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Risk Factors For Cholelithiasis (Gallstones) Among Female Veterans

Mila Pak

RISK FACTORS FOR CHOLELITHIASIS (GALLSTONES) AMONG FEMALE VETERANS

by

Mila Pak
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Master of Science, Barry University

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This dissertation, submitted by Mila Pak in partial fulfillment of the requirements for the Degree of Doctor of Philosophy from the University of North Dakota has been read by the Faculty Advisory Committee under who the work has been done and is hereby approved.

Glenda Lindseth
Glenda Lindseth, Ph.D.

Darla J Adams
Darla Adams, Ph.D.

Jody Ralph
Jody Ralph, Ph.D.

Tomas Petros
Tomas Petros, Ph.D.

Van A. Doze
Van Doze, Ph.D.

This dissertation is being submitted by the appointed advisory committee as having met all of the requirements of the Graduate School at the University of North Dakota and is hereby approved.

Wayne E. Swisher
Wayne E. Swisher, Ph.D.
Dean of the Graduate School

July 29, 2015
Date

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Title Risk Factors for Cholelithiasis (Gallstones) Among Female Veterans

Department College of Nursing

Degree Doctor of Philosophy

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Mila Pak
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ABSTRACT

Background and Purpose: Gallstones affect up to 15% of the U.S. adult population. Women are at greater risk for cholelithiasis, especially if they are overweight, over forty years of age, or have had children. The Veterans Health Administration (VHA) performed 114,653 cholecystectomy surgeries with 107,975 patients diagnosed with cholelithiasis from 2008 to 2013. Female veterans may be at even greater risk for cholelithiasis. However, research with this vulnerable population is sparse. Therefore, the purpose of this study was to examine physiological and environmental risk factors that may be associated with cholelithiasis among female veterans.

Study Design and Theoretical Framework: This retrospective case-control study examined the VHA electronic medical data for possible risk factors associated with cholelithiasis among female veterans. Wittenburg and Lammert's model, describing factors contributing to cholesterol susceptibility, guided this study examining multifactorial influences that may precipitate cholelithiasis in a population of female veterans.

Sample Selection: Data representing samples of ethnically-diverse female veterans over 40 years of age were retrospectively randomly selected from the VHA data between January, 2008 and December, 2013. Study data were retrieved through the Veterans Affairs Informatics and Computing Infrastructure (VINCI) system from 242

patients assigned to each of the study groups based on presence of absence of cholelithiasis diagnosis.

Methods: Demographic, military service, comorbidity, and laboratory test data were analyzed for differences between the cholelithiasis and control groups. Data were further analyzed using multiple regressions to explore the relationship of risk factors to cholelithiasis occurrence.

Results: Tobacco use was significantly ($p < .01$) higher in female veterans with cholelithiasis than those without cholelithiasis. Also higher serum cholesterol ($p < .01$) and hemoglobin A1c ($p < .01$) levels were positively associated with female veterans experiencing cholelithiasis while lower High-Density Lipoprotein (HDL) blood levels were significantly related ($p < .01$) to cholelithiasis occurrence for the women. The women also had higher frequencies ($p < .01$) of hypertension and hepatitis C than those women without cholelithiasis. Results of multiple regression analysis indicated that serum cholesterol, hemoglobin A1c, and HDL levels accounted for 26 % of the variance for risk in female veterans developing cholelithiasis. Also, the women with a history of hypertension and hepatitis C had 2.5 times the risk of developing cholelithiasis than those without hypertension and hepatitis C.

Conclusions and Implications: Tobacco use, higher cholesterol and hemoglobin A1c levels, lower HDL levels, and a history of hypertension and hepatitis C were associated with increased risk for cholelithiasis occurrence in female military veterans. Understanding risk factors associated with cholelithiasis in military female veterans may promote patient-centered care and build preventive strategies in this rising but understudied population.

CHAPTER I

INTRODUCTION

Gallstone disease is one of the most prevalent gastrointestinal diseases and affecting approximately 10-15% of the adult population in the United States. Women are at greater risk (Barbara et al., 1987), especially if they are overweight (Maclure et al., 1989), over 40 years of age (Attili et al., 1997), or had children (Attili et al., 1997). Further, cholelithiasis increases the risk of gallbladder and colorectal cancer (Schernhammer et al., 2003; Siddiqui et al., 2009), especially in women. Between 2008 and 2013, the Veterans Health Administration performed 114,653 cholecystectomy surgeries on 107,975 patients diagnosed with cholelithiasis. While female veterans comprised 14% (2,677) of all cholecystectomy procedures (19,801) in 2011 at the VHA, only 6% of the 514,500 total population enrolled in the VHA database were women during that same year (VHA, 2014). Therefore, female veterans may be at even greater risk for cholelithiasis and cholecystectomies. However, research with this vulnerable population was not found. Furthermore, environmental and occupational risks experienced by these women who have served their country may only further complicate their risks for gallstones. Therefore, the purpose of this study was to examine physiological and environmental risk factors that may be associated with the occurrence of cholelithiasis among female veterans.

Statement of the Problem

Gallstones affect approximately 10-15% of the adult population in the United States and prevalence is rising. Annually, it is estimated that one million patients are newly diagnosed with

cholelithiasis with 1.8 million ambulatory care visits and costing approximately 6.5 billion dollars (Everhart, Khare, Hill, & Maurer, 1999; Shaheen et al., 2006). This trend has increased by greater than 20% over the last three decades, making gallstone disease a leading cause for gastrointestinal hospital admissions (Everhart & Ruhl, 2009; Sandler et al., 2002; Shaffer, 2005).

Although most cholelithiasis (the formation of gallstones) is asymptomatic (Gracie & Ransohoff, 1982), 25-50% of asymptomatic patients eventually develop symptoms and complications (Beckingham, 2001; Gracie & Ransohoff, 1982) that result in a cholecystectomy (removal of gallbladder), the standard care for symptomatic cholelithiasis or in endoscopic retrograde cholangio pancreatography (diagnostic purpose or allowing bile to drain). Many studies have indicated that cholecystectomy surgeries are not benign procedures, although it is one of the most common surgeries in the United States. Approximately 20-40% of patients developed post cholecystectomy syndrome (Yamada, 2013), and complications have been observed in almost 20% of laparoscopic cholecystectomies performed on older adults (Pérez et al., 2006). Many researchers have also been concerned about the causal relationship between cholecystectomy procedures and colon cancer occurrences (Schernhammer et al., 2003; Siddiqui et al., 2009). However, more knowledge of epidemiological characteristics of gallstone formation is greatly needed to better identify preventive strategies.

Cholecystectomies are one of the most frequent surgeries of the Veterans Health Administration (VHA) and symptomatic cholelithiasis is one of the criteria to define disability claims in the military. However, limited studies have been conducted to identify risk factors for cholelithiasis occurrence in the military veteran population. The prevalence of cholelithiasis has increased among patients in the Veterans Health Administration (VHA), especially among female veterans (VHA, 2014).

The female veteran population is projected to increase by 12% within the next five years while the male veteran population is projected to decrease by approximately 27% over the same period (Women Veteran Profile, 2013). Female veterans are serving prolonged military deployments with increasing numbers of women serving in combat. Given their service and sacrifice, the health care needs of female veterans are unique and should be appropriately addressed. There is a great demand to promote the health status of female veterans while decreasing the risks of cholelithiasis or cholecystectomy occurrence by identifying predisposing factors for gallbladder diseases.

Statement of the Purpose

The purpose of this study is to explore multidimensional predisposing factors that may be associated with developing cholelithiasis among military female veterans. The predisposing factors that were collected have been shown in the literature to be associated with cholelithiasis and cholecystectomies, included demographical data, occupational/environmental factors, serum laboratory tests, and comorbidities. The associations of these independent variables and the occurrence of cholelithiasis were examined.

Study Implications

A long-term goal of this proposed study was to identify preventive strategies to improve the health status of military female veterans and decrease their risk for comorbid conditions. The specific aims have been developed to accommodate the purpose of this study.

Specific Aims

In response to the purpose of this study, the following specific aims guided this dissertation study:

Aim 1. Determine the demographic and environmental characteristics of female military veterans with and without cholelithiasis.

Aim 2. Examine differences among metabolic, liver enzyme and serum lipid laboratory data in female military veterans with and without cholelithiasis.

Aim 3. Explore differences between diagnosed metabolic and biliary comorbidities experienced by female military veterans with and without cholelithiasis.

Aim 4. Explore associations among demographic, environmental, laboratory data and diagnosis of comorbid conditions among female military veterans with and without cholelithiasis.

Operational Definitions

The following terms and definitions are explained in relation to the current study.

Table 1. Terms and Definitions for this Study

Concept or Variable	Definitions
Cholelithiasis	Cholelithiasis is defined as patients who were diagnosed with gallstones using an ultrasound technology and these data were recorded in the VHA data using an International Classification of Diseases, Ninth Revision (ICD-9) code of cholelithiasis.
Symptomatic Cholelithiasis	Symptomatic cholelithiasis is defined as a condition when the patient claimed any pain or discomfort related to cholelithiasis, which, in turn, results in a cholecystectomy.
Female Veterans	Female veterans refer to women who have served on active duty in the US Army, Navy, Air Force, Marine Corps, or the Coast Guard but not currently serving on active duty. For this study, female veterans are those who have established veteran status and were approved for eligibility in using the US Veterans Health Administration (VHA).
The VHA Enrolled Female veterans	Military female veterans refers to women who were approved to receive medical benefits and have used services from the VHA, such as a routine check-up, emergency services, inpatient and outpatient care, pharmacy, radiology, and laboratory services. This study included

	female veterans who were seen in the VHA from January 1, 2008 to December 31, 2013.
The VINCI Data	The Veterans Affairs' (VA) Informatics and Computing Infrastructure (VINCI) was created to support research, clinical decision, and business benefits of the US Veterans Health Administration. The VINCI is an effective tool to facilitate researchers' access to the VHA data while ensuring veterans' privacy and confidentiality. The VINCI workspace is a secure, virtual environment that provides resources and tools necessary to conduct studies and analyze data. Additional data requests, data storage, backup, consulting service, statistic tools and data manage software are provided through the VINCI system.

Significance of the Study

Although a significant number of studies have attempted to uncover the risk factors for cholelithiasis and gallstone formation, they still remain unclear. Most studies have sought to identify the association between individual risk factors, such as lipids profile, diet, ethnicity, disease, and drugs, and the occurrence of cholelithiasis. Only a few studies use a multidimensional approach and take into account numerous risk factors related to the occurrence of cholelithiasis. Limited data demands the identification of multifactorial causes of gallstone formation based on military female veterans.

The contribution of this study was to identify predisposing factors of cholelithiasis in female veterans in an effort to identify preventive measures for the disease. Study outcomes may also provide nurses a greater understanding for cholelithiasis and also present guidance for patients diagnosed with gallstones. Using existing data decreases bias that participants might create, and grants a logical, systemic, and cost effective approach to identify the possible association with cholelithiasis among diversely located female veterans. The electronic medical record of the Veterans Health Administration (VHA) is linked with the VHA administrative data,

which is known to have a high level of data element completion and accuracy (Kashner, 1998; Singh, 2009). Moreover, the study data was retrieved from actual electronic medical records of the Veterans Health Administration system (VHA) and may reflect a subset of female veterans in the VHA system. Finally, this study included a nationwide random sample with diverse individuals' medical and surgical histories, thus decreasing selection biases.

Theoretical Framework

The theoretical framework for this study is adapted from Wittenburg and Lammert's (2007) Factors Contributing to Cholesterol Gallstone Susceptibility, which is well suited for understanding gallstone occurrence. The physiological model describes that gallstone formation is due to multifactorial influences. Gallstone disease is identified not by a single gene contribution but as a result of combining factors with the geographical and ethnic differences, a complex genetic predisposition, and their interaction with multiple environmental factors that determine the risk for developing gallstones. This physiological model supports the premise that gallstone formation is multifactorial. Associational factors should also be considered for cholelithiasis occurrence when multiple environmental risk factors surround the patients.

Assumptions

Although multiple logistic regressions do not make assumptions of normality, linearity, or homoscedasticity for the independent variables as linear regression does, the following assumptions may apply for logistic regression.

First, the dependent variable should maintain independence among the dependent variables. The current study met this assumption since the outcomes were dichotomous, 1) with cholelithiasis or 2) without cholelithiasis.

Second, the dependent variable should be classified using dummy coding that "1" is the probability of the event occurring and "0" is the probability of the event not occurring. The dependent variables in this study were coded that "1" with cholelithiasis and "0" without cholelithiasis.

Third, the model should be fitted correctly. The current study used a stepwise method to select only significant variables to maximize the productiveness of the model. Moreover, the Hosmer-Lemeshow test and Chi-square goodness of fit test in SPSS was used to measure how well the logistic model fit the study data.

Fourth, independent variables should be independent from each other. This study used stepwise regression method to demonstrate significant contributing factors associated with cholelithiasis occurrence in female veterans while accounting confounding effects of variables.

Finally, multiple logistic regressions require a larger sample size than linear regressions because maximum likelihood coefficients are less powerful than ordinary least squares in case the smaller sample sizes are used. The sample size should be at least 5-10 cases for each independent variable (Field, 2005). This study accepted over five samples for each independent variable.

Limitations and Delimitations

This study had several limitations:

Study Design

The major limitation of a case-control study is risk (incidence of cholelithiasis) cannot be established directly (Hogue, Gaylor, & Schulz, 1983). Relative risk can only be estimated and cannot be used to draw inferences about the causal relationships between and among the

variables (Hogue, Gaylor, & Schulz, 1983). Retrospective studies may be more apt to selection bias.

Systematic bias could be present if there was a systemic error in how subjects were selected as cases and controls. Systemic bias includes selection bias and information bias. First, increasing the sample size cannot reduce selection bias (Pannucci & Wilkins, 2010). Ideally, drawing homogenous samples should decrease selection bias. For this study, the sample of the study population was drawn from the same database in the Veterans Health Administration and the same population among military female veterans. The case and control groups were planned to be as comparable as possible in all aspects except having cholelithiasis or not.

Second, a possible inadvertent collection of erroneous data could contribute to information bias due to invalid or imprecise study measurement. Patient medical records could contain incomplete and/or inaccurate data depending on the record keeping practices of the medical institutions, resulting in ascertainment bias. However, for this study, the study groups were selected using an ICD code of cholelithiasis, ensuring that the diagnosis was confirmed with an ultrasound (sensitivity 0.97; 95% CI, 0.95–0.99, specificity 0.95; 95% CI, 0.88–1.00) (Shea et al., 1994), and recorded as a patient's diagnosis within the Veterans Health Administration system. Both groups met the inclusion/exclusion criteria to reduce potential misclassification and to maximize the validity of the study.

Finally, hospital-based bias could impact the analysis of potentially confounding variables. In other words, it was hard to determine whether the exposure and cholelithiasis occurrence may be associated with another disease. In this study, controls were selected randomly from existing data while meeting study eligibility. The collection period for clinical record was set from January 1 of 2008 to December 31 of 2013 to reduce the chance for

Berkson's bias. Recall bias, interview bias, and response bias were avoided because of using retrospective medical records based study plan.

Statistical Analyses

The major strengths of this study are the statistical power and statistical methods used. A case-control is a type of study that allows for relative ease of large sample recruitment (Pedhazur & Schmelkin, 1991; Stevens, 2002), and thereby providing sufficient power for the study. One potential limitation of the study was that it might be difficult to control for Type I error simultaneously with the utilization of a multiple unadjusted Odds Ratio. This may increase the rate of false positive findings. Multiple regression methods were used to address confounding and produce adjusted odds ratio.

Another potential limitation of multiple regression study is multicollinearity (Slinker & Glantz, 1985; Tu, Clerehugh, Gilthorpe, 2004) that might make it difficult to identify the change in the dependent variable precisely to one or the other of the independent variables, and may increase Type II errors. Matching the two groups was minimized in this study because investigation of risk factors could be hard if case and controls were matched on a causing factor. In addition, the correlation matrix and independent t-test were performed to check for multicollinearity by the correlation coefficient between two independent variables.

Data Source

A retrospective study involves the analysis of existing data that has been recorded for clinical reasons other than research (Hess, 2004; Tang, 1996). A limitation of retrospective study is that data is collected exclusively from past records and does not follow patients, as is the case with a prospective study. Errors due to confounding and bias are more common in retrospective studies than in prospective studies; however, the methodologies of prospective and retrospective

cohort studies are fundamentally the same. For this study, cases and controls were followed up in the ensuing time period and the starting point of this study was the same as for all cohort studies. For this study, a retrospective study is particularly beneficial to examine possible risk and protection variables in relation to a result that is already established at the start of the study.

Protection of Human Subjects

Study approval was sought from the Institutional Review Board of both the Veterans Health Administration (VHA) in Orlando, Florida and the University of North Dakota. The VHA research committee considered this study as "expedited" because no patient contact or identifiable patient information was required. The Institutional Review Board (IRB) of the Veterans Health Administration requested that the principal investigator obtain course certifications that involved the patients' privacy, confidentiality, and human protection in research to highlight the importance of human rights and human rights' protection in relation to the general research.

The IRB of the University of North Dakota considered this study as "exempted" due to the characteristics of a retrospective study with de-identifiable data use.

This study identified risk factors for cholelithiasis among female veterans. Therefore, the study population was limited only to female veterans who were enrolled with the Veterans Health Administration from January 1, 2008 to December 31, 2013. Males and children were excluded from the study consideration because they were not related to the study purpose. All data was de-identified and study data were monitored by the data security services in the Veterans Health Administration.

Summary

Cholelithiasis is one of the most common but costly digestive diseases affecting 10-15% of the adult population in the United States (Barbara et al., 1987). Women are at greater risk. The Veterans Health Administration data also showed a similar phenomenon of higher cholecystectomy procedure rates in military female veterans in comparison to male veterans. Studies focusing on this vulnerable population and the association with cholelithiasis were not identified in the literature. Therefore, the purpose of this study was to examine physiological and environmental predisposing factors that may be associated with the occurrence of cholelithiasis and cholecystectomy. Information based upon the study outcomes can be used to assist nurses who provide resources, and education for patients diagnosed with gallstones. Additionally, the findings can be used to promote the health status of female veterans while decreasing the risks of cholelithiasis or cholecystectomy occurrence by identifying predisposing factors for gallstone disease.

CHAPTER II

REVIEW OF LITERATURE

The overall objective of this study was to identify possible physiological and environmental risk factors associated with occurrence of cholelithiasis among U.S. military female veterans. Chapter II presents a review of the literature discussing predisposing factors of cholelithiasis occurrence for the current study. This study planned to examine the following study aims:

1) Determine the demographic and environmental characteristics of female military veterans with and without cholelithiasis.
2) Examine differences among metabolic, liver enzyme and serum lipid laboratory data in female military veterans with and without cholelithiasis.
3) Explore differences between diagnosed metabolic and biliary comorbidities experienced by female military veterans with and without cholelithiasis.
4) Explore associations among demographic, environmental, laboratory data and diagnosis of comorbid conditions among female military veterans with and without cholelithiasis.

Literature reviewed in this chapter was accessed via online databases including PubMed, CINAHL, Cochrane, SCOPUS, Academic Search Premier and print editions of peer-reviewed research-based journals. Key search terms used were cholelithiasis (or gallstones) and risk factors (age, gender, ethnicity, diet, obesity, cholesterol, comorbidities, posttraumatic stress

disorder, liver enzymes, etc.) and female veterans and women.

Gallstone disease, cholelithiasis, affects over 6 million men and 14 million women (Everhart, Khare, Hill, & Maurer, 1999) in the United States (Schirmer, Winters & Edlich, 2005; Shaffer, 2005; Tazuma, 2006). It has been recognized as the second most common gastrointestinal discharge diagnosis in U.S. hospitalizations (Peery et al., 2012). Further, there are almost 3,000 gallbladder related deaths reported in the U.S. annually (Everhart & Ruhl, 2009; NIH, 2005). Although cholelithiasis has been one of the most common and costly gastrointestinal disorders, the causes and effects in association with gallstone diseases are not completely understood (Sanders & Kingsnorth, 2007).

The literature review in this chapter includes several topics as background for the current study. Topics included are physiology and characteristics of cholelithiasis, risk factors for gallstone disease, and causes and effects of health with gallstone disease. The section of risk factors is divided into demographic, environmental, pathophysiologic, and comorbidities risk factors. Additionally, the gaps in the literature are identified and discussed following each risk factor. The theoretical framework by Wittenburg and Lammert (2007), "*Factors Contributing to Cholesterol Gallstone Susceptibility*" is explained because this physiological framework was used to guide this study.

The Physiology and Characteristics of Cholelithiasis

Cholelithiasis is stones formed in the gallbladder (Venes, 2013). Although the majority of gallstones are asymptomatic, up to 25% of gallstones cause symptomatic symptoms or severe complications (Freedman, 1993; Halldestam et al., 2004) that include sudden, severe right upper quadrant pain, nausea, vomiting, infection, perforation, or gangrene (Gracie & Ransohoff, 1982). The most common ways to manage symptomatic gallstone diseases are known to be

cholecystectomy and endoscopic or medical treatment of complications. Gallstone size can range from < 1 mm to > 3cm in size (Lowenfels, Walker, Althaus, Townsend, & Domellof, 1989). Depending on the components of the stone, gallstones can be characterized as cholesterol gallstones, brown-colored gallstones, and black pigment gallstones. This study focuses on cholesterol gallstones because it is the most common type in the U.S. The other types of gallstones are most likely related to certain ethnic groups and underlying comorbidities (Sherlock & Dooley, 2002; Vitek & Carey, 2003; Kodaka, Sono, Nakagawa, Kakino, & Mori, 2004).

Risk Factors for Gallstone Disease

Gallstone formation is a complex interaction of genetic, environmental, metabolic, and related conditions. Traditionally, the four "F's"—female, fat, forty and fertile—are considered as risk factors for gallstone diseases (Sherlock, 1963). Being overweight, a sedentary lifestyle, and processed food are contributing factors for cholesterol gallstones (Shaffer, 2006; Tsai et al., 2004a). Cholesterol gallstones have found to be influenced by predisposing factors including female gender, advanced age, ethnicity, a Westernized diet, obesity (Di Ciaula, Wang, Wang, Leonilde & Portincasa, 2010), and certain comorbidities (Andreotti et al., 2008; Atamanalp et al., 2013; Carey & Paigen, 2002; Di Ciaula et al., 2010; Portincasa, Moschetta, & Palasciano, 2006; Venneman & Van Erpecum, 2010). Causes of risk factors have not been completely established although cholelithiasis is one of the most common and costly gastrointestinal disorders to treat (Sanders & Kingsnorth, 2007).

Demographic Risk Factors

Age and gallstones. The prevalence of gallstones increases with age in all racial and ethnic groups. Studies show people age 40 years and older are ten times more likely to develop gallstones (Chen et al., 1998, Einarsson, Nilsell, Leijd, & Angelin, 1985; Festi et al., 2008;

Shaffer, 2005; Volzke et al., 2005). The declined activity of the limiting enzyme, 7α-hydroxylase, is a contributing factor as the aging individual experiences cholesterol saturation and decreasing mobility of the gallbladder emptying (Carulli et al., 1980; Salen, Nicolau, Shefer & Mosbach, 1975). Female veterans over 40 years of age consist of approximately 60% of the entire female veteran population with a median age of female veterans of 49 (Women Veteran Profile, 2013). Thus, the sample for the dissertation study composed of female veterans over 40 years of age.

Gender and gallstones. Women have a higher risk of cholelithiasis than men at all ages (Everhart et al., 1999; Everhart et al., 2002; Racine et al., 2013; Singh, Trikha, Nain, Singh & Bose, 2001). This may be attributed to the fact that female sex hormones, specifically estrogen, may account for gender difference in gallstone formation (Attili et al., 1997; Cirillo et al., 2005). Many studies have demonstrated women having a greater chance of developing gallstones and also of undergoing cholecystectomy procedures in comparison to men of all age groups (Chen et al., 1998; Everhart et al., 1999; Everhart et al., 2002; Racine et al., 2013; Singh, Trikha, Nain, Singh & Bose, 2001).

Estrogen appears to play a role for the gender difference in gallstone formations (Attili et al., 1997; Cirillo et al., 2005). Yet, only a few epidemiologic studies have contributed to findings related to gender, with most of these findings focused on the variation of the female hormone, estrogen (Cirillo et al., 2005; Hulley et al., 1998). The same phenomenon has been observed among patients in the Veterans Health Administration (VHA), especially among female veterans (VHA, 2014). Although female veterans who enrolled in the Veterans Health Administration (VHA) only consist of approximately 6% (514,500) of the total VHA patient population (8,574,198) in 2011 (VetPro 2011), they accounted for 14% (2,677) of all cholecystectomy

procedures (19,801) in the same year. This trend has been observed throughout the current decade (VHA 2014). This study comprises a nationwide random sample of ethnically diverse female veterans with possible physiologic, environmental, and occupational risk factors.

Ethnicity and gallstones. The risk of gallstone diseases differs by race. Cholelithiasis prevalence has been found to be significantly higher in American Pima Indians, especially in the female population (Sampliner et al., 1970). A later study reported 46.3% of American Indian women underwent a cholecystectomy at some point in their lives (Everhart et al., 2002). Some studies found a higher prevalence rate for cholelithiasis in Chile (Covarrubias, Valdivieso, & Nervi, 1984) and in the Mexican-American population (Hanis et al., 1993; Maurer et al., 1989). Other studies also observed certain indigenous populations, particularly in South America and Northern India, have a higher incidence of gallstone disease and gallbladder cancer (Dutta et al., 2005; Hundal & Shaffer, 2014; Misra, Chaturvedi, Misra & Sharma, 2003; Zatonski et al., 1997).

Body weight and gallstones. Obesity is an established contributing factor for gallstone formation. Studies have related high body mass index (BMI) to gallstone diseases (Katsika, Tuvblad, Einarsson, Lichtensten, & Marschall, 2007; Portincasa et al., 2006; Stender, Nordestgaard & Tybjaerg-Hansen, 2013; Volzke et al., 2005). Obese persons have a high ratio of cholesterol to solubilizing lipids (bile acids and phospholipids) (Grundy, Duane, Adler, Aron, & Metzger, 1974; Grundy, Metzger, & Adler, 1972). The high ratio predisposes to crystallization of cholesterol and gallstone formation. In many cases, the amounts of cholesterol entering the bile exceed the solubilizing capacity of the bile acids and phospholipids in the obese population (Bennion & Grundy, 1975). Longitudinal studies reported a significant association between abdominal adiposity and the incidence of symptomatic gallstone disease (Attili et al., 1997; Everhart et al., 1999; Tsai et al., 2004a). Another longitudinal study based on the Nurses' Health

Survey supported participants with higher BMI have higher likelihood to undergo cholecystectomy surgeries (Stampfer et al., 1992). Morbidly obese women (BMI ≥45 kg/m^2) were seven times more likely to have symptomatic gallstones compared to leaner women (BMI ≥30 kg/m^2) (Stampfer et al., 1992).

Environmental Risk Factors

Alcohol use and gallstones. An association between alcohol consumption and gallstone diseases is controversial. Some studies found that moderate alcohol intake lowers gallstone development (Leitzmann et al., 2003; Volzke et al., 2005) due to the mechanism by diminishing bile cholesterol saturation and enhancing HDL-cholesterol levels (Pixley & Mann, 1988). However, other studies have failed to find the same association (Kratzer et al., 1997; Walcher et al., 2010).

Tobacco use and gallstones. Studies examining the association between smoking habits and gallstone formation are also questionable. Studies have found that women who smoked heavily (more than 35 cigarettes per day) had a high prevalence rate for asymptomatic cholelithiasis as well as symptomatic cholelithiasis (Murray, Logan, Hannaford, & Kay, 1994; Stampfer et al., 1992). Other studies have failed to find such a relationship between tobacco use and gallstone development (Katsika et al., 2007; Shaffer, 2006; Walcher et al., 2010). Park et al. (2011) reported that male veterans were more likely to be heavy alcohol drinkers and smokers compared to non-veterans, therefore examining these factors in relation to the cholelithiasis occurrence among female veterans would provide a unique understanding of this study population.

Pathophysiologic Risk Factors

Metabolic factors and gallstones. "Westernized nutrition" (Paigen & Carey, 2002; Tsai, Leitzmann, Willett & Giovannucci, 2008) is a well-known risk factor for gallstone formation (Tsai et al., 2004b; Tsai, Leitzmann, Willett & Giovannucci, 2005b; Tsunoda, Shirai, & Hatakeyama, 2004). Results of other studies have shown a positive relationship between gallstone disease and dietary risk factors such as high calorie consumption (Tsunoda et al., 2004), increased dietary glycemic load (Tsai, Leitzmann, Willett, & Giovannucci, 2005a; Tsai, Leitzmann, Willett, & Glovannucci, 2005b), refined sugar intakes (Alessandrini, Fusco, Gatti, & Rossi, 1982; Misciagna et al., 1999; Moerman, Smeets, & Kromhout, 1994; Scragg, McMichael, & Baghurt, 1984), and chronic hyper-nutrition (Al-Azzawi et al., 2007; Biddinger et al., 2008). However, some studies show cholesterol gallstone formation associated with dietary factors still remain controversial (Andreotti et al., 2008; Halldestam, Kullman & Borch, 2009).

Although numerous study authors have focused their work on how dietary factors are directly related to the increased prevalence of gallstones (Stinton, Myers, & Shaffer, 2010), the actual importance of one's dietary content is unclear and difficult to analyze (Mendez-Sanchez, Zamora-Valdes, Chavez-Tapia, & Uribe, 2007; Tseng, Everhart, & Sandler, 1999). Using the advantage of retrospective data, this study examined the relationship between the occurrence of gallstone disease and biochemical laboratory values, such as fasting glucose, hemoglobin A1C, liver enzymes and lipids profile tests. The serum laboratory tests provided the individuals' indirect diet patterns and made it possible to measure in a more objective way.

Lipids profile and gallstones. A major component of gallstones is cholesterol. The proportion of cholesterol is even more dominant in cholesterol gallstones (Caturelli & Buscarini,

1994). Although numerous studies have tried to identify the relationship between serum laboratory levels of cholesterol and gallstones, the outcomes are still not clear.

Many studies have reported a significant relationship between high serum cholesterol levels and an increased risk for cholelithiasis development (Andreotti, Chen et al., 2008; Atamanalp, Keles, Atamanalp, Acemoglu, & Laloglu, 2013; Khairy, Guraya, & Murshid, 2004; Venneman & Van Erpecum, 2010). Yet, some studies have shown an inverse relationship between serum cholesterol levels and gallstone occurrence (Thijs et al. 1990). Further, studies have reported a relationship between serum Low Density Lipoprotein (LDL) levels and an increased risk for cholesterol gallstone diseases (Fu, Gong, & Shao, 1995; Fu et al., 1997; Han, Jiang, Suo, & Zhang, 2000). Although, other studies did not find the same significant relationship between serum LDL levels and gallstone risk (Andreotti et al., 2008; Tang, 1996).

Correlations have been found between serum High-Density Lipoprotein (HDL) levels and gallstone diseases (Andreotti et al., 2008; Fu et al., 1995; Fu et al., 1997; Halldestam, 2009; Tang, 1996; Thijs et al., 1990). Some studies have reported low HDL levels were highly associated with gallstone risks (Andreotti et al., 2008; Fu et al., 1995) while other studies failed to find the same significant relationship (Fu et al., 1997; Halldestam, 2009; Tang, 1996; Thijs et al., 1990).

Cholesterol gallstone formation is a complex process (Belousou, 2006; Temel & Brown, 2010; Conte, Fraquelli, Giunta, & Conti, 2011). For example, correlations between serum lipids levels and gallstone disease may not have a simple answer. Therefore, a multidimensional approach may be necessary to investigate how serum lipids levels are associated with other environmental factors for developing gallstone formation (Wittenburg & Lammert, 2007).

A study showed that veterans with posttraumatic stress disorder (PTSD) had elevated lipids levels (David, Woodward, Esquenazi, & Mellman, 2004) and women in the general population were twice as likely as men to develop posttraumatic stress disorder (Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Kessler et al., 2005). However, data for the female population in relation to lipid levels and risks for cholelithiasis are very limited.

Comorbidities and Risk Factors

Metabolic comorbidities and gallstones. Metabolic syndrome is a cluster condition that occurs as a combination of high blood pressure, dyslipidemia, abdominal obesity and diabetes. Many studies have identified a positive relationship between metabolic syndrome and gallstone disease (Ahmed et al., 2014; Tsai et al., 2008; Volzke et al., 2005). Metabolic syndromes rates have been observed in societies where "westernized nutrition" prevails. Dietary constituents have also been causally linked to metabolic syndromes (Abete, Astrup. Martinez, Thorsdottir, & Zulet, 2010). It is believed dietary factors are associated with metabolic syndromes with a higher gallstone development rate (Al-Azzawi, Mathur, Swartz-Basile, Nakeeb, & Pitt, 2007; Ruhl & Everhart, 2000).

Because of the clustered characteristics of the syndrome, metabolic syndrome has not been easily diagnosed and it just recently started to be recorded in the Veterans Health Administration data, using International Classification of Diseases (ICD)-10 code. Therefore, this study was not able to retrieve data on female veterans who were diagnosed with metabolic syndrome; however, individual components of the syndromes, such as hypertension, diabetes, dyslipidemia, and obesity were all included.

Biliary comorbidities and gallstones. Chronic hepatitis C virus may be associated with gallstone diseases (Acalovschi, Buzas, & Grigorescu, 2009; Bini & McGready, 2005; Stroffolini,

Sagnelli, Mele, Cottone & Almasic, 2007). Bini and McGready (2005) found male participants who had chronic hepatitis C virus (HCV) infection had higher incidence rate of gallstone diseases. Subsequent studies found a positive relationship between HCV virus and symptomatic cholelithiasis in both the male and female population (Acalovschi, Buzas, & Grigorescu, 2009; Cottone & Almasic, 2007; Stroffolini, Sagnelli, Mele, Cottone & Almasic, 2007). A randomized study also described a close relationship between HCV infection, insulin resistance, and cholesterol gallstones (Acalovschi, Buzas, & Grigorescu, 2009).

Liver cirrhosis and Crohn's disease are also reported to be risk factors for gallstone diseases. Studies have shown these diseases are especially associated with black pigment stones (Lammert & Miquel, 2008; Lapidus, Akerlund, & Elnarsson, 2006; Stinton, Myers, & Shaffer, 2010). It has been found that 25-30% of black-pigmented stones can be attributed to slower gallbladder motility, decreased bile salt absorption, and impairment of bile salt synthesis (Buzas, Chira, Mocan & Acalovschi, 2011; Vitek & Carey, 2003). Padda et al. (2009) reported there were frequent abnormal patterns in liver enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin among patients with symptomatic cholelithiasis. However, the association between those liver enzymes and cholelithiasis development has not been fully identified. This study examined the possible risk factors of liver enzymes that include aspartate aminotransferase, alanine aminotransferase and total bilirubin and their association with cholelithiasis within the study population.

PTSD and gallstones. Posttraumatic stress disorder (PTSD) has been found to be significantly associated with both post deployment physical and chronic mental health disorders (Wachen, 2013; Vogt, Proctor, King, & Vasterling, 2008) among the military population. Female veterans comprise a growing population with high levels of trauma (Zinzow, Grubaugh,

Monnier, Suffoletta-Maierle, & Frueh, 2007), and consequently a high prevalence of PTSD. The PTSD rate is higher for women in civilian accidents and for women who witness death or injury versus men in identical scenarios (Olff, Langeland, Draijer, & Gersons, 2007). While conditions such as PTSD are known to adversely affect quality of life, little is known about the consequential effect on disease occurrence.

A recent report from the Institute of Medicine noted there was sufficient evidence to argue for an association between Gulf War deployment and gastrointestinal disorders, such as irritable bowel syndrome and functional dyspepsia in military personnel (National Research Council, 2010). Few studies have addressed how military trauma or service-connected disabilities are associated with gastrointestinal disorders, although cholelithiasis serves as a military disability criterion. A consequence of developing symptomatic cholelithiasis for military service members can be military disability status. The relationship between gastrointestinal disorders and PTSD in female veterans is notably limited. Thus, this study included the patients' PTSD and disability status in order to determine if occupational risks for cholelithiasis occurrences exists among the female military veteran population.

Military sexual trauma (MST) has been reported to contributes a wide range of negative health outcome that includes anxiety symptoms, increased illicit drug use, and difficulties transitioning home after deployment (Decker et al., 2013; Kimerling et al., 2007; Sadler et al., 2000; Skinner et al., 2000; Stein & Barrett-Connor, 2000). Another study also reported MST contributes to the negative effects on mental and cognitive functioning, and eventually impacts quality of life (Kimerling et al., 2007). However, no study demonstrates MST is associated with an increased risk for gallstone formation. Therefore, this study included the female veterans'

diagnosed MST to determine if MST is an independent risk factor for cholelithiasis occurrence in female veterans.

Causes and Effects of Health with Gallstone Disease

Studies report symptomatic gallstones not only combine ongoing biliary pain but are also attributable to more complicated problems, such as disruption of the gallbladder wall, perforation, or even a rupture of the gallbladder (Gupta & Shukla, 2004). Studies have found a correlation between cholelithiasis and gastrointestinal and pancreatic cancers (Anderson, Potter, & Mack, 1996; Sanders & Kingsnorth, 2007; Schernhammer et al., 2003; Siddiqui et al., 2009). Studies have also found that the overall mortality rates are increased with cholecystectomy surgeries. Although a cholecystectomy is considered one of the most common surgeries in the United States, it is not a benign procedure. Scientific studies have indicated gallbladder surgeries have a high association with gastrointestinal cancers. The studies found significant numbers of patients developed esophageal and colon tumors following cholecystectomy surgeries (Freedman, Ye, Naslund & Lagergren, 2001; Goldacre, Abisgold, Seagroatt & Yeates, 2005; Lagergren, Ye, & Ekbom, 2001; Nogueira et al., 2014; Schernhammer et al., 2003; Shao & Yang, 2005; Siddiqui et al., 2009). Yet other studies have not found a significant relationship between the incidences of tumors resulting from cholecystectomy surgeries (Mercer, Reid, Harrison & Bates, 1995; Reid, Mercer, Harrison & Blates, 1996). In addition, some studies were concerned with the complications of laparoscopic cholecystectomies that were often associated with infection, bleeding, biliary leakage, postoperative complication, anesthesia related complication and possible repeat surgery (Pérez et al., 2006; Pottakkat et al., 2010; Waage & Nilsson, 2006).

Theoretical Framework

With the rising prevalence of cholelithiasis, attention is being increasingly focused on identifying the risk factors associated with cholelithiasis occurrence. An emphasis on identification of principle risk factors facilitates a greater understanding of the pathophysiology of gallstone formation. Wittenburg and Lammert's (2007) Factors Contributing to Cholesterol Gallstone Susceptibility were the primary concepts used herein. The theory's major concepts are defined and the major linkages are identified in the following section.

General Description

The fundamental belief of Wittenburg and Lammert's physiological model is that gallstone formation is due to multifactorial influences. The Wittenburg and Lammert's model indicated, there is a rare chance to develop gallstones based only a single gene. In most cases, gallstones develop as a result of interaction among genetic factors, geographical and ethnic differences, and environmental factors. This indicates that gallstone formation occurs by the interaction among complex genetic predispositions and multiple environmental factors (Wittenburg & Lammert, 2007).

For example, Mexican and American Indian ethnic groups were detected as having human leukocyte antigen allele characteristics that were closely related to gallstone prevalence. Although this was a predisposing factor of a gene, the disease became endemic only with severe environmental changes that occurred after abandoning their traditional lifestyle and adapting a western-type diet. It showed that the genetic variation of the American Indian that increased the ability to store fat was beneficial in times of poverty, but it became detrimental following environmental changes that increased susceptibilities to weight gain, diabetes, and gallstone formation (Wittenburg & Lammert, 2007).

In addition to geographical variation and ethnic differences in gallstone prevalence rates, genetic predisposition was highly associated with gallstone occurrences (Covarrubias, Valdivieso & Nervi, 1984; Hanis et al., 1993; Maurer et al., 1989). Studies reported individuals with family history of gallstones had a two to five-fold increased risk for cholelithiasis among first-degree relatives of a gallstone carrier (Attili et al., 1997; Barbara et al., 1987). These rates were even higher in monozygotic twins at 12% and dizygotic twins at 6% (Gilat, Feldman, Halpern, Dan, & Bar-Meir, 1983; Sarin, Negi, Dewan, Sasan, & Saraya, 1995).

The inflammatory response in chronic liver diseases reduced the capacity of the liver to produce glucuronidate bilirubin. This is the process in which the liver makes bilirubin water-soluble so it can be excreted into the small intestine and be eliminated in stools. Biliary secretion of bile salts is impaired and results in the increased formation of bilirubin gallstones in liver cirrhosis (Conte et al., 1999). In this case, the additional influence of environmental factors to the gallstone risk appears to be somewhat small (Conte et al., 1993). Cholelithiasis is positively associated with the severity of liver disease but not contributed by the cause of cirrhosis (Conte et al., 1999; Conte et al., 1993).

The factors contributing to cholesterol gallstone susceptibility are presented in a diagram (Figure 1). The individual contributing factors do not increase gallstone susceptibility but lead to gallstone development by interacting with each other, as indicated by the arrowheads pointing in both directions.

The above illustrated physiological model, entitled Factors Contributing to Cholesterol Gallstone Susceptibility, guided this study examining gallstone formation as a multifactorial phenomenon. Multiple environmental risk factors that surround patients should be examined in

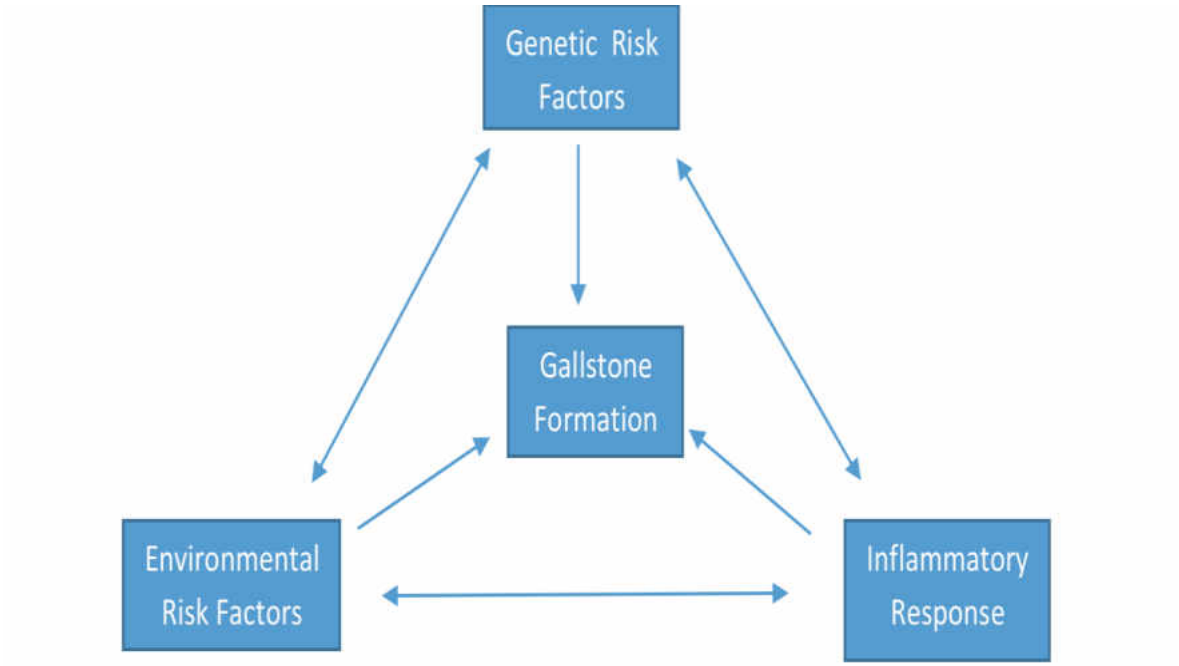

Figure 1. Factors contributing to cholesterol gallstone susceptibility. (Wittenburg & Lammert, 2007)

order to identify the associational factors of cholelithiasis occurrence. Also, geographical variation and ethnic differences should be included in the consideration of identifying predisposing factors associated with gallstone diseases. The application of the physiological model to the current study is explained in Figure 2. This current study consisted of independent variables that are presented in Figure 2, which identifies the relationship between the independent variables and cholelithiasis occurrence among female veterans.

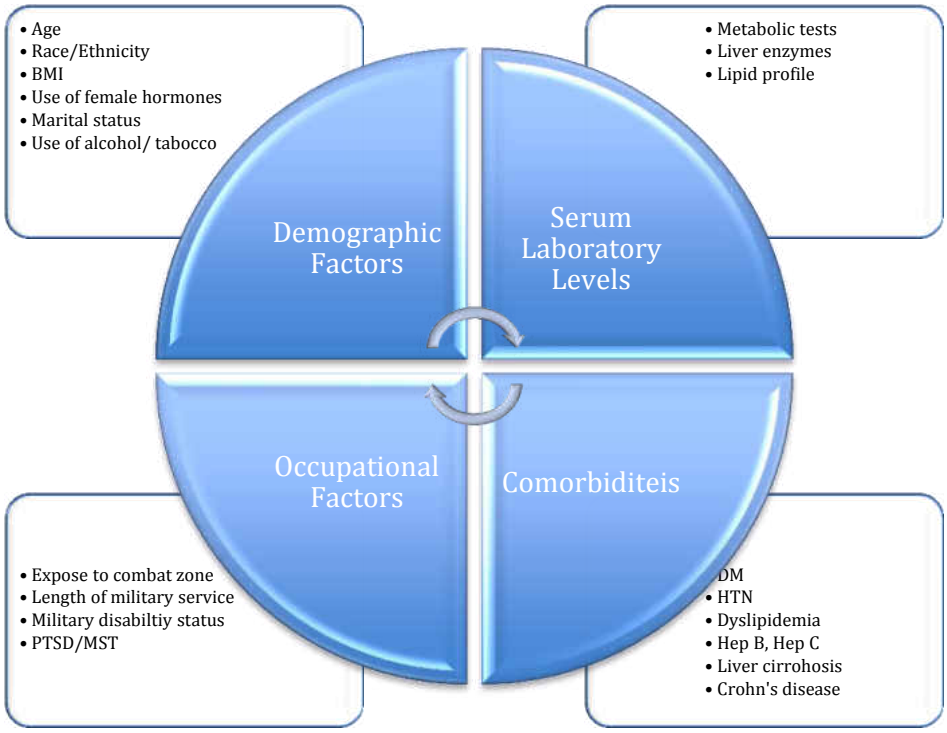

Figure 2. Wittenburg & Lammert's (2007) Factors contributing to cholesterol gallstone susceptibility adapted by Pak (2015). Acronym for diabetes (DM), hypertension (HTN), hepatitis B (Hep B), hepatitis C (Hep C).

Summary

Cholelithiasis is one of the costliest digestive disorders to treat in the United States (American Gastroenterological Association, 2001). Preventive control is a crucial key for reducing chronic cholelithiasis complications. Studies have shown advanced age, female gender, and certain ethnicities are considered to be non-modifiable factors, while serum cholesterols, body weights, and co-existing diseases appears to be modifiable factors for preventing gallstone risks.

Although extensive research literature has tried to identify the risk factors for

cholelithiasis, answers still remain unclear. Studies with a multidimensional approach should be employed to examine populations with cholelithiasis. Further, limited data demands the identification of multifactorial association of gallstone formation in the fast growing population of military female veterans.

The physiological framework of the contributing factors for cholesterol gallstones proposed a significant relationship between multifactorial risk factors and cholelithiasis occurrence. Therefore, cholelithiasis should be understood as a result of combining factors with the geographical and ethnic differences, the associations among multiple environmental factors and the risk for developing gallstones in female veterans were evaluated in this study.

CHAPTER III

METHODOLOGY

This chapter describes the design and research methodology that was used to examine possible relationships between risk factors and the occurrence of cholelithiasis among female veterans. This chapter includes research design, sample and settings, data collection, plan for analysis, data analysis and management, and summary of the study. Data analyses are discussed separately for each of the specific aims.

The overall aims examined in this study are as follows:

1) Determine the demographic and environmental characteristics of female military veterans with and without cholelithiasis.
2) Examine differences among metabolic, liver enzyme and serum lipid laboratory data in female military veterans with and without cholelithiasis.
3) Explore differences between diagnosed metabolic and biliary comorbidities experienced by female military veterans with and without cholelithiasis.
4) Explore associations among demographic, environmental, laboratory data and diagnosis of comorbid conditions among female military veterans with and without cholelithiasis.

Study Design

The study design is a retrospective case control study in which the characteristics of female veterans with and without cholelithiasis were compared and analyzed. A case-control

study design allows for relative ease of large sample recruitment (Pedhazur & Schmelkin, 1991; Stevens, 2002). A retrospective approach contains several benefits including: a) a relatively inexpensive ability to research the readily accessible existing data; b) easier access to conditions where there is a long latency between exposure and disease allowing for the study of rare occurrences; and c) the generation of hypotheses that then could be tested prospectively (Hess, 2004). The retrospective case control study also allows for examination of multiple risk factors associated with the development of cholelithiasis among geographically diverse female veterans with a nationwide random collection of data.

According to the literature, multidimensional risk factors may contribute to cholelithiasis occurrence (Heaton, Braddon, Mountford, Hughes & Emmett, 1991; Wittenburg & Lammert, 2007). Research that aims to identify risk factors for the outcome of the disease should also consider multiple covariates as potential contributors associated with the outcome. For this study, Wittenburg and Lammert's (2007) *Factors Contributing to Cholesterol Gallstone Susceptibility* was used as the theoretical framework. Wittenburg and Lammert conceptualized cholelithiasis as a multifactorial phenomenon resulting from an interaction with multiple predisposing factors. Multiple regressions were planned to explore multiple predisposing risk factors that lead to cholelithiasis development.

Sample and Setting

Eligible female veterans who were over 40 years of age and enrolled in the Veterans Healthcare Administration (VHA) system from January 1, 2008 to December 31, 2013 were considered for inclusion in this study. Only those who had all required information, including demographics, laboratory, medication records, problem lists, and administrative records were included for either the case or control groups. The sample size was determined using calculations

by the G* power 3 software program (Faul, Erdfelder, Lang, & Buchner, 2007). Data constituting a subset of 242 female veterans who were diagnosed with cholelithiasis during the study period were randomly selected to be compared to an equivalent number of controls selected from the pool of patient who had no diagnosis or history of cholecystectomy. The sample size of 484 for two groups was sufficient to meet a statistical power of 80%, and an alpha of 0.05. Therefore, a sample size of 242 subjects in each of the case and control groups was determined to be sufficient to obtain statistical significance.

Inclusion/Exclusion criteria for selection of sample data included:

1) Female veterans who were enrolled in the Veterans Health Administration (VHA) from January 1, 2008 to December 31, 2013 and were over 40 years of age.
2) Female veterans who were seen and had at least one or more of serum laboratory test results during the study period were included.
3) Only female veterans who were diagnosed with cholelithiasis (using ICD-9 Electronic diagnosis designation and recorded as such by the VHA system) during the study period were selected for the case group.
4) Samples were assigned to the control group if they met criteria 1) and 2) they did not have medical or surgical documentation of cholelithiasis or a cholecystectomy during the study period.

Exclusion Criteria

1) Female veterans who had not had medical care by the VHA system between the dates of January 1, 2008 to December 31, 2013 were excluded.
2) Female veterans who were 40 years of age or younger at the time of diagnosis of cholelithiasis or other diagnosis (control) were excluded.

3) Female veterans with no laboratory results during the study time were excluded.

This retrospective case control study examined the relationship among multiple risk factors and cholelithiasis occurrence. The multiple risk factors were considered as independent variables while the occurrence of cholelithiasis was considered as a dependent variable. The independent variables were selected to be studied based upon evidence in the literature of factors associated with cholelithiasis occurrence. The independent study variables included demographic data (age, race, Body Mass Index (BMI), marital status) and environmental factors (length of military service, percentage of military disability, exposure to combat zones, use of alcohol and tobacco, and use of female hormones), metabolic laboratory tests (fasting glucose, hemoglobin A1C), liver enzymes (bilirubin, alanine transaminase (ALT), aspartate aminotransferase (AST)), serum lipid profile (total cholesterol, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), triglycerides), and the diagnosed of comorbidities (diabetes, hypertension, dyslipidemia, hepatitis B, hepatitis C, liver cirrhosis, Crohn's disease, posttraumatic stress disorder (PTSD) and military sexual trauma (MST)). The dependent variable was determined by two groups, female veterans with (case) and without cholelithiasis (control).

Data Collection

This retrospective study was conducted, using a proprietary research database system called the Veteran Affairs Informatics and Computing Infrastructure (VINCI). The VINCI is a nationalized Veterans Health Administration infrastructure system that was developed to improve researchers' access to the VHA data while securing the privacy and data security of the military veteran. Each individualized VINCI virtual setting was named by the principal investigator's last name combined with the study request number. Only the principal investigator

and the principal investigator's appointed personnel, a computer engineer, a data manager, and a data counselor for this study, were allowed to access the data through the VINCI system.

The Veterans Health Administration (VHA) is known to have one of the largest repositories of electronically collected administrative and national healthcare data (Fihn et al., 2013). The VHA's database allows a unique opportunity to study a large segment of the population (military women who have previously served their country) with various age ranges, comorbidities, and clinical epidemiology.

After obtaining the approval from the Institutional Review Boards (IRB) of both at the Veteran Health Administration in Orlando, Florida and the University of North Dakota, the protocol for this study was reviewed by the VHA's National Security Data Service, privacy protection service, and the Veterans Affairs Informatics and Computing Infrastructure (VINCI). Once IRB approvals were obtained from the university and the four VHA agencies, a designated VINCI data manger retrieved a dataset per the principal investigator's inclusion/exclusion criteria, and stored the study cohort in a virtual setting in the VINCI by Structured Query Language (SQL) Server Management System. The International Classification of Diseases 9th Revision (ICD-9) diagnosis codes were used when accessing the VHA data to identify populations of female veterans with cholelithiasis (ICD-9: 574) and with ones who had a history of cholecystectomy (ICD-9: 51.2).

Data samples from 242 military veteran women with and without cholelithiasis were randomly pulled through the VINCI system. The samples were retrieved for these patients who received health care between the dates of January 1, 2008 to December 31, 2013 using a systematic random sampling (LaerdDisseration, 2012). In accessing the VHA data, tables were linked together using a unique numeric identifier in columns. No actual patient identification was

used but national integration control numbers and scrambled social security numbers made it possible to identify the patients.

The samples representing both groups met inclusion criteria (See Figure 3). Data was entered into a Microsoft Excel spreadsheet and numerically coded. The same data was entered twice and compared as a means of minimizing any possible data entry errors. The information was stored in a secure and password-protected server. The detailed process of the sample collection is displayed in Table 1.

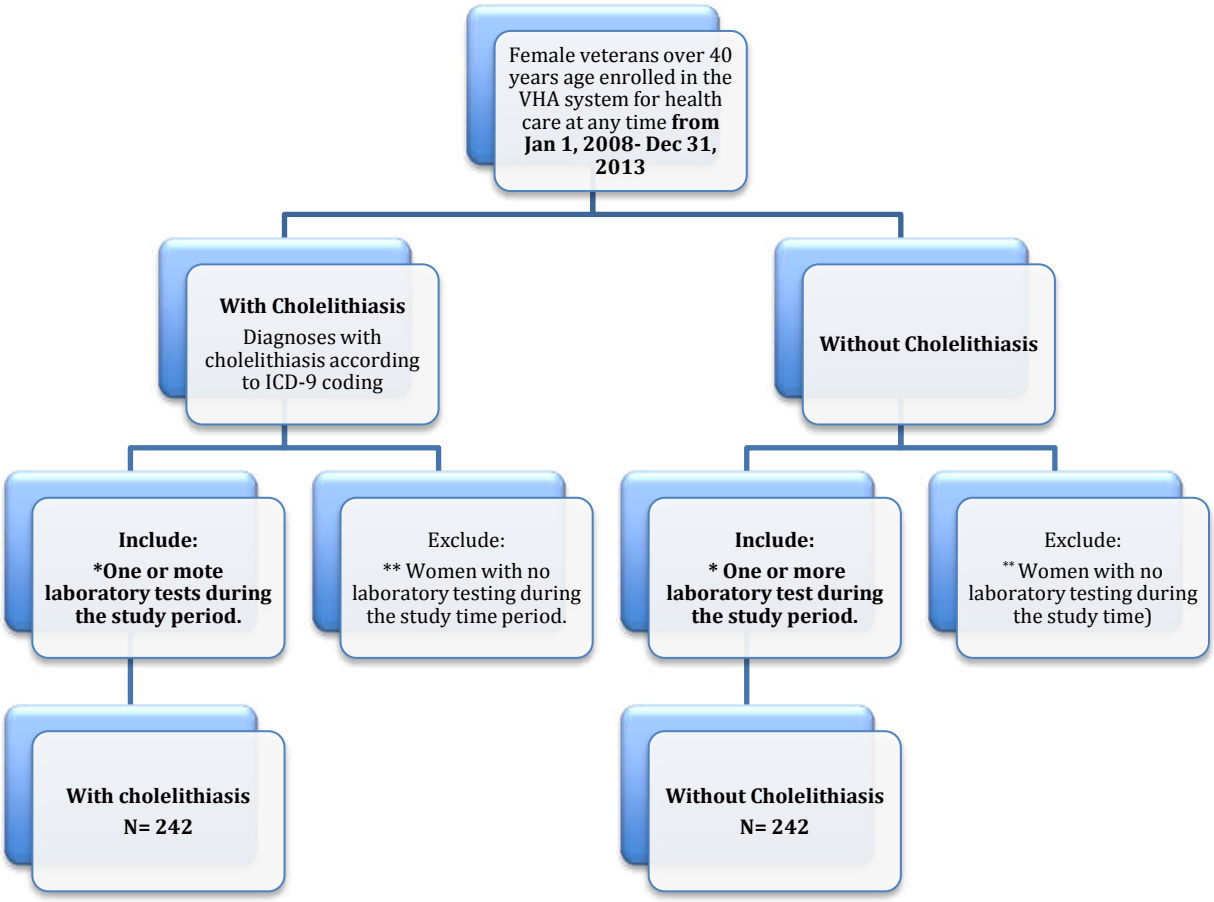

Figure 3. Selection criteria.
Note. *Sufficient data was considered to have at least one or more updated laboratory test results during the study period. Patients' health conditions are updated when test results are reported in the VHA system. * * Insufficient data was considered if no updated laboratory test result were found during the study period.

Table 2. The Process of Scripts for the Sample (Cholelithiasis Group) Data Collection.

Step		Comments
1	Establish base set	Merged the cohort tables, which contain all patients who were seen from January 1, 2008 to December 31, 2013.
2	Identify and remove duplicates from base set	Duplicate data was filtered out using female veterans' unique VHA number associated with scrambled social security number.
3	Add age and exclude those were younger and aged 40 years old when diagnosed of cholelithiasis and excluded without date of birth	Joined the base set to S patient data. S patient data is where the date of birth stored.
4	Add race into base set	Joined the base set to Patient race table where race is stored.
5	Finalize and save out dataset as table "cholelithiasis group"	Ensure this data set included information, such as date of birth, cholelithiasis diagnosis data, age at diagnosis, race.
6	Gather military service information	The table supplied had sparse military service information, and the information was also obtained external data from VetNet. The two datasets were merged, duplicates were excluded, and the results saved after merging into the base set.
7	Add Disability into base set	Joined the base set to the disability table for the test group and excluded duplicates.
8	Add laboratory results into base set	Filtered the results of laboratory tests with keywords of tests' name and excluded the results if they were not within the study period. Then, the laboratory results were merged into the base set.
9	Add disease information (with ICD-9 code) to base set	Detected comorbid diseases using the identified ICD-9 codes for each sample in the base set. Then, the obtained each individual's comorbid diseases were merged into the base set
10	Merge all into one table	Merged all data into one data sheet in Excel.

The process of sample collection for the control group followed the same steps as the cholelithiasis group as shown in Table 1, except step 5. Instead of using cholelithiasis diagnosis data for case group, the control group used a diagnosis date for any other diseases during the study period and the first diagnosis date was included to measure the participant's age.

Throughout this study, the principle investigator's virtual setting in the VINCI was monitored by the designated data manager, the VINCI data security, and the national data security. In addition, the principle investigator's appointed computer for the study was monitored by the VINCI data security, the national data security and the VHA information resources manager in the VHA Orlando, Florida.

Plan for Analysis

Dependent Variables

The two study groups (dependent variables) were: 1) Women diagnosed with cholelithiasis (case group) and coded as Group"1"; and 2) Women not diagnosed with cholelithiasis or did not have cholecystectomy during the study period (control group) and coded as Group '0'. To identify the potential effect of risk factors on the occurrence of cholelithiasis, the female veterans with and without cholelithiasis groups were compared.

Independent Variables

Independent variables were identified and compared against the questionnaire used in Dr. Walter Willett's Health Professionals' Follow-up Study (HPFS) for gallstone disease with Dr. Willett's permission. The HPFS began in 1986 as a prospective study, follow up questionnaires were sent biannually to update participants' health information, such as demographics, medical history, anthropometrics (height, weight and body mass index), life style factors (diet, physical activity, cigarette smoking, and alcohol use), and comorbidities, including gallstone disease (Willett,

2006). The responsiveness to this questionnaire was reported over 90% (Willett, 2006) and the individual variables in the questionnaire were tested in other studies (Martinez-Gonzalez et al., 2004; Leitzmann et al., 1999). Tsai et al.'s prospective study (2004a), abdominal adiposity and gallstone, validated of the body mass index (BMI) and waist circumstances used in the HPFS by comparing 125 participants' self-assessed information to those measured by a technician that demonstrated the validity of BMI in relation to a symptomatic cholelithiasis. The questionnaire has been used extensively in many other gallstone studies (Leitzmann et al., 2003; Tsai, Leitzmann, Willett, & Giovannucci, 2005a; Tsai, Leitzmann, Willett, & Glovannucci, 2005b). The variables for this study were compared and then modified from the questionnaire in the HPFS because it is a retrospective study using electronic medical records.

Demographics. Age, race/ethnicity, Body Mass Index, and marital status were compared to the dependent variable. Age at the time of the disease diagnosis was used as the case sample's age by deducting the time from their birth date. The age of participants in the control sample was measured using the diagnosis of their first disease to be treated during the study time by deducting their birth date. Analyses of frequency rates for cholelithiasis according to intervals of age were arranged in five years increments: the first interval was 41-45 years of age and so on (e.g., 41-45 years, 46-50 years, 51-55 years…76-80 years, >81 years). The control group was matched with the case group based on the age to have similar distribution across confounding variables. A bigger age variation can impact the study outcome since age is one of the strongest risk factor that affects cholelithiasis occurrence. The height and weight when the patients were diagnosed of the disease were selected for case and control group to measure their body mass index (BMI). Body Mass Index (BMI) was calculated using the formula, weight (lb) / height (in^2).

Ethnicity was divided into six groups as listed in the VHA data to include: 1) Caucasian (white), 2) African American (black), 3) Asian, 4) American Indian or Alaska Native, 5) Native Hawaiian or other Pacific Islander, and 6) Unknown. Samples that were recorded in the VHA data as unknown, refused to answer, or unable to identify ethnicities were all labeled as unknown in the ethnicity data. Marital status was identified only with or without spouse since it was listed as such in the VHA data.

Environmental characteristics. Length of military service was measured by deducting the military service end date from the start time and recorded as months. Military disability status was presented as a percentage of the disability in the VHA data, and the total disability percentage was measured by adding all disability rates. Other information, such as use of alcohol and tobacco, use of female hormones, exposure to military combat zones were included to expand the understanding of the women's occupational factors that might have contributed to the development of cholelithiasis. The information about consumption of alcohol or tobacco, use of hormone therapy (contraceptive or postmenopausal female hormone), and exposure to combat zones were listed as binary data because the information were retrieved using ICD-9 code. Therefore, it was only possible to identify whether the female veterans had the exposure "1" or no exposure "0" in the VHA system.

Serum laboratory tests. Serum laboratory tests were retrieved from supplied laboratory data set by putting identified names of tests. Although it was not possible to identify how the samples were obtained and stored in the VHA system, all laboratory tests and result reports at the VHA were followed the federal regulation of the Clinical Laboratory Improvement Amendments (CLIA) (VHA Handbook 1106.01, 2008). CLIA has established quality standards for all laboratory tastings to ensure the accuracy, reliability and timeliness of patient test results

regardless of where the test was performed (VHA Handbook 1106.01, 2008). The value of laboratory tests was collected from the laboratory data using keywords, as displayed in Table 3.

Table 3. Keywords Used to Retrieve the Serum Laboratory Results.

Category	Test	Keywords
Metabolic	Fasting glucose	Fasting glucose, glucose fasting, and serum fasting glucose
	Hemoglobin A1C (HbA1C)	Fasting hemoglobin A1C, fasting serum hemoglobin A1C, and fasting A1C, fasting HbA1C for hemoglobin A1C
Liver Enzymes	Alanine transaminase (ALT)	Alanine transaminase, serum alanine transaminase, fasting alanine transaminase, ALT, serum ALT, Serum glutamic Pyruvate Transaminase, glutamic Pyruvate Transaminase, SGPT, and serum SGPT.
	Aspartate aminotransferase (AST)	Aspartate aminotransferase, serum aspartate aminotransferase, fasting aspartate amionotransferase, AST, serum AST, serum glutamic oxaloacetic transaminase, glutamic oxaloacetic transaminase, SGOT, and serum SGOT
	Bilirubin	Total bilirubin, serum total bilirubin, fasting total bilirubin, and bilirubin total.
Lipid Profile	Total cholesterol, High-density lipoprotein (HDL) cholesterol, Low-density lipoprotein (LDL), triglycerides	Lipid profile, fasting lipid profile, serum lipid profile, total lipid profile, and complete lipid profile

The serum laboratory tests were selected at a time cholelithiasis was diagnosed during the study period for the cholelithiasis group. The laboratory tests at any time during the study period were used for the control group. Mean laboratory values were compared between female veterans with and without cholelithiasis.

Comorbidities. The International Classification of Disease (ICD)-9 codes were used to verify the samples' comorbidities. The selected study samples were verified to contain certain diagnosed comorbidities of diabetics, hypertension, dyslipidemia, hepatitis B, hepatitis C, liver cirrhosis, Crohn's disease, posttraumatic stress disorder, and military sexual trauma. To verify the updated diagnosed of comorbidities, only female veterans who had at least one or more laboratory test results during the study period were included. Patients' health conditions are updated by their physicians when tests are ordered, and results are reported in the VHA system.

Data Analysis and Management

Descriptive statistics were used to compute frequencies, percentages, means and standard deviations of the independent variables. Histogram and bar plots were presented to visualize distributions of the frequency of occurrence for the values. The cholelithiasis group was matched to non-cholelithiasis group based only on age ($\pm$ 5 years) to avoid the findings of the study being confounded by the effects of age. Matching with age is particularly important in order to avoid the latency period for developing cholelithiasis. Each factor of the independent variable was compared and analyzed for the groups of female veterans with and without cholelithiasis, using independent sample t-tests for continuous variables and chi-square (χ^2) tests for categorical variables. Person's product moment correlations were used to investigate the individual relationships between each continuous variable and dependent variable.

As a final step, multiple regression analysis was used to determine risk factors for

cholelithiasis in female veterans while accounting for potential confounding effects (Kleinbaum, Kupper, Muller, & Nizam, 1997; Kutner, Nachtsheim, Neter, & Li, 2004). If there was a significant relationship from the multiple regression, the independent variable could improve the accuracy in predicting values for the dependent variable.

Forward stepwise regressions (Grechanovsky, 1987) were performed to reduce the number of potential effects of confounding variables, with only those variables remaining in the equation that had a significant p value of $\leq .05$. Goodness of fit was performed to verify an overall fit test of the model using chi-square (X^{2a}). Also Odds Ratio (OR) with its 95% confidence interval (95% CI) and R^2 were measured to analyze the strength of the relationship between the set of independent variables and the dependent variable. A statistical significance level was calculated at $p \leq .05$. All statistical data analysis was performed by using the Statistical Package for the Social Science (SPSS version 22, Armonk, NY). The following section describes how this study reduced discrepancies from missing data.

Missing Data

Large data sets, such as the VHA data may contain legitimately missing data (Milbank, 2002). Missing data can potentially skew the results (Cole, 2008), and it is necessary to deal with the missing data. A benefit of a retrospective big data study is that it can include a large number of patients' representative actual patient medical records. Although the missing data in this study was distributed randomly, it had the potential effect of reducing the sample size and power of the study.

For an effective statistical analysis with SPSS, pairwise deletion was used to include all available data in analysis. In order to maintain power, pairwise deletion was useful for this study because of missing values at random distribution. Additionally, comparisons among independent

variables given dependent variables were computed based on mean values of all available data.

Management of Outliers

In order to successfully identify outliers, statistical and graphical methods were used. Independent variables were examined the distribution of observations, and selected as outliers that the values falling at the outer ranges of the distribution. Boxplots and scatterplots were used to detect values outside two of standard deviations of the mean value. Further, the outliers were examined manually to identify the causes of outliers, whether they were from error or uniqueness for accuracy of the data. Finally, the goodness of the fit by SPSS was performed to measure of a better fitting by comparing the baseline including outliers and the model without the outliers. The model, which proved to be a better fit, was chosen for the regressions.

Data Analysis

The Data Analysis plans for each Specific Aim are explained as follows:

Specific aim 1. Determine the demographic and environmental characteristics of female military veterans with and without cholelithiasis.

Descriptive statistics measured risk factors of female veterans with and without cholelithiasis were stratified to visualize what the data was showing. The frequencies and distributions of independent variables were expressed in mean and standard distribution for continuous variables and counts and percentage for categorical variables. Continuous variables included years of age, BMI ratios, months of military service and percentages of military disability. Categorical variables included race, branches of military service, and yes/ no responses to marital status, use of alcohol, tobacco, and female hormones.

Independent sample t-tests were performed to examine the difference between females

with and without cholelithiasis on the given continuous variables. The Chi- Square tests of independence were used to determine the association between two categorical variables. A *p*-value ≤ .05 indicated the variable of interest was significantly different between the case and control groups. A *p*-value ≤ .05 was used to reject the null hypothesis that none of the independent variables were significant. In other words, if at least one of the independent variables is significant, the null hypothesis is rejected. All the statistical analysis was performed in SPSS.

Specific aim 2. Examine differences among metabolic, liver enzyme and serum lipid laboratory data in female military veterans with and without cholelithiasis

The laboratory data were summarized using independent sample t-tests. Mean values of metabolic tests included to fasting glucose, hemoglobin A1C, liver enzymes (alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin) and lipid profile were presented with standard deviations (SD). The mean differences of the laboratory data were compared between female veterans with and without cholelithiasis and the *p*-value associated with each test was reported. Bar plots were reported to show mean comparisons of significant laboratory tests in female veterans with and without cholelithiasis.

A *p*-value ≤ .05 was used to reject the null hypothesis that none of the laboratory tests were significantly associated with cholelithiasis occurrence in female veterans.

Specific aim 3. Explore differences between diagnosed metabolic and biliary comorbidities experienced by female military veterans with and without cholelithiasis

Frequencies of metabolic (diabetes, dyslipidemia, hypertension), biliary (hepatitis B, hepatitis C, liver cirrhosis) and other (Crohn's disease, posttraumatic stress disorder (PTSD), military sexual trauma (MST)) were summarized using descriptive analysis.

Comorbid conditions were referred to as binary variables (either the disease was present or not). These variables were coded for either "0" no disease or "1" had disease. The association between binary variables in female veterans with and without cholelithiasis was measured using the Chi-Square independent test. The *p*-value associated with each test was reported.

A *p*-value ≤ .05 indicated a diagnosed comorbidity was significantly different between females with and without cholelithiasis. A *p*-value ≤ .05 was used to reject the null hypothesis that none of the comorbid conditions were significantly associated with cholelithiasis occurrence in female veterans.

Specific aim 4. Explore associations among demographic, environmental, laboratory data and diagnosis of comorbid conditions among female military veterans with and without cholelithiasis.

The associations among independent (continuous) variables in female veterans and risk for cholelithiasis occurrence were examined using Pearson product moment correlations. The purpose of using statistical correlation was to identify whether there was a significant relationship among independent variables and cholelithiasis occurrence in female veterans. A two-tailed test with a significance level of .05 was used to include the possibility of the relationship in both direction associated with cholelithiasis occurrence. An *r*-value was measured to demonstrate the strength and direction of liner relationships between the continuous variables and cholelithiasis occurrence and *p*-value was also reported. A *p*-value ≤ .05 indicated an independent variable was significantly associated with cholelithiasis occurrence.

Multiple logistic regressions were used to explore associations among the independent variables (use of alcohol, use of tobacco, use of female hormones, and all comorbid diseases) and binary dependent variables (cholelithiasis or no-cholelithiasis). Also multiple linear regressions

were used to evaluate associations among the independent variables, such as laboratory data and the risk of cholelithiasis occurrence. The independent variables were considered for logistic regression analysis based on a liberal alpha of 0.05 from the bivariate comparisons to avoid omission of potentially important variables.

Using stepwise regressions, the individual values of significant variables were identified for the productiveness of the dependent variables. Each associated variable was either entered or removed based on a statistically significant value until they were no longer significantly contribute to the model. Adjusted odds ratio (OR) was obtained through stepwise regression while other risk factors were controlled. The 95% confidence interval (CI) was used to estimate the precision of the adjusted odds ratio.

Summary

In summary, the purpose of this retrospective study was to identify relationships among predisposing risk factors and gallstone occurrence in female veterans. Descriptive analysis was expressed in frequencies and distributions of the data. The differences in female veteran with and without cholelithiasis on given independent variables were calculated using independent t-tests and chi-square tests. Pearson product moment correlations were used to demonstrate the strength and direction of relationships among independent variables and cholelithiasis occurrence in female veterans. Finally, multiple regressions were used to identify risk factors associated with cholelithiasis occurrence while accounting for potential confounding effects.

CHAPTER IV

RESULTS

The purpose of this study was to identify the relationship between predisposing risk factors and cholelithiasis occurrence in military female veterans. The specific aims of the study were to:

1) Determine the demographic and environmental characteristics of female military veterans with and without cholelithiasis.
2) Examine differences among metabolic, liver enzyme and serum lipid laboratory data in female military veterans with and without cholelithiasis.
3) Explore differences between diagnosed metabolic and biliary comorbidities experienced by female military veterans with and without cholelithiasis.
4) Explore associations among demographic, environmental and laboratory data and diagnosis of comorbid conditions among female military veterans with and without cholelithiasis

This chapter presents the findings of this study including: a description of the sample from which the data were derived, results of the descriptive and inferential statistical analysis, along with significant findings for each aim. Statistical analysis was conducted using Statistical Package for the Social Science (SPSS Versions 22, Armonk, NY).

Specific Aims

Specific Aim 1

Aim 1. Determine the demographic and environmental characteristics of female military veterans with and without cholelithiasis.

Demographic characteristics. The medical data for 484 military female veterans aged 41 years and older were examined for this study. Two hundred forty two data of female veterans diagnosed with cholelithiasis from January 1, 2008 to December 31, 2013 were randomly collected for the cholelithiasis group. The same numbers of female veterans without a diagnosis of cholelithiasis or a history of cholecystectomy during the same period were randomly selected for a group without cholelithiasis. The study data were retrieved from the Veterans Health Administration (VHA) database according to the inclusion criteria. Detailed information about the criteria and steps for the data collection were explained in Methods, Chapter III. Demographic data for the sample is reported as follows (Table 4).

Table 4. Demographic Characteristics of Female Veterans With and Without Cholelithiasis.

Characteristics	With Cholelithiasis (n= 242)		Without Cholelithiasis (n= 242)	
	n	%	n	%
Age				
41- 45 yrs	14	5.8	14	5.8
46- 50	38	15.7	38	15.7
51-55	59	24.5	59	24.5
56-60	56	23.1	56	23.1
61-65	33	13.7	33	13.7
66-70	20	8.3	20	8.3
71-75	6	2.4	6	2.4
76-80	5	2	5	2
>81	11	4.5	11	4.5
Total	242	100	242	100

Table 3 cont.

Characteristics	With Cholelithiasis (n= 242) n	%	With Cholelithiasis (n= 242) n	%
Race/ethnicity				
White	167	69	188	77.7
Black or	66	27.3	48	19.8
American	0	0	1	0.4
Asian	1	0.4	1	0.4
Native Islander	4	1.7	4	1.7
Unknown	4	1.7	0	0
Total	242	100	242	100
Marital status				
Yes	8	3.3	19	7.9
No	97	40.5	44	18.2
Unknown	137	56.2	179	74

The intervals of age were set as follows: 41- 50 years, 51-55 years, 56-60 years, 61-65 years, 66-70 years, 71-75 years, 76-80, >81 years. The most prevalent age group at diagnosis was 51 to 60 years of age as shown in Figure 4. The age distribution between the two groups was identical due to the purposive matching based on age.

The mean age of the female veterans with cholelithiasis was 58.41 and the mean age of female veterans without cholelithiasis was 57.41 with a range of ages from 41 to over 81 years. The mean Body Mass Index (BMI) was slightly higher in females with cholelithiasis (M= 31.64, SD= 7.30) than those without cholelithiasis (M=30.56, SD=7.87). However the difference was not statistically significant (t = 1.09, p= .14), as shown in Table 5.

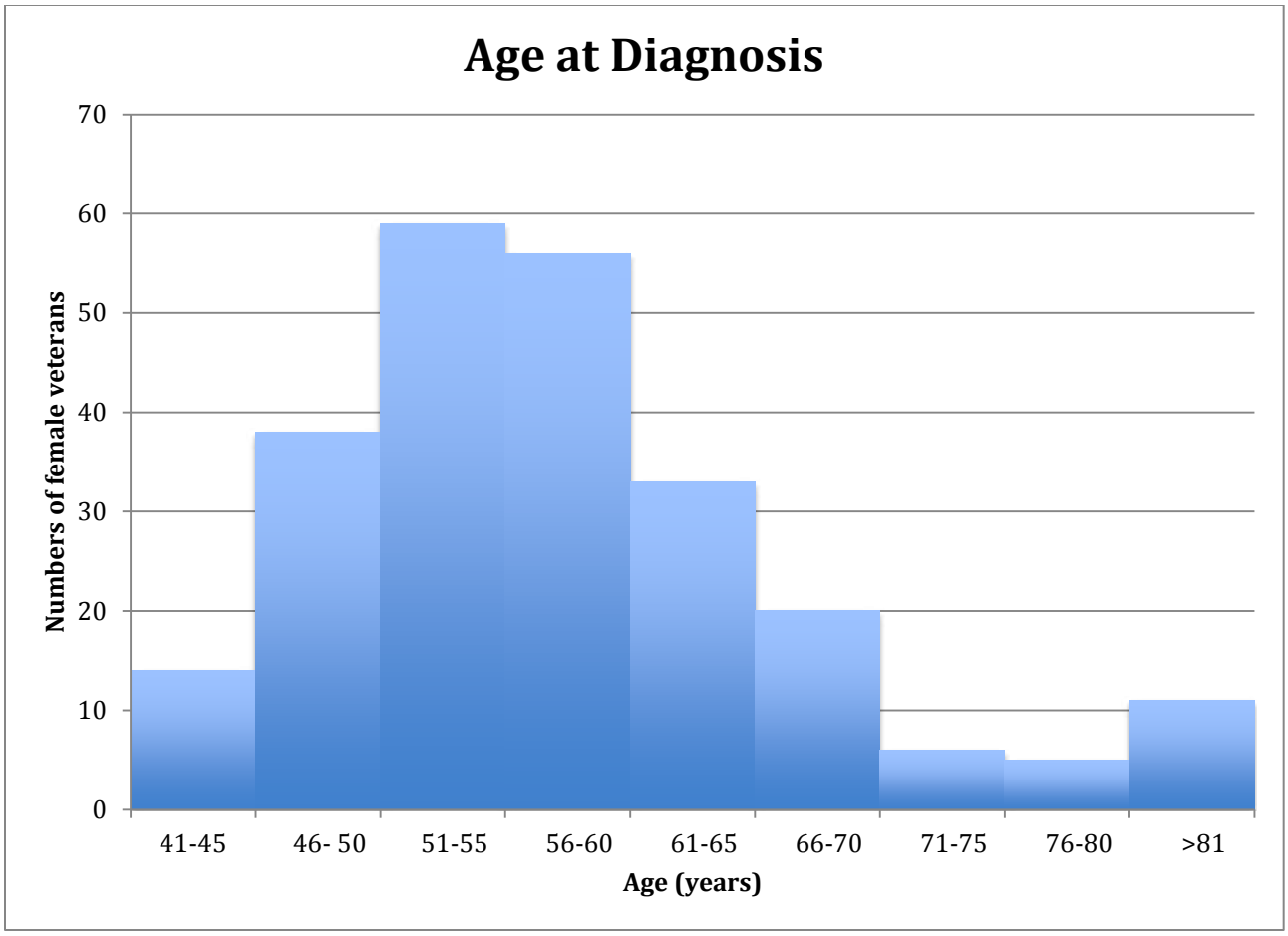

Figure 4. Female veterans' age at diagnosis with cholelithiasis.

Table 5. Age and Weight Comparisons Between Female Veterans With and Without Cholelithiasis.

	n	*M*	*SD*	t	*p*
Age at Diagnosis (years)					
Cholelithiasis	242	58.41	9.97	>1.09	0.28
No-cholelithiasis	242	57. 41	10.05		
Body Mass Indexes					
Cholelithiasis	242	31.64	7.3	>1.49	0.14
No-cholelithiasis	194	30.56	7.87		

The most common ethnic group studied were Caucasian females with and without cholelithiasis. The percentage of Caucasian female veterans with cholelithiasis was 69.0% and those without cholelithiasis was 77.7%. African Americans were the second most common ethnic group studied. Of African American females, 27.3% had cholelithiasis while 19.8% did not. There were not significant differences in ethnicity between two groups. The comparison in ethnicity distribution in females with and without cholelithiasis is presented in Table 6.

Table 6. Frequency of Female Veterans With and Without Cholelithiasis by Ethnic Categories.

Ethnicity	With Cholelithiasis		Without Cholelithiasis	
	n	%	n	%
Caucasian	167	69.0	188	77.7
African American	66	27.3	48	19.8
American Indian	0	0	1	0.4
Native Hawaiian	4	17	4	1.7
Asian	1	.4	1	.4
Unknown	4	1.7	0	0
Total	242	100	242	100

The number of female veterans who were identified as neither Caucasian nor African American was too small to compare the differences between groups. The ethnic distribution of female veterans with and without cholelithiasis is described in Figure 5.

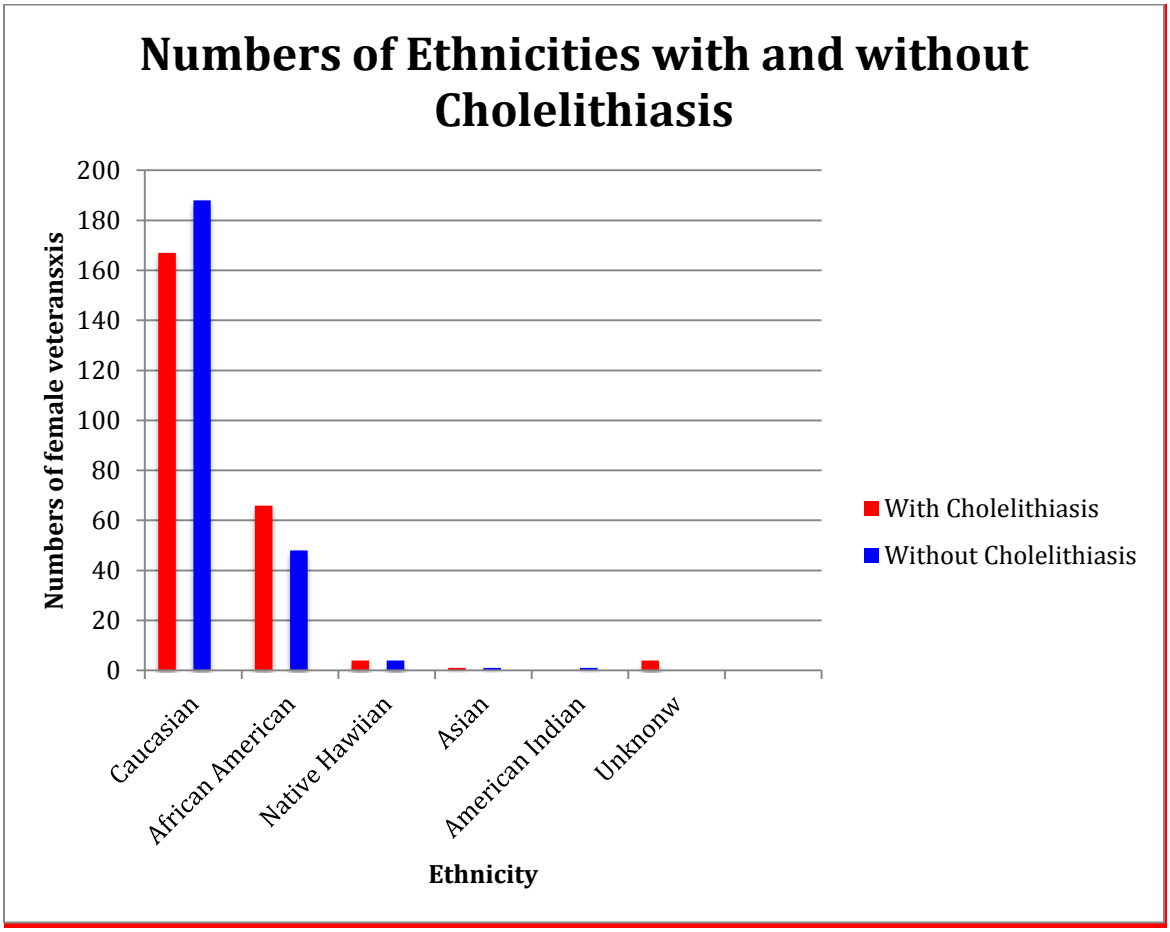

Figure 5. Bar graph representing ethnic groups of female veterans with and without cholelithiasis.

Environmental characteristics. Military female veterans are women who served for any length of time in any military branch. Due to their unique occupational experience, occupational factors may be directly related to women's health. Environmental information, such as the branch of military service for each woman is displayed in Table 7. There was only one female veteran in the cholelithiasis group deployed to warzones; therefore it was not possible to identify whether a warzone exposure contributed to increased risk for cholelithiasis among female veterans.

Table 7. Environmental Characteristics in Female Veterans With and Without Cholelithiasis.

	With Cholelithiasis (n= 242)		Without Cholelithiasis (n=242)	
Characteristics	n	%	n	%
Military branch				
Army	50	20.66	14	5.79
Air Force	19	7.85	10	4.13
Navy	20	8.26	7	2.88
Marine Corp	7	2.89	2	0.82
Other(>2 branch)	2	0.83	1	0.41
Unknown	144	59.50	208	85.95
Total	242	100	242	100
Military Service (months)	95	39.26	34	14.05
Unknown	147	60.74	208	85.95
Total	242	100	242	100
Warzone exposure	1	0.41	0	0
Unknown	241	99.59	242	100
Total	242	100	242	100

A majority of female veterans in both groups served in the Army, with 51.6% of female veterans in the cholelithiasis group and 26.9% in the group without cholelithiasis. Female veterans who served in the Navy had the second highest percentage of cholelithiasis (20.41%) representing the third highest percentage of female veterans without cholelithiasis (13.46%). Air Force female veterans had the third highest percentile of cholelithiasis (19.39%) and the second highest percentage of female veteran without cholelithiasis (19.23%).

Comparison of the service branch served by female veterans is displayed in Figure 6.

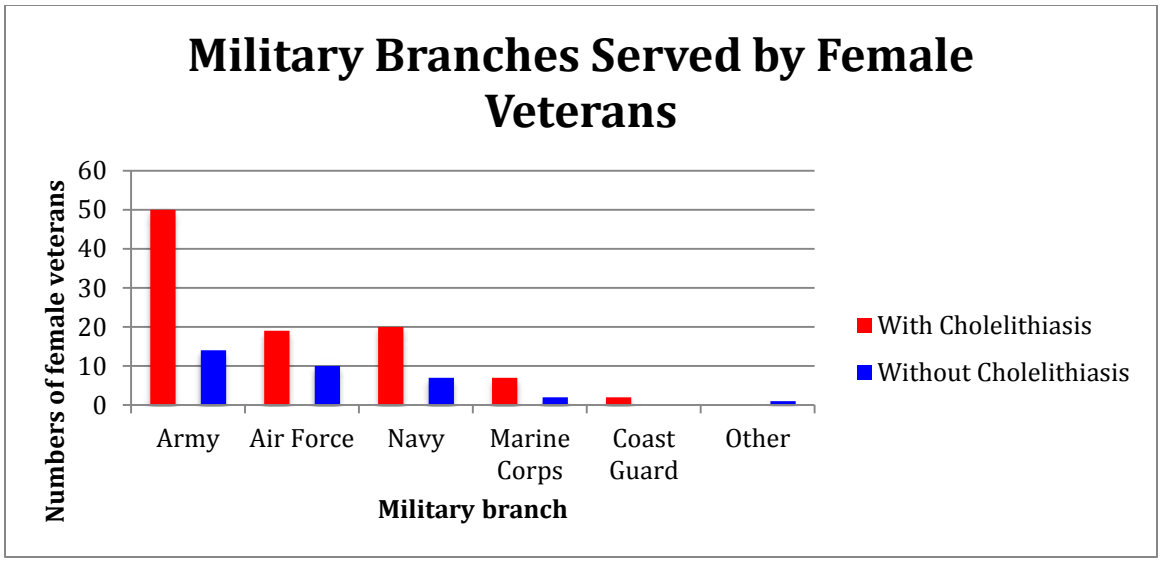

Figure 6. Military branches served by female veterans with and without cholelithiasis.

The length of military service was based on months of service. Military service was longer in females with cholelithiasis (*M*=38.94, *SD*=51.73) than those without cholelithiasis (*M*=28.24, *SD*=17.21) although the difference between the two groups was not statistically significant (t = 1.18, *p* = .24). Mean military disability status was similar between two groups with cholelithiasis (*M*=33.87, *SD*=22.22) and without cholelithiasis (*M*=36.17, *SD*=31.05). There was no significant difference between two groups (t = -.55, *p*= .59) as shown in Table 8.

Table 8. Mean of Environmental Factors in Female Veterans With and Without Cholelithiasis.

	M	*SD*	t	p
Military Service (months)				
Cholelithiasis	38.94	51.73	1.18	0.24
No-cholelithiasis	28.24	17.21		
Military Disability (%)				
Cholelithiasis	32.86	22.22	0.55	0.59
No-cholelithiasis	36.17	31.05		

Note. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$

Military disability status is closely tied to the treatment and care plans for military veterans in the VHA. Military disabilities are the result of a disease or injury that occurred during active military service. The disability status is recoded as a percentage in the VHA and it was examined as such in this study. Total percentage of military disability status for patients was included with varied ranges from 10 to 100%. More numbers of female veterans with cholelithiasis had military disability status (n=65) than females without cholelithiasis (n=23). Total percentage of disability status was higher in females with cholelithiasis than those without cholelithiasis although the difference was not statistically significant (t = .55, p = .59). Figure 7 presents comparisons of the military disability status in both groups.

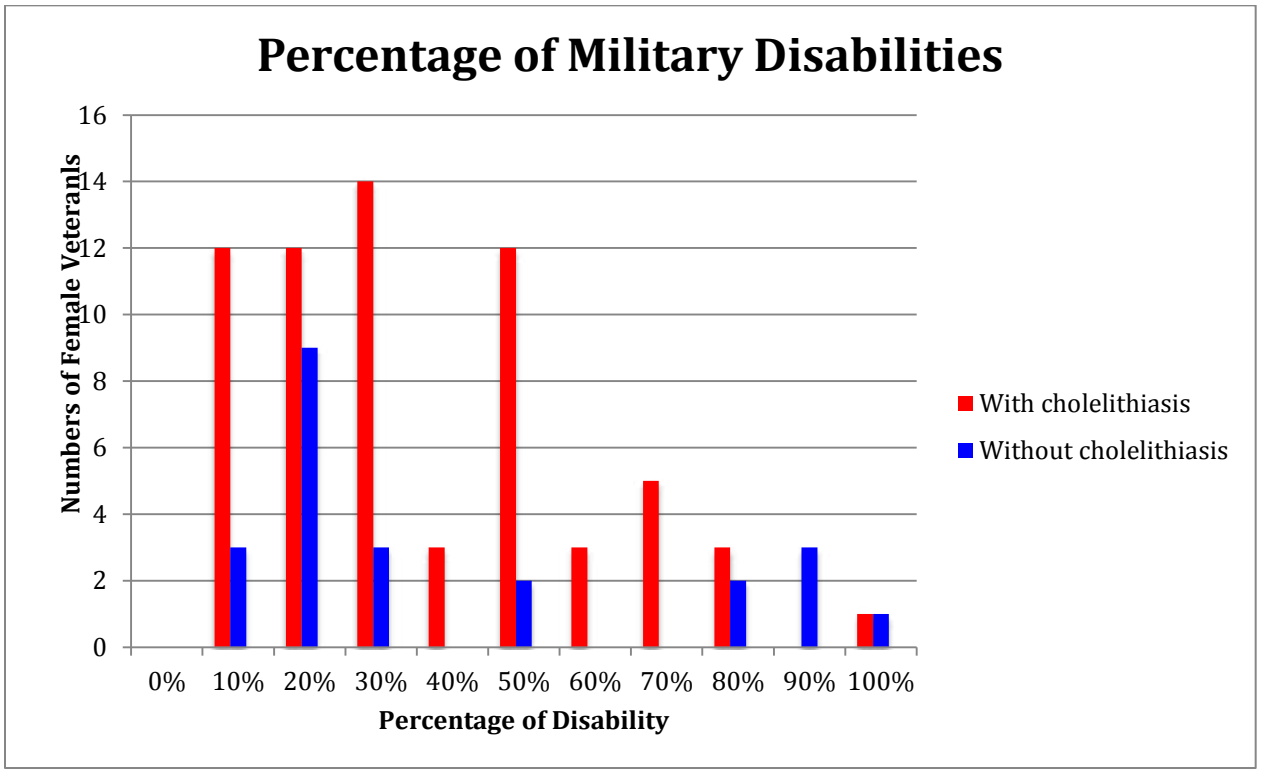

Figure 7. Numbers of military female veterans with and without cholelithiasis and their percentage of disabilities. 0% of disability was listed to show there were no female veterans who had disability rate between 0% to 10%. The minimum disability in this study was reported as 10% and maximum was reported as 100%.

The most common cause of disability status for female veterans with cholelithiasis was posttraumatic stress disorder (n=27). Bipolar disorder (n=6), migraine headache (n=6), and degenerative arthritis of sprain (n=5) were also frequent reasons for disability status in females with cholelithiasis. Degenerative arthritis, hypertensive vascular disease, knee condition, and lumbosacral or cervical strains were the most common causes of disabilities in females without cholelithiasis. The disability conditions are reported for both groups in Table 9.

Table 9. The Most Common Types Of Disabilities Causes in Female Veterans With and Without Cholelithiasis.

With Cholelithiasis			Without Cholelithiasis		
Causes	n	%	Causes	n	%
Posttraumatic disorder	27	11.16	Degenerative-arthritis	4	1.65
Bipolar disorder	6	2.48	Hypertensive-vascular disease	4	1.65
Migraine headache	6	2.48	Knee condition	3	1.24
Degenerative-arthritis of spine	4	1.65	Lumbosacral or –cervical strain	3	1.24
Major depressive-disorder	3	1.24	Paralysis of – sciatic nerve	2	0.83
Knee prosthesis	3	1.24	Limited knee flex	2	0.83
No disability reported	193	79.75	No disability reported	224	92.56
Total	242	100	Total	242	100

The military veteran population has been known to have higher alcohol and tobacco consumption levels compared to civilians (Park et al., 2011). However, many studies do not include female veterans. Data from this study showed that tobacco use was significantly higher ($X^2 = 16.3$, $p < .01$) in females with cholelithiasis (16.94%) than those without cholelithiasis (5.37%). Also, the difference was statistically significant for an increased risk for cholelithiasis. More female veterans with cholelithiasis (4.55%) indicated that they used alcohol in comparison to the female veterans without cholelithiasis (1.65%). However, no statistical significance

(X^2 =3.37, p = .07) was found. As shown in Table 8, use of female hormones was not significantly different in females with and without cholelithiasis (X^2= 1.82, p = .18). The use of alcohol, tobacco, and hormone replacement for female veterans with and without cholelithiasis is listed in Table 10.

Table 10. Frequency of Alcohol, Tobacco, and Hormone Use in Female Veterans With and Without Cholelithiasis.

	n	%	X^2	p
Use of Alcohol				
Cholelithiasis	11	4.55	3.37	0.07
No-cholelithiasis	4	1.65		
Use of Tobacco				
Cholelithiasis	41	16.94	16.34	0.00**
No-cholelithiasis	13	5.37		
Use of Female hormone				
Cholelithiasis	1	0.41	1.82	0.18
No-cholelithiasis	4	1.65		

Note. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$

Specific Aim 2

Aim 2. Examine differences among metabolic, liver enzyme and serum lipid laboratory data in female military veterans with and without cholelithiasis.

The serum laboratory tests used in this study were serum metabolic, liver enzymes and lipid profile laboratory data. Individual test values were compared to female veterans with and without cholelithiasis using independent sample t tests.

Differences between serum metabolic levels in female veterans with and without cholelithiasis. Diabetes is reported to be highly related to cholelithiasis development (De Santis,

et al., 1997; Gielkens et al., 1998; Haffner, Diehl, Mitchell, Ruhl and Everhart, 2000; Shaw et al., 1993; Stern, & Hazuda, 1990). Hemoglobin A1C (HbA1C) and fasting glucose levels are widely used to identify diabetes (American Diabetes Association, 2010; Goldstein et al., 2004; Nathan et al., 2008; World Health Organization, 2006). In this study, females with cholelithiasis (*M*= 7.41, *SD*= 1.67) had a higher mean hemoglobin A1C value than those without cholelithiasis (*M*= 6.09, *SD*= .92) and the difference was statistically significant (t = 7.33, $p < .01$). Mean fasting glucose concentration was not significantly different in females with and without cholelithiasis (t=1.86, $p = .08$). The mean comparison of serum metabolic values is displayed in Table 11.

Table 11. Mean Serum Metabolic Laboratory Levels in Female Veterans With and Without Cholelithiasis.

Variable	n	*M*	*SD*	t	*p*
Glucose					
Cholelithiasis	228	112.10	48.99	1.86	0.08
No-cholelithiasis	147	103.80			
HbAIC					
Cholelithiasis	213	7.41	1.67	7.33	0.00**
No-cholelithiasis	97	6.09	0.92		

Note. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$. HbA1c= Hemoglobin A1c.

Differences among liver enzymes in female veterans with and without Cholelithiasis. Liver enzymes of bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT) were compared in female veterans with and without cholelithiasis. No significant differences were found in AST (t = 1.25, $p = .21$) and ALT levels (t = .33, $p = .75$) between females with and without cholelithiasis. In addition, there were no significant differences in bilirubin levels (t =

.56, p = .57) between the two groups of females. The mean compared the two groups to serum liver enzymes are reported in Table 12.

Table 12. Mean Comparisons of Liver Enzymes in Female Veterans With and Without Cholelithiasis.

Variable	n	*M*	*SD*	t	*p*
Total bilirubin					
Cholelithiasis	226	0.58	0.46	0.56	0.57
No-cholelithiasis	133	0.55	0.23		
AST					
Cholelithiasis	213	28.30	34.87	1.25	0.21
No-cholelithiasis	137	24.49	9.29		
ALT					
Cholelithiasis	228	26.41	20.89	0.33	0.75
No-cholelithiasis	149	25.80	11.43		

Note. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, *AST= Aspartate Transaminase, ALT= Alanine Transaminase*

Differences among lipid profile in female veterans with and without cholelithiasis.

Lipid profiles for total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides were examined between female veterans with and without cholelithiasis. Total cholesterol was significantly higher (t =4.34, p < .01) and HDL values were significantly lower (t = -4.27, p < .01) in females with cholelithiasis. The levels of LDL and Triglycerides were not statistically significant when comparing the female veterans with and without cholelithiasis. Mean comparisons of serum lipids levels in both groups are displayed in Table 13.

Table 13. Mean Comparison of Serum Lipids in Female Veterans With and Without Cholelithiasis.

Variable	n	*M*	*SD*	t	*p*
Total cholesterol					
Cholelithiasis	242	123.69	65.82	4.34	0.00**
No-cholelithiasis	227	98.72	58.40		
HDL					
Cholelithiasis	177	47.13	17.29	-4.27	0.00**
No-cholelithiasis	107	56.28	17.90		
LDL					
Cholelithiasis	127	106.61	38.26	0.88	0.38
No-cholelithiasis	91	101.94			
Triglycerides					
Cholelithiasis	239	153.23	74.91	1.62	0.11
No-cholelithiasis	216	140.60	79.19		

Note. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, *HDL= high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol*

Values of serum total cholesterol are categorized as normal (below 200 mg/dl), borderline (between 200-239 mg/dl) and at risk (above 240mg/dl) (National cholesterol education program, 2001). Although mean levels of total cholesterol in both groups were in a normal range, females with cholelithiasis had higher total cholesterol levels (*M*=124 mg/dl, *SD*= 65.82), than those without cholelithiasis (*M*= 98.72 mg/dl, *SD*=58.40). Serum cholesterol differences in female veterans with and without cholelithiasis group were statistically significant (t = 4.34, $p < .01$).

Levels of HDL were significantly lower in females with cholelithiasis (*M*= 47.12, *SD*= 17.29) than those without cholelithiasis (*M*=56.28, *SD*=17.90). The HDL differences between female veterans with and without cholelithiasis were statistically significant (t=-4.27, $p < .01$). The desired HDL level is > 40 mg/dl (National cholesterol education program, 2001).

Specific Aim 3

Aim 3. Explore differences between diagnosed metabolic and biliary comorbidities experienced by female military veterans with and without cholelithiasis.

Statistical differences in the comorbid conditions experienced by female veterans with and without cholelithiasis were examined using chi-square statistics.

Differences of biliary comorbidities in female veterans with and without cholelithiasis. There were no significant differences in hepatitis B presence in females with and without cholelithiasis. Fourteen females in cholelithiasis group had a history of hepatitis C in comparison to one female in the no-cholelithiasis group. The difference between the two groups was statistically significant ($X^2 = 11.63$, $p < .01$). The frequency of liver cirrhosis was also higher in females with cholelithiasis (n= 13, 5.37%) than those without cholelithiasis (n=0) and the difference was statistically significant ($X^2 = 13.36$, $p < .01$). The comparison of liver diseases between females with and without cholelithiasis is reported in Table 14.

Table 14. Comparison of Biliary Comorbidities in Female Veterans With and Without Cholelithiasis.

	n	%	X^2	p
Hepatitis B				
Cholelithiasis	2	0.83	2.01	0.16
No-cholelithiasis	0	0		
Hepatitis C				
Cholelithiasis	14	5.79	11.63	0.00**
No-cholelithiasis	1	0.41		
Liver Cirrhosis				
Cholelithiasis	13	5.37	13.36	0.00**
No-cholelithiasis	0	0		

Note. $^{*}p = < .05$, $^{**}p = < .01$, $df = 482$

Differences of metabolic comorbidities in female veterans with and without cholelithiasis. Female veterans with cholelithiasis had higher prevalence of diabetes (*n*= 57, *23.55%*) and the differences between two groups were statistically significant (X^2 =28.78, $p <$ .01). The prevalence of dyslipidemia was also higher in females with cholelithiasis (*n*= 86, *35.53%*) and the differences were statistically significant (X^2 = 35.56, $p <$ .01). The prevalence of hypertension was also higher in females with cholelithiasis (*n*=102, 42.15%) than those without cholelithiasis (*n*=38, 15.70%), and the difference reached statistical significance (X^2 = 41.16, $p <$ .01). Although Crohn's disease is an autoimmune disease, it was classified as a metabolic comorbidity for convenient analyses. However, only three females had Crohn's disease, two with cholelithiasis and one without. There was no significant difference between female veterans with and without cholelithiasis and Crohn's disease. (X^2= .34, $p >$ .05). The comparison of metabolic diseases in females with and without cholelithiasis is displayed in Table 15.

Table 15. Comparison of Metabolic Comorbidities in Female Veterans With and Without Cholelithiasis.

Variable	n	%	X^2	*p*
Diabetes				
Cholelithiasis	57	23.55	28.78	0.00**
No-cholelithiasis	15	6.20		
Dyslipidemia				
Cholelithiasis	86	35.53	35.56	0.00**
No-cholelithiasis	30	12.40		
Hypertension				
Cholelithiasis	102	42.15	15.70	0.00**
No-cholelithiasis	38	15.70		
Crohn's Disease				
Cholelithiasis	2	0.83	0.34	0.56
No-cholelithiasis	1	0.41		

Note. $^{*}p = < 0.05$, $^{**}p = < 0.01$, *df =482*

Differences among other comorbidities of female veterans with and without cholelithiasis. Female veterans with cholelithiasis were more frequently diagnosed with posttraumatic stress disorder (PTSD) than females without cholelithiasis (X^2 =12.62, $p < .01$). Military sexual trauma (MST) was also found more frequently in female veterans with cholelithiasis (n=32, 13.22%) than female veterans without cholelithiasis (n= 7, 2.89%). The significant differences are shown in Table 16.

Table 16. Comparison of Other Comorbidities in Female Veterans With and Without Cholelithiasis.

Variable	n	%	X^2	p
PTSD				
Cholelithiasis	32	13.22	12.62	0.00**
No-cholelithiasis	10	4.13		
MST				
Cholelithiasis	32	13.22	17.43	0.00**
No-cholelithiasis	7	2.89		

Note. $^{*}p = < 0.05$, $^{**}p = < 0.01$.*df* =482. *PTSD= Posttraumatic stress disorder, MST=Military sexual trauma*

Overall frequencies of comorbidities were higher in female veterans with cholelithiasis than those without cholelithiasis. The comparison by frequencies is shown in Figure 8.

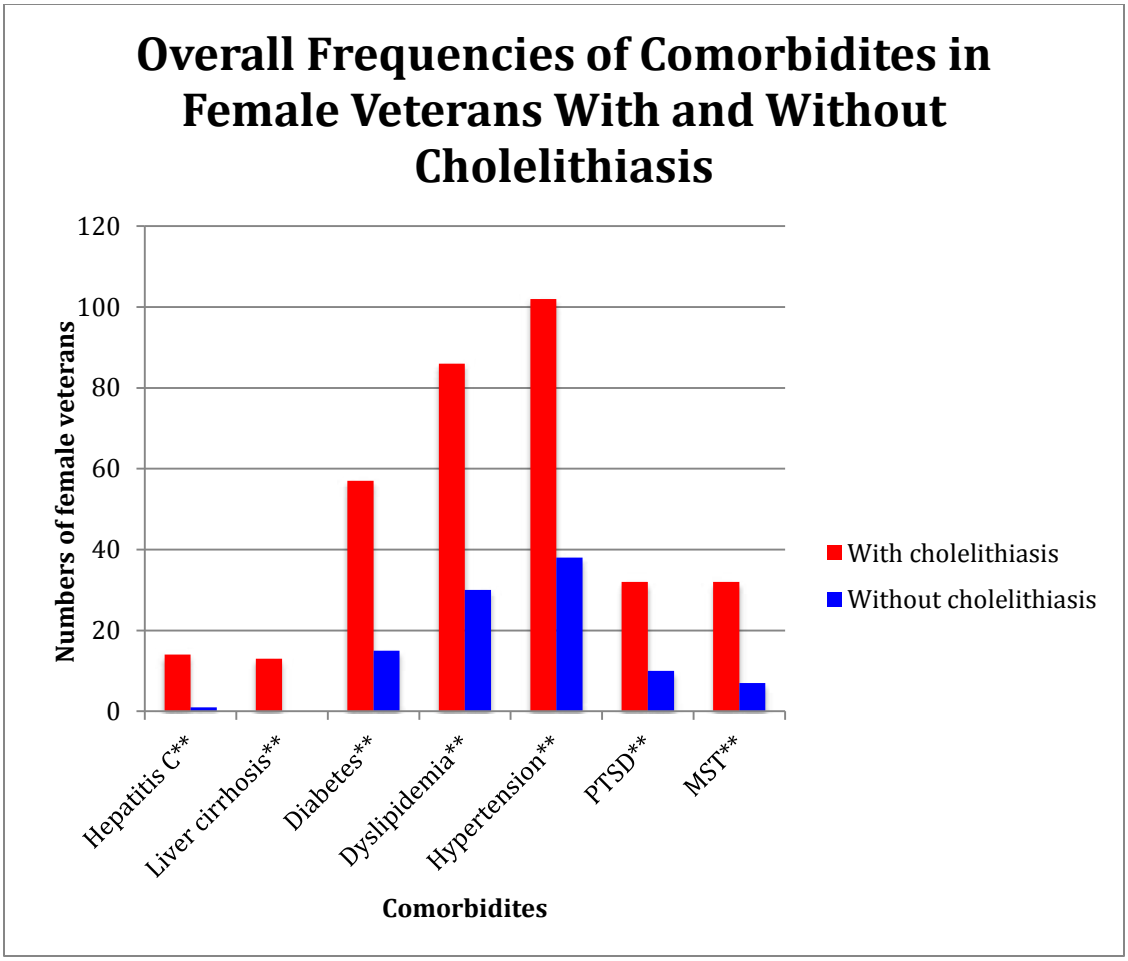

Figure 8. Overall frequency of comorbidities in female veterans with and without cholelithiasis. ** Statistically significant by Chi-square tests.

Specific Aim 4

Aim 4. Explore associations among demographic, environmental, laboratory data and diagnosis of comorbid conditions among female military veterans with and without cholelithiasis

After examining the independent risk factors of female veterans with and without cholelithiasis, the associations of variables related to cholelithiasis were explored using Pearson's correlation coefficients. Inter-correlations of study variables were analyzed and are displayed in Table 16. Age and BMI have major contributing factors for developing cholelithiasis (Shaffer, 2006; Volzke et al., 2005). However age and BMI in this study were not

significantly related to cholelithiasis presence. Similarly, female hormone therapies due to postmenopausal syndrome have reported a close relationship to cholelithiasis development but this study showed no significant relationship with cholelithiasis (Angelin et al., 1992;

Table 16. Intercorrelations Between Cholelithiasis and Predisposing Factors.

variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1 Cholelithiasis Presence	1												
2 Months of Military service	.103	1											
3 BMI	.071	-.186*	1										
4 Percentage of Disability	-.059	-.217	.002	1									
5 Cholesterol	.197**	-.07	.008	-.011	1								
6 HDL	-.246**	-.116	-.098	-.051	.132*	1							
7 LDL	.059	-.137	-.021	-.096	.054	-.001	1						
8 Triglyceride	.076	-.102	.034	.083	.136**	-.357**	.025	1					
9 Glucose	.096	.135	.077	.062	-.009	-.126	-.025	-.009	1				
10 HbA1c	.386**	-.019	.037	.027	.106	-.141*	-.02	.140*	.016	1			
11 Bilirubin	.03	.03	-.088	.081	-.078	.009	.175*	-.122*	.031	-.018	1		
12 AST	.067	-.07	.047	.009	-.002	-.122	.135	.052	.042	-.006	-.011	1	
13 ALT	.017	-.067	.099	.051	-.03	-.105	-.057	.063	.099	-.018	-.014	.844**	1

Note. Intercorrelations represented by Pearson's r coefficient.

$N = 484$; BMI = Body Mass Index; HDL = High Density Lipoprotein; LDL = Low density Lipoprotein; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase

*$p<.05$, **$p<.01$

Henriksson, Einarsson, Eriksson, Kelter, Angelin, 1989; Maurer, Everhart, Knowler, Shawker, & Roth, 1990; Scragg, McMichael, & Seamark, 1984). Alcohol use, military service, and disability status were not significantly associated with cholelithiasis occurrence. Tobacco use was significantly associated with cholelithiasis occurrence ($r = 0.18$, $p < .01$). Lipids have been reported as a controversial factor in relation to cholelithiasis because of inconsistent study findings. Total cholesterol ($r= 0.20$, $p< .01$) and hemoglobin A1C ($r= 0.39$, $p< .01$) in this study were significantly positively related to cholelithiasis. A significant negative interaction was also found between serum high density lipoprotein (HDL) and cholelithiasis occurrence ($r= -0.25$, $p < .01$).

Associations of demographic and environmental factors in relation to cholelithiasis. A step-wise multiple logistic regression analysis was performed to identify the most significant risk factors related to cholelithiasis occurrence. Tobacco use was the only significant association among demographic and environmental factors to cholelithiasis occurrence. The study calculation showed that the likelihood of having cholelithiasis was 3.15 times greater in female veterans with a smoking habit than females without a smoking habit (OR=3.15, $p < .01$).

Associations of serum laboratory values related to cholelithiasis. Variables were analyzed using a linear stepwise regression. Correlational analysis to determine the likelihood of developing cholelithiasis was analyzed using a linear stepwise regression. A stepwise regression was used to maximize the prediction in relation to cholelithiasis occurrence. In a step 1 of analysis, hemoglobin A1C was entered in the regression equation and was significantly related to cholelithiasis occurrence ($R^2= .14$, $p< .01$). HDL was then entered into the equation as the second step. Hemoglobin A1C and HDL together increased the significance of cholelithiasis occurrence ($R^2= .23$, $p < .01$). Total cholesterol was entered as the third step, and the equation showed an

increased prediction for cholelithiasis (R^2= .26, p < .05). Results show as each risk factor was added, the likelihood of cholelithiasis occurrence increased. This indicates that 26% of the variance in predicting the likelihood of having cholelithiasis that was accounted by hemoglobin A1C, HDL, and total cholesterol. Results of the stepwise regression are presented in Table 18.

Table 18. Linear Stepwise Regression in Serum Laboratory Values Associated With Cholelithiasis.

Model	Variable	R^2	Adjusted R^2	R^2 change	Standardized β	Sig.
Step 1	HbA1C	.14	.13	.14	.38	0.00**
Step 2	HbA1C				.32	
	HDL	.23	.21	.08	-.30	0.00**
Step 3	HbA1C				.32	
	HDL				-.32	
	Cholesterol	.26	.24	.04	.20	0.02*

Note. $^{*}p$ = <0 .05, $^{**}p$ = <0 .01. *HbA1C=Hemoglobin A1C, HDL=High- density lipoprotein, Cholesterol= total cholesterol.*

Associations of the significant diagnosed comorbidities (hypertension and hepatitis C) related to cholelithiasis. Of the comorbidities, only hypertension and hepatitis C were included in a stepwise model. These were the only variables that had significant Chi-square test differences while controlling confounding effects. Since none of the independent variables in the analysis had a standard error larger than 2.0, there was no evidence of multicollinearity between independent variables. This model was statistically significant with an overall χ^{2a}=51.02, *Nagelkerke's* R^2 = .13, and p < .01. The results indicate that female veterans with hypertension had 2.68 times the relative risk of developing cholelithiasis (95% CI= 1.69 to 3.59) in comparison to those who did not have hypertension. Also, female veterans with hepatitis C had 8.34 times higher relative risk (95% CI=1.07 to 64.77) compare to who did not have the disease.

The relationships between the diagnosed comorbidities and cholelithiasis are reported in Table 19.

Table 19. Logistic Stepwise Regression Analysis of Diagnosed Comorbidities Associated With Cholelithiasis.

	Comorbidities	*B*	*SE*	*p*	Odds	95% C.I. for Odds Lower	Upper
Step 1	HTN	0.99	0.19	0.00**	2.68	1.85	3.9
Step 2	HepC	2.12	1.05	0.04*	8.34	1.07	64.77
	HTN	0.9	0.19	0.00**	2.46	1.69	3.59

Note. Overall Model χ^{2a}=51.02 with a Nagelkerke pseudo R Square =0.134, and p<0.001, with an overall change in model accuracy from 50% to 63.8%.

Summary

The purpose of this study was to identify the relationship among demographic and environmental factors, serum lipid and liver enzyme concentrations, and associated comorbidities to increased risk for cholelithiasis occurrence among female veterans. Although many studies have reported a significant relationship among age, race, BMI and cholelithiasis occurrence (Everhart et al., 2002; Shaffer, 2005; Torgerson, Lindroos, Naslund, & Peltonen, 2003; Tsai, Leitzmann, Willett, & Giovannucci, 2004), this study did not find the same significant relationships. This study indicated tobacco use to be significantly related ($p< .01$) to the risk for cholelithiasis. Among the serum laboratory tests, mean serum cholesterol ($p< .01$) and hemoglobin A1C were positively associated with cholelithiasis while low HDL levels were significantly associated ($p< .01$) with an increased risk for cholelithiasis occurrence. The comorbid conditions of diabetes, dyslipidemia, hepatitis C, liver cirrhosis, hypertension,

posttraumatic stress disorder, and military sexual trauma occurred more frequently in female veterans with cholelithiasis than females without cholelithiasis. However, only hypertension and hepatitis C ($p < .05$) reached statistical significance while controlling confounding variables.

CHAPTER V

DISCUSSION

The purpose of this study was to identify the relationship between predisposing risk factors and cholelithiasis occurrence in military female veterans. The specific aims for the study were: 1) Determine the demographic and environmental characteristics of female military veterans with and without cholelithiasis; 2) Examine differences among metabolic, liver enzyme and serum lipid laboratory data in female military veterans with and without cholelithiasis; 3) Explore differences between diagnosed metabolic and biliary comorbidities experienced by female military veterans with and without cholelithiasis; 4) Explore associations among demographic, environmental, laboratory data and diagnosis of comorbid conditions among female military veterans with and without cholelithiasis.

In the next section, conclusions and suggestions for each aim of this study were reviewed and the relation to literature was discussed. In addition, nursing implications, future research recommendations, methodological consideration, and limitation were presented. Results of the specific aims that are discussed in the chapters are as follow:

Specific Aim 1

Aim 1. Determine the demographic and environmental characteristics of female military veterans with and without cholelithiasis

The data did not support the differences of demographic and environmental characteristics in military female veterans with cholelithiasis occurrence. Factors including age,

Body Mass Index (BMI), and ethnicity in demographics were not significantly different in female veterans with and without cholelithiasis and no association was found with cholelithiasis. When considering environmental factors, length of military services and percentage of disability status were not significantly different in female veterans with and without cholelithiasis. In addition, use of alcohol and hormone replacement therapy were also not associated with cholelithiasis occurrence.

Tobacco use, on the other hand, was significantly associated with cholelithiasis. Female veterans who had a history of tobacco use had an increased risk for developing cholelithiasis.

Demographic Factors

Female gender (estrogen hormone use) and gallstones. This study only included females. The female gender is a significant risk factor for cholelithiasis development, yet no study was found to identify the risk of cholelithiasis occurrence in military female veterans. Females are almost twice as likely to develop gallstones (Everhart, Khare, Hill, & Maurer, 1999; Nakeeb et al., 2002) and more likely have a cholecystectomy compared with male population (Acalovschi, 2001). The different prevalence between men and women begins to narrow following menopause (Shaffer, 2005). Estrogen is a contributor, therefore parity, oral contraceptive use and estrogen replacement therapy are reported to be risk factors for cholelithiasis (Cirillo et al., 2005; Hulley et al., 1998; Thijs & Knipschild, 1993).

This study identified no relationship between the hormone replacement therapy and contraceptives, but showed a slight but insignificant negative association. Several studies have indicated there is a significant association between hormone replacement therapy (Angelin et al., 1992; Henriksson, Einarsson, Eriksson, Kelter, Angelin, 1989; Maurer, Everhart, Knowler, Shawker, & Roth, 1990), contraceptives (Scragg, McMichael, & Seamark, 1984) and

cholelithiasis occurrence whereas some studies have not found a positive relationship (Barbara et al., 1987). A randomized, double-blinded, placebo-controlled study suggested a greater risk to cholelithiasis, cholecystitis, and gallbladder surgeries in women aged 50 to 79 years with estrogen therapy (Cirillo, 2005). Another large prospective cohort study supported women receiving with oral estrogens alone had a greater risk for cholelithiasis as well as cholecystectomy than women receiving with oral estrogens combined with a progestagen (Racine et al., 2013). Although the effect of estrogen in relation to cholelithiasis development is not fully understood it is believed that estrogen can cause increased excretion of cholesterol into bile (Sanders & Kingsnorth, 2007) and diminish bile salt secretion, thus contributes supersaturation (Acalovschi, 2001) that leads to stasis.

This study did not support the findings of previous studies likely because of a small sample size. The sample size for this study was 484 in comparison to previous studies of 22,579 menopausal women (Cirillo et al, 2005) and 70,928 menopausal women (Racine et al., 2013). In this study, only one female veteran used hormone replacement therapy in the cholelithiasis group and four in the no-cholelithiasis group. Further, these investigators speculated that the relationship between female hormone therapy and cholelithiasis occurrence might be dose-dependent. A short time use or low dose of estrogen use may be associated with a lower risk for cholelithiasis development (Cirillo et al., 2005). This factor was identified in a study by Hulley et al. (1998) in a randomized trial during which post-menopausal women who were taking 0.625 mg of conjugated estrogens and 2.5 mg of medroxyprogesterone acetate had an increased risk of gallbladder disease compared to a placebo group during a 4 year follow-up. Another randomized placebo-controlled trial of the Women's Health Initiative supported that menopausal women who used 0.625 mg of estrogen had a greater risk of gallbladder disease or surgery (Cirillo et al.,

2005). The types, dose and length of the hormone therapy or contraceptives were not included in this study. Additional research may be needed to investigate the effect of hormone replacement therapy and contraceptives use including types, dose, and length of the therapy with a bigger sample size in relation to cholelithiasis in military female veterans.

Age and gallstones. Approximately 40% of the female veterans in the VHA system are under the age of 40 years and about 60% of female veterans are older than 44 years. (http://www.va.gov/vetdata/docs/SpecialReports/Women_Veteran_Profile5.pdf, 2013). The median age of military female veterans in the US is 49 years (http://www.va.gov/vetdata/docs/SpecialReports/Women_Veteran_Profile5.pdf, 2013). The mean age of women in this study was 58 due to the fact that this study included only females veterans aged over 40 years old. Previous studies have reported the prevalence of cholelithiasis increases with age, especially in age groups of women over 40 and the increased risk becomes 4 to 10 times more than females aged younger than 40 years (Shaffer, 2006). A prospective ultrasound-sonographic study supported the risk for developing cholelithiasis increases with age (Chen, 1998). Older female patients present more symptomatic gallstone diseases and as a result, have more cholecystectomies (Shaffer, 2006; Volzke et al., 2005). In this study, 47.6% of female veterans with cholelithiasis were aged 50-60 (47.6%). The studies indicate that during an abdominal work up, cholelithiasis also should be considered in the differential diagnosis, especially in women aged 45-60.

Ethnicity and gallstones. It is reported that about 33% of female veterans are considered a racial minority (any racial group other than white) (Census Bureau, 2011). Demographics in the VHA have shown female veterans consist of Caucasian (67%), African American (20.1%), Hispanic (7.8%), Asian and Native Hawaiian or Pacific Islander (1.8 %), American Indian or

Alaska Native (0.7%), and two or more races (2.7%) (Census Bureau, 2011). The ethnicity of female veterans with cholelithiasis presented in a similar pattern as the veteran distribution of the general VHA, as follows: Caucasian (69%), African American (27.3%), American Indian or Alaska Native (0%), Asian (.4%), Native Hawaiian or Pacific Islander (1.7%) and unknown (1.7%). The result of this study revealed no significant relationship between different ethnicity in female veterans and cholelithiasis occurrence. Previous studies identified ethnicity as an independent risk factor for cholelithiasis development. Prevalence studies have demonstrated North American Indians as having the highest reported rate of cholelithiasis development, affecting 64.1% of women and 29.5% of men (Everhart et al., 2002; Shaffer, 2005).

Body weight and gallstones. Women with severe obesity (BMI > 32 kg/m^2) are six times more likely to develop gallstones compared to non-obese controls (Maclure, Hayes, Colditz, Stampfer, Speizer, & Willett, 1989). The same study indicated that the annual chance of developing gallstones was about 2% in obese women (Maclure, Hayes, Colditz, Stampfer, Speizer, & Willett, 1989). This study supported the previous findings as a higher BMI (*M= 31.64, SD= 7.30*) was found in female veterans with cholelithiasis although the difference was not statistically significant.

Previous studies have demonstrated that obesity is a major factor for cholelithiasis occurrence, especially in females (Heaton, 1991; Everhart & Khare, 1999; Attili, 1997, Friedman, Kalel, & Dawber, 1996). This may be due to an increased hepatic secretion of cholesterol (Shaffer & Small, 1977) relative to a decrease in phospholipids and bile salts, creating supersatulation with cholesterol (Acalovschi, 2001; Angelico, Del Ben, Barbato, Conti, Urbinati, 1997; Amaral & Thompson, 1985; Apstein & Carey, 1996; Shaffer & Small, 1977) that can lead to gallstone formation. Several studies have shown a positive relationship with BMI

(Angelico, Del Ben, Barbato, Conti, & Urbinati, 1997; Attili et al., 1997; Chen et al., 1998; Mendiz-Sanchez, Vega, Uribe, Guevara, Ramos, & Vargas- Vorackova, 1998; Torgerson, Lindroos, Naslund, & Peltonen, 2003; Tsai, Leitzmann, Willett, & Giovannucci, 2004;), although some did not find the relationship (Janzon, Aspelin, Eriksson, Hildell, Trell, & Ostberg, 1985; Thijs, Knipschild, & Leffers, 1992).

The limitation of this study was the use of BMI as a measurement of obesity. More recent studies have found waist circumference and waist-to-hip ratio both to be better indicators obesity compared to BMI alone (Everhart et al., 2002; Tsai, Leitzmann, Willett, & Giovannucci, 2004). Some studies have supported abdominal adiposity as significantly correlated with cholelithiasis occurrence, especially in the female population (Everhart et al., 2002; Hartz, Rupley, & Rimm, 1984; Maclure et al., 1989; Tsai, Leitzmann, Willett, & Giovannucci, 2004). This suggests that waist circumferences and waist-to-hip ratio with BMI should be included in measuring obesity, especially in females. Additional studies are recommended while taking into account the diverse measurement for obesity in relation to cholelithiasis occurrence in military female veterans.

Environmental Factors

Military occupational factors and gallstones. This study did not find a significant relationship between military occupational factors and cholelithiasis occurrence among female veterans, except PTSD and MST that were discussed under comorbid conditions. Studies did not support the relationship between military occupational factors and cholelithiasis occurrence. Length of military services was longer in females with cholelithiasis than those without cholelithiasis but the difference was not significant. The branch of services was also not related

to cholelithiasis occurrence. The most common branch served by the study population with and without cholelithiasis was the Army followed by the Air Force and Navy.

A study reported male veterans with PTSD associated with warzone exposure were found to have abnormal lipids values (Karlovic, Buljan, Martinac, & Marcinko, 2004). However, female veterans were not included in this study. Another study reported PTSD was highly associated with abnormal lipids levels (Kagan, 1999). Many scientific studies have also demonstrated a strong association with abnormal serum lipid levels in people with cholelithiasis (Andreotti, 2008; Atamanalp et al., 2013; Fu, Gong, & Shao, 1995; Halldestam, Kullman, & Borch, 2009; Khairy et al., 2004; Tang, 1996; Thijs, Knipschild, & Brombacher, 1990). This study identified whether the warzone exposure in female veterans was associated with cholelithiasis occurrence. However, there was only one female with cholelithiasis who was exposed to warzone. Military disability is a major gateway to accessing healthcare in the VHA system. The mean percentage of disability status was slightly higher in female veterans with cholelithiasis than those without cholelithiasis. However the relation between military disability status and increased risk for cholelithiasis was not found in this study.

Alcohol use and gallstones. This study was not able to define the impact of alcohol use on cholelithiasis. There was no significant difference in females with and without cholelithiasis in relation to alcohol use. The literature has reported an inverse association between alcohol intake and cholelithiasis occurrence (Attili, Scafato, Marchioli, Marfisi, & Festi, 1998; Leitzmann et al., 1999; Leitzmann et al., 2003; Volzke et al, 2005; Walcher et al., 2010), although some studies have failed to find any relationship (Basso, McCollum, Darling, Tocchi, & Tanner, 1992; Kratzer et al., 1997; Pixley & Mann, 1988; Sahi, Paffenbarger, Hsieh, & Lee, 1998).

Volzke et al. (2005) demonstrated relative risks of daily amount of alcohol consumption being associated with cholelithiasis. The findings of this study showed that men who consumed daily alcohol intakes of more than 60 grams had a significantly lower risk of developing cholelithiasis in comparison to men who consumed less daily alcohol. Studies that included both men and women also supported similar outcomes that frequent moderate alcohol consumption was associated with a lower risk for cholelithiasis occurrence (Leitzmann, et al., 2003; Thornton, J., Symes, C., & Heaton, K, 1983). The risk of cholelithiasis increases in severe alcohol abuse because of damage to the liver and reduced bile salt synthesis (Fornari et al., 1994; Poynard et al., 1995).

These studies supported a hypothesis that alcohol consumption may inhibit cholesterol stone formation by reducing the cholesterol saturation, raising bile salts (Nestel, Simons, & Homma, 1976; Yoshida, McCormick, Swell, & Vlahcevic, 1975) and increasing HDL concentration (Gaziano et al., 1993; Rakic, 1998; Thornton, Symes, & Heaton, 1983). Overall US military veterans are reported to have higher alcohol consumption and higher prevalence of alcohol-related medical problems (Park, 2011) in comparison to male civilians. Unfortunately, studies related to the same issue among female veterans are limited.

Tobacco use and gallstones. The finding of this study revealed a significant relationship between tobacco use and cholelithiasis occurrence in female veterans. Females with tobacco use were 3 times more likely to develop cholelithiasis compared to females who indicated that they did not smoke. Literature was not clear whether or not tobacco use increases the risk of cholelithiasis occurrence. Some studies reported that smokers have a lower tendency to develop cholelithiasis due to a mechanism involving decreased prostaglandin synthesis and mucus production in the gallbladder epithelium (Lindstrom, 1977). However, another study has drawn

the opposite conclusion that heavy smoking (more than 35 cigarettes per day) was an independent risk factor for cholelithiasis occurrence among women (Stampfer, Maclure, Colditz, Manson, & Willett, 1992). A large-scale population-based study of women supported smoking as an important risk factor for developing symptomatic gallstone disease (Murray, Logan, Hannaford, & Kay, 1994).

Specific Aim 2

Aim 2. Examine differences among metabolic, liver enzyme and serum lipid laboratory data in female military veterans with and without cholelithiasis

The findings of this study supported the relationship between serum metabolic levels and increased risks for cholelithiasis. Female veterans with cholelithiasis had a significantly higher hemoglobin A1C (HbA1C) levels than female veterans without cholelithiasis. The difference was significant but no difference was found in serum fasting glucose level. HbA1C was one of the most significant independent indicators to predict cholelithiasis in this study.

There was no association found between serum liver enzyme levels and cholelithiasis among female veterans. Pearson Correlation analysis in this study indicated that AST, ALT and bilirubin were not associated with cholelithiasis occurrence although they are known to be an effective predictor for liver damage (Kaplan, 2002; Tung et al., 2006), especially in patients with hepatitis C and liver cirrhosis (Sheth, Flamm, Gordon, & Chopra, 1998).

Partial support was found for the link between serum lipid levels and cholelithiasis among female veterans. High total serum cholesterol levels and low HDL levels were significantly associated with cholelithiasis. LDL cholesterol and triglycerides levels were not statistically different in females with and without cholelithiasis.

Metabolic Tests (Fasting glucose and Hemoglobin A1C) and Gallstones

Serum fasting glucose levels are widely used as a diagnostic criterion for diabetes (American Diabetes Association, 2010; World Health Organization, 2006). Many studies have indicated the close association between diabetes and increased risk for cholelithiasis (De Santis, et al., 1997; Gielkens et al., 1998; Haffner, Diehl, Mitchell, Stern, & Hazuda, 1990; Shaw et al., 1993), yet serum fasting glucose levels are not commonly evaluated. Previous studies reported that hyperglycemia contributed to reduction of bile secretion from the liver by increasing cholesterol concentration, this then decreases gallbladder motility and leads to gallstone formation (DeBoer, Masclee, & Lamers 1992; Leon, Ferenderes, & Carulli, 1978). Another studies have indicated patients with gallstones had further complications of hyperglycemia and autonomic neuropathy in comparison to patients without gallstones (Fiorucci et al., 1990; Hahm et al., 1996).

Findings of this study indicated that female veterans with higher hemoglobin A1C levels also had a higher risk of developing cholelithiasis in comparison to females with normal hemoglobin A1C values. American Diabetes Association (2010) defines the normal value of hemoglobin A1C as less than 5.7%. The mean hemoglobin A1C level in female veterans with cholelithiasis was 7.41% and 6.09% in those without cholelithiasis. Some studies argue hemoglobin A1C is a better tool to identify a patient's diabetic severity (Nathan et al., 2008; Goldstein et al., 2004). There are very few studies that explore the relationship between hemoglobin A1C and the increased risk for cholelithiasis (Al-Bayati & Kodayer, 2012). The findings of this study revealed gallstones were more prevalent in diabetic patients with increased hemoglobin A1C levels (Al-Bayati & Kodayer, 2012).

The findings of this study were consistent with other established studies that cholelithiasis is a metabolic disease that is also linked to diabetes (De Santis et al., 1997;

Gielkens et al., 1998; Haffner, Diehl, Mitchell, Stern, & Hazuda, 1990; Shaw et al., 1993). This association with diabetes is further discussed in the comorbid conditions section (Please see page 102).

Liver Enzymes (ALT, AST, bilirubin) and Gallstones

The literature describes liver cirrhosis as an independent risk factor for cholelithiasis, with a prevalence rate of 25% to 30% (Acalovschi, Badea, Dumitaccu, & Varga, 1988; Conte, Barisani, Mandelli et al., 1991; Conte, Fraquelli, Fornari et al., 1999). The most sensitive indicators to determine liver cell damage or disease are alanine aminotransferase (ALT) and aspartate aminotransferase (AST). ALT and AST are the most common tests used to measure disease severity and hepatic activity (Kaplan, 2002; Tung et al., 2006), especially in patients with hepatitis C and liver cirrhosis (Sheth, Flamm, Gordon, & Chopra, 1998). In addition, serum bilirubin tests calculated in conjunction with ALT and AST have been used to identify types of liver diseases. This study did not find a significant association between serum liver enzymes and cholelithiasis occurrence in female veterans.

Limited literature was found that identified the relationship between liver enzymes and an increased risk for cholelithiasis. Tung et al. (2006) described that elevated ALT levels may indicate an increased risk of cholelithiasis when type II diabetes is also present. This study suggests integrated diagnosis and therapeutic interventions in early liver cirrhosis may decrease the risk of cholelithiasis (Tung et al., 2006). However, literature was not found that supported liver enzymes as an independent risk factor associated with cholelithiasis. Grau et al.'s study (1999) demonstrated that elevation of ALT, AST, and bilirubin was unrelated to cholelithiasis occurrence but interpretation of biliary tract obstruction (Grau et al., 1999).

Lipid Profile (total cholesterol, HDL, LDL, Triglycerides) and Gallstones

Significant differences were found in serum total cholesterol and HDL in female veterans with and without cholelithiasis. Female veterans with cholelithiasis had significantly higher total cholesterol values than those without cholelithiasis. Previous studies indicated that a high mean total cholesterol level was significantly associated with high prevalent cholesterol gallstone formation (Andreotti, 2008; Atamanalp et al., 2013; Khairy et al., 2004; Halldestam, Kullman, & Borch, 2009). However, some studies argued total cholesterol was inversely associated with cholelithiasis occurrence (Scragg, Calvert, & Oliver, 1984; Thijs, Knipschild, & Brombacher, 1990).

This study indicated that there was a significant association between low HDL cholesterol and an increased risk for cholelithiasis. Normal HDL cholesterol levels are considered to be over 60 mg/dL (National cholesterol education program, 2001). Although both groups with and without cholelithiasis had lower than normal HDL levels, the mean value was significantly lower in females with cholelithiasis (47.13 mg/dL) than those without cholelithiasis (56.28 mg/dL). Previous studies, based on randomized trials, have reported that patients with low HDL levels have a higher risk of developing cholesterol gallstones (Andreotti et al., 2008; Fu, Gong, & Shao, 1995; Tang, 1996; Thijs, Knipschild, & Brombacher, 1990). In contrast, some of the studies failed to find a relationship between low HDL levels and cholelithiasis occurrence (Aulakh, Mohan, Attri, Kaur, & Punia, 2007; Fu et al., 1997; Halldestam, Kullman, & Borch, 2009).

This study did not support a high serum LDL level as a strong indicator for increased risk of cholelithiasis (Fu, Gong, & Shao, 1995; Fu et al., 1997; Halldestam, Kullman, & Borch, 2009; Han, Jiang, Suo, & Zhang, 2000). Epidemiologic studies have indicated high serum levels of LDL were positively associated with increased risk for cholesterol gallstones (Fu, 1997; Han,

2000; Fu, 1995; Halldestam, 2009; Atamanalp, 2013); yet other studies found an inverse association between LDL and cholelithiasis occurrence (Andreotti et al., 2008; Tang, 1996).

In this study, there was no significant correlation among serum triglyceride levels and cholelithiasis occurrence. Studies have reported hypertriglyceridemia observed in obesity, insulin resistance or excessive alcohol consumption have contributed to reduced bile salts, increased biliary cholesterol secretion, delayed gallbladder mortality, and crystal formations in the gallbladder (Jonkers et al., 2003; Lee, LaMonte, & Carey, 1981; Wang, Cohen, & Carey, 2009). Studies to identify the relation between high levels of triglyceride and increased risk for cholelithiasis were limited (Jonkers et al., 2003).

Specific Aim 3

Aim 3. Explore differences between diagnosed metabolic and biliary comorbidities experienced by female military veterans with and without cholelithiasis.

The findings of this study indicated that cholelithiasis is closely related to metabolic disease. More female veterans with cholelithiasis had diabetes, dyslipidemia and hypertension and other comorbid diseases were associated with cholelithiasis occurrence. The prevalence of both hepatitis C and liver cirrhosis was also significantly higher in female veterans with cholelithiasis. A significant relationship was not found between hepatitis B and cholelithiasis occurrence in female veterans. PTSD and MST also had significant associations with cholelithiasis occurrences in female veterans.

Metabolic Diseases and Gallstones

Cholelithiasis is considered a metabolic disease because of its tight relationship with metabolic syndrome (Ata et al., 2011). Metabolic syndrome is a cluster of disorders that include abdominal obesity, high blood pressure, high fasting glucose, increased triglyceride levels and

low HDL cholesterol levels (Eckel, Grundy, & Zimmer, 2005; Mendez-Sanchez et al., 2005). Because metabolic syndromes include obesity, diabetes, hypertension, and dyslipidemia, the mechanism by which it causes gallstone formation is by increasing hepatic cholesterol secretion, reducing bile salt synthesis, and impairing gallbladder motility (Biddinger et al., 2008; Nakeeb, Comuzzi, Al-Azzawi, Sonnenberg, Kissebah, & Pitt, 2006). Although the relationship between diabetes mellitus and the risk for cholelithiasis still remains unclear, several studies have indicated that diabetes is a significant risk factor for cholelithiasis (De Santis et al., 1997; Gielkens et al., 1998; Haffner, Diehl, Mitchell, Stern, & Hazuda, 1990; Shaw et al., 1993). Ruhl and Everhart (2000) reported that patients with insulin-resistant type II diabetes have a 200-300% increased risk for cholelithiasis over patients without diabetes. However, other population-based studies have failed to find the relationship between diabetes and increased risk for cholelithiasis (Barbara et al., 1987; Jorgensen, 1989). This study supported a positive relationship among higher prevalence of diabetes and increased risk factors for cholelithiasis in female veterans.

Although previous studies have indicated a relationship between individual serum cholesterol tests and cholelithiasis occurrence, the relationship between dyslipidemia and the risk for cholelithiasis remains inconclusive (Janzon, Aspelin, Eriksson, Hildell, Trell, & Ostberg, 1985; Thijs, Knipschild, & van Engelshoven, 1990). Some studies have reported significant relationships among abnormal serum lipid levels and an increased risk of cholelithiasis (Andreotti, 2008; Atamanalp et al., 2013; Fu, Gong, & Shao, 1995; Khairy et al., 2004; Halldestam, Kullman, & Borch, 2009; Tang, 1996; Thijs, Knipschild, & Brombacher, 1990). However, other studies did not find the same associations (Andreotti et al., 2008; Aulakh, Mohan, Attri, Kaur, & Punia, 2007; Fu et al., 1997; Halldestam, Kullman, & Borch, 2009; Tang,

1996). The results of this study indicated dyslipidemia was significantly associated with cholelithiasis. Female veterans with cholelithiasis had higher frequencies of dyslipidemia compared to those without dyslipidemia.

Hypertension and Gallstones

Hypertension is a component of metabolic disorder that could be considered to be reasonably association of cholelithiasis. It is unclear whether hypertension is an independent risk factor for cholelithiasis or what mechanisms related to high blood pressure are specifically associated with gallstone formation. Gaziano and associates (1993) have argued that patients who are overweight with increased diastolic pressure had a higher prevalence of cholelithiasis. Another study indicated that patients with blood pressures $\geq$ 130/85 mmHg had a significantly higher risk of cholesterol gallstones (Thijs, Knipschild, & Brombacher, 1990). This study is consistent with previous studies indicating that female veterans with hypertension had a higher relationship with cholelithiasis. Even after controlling confounding variables, hypertension was one of the most significant risk factors for cholelithiasis occurrence in female veterans. This study showed that female veterans diagnosed with hypertension were 2.68 times more likely to develop cholelithiasis than those without hypertension.

Biliary Diseases and Gallstones

The literature has shown that there is a significant relationship between hepatitis C and liver cirrhosis and the increased risks for cholelithiasis (Acalovschi, Badea, Dumitaccu, & Varga, 1988; Conte, Barisani et al., 1991; Conte et al., 1999) and the prevalence increases as liver disease progresses (Conte et al., 1991; Fornari, Civardi, Buscarini, Cavanna, 1990; Fornari, Imberti, Squillante, 1994). Previous studies have demonstrated that cholelithiasis was more prevalent in patients with hepatitis C virus (HCV) (11.7% - 23.3%) than in patients with hepatitis

B (Bini & McGready, 2005; Chang et al., 2005; Stroffolini, Sagnelli, Mele, Cottone, & Almasio, 2007). An Italian study of patients with HCV related cirrhosis were two times more likely to have cholelithiasis in comparison to patients with hepatitis B related cirrhosis (Stroffolini, Sagnelli, Mele, Cottone, & Almasio, 2007). Another population-based study identified the increased risks for cholelithiasis occurred not only in men but also in women who were HCV positive (Acalovschi, Buzas, Radu, & Grigorescu, 2009).

This study supported previous research that hepatitis C was significantly correlated with risk for cholelithiasis while no association was found in female veterans with hepatitis B. Some researchers explained the phenomenon associated with cholelithiasis that HCV infection may have contributed to abdominal adiposity and reduced bile salts, leading to insulin resistance (Acalovschi, Buzas, Radu, & Grigorescu, 2009, Cua, Hui, Kench, & George, 2008; Eguchi et al., 2009) and increased bile cholesterol saturation (Acalovschi, Buzas, Radu, & Grigorescu, 2009).

The results of this study were consistent in finding that liver cirrhosis has a high association with cholelithiasis. Additionally, liver cirrhosis in female veterans was significantly associated with cholelithiasis occurrence (Shaffer, 2006). Buchner and Sonnenberg (2002) study reported that the prevalence of gallstones was in 8% of patients with liver disease compared to 5% of control patients without liver disease. The study also demonstrated that non-alcohol related liver cirrhosis was highly associated with increased risk for cholelithiasis as compared to alcohol-induced liver cirrhosis, which supported Volzke and associates' study hypothesis that a moderate alcohol consumption may protect from gallstone formation. This study did not identify which type of liver cirrhosis was associated with cholelithiasis because it evaluated general risk factors related to cholelithiasis occurrence.

Liver cirrhosis has been established as a risk factor for cholelithiasis (Fornari et al., 1994; Olmo, Garcia, Serra, Maldonada, & Rodrigo, 1997). Studies have found the risk of cholelithiasis was approximately 8 times higher in patients with liver cirrhosis compared to the general population (Fornari et al., 1994; Olmo, Garcia, Serra, Maldonada, & Rodrigo, 1997). The overall prevalence rate for cholelithiasis was at 25-30% in patients with liver cirrhosis (Conte, Fraquelli, Fornari, Lodi, Bodini, & Buscarini, 1999; Conte et al., 1991; Zhang et al., 2006). It is believed liver cirrhosis may contribute to gallstone formation due to abnormal gallbladder motility, reduced hepatic synthesis, and decreased bile salts (Acalovschi, Badea, & Pascu, 1991; Alvaro, Angelico, Gandin, Ginanni, Corradini, & Capocaccia, 1990), leading to increase unconjugated bilirubin (Vitek & Carey, 2003). More than 80 percent of gallstones in liver cirrhosis are pigmented black stones (Diehl, Schwesinger, Holleman, Chapman, & Kurtin, 1995; Schwesinger Kurtin, Levine, & Page, 1985).

Other Comorbid Conditions and Gallstones

Posttraumatic stress disorder (PTSD). The finding of this study indicated female veterans with a diagnosis of PTSD had a higher risk of developing cholelithiasis than those without PTSD. No previous studies were found to support this study outcome. Because dyslipidemia is correlated with cholelithiasis, abnormal lipids values in female veterans with PTSD should be further evaluated. Karlovic et al. (2004) identified military veterans with combat-related PTSD had significantly higher levels of cholesterol, LDL, and triglyceride compared to veterans with combat experiences without PTSD and healthy control. This study also demonstrated serum HDL levels were significantly lower in veterans with combat-related PTSD than those without PTSD or in the healthy control group (Karlovic, Buljan, Martinac, & Marcinko, 2004). Another study also found that veterans with PTSD had significantly higher

cholesterol and lower HDL concentrations in comparison to other groups, such as Vietnam era veterans, substance abuse veterans, and civilians (Kagan, Leskin, Hass, Wilkins, & Foy, 1999).

Although the etiology between high lipid levels and PTSD is unknown, it might be associated with military veterans' diet patterns, stress levels, or activity levels.

Military sexual trauma (MST). MST is a subcomponent of PTSD. It is defined by the US Department of Veterans Affairs as "sexual harassment that is threatening in character or physical assault of a sexual nature that occurred while the victim was in the military regardless of geographic location of the trauma, gender of the victim or the relationship to the perpetrator" (Veterans' Benefits U. S. Code, Section, Title 38, 1720D, 1992) This study showed that the female veterans with cholelithiasis group reported higher rates of MST compared to females without cholelithiasis. Although the association with cholelithiasis was not significant when controlling for confounding factors, this result should be further evaluated.

The literature indicated there is a broad range of negative health outcomes related to MST as well as sexual assault in civilian populations (Kimerling et al., 2007; Sadler et al., 2000; Skinner et al., 2000; Stein & Barrett- Connor, 2000). A recent study showed female veterans with diagnosed of MST have increased risks for anxiety, drug abuse, and higher rates of homelessness compared to female veterans without a history of MST (Decker et al., 2013). Another study reported that MST was an independent cause for decreased mental and cognitive functioning, quality of life, and somatic distress (Kimerling et al., 2007).

The prevalence rate for MST in all eras of service ranges from 0.4% to 63.0% in women and 0.6% to 6.0% in men (Kang et al., 2005; Kimerling et al., 2010; Murdoch et al., 2014; Skinner et al., 2000; Suris & Lind, 2008; Wolfe et al., 1998). The wide range of prevalence is related to variability in sample collection. A study revealed a 0.4% prevalence rate with MST in

women from the Vietnam-era. Consequently, up to 63% of female veterans have sought treatment from a VHA stress disorder clinic (Fontana & Rosenheck, 1998). Studies with nationally collected samples have reported the numbers of military sexual trauma are more frequent in females and younger veterans (Kimerling et al., 2010; Suris & Lind, 2008). MST is also underreported (Department of Veterans Affairs, 2014), with a high suspicion that military sexual disorder is grossly underestimated in the females older than 40 years old.

Specific Aim 4

Aim 4. Explore associations among demographic, environmental, laboratory data and diagnosis of comorbid conditions among female military veterans with and without cholelithiasis.

The findings of this study suggested several predisposing factors were independently associated with cholelithiasis occurrence in female veterans after controlling confounding effects. In this study, tobacco use was found be an independent risk factor for increased risk for cholelithiasis. The result also showed that female veterans who use tobacco had 3.15 times the risk of developing cholelithiasis compared to female veterans who did not use tobacco.

This study's results also revealed that higher hemoglobin A1C levels, higher total cholesterol levels, and lower HDL levels were independently associated with cholelithiasis occurrence. Female veterans with all three factors had a 26% likelihood to develop cholelithiasis.

Although most comorbid conditions including diabetes, dyslipidemia, liver cirrhosis, hepatitis C, posttraumatic stress disorder, and military sexual trauma were highly related to female veterans with cholelithiasis, a significant correlation was not evident when controlling the confounding association between variables. However, hypertension and hepatitis C were identified as independent risk factors for cholelithiasis in female veterans. The result indicated that female veterans with a diagnosis of hypertension had 2.68 times the risk of developing

cholelithiasis compared to female veterans than without. Female veterans diagnosed with hepatitis C had 8.34 times the risk for developing cholelithiasis compared to female veterans without hepatitis. This result required a careful interpretation because of a wide range within the confidence interval (95% CI= 1.07-64.77).

Methodological Consideration

Many researchers believe daily-accumulated electrical medical records often referred to as 'big data' offers great promises for future research. This study is a big data study based on the corporate data warehouse of the VHA system. The approaches in systemic collecting and managing the big data were different from the traditional prospective research or retrospective data study based on chart reviews. This study demanded significant new training and education in order how to retrieve data from the corporate data warehouse as well as how to layout and store the retrieved data, to map and combine pieces of information tables, to comprehend how to filter data, to validate the retrieved cohort, and to analyze the final data in provided virtual setting in the Veterans Affairs Informatics and Computing Infrastructure (VINCI). The challenges of this study included learning all new terms, technologies, techniques, and institutional policies related to a big data study as well as managing interdisciplinary collaboration with a computer engineer, a data manager, data counselor, and data managing agencies.

Despite challenges and difficulties in conducting a big data study, it was extremely valuable to be a part of this massive venture. Research based on the patients' electronic medical data enhances medical practice and public health by investigating their real, accumulated, and objective information in an efficient and timely manner.

Study Limitation

Although this study design was to determine the relationship between predisposing risk factors and cholelithiasis occurrence, some limitations may apply to this study. First, a major limitation was the potential selection bias when filtering data. The study cohort may not be representative of the general female veteran population. Second, missing or incorrect data, especially using retrospective data, might lead to bias due to invalid or imprecise study measurement. The researcher could not control for these errors but acknowledges them in the findings. Third, although this study only includes female veterans, no data was included such as parity, types of hormones, doses, or length of time on female hormone replacement therapy or contraceptives. Therefore, cholelithiasis occurrence in relation to female factors in this study could be underestimated. Fourth, serum laboratory levels were measured at a time when the disease was already present. Therefore, the strength of the relationship between abnormal serum laboratory levels and cholelithiasis occurrence could be underestimated.

Implications for Nursing Science, Practice and Education

The findings of this study provides several points that are especially pertinent to clinicians including nurses and physicians particularly in facilities that provide care to female veterans. Understanding prevalence and risk factors associated with cholelithiasis occurrence is essential for managing patient care and the prevention of gallstone formation (Broulik, Hass, & Adamek, 2005). Education to nurses and physicians may improve understanding of the physiological and scientific background knowledge of cholelithiasis occurrence, and that could serve as a resource when educating patients and patients' family members. Identifying risk factors and prevention strategies related to cholelithiasis should be included in pre-licensure curricula so that nurses better understand the disease and can actively be involved in the

development of care plans specific to a patient with cholelithiasis or has possible risk factors for cholelithiasis.

Additionally, the outcome of the study may contribute to building a strategic plan for preventing cholelithiasis. Due to multiple correlations with environmental factors, patient centered assessment of risk factors for cholelithiasis may be deployed to provide individual strategies to avoid symptomatic cholelithiasis and prevent the need for aggressive treatments or complications. The preventive program should not only include diagnosed disease control but also lifestyle modification aimed at optimizing dietary factors, physical activity and ceasing alcohol and tobacco consumption, especially among women. The outcome of this study may also be useful to guide practitioners towards choosing accurate diagnostic tests, especially in female veterans with unknown abdominal pain.

Recommendations for Future Research

Although the findings of this study identified that several risk factors were associated with increased risk for cholelithiasis occurrence in female veterans, they also raise additional questions that can be the basis for further research.

- The findings of this study indicated that female veterans who used tobacco were at increased risk for cholelithiasis. There is a need to further evaluate the relationship between tobacco use and cholelithiasis occurrence while taking into consideration the types of tobacco used, tobacco frequency and the duration of the smoking habit. Other studies are also needed to investigate the impact of alcohol consumption on gallstone formation among female veterans.
- Findings of this study revealed that high serum hemoglobin A1C levels were significantly associated with an increased risk of cholelithiasis. There is a need to

further examine levels of serum hemoglobin A1C over time and investigate whether the serum levels are associated with clinical symptoms in populations with cholelithiasis. It may be also worth determining whether advanced diabetics with controlled hemoglobin A1C have a higher risk for cholelithiasis.

- Findings of this study identified that lipid levels were associated with an increased risk for cholelithiasis in female veterans. Although cholesterol is a primary contributing factor for cholesterol gallstone formation, the relationship among serum lipids level and an increased risk for cholelithiasis still remains unclear.
  Further studies are needed while taking into consideration the types, size, location, and onset of the gallstones in relation to cholelithiasis occurrence in female veterans. Findings of Jorgensen's (1989) study identified that a newly developed small gallstone may contribute to abnormal serum lipids levels more than a large, slowly developing gallstone. In addition, there is a need to further evaluate the effects of lipid-lowering drugs on the occurrence of cholelithiasis in both women and veterans.
- Findings of this study revealed that hypertension or hepatitis C were significantly associated with an increased risk cholelithiasis. There is a need to further investigate what physiological mechanism associated with high blood pressure leads to the increased risk for cholelithiasis. There is a need to further evaluate the relationship between controlled blood pressure and cholelithiasis occurrence in both women and veterans. Additionally, studies are needed to investigate whether chronic and acute hepatitis C are differently associated with cholelithiasis occurrence.
- The female veteran population is estimated to increase by 12% within the next five years while the male veteran population is projected to decrease by approximately

27% over the same period (Women Veteran Profile, 2013). Given the increase in female veterans serving longer military deployments and increases in warzone exposures, research should further explore factors that influence negative health outcomes in female veterans. Future studies are greatly needed to investigate the relationship between PTSD and increased risk for cholelithiasis occurrence in military female veterans. Considering the established relationship studies among dyslipidemia and increased risk factors for cholelithiasis, there is a need to further examine the degree of PTSD conditions associated with female veterans with symptomatic conditions on cholelithiasis.

Overall Summary and Recommendation

Cholelithiasis is one of the most common and expensive gastroenterological disorders and the prevalence has been rising, especially in women.

This study identified tobacco use, high total cholesterol and hemoglobin A1C levels, low HDL levels and hypertension as independent risk factors for cholelithiasis occurrence in female veterans. Prior to this study, predisposing risk factors associated with cholelithiasis in female veterans had not been investigated although the VHA medical records indicated that the number of female veterans with cholelithiasis and needing cholecystectomy was clearly increasing within the VHA system (VHA, 2014).

The female veteran population will be experiencing high growth rate in the near future. The rising population is understudied and more research will allow health care providers to provide proactive strategies in predicting risk factors for cholelithiasis. Given that a large number of female veterans undergo surgical interventions, preventive strategies may decrease not only unnecessary surgeries but reduce surgical complications and improve quality of life.

APPENDICES

Appendix A
Acknowledgements

This dissertation was not completed without the enthusiastic guidance and encouragement from my advisor and my committee members.

I would like to express my gratitude to my committee chair, Dr. Glenda Lindseth and committee members, Dr. Dalra Adams, Dr. Jody Ralph, Dr. Thomas Petros, and Dr. Van Doze who provided unlimited support throughout this dissertation journey. First and foremost, I would like to thank my advisor, Dr. Glenda Lindseth (University of North Dakota) for her resolute dedication and encouragement to my learning, and enable me to complete this dissertation. She has been an extraordinary mentor, devoting endless guidance, countless hours of reviewing, correcting, commenting, proofreading, and more. This work was not possible without her strong encouragement and passion for guidance. Many thanks to Dr. Darla Adams (University of North Dakota) for her encouragement and enthusiasm throughout this study process. She has been a great cheerleader as she promised at the beginning of this journey offering big hugs whenever I felt in giving up.

I would like to thank you, Dr. Jody Ralph (University of North Dakota) for listening to me and guiding me to overcome obstacles. Without her understanding and encouragement, I would have been lost. Special thanks to Dr. Thomas Petros (University of North Dakota) who was always there for me whenever I had difficulty understanding statistics. I honestly don't understand how he always manages positive attitude despite his uncomfortable physical condition. I would also like to thank Dr. Van Doze (University of North Dakota) for serving on my dissertation committee in his tight schedule. Thank you so much.

Appendix B
IRB Initial Approval (Orlando VA)

Institutional Review Board
Orlando VA Medical Center - 675
5201 Raymond Street • Orlando, FL 32803

IRB APPROVAL - Initial Review

Date: March 27, 2014
From: Mary Beth Shea, Ph.D., Chairperson
Investigator: Mila Pak, MS, CRNA
Protocol: Identifying Risk Factors Cholelithiasis in Military Female Veterans
ID: 00020 Prom#: N/A Protocol#: 14-00020

The following items were reviewed and approved through Expedited Review:

- OVAMC RF 001 Application for New project (02/26/2014)
- OVAMC RF 002 Request for and Determination of Expe (03/17/2014)
- OVAMC RF 005 Application for and Determination of (02/24/2014)
- OVAMC RF 006 Request for and Determination of Waiv (02/24/2014)
- OVAMC RF 007 Request for and Determination of Waiv (03/17/2014)
- OVAMC RF 017 Reviewer Worksheet for Privacy Confid (02/28/2014)
- OVAMC RF 035 Attestation for Adherence to Privileg (03/17/2014)
- OVAMC IRB Form 052 Resources WS Acc Request f/a De (03/17/2014)
- OVAMC RF 053.1 Forms and Documents Checklist Initi (03/18/2014)
- OVAMC RF 054 Scope of Practice (03/18/2014)
- OVAMC RF 055 Site Personnel Delegation of Responsi (03/18/2014)
- Research Financial Conflict of Interest (03/17/2014)
- Correspondence - Correspondence from Professor (02/10/2014)
- Research Protocol Safety Survey (VA Form 10-0398) (03/17/2014)
- Memo from Privacy Officer (03/12/2014)
- VA Form 17.1 Addendum Reviewer Worksheet Privacy (02/28/2014)
- CITI Training (02/26/2014)
- Credentialing Pak (02/25/2014)
- Privacy and ISO Training (06/19/2013)
- HIPAA Training (06/17/2013)
- Research and Development Information System Projec (03/17/2014)
- Research and Development Information System Invest (03/17/2014)
- Curriculum Vitae (03/17/2014)
- Biosketches (03/17/2014)
- Protocol - Identifying Risk Factors of Cholelithiasis (02/24/2014)

Expedited Approval [Expedited under Federal Regulation: 45 CFR 46.110(b)(1)(5) / VA Regulation: 38 CFR 16.110(b)(1)(5)] was granted on 03/27/2014 for a period of 12 months and will expire on 03/26/2015. No Continuing Review is scheduled. This Expedited review will be reported to the fully convened Institutional Review Board on 04/08/2014.

The following other committee reviews are scheduled:
Research & Development Committee [05/02/2014]

Approval by each of the following is required prior to study initiation:
Institutional Review Board

Approval for study initiation is contingent upon your compliance with the requirements of the Research Service for the conduct of studies involving human subjects.

Appendix C
Research Approval (Orlando VA)

Research & Development Committee
Orlando VA Medical Center - 675
5201 Raymond Street • Orlando, FL 32803

APPROVAL - Initial Review

Date: May 2, 2014
From: Radu Clincea, MD, Chairperson
Investigator: Mila Pak, MS, CRNA
Protocol: Identifying Risk Factors Cholelithiasis in Military Female Veterans
ID: 00020 Prom#: N/A Protocol#: 14-00020

The following items were reviewed and approved at the 05/02/2014 meeting:

- OVAMC RF 001 Application for New project (02/26/2014)
- OVAMC RF 002 Request for and Determination of Expe (03/17/2014)
- OVAMC RF 005 Application for and Determination of (02/24/2014)
- OVAMC RF 006 Request for and Determination of Waiv (02/24/2014)
- OVAMC RF 007 Request for and Determination of Waiv (03/17/2014)
- OVAMC RF 017 Reviewer Worksheet for Privacy Confid (02/28/2014)
- OVAMC RF 021 Reviewer Worksheet for New Project Ap (03/27/2014)
- OVAMC RF 021 Reviewer Worksheet for New Project Ap (03/27/2014)
- OVAMC RF 035 Attestation for Adherence to Privileg (03/17/2014)
- OVAMC IRB Form 052 Resources WS Acc Request f/a De (03/17/2014)
- OVAMC RF 053.1 Forms and Documents Checklist Initi (03/18/2014)
- OVAMC RF 054 Scope of Practice (03/18/2014)
- OVAMC RF 055 Site Personnel Delegation of Responsi (03/18/2014)
- Research Financial Conflict of Interest (03/17/2014)
- Correspondence - Correspondence from Professor (02/10/2014)
- Research Protocol Safety Survey (VA Form 10-0398) (03/17/2014)
- Memo from Privacy Officer (03/12/2014)
- VA Form 17.1 Addendum Reviewer Worksheet Privacy (02/28/2014)
- CITI Training (02/26/2014)
- Credentialing Pak (02/25/2014)
- Privacy and ISO Training (06/19/2013)
- HIPAA Training (06/17/2013)
- Research and Development Information System Projec (03/17/2014)
- Research and Development Information System Invest (03/17/2014)
- Curriculum Vitae (03/17/2014)
- Biosketches (03/17/2014)
- Protocol - Identifying Risk Factors of Cholelithiasis (02/24/2014)

This study has been approved by the Research and Development Committee. You may initiate

research upon receipt of an approval letter from the Designated Research Officer.

Approval by each of the following is required prior to study initiation:
Institutional Review Board [Approval Granted 03/27/2014]

Appendix D
Memorandum (VA Final Approval Letter)

Department of Veterans Affairs

Memorandum

Date: May 2, 2014

From: Designated Research Officer

Subj: Final Approval of VA Research

To: Mila Pak, CRNA

1. Your research study entitled *Identifying Risk Factors of Cholelithiasis in Military Female Veterans* (IRB 14-00020) was approved by the Research and Development Committee on May 2, 2014, to be conducted at the Orlando VA Medical Center.

2. You are authorized to begin this study upon receipt of this memorandum.

3. You are required to submit a progress report for continuing review at twelve (12) month intervals as specified by the IRB. Based on the IRB approval date of March 27, 2014, the continuing review date for the first year will be February 10, 2015.

4. You are required to comply with all applicable VA, OVAMC, federal, and state regulations, policies, and procedures including maintenance of all research-related administrative, regulatory and clinical records throughout the conduct of your study

5. Changes to your protocol, associated documents, and study staff must have the prior approval of both the IRB and the Research and Development Committee, prior to implementation.

6. Adverse events and other reportable events must be handled in accordance with the provisions of Research Service Standard Operating Procedures 037, *Reportable Events* and 037a, *Reportable Events Guidance for Investigators.*

7. For information and guidance concerning policies and procedures for the conduct of Research, you may contact Dr. William Fite at William.Fite@va.gov. For questions related to financial and administrative issues, you may contact Mr. Denis Medina at Denismar.Medina@va.gov. For guidance regarding regulatory issues and requirements, you may contact Ms. Barbara Calabrese at Barbara.Calabrese@va.gov.

8. Congratulations on the approval of your study. We wish you every success and stand ready to advise you and assist you in any way we can.

William H. Fite, DSN, ARNP
Designated Research Officer

cc: Research Leadership Group

Appendix E
IRB Approval (University of North Dakota)

UNIVERSITY OF NORTH DAKOTA

UND.edu

DIVISION OF RESEARCH & ECONOMIC DEVELOPMENT

Institutional Review Board
c/o Research Development and Compliance
Twamley Hall, Room 106
264 Centennial Drive Stop 7134
Grand Forks, ND 58202-7134
Phone: 701.777.4279
Fax: 701.777.6708

July 1, 2014

Mila Pak
528 Webster Street
Lake Mary, FL 32746

Dear Ms. Pak:

We are pleased to inform you that your project titled, "Risk Factors of Cholelithiasis in Female Veterans (IRB-201406-501) has been reviewed and approved by the University of North Dakota Institutional Review Board (IRB). The expiration date of this approval is May 2, 2015.

As principal investigator for a study involving human participants, you assume certain responsibilities to the University of North Dakota and the UND IRB. Specifically, any adverse events or departures from the protocol that occur must be reported to the IRB immediately. It is your obligation to inform the IRB in writing if you would like to change aspects of your approved project, prior to implementing such changes.

When your research, including data analysis, is completed, you must submit a Research Project Termination form to the IRB office so your file can be closed. A Termination Form has been enclosed and is also available on the IRB website.

If you have any questions or concerns, please feel free to call me at (701) 777-4279 or e-mail michelle.bowles@research.und.edu.

Sincerely,

Michelle L. Bowles, M.P.A., CIP
IRB Coordinator

MLB/jle

Enclosures

REPORT OF ACTION: EXEMPT/EXPEDITED REVIEW

University of North Dakota Institutional Review Board

Date: 6/27/2014 **Project Number:** IRB-201406-501

Principal Investigator: Pak, Mila

Department: Nursing

Project Title: Risk Factors of Cholelithiasis in Female Veterans

The above referenced project was reviewed by a designated member for the University's Institutional Review Board on 6/27/2014 and the following action was taken:

☐ Project approved. **Expedited Review** Category No. _____
Next scheduled review must be before: _____

☐ **Copies of the attached consent form with the IRB approval stamp dated _____ must be used in obtaining consent for this study.**

☒ Project approved. **Exempt Review** Category No. 4
This approval is valid until MAY 2 2015 as long as approved procedures are followed. No periodic review scheduled unless so stated in the Remarks Section.

☐ **Copies of the attached consent form with the IRB approval stamp dated N/A must be used in obtaining consent for this study.**

☐ Minor modifications required. The required corrections/additions must be submitted to RDC for review and approval. **This study may NOT be started UNTIL final IRB approval has been received.**

☐ Project approval **deferred. This study may not be started until final IRB approval has been received.**
(See Remarks Section for further information.)

☐ Disapproved claim of exemption. This project requires Expedited or Full Board review. The Human Subjects Review Form must be filled out and submitted to the IRB for review.

☐ Proposed project is not human subjects research as defined under Federal regulations 45 CFR 46 or 21 CFR 50 and does not require IRB review.

☐ Not Research ☐ Not Human Subject

PLEASE NOTE: Requested revisions for student proposals MUST include adviser's signature. All revisions MUST be highlighted and submitted to the IRB within 90 days of the above review date.

☒ Education Requirements Completed. (Project cannot be started until IRB education requirements are met.)

cc: Dr. Glenda Lindseth

William A Bruda 6/27/2014
Signature of Designated IRB Member Date
UND's Institutional Review Board

If the proposed project (clinical medical) is to be part of a research activity funded by a Federal Agency, a special assurance statement or a completed 310 Form may be required. Contact RDC to obtain the required documents.

Appendix F
IRB Approval-Continuing Review (Orlando VA)

Institutional Review Board
Orlando VA Medical Center - 675
5201 Raymond Street • Orlando, FL 32803

IRB APPROVAL - Continuing Review

Date: February 4, 2015
From: Mary Beth Shea, Ph.D., Chairperson
Investigator: Mila Pak, MS, CRNA
Protocol: Identifying Risk Factors Cholelithiasis in Military Female Veterans
ID: 00020 Prom#: 0001 Protocol#: 14-00020

The following items were reviewed and approved through Expedited Review:

- OVAMC RF 004 Application for Continuing Review (01/22/2015)
- OVAMC RF 054 Scope of Practice - Ross (01/22/2015)
- OVAMC RF 055 Site Personnel Delegation of Responsi (01/22/2015)
- Research Financial Conflict of Interest - Pak (01/22/2015)
- Research Financial Conflict of Interest - Ross (01/22/2015)
- OVAMC Form 53.4 Checklist for Continuing Review (01/21/2015)
- Staff Training (01/21/2015)
- Research and Development Information System Projec (01/22/2015)
- Curriculum Vitae - Ross (01/21/2015)
- Curriculum Vitae - Pak (01/19/2015)
- OVAMC RF 008 Application to Amend or Modify an App (01/22/2015)
- Worksheet ORC F002 Submissions and Approvals (01/22/2015)
- Worksheet ORC F003 IRB Submissions and Approvals (01/22/2015)
- Worksheet ORC F004 Other Actions (01/22/2015)
- Worksheet ORC F005 Reportable Events (01/22/2015)

Expedited Approval [Expedited under Federal Regulation: 45 CFR 46.110(b)(1)(5) / VA Regulation: 38 CFR 16.110(b)(1)(5)] was granted on 02/03/2015 for a period of 12 months and will expire on 02/02/2016. Your Continuing Review is scheduled for 02/10/2015. This Expedited review will be reported to the fully convened Institutional Review Board on 02/10/2015.

Approval by each of the following is required prior to study continuation:
Institutional Review Board

Approval for study continuation is contingent upon your compliance with the requirements of the Research Service for the conduct of studies involving human subjects.

The Orlando VAMC IRB is not connected with, has no authority over, and is not responsible for human research conducted at any other institution, except where a Memorandum of Understanding specifies otherwise. Separate consent forms, initial reviews, continuing reviews, amendments, and reporting of serious adverse events are required if the same study is conducted at multiple institutions.

Appendix G
IRB Approval-Amendment (Orlando VA)

Institutional Review Board
Orlando VA Medical Center - 675
5201 Raymond Street • Orlando, FL 32803

IRB APPROVAL - Amendment

Date: February 4, 2015
From: Mary Beth Shea, Ph.D., Chairperson
Investigator: Mila Pak, MS, CRNA
Protocol: Identifying Risk Factors Cholelithiasis in Military Female Veterans
ID: 00020 Prom#: 0001 Protocol#: 14-00020

The following items were reviewed and approved through Expedited Review:

- OVAMC RF 008 Application to Amend or Modify an App (01/22/2015)

Expedited Approval [Expedited under Federal Regulation: 45 CFR 46.110(b)(1)(5) / VA Regulation: 38 CFR 16.110(b)(1)(5)] was granted on 02/03/2015. This Expedited review will be reported to the fully convened Institutional Review Board on 02/10/2015.

The Orlando VAMC IRB is not connected with, has no authority over, and is not responsible for human research conducted at any other institution, except where a Memorandum of Understanding specifies otherwise. Separate consent forms, initial reviews, continuing reviews, amendments, and reporting of serious adverse events are required if the same study is conducted at multiple institutions.

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