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Drug Use And Smoking Among Hospitalized Influenza Patients, Connecticut 2011-2014

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DRUG USE AND SMOKING AMONG HOSPITALIZED INFLUENZA PATIENTS, CONNECTICUT 2011-2014

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Table 1. Descriptive statistics for substance abusers hospitalized with influenza, 2013-2014.

	Substance Abuse		
Characteristic	**Yes (N = 61)**	**No (N =900)**	**p**
Demographics			
Age (years)[1]	52.44 ± 11.2	66.48 ± 19.1	<0.001
Sex[2]			0.0375
Female	4.9 (27)[3]	95.1 (521)	
Male	8.2 (34)	91.8 (379)	
Race			
Non- Hispanic White	3.6 (22)	96.4 (594)	<0.001
Non-Hispanic Black	13.0 (25)	87.5 (175)	<0.001
Hispanic	9.6 (11)	90.4 (104)	0.1315
Other	10.0 (3)	90.0 (27)	0.4045
Flu Type			0.0896
Type A	7.0 (55)	93.0 (734)	
Type B	4.0 (6)	96.5 (166)	
Illness Severity Measures			
Length of Stay (days)	6.98 ± 7.6	5.93 ± 9.1	0.3072
Received Antiviral Treatment			0.8526
Yes	80.3 (49)	79.3 (714)	
No	19.7 (12)	20.7 (186)	
Pneumonia Co-Infection			0.5506
Yes	7.5 (10)	6.2 (123)	
No	92.5 (51)	93.8 (777)	
ICU Admission			0.0331
Admitted	10.5 (15)	89.5 (128)	
Not Admitted	5.7 (46)	94.3 (756)	
Mechanical Ventilation			
Yes	13.9 (9)	86.2 (56)	0.0161
No	5.7 (51)	94.3 (840)	
Outcome			
Lived	3.5 (59)	94.3 (848)	0.4423
Died	1.6 (1)	96.7 (31)	
Risk Factors			
Vaccine			0.0594
Yes	4.9 (23)	95.1 (448)	
No	7.9 (37)	92.1 (432)	
Body mass index (kg/m^2)	28.42 ± 7.0	29.96 ± 9.1	0.1384
Smoking Status			<0.001
Current	19.1 (49)	80.9 (208)	
Former	1.9 (6)	98.1 (306)	
Never Smoked	1.5 (6)	98.5 (386)	
Alcohol Abuse			
Yes	23.3 (7)	76.7 (23)	0.0019
No	5.8 (54)	94.2 (877)	

1. Continuous variables are presented as means ± standard deviation.
2. Categorical variables are presented as row percent (n).
3. Numbers/percent may not sum to N/100% due to missing data.

Table 2. Unadjusted and adjusted odds ratios for substance abuse and various characteristics.

Characteristic	N	% Substance Abusers	Unadjusted OR (95% CI)	Adjusted OR (95% CI) [4]
Smoking Status				
Current[5]	257	5.1	15.15 (6.39 – 35.97)	12.29 (5.15 – 29.32) †
Former	312	1.9	1.26 (0.40 – 3.95)	1.58 (0.49 – 5.03) †
Never Smoker	392	1.5	1.00 (reference)	1.00 (reference)
Age (years)				
Under 35	54	0.2	1.00 (reference)	1.00 (reference)
35-49	98	1.3	3.63 (0.78 – 16.86)	2.72 (0.56 –13.11)*
50-64	238	3.9	4.79 (1.12 – 20.51)	3.30 (0.74 – 14.61)*
65-79	235	0.9	1.04 (0.22 – 4.94)	0.93 (0.19 – 4.55)*
80 and over	336	0.1	0.08 (0.01 – 0.87)	0.12 (0.01 – 1.42)*
Sex				
Female	548	2.8	0.58 (0.34 – 0.97)	
Male	413	3.5	1.00 (reference)	
Race				
White	616	3.6	1.00 (reference)	1.00 (reference)
Black	200	12.5	3.86 (2.12 – 7.01)	2.45 (1.30 – 4.61)*
Hispanic	115	9.6	2.86 (1.35 – 6.07)	2.35 (1.06 – 5.22)*
Other				
Body mass index (kg/m^2)				
<25	387	2.7	1.00 (reference)	
25 to <30	224	1.6	0.98 (0.52 – 1.92)	
30+	350	2.1	0.84 (0.46 – 1.54)	
Alcohol Abuse	30	23.3	4.94 (2.03 – 12.03)	1.85 (0.73 – 4.65)*
ICU Admission	143	1.6	1.93 (1.04 – 3.55)	
Pneumonia Co-Infection	133	7.5	1.24 (0.62 – 2.50)	
Mechanical Ventilation	65	15.0	2.65 (1.24 – 5.65)	
Having Flu Vaccine	471	2.5	0.60 (0.25 – 1.03)	
Health Conditions				
Any Lung Condition	252	2.1	1.40 (0.81 – 2.45)	1.64 (0.85 – 3.16)* †
Asthma	218	12.4	2.95 (1.74 – 5.01)	2.01 (1.12 – 3.59)* †
Any Cardiovascular Disease	404	1.4	0.35 (0.19 – 0.66)	0.69 (0.34 – 1.41)* †
Atrial Fibrillation	121	1.7	0.22 (0.05 – 0.92)	0.70 (0.16 – 3.14)* †
Coronary Artery Dis.	179	1.1	0.14 (0.03 – 0.57)	0.23 (0.05 – 0.97)* †
Congestive Heart Fail	144	2.9	0.38 (0.14 – 1.07)	0.62 (0.21 – 1.85)* †
Any Metabolic Disorder	411	1.8	0.49 (0.28 – 0.88)	0.61 (0.33 – 1.12)* †
Thyroid dysfunction	161	1.7	0.24 (0.08 – 0.79)	0.39 (0.12 – 1.32)* †
Kidney Disease	153	3.3	0.45 (0.18 – 1.15)	0.84 (0.31 – 2.26)* †
Immunosuppressed	171	1.8	1.87 (1.04 – 3.36)	1.74 (0.96 – 3.16) †
AIDS	3	66.7	30.47 (2.72 – 341)	
HIV	27	22.2	4.57 (1.78 – 11.78)	3.65 (1.40 – 9.48) †
Liver Disease	52	38.5	13.23 (6.97 – 25.1)	10.79(5.19 22.42)* †

4. Characteristics without adjusted odds ratios reported had no significant independent association with age and/or smoking. Odds ratio adjustments were made according to the key below:
   * Designates adjustment for smoking.
   † Designates adjustment for age.

5. Significant odds ratios are highlighted in darker gray within the table.

Table 3. Relative risk of influenza-associated hospitalization for substance abusers.

SUBSTANCE ABUSE	RELATIVE RISK	95% CI
6.35% OF STUDY POPULATION 1.80% OF CT POPULATION OVERALL	**3.53**	**2.78 – 4.51**

Table 4. Descriptive statistics for current, former, and never smokers hospitalized with influenza, 2013-2014.

	Smokers			
Characteristic	**Current (N = 257)**	**Former (N =312)**	**Never (N =392)**	**p**
Demographics				
Age (years)[6]	53.67 ± 21.2	72.72 ± 15.4	67.07 ± 21.2	<0.001
Sex[7]				0.0246
Female	24.8 (136)[8]	30.7 (168)	44.5 (244)	
Male	29.3 (121)	34.9 (144)	35.8 (148)	
Race				
Non-Hispanic White	20.6 (127)	38.0 (234)	41.4 (255)	<0.001
Non-Hispanic Black	41.5 (83)	24.0 (48)	34.5 (69)	<0.001
Hispanic	30.4 (35)	22.6 (26)	50.0 (54)	0.0552
Other	40.0 (12)	13.3 (4)	46.7 (14)	0.0553
Flu Type				0.1420
Type A	28.0 (221)	31.6 (249)	40.4 (319)	
Type B	20.9 (36)	36.6 (63)	42.4 (73)	
Illness Severity Measures				
Length of Stay (days)	5.40 ± 6.2	5.89 ± 5.7	6.49 ± 12.3	0.3136
Received Antiviral Treatment				0.9769
Yes	79.8 (205)	79.5 (248)	79.1 (310)	
No	20.2 (52)	20.5 (64)	20.9 (82)	
Pneumonia Co-Infection				0.5505
Yes	24.0 (33)	30.1 (40)	45.1 (60)	
No	27.1 (224)	32.9 (272)	40.1 (332)	
ICU Admission				0.4413
Admitted	29.4 (42)	35.7 (51)	35.0 (50)	
Not Admitted	26.8 (215)	32.5 (261)	40.7 (326)	
Mechanical Ventilation				0.0836
Yes	38.5 (25)	27.7 (18)	33.9 (22)	
No	25.8 (230)	32.8 (292)	41.4 (369)	
Outcome				0.4738
Lived	27.0 (245)	32.5 (295)	40.5 (367)	
Died	18.8 (6)	31.3 (10)	50.0 (16)	
Risk Factors				
Vaccine				0.6339
Yes	27.4 (129)	31.0 (146)	41.6 (196)	
No	26.0 (122)	33.9 (159)	40.1 (188)	
Body mass index (kg/m^2)	30.34 ± 8.6	29.86 ± 9.1	29.53 ± 9.18	0.5757
Substance Abuse				<0.001
Yes	80.3 (49)	9.8 (6)	9.8 (6)	
No	23.1 (208)	34.0 (306)	42.9 (386)	
Alcohol Abuse				
Yes	83.3 (25)	6.7 (2)	10.0 (3)	<0.001
No	24.9 (232)	33.3 (310)	41.8 (389)	

6. Continuous variables are presented as means ± standard deviation.
7. Categorical variables are presented as row percent (n).
8. Numbers/percent may not sum to N/100% due to missing data.

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Table 5. Health conditions significantly associated with smoking.

Health Condition	N	% Current Smokers (n)[9]	% Former Smokers (n)[9]	% Never Smokers (n)[9]	p
Any Lung Condition	252	32.3[10] (83)	40.1 (125)	11.2 (44)	<0.001
Asthma	218	30.4 (78)	18.0 (56)	21.4 (84)	0.0015
COPD	232	31.2 (82)	36.5 (114)	9.2 (36)	<0.001
Any Cardiovascular Disease	404	28.4 (73)	54.5 (170)	41.1 (161)	<0.001
Atrial Fibrillation	121	3.5 (9)	18.9 (59)	13.5 (53)	<0.001
Coronary Artery Disease	179	12.5 (32)	28.9 (90)	14.5 (57)	<0.001
Congestive Heart Fail	144	10.5 (27)	20.2 (63)	13.8 (54)	0.0038
Any Metabolic Disorder	411	38.5 (99)	51.0 (159)	39.0 (153)	0.0018
Thyroid dysfunction	161	10.5 (27)	22.4 (70)	16.3 (64)	0.0007
Any Kidney Disease	153	9.3 (24)	18.6 (58)	18.1 (71)	0.0034
Renal Insufficiency	108	5.8 (15)	14.7 (46)	12.0 (47)	0.0031
Dementia	82	1.6 (5)	10.3 (32)	11.5 (45)	<0.001
HIV	27	5.5 (14)	1.0 (3)	2.6 (10)	0.0051
Immunosuppressive Therapy	48	2.0 (5)	6.1 (19)	6.1 (24)	0.0322
Liver Disease	52	10.9 (28)	4.5 (14)	2.6 (10)	<0.001

9. Percent given reflects the prevalence of listed health condition among either current, former, or never smokers. Percents will not add to 100 across rows.

Table 6. Logistic regression model for smokers.

		Model (N=1585)	
Characteristic	**Odds Ratio (95% CI)**	**Beta (SE)**	**p**
Age (years)	0.95 (0.94 – 0.96)	-0.0546 (0.004)	<0.001
Female	0.67 (0.51 – 0.88)	-0.4053 (0.138)	0.0034
BMI	0.98 (0.96 – 0.99)	-0.0211 (0.008)	0.0086
Non-Hispanic Black	1.81 (1.29 – 2.53)	0.5922 (0.172)	0.0006
Hispanic	0.79 (0.51 – 1.22)	-0.2332 (0.221)	0.2903
Outcome (death)	0.86 (0.35 – 2.12)	-0.1530 (0.460)	0.7396
ICU Admission	1.45 (0.98 – 2.16)	0.3720 (0.202)	0.0656
Length of Stay	0.98 (0.96 – 1.00)	-0.0212 (0.012)	0.0684
COPD	4.34 (3.17 – 5.95)	1.4687 (0.161)	<0.001
Atrial Fibrillation	0.40 (0.18 – 0.89)	-0.9249 (0.410)	0.0240
Congestive Heart Failure	41.67 (3.92 – 442.95)	3.7297 (1.206)	0.0020
Immunosuppressed Status	0.51 (0.35 – 0.74)	-0.6814 (0.192)	0.0004
HIV Positive	3.70 (1.60 – 8.52)	1.3070 (0.426)	0.0022
Renal Disease	0.61 (0.40 – 0.94)	-0.4884 (0.219)	0.0259
Liver Disease	2.42 (1.34 – 4.36)	0.8822 (0.302)	0.0034
Interaction terms			
Age*Congestive Heart Failure	0.95 (0.91 – 0.98)	-0.0558 (0.017)	0.0013

Table 7. Relative risk of influenza-associated hospitalization for smokers.

SMOKING	RELATIVE RISK	95% CI
26.7% OF STUDY POPULATION 18.4% OF CT POPULATION OVERALL	1.72	1.55 – 1.92

FIGURES

Figure 1. Adjusted odds ratios for selected conditions and substance abuse.

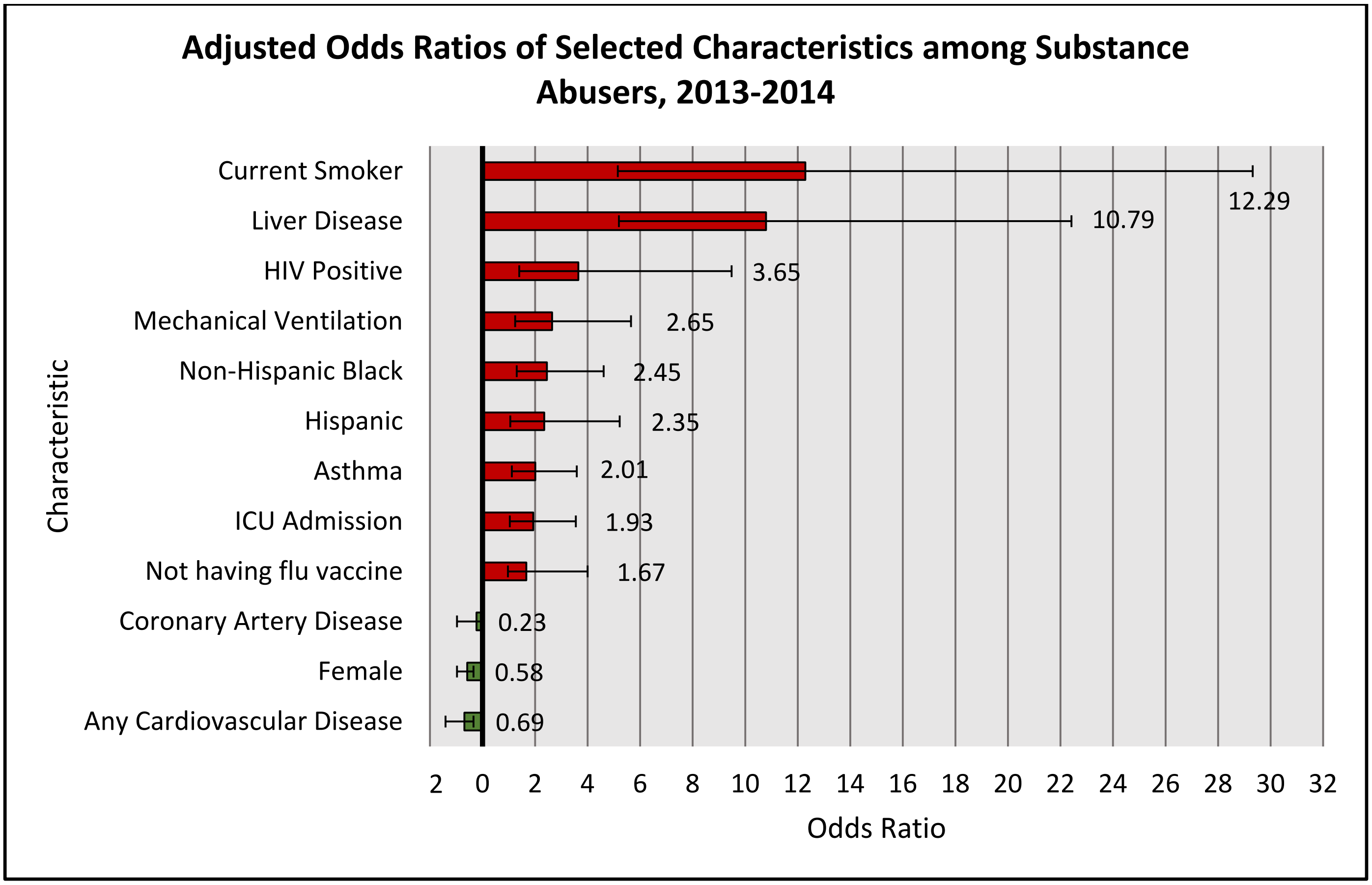


Figure 2. Age distribution of flu-associated hospitalization cases, stratified by substance abuse status.

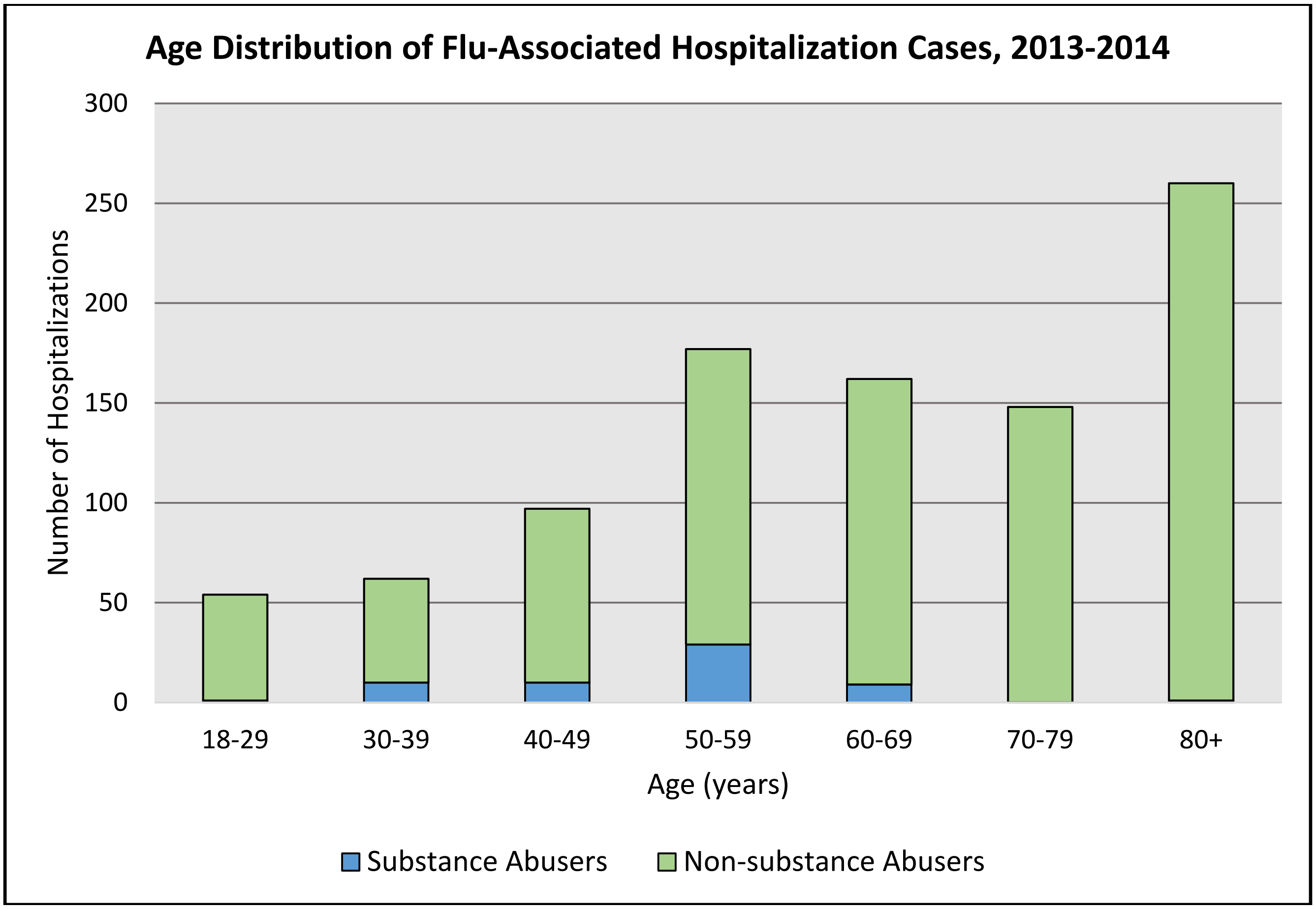


Figure 3. Influenza-associated hospitalization by MMWR week, stratified by substance abuse status.

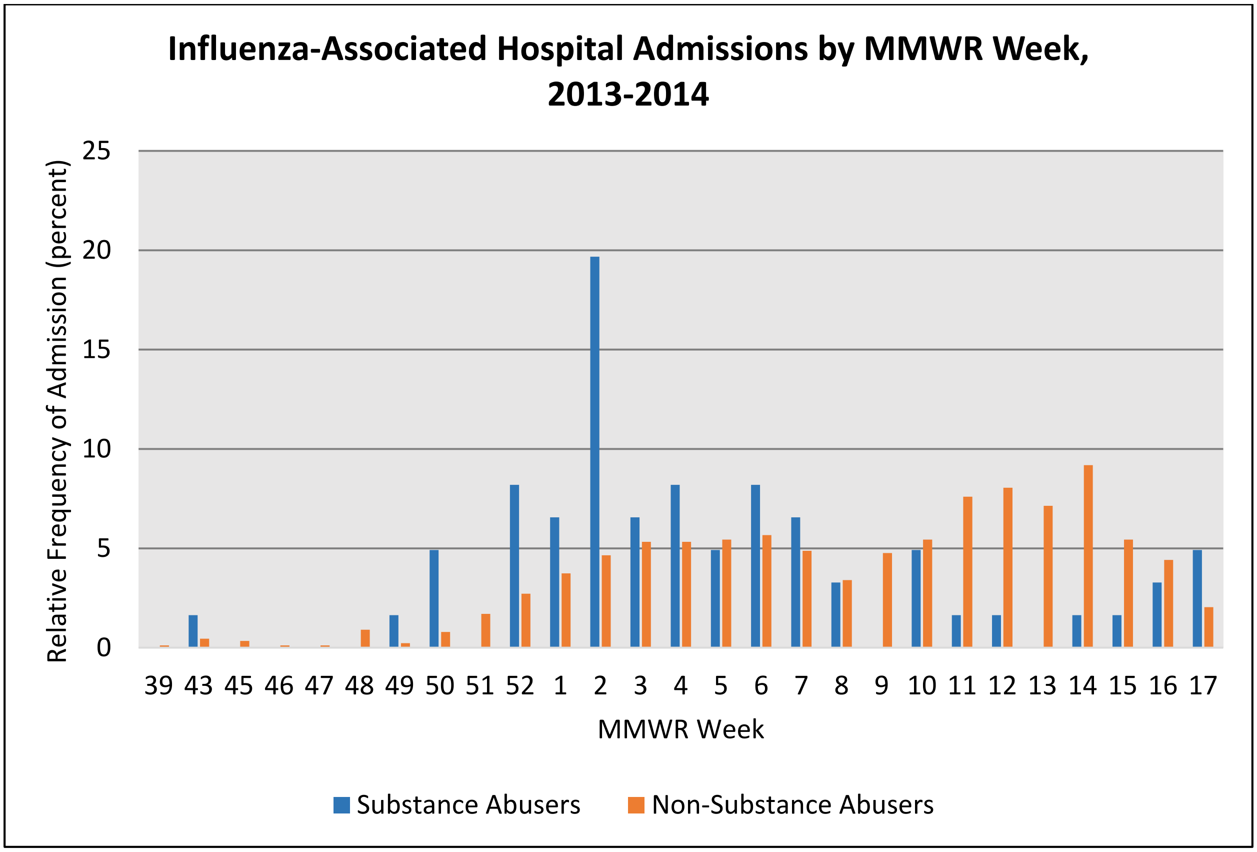
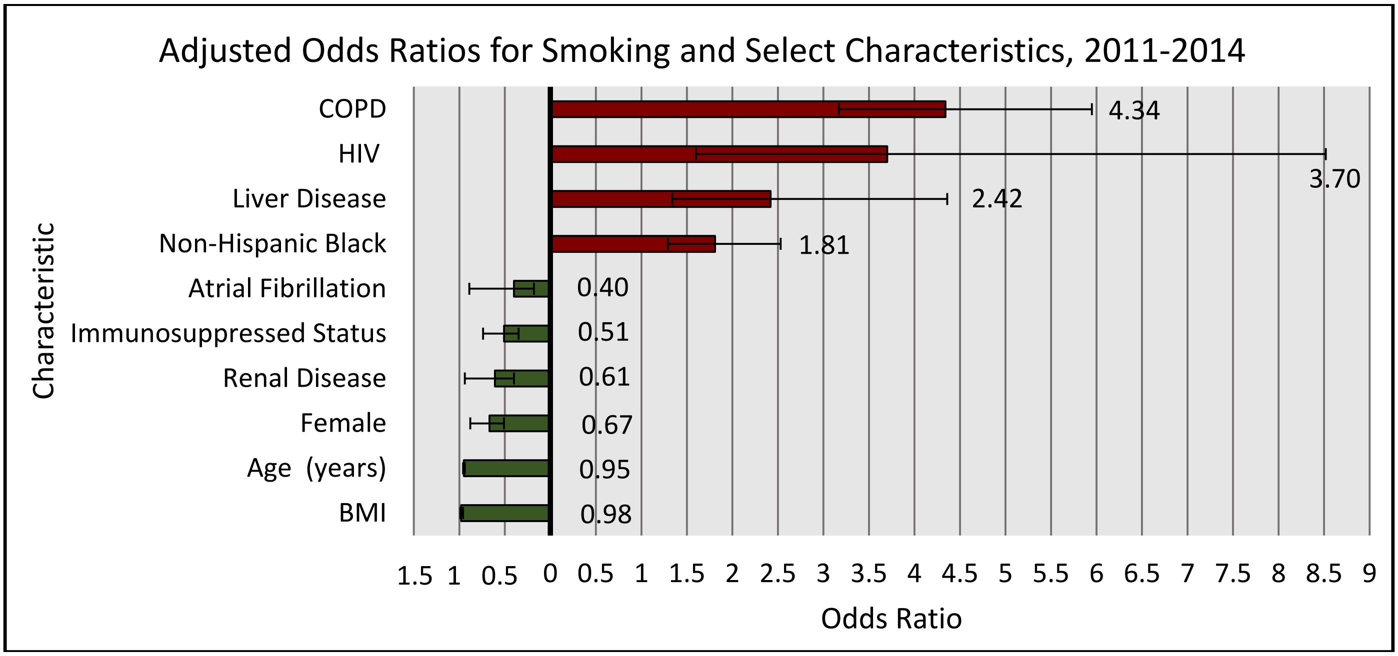


Figure 4. Visual representation of statistically significant odds ratios between smoking and select characteristics.



2. ABSTRACT

INTRODUCTION: Globally, influenza is responsible for 3-5 million cases of severe illness annually. In the United States alone, it is estimated that flu-associated infections account for 3.1 million hospitalized days per year. While the overall impact of flu is relatively well-studied, severe influenza is not well-characterized among the substance abuser and smoker populations.

OBJECTIVES: This study characterizes the risks for and complications associated with serious influenza infection among the substance abuser and smoking populations within Connecticut.

METHODS: Data were obtained via retrospective medical chart review. Cases were individuals within New Haven and Middlesex counties hospitalized with a positive influenza test during the 2011-2012, 2012-2013, and 2013-2014 flu seasons. Smoking and substance use status were analyzed for associations with variables along three main categories: demographics, illness severity measures (e.g. ICU admission, death), and co-morbid conditions. Odds ratios were obtained for statistically significant associations. Logistic regression was used to model risks of smoking.

RESULTS: Of the 961 cases, 61 (6.3%) were substance abusers and 257 (26.7%) were current smokers. On average, substance abusers were 8 years younger upon admission, 1.72 (95% CI 1.03 – 2.94) times more likely to be male than female, 3.86 (95% CI 2.12 – 7.01) times more likely to be black than non-Hispanic white, and faced the highest burden of flu in January. Substance abusers had greater odds of being admitted to the ICU (OR=1.93) and requiring mechanical ventilation (OR=2.65). Smoking status was not significantly associated with increases in illness severity but smokers were at increased risk for COPD (OR=4.34), liver disease (OR=2.42), and HIV (OR=3.70). Overall, substance abusers have 3.53 (95% CI 2.78 – 4.51) times the risk of being hospitalized with an influenza infection than non-drug users, twice the risk of influenza-associated hospitalization for smokers (RR=1.72).

CONCLUSIONS: Influenza hospitalizations are mildly to moderately more severe among substance users. Future directions could include targeted flu vaccine interventions for this population, through programs such as syringe exchange and substance abuse treatment.

3. INTRODUCTION

3.1 Investigation Objectives

The objective of this study was to characterize the population of substance abusers and smokers hospitalized with influenza-associated illnesses in Connecticut, and to assess whether substance use and smoking have an effect on illness severity and outcome.

3.2 The Burden of Influenza

Influenza is a ubiquitous seasonal viral respiratory infection, with an estimated attack rate of 5-10% among adults, and up to 30% in children. Globally, influenza infections result in 3-5 million cases of severe illness and 250,000-500,000 deaths each year [1]. Influenza traditionally has not been the focus of global infectious disease efforts; nor do the annual epidemic cycles often reach the front page of the world news. However, surveillance and research into the disease is a necessary part of global public health for several reasons: the influenza virus infects multiple species, mutates rapidly, disproportionately affects young children and the elderly, and causes large losses in productivity and life-years among adults.

Within the United States, influenza is consistently responsible for substantial morbidity and mortality [2]. The Centers for Disease Control and Prevention (CDC) conducts annual surveillance on flu-related illness and hospitalization, deaths, and disease burden via data collection sites across the country [3]. Because the influenza virus readily mutates and pandemics occasionally occur, it is difficult to reliably estimate the impact of influenza on a year-to-year basis. Researchers have relied on modeling techniques to predict seasonal severity, using data from mortality reports, hospitalizations, and other sources [4–6].

Currently, the best form of preventive protection against influenza is the flu vaccine, changed yearly to reflect the strains predicted to have the highest impact. The World Health Organization (WHO) sets recommendations for the composition of the seasonal flu vaccine [7], and individual countries administer the vaccine according to their own guidelines. Though vaccine efficacy varies from season to season, it was estimated that the 2013-2014 vaccine averted 7.2 million cases of influenza-associated illnesses in the United States alone.

Risk factors that influence flu outcomes and severity have been studied to varying degrees. Children, pregnant women, immunocompromised hosts, and residents of nursing homes have been shown to have increased risk of acquiring influenza [8]. Increased incidence is also seen among low socioeconomic groups and females [9].

Health-risk behaviors also have the potential to be major risk factors for poor health outcomes, but the influence of risk behaviors on influenza is less well-studied. Among alcohol abusers, a large study using data from 2005-2012 found that heavy alcohol consumption was a risk factor for developing severe influenza infections [10]. There have been additional studies conducted in mice that have determined that ethanol consumption was associated with more severe influenza infections [11].

Substance abuse and addiction have great potential to cause increased illness morbidity and mortality, given the associations with long-term risky behaviors and both negative physical and mental health outcomes. This study seeks to explore the relationship between influenza severity, smoking, and substance abuse.

3.3 Smoking and Influenza

The World Health Organization (WHO) cites the tobacco epidemic as one of the biggest public health threats the world has ever faced. Globally, it is estimated that over 1 billion people smoke [12, 13]. Over 5 million deaths per year are directly attributed to tobacco use, and it is estimated that nearly 50% of current tobacco users will die of tobacco-related illnesses [14].

Although smoking rates have declined over the years, as of 2012, an estimated 18.1% of all adults in the United States (approximately 42.1 million people) reported being current smokers [15]. On average, men smoke more than women (20.5% vs. 15.8%), and multi-race individuals and Alaskan Native/Native American individuals report the highest prevalence of smoking (26.1% and 21.8%, respectively). 4.3% of respondents reported using snuff and/or chewing tobacco for at least some days currently [16].

In 2013, the Behavioral Risk Factor Surveillance System (BRFSS) reported a 15.5% (95% CI 14.3-16.7) prevalence of current smokers among adults in Connecticut (n=1058) [17], a lower proportion of smokers than the national average. 10.1% report smoking every day, 5.4% report smoking some days, 28.2% report being former smokers, and 56.3% report never smoking [18]. Connecticut also reports a lower use of chewing tobacco/snuf/snus, with only 1.8% reporting that they use it at least some days [19].

The risk of smoking on influenza outcome and severity is well-characterized. Smoking is associated with a number of respiratory illnesses, both chronic and acute [20]. A 1982 study established a link between smoking and increased risk of epidemic H1N1 [21], and estimated that among smokers with influenza, 40.6% of severe influenza cases were attributable to the risk behavior of smoking itself. Prospective studies on student populations and the elderly estimate odds ratios of 4.1 – 4.4 for incidence of influenza among smokers [22, 23]. Smoking also seems to impact influenza vaccine efficacy as well: vaccinated smokers who lacked hemagglutination-inhibition (HI) antibody prior to vaccination were significantly more susceptible to influenza than non-smokers, and immunity produced by the vaccine waned rapidly [24].

3.4 Substance Abuse and Influenza

A smaller—but no less significant—risk-taking population is illicit drug users: over 15 million people abuse heroin and over 14 million individuals abuse cocaine worldwide. The National Survey on Drug Use and Health, conducted by the Center for Behavioral Health Statistics and Quality, reports on drugs, alcohol, and tobacco use in the civilian, non-institutionalized population over 12 years of age in the United States. This survey reported 22.5 million current substance abusers in the US. 620,000 individuals were current heroin users in 2011 [25]. There is an estimated one million injection drug users (IDUs) in the United States as of 2007 [26]. In Connecticut, it is estimated that there are 66,000 individuals who abuse illicit drugs other than marijuana over the year of the survey (2013) [27].

A review of the literature was conducted to assess the existing evidence surrounding the influence of substance abuse behaviors on influenza risk. Searches were performed on PubMed and Google Scholar using the following keywords: intravenous, injection, injecting, IDU, drug, user, influenza, risk, substance abuse, illicit drug use.

There are very few studies that examine the risk of influenza for the substance abuser population. Most of the existing literature focuses on the increased risk of HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) among the substance abuser population, three infectious diseases associated with unsafe injection practices. Most of the influenza-related work focuses on influenza vaccines: while there is a lack of observational studies on vaccine efficacy in this population, a few studies examine the effectiveness of influenza vaccines on IDUs by measuring seroconversion [40]. In one such study, 409 former IDUs, some of whom were HIV positive, were vaccinated against influenza. Both the HIV positive and HIV negative groups showed no significant changes in CD4 counts as a result of the vaccination, indicating that influenza vaccines may not impair immune function in this group and can be incorporated into regular preventive care for the population [28]. A similar study on former heroin users demonstrated that having a history of substance abuse did not affect immunogenicity of the influenza vaccine in both HIV positive and negative individuals [41]. A systematic review that sought to examine the effects of several different vaccines (including the influenza vaccine) was conducted, but only two studies were used in their analysis of flu vaccine efficacy. Again, the researchers concluded that there was little to no adverse immunological effect of vaccinating the IDU population [40]. An *in vitro* study concluded that methamphetamine reduced influenza viral reproduction [29]. Little is known about the burden associated with severe influenza among substance abusers, on both a molecular and epidemiological level.

3.5 Potential Impact

This project aims to fill the knowledge gap surrounding substance abusers and influenza, and to provide evidence of the illness severity associated with smoking and substance abuse among influenza-associated hospitalization cases. The results of this study can be used to tailor treatment for these populations, make flu vaccination recommendations, and to raise awareness among clinicians that smokers and substance abusers may have unique health needs when it comes to upper respiratory infections.

4. METHODS

4.1 Data Collection

Data were obtained from the Connecticut Emerging Infections Program (CTEIP), which serves as a population-based surveillance site for the Centers for Disease Control and Prevention (CDC)’s Weekly U.S. Influenza Surveillance Report [30]. The CDC’s Influenza Hospitalization Surveillance Network (FluSurv-NET) draws from these surveillance sites to estimate age-specific influenza-related hospitalization rates and to characterize the population hospitalized with severe influenza.

At the CTEIP site, data are collected each year during the flu season (October 1 – April 30) on all individuals within the catchment area of New Haven and Middlesex Counties, who were hospitalized with a laboratory-confirmed positive influenza test [31]. An individual who meets the case definition for surveillance is also assessed, via a retrospective review of his or her medical record, for various demographic factors, over 72 other co-morbid health conditions, details on the duration and course of their influenza-related hospitalization, and their flu vaccination status.

Although the CTEIP collects hospitalization data across all ages, for the purpose of this study pediatric cases (aged under 18 years upon hospital admission) were excluded. For the study’s characterization of substance abuser population hospitalized with influenza, data from the 2013-2014 flu season were used. In this dataset, substance abuse was classified as any note of illicit drug abuse, and recorded under “Other disease conditions,” “Other,” and filled in descriptively. Drug users who were noted to use marijuana exclusively were excluded from the substance abuse category.

To characterize the smoking population, data from 2011-12, 2012-13, and 2013-14 surveillance seasons were used. Medical records for the 2013-2014 flu season were accessed via hospital records (both paper and electronic), MyChart on EpicCare EMR software (Epic Systems Corporation), or collected via hospital visits. Eighteen hospitals within Connecticut contributed to the dataset. Completed datasets for the 2011-2012 and 2012-2013 seasons were collected from CTEIP. Statistical analysis was conducted using SAS Version 9.3 (SAS Institute Inc, Cary, NC).

4.2 Descriptive Statistics for Substance Abusers

First, descriptive statistics for the sample were obtained, with the objective of comparing the substance abuse population to the general influenza-hospitalized population along three main areas: demographics, illness severity, and additional risk factors. The demographic variables examined were age, race, ethnicity, sex, and influenza type (A or B, with some subtype/strain data available). To facilitate analysis, race and ethnicity data were categorized as non-Hispanic white, non-Hispanic black, Hispanic, and other. Age was treated as a continuous variable for characterization purposes and in any modeling. In the case of bivariate association testing, age was stratified into five groups: 18-35, 35-49, 50-64, 65-79, and 80 and over. Illness severity was assessed by examining length of hospital stay in days, whether or not an individual received antiviral treatment, whether or not an individual spent time in the ICU, whether or not a patient received mechanical ventilation or ECMO/bypass, whether the patient died during the hospitalization, and whether or not the patient had pneumonia. An individual was considered to have pneumonia if he or she had a discharge ICD-9 code indicating pneumonia of any origin (ICD-9 codes 480 – 486.xx). Lastly, the population was evaluated for the presence of additional risk factors: smoking status, alcohol abuse status, BMI, and whether or not a patient had received a flu vaccine prior to admission. Smoking status was stratified to three levels: current smokers, former smokers, and never smokers. Alcohol abuse was recorded only if there was direct mention of abuse, addiction, or the need for rehabilitation in the medical chart; it is likely that true alcohol abuse is underestimated in the study due to no recording of binge drinking behavior or sporadic alcohol misuse.

To test for significant differences between the substance abuser and general influenza-hospitalized population with regards to continuous variables, the Student's t-test was used with an α-level of 0.05. The Student's t-test assumes a normal distribution and tests a null hypothesis that there is no statistically significant difference between two means. To verify the normality assumption, all continuous variables (age, BMI, and length of stay) were tested for normality. All continuous variables passed Cramer-von Mises and Anderson-Darling tests ($p<0.005$), indicating that the t-test was an appropriate statistical test.

Testing for significant differences between substance abuse and the general population with regards to categorical variables was performed using the chi-squared test, with a null hypothesis that there was no significant difference between the proportion of substance abusers and non-substance abusers with the characteristic of interest. The significance threshold for all chi-squared tests was also 0.05.

To visualize the time course of influenza associated hospitalizations among substance abusers compared to the general population, an epidemic curve for the two populations was generated. The curve depicts the frequency of hospital admissions among substance abusers compared to non-substance abusers in one week intervals. To correspond with case reporting, number of admissions were totaled by MMWR week (weeks 39-52 in 2013 to weeks 1-17 in 2014).

4.3 Risk Measures for Substance Abuse

After testing for associations between various characteristics and substance abuse status, odds ratios were obtained to describe the magnitude of risk. Tests were performed for all variables included in the descriptive analysis, along with 72 health conditions (see Appendix 1 for full list). A bivariate analysis approach, rather than modeling the data, was chosen to obtain risk measures due to the small sample size of substance abusers within the total population.

Bivariate analysis was carried out using Maentel-Hanszel chi-square tests, which assumes a null hypothesis that the proportion of substance abusers with the characteristic of interest does not differ significantly from the proportion of non-substance abusers with the characteristic. The test also calculates an odds ratio, or the odds that substance abusers are more or less likely to have the characteristic of interest when compared to non-substance abusers. For tests of association in which fewer than five individuals were included per category, Fisher's exact test was used with the same null hypothesis. Both of these tests were carried out with a significance threshold of $p = 0.05$.

Variables that did not include a member of the substance abuse population (for example, history of Guillan-Barre syndrome), were excluded from analysis. Additionally, variables that for which there were only a few substance abusers were excluded due to low sample size. Tests were carried out to the 0.05 level of significance.

Variables that were determined to be effect modifiers or confounders for specific outcomes were adjusted for in the analysis process. To determine confounding or effect modification, the relationship between substance abuse and the variable of interest was stratified along the levels of a third variable (the potential confounder). The Breslow-Day test of homogeneity was used to determine whether differences in stratified odds ratios existed.

To estimate the relative risk of hospitalization as a substance abuser, state and nationwide estimates of these risk behaviors were used. Public data were obtained from the Center for Behavioral Health Statistics' National Survey on Drug Use and Health from the year 2013 to provide estimates of the number of substance abusers over the year in the state of Connecticut. For the purpose of risk estimates, the category "substance abuse other than marijuana" was used. The overall population in Connecticut as well as the population of New Haven and Middlesex counties were obtained from the US Census Bureau's State and County Census QuickFacts [32]. A prevalence of substance abuse within Connecticut was calculated using the survey results and census population data. Assuming that the prevalence of substance abuse within Connecticut was equally distributed throughout the state, this prevalence was used to estimate the number of substance abusers that would be located within the catchment area of New Haven and Middlesex counties.

4.4 Descriptive Statistics for Smoking Population

Descriptive statistics for the smoking population were obtained using the methods detailed in section 2.2. For this analysis, smoking was stratified into three categories: current, former, and non-smokers. Like substance abusers, smokers were also assessed along three main areas: demographics, illness severity measures, and risk factors.

Relative risk of influenza-associated hospitalization for smokers was determined using the methods in section 2.3. Data for smoking prevalence came from the 2013 Behavioral Risk Factor Surveillance System surveys.

4.5 Logistic Regression Modeling

To better understand the relationship between smoking, demographics, co-morbid conditions, and illness severity during flu-association hospitalizations, data from the 2011-2014 surveillance seasons were modeled using logistic regression. For the purposes of the model, smoking was transformed into a binary variable: current and non-smokers (which includes those who have never smoked, as well as those who no longer smoke but may be former smokers). Former and non-smokers exhibited similar age trends upon hospital admission and a similar profile of co-morbid conditions. Because of inconsistencies in reporting substance abuse in the 2011-2012 and 2012-2013 flu season, substance abuse as a risk factor was excluded from model consideration. Additionally, because the alcohol abuse variable was suspected to underreport risk behaviors such as binge drinking, and because alcohol abuse significantly overlapped with smoking, this risk factor was also excluded from the model.

Smoking status was designated as the binary response variable (smoking =1, nonsmoking =0). The explanatory variables for the full model were as follows: age, sex, BMI, race, length of stay, ICU admission, use of mechanical ventilation, use of ECMO, vaccine status prior to admission, type of flu, whether or not the case had pneumonia during hospitalization, and all co-morbid health conditions listed in Appendix 1.

Selection of variables for the model was conducted using a backwards-elimination strategy starting with the full number of explanatory variables. Variables for which there were no smokers were immediately removed from the model. To compare goodness-of-fit between models when model selecting, the Aikake Information Criterion (AIC) score was used. Variable removals that resulted in an AIC score decrease of 2 or greater were considered significant, and the next iteration of the model was run without that variable. Variables were removed sequentially in this manner, starting with those with the highest p-values, until the AIC score did not decrease. Covariates that remained were considered in the final model. Because this was a model designed to explore associative relationships, covariates with p-values that did not meet the significance threshold ($p<0.05$) remained in the model if removal did not decrease the AIC score.

Of the covariates remaining, a correlation matrix was assembled for all variables. If two variables had a Spearman correlation coefficient > 0.2 (or < -0.2), indicating possible collinearity, an interaction term between the two variables was created and tested in the model. Interaction terms that further lowered the AIC score by 2 or more were added into the model.

5. RESULTS

5.1 2013-2014 Sample Characterization

There were a total of 961 individuals over the age of eighteen included in the sample. The population was 56.5% female, 64.1% non-Hispanic white, with an average age of 64.6 (standard deviation ± 19.0) years. 471 individuals (49.0%) were hospitalized despite reporting receiving a flu vaccine sometime between September 2013 and admission. Median hospitalization time was 4 days. Of those individuals, 257 (26.7%) reported being a current smoker, and an additional 312 (32.5%) reported being a former smoker. 61 individuals (6.3%) were substance abusers.

5.2 Substance Abusers

The sample was split into those who were recorded as substance abusers (n=61) and those who had no record of substance abuse (n=900). Across Connecticut, substance abusers were 3.53

times more likely to be hospitalized for influenza-associated illness than non-substance abusers, and are at twice the risk of hospitalization when compared to smokers (see Tables 3 and 7). The full comparison between hospitalized substance abusers and non-substance abusers can be seen in Table 1. Of note, the average age of hospitalized substance abusers was 52.4 years, fourteen years younger than the average age of those who did not report substance abuse (66.5 years, $p<0.001$). Other significant differences were seen across race, with 12.5% of non-Hispanic blacks and 9.6% of Hispanics reporting substance abuse, compared to 3.6% of non-Hispanic whites ($p<0.001$ for non-Hispanic blacks; $p=0.1315$ for Hispanics). Almost twice the proportion of males reported substance abuse than females (8.2% and 4.9%, respectively, $p = 0.0375$).

Illness severity measures differed across both populations as well. Average length of stay among substance abusers was around one day longer than non-substance abusers, though this result was not statistically significant. Substance abusers reported a significantly greater frequency of ICU admissions (10.5% of ICU admissions were substance abusers, while only 5.7% of regular hospitalizations were substance abusers, $p=0.0331$) and mechanical ventilation (13.9% of all incidences of mechanical ventilation were seen in substance abusers, $p=0.0161$). Pneumonia incidence, receipt of antiviral treatment, and survival outcomes during hospitalization were not significantly associated with substance abuse.

While there was no significant association between BMI and substance abuse, substance abusers had an overall lower proportion vaccinated against the flu than non-substance abusers, though this result is not statistically significant ($p=0.0594$). Additionally, substance abusers had a significantly higher frequency of engaging in other measured risk behaviors such as smoking and alcohol abuse. Forty-nine out of the 61 substance abusers were current smokers (80.3%), indicating that the majority of drug users engaged in multiple health-risk behaviors.

5.2.1 Bivariate Analysis

Data analysis to determine any associations between substance abuse and other collected variables was undertaken. All significant associations between substance abuse and their corresponding odds ratios are shown in Table 2.

Smoking as a confounder

Because a large proportion of substance abusers also reported smoking, and there is overwhelming evidence suggesting that smoking is associated with a number of harmful health outcomes, smoking was determined to be a potential confounder for health conditions analysis. The odds ratios for conditions that were independently associated with smoking and substance abuse were adjusted for to account for this confounding effect. Adjusted odds ratios are provided where applicable.

Age as an effect modifier

One concern in the analysis was that age could also be a possible effect modifier within this dataset, given that some of the health conditions analyzed are more common among certain age groups. Unadjusted substance abuse varied considerably across age groups, with those in the 46-60 year range 4.79 times more likely to report substance abuse than individuals under 30. Age, when analyzed as a continuous variable, was independently associated with smoking and all co-morbid conditions of interest.

However, due to the small sample size of the substance abuse population (n=61), the study was not powered to conduct rigorous stratified analyses and present stratified odds ratios.

To adjust for age, a logistic regression model was used to obtain odds ratios between substance abuse (outcome) and various co-morbid conditions (predictors), with age as a continuous predictor variable in the model. If the condition was also independently significantly associated with smoking, smoking was included as a predictor variable as well, resulting in odds ratios that were adjusted for both smoking status and age.

The age distribution of the substance abuse population versus the non-substance abuse population is depicted in Figure 2. Further descriptive information on the age distribution of substance abusers and the correlations between age and various health conditions are included in Appendix 2.

Unadjusted and Adjusted Odds Ratios

Most significantly substance abusers hospitalized with influenza-associated illness have 12.29 [95% CI 5.15 – 29.32] times the odds of being current smokers than non-substance abusers of the same population. Substance abusers were 1.72 times more likely to be male, 2.45 times more likely to be non-Hispanic black, and 2.35 times more likely to be Hispanic (when compared to non-Hispanic whites). Substance abuse status did not significantly differ across age categories, though the highest frequency was seen among 50-64 year olds.

Substance abuse is also a risk factor for several illness severity measures, with substance users 1.93 [95% CI 1.04 – 3.55] times more likely to be admitted to the ICU and 2.65 [95% CI 1.24 – 5.65] times more likely to use mechanical ventilation during hospitalization than non-substance abusers. Of borderline statistical significance was flu vaccination status: those who use illicit drugs are 1.67 times more likely to report not receiving a flu vaccine prior to admission than those who do not. This result, however, had a p-value of 0.0594, and should be interpreted with caution.

Surprisingly, substance abuse was associated with a protective effect for a number of different health conditions, though many of the protective effects lost statistical significance after adjusting for age and/or smoking, where applicable. Most notably, substance abusers had 0.23 times the odds of having coronary artery disease than non-substance abusers ($p<0.05$), though age may explain much of this relationship.

Substance abusers exhibited the largest risks for liver disease (OR=10.79, $p<0.05$), HIV (OR=3.65, $p<0.05$), and AIDS (OR=30.47, $p<0.05$). However, due to the small number of individuals within the study with AIDS (n=3), results for the association with AIDS may not be meaningful.

A visual representation of all statistically significant odds ratios is given in Figure 1.

5.2.2 Hospitalization Epidemic Curve for Illicit Drug Abusers

Visual comparisons between the substance abuser and non-substance abuser populations is difficult due to the disparity in sample size (the non-substance abuser population is nearly 15 times larger). To better visualize the differences in a hospitalization epidemic curve, admission frequency totals per week were presented as proportions of the total population. The epidemic curve for substance abuse is presented in Figure 3. A similar epidemic curve was generated to compare hospital admission patterns between smokers and non-smokers; however, the curves did not appear significantly different (results not shown).

The general incidence of flu-associated hospitalizations in Connecticut during 2013-2014 follows a two-wave pattern, with the first wave peaking around MMWR weeks 4-6 (late January – mid February) and the second wave peaking around MMWR week 14 (April 4-11, 2014, graph not shown). When hospitalization dates are stratified by substance abuse status, differences in the outbreak patterns emerge. Among substance abusers, the “first-wave” pattern is fairly similar, with a notable peak in the proportion of cases around week 2. However, hospitalization incidence during the “second-wave” among substance abusers is diminished, with the proportion of hospitalizations tapering off until MMWR weeks 16-17 (late April).

In the general population, the second wave was marked by an increase in the proportions of Influenza B cases compared to Influenza A. It was hypothesized that, because substance abusers appeared to have less of a second wave of influenza, they may have significantly higher Influenza A cases. However, no association was found between flu type and substance abuse status, as seen in Table 1.

Hospitalization among substance abusers seems highest from late December through February. The large number of hospital admissions during MMWR week 2 (January 11-17, 2014) represents nearly 20% of the total substance abuse population of the sample (n=12).

5.2.3 Relative Risks Compared to General Population

As seen in Table 3, substance abusers make up approximately 1.8% of the overall population within Connecticut. However, the proportion of substance abusers found within the flu-associated hospitalization population (6.34%) is considerably higher. It is estimated that substance abusers have a 3.53 [95% CI 2.78 – 4.51] times greater risk of being hospitalized with influenza than non-substance abusers within New Haven and Middlesex counties in CT.

5.3 Smokers

Smoking status was also assessed to determine whether smoking varied by demographics or risk factors, and had a role in illness severity. The full results can be seen in Table 4, with information about the prevalence of co-morbid conditions among smokers found in Table 5. Variables associated with smoking were similar (but not identical) to the variables associated with substance abuse. The average age at time of admission for smokers was 53.7 years old, significantly lower than former and never smokers (72.3 and 67.1 years, respectively). Smoking was associated with being male ($p=0.0246$) and non-Hispanic black ($p<0.001$).

It is interesting to note that smoking was not significantly associated with any illness severity measures. Average length of stay ranged from 5.4 (±6.2) – 6.5 (±5.7) days among all current, former, and never smokers, and smoking status did not significantly affect survival outcomes of the hospitalization. Smokers also exhibited no significant differences with regards to vaccination status and BMI. As mentioned above, the relationship between smoking and risk behaviors such as alcohol and substance abuse was apparent within this population (Spearman correlation = 0.3152), with the majority of substance and alcohol abusers engaging in smoking as well.

5.3.1 Logistic Regression Model for Smoking

To model the relationship between smoking, illness severity, risk factors, demographics, and co-morbid conditions among those hospitalized for influenza, a logistic regression model was constructed (shown in Table 6). The total sample size used in the model was 1,585 individuals from the years 2011-2014.

A total of sixteen predictor variables comprised the reduced model, which had an R-square value of 0.3408. The model satisfied the Hosmer and Lemeshow Goodness-of-Fit Test, which has a null hypothesis that the final model adequately fits the data. The p-value for this test was 0.5628, indicating that there is not sufficient statistical information to reject the null. Pearson residuals exhibited a random scatter pattern about 0, with most values falling between -2 and 3, and very little visual indication of overdispersion.

The final model included age, sex, race, BMI, hospitalization outcome, ICU admission, length of stay, COPD, atrial fibrillation, congestive heart failure (CHF), immunosuppressed status, HIV, renal disease, and liver disease as predictors, with one interaction term between age and CHF. From the model, odds ratios and 95% confidence intervals were obtained.

Many of the effects in the model were slight: those who were older had 0.95 [95% CI 0.94 – 0.96] times the odds of being a smoker than younger individuals, and those with heavier BMIs had 0.98 [95% CI 0.96 – 0.99] times the odds of being a smoker. Smoking was significantly more common in males, and non-Hispanic blacks had 1.81 [95% CI 1.29 – 2.53] times the odds of being smokers than non-Hispanic whites. Hispanics did not have a statistically significant increase in the probability of being a smoker when compared to non-Hispanic whites. Additionally, hospitalization survival outcomes, ICU admission, and length of stay, while included in the model, were not statistically significant predictors of smoking.

Smokers were shown to be at increased risk for several disease conditions: they had 2.42 [95% CI 1.34 – 4.36] times the odds of having liver disease compared to non-smokers, 3.70 [95% CI 1.60 – 8.52] times the odds of being HIV positive, and 4.34 [95% CI 3.17 – 5.95] times the odds of having COPD. Within this population, smoking represented an enormous risk for congestive heart failure (CHF), with smokers being 41.67 [95% CI 3.92 – 442.95] times as likely to have CHF than non-smokers. However, the wide range in the confidence interval indicates that this odds ratio may not reflect a risk of that magnitude, so this result is to be interpreted cautiously.

Smoking also appeared to be slightly protective against atrial fibrillation (OR=0.40, 95% CI 0.18 – 0.89), having immunosuppressed status (OR=0.51, 95% CI 0.35 – 0.74), and renal disease (OR=0.61, 95% CI 0.40 –0.94). All statistically significant odds ratios from the smoking regression model are displayed in Figure 4.

5.3.2 Relative Risks Compared to General Population and Substance Abusers

The relative risk of flu-associated hospitalization for smokers is presented in Table 6. Smokers make up approximately 18.4% of the overall population within Connecticut, and 26.7% of the 2013-2014 hospitalized influenza population. Smokers have a 1.72 [95% CI 1.55 – 1.92] times greater risk of being hospitalized with influenza than nonsmokers within New Haven and Middlesex counties in CT, assuming an even distribution of smokers throughout the state.

6. DISCUSSION

6.1 Study Findings

The disease burden due to influenza annually results in millions of dollars in lost productivity, millions of hospitalized days, and morbidity and mortality due to severe infection and co-infection. This study offers a descriptive analysis of the burden of influenza among those with high risk behaviors, a group not often studied with regards to influenza infection.

It is important to contextualize the findings in light of a few underlying factors of the study design. First, the population captured in the study are those who were hospitalized with influenza. This does not guarantee that an individual was hospitalized *due to* influenza infection; there may be additional or other reasons that explain hospital admission. However, it is reasonable to assume that the majority of severe influenza cases requiring hospitalization are contained within the study population.

Second, there was the potential of misclassification as a result of the categorization methods used in the 2013-2014 season. The data collection form used for the retrospective chart reviews did not have a specified place to mark drug abuse status, and results were dependent upon the chart reviewer indicating drug use/abuse under the “Other conditions, Other” category. Cases of substance abuse may have been missed due to failure to indicate status on the collection form, failure for the physician to make a note of substance abuse on the medical chart, or concealment of substance abuse status by the patient. It is possible that incidence of substance abuse could be higher among the influenza-associated hospitalized population, which indicates that the relative risk of hospitalization may be underestimated in this study.

Lastly, estimations of risk and illness severity may be confounded by the way substance abusers interact with the health system itself. Substance abusers with no desire to enter rehabilitation are often an isolated population, who may be less likely to seek medical care for serious conditions due to fear of discovery or withdrawal. One partial indicator for delay in seeking care is the receipt of antivirals. Oseltamivir (Tamiflu), the primary antiviral administered for flu in Connecticut, is recommended for those who present within 48 hours of first symptom onset. After the 48 hour window, it is up to physician discretion to administer, but generally regarded as less effective and unadvisable [42]. A significantly lower prescription rate among substance abusers may indicate more substance abusers being admitted past the 48 hour window when compared to the general population, though this is not an exact proxy due to variations in prescription patterns. Both the substance abuser and smoker populations displayed nearly identical proportions of oseltamivir treatment as the general hospitalized population, indicating no difference in treatment patterns. It is possible that substance users may wait to go to the emergency room due to influenza and associated complications until problems become too significant to ignore, resulting in fewer substance abusers being captured within this population. On the other hand, avoidance of the health system may result in poorer health outcomes once substance abusers are hospitalized. This could partially explain the increased risk of ICU admission and mechanical ventilation seen among substance abusers.

Even with these factors taken into consideration, the substance abuser population is unique in many ways. 72.5% of the hospitalizations among substance abusers can be attributed to drug abuse, and substance abusers have a substantially increased risk of being hospitalized compared to the general population. Within the influenza-hospitalized population, substance abuse was also more common among minority demographic groups. The National Survey on Drug Use and Health found no significant differences in substance abuse prevalence across race [16], yet non-Hispanic blacks and Hispanic substance abusers were hospitalized at higher proportions than non-Hispanic whites. This could point to other socioeconomic differences at play among substance abusers that were not measured in this study. Although females in the general population are at higher risk for influenza, there was a far greater proportion of male substance abusers hospitalized than females. The significant gender gap in drug use reflects the national trends that males are more likely to report smoking and substance use than females [33].

Furthermore, substance abusers appeared to be less likely to have a flu vaccine than the general population hospitalized for influenza, which may be related to substance abusers’ reluctance to interact with the health system, as discussed above. Another possible reason for lower vaccination rates could be missed vaccination opportunities through workplace or school-based clinics. A prior study on vaccination rates among the elderly reported that cigarette smoking was associated with decreased likelihood of vaccination [39]. While this may factor into the decreased vaccination coverage among substance abusers—of whom a large number happen to be smokers—it does not explain the fact that smoking status had no association with flu vaccination status within this study population.

A considerable distinguishing factor of substance abusers is the chronological pattern of hospitalizations compared to non-substance abusers. The large spike in cases in MMWR week #2, in which 20% of the substance abuser population was hospitalized, may indicate connections within the community, or a larger outbreak among substance abusers during that time. The study did not have the ability to discern whether or not there were social ties between various members of the substance abusing population, but it is possible that transmission patterns may vary based on social network connections. More research is needed to determine if these patterns are related to social interactions.

Another factor of concern is the significantly earlier age upon hospital admission seen among substance abusers. Given that the prevalence of chronic diseases increases and immune function decreases generally as the population ages, it is expected that a greater number of elderly individuals will experience more severe cases of influenza, resulting in hospitalization. However, it appears that substance abuse contributes to being hospitalized at a substantially younger age (average age upon hospitalization among substance abusers = 52.4 years, compared to 66.4 for non-substance abusers).

The increased illness severity among substance abusers may be partially explained by the connection between immunodeficiency and drug abuse. It is generally well established that injection drug users exhibit a decrease in immune function and are at increased risk for conditions such as HIV and HBV [34]. These findings are supplemented by the increased risk for HIV, AIDS, and immunocompromised status among substance abusers in the study population.

Taken with the evidence and comparisons drawn above, it appears that substance abuse may have at least a partial role in increasing the likelihood of influenza-associated hospitalization, and the severity of the illness once hospitalized. This increased risk, combined with the decreased likelihood of substance abusers to receive flu vaccines, results in a higher burden of disease due to influenza among substance abusers within Connecticut.

It is interesting to note that smokers did not exhibit the same increases in illness severity. While the smoking population shared similar demographic risk factors as substance abusers (more likely to be male, non-Hispanic black, and younger age upon admission), it appears that smokers do not differ much from the general population when it comes to severe influenza. The relative risk of acquiring influenza severe enough to be hospitalized is moderate (RR=1.72). This is affirmed by the extensive literature on smoking's associations with increased severity of respiratory illnesses, though this relative risk is less than half the risk for influenza-associated hospitalizations seen among substance abusers.

It is possible that some of the associations seen between health conditions and smoking found in the logistic regression model are confounded by other risk behaviors. Analysis from the 2013-2014 substance abuser population indicated that substance abusers also have an increased risk of HIV—this may point to an overestimation of HIV risk due to the tight overlap between the substance abuse and smoker population, and the necessary exclusion of substance abuse from the model. It is also possible that alcohol abuse, another variable not included but tightly correlated with smoking, could explain part of the elevated risk of liver disease.

Overall, smokers exhibited a different course of illness and different disease profile. Perhaps the most significant difference between the smoking and substance abuse populations were the effects of illness severity—smoking did not have any associations with measures of severity, while substance abuse seemed to cause increased burden of illness. The comparison between associations provides grounds for treating smokers and substance users as two separate risk groups with differing health needs, despite the large number of substance abusers who also smoke.

6.2 Limitations

Size

First, the small sample size of substance abusers (n=61) prevented the use of more rigorous statistical testing due to low power. Previous years of influenza surveillance data did not collect drug use status upon case hospitalization, which also prevented the use of multi-year data to conduct further analysis. However, the 2014-2015 influenza season data collection includes intravenous drug use as a health condition category, ensuring more rigorous quantification of the population in future years.

Generalizability

The population studied was limited to the relatively small area of New Haven and Middlesex counties, Connecticut. Within New Haven County, the population is 65.8% non-Hispanic white, 14.0% non-Hispanic black, and 16.4% Hispanic, whereas Middlesex County is 85.2% non-Hispanic white, 5.3% non-Hispanic black, and 5.5% Hispanic, with other races making up the remaining population in both counties [32]. The study population (64.1% non-Hispanic white, 20.8% non-Hispanic black, 12.0% Hispanic, 3.1% other) closely resembles the demographics of New Haven County, indicating that the study provides a fairly proportional race/ethnicity representation. The race demographics are not too far off from the U.S. as a whole, which reports 62.6% non-Hispanic whites, 13.2 non-Hispanic blacks, and 17.1% Hispanics [43]. However, the age distribution of the study population is skewed toward the elderly, and has a higher proportion of females represented when compared to males. There is the possibility that the differences in these baseline demographics, as well as any unmeasured demographic variables, may not be generalizable to the rest of the United States.

Confounding

The overlap between the smoking and substance abuser populations is of considerable concern for confounding within the data, particularly for co-morbid conditions. Smoking is linked to a number of adverse health outcomes, including increased incidence of respiratory infections, chronic lung conditions, and heart disease. Examining the individual impacts of each risk behavior side by side, along with smoking-adjusted odds ratios, allows for a clearer picture to emerge.

Evidence indicates that tobacco smokers—especially those who begin smoking during childhood and adolescence—have an increased risk for using substances throughout their lifetime [35, 36].

It is important to note that smoking status was not significantly associated with any disease severity measures in the study, while substance abuse status was. It appears that, while smoking may contribute to adverse health outcomes in general, within this population the added burden of substance abuse increases illness severity, indicating that substance abusers have unique health needs.

Age

Age was an effect modifier in this study. As the population ages, risk of illness increases: according to the North American Association of Central Cancer Registries, aging is associated with increased risk of many cancers, including lung, colon, breast and prostate cancers [37]. Over half of all U.S. adults over the age of 65 are affected by conditions such as arthritis and hypertension. One in three are affected with heart disease, and one in five have diabetes [38]. Due to low sample size among the substance abuser population, there was not enough statistical power to significantly detect differences across age strata. However, the low number of elderly (70+) substance abusers may have affected the associations between substance abuse and certain co-morbid conditions. The protective effects seen among substance abusers for diseases such as coronary artery disease and congestive heart failure could be due to the fact that substance abusers were, on average, eight years younger than the rest of the hospitalized population.

However, the fact that substance abusers were far younger upon hospitalization may point to the burden of substance abuse. Influenza-associated hospitalizations are far more common among the elderly; it is possible that the act of substance abuse itself contributes to earlier hospitalization times among the substance abuse population, rather than any age-associated co-morbid conditions.

6.3 Implications and Future Directions

The findings of this study indicate that substance abusers—and to a lesser extent, smokers—have unique health needs when it comes to severe cases of influenza. Current interventions and impact studies often ignore neglected and hidden populations such as substance abusers; however, this study indicates that substance abusers may need extra public health measures to lessen the burden of sever influenza among the population.

More studies should be conducted to further investigate relationships between influenza severity and drug use. As multiple years of data on substance users becomes available, studies can be undertaken with larger sample sizes to verify the associations observed in this project. Additionally, Connecticut data can be compared to data from other Emerging Infections Program surveillance sites to see whether the substance user population differs across states.

For surveillance purposes, it may be useful to keep track of the time of hospitalization among substance abusers. Weeks or periods with larger-than-average numbers of hospital admissions for this population may point to community-based outbreaks.

Additionally, the decreased vaccination coverage seen among substance abusers could inform future public health efforts. Flu vaccination campaigns may be designed to be more accessible to substance abusers, such as incorporating opt-out vaccine scheduling at existing needle exchange programs or drug treatment programs to ensure higher rates of vaccination.

7. APPENDIX 1.

Table A.1 List of health conditions assessed.

Condition	
Asthma	Plegias/paralysis
Any chronic lung disease	Seizure/Seizure disorder
Cystic fibrosis	Immunocompromised status
Emphysema/COPD	AIDS
Any chronic metabolic disease	HIV
Diabetes	Cancer, in treatment or diagnosed in last 12 months
Thyroid dysfunction	Complement deficiency
Sickle cell disease	Immunoglobulin deficiency
Splenectomy/Asplenia	Immunosuppressive therapy
Thrombocytopenia	Organ transplant
Hemoglobinopathy	Stem cell transplant
Atherosclerotic cardiovascular disease (ASCVD)	Steroid therapy within 2 weeks of admission
Any cardiovascular disease	Any renal disease
Cerebral vascular incident/stroke	Chronic kidney disease
Congenital heart disease	End stage renal disease/Dialysis
Coronary artery disease	Glomerulonephritis
Heart failure/CHF	Nephrotic syndrome
Any neuromuscular disorder	Liver disease
Duchenne muscular dystrophy	Systemic lupus
Muscular dystrophy	Morbidly obese
Multiple sclerosis	Obese
Mitochondrial disorder	Pregnant
Myasthenia gravis	Post-partum
Any neurologic disorder	Dementia
Cerebral palsy	Developmental delay
Cognitive dysfunction	Down syndrome

APPENDIX 2.
Relationship between age, substance abuse, and health conditions.

The age distribution of the substance abuse population vs. the non-substance abuse population is depicted in Figure 2. Nearly half of all substance abusers (n=29, 47.5%) are aged 50-59 years. There was only 1 case under the age of 30, and only 1 over the age of 70.

To depict the general relationship between age and the various health conditions, correlation coefficients are listed in Table A.2 below. Younger age was associated with asthma, smoking, substance abuse, HIV, and having an increased BMI. Older age was associated with atrial fibrillation, coronary artery disease, congestive heart failure, thyroid dysfunction, and renal disease. Very weak to insignificant correlations were seen between liver disease, AIDS, and immunosuppressed status.

This may help to explain the protective effect seen in the associations between substance abuse and coronary artery disease, and metabolic diseases (thyroid dysfunction, diabetes). However, it is also difficult to discern how much of disease onset in this population is due to aging or engagement in risk behaviors such as smoking and substance use.

Table A.2. Correlation between age and select conditions.

Condition	Correlation with Age (Pearson)	p
Asthma	-0.2879	<0.001
Smoking	-0.3472	<0.001
Substance Abuse	-0.1807	<0.001
Atrial Fibrillation	0.3028	<0.001
Coronary Artery Disease	0.2806	<0.001
Congestive Heart Failure	0.2493	<0.001
Thyroid Dysfunction	0.2399	<0.001
Renal Disease	0.1598	<0.001
Immunosuppressed Status	-0.0864	0.0074
AIDS	-0.0454	0.1597
HIV Positive	-0.1002	0.0019
Neurological disorder	-0.1167	<0.001
Liver Disease	-0.0717	0.0263
BMI	-0.1805	<0.001

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9. REFERENCES

1. World Health Organization. (2014). *Influenza (seasonal).* Fact Sheet 211. Accessed from: http://www.who.int/mediacentre/factsheets/fs211/en/

2. World Health Organization. (2014). *Influenza virus infections in humans.* Accessed from: http://www.who.int/influenza/human_animal_interface/virology_laboratories_and_vaccines/influenza_virus_infections_humans_feb14.pdf?ua=1

3. Centers for Disease Control and Prevention. (2015). *Disease Burden of Influenza.* Accessed from: http://www.cdc.gov/flu/about/disease/burden.htm

4. Simonsen, L., Fukuda, K., Schonberger, L. B., & Cox, N. J. (2000). The impact of influenza epidemics on hospitalizations. *Journal of Infectious Diseases*, *181*(3), 831-837. Accessed from: http://jid.oxfordjournals.org/content/181/3/831.full

5. Simonsen, L., Clarke, M. J., Williamson, G. D., Stroup, D. F., Arden, N. H., & Schonberger, L. B. (1997). The impact of influenza epidemics on mortality: introducing a severity index. *American journal of public health*, *87*(12), 1944-1950. Accessed from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1381234/pdf/amjph00511-0042.pdf

6. Glezen, W. P. (1982). Serious morbidity and mortality associated with influenza epidemics. *Epidemiologic reviews*, *4*, 25-44. Accessed from: http://epirev.oxfordjournals.org/content/4/1/25.full.pdf+html?ijkey=fc131f14b994b3e18bc4bfcfc898809ce2ac8352&keytype2=tf_ipsecsha

7. World Health Organization. (2015). Recommended composition of influenza virus vaccines for use in the northern hemisphere. Accessed from: http://www.who.int/influenza/vaccines/virus/recommendations/201502_qanda_recommendation.pdf?ua=1

8. Whitley, R. J., & Monto, A. S. (2006). Prevention and Treatment of Influenza in High-Risk Groups: Children, Pregnant Women, Immunocompromised Hosts, and Nursing Home Residents. *Journal of Infectious Diseases*, *194*(Supplement 2), S133-S138. Accessed from: http://home.smh.com/sections/services-procedures/medlib/Pandemic/Pan_Geriatrics/PanGer_51_Whitely_050309.pdf

9. Tam, K., et al. (2014). "Influenza-related hospitalization of adults associated with low census tract socioeconomic status and female sex in New Haven County, Connecticut, 2007-2011." Influenza Other Respir Viruses.

10. Greenbaum, A., Chaves, S. S., Perez, A., Aragon, D., Bandyopadhyay, A., Bennett, N., ... & Finelli, L. (2014). Heavy alcohol use as a risk factor for severe outcomes among adults hospitalized with laboratory-confirmed influenza, 2005–2012. *Infection*, *42*(1), 165-170. Accessed from: http://www.ncbi.nlm.nih.gov/pubmed/24243481

11. Meyerholz, D. K., Edsen-Moore, M., McGill, J., Coleman, R. A., Cook, R. T., & Legge, K. L. (2008). Chronic alcohol consumption increases the severity of murine influenza virus infections. *The Journal of Immunology*, *181*(1), 641-648. Accessed from: http://www.jimmunol.org/content/181/1/641.abstract?ijkey=d3f34fce8b9ac0b103758e94292450662256d8a5&keytype2=tf_ipsecsha

12. World Health Organization. (2013). *WHO report on the global tobacco epidemic, 2013: enforcing bans on tobacco advertising, promotion and sponsorship*. World Health Organization. Accessed from: http://whqlibdoc.who.int/publications/2011/9789240687813_eng.pdf?ua=1

13. World Health Organization (Ed.). (2009). *Global health risks: mortality and burden of disease attributable to selected major risks*. World Health Organization.

14. World Health Organization. (2014). *Tobacco*. Fact sheet 339. Accessed from: http://www.who.int/mediacentre/factsheets/fs339/en/

15. Centers for Disease Control and Prevention. (2015). *Current Cigarette Smoking Among Adults in the United States*. Accessed from: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/

16. Behavioral Risk Factor Surveillance System. (2013). *Prevalence and Trends Data: Nationwide: (States, DC, and Territories) – 2013 Tobacco Use*. [Data file]. Retrieved from: http://apps.nccd.cdc.gov/brfss/display.asp?cat=TU&yr=2013&qkey=8651&state=US

17. Behavioral Risk Factor Surveillance System. (2013). *Prevalence and Trends Data: Connecticut – 2013 Tobacco Use*. Adults who are current smokers. [Data file]. Retrieved from:http://apps.nccd.cdc.gov/brfss/display.asp?state=CT&cat=TU&yr=2013&qkey=8161&grp=0&SUBMIT4=Go

18. Behavioral Risk Factor Surveillance System. (2013). *Prevalence and Trends Data: Connecticut – 2013 Tobacco Use*. Use of chewing tobacco, snuf, snus. [Data file]. Retrieved from http://apps.nccd.cdc.gov/brfss/display.asp?state=CT&cat=TU&yr=2013&qkey=8171&grp=0&SUBMIT4=Go

19. Behavioral Risk Factor Surveillance System. (2013). *Prevalence and Trends Data: Connecticut – 2013 Tobacco Use*. Use of chewing tobacco, snuf, snus. [Data file]. Retrieved from http://apps.nccd.cdc.gov/brfss/display.asp?state=CT&cat=TU&yr=2013&qkey=8651&grp=0&SUBMIT4=Go

20. Arcavi, L., & Benowitz, N. L. (2004). Cigarette smoking and infection. *Archives of internal medicine*, *164*(20), 2206-2216. Accessed from: http://archinte.jamanetwork.com/article.aspx?articleid=217624

21. Kark, J. D., Lebiush, M., & Rannon, L. (1982). Cigarette smoking as a risk factor for epidemic a (h1n1) influenza in young men. *New England Journal of Medicine*, *307*(17), 1042-1046. Accessed from: http://www.nejm.org/doi/full/10.1056/NEJM198210213071702

22. Finklea, J. F., Sandifer, S. H., & Smith, D. D. (1969). Cigarette smoking and epidemic influenza. *American journal of epidemiology*, *90*(5), 390-399. Accessed from: http://aje.oxfordjournals.org/content/90/5/390.full.pdf

23. Nicholson, K. G., Kent, J., & Hammersley, V. (1999). Influenza A among community-dwelling elderly persons in Leicestershire during winter 1993–4; cigarette smoking as a risk factor and the efficacy of influenza vaccination. *Epidemiology and infection*, *123*(01), 103-108. Accessed from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2810733/pdf/10487646.pdf

24. MacKenzie, J. S., MacKenzie, I. H., & Holt, P. G. (1976). The effect of cigarette smoking on susceptibility to epidemic influenza and on serological responses to live attenuated and killed subunit influenza vaccines. *Journal of Hygiene*, *77*(03), 409-417. Accessed from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2129829/pdf/jhyg00063-0117.pdf

25. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (2011). *Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings.* Accessed from: http://archive.samhsa.gov/data/NSDUH/2k11Results/NSDUHresults2011.htm

26. Virginia HIV Epidemiology Profile. (2011). *Injection Drug Users.* Accessed from: http://www.vdh.virginia.gov/epidemiology/DiseasePrevention/Profile2011/IDU_2011.pdf

27. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (2013). *2012-2013 NSDUH State Estimates of Substance Abuse and Mental Disorders.* [Data file]. Accessed from: http://www.samhsa.gov/data/reports-by-geography?tid=623&map=1

28. Amendola, A., Boschini, A., Colzani, D., Anselmi, G., Oltolina, A., Zucconi, R., ... & Zanetti, A. R. (2001). Influenza vaccination of HIV-1-positive and hiv-1-negative former intravenous drug users. *Journal of medical virology*, *65*(4), 644-648. Accessed from: http://onlinelibrary.wiley.com/doi/10.1002/jmv.2085/abstract;jsessionid=56A8083FD17021270D4FF65F4F9DCB63.f03t01.

29. Chen, Y. H., Wu, K. L., & Chen, C. H. (2012). Methamphetamine reduces human influenza a virus replication. *PloS one*, *7*(11), e48335. Accessed from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0048335#pone-0048335-g008

30. Centers for Disease Control and Prevention. (2015). *2014-2015 Influenza Season Week 13 ending April 4, 2015.* Accessed from: http://www.cdc.gov/flu/weekly/

31. Yale School of Public Health. (2015). *Influenza Hospitalization Surveillance, FluSURV-Net*. CT Emerging Infections Program. Accessed from: http://publichealth.yale.edu/eip/projects/flu.aspx

32. United States Census Bureau. (2015). *QuickFacts*. [Data file]. Accessed from: http://quickfacts.census.gov/qfd/states/09000.html

33. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (2011). *Results from the 2011 National Survey on Drug Use and Health: Gender.* Accessed from: http://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.htm#2.5

34. Maor, P. Y., & Rubinstein, E. (2006). Changing populations: the elderly, injection drug users, health-care-associated and immunocompromised patients. In *Endocarditis* (pp. 23-35). Springer London. Accessed from: http://eknygos.lsmuni.lt/springer/133/23-35.pdf

35. Torabi, M. R., Bailey, W. J., & Majd-Jabbari, M. (1993). Cigarette smoking as a predictor of alcohol and other drug use by children and adolescents: evidence of the "gateway drug effect". *Journal of school health*, *63*(7), 302-306. Accessed from: http://www.ncbi.nlm.nih.gov/pubmed/8246462

36. Johns Hopkins Bloomberg School of Public Health. (2006). *Cigarette Smoking and Drug Use.* Accessed from: http://www.jhsph.edu/news/news-releases/2000/smoking-drugs.html

37. North American Association of Central Cancer Registries (2003). *Incidence rates in selected common cancer sites in adults by age, race/ethnicity, and sex in the selected areas in the United States, 1999-2003.* [Data file]. Accessed from: http://web.archive.org/web/20060925110425/http://seer.cancer.gov/report_to_nation/supplemental/annual_report_75-03_agegroups.pdf

38. Federal Interagency Forum on Aging-Related Statistics. (2012). *Older Americans 2012: Key Indicators of Well-Being.* Accessed from: http://www.agingstats.gov/agingstatsdotnet/Main_Site/Data/2012_Documents/Docs/EntireChartbook.pdf

39. Nichol, K. L., Mac Donald, R., & Hauge, M. (1996). Factors associated with influenza and pneumococcal vaccination behavior among high-risk adults. *Journal of general internal medicine*, *11*(11), 673-677. Accessed from: http://link.springer.com/article/10.1007%2FBF02600158

40. Baral, S., Sherman, S. G., Millson, P., & Beyrer, C. (2007). Vaccine immunogenicity in injecting drug users: a systematic review. *The Lancet Infectious Diseases*, *7*(10), 667-674. Accessed from: http://www.sciencedirect.com/science/article/pii/S1473309907702372

41. Amendola, A., Boschini, A., Colzani, D., Anselmi, G., Oltolina, A., Zucconi, R., ... & Zanetti, A. R. (2001). Influenza vaccination of HIV-1-positive and hiv-1-negative former intravenous drug users. *Journal of medical virology*, *65*(4), 644-648. Accessed from: http://ac.els-cdn.com/S0264410X96000576/1-s2.0-S0264410X96000576-main.pdf?_tid=9c21b3c8-ead1-11e4-a3ab-00000aab0f27&acdnat=1429914851_8cd2fadec79f2903204bc42b5e406a0a.

42. LONG, J. K., MOSSAD, S. B., & GOLDMAN, M. P. (2000). Antiviral agents for treating influenza. *Cleveland Clinic journal of medicine*, *67*(2), 92-95. Accessed from: http://www.ccjm.org/index.php?id=107937&tx_ttnews[tt_news]=349585&cHash=481bc31eb3cf1c5496f64ef983d67067.

43. United States Census Bureau. (2015). USA. *QuickFacts*. [Data file]. Accessed from http://quickfacts.census.gov/qfd/states/00000.html.