DIFFERENTIAL ALL-CAUSE EXCESS MORTALITY OF THE 1918 INFLUENZA PANDEMIC IN THE U.S. REGISTRATION AREA

by

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ABSTRACT

The 1918 influenza pandemic is one of the deadliest events to have occurred in recorded history. This pandemic remains significant to public health due to the potential of a 1918-like pandemic occurring today. The implications of a future influenza similar to that of 1918 necessitate investigation into the mortality of this pandemic. Previous studies examining mortality records in the U.S. during the pandemic found that mortality varied by city and state, and was associated with factors such as sex, age, urbanization, and population density and growth.

The purpose of this study is to evaluate the age- and sex-specific all-cause excess mortality during the 1918 pandemic in the U.S. among twenty-four states with registered mortality data. A secondary objective of the study is to examine the correlations between all-cause excess mortality and suspected determinants of mortality during the pandemic.

This study used mortality data from Vital Statistics reports of the U.S. Census Bureau for states that registered by 1915. Excess mortality was determined by age and sex as the deviation of mortality in 1918-20 from the average mortality rate in 1915-17 and 1921-23.

Overall, the excess mortality rate was the highest in 1918, while in 1919 and 1920 the mortality rates were similar to the non-pandemic rates. With few state exceptions, excess mortality decreased substantially in 1919 and increased in 1920. Younger age groups had higher excess mortality in every year. In 1918, male excess mortality exceeded female excess mortality; however in 1919 and 1920 this was reversed. While some states demonstrated consistent age-

specific and sex-specific patterns of excess mortality compared to the average rates, overall, the excess mortality varied greatly across all states. Population density, urbanization, and male to female ratios were moderately correlated with overall excess mortality, while military enlistment and influenza and pneumonia mortality were weakly correlated with excess mortality rates. These correlations varied by age and sex. The variation in excess mortality and the weak to moderate correlations with suspected determinants of mortality during the 1918 pandemic suggest further investigation of these determinants with regards to predicting excess mortality.

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1.0 INTRODUCTION

Influenza has been responsible for epidemics and pandemics throughout much of recorded history; some of the earliest records of suspected outbreaks date back to the *Corpus Hippocraticum* written in Ancient Greece [1]. More recently, the influenza pandemic of 1918 killed at least 50 million people worldwide and 675,000 Americans [2]. About a third of the world's population was infected, and approximately 2.5 percent of these cases were fatal [3]. While statistics prior to the 20th century are more qualitative than quantitative in nature, it is reasonable to assume influenza has had a material effect on mortality throughout human history.

Over time, improvements to sanitation, medical care, and other factors have resulted in the decrease of infectious disease rates throughout the world. For example, in 1900, infectious diseases caused about 797 deaths per 100,000 in the U.S., primarily from influenza and pneumonia [4]. By 1996, the rate was about 59 deaths per 100,000 in the U.S., roughly an order of magnitude lower, with influenza and pneumonia remaining the leading cause of death, particularly in the elderly [4]. However, while mortality rates have decreased over the past century, seasonal influenza still results in a significant number of deaths each year in the U.S., in addition to causing upper respiratory infections in 5 to 15 percent of the population [2, 5]. The recent pandemic in 2009, while not nearly as deadly as was expected, resulted in 60.8 million cases in the U.S. [6]. To understand and perhaps limit future outbreaks, it is useful to examine the 1918 pandemic and its effects on subsequent occurrence of the disease. Moreover,

with descendants of the 1918 virus still in circulation, and with the world increasingly intertwined, the ability to limit or prevent future outbreaks remains relevant to this day.

2.0 LITERATURE REVIEW

Despite occurring nearly 100 years ago, the 1918 pandemic and factors that contributed to its deadliness can provide inferences for the impact of a pandemic occurring in the modern world. There was not a strong understanding of the cause of the influenza in 1918, and the search for complete understanding of the 1918 strain and its origin continue today. Extensive research has been conducted to attribute the severity of the 1918 pandemic in the U.S. to various aspects of the American life in 1918.

2.1 INFLUENZA VIRAL STRUCTURE

The cause of influenza, and the 1918 pandemic, was discovered in 1931, when virologist Richard Shope isolated Influenza virus A in pigs, and in 1933, Smith, Andrewes, and Laidlaw isolated the first human influenza virus [2]. Influenza has three main types: Influenza A, B, and C viruses, which are classified according to the antigenicity of their nucleocapsids and matrix proteins [7]. While Type B and C viruses have been shown to only infect humans, Influenza A viruses can also infect animals [8].

Influenza A viruses are subtyped according to two surface proteins, Hemagglutinin (H) and Neuraminidase (N) [7]. Hemagglutinin allows the virus to bind to receptor proteins on the host cell; and Neuraminidase is responsible for the spread of progeny viruses [7]. There are 16 varieties of Hemagglutinin and 9 varieties of Neuraminidase [7]. These two proteins are coded

in the virus' single-stranded RNA eight-segment genome, which codes for a total of 11 to 12 proteins [7]. The virus causes symptoms by destroying the epithelial cells of the respiratory tract and reducing the effectiveness of ciliary clearance of mucus [9]. Because the destruction of the respiratory epithelium left people vulnerable to bacterial infection, and antibiotics were not yet available, a majority of deaths during the 1918 influenza pandemic were a result of secondary bacterial infections [10].

2.2 SEASONAL VERSUS PANDEMIC INFLUENZA

Influenza maintains a persistent presence in the human population. Annual recurrence of seasonal influenza occurs as a result of antigenic drift, whereby the virus accumulates mutations as it replicates and results in a modified strain [11]. These slight modifications result in a somewhat predictable pattern of influenza each year. Between 1976 and 2006, seasonal influenza in the U.S. resulted in a range of 3,000 to 49,000 deaths annually, typically among the very young and the elderly [12]. Most people recover from infection due to existing immunity either via prior infection with a similar strain or immunization. Seasonal influenza is easily spread, with a single infection resulting in an average of 1.30 new infections, but it has a low case-fatality rate of about 0.2 percent in developed countries [13].

In contrast, pandemic influenza occurs as a result of larger genetic changes via the process of antigenic shift, when an influenza strain emerges from an animal population with a hemagglutinin and neuraminidase combination that is distinct from strains previously seen in

the human population [11]. The lack of immunity to the newly emerged viral strain provides the potential for a pandemic.

2.3 ORIGIN AND FATE OF THE 1918 STRAIN

The 1918 virus is the earliest influenza virus that has been sequenced; no influenza viruses have been sequenced from before 1918. Researchers are thus unable to compare the 1918 virus to previous viruses. In 2005, virologist Jeffery Taubenberger completed the sequencing of the genome of the 1918 virus using frozen lung tissue from pandemic victims buried in the permafrost of Alaska [2]. All eight gene-segments of the 1918 influenza strain are avian-like, which suggests that the virus had not drifted far from its avian ancestor prior to 1918 [14]. In other words, the virus was probably in the avian population just prior to the 1918 outbreak. This is atypical, as the virus usually has a non-human mammalian (typically swine) intermediary between the avian virus and the human virus [15]. While there were reports of simultaneous influenza outbreaks in swine populations during the 1918 pandemic, research has not yet been able to establish a relationship between these outbreaks and the 1918 pandemic.

Interestingly, a common thread among the later influenza pandemics of 1957, 1968, and 2009 is that these influenza strains were descendants of the 1918 virus [16]. Lineages of the 1918 viral strain are believed to persist in avian, swine, and human populations, accumulating mutations until a new strain, capable of causing influenza outbreaks, emerges [16]. However, these descendants have shown reduced pathogenicity relative to the original 1918 strain. Moreover, influenza pandemics prior to 1918 apparently did not match the severity of the 1918

outbreak. A pandemic in 1889 resulted in about one million deaths, and resembled more recent influenza outbreaks in that it had higher mortality rates among the very young and the elderly [17]. Uniquely, the 1918 influenza pandemic had a W-shaped age-specific mortality rate, with an additional high mortality rate among people ages 20 to 40 years.

Because the 1918 influenza strain is the earliest strain that has been sequenced, determining its origin is somewhat problematic. When the pandemic hit, it occurred almost simultaneously in three different locations around the world: Europe, North America, and Asia. If the 1918 virus was a founder virus that emerged from an avian host, epidemiologically we would normally be able to observe and document its spread. The fact that the virus emerged in three different locations virtually simultaneously suggests that it may have already been circulating globally undetected. Despite the simultaneous outbreaks, there is general consensus that the virus originated in one of these three locations.

Although popular because of conditions related to the war, a European origin is not considered likely. Although for propaganda purposes it may have been expedient to blame it on the Germans or that it originated in Spain (so-called “Spanish Flu”), there is little epidemiological evidence of a European origin. In the 1990s, virologist John Oxford did observe that there had been outbreaks of respiratory disease in the British Army in late 1916 and early 1917, and posited that trench warfare conditions created a unique environment for emergence of a new strain of the virus [18]. Oxford believed that the pandemic in the fall of 1918 resulted from soldiers returning home after the war, bringing the influenza virus with them. This theory is somewhat problematic in that the demobilization of troops did not largely begin until after the pandemic had begun. Moreover, German troops did not return home until November 1918, the British and Canadian troops did not demobilize until the winter of

1918/1919, and American troops were still returning to the U.S. in August of 1919 [19]. As such, the likelihood of the virus originating in Europe and spreading via troop demobilization is small.

A second origin theory is that the pandemic began in North America. The military was the first population in the U.S. to show signs of the disease, although this is likely due to an increased vigilance of influenza cases within the military after the Army Surgeon General had commissioned a committee tasked with the prevention of infectious diseases in army training camps [20]. An early outbreak of influenza in March 1918 at Camp Funston in Kansas was theorized as the origin of the pandemic., as more than one thousand men at the camp were hospitalized with influenza, with about 20 percent of cases developing pneumonia [20]. However, Camp Funston and overall the U.S. military, is generally not believed to be the source of the deadlier virus that would hit a few months later, as there had been more severe waves of influenza occurring in military camps across the country before the March 1918 outbreak. Moreover, the March outbreaks of influenza exhibited morbidity and mortality rates that were nowhere near those of the overall pandemic.

By way of example, the March outbreak exhibited hospital admission rates for respiratory diseases per 1,000 soldiers of 363.91 for white soldiers and 582.16 for African-American soldiers [19]. During the influenza pandemic in the fall of 1918, the Army saw peak admission rates per 1,000 soldiers at 1,978.15 for white soldiers and 1,548.95 for African-American soldiers during October [19]. The contrast between the severities of these influenza outbreaks suggests that Kansas, and North America overall, was not the origin of the pandemic.

The virus most likely originated in Asia, and specifically, China. There were multiple reports of outbreaks of a deadly respiratory disease in regions of China during the winter of

1917/1918. Like many early reports of the influenza pandemic, these outbreaks in China were reported as outbreaks of pneumonic plague. When the global pandemic began in the fall of 1918, it was much less devastating in China than what could have been expected for such a dense population. Compared to cities like New York and London, where the influenza mortality rates largely spiked, Hong Kong experienced relative immunity to the disease, suggesting that it had seen the virus earlier [19]. However, due to incomplete records, China cannot be confirmed as the origin of the pandemic.

2.4. PANDEMIC MORTALITY

Determining how and why mortality rates varied so greatly across the country has been the subject of extensive research. In 1900, the U.S. Department of Commerce Census Bureau began annual reports of mortality in a registration area [21]. This area consisted of states and cities that adopted recommended death certificates, which allows for accurate accounts of at least ninety percent of the deaths in the area [22]. In 1918, the registration area included 30 states, the District of Columbia, and 27 cities in non-registered states [21]. The accurate reporting of mortality within the area is a key component to understanding the geographic variance of mortality during the 1918 influenza pandemic.

2.4.1 PANDEMIC MORTALITY ACROSS U.S. STATES

Mortality due to the influenza pandemic varied globally, as well as among the individual states. One study compared the overall excess mortality during the pandemic years of 1918-1920 after adjusting for per-head income and latitude with the average mortality rates in 1915-17 and 1921-23 in 27 countries. In the study, the U.S. was further subdivided into the 24 states with complete registration data.

Overall, the U.S. had an adjusted excess mortality rate of 0.39 deaths per 100 people, with measureable differences between the states (Table 1) [23]. Wisconsin exhibited the lowest adjusted excess mortality rate at 0.25 deaths per 100 people, compared to Colorado which had the highest adjusted excess mortality rate at 1.00 deaths per 100 people [23].

Table 1: Estimated Excess Pandemic Mortality by U.S. State, Adjusted for per-head income and latitude [23]

Location	Estimate	95% Confidence Interval
Colorado	1.00%	(0.94, 1.05)
Connecticut	0.66%	(0.63, 0.69)
Indiana	0.34%	(0.31, 0.36)
Kansas	0.35%	(0.32, 0.38)
Kentucky	0.50%	(0.48, 0.52)
Maine	0.40%	(0.36, 0.45)
Maryland	0.72%	(0.69, 0.75)
Massachusetts	0.64%	(0.62, 0.66)
Michigan	0.26%	(0.24, 0.28)
Minnesota	0.40%	(0.37, 0.43)
Missouri	0.39%	(0.37, 0.41)
Montana	0.75%	(0.70, 0.79)
New Hampshire	0.64%	(0.59, 0.68)
New Jersey	0.63%	(0.61, 0.65)
New York	0.44%	(0.43, 0.44)
North Carolina	0.76%	(0.73, 0.79)
Ohio	0.36%	(0.35, 0.37)
Pennsylvania	0.81%	(0.80, 0.82)
Rhode Island	0.66%	(0.61, 0.70)
Utah	0.48%	(0.41, 0.55)
Vermont	0.60%	(0.53, 0.67)
Virginia	0.47%	(0.45, 0.50)
Washington	0.53%	(0.49, 0.57)
Wisconsin	0.25%	(0.23, 0.27)
United States	**0.39%**	**(0.39, 0.39)**

One study conducted to assess state to state variability looked at Kentucky death certificates between 1911 and 1919. A cyclical Serfling regression model was fitted to daily all-cause deaths to incorporate the seasonality of influenza outbreaks. The excess influenza-associated mortality rate was determined as the difference between the model-predicted mortality and the observed mortality. Between 1911 and 1919, a total of 310,363 deaths were reported in Kentucky, with about half of the death certificates listing primary and contributing

causes of death [24]. In 1918, 37 percent of death certificates listed respiratory causes on the death certificate, compared to 18 to 19 percent in previous years [24]. Overall, the 1918 pandemic caused approximately 13,027 excess deaths in Kentucky, or an excess mortality rate of 0.54 deaths per 100 people [24]. The uniquely detailed database of death certificates from Kentucky used in this study allowed researchers to gain an in-depth understanding of the occurrence of the influenza pandemic within the state, which may mimic what was occurring throughout the country.2.4.2 pandemic mortality across U.S. cities

2.4.2 PANDEMIC MORTALITY ACROSS U.S. CITIES

Mortality records maintained during the pandemic reported weekly deaths in major U.S. cities, including those due to influenza. In August of 1919, Raymond Pearl published one of the first studies of the 1918 pandemic in the U.S. While he acknowledged that the pandemic was likely not over (as there were milder waves of influenza that continued even into the early 1920s) there was a substantial amount of data available regarding the 1918 fall wave in major U.S. cities from the U.S. Census Bureau's Weekly Health Index records. Pearl studied all-cause mortality, acknowledging the assumption that "any deviation of the curves of total mortality from their normal course during the epidemic was due entirely to causes inherently associated with the epidemic itself" [25]. He found that the impact of the pandemic varied among U.S. cities, as shown in Figure 1. Philadelphia and Baltimore had the highest peak mortality rates at 158.3 and 148.3 mortalities per 1,000 residents, respectively [25]. The cities with the lowest peak mortalities were Grand Rapids at 31.6 and Minneapolis at 33.1 per 1,000 [25]. The Census

Bureau also published a report of the excess mortality among these cities during the 25-week period prior to March 1, 1919. Nashville had the highest excess mortality rate at 7.8 per 1,000, closely followed by San Francisco at 7.5 per 1,000 [25]. Grand Rapids had the lowest excess mortality rate at 1.5 per 1,000 [25]. Overall, the average 25-week excess mortality rate among these cities was 4.75 per 1,000 [25]. Pearl found that the mean date for a peak in mortality was October 23, 1918 [25]. Thirty-one of the 40 cities studied had peaked in their mortality before November 2, 1918 [25]. Most cities reached their peak mortality rates in their first wave of the pandemic, however Milwaukee, Kansas City, and St. Louis had a higher maximum mortality rate in their second wave [25]. Upon reaching peak mortality, it took an average of 8 weeks for these cities to return to their normal mortality rates [25].

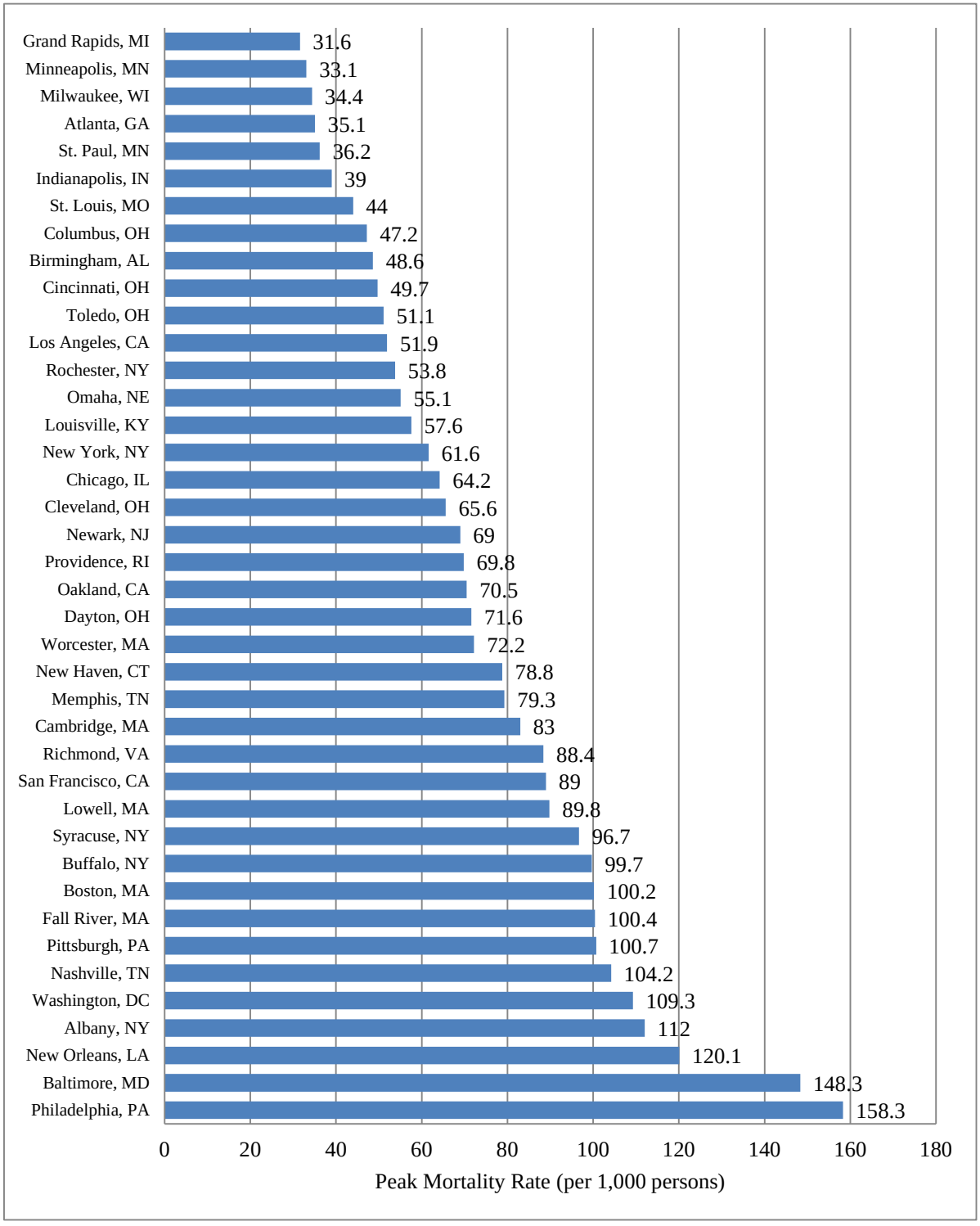

Figure 1: Peak Mortality Rates per 1,000 Persons across U.S. Cities [25]

A week after Pearl published his findings, W.H. Frost, an epidemiologist in charge of the U.S. Public Health Service's investigation of the 1918 pandemic, published his paper "The Epidemiology of Influenza." Frost acknowledged that the pandemic was first recognized in Boston in September. Within two weeks of the disease showing up in Boston, most of the major cities on the Atlantic coast had experienced epidemics [26]. Within four weeks of the epidemic in Boston it reached San Francisco, the longest interval between peaks in U.S. major city [26]. There were differences in the epidemics in different cities. While Philadelphia experienced a sharp, abrupt increase in mortality, New York City had a less explosive curve, with a high mortality rate which lasted longer [26]. In the Midwest, more gradual mortality curves were common [26]. Pearl and Frost were only the start of researchers who would use city data to examine the impact of the influenza pandemic.

Rodolfo Acuna-Soto, Cécile Viboud, and Gerardo Chowell examined mortality in cities in the years leading up to and during the pandemic, in an effort to determine how previous influenza mortality might the impact the 1918 pandemic. They used vital statistics from the U.S. Census Bureau for the 66 largest cities in the U.S., accounting for 25.4 percent of the population [27]. Their research showed that in the years leading up to the pandemic (1910 to 17), the average pneumonia mortality rate varied from 64 to 266 deaths per 100,000 in the cities [27]. During these years the influenza mortality rate ranged from 3 to 38 per 100,000 in the cities [27]. In 1918 the average influenza mortality rate increased between 10 and 129 times the pre-pandemic rates, while the pneumonia mortality rate only increased by 1.2 to 3.6 times [27]. They found that the average pneumonia mortality rates in the cities during the pre-pandemic years significantly correlated with the pneumonia mortality rates during the pandemic, as shown in Figure 2 [27]. In comparison, the average influenza mortality rates during the pre-pandemic

years were only weakly correlated with the rates during the pandemic, as shown in Figure 3 [27]. They also found a significant correlation between influenza and pneumonia mortality rates, which supports the long known interaction between the influenza virus and bacterial pneumonia during the 1918 pandemic [27].

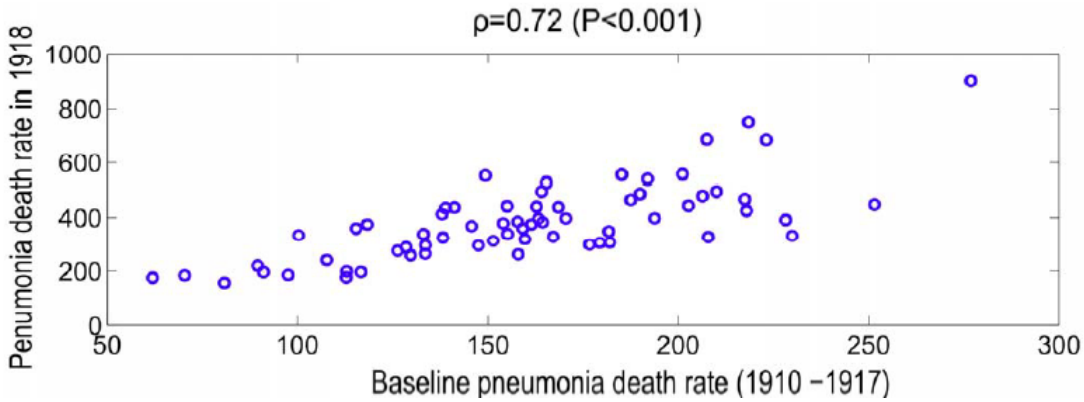

Figure 2: Correlation between Baseline and Pandemic Pneumonia Mortality Rates [27]

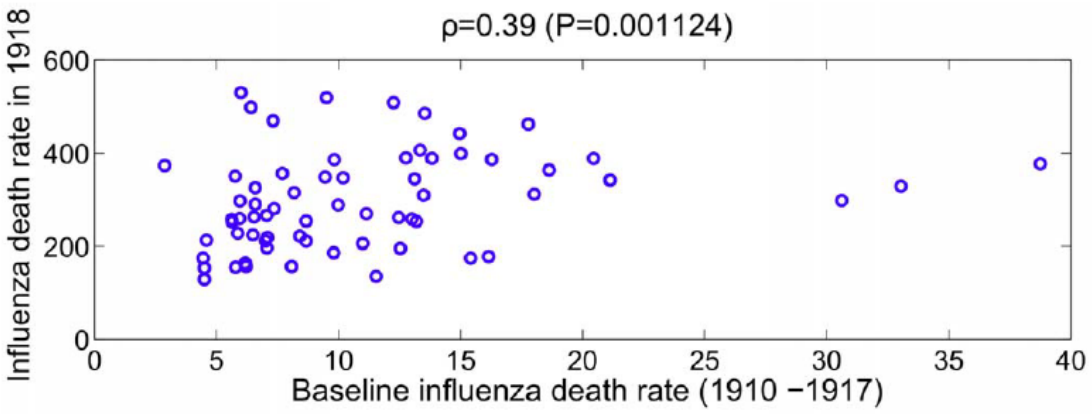

Figure 3: Correlations between Baseline and Pandemic Influenza Mortality Rates [27]

In his book Epidemic Influenza: A Survey, bacteriologist Edwin Jordan particularly noted the difficulty in determining a case-fatality rate for the pandemic due to the lack of reporting of influenza cases. Studies that did examine case-fatality rates relied on house-to-house surveys. In Oswego, NY the case-fatality rate among 12,952 surveyed persons was found to be 2.4 percent, and among 20,473 persons in Watertown, NY it was found to be 3.1 percent [28]. A house study in Boston of 10,050 persons found a case-fatality rate of 2.47 percent, and one in New Britain, CT, of 2,757 persons, found a rate of 3.9 percent [28]. Other studies had been conducted in the military; however the case-fatality rates were believed to be higher than the reported rates due to a lack of reporting milder cases [28]. The case-fatality rate due to influenza and pneumonia among American Expeditionary Forces was 6.06 percent based on 220,971 reported cases between July 1, 1917 and April 19, 1919 [28]. The U.S. Navy in the New York region reported a case-fatality rate of 4.35 percent, and in the Washington region it was 1.46 percent during the same time period [28]. The differences in military case-fatality rates could have been due to a number of factors, including crowding of training camps, availability of medical personnel, and control measures put into place on military bases.

Following the fall and winter peaks in influenza and pneumonia deaths, the U.S. Public Health Service conducted house-to-house surveys of 146,203 persons in 35 cities to determine patterns in mortality. In each city, ten to twenty districts were surveyed to represent the city [29]. The age, sex, and race of every member of each household were recorded, in addition to their experience during the pandemic. Experience was grouped into three categories: influenza, pneumonia, and “doubtful” [29]. The number of “doubtful” cases was so small that it was determined to not have any influence on the study. The overall combined rate of influenza, pneumonia and “doubtful” cases in the surveyed regions was 294 per 1,000 persons [29]. The

incidence rates per 1,000 persons were 17.6 for pneumonia, 239 for influenza, and 21.5 for "doubtful" [29]. The mortality rate per 1,000 in the canvassed area from September to December was 4.99, compared to a rate of 5.04 reported in 35 registered large cities [29]. The survey showed that the case-fatality rates varied greatly between locations from 0.78 percent in San Antonio to 3.14 percent in New London [29]. One of the main objectives of research regarding the 1918 pandemic is determining the cause of geographic differentials in mortality, which may have been influenced by several different potential factors.

2.5 PREDICTORS OF 1918 PANDEMIC MORTALITY

Mortality in the U.S. during the 1918 influenza pandemic varied across states and cities. For example, Pennsylvania experienced over twice the estimated excess mortality of its neighbor, Ohio [23]. Also, western states were less affected than those in the eastern U.S. Potential explanations for these differences include preparedness (*e.g.,* western cities had more time to implement prevention measures before the pandemic arrived) or diminishing virulence as the virus spread westward, with western cities not experiencing the same strain. However, geographic location alone is not sufficient to explain the differences in mortality; other factors, discussed below, contributed to the observed variation.

2.5.1 AGE

Shifts in age distribution may have played a role in the impact of the pandemic in the U.S. In 1900, half of the U.S. population was younger than 22.9 years old [30]. About 12 percent was under 5 years old [30]. This pattern continued through the 1920s, until decreasing fertility rates during the Great Depression led to shifts in the age distribution. The 65 years or older population was the smallest age group at the beginning of the century, at about 4.1 percent [30]. Overall, the South was the youngest region of the country due to its high fertility rate [30]. The Northeast and the Midwest were closely tied for the oldest region of the country. The Northeast had the highest proportion of its population being 65 years or older in 1900, but was overcome by the Midwest from 1910 to 1940 [30]. These differences in age distribution between states may provide insight into why some states or regions experienced higher mortality during the pandemic.

The age distribution of mortalities during the 1918 pandemic distinguishes it from most other influenza pandemics. Typically influenza has a U-shaped curve for mortality, with most deaths occurring in the young and the elderly, whereas the 1918 influenza was characterized by a W-shaped mortality curve, as shown in Figure 4. The influenza and pneumonia mortality rates for 15 to 34 year olds was nearly 20 times what it had been during seasonal influenzas in years prior to 1918 [15]. Approximately 99 percent of the excess mortality during the pandemic was in the portion of the population under 65 years old [15]. This shift in the mortality age curve resulted in a temporary 11.8 year reduction in life expectancy for both males and females [31]. However, after the pandemic, the male life expectancy recovered sooner than the female life expectancy [31].

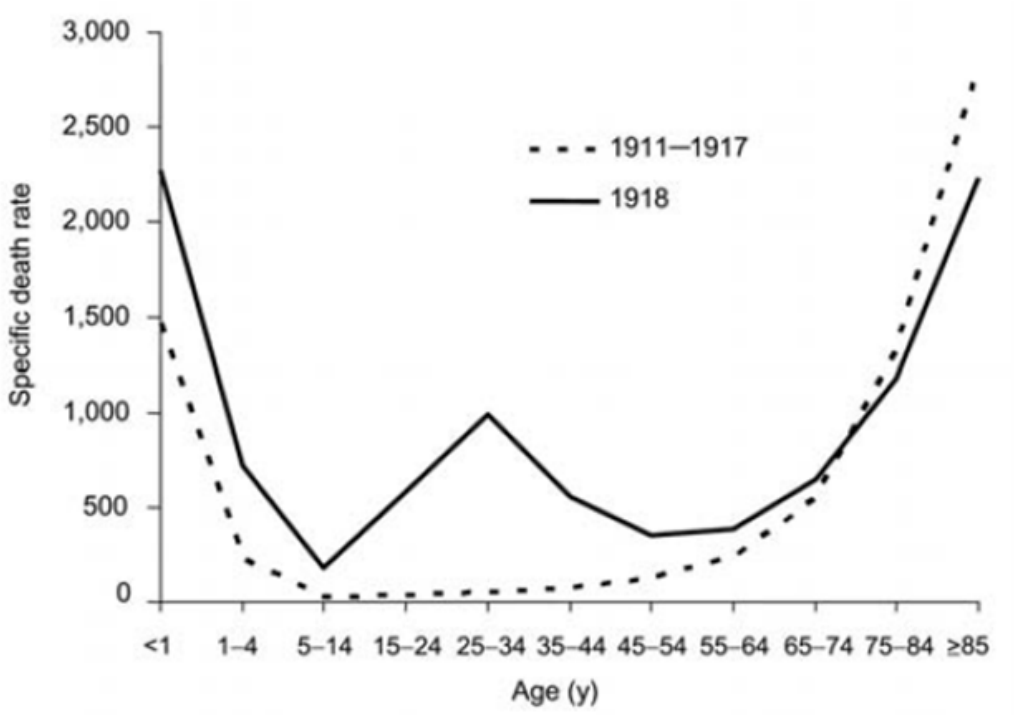

Figure 4: Mortality per 100,000, by Age, in the U.S. in Pre-Pandemic Years (1911-1917) and in 1918 [16]

The effects of the 1918 pandemic in Kentucky were further broken down when the population was split into age categories. Overall, infants under one year old experienced the highest influenza-associated excess mortality [24]. The common W-shaped mortality curve showed three distinct breakpoints in Kentucky. There was a minimum of 15 deaths per 10,000 at 9.7 years of age, a maximum of 80 deaths per 10,000 at 25.6 years of age, and another minimum of 7 deaths per 10,000 at 57.8 years of age [24]. The pattern of mortality with age in Kentucky during the pandemic reflects similar patterns seen globally.

There are many hypotheses regarding the abnormal age distribution of influenza-related deaths that occurred during the 1918 influenza pandemic. One explanation is that the proportion

of deaths that occurred in the 65 years and older group was due to previous immunity bestowed upon them from a prior strain of influenza. The ability to investigate this hypothesis is difficult due to the lack of genetic knowledge of previous influenza outbreaks. Another hypothesis for explaining the age-specific mortality is the immune response generated in young, healthy individuals in comparison to the elderly or others with weaker immune systems. This hypothesis suggests that the immune systems of healthy individuals reacted to the 1918 virus with such a strong response that it caused severely damaging inflammation, which could have put these individuals at a higher risk of dying [32]. Whatever the explanation, age played an important role in determining mortality during the 1918 influenza pandemic.

2.5.2 GENDER

The gender distribution changed greatly in the first half of the century. In 1910, the U.S. was a predominately male population with approximately 2.7 million more males than females [30]. This was mainly due to a higher proportion of male immigrants entering the U.S., and the tendency for younger populations to be more male as compared to older populations [30]. By 1950, the sex ratio had shifted to females outnumbering males by about 1.0 million [30]. The West was the most predominately male region in the country in 1900 and 1910 due to the Western expansion being driven by male-dominated industries [30]. The lowest sex ratio was in the Northeast throughout the entire 20th century [30].

The case-fatality rates during the 1918 pandemic among men and women varied in age distribution. The male case-fatality rate was lower than the female rate at ages below 15 and

above 60 [28]. The female case-fatality rate was lower than the male rate for the ages between 15 and 60 [28]. The greatest difference between male and female case-fatality rates was between the ages of 20 and 40 [28]. Overall the peak in young adults was higher in males than females, yet both groups had a significant peak, which suggests that whatever factor caused the peak in males was also affecting females [29]. In Kentucky males aged 15 to 50 were found to have excess mortality rates 20 to 80 percent higher compared to females in the same age category [24].

2.5.3 MILITARY PANDEMIC MORTALITY

World War I was another factor that influenced mortality during the pandemic. When President Woodrow Wilson's declared war against Germany on April 6, 1917, there were about 126,000 men serving in the Army [33]. With a substantial increase needed to win the war, three drafts were conducted, resulting in mobilizing over 4 million American troops [34]. This mass entry of young American men into the military resulted in the overcrowding of under-prepared training camps in the U.S. These camps experienced outbreaks of measles, influenza, pneumonia, and other communicable diseases. Throughout the war there would be nearly 330,000 American casualties, with about 117,000 deaths [34]. While overall, World War I was the first war with more deaths due to battle than disease, the later months of the war had more infectious disease deaths than on the battlefield (*i.e.,* during the 1918 pandemic) [35]. Overall, about half of the deaths of American troops during the war would be attributed to accidents and diseases [34].

One of the unique aspects of the aforementioned Kentucky study was that it examined every individual death certificate. Military death reports commonly present a problem due to the tendency for members of the military to be moved to other regions of the country. The question for mortality reporting then becomes which state is listed in the vital statistics, which varies from the state they were originally from, the state they were trained in, the state they died in, etc. Death certificates give researchers access to more specific data than what is listed in vital statistic reports. This study found that approximately 30 percent of soldiers who died in Kentucky were residents of another state, which could have altered the mortality rate reported for young men in Kentucky [24]. When the non-resident deaths are removed, the mortality rate for young men in Kentucky is lowered and the age breakpoint then shifts from 26 years to 32 years of age [24]. However, this adjusted mortality rate could be an underestimate in Kentucky because it also excludes Kentucky residents who were training out-of-state or involved in combat [24]. Between October and December of 1918, military deaths accounted for 31.8 percent of the respiratory-related deaths in Kentucky among men aged 18 to 35 years [24]. Due to the influence of the military, the study considered mortality among women to be the most accurate representation of excess mortality by age in Kentucky. Since women also had a large peak in mortality in the 24 to 26 age category and were not drafted into the military, it is likely that other factors were contributing to the peak in young adult mortality.

Another military population that was largely affected by the pandemic was the nurses and physicians. In November 1918 there were about 21,000 nurses and 31,000 medical officers in the U.S. military, either stateside or overseas [36]. During the pandemic from September 1918 to February 1919, nurses in the military had a crude mortality rate of 1.05 percent, which was nine times higher as compared to their equivalents in the British Army [36]. Moreover,

nurses serving in the U.S. had a mortality rate twice as high as those serving overseas [36]. U.S. Army medical officers had a mortality rate of 0.68 percent during the pandemic, with the states-assigned proportion having a rate twice as high as physicians in the U.S. in general [36]. Overall, the military nurses had mortality rates approximately 40 percent higher than the rates among medical officers [36]. The difference between these mortality rates was attributed to two likely causes, varied exposure to secondary bacterial infections and varied immunity once exposed [36]. The overcrowding of U.S. training camps likely explains why members of the military stationed stateside had mortality rates much higher than those stationed in Europe. This difference was the most extreme among soldiers, with pneumonia and influenza mortality rates being four times greater among those stationed in the U.S. compared to those stationed in Europe [36].

2.5.4 POPULATION DENSITY

Pandemic spread depends significantly on the proximity of infected persons to susceptible individuals, which can be illustrated by population density. In 1900, Rhode Island was the most densely populated state in the U.S., with a population density of 401.6 people per square mile [30]. Conversely, 14 states had population densities of fewer than 10, including Florida and California [30]. Among cities, New York, the most densely populated throughout the 20th [30]. This close-proximity of people enabled the pandemic to rapidly disseminate through populations.

Economist Thomas Garrett found that state population density in 1910 was significantly correlated with influenza mortality rates (correlation coefficient = 0.447) [37]. However, the influenza mortality rates in 1915 had a stronger correlation to population density compared to the 1918 rates (correlation coefficient = 0.632) [37]. This suggests that state population density had less influence during the 1918 pandemic compared to non-pandemic years [37].

2.5.5 URBAN VERSUS RURAL

In the early part of the 20th century, population shift from rural (*i.e.,* farming) to urban (*i.e.,* industrial jobs) living was underway. Overall, about 12.5 percent of the U.S. population was living in the 10 largest cities in 1900 [30]. This proportion grew to 15.5 percent by 1930 [30], The Northeast had the highest proportion of people living in cities compared to any other region in the U.S. for the entirety of the twentieth century [30]. In 1910, over half of the Northeast's population was living in metropolitan areas, compared to a quarter of the Midwest and the West, and about a tenth of the South [30]. In 1910, only five states, Massachusetts, Maryland, New Jersey, New York and Rhode Island, had a majority of their population living in cities [30]. Forty years later this number had tripled to 15 states [30]. In 1910, thirty-three states had less than a quarter of their population living in cities [30]. For the most part, the pattern of urbanization among the states was consistent throughout the twentieth century. California, Connecticut, Maryland, Massachusetts, New Jersey, New York, and Rhode Island were consistently among the states with the highest percentage its population living in urban areas

[30]. Idaho, North Dakota, South Dakota, Vermont, and Wyoming were consistently among the states with the lowest percentage of their population living in urban areas [30].

A difference in mortality may be observed between rural and urban areas of the U.S. In Indiana and Kansas the mortality rates for pneumonia and influenza were higher in cities than in rural areas [28]. From September to December 1918, the mortality rates for all ages per 100,000 in Indiana cities was 1,143.6 for females and 1,066.6 for males, as compared to rural regions, where the rates were 776.6 for females and 749.9 for males [28]. In Kansas the mortality rates were similar, 1,167.2 for females and 1,223.0 for males in cities, and 741.4 for females and 799.7 for males in rural areas [28]. Interestingly, prior to the pandemic, influenza mortality rates in Kansas and Indiana were higher in rural regions than in urban areas. Jordan noted this reversal, stating that regions previously affected by influenza outbreaks (in this case rural regions of Kansas and Indiana), would be less severely affected by the pandemic due to bestowed immunities. Connecticut also experienced a higher mortality in cities compared to smaller communities [28].

2.5.6 POPULATION GROWTH

Raymond Pearl suspected that population growth between 1900 and 1910 could have impacted the severity of the pandemic in major U.S. cities. In 1900 there were 76 million people living in the U.S., with about a quarter of the population living in cities [30]. The largest percent increase (at 21%) in the population in the 20th century occurred from 1900 to 1910, mainly due to high birth and immigration rates [30]. Nearly half of the states had fewer than 1 million residents in

1900, and New York and Pennsylvania were the only states with populations of at least 5 million [30]. Overall, California saw the greatest increase in population throughout the 20th century, accounting for one-sixth of the total population growth in the country [30].

Pearl found that the correlation coefficient between the epidemic severity in 1918 and population growth from 1900 to 1910 was -0.327±0.096, demonstrating that cities that had large population growth were hit less by the pandemic in comparison to cities with little growth [25]. This indicates that established older cities with large populations that experienced little growth were hit harder by the pandemic compared to younger, smaller cities that had experienced more growth [25].

Acuna-Soto, et al. found that influenza mortality counts were associated with population size, indicating that smaller cities experienced higher influenza mortality rates [27]. This finding supports Pearl's early conclusions, that large, established cities were less impacted by the pandemic compared to smaller cities. The mortality differences between large cities and small cities could be attributed to differences in medical care, socio-economic status, and previous baseline levels of disease in the cities [27].

2.5.7 ECONOMIC CONDITIONS AND RACE

There was an observed relationship between economic conditions and pandemic mortality rates. One study found that when the population was divided into four income groups, the case-fatality rate was almost twice as high in the lowest income group compared to the highest income group [38]. The Metropolitan Life Insurance Company reported that of their three main

classes of clients during the 1918 pandemic, industrial (*e.g.*, low-income) policy-holders had the highest mortality rate, as compared to the intermediate and ordinary policy-holders [28]. However, the difference among these classes of policy-holders was likely due to the race-based insurance practices common in many states [39]. These practices greatly disadvantaged black Americans who, if offered, paid higher rates than whites and represented a large percent of industrial policy-holders [39]. The racial breakdown of mortality statistics during the 1918 pandemic are not as detailed as modern statistics, however during the pandemic, mortality rates were reported to be higher in non-whites compared to whites [37]. Of the cities for which a racial breakdown of influenza mortality was available, non-whites had mortality rates as high as twice those of whites [37]. The difference between white and non-white mortality rates likely resulted from differences in the availability of healthcare and a disproportionate amount of non-whites living in densely-populated urban areas [37].

2.6 LIMITATIONS OF HISTORICAL DATA

Many complications hinder the accuracy of studies trying to calculate the impact of the 1918 influenza. There were regions of the world, especially in Africa and Asia, which did not maintain death records. In the U.S. in 1918 there were only thirty registration states that reported deaths of influenza and pneumonia. The reliability of these records has also been questioned due to the ability of physicians in 1918 to correctly assess and/or report the cause of death. While the International Classification of Diseases existed in 1918, it was not widely used, resulting in a poor standardization of records, especially at the beginning of the pandemic, when

influenza was not a reportable disease [28]. The pandemic left people vulnerable to bacterial infections, leading to a high mortality due to bacterial pneumonia. This led to an increase in the mortality due to both influenza and pneumonia, but infected people also died of related renal failure, liver failure, hemorrhaging, and other complications [20]. Nearly fifty percent of total excess mortality during influenza epidemics has been attributed in death records to causes other than pneumonia and influenza, particularly cardiovascular diseases [40]. The complications from the influenza have led many researchers to use the all-cause mortality records instead of the influenza and pneumonia records. While using influenza and pneumonia records may lead to an underestimation of the mortality rate during the pandemic, the all-cause records could lead to an overestimation of the mortality rate. Perhaps a benefit of the sheer magnitude of the pandemic is that the use of either of these records will clearly show the deviation from the normal that occurred in 1918.

The main challenge with the U.S. Census Bureau's vital statistics was differential mortality reporting. Registration of areas was much more developed in urban, as compared to rural regions of the country, due largely on the regional laws regarding use of death certificates. Acuna-Soto, et al. made the assumption that the reporting and coding of deaths was homogenous across all regions of the study. They also discussed the use of annual, as compared to weekly or monthly, data to calculate excess mortality. Despite the decreased accuracy when using annual data, they found that their results were similar to estimates for cities where weekly data was available, such as New York City.

3.0 SUMMARY

Influenza has been responsible for epidemics and pandemics throughout history. However, prior to the 1918 pandemic, influenza mortality was limited to historical literature and personal accounts. The availability of vital statistics from the U.S. Census Bureau provided the foundation for a quantitative evaluation of the 1918 pandemic.

During the pandemic there was an overall per-head income and latitude-adjusted excess mortality rate of 0.39 deaths per 100 people in the U.S., however adjusted excess mortality rates varied greatly by state, ranging from 1.00 per 100 in Colorado to 0.25 per 100 in Wisconsin [23]. Moreover, unique to the 1918 pandemic, and in contrast with prior outbreaks that mostly affected the young and the elderly, was a W-shaped mortality curve, with high mortality rates in the 20 to 40 year old cohort.

Factors suspected to have affected mortality in the 1918 pandemic include the presence of large military populations living in close proximity as a result of World War I, an overall increase in population density and growth within crowded urban areas, economic class, and sex. Consensus has yet to be reached on how these and perhaps other factors affected mortality from the pandemic.

Thus, there is variation in mortality by state, as well as by age and sex. Presumably, the factors affecting overall mortality did not have equal influence on state- and age-specific mortality distributions during all years of the pandemic. For instance, while population density has been found to be correlated with state mortality, this effect has not yet been shown to be

consistent among all age groups and sexes. If there were differences in the effects of these factors by age group or sex across the states, it could explain why some states were more severely affected by the pandemic than others. Due to the remaining presence of descendants of the 1918 influenza strain and the remaining burden of influenza on the U.S. population, factors that explain mortality variety during the pandemic may affect the public health approach that is taken to future outbreaks of influenza.

4.0 SPECIFIC AIMS

There is a lack of literature regarding differential excess mortality by age and sex for each state during the 1918 pandemic. In addition, factors that could be influential in the varying mortality have not been investigated regarding differences by age group, sex and state. Due to these gaps in knowledge, the following specific aims will be addressed:

4.1 SPECIFIC AIM 1

1. Describe the overall all-cause excess mortality rates in 1918, 1919, and 1920 as well as the cumulative excess mortality rates in the U.S. during the 1918 influenza pandemic.
2. Describe all-cause excess mortality rates by age (under 5, 5 to 9, 10 to 49, and 50 and older) and by sex in 1918, 1919, and 1920 as well as the cumulative pandemic period.
3. Compare state-specific all-cause excess mortality rates with the average in the study population for both annual total excess mortality rates and sex- and age-specific excess mortality rates.

4.2 SPECIFIC AIM 2

Determine the correlation of total all-cause excess mortality, sex-specific cumulative excess mortality and age-specific cumulative excess mortality with the following variables:

Population Density

Male to Female Population Ratio

Percent of the Population Living in Urban Areas

Percent of the Population Enlisted in the Military

Percent Mortality among Military Personnel due to Influenza and Pneumonia

5.0 METHODS

To address each of the specific aims, mortality reports and decennial census data were used to examine excess mortality and potential predictors of mortality.

Vital statistic data provided by the U.S. Department of Commerce Census Bureau were used only for states that were registered by 1915. States that had not adopted mortality registration laws to standardize reports, and were therefore not part of the U.S. registration area, were not included in this study. This also excluded territories that had not joined the union, which included New Mexico, Arizona, Hawaii and Alaska. After exclusion of these states, the following 24 states were included in the study:

California	Massachusetts	Ohio
Colorado	Michigan	Pennsylvania
Connecticut	Minnesota	Rhode Island
Indiana	Missouri	Utah
Kansas	Montana	Vermont
Kentucky	New Hampshire	Virginia
Maine	New Jersey	Washington
Maryland	New York	Wisconsin

Mortality rates were estimated using mortality count data from the annual vital statistics reports and state populations from the decennial censuses in 1910, 1920 and 1930. The intercensal state populations were estimated assuming a linear trend between the decennial censuses following the procedure of the U.S. Department of Commerce methods in 1920 [41]. In addition to the overall mortality rate, mortality rates were estimated for four age groups: less than 5 years, 5 to 9 years, 10 to 49 years, and 50 years and older.

5.1 SPECIFIC AIM 1 METHODS

To address Specific Aim 1, excess mortality by age and sex for each state was estimated using the average mortality rate for the period surrounding the pandemic: 1915-17 and 1921-23 as a baseline mortality rate [23]. The total excess mortality during the pandemic period was the difference between the average mortality rates in 1915-17 and 1921-23, and the mortality rate during each year of the pandemic (1918, 1919, and 1920), and was reported as per 100,000 people. This method was repeated for the mortality rates of both sexes and each age group (0-5, 5-9, 10-49, >50). The cumulative excess mortality rate was calculated as the sum of the total excess mortality rates during each pandemic year and was reported per 100,000 person-years (p-y).The method of using 1915-17 and 1921-23 as the baseline mortality rates is effective because it captures any deaths due to the pandemic that occurred in years after the peak pandemic incidence in 1918 [23].

5.2 SPECIFIC AIM 2 METHODS

In order to address Specific Aim 2, the correlation between total excess mortality and cumulative age- and sex-specific excess mortality, and the predictors of interest (population density, male to female ratio, percent of the population in urban areas, military enlistment, and military mortality) were explored.

All excess mortality estimates were hypothesized to be higher in states with greater population densities. Data on population density was provided in the 1910 census and the 1920

census [42, 43]. The average population density for each state during the pandemic was estimated assuming a linear trend between 1910 and 1920.

All estimates of excess mortality were hypothesized to be higher in states with high male to female ratios were hypothesized to have higher excess mortality rates compared to states with lower ratios. The male to female ratio by age group for each state was estimated using male population size and overall population size provided in the 1910 and 1920 census [42, 43]. The average ratio during the pandemic years was estimated assuming a linear trend in the ratio over the decade.

Excess mortality was hypothesized to be higher in states with a greater percent of the population living in urban areas. Data regarding percent of the population living in urban areas was provided in the 1910 and 1920 censuses [42, 43]. Urban areas were classified as "all incorporated places (and all towns in Massachusetts, Rhode Island, and New Hampshire) having 2,500 inhabitants or more" with the remainder of the country being considered rural [42]. An assumed linear trend was used to estimate the average percent of the population living in urban areas during the pandemic years.

States with higher military enlistment were hypothesized to have higher excess mortality rates compared to states with lower military enlistment. This relationship was examined using two different estimates of the percent military enlistment by state. The first estimate used the number of soldiers coming from each state reported in an annual report of the Secretary of War in 1918 summarized in the 1918 Statistical Abstract [44]. The second estimate used the enlistments and inductions into the armed forces between April 2, 1917 and October 31, 1918 under the first and second drafts which were provided in a report of the Provost Marshal General to the Secretary of War summarized in the Statistical Abstract of 1918 [44]. Each of these

enlistment numbers were used with the estimated total state population to determine what percent of the population enlisted in the military during World War I.

States that had higher proportion of military deaths due to influenza and pneumonia were hypothesized to have higher excess mortality rates compared to states with lower military deaths due to influenza and pneumonia. Data regarding military death in 1917 (after April 6), 1918 and 1919 was obtained from the vital statistics reports in 1917, 1918 and 1919 provided by the U.S. Census Bureau Department of Commerce [45-47]. The pneumonia and influenza specific mortality and the overall mortality among military personnel for each state were used to estimate the average proportion of military deaths during the pandemic in each state that was due to influenza and pneumonia.

The relationship between annual total excess mortality and each of the variables of interest was explored using Spearman Correlation coefficients. The correlations between these variables and sex- and age-specific excess mortality were also determined for both the cumulative excess mortality and the total excess mortality in 1918.

6.0 RESULTS

6.1 CUMULATIVE ALL-CAUSE EXCESS MORTALITY

The cumulative excess mortality occurring in the study population for the pandemic period from 1918 to 1920 varied across the states. On average, the cumulative excess mortality rate in the study population was 528.51 deaths per 100,000 person-years (p-y). The highest cumulative excess mortality rate occurred in Colorado, at 968.29 deaths per 100,000 p-y. The lowest cumulative rate occurred in Maine at 162.37 deaths per 100,000 p-y.

6.2 CUMULATIVE ALL-CAUSE EXCESS MORTALITY BY AGE

The variation in cumulative excess mortality for 1918 to 1920 across the states by age group is shown in Table 2. The highest cumulative excess mortality rate during the pandemic period occurred among person 5 to 9 years old, at an average rate of 1,417.3 deaths per 100,000 p-y. This age group also showed the greatest range of excess mortality rates, with an overall difference of 2,397.06 deaths per 100,000 p-y between the highest rate (2,557.41 deaths per 100,000 person-years in Colorado) and the lowest rate (160.4 deaths per 100,000 p-y in Kansas). The cumulative excess mortality rates among people under 5 years old and between 10 and 49 years old were fairly similar, at 771.8 and 710.7 deaths per 100,000 p-y, respectively. The group of 50 years and older had the lowest average cumulative excess mortality rate, at -179.9 deaths per 100,000 p-y. This pattern of cumulative excess mortality by age occurred in many of the

states of interest; however some states, such as Virginia and Kansas had cumulative excess mortality rates dissimilar to the averages.

Table 2: Cumulative Age-Specific All-Cause Excess Mortality for 1918 to 1920 (per 100,000 person-years)

State	0-5	5-9	10-49	50+
Maryland, MD	1823.32	2113.9	901.2	-292.23
Pennsylvania, PA	1176.24	1913.56	1043.54	-84.67
Rhode Island, RI	1151.38	1838.75	1221.4	-624.35
Massachusetts, MA	1133.43	1547.31	833.3	-200.56
Connecticut, CT	1059.38	1740.97	915.85	-439.14
New Jersey, NJ	1013.58	1674.58	835.85	-163.69
Kentucky, KY	1003.69	382.69	632.55	-31.06
Michigan, MI	942.88	1178.83	501.7	-81.2
Colorado, CO	898.6	2557.41	1309.41	112.12
Virginia, VA	885.74	266.05	718.52	1618.81
Indiana, IN	759.97	1316.2	564.68	-255.4
Washington, WA	739.95	1427.3	452.56	112.39
Ohio, OH	703.91	1445.49	647.42	-315.38
Vermont, VT	683.95	1546.94	803.99	-575.76
New York, NY	659.74	1569.96	669.99	-292.01
Missouri, MO	606.55	288.28	-525.68	-155.89
Kansas, KS	592.75	160.35	497.91	-271.75
Maine, ME	468.28	1477.16	351.38	-463.6
Wisconsin, WI	449.43	1141.05	510.83	-505.47
Montana, MT	445.37	1961.94	978.27	-468.36
California, CA	408.55	1798.42	772.17	-141.77
Minnesota, MN	407.01	1289.57	606.02	-142.22
Utah, UT	342.11	1620.85	889.41	-405.83
New Hampshire, NH	167.08	1757.88	924.83	-250.48
Average	**771.79**	**1417.31**	**710.71**	**-179.9**

6.3 CUMULATIVE ALL-CAUSE EXCESS MORTALITY BY SEX

The cumulative excess mortality by state for males and females is shown in Table 3. The average cumulative excess mortality rate among males was 527.90 deaths per 100,000 p-y, which was much lower than the cumulative female excess mortality rate, at 612.29 deaths per 100,000p-y. Colorado had both the highest male and female cumulative excess mortality rates of the study population, at 1,012.69 and 975.66 deaths per 100,000 p-y. Wisconsin had the lowest male cumulative excess mortality rate at 266.88 deaths per 100,000 p-y. Vermont had the lowest female cumulative excess mortality rate, at 364.8 deaths per 100,000 p-y. The male and female cumulative excess mortality rates were more similar in New Hampshire, with a difference of only 8.74 deaths per 100,000 p-y. The rates were most dissimilar in Michigan, with a difference of 330.59 deaths per 100,000 p-y. There were only six states (CO, PA, MT, NH, RI and VA) where the cumulative rate among males was higher than the cumulative rate among females. On average, the female rate was 84.39 deaths per 100,000 p-y higher than the male rate.

Table 3: Cumulative Sex-Specific All-Cause Excess Mortality for 1918 to 1920

(per 100,000 person-years)

	Male	Female
Colorado, CO	1012.69	975.66
Pennsylvania, PA	871.81	796.83
Maryland, MD	709.13	863.93
Montana, MT	666.13	619.49
New Jersey, NJ	649.61	764.58
Connecticut, CT	635.11	734.00
Massachusetts, MA	616.91	691.69
Washington, WA	614.56	665.30
California, CA	590.41	662.33
Utah, UT	574.05	594.86
Kentucky, KY	562.95	610.50
New Hampshire, NH	552.74	544.00
Rhode Island, RI	534.09	693.91
Virginia, VA	519.94	488.34
Vermont, VT	475.86	364.86
New York, NY	445.91	610.88
Ohio, OH	444.60	512.21
Minnesota, MN	359.72	534.53
Kansas, KS	348.04	451.54
Michigan, MI	337.65	668.24
Indiana, IN	306.59	521.77
Maine, ME	295.09	454.76
Missouri, MO	279.10	481.22
Wisconsin, WI	266.88	389.58
Average	**527.90**	**612.29**

6.4 ANNUAL TOTAL ALL-CAUSE EXCESS MORTALITY

The total excess mortality varied quite a bit by year, as seen in Table 4. In 1918, the average excess mortality rate was 489.78 deaths per 100,000 people. The highest rate occurred in Pennsylvania, at 831.24 deaths per 100,000. The lowest rate was 258.94 deaths per 100,000 in Washington. In 1919 the average excess mortality rate was 2.26 deaths per 100,000. The highest rate occurred in Kentucky, at 80.49 deaths per 100,000, and the lowest rate occurred in New Hampshire, at -75.73 deaths per 100,000. In 1920 the average excess mortality rate was 36.47 deaths per 100,000. The highest rate was in Colorado, at 220.26 deaths per 100,000, while the lowest rate occurred in Maine, at -37.80 deaths per 100,000. Every state demonstrated the pattern of decreasing excess mortality between 1918 and 1919, and increasing excess mortality between 1919 and 1920. The average decrease between 1918 and 1919 was 310.86 deaths per 100,000. The greatest decrease occurred in Pennsylvania, decreasing by 864.76 deaths per 100,000. Washington had the lowest decrease between 1918 and 1919, at 205.38 deaths per 100,000. The average increase from 1919 to 1920 was 79.30 deaths per 100,000. The greatest increase was in Rhode Island, at 178.03 deaths per 100,000. The greatest decrease between 1919 and 1920 occurred in Kentucky, decreasing by 96.50 deaths per 100,000. Only six states (CA, KY, MD, NJ, NY and VA) had excess mortality rates that continually decreased.

Table 4: Annual Total All-Cause Excess Mortality by Pandemic Year

(per 100,000 people)

State	**1918**	**1919**	**1920**
Pennsylvania, PA	831.24	-33.52	8.89
Maryland, MD	757.68	27.71	-33.61
Montana, MT	694.79	36.23	-88.59
Colorado, CO	685.37	62.66	220.26
New Jersey, NJ	680.64	-7.96	-21.25
Connecticut, CT	677	-28.12	-4.95
Rhode Island, RI	663.24	-7.84	170.19
Massachusetts, MA	660.52	-26.21	-7.88
New Hampshire, NH	627.29	-75.73	-20.76
New York, NY	487.46	-1.2	-3.58
Virginia, VA	485.81	33.74	-19.23
Kentucky, KY	455.19	80.49	-16.01
California, CA	425.76	56.95	47.07
Vermont, VT	418.89	-66.17	63.24
Ohio, OH	395.65	18.4	25.63
Utah, UT	379.03	69.13	114.19
Missouri, MO	360.42	-35.85	36.63
Minnesota, MN	322.26	41.71	61.68
Indiana, IN	319.97	0.96	71.03
Maine, ME	316.94	-116.76	-37.8
Kansas, KS	308.12	-33.81	24.97
Wisconsin, WI	272.43	-9.39	39.59
Michigan, MI	270.15	15.26	150.52
Washington, WA	258.94	53.57	95.07
Average	**489.78**	**2.26**	**36.47**

6.5 TOTAL ALL-CAUSE EXCESS MORTALITY BY AGE

The age-specific excess mortality rates changed annually, as shown in Figure 5. Compared to the cumulative excess mortality rate, the total excess mortality in 1918 was highest in the under 5 population, at an average rate of 806.70 deaths per 100,000. The lowest average excess mortality rate in 1918 was among persons 50 years of age and older, at 120.8 excess deaths per 100,000 people.

The age group with the highest average excess mortality rate in 1919 was the group of 5 to 9 years of age, at 321.2 deaths per 100,000 people. The lowest rate was among people 50 years or older, at -240.6 deaths per 100,000 people.

The excess mortality rates in 1920 demonstrated age patterns similar to that of 1919. The highest rate was once again among 5 to 9 year olds (301.8 deaths per 100,000 people) and the lowest rate was among those 50 year or older (-60.0 deaths per 100,000 people).

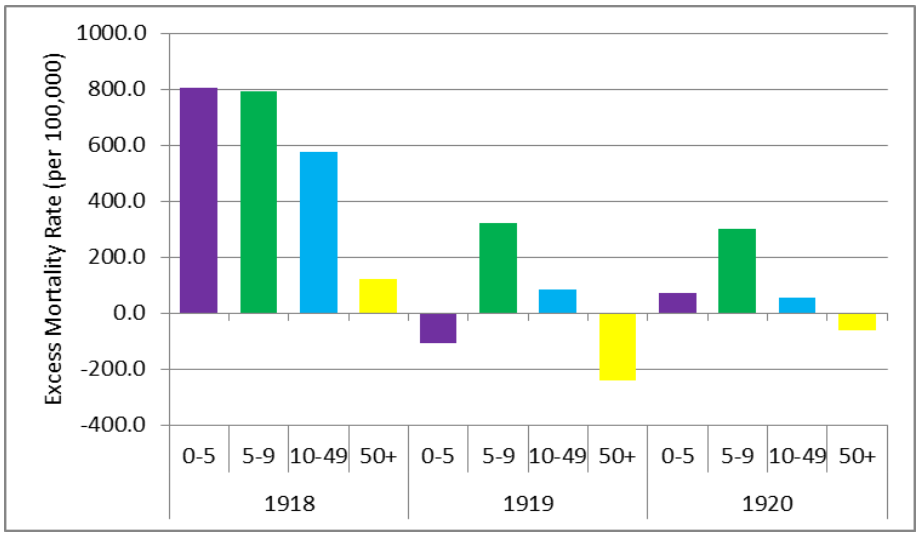

Figure 5: Average Total Annual All-Cause Excess Mortality by Age and Pandemic Year

6.6 TOTAL ALL-CAUSE EXCESS MORTALITY BY SEX

The sex-specific excess mortality rates also changed annually, as shown in Figure 6. In 1918 the average excess mortality rate among males was higher than the rate among females (537.48 vs. 471.13 deaths per 100,000). In 1918, Pennsylvania had the highest male rate (952.4 deaths per 100,000) and Michigan had the lowest male rate (266.39 deaths per 100,000). Maryland had the highest female rate in 1918 at 740.16 deaths per 100,000 while Wisconsin had the lowest female rate at 273.73 deaths per 100,000. The greatest difference between the male and female rates in 1918 was in Montana, where the male rate was 276.79 deaths per 100,000 higher. The male and female rates were most similar in Kansas, at 344.71 and 337.00 deaths per 100,000. Indiana, Maine, Michigan, and Minnesota were the only states where the female rate exceeded the male rate.

In 1919, the average excess mortality rate among females was much higher than the rate among males (52.80 vs. -14.6 deaths per 100,000). Washington had both the highest male and female rates in 1919, at 106.01 and 159.40 deaths per 100,000. New Hampshire had the lowest male rate in 1919, at -108.12 deaths per 100,000, while Vermont had the lowest female rate, at -52.20 deaths per 100,000. Michigan had the greatest difference between the male and female rates, with the female rate being 144.13 deaths per 100,000 higher than the male rate. Kentucky had the most similar male and female rates, at 93.88 and 111.84 deaths per 100,000. In 1919, Virginia was the only state where the overall male rate was higher than the female rate.

The average excess mortality rates in 1920 were again higher among females than males (88.36 vs. 5.02 deaths per 100,000). Colorado had the highest male and female excess mortality rates in 1920, at 203.64 and 258.37 deaths per 100,000. Montana had the lowest male and female

excess mortality rates, at -136.33 and -24.64 deaths per 100,000. The greatest difference was in Connecticut, where the female rate was 154.10 deaths per 100,000 higher than the male rate. The rates were most similar in New Hampshire, where the male rate was 3.27 deaths per 100,000 lower than the female rate.

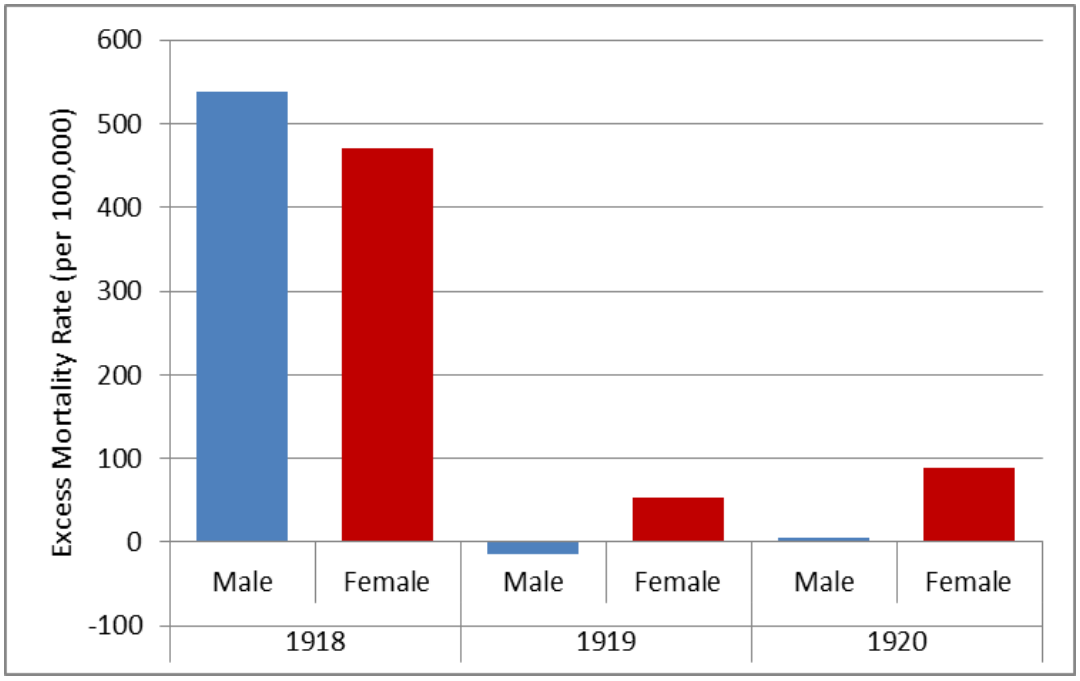

Figure 6: Average Total Annual All-Cause Excess Mortality by Sex and Pandemic Year

6.7 COMPARISON OF TOTAL ALL-CAUSE EXCESS MORTALITY TO AVERAGE

Figure 7 shows the annual excess mortality in each state compared to the study population annual average. The average total excess mortality rate during the pandemic varied from 489.78 deaths per 100,000 in 1918, to 2.26 deaths per 100,000 in 1919 and 36.47 deaths per 100,000 in

1920. More states were below the average in each year of the pandemic, with median excess mortality rates of 440.47, -0.12 and 25.30 deaths per 100,000. Colorado was the only state that was consistently above the average total excess mortality rate, while New York, Maine and Kansas were consistently below the average excess mortality rate. In general, states that were above the average rate in 1918 were more likely to be below the average in 1919, while states that were below the 1918 average were about equally likely to be above or below the 1919 average. States that were above the average in 1918 were more likely to be below the average in 1920, while states below the average in 1918 were more likely to be above the average in 1920.

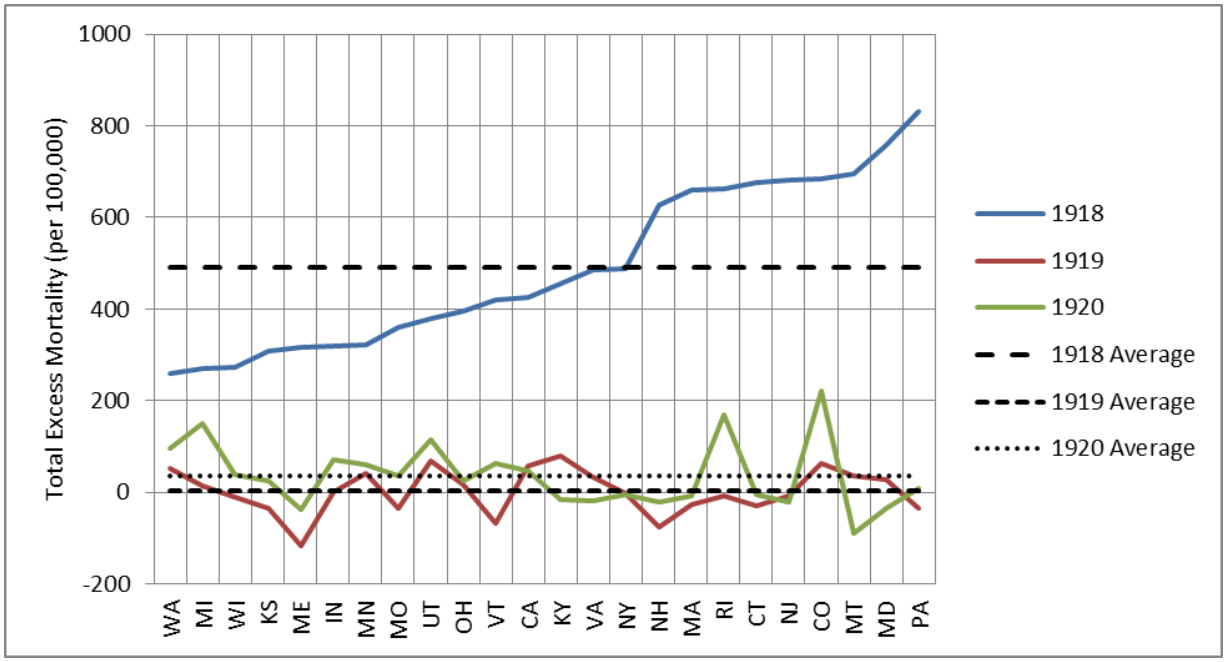

Figure 7: State Total Excess Mortality and Annual Averages by Pandemic Year

6.8 COMPARISON OF CUMULATIVE AGE-SPECIFIC ALL-CAUSE EXCESS MORTALITY TO AVERAGE

Figure 8 shows the age-specific annual excess mortality rates in the states compared to the study population average. In the 0-5 age group, there were no states that were consistently above or below the average throughout the pandemic period. Among the 5-9 age group, ten states were consistently above the average (CA, CO, CT, ME, MD, NH, NY, PA, RI and UT), while five states were consistently below the average (KS, KY, MO, VA, and WI). Among the 10-49 age group, Rhode Island and Colorado were consistently above the average, while Missouri, Kansas, and Maine were consistently below the average. Among the 50+ age group Colorado, Kentucky and Virginia were consistently above the average, whereas Connecticut, Maine, Montana, Rhode Island, Vermont and Wisconsin were consistently below the average.

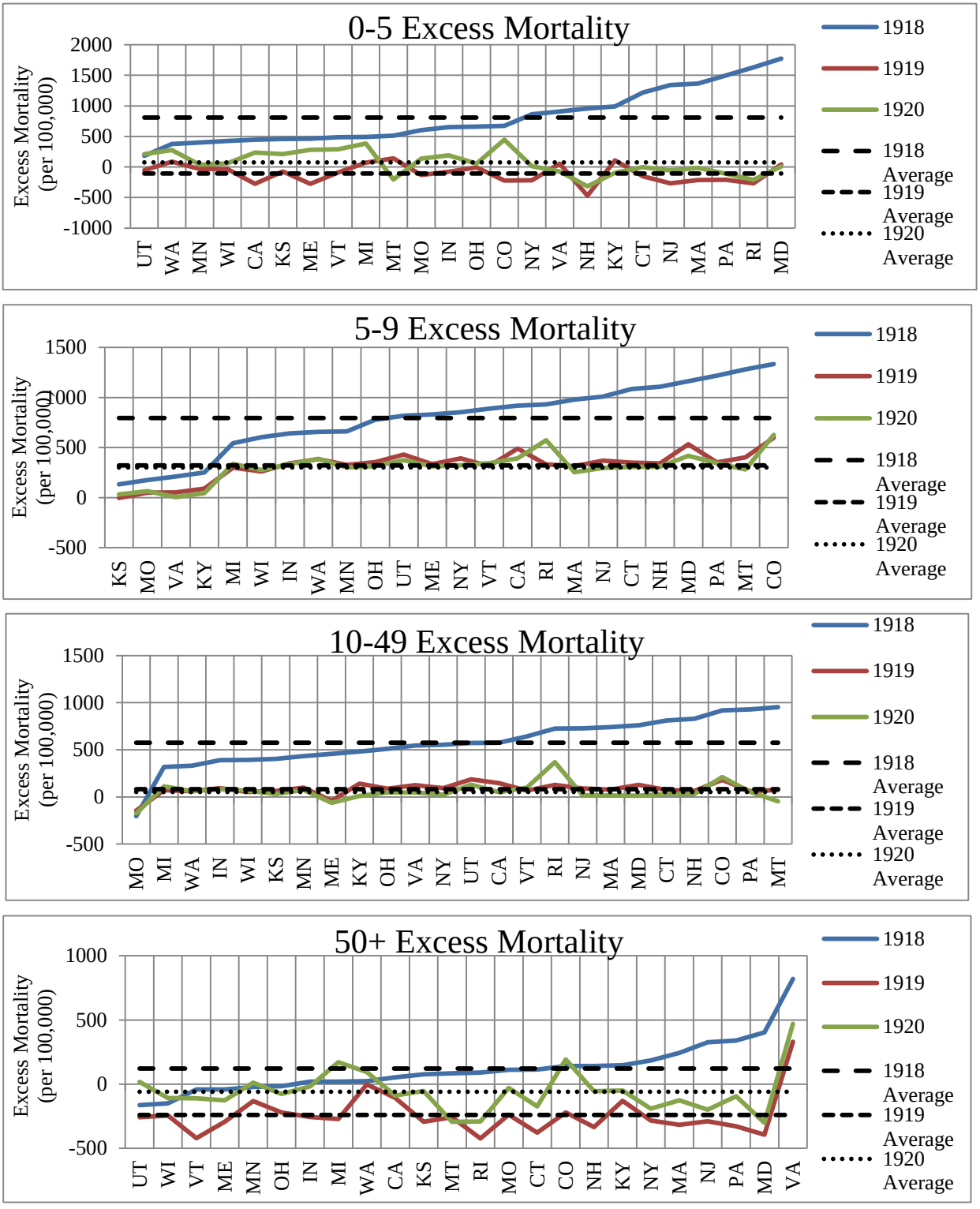

Figure 8: Annual Total Excess Mortality by State by Age and Pandemic Year

6.9 COMPARISON OF CUMULATIVE SEX-SPECIFIC ALL-CAUSE EXCESS MORTALITY TO AVERAGE

Figure 9 shows the annual total excess mortality by state in males and females, compared to the averages in the study population. The average male excess mortality rate was 537.48 deaths per 100,000 in 1918, -33.64 deaths per 100,000 in 1919, and 104.9 deaths per 100,000 in 1920. Colorado consistently had male excess mortality rates above the average, while Missouri and New York consistently had rates below the average. The average female excess mortality rate was 471.13 deaths per 100,000 in 1918, 52.80 deaths per 100,000 in 1919, and 88.3624 deaths per 100,000 in 1920. Colorado was the only state consistently above the average, while Massachusetts, Virginia, and Wisconsin were consistently below it.

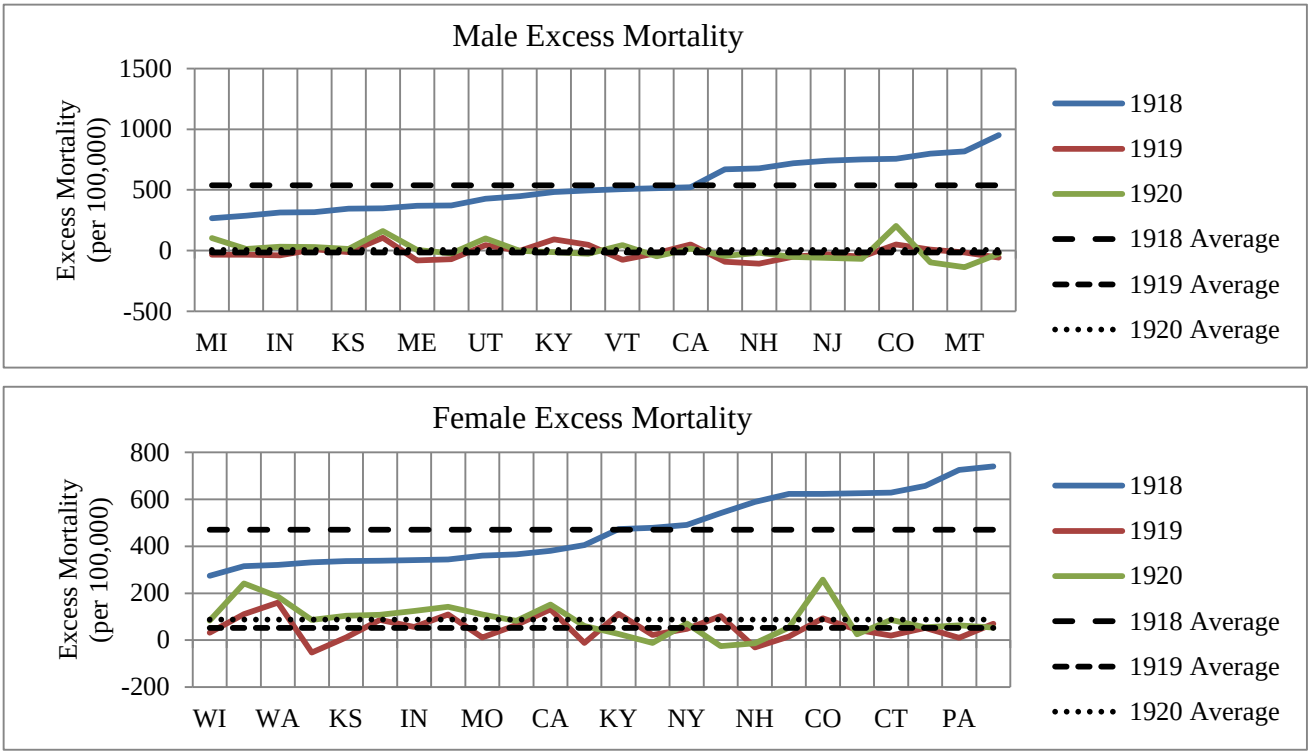

Figure 9: Annual Total Excess Mortality by State by Sex and Pandemic Year

6.10 CORRELATION TO POTENTIAL DETERMINANTS OF MORTALITY

The Spearman Correlation coefficients and p-values for the variables of interest and the annual total excess mortality, and cumulative and 1918 age- and sex-specific excess mortality are shown in Table 5. The correlation between total excess mortality and population density was the strongest in 1918, at 0.5284, indicating a positive relationship between population density and total excess mortality in 1918. The correlation was weaker and negative in both 1919 and 1920. The correlation between population density and total excess mortality was not significant in any of the pandemic years. In 1918, population density was significantly correlated with the total excess mortality in the 0-5 and 50+ age groups. All other age groups were not statistically significantly correlated with population density at varying strengths of negative and positive correlations. In 1918, the female excess mortality was significantly correlated with population density (rho = 0.4983, p-value = 0.0132), while the male excess mortality rate was not (rho = 0.2565, p-value = 0.2263). Population density was only significantly correlated with cumulative excess mortality in the 0-5 age group, and neither of the sexes.

The correlation between total excess mortality and percent of the population living in urban areas was similar to that of population density, in that the strongest correlation occurred in 1918 (rho = 0.3652), and it was lower in 1919 and 1920 (rho = -0.1339 and 0.0896). There was no significant correlation between total excess mortality and percent of the population living in urban areas in any year of the pandemic. In 1918, the 5-9 age group was the only age group with a significant correlation with urbanization (rho = 0.5104, p-value = 0.0108). All other age groups had weaker correlations, with the over 50 age group having the weakest correlation. In 1918, the 0-5 and 5-9 age groups had significant correlations between total excess mortality and

urbanization. The cumulative male excess mortality rate was not significantly correlated with urbanization, however the cumulative female excess mortality rate was significantly correlated, with a correlation coefficient of 0.6183 (p-value = 0.0013). Similarly, in 1918, the female total excess mortality was significantly correlated with urbanization, while the male excess mortality was not.

The correlation between male to female ratio and total excess mortality was moderately strong in 1918, however indicated a negative relationship. The correlation was stronger in 1919, at 0.6460, and indicated a positive relationship. The correlation weakened to 0.4185 in 1920. The correlation between average male:female ratio and total excess mortality was significant in 1919 and 1920. Male to female ratio was not significantly correlated with the cumulative excess mortality age groups. The strongest correlation was in the under 5 age group, with a correlation coefficient of -0.4026 (p-value = 0.0511). Male to female ratio was not significantly correlated with male or female cumulative excess mortality, both correlations were weak. In 1918, the male:female ratio was significantly correlated with the total excess mortality in the 0-5 and 50+ age group. Male:female ratio was significantly correlated with the female total excess mortality in 1918, but not with the male total excess mortality in 1918.

The strength of the correlation between percent military deaths due to influenza and pneumonia and total excess mortality increased in strength from 1918 to 1920; however the correlation was never significant. In 1918 and 1920 the correlation indicated a negative relationship with total excess mortality. In 1919 the correlation indicated a positive relationship. The strongest correlation between percent military deaths due to influenza and pneumonia and cumulative excess mortality occurred among the 5-9 age group, however this correlation and those all other age groups were insignificant. The correlations with male and female cumulative

excess mortality were also insignificant. The correlation between percent military deaths due to influenza and pneumonia and excess mortality in 1918 was not significant for any of the age groups or either of the sexes.

Military enlistment as soldiers was weakly correlated with total excess mortality. The correlation was negative in 1918 and positive in 1919 and 1920. Military enlistment with the first and second drafts was also not significantly correlated with total excess mortality during any of the pandemic years. Similar to the other enlistment measure, the correlation with total excess mortality was negative in 1918, and stronger and positive in 1919 and 1920. Both enlistment measures were insignificantly correlated with cumulative excess mortality in all age groups and both sexes. Neither of the military enlistment measures were significantly correlated with age- and sex-specific excess mortality in 1918. However, Montana had a much higher enlistment rate than the other states of interest. When removing Montana from the study population, the percent of the population enlisted with the 1st and 2nd drafts was significantly correlated with excess mortality in 1919, and both enlistment measures were significantly correlated with excess mortality in 1920. Removing Montana from the study population did not affect the correlation between military enlistment and any of the age- and sex-specific excess mortality rates.

Table 5: Spearman Correlation Coefficients of Total Excess Mortality and Cumulative Sex- and Age-Specific Excess Mortality with Various Factors

		Population Density	% Population Living in Urban Areas	Male:Female Ratio	Percent Military Mortality Due to Influenza and Pneumonia	Military Enlistment as Soldiers	Military Enlistment with 1st and 2nd Drafts
Total Excess Mortality	**1918**	0.3696	0.3652	-0.3635	-0.0643	-0.1191	-0.0183
	p-value	0.0755	0.0793	0.0808	0.7652	0.5793	0.9325
	1919	-0.3235	-0.1339	0.4430	0.1487	0.3200	0.3930
	p-value	0.1231	0.5327	0.0345	0.4880	0.1274	0.0574
	1920	-0.1835	0.0896	0.4165	-0.3096	0.2270	0.2913
	p-value	0.3908	0.6773	0.0429	0.1410	0.2862	0.1673
Cumulative Excess Mortality	**0-5 yrs**	0.7183	0.3922	-0.4026	0.0009	-0.3009	-0.2148
	p-value	0.0001	0.0580	0.0511	0.9968	0.1531	0.3135
	5-9 yrs	0.0757	0.5104	-0.0078	-0.2583	-0.0600	0.1904
	p-value	0.7253	0.0108	0.9710	0.2230	0.7806	0.3728
	10-49 yrs	0.1939	0.3861	-0.1904	-0.1904	-0.0765	0.0739
	p-value	0.3639	0.0624	0.3728	0.3728	0.7223	0.7314
	>50 yrs	-0.0913	-0.0878	0.1626	0.0061	0.0513	0.0870
	p-value	0.6713	0.6832	0.4478	0.9775	0.8118	0.6862
	Male	0.0600	0.3191	0.0157	0.1026	-0.0626	0.2374
	p-value	0.7806	0.1285	0.9421	0.6333	0.7713	0.2640
	Female	0.3530	0.6183	-0.0383	-0.2461	0.0400	0.3226
	p-value	0.0906	0.0013	0.8591	0.2464	0.8528	0.1242
1918 Total Excess Mortality	**0-5 yrs**	0.7904	0.4783	-0.6939	-0.1383	-0.3997	-0.3626
	p-value	<0.001	0.0181	0.0020	0.5194	0.0605	0.0816
	5-9 yrs	0.1252	0.4764	-0.0687	-0.2113	-0.0809	0.1609
	p-value	0.5599	0.0203	0.7498	0.3216	0.7072	0.4527
	10-49 yrs	0.1461	0.3296	-0.2078	-0.0591	-0.1243	0.0365
	p-value	0.4958	0.1158	0.3298	0.7837	0.5626	0.8655
	>50 yrs	0.5157	0.3061	-0.5487	0.0009	-0.2704	-0.1800
	p-value	0.0099	0.1458	0.0055	0.9968	0.2012	0.4000
	Male	0.2565	0.3791	-0.2800	-0.0113	-0.1739	0.0296
	p-value	0.2263	0.0677	0.1851	0.9582	0.4164	0.8909
	Female	0.4983	0.4852	-0.5191	-0.1635	-0.2357	-0.0791
	p-value	0.0132	0.0162	0.0093	0.4453	0.2676	0.7132

7.0 DISCUSSION

This study found that most of the excess mortality due to the influenza pandemic occurred in 1918, and in the two years following the pandemic, mortality was below the baseline average mortality that was seen in 1915-17 and 1920-23. This was shown in the largely negative excess mortality rates in 1919 and 1920 in the study population. Unlike previous research, this study suggests that all-cause excess mortality in the states only occurred in the year of the pandemic, and after the virus cycled through the population, the state mortality rates quickly return to the baseline rates.

The results of this study also show age-specific excess mortality patterns similar to what has been previously found. Most of the excess mortality in 1918 occurred in the younger age groups (with the highest excess mortality rate occurring among the 0-5 age group). The lowest excess mortality rates were consistently in the 50 and older age group. The 5-9 and 10-49 age groups had similar patterns of decreasing excess mortality in both 1919 and 1920, while the excess mortality in the 0-5 and 50+ age group decreased in 1919 and increased in 1920.

In 1918, the average excess mortality rate was higher in males than females. However, in 1919 and 1920, the excess mortality was higher in females. The 1918 pattern occurred in every state except for Maine, Michigan and Indiana, where the male rate was lower than the female rate. In 1919, the only state where the female rate was lower than the male rate was in Virginia. Every state in 1920 had the female rate higher than the male rate. These findings support previous research that the male excess mortality during the pandemic was higher than the female

excess mortality rate during the pandemic. However, after the waves of the pandemic ended in 1918, the excess mortality was higher among women than men. This suggests that after the waves of influenza ended, the male mortality rates returned to normal faster than the female mortality rates, which were still elevated in 1919 and 1920. It has previously been found that after the pandemic decreased life expectancies, the male life expectancy rebounded faster than the female life expectancy [31]. The changes in sex-specific excess mortality rates from 1918-20 found in this study correlate with this previous research.

The correlations between excess mortality and population density, urbanization, male to female ratio, military mortality due to influenza and pneumonia, and military enlistment were, for the most part, weak and insignificant. While previous studies have found that influenza mortality in 1918 was significantly correlated with population density, in this study population density was only found to be significantly correlated with cumulative all-cause excess mortality in the 0-5 age group. While urban areas have previously been found to have higher mortality rates during the pandemic than rural areas, the percent of the population living in urban areas was significantly correlated only in the 5-9 age group. The average male to female ratio was significantly correlated with the excess mortality rate in 1919 and 1920. These correlation coefficients indicated that populations with more males than females had higher excess mortality rates despite the observation that in 1919 and 1920, the female excess mortality rate was higher than the male excess mortality rate. During the pandemic, military populations were found to have much higher mortality rates than the civilian population, however in this study, neither mortality in the military due to influenza and pneumonia nor military enlistment were found to be significantly correlated with excess mortality.

7.1 STRENGTHS AND WEAKNESSES OF APPROACH

The use of historical data in this study produces some limitations. The data came from two historical sources: the U.S. decennial censuses in 1910, 1920 and 1930, and the annual vital statistics reports in 1915-1923. Intercensal linear trends were used to estimate the population and covariate values for the years of interest. While this was a method traditionally used during this period and in more recent studies to estimate intercensal trends in population, modern estimates of intercensal population rely on data regarding annual births, deaths, emigration, immigration, and net military movement [48]. Using the linear method likely resulted in an overestimation of the U.S. population during the pandemic, largely due to circumstances surrounding the World War [41]. Data regarding the military population during the pandemic were also problematic due to the decennial censuses. The 1910 census was conducted prior to the war, when there fewer than 200,000 men serving in the army, and the 1920 census was conducted after the war, when most of the 4,000,000 troops had returned home. Therefore the censuses cannot provide accurate estimates of the military population in each state during the pandemic. The estimations of the population during the years of interest therefore include both the civilian and military population. So when using the vital statistics reports, which exclude military deaths, the estimated excess mortality rates were likely underestimates of the true rates, since the two measures are not based on the same population.

As was previously mentioned, vital statistics reports are only available for areas in the country that adopted death registration laws and recommended death certificates that account for at least 90 percent of mortality in the area. In 1915, there were only twenty-four registered states, which accounted for approximately two-thirds of the U.S. population during the pandemic.

Excluding states that were not registered by 1915 may have introduced bias in terms of what states had legislations in place that could be readily altered to adopt new death registration laws. The states that were included in the study may not by representative of the entire country during the pandemic in terms of both excess mortality rates and the demographic variables of interest. Since these states were not registered during the pandemic, it is not possible to get an accurate estimate for the average excess mortality at the national level. The states that were included in this study can therefore only be compared to their average, and not what was occurring in the entire country.

Another limitation of this study using historical data is the availability of data. As previous studies have found, economics were an important factor for influencing mortality during the pandemic. However, data regarding economic conditions at the state level are not available, so this study was not able to adjust for factors such as per-head income. The economy of the states likely varied, so not being able to adjust for this is a large limitation of this study. Race was also considered to be an important factor in mortality during the pandemic, however, due to changes in the approach towards race in the census, race-specific excess mortality rates would not be accurate, and would also not be translatable to race-specific rates today.

Due to the lack of complete, accurate data for the U.S. during the pandemic, this study is limited in identifying the reasons for heterogeneity of the mortality due to the pandemic. While the differences in mortality could be real, they could also be artefacts due to differences in reporting and the public health environment during the period of interest. While the examination of mortality at the state-level is significant for the development of state-wide public health policies, there can be large heterogeneity within the state affecting the observations made at the state-level. For example, while this study examined the effect of state population density on

excess mortality rates, city-level population density may demonstrate a different relationship between population density and excess mortality. In order to fully understand excess mortality at the state level, further indicators of within-state heterogeneity would need to be taken into consideration.

There were, however, some advantages to the approach taken in this study. Excess mortality takes into consideration the mortality rate in the state prior to the pandemic, and explicitly demonstrates how the pandemic altered the mortality in state. Many previous studies have simply looked at mortality rates during the pandemic, which do not show how mortality changed during the pandemic. By using all-cause excess mortality, instead of cause-specific excess mortality, this study captures all causes of death that could be attributed to the pandemic, including liver and renal failure. It is also not impacted by the failure of physicians to correctly determine the cause of death. Since only states that were registered by 1915 were used in this study, the data from these states can be assumed to be fairly accurate regarding the number of deaths that occurred during each year of interest. Using 1915-17 and 1921-23 as the baseline years for mortality rates is a method that has been previously used in studies to examine the mortality during the pandemic. This method not only captures pandemic-related deaths that could have occurred after 1918, but also provides an accurate estimate of the average mortality rate during the years closest to the pandemic.

7.2 FUTURE DIRECTIONS

There has been a large amount of research done regarding mortality and risk factors during the 1918 influenza pandemic. However, the age- and sex-specific effects of these risk factors have not been fully examined. In order to fully understand how factors such as population density, urbanization, male to female ratio, and military mortality and enlistment influenced the mortality patterns observed during the pandemic, the individual effects of these factors would need to be examined. While correlations provide preliminary assessments of the relationship between excess mortality and these factors, they do not take into consideration the associations between these factors, which could be assessed using multivariate regression.

7.3 SUMMARY

The influenza pandemic that struck the world in 1918 killed an estimated 675,000 Americans. This study reiterated findings from previous research regarding the patterns of excess mortality in the U.S. However, it also showed that these patterns changed after the waves of influenza ended. The age- and sex-specific excess mortality rates in 1918 were greatly different from the rates that occurred in 1919 and 1920. Certain states experienced consistent patterns of excess mortality, Colorado, for example, had higher excess mortality than the average in every year of the study. While many of the correlations between excess mortality and the factors of interest were weak, some factors were significant, which prompts for further investigation of these relationships.

The 1918 pandemic was one of the deadliest events to occur in human history. In the nearly 100 years that have passed, large medical advances have occurred that dramatically decreased the presence of infectious diseases in the developed world. However, influenza remains a persistent presence in the population, and due to the ability of the influenza virus to evolve, there remains the possibility for the emergence of an influenza strain similar to that of 1918. In order to fully anticipate the repercussions of a 1918-like pandemic occurring today, it is important to understand the factors that influenced mortality during the 1918 pandemic. While this study conducted a thorough investigation into the patterns of excess mortality during the 1918 pandemic, further investigation is required to examine the effects of factors such as population density, urbanization, etc. on these patterns of excess mortality.

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