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THESIS

QUANTIFYING THE RELATIONSHIP BETWEEN AGE-RELATED COMORBIDITIES AND QUALITY-OF-LIFE MEASURES AMONG HIV-POSITIVE ACTIVE DUTY U.S. MILITARY

by

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13. ABSTRACT (maximum 200 words)

Human immunodeficiency virus (HIV) is a well-studied disease that remains prevalent in the United States. While the risk of death from HIV has decreased, the disease still claims lives each year. Beyond mortality rates, there is great interest in understanding and improving health-related quality of life (HRQOL) in infected persons. HRQOL is driven by an individual's health perceptions, physical functionality, and psychological well-being, and is influenced by community and environmental indicators.

Studies of HRQOL are generally associated with healthcare use, disability diagnoses, assessment of behavioral risk, and common health outcomes: mortality and morbidity. The HRQOL of U.S. military members infected with HIV is a prevalent area of research. Increased understanding of service members infected with HIV, and subsequently how their quality of life persists with the disease, is critical for maintaining and improving military readiness and capabilities. The purpose of this study is to further analyze the association between age-related comorbidities and quality-of-life measures specifically among HIV-positive active duty service members.

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ABSTRACT

Human immunodeficiency virus (HIV) is a well-studied disease that remains prevalent in the United States. While the risk of death from HIV has decreased, the disease still claims lives each year. Beyond mortality rates, there is great interest in understanding and improving health-related quality of life (HRQOL) in infected persons. HRQOL is driven by an individual's health perceptions, physical functionality, and psychological well-being, and is influenced by community and environmental indicators.

Studies of HRQOL are generally associated with healthcare use, disability diagnoses, assessment of behavioral risk, and common health outcomes: mortality and morbidity. The HRQOL of U.S. military members infected with HIV is a prevalent area of research. Increased understanding of service members infected with HIV, and subsequently how their quality of life persists with the disease, is critical for maintaining and improving military readiness and capabilities. The purpose of this study is to further analyze the association between age-related comorbidities and quality-of-life measures specifically among HIV-positive active duty service members.

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LIST OF ACRONYMS AND ABBREVIATIONS

AA	African American
AFI	Air Force Instruction
AIC	Akaike's Information Criterion
AIDS	acquired immunodeficiency syndrome
AR	Army Regulation
ART	antiretroviral therapy
CD4	disease fighting cell of the human immune system
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DOA	Department of the Army
DOD	Department of Defense
DNIF	duty not including flight
GLM	generalized linear model
HAART	highly active antiretroviral therapy
HETU	HIV Evaluation and Treatment Unit
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HST	Health Systems Trust
IDCRP	Infectious Disease Clinical Research Program
IDES	Integrated Disability Evaluation System
ID-IRB	Infectious Disease - Institutional Review Board
IQR	interquartile range
MCS	mental component score
MCSS	mental component summary score
M&RA	Manpower & Reserve Affairs
NBIMC	Navy Bloodborne Infection Management System
NHS	U.S. Military HIV Natural History Study
NIH	National Institute of Health
NMCPHC	Navy and Marine-Corps Public Health Center

NPI	non-protease inhibitor
OCD	obsessive-compulsive disorder
PCS	physical component score
PCSS	physical component summary score
PHA	preventive health assessment
PI	protease inhibitor
RC	reserve component
RMF	regional medical facility
SECAF	Secretary of the Air Force
SECNAVINST	Secretary of the Navy Instruction
STI	sexually transmitted infection
UNAIDS	Joint United Nations Programme on HIV/AIDS
USA	United States Army
USAF	United States Air Force
USMC	United States Marine Corps
USN	United States Navy
USU	Uniformed University of the Health Sciences
VL	viral load

EXECUTIVE SUMMARY

The goal of this study is to quantify a relationship between age-related comorbidities and Health Related Quality of Life (HRQOL) among active duty U.S. military. Using a survey, the Short Form – 36 (SF-36) developed by RAND, univariate and multiple regression model building techniques were used to illustrate both intuitive and insightful relationships between the dependent and independent variables of interest. The dependent variables included Physical Component Summary Scores (PCSS), Mental Component Summary Scores (MCSS), and a binary representation of those patients who scored in the highest quintile of either of the aforementioned variables.

The Natural History Study (NHS) has been tracking the HIV positive U.S. military population for decades as HIV is a serious threat to operational sustainability. The cohort study is conducted through the Uniformed Services University of the Health Science Infectious Disease Clinical Research Program and is comprised of an especially unique population; its racial/ethnic diversity, younger average age, health, education, consistent access to healthcare, and regular HIV screenings set the NHS cohort apart from civilians (CDC 2015). The uniqueness of this cohort also extends to transmission risks. Drug use testing is frequent in the military and policies against drug use are strictly enforced. As such, a large majority of HIV transmissions in this cohort are presumed to be from sexual relations.

The main research questions focus on specifically identifying which comorbidities affects a patient's physical or mental quality of life. In order to quantify these relationships, binary variables were created to represent whether a patient had been diagnosed with each comorbidity (i.e., specific diagnosis). Next, binary variables were created to denote whether each patient had ever been diagnosed with each category of comorbidity (e.g., viral). Each of the 49 diagnoses identified in the cohort can be classified under 1 of the 10 categories of diagnoses. In an effort to increase the practicality of this study, those newly created variables representing specific diagnoses and categories were only populated with patient diagnoses occurring within 24 months prior to the survey date. The logical justification for the 2-year limit is that diagnoses

beyond a certain time window before the survey date would not be reflected in a patient's personal account of their current health status.

Univariate analysis were conducted to estimate the effect of each independent variable on the 3 dependent variables. Variables encompassing demographic information, general clinical information, diagnosis categories, and specific diagnoses represent the independent variables of initial interest. The univariate analyses initially employed a conservative, purposeful predictor selection approach (p-value < 0.1) to identify candidate predictor variables included in the full multiple regression model. Separate multiple regression models were constructed for each dependent variable based on the independent variables which were significant in the univariate models. One model included all significant demographic, general clinical, and specific diagnoses variables and the other included diagnosis categories in place of the specific diagnoses. The 6 models, 2 for each dependent variable, were created in an effort to reduce the multicollinearity due to the inherent linear dependence of the specific diagnoses and their respective categories. Backward elimination using AIC and minimal extractions of remaining variables with non-significant p-values facilitated the construction of the final multiple regression models representing the relationship between the comorbidities and an HIV positive active duty military personnel's HRQOL (Venables and Ripley 2002).

Age, sex, rank and race were the most common demographic predictors among the 6 models. Treatment options were significant only in predicating the log-odds of a patient scoring in the highest quintile of either PCSS or MCSS. However, the relationship between comorbidities and HRQOL remains the focal point of this study.

The comorbidities, which yielded significant influence on MCSS in this cohort included categories of respiratory and psychological illness and specific diagnoses of major depression, chronic obstructive pulmonary disease (COPD), methamphetamine use, and squamous cell (skin) cancer. While there was statistically no difference in the mean ages in most of these comorbidities, the mean age of patients with cancer was 5.9 years older than patients without (95% CI: 5.7, 11.5). Those comorbidities influencing PCSS include the category of bacterial illness and the specific diagnoses of anxiety and prostate cancer. However, the personnel with a bacterial infection are

significantly younger than those without. There is no significant difference in the mean age of personnel with either anxiety or prostate cancer and those without either. Among the quintile models, a cancer diagnosis rendered a significant negative effect on a patient's log odds of being in the highest quintile of either MCSS or PCSS. Similar to the category cancer, patients diagnosed with basal skin cancer had a mean age of 5 years older than those not diagnosed with the disease (95% CI: 6.7, 16.1). In total, 12 identified comorbidities among categories and specific diagnoses are found to significantly affect the physical and mental health of active duty HIV positive patients.

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I. BACKGROUND

The human immunodeficiency virus (HIV), is a well-studied disease which remains prevalent in the United States. If left untreated, HIV disease progression can eventually lead to severe disease—acquired immunodeficiency syndrome (AIDS) (Centers for Disease Control and Prevention 2015 [CDC]). HIV afflicts its hosts by attacking their immune systems (CDC 2015). The CD4 cells, one type of T cells, help fight infection in the human body; as the virus kills CD4 cells, afflicted persons grow increasingly susceptible to opportunistic illness and disease. However, antiretroviral therapy (ART) has been administered with tremendous success in mitigating the damaging effects of HIV (CDC 2015).

A. HIV QUANTIFIED AS AN EPIDEMIC IN GENERAL POPULATION

In 2014, according to the CDC, approximately 1.1 million persons were living with HIV in the U.S.; fifteen percent of whom were unaware of their infection (CDC 2015). The majority of those living with HIV in the U.S. are members of specific at-risk groups, including injection drug users, female sex workers, and men who have sex with men. Regarding race and ethnicity, the CDC also reports that African Americans are the largest proportion of infected persons, at 45 percent of total infections, though they only represent 15 percent of the total U.S. population (CDC 2015). Similarly, Latinos make up 24 percent of all infections, though only 18 percent of the U.S. population. The disease afflicts mostly urban areas and the likelihood of transmission trends with lifestyle choices, and according to the CDC, MSM are most at-risk. Approximately 80 percent of all infections in 2014 were among MSM, 23 percent of all infections were among heterosexuals, injection drug users made up about 5 percent, and MSM who also injected drugs comprised the remaining (CDC 2015).

B. HIV TREATMENT/PREVENTION

ART has been used with great success in preventing disease progression through its effect on viral suppression (VS). VS is defined as a very low viral load (VL), or amount of HIV replicates in the blood. Viral loads are deemed 'undetectable' when the amount of HIV in the patient's system is low enough that instruments cannot measure (CDC 2015). It should be noted that VL and CD4 are inversely related—as viral load increases, a patient's CD4 will decrease. And if a patient's CD4 drops below 200 cells/m^3 they have progressed to severe HIV disease: AIDS (CDC 2015). Strict adherence to ART reduces the chances of progressing from the first stage of HIV—acute HIV infection—through the second and third: clinical latency and AIDS, respectively. Without access or adherence to ART, AIDS will continue to claim lives each year, with 6,721 deaths in the U.S. in 2014. It remains the eighth leading cause of death in persons aged 25–34 and the 9th for those aged 35–44 (CDC 2015).

C. QUALITY-OF-LIFE RESEARCH IN GENERAL POPULATION

As rates of death decline, the prevalence of HIV will continue to increase, demanding a better understanding of how to improve Health Related Quality of Life (HRQOL) in persons infected (CDC 2015). HRQOL is driven by an individual's health perceptions, physical functionality, and psychological well-being (Healthy People 2020). HRQOL is also influenced by community and environmental indicators, which impact both the mental and physical status of patients (Boehmer et al. 2003). Boehmer et al. found that measures of HRQOL are generally associated with health care use, disability diagnoses, assessment of behavioral risk, and common health outcomes: mortality and morbidity (Boehmer et al. 2003).

D. QUALITY-OF-LIFE RESEARCH IN MILITARY

To better understand how HIV affects HRQOL in service members, there must be a frame of reference for quality of life measures for all service members in the military at-large. Prior research has shown that active duty service members score lower on HRQOL surveys compared to the civilian, or even reservist and retired, populations (Boehmer et al. 2003), suggesting worse self-assessed quality of life among active duty

personnel. Specifically, compared to persons with no military service, veterans are negligibly different in self-reported HRQOL, reservists score higher, and active duty members score the lowest. However, there are disparities between genders within the active duty personnel. In fact, researchers have suggested that the "healthy soldier" effect, where the standard for health and vitality is above average, is seen in reservist and male active duty personnel, though for female active duty personnel their scores remain the lowest (Boehmer et al. 2003).

E. QUALITY-OF- LIFE RESEARCH IN HIV + GENERAL POPULATION

While the general population has a higher self-reported HRQOL than the military cohort, those infected with HIV in the general population exhibit lower scores than those without HIV (Boehmer et al. 2003). Mannheimer et al. (2010) found that strict adherence to ART yielded an opportunity for significant HRQOL improvement for patients equipped with the means of consistent treatments (Mannheimer et al. 2010). Baseline HRQOL scores for HIV-positive patients were comparable to the baseline scores reported in other studies of HIV-positive patients. However, among those who strictly adhered to ART, their scores drastically improved within the first four months (Mannheimer et al. 2010). Over the span of one year, 100 percent adherence resulted in distinguishable variation from those with inferior adherence. Furthermore, 80 percent adherence led to minimal quality of life improvement, while less than 80 percent adherence to ART led to a decrease in HRQOL scores (Mannheimmer 2010).

F. UNIQUENESS OF MILITARY COHORT

Military healthcare is unique in providing thorough education, care, and treatment of HIV through its universal healthcare delivery system. Unlike the general population, which is usually unaware of its seroconversion date, service members are subject to approximately biennial HIV screenings. The frequency of screening reduces the ambiguity of seroconversion date drastically in comparison to the civilian population. Furthermore, compared to the general population, military personnel are younger, healthier, and have universal access to medical care. The military cohort is also relatively educated, with the enlisted population possessing at least a high school diploma or

equivalent thereof, and the officer corps holding at least a bachelor's degree. Understanding military personnel's educational background is important as this can affect HRQOL measures. Generally, it can be assumed that the transmission of HIV within the military excludes injection drug use, as less than one percent of active duty patients report use (Emuren et al. 2017). As such, the predictors of HRQOL and HIV transmission that apply to the general population, do not all apply to the military.

G. QUALITY-OF-LIFE RESEARCH IN HIV + MILITARY COHORT

The HRQOL of U.S. military members infected with HIV is a growing area of research. Increased understanding of service members infected with HIV and, subsequently, how their quality of life persists with the disease can improve military readiness and capabilities. The universal access to healthcare and vitality of the active duty cohort has spurred research in the search of predictors for HRQOL among HIV positive military personnel. Emuren et al. (2017) found many predictors which influenced HRQOL in HIV-positive military personnel to include: age, race/ethnicity, gender, education, income, ART adherence, CD4 count, presence of AIDS and comorbidities, and access to health care. Physical component scores (PCS) of HRQOL, a measure of quality of physical life, were driven predominantly by age, CD4 cell counts less than 200 cells/m^3, lower military rank or being civilian/retired, AIDS diagnoses, marriage, and mental and medical comorbidities. Concurrent with previous studies such as Boehmer et al. (2003), Emuren et al. (2017) found that females tended to score lower on HRQOL than men. Lower mental component scores (MCS) were found to be associated with CD4 cell counts less than 200 cells/mm^3, mental comorbidities, and AIDS diagnoses-similar to PCS variables. Older age and being African American were predictive of higher MCS scores, however. This may suggest the confounding role comorbidities can play in measuring HRQOL among HIV positive patients, specifically age-related conditions (Emuren et al. 2017).

H. COMORBIDITIES IN HIV + GENERAL POPULATION

Age-related comorbidities are more prevalent in HIV-positive populations. In a study specifically focused on quantifying the health impact of HIV, Rajasuriar et al. (2017) found that HRQOL was 2.2 times poorer, mortality risk was 4 times greater, and healthcare use was 5 times more frequent in an HIV-positive population when compared to an uninfected population. Geriatric conditions were noticeably more prevalent in this same HIV-infected population, characterized as follows: gait/balance abnormalities, malnourishment, frailty, vision impairment, urinary incontinence, polypathology, polypharmacy, depression, cognitive impairment, and functional disability. Furthermore, the HIV-infected population had a median of two geriatric conditions, while the uninfected had one. Concluding evidence from the study suggests a significantly higher proportion—approximately 1.4 times greater—of HIV-positive persons exhibiting multiple geriatric conditions regardless of age than members of the uninfected population (Rajasuriar et al. 2017).

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II. DATA INTRODUCTION

A. CURRENT MILITARY POLICY

The "United States Natural History Study" (Infectious Disease Clinical Research Program [IDCRP] 2015) provides information on HIV status, progression, and treatment options from which the Department of Defense (DOD) and each service branch develop respective policies. However, while the DOD sets forth its own minimum HIV response provisions, each Service Secretary has drafted independent-albeit highly correlated-policy memorandums regarding response plans.

The DOD establishes general policy guidelines regarding service members infected with HIV. Foremost, infected civilians are deemed unfit for service, therefore do not meet "accession standards" for service in the U.S. military (DOD 2015). Communicable disease, afflictions potentially requiring medical treatment that would result in immoderate time lost from service, or diseases with high probability of leading to medical separation, result in denial of accession. However, set forth by DOD regulation, no service member currently serving can be legally separated solely based on HIV status (CDC 2015). Though "no adverse personnel action" is permitted by law, formal legal action follows any service member's failure to inform sexual partners of their HIV status. Disclosure policies align with multiple U.S. state laws outlining disclosure policies and confidentiality limitations (CDC 2017). DOD regulation also guarantees standards of care coinciding with those in place for chronic and progressive diseases. Following a positive HIV diagnosis, patients are medically evaluated to determine duty status. In certain instances, persons who are medically separated or deemed unfit for duty are subject to assignment limitations (DOD 2014). HIV-infected persons are non-deployable except in the case of a waiver by the Combatant Commander advised by medical personnel (DOD 2014). While the DOD has established baseline regulations regarding HIV-positive service members, each individual branch drafts service-specific policies, as well.

The Department of the Navy, in accordance with DOD policy, bars HIV positive potential accessions from entry. Testing of current service members also continues throughout their careers. Active Components (AC) are tested for HIV every 25 months, excluding unique circumstances such as sexually transmitted infection (STI) diagnoses (DOD 2014). An HIV test follows every STI discovery in AC and Reserve Components (RC) (Secretary of the Navy 2012). RC members are tested on the same interval as AC members, except when they are called to active duty for more than a 30-day period. HIV screenings are mandatory before every permanent change of station and every call to active duty from the reserves (DOD 2014). Similar to DOD policy, medical evaluation immediately follows serological evidence of HIV in order to determine medical eligibility for continued service. Sailors attend the HIV Evaluation and Treatment Unit (HETU) and the Navy Bloodborne Infection Management Center (NBIMC). Marines are regulated by Manpower and Reserve Affairs (M&RA). All members of the USN will have access to appropriate, timely, and consistent medical care. In addition to proper care, infected persons also receive training on transmission prevention and the legal consequences of failing to take appropriate precautions (DOD 2014). While the Department of the Navy works to mitigate the influence of infection on a person's career trajectory, some statutes are steadfast. The DOD permits certain individual cases to serve overseas, or in deployable units, because the CDC has found no risk in transmission via daily activities (SECNAV 2012). Furthermore, the Navy has made an investment in the training of each service member, and the lack of deployments limits the competitiveness of that sailor's or Marine's promotion portfolios. If, however, the disease progresses to advanced stages, DOD refers service members to Integrated Disability Evaluation System (IDES) (DOD 2014).

The United States Army (USA) has recently adapted its testing policy, aligning with that of the Navy screening for HIV every two years instead of every five (Department of the Army [DOA] 2014). The Army tests all active duty, Army National Guard, and United States Army Reserve on the same interval. Similar to the Navy, reservists called to active duty for more than 30 days will be tested for HIV, as well (DOA 2014). The Army will counsel all HIV infected persons and their spouses

immediately upon their first positive test. However, USA policy dictates that each HIV positive diagnosis will be retested by a separate blood draw. The Army, in accordance with DOD policy similar to the Navy, does not separate infected active duty persons because of HIV status (DOA 2014). All active duty members must prove their individual ability to perform duties to ensure retention, but Active Duty Operational Support members are automatically referred to Release from Active Duty. Active duty and active guard reserve receive medical evaluations at a minimum, and active duty members will be separated if deemed unfit for duty. For active duty soldiers who pass the fitness for duty criteria, duty station and operability limitations still apply. Select reserve and non-deployable billets are available, though grade, MOS, and community restraints exist. Annual revaluation determines an active duty soldier's potential for serving under different capacities. However, soldiers are financially responsible for each new evaluation (DOA 2014). While policy is strict, the Army does attempt to care for HIV infected persons and their families; most notably the Army automatically enrolls dependents in the Exceptional Family Member Program- AR 608–75 (DOA 2014). Further enrollment in Army funded Child, Youth, and School Services are decided on individual basis.

Similarly, the United States Air Force (USAF) focuses on balancing care for HIV infected service members and ensuring optimal unit functionality. The USAF tests all service members every two years during Preventive Health Assessments (PHA) and advocates education on prevention techniques. Akin to the Army, certain service classifications are subject to different regulations. For example, upon medical evaluation to determine status of continued military service the USAF send Air Nation Guard members to "non-mobility, non-deployable" positions (Secretary of the Air Force [SECAF] 2014). Those in the Air Reserve Component progress similarly to persons diagnosed with chronic illness. While the USAF refers all service members to San Antonio Military Medical Clinic upon first positive diagnosis, the active duty Air Force constituents are required to return six months post initial visit and every subsequent year while on active duty. If Air Reserve Components and Air National Guard members pass the initial Line of Duty assessment, they are free to continue care at Regional Medical

Facilities (RMF). However, if they fail, the USAF sends them to civilian HIV specialists. The USAF also offers counseling to legal beneficiaries and does not separate persons on seropositivity alone (SECAF 2014). The USAF confines infected persons to Continental United States (CONUS)—to include Alaska, Hawaii, and Puerto Rico- billets similarly to the other branches. USAF also places each member with HIV on a Duty Not Including Flying (DNIF list and restricts them to non-mobility commands (SECAF 2014).

When comparing each branch of service to each other, the differences are limited mostly to treatment facility location. Perhaps more important, the commonalities are far more numerous. Each branch reports to the DOD using the CDC's and NHS' HIV guidelines to develop respective policies.

B. INTRODUCTION OF COHORT

The U.S. Military HIV Natural History Study (NHS) has been collecting data on HIV infected persons in the U.S. military for over thirty years, beginning in 1986 (IDCRP 2015). A groundbreaking study group, NHS has provided information for policy makers in the military and clinical care where there was otherwise none. NHS is administered by the Uniformed Services University of the Health Sciences (USU) Infectious Disease Clinical Research Program (IDCRP 2015). NHS has collected data on an aggregate 6,000 active duty military personal since 1986. The population comprises U.S. military beneficiaries who are HIV positive, 18 years or older, and willing and able to provide informed consent. The cohort excludes incarcerated persons and those who are unable to provide informed consent.

As discussed previously, the military makes for a special study group. With 1,498 currently active duty members in the cohort as of May 2016, the NHS demographic guarantees racial and ethnic diversity. The cohort comprises young, educated, and active subjects, 87 percent of whom have approximate seroconversion dates (IDCRP 2015). This high percentage of known seroconversion date is a function of the military's policy of screening for HIV every 1–2 years. Once the DOD diagnose each individual with HIV, service members continue to have access to the military healthcare system: free medications and regular clinical appointments with rare exceptions.

C. SURVEY TOOLS

The Short Form 36 (SF-36) was used to gather information on the NHS cohort between 2006 and 2010. The SF-36 is a survey developed by RAND over multiple years of investigative studies within the Medical Outcome Study (Healthy People 2017). During this time, RAND perfected a set of generic, coherent, and easily administered quality-of-life-measures. Based on patient self-reporting, the survey is used by Medicare and other managed care organizations globally in efforts to quantify the physical and mental health of adults (Healthy People 2017). Calculated based on computer algorithms and used to quantify quality of life measures for patients, Physical Component Scores (PCS) and Mental Component Scores (MCS) project a person's health (NHS). The resulting scores are then used to calculate both physical component summary scores (PCSS) and mental component summary scores (MCSS) using a standard algorithm.

D. COLLECTING AND CLEANING

Receiving the data via comma-separated values (csv) files from IDCRP Data Collection and Analysis Center, they were imported into the statistical programming environment R for analyses (R Core Team 2016). Each patient in the data is identified by a random pin code in order to protect their identity in accordance with the Infectious Disease Institutional Review Board (ID-IRB) and DOD approval of protocol for human subjects' participation. The original data had information for each of the 1730 patients on their respective survey dates, CD4 counts, treatments, AIDS diagnoses, sex, HIV duration, age, viral load, race, and most importantly MCSS and PCSS. Both PCSS and MCSS had 11 missing values among the 1728 patients, and VL had 1 missing value. An additional column included a factor variable classifying CD4 count into 3 levels—less than 200 cells/m^3, between 200–499 cells/m^3, and greater than 499 cells/m^3.

Further manipulation of the data for the purposes of this analysis excluded the continuous CD4 counts in favor of solely using the three level CD4 count, because of its direct applicability to AIDS research: counts below 200 cells/m^3 are used to diagnose AIDS. Additional csv files containing the branches of service for each patient, category of diagnoses, and specific diagnoses for each patient were merged with the original data

set via pin codes. After the merge and the discovery of duplicated pins in the original data set, 1,728 rows of patients remained. The merge added columns denoting the branch of service, data of each category of diagnoses, and date of each specific diagnoses.

Aligning with the goal of this analysis—quantifying the relationship between age-related comorbidities and HRQOL—additional binary columns were constructed for each diagnoses and its category. Initially, the new indicator variables were populated contingent upon whether a patient was diagnosed with the respective category of diagnosis within 12 months prior to the survey date. However, the columns were far too sparse, so the time was extended to 24 months. Schizophrenia, breast cancer, oral cancer, obsessive-compulsive disorder (OCD) still had no data for any patient within two years of their survey dates. Columns of total mental and total medical comorbidities were also added to track the potential influence of compounding comorbidities.

PCSS and MCSS, the patient's health indicators, initially represented the only dependent variables in this analysis. However, as the research progressed, so too did an interest in observing which factors influenced the healthier proportion of the cohort. Therefore, PCSS and MCSS were divided into quintiles and a new indicator column denoted which patients fell into the highest 20 percent of the most mental or physical scores. Regression techniques were thus employed using PCSS, MCSS, and the highest quintile of either as dependent variables in an effort to both discover and quantify a relationship between these dependent variables and the factors that influence them.

E. STATISTICAL METHODS

Simple linear regression estimated the effects of each predictor in the data set using PCSS and MCSS as response variables. Two separate multiple regression models were built for each dependent variable: one using the significant categories of diagnoses as predictors and one using the significant specific diagnoses as predictors. Additionally, significant demographic and general clinical predictors were included in each model. Using two separate models, one for categories of diagnoses and one for specific diagnoses, helped mitigate the risk of multicollinearity due to the linear dependence between the categories and diagnoses. Using the highest quintile of either MCSS or

PCSS, a logistic regression was used to summarize the data using similar techniques as the linear regression: one model for using categories and one using specific diagnoses.

For the purposes of developing the initial multiple regression models, $p < 0.1$ in the univariate models determined significance. Using the univariate analysis approach with a higher level of significance helps identify potential confounding variables while not necessarily missing potentially important predictors (Bendel and Affifi 1977, Mickey and Greenland 1989). However, setting $p < 0.05$ in a univariate analysis is risky, because there is some chance variables could be misidentified as unimportant (Bendel and Affifi 1989, Mickey and Greenland 1989). While a variable may not be significant at the $p < 0.05$ in univariate analysis, it could potentially be significant in a multiple regression analysis (Mickey and Greendland1989). In order to mitigate the chance of removing potentially significant variables in a multiple regression model, the univariate p-value cutoff was raised to $p < 0.1$. In the multiple regression analyses, non-significant predictors ($p < 0.5$) were removed, but only if they were also determined *not* to be confounders. Confounding in the multiple regression model was identified if any of the coefficient estimates changed by at least 25 percent after removal of the non-significant predictor (Bendel and Affifi 1977, Mickey and Greenland 1989). In this analysis, no confounding variables were removed during the multiple regression model selection.

Full models were populated with all significant predictors ($p < 0.1$) from the univariate models, and the backwards elimination using Akaike's Information Criterion (AIC) was used to help select the final model (Venables and Ripley 2002). The predictive quality of each multiple regression model is measured with R^2 and Psuedo-R^2 values for the linear and logistic models respectively (see Tables 20–25).

Additional model assumption diagnostics were performed analyzing normality and heteroscedasticity (see the Appendix). As a result of non-linearity and the potential presence of heteroscedasticity, we considered a secondary analysis in which we transformed the response variables PCSS and MCSS. We explored log, squared, and a power transformation estimated using the Box-Cox methods. For further details, see the Appendix (Secondary Analysis using Power Transformations). In general, the Box-Cox transformation found lambda estimates to be roughly 2–3. For ease of interpretation, we

have retained untransformed models, but for transparency purposes the transformed models are described in the appendix. Interaction terms were considered in the final models, but none were found to be both statistically and practically meaningful.

F. PRIOR ANALYSES

NHS has been analyzed for decades in attempts to better understand the various elements of a disease which infects such a significant proportion of the globe (Beyrer et al. 2012). Knowledge of transmission mediums, disease progression, and treatment options have consequently been developed with great success (Emuren et al. 2012). However, in addition to clinical outcomes, a better understanding of quality of life has developed in recent years. Additional studies have quantified a relationship between both HRQOL scores and hospitalization and HRQOL and ART (Emuren et al. 2012). This study intends to build on prior studies and specifically quantify the relationship between unique comorbidities and HRQOL in HIV positive service members.

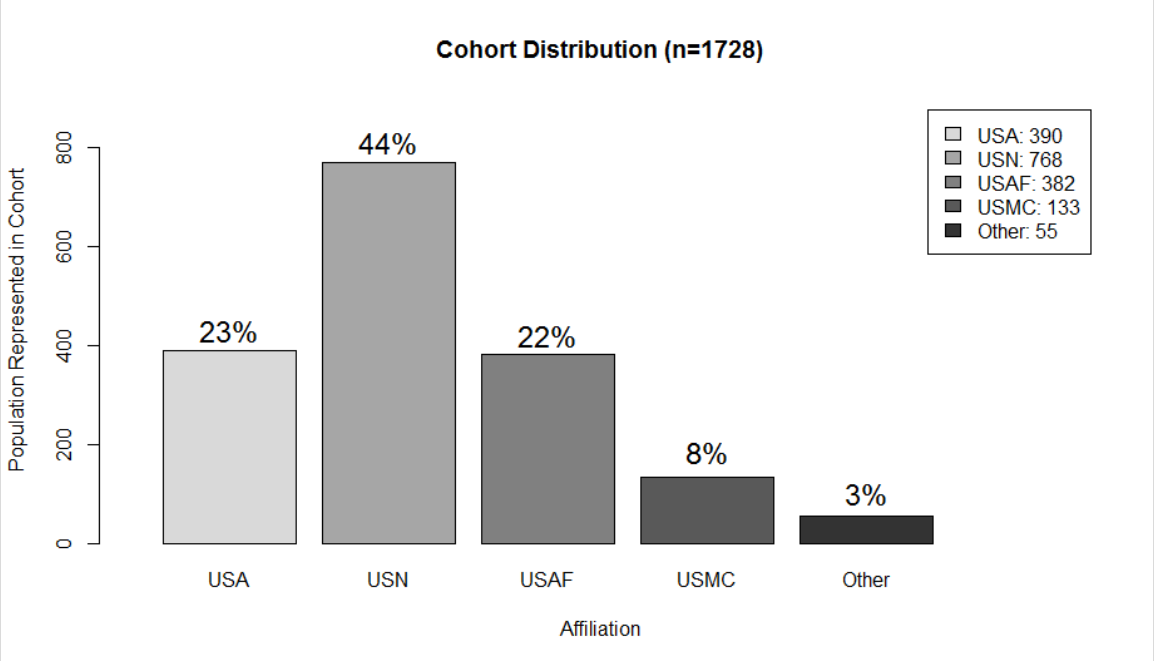
Emuren et al. previously used a multiple linear regression to estimate association between selected variables and HRQOL in an effort to understand the effect of ART on HRQOL within the NHS cohort. Researchers found that ART and HRQOL were significantly related and predictors of HRQOL included clinical measures such as CD4 count levels less than 200 cell/m^3 and AIDS diagnoses, and demographics including gender, marital status, age, race, and rank. The authors concluded that there are modifiable factors associated with HRQOL among the NHS cohort and that the determination of which specific comorbidities were influential in the patients' HRQOL needed further analysis (Emuren et al. 2017). Lastly, prior research has found that HRQOL summary scores can be predictive of various causes of hospitalization in the NHS cohort (Emuren et al. 2012). Again, this emphasizes the importance of understanding the dynamics of a history of specific comorbidities and HRQOL among HIV-positive populations.

III. DESCRIPTIVE STATISTICS

A. DEMOGRAPHICS

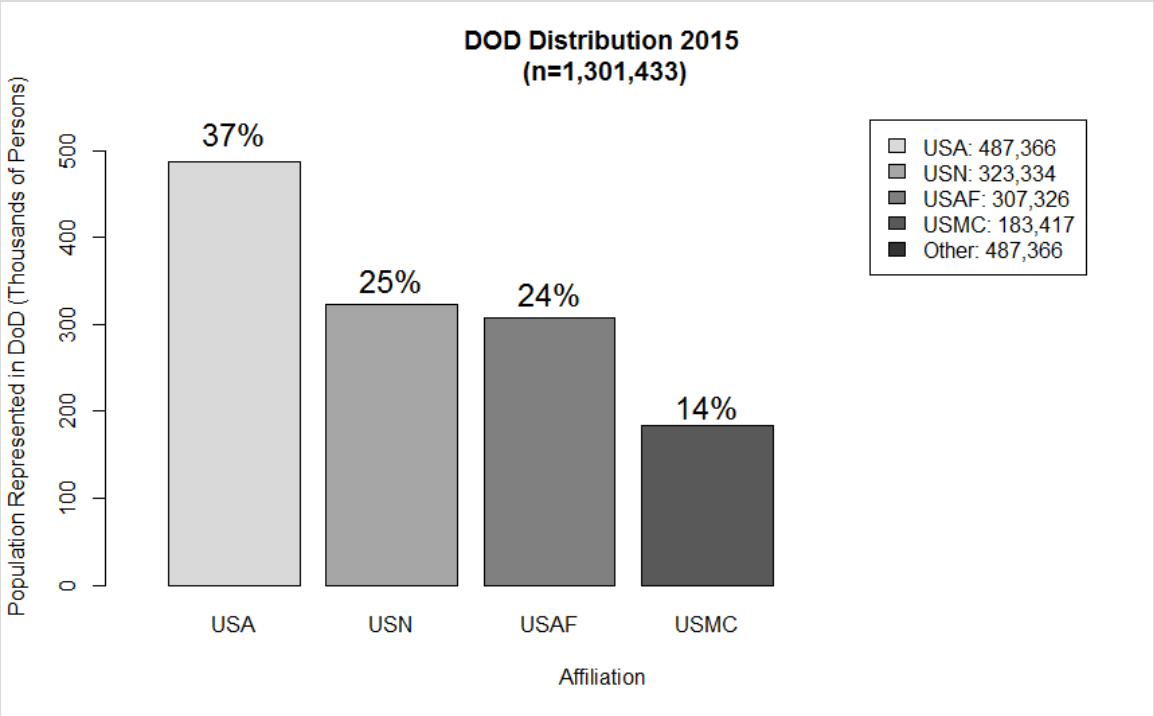
The observed cohort used in this analysis contains 1,728 patients spanning every branch of service in the DOD further including various civilian positions, not active, and reserve persons. Initial analyses compared the percentages of each branch of service in the cohort to those percentages in the larger DOD. Noticeably the representative percentages in the NHS cohort are skewed in comparison. For example, Figures 1 and 2 show the USN accounts for 44 percent of patients in the study cohort, while the entirety of the USN only accounts for 25 percent of active duty military currently serving (DOD 2014).

1. General Statistics



USA: United States Army, USN: United States Navy, USAF: United States Air Force, USMC: United States Marine Corps. All analyses were carried out with the Natural History Study data set.

Figure 1. Branch of Service Distribution in Cohort

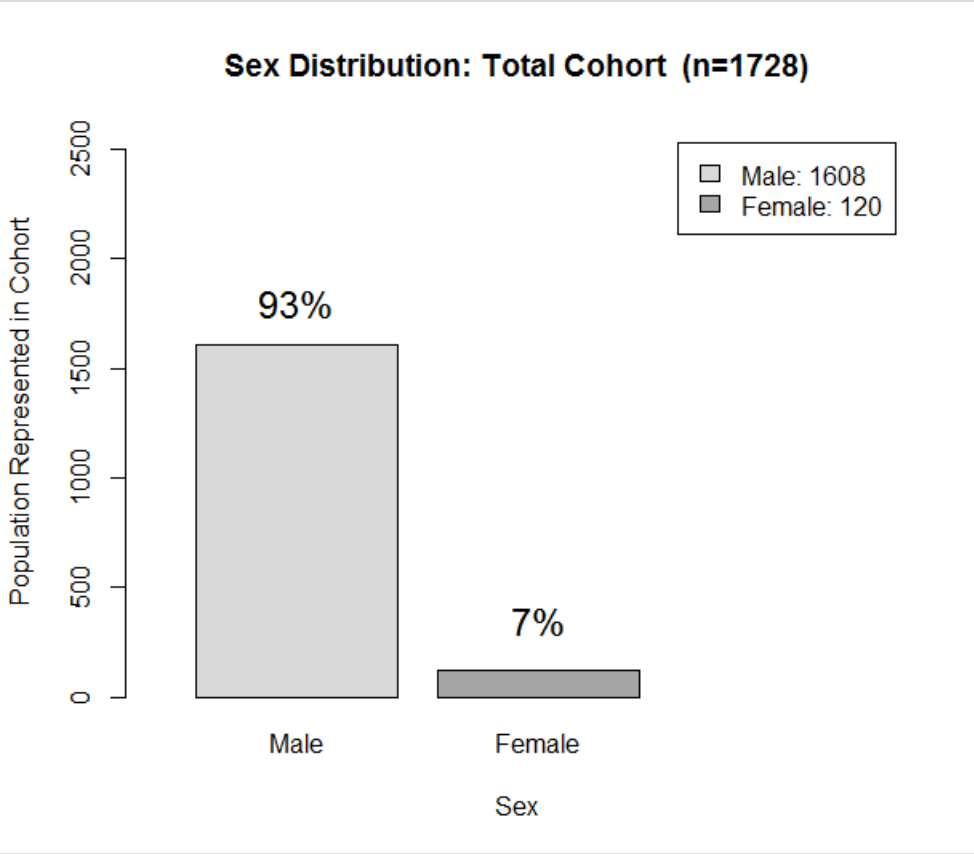


USA: United States Army, USN: United States Navy, USAF: United States Air Force, USMC: United States Marine Corps. All analyses were carried out with the Natural History Study data set.

Figure 2. Branch of Service Distribution across DOD

2. Sex Demographics

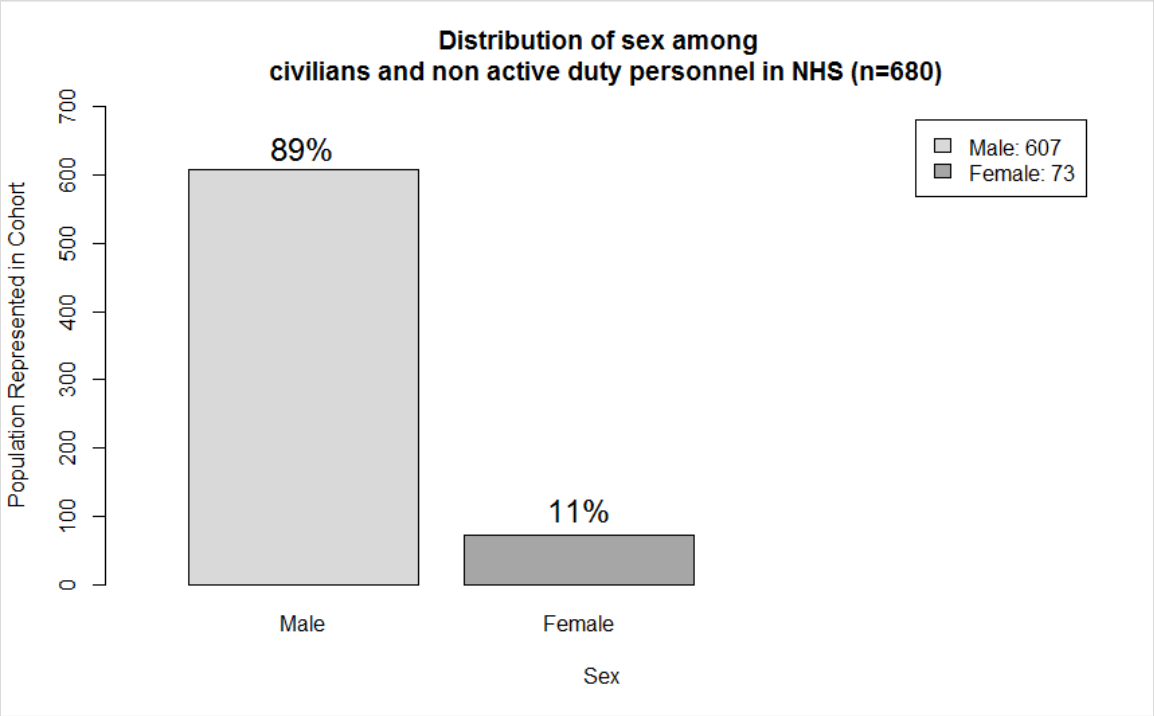
The NHS cohort represents a skewed ratio of males to females when compared to the distribution of genders in the DOD. In this cohort, 93 percent were males compared to only 7 percent females, as seen in Figure 3. However, the total force in the DOD contains a comparably smaller percentage of males (85 percent) than females (15 percent). Overall, 201,413 females and 1,100,030 males represent the 1,301,443 active duty service members as of 2015 (DOD 2014).



All analyses were carried out with the Natural History Study data set.

Figure 3. Distribution of Sex in Cohort

While 95 percent or more of officers and enlisted were males, the civilian and non-active duty representatives in the cohort have the highest percentage of females at 11 percent, perhaps reflecting spouses of active duty service members (see Figure 4).

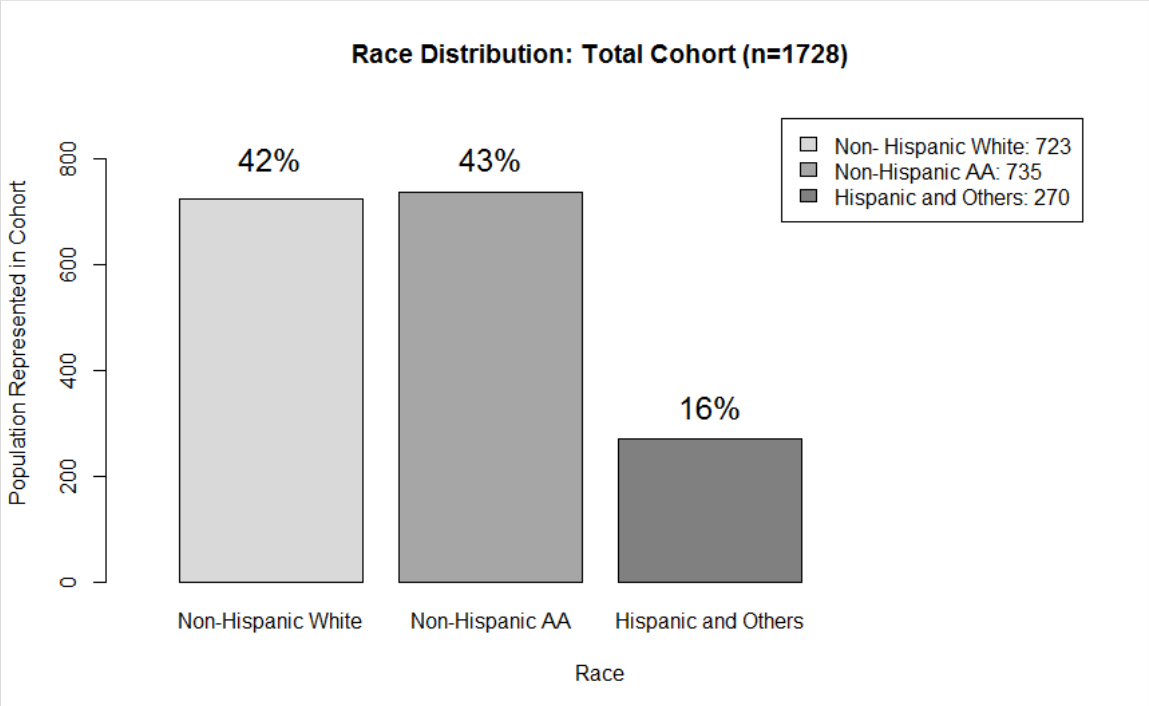


All analyses were carried out with the Natural History Study data set.

Figure 4. Distribution of Sex among Civilians and Non–active Duty Personnel in NHS

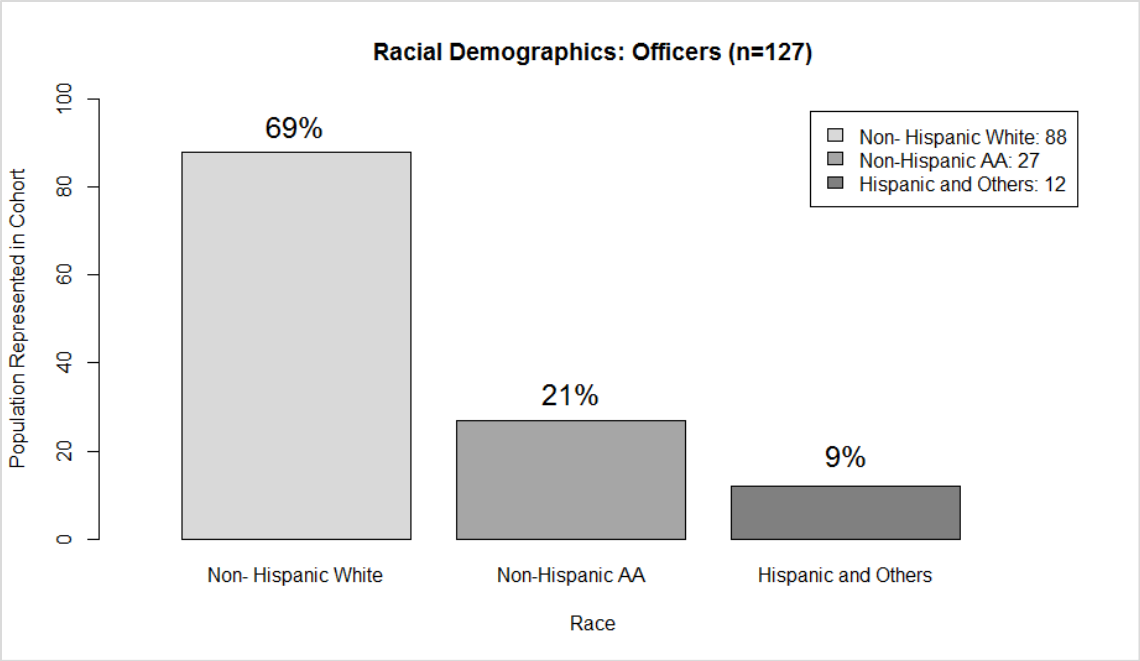
3. Racial Demographics

Self-identified racial minorities (i.e., black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multi-racial, or other/unknown) currently constitute approximate 31 percent of the total active duty service members across the DOD (DOD 2014). However, racial minorities represent well over half (59 percent) of the total population in NHS. Figure 5 illustrates the distribution of race across the entire cohort, while Figures 6–8 illustrate the distribution of race by rank. Officers have the lowest percentage of ethnic minority representation at 30 percent (see Figure 6), while 65 percent of enlisted are minorities (see Figure 7). It follows that 54 percent of the civilian and non-active duty self-identified as ethnic minority (see Figure 8).



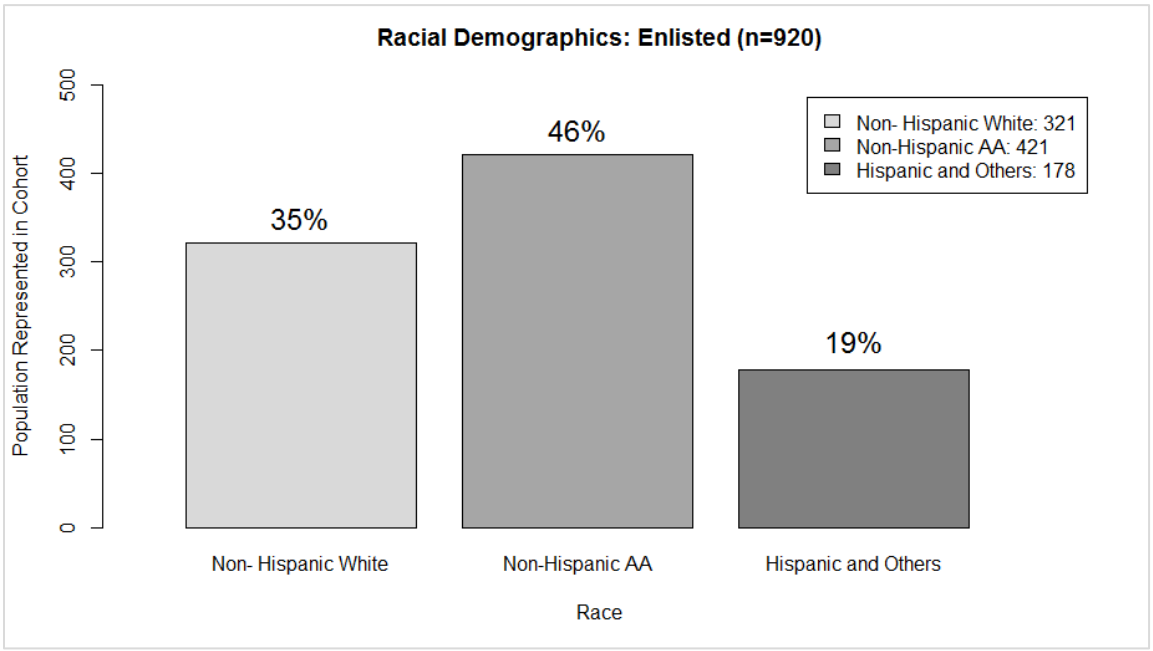
Non-Hispanic AA: Non-Hispanic African American. All analyses were carried out with the Natural History Study data set.

Figure 5. Distribution of Races across the Entire Cohort Population



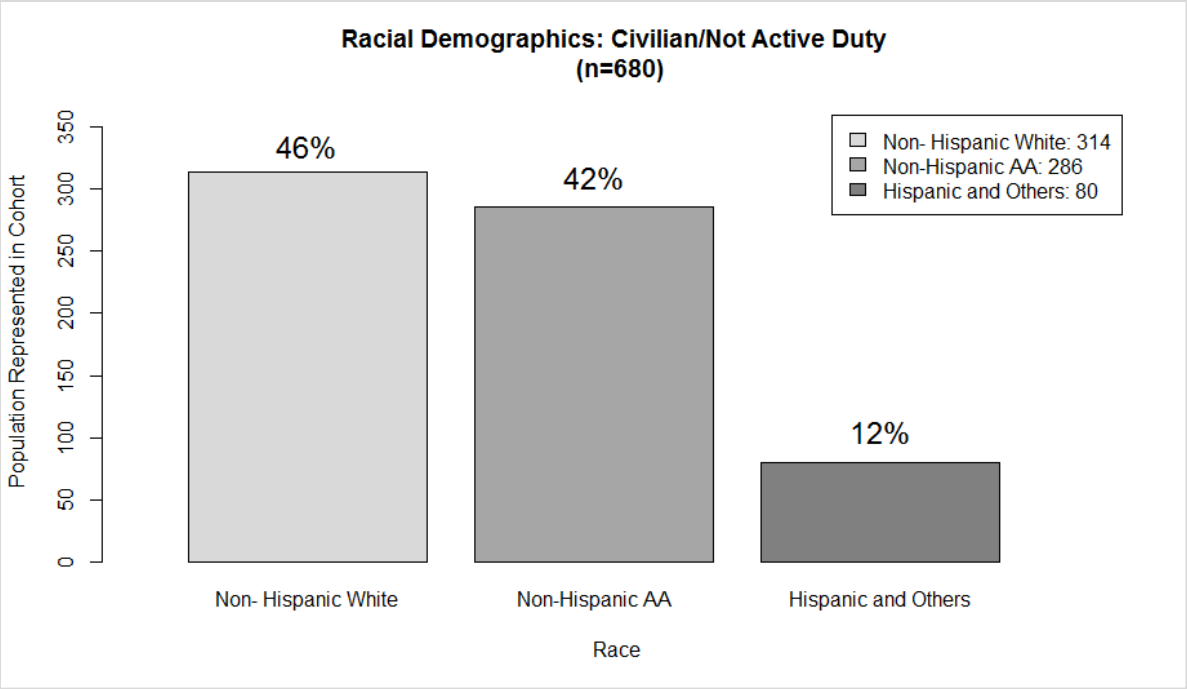
Non-Hispanic AA: Non-Hispanic African American. All analyses were carried out with the Natural History Study data set.

Figure 6. Racial Demographics among Officers in Cohort



Non-Hispanic AA: Non-Hispanic African American. All analyses were carried out with the Natural History Study data set.

Figure 7. Racial Demographics among Enlisted in Cohort

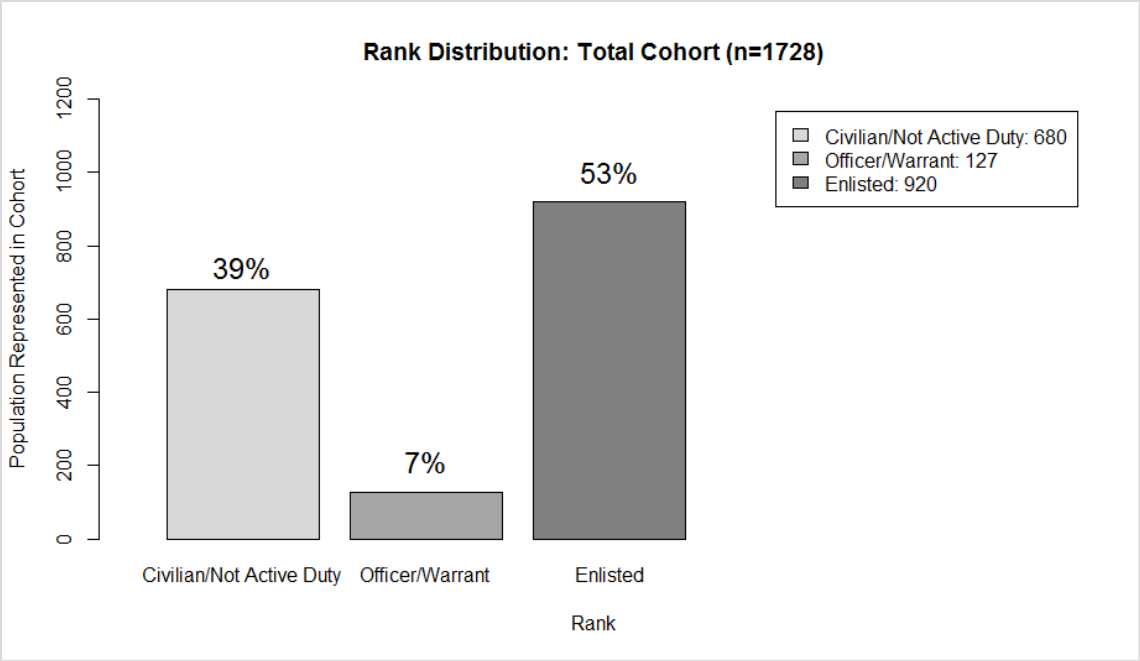


Non-Hispanic AA: Non-Hispanic African American. All analyses were carried out with the Natural History Study data set.

Figure 8. Racial Demographics among Civilian and Non–active Duty Personnel in Cohort

4. Rank Demographics

The observed cohort has a higher percentage of enlisted compared to officers than the overall DOD. Enlisted number 920 of 1047 total active duty in this cohort at 53 percent while officers number 127 at 7 percent. Enlisted personnel comprise 82.3 percent (1,070,653) and officers comprise 17.7 percent (230,790) of the DOD (DOD 2014). Figure 9 depicts the distribution of rank across the cohort. Across the entire DOD, one officer serves 4.6 enlisted, with ratios varying slightly between branches (DOD 2014). The Army has one officer for every 4.1 enlisted, the Air Force has one officer for every 4.0 enlisted, and the Navy has one officer for every 5.0 enlisted personnel. The highest ratio of enlisted to officers is claimed by the Marine Corps with one officer for every 7.9 enlisted personnel. In the NHS cohort, there is one officer for every 7.2 enlisted personnel.



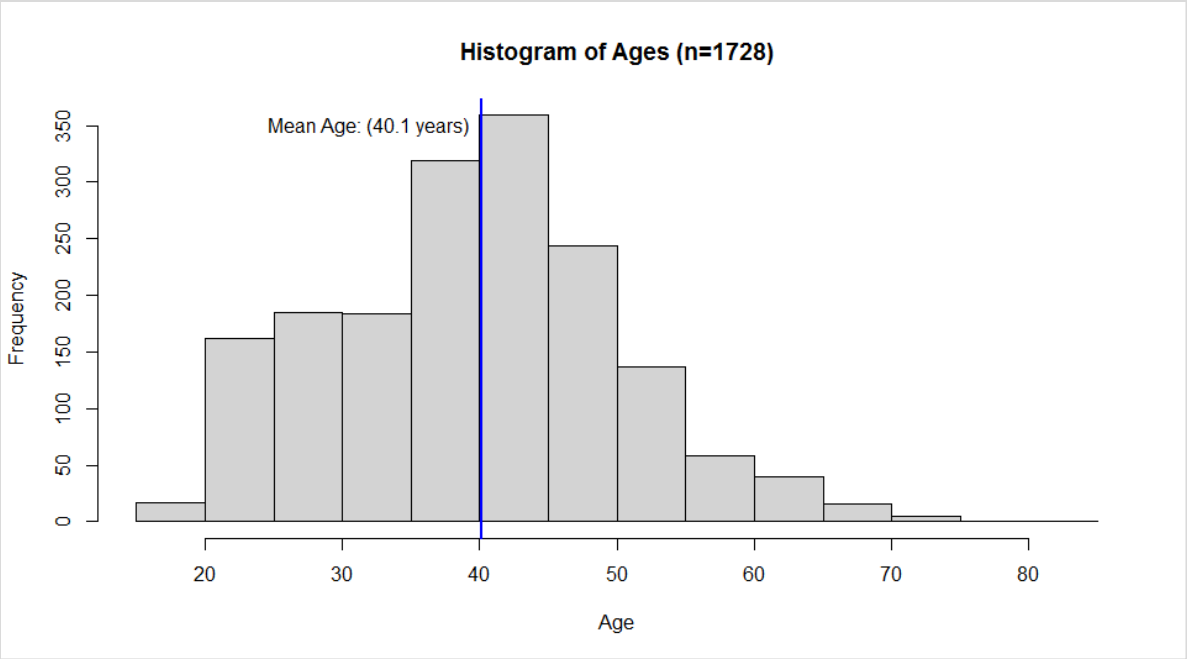
All analyses were carried out with the Natural History Study data set.

Figure 9. Cohort Rank Demographics

5. Age Demographics

The mean age of persons in this cohort at the time of the survey is much higher than the mean age of active duty personnel across the DOD. Figure 10 is a histogram of the age spread across the cohort. Overall, the mean age of our cohort is 40.1 years of age, while the mean age in the DOD Active Duty force is 28.5 years. Further, the mean age of enlisted personnel is 27.2 years and officers is 34.7 years in the DOD.

Across the DOD, over one-half of all Active Duty enlisted personnel are 25 years old or younger (DOD 2014). The age break down continues with 26 to 30 years (21.7 percent), 31 to 35 years (14.0 percent), 36 to 40 years (8.8 percent), and (5.3 percent) 41 years or older. Officers younger than 25 years old make up only 13.8 percent of the total population across the DOD. The largest percentages of officers are over 41 years of age (25.3 percent) followed by those between 26 to 30 years old (22.4) and finally 31 to 35 years old (20.8 percent) (DOD 2014).

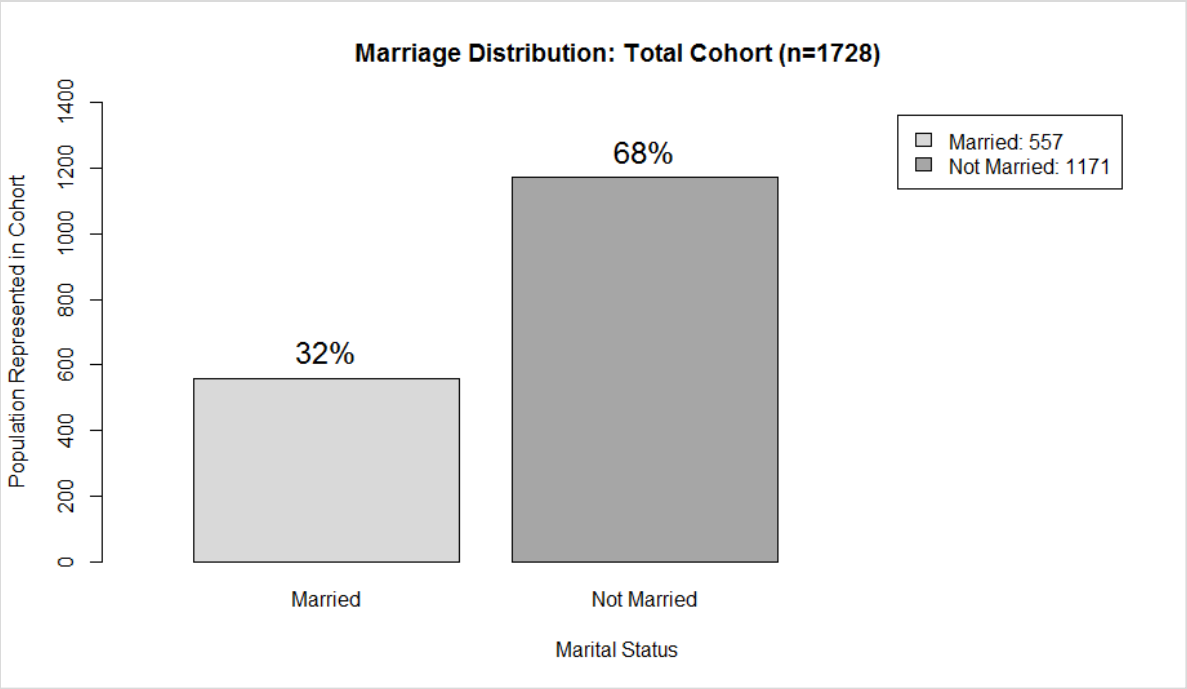


All analyses were carried out with the Natural History Study data set.

Figure 10. Histogram of Age Distribution in Cohort at Time of Survey

6. Marital Demographics

The most prevalent transmission methods of HIV in this cohort is sexual contact and a higher percentage of this cohort is not married compared to the DOD (see Figure 11). Across the DOD, 54.3 percent of active duty military members are married. Over half (51.1 percent) of enlisted members and 69.6 percent of officers were married as of 2015 (DOD 2014). The study cohort is represented by over two thirds (68 percent) of its population not married.



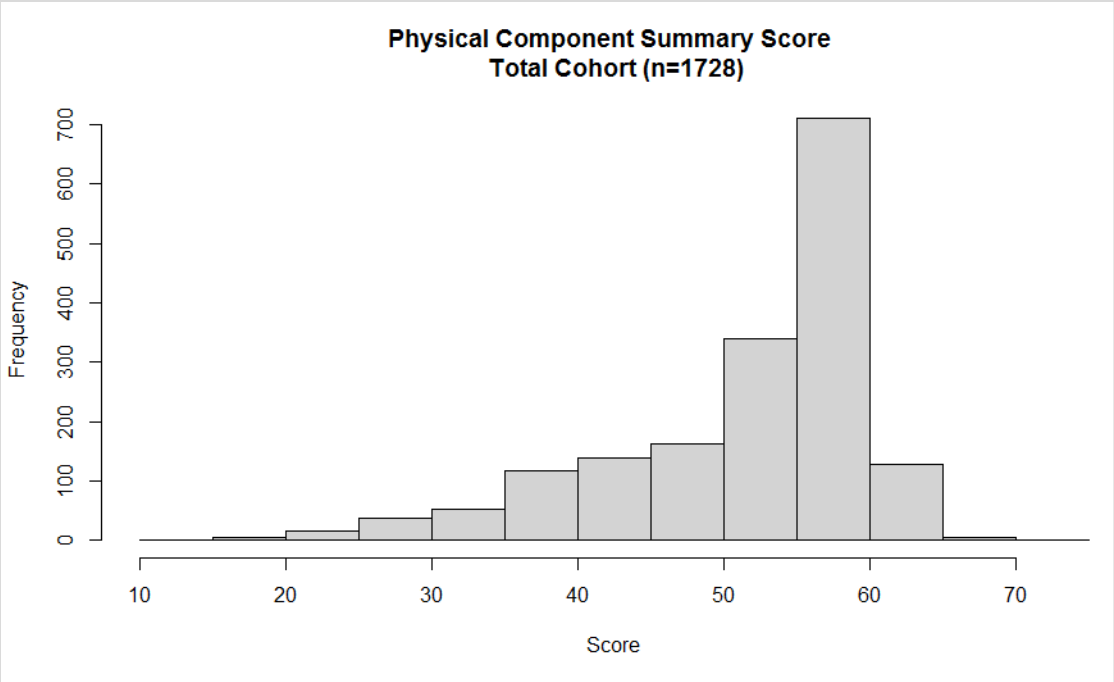
All analyses were carried out with the Natural History Study data set.

Figure 11. Marriage Distribution in Cohort

B. BASIC HEALTH

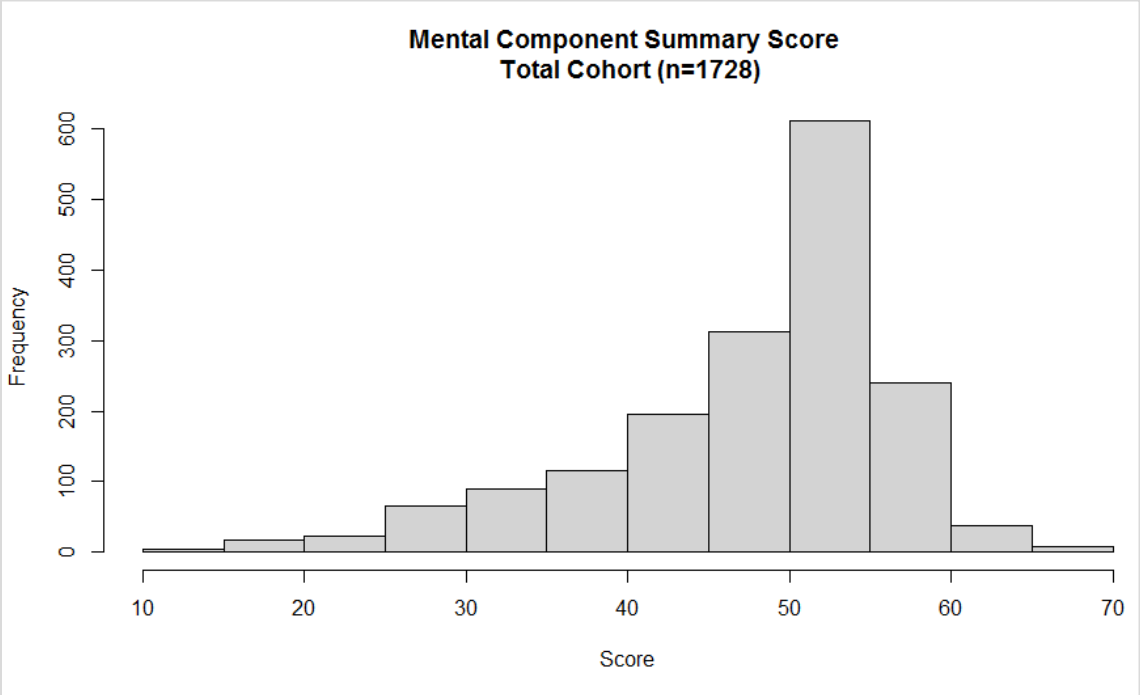
1. Physical and Mental Component Summary Scores

Figures 12 and 13 illustrate the spread of PCSS and MCSS across the entire cohort. PCSS and MCSS have similar distributions, though the MCSS is slightly lower on average with a median of 50.3 and an IQR of 43.45–53.85. The PCSS median, however, is 54.88 with an IQR of 46.94–57.97.



All analyses were carried out with the Natural History Study data set.

Figure 12. Histogram of Physical Component Summary Score for Cohort

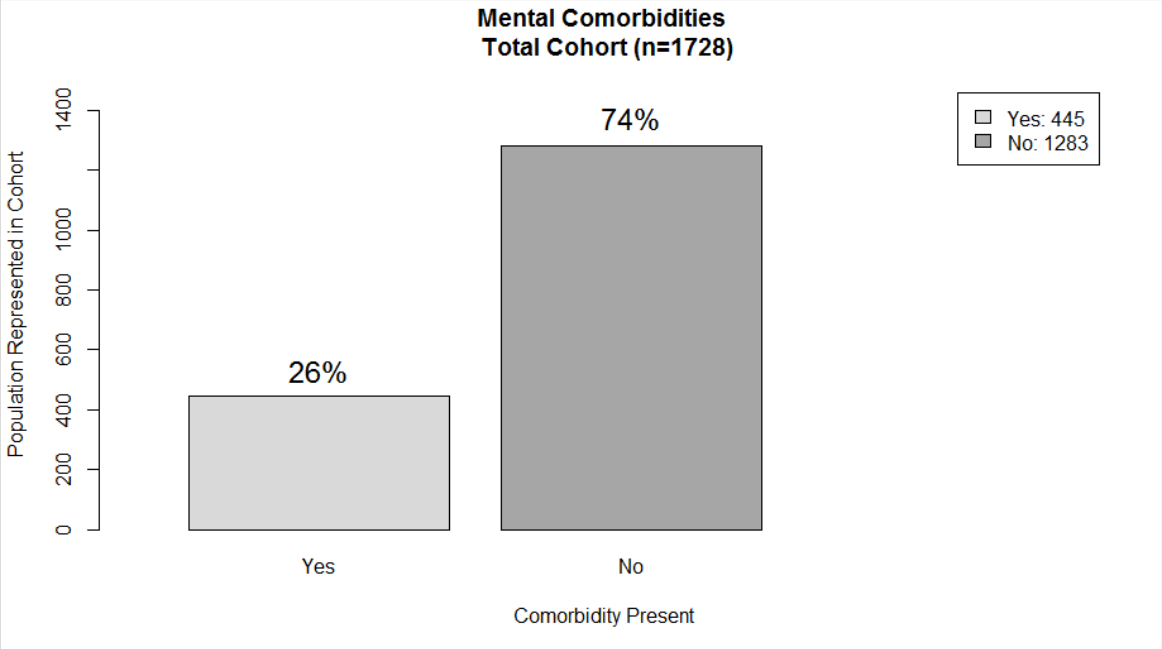


All analyses were carried out with the Natural History Study data set.

Figure 13. Histogram of Physical Component Summary Score for Cohort

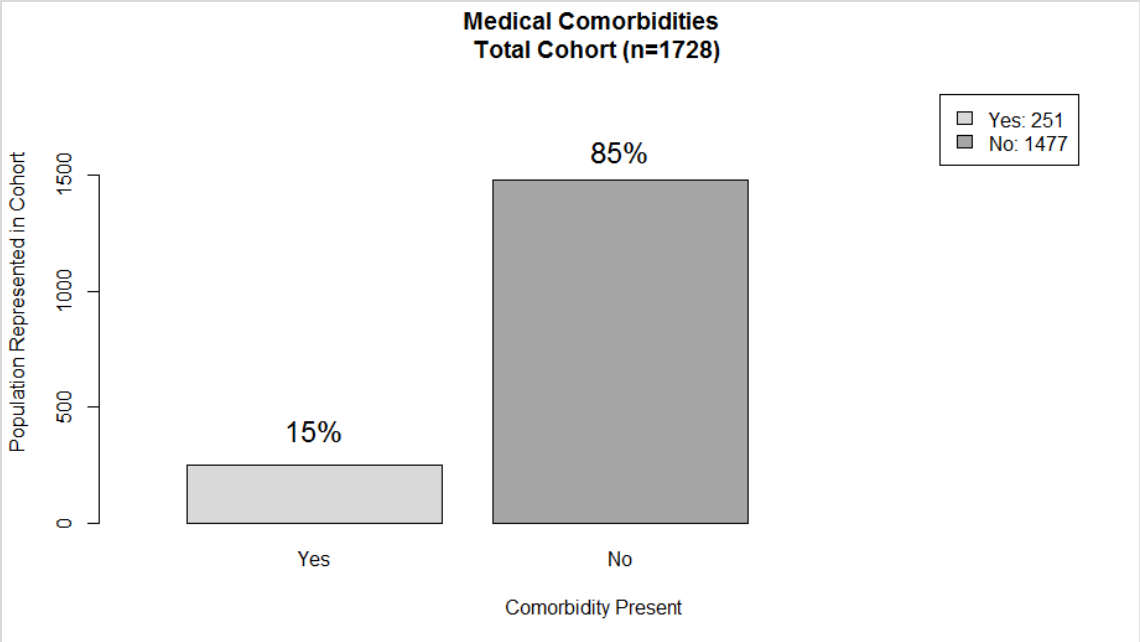
2. Comorbidities

An integral focus of this analysis is quantifying a relation between HRQOL, specifically using the aforementioned MCSS and PCSS, with the following medical and mental comorbidities. Figures 14 and 15 show the prevalence of mental and medical comorbidities across the entire cohort at the time of the survey. Approximately three-quarters of the NHS patients did not have a mental or a medical comorbidity at the time of the survey, though medical comorbidities were less common than mental (15 percent versus 26 percent, respectively).



All analyses were carried out with the Natural History Study data set.

Figure 14. Distribution of Total Cohort Afflicted with Mental Comorbidities



All analyses were carried out with the Natural History Study data set.

Figure 15. Distribution of Total Cohort Afflicted with Medical Comorbidities

Table 1 illustrates the category classification and prevalence of each comorbidity in the cohort. The vast majority of comorbidities are categorized by psychological (mental), viral (physical), and bacterial (physical). Specifically, 23 percent of the cohort had a bacterial comorbidity at some time during follow up prior to the survey, while 16 percent of the cohort had a psychological comorbidity diagnosis at some time before the survey. Those two categories of comorbidities remain the most commonly reported within 24 and 12 months prior to the survey, as well. The psychological comorbidities are more chronic, while the bacterial comorbidities are likely more acute and transient with treatment, thus the decreased relative frequency in more recent months prior to the survey.

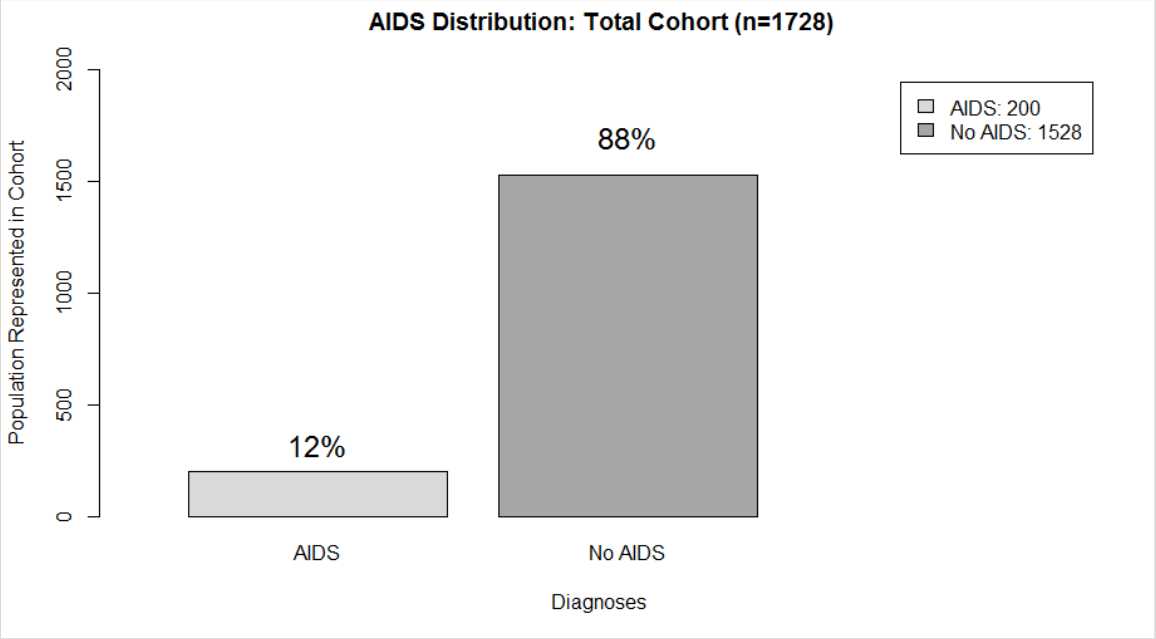
Table 1. Frequency and Prevalence (Percent out of 100) of Individual Comorbidity Categories

Category	<12 months	<24 months	Ever
GI	0.06	0.12	0.29
Respiratory	0.12	0.35	0.64
Cardiovascular	0.69	1.16	2.95
Genitourinary	0.75	1.22	2.08
Endocrine	0.46	1.10	3.18
Psychological	4.69	8.22	16.26
Cancer	1.91	3.13	6.02
Viral	2.89	4.63	7.06
Mycobacterial	0.17	0.17	0.41
Bacterial	4.57	10.42	22.57

GI: Gastrointestinal. All analyses were carried out with the Natural History Study data set

3. HIV Descriptive

CD4 counts, or a measurement of T-cells, is a method of determining HIV progression in patients. The number of T-cells in a person's body is an indication of how well their immune system is functioning; consequently, lower CD4 counts are a sign of progressive HIV and potentially AIDS. Figure 16 shows the distribution of the cohort who has ever had an AIDS diagnosis. There were no notable differences between branches in terms of a history of AIDS diagnoses; roughly, 12 percent across all branches had a history of AIDS.

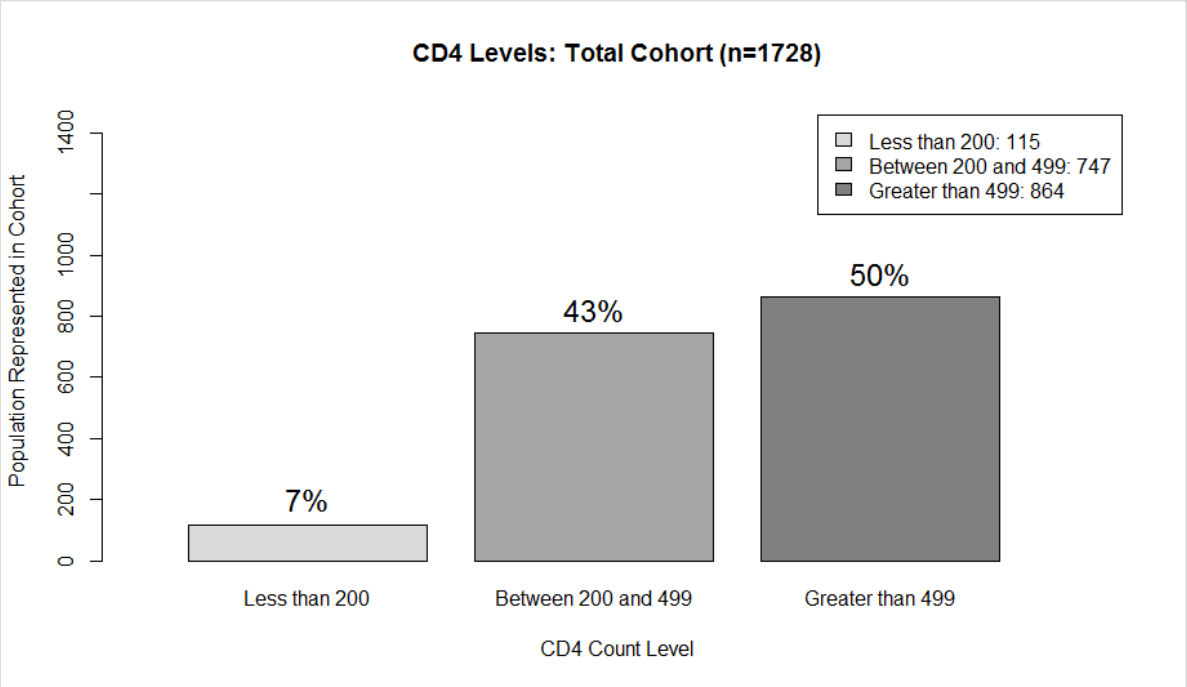


All analyses were carried out with the Natural History Study data set.

Figure 16. AIDS Distribution across Entire Cohort

One criteria for an AIDS diagnosis is when a patient's CD4 count drops below 200. Normal ranges fluctuate between 500–1500 cells/m^3. CD4 counts at the time of the survey identify the immune status of each patient when reporting their quality of life. The cohort further categorizes into three levels of CD4 counts: below 200 cells/m^3, between 200 and 499 cells/m^3, and above 499 cells/m^3. Figure 17 shows the percentages of the cohort which fall into each range. Notably, 7 percent of the cohort at the time of the

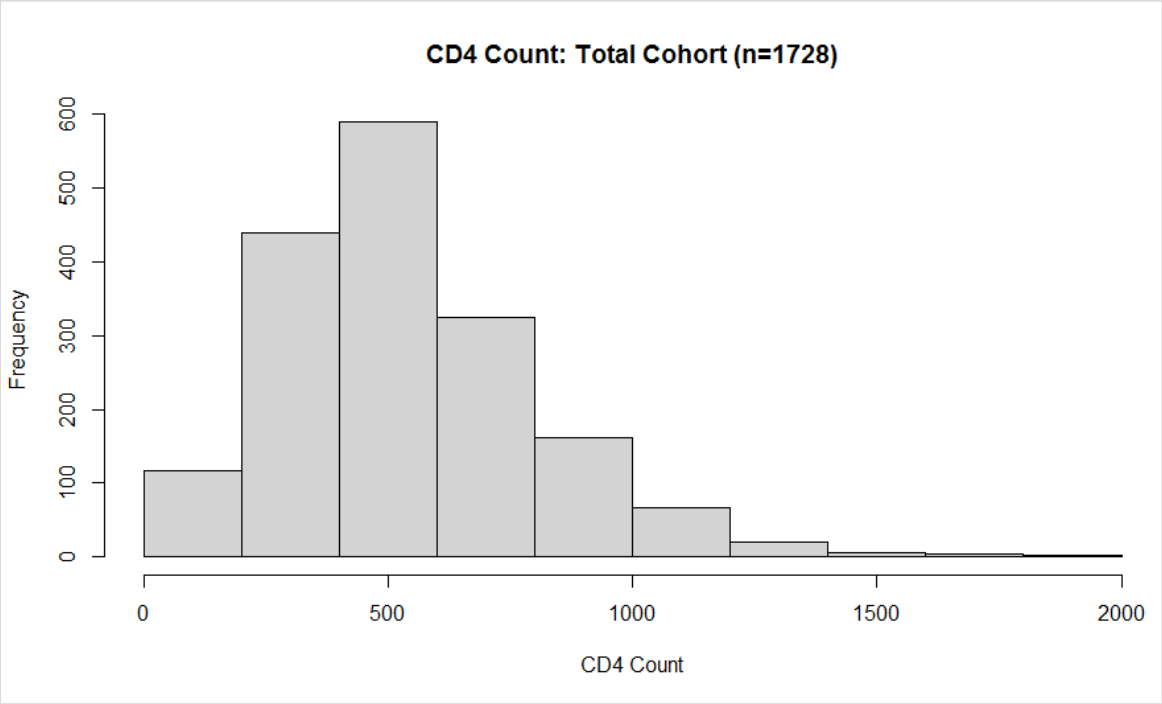
survey was severely immune-compromised and 43 percent of the cohort mildly-moderately compromised.



All analyses were carried out with the Natural History Study data set.

Figure 17. Distribution of the Three Levels of CD4 Count Stratified in the Study for Entire Cohort

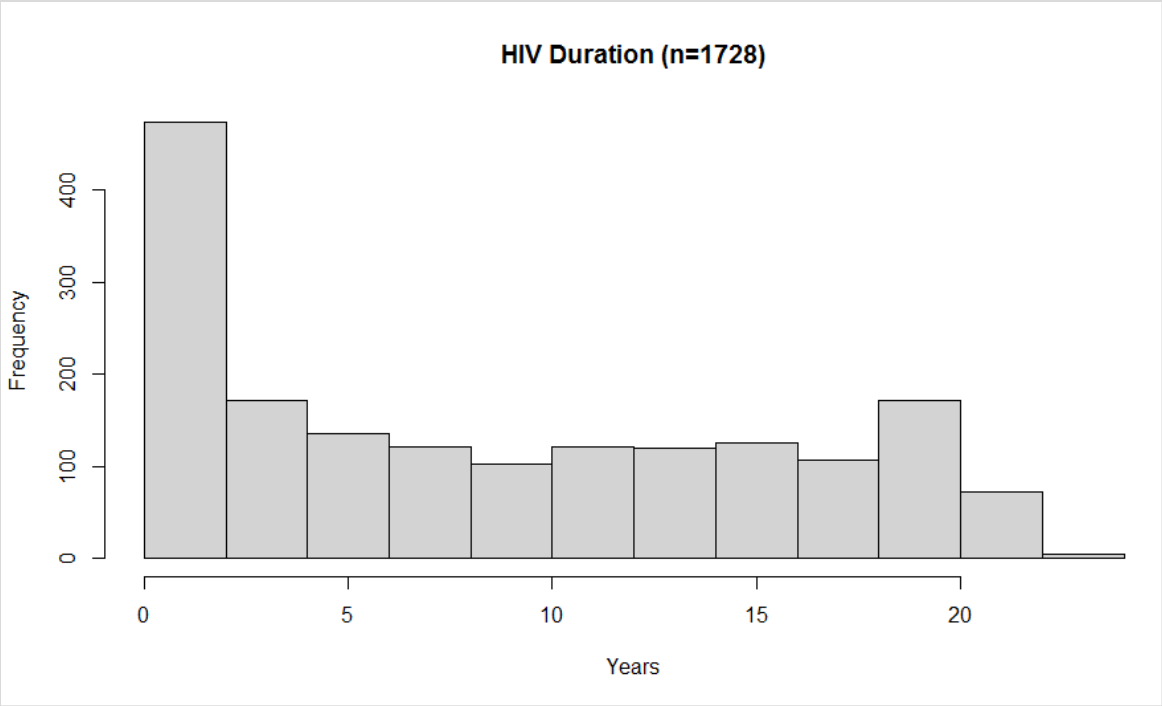
Figure 18 depicts a histogram, which emphasizes the distribution of CD4 counts concentrated around 500 cells/m^3. In later analyses, CD4 counts above this point of concentration significantly influences estimates of PCSS and MCSS.



All analyses were carried out with the Natural History Study data set.

Figure 18. Histogram of CD4 Counts for Entire Cohort

Similarly, Figure 19 depicts a histogram of HIV duration, also later found to be a statistically significant predictor of mental and physical health. The diagnosis of HIV for the majority of patients in this cohort was within five years. However, there appears to be a relatively constant number of patients at duration level with a small spike just before twenty years since seroconversion.



All analyses were carried out with the Natural History Study data set.

Figure 19. Histogram Depicting Distribution of Total Years Persons in Cohort Have Been HIV Positive

IV. RESULTS AND ANALYSIS

Initial review of the data included descriptive statistics by which categorized predictor variables and simple explanatory plots illustrated general tendencies of the data. Follow-on analyses aimed to identify those predictors that influenced PCSS and MCSS. All scores are calculated using the SF-36 survey questions. Responses are gathered and a previously validated algorithm calculates the MCSS and PCSS on a 0–100 scale (Healthy People 2017). The linear models then capture each combination of independent and dependent variables' effect on where a patient scores on this scale.

The goal of the analyses is to quantify a relationship between age-related comorbidities and HRQOL. Therefore, specifically developed independent binary variables denote which of the forty-nine specific comorbidities and ten clinical categories affect each patient. Initially, each of these 59 variables populated columns of the data set conditioned on diagnoses within 12 months prior to the survey date. In Table 2, the prevalence of the most common specific comorbidities in this cohort are highlighted, using ever a historical diagnosis, a diagnosis within 24 months, and within 12 months of the survey. Expectedly, the most recent window of opportunity has a smaller prevalence of all comorbidities as the time of follow-up is reduced relative to the other windows of follow-up (i.e., within 24 months and ever).

Table 2. First 7 Diagnoses' Prevalence (Percent out of 100) for Purposes of Illustrated Increase Sparsity as Time from Survey Date Decreases

Diagnosis	<12 months	<24 months	Ever
Syphilis Latent	0.81	2.43	7.64
Gonorrhea	0.81	1.68	4.34
Diabetes Mellitus	0.46	1.10	3.18
Major Depression	1.97	3.65	6.66
Alcohol Abuse	0.81	1.45	2.43
Chlamydia	1.27	3.47	8.45
Anxiety	1.04	1.79	3.99

All analyses were carried out with the Natural History Study data set.

Univariate models that yielded covariates with p values < 0.1 populated subsequent full multiple regression models. The threshold at 0.1 is a conservative attempt to create complete multiple regression models. In the end, the intent is for the multiple regression models to more thoroughly, yet pragmatically, describe the relationships between the response variables and independent variables.

A. PHYSICAL COMPONENT SUMMARY SCORES

Univariate models of PCSS resulted in 32 independent variables significant at the alpha=0.1 level. Amongst those, 5 were demographic predictors, 5 were clinical categories, 10 were specific clinical diagnoses, and twelve were general clinical characteristics (see Tables 3–6). Age was the only demographic predictor associated with lower PCSS score, albeit with a low coefficient of -0.20 (see Table 3). The univariate analyses also revealed 3 demographic predictors that positively influenced PCSS to include rank, gender, and marital status, in decreasing order of coefficients. The categories of diagnoses associated with lower PCSS score included cardiovascular, endocrine, cancer, and viral infections, in order of decreasing coefficients (see Table 4). The specific clinical diagnoses significantly reducing PCSS score included congestive heart failure, prostate cancer, cerebrovascular, anal cancer, coronary artery disease, diabetes, and herpes, in order of decreasing coefficients (see Table 5). The general clinical predictors negatively influencing PCSS included a history of an AIDS diagnosis, ART class, the total historical mental or medical comorbidities, VL, and duration of HIV

disease (see Table 6). Lastly, analyses found CD4 count positively influencing PCSS in the univariate analyses.

Table 3. Demographics: PCSS

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Gender			
Female	*Ref*	*Ref*	
Male	2.19	0.001	*
Age	-0.20	< 0.001	*
Marital Status			
Married	*Ref*	*Ref*	
Not Married	1.76	< 0.001	*
Rank			
Civilian/not Active Duty	*Ref*	*Ref*	
Enlisted	4.00	< 0.001	*
Officer/Warrant	5.98	< 0.001	*
Race-Ethnicity			
Non-Hispanic White	*Ref*	*Ref*	
Hispanic and Others	0.38	0.555	
Non-Hispanic AA	0.05	0.917	
Branch of Service			
Other (service)	*Ref*	*Ref*	
USA	-1.61	0.220	
USAF	-0.42	0.752	
USMC	-0.36	0.808	
USN	0.76	0.550	

Non-Hispanic AA: Non-Hispanic African Americans, USA: United States Army, USN: United States Navy, USAF: United States Air Force, USMC: United States Marine Corps. All analyses were carried out with the Natural History Study data set.

Expected PCSS values are 2.19 points higher for males compared to females in this cohort ($p < 0.001$). As age increases, PCSS can be expected to decrease by 0.2 points ($p < 0.001$), which results in approximately one PCSS point for every five years gained in age. While statistically significant, this does not have much practical significance in terms of estimating PCSS. Patients in the cohort who are not married have expected PCSS values 1.76 points higher than those patients who are married ($p < 0.001$). Lastly,

compared to civilian and not active duty patients, enlisted patients' expected PCSS values are 4 points higher ($p < 0.001$) and officers have nearly 6 points higher ($p < 0.001$).

Table 4. Clinical Categories: PCSS

Independent Variable	Coefficient	p-Value	p-Value < 0.1
GI	-7.75	0.228	
Respiratory	-5.47	0.141	
Cardiovascular	-6.34	0.002	*
Genitourinary	-2.91	0.165	
Endocrine	-4.46	0.033	*
Psychological	0.05	0.946	
Cancer	-2.99	0.017	*
Viral	-1.87	0.075	*
Mycobacterial	-5.69	0.376	
Bacterial	3.00	< 0.001	*

GI: gastrointestinal. All analyses were carried out with the Natural History Study data set.

Those patients with diagnoses that fall under the category of cardiovascular diseases can expect PCSS values to drop by 6.34 points ($p = 0.002$) relative to those without a cardiovascular disease history. Patients with a history of diagnoses that classify as endocrine, have a reduced PCSS value by an estimated 4.46 points ($p = 0.033$) when compared to those without that disease history. Similarly, a patient diagnosed with any cancer has expected PCSS value reduced by 2.99 points ($p = 0.017$) relative to those without that diagnosis history. Additionally, a history of viral diagnoses reduce expected PCSS values by 1.87 points ($p = 0.075$).

Clinical categories which positively influenced PCSS include bacterial infections. Expected PCSS estimates increase by 3 points ($p < 0.001$) in the presence of a history of bacterial infection when compared to those without such history. Correspondingly, certain STIs were also significantly associated with an increasing PCSS value (see Table 5).

Table 5. Clinical Diagnoses: PCSS

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Congestive Heart Failure	-16.51	0.069	*
Interstitial Nephritis	2.32	0.798	
Diabetes	-4.46	0.033	*
Major depression	-2.32	0.048	*
Alcohol abuse	0.51	0.786	
COPD	-5.47	0.141	
Anxiety	3.75	0.025	*
Bipolar	2.80	0.663	
PTSD	1.99	0.564	
Suicide attempt	2.74	0.461	
Cirrhosis	-7.75	0.228	
Anal Cancer	-7.66	0.017	*
Acute Renal Failure	-3.33	0.144	
Cervical Cancer	-9.85	0.278	
Cocaine	-0.39	0.923	
Marijuana	1.05	0.908	
Methamphetamines use	-10.38	0.106	
Drug abuse (other)	-2.94	0.648	
Herpes	-2.33	0.057	*
Hepatitis (acute/resolved)	-1.07	0.740	
Hepatitis C	2.43	0.423	
Hepatitis B	-5.16	0.205	
Tuberculosis	-5.69	0.376	
Cerebrovascular	-8.86	0.051	*
Coronary Artery	-6.32	0.022	*
Myocardial Infarction	2.29	0.722	
Peripheral Artery	-4.47	0.487	
Lymphoma Non-Hodgkin's	5.90	0.516	
Lymphoma Hodgkin's	1.35	0.834	
Kaposi's Sarcoma	-7.08	0.271	
Basal Cell (skin)	-3.26	0.130	
Colon Cancer	0.57	0.950	
Lung Cancer	-11.18	0.219	
Melanoma	7.69	0.398	
Multiple Myeloma	5.46	0.396	
Prostate Cancer	-12.57	0.002	*
Squamous Cell (skin)	2.19	0.526	
Other cancer	-0.38	0.912	

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Syphilis (latent)	2.98	0.038	*
Gonorrhea	4.39	0.010	*
Chlamydia	2.53	0.034	*
Syphilis (primary)	2.60	0.286	
Syphilis (secondary)	1.64	0.270	
Syphilis (tertiary)	1.03	0.873	
HIV Nephropathy	-2.11	0.743	

COPD: chronic obstructive pulmonary disease, PTSD: post-traumatic stress disorder, HIV: human immunodeficiency virus. All analyses were carried out with the Natural History Study data set.

Diagnosis of congestive heart failure had the most influence on PCSS, negatively influencing PCSS scores by 16.5 points ($p = 0.069$). The next most influential clinical diagnosis on PCSS is prostate cancer, reducing expected scores by 12.6 points ($p = 0.002$) when compared to others without that diagnosis history. Cerebrovascular disease, anal cancer, and coronary artery disease all appear to have comparable reduction effects, reducing expected PCSS values by 8.86 ($p = 0.051$), 7.66 ($p = 0.017$), and 6.32 ($p = 0.022$) respectively. The presence of diabetes reduces expected PCSS values by an estimated 4.46 points ($p = 0.033$), as well. Interestingly, major depression and anxiety, generally associated with mental comorbidities, each also reduce expected PCSS scores significantly. Diagnoses of major depression can lower expected PCSS by 2.3 points ($p = 0.048$) and anxiety can lower PCSS by 3.75 points ($p =0.025$).

Again, three bacterial diagnoses increase the expected PCSS values significantly. Syphilis (latent) increases expected PCSS vales by 2.98 points ($p = 0.038$), gonorrhea by 4.39 points ($p = 0.01$), and chlamydia by 2.53 points ($p = 0.034$). Again, this may be an artifact of age, as the mean age of those with a history of recent STI, 35.45 years, is significantly lower than the mean age of those without, 40.22 years ($p < 0.001$).

Table 6. Clinical General: PCSS

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Total Mental Diagnoses	-2.72	< 0.001	*
Total Medical Diagnoses	-0.72	< 0.001	*
Treatment Class			
Not Treated	*Ref*	*Ref*	
Not Currently Treated	-3.77	< 0.001	*
NPI	-2.22	< 0.001	*
PI	-4.66	< 0.001	*
History of AIDS Diagnosis	-6.11	< 0.001	*
HIV Duration	-0.29	< 0.001	*
VL	0.29	0.095	*
CD4 Levels			
CD4 count below 200	*Ref*	*Ref*	
CD4 count 200 – 499	6.62	< 0.001	*
CD4 count 500+	7.38	< 0.001	*

PI: protease inhibitor, NPI: non-protease inhibitor. All analyses were carried out with the Natural History Study data set.

The total number of mental and medical diagnoses have each shown to be significant predictors of PCSS in univariate analyses (see Table 6). With each additional diagnosis of mental comorbidity, the expected PCSS score decreases by 2.72 points ($p < 0.001$). Likewise, with each additional medical comorbidity, PCSS drops by 0.72 points ($p < 0.001$). Interestingly, patients with any type of treatment history all had significantly reduced PCSS values (p values < 0.001) relative to those patients without any HIV treatment history. This is likely due mostly to treatment initiation criteria during the majority of survey dates being contingent on AIDS symptoms. As a history of an AIDS diagnosis has a negative influence on PCSS values (p value < 0.001), this also reflects the subset of individuals in the cohort who would have been eligible to initiate treatment. The sicker the patient, the more likely they are to initiate treatment, a facet captured in these univariate analyses. HIV duration is also seen to reduce PCSS, though similar to age, the practical significance is unknown (reduction of PCSS values by -0.29; $p < 0.001$).

CD4 levels are useful indicators of immune health. Therefore, higher counts imply greater health. Patients whose CD4 counts are between 200 and 499 have increased

PCSS values by 6.62 points ($p < 0.001$) while those with CD4 counts greater the 499 have increased PCSS values of 7.38 ($p < 0.001$), when they are compared to those patients whose CD4 is less than 200 at the time of the survey.

B. MENTAL COMPONENT SUMMARY SCORE

Twenty independent variables were found to significantly influence MCSS in univariate analyses: 5 demographics variables, 3 categories of diagnosis, 8 specific diagnosis and 6 general clinical variables. Those demographic independent variables include race (specifically non-Hispanic African Americans), rank (specifically enlisted), and age in order of decreasing coefficient estimates (see Table 7). Categories of comorbidities affecting significant negative change on MCSS were respiratory, psychological, and viral illness in decreasing order of influence estimates (see Table 8). Specific diagnosis found to have significant negative impact include Methamphetamines use, suicide attempt, chronic obstructive pulmonary disease (COPD), squamous cell (skin) cancer, anxiety, major depression, alcohol abuse, and herpes (see Table 9). Three of the general clinical variables negatively influence MCSS: total mental diagnosis, AIDS, and viral load. However, analyses found CD4 count significantly increasing MCSS estimates as counts increased.

Table 7. Demographics: MCSS

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Gender			
Female	*Ref*	*Ref*	
Male	0.63	0.465	
Age	0.045	0.031	*
Marital Status			
Married	*Ref*	*Ref*	
Not Married	0.35	0.465	
Rank			
Civilian/not Active Duty	*Ref*	*Ref*	
Enlisted	0.83	0.074	*
Officer/Warrant	1.35	0.127	
Race-Ethnicity			
Non-Hispanic White	*Ref*	*Ref*	
Hispanic and Others	-0.77	0.239	
Non-Hispanic AA	1.81	< 0.001	*
Branch of Service			
Other (service)	*Ref*	*Ref*	
USA	0.794578	0.551	
USAF	0.452977	0.734	
USMC	-0.06201	0.967	
USN	0.409593	0.751	

Non-Hispanic AA: Non-Hispanic African Americans, USA: United States Army, USN: United States Navy, USAF: United States Air Force, USMC: United States Marine Corps. All analyses were carried out with the Natural History Study data set.

Age is a significant predictor of MCSS as it was for PCSS (see Table 7). While statistically significant ($p = 0.031$) its practical significance is negligible-- 0.045 MCSS points for every year gained in age. MCSS is again influenced by rank, specifically, the expected MCSS for enlisted are 0.83 points higher than civilian or active duty patients ($p = 0.074$). Race is also a determinant of MCSS in that non-Hispanic African Americans have expected MCSS scores 1.81 points higher than non-Hispanic Whites ($p < 0.001$).

Table 8. Clinical Categories: MCSS

Independent Variable	Coefficient	p-Value	p-Value < 0.1
GI	4.10	0.527	
Respiratory	-9.07	0.016	*
Cardiovascular	-0.82	0.690	
Genitourinary	-2.06	0.331	
Endocrine	-2.08	0.326	
Psychological	-5.59	< 0.001	*
Cancer	-1.66	0.191	
Viral	-1.87	0.076	*
Mycobacterial	-3.82	0.557	
Bacterial	-0.12	0.870	

GI: gastrointestinal. All analyses were carried out with the Natural History Study data set.

Categories of respiratory, psychological and viral diagnoses have the most significant effect on MCSS (see Table 8). Respiratory diagnoses have the greatest effect, lowering MCSS an expected 9.07 points ($p = 0.016$). Psychological diagnoses, unsurprisingly, have a noticeable negative impact, as well, lowering scores by 5.59 points ($p < 0.001$). Finally, viral diagnoses lower expected MCSS by 1.87 points ($p = 0.076$).

Table 9. Clinical Diagnoses: MCSS

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Congestive Heart Failure	2.16	0.814	
Interstitial Nephritis	4.54	0.621	
Diabetes	-2.08	0.326	
Major depression	-5.36	0.000	*
Alcohol abuse	-3.46	0.067	*
COPD	-9.07	0.016	*
Anxiety	-6.54	0.000	*
Bipolar	-9.62	0.138	
PTSD	-2.01	0.562	
Suicide attempt	-9.39	0.012	*
Cirrhosis	4.10	0.527	
Anal Cancer	-3.07	0.346	
Acute Renal Failure	-2.83	0.219	
Cervical Cancer	2.51	0.784	
Cocaine	-1.30	0.753	
Marijuana	-4.20	0.647	
Methamphetamines use	-20.47	0.002	*
Drug abuse (other)	-3.56	0.584	
Herpes	-2.73	0.027	*
Hepatitis (acute/resolved)	-2.87	0.378	
Hepatitis C	2.47	0.420	
Hepatitis B	1.97	0.632	
Tuberculosis	-3.82	0.557	
Cerebrovascular	-2.46	0.593	
Coronary Artery	0.42	0.880	
Myocardial Infarction	3.04	0.640	
Peripheral Artery	-9.65	0.137	
Lymphoma Non Hodgkin’s	3.95	0.667	
Lymphoma Hodgkin’s	2.82	0.664	
Kaposi’s Sarcoma	-5.85	0.368	
Basal Cell (skin)	-1.55	0.475	
Colon Cancer	3.32	0.718	
Lung Cancer	-8.72	0.342	
Melanoma	10.19	0.267	
Multiple Myeloma	5.32	0.413	
Prostate Cancer	0.33	0.936	
Squamous Cell (skin)	-6.68	0.055	*
Other cancer	-1.71	0.623	

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Syphilis (latent)	1.00	0.489	
Gonorrhea	-2.47	0.151	
Chlamydia	-0.13	0.913	
Syphilis (primary)	-1.39	0.574	
Syphilis (secondary)	1.40	0.353	
Syphilis (tertiary)	3.18	0.625	
HIV Nephropathy	0.87	0.894	

COPD: chronic obstructive pulmonary disease, PTSD: post-traumatic stress disorder, HIV: human immunodeficiency virus. All analyses were carried out with the Natural History Study data set.

The diagnoses most significantly influencing a patient's mental score are intuitive. Psychological diagnosis of major depression and anxiety lower expected MCSS by 5.36 points ($p < 0.001$) and 6.54 points ($p < 0.001$) respectively (see Table 9). Suicide attempts have an extensive, albeit expected, impact of lowering MCSS an expected 9.39 points ($p = 0.012$). Alcohol and drug abuse are also significant players, while not to the same degree. Alcohol abuse lowers MCSS by an expected 3.46 points ($p = 0.067$) while Methamphetamines use lowers expected MCSS by 20.47 points ($p = 0.002$). COPD lowers MCSS by an expected 9.07 points ($p = 0.016$) and squamous cell (skin) cancer reduces by 6.68 points ($p = 0.055$). The only STI significantly linked with MCSS was herpes, lowering expected MCSS by 2.73 ($p = 0.27$).

Table 10. Clinical General: MCSS

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Total Mental Diagnoses	-4.27	< 0.001	*
Total Medical Diagnoses	-0.22	0.119	
Treatment Class			
Not Treated	*Ref*	*Ref*	
Not Currently Treated	-0.94	0.275	
NPI	1.25	0.033	*
PI	0.35	0.565	
History of AIDS Diagnosis	-2.04	0.003	*
HIV Duration	0.004	0.883	
VL	-0.59	< 0.001	*
CD4 Levels			
CD4 count below 200	*Ref*	*Ref*	
CD4 count 200 – 499	2.24	0.015	*
CD4 count 500+	3.35	< 0.001	*

PI: protease inhibitor, NPI: non-protease inhibitor, VL: viral load. All analyses were carried out with the Natural History Study data set.

General clinical measurements, total mental comorbidities, treatment administration, AIDS diagnosis, VL, and CD4 count each significantly influence MCSS (See Table 10). As to be expected, increasing the number of mental comorbidities lowers MCSS (-4.27 points; $p < 0.001$). Patients diagnosed with AIDS had expected MCSS 2.04 points lower than those without an AIDS diagnosis ($p = 0.003$). Increasing viral load also drops MCSS by 0.59 points per unit increase ($p < 0.001$).

Interestingly, administering treatments increases estimated MCSS, contrary to observations seen with respect to PCSS. The introduction of NPI raises MCSS by 1.25 ($p = 0.033$), compared to those patients never treated. The effect of CD4 count, however, is consistent between PCSS and MCSS analyses. CD4 counts between 200 and 499 can be expected to raise MCSS by 2.24 points ($p = 0.015$) and measurements over 499 can be expected to raise MCSS by 3.35 points ($p < 0.001$).

C. QUINTILE GLMS

Nineteen independent variables significantly influence whether a patient fell into the highest quintile of either MCSS or PCSS. Among those included, 5 were demographic, 3 were categories of diagnosis, 3 were specific diagnoses, and 8 were general clinical variables (see Tables 11–14). Independent demographic variables significantly increasing the log odds of a patient falling in the highest quintile of MCSS or PCSS include being male, enlisted, officer/warrant, and non-Hispanic African American (see Table 11). Increasing age reduces log odds of falling in the highest quintile, though not practically significantly (β = -.008: p = 0.093). Psychological and cancer were two categories of diagnosis found to negatively influence the log-odds, while bacterial diagnosis were found to increase log-odds of a patient scoring in the highest quintile. However, the cause of bacterial infections raising log odds is rooted in the relation between age and contraction of STIs. The mean age of patients with a bacterial infection diagnosis within the 24 months prior to the survey date is 33.57 years old while those not diagnosed is 40.87 years old (95 percent CI: [5.78, 8.79]). Akin to the significant categories, the specific significant diagnoses include major depression, basal cell (skin) cancer, and herpes (see Table 13). General clinical independent variables with significant influence are total mental or medical diagnosis, specific treatments, AIDS diagnoses, HIV duration, and CD4 count.

Table 11. Demographics: Quintiles

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Gender			
Female	*Ref*	*Ref*	
Male	0.37	0.075	*
Age	-0.008	0.093	*
Marital Status			
Married	*Ref*	*Ref*	
Not Married	0.10	0.342	
Rank			
Civilian/not Active Duty	*Ref*	*Ref*	
Enlisted	0.21	0.054	*
Officer/Warrant	0.67	< 0.001	*
Race-Ethnicity			
Non-Hispanic White	*Ref*	*Ref*	
Hispanic and Others	0.22	0.144	
Non-Hispanic AA	0.38	< 0.001	*
Branch of Service			
Other (service)	*Ref*	*Ref*	
USA	-0.07	0.828	
USAF	-0.11	0.704	
USMC	-0.04	0.894	
USN	0.049	0.866	

Non-Hispanic AA: Non-Hispanic African Americans, USA: United States Army, USN: United States Navy, USAF: United States Air Force, USMC: United States Marine Corps. All analyses were carried out with the Natural History Study data set.

The data was coerced into quintiles for the purposes of logistic regression where an independent binary variable represents whether a patient has scored in the highest quintile for either PCSS or MCSS. Among those variables which significantly influence whether a patient will score in the highest quintile is sex (see Table 11). Specifically, the log odds of males scoring in the highest quintile is .37 that of females ($p = 0.075$). Additionally, for every year increase in age, the log odds of falling in highest quintile reduces by 0.008 ($p = 0.093$). For enlisted, the log odds of being in the highest quintile of either MCSS/PCSS is 0.21 times the log odds for civilians/not active duty ($p = 0.054$), while the log odds for officers is 0.67 that of civilians/not active duty ($p < 0.001$). The

log odds of non-Hispanic African Americans are also .38 times that of non-Hispanic White patients ($p < 0.001$).

Table 12. Clinical Categories: Quintiles

Independent Variable	Coefficient	p-Value	p-Value < 0.1
GI	-12.99	0.973	
Respiratory	-13.99	0.969	
Cardiovascular	-0.52	0.313	
Genitourinary	-0.59	0.253	
Endocrine	-0.45	0.386	
Psychological	-0.39	0.047	*
Cancer	-0.80	0.019	*
Viral	-0.34	0.175	
Mycobacterial	-12.99	0.966	
Bacterial	0.27	0.088	*

All analyses were carried out with the Natural History Study data set.

Categories influencing the log odds of falling in the highest quintile include psychological, cancer, and bacterial diagnoses (see Table 12). A diagnosis with a psychological disorder decreases the log odds of scoring in the highest quintile by 0.39 ($p = 0.047$) compared to those without. Similarly, cancer diagnoses decrease log odds by 0.80 ($p = 0.019$). However, a history of bacterial infections (driven mostly by STIs, presumably) increased the patient's log odds of scoring in the highest quintile by 0.27 ($p = 0.088$).

Table 13. Clinical Diagnoses: Quintiles

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Congestive Heart Failure	-11.99	0.971	
Interstitial Nephritis	-11.99	0.971	
Diabetes	-0.45	0.386	
Major depression	-0.79	0.012	*
Alcohol abuse	-0.18	0.684	
COPD	-13.99	0.969	
Anxiety	0.39	0.280	
Bipolar	14.15	0.970	
PTSD	-1.21	0.261	
Suicide attempt	-1.03	0.347	
Cirrhosis	-12.99	0.973	
Anal Cancer	-0.52	0.525	
Acute Renal Failure	-0.38	0.474	
Cervical Cancer	-11.99	0.971	
Cocaine	-0.81	0.470	
Marijuana	-11.99	0.971	
Methamphetamines use	-12.99	0.973	
Drug abuse (other)	-12.99	0.973	
Herpes	-0.58	0.061	*
Hepatitis (acute/resolved)	-1.37	0.200	
Hepatitis C	0.81	0.230	
Hepatitis B	0.99	0.279	
Tuberculosis	-12.99	0.966	
Cerebrovascular	-12.99	0.961	
Coronary Artery	-0.40	0.553	
Myocardial Infarction	0.58	0.681	
Peripheral Artery	0.58	0.681	
Lymphoma Non Hodgkin's	-11.99	0.971	
Lymphoma Hodgkin's	0.58	0.681	
Kaposi's Sarcoma	-12.99	0.973	
Basal Cell (skin)	-2.27	0.028	*
Colon Cancer	-11.99	0.971	
Lung Cancer	-11.99	0.971	
Melanoma	13.15	0.968	
Multiple Myeloma	-12.99	0.973	
Prostate Cancer	0.18	0.848	
Squamous Cell (skin)	-0.34	0.688	
Other cancer	-0.34	0.688	

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Syphilis (latent)	0.50	0.112	
Gonorrhea	0.09	0.816	
Chlamydia	-0.04	0.885	
Syphilis (primary)	0.88	0.106	
Syphilis (secondary)	0.22	0.499	
Syphilis (tertiary)	0.58	0.681	
HIV Nephropathy	-12.99	0.973	

COPD: chronic obstructive pulmonary disease, PTSD: post-traumatic stress disorder, HIV: human immunodeficiency virus. All analyses were carried out with the Natural History Study data set.

The psychological disorder influencing a patient's log odds of scoring in the highest quintile is major depression diagnosis–reducing the log odds by .79 (p = 0.012) (see Table 13). A history of the bacterial infection herpes reduces the patient's log odds by 0.58 (p = 0.061). Finally, basal cell (skin) cancer reduces the log odds by 2.27 (p = 0.28).

Table 14. Clinical General: Quintiles

Independent Variable	Coefficient	p-Value	p-Value < 0.1
Total Mental Diagnoses	-0.58	< 0.001	*
Total Medical Diagnoses	-0.07	0.031	*
Treatment Class			
Not Treated	*Ref*	*Ref*	
Not Currently Treated	-0.64	0.002	*
NPI	0.01	0.942	
PI	-0.24	0.076	*
History of AIDS Diagnosis	-0.61	< 0.001	*
HIV Duration	-0.01	0.089	*
VL	-0.05	0.212	
CD4 Levels			
CD4 count below 200	*Ref*	*Ref*	
CD4 count 200 – 499	0.50	0.029	*
CD4 count 500+	0.75	0.001	*

PI: protease inhibitor, NPI: non-protease inhibitor. All analyses were carried out with the Natural History Study data set.

Total mental and medical comorbidities reduce the log odds of scoring in the highest quintile by 0.58 ($p < 0.001$) and 0.07 ($p = 0.031$), respectively (see Table 14). Patients treated with protease inhibitors (PI) have a reduced log odds of scoring in the highest quintile by 0.24 ($p = 0.076$). Patients having ever been diagnosed with AIDS have reduced log odds of scoring in the top fifth by 0.61 ($p < 0.001$). And, HIV duration decreased the log odds by 0.01 ($p = 0.089$) for every year increase. CD4 counts between 200 and 499 are expected to increase log odds by .50 ($p = 0.029$) and counts greater than 499 are expected to increase log odds by 0.75 compared to those patients with CD4 cell counts below 200 ($p = 0.001$).

Table 15. Demographics: Independent Variables' Significance across Dependent Variables

Independent Variable	**Quintile**	**PCSS**	**MCSS**
Gender			
Female	*Ref*	*Ref*	*Ref*
Male	*	*	
Age	*	*	*
Marital Status			
Married	*Ref*	*Ref*	*Ref*
Not Married		*	
Rank			
Civilian/not Active Duty	*Ref*	*Ref*	*Ref*
Enlisted	*	*	*
Officer/Warrant	*	*	
Race-Ethnicity			
Non-Hispanic White	*Ref*	*Ref*	*Ref*
Hispanic and Others			
Non-Hispanic AA	*		*

Non-Hispanic AA: Non-Hispanic African Americans. All analyses were carried out with the Natural History Study data set.

Certain predictor variables were found to be significant in estimating each of the three analyzed response variables (highest quintile of either PCSS or MCSS, PCSS, and MCSS) (see Table 15–18). Age is the only covariate which appears as significant with all the response variables. However, its practical significance remains unclear.

Table 16. Categories: Independent Variables' Significance across Dependent Variables

Independent Variable	**Quintile**	**PCSS**	**MCSS**
Respiratory			*
Cardiovascular		*	
Endocrine		*	
Psychological	*		*
Cancer	*	*	
Viral		*	*
Bacterial	*	*	

All analyses were carried out with the Natural History Study data set.

There is no single diagnosis category with a statistically significant estimate for all of the three dependent variables. However, psychological diagnoses appear to be associated with both the highest quintile and MCSS alone (see Table 16). Likewise, cancer and bacterial each appear to be associated with both highest quintile and PCSS alone. Viral infections was a significant predictor for both PCSS and MCSS models.

Table 17. Diagnoses: Independent Variables' Significance across Dependent Variables

Independent Variable	**Quintile**	**PCSS**	**MCSS**
Congestive Heart Failure		*	
Diabetes		*	
Major depression	*	*	*
Alcohol abuse			*
COPD			*
Anxiety		*	*
Suicide attempt			*
Anal Cancer		*	
Methamphetamines use			*
Herpes	*	*	*
Cerebrovascular		*	
Coronary Artery		*	
Basal Cell (skin)	*		
Prostate Cancer		*	
Squamous Cell (skin)			*
Syphilis (latent)		*	
Gonorrhea		*	
Chlamydia		*	

COPD: chronic obstructive pulmonary disease, HIV: human immunodeficiency virus. All analyses were carried out with the Natural History Study data set.

Major depression and herpes are the only specific diagnoses that appear as significant variables for estimating each dependent variable (see Table 17). Likewise, bacterial is included in the PCSS model built with categories. However, while herpes was included using the stepAIC ( ) function in R, its p value was not significant at the alpha =

0.05 level and its removal from the model did not influence AIC (Venables and Ripley 2002). Therefore, herpes was dropped as an estimator for PCSS.

Table 18. General Clinical: Independent Variables' Significance across Dependent Variables

Independent Variable	Quintile	PCSS	MCSS
Total Mental Diagnoses	*	*	*
Total Medical Diagnoses	*	*	
Treatment Class			
Not Treated	*Ref*	*Ref*	*Ref*
Not Currently Treated	*	*	
NPI		*	*
PI	*	*	
History of AIDS Diagnosis	*	*	*
HIV Duration	*	*	
VL		*	*
CD4 Levels			
CD4 count below 200	*Ref*	*Ref*	*Ref*
CD4 count 200 – 499	*	*	*
CD4 count 500+	*	*	*

PI: protease inhibitor, NPI: non-protease inhibitor. All analyses were carried out with the Natural History Study data set.

Interestingly, total mental comorbidities is significant across all three dependent variables, but total medical comorbidities is not significant for MCSS (see Table 18). A history of an AIDS diagnosis significantly influences a patient's estimated MCSS and PCSS scores, and their log odds for falling in the highest quintile of either one. Similarly, VL and CD4 count each influence the three response variables and will be considered in subsequent multiple regression models. The following multiple regression models have been subdivided into six total models. For each dependent variable there have been two separate multiple regression models fit: one model includes all significant demographic, diagnosis categories, and general clinical covariates; the other is the proceeding model included all specific diagnoses in lieu of diagnosis categories. The purpose for separating these models is to observe specific influence of each diagnosis within the overarching

category, yet still observe the larger impacts of each group of specific comorbidity. Furthermore, by separating diagnoses from their categories mitigates the potential risk for inherent multicollinearity.

D. MULTIPLE REGRESSION MODELS

The goal of this analysis is to quantify the relationship between age-related comorbidities and quality of life. The final multiple regression models selected by backward elimination using AIC yielded some covariates that were not significant at an alpha=0.05 level because the function does not explicitly consider the significance of individual predictors in the model. Therefore, AICs were compared between the step( ) function selected models and models without the non-significant covariates. Prior research has found that, in general, if the difference in AICs is less than 2, the models can be considered similar (Burnham 1998). Therefore, the models were assumed to be relatively the same and insignificant covariates were dropped. The first model uses diagnosis categories (see Table 19) and the second using specific diagnoses (see Table 20) in order to estimate patient mental health scores. Comorbidities under the realm of respiratory and psychological have the greatest influence of those categories represented by patients in this cohort. A diagnosis of a respiratory comorbidity can be expected to lower a patient's MCSS by 0.811 points ($p = 0.021$), while a psychological comorbidity can be expected to lower MCSS by 1.68 points ($p = 0.036$), while holding other covariates fixed. The total number of mental comorbidities, classified as a general clinical variable in this study, is expected to lower a patient's estimated MCSS by 3.96 points ($p < 0.001$) for every additional comorbidity, while holding all other covariates fixed. The R^2 value for the MCSS categories model was 0.15, which suggests that about 15 percent of the variance of MCSS is explained by this model.

Table 19. Mental Component Summary Score: Multiple Regression Model with Diagnosis Categories as Independent Variables

Independent Variable	Estimate	P Value
Age	0.10	< 0.001
Rank		
Civilian/ not Active Duty	*Ref*	*Ref*
Enlisted	1.05	0.044
Officer/Warrant	0.43	0.611
Race		
Non-Hispanic white	*Ref*	*Ref*
Hispanic and Others	-0.50	0.421
Non-Hispanic AA	1.54	0.001
Respiratory	-8.11	0.021
Psychological	-1.68	0.036
Total Mental Diagnoses	-3.96	< 0.001
CD4 Levels		
CD4 count below 200	*Ref*	*Ref*
CD4 count 200 – 499	1.30	0.136
CD4 count 500+	2.26	0.009

Non-Hispanic AA: Non-Hispanic African Americans. All analyses were carried out with the Natural History Study data set.

Those specific diagnoses of comorbidities which most significantly influence a patient's mental health include major depression, COPD, Methamphetamines use, the total number of mental comorbidities and squamous cell (skin) cancer (see Table 20). Squamous cell skin cancer was selected using the stepAIC ( ) and, while it does not have a significant p value, it could not be dropped from the model, because its removal lowered the AIC by more than two points (Venables and Ripley 2002). Major depression is expected to lower a patient's MCSS by 1.93 points ($p = 0.087$) when compared to those without major depression, while holding the other covariates fixed. COPD, a respiratory comorbidity, is expected to lower scores by 8.08 ($p = 0.021$), when compared to those without COPD, and Methamphetamines is expected to lower scores by 15.70 ($p = 0.0087$) when compared to those without a history of Methamphetamines use, holding other covariates fixed. Total mental health comorbidities are estimated to drop MCSS by 4.07 points ($p < 0.001$), while holding other variables constant. Age is seen again as a significant predictor ($p < 0.001$), however, its estimate of 0.07 points for every age

increase does not practically influence MCSS estimates. An AIDS diagnosis lowers expected PCSS by 2.78 points ($p < 0.001$). CD4 counts between 200 and 499 yield statistically insignificant estimates, counts above 499 points are expected to raise scores 2.35 points higher than those with counts under 200 ($p < 0.006$). The MCSS model using specific diagnoses yields an R^2 of 0.15, suggesting that this model explains about 15 percent of all variance in the response.

Table 20. Mental Component Summary Score: Multiple Regression Model with Specific Diagnoses as Independent Variables

Independent Variable	Estimate	P Value
Age	0.07	< 0.001
Race		
Non-Hispanic white	*Ref*	*Ref*
Hispanic and Others	-0.60	0.343
Non-Hispanic AA	1.53	0.001
Major Depression	-1.93	0.087
COPD	-8.08	0.021
Methamphetamines use	-15.70	0.009
Squamous cell (skin)	-4.98	.123
Total Mental Diagnoses	-4.07	< 0.001
CD4 Levels		
CD4 count below 200	*Ref*	*Ref*
CD4 count 200 – 499	1.38	0.111
CD4 count 500+	2.35	0.006

COPD: chronic obstructive pulmonary disease, Non-Hispanic AA: Non-Hispanic African Americans All analyses were carried out with the Natural History Study data set.

Table 21. Physical Component Summary Score: Multiple Regression Model with Diagnoses Categories as Independent Variables

Independent Variable	Estimate	P Value
Sex		
Female	*Ref*	*Ref*
Male	2.19	0.008
Age	-0.13	< 0.001
Marital Status		
Married	*Ref*	*Ref*
Not Married	1.05	0.018
Rank		
Civilian/ not Active Duty	*Ref*	*Ref*
Enlisted	1.11	0.034
Officer/Warrant	3.39	< 0.001
Bacterial	1.38	0.044
Total Mental Diagnoses	-1.99	< 0.001
History of AIDS Diagnosis	-2.80	< 0.001
CD4 Levels		
CD4 count below 200	*Ref*	*Ref*
CD4 count 200 – 499	4.33	< 0.001
CD4 count 500+	5.38	< 0.001

All analyses were carried out with the Natural History Study data set.

The multiple regression models predicting PCSS estimates were calculated the same way as the MCSS. The initial multiple regression model is built using categories of comorbidities (see Table 21). Bacterial diagnosis is the only category that made it to the final model using backward elimination and AIC with a relatively influential estimate of 1.38 points increase of PCSS for those with a bacterial diagnosis when compared to those without the diagnosis, holding all other variables constant. As noted earlier, bacterial infections are highly correlated with younger ages of contraction and therefore, healthier. While sex was not significant in the MCSS models, being male increases the PCSS estimate of a patient by 2.19 points ($p = 0.008$), while holding the other variables constant. A patient who is married increases their PCSS estimate by 1.05 points compared to those who are not married ($p = 0.018$), adjusting for all other variables. While enlisted status is not a significant predictor, being an officer increases a patient's PCSS estimate by 3.39 points ($p < 0.001$) compared to civilians/not active duty. AIDS

and CD4 counts are, again, significant predictors of the dependent variable estimates. An AIDS diagnosis lowers expected PCSS by 2.80 points ($p < 0.001$) when compared to those without an AIDS diagnosis. CD4 counts between 200 and 499 are expected to increase PCSS by an estimated 4.33 points ($p < 0.001$) compared to those with counts below 200 cell/m^3. Patients with counts above 499 points are expected to have scores 5.38 points higher than those with counts under 200 ($p < 0.001$). The R^2 value for the PCSS categorical multiple regression model is 0.16, suggesting that the model explains just over 16 percent of the variance in PCSS.

Table 22. Physical Component Summary Score: Multiple Regression Model with Specific Diagnoses as Independent Variables

Independent Variable	Estimate	P Value
Sex		
Female	*Ref*	*Ref*
Male	2.38	0.004
Age	-0.13	< 0.001
Marital Status		
Married	*Ref*	*Ref*
Not Married	1.10	0.013
Rank		
Civilian/ not Active Duty	*Ref*	*Ref*
Enlisted	1.09	0.036
Officer/Warrant	3.24	< 0.001
Anxiety	5.18	0.001
Prostate Cancer	-10.09	0.007
Total Mental Diagnoses	-2.13	< 0.001
History of AIDS Diagnosis	-2.66	< 0.001
CD4 Levels		
CD4 count below 200	*Ref*	*Ref*
CD4 count 200 – 499	4.46	< 0.001
CD4 count 500+	5.48	< 0.001

All analyses were carried out with the Natural History Study data set.

Specific comorbidities represented in the PCSS multiple regression model include anxiety and prostate cancer (see Table 22). A diagnosis of anxiety raises estimated PCSS by 5.18 points ($p < 0.001$) when compared to those without that diagnosis, holding other variables constant. It may be that those who have anxiety, a generally chronic illness, are treated, perhaps influencing a patient's perception of their own physical health. Prostate cancer, however, is expected to reduce a patient's PCSS by 10.09 points ($p = 0.007$). Again, males are expected to have an estimated 2.38 points higher PCSS that females ($p < 0.001$), holding other variables constant. Enlisted personnel are expected to have an estimated PCSS 1.09 points higher ($p = 0.036$) and officers are expected to have 3.24 points higher PCSS than civilians/not active duty ($p < 0.001$). Patients who are not married have an expected increase in PCSS by 1.10 over those who are married ($p = 0.013$). In this model, CD4 counts between 200 and 499 are expected to raise PCSS by 4.46 points higher than patients with counts under 200 ($p < 0.001$), holding other variables constant. Likewise, patients with counts over 499 are expected to raise PCSS 5.48 points higher ($p < 0.001$). The R^2 value for the PCSS specific diagnoses multiple regression model is 0.16—a model that explains just over 16 percent of the variance in PCSS.

Table 23. High Quintile: Multiple Regression Modeling Log Odds of a Patient Falling within the Highest Quintile of either MCSS or PCSS Using Diagnosis Categories as Independent Variables

Independent Variable	Estimate	P Value
Gender		
Female	*Ref*	Ref
Male	0.45	0.040
Rank		
Civilian/ not Active Duty	*Ref*	*Ref*
Enlisted	0.021	0.861
Officer/Warrant	0.53	0.010
Race		
Non-Hispanic white	*Ref*	*Ref*
Hispanic and Others	0.23	0.138
Non-Hispanic AA	0.41	< 0.001
Cancer	-0.73	0.037
Total Mental Diagnoses	-0.52	< 0.001
Treatments		
Never Treated	*Ref*	*Ref*
Not Currently Treated	-0.45	0.042
NPI	0.07	0.620
PI	-0.02	0.921
CD4 Levels		
CD4 count below 200	*Ref*	*Ref*
CD4 count 200 – 499	0.401	0.010
CD4 count 500+	0.63	0.009

PI: protease inhibitor, NPI: non-protease inhibitor, Non-Hispanic AA: Non-Hispanic African Americans. All analyses were carried out with the Natural History Study data set.

Cancer was the only comorbidity category found to be statistically significant in predicting a patient's likelihood of falling into the highest quintile of MCSS or PCSS included (see Table 23). If a patient were to be diagnosed with cancer they are 0.73 times less likely to fall into the highest quintile of either mental or physical health amongst all patients in the cohort ($p = 0.037$), holding all other variables fixed. Males are 0.45 times more likely to fall into the highest quintile than females ($p = 0.040$) and officers are 0.53 times more likely than civilians/not active duty ($p = 0.010$), holding other variables fixed. African Americans are 0.41 times more likely than non-Hispanic Whites to fall into the highest quintile ($p < 0.001$). Those patients who are not currently being treated are .45 times less likely to fall into the highest quintile than those who were never treated

(p = 0.042), holding all other variables constant. This is consistent with the treatment requirements during the majority of survey dates collected which specify a patient only be treated if they showed symptoms of AIDS. Therefore, a patient who has shown signs of AIDS (i.e., treated) is less likely to score well than a patient who has never shown signs of AIDS (i.e., untreated). However, those patients with CD4 counts above 499 cells/m^3 are 0.63 times more likely to score in the highest quintile than those with counts below 200, holding all other variables constant. The quantile GLM using categories had a pseudo R^2 value of 0.05, suggesting poor prediction capabilities of the model.

Table 24. High Quintile: Multiple Regression Modeling Log Odds of a Patient Falling within the Highest Quintile of either MCSS or PCSS Using Specific Diagnoses as Independent Variables

Independent Variable	Estimate	P Value
Sex		
Female	*Ref*	*Ref*
Male	0.45	0.039
Rank		
Civilian/ not Active Duty	*Ref*	*Ref*
Enlisted	0.028	0.82
Officer/Warrant	0.54	0.009
Race		
Non-Hispanic white	*Ref*	*Ref*
Hispanic and Others	0.22	0.157
Non-Hispanic AA	0.39	0.001
Basal Cell (skin)	-2.15	0.039
Total Mental Diagnoses	-0.52	< 0.001
Treatments		
Never Treated	*Ref*	*Ref*
Not Currently Treated	-0.45	0.041
NPI	0.068	0.63
PI	-0.02	0.901
CD4 Levels		
CD4 count below 200	*Ref*	*Ref*
CD4 count 200 – 499	0.40	0.103
CD4 count 500+	0.63	0.009

PI: protease inhibitor, NPI: non-protease inhibitor, Non-Hispanic AA: Non-Hispanic African. Americans. All analyses were carried out with the Natural History Study data set.

Similar variables to those included in the category high quintile multiple regression model are included in the diagnoses multiple regression model (see Table 24). Here, the specific comorbidities found to statistically influence probability of scoring in the highest quintile includes basal cell (skin) cancer. A diagnosis results in a 2.15 times less likely chance of scoring in the highest quintile compared to those patients who are not diagnosed with basal cell cancer ($p = 0.039$). Males are again 0.45 times more likely than females ($p = 0.039$) and officers are 0.54 times more likely than civilians/not active duty ($p = 0.009$), adjusting for all other variables in the model. African Americans, too, are again more likely than non-Hispanic Whites to score in the highest quintile (log odds of 0.39; $p = 0.001$). For every additional mental comorbidity, the log odds of being in the highest quintile decrease by 0.52 ($p < 0.001$), holding all other variables fixed. Consistent with the argument posed for the previous multiple regression model, patients classified as not currently treated are 0.45 times less likely to score high as those who have never been treated ($p = 0.041$), holding all other variables fixed. CD4 count above 499 cells increases a person's probability by 0.63 ($p = 0.009$) when compared to those whose CD4 is below 200, while holding all other variables fixed. The pseudo R^2 for the quintile models using specific diagnoses is 0.05, again suggesting poor predictive abilities of the model.

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V. CONCLUSION

The main intent of this study is to quantify a relationship between age-related comorbidities and HRQOL among active duty U.S. military HIV patients. This effort concluded with 6 multiple regression models comprised of predictors estimating the physical and mental health of patients as calculated by the SF-36. Among those predictors included in these models, some were demographic and general clinical data, but each model also included identified comorbidities of interest.

A. HIGHLIGHTED RESULTS FROM MODELS EXPLAINED

Interesting results were discovered while fitting these models. The initial univariate models used to prescribe formal multiple regression models elicited a trend between positive physical health scores and patients' diagnoses with sexually transmitted diseases. Originally, this appears contradictory to a basic understanding of bacterial infections and how they affect the human body. However, deeper statistical investigation found a relationship between age and STIs. Naturally, younger patients tend to be healthy and report healthier scores on the SF-36. Younger patients are also more susceptible to contracting STIs (Downing-Matibag, Geisinger 2009). According to the t test, the difference in mean ages between those without a diagnosed bacterial infections and those with a history of diagnosis is 9.56 years (95 percent CI: 5.78, 8.79). The association between bacterial infections, specifically STIs and higher HRQOL scores, may be an artifact of the influence age has on this relationship.

Additionally, the multiple regression models derived from this study have notably small R^2 for the linear models and pseudo- R^2 for the logistic regression models. However, these results are common when creating models based upon mental and physical health scores derived from SF-36 surveys (Abelson 1985). Specifically, other studies have found predicting mental health results from SF-36 MCSS have notoriously yielded low R^2 (Abelson 1985).

B. MILITARY IMPLICATIONS

Most notably, perhaps, is the lack of differences between services and patient care. Branch of service was not significant in any univariate or multiple regression model. Moreover, this study suggests that the standard of care across all branches of the U.S. military is similar and all chains of command are caring for their service members effectively.

Initially, the influence of illicit drugs on the cohort members' risk for HIV was believed to be minimal due to frequent drug testing. However, Methamphetamines amphetamine use was found to be a significant predictor in the models. In fact, a history of a use of Methamphetamines is estimated to reduce MCSS scores by 15.7 points ($p < 0.009$); for a cohort that is not expected to be using drugs, this is an issue in need of attention.

The only predictors seen in all six models are CD4 count and total number of mental diagnoses. This is likely due to the fact that a high CD4 count is an extremely strong indicator of immune health and, therefore, means HIV is not currently exhibiting a significant effect on that patient. In all cases, the CD4 count above 500 indicated significant positive estimates. The estimate on both PCSS and MCSS reduces as the total number of mental diagnoses increase.

Age, sex, rank and race were each the next most common predictors among the 6 models. Lower ages, intuitively, yielded positive estimates for each of the models. Males had a higher estimate in predicting physical quality of life scores and were found to have a higher probability of being in the highest quintile of either mental or physical quality of life than their female counterparts. The "healthy soldier effect" may partially explain these differences—that is, there are physical standards for active duty service members to retain a higher level of physical fitness. Further, the healthy soldier effect is seen more often in men than women (Boehmer et al. 2003). Moreover, there is no significant difference in mean age between males and female (t test reporting a $p < 0.131$), so age is not likely a contributing factor to these differences in quality of life measures. Rank, specifically officers, is seen as a significant positive predictor in 5 of the 6 models when

compared to their civilian counterparts. Further, officers had better quality of life scores than the enlisted personnel relative to their civilian counterparts. In general, the selection criteria for commission surpass those of enlisted. Qualifying entry standards for officers in the U.S. military are more stringent and result in a population of individuals, on average, more physically fit and more highly educated than the enlisted population. This more selective attrition process may highlight the presence of officer-ship over enlisted in the present models. Lastly, race seems to be an important factor in the performed models. Specifically, African Americans were consistently estimated to have higher MCSS scores in the univariate and multiple regression models than the White personnel. The reasons for these differences are not clear, but may be reflective of younger age or gender differences in the cohort.

Treatments are an obvious predictor of disease progression and quality of life, though the only multiple regression models in which treatments were included were the quintile models. Not surprisingly, the estimates for treatment yield naively counterintuitive results. Receiving some treatment and stopping results in lower log odds of a patient scoring in the highest quintile of either PCSS or MCSS when compared to those who never start treatment. This, however, is likely due to changing treatment initiation guidelines. During the time of the survey, patients only received treatment contingent upon whether they exhibited symptomatic AIDS or were moderately immune-impaired. Therefore, the only people to receive treatment had very low CD4 counts, which underscores how unhealthy they were at treatment initiation. Therefore, members of this HIV cohort, with access to free universal healthcare, who have never had treatment are likely healthier than those who have started treatment at some point in time during follow-up. The treatment policy in 2015 changed to recommend treatment for all with HIV, regardless of immune status, and subsequent analyses should no longer be affected by this counterintuitive effect.

In total, this study identified 12 comorbidities among categories and specific diagnoses significantly affecting the physical and mental health of active duty HIV positive patients. The comorbidities which yielded significant influence on MCSS in this cohort, included categories of respiratory and psychological illness and specific

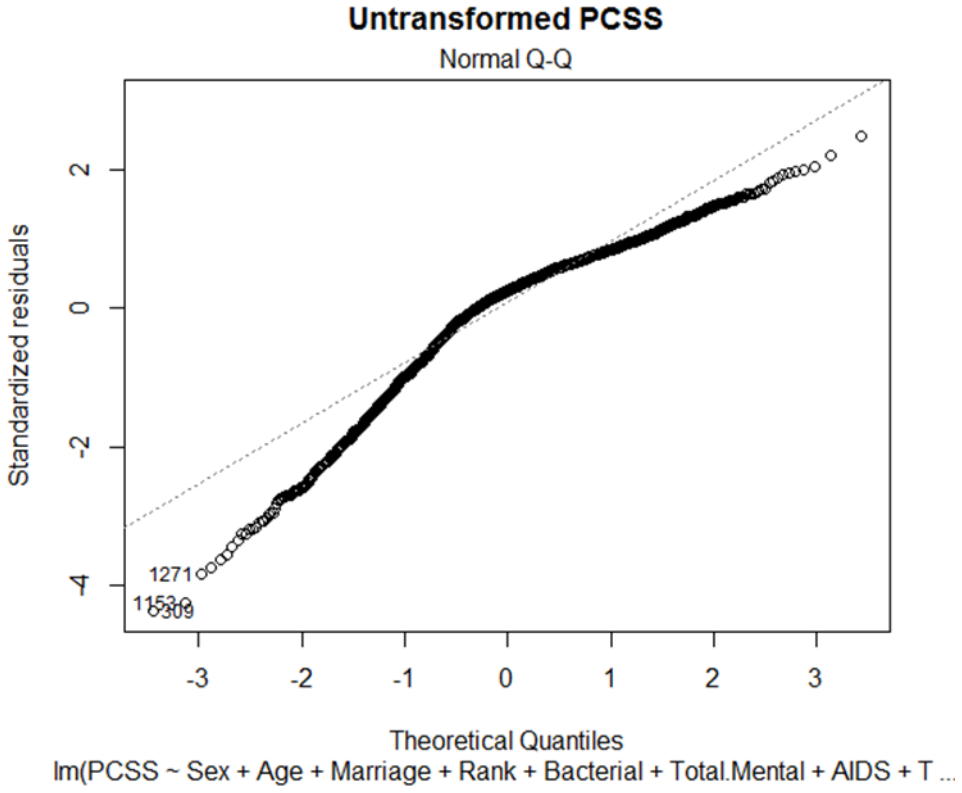
diagnoses of major depression, COPD, Methamphetamines use, and squamous cell skin cancer. While there was no difference in the mean ages in most of these comorbidities, the mean age of patients with cancer was 5.9 years older than patients without (95 percent CI: 5.7, 11.5). Those comorbidities influencing PCSS include the category of bacterial illness and the specific diagnoses of anxiety and prostate cancer. As previously noted, patients with bacterial infections, predominately STIs, were significantly younger than patients without bacterial infections ($p < 0.001$). No differences in age were noted between patients with and without anxiety or prostate cancer. Among the quintile models, cancer, specifically basal skin cancer, rendered a significant negative effect on a patient's log odds of being in the highest quintile of either MCSS or PCSS. This may be, again, a factor of age as patients diagnosed with basal skin cancer had a mean age of 5 years older than those not diagnosed with the disease (95 percent CI: 6.7, 16.1).

C. FUTURE STEPS

Even with low R^2 values in our models, these findings could have important implications. For example, the present models found multiple predictors that were modifiable, or addressable. Further even if the variance in the mental or physical quality of life response variables is only minimally affected by these factors, they could still play an important role in improving HIV patients' quality of life. Anecdotally, high R^2 values are uncommon in studies of social sciences due to the complexity of social phenomena. The sparsity of data in the comorbidity columns could have played a factor in the low R^2 values. However, if one were to consider diagnoses of more than two years prior to the survey, the data would arguably be impractical. Ultimately, if the goal is prediction, adding more patients to the cohort may be necessary to derive better predictive results. If the goal is identification of avenues of intervention for HIV+ patients, lower predictability may be of less consequence.

APPENDIX. MODEL ASSUMPTION TESTING SECONDARY ANALYSIS USING POWER TRANSFORMATIONS

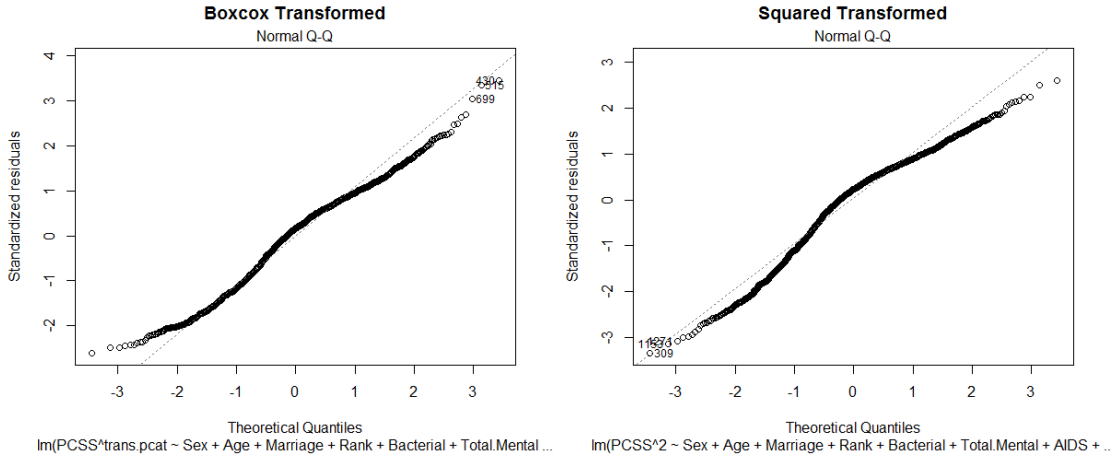
Initial linear model diagnostics yielded no obvious concerns with multicollinearity, and independence. There was, however, a concern with the normality and heteroscedasticity assumptions. For simplicity, the PCSS multiple regression model using illness categories will be used as a surrogate for the other 5 models. Figure 20 depicts the normal quantile-quantile plot of the standardized residuals for the PCSS model. Two transformations were employed in an effort to address these potentially failed assumptions. Box-Cox and a simple square transformation, though they did not align directly, both yielded very similar visual representations of normal distribution data.



All analyses were carried out with the Natural History Study data set.

Figure 20. Untransformed PCSS Dependent Variable: Normality Analysis

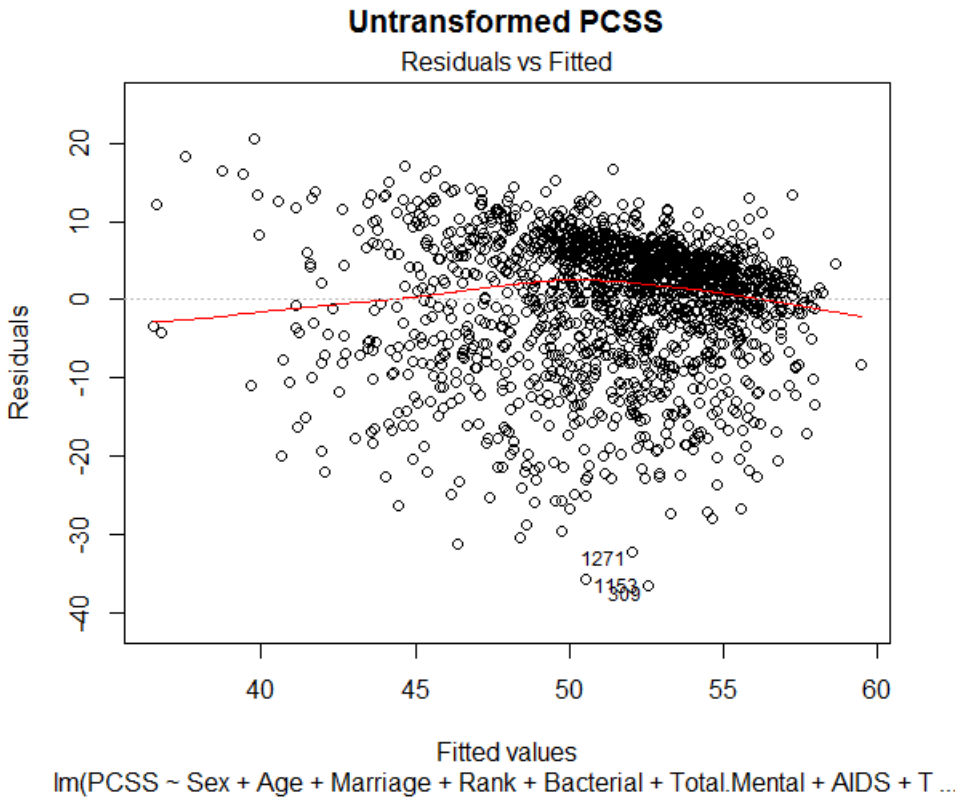
The Box-Cox transformation called for a transformation of the power 3.6. Figure 20 depicts the similarity between the Box-Cox transformed normal plot and the square transformed normal plot. The R^2 do not differ significantly either. The R^2 for the untransformed model is .1552, while the Box-Cox transformed is .1477 and the square transformed is .1546.



All analyses were carried out with the Natural History Study data set.

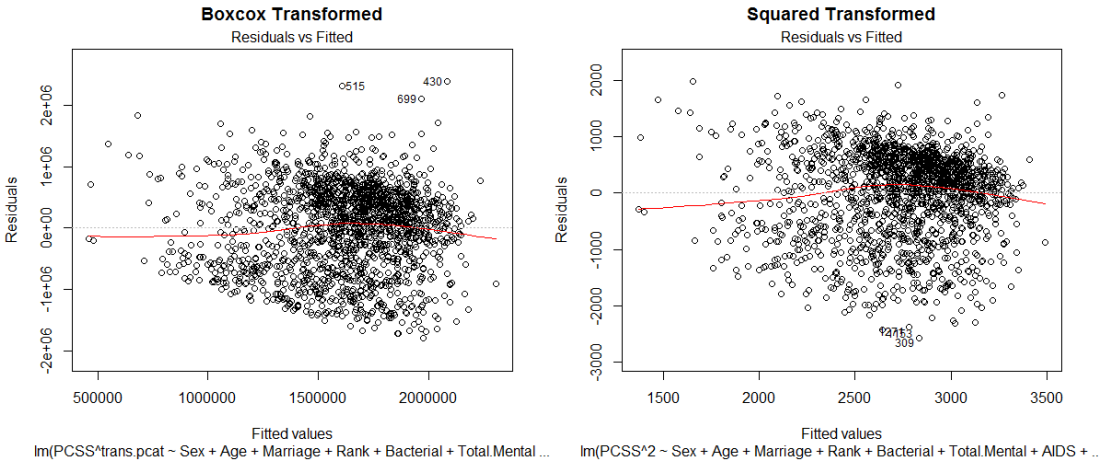
Figure 21. PCSS Transformations: Box-Cox ($PCSS^{3.6}$) versus Squared ($PCSS^2$) Normality Analysis

When reviewing the residual versus fitted plots, possible heteroscedasticity was identified. Heavy tails and a left-skewed response variable, PCSS, causes unequal variance seen in Figure 21. Box-Cox and the squared transformation reduces the visual heteroscedasticity seen in Figure 22, but the overall model fit still remains relatively unchanged. Moreover, further analysis conducted using the Breusch-Pagan test for heteroscedasticity, using the function bptest (), suggested that the heteroscedasticity was still present, though its presence was not strong (p = .01325). Specifically, neither the square, nor the Box-Cox transformations were able to remove the presence of heteroscedasticity as determined by the Breusch-Pagan test (Zeiles and Hothorn 2002).



All analyses were carried out with the Natural History Study data set.

Figure 22. PCSS Untransformed Dependent Variable: Heteroscedasticity Analysis



All analyses were carried out with the Natural History Study data set.

Figure 23. PCSS Transformations: Box-Cox ($PCSS^{3.6}$) versus Squared ($PCSS^{2}$) Heteroscedasticity Analyses

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