CAN MEDICAL MARIJUANA STEM INCREASES IN DRUG RELATED DEATH-RATES: A TIME-SERIES CROSS-SECTION ANALYSIS

by

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ABSTRACT

Opioid and heroin use has increased dramatically over the past two decades. This issue has public health significance as overdose rates and usage rates of these drugs have never been higher. This increase in use has been driven primarily by availability. The population considered most at risk for opioid/heroin abuse is young, white males. There is a significant comorbidity in opioids and alcohol and alcohol abuse has increased among this young white male population as well. There is evidence that the presence of medical marijuana in states is associated with lower rates of overdose from opioids and heroin. There is also evidence that marijuana acts as a substitute for alcohol in places where it is legal. The objective of this study is to look at the association between overdose rates by state, related to opioids, heroin or alcohol and the presence of medical marijuana in those states. We want to evaluate how state policies, like the presence of prescription drug monitoring programs, as well as socio-economic factors affect the rate of these deaths. Fixed-effect linear models were fit in order to do primary and secondary analyses of medical marijuana's effects on overdose deaths.

Medical marijuana was found to have a positive effect on the rates of overdoses related to opioids, heroin or alcohol. A secondary analysis showed a negative cumulative year effect. This suggests that overdose rates are initially higher in places that have legalized medical marijuana but that as time passes overdose rates fall. The actual magnitude of the effects of medical marijuana is small when compared to our socio-economic covariates. These results suggest that

marijuana policy, while potentially useful in combating this drug epidemic, is less important than socio-economic factors in curbing overdose deaths.

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1.0 INTRODUCTION

1.1 PROBLEM

Since the mid-1990s prescription opioid and heroin abuse have increased in a dramatic fashion. This opioid crisis, along with a corresponding increase in alcohol abuse has contributed to a rising death rate amongst middle-aged white Americans. Trends in this increase in the death rate have emerged. According to the CDC, "Drug overdose death rates in the United States have more than tripled since 1990 and have never been higher. In 2008, more than 36,000 people died from drug overdoses, and most of these deaths were caused by prescription drugs" [6] Furthermore, according to the NIH's National Institute on Drug Abuse, or NIDA, "…an estimated 52 million people (20 percent of those aged 12 and older) have used prescription drugs for nonmedical reasons at least once in their lifetimes," and, "…about 1 in 12 high school seniors reported past-year nonmedical use of the prescription pain reliever Vicodin in 2010, and 1 in 20 reported abusing OxyContin". [25] According to NIDA's National Survey Results on Drug use, in 2003 opioid analgesics were the second most abused drug amongst high school seniors, behind marijuana. [14] In the period from 1998 to 2002, mentions of opioid analgesics in medical examiner cases increased in 28 of 31 reporting areas of the United States. [13]

It is clear that opioid abuse is a major public health issue affecting the United States. In addition to the increases in drug abuse and overdose deaths, this issue has had a significant

economic impact. Based on estimates from the 2007 National Survey on Drug Use and Health (NSDUH), total societal costs to the US were said to be about $55.7 billion in that year. (12) In order to fully address the problem of opioid abuse and increasing heroin abuse it is important to understand how this form of drug abuse manifests itself in the US.

1.2 REASONS

One of the biggest driving factors in opioid abuse is the availability of opioid analgesics. According to the CDC, "Sales of prescription opioids in the U.S. nearly quadrupled from 1999 to 2014," and deaths related to those drugs have increased similarly. [10] From 1990 to 1996 the biggest increases in prescribed opioids were for oxycodone, 402% increase, fentanyl, 226%, hydromorphone, 96% and morphine, 783%. [16] The connection between the increasing amounts of prescription drugs in the American populous and the increasing number of deaths related to those drugs is apparent. Opioid analgesics are prescribed in two ways: for short-term and long-term pain management. Addiction and abuse are generally rare for patients on a short-term opioid prescription. Long-term patients on the other hand, are at a significantly increased risk for addiction. [15] Though short-term pain management patients do not experience an increased risk of drug abuse and addiction, the presence of pain medication in a household does pose a source of risk for other members of the home. [26]

Availability of opioids is only one explanation for increases in opioid abuse. In a study of VA patients from 2000 to 2005, researchers looked at risk factors for opioid abuse among veterans. They found that a diagnosis of non-opioid substance abuse was the strongest predictor of opioid abuse and addiction. They also found that mental health disorders were strong

predictors; the fact that there are so many more patients with mental health disorders, in this study at least, suggests that mental health disorders account for more of the attributable risk for opioid abuse and addiction than non-opioid substance abuse. [27]

In order to deal with the increases in opioids abuse it is important to understand which portion of the population is most at risk for opioid abuse and addiction. It has been shown that certain factors are positively associated with opioid abuse: patients with multiple opioid prescriptions from multiple pharmacies and doctors, patients who refill their prescription opioids early, and other measures of actual drug use are the best predictors of opioid abuse. Apart from actual usage, certain demographic factors are also very much associated with opioid abuse: young white men, 18-34, are at higher risk for opioid abuse than others. [17] There is comorbidity in opioids and alcohol. In fact, there is comorbidity in alcohol with most illicit drugs. In the context of opioid abuse, alcohol is an important drug to also consider, as alcohol use in conjunction with opioid use is very dangerous and accidental overdoses when the two substances are combined are not uncommon. A study of drug overdoses in New Mexico found that over the time period 1990-2005 there was a 196% increase in single-drug category overdose deaths that was driven primarily by heroin alone and opioids alone. The same study also found that there was a 148% increase in multiple-drug category overdose deaths and that this was fueled mainly by heroin/alcohol and heroin/cocaine. [20] It is interesting to note that young men in the US are also at increased risk for alcohol abuse and dependence, similar to how they are at increased risk for opioid abuse. A study using results from the National Epidemiologic Survey on Alcohol and Related Conditions found that alcohol abuse and dependence are both more prevalent among young men, particularly whites and those with a low income. [18]

Based on all of this information we can identify the most pressing drug abuse issue in the US. Prescription opioid abuse has been a growing issue for much of the last two decades and heroin abuse has seen a similar trend, as opioid abusers eventually turn to the cheaper and more potent alternative. Opioids and heroin have a significant comorbidity with alcohol and the combination of the two substances has had an increasing contribution to overdose deaths. The demographic considered most at risk for abuse and dependence on opioids and alcohol are young men, typically in the 18-34 age range and typically with some kind of risk factor for drug abuse such as being on a long term pain management program, having mental health issues, or having abused drugs in the past. In addition, particularly for alcohol, poor whites are considered more at risk for drug abuse and dependence.

1.3 POSSIBLE SOLUTIONS

There is evidence that the legalization of medical marijuana is correlated with a reduction in the increasing rate of heroin overdoses. [3] Other studies have shown links between marijuana use and a decreased need for opioids, at least in long term palliative care [4] as well as a decreased rate of alcohol related traffic fatalities.[7] Legalized medical marijuana can be thought of as a stand in for more liberal attitudes towards marijuana and drug use in general.[2] Based on these findings, it may be appropriate to think of marijuana use as having some kind of protective effect when it comes to opioid/heroin and alcohol abuse.

Conversely, the opposite could be true. States that have legalized medical marijuana tend to have more lax attitudes towards drug use as well as a greater prevalence of marijuana use among the high school aged population. Studies have shown that the younger an individual is at

the onset of marijuana or alcohol use, the more likely they are to abuse drugs in the future. [2,21,5] In this case it could be argued that medical marijuana laws are evidence of a more at risk population for drug abuse and that the presence of such laws are indicative of a populous that is more likely to abuse and therefore suffer the ill effects of opioids, heroin and alcohol.

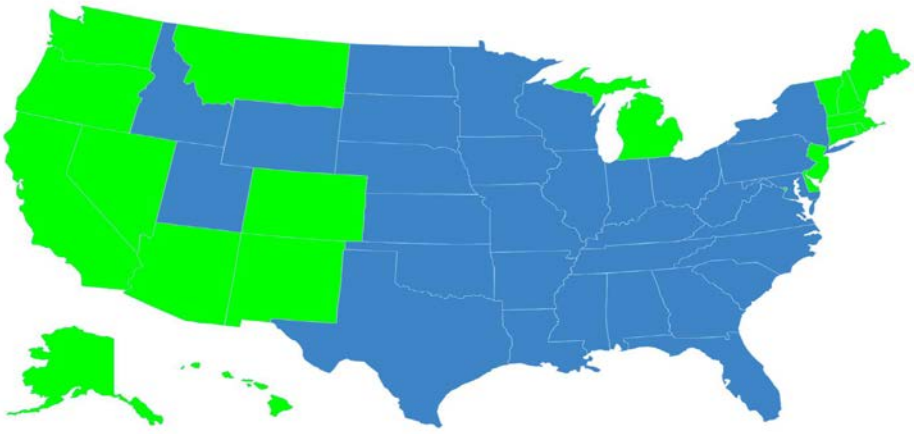

Figure 1. States with medical marijuana laws during the study period

1.4 OBJECTIVE

The primary objective of this study is to look at the relationship between overdose deaths related to alcohol and drug abuse, specifically prescription opioids and heroin, and the presence of statewide medical marijuana laws. If the presence of legal medical marijuana is associated with a reduction in these types of deaths than it could be evidence that marijuana could be considered a substitute for opioids and heroin both medically, in the treatment of pain, chronic and otherwise, and recreationally, where the negative health effects of marijuana are far less severe than those of opioids and heroin. A reduction in the volume of prescription drugs would

lead to a decrease in abuse of prescription drugs and lead to fewer individuals progressing from opioids to heroin. Secondary objectives include measuring the impact of factors such as poverty and education on overdoses from drug and alcohol abuse. The hope in building this model is to measure not only the impact of both state-wide policies, MMLs and PDMPs, but also to measure the impact of socio-economic factors.

1.5 DATA SOURCES

Data were obtained on all 50 states plus the District of Columbia (N=51) from the time period 2003-2014 (T=12) on a number of state policies, socio-economic factors and non-intentional overdose deaths with either an opioid, heroin, or alcohol contributing cause of death. The state policies that are of primary concern are implementation of medical marijuana laws (MMLs) and/or prescription drug monitoring programs (PDMPs).[9] PDMPs are designed to track the prescribing and dispensing of prescription drugs to patients and can give prescribers information on a patient's prescription drug history as well as monitor suspected abuse and diversion, such as selling drugs.[11] This information better allows states to find out which individuals are engaged in the drug using behaviors described earlier: having multiple opioid prescriptions from multiple pharmacies or doctors.[17]

Besides this policy information, data on socio-economic factors including education level, individuals in poverty and insurance status were obtained from the Census Bureau over the study period. Individuals at risk for drug abuse tend to have a lower income than those considered less at risk. Poverty and education level are very closely related and insurance status gives us an idea of the portion of each state's population receiving adequate healthcare.

Overdose data by year and state was obtained from the CDC's WONDER database. Of interest are non-intentional overdose deaths with a contributing cause of death pertaining to either opioids, heroin and other narcotics, or alcohol.

The overdose mortality rate for deaths related to opioid analgesics, heroin and alcohol in the years 1999 to 2014 for every state was abstracted from the Center for Disease Control's Wide-ranging Online Data for Epidemiologic Research interface for multiple-cause of death. Opioid analgesic and heroin overdose deaths were defined as overdoses of any intent (*International Statistical Classification of Diseases,10th revision* [*ICD-10*], codes X40-X45 and Y10-Y15) where either an opioid analgesic, heroin or narcotic, or alcohol were coded for (extension codes T40.0-T40.4, T36-T39, T50.9, T151.0-T151.9). This captures overdose deaths where an opioid was involved including cases related to polypharmacy, illicit narcotics and alcohol.

State-level time varying economic factors were also obtained from the U.S. Census Bureau. These include individuals in poverty, insurance status and education levels by state with racial breakdowns. In addition to these three demographic and socio-economic measures, data was also obtained on which states have prescription drug monitoring programs (PDMPs) [9] as well as which states have medical marijuana laws (MMLs) and in what years these programs and laws were implemented.

2.0 METHODS

2.1 NORMAL FIXED-EFFECTS MODELS

The data used in this study was time-series cross-sectional (TSCS) and consisted of comparable time-series data observed over a number of units. In this case our time-series was each year 2003 to 2014 and our units were all 50 states plus Washington D.C.; N=51 and T=12. TSCS data resembles panel data and both are forms of multilevel or hierarchical data whereby lower-level observations are grouped by some characteristic of interest, in this case states.[22] There are several advantages to analyzing TSCS data, according to Worrall and Pratt's paper, "Estimation Issues Associated with Time-Series—Cross-Section Analysis in Criminology." TSCS estimation typically reduces estimation bias, allows for the specification of multiple models and reduces the problems from data multicollinearity.[24]

The TSCS models were based on the generic form:

$$y_{i,t} = x_{i,t}\beta + \varepsilon_{i,t} ; \qquad i = 1, \ldots, N; \quad t = 1, \ldots, T \qquad (1)$$

$$y_{i,t} \sim N(\mu, \sigma^2)$$

$y_{i,t}$ is the log of the age-adjusted death rate related to overdose/100,000 population for state i at time t. $x_{i,t}$ is a vector of covariate data for state i at time t and β is the coefficient on that covariate. $\varepsilon_{i,t}$ is the error term.

This assumed a rectangular data structure, each of N units was observed for all T times. This model assumed no error structure for $\varepsilon_{i,t}$, error terms were considered independent for all *i* and *t*. This simple model represented a good method of estimating TSCS data. Units were fixed, not sampled, and N was neither too small nor too large, falling near the middle of the general rule that N=10 to 100. T was also large enough (>10) so that time-averages made sense.

Equation (1) provided a good model based on the assumption that all units were fit by the same model with the only variation between units being the independent variables, $x_{i,t}$. Equation (1) failed to account for heterogeneity between units however. The simplest way to account for heterogeneity between units was to allow for the inclusion of an intercept value for each unit, α_i, which represents the fixed effects of state *i* on the dependent variable. A fixed effects model can be expressed simply as:

$$y_{i,t} = x_{i,t}\beta + \alpha_i + \varepsilon_{i,t} ; \qquad i = 1, \ldots, N; \quad t = 1, \ldots, T \qquad (2)$$

$$\alpha_i \sim N(0, \sigma^2_\mu)$$

That is, the fixed effects intercept only shifted the regression line for each specific unit up or down, regression lines for each state remained parallel. This allows us to estimate the effect of state-level time-varying factors across all states while still accounting for differences across states.

We use fixed-effect models when we are mainly interested in variables that change over time, in this case measures of poverty, insurance coverage, and education, as well as the presence of prescription drug monitoring programs (PDMPs) and medical marijuana laws (MMLs). In a fixed-effect model each unit, or state, has its own characteristics that may or may not have an effect on the independent variables. This kind of state-level heterogeneity is generally described as some prevalent attitude or condition present in the state that is difficult to measure. For

example, two states could lean conservative politically, but this is not necessarily a good representation of both states' underlying attitudes towards drug policy. Alaska and Texas are similar electorally but have totally opposite medical marijuana laws over the study period. It would be inaccurate to model both states exactly the same and introducing a fixed-effect model allows for differences between individual unit models.

This concept of introducing fixed effects to a model extends beyond just the units, or states, measured and can be applied to the time factors in the study. The study period here is 2003 to 2014, and while overdose rates have risen throughout that time period, they have not necessarily risen uniformly from year-to-year or state-to-state or even region-to-region. Time fixed-effects are treated the same as unit fixed-effects, another intercept value is included in order to represent the fixed effects of each year within the study period and their effect on the dependent variable. A model with both unit and time fixed-effects can be expressed as:

$$y_{i,t} = x_{i,t}\beta + \alpha_i + \varphi_t + \varepsilon_{i,t}\ ; \qquad i = 1, \ldots, N; \quad t = 1, \ldots, T \qquad (3)$$

$$\varphi_t \sim N(0, \sigma^2_\mu)$$

Where φ_t behaves in the same way that α_i does, except φ_t applies to time-effects.

In this type of model we assume a correlation between the error term and a unit's independent variables in order to account for the unseen fixed-effects of a specific unit. The fixed-effects remove the effect of those time-invariant characteristics to better estimate the effect of our independent variables on our outcome variables. The simplest way to test for heterogeneity and the need to include fixed-effects is to use a Hausman test to compare the F statistics from equation (3), the model with the fixed-effect intercepts, to equation (1), the model without the fixed-effect intercept. When deciding between including both unit and time fixed-

effects we can look at the F statistics comparing equation (2) to (1) and comparing (3) to (1) and decide which model better represents the data.

2.2 POISSON FIXED-EFFECTS MODELS

The concept of fixed-effects regression is not limited solely to linear models. Fixed-effects can be applied to other regression models and in this case we have considered the possibility that a Poisson model is potentially more appropriate for the data used in this study. The generic form of this model can be expressed as:

$$E[y_{it} \mid x_{it}] = \mu_{it} = \exp(x'_{it}\beta) \qquad (4)$$

Where μ_{it} is the dependent variable of interest, in this case the log of the age-adjusted death rate/100,000 population and $x_{i,t}$ is a vector of explanatory variables for unit i at time t. As in the linear fixed-effects models we can model the unobserved heterogeneity between units and years, expressed in α_i and φ_t as individual and time specific effects. That effect is multiplicative in the conditional mean rather than additive, as expressed here:

$$E[y_{it} \mid x_{it}; \alpha_i, \varphi_t] = \mu_{it} = \alpha_i \varphi_t \exp(x'_{it}\beta) \qquad (5)$$

Note: an intercept term is not expressed as it is folded into the fixed-effects terms.[29]

In a random-effects model we would treat the panel data as a single cross-section and estimate our parameters of interest after making some assumption about the distributions of α_i.and φ_t. The fixed-effects model makes minimal assumptions about α_i or φ_t. This approach can be justified by the fact that if there were only a few individuals observed over many time periods, then all α_i's and φ_t's could be treated as parameters to be estimated.[30]

In summary, fixed-effects models have broader extensions than just linear regression and panel data, or time-series cross-sectional data, can be modeled using many techniques while still accounting for and measuring unobserved heterogeneity between units and time periods.

2.3 PRIMARY/SECONDARY MML ANALYSIS AND FINAL MODELS

Model diagnostics were used to assess the appropriateness of a Normal model versus a Poisson model. Distributions of dependent variables, AIC/BIC measures, as well as residual plots were compared in order to choose the best method of estimation. We also looked at multicollinearity between our socio-demographic variables. Based on these various measures we concluded that a linear TSCS fixed-effects regression model based on a Normal distribution was most appropriate for these data.

Using linear time-series cross-sectional regression models, we analyzed the association between medical marijuana laws and opioid and alcohol related deaths. For our dependent variable we used the log of the age-adjusted death rate per 100,000 population related to opioid and/or alcohol use. The primary independent variable of interest is the presence of medical marijuana laws, which are modeled in two ways. In the first regression model a state and year-specific indicator variable was included for the presence of medical cannabis laws. All years prior to passage are coded as 0 and all years after passage are coded as 1. Because laws could be passed at different times during a specific year, the year of passage is coded as a fraction. For example, a cannabis law passed on July 1st would be coded as 0.5 in that year.

In the second model we allowed the effect of medical marijuana laws to vary based on time elapsed since the passage of the law. In order to account for delays in patient registration,

distribution of identification cards and establishment of dispensaries, where applicable, we included a variable of years since implementation of MMLs. This allowed us to measure the cumulative effect of multiple years of legal medical marijuana.

These models were fit two different ways. First, demographic data was used for each state's total population; annual poverty rates, education level and insurance status were taken from all residents of each state. Second, this same demographic data was used but for the white population only. As stated earlier there is evidence to suggest that this problem disproportionately effects the white population and fitting each model with demographic data from the total population and just the white population allowed us to look at these differences.

Finally, this same two model analysis, for both the total population and the white population was run again, this time on death rates corresponding only to opioid and heroin related deaths, without alcohol. This was done in order to look at the problem of drug abuse without the effects of polypharmacy and to see if there were significant differences in how our model predicted these drug abuse deaths.

To review, a total of eight models were fit. We can divide these up by the cause of death, opioids, heroin and/or alcohol or opioids and heroin only. Primary and secondary MML analysis were carried out and models were fit with socio-demographic data from the total population and again for the white population only. These eight models are listed in table 1.

Table 1. All eight models fit for both overdose categories, two levels of MML analysis and population subgroups

Cause of Death	Primary MML analysis	Secondary MML analysis
Opioids, heroin and/or alcohol	Total Pop.	Total Pop.
	White Pop.	White Pop.
Opioids and heroin only	Total Pop.	Total Pop.
	White Pop.	White Pop.

Models were fit using seven state level factors:

1. Annual percentage of state population living in poverty
2. Annual percentage of state population with no more than a high school diploma
3. Annual percentage of state population with health insurance
4. An interaction term of 1. And 2.
5. Medical marijuana laws (MML) by state
6. Presence of prescription drug monitoring programs (PDMP) by state
7. State-specific years since implementation of MML

Number 3, the annual percentage of state population with health insurance, was removed from the final models as it added little to the model and was not significant. Number 7, our years since implementation of MMLs variable is only included in the secondary MML analysis.[3]

All analysis was done in SAS for a combination of cross-sectional and time-series data, otherwise known as panel data. Two-way fixed effects models fit with the intercept suppressed were fit. Primary MML analysis models can be represented by following equation:

$$Y_{it} = \alpha_N + \varphi_t + \beta_1(\%\ \text{Population in Poverty}) + \beta_2(\%\ \text{Population Finished no more than HS}) + \beta_3(\%\ \text{Poverty} * \%\ \text{Finished HS}) + \beta_4(\text{MML}) + \beta_5(\text{PDMP}) + \varepsilon_{it}$$

Secondary MML analysis models can be represented by the following equation:

$$Y_{it} = \alpha_N + \varphi_t + \beta_1(\%\ \text{Population in Poverty}) + \beta_2(\%\ \text{Finished HS}) + \beta_3(\%\ \text{Poverty} * \%\ \text{Finished HS}) + \beta_4(\text{MML}) + \beta_5(\text{PDMP}) + \beta_6(\text{years since MML implementation}) + \varepsilon_{it}$$

3.0 RESULTS

3.1 DISTRIBUTIONS AND DESCRIPTIVES

Eight states had medical marijuana laws prior to the beginning of the study period in 2003. Twelve more states, including Washington D.C., passed MMLs at some point during the study period, 2003-2014. Figure 2 shows the mean age-adjusted death rates for states with and without MMLs were plotted over the study period.

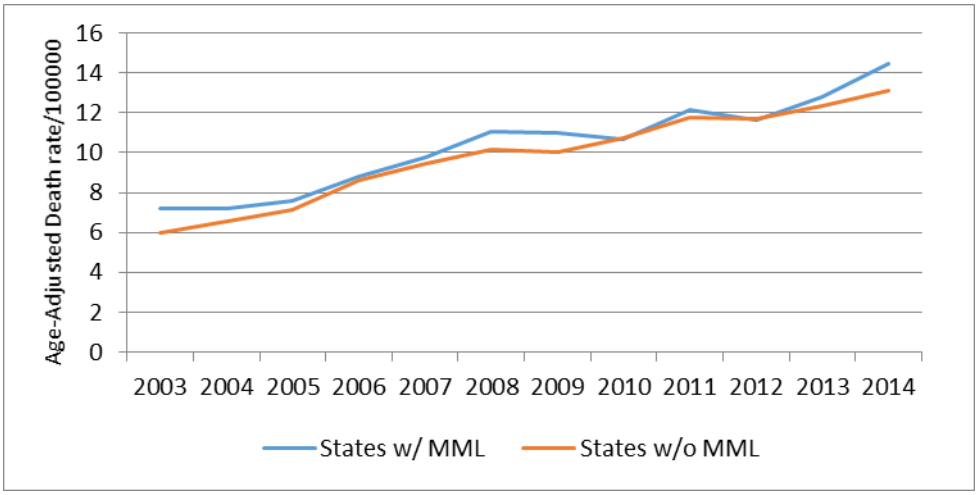

Figure 2. Mean age-adjusted death rates by state MML policy

In order to analyze the distribution of overdose deaths across the nation, the natural log of the age-adjusted death rate/100,000 population was plotted over the entire study period for both

causes of death, those relating to opioids, heroin or alcohol, or those relating to opioids or heroin only. The distributions of the dependent variables are pictured in figures 3 and 4.

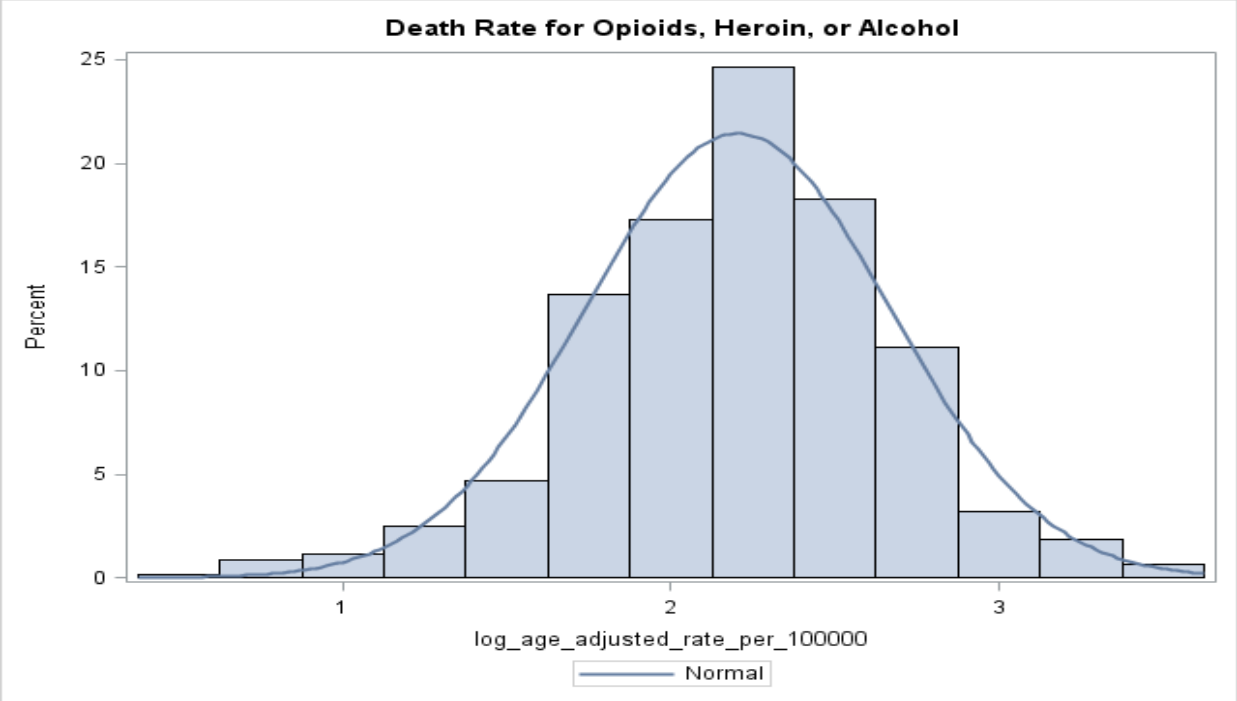

Figure 3. Distribution of overdose deaths related to opioids, heroin or alcohol, 2003-2014

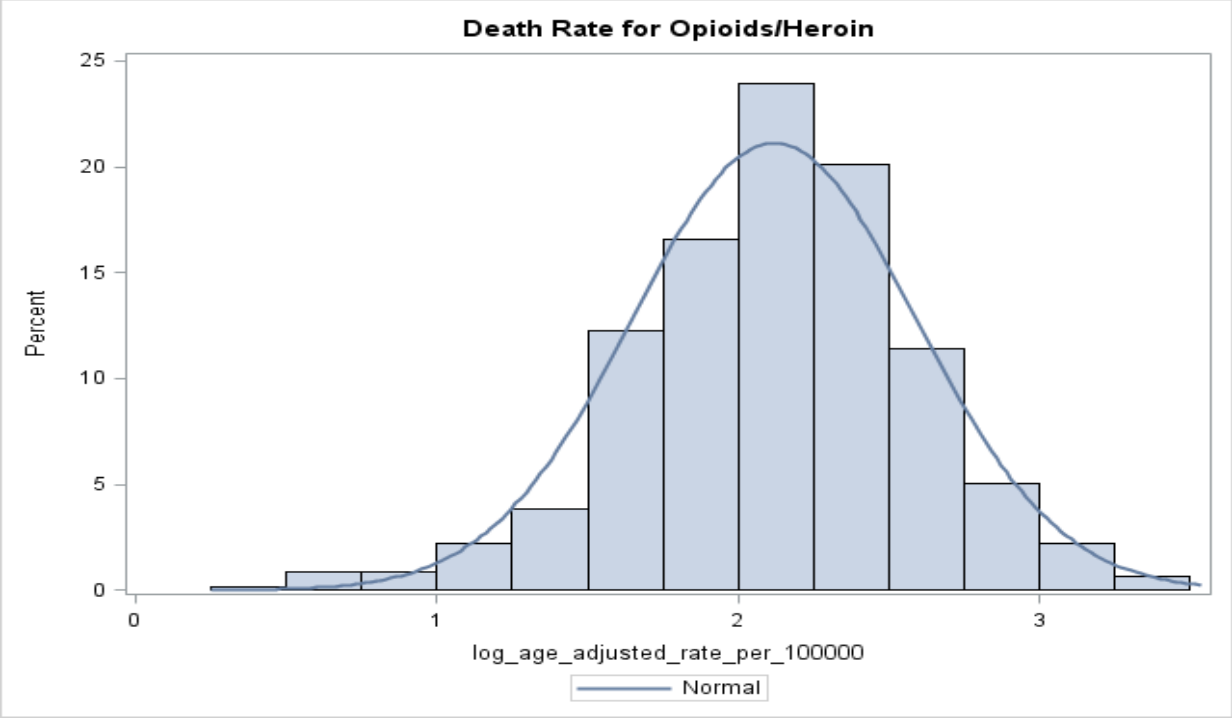

Figure 4. Distribution of overdose deaths related to opioids and heroin only, 2003-2014

The distribution of the log of the age-adjusted death rate appears normal but we want to evaluate whether or not we can treat this data as normally distributed. Figures 5 and 6 show Q-Q plots of our data. There appears to be a slight right-skewedness to the distributions of our outcome data. A Shapiro-Wilk test of normality rejects the assumption of normality (p=<.05) for both outcomes, but this test is sensitive to small sample sizes; here our N is only 51. For this reason we consider both Normal and Poisson models.

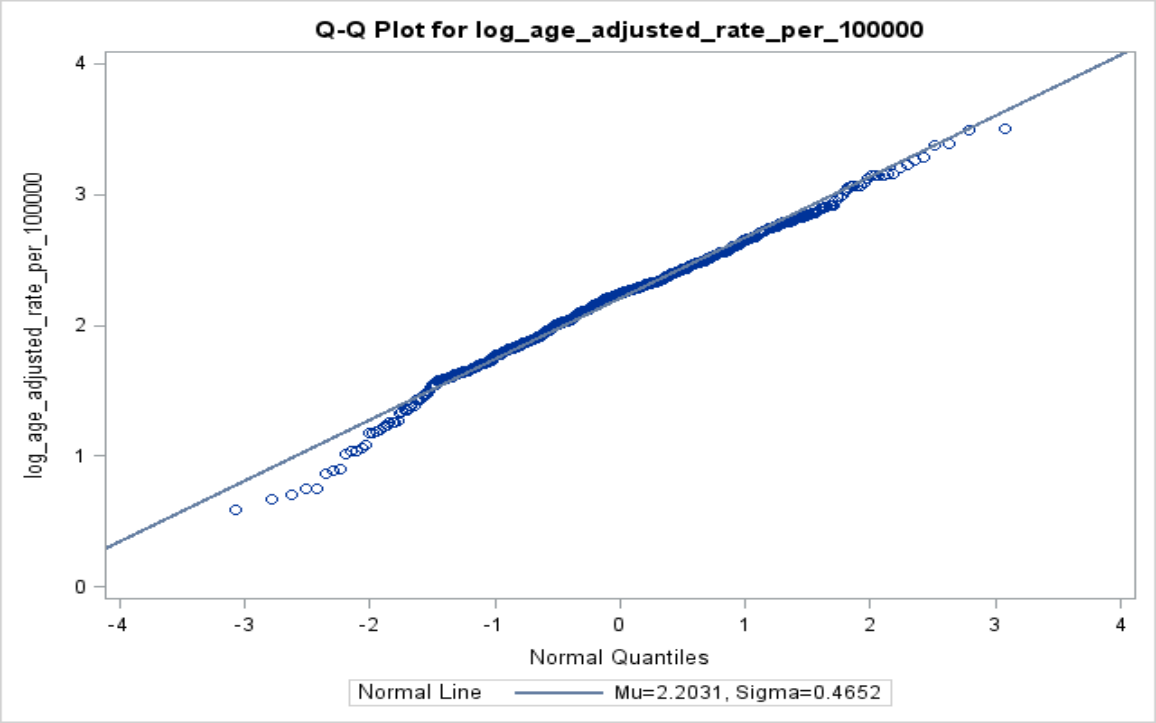

Figure 5. Q-Q plot of log age-adjusted death rate/100,000 for overdoses related to opioids, heroin or alcohol

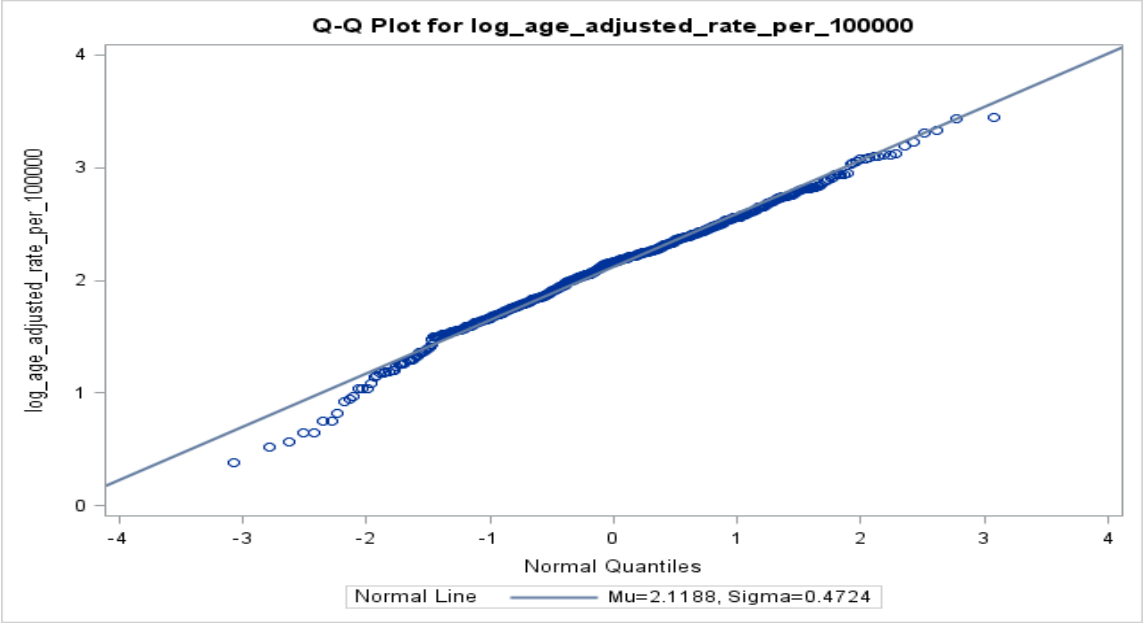

Figure 6. Q-Q plot of log age-adjusted death rate/100,000 for overdoses related to opioids and heroin only

In order to look at some of our demographic data in states with and without MMLs the percentage of states' population living in poverty as well as percentage of states' population having finished no more than high school were plotted over the study period in Figures 7 and 8.

The most striking feature from these figures is the difference in education in states with MMLs. Overdose rates related to opioids, heroin or alcohol as well as the percentage of a state's population living in poverty are not drastically different when we compare states with and without MMLs. Education, however, had a much higher percentage of the population from states without MMLs having finished no more than high school. Regardless of these differences a few trends emerge: overdose deaths are rising everywhere, poverty is getting worse and education levels, as measured by percentage of residents completing more than just a high school diploma, are rising.

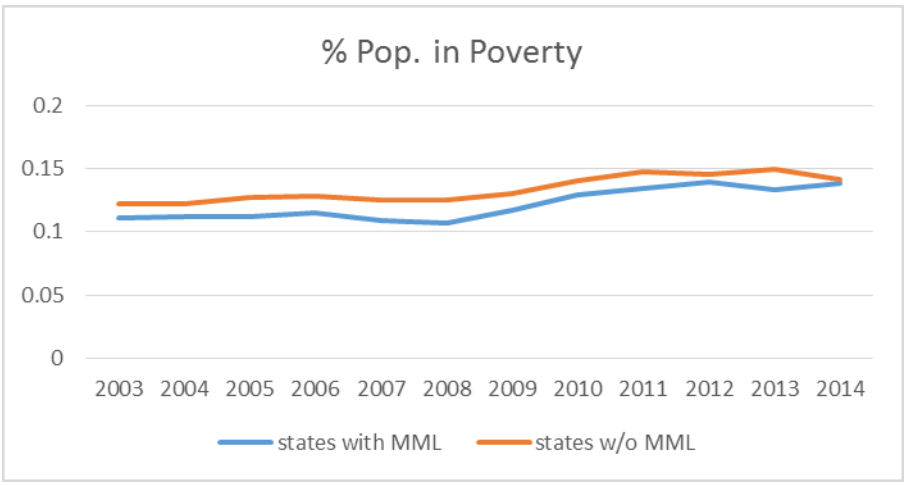

Figure 7. Percentage of population living in poverty by state MML policy

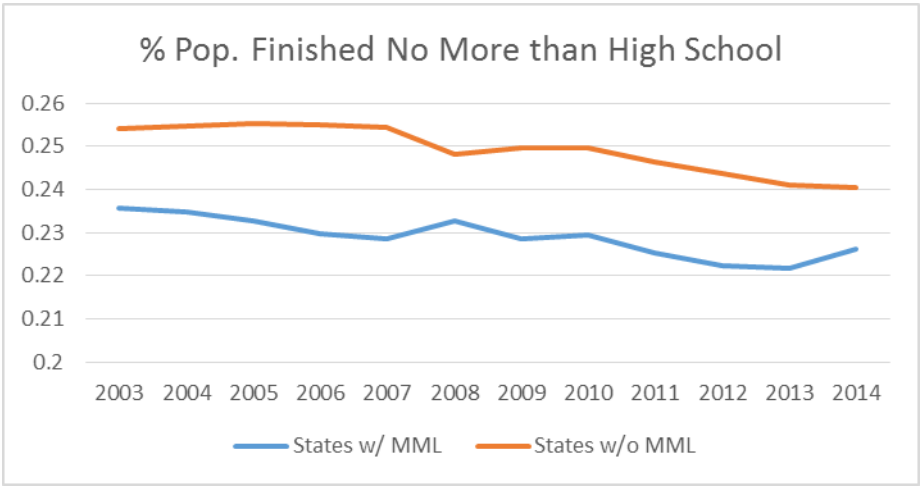

Figure 8. Percentage of population with no more than a high school diploma by state MML policy

Important results are abstracted in tables 1-5. Tables 1-4 contain coefficients, standard deviations and p-values for covariates used in the 8 different fixed-effect linear models discussed earlier. Because of questions about the normality of our outcome variable, models were also fit using fixed-effects Poisson regression and compared on the basis of AIC and BIC, which is shown in table 5. It should be noted that while the magnitude and significance of predicted

coefficients were not uniform between the Normal and Poisson models, the direction, both positive and negative, of those coefficients were the same.

3.2 OPIOIDS, HEROIN OR ALCOHOL RESULTS

In the first model, illustrated in table 2, results show that the presence of MMLs is positively associated with overdose deaths related to opioids, heroin or alcohol when using covariates from the full population as well as the white population. The interaction term of education and poverty is also positively associated with these overdose deaths but at a much greater value. PDMPs are negatively associated with overdose deaths but aren't statistically significant in this analysis.

Table 2. Primary MML analysis for cause of death codes related to opioids, heroin, or alcohol

Covariates	All	White	
% Population in Poverty	-8.88963 (3.0106) 0.0033	-11.0721 (2.6003) <.0001	Coeff. (Std Dev) p-value
% Population w/ no more than HS diploma	-5.73844 (1.7658) 0.0012	-5.0013 (1.291) 0.0001	
Interaction term (Poverty and Education)	36.8561 (12.1223) 0.0025	46.62059 (10.7353) <.0001	
MML	0.151224 (0.0389) 0.0001	0.145903 (0.0383) 0.0002	
PDMP	-0.03361 (0.0297) 0.2582	-0.0389 (0.0293) 0.1851	

Opioids, Heroin or Alcohol (Primary MML Analysis)

Table 3 shows a secondary analysis of MMLs based on the same models as in table 2, except for the inclusion of an additional covariate. A years-since-implementation of MMLs variable is added to the model to gain some perspective about the cumulative, multi-year effects of MMLs. In this secondary analysis the years since implementation variables has a negative effect on overdose deaths, suggesting that multiple consecutive years of MMLs has a beneficial effect with respect to overdoses related to opioids, heroin, and alcohol. The effects of covariates are similar in direction and magnitude, regardless of whether they are taken from the full population or the white population.

Table 3. Secondary MML analysis for cause of death codes related to opioids, heroin, or alcohol

Covariates	All	White	
% Population in Poverty	-6.82718 (2.96) 0.0215	-9.05053 (2.5671) 0.0005	Coeff. (Std Dev) p-value
% Population w/ no more than HS diploma	-4.19462 (1.7453) 0.0166	-3.79731 (1.2808) 0.0032	
Interaction term (Poverty and Education)	28.62075 (11.9169) 0.0167	38.05519 (10.6047) 0.0004	
MML	0.200756 (0.0391) <.0001	0.195037 (0.0386) <.0001	
PDMP	-0.02736 (0.029) 0.3454	-0.03101 (0.0287) 0.2796	
# Years of MML Implemented	-0.02753 (0.00513) <.0001	-0.02674 (0.0051) <.0001	

Opioids, Heroin or Alcohol (Secondary MML Analysis)

3.3 OPIOIDS/HEROIN ONLY RESULTS

Tables 4 and 5 show results for similar models to tables 2 and 3, except the outcome variable here is changed to the log of overdose deaths related to opioids or heroin only. These models give much the same results as presented in tables 2 and 3, positive associations between MMLs and overdose deaths but negative associations when accounting for multiple years of legalization. The interaction term of education and poverty is still the most positively significant variable and the largest in magnitude. The main difference between these models and those presented in tables 2 and 3 is that PDMPs are now statistically significant, which makes a certain amount of sense as alcohol overdoses are now omitted from the outcome variable. Table 6 contains AIC and BIC values for the Normal based models that are abstracted out in tables 2 through 5 as well as for the Poisson based models that we considered. It is clear from those results that the Normal based fixed-effects models better fit the data. Residual diagnostics for all eight models fit are in figures 11-18 in the appendix.

Table 4. Primary MML analysis for cause of death codes related to opioids and heroin only

Covariates	All	White	
% Population in Poverty	-9.32898 (3.1399) 0.0031	-10.6291 (2.816) 0.0002	Coeff. (Std Dev) p-value
% Population w/ no more than HS diploma	-6.37582 (1.8403) 0.0006	-5.31207 (1.3734) 0.0001	
Interaction term (Poverty and Education)	39.44566 (12.6382) 0.0019	45.70408 (11.5654) <.0001	

Table 4 Continued			
MML	0.149808 (0.0406) 0.0002	0.148435 (0.0402) 0.0002	
PDMP	-0.06201 (0.0309) 0.0002	-0.06777 (0.0306) 0.0274	

Opioids or Heroin (Primary MML Analysis)

Table 5. Secondary MML analysis for cause of death codes related to opioids and heroin only

Covariates	All	White	
% Population in Poverty	-7.1716 (3.0841) 0.0204	-8.37766 (2.7781) 0.0027	Coeff. (Std Dev) p-value
% Population w/ no more than HS diploma	-4.7488 (1.8174) 0.0092	-3.99371 (1.3618) 0.0035	
Interaction term (Poverty and Education)	30.79889 (12.4129) 0.0134	36.18615 (11.4176) 0.0016	
MML	0.202031 (0.0407) <.0001	0.199911 (0.0404) <.0001	
PDMP	-0.05544 (0.03031) 0.0663	-0.05954 (0.0299) 0.047	
# Years of MML Implemented	-0.02898 (0.00533) <.0001	-0.02837 (0.00532) <.0001	

Opioids or Heroin (Secondary MML Analysis)

Table 6. AIC/BIC comparison of linear models vs. poisson models

		Primary MML analysis		Secondary MML analysis	
Cause of Death	**Model**	**AIC**	**BIC**	**AIC2**	**BIC3**
Opioids, heroin, alcohol (all)	Normal	-321.865	-22.8739	-351.522	-48.1337
	Poisson	1753.022	2047.6163	1754.55	2053.5413
Opioids, heroin, alcohol (white)	Normal	-330.963	-31.9715	-359.189	-55.8005
	Poisson	1752.957	2047.5515	1754.503	2053.4942
Opioids and heroin only (all)	Normal	-272.119	26.4172	-302.56	0.3669
	Poisson	1720.449	2014.5951	1721.935	2020.4711
Opioids and heroin only (white)	Normal	-276.758	21.7788	-305.985	-3.0587
	Poisson	1720.426	2014.5719	1721.924	2020.4601

4.0 ANALYSIS/DISCUSSION

The most striking result is that our model shows a positive relationship between the presence of MMLs in a state and the log of the age-adjusted death rate related to opioids or alcohol. This is the opposite of what was found in Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010.[3] There are a number of explanations for this. First, ICD codes used to examine overdose deaths are not uniform. The codes used in this study include alcohol related deaths as well as a more comprehensive list of extension codes that we believe captures a more complete picture of the drug abuse issue. Second, even though the independent variables used in the two studies are similar they are not the same. Here we are interested in education, poverty and how the two interact with each other, rather than just the state unemployment rate. Also, while both studies include MML and PDMP policies, we do not consider prescription drug ID laws or state oversight of pain management clinics.

It should be noted that even though this model found a positive association between MMLs and opioid and/or alcohol related deaths, it is a very small association, especially when compared to the other covariates included in the model. The interaction term of percentage population that has finished no more than high school and percentage living in poverty was both positive and extremely large. In this context it is perhaps more appropriate to say that MMLs and attitudes towards marijuana in general have little effect on overdose deaths related to opioids or alcohol, especially compared to education and poverty levels. As discussed earlier MMLs are

considered an indicator of more lax attitudes towards marijuana use and this corresponds with a higher rate of use amongst high school students.[2,1] Drug and alcohol abuse at young ages corresponds with higher rates of abuse and dependence later in life.[21,5] Taking this into consideration, we might explain the positive association between MMLs and overdose deaths as the naturally occurring consequence of a population that is at a higher risk for drug abuse in general.

This explanation seems to be more reasonable when we look at the secondary analysis of MMLs. Years since implementation has a negative effect on overdose rates meaning that multiple consecutive years of legal medical marijuana correspond with lower overdose rates. This corroborates the conclusions found in Bachhuber, et al.'s work.[3] Though their work sought to provide a coefficient for each year post-MML passage, our study sought to provide a single coefficient based on the number of years a state had MMLs in place.

It's important to look at these results in the context of other studies as well. The study State Medical Marijuana Laws and the Prevalence of Opioids Detected Among Fatally Injured Drivers [28] looked at automobile fatalities from 1999-2013 in states with and without MMLs. Researchers found that in states with operational MMLs that opioid positivity, or drivers that tested positive for some opioid in fatal crashes, was significantly reduced in 21 to 40 years-olds. Furthermore, in the study Medical Marijuana Laws, Traffic Fatalities, and Alcohol Consumption [7] found a nearly 12 percent decrease in any-BAC fatal crashes-per-100,000 licensed drivers and a 14 percent decrease in high-BAC fatal crashes-per-100,000 licensed drivers in states with MMLs. This study also found that the legalization of medical marijuana is associated with a decrease in alcohol consumption especially among 20 – 29 year olds.[7]

Based on the results of this study it is reasonable to draw a number of conclusions. First, there is a clear positive relationship between MMLs and a higher rate of opioid, heroin and alcohol overdose rates but this relationship is small and likely due to the attitudes and behaviors that are necessarily present in order to get medical marijuana legalized. Every subsequent year after the passage of MMLs is associated with a stronger negative effect on these kinds of overdoses. We interpret this to mean that over time, as patients get registered, identification cards get dispersed, dispensaries open and the practice of prescribing and using medical marijuana becomes more commonplace, that the beneficial effects of medical marijuana with regards to overdose deaths become more pronounced. When considering these conclusions in the context of similar research, the idea that marijuana acts as a substitute for opioids, heroin and alcohol seems reasonable.

Besides just focusing on the effect of MMLs on overdose deaths, understanding the effects of the demographic variables included in the models is also important. The inclusion of an interaction term, between the percentage of a state's population living in poverty and the percentage of a state's population with no more than a high school diploma, has a large positive effect on overdose deaths in all eight models specified. The size of this effect is quite large in all cases and dwarfs the individual negative coefficients present on poverty and education by themselves. This suggests that the overdose problem cannot be said to relate solely to poverty or education level. It would be incorrect to say that poverty by itself is an adequate predictor of these kinds of overdoses. Instead, our models seem to reinforce what has been posited by other studies, that the most at-risk groups for this kind of drug abuse are lower income whites with relatively little education.[18]

There are a few limitations to this analysis to consider when evaluating the results of this study. First, individuals' ability to cross state lines is unaccounted for in this analysis. State-wide policies, specifically the presence of PDMPs, could affect the behaviors of drug-users and suppliers that live in relatively close proximity to state borders. Furthermore, this study did not account for differences in states' MML policies. No distinction was made between states with MMLs during the study period, despite the fact that MMLs were not uniform in states where they were present. Lastly, since this analysis was done at the state level it is hard to make any conclusions based on urban vs. suburban and/or rural areas. States are not homogenous within themselves and it would be interesting to look at differences between urban and rural populations.

In the future a number of next steps could be considered to further this analysis. It would be very useful to look at death-rates at the county-level rather than just the state-level, in order to account for differences in urban and rural populations. Analysis at this level can be difficult as more data is suppressed in lower-population subgroups however. This concept could be extended to look at quarter-year time intervals rather than full years as well. It would also be interesting to look at differences in MMLs. As stated earlier no distinction was made for differences in state-wide MMLs and a more granular analysis of these policies could be very illuminating.

In addressing the growing problem of overdoses related to opioids, heroin and/or alcohol, it is important to take into account the issues and conditions that have most influenced this problem. The conclusion of this study, and others that show that MMLs have a beneficial effect on overdoses, abuse rates and traffic fatalities related to opioid, heroin and alcohol abuse, should not be that medical marijuana is a cure-all for these issues. Instead, a more appropriate conclusion would be that while there is evidence that the presence of medical marijuana is

beneficial in reducing overdose deaths and drug abuse, material conditions such as poverty and education level are still much more important in predicting these problems. A public health approach to the issue of overdoses related to opioids, heroin or alcohol should be two pronged. First, efforts should be made to make drug policy more lenient. Marijuana has been shown to be a substitute, if an imperfect one, for both opioids and alcohol, and has reduced problems associated with these two substances. More leniency towards opioid and heroin abuse also has the added benefit of possibly saving the lives of more drug abusers. Second, it is clear that the most positive change would come from improving education and reducing poverty in areas hit hardest by this drug epidemic. This may fall outside the purview of public health, but it is clear that poverty and education are the two areas where improvement would see opioid, heroin and alcohol related deaths fall.

APPENDIX: TABLES AND REGRESSION DIAGNOSTICS

Table 7. Overdose deaths with cause of death codes for opioids, heroin or alcohol by state

Age-Adjusted Death rate/100000

State	Year											
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
AL	3.29	4.47	4.71	6.8	9.33	11.4	11.8	9.86	10.8	10.2	11.2	13.8
AK	10.2	10.2	8.94	9.56	10.9	19.7	17.2	13.4	14.8	14.5	15	16.4
AZ	9.02	9.41	9.83	10.5	11.2	11	12.9	14.5	13.9	14.3	15.7	14.9
AR	4.2	5.65	6.49	7.64	8.49	10.4	10.7	9.8	9.9	10.1	8.16	10
CA	5.91	5.9	5.97	6.2	7.71	7.87	8.4	8.19	8.28	7.46	8.32	8.24
CO	6.86	6.24	8.17	8.64	10.9	11.2	11.8	10.2	13	12	11.9	12.3
CT	6.34	7.11	6.02	7.87	9.2	8.7	8.31	7.6	8.04	9.12	13.6	15.7
DE	6.76	4.86	5.53	7.61	9.16	12.5	11.9	13.3	13.8	12.1	16.3	17.1
DC	5.15	7.5	3.85	6.57	4.67	6.23	.	9.7	9.88	9.17	10.7	12.3
FL	9.06	9.38	9.7	10.4	11.8	12.9	13.6	13.6	12.6	10.3	9.84	10.5
GA	4.97	5.2	5.62	6.74	7.61	7.81	8.39	8.74	8.81	8.42	8.48	9.29
HI	3.52	4.71	5.59	3.97	6.62	5.81	5.91	6.14	7.84	5.73	6.05	5.52
ID	5.21	5.15	5.17	7.02	7.08	7.6	8.6	9.15	9.19	9.96	10.2	9.56
IL	3.31	4.19	4.59	7.5	6.3	7.35	8.23	7.54	7.49	8.13	9.74	11
IN	5.03	6.34	7.51	8.71	10.3	11.4	12.4	11.6	13.1	13.6	14.5	16.3
IA	1.81	2.12	2.97	4.18	4.32	5.55	5.53	6.58	6.35	7.16	7.43	7.63
KS	3.83	5.78	6.16	6.5	7.4	6.98	9.52	7.66	8.29	9.23	9.98	10
KY	11.5	10.7	13	14.6	15.2	16.3	16.5	21.9	23.6	23.1	21.6	23.2
LA	9.5	9.8	12.1	13.6	16	12.9	11.4	11.7	11	10.6	15.4	14.3
ME	7.76	8.94	9.64	9.84	10.2	11.6	10.7	8.18	8.86	9.22	11	15.5
MD	3.25	4.63	5.46	7.38	9.29	8.75	9.37	9.17	9.66	11.2	12.3	15.6
MA	3.38	3.45	4.31	6.75	8.16	7.42	7.66	7.35	8.27	9.04	10.4	15.7
MI	5.22	6.23	7.16	8.98	9.77	10.4	12.3	11.5	12.6	11.9	13.8	16
MN	2.75	2.89	3.26	3.89	4.98	6	6.66	6.09	7.57	7.04	7.91	7.52
MS	5.98	6.47	7.06	9.94	9.62	9.84	9.67	9.64	9.34	9.82	9.66	10.4

Table 7 Continued

MO	6.74	6.94	7.66	9.32	9.53	11.1	11.8	14.1	12.9	12.9	14.1	15.2
MT	8.32	8.37	7.24	7.29	9.49	12.5	12.4	9.31	12	9.54	10.2	9.21
NE	2.11	1.96	3.5	3.86	4.21	4.88	5.34	5.65	6.51	6.11	5.33	5.34
NV	8.79	10	11	11.1	13.6	14.4	15.7	16.3	18.2	16.9	15.6	14.5
NH	5.54	5.26	6.78	7.1	9.41	6.58	10.1	9.04	11.2	11.4	12.1	23.3
NJ	6.04	4.85	6.68	7.4	6.72	7.09	2.47	8.74	10.3	12.1	13.1	12.8
NM	16.9	14.5	16.6	18.4	20.6	24.6	21.4	21.5	25.3	23.6	21.5	26.2
NY	2.37	2.02	2.44	5.17	5.81	6.38	6.22	6.21	7.83	8.58	9.26	9.54
NC	6.39	6.75	7.68	7.95	8.56	9.89	10.3	8.99	10.8	10.2	10.1	11.2
ND	.	.	.	.	3.76	5.93	4.89	3.51	.	.	.	6.22
OH	5.22	7.66	8.29	10.5	11.9	13.2	9.46	14.3	15.4	16.8	18.5	22.8
OK	8.61	10.9	10.5	13.1	16.3	14.2	19.1	17.4	17	17.6	18	17.4
OR	6.52	6.18	6.55	8.69	9.98	10.2	10.1	9.92	10.7	9.55	9.06	9.72
PA	9.67	10.6	11.3	11.5	12.4	13	13.2	13.3	16.3	16.8	17.3	19.8
RI	6.25	4.91	6.62	9.87	9.03	11.7	10.1	11.9	14.9	15.6	18.4	21.2
SC	4.99	6.51	7.76	9.3	9.33	9.96	11.3	12.1	11	10.1	11	12.5
SD	.	3.55	2.83	4	2.84	5.63	5.24	5.18	5.54	4.84	6.14	5.6
TN	8.05	9.13	10.3	11.4	12	11.9	12.1	13.6	14	14.4	15.1	16.4
TX	4.98	5.08	5.51	6.37	6.57	6.27	7.5	7.28	7.65	6.65	6.69	7.02
UT	12.7	11.9	15.7	15.1	17.3	16	16	14.2	16.8	18.3	18	18.2
VT	7.79	5.94	5.38	9.16	7.14	9.49	7.67	6.47	9.56	8.21	12.6	12.1
VA	5.07	5.11	5.09	5.37	6.34	6.85	6.6	5.42	7.38	6.8	8.06	9.03
WA	8.13	9.46	9.46	10.4	11.3	11.8	11.9	10.2	11.3	10.9	11.2	10.6
WV	12.6	15.1	8.59	17.4	20.1	23.2	11.1	26.8	33.2	29.4	29.7	32.8
WI	4.4	4.89	5.9	7.18	8.63	8.22	8.36	8.74	9.71	10.5	12.8	12.7
WY	.	5.34	.	5.42	8.64	13.1	10.3	12.9	12.6	11.5	14.3	15.5

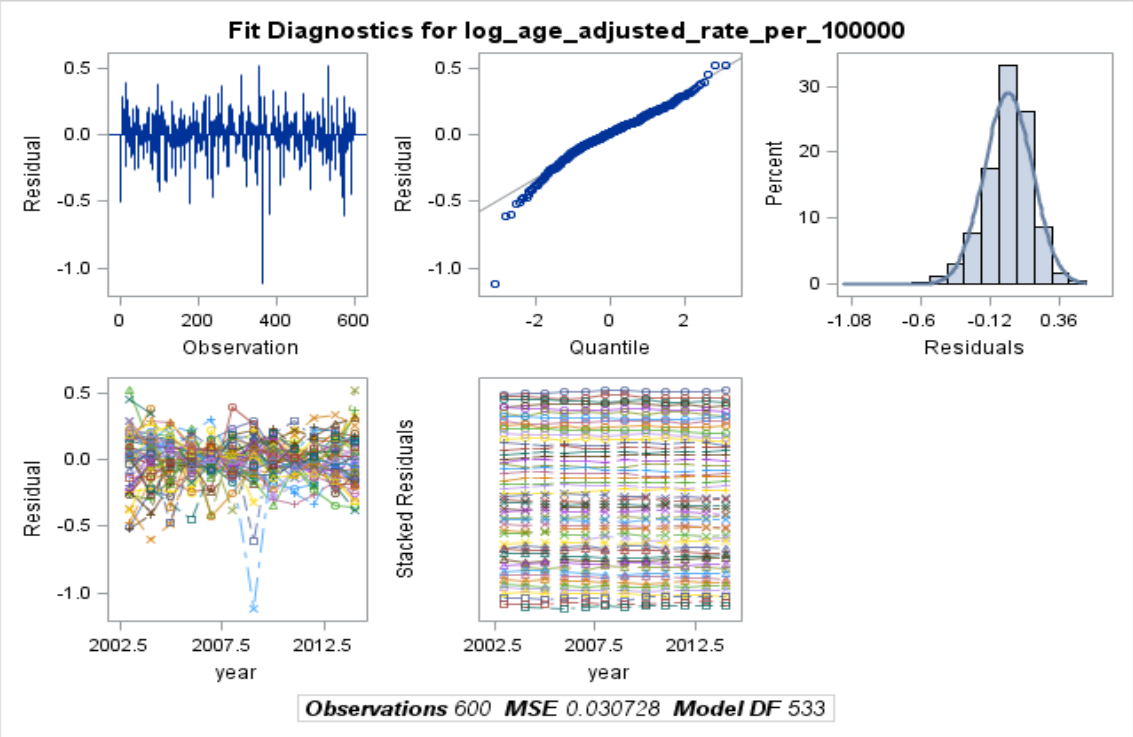

Figure 9. Residual diagnostics for opioid, heroin and alcohol primary overdose model, full population

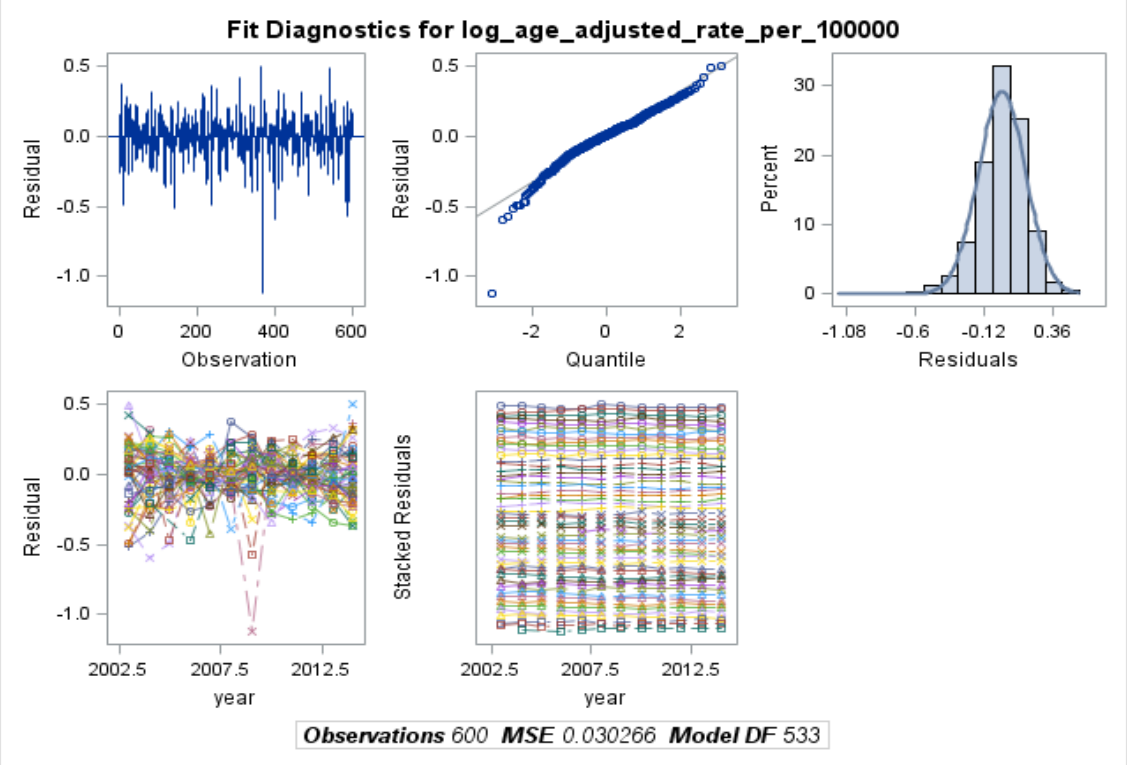

Figure 10. Residual diagnostics for opioid, heroin and alcohol primary overdose model, white population

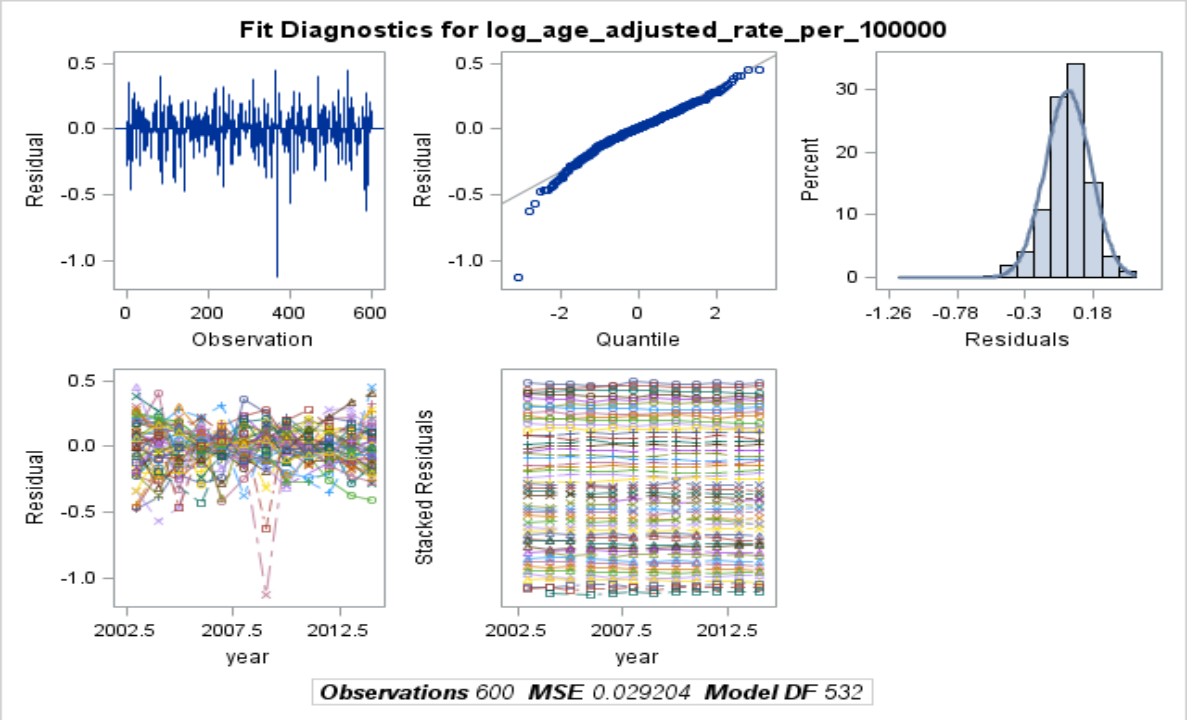

Figure 11. **Residual diagnostics for opioid, heroin and alcohol secondary overdose model, full population**

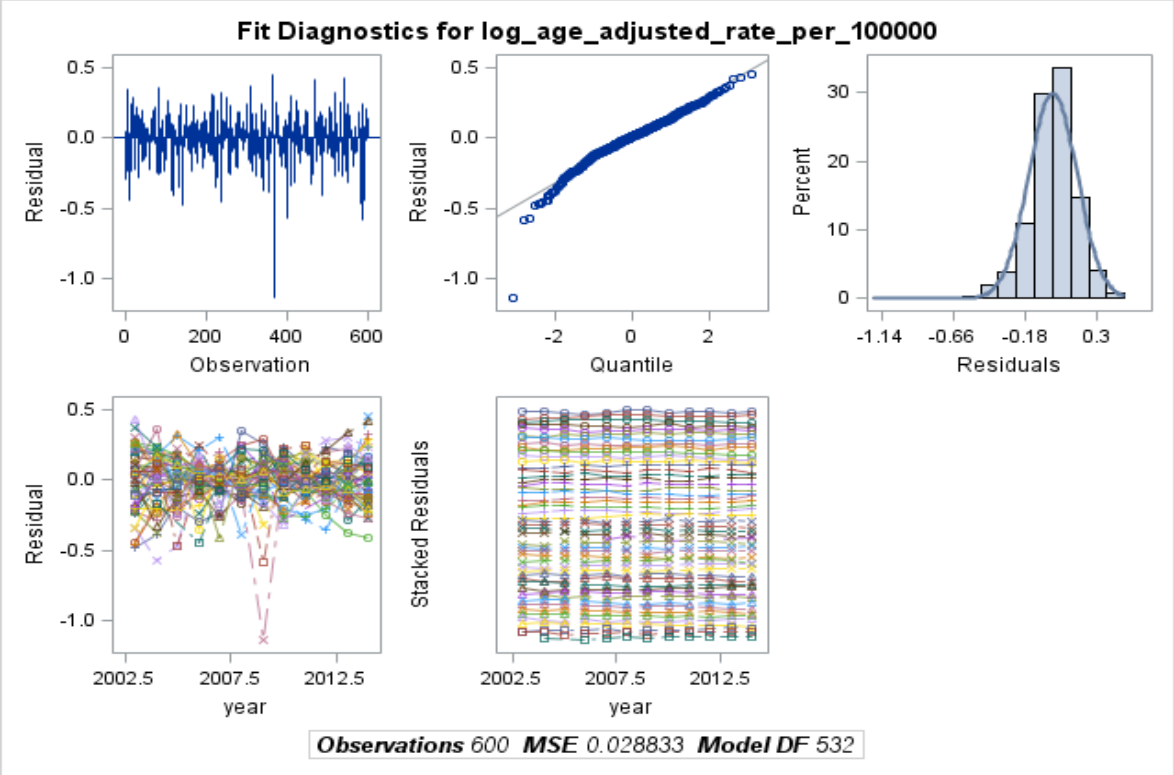

Figure 12. **Residual diagnostics for opioid, heroin and alcohol secondary overdose model, white population**

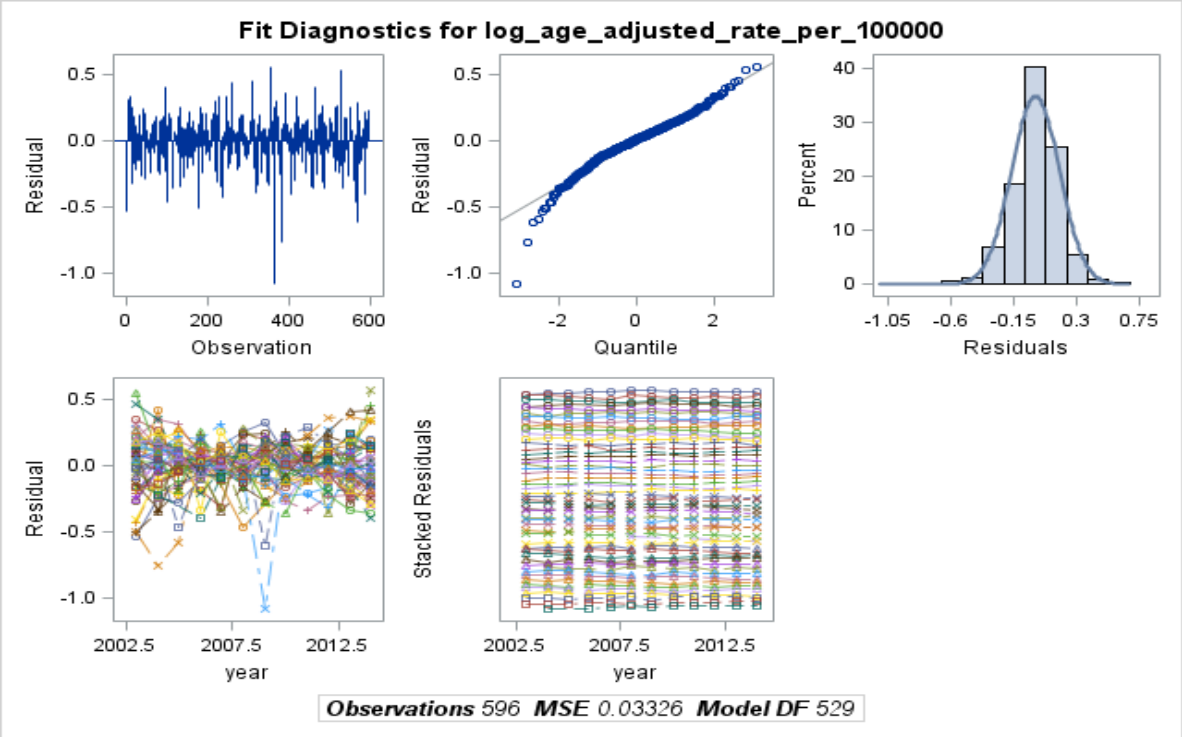

Figure 13. **Residual diagnostics for opioid and heroin primary overdose model, full population**

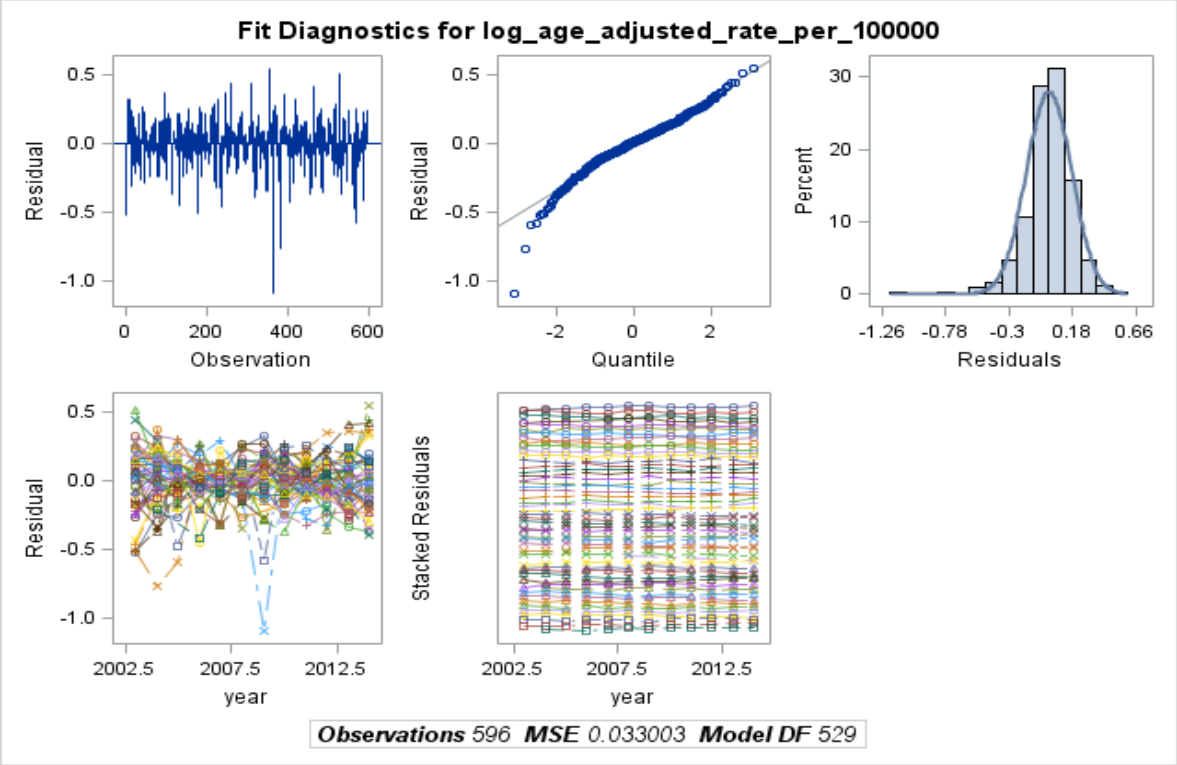

Figure 14. **Residual diagnostics for opioid and heroin primary overdose model, white population**

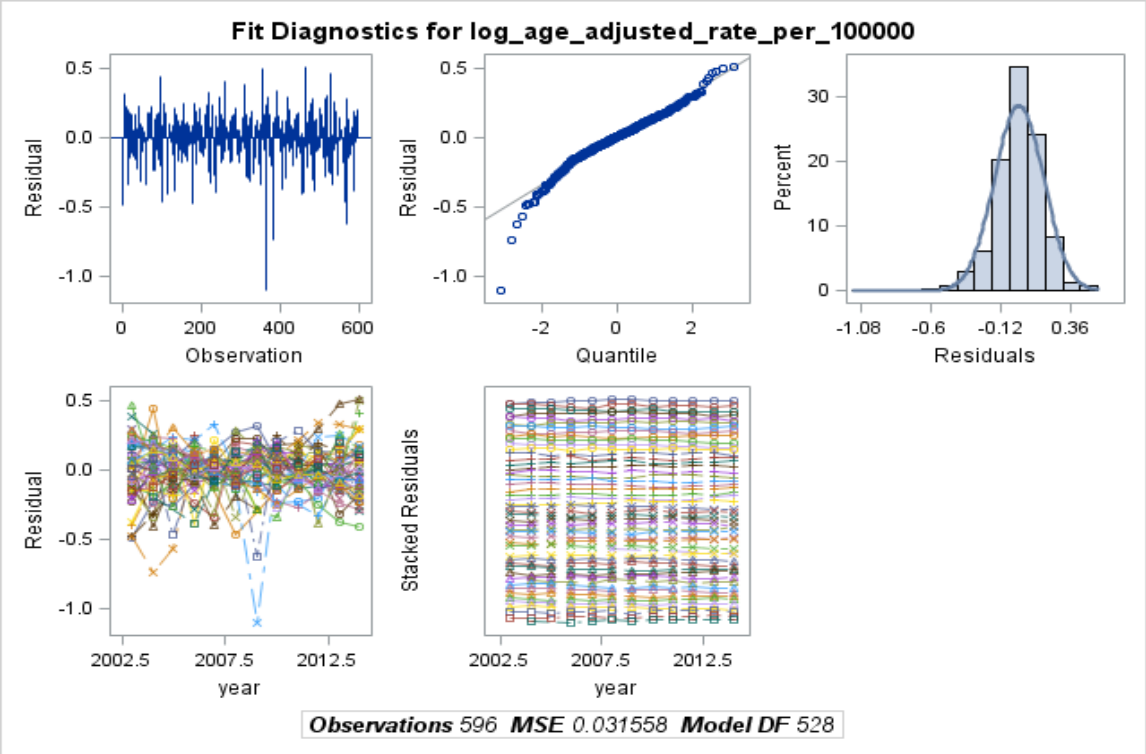

Figure 15. **Residual diagnostics for opioid and heroin secondary overdose model, full population**

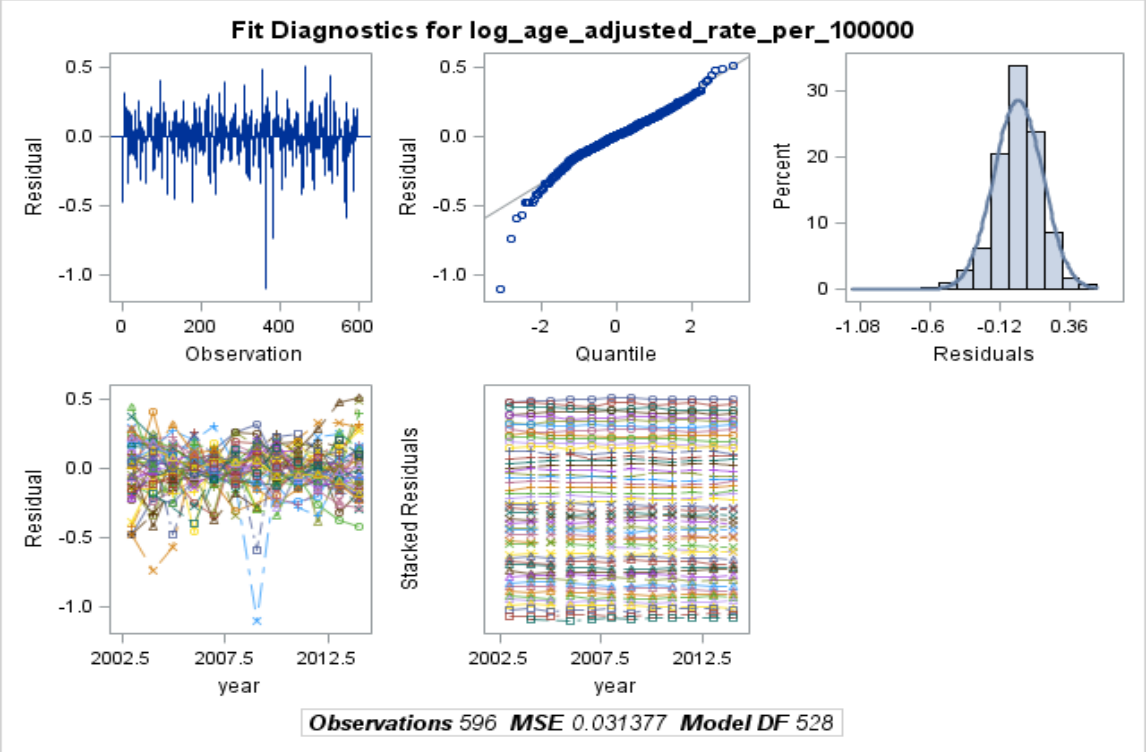

Figure 16. **Residual diagnostics for opioid and heroin secondary overdose model, white population**

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