Title
The Effect of BMI on Community-Acquired Pneumonia Incidence and Mortality in Veterans

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Publication Date
2017

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

The Effect of BMI on Community-Acquired Pneumonia Incidence and Mortality in Veterans

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science in Epidemiology

by

Katelyn Chandler Corey

2017

ABSTRACT OF THE THESIS

The Effect of BMI on Community-Acquired Pneumonia Incidence and Mortality in Veterans

by

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Master of Science in Epidemiology

University of California, Los Angeles, 2017

Professor Katherine J. Hoggatt, Co-Chair

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This study aimed to assess the effect body mass index (BMI) has on community-acquired pneumonia (CAP) incidence and mortality in the Veteran Healthcare System. A historical cohort of 3,606,564 subjects was identified between fiscal year 2010-2012, and was followed until the end of fiscal year 2015 for the outcomes of CAP and 30-day all-cause mortality post-CAP infection. A total of 210,408 cases of CAP were identified during follow-up. Men who were overweight or obese had a protective effect on CAP incidence, while women were at a slight increased risk. A sub-cohort, made up of those diagnosed with CAP, was analyzed for the association of BMI and 30-day all-cause mortality. For overweight and obese men and women there was a decrease in mortality in the 30-days post-CAP infection, supporting previous findings of the “obesity paradox”. However, new evidence has come to light that may reverse the “obesity paradox” in future studies.

The thesis of Katelyn Chandler Corey is approved.

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2017

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ACKNOWLEDGEMENTS

I would like to thank my committee for their continuous support and critique of this master's thesis, which molded it into the manuscript presented. I especially would like to honor my advisor, Dr. Katherine J. Hoggatt, who took on this project with me and taught me good work and research ethics every step of the way. If it were not for her encouragement and her unfailing belief in my abilities, I would not be where I am today. I would also like to acknowledge those colleagues, peers, friends, and family members who talked over concepts with me, read my drafts, and made sure that all the I's were dotted before the manuscript was submitted: Ryan T. Davis, Elizabeth L. Corey, Christopher R. Corey, Stella Jouldjian, and Nicole J. Cunningham.

1. INTRODUCTION

1.1 Background

Pneumonia still plagues the advanced medical treatment and healthcare system of the United States, with an annual incidence of 7-8 cases per 1,000. It is the second leading cause of hospitalization.[1,2] Most pneumonia cases are Community-Acquired Pneumonia (CAP), which is a pneumonia infection that is not associated with any type of hospital care. A suspected 30-50% of these cases are caused by *Streptococcus*, which is covered by forms of the Pneumococcal Conjugate Vaccine (PCV).[3] Even though these PCVs have been in circulation since 2000, pneumonia is still the eighth leading cause of mortality in the U.S.[4] About 20-25% of CAP cases are hospitalized, creating a large inpatient burden on hospital staff and finances that could be decreased through proactive vaccination.[5] Though there are vaccines to prevent specific types of CAP infections they are usually only recommended for young children, the immune compromised, and people over the age of 65.

Recent studies have reported associations between an overweight and obese Body Mass Index (BMI) and CAP incidence.[4,6-10] Individuals who have high BMI (overweight or obese) may have an increased susceptibility to infection due to differing inflammation responses in comparison to individuals with a normal BMI I.[11,12] BMI is a proxy for measuring adiposity.[13] Though BMI is prone to measurement error and is not a perfect predictor of adiposity, it is important to look at BMI as a clinical measure that can be associated with infections and be used as an indicator for health interventions. The literature has shown both overweight and obese BMI have, in some cases, an increased risk of CAP, but decreased risk of mortality post-CAP.[4,6-10] The concept that overweight/obese individuals are at a decreased risk of mortality after disease diagnosis is known as the “obesity paradox”.

The "obesity paradox" is not unique to CAP – other observational studies have reported results consistent with this "paradox" for diseases other than CAP (i.e. lung cancer, pulmonary hypertension, coronary revascularization, and kidney disease).[14-19] However, because CAP is a common infection with severe consequences, it is important to assess BMI as a possible indicator for increased vaccination with PCV or treatment, and, in turn, examine the extent to which the "obesity paradox" is present for CAP incidence and mortality.

Within the Veteran Health Administration (VA) Healthcare System, data are generated for over 6 million patients per year, creating an opportunity to study this relationship in a large source population. There were approximately 34,000 cases of CAP diagnosed via x-ray in 7.7 million person-years in 2011.[5] Pneumonia accounts for 6.1-7.0% of hospitalizations for patients over 65 in the VA.[2] Additionally, for the three months post-CAP, the medical costs per patient per month for Veterans was an average of $7,154 (median $3,174), while the cost for VA healthcare prior to CAP was only $1,020 (median $381). [5]

BMI is not currently recognized as a risk factor for CAP. Additionally, US Veterans have an overweight/obese prevalence of about 70-78%. [20] The current VA pharmacy recommendations state that those patients who are immune-compromised (i.e. chronic heart disease, chronic lung disease, diabetes mellitus, alcoholism, smoking, HIV, solid organ transplant, etc.) or 65 years and older should receive the PCV 13 or PCV23 valent. [21] Though there are high vaccination rates (90.5%) among eligible patients, there is still a burden of pneumonia cases in the VA system.[22] Thus, there may be a BMI group of patients at increased risk for CAP and who are not receiving the PCV based on current VA pharmacy

recommendations.

The purpose of this study is to identify whether there is a relationship between BMI and CAP incidence and mortality, and subsequently, identify a group of VA patients who may be at increased risk for CAP incidence and mortality based on their BMI status, thereby allowing clinicians to recommend PCV to a wider group of people. The VA patient population has a high prevalence of overweight/obese BMI and constitutes an ideal study group in which to examine the independent effects of BMI factors on CAP incidence and mortality.

1.2 Study Description

A cohort of 3,606,564 male and female Veteran patients was identified from VA electronic health record (EHR) data for fiscal years (FY) FY2010-FY2012. The cohort was then followed in historical time until FY2015 to estimate the effect of BMI on two outcomes: acquisition of CAP and mortality after CAP infection. This study was approved by the VA Greater Los Angeles Institutional Review Board.

1.3 Study Aims and Hypotheses

This study aimed to estimate the effect of BMI on CAP and 30-day all-cause mortality following a CAP infection. It was expected that Veterans with a BMI of overweight or obese would have a higher rate of CAP than Veterans with a BMI of normal or underweight. Patients who were overweight or obese were hypothesized to have a lower 30-day mortality rate after CAP in comparison to patients who are of normal or underweight BMI.

2. METHODS

2.1 Data Source

Subjects were identified from EHR data in the VA Corporate Data Warehouse (CDW) via the VA Informatics and Computing Infrastructure (VINCI). The CDW is a continuously updated relational database that contains medical records, employee information, and financial data on the VA system. The data for the analysis included demographics, ICD-9-CM diagnosis codes, and the locations in which patients receive care (e.g., an outpatient clinic encounter vs. an inpatient stay).

2.2 Cohort Selection

In this study, there was an open enrollment into the cohort between FY2010-FY2012, which allowed for new VA users in this period to become part of the study cohort. Subjects who entered the cohort had to be a VA health system user for the year prior to cohort entry (the patient's "qualifying year"). During the qualifying year, the patient had to have at least one outpatient visit every six months. After the minimum qualifying year had passed, a patient could enter the cohort through an additional encounter with the VA system. The cohort entry period (FY2010-FY2012) was broken up into six six-month period timeslots (October 1st – March 31st and April 1st – September 30th) for cohort entry. During this time, there were 7,063,747 unique Veteran healthcare users, and 4,227,186 had been VA users for a qualifying year and were considered for inclusion in the cohort. The following inclusion criteria for cohort entry were applied. An eligible patient must have been: 1) a Veteran, 2) aged 18 or older at his or her qualifying visit, and 3) used the VA healthcare system as an outpatient at least once every six months for a year prior to cohort entry. The

medical encounter that made the Veteran patient eligible for the study could occur with a primary care physician, nurse, pharmacy, or any other outpatient encounter in the VA system. Otherwise eligible patients were excluded from analysis if they did not have a valid height measurement of 4-7ft between the years of FY2002-FY2015, did not have a valid weight measurement between 75-700lb within ±365 days of cohort entry, if they had a pneumonia diagnosis within the previous year prior to enrollment into the cohort, or if they had a date of death prior to cohort entry.[23] A total of 3,978,156 qualified for the study cohort based on the inclusion and exclusion criteria. From this initial cohort, an additional 371,592 (9.3%) of the original 3,978,156 were dropped from analysis due to missing demographics for the patient (i.e. missing homeless status, age, sex, or race/ethnicity), resulting in a dataset with observations for 3,606,564 patients for a complete case analysis. Since the mode of analysis is regression, complete case analysis is an unbiased method of looking at an association between BMI and CAP if missing demographics was independent from CAP outcome, conditional on BMI. Additionally, introducing imputation of demographics could introduce more bias, which is why complete case analysis was chosen for this study. The section criteria for the cohort is diagramed in Figure 1.

Patients in the cohort were followed until CAP outcome, the end of FY2015, or death. To account for possible attrition from the VA system, patients were considered lost to follow-up if subjects did not have an encounter with the VA during each subsequent six-month period after cohort entry. Patients who were considered to be lost to follow-up were assigned a censoring date corresponding to the date of the last encounter during the study period.

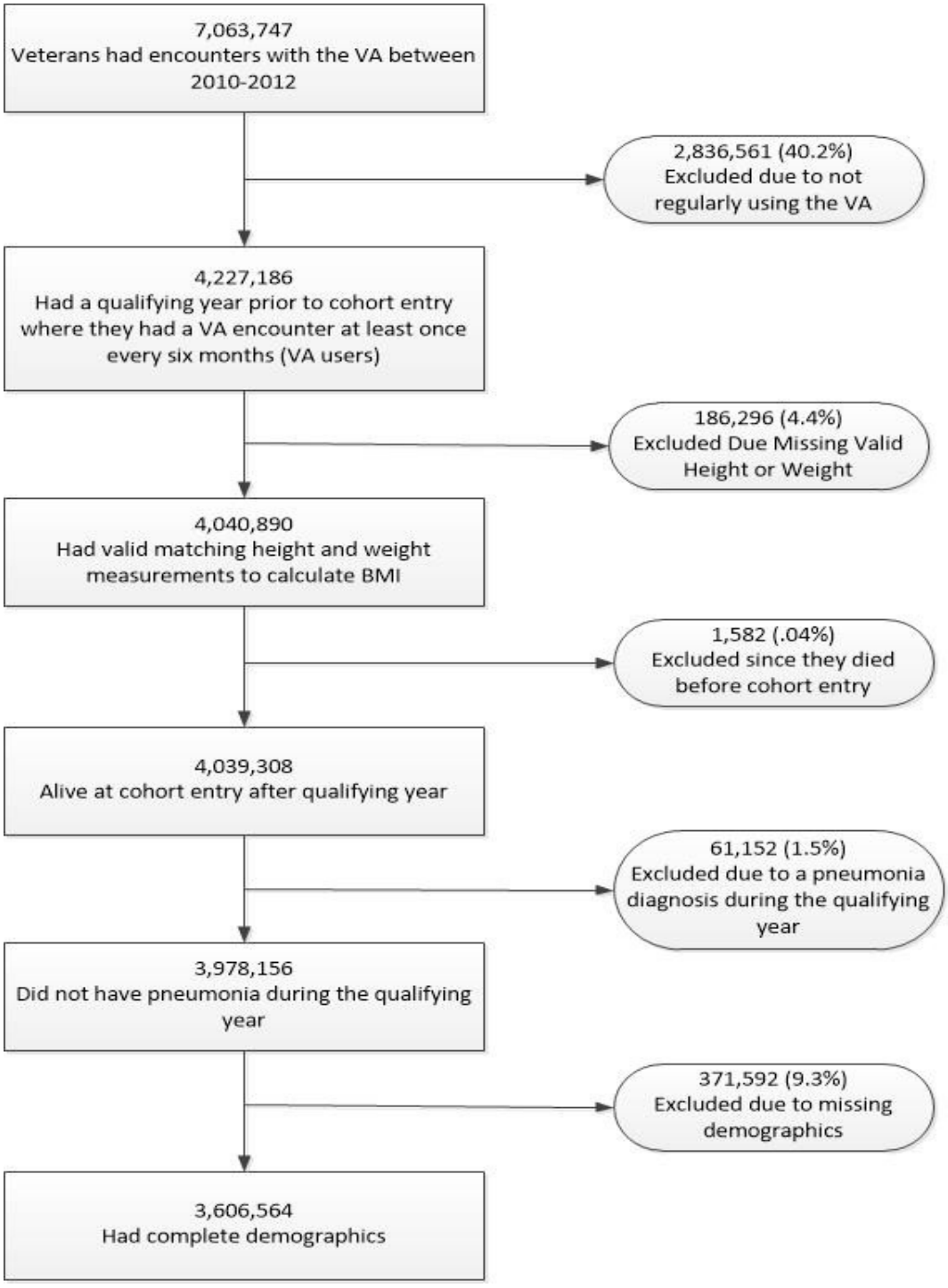

Figure 1. Cohort Selection Criteria

A subcohort was created from those who developed CAP during follow-up (FY2010-FY2015) were included in an analysis to explore 30-day mortality after -CAP infection. Therefore, all the inclusion and exclusionary criteria that applied to the cohort are the same for the CAP subcohort, with the addition that a patient must have been diagnosed with CAP between FY2010-FY2015. The total CAP subcohort population was 210,408 subjects. In the CAP subcohort, there was assumed to be no loss to follow-up since the outcome of interest was all-cause mortality, and the CDW keeps a record of nearly all Veteran mortalities.[24]

2.3 Variables

The exposure of interest was BMI, and in order to calculate BMI methods from Breland et al were utilized as noted above. [23] Height data was obtained under the assumption that height did not significantly change over time. Weight data was obtained under a similar assumption, though weight can change significantly over short periods of time. Height and weight measurements were used to calculate BMI, which was broken up into the four exposure groups. A BMI of <18.5 was underweight, a BMI of 18.5-24.9 was normal weight, 25-29.9 was overweight, and a BMI of 30 or greater was obese.

The outcomes of interest, CAP and 30-day mortality post-CAP, were measured in the following manner. A patient was determined to have classified as having CAP if he or she had an outpatient encounter with a documented ICD-9 diagnosis code between 480-487 (Appendix 1) during follow-up (FY2010-FY2015). However, of the 210,408 patients with a pneumonia diagnosis, only 3,024 (1.44%) had a hospitalization in the VA system which lasted over two days where pneumonia was diagnosed 2-90 days after hospital admission.[25]

Therefore, misclassification of hospital-acquired pneumonia as CAP seems unlikely in this population. Patients who were classified as having CAP were followed for additional 30 days for mortality. It was assumed there was no loss to follow-up since the VA has near complete death records. If a patient did not have a date of death within 30 days of CAP diagnosis, the patient was considered to have not died within those 30 days.[24]

Baseline measurements of comorbidities, demographics, and other risk factors that were controlled for during analysis were collected during the qualifying year prior to cohort entry and on the qualifying visit that entered the individual into the cohort from the MedSAS database. If a subject had a diagnosis (i.e. from the Charlson index, asthma, drug use disorder, etc. as seen in Appendix 1) during the previously specified period, then they were a designated to have that diagnosis. If there was no diagnosis during the qualifying year or qualifying visit, then a person was considered to not have that diagnosis. The Charlson Index score that was recently updated by Quan, et al was used to control for comorbid conditions.[26] The index ideal for controlling for comorbidities due to the fact that it covered diagnoses indicated as risk factors for CAP by McLaughlin et al.[5] The intention was to follow the methods used by Kornum, et al, who used the Charlson Index while looking at CAP incidence and mortality. Though the Charlson Index is a scoring system usually used to predict mortality, it contains comorbid risk factors for CAP, which makes it versatile in controlling for these comorbid conditions when looking at CAP incidence.

This method was additionally chosen in lieu of using dummy variables for each comorbid chronic disease, since it prevents sparse data in some of the less frequent diagnoses.

The demographics collected included race/ethnicity, age, sex, and homeless status. The race/ethnicity, age, and sex variables were controlled for in analysis due to their

association with both BMI and CAP.[4-9,27]Age was treated as a continuous variable during analysis. Homeless status was added since homeless individuals are known to have increased risk factors for CAP, such as higher rates of comorbidities and substance use disorders.[28,29] All demographic variables, except for race/ethnicity, were collected on the date of cohort entry. Race/ethnicity was collected as the first not null measurement closest to the cohort entry date between FY2002-FY2015. This was done to prevent a large percent of the cohort from being excluded based on one variable. If race/ethnicity was collected on the cohort entry date, then 24% of the cohort would have been excluded from analysis. This method decreased the proportion to be excluded to about 10%.

2.4 Analysis

A semi-parametric Cox model was used to assess the effect of BMI on CAP acquisition. Patients were classified according to their BMI (underweight, overweight, and obese vs. normal weight). Because patients can leave the VA Healthcare System and seek non-VA care elsewhere, patients were censored on the date of their last VA contact if they have a six-month period with no VA encounter. Patients who were continuously enrolled but did not experience the index event were censored at date of death or the end of FY2015. Confounders of the effect of BMI on CAP (e.g. tobacco use disorder, age, sex, homelessness, immune compromising diseases identified in the Charlson Index, etc.) were identified through literature review and were controlled for in the analysis. Prior studies had examined the association between BMI and CAP separately for men and women.[4,9] A similar method was applied here by creating product terms for sex and BMI category, which were entered in the model to examine heterogeneity by sex in the association between BMI

and CAP. Lastly, to test the proportional hazards assumption that the Cox model makes, the Schoenfeld residuals were plotted against time and a Loess smoother was applied. To determine if the proportional hazards assumption had been met, the Loess smoother should show no relationship between time and the residuals (i.e. a linear association with no slope).

The effect of BMI on 30-day mortality post-CAP infection was also estimated analyzed using a Cox model. Like the previous Cox model, a product terms for sex and BMI category was utilized, which used to examine heterogeneity by sex in the association between BMI and mortality post-CAP. The hypothesis was that the BMI and sex interaction may carry over as a risk factor for mortality post-CAP and not just for CAP incidence. The same covariates were controlled for as in the Cox model for CAP incidence. A logistic regression was performed as a sensitivity analysis to determine if results from the Cox model were comparable to results reported in the literature that were obtained from logistic regression models. The Schoenfeld residuals were plotted against time for the subcohort to test for the Cox model's proportional hazards assumption, with the hope there is no association between time and residuals based on the Loess smoother.

3. RESULTS

3.1 Cohort Description:

The final cohort consisted of 3,978,156 patients, with 3,606,564 (90.7%) with non-missing demographic data were included in the analysis. The majority of the cohort was predominately male Veterans (93.8%) had an average age of 62.0 (SD 14.9). The most common racial/ethnic groups represented in the study were Non-Hispanic White, Non-Hispanic African American, and Hispanic with 75.1%, 16.4%, and 5.8% respectively. The remainder of the race/ethnicity categories had less than 1% in each group. Of those selected

for the cohort, only 13,597 (0.4%) were homeless at cohort entry. Based on the Charlson Index Score calculated for each participant, 63.4% had no chronic diseases that would give them a score higher than 0. The most common scores above 0 were 1, 2, and 3 as shown in Table 1. The frequencies of the specific diagnoses for the Charlson Index in the cohort can be found in Appendix 2 for the cohort and Appendix 3 for the subcohort. Risk factors for CAP that were considered, aside from the Charlson Index score, were alcohol use disorder, tobacco use disorder, drug use disorder, and asthma.[4,5,26,27,30] In Table 1, each of the risk factors are broken up into the four BMI categories, underweight BMI, normal BMI, overweight BMI, and obese BMI. The cohort was distributed with 0.9% underweight, 18.8% normal weight, 37.1% overweight and 43.1% obese. During follow-up, 210,408 (5.8%) of the cohort developed CAP. This is a cumulative incidence of CAP from FY2010-FY2015. The proportion of CAP cases per year in the cohort ranged from 0.8-1.1%. For the patients who did not have an event of CAP, 74.1% were lost to follow-up prior to the end of the study (end of FY2015) and 16.4% died.

3.2 Risk of Cap Based on BMI Status:

The results from both univariate and a multivariate Cox model are shown in Table 2. BMI categories of underweight, overweight, and obese were compared to the reference category of normal BMI. Underweight BMI had an increased rate of CAP in the cohort for both men and women, with hazard ratios (HR) of 1.78 (95% CI = 1.72, 1.84) and 1.48 (95% CI = 1.29, 1.70), respectively, in comparison to normal BMI in the multiple regression model. However, the association between overweight/obese BMI and CAP differed

TABLE 1	Characteristics of the Cohort									
	BMI Group									
	<18.5		18.5-24.9		25-29.9		30+		Total	
	Mean	(Sd)	Mean	(Sd)	Mean	(Sd)	Mean	(Sd)	Mean	(Sd)
Age	65.6	15.1	63.8	17.0	63.1	15.2	60.2	13.4	62.0	14.9
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Sex										
Female	2,961	9.3	53,906	7.9	67,799	5.1	97,406	6.3	222,072	6.2
Male	28,967	90.7	624,932	92.1	1,271,902	94.9	1,458,691	93.7	3,384,492	93.8
Race/Ethnicity										
White	21,827	68.4	502,416	74.0	1,016,870	75.9	1,166,978	75.0	2,708,091	75.1
African American	7,756	24.3	119,809	17.7	204,387	15.3	260,625	16.8	592,577	16.4
Hispanic	1,569	4.9	36,820	5.4	80,881	6.0	88,008	5.7	207,278	5.8
Asian	229	0.7	6,833	1.0	10,799	0.8	5,876	0.4	23,737	0.7
Native American	128	0.4	3,158	0.5	7,041	0.5	9,781	0.6	20,108	0.6
Hawaiian/Pacific Islander	221	0.7	5,780	0.9	12,104	0.9	15,253	1.0	33,358	0.9
Multi-Race/Ethnicity	198	0.6	4,022	0.6	7,619	0.6	9,576	0.6	21,415	0.6
Homeless	254	0.8	3,782	0.6	4,714	0.4	4,847	0.3	13,597	0.4
Charlson Index Score										
0	13,158	41.2	404,540	59.6	875,301	65.3	992,359	63.8	2,285,358	63.4
1	8,726	27.3	116,782	17.2	203,782	15.2	271,131	17.4	600,421	16.7
2	4,964	15.6	93,721	13.8	169,745	12.7	181,074	11.6	449,504	12.5
3	3,252	10.2	37,498	5.5	54,925	4.1	68,905	4.4	164,580	4.6
4	1,007	3.2	16,212	2.4	22,950	1.7	26,702	1.7	66,871	1.9
5	460	1.4	5,246	0.8	6,695	0.5	8,824	0.6	21,225	0.6
6	232	0.7	3,195	0.5	4,254	0.3	4,690	0.3	12,371	0.3
7+	129	0.4	1,644	0.2	2,049	0.2	2,412	0.2	6,234	0.2
CAP Risk Factors										
Alcohol Use Disorder	5,206	16.3	81,995	12.1	113,684	8.5	105,648	6.8	306,533	8.5
Other Drug Use Disorder	1,402	4.4	30,954	4.6	41,452	3.1	37,720	2.4	111,528	3.1
Tobacco Use Disorder	12,281	38.5	178,759	26.3	245,810	18.4	239,513	15.4	676,363	18.8
Asthma Diagnosis	895	2.8	21,053	3.1	46,164	3.5	70,319	4.5	138,431	3.8
Outcome										
CAP Diagnosis	3,476	10.9	44,742	6.6	71,216	5.3	90,974	5.9	210,408	5.8
Total	31,928	0.9	678,838	18.8	1,339,701	37.1	1,556,097	43.1	3,606,564	100

TABLE 2	Hazard Ratios of Risk Factors for Community-Acquired Pneumonia (n=3,606,564)			
	Univariate		Multivariate	
Variables	HR (95%CI)	P-Value	HR (95%CI)	P-Value
Age	1.02 (1.02-1.02)	<.0001	1.02 (1.02-1.02)	<.0001
Sex				
Female	1.00 *	.	1.00 *	.
Male	1.21 (1.19-1.24)	<.0001	1.10 (1.05-1.14)	<.0001
Race/Ethnicity				
White	1.00 *	.	1.00 *	.
African American	0.85 (0.84-0.86)	<.0001	0.86 (0.85-0.88)	<.0001
Hispanic	0.87 (0.85-0.89)	<.0001	0.96 (0.94-0.98)	<.0001
Asian	0.86 (0.81-0.91)	<.0001	1.02 (0.96-1.08)	0.5791
Native American	1.04 (0.99-1.10)	<.0001	1.14 (1.08-1.20)	<.0001
Hawaiian/Pacific Islander	0.86 (0.83-0.90)	0.1241	0.90 (0.86-0.95)	<.0001
Multi-Race/Ethnicity	1.01 (0.96-1.07)	0.6061	1.04 (0.98-1.10)	0.1740
Homeless	1.38 (1.31-1.46)	<.0001	1.27 (1.20-1.35)	<.0001
Charlson Index Score				
0	1.00 *	.	1.00 *	.
1	2.14 (2.12-2.16)	<.0001	1.95 (1.92-1.97)	<.0001
2	1.82 (1.79-1.84)	<.0001	1.65 (1.63-1.67)	<.0001
3	3.37 (3.32-3.42)	<.0001	2.90 (2.85-2.94)	<.0001
4	3.25 (3.18-3.33)	<.0001	3.01 (2.94-3.08)	<.0001
5	4.74 (4.59-4.91)	<.0001	4.13 (3.99-4.27)	<.0001
6	3.50 (3.34-3.68)	<.0001	3.31 (3.15-3.48)	<.0001
7+	4.93 (4.64-5.25)	<.0001	4.52 (4.24-4.81)	<.0001
BMI Group for Women				
<18.5	1.80 (1.67-2.07)	<.0001	1.48 (1.29-1.70)	<.0001
18.5-24.9	1.00 *	.	1.00 *	.
25-29.9	0.95 (0.90-1.00)	0.0527	0.96 (0.91-1.01)	0.1078
30+	1.13 (1.08-1.19)	<.0001	1.12 (1.06-1.17)	<.0001
BMI Group for Men				
<18.5	2.08 (2.01-2.16)	<.0001	1.78 (1.72-1.84)	<.0001
18.5-24.9	1.00 *	.	1.00 *	.
25-29.9	0.71 (0.70-0.72)	<.0001	0.78 (0.77-0.79)	<.0001
30+	0.71 (0.70-0.72)	<.0001	0.81 (0.80-0.82)	<.0001
Alcohol Use Disorder	1.11 (1.10-1.13)	<.0001	1.08 (1.06-1.10)	<.0001
Other Drug Use Disorder	1.13 (1.10-1.15)	<.0001	1.25 (1.22-1.27)	<.0001
Tobacco Use Disorder	1.31 (1.29-1.32)	<.0001	1.31 (1.30-1.33)	<.0001
Asthma Diagnosis	1.53 (1.50-1.56)	<.0001	1.07 (1.05-1.09)	<.0001

*** = Reference category used during analysis**

between men and women. For men, there was an inverse association between overweight or obese BMI and CAP incidence, with HR=0.78 (95% CI = 0.77, 0.79) for overweight BMI in comparison to normal BMI and HR=0.81 (95% CI = 0.80, 0.82) for obese BMI in comparison to normal BMI in the multivariate model. Among women, an overweight BMI had a weak inverse association with CAP (HR=0.96; 95% CI = 0.91, 1.01) in comparison to normal BMI, while an obese BMI had a weak positive association with CAP (HR=1.12; 95% CI = 1.06, 1.17). The proportional hazards assumption for the multiple-variable Cox regression model was assessed with a plot of the Schoenfeld residuals against time. This yielded a flat Loess smoothed line at the x-axis (where y=0) with only a slight deviation from linearity at the start of the line and with a slope of zero (graph not shown), indicating that the assumptions of the Cox model are reasonable for this data.

3.3 Subcohort Description:

The subcohort was made up of the 210,408 CAP patients identified in the cohort. The average age of the subcohort was 65.1 (SD 13.2) with a majority being male (94.6%). The most common racial/ethnic groups in the subcohort were primarily Non-Hispanic White, Non-Hispanic African American, and Hispanic with 76.4%, 15.5%, and 5.5% respectively. Again, each of the remaining race/ethnicity categories represented less than 1% of the subcohort. In comparison to the original cohort, which had 63.4% with a Charlson score of 0, the CAP subcohort has only 41.9% with a Charlson score of 0. Additionally, there is a slight increase in alcohol use disorder, tobacco use disorder, and drug use disorder in the subcohort in comparison to the prevalence in the main cohort (Table 3). Asthma had a 150% increase in prevalence from the cohort to the CAP

TABLE 3	Characteristics of the Subcohort				
	BMI Group				
	<18.5	18.5-24.9	25-29.9	30+	Total
	Mean (Sd)	Mean (Sd)	Mean (Sd)	Mean (Sd)	Mean (Sd)
Age	67.7 13.0	67.8 14.2	66.4 13.5	62.6 12.1	65.1 13.2
	N (%)	N (%)	N (%)	N (%)	N (%)
Sex					
Female	220 6.3	2,374 5.3	3,059 4.3	5,739 6.3	11,392 5.4
Male	3,256 93.7	42,368 94.7	68,157 95.7	85,235 93.7	199,016 94.6
Race/Ethnicity					
White	2,421 69.7	33,260 74.3	54,850 77.0	70,171 77.1	160,702 76.4
African American	771 22.2	7,743 17.3	10,307 14.5	13,702 15.1	32,523 15.5
Hispanic	208 6.0	2,584 5.8	4,127 5.8	4,656 5.1	11,575 5.5
Asian	21 0.6	324 0.7	474 0.7	290 0.3	1,109 0.5
Native American	16 0.5	201 0.5	394 0.6	651 0.7	1,262 0.6
Hawaiian/Pacific Islander	21 0.6	362 0.8	620 0.9	870 1.0	1,873 0.9
Multi-Race/Ethnicity	18 0.5	268 0.6	444 0.6	634 0.7	1,364 0.7
Homeless	25 0.7	352 0.8	429 0.6	468 0.5	1,274 0.6
Charlson Index Score					
0	918 26.4	16,810 37.6	31,261 43.9	39,167 43.1	88,156 41.9
1	1,243 35.8	11,964 26.7	17,145 24.1	23,181 25.5	53,533 25.4
2	536 15.4	7,354 16.4	11,465 16.1	13,714 15.1	33,069 15.7
3	497 14.3	5,092 11.4	6,798 9.6	8,788 9.7	21,175 10.1
4	127 3.7	1,969 4.4	2,685 3.8	3,630 4.0	8,411 4.0
5	97 2.8	893 2.0	1,023 1.4	1,455 1.6	3,468 1.7
6	37 1.1	397 0.9	528 0.7	629 0.7	1,591 0.8
7+	21 0.6	263 0.6	311 0.4	410 0.5	1,005 0.5
Risk Factors for CAP Mortality					
Alcohol Use Disorder	602 17.3	5,736 12.8	7,043 9.9	6,998 7.7	20,379 9.7
Other Drug Use Disorder	167 4.8	2,218 5.0	2,832 4.0	2,833 3.1	8,050 3.8
Tobacco Use Disorder	1,465 42.2	13,917 31.1	16,343 23.0	17,787 19.6	49,512 23.5
Asthma Diagnosis	131 3.8	2,180 4.9	3,947 5.5	6,652 7.3	12,910 6.1
Outcome					
30-Day Mortality Post CAP	404 11.6	2,845 6.6	2,914 4.1	2,413 2.7	6,676 4.1
Total	3,476 1.7	44,742 21.3	71,216 33.8	90,974 43.2	210,408 100

subcohort, with 3.8% in the cohort and 6.1% with asthma in the subcohort. The BMI categories, as seen in Table 3, have 1.7% underweight BMI, 21.3% normal BMI, 33.8% overweight, and 43.2% obese BMI. This is an increase in underweight and normal BMI proportions in the subcohort compared to the original cohort. In the subcohort, 6,676 (4.1%) died within 30-days after CAP diagnosis.

3.4 Risk of 30-Day All-Cause Mortality Post-CAP based on BMI Status:

The results of univariate and multivariate Cox models are found in Table 4. The Cox model was found to have very similar estimates as those seen in the logistic model (logistic model not shown), making the Cox model of the subcohort comparable to logistic models in the literature. The normal BMI group was used as the reference group in the subcohort Cox model. Both men and women with underweight BMI were at an increased risk of 30-day mortality post-CAP, with hazard ratios of 1.81 (95% CI = 1.63, 2.01) and 2.59 (95% CI = 2.37, 4.91), respectively, in comparison to normal BMI. Though both overweight BMI groups for men and women had null associations with mortality in the multivariate model -- men had an HR of 0.69 (95% CI = 0.65, 0.79) and women had an HR of 0.78 (95% CI = 0.51, 1.20) in comparison to normal BMI -- the 95% confidence interval for women is much larger than that for the men. However, the inverse association was stronger in both obese BMI groups for men and women in the multivariate model, with HR 0.56 (95% CI = 0.53, 0.59) and HR 0.61 (95% CI = 0.40, 0.92) respectively in comparison to normal BMI. Lastly, the Schoenfeld residual plot against time with the Loess smoother showed a smooth linear line at the x-axis (graph not shown), indicating the data met the model assumptions of proportional hazards.

TABLE 4	Hazard Ratios of 30-day All-Cause Mortality Post Community-Acquired Pneumonia (n=210,408)			
	Univariate		**Multivariate**	
Variables	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**
Age	1.01 (1.01-1.01)	<.0001	1.05 (1.05-1.06)	<.0001
Sex				
Female	1.00 *	.	1.00 *	.
Male	3.49 (2.96-4.12)	<.0001	1.94 (1.44-2.62)	<.0001
Race/Ethnicity				
White	1.00 *	.	1.00 *	.
African American	0.85 (0.80-0.90)	<.0001	1.02 (0.95-1.08)	0.6138
Hispanic	1.38 (1.28-1.50)	<.0001	1.36 (1.25-1.47)	<.0001
Asian	0.49 (0.33-0.74)	0.0007	0.48 (0.32-0.72)	0.0004
Native American	0.63 (0.44-0.88)	0.0070	0.83 (0.59-1.17)	0.2778
Hawaiian/Pacific Islander	1.00 (0.80-1.25)	0.9876	1.09 (0.87-1.36)	0.4704
Multi-Race/Ethnicity	0.84 (0.63-1.12)	0.2409	0.97 (0.73-1.29)	0.8573
Homeless	0.66 (0.48-0.92)	0.0145	1.00 (0.72-1.40)	0.9998
Charlson Index Score				
0	1.00 *	.	1.00 *	.
1	1.18 (1.11-1.25)	<.0001	1.05 (0.99-1.12)	0.0856
2	1.90 (1.80-2.02)	<.0001	1.48 (1.40-1.57)	<.0001
3	1.94 (1.82-2.08)	<.0001	1.45 (1.35-1.55)	<.0001
4	2.07 (1.89-2.28)	<.0001	1.65 (1.50-1.81)	<.0001
5	2.64 (2.33-3.00)	<.0001	1.95 (1.72-2.22)	<.0001
6	2.31 (1.91-2.80)	<.0001	2.06 (1.70-2.50)	<.0001
7+	2.48 (1.97-3.12)	<.0001	2.52 (2.00-3.18)	<.0001
BMI Group for Women				
<18.5	2.99 (1.58-5.66)	0.0008	2.59 (1.37-4.91)	0.0034
18.5-24.9	1.00 *	.	1.00 *	.
25-29.9	0.69 (0.45-1.06)	0.0866	0.78 (0.51-1.20)	0.2546
30+	0.44 (0.29-0.66)	<.0001	0.61 (0.40-0.92)	0.0182
BMI Group for Men				
<18.5	1.81 (1.63-2.01)	<.0001	1.81 (1.63-2.01)	<.0001
18.5-24.9	1.00 *	.	1.00 *	.
25-29.9	0.61 (0.58-0.64)	<.0001	0.69 (0.65-0.73)	<.0001
30+	0.40 (0.38-0.42)	<.0001	0.56 (0.53-0.59)	<.0001
Alcohol use Disorder	0.76 (0.70-0.82)	<.0001	1.17 (1.07-1.27)	0.0005
Other Drug use Disorder	0.48 (0.41-0.55)	<.0001	0.80 (0.69-0.93)	0.0041
Tobacco use Disorder	0.85 (0.81-0.89)	<.0001	1.21 (1.15-1.29)	<.0001
Asthma Diagnosis	0.55 (0.49-0.61)	<.0001	0.65 (0.58-0.73)	<.0001

*** = Reference category used during analysis**

4. DISCUSSION

4.1 Findings and Literature Comparisons

It was found that men and women differ in BMI association to CAP incidence when the BMI is overweight or obese. Men have a protective association with overweight and obese BMI in comparison to normal BMI, while women had a null association between overweight BMI and CAP and a slight increase risk of CAP with an obese BMI in comparison to normal BMI. With regards to 30-day all-cause mortality post-CAP infection, the "obesity paradox" still exists for men for both overweight and obese BMIs, while it is only present for women in obese BMIs. Men have a strong protective association between overweight and obese BMI and 30-day mortality, while women only have a strong protective effect for obese BMI. For women, the overweight BMI is not significant and has a large confidence interval for 30-day mortality. The one constant for both men and women though was that individuals with an underweight BMI were at an increased risk for both CAP incidence and 30-day all-cause mortality.

The discrepancy in the results based on the previous literature was that overweight and obese BMI were expected to have an increased risk of CAP based on the concept that obese individuals are at an increased risk of infections.[11,12] However, his is not seen in observation studies including this one.[4,8,9] The results clearly differ in the Cox model for men and women, where women's results are consistent with the hypothesis that obese individuals are at an increased risk for infections. Other observational studies have documented protective values for overweight and obese BMIs. For example, Jackson et al observed that their overweight BMI group had a hazard ratio of 0.75 (95% CI = 0.58, 0.95) for their clinical model and 0.77 (95% CI = 0.60, 0.98) for their EHR model in comparison

to the reference group (BMI 18.5- 24.9).[27] They split their obese patients group into two categories, BMI of 30-34.9 and ≥35. Both obese BMI groups in Jackson et al had inverse associations with pneumonia in the clinical and EMR models. Additionally, a case-control study looking at statin as a pneumonia risk factor, found overweight BMI to have an odds ratio of 0.70 (95% CI = 0.60, 0.82) and obese BMI to have an odds ratio of 0.81 (95% CI = 0.66, 0.99) in comparison to those with BMIs under 25.[7]

Other studies have found support for the biological argument that overweight and obese individuals are at increased risk of infections. When looking at the risk of hospitalizations due to pneumonia in men, moderate obesity (BMI 30-34.9) and severe obesity (BMI ≥35) had HRs of 1.4 (95% CI = 1.2, 1.7) and 2.0 (95% CI = 1.4, 2.8), respectively, compared to a reference as BMI 22.5-24.9 [4]. However, Kornum et al states that all risk increases due to obesity were gone after controlling for other chronic diseases.[4] These results may not be entirely comparable as their outcome is hospitalization from pneumonia rather than pneumonia incidence. Hospitalization may differ from what determines if a person gets the disease. be affected by variables other than those that cause pneumonia. There is additional support in the literature for the hypothesis that an overweight or obese BMI increases CAP incidence, but the association is mainly seen among women.[9] The findings of Baik, et al support the differing results for men and women in this study of Veterans.[9]

The results of BMI's effect on 30-day all-cause mortality post-CAP are similar to that of Kornum et al, which looked at 30-day mortality after pneumonia hospitalization.[4] For men with moderate obesity (BMI 30-34.5) and severe obesity (BMI ≥35) Kornum et al had HR 0.9 (95% CI = 0.50, 1.7) and 0.8 (95% CI = 0.2, 2.7) respectively in comparison to BMI

22.5-24.9. Women in the same study had HR 0.6 (95% CI = 0.2, 1.6) and 0.9 (95% CI = 0.3, 2.8) for moderate and severe obesity.[4] The logistic model performed in Corrales-Medina et al makes an apt comparison as mortality is rare in the study population [6]. Their finding was with a continuous variable of BMI for 30-day mortality after pneumonia, with an odds ratio 0.88 (95% CI = 0.81, 0.96). [6] The "obesity paradox" could be explained by the increase in what is considered to be the healthy BMI, the BMI with the lowest mortality rate.[15] The study by Wang et al showed that the BMI with the lowest mortality rate increased from 23.9 in 1986-89 to 28.6 in 2005-9.[15] Since the new healthy BMI was in the overweight group, this could explain why there is decreased mortality in this study in comparison to normal BMI. Additionally, a previous study argued there was biological possibility for the increased survival rates of overweight and obese individuals in relation to CAP and other disease where the "obesity paradox" has been observed.[19] However, this thought differs with the population-based evidence that overweight and obese BMI individuals live shorter lives and are at an increased risk of mortality.[14,15]

4.2 Strengths and Limitations

The overwhelming strength of this study was the access to the VA electronic medical records. The VA provided an ample subject population that far exceeded the previous studies on this topic, including a meta-analysis of over 1.5 million subjects.[8] As a result of the large sample, this study had high power to look at the association of BMI and CAP incidence and mortality. The use of the VA database facilitated control of many different risk factors of CAP through the Charlson Index, other drug use disorders, tobacco use disorder, and asthma, among other conditions. The inclusion of demographic and

social factors as covariates, including homeless status, allowed for better control of confounders. Additionally, using a sample of VA healthcare users will make these results generalizable to the total VA user population. Therefore, any medical recommendations made based on this sample could be applied to all those who use the VA healthcare system. Due to the differences between Veterans and the general population, it is unclear if these results can be extended for individuals outside the VA. However, there are limitations to this study. Only outpatient medical records were used, there was no control for patients who were hospitalized prior to CAP diagnosis in the CAP incidence analysis, and patients hospitalized after CAP was not controlled for in the mortality analysis. This may mean that some of the CAP cases were hospital acquired, but only 3,024 (1.44%) CAP patients in the cohort were hospitalized for two days and were diagnosed with CAP between 2 to 90 days after hospitalization.[25] Controlling for CAP cases that were hospitalized after diagnosis may have been useful in controlling for the severity of pneumonia in the mortality analysis. Selection bias may have been introduced when excluding individuals who did not have matching height and weight data (4.4% excluded) and missing demographics (an additional 9.3% excluded after those who had pneumonia or who died prior to cohort entry were excluded). An additional type of selection bias could have occurred due to the independent censoring assumption made during analysis (i.e. it was assumed that there was no association between those who were censored and the outcome of CAP or its covariates). Imputation was not used to prevent these biases; instead, complete case analysis was performed. Tobacco use disorder was used as a proxy variable for smoking since smoking is a true risk factor for pneumonia. Not all subjects who smoke will have been captured by the tobacco use disorder diagnosis control variable. It has been suggested that correctly controlling for

smoking can reverse the "obesity paradox", but the estimate of 18.6% in this study for tobacco use disorder is not far from the 20% Veteran smoking population.[31,32] Therefore, a better capture of smokers may not have changed the BMI association seen in the results. Additionally, though patients were excluded if they had pneumonia during the qualifying year, a history of pneumonia was not collected past one year prior to cohort entry. Vaccination status was also not collected or controlled for during analysis.

Lastly, one major limitation that was recently discovered was how BMI was collected for analysis. In the previous literature, all studies that have looked at BMI and CAP, or BMI and another disease, with the outcome of mortality, have based the BMI measure on a baseline BMI made around cohort entry.[4,6-10,16-19] This method has been shown to create the "obesity paradox" as it does not control for BMI history.[33] Yu et al used the highest BMI in a 16 year period and this reversed the "obesityparadox".[33] Though a 16 year period may not be feasible for every study, using a time range and taking the highest BMI measure could be a better method of measuring BMI in relation to disease related mortalities.

4.3 Conclusions and Future Directions

Though the findings of this study support the existing literature on the association between BMI and CAP incidence and mortality, these findings do not support the literature that strongly indicates that overweight and obese BMI statuses lead to increase rates of infection and mortality.[11,12,14,15] In the end, it can be said that an underweight BMI puts an individual at a greater risk of CAP incidence and 30-day all-cause mortality post-CAP, which identifies a risk group not currently recommended for PCV. However, based on the

new evidence on the flaw in BMI determination, it is unclear if there is truly a protective effect for overweight and obese BMI for CAP incidence and mortality.[33] To explore this possibility, the data from this study could be analyzed with new BMI groups based on a larger time period prior to cohort entry and having the BMI groups be based on the maximum BMI measure. Additionally, utilizing inpatient records could be useful in determining if a case of pneumonia is CAP or hospital-acquired pneumonia and it would help control for CAP severity if individuals were hospitalized after CAP diagnosis. The question about the true existence of the "obesity paradox" has not yet been answered. There is hope that this research has entered a new stage of BMI identification in studies, which will get researchers one step closer to learning how BMI effects mortality.

5. APPENDIX

APPENDIX 1	ICD-9 Codes Used For Baseline Diagnoses
Diagnosis	**ICD-9 Codes**
Charlson Comorbidities Index (score)	
Congestive Heart Failure (2)	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.7, 425.8, 425.9, 428
Dementia (2)	290, 294.1, 331.2
Chronic Pulmonary Disease (1)	416.8, 416.9, 490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 506.4, 508.1, 508.8
Connective Tissue Disease-Rheumatic Disease (1)	446.5, 710.0, 710.1, 710.2, 710.3, 710.4, 714.0, 714.1, 714.2, 714.8, 725
Mild Liver Disease (2)	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571, 573.3, 573.4, 573.8, 573.9, V427
Diabetes with complications (1)	250.4, 250.5, 250.6, 250.7
Paraplegia and Hemiplegia (2)	334.1, 342, 343 , 344.0, 344.1, 344.2, 344.3, 344.4, 344.5, 344.6, 344.9
Renal Disease (1)	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 585, 586, 588.0, V420 , V451, V56
Cancer (2)	140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 170, 171, 172, 174, 175, 176, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 200, 201, 202, 203, 204, 205, 206, 207, 208, 238.6
Metastatic Carcinoma (4)	196, 197, 198, 199
Moderate or Severe Liver Disease (6)	456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8
HIV/AIDS (4)	042, 043, 044
Other Pneumonia Risk Factors	
Asthma	493
Alcohol Use Disorder	291, 303, 305.0
Drug Use Disorders	
Cocaine Dependence or Abuse	304.2, 305.6
Opioid Dependence or Abuse	304.0, 304.7, 305.5
Cannabis Dependence or Abuse	304.3, 305.2
Stimulant Dependence	304.4
Tobacco Use Disorder	305.1
All CAP Diagnoses	
Pneumonia	480, 480.0, 480.1, 480.2, 480.3, 480.8, 480.9, 481, 481.0, 482, 482.0, 482.1, 482.2, 482.3, 482.30, 482.31, 482.32, 482.39, 482.40, 482.4, 482.41, 482.42, 482.49, 482.8, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483, 483.0, 483.1, 483.8, 484, 484.6, 485, 486, 487

APPENDIX 2	Charlson Index Diagnosis Frequency for the Cohort									
	BMI Group									
	<18.5		18.5-24.9		25-29.9		30+		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Congestive Heart Failure	1,719	5.4	30,973	4.6	53,798	4.0	84,374	5.4	170,864	4.7
Chronic Pulmonary Disease	11,527	36.1	124,188	18.3	179,942	13.4	228,879	14.7	544,536	15.1
Dementia	706	2.2	10,316	1.5	11,184	0.8	6,329	0.4	28,535	0.8
Connective Tissue Disease-Rheumatic Disease	587	1.8	10,791	1.6	18,199	1.4	18,478	1.2	48,055	1.3
Mild Liver Disease	1,274	4.0	23,665	3.5	38,200	2.9	42,911	2.8	106,050	2.9
Diabetes with Complications	808	2.5	22,640	3.3	63,996	4.8	133,296	8.6	220,740	6.1
Paraplegia and Hemiplegia	765	2.4	6,800	1.0	8,381	0.6	8,110	0.5	24,056	0.7
Renal Disease	1,790	5.6	37,597	5.5	70,214	5.2	86,311	5.6	195,912	5.4
Cancer	5,536	17.3	81,136	12.0	138,014	10.3	127,234	8.2	351,920	9.8
Metastatic Carcinoma	.	.	.	.	.	.	.	.	.	.
Moderate or Severe Liver Disease	102	0.3	2,049	0.3	3,350	0.3	4,041	0.3	9,542	0.3
HIV/AIDS	498	1.6	7,602	1.1	7,412	0.6	4,098	0.3	19,610	0.5

APPENDIX 3	Charlson Index Diagnosis Frequency for the Subcohort									
	BMI Group									
	<18.5		18.5-24.9		25-29.9		30+		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Congestive Heart Failure	248	7.1	3,823	8.5	6,152	8.6	10,499	11.5	20,722	9.9
Chronic Pulmonary Disease	1,806	52.0	15,897	35.5	20,491	28.8	27,239	29.9	65,433	31.1
Dementia	81	2.3	995	2.2	972	1.4	571	0.6	2,619	1.2
Connective Tissue Disease-Rheumatic Disease	81	2.3	1,160	2.6	1,702	2.4	1,882	2.1	4,825	2.3
Mild Liver Disease	148	4.3	2,038	4.6	2,927	4.1	3,344	3.7	8,457	4.0
Diabetes with Complications	91	2.6	2,301	5.1	5,819	8.2	12,915	14.2	21,126	10.0
Paraplegia and Hemiplegia	98	2.8	734	1.6	838	1.2	822	0.9	2,492	1.2
Renal Disease	222	6.4	3,948	8.8	6,487	9.1	8,448	9.3	19,105	9.1
Cancer	707	20.3	7,785	17.4	10,572	14.8	10,495	11.5	29,559	14.1
Metastatic Carcinoma	.	.	.	.	.	.	.	.	.	.
Moderate or Severe Liver Disease	8	0.2	179	0.4	294	0.4	416	0.5	897	0.4
HIV/AIDS	96	2.8	972	2.2	815	1.1	516	0.6	2,399	1.1

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