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Vitamin K Deficiency and Ischemic Stroke in Atrial Fibrillation Patients on Warfarin

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Walden University
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Abstract

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by

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MA, Central Michigan University, 2009
BS, Central Michigan University, 2004

Dissertation Submitted in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy
Public Health

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Abstract

Individuals with poor nutritional vitamin K status can suffer from atrial fibrillation (AF) due to misinterpretation of warfarin instructions by healthcare providers. The purpose of this quantitative study was to determine if there was an association between inadequate dietary vitamin K intake in AF patients and stroke outcomes to address the lack of research surrounding stroke outcomes in patients with true vitamin K deficiency. Grounded in the health belief model, this study assessed if individual beliefs from health education influenced the nutritional quality of their diet and health outcomes. The study is a secondary data analysis of the Framingham Heart Study. Longitudinal data from the *Offspring* cohort collected from 1971 to 2014 were included. All AF patients with no prior history of stroke were eligible, resulting in a sample size of 471. The association between dietary vitamin K, serum vitamin K levels, and stroke outcomes was analyzed using bivariate regression analyses and multivariate regression analysis. There was an increased risk for ischemic stroke was seen with lower dietary intake levels (OR 1.18 – 1.46) and lower serum vitamin k levels (OR 1.32 – 1.47) while controlling for age, gender, education level, income level, smoking status, alcohol abuse, diabetes mellitus, high blood pressure, high cholesterol, and obesity; however, results are not statistically significance ($p > .05$). The findings can promote positive social change by informing care protocols and policies on safe levels of vitamin K foods to consume and health improvement programs for routine vitamin K monitoring in the population, resulting in a reduction in population mortality rates for heart attack and stroke.

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Dedication

This dissertation is dedicated to my father, Robert McDonald, without whom this study would never have happened. His strength to overcome hardship and continue living is phenomenal and continues to provide inspiration not just to his wife and children but to his grandchildren as well.

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Chapter 1: Introduction to the Study

Introduction

Nutritional adequacy in an individual's diet can impact both short and long-term health outcomes. There are several factors that could influence nutrient intake and metabolism, including specific disease processes, medications, socioeconomic status, geographic location, and nutritional habits. Vitamin K is a fat-soluble vitamin often overlooked in deficiency states. Longitudinal studies reported the average individual consumes above the recommended dietary intake, upholding the thought that vitamin K deficiency in the population is low (Zwakenberg et al., 2017). Many longitudinal observational studies used healthy populations and excluded individuals that would be at considerable risk for vitamin K deficiency, including individuals on warfarin, a vitamin K agonist. Cross-sectional surveys offered more insight since they tended to include individuals in both good and fair health. While the average intake of Americans was 110 ug/day, the National Health and Nutrition Examination Survey (NHANES) reported that less than 40% of Americans met the recommended daily intake of 120 ug/day for men and 90 ug/day for women, which led to an increased mortality risk (Chen et al, 2019: Han et al., 2019; Harshman et al., 2017). The results of the study showed the variability in vitamin K intake among the general population could impact health studies when grouping all individuals together.

Any nutritional deficiency is a cause for concern due to the risk for adverse health outcomes. This is especially true when dealing with food-drug interactions because of chronic disease management. Atrial fibrillation (AF) is an irregular heart rhythm that is often managed by anticoagulants to prevent strokes. One such anticoagulant is warfarin, a vitamin K agonist. Individuals on long-term vitamin K agonist treatment could end up with vitamin K insufficiency (Yuji et al., 2020). Vitamin K foods include phylloquinones, a prenylated naphthoquinone manufactured by plants, and menaquinones, a compound produced by bacteria in the large intestine. Researchers found that vitamin K insufficiency could lead to cardiovascular disease risk due to arterial stiffness (Yuji et al., 2020); however, low levels of phylloquinone have also been associated with higher mortality rates (Shea et al., 2020). Teenagers with lower vitamin K intakes had a three times higher risk for left ventricular hypertrophy (Douthit et al., 2017). There is potential that any increased arterial stiffness resulting from vitamin K deficiency could be associated with future strokes.

Understanding of health principles plays a critical role in preventing adverse health outcomes. Patients taking anticoagulants may lack the proper understanding of their treatment (Magon et al., 2020). Individuals with uncontrolled anticoagulation suffered from lower treatment satisfaction, lower self-efficacy, higher levels of distress, more daily hassles, and more strained social relationships (Varona et al., 2020). A better understanding of the nutritional implications of vitamin K deficiency can lead to improved nutrition education strategies to maintain adequate vitamin K intakes, as well as lead to potential changes in medication regiments to improve coagulation status and lower the risk for adverse health outcomes.

A critical part of healthcare is following evidenced-based practices. The current practice recommendations for outpatient anticoagulant treatment with warfarin discussed only monitoring blood clotting (Wigle, et al., 2019). One way to measure blood clotting is by the international normalized ratio (INR). The effective range for someone on warfarin is 2.0 to 3.0 (Mayo Clinic, 2020). If the INR increases above 3.0, this could be a sign of vitamin K deficiency causing the blood to clot to slowly; however, if the level is less than 2.0, that could signal too much vitamin K in the diet leading to blood clotting too quickly (Mayo Clinic, 2020). General practice recommendations are to monitor labile INR monthly and stable INR levels every three months, as well as maintaining a consistent intake of vitamin K foods (Wigle et al., 2019). There is no mention as to what constitutes an appropriate amount to consume while on warfarin treatment, or the assessment of vitamin K biochemically. Through this investigation, the hope is there can be better examination of the association between true subclinical vitamin K deficiency and stroke outcomes in AF patients that take anticoagulants.

Understanding the basics of atrial fibrillation (AF) can help improve the understanding of increased stroke risk. Atrial fibrillation can be valvular, as with mitral valve issues, or non-valvular, as with high blood pressure or heart disease (Hawkes & Rabinstein, 2018). In normal heart rhythm, the coordination of electrical impulses in the heart move blood from the atrium into the ventricles, and then in turn to the body at a constant rate; however, in AF, those electrical impulses become inconsistent leading to ineffective blood flow from the heart into the tissues (National Institute of Neurological Disorders and Stroke [NINDS], 2019). Since blood flow is disrupted, blood starts to pool in the heart in either the atria or ventricles, which could cause blood clots to form

(NINDS, 2019). In severe cases of AF, those blood clots could leave the ventricles and travel through the body to the brain causing a stroke (NINDS, 2019).

Two types of strokes that can occur in AF individuals are ischemic and hemorrhagic strokes. Ischemic strokes could occur when there are blockages in the brain blocking blood flow, such as with plaque or clots; hemorrhagic strokes are caused by damaged arteries that rupture or release blood into the brain (CDC, 2021). Researchers stated previously that the risk for ischemic stroke may be up to three times higher with valvular atrial fibrillation (VAF) versus nonvalvular atrial fibrillation (NVAF), depending on the number of risk factors (5-fold with NVAF versus 17-fold with VAF) (Ahmad & Wilt, 2016; Hawkes & Rabinstein, 2018). Approximately 14% of strokes are the result of AF complications (CDC, 2020a), and regardless of the underlying cause, the risk is exceedingly high with AF patients since many have multiple silent strokes over the years according to the National Institutes of Neurological Disorders and Stroke (NINDS, 2019).

The primary treatment to prevent strokes in NVAF remains oral anticoagulants (OAC) in the form of vitamin K agonists (VKAs), such as warfarin, novel oral anticoagulants (NOACs), or direct oral anticoagulants (DOACs). Warfarin treatment induces vitamin K restriction, which could cause a deficiency state leading to further bleeding and hemorrhage risk if not appropriately monitored (ODS, 2020). The risk for intracerebral hemorrhage from those on anticoagulation is eightfold (Hawkes & Rabinstein, 2018). Nutritional epidemiology plays a vital role in assessing the association between nutritional intake and health status (Lachat et al., 2016).

This chapter provided the preface for this study. The background section reviewed the evidence surrounding vitamin K deficiency, atrial fibrillation, coagulation factors, medication treatment and compliance, and stroke outcomes, as well as the gaps in the current literature. The problem statement addressed the impact that the problem has on current medical practice, as well as how addressing the problem can improve quality of life through improvements in assessment and education. The purpose provided a brief methodology and intent of the study's underlying variables. The research questions and hypotheses were laid out and explained using a theoretical foundation. Finally, there was a brief update of the methodology, scope, assumptions, and limitations of the study.

Background

Atrial fibrillation is a complex heart issue affecting millions of individuals every year. According to the CDC (2020a), AF is a type of heart arrhythmia where the heart beats too slow, too fast, or is irregular. Nonvalvular heart disease occurs when arrythmias are caused by high blood pressure, sleep apnea, lung disease, hyperthyroidism, and severe illnesses (Nall, 2019). The main cause for nonvalvular AF is uncontrolled high blood pressure. The CDC reported that approximately 20% of all AF cases could be attributable to high blood pressure, making them nonvalvular forms of AF (2020a). Some of the other risk factors for AF included adults over 80 years age, family history of AF, gender, European descent (race/ethnicity), alcohol use, illegal drug use, endurance sports, smoking, stress, past medical history (high blood pressure, diabetes, heart failure, heart disease, kidney disease), obesity, and surgery (heart, lung, esophagus) (CDC, 2020a; NHLBI, n.d.-b). According to the CDC (2020a), more than 12 million individuals are estimated to develop AF by 2030. As understanding of the risk factors increases, medical providers can monitor the incidence and prevalence of AF in the community leading to improvements in preventive health treatment.

While the symptoms are remarkably like other maladies, medical professionals can monitor for specific signs that could indicate an individual has AF. Some of the signs for AF included heart palpitations, lightheadedness, extreme fatigue, shortness of breath (SOB), chest pain, and irregular heartbeat (CDC, 2020a). Other signs included tachycardia, where the heart rate can be as high as 400 beats per minute (NHBLI, n.d.). In a review of 14 studies, dyspnea, heart palpitations, and fatigue were the three most common symptoms associated with AF (Gleason et al., 2018).

The cost of AF is high, both in terms of financial costs and mental and physical costs. More than 450,000 hospitalizations occur annually related to AF (CDC, 2020a). With the current death rate around 158,000 every year in the United States, the death rate increased annually for the past 20 years (CDC, 2020a). One of the largest costs associated with AF is the cost for anticoagulants to prevent clotting events, but uncontrolled monitoring of anticoagulants can increase the risk for those same clotting events. In the U.S., the annual lifetime costs per person in the U.S. associated with preventing ischemic and hemorrhagic strokes through prescriptions without insurance ranged from $40,000 for aspirin to $67,000-$72,000 for the newer anticoagulants, dabigatran and rivaroxaban (Witte et al., 2021). The rising costs of prescriptions in the U.S. is alarming since not all individuals have access to health insurance, which could decrease annual costs to $2,500 to $13,000 for these same medications that equate to $210 to $1,100 monthly (Witte et al., 2021). Even with insurance, many low-income families cannot afford the costs of these newer medications, which could be more effective than the traditional warfarin at prevention of ischemic strokes.

Ischemic stroke is a major complication of atrial fibrillation and can be debilitating, not just in terms of health but also economically. In terms of health, strokes, ischemic and hemorrhagic, are one of the major causes of disability in the U.S. (CDC, 2020b). While the average global cost for inpatient hospitalization was around $4,000 for ischemic stroke (Puumalainen et al., 2020), the average patient in the United States could expect to spend, at minimum, four times as much as their global counterparts, with AF patients spending up to $7,000 more on costs than those without AF (Claxton et al., 2018; Doshi et al., 2021; Yousufuddin et al, 2020). Of the total costs associated with stroke treatment, 62% relates to lost productivity, 19% relates to inpatient care, 16% relates to homecare, and 3% relates to rehabilitation.

The primary treatment of choice to prevent ischemic strokes in AF patients is oral anticoagulation in the form of vitamin K agonists (VKA), direct oral anticoagulants (DOAC), or non-vitamin K (previously novel) oral anticoagulants (NOAC). The use of anticoagulants in AF patients has reduced the risk for ischemic stroke by 50-67% (NINDS, 2019; Rutrick et al., 2021). As with any type of medication used for specific reasons, the distinct types of anticoagulants have different modes of action, as well as pros and cons, to their treatment. Additionally, healthcare providers follow different protocols when prescribing oral anticoagulants, where 64% preferred DOACs versus 38% warfarin; there are also differences in the decisions to start the medications

(Rybinnik et al., 2020). While warfarin is widely trusted due to its length of time on the market, cost-effectiveness, and proven ability to prevent ischemic strokes, there is a major drawback in that individuals undergo monthly biochemical tests for clotting factors, as well as the need to limit the amount of vitamin K in their diet due to potential interactions with the medication (Pritchett et al., 2020). Much controversy surrounds the continued use of warfarin, a VKA, since some studies have shown less therapeutic benefits than with the newer oral medications (e.g., DOAC and NOAC). One common issue is that medication compliance among warfarin patients has measured between 20-70%, thus increasing the risk for ischemic strokes (Anguita Sánchez et al., 2020; Barrios et al., 2015; Falk et al., 2020; Ng et al., 2020).

Diet has always been an identified complication surrounding warfarin effectiveness. Patients have high perceptions of food restriction related to healthcare education, which impacts many cultural diets as well (Pandya & Bajorek, 2017). Barrios et al. (2015) reported that about 40% of the poor use with warfarin was related to dietary factors. This has been challenged by others where normal intakes of vitamin K did not impact the INR, compared with individuals consuming over 250 µg daily of vitamin K foods (Lurie et al., 2010; Violi et al., 2016). Table 1 provides a listing of foods that contain at least 10% of the recommended daily value for vitamin K intake (Office of Dietary Supplements, 2021).

Table 1

Vitamin K (Phylloquinone) Content of Selected Foods

Food	Micrograms (mcg) per	Percent *DV
Natto, 3 ounces (as MK-7)	850	708
Collards, frozen, boiled, ½ cup	530	442
Turnip greens, frozen, boiled, ½ cup	426	355
Spinach, raw, 1 cup	145	121
Kale, raw, 1 cup	113	94
Broccoli, chopped, boiled, ½ cup	110	92
Soybeans, roasted, ½ cup	43	36
Carrot juice, ¾ cup	28	23
Soybean oil, 1 tablespoon	25	21
Edamame, frozen, prepared, ½ cup	21	18
Pumpkin, canned, ½ cup	20	17
Pomegranate juice, ¾ cup	19	16
Okra, raw, ½ cup	16	13
Salad dressing, Caesar, 1 tablespoon	15	13
Pine nuts, dried, 1 ounce	15	13
Blueberries, raw, ½ cup	14	12
Iceberg lettuce, raw, 1 cup	14	12
Chicken, breast, rotisserie, 3 ounces (as MK-4)	13	11

Note: Office of Dietary Supplements, 2021

In the past, historical research recorded many individuals being in a deficiency state with vitamin K because of recommendations by healthcare providers to restrict vitamin K foods when taking warfarin (Kamali et al., 2009; Kim et al., 2015; Takada et al., 2014). There is an issue with individual health beliefs stemming from the lack of understanding of what constitutes a balanced vitamin K intake and how vitamin K intake impacts warfarin treatment (Pandya & Bajorek, 2017). Documented reports of an association between vitamin K deficiency, elevated INR above 4.0, and bleeding risk hold true for the potential for hemorrhagic side effects such as intracranial bleeds and hematuria (Kim et al., 2015; Mohammed et al., 2016). Vitamin K deficiency increased the need for scheduled INR checks by 20% compared to individuals with higher intakes of vitamin K in their diet (Kim et al., 2015). In the same thought, proper education using a structured diet approach with individuals decreasing vitamin K intake by half with INR less than 2.0 and doubling their intake if the INR was greater than 3.0 led to more stability in INR levels, showing the crucial role of health beliefs with nutrition education (Lurie et al., 2010). Unfortunately, due to these food restrictions, over half of patients preferred to switch from warfarin to new anticoagulants for more dietary freedom (Pandya & Bajorek, 2017).

Vitamin K has several functions within the human body impacting the vascular system and coagulation pathways. The primary physiological function known to providers is the role of vitamin K in the clotting cascade. Vitamin K is the cofactor for several vitamin K-dependent proteins including factors II, VII, IX, and X, as well as protein C, S, and Gas6, a growth arrest-specific protein member of the vitamin K-dependent family of proteins that are expressed in many human tissues, helping to regulate several biological processes in cells (Booth & Centurelli, 1999; Kamali et al., 2009; McCann & Ames, 2009). Individuals must maintain adequate vitamin K intake to maintain all physiological functions. As dietary vitamin K intakes decrease, serum vitamin K levels fall, causing a shortage in the availability of vitamin K and leading to the development of poor health outcomes.

One such impairment associated with vitamin K deficiency is the role of vitamin K in the regulation of bone metabolism. When there is adequate vitamin K in the body, vitamin K-dependent proteins help maintain bone structure and lower plaque buildup in the coronary arteries (Fulton et al., 2016; Lees et al., 2019; Theuwissen et al., 2012). When sufficient vitamin K is not available in the body, vitamin K dependent proteins cannot maintain those biological processes, thus leading to buildup in vascular calcification (VC) from the calcium released in the body from bone loss. Strokes have occurred in the past because of inadequate vitamin K intake leading to undercarboxylation of MGP, which in turn causes increased VC (ODS, 2020). Furthermore, some studies surrounding inadequate menaquinone and phylloquinone intakes have been associated with calcification throughout the coronary arteries (ODS, 2020). As individuals are repleted with vitamin K, their levels of vascular calcification decreased between 10-60% (Fulton et al., 2016; Lees et al., 2019; Theuwissen et al., 2012).

While not proven, an individual on warfarin for over 10 years developed large areas of VC despite his INR being in the therapeutic range most of that time (Wahlqvist et al., 2013). Wahlqvist et al. (2013) suggested that adequate vitamin K intake may help to reverse VC caused by warfarin administration. Despite the number of patients on warfarin decreasing, inadequate dietary intake is still a problem with more than 14 million prescriptions of warfarin in the U.S. annually in 2018 (Kane, 2020). As patients become more vitamin K deficient, various biological processes become altered to maintain anticoagulation pathways.

Proper nutrition is critical to health. Inadequate dietary vitamin K raised all-cause mortality over 1.5x when vitamin K and vitamin D are low compared with normal intakes as well as identified issues with left ventricular mass function (Dal Canto et al., 2020). The role of vitamin K and ischemic stroke risk is controversial within the literature. This controversy may result from the different methodologies in each study. After adjusting for various confounding variables, one study found a small 2% decreased risk for ischemic stroke outcomes with higher phylloquinone intake levels (greater than 242 µg daily) compared to low intakes (< 109 µg daily), which is considered adequate for women (Erkkilä et al., 2005). Another study looking at intakes over 200 µg daily reported a 40% increased risk for large artery atherosclerotic stroke (Larsson et al., 2018). A study that looks at vitamin K deficiency versus adequacy could return different results. Indeed, Violi et al. (2016) reported that most studies looking at an association between vitamin K intakes and stroke risk or CV events use levels greater than 100 µg daily. For example, menaquinone and phylloquinone intakes were found to have no significance on ischemic stroke, despite up to a 10% decreased risk with menaquinone supplementation and up to 20% decreased risk with phylloquinone supplementation; however, individuals in the study were noted to have an inadequate vitamin K intake by current U.S. dietary standards with phylloquinone intakes of 96 µg daily and menaquinone intake of 29.5 µg daily (i.e., no deficiency states) (Vissers et al., 2013). Unfortunately, the more current research has not clarified the issue.

Problem Statement

While there is much research available relating to ischemic stroke risk factors, there continues to be gaps in the current knowledge. Several studies reported conflicting information related to the actual association between vitamin K deficiency and VKAs in the atrial fibrillation population (Anguita Sánchez et al., 2020; Barrios et al., 2015; Erkkilä et al., 2005; Kim et al., 2015; Lurie et al., 2010; Vermeer & Braam, 2001; Violi et al., 2016; Vissers et al., 2013). More current research has not helped with improving knowledge. Researchers found significant differences in vitamin K deficiency with patients on anticoagulation where those on VKAs had worse levels of vitamin K deficiency ($p < 0.001$) (De Vriese et al., 2020). Despite the differences in vitamin K deficiency levels, there were no significant differences in stroke incidence with only five ischemic strokes in the VKA group, compared with 1 or 2 ischemic strokes in non-VKA groups (De Vriese et al., 2020). In another study, Xu et al. (2019) acknowledged an increased risk for total stroke ($p=0.05$), but the risk was not specific to ischemic stroke ($p=0.087$) or hemorrhagic stroke ($p=0.681$) in patients with elevated levels of vitamin K deficiency. The risk for cardiovascular events (CVEs), including stroke, was 1.85x higher for those with higher levels of vitamin K deficiency (CI 1.07-3.17) after adjustment for confounders (Xu et al., 2019).

There are several issues when looking at the conflicting information surrounding vitamin K deficiency and stroke outcomes. The current research does not have sufficient power to detect significant differences between groups due to the small number of participants in groups. Some of the research was conducted using cross-sectional surveys looking at only one point in time with only one measurement of vitamin K status. Some studies excluded patients on VKA, which can increase vitamin K deficiency risk due to dietary restrictions. This study attempted to address the gap in clinical practice surrounding the association between vitamin K deficiency resulting from VKA use in AF patients on warfarin and stroke outcomes.

Purpose

The purpose of this proposed study was to investigate the association between vitamin K deficiency from elimination diets (defined as vitamin K intakes below the recommended Adequate Intake by gender daily) and the risk for ischemic stroke in AF patients on warfarin. This study was quantitative based on secondary data from the Framingham Heart Study and utilized a retrospective study design. The health belief model provided the framework for this study to assess the implications of inadequate vitamin K intakes on ischemic stroke outcomes for AF patients on warfarin. Information from the *Offspring cohort* provided the relevant data from Framingham, Massachusetts (MA) with over 39 years of data from 1975-2014 to determine if vitamin K deficiency association exists with ischemic stroke outcomes in AF patients on warfarin.

Research Questions and Hypotheses

Bivariate Research Questions

RQ1: Is there an association between dietary vitamin K intake below the daily adequate intake (AI) for gender and ischemic stroke in AF patients on warfarin?

H_{01} –there is no association between dietary vitamin K intake below the daily adequate intake (AI) for gender and ischemic stroke in AF patients on warfarin.

H_1 –there is an association between dietary vitamin K intake below the daily adequate intake (AI) for gender and ischemic stroke in AF patients on warfarin.

RQ2: Is there an association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin?

H_{02} – there is no association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin.

H_2 –there is an association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin.

Multivariate Research Questions

RQ3: Is there an association between vitamin K subclinical deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin controlling for age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity.

H03 – There is no association between vitamin K subclinical deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin controlling for age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity.

H3 – There is an association between vitamin K subclinical deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin controlling for age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity.

Each covariate in RQ3 will have their own bivariate regression analysis with the ischemic stroke outcome before the final multivariate regression analysis is conducted. If any covariate has a p-value > 0.05, those covariates will not be in the final multivariate analysis above.

Theoretical and Conceptual Framework

Health belief plays a critical role in health behaviors, including disease management. In the 1950s, the Health Belief Model (HBM) was introduced to help understand the failure of individuals to adopt disease prevention strategies or screening tests for the early detection of disease. Several factors were investigated, among them perceptions of disease susceptibility, severity, benefits to treatment, and barriers to treatment impacted their self-management behaviors (Chang et al., 2018; Long et al., 2017; Sullivan et al., 2009). Perceived susceptibility surrounds identification of odds of an individual having a stroke if they do not follow their vitamin K restriction (Chang et al., 2018; Sullivan et al., 2009). Perceived severity looks at how severe do individuals assume a stroke will be if they do not follow dietary restrictions as advised by their medical providers (Chang et al., 2018; Long et al., 2017; Sullivan et al., 2009). Individuals will ask, “What is the perceived benefit to dietary restriction?” (Chang et al., 2018; Long et al., 2017; Sullivan et al., 2009). Finally, perceived barriers would have individuals considering what would keep them from restricting the vitamin K in their diet (Chang et al., 2018; Long et al., 2017; Sullivan et al., 2009).

A barrier to consider could be an individual’s belief that eating green, leafy vegetables helps reduce the risk of cancer or heart disease, or that the restriction would be an infringement on their cultural heritage for eating foods high in vitamin K. A couple of additional constructs added in later years included an individual’s ability to maintain their dietary restriction (self-efficacy), the attitude of their family or peers to dietary restriction to prevent strokes (social norms), and actions that could alter their behavior (cues to action) (Chang et al., 2018; Long et al., 2017; Sullivan et al., 2009). Self-efficacy is an individual's ability to adequate restrict vitamin K based on generic recommendations to limit the vitamin K in their diet, or confusion in nutrition education between healthcare providers. Additional cues for action that can lead a patient to follow the advice and restrict too much could the desire for a longer life to spend more time with their family or the monthly PT/INR checks that provide direction on whether to increase or decrease their intake based on the biochemical values.

Research using the HBM shows the impact of individual perceptions on self-management. Sullivan et al. (2009) found that perceived benefits and self-efficacy were major contributors to improved self-management. In another study, the researchers found that individuals thought unhealthy diet patterns were a perceived barrier to self-management, as well as a perceived lack of control over their treatment. Conversely, perceived susceptibility and perceived barriers were major contributors to behavior change around cultural competence and health beliefs (Chang et al., 2018). Presently, pharmacists, dietitians, and physicians provide different education on warfarin and diet maintenance. There is a lack of vitamin K testing during warfarin treatment, associated with unknown deficiency states. In individuals with poor comprehension and lack of physician care, the potential for medication and diet errors increased substantially (Zhang, 2017). Nutrition education based on the HBM can improve diet compliance to prevent future disease (Araban et al., 2017). In using the HBM model for this study, nutrition education would focus on increasing awareness by providing statistics on the disease (susceptibility), information on complications (severity), importance of consuming vitamin K foods (benefits), group discussions on what prevents successful adaption (barriers), and demonstration as well as role models to describe the proper way to maintain vitamin K intake while minimizing the risk for stroke (self-efficacy). The study proposes that by determining what constitutes adequate intake, healthcare providers can be on the same page with education, thereby improving patient understanding.

Table 2

Theoretical Framework and Study Variables

Theoretical Framework Title: Health Belief Model	**Proposed Study Title: Vitamin K Deficiency and Stroke in Atrial Fibrillation Patients on Warfarin**	**Variable Nature/Coding Scheme**
Perceived barrier	Dietary Vitamin K intake	C, D, N; vitamin K intake as reported in mcg per day where 0 = intake > 120 mcg/day for men (> 90 mcg/day for women) and 1 = intake < 120 mcg/day for men (<90 mcg/day for women)
Cues to action	Subclinical vitamin K deficiency	C, D, N; vitamin K assay levels where 0 = levels > 0.30 nmol/L and 1 = levels < 0.30 nmoL/L
Perceived barrier	Age	CO; 18 – 95 years
Perceived barrier	Gender	C, D, N; 0=male, 1 = female
Perceived barrier	Race/Ethnicity	C, N; 1 = Caucasian, 2 = Black, 3 = Hispanic/Latino, 4 = Asian, 5 = Pacific Islander, 6 = American Indian/Alaskan Native, 7 = Other
Self-efficacy	Education status	C, O; 1 = Less than high school, 2 = High school, 3 = Some college, 4 = Associates or bachelor’s degree, 5 = Graduate Degree

(*table continues*)

Theoretical Framework Title: Health Belief Model	Proposed Study Title: Vitamin K Deficiency and Stroke in Atrial Fibrillation Patients on Warfarin	Variable Nature/Coding Scheme
Self-efficacy	Income	C, O; 0 = high (> $75,000 annually), 1 = medium ($25,000 - $75,000 annually), and 2 = low (<$25,000 annually)
Perceived barrier	Smoking status	C, D, N; 0 = never smoked, 1 = former or current smoker
Perceived barrier	Alcohol intake	C, D, N; 0 = no, 1 = yes
Perceived barrier	Diabetes mellitus	C, N; 0 = no, 1 = yes
Perceived barrier	High blood pressure	C, D, N; 0 = no, 1 = yes
Perceived barrier	High cholesterol	C, D, N; 0 = no, 1 = yes
Perceived barrier	Heart disease	C, D, N; 0 = no, 1 = yes
Perceived barrier	Body mass index (BMI)	C, O; 1 = underweight, 2 = normal weight, 3 = overweight, 4 = obese, 5 = severe obesity
Perceived susceptibility	Ischemic Stroke	C, D, N; 0 = no stroke, 1 = stroke event

Note. C = Categorical, CO = Continuous, D = Dichotomous, N = Nominal, O = Ordinal, R = Ratio

Nature of the Study

This proposed study was a quantitative, retrospective longitudinal cohort study utilizing secondary data analysis from the Framingham Heart Study (1948). Data collection on atrial fibrillation status, stroke status, vitamin K levels, nutritional intake via food frequency questionnaires, and demographics came from the original and offspring cohorts with data from over 70 years to review. The outcome variable for all research questions was the presence of ischemic stroke (Yes/No). The independent variables were dietary vitamin K intake and subclinical vitamin K deficiency. The covariates were age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, ischemic heart disease, and body mass index. When comparing the differences in vitamin K intake and subclinical vitamin K deficiency in AF subjects on warfarin with and without stroke, many of the variables were categorical in nature, leading to the use of Pearson’s Chi-square inferential analysis to check the independence between variables. When looking at the association between vitamin K and stroke risk, a bivariate as well as multivariate logistic regression was used to assess the association between each variable and the outcome at a time as well as modelling, respectively. All covariates were included in the multivariate logistic regression and stepwise regression. The quantitative findings should help provide more clarity about the association between dietary vitamin K intake and stroke outcomes in NVAF patients on warfarin.

Data came from the Framingham Heart Study's Offspring cohort (n = 5,124) available from BioLINCC through the Centers for Disease Control and Prevention (CDC). The data included variables compiled from all exams compiled from years 1971 to 2014. There was data collection on demographics, atrial fibrillation diagnosis, stroke diagnosis, dietary vitamin K intakes via food frequency questionnaires, and serum vitamin K levels. All participant information received from the gatekeepers was de-identified. Some of the data was transformed into binomial data points for regression analyses. Inclusion criteria was diagnosis of AF in the offspring cohorts. Exclusion criteria included prior cerebrovascular accident (CVA) or similar event prior to AF diagnosis and prior use of warfarin before AF diagnosis. Covariate information collection included age, gender, education level, socioeconomic status, prior medical history (diabetes, high blood pressure, high cholesterol, and heart disease), smoking status, alcohol intake, and body mass index (BMI).

Definitions

General

Atrial fibrillation. A condition in which the heart is unable to maintain a normal rhythm because of physiological changes, leading to increased risk for cardiovascular disease (CDC, 2020a).

Dietary recall. Method of assessing nutritional status of individuals based on oral intake over a specific period, most often between 24 to 72 hours with a combination of weekdays and weekends.

Primary Variables

Anticoagulants. Medication prescribed by a licensed medical practitioner to prevent clotting by various physiological mechanism to minimize the risk of stroke (American Heart Association, n.d.).

Dietary vitamin K. Fat-soluble vitamin with low physiologic stores that has important roles in coagulation and bone metabolism using vitamin K-dependent proteins. Other names include phylloquinone and menaquinone (Lab Tests Online, 2020b).

PT/INR assays. Biochemical test that provides information on bleeding and clotting disorder (PT) and medication effectiveness of anticoagulants (INR). PT is prothrombin time, whereas INR is international normalized ratio (Lab Tests Online, 2020a).

Stroke. Acute disease process where a clot forms and blocks the flow of blood to the heart or brain potentially causing severe physical and mental disability or death (CDC, 2017).

Vitamin K assays. Biochemical laboratory test used to verify the nutritional analysis of dietary recalls for vitamin K intake (Lab Tests Online, 2020b).

Covariables

Age. A participant's chronological age; as the individual ages, their risk for stroke increases (CDC, 2017).

Alcohol Abuse. Intake above the recommended guidelines of one beverage per night for females and two beverages per night for males (CDC, 2017).

Diabetes mellitus. Chronic disease condition in which the body has an inability to process sugars, leading to elevation in the blood stream and potential microvascular changes such as kidney disease, eye disease, and heart disease when left untreated (CDC, 2017).

Ethnicity. A person's cultural heritage which can potentially impact their levels of risk for different chronic diseases (CDC, 2017).

*Heart Disease***.** Any condition that weakens the heart muscle such as coronary artery disease, atrial fibrillation, valve defects, irregular heartbeat, and enlarged heart increase the risk for stroke (CDC, 2017).

*High Blood Pressure***.** Pressure in the vasculature system becomes too high, leading to an increased stroke risk (CDC, 2017).

*High Cholesterol***.** Excessive fat intake leads to atherosclerosis build up in the arteries, thus increasing the pressure in the vascular system as well as causing blockages leading to an increased stroke risk (CDC, 2017).

*Physical Inactivity***.** Condition where the participant is inactive, which leads to chronic medical issues such as high blood pressure, high cholesterol, diabetes, obesity, and stroke (CDC, 2017).

*Obesity***.** Excessive body weight often measured by body mass index, which can lead to high blood pressure, high cholesterol, and diabetes, thus increased stroke risk (CDC, 2017).

Sex. Gender of the participant, where females have a higher risk for stroke than males (CDC, 2017).

Sickle Cell Disease. Process in which irregular size blood cells can block arteries and cause a stroke (CDC, 2017).

Tobacco Use. The use of nicotine-based products, which can lead to high blood pressure and decreased oxygenation in the blood (CDC, 2017).

Assumptions

There are several assumptions that must be accepted. This quantitative study took on a positivist view. First, the data for the study was requested from a single population in Massachusetts with no measurements from individuals outside the area. The assumption was that all individuals had the same experiences and cultural perspectives since they were from the same geographic location. Next, the information was assumed to be gathered by personnel as part of standard treatment, thus helping the researcher remain independent of the study. A third assumption was that based on the data provided, the study would provide an explanation of the association between dietary vitamin K intake and stroke outcomes with all other covariates remaining stable. A fourth assumption is that the measurements taken from valid and reliable instruments, including biochemical testing results and nutritional intake guidelines. Finally, the participants of the study are assumed to have volunteered and provided accurate nutritional information on dietary recalls to the best of their knowledge and relayed this information honestly.

Scope and Delimitations

This study was primarily focused on better understanding the association between vitamin K deficiency below the daily AI for gender and ischemic stroke outcomes in atrial fibrillation patients on warfarin. The focus is important since nutrition education on warfarin and vitamin K interactions lacks consistency across disciplines, leading to health belief issues and poor health outcomes. The study followed the HBM framework looking at the associations between individual perceptions and choices on health outcomes. This secondary data analysis included all participants of the Framingham Heart Study with a diagnosis of atrial fibrillation (AF) and no prior cerebrovascular accident or transient ischemic accident. All participants will be from the Framingham, MA vicinity, which limited the ability to generalize the results to other geographic locations. Generalization was also be limited by and individuals with a diagnosis of AF.

Limitations

Potential barriers to using secondary data can include missing information and miscoded information. Bias could have entered the study results through missing and miscoded information. Another source of bias in this study was that of participant/design bias, since most participants in the Framingham Heart Study are of European descent. The study attempted to minimize this bias in later years by adding cohorts with more variety in ethnicity through the Omni cohorts (Framingham Heart Study, n.d.). Sampling bias could be an issue since the sample was based on a simple 2/3 sampling ratio in 1950 (D'Agostino & Kannel, 1989). According to D'Agostino & Kannel (1989), participants were invited to participate based on a random selection of households within eight precincts through family size and serial order of address. The researchers of the Framingham Heart Study attempted to decrease this issue through the addition of new cohorts and sampling techniques.

A final challenge to conducting the research was adequate computing capabilities on the home computer to store the data while maintaining patient privacy guidelines as put forth by the Framingham Heart Study. This limitation could have led to limiting the number in the sample to be able to do the analysis. Another concern was that secondary data could be too general or vague. Secondary data may not always reflect the larger population and finding an adequate sample to generate actionable results can be problematic. At the same time, a major advantage of secondary data, beyond its economy in this case, is the ability to explore the research questions, as the Framingham heart study has adequate history and population to circumvent many of these concerns, has a wide breadth of data available, is longitudinal, and the data collection process by design maintains a significant level of expertise and professionalism.

Significance

This proposed study identified a gap in the current literature. Current research is formulated mostly around adequate vitamin K intakes, whereas the proposed study looked at the association between dietary vitamin K intake and ischemic stroke outcomes in AF patients. Additionally, current research inclines to view populations as a distinct group in terms of vitamin K intake. In contrast, this proposed study examined a subset of the population: AF that has a significantly increased risk for stroke over the general population. This study addressed the validity of current guidelines for consistent vitamin K intake in warfarin treatment guidelines and attempted to provide more clear-cut guidelines for what constitutes adequate intake without increasing risk for strokes.

Any nutritional deficiency is cause for concern due to the risk for adverse health outcomes. Individuals on long-term vitamin K agonist treatment could end up with vitamin K insufficiency (Yuji et al., 2020). Vitamin K insufficiency could lead to cardiovascular disease risk due to arterial stiffness (Yuji et al., 2020); however, low levels of phylloquinone have been associated with higher mortality rates (Shea et al., 2020). For example, teenagers with lower vitamin K intakes had a three times higher risk for left ventricular hypertrophy (Douthit et al., 2017).

Any study should be relevant to the population under investigation. Several ways that this study could impact the population for positive social change include better nutritional care, improved healthcare monitoring, improved protocols for the use of anticoagulants, improved patient education, and improved economic impact on the community (Freudenberg, 2006). The primary focus of nutritional epidemiology is to minimize malnutrition and improve health outcomes (Lachat et al., 2016). Health beliefs plays a critical role in preventing adverse health outcomes. In the anticoagulant population, many individuals lack proper understanding of their treatment (Magon et al., 2020). Individuals with uncontrolled anticoagulation suffer from lower treatment satisfaction, lower self-efficacy, higher levels of distress, more daily hassles, and more strained social relationships (Varona et al., 2020). A better understanding of the nutritional implications of vitamin K deficiency could lead to improved nutrition education strategies to maintain adequate vitamin K intakes, as well as potential changes in medication regiments to improve coagulation status and lower the risk for adverse health outcomes. Building community capacity through partnerships with pharmacies, healthcare organizations, and dietitians can improve warfarin education through consistent messages from all providers with improvements in monitoring and evaluation (Vest et al., 2020).

Summary

Vitamin K deficiency plays a critical role in the prevention of cardiovascular events. The risk for ischemic stroke is higher in AF patients and the costs associated with stroke can climb as high as $70,000 annually for hospital costs, rehabilitation costs, and personal home care. The main way to prevent stroke in AF patients is using anticoagulants, but the risk for ischemic stroke varies by the different forms of anticoagulation. The issues of dietary and medication noncompliance are high with VKAs versus DOACs related to confusion in health education by providers and patient’s understanding. More research is needed since current research focuses on general populations, normal levels of vitamin K intakes, are not necessarily specific to the AF population, may exclude VKA patients, may not have sufficient power to detect differences due to small outcomes, and the differences in nutrient deficiencies resulting from chronic disease. This study focused on the HBM to determine the extent of health education issues in a retrospective, longitudinal review of the Framingham Heart Study over the past 20 years. A regression analysis controlling for different social determinants of health helped to improve the understanding of the impact of vitamin K deficiency on ischemic stroke. The potential for positive social change exists through the improvement of health education, disease management, and economic costs to patients and healthcare systems. In the next section, a thorough review of current literature discussed the background more thoroughly regarding dietary vitamin K, atrial fibrillation, and ischemic stroke risk.

Chapter 2: Literature Review

Introduction

Understanding the impact of health beliefs related to patient education can be challenging due to the multifactorial nature of disease management. Nutrition, specifically vitamin K deficiency, plays a critical role in preventing stroke. In the prior chapter, research discussing the benefits of vitamin K supplementation to reduce the risk for stroke was noted, but the results were conflicting and ambiguous. Many of the issues could be attributed to research design since many of the studies utilized general populations with healthy vitamin K intakes. Other issues included cross-sectional studies that only looked at one point in time for dietary intake, which can change by the season and region. Many samples initially had adequate power, but too few individuals were experiencing the outcome in the studies to show an association. Some studies excluded those taking warfarin, which can be a primary cause for vitamin K deficiency. Alternately, other studies used patient populations with different chronic diseases, which can alter the metabolism of vitamin K foods. Additionally, warfarin patients experience confusion from differences in vitamin K education by providers. There is a need to address the gap of whether there is a true association between vitamin K deficient diets and ischemic stroke risk in the AF population. The upcoming chapter discusses the strategy used to conduct the literature review, explained the impact of the Health Belief Model on health education and disease management, and looked at the association between vitamin K deficiency and ischemic stroke risk in AF patients on warfarin. Additionally, a thorough review of AF causes, statistics, risk factors, symptoms, and burden provided the background to the discussion on stroke prevention in AF patients using anticoagulants. Finally, there was a quick discussion on vitamin K pathophysiology and nutritional needs.

Literature Review Strategy

To better prepare for conducting a thorough literature review, I met with the research librarian in the health professions department of Walden Library. After the meeting, the article search was conducted using APA PsycInfo, BioMed Central, CINAHL, Embase, Google Scholar, MEDLINE, ProQuest Health and Medical Collection, ProQuest Nursing and Allied Health Database, PubMed, SAGE Journals, Science Direct, and Thoreau. Keyword searches were kept broad to return as many articles as possible using the following keywords in various truncated forms: *atrial fibrillation, stroke, cerebrovascular accident, transient ischemic attack, ischemic stroke, hemorrhagic stroke, cardiovascular, vascular calcification, vitamin K, phylloquinone, menaquinone, Framingham Heart Study, Health Belief Model (HBM), warfarin, coumadin, anticoagulants, direct oral anticoagulant, novel oral anticoagulants, dietary intake, nutritional intake, intake, signs and symptoms, statistics, epidemiology, risk factors, burden, function*, and *deficiency*. To narrow the search further, the findings were limited to English, peer-reviewed, and within the last five years. Upon receipt of the initial article search results, abstracts were reviewed for new keywords and bibliographies for possible seminal works. The “subject” function was used to further limit the results by subject for more pertinent research. All articles that had full-text options available were reviewed using Walden Library.

Theoretical Framework

Health Belief Model

The Health Belief Model (HBM) is one of the most powerful tools in research to determine the framework of a study (Rosenstock, 1974). HBM had four original constructs: perceived susceptibility, perceived severity, perceived benefits, and perceived barriers, with the concept that an individual with high perceptions of susceptibility, severity, and benefits with lower perceived barriers would be more likely to adhere to positive health behaviors (Sulat et al., 2018). The perception of having a negative health outcome such as a stroke impacted behavior change by 15% (Sulat et al., 2018). Unfortunately, there was a lack of research available surrounding the perception of stroke risk in atrial fibrillation patients non-compliant with dietary vitamin K restrictions. While important, perceived severity had the least impact on a patient's ability to make healthy behavior changes, only having affected behaviors 8% as compared with barriers impacting behaviors at 20% (Sulat et al., 2018). According to Sulat et al. (2018), perceived benefits impacted behavior change 13% compared to the other constructs.

While no study was found related to diet compliance and stroke, diabetics with optimal diet control had high perceived benefits in terms of less long-term consequences ($r = -0.22$) and fewer symptoms ($r = -0.28$) (Broadbent et al., 2011). Chen et al. (2019) reported that there was a high perceived benefit for anticoagulant use with a mean score of 20.1 out of 25, with higher scores equating higher perceived benefits. Perceived barriers have been the most important predictor of behavior change, accounting for 100% of preventive health behaviors related to medical advice adherence (Sulat et al., 2018).

Perceived barriers included drug interactions, forgetting to take the medications, diet interactions, activity restrictions, impact on work life, and health belief issues (Chen et al., 2019). Despite these barriers, Chen et al. (2019) found a mean score of 1.1 out of 10, where higher scores were equivalent to more barriers. Additionally, the perceived adherence was 8.8 out of a range of 7-28 with higher scores meaning worse adherence resulting from the barriers (Chen et al., 2019).

A couple of other concepts associated with the HBM include cues to action, locus of control, and self-efficacy. Sulat et al. (2018) reported that the literature surrounding predictive behaviors associated with cues to action and self-efficacy were limited. One of the ways that self-efficacy can improve health beliefs is through video narratives, which have been shown to improve medication compliance through the ability to associate with other individuals dealing with the health outcome under investigation (Appalasamy et al., 2020). Chen et al. (2019) reported a prominent level of self-efficacy among anticoagulated patients at a mean score of 32.9 (range 13-39), with higher scores consistent with higher self-efficacy values. Fernandez et al. (2016) found elevated levels of health beliefs positively associated with perceptions of control over an individual's health condition ($p < 0.001$). Broadbent et al. (2011) found optimal diet compliance in diabetics positively associated with higher locus of control ($r = 0.20$) and self-efficacy for disease management ($r = 0.23$). With over 50% of study participants failing to understand the importance of anticoagulation, a mean knowledge scale score of 35.9 out of 100 visualized the issues with poor health beliefs in the population (Chen et al., 2019). Presently, there is extraordinarily little to no research available on the use of the HBM to explain the impact of nutritional health beliefs related to anticoagulation therapy and prevention of stroke in atrial fibrillation patients.

Literature Review Related to Key Variables and/or Concepts

Independent Variables

Some medications have nutritional restrictions. The dietary restrictions for warfarin have been couched in terms such as *consistent*, *limit*, and *restri*ct. No two healthcare provider educations are the same. Some providers mention all vitamin K foods, whereas other providers may state to avoid or limit green leafy vegetables. The confusion from these educations, as well as cultural preferences, is a major reason for treatment failure. There is also literature showing that the impact of nutritional deficiency by type of vitamin K may be a factor as well in the causation of ischemic and hemorrhagic strokes.

Dietary Vitamin K Intake

Vitamin K foods are discussed in terms of vitamin K1 (phylloquinones) and vitamin K 2 (menaquinones). There are differences in the source and functions by vitamin K type. Having a better understanding of these differences could help improve the education that providers give their patients and improve treatment compliance with VKAs. There are detailed guidelines for the recommended daily adequate intake (AI) for vitamin K, which differs between men and women. The AI for men is 120 mcg daily, and for women, 90 mcg daily (ODS, 2020). The authors went on to describe how the vegetable servings were significantly different, with those meeting the RDI consuming on average 4.36 servings of vegetables daily and those not meeting the RDI only consuming

1.43 servings daily (Wessinger et al., 2020). An overall analysis revealed that those not meeting the AI consumed, on average, 55 mcg daily, as compared with those meeting the AI consuming 330 mcg daily (Wessinger et al., 2020). While the percentage of individuals not meeting the AI for vitamin K between 2003 – 2016 decreased, approximately 67% of participants overall failed to meet the AI for vitamin K intake (Han et al., 2019). Chen and associates (2019) confirmed these findings in a report that 62% of participants failed to meet the AI for vitamin K. Despite having clear guidelines, the actual intakes vary by geographic region, age, cultural differences, and socioeconomic factors, just to name a few barriers.

While overall consumption is important, the balance of vitamin K products between phylloquinones and menaquinones is just as important for biological health. Vitamin K1 is found in foods containing phylloquinones. When providers and patients think back to basic science, *phyllo* often suggests plants. Phylloquinones are the main source of vitamin K from green leafy vegetables in our diet (ODS, 2020). These foods include spinach, collard greens, turnip greens, and other lettuces. The amount of vitamin K consumed depends on the serving size, preparation method, and type of food (e.g., iceberg lettuce versus spinach). When comparing groups with high intake versus those with low intake, 60% of the phylloquinone intake in those with high intake came from vegetables (Harshman et al., 2017). Additionally, Harshman et al. (2017) discovered that low phylloquinone intake was associated with inadequate vegetable intake (less than 2 cups daily). Harshman and colleagues (2017) reported that less than 2 cups of vegetable daily were associated with mean intakes between 78.0 – 80.8 mcg/day, as compared with individuals consuming greater than 2 cups of vegetables daily associated with mean intakes between 195 – 223 mcg/day. These studies looked at one point in time (cross-sectional) though, which does not necessarily show changes over the years. Also, the research did not include individuals on VKAs, which may lower intakes even more than reported.

Menaquinones are the major source of vitamin K2. While our bodies produce menaquinones in the intestine through bacterial processes, individuals can also consume vitamin K2 through fermented vegetable and animal products (ODS, 2020). These foods include natto (fermented soybeans), dairy products (fermented cheeses, sour cream, cream cheese, heavy cream, butter), egg yolks, cured meats (pepperoni, salami, pork sausage, kielbasa), ground beef, and chicken products (wings, thighs, and drumsticks). Menaquinone-4 (MK-4) is converted from the phylloquinones found in vitamin K1 foods in the human intestine (ODS, 2020). Unfortunately, there are not enough studies available looking into actual food intake from menaquinones as opposed to supplemental menaquinone intake. The use of food versus supplement can change the absorption rate of any nutrient.

While vitamin K is a fat-soluble vitamin, the liver does not store much of the nutrient when compared to vitamins A, E, and D. The body only retains about 30-40% of the ingested vitamin K amounts (ODS, 2020). Turck et al. (2017) found that the average storage of vitamin K in the body was around 0.55 mcg/kg of body weight, or 40 mcg/day for a 150-lb person, to be considered healthy. Unfortunately, the absorption of vitamin K foods is not as efficient, with the absorption rate being somewhere between 4-23% in historical studies (Turck et al., 2017). The current recommendations from the European Union would be for everyone to have 70 mcg/day, but that may not be enough to stop a deficiency state if a person is only absorbing 20% of the nutrients. According to Turck et al. (2017), vitamin K deficiency developed in as little as 2-3 weeks with inadequate vitamin K intake from the diet and may need as much as 100 mcg daily of phylloquinones alone to replete the body stores. These issues with absorption and storage become compounded when warfarin patients start eliminating phylloquinones from their diet after they are advised to lower their intakes of vitamin K foods.

Subclinical Vitamin K Deficiency and Cardiovascular Event Risk

Vitamin K has several physiological functions within the human body that helps explain the various forms of vitamin K (i.e., phylloquinones, menaquinone-4, menaquinone-7, etc.). While limiting vitamin K is beneficial for patients on warfarin to lower the clotting factors, limiting too much can lead to a deficiency state, thus altering other biological functions. As healthcare providers, the provider has a responsibility to understand how the medication they prescribe could potentially impact all the physiological functions of their patient considering their cultural practices as well as their biological health. Vitamin K’s impact on physiological health occurs through its role in vitamin K dependent proteins, which function as gateways to further biological cascade functions. Ideally, classic research reported that an intake of 150 mcg daily is crucial to maintaining critical vitamin K pathways (Murray, 2004).

The average intake in the United States historically was documented as 70-80 mcg daily, which is well below the recommendations of 90-120 mcg daily (McCann &

Ames, 2009). In a classic study looking at the impact of a vitamin K deficient diet in rats, Kamali et al. (2009) was able to show that after two weeks on a vitamin K deficient diet, factor II activity decreased over 80%, and further to zero when warfarin was added. Additionally, Kamali et al. (2009) found that while no significant change was seen with factor V, there was another significant decrease in factor VIII of 40%, and factor VIII of 30%, as well as a decrease in factor VIII activity with vitamin K deficient diets plus warfarin.

Vitamin K maintains a presence in bone metabolism through its role with osteocalcin. Osteocalcin acts through vitamin K dependent proteins to balance bone turnover and mineralization (ODS, 2020). As vitamin K levels drop in the body due to insufficient diets, calcium is lost from the bone into the vascular system leading to calcification (ODS, 2020). In a meta-analysis conducted by Lees et al. (2019), the researchers found that vitamin K supplementation decreased calcification by 9.1% (CI 0.5 – 17.7%), thus finding a significant association between vitamin K deficiency and cardiovascular (CVD) mortality (HR 0.45, CI 0.07 – 0.83). In current research, Dai et al. (2021) found associations between vitamin K deficiency and all-cause mortality (sub-HR 1.17, CI 1.01 – 1.37) but not with CVD mortality (sub-HR 1.19, CI 0.90 – 1.55). These findings helped corroborate the findings from Chen et al. (2019) where the RR associated with adequate vitamin K intake and lower CVD mortality was 0.68 (CI 0.54 – 0.86) and 0.79 (CI 0.69 – 0.92) for all-cause mortality. Vitamin K deficiency increased both coronary calcification (sub-HR 1.22, CI 1.01 – 1.48) and arterial calcification (sub-HR 1.27, CI 1.01 – 1.60) (Dai et al., 2021). In a mouse model, van Gorp et al. (2021)

positively associated use of warfarin with higher levels of plaque calcification (r = 0.72) 73% times higher than use with a DOAC (warfarin = 7.2x, DOAC = 1.9x). Jespersen et al. (2020) also reported a 1.54x increased risk (CI 1.21-1.96) for vascular calcification with increasing levels of vitamin K deficiency in a cross-sectional study of the general population. The heterogeneity between the studies helps show the controversial nature of vitamin K deficiency being associated with calcification which could lead to future strokes.

Vitamin K can be assessed through prothrombin time (PTT), which is part of the monthly warfarin tests, or phylloquinone (Vitamin K1). Liquid chromatography, used for vitamin K1 and well as menaquinone testing, can be extremely expensive which is why medical providers do not traditionally use these tests. PTT is the primary tests and less costly which makes it the better choice for testing when dealing with monthly lab draws; however, it is not an accurate assessment of physiological stores or intake of vitamin K. In terms of phylloquinone levels, a healthy range would be 0.29-2.64 nmol/L to match the recommended dietary intakes of 120 mcg/day for men and 90 mcg/day for women (ODS, 2020). Assessing vitamin K status becomes hard when values differ between nations with the European Union recommending only 70 mcg/day for all adults compared to the U.S. recommendations of 120 mcg/day for men and 90 mcg/day for women. Additionally, many researchers are starting to look at precursors of vitamin K dependent proteins to assess vitamin K status, but there are no true references ranges available for assessment (Turck et al., 2017). This gap in reference materials leads to methodology issues when studies use general populations with adequate intake to study deficiency states.

There are several conditions which could lead to vitamin K deficiency states. Infants may be vitamin K deficient directly after birth which is the reason for providers giving infants vitamin K injections directly after their birth (ODS, 2020). Individuals with malabsorptive disorders could have vitamin K deficiency due to alterations in the intestinal membrane seen with cystic fibrosis, celiac disease, ulcerative colitis, short bowel syndrome, and bariatric surgery (ODS, 2020). Similarly, certain medication could cause a deficiency state because of their mechanisms of action. While warfarin is the most widely recognized for decreasing vitamin K intake, bile acid sequestrants and weight loss medications (Orlistat) could decrease vitamin K as well through their alterations in gut permeability. Unfortunately, many population-based studies do not consider the impact of chronic disease states or medications on nutrient intake when conducting their analyses.

Dependent Variables (Ischemic Stroke)

One of the major debilitating complications of AF is stroke. Stroke is currently the fifth leading cause of death in the United States (U.S.) (CDC, 2020b). Individuals suffering from AF have a 4-6x increased risk for stroke on average with AF being identified as primary cause of all strokes at least 14% of the time (CDC, 2020a; NINDS, 2019). Annually, there are 795,000 strokes in the U.S. (CDC, 2020b). A recent study reported that over 15 years, the relative percentage of AF hospitalizations for stroke was 4.8% with the top risk factors for admission in those patients being high blood pressure, advanced age, and chronic lung disease (Doshi et al., 2021). The frequency of IS was determined to be 38.9 per 1000 which was a significant increase over the prior 15 years ($p < 0.001$) (Doshi et al., 2021). As discussed earlier, there was a notably higher percentage of IS patients in the Southern U.S. versus other geographic areas (37.5% versus 18.9-23.2%) (Doshi et al., 2021). Like other chronic diseases, there is a strong regional influence with a higher percentage of strokes annually located in Alabama, Arkansas, Georgia, Indiana, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, and Virginia (Claxton et al., 2018). Originally coined the "stroke belt," the area had stroke rates 10% higher than the national average in the 1980s, but the gap has narrowed to around 5% since the 1999 legislation to reduce minority disparities (Claxton et al., 2018; Odlum et al., 2020). Stroke can be further described as ischemic, hemorrhagic, or as a transient ischemic attack.

Types of Strokes

Ischemic stroke is caused when blood clots block the arteries leading to the brain (CDC, 2020b). Approximately 87% of all ischemic strokes are caused by AF (CDC, 2020b). Mortality rates among ischemic stroke patients increased the longer the time from the event with 3% within the hospital to 26% at one year post event (Gardener et al., 2021). When hospitals follow the 10-performance metrics (Table 2) for ischemic stroke developed by the CDC, AHA, and Joint Commission (JC), health outcomes improved 112% over 10 years (Overwyk et al., 2021). One major area of disparity amongst stroke care was incomplete care for those with AF (10% lower than those without AF) (Overwyk et al., 2021). When reviewing quality of life indicators (QOL), IS patients had significant associations between QOL and follow-up visits, physiotherapist visits, and musculoskeletal complications (p=0.025 for all) (Overwyk et al., 2021). Over the course of 11 years from 2004 to 2015, there was a 40% increase in the prevalence of AF in Melbourne, Australia (Yang et al., 2017). During the same period, individuals with AF experienced a 57% increase in ischemic stroke (Yang et al., 2017). When looking further into individuals with AF that had ischemic strokes, there was a 43% increase in cardiometabolic strokes during those 11 years (Yang et al., 2017).

Transient ischemic attacks (TIA) are small ischemic strokes with symptoms lasting less than 24 hours and no evidence of a stroke on imaging (Rutrick et al, 2021). As with ischemic strokes, TIA had significant improvements in 10 years with hospital performance metrics where stroke rates decreased from 4.6 to 3.6 per 100,000 U.S. adults (Tabbalat et al., 2021). Rutrick et al. (2021) reported that more than 20% of all strokes have been preceded by TIA.

Hemorrhagic stroke (HS) could occur when blood vessels or arteries rupture from high blood pressure or aneurysms (CDC, 2020b). When the blood floods the surround tissues, the stroke is considered an intracerebral hemorrhagic stroke (IHS) (CDC, 2020b). In patients with HS, there was a 76% improvement overall with use of the performance metrics put out by the CDC, AHA, and JC (Overwyk et al., 2021). One of the major gaps in risk factors for stroke is population specific data such as atrial fibrillation risk factors alone versus all the population.

Table 3

Gold Standard Evidenced-Based Stroke Protocol

Stroke Performance Measure	**Evidenced based protocol for gold standard care**		
	Ischemic stroke	**Hemorrhagic stroke**	**Transient ischemic attack**
IV Alteplase given when indicated	X		
Venous thromboembolism prophylaxis (VTE)	X	X	
Antithrombotic therapy within 48 hours	X		X
Dysphagia screen	X	X	
Discharged on statin medication	X		X
Discharged on antithrombotic therapy	X		X
Anticoagulation for atrial fibrillation	X		X
Stroke education	X	X	X
Smoking cessation counseling	X	X	X
Rehabilitation assessment	X	X	

Note. IV = intravenous. Adapted from "Defect-Free Care Trends in the Paul Coverdell National Acute Stroke Program, 2008-2018," by K. J. Overwyk, X. Yin, X. Tong, S. M. C. King, and J. L. Wiltz, 2021, *American Heart Journal, 232*, p. 177–184**. (**https://doi.org/10.1016/j.ahj.2020.11.010**)**

Covariates

Age

When analyzing information, health care providers need to consider the ramifications of chronological age. Regarding strokes in AF patients, at least 25% of those strokes occur in patients over 80 years of age (NINDS, 2019). The largest area of disparity amongst stroke care was for those aged 18-54 (9-28% lower than other age groups) (Overwyk et al., 2021). Mortality rates associated with stroke increased with those older than 55 years (aOR 1.12 – 5.01) (Tabbalat et al., 2021). Researchers continue to report the impact of age on stroke risk with a study looking at two large databases estimated the risk for stroke between 1.66 – 2.76 for individuals over 65 years age (Wang et al., 2020).

Inadequate vitamin K intake is not just in the general population. Keller et al. (2018) reported >97% of the long-term care residents in Canada had intakes below adequate with median intakes between 51.2 – 55.4 mcg daily. Harshman et al. (2017) reported the lowest intake of vitamin K in men was for ages 51 and older (31-38% meeting the AI). Han et al. (2019) added to the findings showing men ages 19-45 years had the lowest intake; however, the calorie intake also decreased over the 13-year study period as well which could confound the results. Stroke education was lowest with those older than 75 years (Overwyk et al., 2021). These disparities in stroke outcomes, vitamin K intakes, and health education need to be addressed in research that will control the different risk factors, so outcomes are consistent.

Alcohol

Differences in alcohol intake impact health outcomes because of its impact on the internal organs. Previous research looking at heavy alcoholic intake and stroke risk reported the risk for all stroke was higher than light alcoholic intake (OR 1.93; 95% CI 1.21-3.08) (Bassand et al., 2018). One study comparing alcoholic intake measured by the fatty liver index where elevated levels equal low alcoholic intake found that low intake was positively associated with reduced overall stroke risk in men but not women (p=0.09) (Alexander et al., 2018). Lower consumption of alcohol within 30 days was found to decrease the risk for all stroke by close to 40% (OR 0.63; 95% CI 0.51-0.79) (Tshiswaka et al., 2019). Another study found alcohol had no impact on total stroke risk (p=0.856) (Ren & Fu, 2021). The lack of standardization in measuring alcohol intake as well as using cross-sectional studies impacts the results of these studies. Using regression analysis to help control for this confounding variable should reduce the impact on the proposed study.

Diabetes

As with other covariates, there are mixed results on the impact of diabetes and stroke risk. Societies that have a diabetes rate higher than 10.95% have a slightly increased risk for stroke but this was not significant related to the databases in use (Wang et al., 2020). While there have been improvements in the mortality rates (19-48% reduced risk) following stroke in diabetics with Hispanic ancestry, high blood pressure, dyslipidemia, and smoking history, these changes were attributed to changes in screenings and documentation, more precise targeted risk factor modification, increased primary and secondary prevention strategies, and improvements in cardiovascular medications (Tabbalat et al., 2021). The mortality risk for diabetics after stroke increased with age (aOR 1.12 – 5.01), renal failure (aOR 1.28 – 2.10), and coronary artery disease (aOR 1.05 – 1.27) (Tabbalat et al., 2021). One study analyzing the impact of diabetes on all strokes by cluster or by predefined diagnosis found positive associations but by wide margins where a cluster model reported 28x the risk for all stroke versus only 2x the risk for all stroke with predefined diagnosis (Ren & Fu, 2021). Despite the findings of Tshiswaka et al. (2019), a significant association was found between diabetes and all stroke (OR 1.43; 95% CI 1.15-1.78; p <0.01) and a global study of AF patients (OR 1.23; 95% CI 1.03 – 1.47) (Bassand et al., 2018). No significance was found in a later study between all types of recurrent stroke and diabetes (OR 0.069; 95% CI 0.339–1.096) (Sarif et al., 2020). More longitudinal studies are needed to confirm these results from the cross-sectional studies which only look at disease states at one point in time with different individuals.

Education

Health education is a critical component of preventive health outcomes. Stroke education had the largest improvement over the 10 years with a 64% increase (Overwyk et al., 2021). Individuals taking warfarin must be able to understand the differences between consistent intake and no intake of vitamin K foods. Harshman et al. (2017) discovered that low phylloquinone intake was associated with poor education (less than high school). Wang and associates (2020) found that regions with a high school graduation rate lower than 83% had a significantly increased risk for stroke (OR 1.03, CI 1.02 – 1.04). In a recent study, Ali (2018) found that only 20% of IS participants could read and write which could have a significant impact on their ability to understand directions. There was a 113% overall improvement in TIA over the intervening years with an 81% improvement in stroke education and 29% improvement in patients being discharged on statin medications (Overwyk et al., 2021). In HS, the main improvements in care were seen with stroke education (74.9% increase) and dysphagia screening (18.6% increase) (Overwyk et al., 2021). There remains a lack of knowledge in general research surrounding patient understanding of the vitamin K diet and warfarin treatment.

Gender

Gender plays a modulating role in stroke outcomes. When comparing gender, women had a higher risk for premature atherosclerotic cardiovascular disease (ASCVD) than men (aOR 2.13 versus aOR 1.49; $p<0.01$ each) (Mahtta et al., 2021). Previous age-standardized rates for the incidence of stroke in AF patients were 3.19 – 3.79 per 1,000 per years (Claxton et al., 2018). These rates were higher among women in the majority of the 10 regions identified with rates between 3.42 – 4.62 per 1,000 person years (Claxton et al., 2018). Men, however, were reported as being 2.61 – 3.41 per 1,000 person years in most regions (Claxton, et al., 2018). Yong et al. (2020) supported these findings with the stroke rate in women being significantly higher than men in the U.S. (10.9 versus 7.2; $p < 0.0001$). Research by Wang et al. (2020), however, determined that the risk for ischemic stroke was lower in females versus males (OR 0.95, 95% CI 0.94 – 0.96).

The largest area of disparity amongst stroke care for those not receiving complete care were women (6% lower than men) (Overwyk et al., 2021). Some of the health disparities associated with oral anticoagulants (OAC) include women being less likely to receive OAC treatment than men (50% versus 43%) (Yong et al., 2020). Women were found to have higher rates of hospitalization for stroke than men (aHR 1.06) (Yong et al., 2020).

Vitamin K intakes varied as well by geographic region and ancestry. In a recent study by Wessinger et al. (2020), 82% of participants failed to meet the RDI for vitamin K intake with men consuming on average 100 mcg daily and women 89 mcg daily. These findings were corroborated by Harshman et al. (2017) that reported only 43% of men and

62.5% of women met nutritional adequacy for vitamin K intake. Over a 13-year period, vitamin K intakes decreased by a minimum of 13-20% versus men by a minimum of 1-10% (Han et al., 2019). Due to the nature of the variable, the main limitation to studying gender and ischemic stroke is the lack of current research looking at gender-based differences in the AF populations. The proposed study will provide an update on the impact of gender and IS stroke risk in atrial fibrillation patients on warfarin.

High Blood Pressure (HTN)

Another chronic disease that impacts ischemic stroke health outcomes is hypertension. Recent studies have reported an association between high blood pressure and stroke (aOR 2.295 – 3.60) (Ren & Fu, 2021; Tshiswaka et al., 2019). Other studies have found no association between HTN and recurrent stroke risk for all strokes or in a global AF study looking at all strokes (Bassand et al., 2018; Sarif et al., 2020). Overwyk and associates (2021) were able to report a marginally increased risk for IS in patients with HTN as 1.02 (95% CI 1.00 – 1.04). A couple of limitations to the studies are the cross-sectional nature and inadequate power to detect any significance due to ischemic strokes being a rare outcome. A longitudinal study should provide the power needed if the sample size is large enough.

High Cholesterol (HLD)

High cholesterol is a confounder when dealing with any study looking at ischemic stroke risk since elevated levels of cholesterol can cause plaque build-up and all types of strokes. When comparing HLD to all strokes, HLD was found to be significantly associated with stroke outcomes (Ren & Fu, 2021; Sarif et al., 2020). The risk for all stroke in patients with HLD was 1.75 (95% CI 1.39-2.19; p <0.001) (Tshiswaka et al., 2019). When looking at IS specifically, patients with HLD experienced a 16% increase in IS (p<0.001) (Agarwal et al., 2017) and a marginal increased odd for IS (OR 1.06; 95% CI 1.04-1.07) (Overwyk et al., 2021). To control for this confounder, a multivariate regression will be used for the proposed study.

Income

The social determinants of health (SDH) have major impacts on income and health. The SDH can include age, race, financial status, education status, food security, substance use, and disease states. In a 13-year study, Han and associates (2019) reported that low socioeconomic status (SES) was associated with lower vitamin K intake where low SES only met vitamin K adequacy in 2015-2016 at least 50% of the time versus high SES meeting vitamin K adequacy at least 80% of the time (p < .001). Low SES was determined by a poverty income ratio (PIR) where the lower the ratio the lower the income levels with low PIR < 1.30 and high PIR > 3.5 (Han et al., 2019). Ren and Fu (2021) confirmed this association with stroke patients having a PIR of 2.23 (95% CI 1.42-4.79) compared to non-stroke patients with a PIR of 3.22 (95% CI 1.78-5.00). Another determinant associated with ischemic stroke included unemployment rates above 7.25% (OR 1.01) (Wang, et al., 2020). Soliman et al. (2017) found in the past that unemployment was a modifier for stroke risk in AF patients with the unemployed having a 12.3% association with prior stroke history versus employed individuals at 2.2% (p<0.001). Prior stroke decreased with an increase in income levels from 4.0% to 3.5% in the first quartile versus the fourth quartile (Matetic et al., 2020). Harshman et al. (2017)

discovered that low phylloquinone intake was associated with individuals making less than $25,000 annually. One thing that Wang and associates (2020) did not find was an association between food insecurity rates above the national average (14.75%) and stroke risk (OR 1.00, CI 0.99 – 1.01). The contrasting results suggest the veracity of the representativeness of the data used for investigation.

Obesity

There is conflicting information surrounding the impact of weight on ischemic stroke risk in the U.S. Ren & Fu (2021) and Tshiswaka et al. (2019) failed to find an association between weight and all stroke (95% CI 0.36-1.30; p=0.063). Agarwal et al. (2017) did find a positive association between obesity and all stroke over 10 years with a 205% increase in obesity rates for individuals having any type of stroke (p<0.001). Another issue is the nutritional adequacy of vitamin K intake in obese individuals. Harshman et al. (2017) found higher levels of vitamin K adequacy in women versus men among the obese population (62.5% versus 43.9%), and Han et al. (2019) found a significantly increased intake between normal weight (55-57%) and obese (65%) individuals (p<0.001). The conflicting nature of the results may be due to the inadequate power in the study and differences in weighing techniques. Longitudinal studies using multivariate regression should help control for the potential of confounding by this covariate.

Race and Ethnicity

Race and ethnicity are often studied together which makes separating these variables undesirable. An analysis of over 4 million participants revealed a 15% increase in stroke among Black Americans leading to a 7% worsening gap between the Black American and Caucasian populations over the past 20 years; however, the gap in stroke rates between Hispanic and Caucasian populations improved by 4% over the same period (Odlum et al., 2020). More recently there was a significant difference in the risk of overall stroke between Caucasians (71% stroke rate) and Black American (91.9% stroke rate) populations ($p = 0.001$) (Noorbakhsh-Sabet et al., 2018). These variations between populations and stroke risk carried over to vitamin intakes as well.

While African Americans, Mexican Americans, Hispanics, and Asians tend to have prominent levels of vitamin K intake, Caucasians tend to fall below the RDI (Harshman et al., 2017). Harshman et al. (2017) discovered that low phylloquinone intake was associated with Caucasian ethnicity. Prior studies reported men and those of Hispanic ancestry having the lowest intakes of vitamin K ($p < .001$) (Han et al., 2019; Harshman et al., 2017). Black Americans had high rates of stroke if the percentage of Black Americans was higher than 11.37% (OR 1.50, CI 1.48 – 1.51) (Wang et al., 2020). One of the key issues with the research is the impact of the databases used to gather geographic data and whether that data is representative of the region or not. Another limitation is the use of food recalls which are often fallible and only measure one point in time. The current proposed study will use biochemical values to validate the food diaries.

Smoking

Different disease states and substance abuse issues impact someone’s odds of having any stroke. Individuals with AF have a 20% risk for ischemic stroke, but that risk increases to 33% if they have even one identified risk factor for any stroke such as smoking, alcohol abuse, obesity, high blood pressure, heart attack, or diabetes (Staerk et al., 2018). Another area of concern is societies with smoking rates of more than 21.23% showing a marginally increased risk for all strokes (OR 1.02, CI 1.01 – 1.03) (Wang et al., 2020). Studies do not always agree as seen by recent studies that reported smoking rates for stroke patients versus those without stroke as nonsignificant (p=0.081) and not associated with recurrent ischemic strokes (95% CI 0.436 – 1.980) or all stroke in AF patients (aOR 1.27; 95% CI 0.96-1.68) (Bassand et al., 2018; Ren & Fu, 2021; Sarif et al., 2019). Other studies reported associations between smoking and pre-atherosclerotic cardiovascular disease (ASCVD) (aOR 1.97; 95% CI 1.94-2.00) and between those that smoked versus those that never smoked and all stroke risk (OR 0.58; 95%CI 0.45-0.75; p < 0.001) (Mahtta et al., 2021; Tshiswaka et al., 2019). The incongruence between studies as well as the use of cross-sectional studies undermines the functionality of the data. Using a longitudinal study will help improve associations between smoking and ischemic stroke risk.

Association Between Vitamin K Deficiency and Stroke Risk

While significant research has been conducted into vitamin K deficiency and stroke risk, the research has been controversial with mixed results. Some of the controversy surround the type of vitamin K studied, the average intake of vitamin K consumed was adequate versus deficient, and not enough participants to find any true significance. In more recent research, phylloquinone intake was found to improve the risk for coronary heart disease (CHD) at adequate intake levels with averages around 83 mcg daily by 52% (aHR 0.48); however, the reduced risk for CHD goes away with higher intakes showing that excessive phylloquinone intake or supplementation is not warranted (Haugsgjerd et al., 2020). Additionally, menaquinone intakes on average around 15 mcg daily were found to have no association with CHD (Haugsgjerd et al., 2020).

Conceptual Framework and Statistical Plan

The proposed study followed the HBM using a longitudinal, retrospective analysis of secondary data from the Framingham Heart Study (FHS). Using the constructs from the HBM and the variables for the study, participant outcomes looked at their perceived susceptibility to ischemic stroke based on their vitamin K intake. Some of the perceived barriers were measured in the proposed study included dietary vitamin K intake, age, gender, race, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, heart disease, and body mass index. These variables are barriers to stroke because they can be risk factors as well and due to the influence of cultural, regional, and social factors impacting nutritional intake. The cue to action would be subclinical vitamin K deficiency as individuals could view this to adjust their diet to become more consistent in their intake when taking warfarin. Participants' ability to understand medical nutrition orders as well as adjust intakes, self-efficacy, are impacted by their education and income levels. All these constructs help to define what this study is trying to measure: the impact of nutritional deficiencies on ischemic stroke outcomes when controlling for other risk factors and barriers.

The proposed study looked to provide higher-level evidence to improve scientific knowledge using a longitudinal study with bivariate and multivariate logistic regression analyses. Previous studies may lack adequate power due to their cross-sectional nature, only looking at food recalls, having populations with adequate vitamin K intake to begin with, and not controlling for the different risk factors for ischemic stroke. The FHS is a longitudinal study with a high retention rate, highly trained medical professionals, measures three generations of participants for heart disease with multiple measurements, uses standardized terminology for heart disease, and maintained extensive quality control and reproducibility through multiple research studies (Tsao & Vasan, 2015). The main weakness of the FHS is that the original and offspring cohorts were all white and of European descent (Tsao & Vasan, 2015). The proposed study used the *Offspring* cohort spanning over 43 years from 1971 to 2015 (Tsao & Vasan, 2015).

Since the proposed study dealt with a dichotomous, categorical outcome variable, continuous/categorical independent variables, and looking for probabilities for ischemic stroke, the study utilized bivariate and multivariate logistic regression analyses which will also help to control for confounding variables. Both types of logistic regression require the dependent variable to be categorical but allow multiple independent variables that are either categorical or continuous. The analyses generated the probability of participants having an ischemic stroke given the explanatory factors listed in the research questions. Some of the strengths to using logistic regression include no need for a linear association, equal variance not required, normal distribution not required, being more appropriate for fixed time frames, improved accuracy; addressing relative and absolute risk, less influence by research design, and estimates are smoothed (Hanson, 2022). According to Hanson (2022), the inherent weakness to logistic regression includes difficult to interpret results, odds ratios may be less intuitive, and the association between the explanatory variables and outcome variable may not always be logical which needs to be accounted for in the results.

Conclusion

The research surrounding the association between vitamin K deficiency and ischemic stroke is controversial. Atrial fibrillation patients restrict their diets due to medication complications with warfarin which may be leading to deficiency states and risk for IS due to poor health beliefs from ongoing patient education. The Health Belief Model helps to identify how an individual's perceptions, beliefs, barriers, and self-efficacy can impact their diet. While there may be an association between vitamin K deficiency and cardiovascular or all-cause mortality, few studies are available looking specifically at stroke risk. Some of the issues surrounding the present literature is the lack of homogeneity in research design, studies were conducted with other disease states which can change the biochemical processes compared with atrial fibrillation patients, the samples may have been too small to detect a significant association between vitamin K deficiency and IS, IS may not have been the primary outcome, some studies used samples with normal vitamin K intake compared to deficiency states, and lack of reference ranges for many vitamin K deficiency tests makes it hard to identify a true deficiency state. This study looked specifically at atrial fibrillation patients on warfarin and the association between dietary vitamin K intake and ischemic stroke risk. In the next chapter, the research design and methods are explained. A thorough review of the Framingham Heart Study procedures are discussed to provide an understanding of the nature of the prospective cohort study that is conducted in Framingham, MA. The data collection, variables, and analysis were further explained as well as the power for the study to detect an association between vitamin K deficiency and stroke in atrial fibrillation patients on warfarin. Finally, the research ethics and privacy were reviewed.

Chapter 3: Research Method

Introduction

In the previous chapter, there was conflicting information between past and current research with vitamin K deficiency, VKAs, and stroke risk in the AF population. These conflicts were mostly related to small studies lacking adequate power due to the rare outcome of stroke, research at one point in time (cross-sectional), excluding individuals on VKAs, research that did not include the AF population, and research from other countries with distinct cultural traits. Stroke is one of the outcomes followed by the Framingham Heart Study. The Framingham Heart Study (FHS) is a prospective, longitudinal cohort that will be discussed in further detail. This study will be a secondary analysis of the *Offspring cohort*.

Information was collected from self-administered questionnaires, food frequency questionnaires, and medical questionnaires. The purpose of this study was to determine if there is an association between dietary vitamin K deficiency in AF patients on warfarin and ischemic stroke. Information was provided on the number of exams the cohorts have been through, as well as the sampling frame. This quantitative study used binary logistic regression, multivariate regression, and Pearson’s chi-square analyses to determine if an association exists. The ethical considerations and limitations of the study were considered, including patient consent, data storage, self-reporting bias, sampling bias, and limitation inherent with archival data collections. This chapter provides a thorough review of the research design and variables on the data collected through various questionnaires at each exam, as well as the number of individuals that have completed the exams through 2019 to better fill in the gap from prior research studies.

Research Design and Rationale

Variables

This study had two main priori independent variables and one outcome variable. This study assessed the association between several covariates to help control for any confounding in the study. The purpose of the study was to identify if there was an association between vitamin K deficiency and stroke outcomes initially, and after controlling for confounding factors. At the end of the variable descriptions, Table 4 shows a condensed view of the variables, their role in the study, the measurement level, and the associated statistical test.

The first main priori independent variable was Dietary Vitamin K intake. This variable was measured in micrograms (mcg) per day. The variable was accessed using the vr_ffreq_ex08_1_0615s dataset. The two ratio variables used for this study were from oils (dihydovitamin K: NUT_DVITK) and dark green leafy vegetables without supplements (phylloquinone vitamin K1 without supplements: NUT_VITKWO). The range of NUT_DVITK was 0.02 – 133.48 mcg/day. The range for NUT_VITKWO was 9.02 – 2112.24 mcg/day. These measurements were taken from a food frequency interview as part of the FHS surveys to monitor the average intake of dietary vitamin K intake through their lifespan and compare this against stroke outcomes. The two variables were recoded to one dietary vitamin K intake variable (DVITK) by adding them together. The new independent variable was recategorized to a dichotomous variable and classified as having adequate intake (0 = vitamin K intake > 120 mcg per day for men and > 90 mcg per day for women: 1 = vitamin K intake < 120 mcg per day for men and < 90 mcg per day for women). These ranges were chosen from the U.S. national recommendations for people (ODS, 2021).

The second main priori independent variable was Serum Vitamin K. The variable came from the VITK1_7s dataset from exam 7. The blood was processed at the Vitamin K laboratory at Tufts New England Medical Center and measured in nmol/L. The current range of the measurement was between 0.05 – 35.02 nmol/L in the FHS. The variable was renamed VITK in this retrospective data analysis and was used to analyze any associations between biochemical levels of vitamin K and ischemic stroke outcomes. The independent variable was recoded into a dichotomous variable where 0 = levels > 0.30 nmol/L and 1 = levels < 0.30 nmol/L based on national lab recommendations.

The dependent variable, ischemic stroke, was a nominal level variable. The variable was from the vr_svstk_2018_a_1269s dataset that provided information from survival and status updates following all strokes through 2018 for the original, offspring, generation 3, new offspring spouse, omni 1, and omni 2 cohorts. Only data from the offspring cohort was requested through the IDTYPE variable, which coded the offspring cohort = 1. To determine if any stroke occurred, the variable STROKE was coded as no (0) or yes (1). For all identified participants having a stroke, the variable STROKE_TYPE identified the type of stroke they had where the variable was coded as definite CVA at exam 1 (10), atherothrombotic infarction of brain (11), cerebral embolism (13), intracerebral hemorrhage (14), subarachnoid hemorrhage (15), other

CVA (16), CVA type unknown (17), and questionable CVA at exam 1 (19). Any participants coded as 10 or 19 were excluded from the study to reduce the risk of confounding. A new dependent variable (STROKE) was recoded as a nominal variable from the STROKE_TYPE variable looking solely at cerebral embolism where the originally coded 11, 14, 15, 16, and 17 became “no” (0) and originally coded 13 will be recoded to “yes” (1).

Some of the genetic confounders in the current study included age, gender, and race/ethnicity. Age and gender were taken from the vr_wkthru_ex09_1_1001s dataset. Age was the first covariate and corresponds to AGE8. The age was calculated at examination 8, and it ranges between 40-93 years at that exam. The variable was a ratio measurement, which was recategorized to an ordinal variable for the current study. Gender was the second covariate and corresponded to SEX, describing the sex of the participant. The sex was a nominal level measurement and coded as either Male (1) or Female (2). The covariate remained coded as a nominal level variable for this study. Race/Ethnicity was the next covariate, which was taken from the vr_raceall_2008_a_0712s dataset. The original variable for the dataset was from RACE_CODE with the following coding: White (W), Black (B), Hispanic or Latino (H), no Hispanic or Latino (E), Asian (A), Native Hawaiian/Pacific Islander (P), American Indian/Alaskan Native (N), Asian Indian/Pacific Islander (X), Other (O), No Answer (R), and unknown (*).

Some of the sociodemographic confounders for ischemic stroke included education status and income. The education variable came from the ex1_8s dataset with a variable code H708. Education level was an ordinal level covariate that asked, “what is the highest degree or level of school have you completed.” The variable was coded as 0 = no school, 1 = grades 1-8, 2 = grades 9 – 11, 3 = completed high school or GED, 4 = some college but no degree, 5 = technical school certificate, 6 = associates degrees, 7 = bachelor’s degree, 8 = graduate or professional degree, or prefer not to answer (.). The covariate was recoded to 1 = less than high school (HS), 2 = HS or GED, 3 = some college, 4 = associates or bachelor’s degree, and 5 = graduate degree for the current study. The income variable looked at the income group best representing the participants combined family income over the past 12 months. The corresponding Variable ID was PY125. The variable was coded as either 1 = no income, 2 = Less than $5,000, 3 = $5,000 - $9,000, 4 = $10,000 - $14,000, 5 = $15,000 - $19,0000, 6 = $20,000 - $24,000, 7 = $25,000 - $29,000, 8 = $30,000 - $34,000, 9 = $35,000 - $39,000, 10 = $40,000 - $44,000, 11 = 45,000 - $50,000, or 12 = Greater than $50,000. The variable was recoded to 1 = Low Income (Less than $25,000 annually), 2 = Medium Income ($25,000 - $50,000), or 3 = High Income (Greater than $50,000).

The current study controlled for substance abuse identified from smoking and alcohol use. The data came from the dataset vr_wkthru_ex09_1_1001s. Smoking came from the CURRSMK8 variable, which asked if the participant is currently smoking at exam 8. The variable was a dichotomous variable where 0 = not a current smoker, and 1 = current smoker, with 2,107 missing data points. Alcohol use was a covariate taken from variable IDs, h081 and h082, from the ex1_8s dataset. H081 asked, “Over the past year, on average, on how many days per week did you drink an alcohol beverage of any type?”

H082 asks, “Over the past year, on a typical day when you drink, how many drinks do you have?” Both variables were ratio variables. To identify chronic alcohol use versus social use, a new dichotomous variable was created (ALCOHOL) where 0 = no and 1 = yes. Anyone that listed H081 as 0 (none) were listed as 0 on the new variable. For those that had identified drinking on H081, H082 was used to identify how much the participant consumed, relative to weekly alcoholic intake recommendations (less than 7 standard drinks per week for women and 14 drinks per week for men). If they exceeded their recommended standard drinks per week, they were coded as yes (1) for the ALCOHOL variable; otherwise, they were coded as no (0) for the new variable.

The study looked at covariates related to chronic disease as confounders for ischemic stroke including diabetes mellitus (DM), high blood pressure (HTN), high cholesterol (HLD), and obesity. The variables were taken from the vr_wkthru_ex09_1_1001s dataset. Obesity was coded as BMI8, which measured the body mass index (BMI) of participants with a range of 13.76 – 56.33 kg/m^2 and 2,218 missing data points. The variable was recoded as an ordinal variable where 1 = Underweight (<18.5 kg/m2), 2 = Normal Weight (18.5 – 24.9 kg/m2), 3 = Overweight (25.0 – 29.9 kg/m2), 4 = Obesity (30.0 – 39.9 kg/m2), and 5 = Severe Obesity (> 40.0 kg/m2). DM came from the variable DMRX8, which asked participants if they were receiving treatment for diabetes at exam 8. The variable was a dichotomous variable coded as 0 = no and 1 = yes with 2,243 missing data points. HTN came from the variable HRX8, which asked participants if they are receiving treatment for hypertension at exam 8. The variable was coded as a dichotomous variable where 0 = no and 1 = yes with

2,106 missing data points. HLD came from the variable LIPRX8, which asked participants if they received treatment for hyperlipidemia at exam 8. The variable was a dichotomous variable coded as 0 = no and 1 = yes with 2,106 missing data points. The coding remained the same for the current study.

To identify the appropriate population, atrial fibrillation patients on warfarin, the vr_afcum_2019_a_1186s dataset was used for identification purposes. To merge all the data appropriately, the variable, SHAREDID, was requested, which was the ID assigned to all participants in each dataset. The ID TYPE helped to identify the appropriate cohort where the offspring cohort = 1 with 11,805 participants. The RHYTHM variable helped identify all participants with atrial fibrillation (1), which was 11,356 participants. The population was further restricted using ATHROMRX to identify participants taking warfarin (1), which totaled 8,149 participants through the full FHS. As previously stated, when discussing the stroke variable, any participants with a history of stroke prior to entering the FHS were excluded from the study. Table 4 provides a look at the association between the variables, measurement levels, role in the study, and statistical test for analysis.

Table 4

Study Variable Characteristics

Variable Name	Measurement Level	Role in Study	Statistical Test
Stroke	Dichotomous	DV	Simple & Multivariate Logistic Regression
Dietary Vitamin K	Dichotomous	IV	Simple Logistic Regression
Serum Vitamin K	Dichotomous	IV	Simple Logistic Regression

(*table continues)*

Variable Name	**Measurement Level**	**Role in Study**	**Statistical Test**
Age	Ratio	CV	Pearson’s Chi Square
Gender	Nominal	CV	Pearson’s Chi Square
Race/Ethnicity	Nominal	CV	Pearson’s Chi Square
Education Level	Ordinal	CV	Pearson’s Chi Square
Income Level	Ordinal	CV	Pearson’s Chi Square
Smoking Use	Dichotomous	CV	Pearson’s Chi Square
Alcohol Use	Dichotomous	CV	Pearson’s Chi Square
Diabetes Mellitus	Dichotomous	CV	Pearson’s Chi Square
High Blood Pressure	Dichotomous	CV	Pearson’s Chi Square
High Cholesterol	Dichotomous	CV	Pearson’s Chi Square
Body Mass Index	Ordinal	CV	Pearson’s Chi Square
Atrial Fibrillation	Nominal	Sample identification	
Warfarin	Nominal	Sample identification	

Note. CV = covariate, DV = dependent variable, IV = independent variable

Research Design

This study was a retrospective, secondary data analysis with participants ranging in age from 32-93 at their last examination. A secondary data analysis of data from the first three examinations was collected from the *Offspring cohort*, which helped provide a timeline to determine if the primary outcome (ischemic stroke) occurred after the appearance of AF diagnosis and vitamin K deficiency for patients on warfarin. By using the first three examinations’ data, we were able to exclude participants that had strokes prior to AF, as well as track the diagnosis of AF, initiation of anticoagulation, and diagnosis of stroke. One of the benefits of a secondary data analysis was that the data was already collected so the only time constraints involved in this study were the time it took to request the data from the stakeholders, as well as the time to review everyone for inclusion or exclusion into the study. Using longitudinal studies is a fantastic way to improve evidence-based practices since researchers can see when the outcomes occur naturally in the environment. At the same time, professionals need to remember that observational studies can have many confounders due to their nature.

Research Methodology

Population

The Framingham Heart Study (FHS) is an ongoing critical study on cardiovascular health. The study started enrolling residents from Framingham, MA, and the surrounding area in 1948 (FHS, n.d.). Presently, the study is monitored by the NBHLI (FHS, n.d.). The overarching goal of the FHS is to identify common risk factors associated with cardiovascular disease (CVD) risk (FHS, n.d.). With over 14,000 participants spanning three generations, the FHS is one of the most well-known longitudinal studies enrolling individuals with no prior signs of symptoms of CVD, myocardial infarction (MI), or stroke (FHS, n.d.; NBHLI, n.d.-c). Everyone participates in a variety of assessments including physical exams, biochemical exams, lifestyle interventions, and past medical history, all of which are collected every two to six years (NBHLI, n.d.-c). While the initial study in the 1940s started with individuals of European descent, the researchers are making a concentrated effort to expand the study to include other ethnicities including African American, Hispanic, Asian, Pacific Islander, and Native American (NBHLI, n.d.-c). The study has produced major findings and associations between hypertension, hyperlipidemia, and CVD with more than 3000 articles in the past 40 years (NBHLI, n.d.-c).

Sampling Procedures

The FHS followed a systemic recruitment using the town of Framingham, MA for their research base. Framingham was chosen due to its ability to provide an adequate sample size, convenience to study the sample, ethnically and socioeconomically diverse population, stable population over time, convenience to the medical center and research support staff, support within the community from medical providers and the public health department, and prior success with a 30-year longitudinal study on tuberculosis (D'Agostino & Kannel, 1989). According to D'Agostino and Kannel (1989), the FHS followed a 2/3 convenience sampling ratio, using a desired sample of 6,000 in a town of 10,000 participants eligible to enroll between the ages of 30-59 years. Enrollment was achieved by dividing the eight separate precincts by family size and geographic location and then sending letters of enrollment to two out of every three families in each precinct (D'Agostino & Kannel, 1989). Personal contacts were used to encourage enrollment; however, volunteers had to be added after the fact to best alter the randomization and meet the desired minimum enrollment of 5,000 participants (D'Agostino & Kannel, 1989). As the years advanced, participants from each family were encouraged to participate in the Offspring, Third Generation, and New Offspring Spouse cohorts. The inclusion criteria were described above for the newer cohorts. No exclusion criteria were found for the original data collection.

Power Analysis (Sample Size Calculations)

To achieve an appropriate level of statistical inference, G*power (Faul et al., 2009) was used for the power calculations to determine the sample size needed for this archival data analysis plan. Prior literature reported an $r^2 = 0.33$. This was validated by averaging the risk from 7 studies ranging from 9% - 85% which also came back 33%. The alpha (α) was set at 0.05, and the power (β) was set to .0.95. Using information from previous literature, a sample size using logistic regression returned a sample size of 312 participants. Table 5 provides a brief look at the power analysis used for the current study.

Table 5

Sample Size Calculations

Analysis	Input	Output
z test: Logistic regression	Tails (one) Odds ratio = 1.5 Pr(Y=1|X=1) H0 = 0.33 α err prob = 0.05 Power (1-β err prob) = 0.95 R^2 other X = 0 X distribution = Normal X parm μ = 0 X parm σ = 1	312

Archival Data Collection

This retrospective study used data from the *Offspring cohort* living in or near Framingham, Massachusetts (MA). The original cohorts started with 5,124 participants which has since decreased to 2,430 participants as of 2014 equating to about a 52% loss. The importance of the FHS is the critical analysis it provides of familial health through the generations. Twenty-three years after the original cohort was enrolled, the *Offspring* cohort enrolled individuals between 1971-1975 (FHS, n.d.-c). The cohort is comprised of

Caucasian participants that had at least one parent in the original cohort and enrolled 5,124 participants (FHS, n.d.-c).

Data Collection

Data was collected from participants at examinations held every two years over the course of a twenty-year study (D'Agostino & Kannel, 1989). For this study, participants from the Offspring cohort were selected based on their AF status. All individuals diagnosed with AF with no prior history of stroke were eligible for the data collection. The sample was further constrained by the type of anticoagulation used to prevent strokes excluding participants not on warfarin. All participants with a history of stroke prior to AF diagnosis were excluded from this retrospective analysis of archival data. The Walden University institutional review board (IRB) application approved the application for research May 2022, and the investigator received approval through BioLINCC to conduct the research after the data use agreement was signed May 2022. The online application included the study protocol, IRB approval, biographical sketch, reference materials, and abstract. Table 6 provides a quick look at the datasets and the variables requested.

Table 6

List of Requested Datasets and Variables from Framingham Heart Study

Dataset	Variables
vr_afcum_2019_a_1186d	IDTYPE, SHAREID, RHYTHM, ATHROMRX
vr_svstk_2018_a_1269d	IDTYPE, SHAREID, STROKE, STROKE_TYPE
vr_ffreq_ex08_1_0615d	SHAREID, NUT_DVITK, NUT_VITKWO
1_vitk_ex07_1_0024d	SHAREID, VITK

(*table continues)*

Dataset	Variables
vr_wkthru_ex09_1_1001s	SHAREID, SEX, AGE8, BMI8, CURRSMK8, DMRX8, HRX8, LIPRX8
vr_raceall_2008_a_0712s	IDTYPE, SHAREID, RACE_CODE
ex1_8s	SHAREID, H081, H082, H708

Instrumentation and Organizational Constructs

Participants of the FHS went through several examinations over the course of their 20-year participation in the study. One of the questionnaires they filled out for nutrition was the Willett Food Frequency Questionnaire (FFQ) that was developed by Harvard University (Lin et al., 2019). This FFQ was used in 2015 to develop the Dietary Guidelines for Americans Adherence Index (DGAI) to monitor the ability of Americans to adhere to a healthy diet (Lin et al., 2019). The FFQ is a four-page questionnaire containing 126 food items (Subar et al., 2001). To evaluate the validity of the questionnaire, the FFQ was mailed to 127 individuals twice with a one-year gap (Lin et al., 2019). The intraclass correlations for the first year for individual nutrients ranged from 0.47-0.80 and during the second year ranged from 0.28-0.86 (Lin et al., 2019). A prior study reported a response rate of 82% with the FFQ and correlation coefficients ranging from 0.58 (women) to 0.63 (men) (Subar et al., 2001). Another comparison between the Willett and block FFQ given to two separate samples revealed the Willett FFQ had a 70% response rate with correlation coefficients between 0.52 – 0.92 (Caan et al., 1998). There was a moderate amount of internal reliability as seen over the last twenty years with correlation coefficients.

The FFQ was developed by the Harvard T. H. Chan School of Public Health at Harvard University with the latest updates in 2015 (Harvard University, 2015). The Harvard Willett FFQ is divided into nine sections. These sections include vitamins, dairy foods, fruits, vegetables, eggs/meats/fish, cereals/breads/starches, beverages, sweets/baked goods/miscellaneous, and diet changes (Harvard University, 2015). The foods are listed with portions sizes (example: Kale, mustard, or chard greens, ½ cup) with options for never, less than once per month, 1-3 times per month, once per week, 2-4 times per week, 5-6 times per week, and 1 or more servings per day (Harvard University, 2015). The information collected from the FFQ were then translated by trained nutrition personnel into dietary intakes based on the serving sizes entered. The Offspring cohort completed three rounds of the FFQ during examinations 3, 5, and 6. This study focused on foods with vitamin K content.

Data Analysis Plan

The data analysis for this protocol utilized the Statistical Package for Social Sciences (SPSS v.27). The initial sample expected was approximately 3,500 individuals. This sample was reduced once individuals with AF were identified and participants with a history of stroke prior to AF diagnosis were removed from the analysis. The current response rate for examination three for the three cohorts was 76%. There was some bias due to the higher amount of Caucasian ancestry in the cohorts. The variables were examined for missing data. Any variable with over 10% of missing data would go through multiple imputation.

Research Questions

Bivariate Research Questions

RQ1: Is there an association between dietary vitamin K intake below the daily adequate intake (AI) by gender and ischemic stroke in AF patients on warfarin?

H_{01} –there is no association between dietary vitamin K intake below the daily adequate intake (AI) by gender and ischemic stroke in AF patients on warfarin.

H_1 –there is an association between dietary vitamin K intake below the daily adequate intake (AI) by gender and ischemic stroke in AF patients on warfarin.

RQ2: Is there an association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin?

H_{02} – there is no association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin.

H_2 –there is an association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin.

Multivariate Research Questions

RQ3: Is there an association between subclinical vitamin K deficiency less than 0.30 nmol/L and ischemic stroke in AF patients on warfarin controlling for age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity?

H_{03} – There is no association between subclinical vitamin K deficiency less than 0.30 nmol/L and ischemic stroke in AF patients on warfarin controlling for age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity.

H_3 – There is an association between subclinical vitamin K deficiency below 0.30 nmoL/L and ischemic stroke in AF patients on warfarin controlling for age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity.

Note: Each covariate in RQ3 had their own correlational analysis with the ischemic stroke outcome before the final multivariate regression analysis was conducted. All covariates were included in the final multivariate analysis. Table 7 provides an overview of the hypothesis and statistical plan.

Table 7

Hypotheses and Statistical Analyses

Hypothesis & Measures	**Dietary vitamin K intake will have a linear association with IS**	**Subclinical vitamin K will have a linear association with IS**	**Vitamin K, vitamin K subclinical deficiency, and IS will have a linear association with controlling for IS risk factors**
Ischemic Stroke	DV	DV	DV
Vitamin K (mcg)	IV		
Vitamin K (nmol)		IV	IV
Age			CV
Gender			CV
Race/Ethnicity			CV
Education			CV
Income			CV
Smoking			CV
Alcohol			CV
DM			CV
HTN			CV
HLD			CV

(*table continues*

Hypothesis & Measures	**Dietary vitamin K intake will have a linear association with IS**	**Subclinical vitamin K will have a linear association with IS**	**Vitamin K, vitamin K subclinical deficiency, and IS will have a linear association with controlling for IS risk factors**
BMI			CV
Statistical Analysis	Simple Logistic Regression	Simple Logistic Regression	Multivariate Logistic Regression

Note. Diabetes Mellitus (DM), High Blood Pressure (HTN), High Cholesterol (HLD), Obesity (BMI), Dependent Variable (DV), Independent Variable (IV), Covariate (CV)

Statistical Tests

Assumptions of Normality, Collinearity, Independence, Linearity, and Outliers

The logistic regression analysis has five assumptions that were assessed: normality, multicollinearity, independence of observations, linearity of IV and log odds, and outliers that could influence the data analysis. While the assumption of normality is typically void with logistic regression, the test was conducted on the bivariate outcome variable. All independent variables and covariates were evaluated for collinearity using the variance inflation factor (VIF) (Table 8). The independence of observations was assessed using a Q-Q plot. To evaluate the linearity of the IV and log odds, the proposed study looked at the Box-Tidwell test. Finally, to analyze for potential issues from outliers, the Cook's Distance test was used.

Table 8

Collinearity Statistics

Variable	Tolerance	VIF
Vitamin K (mcg/day)		
Vitamin K (nmol/L)		

Descriptive Statistics

Baseline data were reported for all variables. All categorical variables were reported as counts and percentages in a frequency distribution table. Any ordinal level variables were reported using medians. All continuous variables were reported as means with standard deviation.

Bivariate Analyses

Analytical studies of the baseline data were conducted using Pearson's Chi-Square analysis to determine if any independent variable or covariate was significantly different between those with or without ischemic stroke. Table 9 provides a sample bivariate analysis table that will be used in the current study.

Table 9

Baseline Data Information and Person's Chi-Square Analysis Test

Variable	Stroke (Yes)	Stroke (N)	χ^2	***P* value**
Dietary vitamin K intake				
Subclinical vitamin K level				
Age (year)				
Gender (%)				
Race/Ethnicity (%)				
Caucasian				
Hispanic				
Education Level (%)				
None				
HS or GED				
Some College				
Undergraduate Degree				
Graduate Degree				

(*table continues)*

Variable	Stroke (Yes)	Stroke (N)	χ^2	*P* value
Active Smoker (%)				
Alcohol Abuse (%)				
DM (%)				
HTN (%)				
HLD (%)				
BMI (kg/m²)				

This study had three inferential research questions that were conducted using logistic regression analysis. The statistical significance was set to 0.05 and confidence intervals were used to determine effect size. The primary research question analyzed the association between dietary vitamin K intake adequacy by gender and ischemic stroke outcomes (both dichotomous variables). A simple logistic regression analysis identified if there are any significant differences between individuals with or without dietary vitamin K deficiency and ischemic stroke outcomes. The second inferential question looked at the association between subclinical vitamin K deficiency and ischemic stroke outcomes (both dichotomous variables). Another simple logistic regression was used to identify any significant differences between participants with or without subclinical vitamin K deficiency and ischemic stroke outcomes. The main difference between the two questions was to determine if ischemic stroke outcomes differ by dietary vitamin K intake versus subclinical vitamin K deficiency (Table 10).

Table 10

Bivariate Logistic Regression Analyses

Variable	β	S.E.	Wald	Df	*p*	OR	CI
Dietary Vitamin K							
Serum Vitamin K							

Multivariate Logistic Regression Analysis

A final third inferential question controlled for the previously mentioned covariates and independent variables to determine if a true association exists between vitamin K deficiency and ischemic stroke outcomes. The final question was assessed using a multivariate logistic regression analysis. Table 11 provides an example of reporting the results from the multivariate logistic regression analyses.

Table 11

Multivariate Logistic Regression Analyses

Variable	β	S.E.	Wald	Df	*p*	OR	CI
Vitamin K							
Age							
Gender							
Race/Ethnicity							
Education Level							
Income Level							
Smoking Use							
Alcohol Use							
DM							
HTN							
HLD							
Obesity							

Threats to Validity

Internal

There are potential internal threats to validity to consider when dealing with archival data, including longitudinal studies. Maturation may have occurred in the study since the FHS follows individuals for close to 20 years. As individuals are diagnosed with chronic diseases, there is a tendency to improve lifestyle factors to improve their health. In this study, that could mean individuals are decreasing their vitamin k intakes to minimize complications with antithrombotic medications. Another threat to internal validity is the lack of an ethnically diverse population. One way to minimize this risk is to be sure to not generalize the findings to other ethnically diverse groups. Mortality is another threat leading to attrition that can be managed if the sample is large enough. The *Offspring cohort* had over 5,000 participants and by the end of 2014 still had over 2,000 individuals enrolled making it a robust cohort.

External

Potential threats to external validity include inability to generalize the results to more ethnically diverse populations since the cohort is predominantly Caucasian. Another threat is the inability to generalize to other states or nations since the cohort is from MA which will have distinct cultural impacts than someone living in the Southern United States, or someone living in Europe. These risks can be minimized using the newer *Omni 1 and Omni 2* cohorts once they have enough examinations completed.

Ethical Procedures

Informed Consent and Access to Archival Data

Permissions to use archival data through the FHS was requested through the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) that is part of the National Institutes of Health – National Heart, Lung, and Blood Institute website. The site required the principal investigator to fill out the data request form and submit an approved protocol, IRB approval, resume, reference materials, and abstract. Original informed consent (IC) for participation in the FHS was collected from participants at the beginning of each examination (FHS, n.d.-b). Participants had the option to choose which examinations they would participate in at each examination after a thorough review was completed by the research support staff. The protocol went through IRB review with Walden University. All data was de-identified and kept on an encrypted thumb drive. There were no ethical violations with this secondary data analysis of the FHS.

Summary

To summarize, this study was a retrospective analysis of secondary data from the Framingham Heart Study with particular interest in the *Offspring* cohort with data from 1971-2014. While the original cohort still has over 2,000 participants, this study only needed about 312 participants. All participants from the cohort with a diagnosis of AF with no prior stroke were eligible for this new study. The study concentrated on identifying associations between dietary vitamin K deficiency, subclinical vitamin K deficiency, and ischemic stroke outcomes using multivariate linear regression to control for confounders as well as running Pearson correlations and chi-square statistics. All data was accessed using BioLINCC with expedited IRB approval and approval from the FHS staff. The data was de-identified and maintained on a password, encrypted, USB-thumb drive to maximize security and maintain patient anonymity. The limitations to secondary data analysis and strengths of using longitudinal data were discussed with the study results coming up in the next chapter.

Chapter 4: Results

Introduction

In Chapter 3, the research plan for this study was discussed, along with the research questions, hypotheses, analysis, data collection methods, and populations. The purpose of this study was to determine if there is an association between vitamin K deficiency and ischemic stroke outcomes in atrial fibrillation patients on warfarin. In Chapter 4, the research questions and hypotheses are restated. A description of the study population will provide information on changes to the research plan, as well as the process to access the Framingham Heart Study data. Next, a description of the variables and frequency tables, along with a correlational Pearson's Chi-Square analyses, will reveal which independent variables to include in the final regression model. Finally, the results section will provide analysis surrounding the statistical assumptions, each individual bivariate research question, and the multivariate research question. The chapter will close with a summary of the results before moving into the discussion chapter.

Research Questions and Hypotheses

Bivariate Research Questions

RQ1: Is there an association between dietary vitamin K intake below the daily adequate intake (AI) by gender and ischemic stroke in AF patients on warfarin?

H_{01} –there is no association between dietary vitamin K intake below the daily adequate intake (AI) by gender and ischemic stroke in AF patients on warfarin.

H_1 –there is an association between dietary vitamin K intake below the daily adequate intake (AI) by gender and ischemic stroke in AF patients on warfarin.

RQ2: Is there an association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin?

H_{02} – there is no association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin.

H_2 –there is an association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin.

Multivariate Research Questions

RQ3: Is there an association between subclinical vitamin K deficiency less than 0.30 nmol/L and ischemic stroke in AF patients on warfarin controlling for age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity?

H_{03} – There is no association between subclinical vitamin K deficiency less than 0.30 nmol/L and ischemic stroke in AF patients on warfarin controlling for age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity.

H_3 – There is an association between subclinical vitamin K deficiency below 0.30 nmoL/L and ischemic stroke in AF patients on warfarin controlling for age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity.

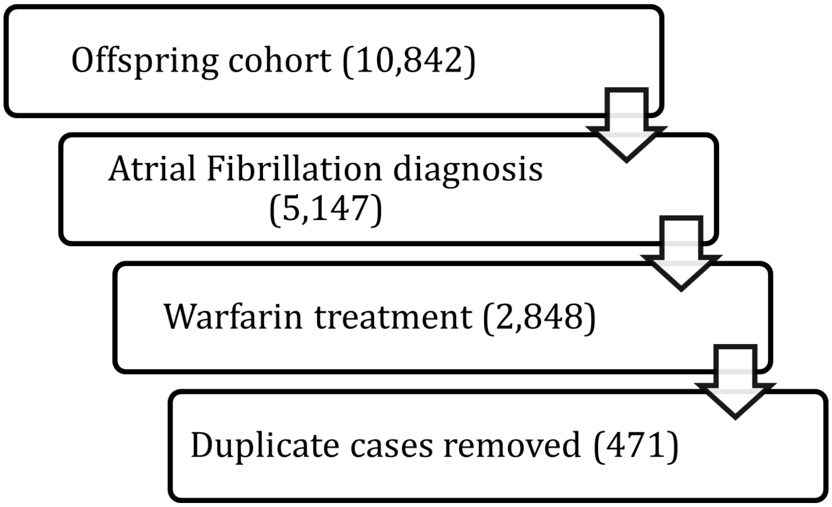
Data Collection

Description of the Study Population

The Offspring cohort entered the Framingham Heart Study between 1971-1975. While most of the analyses performed were related to data collected between 2005-2008, some variables were from overall population analysis between 1971-2014 over nine exams. The original dataset contained 5,124 individuals, which reduced to 471 subjects after adjusting for atrial fibrillation and warfarin status (Figure 2). The sample size estimation was 312, revealing an adequate sample size to run the analyses.

Figure 1

Process for Identifying Study Population



Once the final merge was complete and ready for analysis, a missing data analysis reviewed 73% of variables were missing data, 72% of cases had incomplete data, and 24% of individual values were missing from the dataset. No patterns were found in the missing data. Once variables were converted into the proper format as discussed in Chapter 3, multiple imputations were used to fill in the missing values.

Changes to the Proposal

A few minor changes were necessary from the original research plan. The initial race and ethnicity variable was changed to two separate variables (RACE and ETHNICITY). Neither variable was recoded, as > 99% of variables were either Non-Hispanic (ETHNICITY) and White (RACE). The original income variable was also removed, and another variable was chosen, PY125 from the *q_psych_ex03_1_0167d* dataset measuring total family income at exam 3. The new variable had 12 values ranging from no income (0) to more than $50,000 (12). These values were recoded into a new variable (INCOME) where 1 = Low Income (less than $25,000 annually), 2 = Medium Income ($25,000-$50,000 annually), or 3 = High Income (more than $50,000 annually). Additionally, two new quartile variables were created for the total dietary vitamin K intake (DVITK_CAT) and serum vitamin K level (VITK_CAT). The dataset was split by file using the variable SEX and frequencies with quartiles were run to identify the quartile ranges by gender.

Data Access and Acquisition

To access the Framingham Heart Study, researchers must request the data through BioLINCC. The request required a finalized proposal, IRB approval, and a signed data use agreement between the university and National Institutes of Health. Data access was requested in April 2022 and approved in May 2022 with the release of requested data. Data was sent via secure email and downloaded onto an encrypted portable drive. All *Offspring* cohort datasets were sent.

To prepare the data, I located each dataset, removed the variables not required, renamed the new datasets, and stored them in a separate folder on the encrypted drive. Next, I removed any ID_TYPE from each dataset that was not equal to “1,” which was the *Offspring* cohort identifier. I was able to locate these records easily by sorting the variable by ascending and removing all codes not equal to “1.”

Another issue was that one of the datasets had multiple records per individual due to the recurrent exams. First, I located only the atrial fibrillation patients that were on warfarin. Next, I used the *Identify Duplicate Cases* function to identify duplicates and only keep the primary cases. Once that was completed, all datasets were merged one at a time to another, using a new name for the dataset each time until all datasets were merged using the SHAREID variable, which is the unique identifier in the study for each participant. Once the files were merged, labels were updated, and variables recoded per the research plan in Chapter 3 with only minor variations to the plan as noted above.

Descriptive Analysis of Variables

While the overall sample size was 471, several of the variables were missing data. The file was split by the sample as determined by dietary vitamin K adequacy. Of the 471 participants, 77 participants had adequate dietary vitamin K intake, 194 participants had inadequate intake, and 200 participants were missing data. This section will provide a quick synopsis of each variable as it relates to the full sample, the pertinent measures of central tendency, and the variations in missing data. The review will start with the dependent variable, then move to the independent variables, and then each of the covariates.

Ischemic Stroke

Considering the full sample (n=471), only 13.8% (n =65) had an ischemic stroke identified after they started the study (Table 12). When looking at the original stroke type, 79% (n = 372) had no stroke, 5.7% (n = 27) had an atherothrombotic infarction of the brain, 13.8% (n = 65) had a cerebral embolism (i.e., ischemic stroke), 1.3% (n = 6) had an intracerebral hemorrhage, and 0.2% (n =1) had an unidentified CVA. Further analysis by dietary vitamin K adequacy revealed that 11 participants (14.3%) with inadequate dietary vitamin K intake had an ischemic stroke as compared to 21 (10.8%) of participants with adequate vitamin K intake.

Table 12

Percentage of Individuals with Ischemic Stroke

		Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	No Ischemic Stroke	406	86.2	86.2	86.2
	Ischemic Stroke Present	65	13.8	13.8	100.0
	Total	471	100.0	100.0	

Dietary Vitamin K Intake

The recommended intake for vitamin K foods is between 90 – 120 mcg per day based on gender for adults. In this study, the average intake from oils was 22.01 (min 2.85, max 83.74, *SD* 15.09) and greens (phylloquinones) was 167.10 (min 211.54, max 1918.89, *SD* 170.11). The average total intake was calculated as 189.11 (min 33.83, max 1954.50, *SD* 171.46). Women consumed more overall vitamin K intake than men (μ = 210.02 mcg/day versus μ = 175.46 mcg/day). When broken down into adequate versus inadequate intake by gender, 65.2% of men (n = 107) and 81.3% of women (n = 87) met their recommended daily intake. The average intake for individuals with adequate intake was 230 mcg daily versus 85 mcg daily for those with inadequate intake (p < .001). There was only one missing value for this variable.

Table 13

Descriptive Analysis of Dietary Vitamin K Intake

		Vitamin K (Oils), mcg	Vitamin K (Greens), mcg	Combined Vitamin K, mcg
N				
	Valid	271	271	271
	Missing	200	200	200
Mean		22.01	167.10	189.11
Std. Deviation		15.09	170.11	171.46
Minimum		2.85	21.54	33.83
Maximum		83.74	1918.89	1954.50
Percent Deficiency				
	Male			34.8%
	Female			18.7%

Serum Vitamin K Levels

The recommended level for serum vitamin K is greater than 0.30 nmol/L. The average level for the *Offspring cohort* with atrial fibrillation on warfarin was 1.67 nmol/L (min 0.05, max 35.02, *SD* 2.91). When comparing by gender, the average serum value for men was 1.69 nmol/L (*SD* 3.24) versus 1.63 nmol/L (*SD* 1.95) for women. When comparing inadequacy of vitamin K intake, only 7.4% of men and 9.8% of women had inadequate dietary vitamin K intake as measured by serum phylloquinone levels. There was only one missing value for the variable. When breaking down the data by dietary vitamin K adequacy, 101 participants out of 109 (92.7%) with adequate dietary intake met the guidelines for adequacy of serum levels. Furthermore, 29 participants out of 33 (87.9%) that had inadequate dietary vitamin K intake showed adequacy by serum levels.

Table 14

Descriptive Analysis of Serum Vitamin K Levels

		Cohort	**Male**	**Female**
N				
	Valid	209	148	61
	Missing	262	137	124
Mean		1.67	1.69	1.63
Std. Deviation		2.91	3.23	1.95
Minimum		.05	.05	.05
Maximum		35.02	35.02	12.42
Vitamin K Status				
	Adequate	91.9%	92.6%	90.2%
	Deficient	8.1%	7.4%	9.8%

Covariates

Age. The age was recorded at exam 8 for this analysis. The mean age for the data was 71.75 years (SD 8.46) with a spread of 51-92 years. There was a total of 161 missing data points. The data were further analyzed by gender. Men had an average age of 70.48 years (*SD* 8.310) with a spread of 52-92 years with 98 missing data points. Females had an average age of 73.68 years (*SD* 8.353) with a spread of 51-90 years and 62 missing data points. When comparing age by presence of an ischemic stroke, the mean age of those with an ischemic stroke was 75.00 years (*SD 7.899*) with a spread of 53-90 years and a total of 29 missing data points. Those without an ischemic stroke had an average age around 71.32 years (*SD* 8.452) with a spread of 51-92 years and 132 missing values.

All data points were showing normal distribution with skewness and kurtosis between -2 and +2 for each type of variation.

Table 15

Descriptive Analysis of Age Variable in Years

	N	Mean	Std. Deviation	Minimum	Maximum
Overall					
Valid	310	71.75	8.46	51	92
Missing	161				
Gender					
Male	187	70.48	8.31	52	92
Female	123	73.68	8.35	51	90
IS Status					
Absent	274	71.32	8.45	51	92
Present	36	75.00	7.90	53	90

Gender. There was a total of 470 valid data points with 60.5% of the sample being male and 39.4% being female. There was only one missing data point. Women were noted to have a higher percentage of ischemic stroke compared to men (53.88% versus 46.2%). Men were noted to have higher levels of dietary vitamin K inadequacy than women (74.0% versus 26.0%).

Table 16

Descriptive Analysis of Gender Variable

	N	Frequency (%)	Ischemic Stroke Presence (%)	Vitamin K Deficiency (%)
Male	285	60.6	46.2	74.0
Female	185	39.4	53.8	26.0

Race/Ethnicity. Out of 471 participants, 41.4% did not identify as either Hispanic or non-Hispanic. Out of the remaining 276 participants, the overwhelming majority was non-Hispanic at 58.2%, with only two individuals identifying as having Hispanic ancestry (0.4%). Out of 471 participants, 35.2% did not identify their racial category (n = 166). Of the remaining 305, most participants identified as being White (64.1%) with only three identifying as Other (0.6%). When breaking the data out further by presence of ischemic stroke, 49.2% identified as non-Hispanic, and 50.8% identified with being White.

Table 17

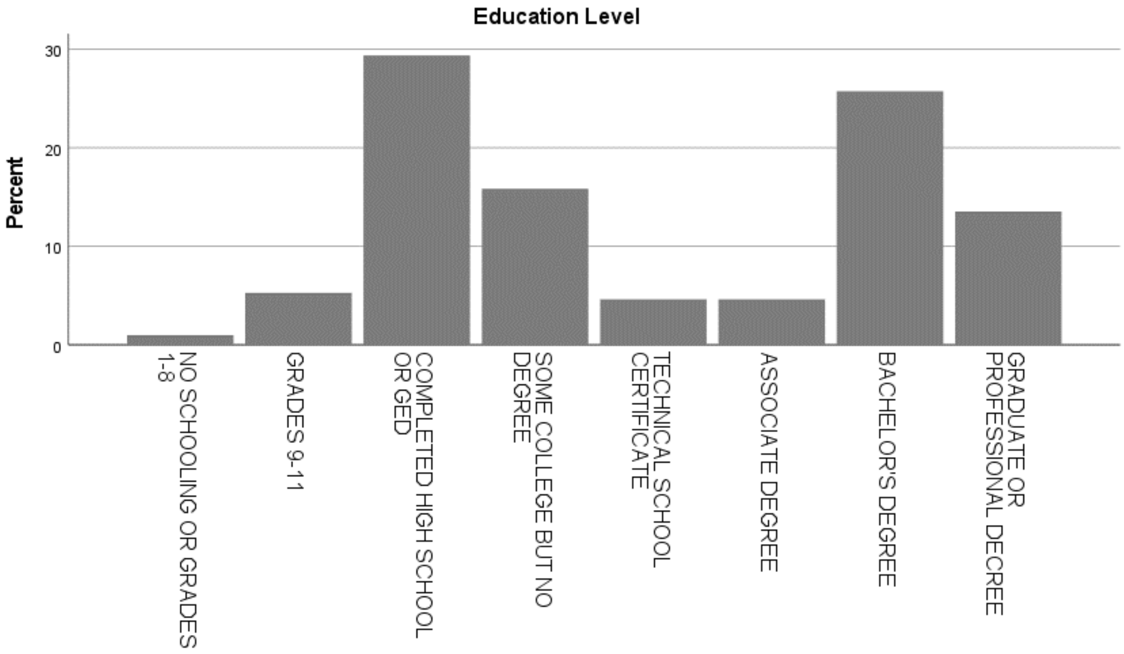
Descriptive Analysis of Race and Ethnicity Variables

	Ethnicity (%)	**Race (%)**
Full cohort	Hispanic/Latinx 0.4%	White 64.1%
	Non-Hispanic 58.2%	Other 0.6%
Presence of Ischemic Stroke		White 50.8%
	Non-Hispanic 49.2%	Other 1.5%

Education Level. Out of 471 participants, 303 provided information on their education level (64.3%) with 6.3% never completing high school, 29.3% completing high school or their GED, 15.9% completing some college coursework, 35.0% completing some form of undergraduate degree or certificate program, and 13.5% attaining a graduate degree. Individuals with an ischemic stroke were identified as 38.2% with a high school diploma or GED, 5.9% with some college, 44.1% with some form of undergraduate degree or certificate, and 11.8% with a graduate degree. When comparing education level by dietary vitamin K adequacy, the median level of education was higher for those with adequate intake versus inadequate intake (some college versus having an undergraduate degree).

Figure 2

Education Level of Atrial Fibrillation Participants on Warfarin in Offspring Cohort



Income Level. Data was obtained from 62% of participants on their total family income annually before taxes (n=292). Those identified as having low-income levels (< $25,000 annually) accounted for 15.4% of the sample. Those in the middle-income category earned between $25,000 to less than $50,000 annually accounted for 55.1% of the sample. The rest of the sample earned more than $50,000 annually (29.5%). Those with an ischemic stroke were classified as 15.4% low-income, 56.4% middle-income, and 28.2% high-income. Those with inadequate dietary vitamin K intake tended to have lower income levels.

Table 18

Percentage of Participants at Different Income Levels

		Low Income (<$25K)	Middle Income ($25K - $50K)	High Income (>$50K)
Full Sample		15.4%	55.1%	29.5%
Ischemic Stroke				
	Yes	15.4%	56.4%	28.2%
	No	15.4%	54.9%	29.6%
Dietary Vitamin K				
	Adequate	9.2%	57.0%	33.8%
	Deficient	18.2%	52.7%	29.1%

Smoking Status. Someone was identified as being an active smoker if they smoked anything during the year prior to exam 8. During the exam, 3.0% (n=14) were identified as being active smokers. When considering those only with ischemic stroke, 1.5% versus 3.2% (no ischemic stroke) were identified as being active smokers. Individuals with inadequate dietary vitamin K intake had higher levels of smoking versus individuals with adequate dietary vitamin K intake (7.8% versus 3.1%).

Table 19

Descriptive Analysis of Smoking Status of Sample

		Active Smokers (%)
Overall Cohort		14 (3.0%)
Ischemic Stroke		
	Absent	13 (3.2%)
	Present	1 (1.5%)
Dietary Vitamin K Intake		
	Adequate	6 (3.1%)
	Deficient	6 (7.8%)

Alcohol Status. Alcohol abuse was identified as any individual exceeding the recommended weekly alcoholic beverage intake by gender. During the exam after considering the 163 missing data points, 6.4% (n=30) were determined to have an active alcohol abuse problem. When comparing ischemic stroke outcomes, individuals with ischemic stroke had lower levels of alcohol abuse (4.6%) versus those without an ischemic stroke (6.7%) when removing the missing data points. Individuals with adequate dietary vitamin K intake had lower levels of alcohol abuse (8.8%) compared with those with inadequate dietary vitamin K intake (14.3%).

Table 20

Descriptive Analysis of Alcohol Abuse in Sample

		Active Alcohol Abuse (%)
Overall Cohort		30 (6.4%)
Ischemic Stroke		
	Absent	27 (6.7%)
	Present	3 (4.6%)
Dietary Vitamin K Intake		
	Adequate	17 (8.8%)
	Deficient	11 (14.3%)

Diabetes Mellitus. During exam 8, 64.5% of participants (n=304) provided information on their diabetes status. At the time of exam 8, 11.7% of participants (n=55) identified as being under treatment for diabetes. Those participants that had an ischemic stroke reported 6.2% being treated for diabetes. Individuals with adequate dietary vitamin K intake had higher levels of DM (18.6%) compared with those with inadequate dietary vitamin K intake (14.3%).

Table 21

Descriptive Analysis of Diabetes Treatment Among Sample

		Active Treatment for Diabetes (%)
Overall Cohort		55 (11.7%)
Ischemic Stroke		
	Absent	51 (12.6%)
	Present	4 (6.2%)
Dietary Vitamin K Intake		
	Adequate	36 (18.6%)
	Deficient	11 (14.3%)

High Blood Pressure. Just over 65% of participants (n=310) provided information on blood pressure status. Of the 310 participants, 45.2% (n=213) reported being treated for high blood pressure. When comparing participants receiving treatment for high blood pressure by ischemic stroke outcomes, 41.5% of ischemic stroke patients and 45.8% of non-stroke participants received treatment for high blood pressure. Individuals with adequate dietary vitamin K intake had lower levels of HTN (67.5%) compared with those with inadequate dietary vitamin K intake (74.0%).

Table 22

Descriptive Analysis of Active Treatment for High Blood Pressure (HTN) Among Sample

		Active Treatment for HTN (%)
Overall Cohort		213 (45.2%)
Ischemic Stroke		
	Absent	186 (45.8%)
	Present	27 (41.5%)
Dietary Vitamin K Intake		
	Adequate	131 (67.5%)
	Deficient	57 (74.0%)

High Cholesterol. Just over 65% of participants (n=309) provided information on cholesterol status. Of the 309 participants, 37.8% (n=178) identified as receiving treatment for high cholesterol. When comparing participants receiving treatment for high cholesterol by ischemic stroke outcomes, 29.2% of ischemic stroke participants versus 39.2% of non-stroke participants received high cholesterol treatment. The levels of HLD between those with and without adequate dietary vitamin K intake were stable around 58%.

Table 23

Descriptive Analysis of Active Treatment for High Cholesterol (HLD) Among Sample

		Active Treatment for HLD (%)
Overall Cohort		178 (37.8%)
Ischemic Stroke		
	Absent	159 (39.2%)
	Present	19 (29.2%)
Dietary Vitamin K Intake		
	Adequate	112 (57.7%)
	Deficient	45 (58.4%)

Body Mass Index. Over 60% of participants (n=289) had available weights to calculate BMI. The average BMI was 30.01 kg/m^2 (*SD* 5.95) with a spread from 16.86 kg/m^2 to 53.72 kg/m^2. The average BMI for individuals with an ischemic stroke was 29.78 kg/m^2 versus 30.04 kg/m^2 without a stroke. Further analysis showed less than 1% underweight, 10.2% normal weight, 24.2% overweight, 22.3% obese, and 4.0% severely obese for the full sample. When analyzing the information by presence of ischemic stroke, of the 33 participants that had an ischemic stroke, no participant was underweight, 7.7% were normal weight, 21.5% were overweight, 20.0% were obese, and 1.5% were severely obese. The median BMI category (Overweight) was the same regardless of dietary vitamin K status.

Table 24

Descriptive Analysis of Mean Weight and Weight Categories by Full Sample, Presence of Ischemic Stroke, and Presence of Vitamin K Deficiency

	Full Sample (%)	Presence of Ischemic Stroke (%)	Vitamin K Intake Deficiency (%)
Mean weight (kg/m^2)	30.01	29.78	29.21
Underweight	3 (0.6%)	-	1 (1.3%)
Normal Weight	48 (10.2%)	5 (7.7%)	10 (13.0%)
Overweight	114 (24.2%)	14 (21.5%)	30 (39.0%)
Obesity	105 (22.3%)	13 (20.0%)	29 (37.7%)
Severe Obesity	19 (4.0%)	1 (1.5%)	6 (7.8%)
Median Weight Category	Overweight	Overweight	Overweight

Results

Statistical Assumptions

A binomial logistic regression was performed to ascertain the effects of dietary vitamin K adequacy, serum vitamin K adequacy, age, race, ethnicity, gender, income, education level, smoking status, alcohol abuse, diabetes mellitus, hypertension, hyperlipidemia, and obesity on the likelihood that atrial fibrillation participants would have an ischemic stroke. There were seven assumptions considered before running the analysis and prior to multiple imputation

Assumption 1: One Dependent, Dichotomous Variable

The outcome variable for this study was the presence or absence of ischemic stroke. The variable was coded as 0 = absent of ischemic stroke and 1 = presence of ischemic stroke. Assumption for one dependent, dichotomous variable was met.

Assumption 2: One or More Independent Variables Measured on Continuous or Nominal Scales

There were two primary independent variables, dietary vitamin k intake and serum vitamin K intake, as well as thirteen covariates. The two primary variables were analyzed as dichotomous variables, ordinal variables (by quartile), and continuous variables. The covariates were measured as either dichotomous variables, ordinal variables, or continuous variables. Assumption for one or more independent variables measured on different scales was met.

Assumption 3: Independence of Observations, Mutually Exclusive and Exhaustive Nominal and Dichotomous Variables (Univariate Analysis)

To determine if there was any association between the independent variables based on ischemic stroke status, a correlation analysis using either Chi-Square Test of Homogeneity/Association (two dichotomous variables), Point Biserial Correlation (one dichotomous DV and one continuous IV), or Cochran-Armitage (one dichotomous DV and one ordinal IV) were conducted based on the variable measurement. All tests were conducted on the original data prior to multiple imputation for missing variables.

A chi-square test for association was conducted between dietary vitamin K adequacy and ischemic stroke outcomes. All expected cell frequencies were greater than five. There was no statistically significant association between dietary vitamin K adequacy and ischemic stroke outcomes, $\chi^2 = .634$, $p = .426$.

A chi-square test for association was conducted between serum vitamin K adequacy and ischemic stroke outcomes. One expected cell frequency was less than five.

As a result of the one frequency less than 5, the Fisher's Exact Test was reviewed. There was no statistically significant association between serum vitamin K adequacy and ischemic stroke outcomes, $p = .670$.

A point-biserial correlation was run between ischemic stroke outcomes and age. There was a statistically significant correlation between ischemic stroke outcomes and age, $r_{pb}(469) = .139$, with individuals with ischemic stroke outcomes being older than those without ischemic stroke, $M = 75.00$ ($SD = .62.400$) vs. $M = 71.32$ ($SD = 8.452$).

A chi-square test for association was conducted between gender and ischemic stroke outcomes. All expected cell frequencies were greater than five. There was a statistically significant association between gender and ischemic stroke outcomes, $\chi^2 = 6.630$, $p = .010$. There was a mildly strong association between gender and ischemic stroke outcomes, $\varphi = 0.119$, $p = .010$.Gender was not included in the multiple imputation as there were less than 10% missing values.

A chi-square test for association was conducted between race and ischemic stroke outcomes. Some expected cell frequencies were less than five. No Fisher's Exact Test statistic was provided so the Pearson Chi-Square test statistic is reported. There was a statistically significant association between race and ischemic stroke outcomes, $\chi^2 = 6.373$, $p = .041$. Race was not included in the multiple imputation as it was a nominal level variable.

A chi-square test for association was conducted between ethnicity and ischemic stroke outcomes. Some expected cell frequencies were less than 5. No Fisher's Exact Test statistic was provided so the Pearson Chi-Square test statistic is reported. There was no statistically significant association between ethnicity and ischemic stroke outcomes, $\chi^2 = 2.995$, $p = .228$. Ethnicity was not included in the multiple imputation as it was a nominal level variable.

A Cochran-Armitage test of trend was run to determine whether a linear trend exists between the education level and ischemic stroke outcomes. The education levels were no high school degree ($n = 19$), high school or GED ($n = 89$), some college ($n = 48$), undergraduate degree or certificate ($n = 106$) and graduate degree ($n = 41$), and the proportion of individuals having an ischemic stroke was 0.0%, 14.6%, 4.2%, 14.2%, and 9.8%, respectively. The Cochran-Armitage test of trend did not show a statistically significant linear trend, $p = .627$.

A Cochran-Armitage test of trend was run to determine whether a linear trend exists between the income level and ischemic stroke outcomes. The income levels were low income ($n = 45$), middle income ($n = 161$), and high income ($n = 86$), and the proportion of individuals having an ischemic stroke was .33, .137, and .128, respectively. The Cochran-Armitage test of trend did not show a statistically significant linear trend, $p = .900$.

A chi-square test for association was conducted between active smoking use and ischemic stroke outcomes. One expected cell frequency was less than five so the Fisher's Exact Test is reported. There was no statistically significant association between active smoking status and ischemic stroke outcomes, $p = 1.000$.

A chi-square test for association was conducted between alcohol abuse status and ischemic stroke outcomes. One expected cell frequency was less than five so the Fisher's

Exact Test is reported. There was no statistically significant association between alcohol abuse status and ischemic stroke outcomes, $p = 1.000$.

A chi-square test for association was conducted between DM and ischemic stroke outcomes. All expected cell frequencies were greater than five. There was no statistically significant association between DM and ischemic stroke outcomes, $\chi^2 = 1.343$, $p = .247$.

A chi-square test for association was conducted between high blood pressure and ischemic stroke outcomes. All expected cell frequencies were greater than five. There was no statistically significant association between high blood pressure and ischemic stroke outcomes, $\chi^2 = .750$, $p = .387$.

A chi-square test for association was conducted between high cholesterol and ischemic stroke outcomes. All expected cell frequencies were greater than five. There was no statistically significant association between high cholesterol and ischemic stroke outcomes, $\chi^2 = .389$, $p = .533$.

A Cochran-Armitage test of trend was run to determine whether a linear trend exists between BMI category and ischemic stroke outcomes. The BMI categories were underweight ($n = 3$), normal weight ($n = 48$), overweight ($n = 114$), obese ($n = 105$) and severe obesity ($n = 19$), and the proportion of individuals having an ischemic stroke was .000, .104, .123, .124, and .053, respectively. The Cochran-Armitage test of trend did not show a statistically significant linear trend, $p = .972$.

Table 25

Correlational Analyses of Independent Variables by Ischemic Stroke Outcomes

Independent Variable	**No Ischemic Stroke (n=406)**	**Presence of Ischemic Stroke (n=65)**	**test statistic**	***P* value**
Dietary Vitamin K Adequacy (%) [a]	66 (24.4%)	11 (4.1%)	.634	.426
Serum Vitamin K Adequacy (%) [b]	15 (7.2%)	2 (1.0%)		.670
Age (SD) [c]	71.32 (8.452)	75.00 (62.400)	.139	.014
Gender (%) [a]				
Male	255 (54.3%)	30 (6.4%)	6.630	.010
Female	150 (31.9%)	35 (7.4%)		
Race/Ethnicity (%) [a]				
White	269 (57.1%)	33 (7.0%)	6.373	.041
Non-Hispanic	242 (51.4%)	32 (6.8%)	2.955	.228
Education Level (%) [d]				
None	19 (100.0%)	0 (0.0%)	.236	.627
HS or GED	76 (85.4%)	13 (14.6%)		
Some College	46 (95.8%)	2 (4.2%)		
Undergraduate Degree	91 (85.8%)	15 (14.2%)		
Graduate Degree	37 (90.2%)	4 (9.8%)		
Income Level (%) [d]				
< $25,000	39 (86.7%)	6 (13.3%)	.016	.900
$25,000 - $49,999	139 (86.3%)	22 (13.7%)		
Over $50,000	75 (87.2%)	11 (12.8%)		
Active Smokers (%) [b]	13 (4.2%)	1 (0.3%)		1.000
Alcohol Abuse (%) [b]	27 (8.8%)	3 (1.0%)		1.000
DM (%) [a]	51 (16.8%)	4 (1.3%)	1.343	.247
HTN (%) [a]	186 (60.0%)	27 (8.7%)	.750	.387
HLD (%) [a]	159 (51.5%)	19 (6.1%)	.389	.533
BMI (%) [d]				
Underweight	3 (100%)	0 (0.00%)	.001	.972
Normal	43 (89.6%)	5 (10.4%)		
Overweight	100 (87.7%)	14 (12.3%)		
Obese	92 (87.6%)	13 (12.4%)		
Severe Obesity	18 (94.7%)	1 (5.3%)		

Note: Test statistics were calculated by Chi-Square Test of Association [a], Fisher's Exact Test [b], Point Biserial Correlation [c], and Cochran-Armitage Test [d]

Assumption 4: Minimum of 15 Cases per Independent Variable

The two main independent variables in the study had 271 cases (dietary vitamin K adequacy) and 209 cases (serum vitamin K adequacy). Of the covariates, the lowest covariate sample size was body mass index (n=289), and the highest covariate sample size was gender (n=470). Assumption for more than 15 cases per independent variable was met.

Assumption 5: Linearity

Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure. A Bonferroni correction was applied using all three terms in the model resulting in statistical significance being accepted when $p < .01667$ (Tabachnick & Fidell, 2014). Based on this assessment, the continuous independent variable, age, was found to be linearly related to the logit of the dependent variable (p = .959).

Assumption 6: Multicollinearity

Multicollinearity was assessed by VIF. All independent variables had VIF < 2.00 showing no signs of multicollinearity in the data (Table 26).

Table 26

Test for Multicollinearity

Variable	Tolerance	VIF
Dietary Vitamin K	.892	1.121
Serum Vitamin K	.891	1.123

Assumption 7: No Significant Outliers

All cases were analyzed for significant outliers by looking at the ZResidual from the Casewise List. There were 5 standardized residuals with values of 2.556, 3.390, 3.530, 3.626, and 4.671, which were kept in the analysis.

Prior to running the final bivariate and multivariate logistic regression tests, multiple imputation was conducted to replace missing values for the following variables:

AGE8, CURRSMK8, DMRX8, HRX8, LIPRX8, DVITK_AGE, VITK2, EDUCATION, ALCOHOL_GENDER, BMI, and INCOME.

Research Question 1 Statistical Analysis: Dietary Vitamin K and Ischemic Stroke

RQ1: Is there an association between dietary vitamin K intake below the daily adequate intake (AI) by gender and ischemic stroke in AF patients on warfarin?

A bivariate logistic regression was performed to ascertain the effects of dietary vitamin K adequacy on the likelihood that atrial fibrillation patients on warfarin would have an ischemic stroke. The logistic regression model was a poor fit and not statistically significant, $\chi^2(1) = .614$, $p = .433$. There was no statistically significant association between dietary vitamin K below the daily adequate intake (AI) by gender and ischemic stroke in AF patients on warfarin $\chi^2(1) = .614$, $p = .665$.

Table 27

Bivariate Logistic Regression between Dietary Vitamin K Adequacy and Ischemic Stroke Outcomes

Variable	β	S.E.	*p*	Odds Ratio	95% CI for Odds Ratio
Dietary Vitamin K	.150	.344	.665	1.162	.582 – 2.316
Constant	- 1.877	.173	.000	.153	.109 - .215

When analyzing the effect of vitamin K adequacy by quartile on the likelihood that atrial fibrillation patients on warfarin would have an ischemic, the model fit improved but was still not statistically significant, $\chi^2(3) = 5.797$, $p = .1.22$. The model was a poor fit explaining only 4.1% (Nagelkerke R^2) of the variance in ischemic stroke outcomes and correctly classified 88% of cases. There was no statistically significant association between dietary vitamin K by quartile and ischemic stroke in AF patients on warfarin with patients with the lowest vitamin K intake (men < 106 mcg daily, women < 111 mcg daily) having only a mild increased risk for an ischemic stroke as compared with individuals with the highest intake (men > 196 mcg daily, women > 252 mg daily), *p* = .129, 95% CI [.845, 3.754].

Table 28

Vitamin K Adequacy Levels by Quartile and Ischemic Stroke Outcomes

Variable	β	S.E.	*p*	Odds Ratio	95% CI for Odds Ratio
Dietary Vitamin K Quartile 1	.577	.380	.129	1.782	.845 – 3.754
Dietary Vitamin K Quartile 2	.349	.563	.542	1.418	.439 – 4.582
Dietary Vitamin K Quartile 3	.381	.446	.395	1.464	.602 – 3.565
Constant	- 2.164	.306	<.001	.115	.063 - .211

Finally, when conducting a bivariate logistic regression analysis by total dietary vitamin K intake (continuous IV), the logistic regression model was statistically significant, $\chi^2(1) = 5.$, $p = .021$. The model explained 3.8% of the variance in ischemic stroke outcomes (Nagelkerke R^2) and correctly classified 88.2% of cases when considering vitamin K deficiency. There was no statistically significant association between overall dietary vitamin K daily intake and ischemic stroke outcomes in AF patients on warfarin, *p* = .131, 95% CI [.995, 1.001]

Table 29

Bivariate Logistic Regression between Combined Dietary Vitamin K Intake (mcg/day) and Ischemic Stroke Outcomes

Variable	β	S.E.	*p*	Odds Ratio	95% CI for Odds Ratio
Dietary Vitamin K	- .002	.001	.131	.998	.995 – 1.001
Constant	- 1.466	.261	< .001	.231	.138 - .386

Research Question 2 Statistical Analysis: Serum Vitamin K and Ischemic Stroke

RQ2: Is there an association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin?

A bivariate logistic regression was performed to ascertain the effects of serum vitamin K adequacy on the likelihood that atrial fibrillation patients on warfarin would have an ischemic stroke. The logistic regression model was not statistically significant, $\chi^2(1) = .097$, $p = .755$. There was no statistically association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin, $p = .859$; 95% CI [.277, 4.627].

Table 30

Bivariate Logistic Regression between Subclinical Vitamin K Deficiency Below 0.30 nmol/L and Ischemic Stroke Outcomes

Variable	β	S.E.	*p*	OR	CI
Serum Vitamin K	.123	.686	.859	1.131	.277 – 4.627
Constant	- 1.844	.142	.000	.158	.120 - .209

When analyzing the effect of serum K adequacy by quartile on the likelihood that atrial fibrillation patients on warfarin would have an ischemic stroke by bivariate ordinal regression, the model fit improved but was still not statistically significant, $\chi^2(3) = 2.318$, $p = .509$. The model was a poor fit only explaining 2.4% (Nagelkerke R^2) of the variance in ischemic stroke outcomes. There was no statistically association between subclinical vitamin K deficiency by quartile and ischemic stroke in AF patients on warfarin. While not statistically significant, there was a lower risk for ischemic stroke with quartile 2 (OR = 1.32) versus quartile 1 (OR = 1.47) and quartile 3 (OR = 1.46) when the exp(*B*) was inverted due to being less than 1.

Table 31

Bivariate Logistic Regression between Subclinical Vitamin K Deficiency Quartile and Ischemic Stroke Outcomes

Variable	β	S.E.	*p*	OR	CI
Quartile 1	- .388	.412	.347	.679	.302 – 1.524
Quartile 2	- .276	.548	.621	.759	.239 – 2.411
Quartile 2	- .379	.430	.380	.685	.292 – 1.607
Constant	- 1.668	.196	< .001	.189	.128 - .277

Finally, when conducting a bivariate logistic regression analysis by serum vitamin K level (continuous IV), the logistic regression model was not statistically significant, $\chi^2(1) = .046$, $p = .830$. There was no statistically association between serum vitamin K deficiency and ischemic stroke in AF patients on warfarin, $p = .748$; 95% CI [.923, 1.118].

Table 32

Bivariate Logistic Regression between Subclinical Vitamin K Deficiency (nmol/L) and Ischemic Stroke Outcomes

Variable	β	S.E.	*p*	OR	CI
Serum Vitamin K	.016	.049	.748	1.016	.923 – 1.118
Constant	- 1.871	.182	.000	.154	.108 - .220

Research Question 3 Statistical Analysis

RQ3: Is there an association between subclinical vitamin K deficiency less than 0.30 nmol/L and ischemic stroke in AF patients on warfarin controlling for age, gender, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity?

A multivariate logistic regression was performed to ascertain the association of vitamin K subclinical deficiency less than 0.30 nmol/L, age, gender, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity on the likelihood that atrial fibrillation patients on warfarin would have an ischemic stroke. The data was analyzed in its original format as well as with imputed data. The data went through 5 iterations for imputation due to several variables having up to 55% of missing data. The pooled multivariate logistic regression model was not statistically significant, $\chi^2(18) = 18.453$, $p < .426$. The model explained 37.4% (Nagelkerke R^2) of the variance in ischemic strokes and correctly classified 92.9% of the cases. Normality testing was reviewed by looking at the Q-Q plots for all variables. All variables had less than 5 outliers noted with dietary vitamin K intake (mcg/day) and serum vitamin K levels (nmol/L) having slightly skewed distributions.

Of the twelve predictor variables, there was one statistically significant predictor variable: gender; with the risk for ischemic stroke increasing in females 2.224 times more than in males ($p = .011$, 95% CI 1.200 – 4.123). Every ten years, the risk for IS increased from 1.318 to 2.606 over 30 years starting at age 60, but this finding was not statistically significant (*p* > .05). When comparing the risk for IS by education levels, individuals with some college education had 2.74 times the risk for IS versus individuals with graduate degrees (*p* > .05). Individuals with a high school diploma, GED, or less than high school education had a 1.77x increased risk for IS versus those with a graduate degree (*p* > .05). Compared to individuals making over $50,000 annually, the risk for IS increased from 1.12 – 1.30 times as the income level dropped (*p* > .05). The impact of chronic disease and substance abuse increased the risk for IS between 1.23 – 1.60 times but this was not statistically significant (*p* > .05). As individuals gain weight the risk for IS increases from 1.92 – 2.15 times that of individuals that are normal weight, but this finding was not statistically significant (*p* > .05).

While neither vitamin K variables reached statistical significance, dietary vitamin K deficiency was found to increase the risk for IS by 33%; while inadequate serum vitamin K levels increased IS risk by 23.6% (*p* > .05). There was no statistically significant association between subclinical vitamin K deficiency and ischemic stroke when controlling for age, gender, education, income level, smoking status, alcohol abuse status, treatment for diabetes, treatment for hypertension, treatment for hyperlipidemia, and weight.

Table 33

Multivariate Logistic Regression of Imputed Data by Dichotomous Independent Variables and Dichotomous or Ordinal Covariates

Variable	β	S.E.	*p*	OR	CI
Dietary Vitamin K	.285	.405	.488	1.330	.580 – 3.049
Serum Vitamin K	.212	.707	.766	1.236	.293 – 5.223

(*table continues)*

Variable	β	S.E.	*p*	OR	CI
Age					
60-69 years	.276	.775	.722	1.318	.286 – 6.064
70-79 years	.866	.761	.256	2.378	.530 – 10.678
80+ years	.958	.874	.278	2.606	.454 – 14.953
Gender	.799	.314	.011	2.24	1.200 – 4.123
Education Level					
HS/GED or less	-.572	.556	.309	.565	.185 – 1.724
Some College	-1.008	.816	.232	.365	.066 – 2.010
Undergraduate	-.056	.467	.906	.946	.364 – 2.457
Income Level					
Less than $25,000	.110	.650	.868	1.116	.282 – 4.409
$25,000 - $50,000	.261	.524	.627	1.298	.418 – 4.033
Smoking Use	-.360	1.026	.726	.698	.093 – 5.264
Alcohol Use	-.230	.705	.745	.795	.198 – 3.192
DM	-.469	.639	.468	.625	.170 – 2.297
HTN	.287	.451	.532	1.332	.519 – 3.414
HLD	-.208	.399	.604	.812	.366 – 1.801
BMI					
Overweight	.654	.777	.417	1.923	.352 – 10.496
Obese	.766	.709	.294	2.152	.487 – 9.515

Further multivariate logistic regression by quartiles was performed to ascertain the association of dietary vitamin K quartiles, vitamin K subclinical quartiles, age, gender, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity on the likelihood that atrial fibrillation patients on warfarin would have an ischemic stroke. The data was analyzed in its original format as well as with imputed data. The data went through 5 iterations for imputation due to several variables having up to 55% of missing data. The original logistic regression model was not statistically significant, $\chi^2(22) = 25.079$, $p < .293$. The original model explained 49.2% (Nagelkerke R^2) of the variance in ischemic strokes and correctly classified 93.9% of cases.

Of the twelve predictor variables, there was one statistically significant predictor variable: gender; with the risk for ischemic stroke increasing in females 2.063 times more than in males ($p = .024$, 95% CI 1.101-3.867). Every ten years, the risk for IS increased from 1.22 – 2.50 times over 30 years starting at age 60, but this finding was not statistically significant ($p > .05$). When comparing the risk for IS by education levels, individuals with some college education had 2.78 times the risk for IS versus individuals with graduate degrees ($p > .05$). Individuals with a high school diploma, GED, or less than high school education had a 1.75x increased risk for IS versus those with a graduate degree ($p > .05$). Compared to individuals making over $50,000 annually, the risk for IS increased from 1.03 – 1.24 times as the income level dropped ($p > .05$). The impact of chronic disease and substance abuse increased the risk for IS between 1.23 – 1.56 times but this was not statistically significant ($p > .05$). As individuals gain weight the risk for IS increases from 1.93 – 2.15 times that of individuals that are normal weight, but this finding was not statistically significant ($p > .05$).

While neither vitamin K variables reached statistical significance, dietary vitamin K deficiency was found to increase the risk for IS from 34% to 81% as the levels dropped ($p > .05$); while inadequate serum vitamin K levels increased IS risk from 27 – 47% as the serum levels fell below adequate levels ($p > .05$). The lowest risk for IS was found with dietary intake levels between 144 – 197 mcg daily for men and 140 – 253 mcg daily for women ($p = .501$, OR 1.337, 95% CI .573 – 3.121). The lowest risk for IS was found with serum vitamin K levels between 0.58 – 1.06 nmol/L (*p* = .689, OR 1.27, 95% CI .37 – 4.37). There was no statistically significant association between subclinical vitamin K deficiency and ischemic stroke when controlling for age, gender, education, income level, smoking status, alcohol abuse status, treatment for diabetes, treatment for hypertension, treatment for hyperlipidemia, and weight.

Table 34

Multivariate Logistic Regression of Imputed Data by Independent Variable Quartiles and Dichotomous or Ordinal Covariates

Variable	β	S.E.	*p*	OR	CI
Dietary Vitamin K					
Quartile 1	.594	.441	.181	1.810	.755 – 4.342
Quartile 2	.435	.587	.466	1.545	.459 – 5.200
Quartile 3	.290	.431	.501	1.337	.573 – 3.121
Serum Vitamin K					
Quartile 1	-.336	.464	.470	.715	.285 – 1.792
Quartile 2	-.238	.584	.689	.788	.229 – 2.710
Quartile 3	-.387	.477	.421	.679	.261 – 1.768
Age					
60-69 years	.197	.740	.790	1.218	.285 – 5.200
70-79 years	.814	.738	.270	2.257	.529 – 9.625
80+ years	.914	.852	.286	2.498	.459 – 13.575
Gender	.724	.319	.024	2.063	1.101 – 3.867
Education Level					
HS/GED or no HS degree	-.561	.594	.352	.571	.170 – 1.913
Some College	-1.022	.818	.225	.360	.066 – 1.976
Undergraduate	-.048	.478	.920	.953	.357 – 2.541
Income Level					
Less than $25,000	.032	.683	.963	1.033	.240 – 4.437
$25,000 - $50,000	.212	.555	.709	1.237	.365 – 4.184
Smoking Use	-.349	1.043	.738	.705	.090 – 5.520
Alcohol Use	-.280	.702	.691	.756	.190 – 3.010
DM	-.450	.643	.490	.638	.172 – 2.365
HTN	.229	.469	.632	1.257	.467 – 3.381

(*table continues)*

Variable	β	S.E.	p	OR	CI
HLD	-.211	.443	.638	.810	.327 – 2.007
Obesity					
Overweight	.657	.810	.435	1.929	.324 – 11.471
Obese	.763	.761	.332	2.145	.423 – 10.889

Further multivariate logistic regression was performed to ascertain the association of total dietary vitamin K intake (mcg/day), vitamin K subclinical (nmoL/L), age, gender, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity on the likelihood that atrial fibrillation patients on warfarin would have an ischemic stroke. The data was analyzed in its original format as well as with imputed data. The data went through 5 iterations for imputation due to several variables having up to 55% of missing data. The original logistic regression model was not statistically significant, $\chi^2(18) = 22.595$, $p < .207$. The original model explained 44.9% (Nagelkerke R^2) of the variance in ischemic strokes and correctly classified 91.8% of.

Of the twelve predictor variables, there was one statistically significant predictor variable: gender; with the risk for ischemic stroke increasing in females 2.15 times more than in males ($p = .018$, 95% CI 1.144 – 4.044). Every ten years, the risk for IS increased from 1.20 – 2.41 times over 30 years starting at age 60, but this finding was not statistically significant ($p > .05$). When comparing the risk for IS by education levels, individuals with some college education had 2.76 times the risk for IS versus individuals with graduate degrees ($p > .05$). Individuals with a high school diploma, GED, or less than high school education had a 1.73x increased risk for IS versus those with a graduate degree ($p > .05$). Compared to individuals making over $50,000 annually, the risk for IS increased from 1.05 – 1.28 times as the income level dropped ($p > .05$). The impact of chronic disease and substance abuse increased the risk for IS between 1.26 – 1.56 times but this was not statistically significant ($p > .05$). As individuals gain weight the risk for IS increases from 1.96 – 2.20 times that of individuals that are normal weight, but this finding was not statistically significant ($p > .05$).

While neither vitamin K variables reached statistical significance, every unit decrease in dietary vitamin K intake results in a minute increase in the risk for IS ($p = .120$, OR 1.002, 95% CI .999 – 1.005); while every unit increase in serum vitamin K levels increased IS risk by 2.6% ($p = .657$, OR 1.026, 95% CI .916 – 1.150). There was no statistically significant association between subclinical vitamin K deficiency and ischemic stroke when controlling for age, gender, education, income level, smoking status, alcohol abuse status, treatment for diabetes, treatment for hypertension, treatment for hyperlipidemia, and weight.

Table 35

Multivariate Logistic Regression of Imputed Data by Continuous Independent Variables and Dichotomous or Ordinal Covariates

Variable	β	S.E.	*p*	OR	CI
Dietary Vitamin K	-.002	.001	.120	.998	.995 – 1.001
Serum Vitamin K	.026	.058	.657	1.026	.916 – 1.150
Age					
60-69 years	.181	.738	.806	1.199	.282 – 5.098
70-79 years	.773	.741	.298	2.167	.504 – 9.316
80+ years	.880	.864	.312	2.412	.430 – 13.535
Gender	.766	.320	.018	2.151	1.144 - 4.044

(*table continues)*

Variable	β	S.E.	*p*	OR	CI
Education Level					
HS/GED or no HS	-.549	.558	.330	.578	.188 – 1.775
Some College	-1.017	.839	.242	.362	.062 – 2.116
Undergraduate	-.039	.469	.934	.962	.369 – 2.509
Income Level					
Less than $25,000	.046	.677	.947	1.047	.246 – 4.452
$25,000 - $50,000	.249	.507	.631	1.283	.434 – 3.794
Smoking Use	-.373	1.039	.720	.689	.088 – 5.359
Alcohol Use	-.233	.693	.737	.792	.203 – 3.096
DM	-.447	.655	.500	.639	.169 – 2.435
HTN	.250	.455	.589	1.284	.495 – 3.328
HLD	-.233	.414	.576	.792	.344 – 1.824
Obesity					
Overweight	.670	.799	.419	1.955	.337 – 11.344
Obese	.789	.746	.307	2.201	.449 – 10.787

Summary of Data Analyses

Over the course of Chapter 4, the results of the bivariate and multivariate research questions were analyzed. Information was revealed about changes to the protocol, original data analysis, and imputed data analysis due to over 55% of the data of several variables missing. There was no statistically significant association between dietary vitamin K intake below the daily adequate intake (AI) by gender and ischemic stroke in AF patients on warfarin. There was no statistically significant association between subclinical vitamin K deficiency below 0.30 nmol/L and ischemic stroke in AF patients on warfarin. There was no statistically significant association between vitamin K subclinical deficiency less than 0.30 nmol/L and ischemic stroke in AF patients on warfarin controlling for age, gender, race/ethnicity, education status, socioeconomic status, smoking status, alcohol intake, diabetes mellitus, high blood pressure, high cholesterol, and obesity. Due to the nature of the data and imputed data further analysis was conducted by quartiles (dietary vitamin K intake and serum vitamin K levels) as well as by continuous levels (mcg/day and nmoL/L).

Further analysis of dietary vitamin K intakes and serum vitamin K levels was analyzed by quartile to determine if there was a difference in the association of vitamin K deficiency and ischemic stroke outcomes. When reviewing dietary vitamin K intake by quartile, there was no statistically significant association between individuals with the lowest quartile dietary vitamin K intake (men < 106 mcg daily and women < 111 mcg daily) had 1.78 times increased risk for ischemic stroke versus individuals with the highest quartile of intake (men > 196 mcg daily, women > 252 mg daily) (*p* = .129). No statistically significant association was found between the different quartiles of serum vitamin K levels and ischemic stroke outcomes; however, there results did show 1.47 times higher odds for ischemic stroke in the lowest quartile serum vitamin K levels as compared to the highest quartile serum vitamin K levels [*p* = .347; 95% CI (.87, 3.31)].

A final analysis analyzing total dietary vitamin K intake (mcg/day) and serum vitamin K intake (nmoL/L) revealed comparable results. The statistical results showed that for every mcg/day drop in total dietary vitamin K intake, there was 0.5% increased odds for ischemic stroke [*p* = .131; 95% CI (.995, 1.001)]. While that does not seem like much, the results extrapolated out would show that a 10 mcg/day decrease in total dietary vitamin K intake could result in 5% increased ischemic stroke outcomes. Every nmol/L drop in serum vitamin K resulted in 2% increased odds of ischemic stroke outcomes [(*p* =

.748; 95% CI (.923, 1.118)]. Like total dietary vitamin K intake, a 10 nmoL/day drop in serum vitamin K could result in 20% increased odds for developing an ischemic stroke.

When controlling for other factors related to ischemic stroke outcomes, there were no significant associations between total dietary vitamin K intake or serum vitamin K levels and ischemic stroke outcomes ($p > .05$). As total dietary vitamin K levels increase there is a general decrease in the odds for ischemic stroke with the safest level being around 106-144 mcg daily for men and 111-140 mcg daily for women [Exp(*B*) = 2.613, 95% CI (.515, 13.263)]. As serum vitamin K levels increase there is a decrease in the odds of ischemic stroke outcomes with the safest levels appearing to be .058 – 1.06 nmol/L [Exp(*B*) = .214, 95% CI (.022, 2.074)]. When analyzing total dietary vitamin K intake in mcg/day while controlling for all other predictor variables, the risk for ischemic stroke increases for each unit decrease in total dietary vitamin K intake [$p = .107$, Exp*(B)* = .995, 95% CI (.989, 1.001)]. For every unit increase in serum vitamin K levels, the risk for ischemic stroke decreases [$p = .428$, Exp*(B)* = 1.061, 95% CI (.915, 1.231)]. The only consistent independent variable with statistical significance through all the testing was age where the risk for ischemic stroke would increase by 10% every 10 years (starting at age 51).

Chapter 5 will discuss these findings in more detail. There will be a discussion on the findings in relation to other works as well as strengths and limitations to the current study. A description of potential research avenues as well as practice recommendations will close out the discussion section with a goal towards positive social change.

Chapter 5: Discussion

Summary

The purpose of this research was to investigate the association between vitamin K deficiency from elimination diets and the risk for ischemic stroke in Atrial Fibrillation patients on warfarin. The study was a quantitative, retrospective analysis of secondary data from the Framingham Heart Study *Offspring* cohort. The study was conducted to determine if patients taking warfarin long-term had an increased risk for ischemic stroke resulting from extremely low vitamin K intakes. In conducting the research using dichotomous IV, quartile based IV, and continuous IV, no statistically significant association was found between dietary vitamin K deficiency, subclinical vitamin K deficiency, and ischemic stroke outcomes with and without controlling for other risk factors for ischemic stroke. One thoughtful note, however, is that when reviewing the analysis from dichotomous IV and quartile based IV, there was a definitive increased risk for ischemic stroke outcomes compared with adequate nutritional intake and adequate biochemical levels. The following chapter will review the findings of this current study against prior research, discuss the limitations of the study, review recommendations for future studies and clinical practice, as well as discuss the implications on positive social change.

Conceptual Framework

The conceptual framework for the current study looked at the impact of inadequate vitamin K diets leading to subclinical vitamin K deficiency and increasing the risk for cardiovascular outcomes, such as ischemic stroke. The thought process was that as the levels of vitamin K decreased in the body, there would not be enough vitamin K available in the circulatory system to maintain all the biochemical pathways for health (McCann & Ames, 2009; Vermeer & Braam, 2001). Therefore, the available vitamin K would be primarily shunted to essential life functions, such as in this case, coagulation. Because vitamin K participates in the maintenance of bone metabolism, the concept is that if there is not enough vitamin K available within the body, bone homeostasis would start to decline, thus leading to calcium being released in the body. This excess calcium would then start to form plaque, leading to an increased risk for ischemic stroke.

Because ischemic stroke risk involves several factors, the current study tried to control for factors that would have impacts on vitamin K intake as well. These included age, gender, education status, income status, substance abuse, and co-morbidities. These specific factors could alter vitamin K intake through the ability to purchase foods, availability of foods high in vitamin K, cooking ability, cultural preferences, competing dietary restrictions, and decreased dietary intake results from excessive substance abuse issues. With these factors in mind, the present study was developed to better understand the impact of vitamin K deficiency (both dietary and clinically) on ischemic stroke outcomes in patients that were already on vitamin K restrictive diets.

Comparison to Previously Published Studies

Several studies have been conducted in the past looking at the impact of vitamin K on cardiovascular outcomes. This study attempted to fill in some of the gaps in the literature surrounding the impact of vitamin K deficient diets specifically on ischemic stroke outcomes to increase knowledge in the profession and improve outcomes of warfarin treatment protocols.

Dietary Vitamin K

When reviewing the impact of dietary vitamin K adequacy on ischemic stroke outcomes, the current study disproved two studies while extending the results of several others. Wessinger et al. (2020) found that over 80% of post-stroke patients had inadequate intakes with average intakes around 45 mcg/day; however, the current study found a lower percentage of ischemic stroke patients with inadequate intakes with an average intake 3x higher than Wessinger et al. (2020). Haugsgjerd et al. (2020) found that the risk for CHD increased with higher levels of vitamin K intake; however, the current study found that higher intakes of dietary vitamin K had lower risks for ischemic stroke compared with lower intakes.

The current study extended the findings from Han et al. (2019) and Chen et al. (2019), finding that individuals on warfarin had elevated levels of inadequate vitamin K intake, which was similar in the general population. This study revealed similar findings with inadequate vitamin K intakes in populations with an average age of 71 years compared with over 90% of LTC residents having inadequate intakes (Keller et al., 2018). Additionally, prior research found higher intakes of vitamin K maintained vitamin K pathways, which the current study confirmed showing increased odds for ischemic stroke as the levels of vitamin K intake decreased (Murray, 2004). Finally, Douthit et al. (2017) found that lower vitamin K intakes had higher levels of heart dysfunction as compared to higher intakes. The current study extended those findings by determining that warfarin patients with inadequate vitamin K intakes had lower levels of high blood pressure, but the levels of high cholesterol were like those with adequate vitamin K intake, although neither finding was statistically significant.

Some of the prior research studies did conduct multivariate analyses that were either disconfirmed, confirmed, or extended by the current study. Three studies in the past analyzing associations between vitamin K adequacy and cardiovascular outcomes found vitamin K diets around 90-120 mcg daily had a reduced risk for cardiovascular outcomes (Chen et al., 2019; Haugsgjerd et al., 2020; Shea et al., 2020). Whereas, this study found lower vitamin K intakes had increased risk for ischemic stroke. Several studies found no statistically significant association between vitamin K deficiency and ischemic stroke or other cardiovascular outcomes, which was confirmed by the current study (Dai, et al., 2021; Del Canto, et al., 2020; Erkkila et al., 2005; Larsson et al., 2018; Vissers et al., 2013; Xu et al., 2019; Zwakenberg et al., 2017). This study extended these findings though by showing that ischemic stroke outcomes do increase with lower intakes of dietary vitamin K and serum vitamin K levels.

Serum Vitamin K

Several studies in the past analyzed the impact of serum vitamin K levels on cardiovascular outcomes. The current study attempted to extend the knowledge of current literature by determining the impact of subclinical vitamin K deficiency, as measured by serum phylloquinone levels, on ischemic stroke outcomes. The measures with most of the other studies utilized different vitamin K clinical laboratory tests. The current study helps extend those findings. The Office of Dietary Supplements (2020) reported that a healthy level of serum intake should be 0.29 – 2.64 nmol/L. The current study confirmed that warfarin patients, on average, met this goal. Interestingly, the current study disconfirmed the findings by Kim et al. (2015) that vitamin K levels dropped significantly after warfarin initiation, as the current study showed adequate levels of intake on average among warfarin patients when compared to the recommendations from ODS (2020). Additionally, the current study found inconsistencies in vitamin K adequacy between dietary and serum levels, which extends the information from Shea et al. (2020) looking at the differences in mean serum levels based on dietary vitamin K intakes. In confirmation of Takada et al. (2014) and De Vriese et al. (2020), low phylloquinone concentrations did increase the risk for ischemic stroke, but the results were not statistically significant.

Age

Prior research has shown that as individuals age, they have an increased risk for ischemic stroke, as well as all other strokes. The risk for stroke increased over the age of 65 years and particularly in those over 80 years (NINDS, 2019; Wang et al., 2020). The current study confirmed these findings and even extended the findings, showing high risks for strokes in those over 80 years. Other researchers found lower intakes of vitamin K foods as individuals between 50-60 years (Harshman et al., 2017; Keller et al., 2018). This study confirmed those two studies, showing average intakes below the AI in individuals 50-59 years as compared to the highest intake over the AI in individuals 70-79 years. Mean intakes were similar in the lowest quartiles between the Keller et al. (2018) study and this study. While the findings were not statistically significant, there were narrow confidence intervals and noticeable changes between the different age groups by decade.

Alcohol Abuse

The research surrounding alcohol consumption and ischemic stroke in the past has been mixed. Bassand et al. (2018) was able to show an increased risk for all stroke with heavy alcohol use. The current study extended these findings by showing an increased risk for ischemic stroke in those with alcohol abuse higher that other types of stroke. Alexander et al. (2018) and Ren & Fu (2021) had mixed reviews concerning alcohol intake and total stroke risk. Alexander et al. (2018) found a lower risk for stroke with lower intake, whereas Ren & Fu (2021) did not find a statistically significant difference between alcohol intake and stroke risk. While the current study also did not find statistical significance, there was a noticeable increased risk for ischemic stroke with alcohol abuse with concurrent narrow confidence interval ranges.

Diabetes Mellitus

Poor diabetes control damages small vessels and increases the risk for all strokes. Tshiswaka et al. (2019) and Bassand et al. (2018) found positive associations between diabetes, atrial fibrillation, and stroke outcomes. The current research extended these findings to include an extensive increased risk for ischemic stroke in those receiving diabetes treatment. Sarif et al. (2020) did not find an association between diabetes and stroke in the past, but they did notate an insignificant increase in the risk for stroke. The current study extended these findings to include a substantial increase in risk for ischemic stroke with diabetes treatment. While the findings were significant with narrow confidence intervals, there was not a statistically significant association between diabetes mellitus treatment and ischemic stroke when controlling for other potential risk factors.

Education

Education has played a key role in past research in the sense of the ability to understand healthcare provider guidance, or as the level of functional knowledge they may possess. Harshman et al. (2017) found that individuals with less education had lower vitamin K intakes. This was disconfirmed by the current study where individuals with a HS degree had the lowest intake as compared to those with no HS degree having adequate intake of vitamin K foods. Wang et al. (2020) reported higher rates of all strokes for those without a high school diploma. The current research extended those findings by identifying a much substantially higher risk for ischemic stroke with lower education levels with narrow confidence intervals.

Gender

Gender continued to be the only variable that had a statistically significant impact on ischemic stroke risk, which has been seen in similar research studies. Claxton et al. (2018) found a significant higher risk for stroke in women over men, which was confirmed by the current study. While the current study confirmed the increased risk for ischemic stroke in women compared to men, the study revealed a substantial increased risk for ischemic stroke as compared to the Yong et al. (2020) study. Interestingly, the current study denied the findings of Wessinger et al. (2020) that women had lower average daily intakes of vitamin K with women having over almost 30 mcg daily more intake than men. The current study did confirm and extend the findings of Harshman et al. (2017) that women had higher percentages of adequate intake of vitamin K than men.

Hypertension

Several studies in the past looked at the association between high blood pressure (HTN) and stroke risk. There have been mixed reviews, with Ren & Fu (2021) and Tshiswaka et al. (2019) confirming the existence of an association between HTN and stroke, versus Bassand et al. (2018) and Sarif et al., 2020) finding now association between them. The current study confirmed and extended the findings of Ren & Fu (2021) and Tshiswaka et al. (2019) by showing an elevated risk for ischemic stroke in those receiving treatment for HTN. While not statistically significant, the confidence intervals were narrow, and the odds ratios were moderately elevated.

Hyperlipidemia

Prior research has been set showing positive associations between hyperlipidemia (HLD) and stroke. Ren & Fu (2021), Sarif et al. (2020), and Tshiswaka et al. (2019) all found positive associations between HLD and all strokes. The only difference between the three studies and the current study was that the current research looked specifically at ischemic stroke, which also found a moderately increased risk for ischemic stroke for individuals receiving HLD treatment. The current study did confirm the findings of Agarwal et al. (2017) and Overwyk et al. (2021), showing a moderately higher risk for ischemic stroke than the prior research studies. While there was no statistical significance to the current research, there was a moderate association with narrow confidence interval ranges.

Income

There is no surprise that lower income levels have increased risks for chronic disease. The current study extended the dearth of research by providing information on a mild increase in the risk for ischemic stroke with lower income levels. The current study confirmed the findings of Han et al. (2019) and Harshman et al. (2017) that lower incomes had lower intakes of vitamin K deficiency. This is not surprising as vitamin K foods are often found in higher amounts in green leafy vegetables, which may be more costly for lower income families compared to standard frozen vegetables. Another consideration is that northern U.S. diet patterns may not have as many green leafy vegetables in their diets as compared to southern U.S. diet patterns. While the findings were not statistically significant, there were mild associations between low-income families making less than $25,000 annually and ischemic stroke risk.

Obesity

In the past, Ren & Fu (2021) and Tshiswaka et al. (2019) found no association between weight differences and all stroke risk. Agarwal challenged this et al. (2017), who did find a statistically significant association between obesity and stroke risk. The current study confirmed findings by Agarwal et al. (2017) and extended those findings to ischemic stroke risk with a significant increase in the risk for ischemic stroke as individuals gain weight. The current research confirmed that obese participants have excessive intakes of vitamin K, which could lead to hemorrhagic consequences. While the findings were not statistically significant, the associations were significant for risk of ischemic stroke in overweight and obese subjects with narrow confidence intervals.

Race/Ethnicity

Prior research has mostly revolved around Caucasians, African Americans, and Hispanics in the U.S. The increased risk for total stroke in African Americans compared to Caucasians has been noted in prior research (Noorbakhsh-Sabet et al., 2018; Odlum et al., 2020). Han et al. (2019) and Harshman et al. (2017) both have discussed the lower intakes of vitamin K among Hispanic and White Americans, respectively. The current study results could not be extrapolated to African Americans or Hispanics as most of the *Offspring* cohort reporting on race and ethnicity were predominantly Caucasian and non-Hispanic. The current study did confirm a lower intake amongst White, Non-Hispanic participants as opposed to other race/ethnicity combinations like the findings of Han et al. (2019) and Harshman et al. (2017). In the current study, White/Hispanic participants were the predominant participants to have the most ischemic strokes.

Smoking Status

Previous studies often report on the associations between smoking status and either stroke or cardiovascular disease risk. Although Bassand et al. (2018), Ren & Fu (2021), and Sarif et al. (2019) found no associations between smoking and ischemic stroke risk, positive moderate to high associations were reported with cardiovascular disease and total risk by Mahtta et al. (2021) and Tshiswaka et al. (2019). The current study had no statistically significant associations like Bassand et al. (2018), Ren & Fu (2021), and Sarif et al. (2019), but there were moderate associations between participants with smoking habits and ischemic stroke risk extending the findings of Mahtta et al. (2021) and Tshiswaka et al. (2019). The confidence intervals for these findings were narrow like other covariates, but these narrow intervals could be related to the larger sample size.

Ischemic Stroke

While prior research often excluded participants that were on VKAs, such as warfarin, the current study focused solely on warfarin patients to better understand the impact of the medication on dietary vitamin K intakes. Several studies did not have adequate power resulting from small sample sizes, but the current study utilized information from the *Offspring* cohort of the Framingham Heart Study that provided information for over 471 individuals. The study utilized multiple imputation to replace missing values instead of listwise deletion which could have reduced the power of the current study. Finally, as Lin et al. (2019) reported, the *Offspring* and *3rd Generation* cohorts from the Framingham Heart Study had a 16% CVD rate which provided ample data on CVD outcomes. The current study had an ischemic stroke rate among warfarin patients of 13.8%. The next section will focus solely on the interpretation of the current study findings.

Interpretation of Findings

The current study utilized three different methods to analyze vitamin K deficiency and ischemic stroke outcomes. Vitamin K adequacy was measured as a dichotomous variable, a quartile-based variable, and a continuous variable. All tests were not statistically significant; however, there were still findings which need to be considered for future practice. Inadequate dietary vitamin K intake as measured by a continuous variable had no statistically significant association with ischemic stroke outcomes. When analyzed by the AI for gender, there had a 16% increased risk for ischemic stroke. When analyzed by quartiles, the risk for ischemic stroke increased 45-78% compared with those that had adequate intakes.

This association continued when analyzing vitamin K deficiency by serum levels of phylloquinone. While the continuous serum vitamin K variable revealed no association with ischemic stroke outcomes, when changed to a dichotomous variable, inadequate serum vitamin K had a 13% increased risk for ischemic stroke. The risk for ischemic stroke was even more evident when reviewing quartiles with prominent levels of serum vitamin K increasing the risk by 5.29 times versus lower levels increasing risk 31-47%. The results show that while serum vitamin K is associated with ischemic stroke the impact can be marginalized by the level in the blood.

The multivariate analysis reported statistically significant associations between gender and ischemic stroke with females have 2x the risk for stroke versus men. The findings of increased risk for ischemic stroke based on dichotomous and quartile-based vitamin K variables remained in the multivariate analyses as well; however, those findings continued to be not statistically significant. While the findings of the study were not statistically significant, the results did show the impact of various levels of vitamin K on ischemic stroke outcomes.

Something to consider when interpreting the current findings to prior research is the cohort used. While the Framingham Heart Study is a gold-standard study for analyzing health outcomes over time, the time period can be a significant confounder to any interpretation. The *Offspring* cohort would have been enrolled between the 1990's to around 2010. The events that occurred during those years as well as the lifestyle of that generation of the study would be vastly different from a study using younger participants. This generational difference should be considered carefully when interpreting the findings further.

Theoretical Foundation

The current study was based on the Health Belief Model that tried to discern the impact of individual behaviors on adopting lifestyle changes to improve the risk for acute and chronic diseases (Rosenstock, 1974). Some of the factors impacting health behaviors include the perceptions of disease susceptibility, disease severity, benefits of complying with treatment recommendations, and barriers to implementing the recommendations (Chang et al., 2018; Long et al., 2017; Sullivan et al., 2009). The HBM can be used in nutrition education to improve dietary compliance (Araban et al., 2017).

The current study used the HBM to increase the awareness of vitamin K deficiency and ischemic stroke outcomes by providing statistics related to the impact of following dietary recommendations for vitamin K restriction while on warfarin. The study helped to identify the safest level of vitamin K intake that providers can discuss with their patients while controlling for barriers such as lack of education or cooking knowledge, competing dietary restrictions from other co-morbidities, cultural preferences, and inadequate intakes from substance abuse issues. With over 50% of patients on warfarin failing to understand their diet (Chen et al., 2019), these findings can help patients better understand how much vitamin K food intake would be safe to consume instead of restricting all vitamin K foods.

Limitations

There are several limitations to the study to consider. The study cannot be generalized to the general population as the study was very narrow in focus. The current study had older adults (average age 71 years), primarily of European descent, and from the Massachusetts region of the United States. Additionally, the study focused solely on atrial fibrillation patients on warfarin. As a result, the findings cannot be extrapolated to other atrial fibrillation patients on other anticoagulants. While these findings could be generalized to anyone on warfarin, professionals should exercise caution as different disease processes affect nutrient metabolism differently. One final thought on generalization to all patients with inadequate intake would be that the current study could have misclassified some individuals as 37 participants had serum values that were incongruous with dietary values. In terms of validity and reliability, there are no perceived issues with the validity of the Framingham Heart Study. As discuss in prior sections, the FHS had a high retention rate, highly trained professionals, followed participants for over 43 years, took multiple measurements, created standardized terminology, and reported extensive quality control and reproducibility through multiple research studies (Tsao & Vasan, 2015). While the length of time on warfarin, different ethnicities, and geographic location can impact vitamin K levels, these factors were not studied as they were not available within the FHS data collection. While ethnicity was available, 99% of the participants with recorded information in this study were of European descent.

Recommendations for Further Analysis or Study

Longitudinal studies help provide the much-needed perspective on warfarin, vitamin K intake, and ischemic stroke risk since they follow patients over time. The FHS had over 40 years of data with the *Offspring* cohort alone. Based on the findings of the current study, future research should take a broader look at all participants within the Framingham Heart Study to compare vitamin K deficiency and ischemic stroke outcomes, controlling for atrial fibrillation and anticoagulants. FFQ exams from the FHS help track any changes in the dietary vitamin K intake over the 40 years. The FHS measured the dietary guideline adherence index (DGAI) for everyone which could be another way of measuring vitamin K status in the future. Another recommendation would be finding a study that has a more diverse sample size or merge several studies in a meta-analysis if some could be found with the same variables. Additionally, if the variables are different between studies, the research could recode the information into a new variable to conduct the analysis. An example would coding the variables as adequate intake versus inadequate intake for the final analysis. Serum phylloquinone levels are not considered the gold standard for determining vitamin K adequacy, so conducting future research with gold standard laboratory testing would be crucial. Adding a time component to any future research project could help determine if there is an association between the amount of time someone is on warfarin, vitamin K adequacy, and ischemic stroke outcomes. One change that could help would be adding serial vitamin K measures in longitudinal studies as well for tracking deficiency states.

Implications for Positive Social Change

This study has several implications for positive social change. The study can impact social change at the individual level by providing an increased awareness for vitamin K adequacy and what is considered a safe intake level while taking warfarin. Based on the results of the study, patients with AF on warfarin could consume between 110 – 140 mcg daily and maintain the lowest risk for ischemic stroke. At the family level, having a better understanding of the safe level to consume can increase family involvement with care management through cooking as well as monitoring for signs of any stroke in long-term warfarin patients to help determine if physicians should change the medication prior to a stroke occurring. This finding helps to prove that restriction below the AI is not recommended for these patients. Having an adequate intake could help stabilize coagulation indices as well as lower their risk for stroke.

At the organization level, healthcare professionals can provide a more thorough education on a safe level of vitamin K to consume versus restricting all foods. Physicians could potential order quarterly or annual serum vitamin K levels to monitor for deficiency states in long-term warfarin patients. Based on the results of the study, physicians could start AF patients at high-risk for vitamin K deficiency on routine monitoring annually. They could then adjust that monitoring based on a safe level between 0.58 – 1.06 nmol/L. Dietitians could develop cooking classes to help individuals learn to cook different vitamin K foods, and communities could improve access to vitamin K foods through local farmer's markets and community gardens.

When considering the totality of the research surrounding vitamin K deficiency and ischemic stroke outcomes in AF patients on warfarin at the society level, healthcare organizations could develop protocols regulating the treatment of warfarin which could include regular serum vitamin K checks when vitamin K deficiency is questioned, educate on safe levels of vitamin K foods to consume versus restriction, and have patients attend cooking classes that will teach them how to prepare meals for consistent intakes. This increased education and awareness of safe levels to consume and improvements in monitoring can help reduce the risk for ischemic stroke in atrial fibrillation patients on warfarin.

HBM looks at individuals understanding the risk and benefits of different health outcomes. Many warfarin patients lack the understanding surrounding consistent vitamin K intake and need better education as a result. The education needs to include healthcare providers since many may not realize the differences between consistent intake and restriction as well as the impact of restriction on ischemic stroke outcomes. By moving away from educations focused on “restriction” or “consistent” intake to actual levels, patients can have a better understanding and control of the impact of what they eat on their health outcomes.

Conclusions

Nutrition plays a critical role in human physiology. Many factors affect dietary intake including medications, access to healthy food, ability to buy food, and ability to prepare foods. Many patients and healthcare providers lack the proper education on what adequate and consistent vitamin K intake for patients on warfarin looks like. More education for healthcare professionals on adequate vitamin K intake and the impact of long-term warfarin use and ischemic stroke risk need to be considered when making treatment decisions. Healthcare providers need to monitor biochemical vitamin K levels quarterly or annually to determine if patients are deficiency and need changes in anticoagulants as a result. One of the best sayings in management is that when you give a person a carrot (verbal education on limiting vitamin K intake), they may struggle; but give them the seeds to grow their carrot (information on risks, benefits, foods, and cooking ability), then watch that individual learn and grow while maximizing their health benefits. In the case of vitamin K intakes, the safest level to consume while minimize adverse health outcomes would be 106 – 143 mcg daily for men and 111-139 mcg daily for women. With this information, healthcare professionals can develop new handouts displaying actual vitamin K levels of select foods and help patients better understand how to manage their diet while minimize the risk for ischemic stroke.

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