat, and presence of diabetes, HTN, CVD (excluding HTN), and cancer at enrollment. A total of 394 CVD deaths were reported. Compared with those participants with a caffeine intake of < 100 mg/day, the HRs for CVD mortality were significantly lower in the participants with a caffeine intake of 100-200 mg/day (HR, 0.63; 95% CI, 0.45-0.88; $p = 0.008$), and those with a caffeine intake of > 200 mg/day (HR, 0.70; 95% CI, 0.53-0.94; $p = 0.02$).

Table 4

Hazard Ratios for Caffeine Intake and CVD Mortality

Variables	CVD HR (95% CI)	*p* value
Age		
20-34	1.00	
35-50	20.92 (4.55-96.18)	<.001
> 50	73.35 (17.36-309.85)	<.001
Gender		
Female	1.00	
Male	2.77 (2.13-3.60)	<.001
Race		
White	1.00	
Black	0.62 (0.43-0.88)	.009
Hispanic	0.48 (0.30-0.77)	.002
Other	0.42 (0.21-0.84)	.02
Education		
postgraduate	1.00	
<high school	1.92 (1.22-3.01)	.005
High school	1.57 (1.01-2.45)	.05
Some college	1.38 (0.88-2.17)	.16
Income		
>75,000	1.00	

Variables	CVD HR (95% CI)	*p* value
<15,000	2.78 (1.61-4.78)	<.001
15,000-25,000	2.12 (1.24-3.63)	.006
25,000-35,000	1.74 (0.99-3.08)	.06
35,000-55,000	1.95 (1.16-3.28)	.01
55,000-75,000	1.25 (0.73-2.15)	.41
BMI		
18.5-24.9	1.00	
<18.5	0.86 (0.30-2.47)	.77
25-29.9	0.64 (0.43-0.97)	.03
≥ 30	0.58 (0.41-0.81)	.002
HTN		
Yes	1.53 (1.07-2.17)	.02
Diabetes		
Yes	2.11 (1.58-2.81)	<.001
Cancer		
Yes	1.28 (1.02-1.61)	.04
CVD (excluding HTN)		
Yes	3.57 (2.64-4.82)	<.001
Smoke		
Yes	1.25 (0.97-1.61)	.08
Energy	0.93 (0.82-1.06)	.27

Variables	CVD HR (95% CI)	*p* value
Carbohydrates	1.19 (0.73-1.94)	.48
Fat	1.01 (0.91-1.13)	.25
Protein	0.97 (0.88-1.07)	.58
Caffeine Intake (mg/day)		
<100	1.00	
100-200	0.63 (0.45-0.88)	.008
>200	0.70 (0.53-0.94)	.02

Summary

This chapter presented the findings of this study, including the characteristics of the study participants by caffeine intake, the prevalence of chronic illness among the study participants, and the HRs and 95% CIs for the effects of caffeine consumption on CVD mortality adjusted for age, race, gender, education, income, BMI, smoking status, total daily intake of energy, carbohydrates, protein, and fat, and presence of diabetes, HTN, CVD (excluding HTN), and cancer at enrollment.

CHAPTER 5

DISCUSSION

The NHANES 1999-2014 database was used to examine the association between daily caffeine intake and CVD mortality (obtained from the 2015 Public-use LMF) after adjusting for age, race, gender, education, income, BMI, smoking status, total daily intake of energy, carbohydrates, protein, and fat, and presence of diabetes, HTN, CVD (excluding HTN), and cancer at enrollment. Compared with those participants with a caffeine intake of < 100 mg/day, those who consumed 100-200 mg/day had a 37% lower risk of CVD death after adjusting for the potential confounders; those who consumed > 200 mg/day had a 30% lower risk of CVD death.

Higher caffeine intake (compared to < 100 mg/day) was associated with lower CVD mortality in the present study. This finding is consistent with several larger, more recent studies and meta-analyses. In the Alpha Omega Trial (van Dongen et al., 2017), compared to those who consumed 0-2 cups (1 cup = 125 ml) of coffee per day, the HRs for CVD mortality was 0.66 (95% CI, 0.52-0.85; $p = 0.03$) for those consuming 2-4 cups of coffee per day, and 0.69 (95% CI, 0.53-0.90; $p = 0.03$) for those consuming > 4 cups of coffee per day. In the National Institutes of Health-AARP Diet and Health study (Freedman et al., 2012), compared to those with no coffee intake, the HRs for CVD mortality for people consuming 2-3 cups of coffee per day were 0.85 (95% CI, 0.76-0.95; $p < 0.001$) for women, and 0.86 (95% CI, 0.79-0.94; $p = 0.03$) for men. In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (Loftfield, Freedman et al., 2015), the HRs for CVD mortality was 0.74 (95% CI, 0.64-0.86; $p < 0.0001$) for those consuming 2-3 cups of coffee per day compared to those non-coffee drinkers. Kim et al. (2019) pooled 31 studies including 2,631,398 participants and 81,188 CVD deaths and found inverse

association between coffee intake and CVD mortality with the lowest HR at 0.83 (95% CI, 0.80-0.87; $p < 0.0001$) for intake of 2.5 cups/day compared to those non-coffee drinkers. Crippa et al. (2014) pooled 21 studies including 997,464 participants and found inverse association with the lowest HR at 0.79 (95% CI, 0.74-0.84; $p < 0.001$) for intake of 3 cups/day compared with no coffee consumption.

The mechanism of this inverse association between caffeine intake and CVD mortality is not clear. Although caffeine has been considered a risk factor for CVD, a recent animal study suggests that caffeine may protect and repair myocardium through the action of mitochondrial p27, which was known as an inhibitor of the cell cycle (Ale-Agha et al., 2018). Caffeine also promotes the repair of endothelial function (Spyridopoulos et al., 2008) and has anti-inflammatory (Renner et al., 2007) and bronchodilator effects (Gong et al., 1986). Caffeine decreases the risk of depression (Lucas et al., 2011), and depression was associated with higher risk of CVD mortality (Meng et al., 2020). Caffeine has protective effects against some types of cancer (Bøhn et al., 2014), and cancer patients have a higher risk of dying from CVD (Sturgeon et al., 2019). Caffeine helps reduce symptoms of Parkinson's disease (Ludwig et al., 2014), and control weight, which will reduce the risk of metabolic syndrome (Heckman et al., 2010). Although regular caffeine intake increases BP, when ingested through coffee, the pressure effect is small (Noordzij et al., 2005). This pressure effect mainly affects naïve drinkers (Corti et al., 2002) and only for about 3 hours (Robertson et al., 1978). The half-life of caffeine is 3-7 hours (Massey, 1998). For people with slower caffeine metabolism, coffee increases the risk of HTN, but for people with faster caffeine metabolism, it decreases the risk of HTN (Palatini et al., 2009). Since HTN is the single largest risk factor for CVD mortality in the US and accounted for 45%

of all CVD deaths in 2005 (Virani et al., 2020), the effects caffeine has on BP might contribute to our understanding of this inverse association between caffeine intake and CVD mortality. It was also reported that people had lower heart rates after caffeine consumption (Hartley et al., 2004).

Seventy-one percent of caffeine intake comes from coffee in the US diet (Frary et al., 2005). Coffee is a complex beverage containing more than 1,000 biologically active compounds (Cano-Marquina et al., 2013). One of the compounds in coffee, chlorogenic acid has been shown to decrease the rate of glucose absorption (van Dam & Hu, 2005), reduce LDL oxidation (Rebello & van Dam, 2013), and lower BP (Yamaguchi et al., 2008). It may also reduce inflammation and oxidative stress during the process of atherosclerosis (Rebello & van Dam, 2013). Pyridinium compounds, which are formed upon trigonelline pyrolysis and coffee roasting, may contribute to the beneficial effect due to their antithrombotic properties (Kalaska et al., 2014). However, diterpenes (cafestol and kahweol) found mainly in unfiltered coffee are associated with high total cholesterol level (Urgert & Katan, 1997), although most Americans drink filtered coffee (Gardener et al., 2013).

Higher coffee consumption is associated with improved insulin sensitivity (Arnlov et al., 2004), as well as lower levels of liver enzymes and inflammatory markers (Xiao et al., 2014). Coffee intake was associated with lower incidence for type 2 diabetes (Huxley et al., 2009; van Dam & Hu, 2005), which is consistent with the current study. The current study showed that higher caffeine intake was associated with a lower prevalence of diabetes at enrollment ($p < .001$). Coffee intake improves lung function (Nettleton et al., 2009), and is associated with a lower relative risk of depression (Lucas et al., 2011).

People develop tolerance to coffee after only 4-5 days of administration (Ammon et al., 1983; Robertson et al., 1981), although not all coffee drinkers develop this tolerance (Lovallo et al., 2004). It is suggested that research studies should separate regular coffee drinkers from pure naïve participants (Cano-Marquina et al., 2013) since they may respond differently, but this kind of research study has not been carried out maybe due to the challenges of finding such participants.

One possible explanation for the observed inverse association between caffeine intake and CVD mortality is that participants who have chronic disease at enrollment may decrease or abstain from caffeine consumption. However, some previous studies reported inverse association between coffee intake and CVD mortality even when they excluded people with CVD or other chronic disease at enrollment (Andersen et al., 2006; Freedman et al., 2012; Gunter et al., 2017).

Even though the findings from this study are consistent with some of the larger more recent studies (Freedman et al., 2012; Loftfield et al., 2018; van Dongen et al., 2017), the results of earlier smaller studies (Loomba et al., 2016; Tsujimoto et al., 2017) have been highly variable. One of the reasons is that most studies were categorizing participants based on how many cups of coffee they consumed each day (Freedman et al., 2012; Loftfield et al., 2018); only one study was using daily caffeine intake (mg/day; Tsujimoto et al., 2017) to categorize the participants. The cup size was not standardized with some studies using 240 ml (Andersen et al., 2006; Lopez-Garcia et al., 2011; Odegaard et al., 2015) while others using 125 ml (van den Brandt, 2018; van Dongen et al., 2017), 150 ml (Grosso et al., 2016), or 170 ml (Greenberg et al., 2007; Mineharu et al., 2011). Some researchers did not specify how many ml was in a cup (Freedman et al., 2012; Yamakawa et al., 2019). Besides, the caffeine content in each cup of coffee varies.

In Canada, a home-made cup of coffee can contain 30-175 mg caffeine (Gilbert et al., 1976). In the US, the standard value of caffeine quantity is 96 mg for an 8-oz cup of ground roasted coffee, 64 mg for instant coffee, 48 mg for tea, 30 mg for a 12-oz cola, 64 mg/oz for espresso, and 3 mg for decaffeinated coffee (Barone & Roberts, 1996; T. W. Crozier et al., 2012; US DHHS & DOA, 2015). However, these values were not being used consistently; Greenberg et al. (2007) used the following values for caffeine content: 159 mg for each serving of ground caffeinated coffee, 83 mg for instant caffeinated coffee, 42 mg for colas, 36 mg for regular tea, and 6 mg for chocolate snacks. For mortality rates, different studies have included different mortality codes, which could also affect the results of the study.

Adjusting confounding variables has a large impact on the HRs of mortality (Freedman et al., 2012). It has been established that coffee intake is associated with smoking (Freedman et al., 2012; Lopez-Garcia et al., 2008), so smoking status was adjusted in this analysis. Drinking coffee is also a lifestyle habit, which is why this analysis adjusted for educational level, income, BMI, medical history, and dietary confounders. However, this inverse association between caffeine intake and CVD mortality could reflect residual confounding by other unmeasured or poorly measured confounders.

Strengths

The current study used a nationally representative sample of the US civilian non-institutionalized population (NHANES database 1999-2014). First, it had a large sample size (n = 21,938), including both genders and a wide age range from 20 to 85 years. Second, it included a multi-ethnic group and a long follow-up period (16 years). Third, it included the most recent data set which was also linked to mortality data providing important clinical outcome measures.

Fourth, the NHANES database includes detailed information on many confounding variables allowing controlling for several known predictors of mortality, such as smoking status, BMI, presence of HTN, diabetes, CVD (excluding HTN), and cancer at enrollment. Finally, this study categorized participants based on how many milligrams of caffeine they consumed daily instead of how many cups of coffee, which is more accurate. These strengths made it possible to perform a robust multivariate Cox's proportional hazards regression analysis.

Limitations

First, this is a secondary data analysis using the NHANES database. The data was not collected to answer this specific research question. The PI was not involved in the data collection process and had no control over what variables were contained in the dataset.

Second, there may be measurement errors because caffeine intake was self-reported. It was collected by one or two 24-hour dietary recalls depending on the different NHANES cycles. It was suggested that 24-hour dietary recalls underreport the intakes (Slimani et al., 2000), so comparison between the current study and a representative sample of the US consumers (Mitchell et al., 2014) was conducted. For example, for age group 25-34, the mean caffeine intake for the current study was 166 mg/day, and the mean caffeine intake for Mitchell et al. (2014) was 137 mg/day.

Third, despite efforts to control confounding by a few measured predictors of mortality, including smoking status, BMI, presence of HTN, diabetes, CVD (excluding HTN), and cancer at enrollment, the possibility of residual confounding remains. However, the results of the current study reinforced previous studies with similar findings. Future studies should consider controlling for physical activity, alcohol intake, menopausal status, red meat, fruit, and vegetable

consumption (Freedman et al., 2012; Gunter et al., 2017). Physical activity was not adjusted in this analysis because NHANES used inconsistent measurement during the 1999-2014 study period.

Conclusions

In conclusion, in this large multi-ethnic population, higher caffeine intake (compared to < 100 mg/day) was associated with lower CVD mortality. Further research is needed to figure out the mechanism of this inverse association. Even though the current study cannot prove cause-effect relationship between caffeine intake and CVD mortality, it provided further evidence for the protective effects of moderate caffeine consumption. The finding of this study supports the 2015-2020 US Dietary Guidelines, which suggested that moderate coffee consumption (three to five 8-oz cups/day or up to 400 mg/day of caffeine) can be a part of a healthy diet.

Nursing Implications

Nursing Practice

There are many misconceptions regarding caffeine and cardiovascular health that can lead to confusion about whether caffeine consumption can be a part of a healthy diet. For example, some people think caffeine is harmful for cardiovascular disease. These misconceptions exist among health care professionals and nonprofessionals. Nurses spent more time than any other health care professionals teaching patients. Bedside nurses need the most up-to-date and evidence-based knowledge to be able to provide quality education. The finding from this study will help clarify some of these misconceptions. It increases our knowledge and understanding of benefits of caffeine. Caffeine consumers would be happy to learn this finding.

They should not have to give up caffeine due to some misconceptions. This research finding will also provide recommendations for future dietary guidelines.

Nursing Research

This is the first study that reported higher caffeine intake (compared to < 100 mg/day) is associated with lower CVD mortality. Previous studies attributed the inverse association between coffee intake and CVD mortality to the antioxidants instead of caffeine (Freedman et al., 2012; Loftfield et al., 2018). This new finding will lead to more research examining the benefits of caffeine. Future research should figure out the mechanism of the inverse association between caffeine intake and CVD mortality and examine possible harmful effects with heavy caffeine consumption. For example, researchers may examine the association between metabolic biomarkers and caffeine intake to figure out the mechanism, since some of the metabolic biomarkers are associated with CVD mortality. Future researchers should conduct longitudinal prospective studies to examine the association between caffeine intake and CVD mortality and figure out if there is cause-effect relationship.

Summary

This chapter discussed key findings of this study and compared these findings with previous research studies. Possible mechanisms of the inverse association between caffeine intake and CVD mortality were presented. This chapter also discussed the strengths and limitations of this study and presented the conclusions and nursing implications for practice and research.

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Appendix

The Institutional Review Board Exemption

Hello Juan,

Thank you for reaching out. As long as you are solely accessing the parts of the data set that are public (i.e., readily available on the website), then you do not need to gain IRB approval as this does not qualify as human subjects research. Please see the following charts for more information: https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts/index.html#c1. In your case, you are not interacting with the subjects (as this is secondary use of data), and the information is not individually identifiable or private.

Should you decide to request information that would be individually identifiable or private, you would need to gain IRB approval. Otherwise, you are clear from an IRB perspective. Please let me know if you have any questions!

Thank you,

Christina Morris

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