Supplementary material for: A modeling study of the opioid epidemic for vulnerable communities in Knoxville, Tennessee

Kimberlyn Eversman[1], Adam Spannaus[3], Ryan Campbell[1], Leigh Pearcy[4], Jodie Trafton[5], AnujKapadia[3], and W. Christopher Strickland[1,2]

[1]Department of Mathematics, University of Tennessee, Knoxville, 37916, TN, USA
[2]Department of Ecology and Evolutionary Biology, University of Tennessee, Knoxville, 37916, TN, USA
[3]Computational Sciences and Engineering Division, Oak Ridge National Laboratory, Oak Ridge, 37830, TN, USA
[4]Department of Psychiatry, University of Pittsburgh, Pittsburgh, 15213, PA, USA
[5]Office of Mental Health, Veterans Health Administration, Palo Alto, 94025, GA, USA

1 Additional Background

1.1 Substance Use Disorder and Addiction Terminology

To discuss the opioid epidemic, it is important to have clear definitions of both substance use disorder (SUD) and addiction. According to the American Psychological Association (APA), SUD is defined as a cluster of physiological, behavioral, and cognitive symptoms associated with the continued use of substances despite substance-related problems, distress, and/or impairment, such as impaired control and risky use [2]. Previously in the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV), SUD was broken down into two diagnoses of substance abuse and substance dependence, where dependence was placed above abuse in a hierarchy by stipulating that abuse should not be diagnosed when dependence was present [7, 12]. However, in DSM–5, the SUD diagnosis combines and replaces the previous diagnoses of substance abuse and substance dependence [1]. It defines SUD using the following 11 criteria:

1. The individual may take the substance in larger amounts or over a longer period than was originally intended.

2. The individual may express a persistent desire to cut down or regulate substance use and may report multiple unsuccessful efforts to decrease or discontinue use.

3. The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects.

4. The individuals may experience cravings, which are manifested by an intense desire or urge for the drug that may occur at any time but is more likely when in an environment where the drug previously was obtained or used.

5. Recurrent substance use may result in a failure to fulfill major role obligations at work, school, or home.

6. The individual may continue substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.

7. Important social, occupational, or recreational activities may be given up or reduced because of substance use.

8. The individual may have recurrent substance use in situations in which it is physically hazardous.

9. The individual may continue substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

10. The individuals may develop tolerance signaled by requiring a markedly increased dose of the substance to achieve the desired effect or a markedly reduced effect when the usual dose is consumed.

11. The individuals may experience withdrawal, which is a syndrome that occurs when blood or tissue concentrations of a substance decline in an individual who has maintained prolonged, heavy use of the substance.

Criteria 1-4 deal with impaired control, criteria 5-7 with social impairment, criteria 8-9 with risky use, and criteria 10-11 with pharmacological criteria. A mild SUD is defined as having two to three symptoms, a moderate SUD as having four to five symptoms, and a severe SUD as having six or more symptoms.

Although the term "addiction" is not explicitly listed in the DSM–5, it is commonly regarded as a severe manifestation of SUD [20]. The National Institute on Drug Abuse defines addiction as a chronic, relapsing condition marked by compulsive drug-seeking and usage despite harmful consequences [21].

1.2 Effects of the COVID-19 Pandemic on Data Collection

We must acknowledge the changes and limitations in data collection that resulted from the COVID-19 pandemic and how this affects our understanding of the role it played in the opioid epidemic. A key source of data on OUD is the National Survey on Drug Use and Health (NSDUH), administered by the Substance Abuse and Mental Health Services Administration (SAMHSA). There is no state-level data for the 2019-2020 period due to methodological challenges in combining data from 2019 and 2020, which stemmed from the suspension of in-person data collection in 2020 [23]. Although web interviews were eventually conducted to continue data collection in 2020, there are known differences in how people respond to surveys administered online versus in person. The demographics of web respondents (e.g., by gender, race, education, etc.) differed from those of in-person respondents, and in-person respondents were more likely to be users of certain substances and were more likely to have experienced mental health issues. This created a "mode effect," complicating data consistency.

Furthermore, comparing national-level NSDUH data from before and after 2020 is problematic for several reasons [24]. SAMHSA opted to continue using a multi-mode data collection approach, incorporating both in-person and web interviews in 2021. This shift significantly altered the survey results, making them incomparable, even after weighing (adjusting) the data for demographic differences between the two respondent groups. Additionally, prior to 2021, the NSDUH used the fourth edition of the DSM–IV to diagnose SUD, whereas it now uses the DSM–5, which, as we discussed earlier, employs different diagnostic criteria. Another significant change is that, before 2021, the survey only asked individuals misusing prescription drugs more in-depth questions to determine if they have SUD. Since 2021, they have started asking more in-depth questions of both those who have misused prescription drugs and those who are using prescription drugs but are not misusing them to determine if they have a SUD. This enables them to identify milder cases of SUD (those who met only two or three SUD criteria from DSM–5).

1.3 Previous Work

The motivation for our ODE system comes from Phillips, Lenhart, and Strickland [28], which was inspired by Battista, Pearcy, and Strickland [6]. Battista, Pearcy, and Strickland created an ODE system for the national population consisting of four compartments: susceptibles, prescribed users, addicts, and individuals in treatment. Parameters were drawn from existing literature, and simulations were run to compare the model's predicted opioid overdose deaths with real-world data, validating the model's accuracy. They found that an addiction-free equilibrium could only be obtained for their model under the assumption that prescribed users did not become addicted to their own prescriptions and that there were no addictions that came from excess prescription drugs. While these assumptions were unrealistic, they revealed that, under these conditions, the basic reproduction number $\mathcal{R}_0$ was less than one, implying that the opioid epidemic could not persist without primary and secondary addiction. Furthermore, a Sobol sensitivity analysis showed that the addiction class was most sensitive to the rates of prescription completion and treatment entry. Higher values for these rates

were critical for reducing the addicted population. By focusing on key parameters that had the potential to be feasibly managed, the model shows that the addicted population could decrease in 10 years, given proper rates of prescription completion, treatment entry, and treatment completion. They concluded that effective intervention efforts should prioritize prescription completion and treatment entrance rates, followed by prescription rates and treatment completion.

Building on Battista, Pearcy, and Strickland's model, Phillips, Lenhart, and Strickland incorporated the role of heroin and fentanyl in the opioid epidemic. They expanded the addiction class into two distinct groups: prescription opioid addicts and heroin/fentanyl addicts, resulting in a five-class ODE model: susceptibles, prescription opioid users, prescription opioid addicts, heroin/fentanyl addicts, and stably recovered individuals. Previous models had not explicitly accounted for the connection between prescription opioid addiction and heroin/fentanyl addiction. In addition, Phillips et al. deviated from Battista et al. by defining a "stably" recovered class, consisting of individuals who had completed treatment and remained relapse-free for at least 4 weeks—a benchmark chosen due to the high relapse rates within the first month after treatment. To narrow the scope of their analysis, Phillips et al. focused on Tennessee instead of the national level, using state-level data on opioid prescriptions, overdoses, and heroin use to estimate parameters. They found that an addiction-free equilibrium could only be obtained for their model under the strict assumption of either ending all prescriptions for opioids or ending all prescription-based addiction (making the only way to become addicted to prescription opioids through illicit purchases). This was consistent with the unrealistic assumptions in Battista et al. However, they found that $\mathcal{R}_0$ was greater than one, indicating that the epidemic could be sustained by black market sales alone. Their model revealed that heroin and fentanyl had become the primary drivers of the opioid epidemic in Tennessee, with projections showing that addiction and overdose deaths related to heroin and fentanyl would continue to rise in the coming years (2020-2022), even as prescription opioid addiction decreased. They projected their model forward to 2023 and conducted a sensitivity analysis to identify the parameters most influential to the sizes of the compartments at the end of this period. This analysis helped pinpoint the most effective management strategies for reducing addicted individuals and overdose deaths. The most successful approaches, according to their findings, involved targeting treatment availability, monitoring stably recovered individuals to prevent relapse, and increasing efforts to reduce opioid overdose fatalities (e.g., expanding Naloxone distribution).

2 Model Formulation

2.1 Initial Model

The model consists of five general population subgroups (S_G, P_G, A_G, F_G, R_G) and six community population subgroups (S_C, S_H, P_C, A_C, F_C, R_C) within the general population groups. We assume that the individuals in each of the classes are homogeneous for the simplicity of a starting model. These are all measured as proportions of the entire general

population and community populations, respectively, so that

$$1 = S_G + P_G + A_G + F_G + R_G, \text{ and}$$
$$1 = S_C + S_H + P_C + A_C + F_C + R_C.$$

The general population compartments are characterized as follows:

1. Susceptibles S_G: represents individuals in the general population who are not taking prescribed opioids nor using fentanyl/heroin. We only consider the portion of the population aged 12 and older.

2. Prescription opioid users P_G: represents individuals in the general population who are prescribed opioids by a health care provider and take them in a manner not constituting an opioid use disorder as defined above (some misuse is possible, as long as it is in a manner such that potential for immediate harm is negligible).

3. Prescription opioid use disorder A_G: represents individuals in the general population who have a prescription opioid use disorder (POUD) as described but not using fentanyl/heroin. They may be actively in treatment for opioid use disorder and are still considered in this class for one month after being discharged from treatment, regardless of current use.

4. Fentanyl/heroin use disorder F_G: represents individuals in the general population who have fentanyl/heroin use disorder (FHUD) or are actively in treatment for opioid use disorder, including fentanyl/heroin. Individuals remain in this class for at least one month after being discharged from treatment, regardless of current use.

5. Stably recovered individuals R_G: represents individuals in the general population who complete treatment for opioid use disorder and do not relapse within one month after treatment is over, and therefore, we consider them to be in a "stable" recovery state. In cases where treatment is not a well-defined, discrete event (e.g., ongoing counseling, group support, solo attempts at recovery), one month without relapse alone characterizes inclusion in R_G versus A_G or F_G.

The community population compartments are characterized as follows:

1. Susceptibles without chronic pain S_C: represents individuals in the community who are not taking prescribed opioids nor using fentanyl/heroin. These individuals are also not experiencing chronic pain (pain lasting more than three months), though they might be experiencing acute pain (pain that lasts less than a month) or subacute pain (pain that lasts one to three months).

2. Susceptibles with chronic pain S_H: represents individuals in the community who are not taking prescribed opioids, nor using fentanyl/heroin, but have chronic pain (i.e., they are "hurt").

3. Prescription opioid users P_C: represents individuals in the community who are prescribed opioids by a health care provider and take them in a manner not constituting an opioid use disorder as defined above (some misuse is possible, as long as it is in a manner such that potential for immediate harm is negligible).

4. POUD A_C: represents individuals in the community who have POUD as described but not using fentanyl/heroin. They may be actively in treatment for opioid use disorder and are still considered in this class for one month after being discharged from treatment, regardless of current use.

5. Fentanyl/heroin use disorder F_C: represents individuals in the community who have FHUD or are actively in treatment for opioid use disorder, including fentanyl/heroin. Individuals remain in this class for at least one month after being discharged from treatment, regardless of current use.

6. Stably recovered individuals R_C: represents individuals in the community who complete treatment for opioid use disorder and do not relapse within one month after treatment is over, and therefore, we consider them to be in a "stable" recovery state. In cases where treatment is not a well-defined, discrete event (e.g., ongoing counseling, group support, solo attempts at recovery), one month without relapse alone characterizes inclusion in R_C versus A_C or F_C.

Due to the addictiveness of fentanyl and heroin, we assume that there are no casual users. If someone is using illicit fentanyl or uses fentanyl outside of the strict setting prescribed by their healthcare provider, they are considered to have a fentanyl use disorder. Additionally, due to the nature of heroin often being laced with fentanyl (knowingly or unknowingly to the user), we group those with fentanyl and heroin use disorders in the model.

In one study of 109 patients admitted to a residential addiction treatment service for detoxification, they found that 91% of patients reported a relapse after discharge [35]. Most of these occurrences took place within the first month, as 71% had relapsed within one month. Thus, due to the difficulties in recovery from OUD and the high rate of relapse, we use one month of no relapse after treatment as the benchmark for being stably recovered.

We denote the positive initial conditions for the model as $S_{G0} := S_G(0)$, $P_{G0} := P_G(0)$, $A_{G0} := A_G(0)$, $F_{G0} := F_G(0)$, $R_{G0} := R_G(0)$, $S_{C0} := S_C(0)$, $S_{H0} := S_H(0)$, $P_{C0} := P_C(0)$, $A_{C0} := A_C(0)$, $F_{C0} := F_C(0)$, and $R_{C0} := R_C(0)$. The system of ODEs describing the general population model is provided in (1), and (2) provides the system of ODEs describing

the community model.

$$
\begin{cases}
\dfrac{dS_G}{dt} = & -\alpha_G S_G - \beta_{GA} S_G A_G - \beta_{GP} S_G P_G - \theta_{S_G} S_G F_G + \varepsilon_G P_G \\
& + \mu \left(P_G + A_G + F_G + R_G \right) + \mu_A A_G + \mu_F F_G \\
\dfrac{dP_G}{dt} = & -\varepsilon_G P_G - \mu P_G - \gamma P_G - \theta_P P_G F_G + \alpha_G S_G \\
\dfrac{dA_G}{dt} = & -\zeta A_G - \theta_A A_G F_G - \left(\mu + \mu_A \right) A_G + \beta_{GA} S_G A_G + \beta_{GP} S_G P_G \\
& + \gamma P_G + \sigma R_G \dfrac{\lambda_A A_G + \left(1 - \lambda_F \right) F_G}{A_G + F_G + \omega} \\
\dfrac{dF_G}{dt} = & -\nu F_G - \left(\mu + \mu_F \right) F_G + \theta_{S_G} S_G F_G + \theta_P P_G F_G + \theta_A A_G F_G \\
& + \sigma R_G \dfrac{\left(1 - \lambda_A \right) A_G + \lambda_F F_G}{A_G + F_G + \omega} \\
\dfrac{dR_G}{dt} = & -\sigma R_G \dfrac{\lambda_A A_G + \left(1 - \lambda_F \right) F_G}{A_G + F_G + \omega} - \sigma R_G \dfrac{\left(1 - \lambda_A \right) A_G + \lambda_F F_G}{A_G + F_G + \omega} - \mu R_G \\
& + \zeta A_G + \nu F_G
\end{cases}
. \qquad (1)
$$

$$
\begin{cases}
\dfrac{dS_C}{dt} = & -\left[kF_G + (1-k)F_C\right]\theta_{S_C}S_C - \rho_C S_C - \left[kA_G + (1-k)A_C\right]\beta_{CA}S_C \\
& -\left[kP_G + (1-k)P_C\right]\beta_{CP}S_C - \alpha_C S_C + \rho_H S_H + \varepsilon_C P_C \\
& +\mu\left(S_H + P_C + A_C + F_C + R_C\right) + \mu_A A_C + \mu_F F_C \\
\dfrac{dS_H}{dt} = & -\left[kA_G + (1-k)A_C\right]\beta_{HA}S_H - \left[kP_G + (1-k)P_C\right]\beta_{HP}S_H \\
& -\rho_H S_H - \alpha_H S_H - \left[kF_G + (1-k)F_C\right]\theta_{S_H}S_H - \mu S_H \\
& +\rho_C S_C + \varepsilon_H P_C \\
\dfrac{dP_C}{dt} = & -\varepsilon_C P_C - \varepsilon_H P_C - \gamma P_C - \left[kF_G + (1-k)F_C\right]\theta_P P_C - \mu P_C \\
& +\alpha_H S_H + \alpha_C S_C \\
\dfrac{dA_C}{dt} = & -\left[kF_G + (1-k)F_C\right]\theta_A A_C - \zeta A_C - \left(\mu + \mu_A\right)A_C \\
& +\left[kA_G + (1-k)A_C\right]\beta_{CA}S_C + \left[kP_G + (1-k)P_C\right]\beta_{CP}S_C \\
& +\left[kA_G + (1-k)A_C\right]\beta_{HA}S_H + \left[kP_G + (1-k)P_C\right]\beta_{HP}S_H \\
& +\gamma P_C + \sigma R_C\dfrac{\lambda_A A_G + (1-\lambda_F)F_G}{A_G + F_G + \omega} \\
\dfrac{dF_C}{dt} = & -\nu F_C - \left(\mu + \mu_F\right)F_C + \left[kF_G + (1-k)F_C\right]\theta_{S_C}S_C \\
& +\left[kF_G + (1-k)F_C\right]\theta_{S_H}S_H + \left[kF_G + (1-k)F_C\right]\theta_P P_C \\
& +\left[kF_G + (1-k)F_C\right]\theta_A A_C + \sigma R_C\dfrac{(1-\lambda_A)A_G + \lambda_F F_G}{A_G + F_G + \omega} \\
\dfrac{dR_C}{dt} = & -\sigma R_C\dfrac{\lambda_A A_G + (1-\lambda_F)F_G}{A_G + F_G + \omega} - \sigma R_C\dfrac{(1-\lambda_A)A_G + \lambda_F F_G}{A_G + F_G + \omega} - \mu R_C \\
& +\zeta A_C + \nu F_C
\end{cases}
. \qquad (2)
$$

The parameters in this model represent transition rates from one class to another or births and deaths. All per capita yearly rates (units 1/year) are represented below for the general population model:

- $\alpha_G S_G$: rate at which susceptible individuals are prescribed opioids
- $\beta_{GA} S_G A_G$: rate at which susceptible individuals develop POUD primarily by illicit purchases or interaction with individuals in the general population with POUD
- $\beta_{GP} S_G P_G$: rate at which susceptible individuals develop POUD primarily by using left-over or stolen prescription drugs
- $\theta_{S_G} S_G F_G$: rate at which susceptible individuals develop FHUD by illicit purchases or interaction with individuals who have FHUD
- $\varepsilon_G P_G$: rate at which individuals return to the susceptible class after being prescribed opioids and finishing their prescription without developing an OUD

- $\mu S_G, \mu P_G, \mu A_G, \mu F_G, \mu R_G$: natural death rates, balanced with birth into S_G
- $\mu_A A_G$: overdose death rate for individuals with POUD
- $\mu_F F_G$: overdose death rate for individuals with FHUD
- γP_G: rate at which prescribed opioid users develop a POUD
- $\theta_P P_G F_G$: rate at which prescription opioid users develop FHUD
- $\sigma R_G \frac{\lambda_A A_G + (1-\lambda_F) F_G}{A_G + F_G + \omega}$: rate at which individuals transition from the recovered class into the POUD class due to relapse. Individual history is not tracked in the model, so the transition is proportional to $\frac{\lambda_A A_G + (1-\lambda_F) F_G}{A_G + F_G + \omega}$, where $\lambda_A, \lambda_F \in [0, 1]$ are used to skew the results towards A_G or F_G, respectively. We include a perturbation term ω for the case that $A_G = F_G = 0$.
- ζA_G: rate at which those with POUD stably recover
- $\theta_A A_G F_G$: rate at which those with POUD develop FHUD
- $\sigma R_G \frac{(1-\lambda_A) A_G + \lambda_F F_G}{A_G + F_G + \omega}$: rate at which individuals transition from the recovered class into the fentanyl class due to relapse. Individual history is not tracked in the model, so the transition is proportional to $\frac{(1-\lambda_A) A_G + \lambda_F F_G}{A_G + F_G + \omega}$, where $\lambda_A, \lambda_F \in [0, 1]$ are used to skew the results towards A_G or F_G, respectively. We include a perturbation term ω for the case that $A_G = F_G = 0$.
- νF_G: rate at which individuals with FHUD stably recover

All per capita yearly rates (units 1/year) are represented below for the community population model:

- $\rho_C S_C$: rate at which susceptible individuals without chronic pain develop chronic pain
- $\rho_H S_H$: rate at which susceptible individuals with chronic pain no longer have chronic pain
- $\alpha_H S_H$: rate at which susceptible individuals with chronic pain are prescribed opioids
- $\alpha_C S_C$: rate at which susceptible individuals without chronic pain are prescribed opioids
- $[kA_G + (1-k)A_C]\,\beta_{CA} S_C$: rate at which susceptible individuals without chronic pain develop POUD primarily by illicit purchases or interaction with individuals in the general population with POUD
- $[kA_G + (1-k)A_C]\,\beta_{HA} S_H$: rate at which susceptible individuals with chronic pain develop POUD primarily by illicit purchases or interaction with individuals who have POUD
- $[kP_G + (1-k)P_C]\,\beta_{CP} S_C$: rate at which susceptible individuals without chronic pain develop POUD primarily by using left-over or stolen prescription drugs

- $[kP_G + (1-k)P_C]\,\beta_{HP} S_H$: rate at which susceptible individuals with chronic pain develop POUD primarily by using left-over or stolen prescription drugs
- $[kF_G + (1-k)F_C]\,\theta_{S_C} S_C$: rate at which susceptible individuals without chronic pain develop FHUD by illicit purchases or interaction with individuals who have FHUD
- $[kF_G + (1-k)F_C]\,\theta_{S_H} S_H$: rate at which susceptible individuals without chronic pain develop FHUD by illicit purchases or interaction with individuals who have FHUD
- $\varepsilon_C P_C$: rate at which individuals move to the susceptible without chronic pain class after being prescribed opioids and finishing their prescription without developing an OUD and with having their chronic pain resolved
- $\varepsilon_H P_C$: rate at which individuals return to the susceptible with chronic pain class after being prescribed opioids and finishing their prescription without developing an OUD and without having their chronic pain resolved
- $\mu S_C, \mu S_H, \mu P_C, \mu A_C, \mu F_C, \mu R_C$: natural death rates, balanced with birth into S_C
- $\mu_A A_C$: overdose death rate for individuals with POUD
- $\mu_F F_C$: overdose death rate for individuals with FHUD
- γP_C: rate at which prescribed opioid users become individuals with POUD
- $[kF_G + (1-k)F_C]\,\theta_P P_C$: rate at which prescribed opioid users become individuals with FHUD
- $\sigma R_C \frac{\lambda_A A_G + (1-\lambda_F)F_G}{A_G + F_G + \omega}$: rate at which individuals transition from the recovered class into the POUD class due to relapse. Individual history is not tracked in the model, so the transition is proportional to $\frac{\lambda_A A_G + (1-\lambda_F)F_G}{A_G + F_G + \omega}$, where $\lambda_A, \lambda_F \in [0,1]$ are used to skew the results towards A_C or F_C, respectively. We include a perturbation term ω for the case that $A_G = F_G = 0$.
- ζA_C: rate at which those with POUD stably recover
- $[kF_G + (1-k)F_C]\,\theta_A A_C$: rate at which individuals with POUD develop FHUD
- $\sigma R_C \frac{(1-\lambda_A)A_G + \lambda_F F_G}{A_G + F_G + \omega}$: rate at which individuals transition from the recovered class into the FHUD class due to relapse. Individual history is not tracked in the model, so the transition is proportional to $\frac{(1-\lambda_A)A_G + \lambda_F F_G}{A_G + F_G + \omega}$, where $\lambda_A, \lambda_F \in [0,1]$ are used to skew the results towards A_C or F_C, respectively. We include a perturbation term ω for the case that $A_G = F_G = 0$.
- νF_C: rate at which individuals with FHUD stably recover

Although the model does not explicitly account for drug sellers, we acknowledge that they play a role in the development of OUD, even though the individuals involved in drug selling may not necessarily have OUD themselves. We assume that as the number of individuals

with OUD increases, the demand for drug sellers rises, leading to greater availability of opioids. This, in turn, increases exposure to illicit opioid sales, thereby contributing to the proliferation of OUD cases. This dynamic is captured by the interaction terms involving β_{GA}, β_{CA}, β_{HA}, θ_{S_G}, θ_{S_H}, and θ_{S_H}, all of which grow with the A and F classes.

Since we cannot track whether individuals in the recovered classes previously had POUD or FHUD, we use the proportion of individuals in each OUD class at the time of relapse to determine the class into which they relapsed. While this approximation relies on current class proportions rather than the proportions at the time of recovery, it offers a reasonable estimate. Unlike Phillips et al.'s model [28], our model introduces the parameters λ_A and λ_F, allowing skewed relapse rates into the POUD or FHUD classes. For example, this means that even if POUD is more prevalent, individuals who relapse after stable recovery might be more likely to relapse into FHUD, and vice versa. These parameters give us the flexibility to model such behaviors.

We have not included an interaction term between the P and A classes, assuming that individuals with POUD are more likely to develop the disorder from their own prescriptions than from external sources. Additionally, we assume that individuals who have recovered from OUD have different transition rates into the A and F classes compared to the S class (i.e., they are more likely to transition into an OUD class than someone who has never had an OUD). As a result, there is no direct transition between the R and S classes.

By modeling both the community and the surrounding general population, we can explore how the general availability of opioids and fentanyl/heroin influences the community of interest. The impact of the broader general population on the community is reflected in the following interaction terms: $\theta_{S_C} S_C F_G$, $\beta_{CA} S_C A_G$, $\beta_{CP} S_C P_G$, $\beta_{HA} S_H A_G$, $\beta_{HP} S_H P_G$, $\theta_{S_H} S_H F_G$, $\theta_P P_C F_G$, and $\theta_A A_C F_G$.

The S_C class includes individuals with no pain, acute pain, or subacute pain, while the S_H class encompasses those with chronic pain. Acute pain is defined as pain lasting less than a month, typically due to injury, trauma, surgery, or infection, while subacute pain lasts from one to three months [8]. Chronic pain, on the other hand, persists for more than three months and can arise from various causes, including disease, injury, medical treatment, or inflammation. Unresolved acute or subacute pain can sometimes progress into chronic pain [4]. Both S_C and S_H classes may be prescribed opioids (transitioning into the P_C class). However, it is reasonable to assume that individuals in the S_H class are more likely to be prescribed opioids to manage their chronic pain on top of possibly being prescribed opioids for events like minor injury or surgery, like in the S_C class. Nevertheless, we stratify the susceptible community into S_C and S_H to model how access to additional resources, such as therapy, physical therapy, or exercise, could help reduce the number of individuals being prescribed opioids.

Finally, it is reasonable to assume that a community might have more influence on its members than the surrounding general population does. Thus, the interaction terms, like the transition from the A_C class to the F_C class, are as such

$$k\theta_A A_C F_G + (1-k)\theta_A A_C F_C, \tag{3}$$

where k is a constant. In (3), we see that if $k = 0$, the interactions the community have

are exclusively within their community: They are segregated from the general population. If $k = 1$, there is no discrimination or preference between interacting with those in or out of the community: They interact with everyone equally.

3 Numerical Results

3.1 Data Calculations

We apply the model to the Knoxville, TN Metropolitan Statistical Area (MSA), which includes nine counties: Anderson, Blount, Campbell, Grainger, Knox, Loudon, Morgan, Roane, and Union, covering the years 2016 to 2019. As part of the Appalachian region, this area was notably impacted by the opioid epidemic [3, 17]. Analyzing this region allows us to examine the model on a more localized scale rather than the broader national or state levels explored in previous studies. Furthermore, considering the entirety of the Knoxville MSA provides diversity between urban and rural areas, compared to focusing only on one county.

We begin the model in 2016 because, between 2015 and 2016, overdose deaths from synthetic opioids (such as fentanyl) surpassed those from heroin and prescription opioids nationally, a trend that has continued since [9]. We conclude the model in 2019 due to the absence of post-COVID-19 data. As more post-pandemic data becomes available, we plan to extend the model to include future years. However, given the profound impact COVID-19 had on both the United States and the opioid crisis, a separate model will likely be needed to address the post-COVID-19 era.

An explanation of the data's origin and the processing steps taken to fit the model is provided below. A summary of the yearly and quarterly estimates for the number of individuals in each category is presented in Table 1 and Table 3, respectively. A summary of the yearly overdose estimates can be seen in Table 2.

Total Population 12 Years and Older

We obtain the total population estimates by county for July 1st of the years 2010-2022 and aggregate the counties of interest together to provide us with the Knoxville MSA area [58, 59]. To be consistent with the other data sets, we are concerned with the population on January 1st of each year that is age 12 and older. We use a cubic interpolation to estimate the total population for January 1st of each year.

To estimate the population that is age 12 and older, we use period life tables for years 2016, 2017, 2019, and 2020, which provide the death probability, defined as the probability of dying within one year, of a person born on January 1st for males and females separately [38, 39, 40, 41]. Using this information, we create two Leslie matrices, one for males and one for females, for each of these years. Each row corresponds to an integer age from the period life table. We assume that the death rate for each age equals the birth rate from that age into age zero; thus, the death probabilities provide the fecundity rates. The survival probability along the off-diagonal of the Leslie matrix is then equal to one minus the death probability. Normalizing the dominant eigenvector of each matrix such that the vector sums

Table 1: Yearly estimates for the number of individuals in each category listed for years 2016-2022. **Bolded numbers** are data used directly in parameter estimation in Section 3.3.

Knoxville MSA Yearly Data	2016	2017	2018	2019	2020	2021	2022
Total Population	864,069	872,431	880,795	887,859	898,921	911,688	923,579
Total Population 12+	**677,952**	**684,276**	**690,529**	**695,749**	707,974	718,061	727,406
Fentanyl/Heroin Users	808	812	758	504	-	-	-
FHUD	**534**	**598**	**494**	**297**	-	-	-
POUD	3,148	**1,436**	**1,375**	**1,123**	-	-	-
Prescription Opioid Users (including OUD)	232,570	220,139	198,144	183,657	167,840	164,897	158,747
Prescription Opioid Users (excludes OUD)	**231,176**	**219,503**	**197,535**	**183,160**	-	-	-

Table 2: Yearly overdose estimates for years 2016-2021. **Bolded numbers** are data used directly in parameter estimation in Section 3.3.

Knoxville MSA Yearly Data	2016	2017	2018	2019	2020	2021
Fatal Overdoses Involving All Opioids	244	306	307	281	432	654
Fatal Overdoses Involving Fentanyl	55	150	191	190	357	588
Fatal Overdoses Involving Heroin	31	61	87	67	83	56
Fatal Overdoses Involving Prescription Opioids	163	153	122	106	97	139
Nonfatal Overdoses Involving Heroin	387	764	902	683	863	1,110
Nonfatal Overdoses Involving All Opioid Overdose Excluding Heroin	773	759	682	593	659	917
POUD Fatal Overdoses	**73**	**69**	**55**	**48**	44	62
FHUD Fatal Overdoses	**146**	**167**	**163**	**144**	221	316

Table 3: Quarterly estimates for those who have had prescriptions for opioids. **Bolded numbers** are data used directly in parameter estimation in Sections 3.3.

Quarter	State-level Presc. Opioid Users (including OUD)	Knox. MSA Presc. Opioid Users (including OUD)	Knox. MSA Presc. Opioid Users (excluding OUD)
2016 Q1	1,959,678	85,102	**84,592**
2016 Q2	1,935,484	84,051	**83,548**
2016 Q3	1,899,194	82,475	**81,981**
2016 Q4	1,854,839	80,549	**80,067**
2017 Q1	1,790,323	78,072	**77,847**
2017 Q2	1,770,162	77,192	**76,969**
2017 Q3	1,721,775	75,082	**74,866**
2017 Q4	1,665,323	72,621	**72,412**
2018 Q1	1,572,581	69,228	**69,016**
2018 Q2	1,568,549	69,050	**68,838**
2018 Q3	1,471,775	64,790	**64,591**
2018 Q4	1,447,581	63,725	**63,530**
2019 Q1	1,395,162	62,568	**62,399**
2019 Q2	1,370,968	61,483	**61,317**
2019 Q3	1,350,807	60,579	**60,416**
2019 Q4	1,314,517	58,952	**58,793**
2020 Q1	1,262,097	55,992	-
2020 Q2	1,209,678	53,667	-
2020 Q3	1,282,259	56,887	-
2020 Q4	1,254,033	55,635	-

to one gives us the stable age structure for each sex. The sum of the vector elements that correspond to ages 12 and older then estimates the proportion of the population that is 12 and older for that sex. Simply multiplying this by the corresponding population estimate for that sex and adding the two together gives us the total population estimate for those aged 12 and older. To estimate the total population of those aged 12 and older in 2018, we take the averages for 2017 and 2019 and multiply them by the total population in 2018. For 2021 and 2022, we used the proportion from 2020. The resulting data may be seen in Table 1.

Prescription Opioid Fatal Overdoses and POUD Fatal Overdoses

In 2016, there were 174 fatal drug overdoses involving prescription opioids for residents of the Knoxville MSA; in 2017, there were 153; in 2018, there were 122; in 2019, there were 106; in 2020, there were 97; and in 2021 there were 139 [26]. Overdose deaths are determined by ICD-10 codes or literal text derived from death certificates and are listed as the underlying cause of death in the Tennessee Death Statistical Files [27]. To qualify as a fatal drug overdose involving prescription opioids, the death must meet all drug overdose criteria and contain either the code for acute poisoning by natural or semi-synthetic opioids or the code for acute poisoning by methadone as a contributing cause of death. This data accounts for individuals of all ages, but we assume the number of residents who have overdosed under the age of 12 is negligible.

In 2019, out of the total 515 fatal prescription opioid overdoses that occurred in Tennessee, 59 also involved heroin, and 227 also involved fentanyl [25]. This leaves us with at least 229 fatal prescription opioid overdoses in Tennessee that did not involve fentanyl or heroin. Note this might be underestimated since individuals who overdosed on prescription opioids, heroin, and fentanyl would be counted in both the fatal overdoses involving prescription opioids and heroin and the fatal overdoses involving prescription opioids and fentanyl. This gives us a rough estimate that in 2019, roughly $229/515 \approx 44.5\%$ of fatal prescription opioid overdoses did not involve fentanyl or heroin. We note that the number of fatal overdoses involving fentanyl was relatively close between 2016 and 2019 but nearly doubled in 2020 and 2021, so this is not the best estimate for 2020-2021. However, we use this estimate for 2016-2021 until additional polydrug data becomes available. So we take 44.5% of the number of fatal drug overdoses involving prescription opioids for the Knoxville MSA for each of these years to estimate the number of fatal overdoses involving prescription opioids but excluding fentanyl/heroin for residents of the Knoxville MSA for 2016-2021. Note that this might be an overestimate for the number of individuals who died of an overdose with POUD since this includes those who overdosed on prescription opioids but did not necessarily have POUD as well. However, we assume that this roughly balances out the potential underestimate from using the polydrug data and use this for the estimated number of fatal overdoses for those with POUD, as can be seen in Table 2.

Fentanyl/Heroin Fatal Overdoses

The total number of fatal overdoses involving all opioids, fatal overdoses involving fentanyl, and fatal overdoses involving heroin in the Knoxville MSA are listed in rows one, two, and

three of Table 2, respectively [26]. Overdose deaths are determined by ICD-10 codes or literal text derived from death certificates and are listed as the underlying cause of death in the Tennessee Death Statistical Files [27]. To qualify as a fatal drug overdose involving fentanyl, the death must meet all drug overdose criteria and contain the text 'FENTAN', 'FANTAN', or 'FENTA' written in the cause of death on the death certificate. To qualify as a fatal drug overdose involving heroin, the death must meet all drug overdose criteria and contain acute poisoning by heroin as a contributing cause of death. To qualify as a fatal drug overdose involving all opioids, the death must meet all drug overdose criteria and contain at least one of the following codes for

- acute poisoning by opium,
- acute poisoning by heroin,
- acute poisoning by natural to semi-synthetic opioids,
- acute poisoning by methadone,
- acute poisoning by synthetic opioids other than methadone, or
- acute poisoning by other or unspecified narcotics

as a contributing cause of death or contain the text 'FENTAN', 'FANTAN', or 'FENTA' written in the cause of death on the death certificate. This data accounts for individuals of all ages, but we assume the number of residents who have overdosed under the age of 12 is negligible.

Since those who are accounted for in fatal overdoses involving fentanyl and those who are accounted for in fatal overdoses involving heroin are not mutually exclusive, we do not want to double-count them by simply summing their totals together to get the total number of fatal overdoses involving fentanyl or heroin. Instead, we take the total number of fatal overdoses involving all opioids and subtract the estimate for the total number of fatal overdoses of those with POUD. However, we note that this estimate might include fatal overdoses involving non-opioids (such as cocaine or methamphetamine) being laced with fatal amounts of fentanyl. Thus, this has the potential to overestimate the fatal overdose risk of those with FHUD. To offset this potential overestimate, we look at 2019, where we know out of the total 1087 fatal overdoses involving fentanyl in Tennessee, 319 also involved psychostimulants (including methamphetamine) and 192 also involved cocaine [25]. Thus, at least 576 fatal fentanyl overdoses in Tennessee did not involve psychostimulants or cocaine. Note that this might be an underestimate as an individual who overdosed on fentanyl, psychostimulants, and cocaine would be counted in both the fatal overdoses involving fentanyl and psychostimulants and the fatal overdoses involving fentanyl and cocaine. This gives us an estimate that roughly $(1087 - 576)/1087 \approx 47.0\%$ of fatal fentanyl overdoses also involved psychostimulants or cocaine in 2019. Note that the number of fatal overdoses involving fentanyl was relatively the same between 2016 and 2019 but nearly doubled in 2020 and 2021, so this isn't the best estimate for 2020-2021. Until more data becomes available, though, we use this estimate for 2016-2021. Thus, to get the final estimate for the number of fatal FHUD overdoses for the

Knoxville MSA, we take the total number of fatal overdoses involving all opioids, subtract the estimate for the total number of fatal overdoses of those with POUD, and subtract 47.0% of the number of fatal overdoses involving fentanyl for 2016-2021 as can be seen in Table 2.

Fentanyl/Heroin Users and Fentanyl/Heroin Use Disorder

The 2015/2016 average number estimate of individuals 12 and older who have used heroin in the past year is 14000 for Tennessee [44]. For 2016/2017 it is 19000, for 2017/2018 it is 18000, and for 2018/2019 it is 17000 [49, 51, 54]. We use the greater of the 2 years as the estimates. For example, the 2015/2016 average is used to represent the 2016 estimate. Unfortunately, the estimates for 2019/2020 are no longer available due to methodological concerns with combining 2019 and 2020 data [55]. There is however preliminary data that tells us that in 2021, the average number of individuals 18 and older who have used heroin in the past year is 55000 for Tennessee [56]. Note that youths aged 12 to 17 are not included in this estimate because past year heroin use was extremely rare among youths aged 12 to 17 in the 2021 NSDUH. It also is important to note that because the 2021 estimate is based on a single year of data instead of the usual two-year estimate, there is a greater variance around the estimate for this year.

Finally, it is estimated that in 2016, 626,000 individuals 12 and older in the past year had heroin use disorder, and 948,000 individuals 12 and older have used heroin in the past year in the United States [45, 48]. For 2017 there were 652,000 and 886,000, for 2018 there were 526,000 and 808,000, and for 2019 there were 438,000 and 745,000 individuals 12 and older who had heroin use disorder and used heroin in the past year, respectively [45, 48, 52, 53].

The data covers residents of households, noninstitutional group quarters (e.g., shelters, rooming houses, dormitories), and civilians living on military bases but does not include homeless people who do not use shelters, military personnel on active duty, and residents of institutional group quarters, such as jails or prisons and long-term hospitals. The survey is conducted using an audio computer-assisted self-interviewing program which is designed to provide the respondent with a highly private and confidential means of responding to questions and increases the level of honest reporting of illicit drug use and other sensitive behaviors [42]. We note that this data is self-reported and thus runs the risk of under-reporting the use of illicit drugs.

The NSDUH categorizes respondents who used heroin in the past 12 months as having a heroin use disorder if they met DSM–IV criteria for either dependence or abuse of heroin [50]. There are seven possible dependence criteria for heroin:

1. spent a lot of time engaging in activities related to use of the drug,
2. used the drug in greater quantities or for a longer time than intended,
3. developed tolerance to the drug,
4. made unsuccessful attempts to cut down on use of the drug,
5. continued to use the drug despite physical health or emotional problems associated with use,

6. reduced or eliminated participation in other activities because of use of the drug, and
7. experienced withdrawal symptoms when respondents cut back or stopped using the drug.

Dependence is defined as meeting three or more of these seven criteria. Respondents who used heroin in the past 12 months and did not meet the dependence criteria for heroin were defined as having abuse for heroin if they reported one or more of the following:

1. problems at work, home, or school because of use of the drug;
2. regularly using the drug and then doing something physically dangerous;
3. repeated trouble with the law because of use of the drug; and
4. continued use of the drug despite problems with family or friends.

Using the available overdose data (as seen in Table 2), we determined the percentage of nonfatal overdoses involving heroin in Tennessee that took place in Knoxville MSA for each available year. Similarly, we also determined the percentage of fatal overdoses involving fentanyl and the percentage of fatal overdoses involving heroin that took place in Knoxville MSA for each year. Averaging these three percent for each year and multiplying them times the corresponding year's estimate of individuals 12 and older who have used heroin in the past year in Tennessee gives us an estimate of the number of individuals 12 and older who used heroin in the past year for the Knoxville MSA as can be seen in Table 1.

Finally, we determine the ratio of the number of individuals 12 and older who have had heroin use disorder in the past year to the number of individuals 12 and older who have used heroin in the past year from the national data. Multiplying this ratio for each year with the final estimated number of individuals 12 and older who used heroin in the past year in the Knoxville MSA gives us an estimate of the total number of individuals 12 and older who have heroin use disorder in the Knoxville MSA, as can be seen in Table 1.

Note there is currently no data available on fentanyl users or those with fentanyl use disorder in Tennessee. The estimations here mainly draw from available heroin data. Thus, these estimations are likely underestimated.

Prescription Opioid Use Disorder

The 2015/2016 average number estimate of individuals 12 and older who have had "pain reliever use disorder" in the past year is 48000 for Tennessee. For 2016/2017, it is 42000; for 2017/2018, it is 42000; and for 2018/2019, it is 39000. We use the greater of the two years for that year's estimate.

The data covers residents of households, noninstitutional group quarters (e.g., shelters, rooming houses, dormitories), and civilians living on military bases but does not include homeless people who do not use shelters, military personnel on active duty, and residents of institutional group quarters, such as jails or prisons and long-term hospitals. The survey

is conducted using an audio computer-assisted self-interviewing program which is designed to provide the respondent with a highly private and confidential means of responding to questions and increases the level of honest reporting of illicit drug use and other sensitive behaviors [42]. We note that this data is self-reported and thus runs the risk of under-reporting the use of illicit drugs.

The NSDUH categorizes respondents who have misused pain relievers in the past 12 months as having a pain reliever use disorder if they met DSM–IV criteria for either dependence or abuse of pain delivers [50]. There are seven possible dependence criteria for pain relievers:

1. spent a lot of time engaging in activities related to use of the drug,
2. used the drug in greater quantities or for a longer time than intended,
3. developed tolerance to the drug,
4. made unsuccessful attempts to cut down on use of the drug,
5. continued to use the drug despite physical health or emotional problems associated with use,
6. reduced or eliminated participation in other activities because of use of the drug, and
7. experienced withdrawal symptoms when respondents cut back or stopped using the drug.

Dependence is defined as meeting three or more of these seven criteria. Respondents who used misused pain relievers in the past 12 months and did not meet the dependence criteria were defined as having abused pain relievers if they reported one or more of the following:

1. problems at work, home, or school because of use of the drug;
2. regularly using the drug and then doing something physically dangerous;
3. repeated trouble with the law because of use of the drug; and
4. continued use of the drug despite problems with family or friends.

To estimate the number of people 12 and older in the Knoxville MSA that have had pain reliever use disorder in the past year, we use a method similar to the method used for fentanyl/heroin users. Using the available overdose data (as seen in Table 2), we determined the percentage of nonfatal overdoses involving all opioid overdoses excluding heroin in Tennessee that took place in Knoxville MSA for each available year. Similarly, we also determined the percentage of fatal overdoses involving prescription opioids that took place in Knoxville MSA for these years. Averaging these two percent for each year and multiplying them times the corresponding year's estimate of individuals 12 and older who have had prescription pain reliever use disorder in the past year in Tennessee gives us an estimate of the number of individuals 12 and older who have had prescription pain reliever use disorder in the past year for the Knoxville MSA.

People who use heroin consistently seldom continue using prescription opioids for a variety of reasons, including the availability of heroin, heightened scrutiny by health care providers, and the lower price of heroin [19]. We thus assume the number of individuals with FHUD represented in the estimate of those who have had prescription pain reliever use disorder in the past year is negligible. Thus, row 5 of Table 1 is the final estimate for the number of individuals with POU in the Knoxville MSA.

Prescribed Opioid Users (includes Opioid Use Disorder)

The total number of people who have filled an opioid prescription for the Knoxville MSA for 2016-2022 is given in Table 1. This data comes from Tennessee's Controlled Substance Monitoring Database (CSMD) [26]. This data accounts for individuals of all ages, but we assume the number of residents who have filled a prescription under the age of 12 is negligible. In addition, though we know that these residents are filling their prescriptions for opioids, we do not know if they are taking them or if they are selling or sharing them.

Prescribed Opioid Users (excludes Opioid Use Disorder)

One study using 2015 NSDUH estimates found that among adults who have had POU within the past 12 months, 44.3% obtained prescription opioids for their most recent episode of misuse from one or more physicians [11]. Taking 44.3% of the number of individuals with POU gives us an estimate for the number of people with POU who have prescriptions. We subtract this number from the total number of people with a prescription for opioids to determine the number of people who have a prescription for opioids but do not have POU, as can be seen in Table 1.

Quarterly Prescribed Opioid Users (excludes Opioid Use Disorder)

The Tennessee Department of Health has state-wide estimates for the number of residents receiving opioids for pain quarterly from 2016-2020 [25]. In the report, a graph is given without specific numbers. Using WebPlotDigitizer, we estimate the numbers from this graph as seen in column 1 of Table 3 [31].

To estimate the number of residents receiving opioids for pain for the Knoxville MSA, we determine the proportion of the population with an opioid prescription (including individuals with an opioid use disorder) from the yearly data and then multiply this ratio for each quarter in the year, as can be seen in column 3 of Table 3. Note that this estimate included those who may have opioid use disorder.

To then estimate the number of residents with prescriptions for opioids without opioid use disorder, we first calculate the ratio of residents with a prescription for opioids (including individuals with an opioid use disorder) for that quarter compared to the entire year. We then multiply this ratio by the yearly estimate of prescribed opioid users excluding opioid use disorder (row 7 of Table 1). The result is in column 4 of Table 3. Again, we note that though we know that these residents are filling their prescriptions for opioids, we do not know if they are taking them or if they are selling or sharing them.

3.2 Parameter Calculations

We calculate the death rate (μ) and the overdose death rates (μ_A and μ_F) from available mortality information.

We calculate the continuous-time POUD death rate and the continuous-time FHUD death rate in the year 2017 since we have a reasonable estimate for the number of fatal overdoses of those with POUD, and it is in the middle of the pre-COVID time range. From Table 2 and Table 1, we see that in 2017, 69 individuals died of a fatal overdose with POUD and a total of 3148 individuals had POUD. Thus, $(3148 - 69)/3148 \approx 0.978$ of the total POUD population from 2017 remains at the start of 2018. If we let A_0 be the total proportion of the population with POUD in 2017, then we may determine μ_A with the equation

$$\frac{3148 - 69}{3148} A_0 = A_0 e^{-\mu_A t}$$

with $t = 1$. This gives us that $\mu_A \approx 0.0222$. Similarly, from Table 2 and Table 1, we see that in 2017, 167 individuals died of a fatal overdose with FHUD, and a total of 598 individuals had FHUD. If we let F_0 be the total proportion of the population with FHUD in 2017, then we determine μ_F with the equation

$$\frac{598 - 167}{598} F_0 = F_0 e^{-\mu_F t}$$

with $t = 1$. This gives us that $\mu_F \approx 0.327$.

In 2017, the total number of deaths in the Knoxville MSA was 9948 [57]. We assume that the number of individuals under the age of 12 who died is negligible. Subtracting off the number of individuals who died in 2017 of an overdose with POUD or FHUD leaves us with 9712 deaths. From Table 1, we see that in 2017, the total population of the Knoxville MSA 12 and older was 684,276. If we let T_0 be the total proportion of the population 12 and older in 2017, then using the equation

$$\frac{684276 - 9712}{684276} T_0 = T_0 e^{-\mu t}$$

we get that $\mu \approx 0.0143$, the continuous-time natural death rate.

Finally, since ω is used to keep from dividing by zero in the case that A_G and F_G are zero, we let it be 10^{-10}.

These assumed values are shown in Table 4. For the remaining parameters, we will need to determine ranges from which to estimate them.

Table 4: Assumed parameters calculated from mortality data.

Parameter	Assumed Value	Units
μ	0.0143	$\frac{1}{\text{year}}$
μ_A	0.0222	$\frac{1}{\text{year}}$
μ_F	0.327	$\frac{1}{\text{year}}$
ω	10^{-10}	dimensionless

Table 5: Parameter ranges used in parameter estimation and the reason for choosing said ranges.

Parameter	Range	Reasoning for Choice of Range
$\tilde{b}_G$	[0.1,0.5]	Based on the order of magnitude for α in [6] and $\tilde{b}_G$ in [28].
$\tilde{m}_G$	[-0.1,-0.001]	Based on the order of magnitude of $\tilde{b}_G$ with the possibility of a smaller order of magnitude. Note it is negative due to the decline in prescribing rates.
β_{GA}	$[0.001, 0.1]$	See calculations in Section 3.3.1.
β_{GP}	$[0.0001, 0.01]$	See calculations in Section 3.3.1.
θ_{S_G}	$[0.001, 0.5]$	See calculations in Section 3.3.1.
θ_P	$[0.001, 1]$	See calculations in Section 3.3.1.
θ_A	$[30, 50]$	See calculations in Section 3.3.1.
ε_G	$[0.333, 52]$	See calculations in Section 3.3.1.
γ	$[1.0 \times 10^{-5}, 0.1]$	Estimate based on the value in [28] with a decreased lower bound since in the parameter estimation of [28], γ always hit its lower bound.
ζ	$[0.001, 0.9]$	See calculations in Section 3.3.1.
ν	$[0.001, 0.9]$	See calculations in Section 3.3.1.
σ	$[0.1, 2]$	See calculations in Section 3.3.1.
λ_A	[0,1]	Used to skew the results of relapsing towards the A classes. We have no prior knowledge of this value, so allow it to range from zero to one. If λ_A and λ_F are both one, then we have the same relapse transition as in [28].
λ_F	[0,1]	Used to skew the results of relapsing towards the F classes. We have no prior knowledge of this value, so allow it to range from zero to one. If λ_A and λ_F are both one, then we have the same relapse transition as in [28].
P_{G0}	[0.001,0.4]	Assume no greater than 40% of the population since the total proportion of prescribed users within 2016 was $\frac{231176}{677952} \approx 0.34$.
A_{G0}	$[1.0 \times 10^{-4}, 0.01]$	Assume no greater than 1% of the population since the total proportion of people with POUD within 2016 was $\frac{3148}{677952} \approx 0.0046$.
F_{G0}	$[1.0 \times 10^{-5}, 0.01]$	Assume no greater than 1% of the population since the total proportion of people with FHUD within 2016 was $\frac{534}{677952} \approx 0.00079$.
R_{G0}	$[1.0 \times 10^{-5}, 0.1]$	Assume no greater than 10%.

3.3 Parameter Estimation

The remaining parameters must be estimated. We do this using the weighted least squares method and thus must first determine initial parameter ranges for these parameters.

Since there is an overall decrease in prescribing opioids in the time frame of the model, we have made the prescribing rate parameter α_G a linear function time such that

$$\alpha_G(t) = \tilde{m}_G \cdot t + \tilde{b}_G.$$

Additionally, since the data only tells us the number of individuals in the P_G, A_G, and F_G classes at some point in 2016, not the number of individuals at the start of 2016, we must estimate the initial values of all the classes and the parameters.

The upper and lower bounds of these parameter ranges are given in Table 5, as well as the explanation for this range choice. Some parameters require additional explanation, which are described below.

3.3.1 Parameter Bounds

Parameters β_{GP} and β_{GA}

We were unable to find data or literature on these parameters at the MSA or state levels, so we use national-level data to approximate them.

We first wish to estimate the number of people who developed POUD in the past year. We know that in 2016, there were 2,139,000 individuals 12 and older who initiated misuse of pain relievers in the past year in the US [47]. We assume that pain relievers are synonymous with prescription opioids. We are interested in how many of these individuals developed a POUD in 2016. To determine this, we know that in 2016, there were 11,517,000 individuals 12 and older who misused pain relievers in the past year in the US and that there were 1,753,000 individuals 12 and older who had pain reliever use disorder in the past year in the US [45, 48]. We then determine the ratio of individuals with pain reliever use disorder in the past year to individuals who misused pain relievers in the past year so that we may multiply this by the number of individuals who initiated misuse of pain relievers in the past year. This gives us an estimate of the number of individuals who developed POUD in the past year. For 2016, we multiply the ratio

$$\frac{1,753,000 \text{ individuals with pain reliever use disorder}}{11,517,000 \text{ individuals who misused pain relievers}} \approx 0.152$$

times 2,139,000 to get 325,577 individuals 12 and older who developed POUD in the past year in the US.

In 2016, it was found that 53.0% of individuals 12 and older who misused pain relievers in the past year obtained the pain relievers for their most recent misuse from a friend or relative [43]. This includes being given, buying, or taking from a friend or relative. In addition, in 2016, the total US population of 12 and older was 269,430,000 [46]. Thus in 2016,

$$\frac{325,577 \text{ developed POUD}}{269,430,000 \text{ total population}} * \frac{0.530 \text{ opioids obtained from friend/relative}}{\text{opioid source} * \text{year}} \approx 6.40 * 10^{-4}$$

is the proportion of individuals 12 and older who developed POUD by obtaining opioids from extra prescriptions that were available that year. We define $S_G[2016]$ and $P_G[2016]$ as the total proportion of the population that was in S_G and P_G at some point over the year 2016, respectively. Since we have no information about how $S_G(t)$ and $P_G(t)$ changed within 2016, we assume that they are constant within the year. Thus to determine the total flux from S_G into A_G due to obtaining opioids from extra prescriptions that were available, we integrate $\beta_{GP} S_G P_G$ from the start of 2016 to the end of 2016, which gives us $\beta_{GP} S_G[2016] P_G[2016]$ since we assumed that S_G and P_G are constant in 2016. From Table 1, we see that $P_G[2016] = 231,176/677,952$. Therefore

$$\beta_{GP} S_G[2016] P_G[2016] = 6.40 * 10^{-4} S_G[2016]$$

gives us that $\beta_{GP} \approx 0.00188$.

In the same survey, it was found that 6.0% of individuals 12 and older who misused pain relievers in the past year bought the pain relievers for their most recent misuse from a drug

dealer or other stranger [43]. Thus for 2016,

$$\frac{325,577 \text{ developed POUD}}{269,430,000 \text{ total population}} * \frac{0.060 \text{ opioids obtained from black market}}{\text{opioid source} * \text{year}} \approx 7.25 * 10^{-5}$$

is the rate at which individuals 12 and older develop POUD by obtaining opioids from the black market for that year. We define $A_G[2016]$ as the total proportion of the population that was in A_G at some point over the year 2016. Similar to before, we assume that $A_G(t)$ is constant over 2016 since we have no information about how it changes within 2016. Thus to determine the total flux into A_G from S_G due to obtaining opioids from the black market, we integrate $\beta_{GA} S_G A_G$ from the start of 2016 to the of 2016, which gives us $\beta_{GA} S_G[2016] A_G[2016]$ since we assume that S_G and A_G are constant in 2016. From Table 1, we see that $A_G[2016] = 3,148/677,952$. Therefore

$$\beta_{GA} S_G[2016] A_G[2016] = 7.25 * 10^{-5} S_G[2016]$$

gives us that $\beta_{GA} \approx 0.0156$.

Parameters θ_{S_G}, θ_P, and θ_A

One national study consisting of 609,000 participants aged 12-49 found that of individuals who reported past year dependence/abuse of pain relievers, 4.83% of them initiated heroin use on average from 2009-2011 [18]. We assume that the individuals who reported past year dependence/abuse of pain relievers fall into the A_G class. In 2016, it is estimated that 626,000 individuals 12 and older in the past year had heroin use disorder, and 948,000 individuals 12 and older have used heroin in the past year in the United States [45, 48]. This gives us 313/474 of individuals 12 and older who used heroin in the past year had heroin use disorder. We assume that 313/474 of the 4.83% of individuals who initiated heroin developed heroin use disorder, which is approximately 3.1894% of the individuals. We define $A_G[2016]$ and $F_G[2016]$ as the total proportion of the population that was in the A_G and F_G class at some point in 2016, respectively. Note that this is the number of unique individuals, so if someone entered and left the A_G class multiple times, they are still only counted once in $A_G[2016]$ and similarly for $F_G[2016]$. Thus $A_G[2016]$ and $F_G[2016]$ are equal to the integral of $A_G(t)$ and $F_G(t)$ over the year 2016, respectively. Since we have no information about how $A_G(t)$ and $F_G(t)$ changed within 2016, we assume that they are constant within the year. To determine the total flux from A_G into F_G, we integrate $\theta_A A_G F_G$ from the start of 2016 to the end of 2016, which gives us $\theta_A A_G[2016] F_G[2016]$ since we assumed A_G and F_G are constant within 2016. From Table 1, we see that $F[2016] = 534/677,952$. Therefore

$$\theta_A A_G[2016] F_G[2016] = 0.0483(313/474) A_G[2016]$$

gives us that $\theta_A = 40.492$. We allow θ_A to range between 30 and 50.

The same study also found that 0.02% of individuals who had no prior pain reliever misuse transitioned to heroin use in the past year on average from 2009-2011 [18]. We make the assumption that these individuals who reported no prior pain reliever misuse fall into the S_G class, though the S_G class does not exclude those who have misused pain relievers (only

those with pain reliever use disorder). Thus the actual percentage might be higher. Similarly to before, we assume that 313/474 of the 0.02% of individuals who transitioned to heroin use in the past year developed heroin use disorder, which is approximately 0.0132% of the individuals. We now define $S_G[2016]$ as the proportion of the population that was in S_G at some point in 2016 which is equal to the integral of $S_G(t)$ over the year 2016. As with θ_A, we have that

$$\theta_{S_G} S_G[2016] F_G[2016] = 0.0002(313/474) S_G[2016],$$

giving us that $\theta_{S_G} = 0.168$. We allow θ_{S_G} to range from 0.001 to 0.5 to account for the assumptions we have to make.

Finally, the same study found that 0.34% of individuals who had prior non-medical pain reliever misuse but no dependence/abuse in the past year transitioned to heroin averaged from 2009-2011 [18]. For the sake of finding bounds for θ_P, we assume that the individuals who had prior non-medical pain reliever misuse but no dependence/abuse are individuals in the class P_G who have misused their prescription but do not have a POUD. In 2015, it was estimated that 12.8% of past-year users of pain relievers misused pain relievers [22]. Note that this could include those with a POUD. It could also include those with current or past misuse, but we assume around 12.8% of those in P_G misuse their prescription. We define $P_G[2016]$ as the proportion of population that was in the class P_G at some point in the year 2016. Thus, similarly to before with,

$$\theta_P P_G[2016] F_G[2016] = 0.0034(0.128) P_G[2016],$$

gives us that $\theta_P = 0.553$. Thus, we allow θ_P to range from 0.001 to 1 to account for the assumptions.

Parameters ζ and ν

One study from 2019, found that out of those who needed treatment for OUD in the past year 27.8% received medication for OUD and another 15.3% of people received other treatment for OUD without medication [16]. Someone was considered in need of treatment if they met one of the following three criteria: (1) past-year heroin or prescription pain reliever abuse or dependence (i.e., past-year OUD), (2) received medication for OUD in the past year, or (3) past-year or current specialty treatment episode for heroin or prescription pain relievers. Another study conducted with opioid-dependent patients admitted to a residential addiction treatment service found that 71% relapsed within a month of discharge and 91% relapsed at some point after discharge [36].

To estimate ζ, the rate of stability recovering from the POUD class, we first want to determine a lower bound for the proportion of those in A_G that remain in A_G after one year. We know that only about 43.1% of those in A_G go to treatment, so then at least 56.9% of those in A_G stay in A_G for the entire year. Out of the 43.1% that go to treatment, 71% relapse in a month, thus staying in A_G. Therefore $0.569 + 0.431(0.71) = 0.87501$ is the proportion that stays in A_G throughout the year. If we let A_0 be the total POUD population in 2019, then we may determine ζ with the equation

$$0.87501 A_0 = A_0 e^{-\zeta t}$$

with $t = 1$. This gives us that $\zeta \approx 0.134$.

To find an upper bound for the proportion of those in A_G that remain in A_G after one year, suppose that the 91% that relapse at some point after discharging all relapse within the year. We then have that $1 - 0.71 = 0.29$ proportion that has not relapsed after one month and that $0.91 - 0.71 = 0.20$ is the proportion that moved to R_G from not relapsing after treatment for more than a month but ended up relapsing within the year. Thus $0.431(0.29)(0.20) = 0.024998$ is the proportion that moves from A_G to R_G but ends up back in A_G within the year. Therefore $0.87501 + 0.024998 = 0.900008$ is the proportion that stays in A_G throughout the year. Using similar methods to before, we estimate that $\zeta \approx 0.105$. Note that this estimation applies to ν, the rate of stability recovering from the FHUD class, as well since the studies available were on opioids in general, including prescription opioids and heroin.

Parameter σ

A study conducted with opioid-dependent patients admitted to a residential addiction treatment service found that 92% of those who relapsed returned to treatment with a median gap from relapse to re-entry of four months [36]. Of this 92%, it is unknown how many of these individuals transitioned to the R_G class at all (i.e., did not relapse within the first month). We also were not able to find rates on lifetime recoveries (i.e., people transitioning to R_G and staying there). Thus, we assume that between 20% and 80% of those in R_G at the start of the year are in R_G by the end of the year.

Let $\omega = 0$ since it is only used to keep from getting a zero denominator. Then adding the two relapse rates gives us

$$\sigma R_G \frac{\lambda_A A_G + (1 - \lambda_F) F_G}{A_G + F_G} + \sigma R_G \frac{(1 - \lambda_A) A_G + \lambda_F F_G}{A_G + F_G} = \sigma R_G \frac{A_G + F_G}{A_G + F_G} = \sigma R_G.$$

Thus we can model the change over time out of R_G as simply $R' = -\sigma R_G$. Thus, if we suppose that only 20% of those in R_G at the start of the year are in R_G at the end of the year, we can determine σ with the equation

$$0.20 R_0 = R_0 e^{-\sigma t}.$$

Taking t to be one, this gives us that $\sigma \approx 1.61$. By similar methods, if we suppose that only 80% of those in R_G at the start of the year are in R_G at the end of the year, then $\sigma \approx 0.223$.

Parameter ε_G

A study from 2017 found that approximately 70% of patients' initial opioid prescription is a week or less, and only 7.3% are given an initial opioid prescription for more than 30 days. At one year, only 6.0% of patients were still continuing this prescription, and even fewer still had a prescription at three years (only 2.9%) [34].

To determine the upper bound on ε_G, the rate at which people are ending their prescription for opioids without developing any kind of opioid use disorder, let us consider that the average

length of time people are taking a prescription is one week (1/52 years). If we assume that the transition from the P_G into S_G is a Poisson process, then the length of time between transitions follows the exponential distribution with the average time between transitions being ε_G. Thus, an upper bound for ε_G is 52. If we consider the average length of time people are taking a prescription is 3 years, then we get a lower bound of 1/3 for ε_G.

3.3.2 Least Squares for Parameter Estimation

To fit the remaining parameters, we use the weighted least squares method. The objective is to minimize the sum of the squared differences between the data and the model. Since the magnitude of the data varies widely, we weigh each term in the objective by the inverse of the size of the data squared.

The data utilized (shown in bold in Table 1 and Table 2) is the following proportions out of the total Knoxville MSA for each year:

- the proportion of prescription opioid users without opioid use disorder (years 2016-2019),
- the proportion of individuals with POUD (years 2017-2019),
- the proportion of individuals with FHUD (years 2016-2019),
- the proportion of fatal POUD overdoses (years 2017-2019; excluding 2016 which was an outlier and not repressive of the trend), and
- the proportion of fatal FHUD overdoses (years 2016-2019).

This represents the proportion of individuals in class P_G at some point during each of the years 2016-2019, the proportion of individuals in class A_G at some point during each of the years 2017-2019, and the proportion of individuals in class F_G at some point during each of the years 2016-2019 along with the proportion of individuals dying of an overdose out of the A_G and F_G classes for each of the years 2016-2019, respectively. The proportion of individuals with POUD in 2016 was considered an outlier when compared to the rest of the data and was not used in the parameter estimation. In addition, quarterly data on the proportion of the total Knoxville MSA who are prescription opioid users without opioid use disorder for years 2016-2019 (shown in bold in Table 3) was utilized. This results in a total of 35 data points.

This data represents the number of people in the classes at any point throughout the year (or quarter), even if they were in the class for less than a year (or quarter). For example, if someone is taking a prescription for opioids and then develops POUD all within 2016, they would be accounted for in both the 2016 prescription opioid users (excludes opioid use disorder) data and the 2016 POUD data. Also, note that the data only tells us about the number of unique individuals that enter a class; if someone enters and leaves a class multiple times throughout the year, they are still only counted once in that class due to the course yearly data. Thus, for each year and each class, we need to determine the number

of individuals at the start of the year and the number of individuals who entered that class throughout the year. We are not interested in the number of individuals leaving the classes each year since we have no data to compare this to (except for overdose deaths in the A_G and F_G classes).

From the model, we need to determine the proportion of individuals who have had prescriptions for opioids (and not an opioid use disorder) at any time throughout the year for each year. Thus, we determine the value of the P_G class at the start of the year and the proportion of individuals who entered the P_G class at any time throughout the year. We define $X_G(t)$ such that $\int_0^t X_G'(t)dt = \int_0^t \alpha_G S_G(t)dt$ and $X_G(0) = 0$, where t is measured in years and $t = 0$ is the start of 2016. Using the fundamental theorem of calculus, we then have that $\int_0^t \alpha_G S_G(t)dt = X_G(t) - X_G(0) = X_G(t)$. In other words, $X_G(t)$ is the proportion of individuals who have entered the P_G class at time t since time zero. Therefore, for 2016-2019, we have the following:

- 2016: $P_G(0) + \int_0^1 \alpha_G S_G(t)dt = P_{G0} + X_G(1)$
- 2017: $P_G(1) + \int_1^2 \alpha_G S_G(t)dt = P_G(1) + \int_0^2 \alpha_G S_G(t)dt - \int_0^1 \alpha_G S_G(t)dt = P_G(1) + X_G(2) - X_G(1)$
- 2018: $P_G(2) + \int_2^3 \alpha_G S_G(t)dt = P_G(2) + \int_0^3 \alpha_G S_G(t)dt - \int_0^2 \alpha_G S_G(t)dt = P_G(2) + X_G(3) - X_G(2)$
- 2019: $P_G(3) + \int_3^4 \alpha_G S_G(t)dt = P_G(3) + \int_0^4 \alpha_G S_G(t)dt - \int_0^3 \alpha_G S_G(t)dt = P_G(3) + X_G(4) - X_G(3)$

We define

$$\text{Data1} = \begin{bmatrix} 231176/677952 \\ 219503/684276 \\ 197535/690529 \\ 183160/695749 \end{bmatrix}$$

as the vector of values that represents the total proportion of the population in the P_G class at some point throughout the years 2016-2019 from the data. We also define

$$\text{Estim1} = \begin{bmatrix} P_{G0} + X_G(1) \\ P_G(1) + X_G(2) - X_G(1) \\ P_G(2) + X_G(3) - X_G(2) \\ P_G(3) + X_G(4) - X_G(3) \end{bmatrix}$$

as the total proportion of the population that the model simulates being in the P_G class at some point throughout the years 2016-2019. The vector

$$\text{Diff1} = \text{Data1} - \text{Estim1}$$

defines the difference between the actual values and the model simulated values for the P_G class for each of the years. Thus, to get the weighted error, we calculate

$$\frac{\sum_{i=0}^{3} \text{Diff1}_i^2}{\sum_{i=0}^{3} \text{Data1}_i^2},$$

where Diff1_i and Data1_i are the ith component of the difference and data vectors, respectively.

From the model, the proportion of individuals who have had POUD at any time throughout the year for each year is determined by the value of the A_G class at the start of the year and the proportion of individuals who entered the A_G class at any time throughout the year. We define $Y_G(t)$ such that

$$\int_0^t Y_G'(t)dt = \int_0^t \left(\beta_{GA} S_G A_G + \beta_{GP} S_G P_G + \gamma P_G + \sigma R_G \frac{\lambda_A A_G + (1-\lambda_F) F_G}{A_G + F_G + \omega}\right) dt$$

and $Y_G(0) = 0$, where t is measured in years and $t = 0$ is the start of 2016. Thus, $Y_G(t)$ tells us the proportion of individuals who have entered the A_G class at time t since time zero. Therefore, for 2017-2019, we have the following:

- 2017: $A_G(1) + \int_1^2 \left(\beta_{GA} S_G A_G + \beta_{GP} S_G P_G + \gamma P_G + \sigma R_G \frac{\lambda_A A_G + (1-\lambda_F) F_G}{A_G + F_G + \omega}\right) dt = A_G(1) + Y_G(2) - Y_G(1)$
- 2018: $A_G(2) + \int_2^3 \left(\beta_{GA} S_G A_G + \beta_{GP} S_G P_G + \gamma P_G + \sigma R_G \frac{\lambda_A A_G + (1-\lambda_F) F_G}{A_G + F_G + \omega}\right) dt = A_G(2) + Y_G(3) - Y_G(2)$
- 2019: $A_G(3) + \int_3^4 \left(\beta_{GA} S_G A_G + \beta_{GP} S_G P_G + \gamma P_G + \sigma R_G \frac{\lambda_A A_G + (1-\lambda_F) F_G}{A_G + F_G + \omega}\right) dt = A_G(3) + Y_G(4) - Y_G(3)$

We define

$$\text{Data2} = \begin{bmatrix} 1436/684276 \\ 1375/690529 \\ 1123/695749 \end{bmatrix}$$

as the vector of values that represents the total proportion of the population in the A_G class at some point throughout the years 2017-2019 from the data and define

$$\text{Estim2} = \begin{bmatrix} A_G(1) + Y_G(2) - Y_G(1) \\ A_G(2) + Y_G(3) - Y_G(2) \\ A_G(3) + Y_G(4) - Y_G(3) \end{bmatrix}$$

as the total proportion of the population that the model simulates being in the A_G class at some point throughout the years 2017-2019. The vector

$$\text{Diff2} = \text{Data2} - \text{Estim2}$$

defines the difference between the actual values and the model simulated values for the A_G class for each of the years. Thus, to get the weighted error, we calculate

$$\frac{\sum_{i=0}^3 \text{Diff2}_i^2}{\sum_{i=0}^3 \text{Data2}_i^2},$$

where Diff2_i and Data2_i are the ith component of the difference and data vectors, respectively.

From the model, the proportion of individuals who have had FHUD at any time throughout the year for each year is determined by the value of the F_G class at the start of the year and the proportion of individuals who entered the F_G class at any time throughout the year. We define $Z_G(t)$ such that

$$\int_0^t Z_G'(t)dt = \int_0^t \left(\theta_{S_G} S_G F_G + \theta_P P_G F_G + \theta_A A_G F_G + \sigma R_G \frac{(1-\lambda_A)\, A_G + \lambda_F F_G}{A_G + F_G + \omega}\right) dt$$

and $Z_G(0) = 0$, where t is measured in years and $t = 0$ is the start of 2016. Thus, $Z_G(t)$ tells us the proportion of individuals who have entered the F_G class at time t since time zero. Therefore, for 2016-2019, we have the following:

- 2016: $F_G(0) + \int_0^1 \left(\theta_{S_G} S_G F_G + \theta_P P_G F_G + \theta_A A_G F_G + \sigma R_G \frac{(1-\lambda_A)A_G + \lambda_F F_G}{A_G + F_G + \omega}\right) dt = F_{G0} + Z_G(1)$
- 2017: $F_G(1) + \int_1^2 \left(\theta_{S_G} S_G F_G + \theta_P P_G F_G + \theta_A A_G F_G + \sigma R_G \frac{(1-\lambda_A)A_G + \lambda_F F_G}{A_G + F_G + \omega}\right) dt = F_G(1) + Z_G(2) - Z_G(1)$
- 2018: $F_G(2) + \int_2^3 \left(\theta_{S_G} S_G F_G + \theta_P P_G F_G + \theta_A A_G F_G + \sigma R_G \frac{(1-\lambda_A)A_G + \lambda_F F_G}{A_G + F_G + \omega}\right) dt = F_G(2) + Z_G(3) - Z_G(2)$
- 2019: $F_G(3) + \int_3^4 \left(\theta_{S_G} S_G F_G + \theta_P P_G F_G + \theta_A A_G F_G + \sigma R_G \frac{(1-\lambda_A)A_G + \lambda_F F_G}{A_G + F_G + \omega}\right) dt = F_G(3) + Z_G(4) - Z_G(3)$

We define

$$\text{Data3} = \begin{bmatrix} 534/677952 \\ 598/684276 \\ 494/690529 \\ 297/695749 \end{bmatrix}$$

as the vector of values that represents the total proportion of the population in the F_G class at some point throughout the years 2016-2019 from the data and define

$$\text{Estim3} = \begin{bmatrix} F_{G0} + Z_G(1) \\ F_G(1) + Z_G(2) - Z_G(1) \\ F_G(2) + Z_G(3) - Z_G(2) \\ F_G(3) + Z_G(4) - Z_G(3) \end{bmatrix}$$

as the total proportion of the population that the model simulates being in the F_G class at some point throughout the years 2016-2019. The vector

$$\text{Diff3} = \text{Data3} - \text{Estim3}$$

defines the difference between the actual values and the model simulated values for the A_G class for each of the years. Thus, to get the weighted error, we calculate

$$\frac{\sum_{i=0}^3 \text{Diff3}_i^2}{\sum_{i=0}^3 \text{Data3}_i^2},$$

where Diff3_i and Data3_i are the ith component of the difference and data vectors, respectively.

From the model, the proportion of individuals with POUD that overdose at any time throughout the year for each year is determined by those who die via an overdose out of the A_G class. We define $J_G(t)$ such that $\int_0^t J_G'(t)dt = \int_0^t \mu_A A_G dt$ and $J_G(0) = 0$, where t is measured in years and $t = 0$ is the start of 2016. Thus, $J_G(t)$ tells us the proportion of individuals with POUD who have died of an overdose at time t since time zero. Therefore, for 2016-2019, we have the following:

- 2016: $\int_0^1 \mu_A A_G dt = J_G(1) - J_G(0) = J_G(1)$
- 2017: $\int_1^2 \mu_A A_G dt = J_G(2) - J_G(1)$
- 2018: $\int_2^3 \mu_A A_G dt = J_G(3) - J_G(2)$
- 2019: $\int_3^4 \mu_A A_G dt = J_G(4) - J_G(3)$

We define

$$\text{Data4} = \begin{bmatrix} 73/677952 \\ 69/684276 \\ 55/690529 \\ 48/695749 \end{bmatrix}$$

as the vector of values that represents the total proportion of the population dying of an overdose with POUD at some point throughout the years 2016-2019 from the data and define

$$\text{Estim4} = \begin{bmatrix} J_G(1) \\ J_G(2) - J_G(1) \\ J_G(3) - J_G(2) \\ J_G(4) - J_G(3) \end{bmatrix}$$

as the total proportion of the population leaving the A_G class due to a fatal overdose at some point throughout the years 2016-2019. The vector

$$\text{Diff4} = \text{Data4} - \text{Estim4}$$

defines the difference between the actual values and the model simulated values for each of the years. Thus, to get the weighted error, we calculate

$$\frac{\sum_{i=0}^{3} \text{Diff4}_i^2}{\sum_{i=0}^{3} \text{Data4}_i^2},$$

where Diff4_i and Data4_i are the ith component of the difference and data vectors, respectively.

From the model, the proportion of individuals with FHUD that overdose at any time throughout the year for each year is determined by those who die via an overdose out of the F_G class. We define $K_G(t)$ such that $\int_0^t K_G'(t)dt = \int_0^t \mu_F F_G dt$ and $K_G(0) = 0$, where t is measured in years and $t = 0$ is the start of 2016. Thus, $K_G(t)$ tells us the proportion of individuals with FHUD who have died of an overdose at time t since time zero. Therefore, for 2016-2019, we have the following:

- 2016: $\int_0^1 \mu_F F_G dt = K_G(1) - K_G(0) = K_G(1)$
- 2017: $\int_1^2 \mu_F F_G dt = K_G(2) - K_G(1)$
- 2018: $\int_2^3 \mu_F F_G dt = K_G(3) - K_G(2)$
- 2019: $\int_3^4 \mu_F F_G dt = K_G(4) - K_G(3)$

We define

$$\text{Data5} = \begin{bmatrix} 146/677952 \\ 167/684276 \\ 163/690529 \\ 144/695749 \end{bmatrix}$$

as the vector of values that represents the total proportion of the population dying of an overdose with FHUD at some point throughout the years 2016-2019 from the data and define

$$\text{Estim5} = \begin{bmatrix} K_G(1) \\ K_G(2) - K_G(1) \\ K_G(3) - K_G(2) \\ K_G(4) - K_G(3) \end{bmatrix}$$

as the total proportion of the population leaving the F_G class due to a fatal overdose at some point throughout the years 2016-2019. The vector

$$\text{Diff5} = \text{Data5} - \text{Estim5}$$

defines the difference between the actual values and the model simulated values for each of the years. Thus, to get the weighted error, we calculate

$$\frac{\sum_{i=0}^{3} \text{Diff5}_i^2}{\sum_{i=0}^{3} \text{Data5}_i^2},$$

where Diff5_i and Data5_i are the ith component of the difference and data vectors, respectively.

Finally, we now need to determine the proportion of individuals who have had prescriptions for opioids and not an opioid use disorder at any time throughout the quarter for each quarter of the year. Similar to before, we determine the value of the P_G class at the start of each quarter and the proportion of individuals who entered the P_G class at any time throughout the year. Recall we defined $X_G(t) = \int_0^t \alpha_G S_G(t) dt$ as the proportion of individuals who have entered the P_G class at time t since time zero (the start of year 2016). Thus, for each quarter of 2016-2019, we have the following:

- 2016 Q1: $P_G(0) + \int_0^{0.25} \alpha_G S_G(t) dt = P_{G0} + X_G(0.25)$
- 2016 Q2: $P_G(0.25) + \int_{0.25}^{0.50} \alpha_G S_G(t) dt = P_G(0.25) + X_G(0.50) - X_G(0.25)$
- 2016 Q3: $P_G(0.50) + \int_{0.50}^{0.75} \alpha_G S_G(t) dt = P_G(0.50) + X_G(0.75) - X_G(0.50)$

- 2016 Q4: $P_G(0.75) + \int_{0.75}^{1} \alpha_G S_G(t)dt = P_G(0.75) + X_G(1) - X_G(0.75)$
- 2017 Q1: $P_G(1) + \int_{1}^{1.25} \alpha_G S_G(t)dt = P_G(1) + X_G(1.25) - X_G(1)$
- 2017 Q2: $P_G(1.25) + \int_{1.25}^{1.50} \alpha_G S_G(t)dt = P_G(1.25) + X_G(1.50) - X_G(1.25)$
- 2017 Q3: $P_G(1.50) + \int_{1.50}^{1.75} \alpha_G S_G(t)dt = P_G(1.50) + X_G(1.75) - X_G(1.50)$
- 2017 Q4: $P_G(1.75) + \int_{1.75}^{2} \alpha_G S_G(t)dt = P_G(1.75) + X_G(2) - X_G(1.75)$
- 2018 Q1: $P_G(2) + \int_{1}^{2.25} \alpha_G S_G(t)dt = P_G(2) + X_G(2.25) - X_G(2)$
- 2018 Q2: $P_G(2.25) + \int_{2.25}^{2.50} \alpha_G S_G(t)dt = P_G(2.25) + X_G(2.50) - X_G(2.25)$
- 2018 Q3: $P_G(2.50) + \int_{2.50}^{2.75} \alpha_G S_G(t)dt = P_G(2.50) + X_G(2.75) - X_G(2.50)$
- 2018 Q4: $P_G(2.75) + \int_{2.75}^{3} \alpha_G S_G(t)dt = P_G(2.75) + X_G(3) - X_G(2.75)$
- 2019 Q1: $P_G(3) + \int_{1}^{3.25} \alpha_G S_G(t)dt = P_G(3) + X_G(3.25) - X_G(3)$
- 2019 Q2: $P_G(3.25) + \int_{3.25}^{3.50} \alpha_G S_G(t)dt = P_G(3.25) + X_G(3.50) - X_G(1.25)$
- 2019 Q3: $P_G(3.50) + \int_{3.50}^{3.75} \alpha_G S_G(t)dt = P_G(3.50) + X_G(3.75) - X_G(1.50)$
- 2019 Q4: $P_G(3.75) + \int_{3.75}^{4} \alpha_G S_G(t)dt = P_G(3.75) + X_G(4) - X_G(3.75)$

Since we do not have the total population of the Knoxville MSA for each quarter of the year, we keep the total population constant for each year. Thus, we define

$$\text{Data6} = \begin{bmatrix} 84592/677952 \\ 83548/677952 \\ 81981/677952 \\ 80067/677952 \\ 77847/684276 \\ 76969/684276 \\ 74866/684276 \\ 72412/684276 \\ 69016/690529 \\ 68838/690529 \\ 64591/690529 \\ 63530/690529 \\ 62399/695749 \\ 61317/695749 \\ 60416/695749 \\ 58793/695749 \end{bmatrix}$$

as the vector of values that represents the total proportion of the population in the P_G class at some point throughout the quarter in the years 2016-2019 from the data and define

$$\text{Estim6} = \begin{bmatrix} P_{G0} + X_G(0.25) \\ P_G(0.25) + X_G(0.50) - X_G(0.25) \\ P_G(0.50) + X_G(0.75) - X_G(0.50) \\ P_G(0.75) + X_G(1) - X_G(0.75) \\ \vdots \\ P_G(3.75) + X_G(4) - X_G(3.75) \end{bmatrix}$$

as the total proportion of the population that the model simulates being in the P_G class at some point throughout the quarter in the years 2016-2019. The vector

$$\text{Diff6} = \text{Data6} - \text{Estim6}$$

defines the difference between the actual values and the model simulated values for the P_G class for each of the quarters throughout the years. Thus, to get the weighted error, we calculate

$$\frac{\sum_{i=0}^{15} \text{Diff6}_i^2}{\sum_{i=0}^{15} \text{Data6}_i^2},$$

where Diff6_i and Data6_i are the ith component of the difference and data vectors, respectively.

Therefore, the final objective function we wish to minimize is

$$\sum_{j=1}^{3} \frac{\sum_{i=0}^{3} \text{Diffj}_i^2}{\sum_{i=0}^{3} \text{Dataj}_i^2} + \frac{\sum_{i=0}^{3} \text{Diff4}_i^2}{\sum_{i=0}^{3} \text{Data4}_i^2} + \frac{\sum_{i=0}^{3} \text{Diff5}_i^2}{\sum_{i=0}^{3} \text{Data5}_i^2} + \frac{\sum_{i=0}^{15} \text{Diff6}_i^2}{\sum_{i=0}^{15} \text{Data6}_i^2}.$$

To minimize the objective function, we randomly draw multiple points from uniform distributions over the parameter ranges (provided in Table 5). Since some of these parameter ranges are on a very small scale, we use a log scale for β_{GA}, β_{GP}, θ_{S_G}, θ_P, γ, and ν to give us a more accurate estimation. Using the minimize function with the Sequential Least Squares Programming (SLSQP) method from the scipy.optimize package in Python with the bounds listed in Table 5, we then calculate the local minima of those points. The parameter set that minimizes the objective function the most out of the calculated local minima is then the global minimum. Approaching the problem this way allows us to parallelize calculating the local minima.

Recall that α_G is a decreasing linear function such that $\alpha_G(t) = \tilde{m}_G t + \tilde{b}_G$ and we want to ensure that α_G remains non-negative. Thus, when generating initial points within the parameter ranges, if $\tilde{m}_G$ and $\tilde{b}_G$ result in a negative value for α_G at the final time, we reselect these parameters from the uniform distribution until α_G at the final time is non-negative. We also specify this as a constraint for the scipy.optimize.minimize function. Since constraints are needed, this is one of the reasons we use the SLSQP method for the local minima.

We considered two cases: 1.) where μ_A and μ_F are predetermined constants and 2.) where μ_A and μ_F are estimated constants. For each, we use 1000 starting points to determine the local minimas. We run the model from the start of 2016 to the start of 2020 (the end of 2019), a total of four years.

3.3.3 Case 1: μ_A and μ_F are predetermined constants.

We estimate a total of 18 inputs, which includes parameters and initial conditions, where $\tilde{m}_G$ and $\tilde{b}_G$ are both estimated for parameter α_G. The ranges of these parameters can be seen in Table 5. An additional four assumed constant parameters (including μ_A and μ_F for now) can be seen in Table 4.

Of 1000 runs, 995 converged with a final objective function value of 0.920. The resulting estimated parameter values are in Table 6. Figure 1 shows the fit of the model to the data. The solution curves using the parameter values from Table 6 are shown in Figure 2.

3.3.4 Case 2: μ_A and μ_F are estimated constants.

In Figure 1, the solution does not fit the fatal overdose data very well. Thus, in Case 2, instead of assuming the values of μ_A and μ_F, we estimate these parameters as well. This creates a total of 20 parameters and initial conditions to estimate, where α_G is still a linear function of time with slope $\tilde{m}_G$ and y-intercept $\tilde{b}_G$. In the parameter estimation, we let $[0.001, 1.0]$ be the range for both μ_A and μ_F. The parameters μ and ω are still assumed with values from Table 4. Table 5 contains the remaining parameter ranges.

Out of 1000 runs, 974 converged for a final objective function value of 0.276. Table 7 shows the resulting estimated parameter values. Figure 3 shows the fit of the model to the data. The solution curves using the parameter values from Table 7 are shown in Figure 4.

3.4 Comparison of Models with AIC

While the model appears to fit the data better in Case 2 rather than in Case 1, as can be seen in Figure 3 and Figure 1, Case 2 is still estimating two additional parameters. The more parameters we estimate, the better the model fit should appear; however, this also runs the risk of overfitting and making the model unnecessarily complex. To determine which of the model cases is better, we compute each model's Akaike information criterion (AIC) score. While meaningless by itself, the AIC score enables us to compare the quality of the models to one another. The AIC score rewards a model's fit to the data while penalizing the addition of extra parameters to estimate. The lower the AIC score, the better the model. The AIC score for weighted least squares regression analysis is defined as

$$\text{AIC} = N \ln\left(\frac{OF}{N}\right) + 2K,$$

where N is the total number of data points the model is fitting to, OF is the sum of weighted squares residuals (i.e., the objective function we are minimizing when performing weighted least squares), and K is the total number of estimated parameters (i.e., the total number of model parameters plus one since we are estimating the value of OF) [5].

In the model, we have $N = 35$ data points. In Case 1, we have $K_1 = 18 + 1 = 19$ total number of parameters to estimate, and in Case 2, we have $K_2 = 20 + 1 = 21$ total number of parameters to estimate.

Table 6: The values of the parameters that were estimated for Case 1 in Section 3.3.3 where μ_A and μ_F are assumed constant parameters.

Input	**Estimated Value**	**Units**
$\tilde{m}_G$	-0.0288	$\frac{1}{\text{year}}$
$\tilde{b}_G$	0.332	$\frac{1}{\text{year}}$
β_{GA}	0.001	$\frac{1}{\text{year}}$
β_{GP}	0.0001	$\frac{1}{\text{year}}$
θ_{S_G}	0.001	$\frac{1}{\text{year}}$
θ_P	0.00101	$\frac{1}{\text{year}}$
θ_A	50.0	$\frac{1}{\text{year}}$
ε_G	7.01	$\frac{1}{\text{year}}$
γ	1×10^{-5}	$\frac{1}{\text{year}}$
ζ	0.012	$\frac{1}{\text{year}}$
ν	0.001	$\frac{1}{\text{year}}$
σ	1.3	$\frac{1}{\text{year}}$
λ_A	1×10^{-10}	$\frac{1}{\text{year}}$
λ_F	1.0	$\frac{1}{\text{year}}$
P_{C_0}	0.0431	dimensionless
A_{C_0}	0.00227	dimensionless
F_{C_0}	0.000434	dimensionless
R_{C_0}	0.000538	dimensionless

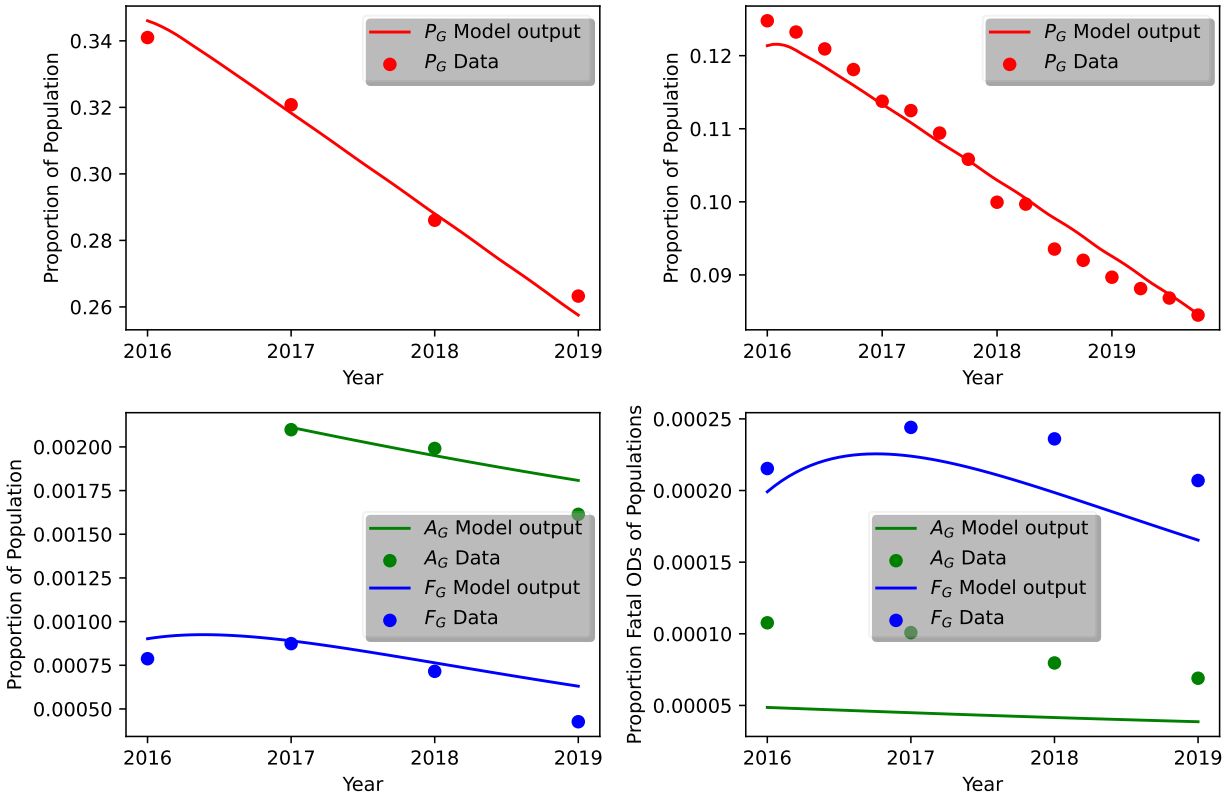


Figure 1: Model simulation fit to data for Case 1 parameter estimation, where μ_A and μ_F are assumed constant parameters. This figure's data includes yearly prescription opioid data, quarterly prescription opioid data, yearly POUD data, yearly FHUD data, yearly POUD fatal overdose data, and yearly FHUD fatal overdose data.

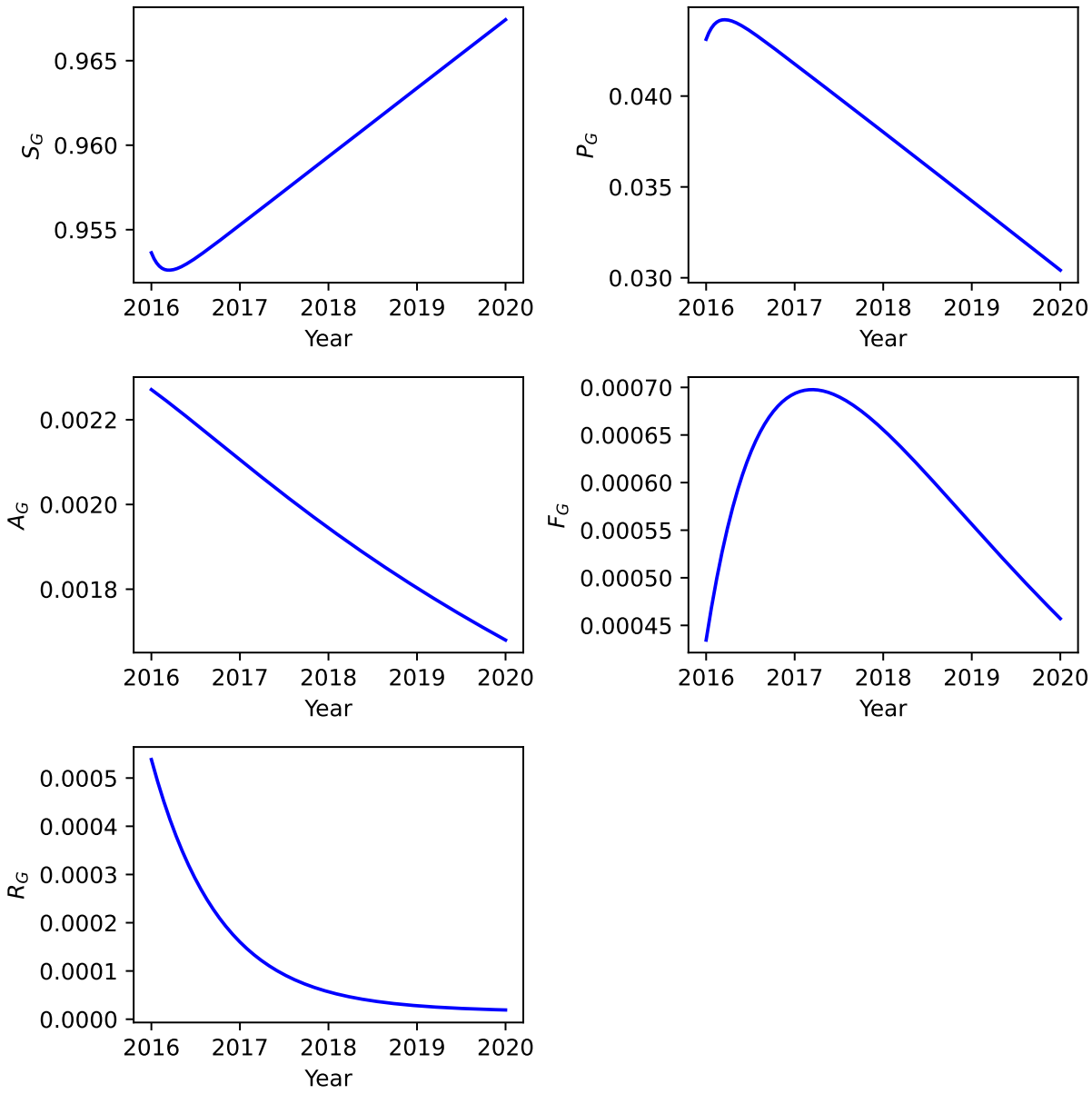


Figure 2: Solution curves using the parameter values from Table 6 from the Case 1 parameter estimation where μ_A and μ_F are assumed constant parameters.

Table 7: The values of the parameters estimated for Case 2 in Section 3.3.4 where μ_A and μ_F are estimates parameters.

Input	**Estimated Value**	**Units**
$\tilde{m}_G$	-0.0288	$\frac{1}{\text{year}}$
$\tilde{b}_G$	0.332	$\frac{1}{\text{year}}$
β_{GA}	0.001	$\frac{1}{\text{year}}$
β_{GP}	0.0001	$\frac{1}{\text{year}}$
θ_{S_G}	0.00111	$\frac{1}{\text{year}}$
θ_P	0.0101	$\frac{1}{\text{year}}$
θ_A	48.9	$\frac{1}{\text{year}}$
ε_G	7.0	$\frac{1}{\text{year}}$
γ	1.16×10^{-5}	$\frac{1}{\text{year}}$
ζ	0.0536	$\frac{1}{\text{year}}$
ν	0.00319	$\frac{1}{\text{year}}$
σ	0.97	$\frac{1}{\text{year}}$
λ_A	0.00633	$\frac{1}{\text{year}}$
λ_F	1.0	$\frac{1}{\text{year}}$
P_{C_0}	0.0432	dimensionless
A_{C_0}	0.00246	dimensionless
F_{C_0}	0.000339	dimensionless
R_{C_0}	0.000508	dimensionless
μ_A	0.0471	$\frac{1}{\text{year}}$
μ_F	0.471	$\frac{1}{\text{year}}$

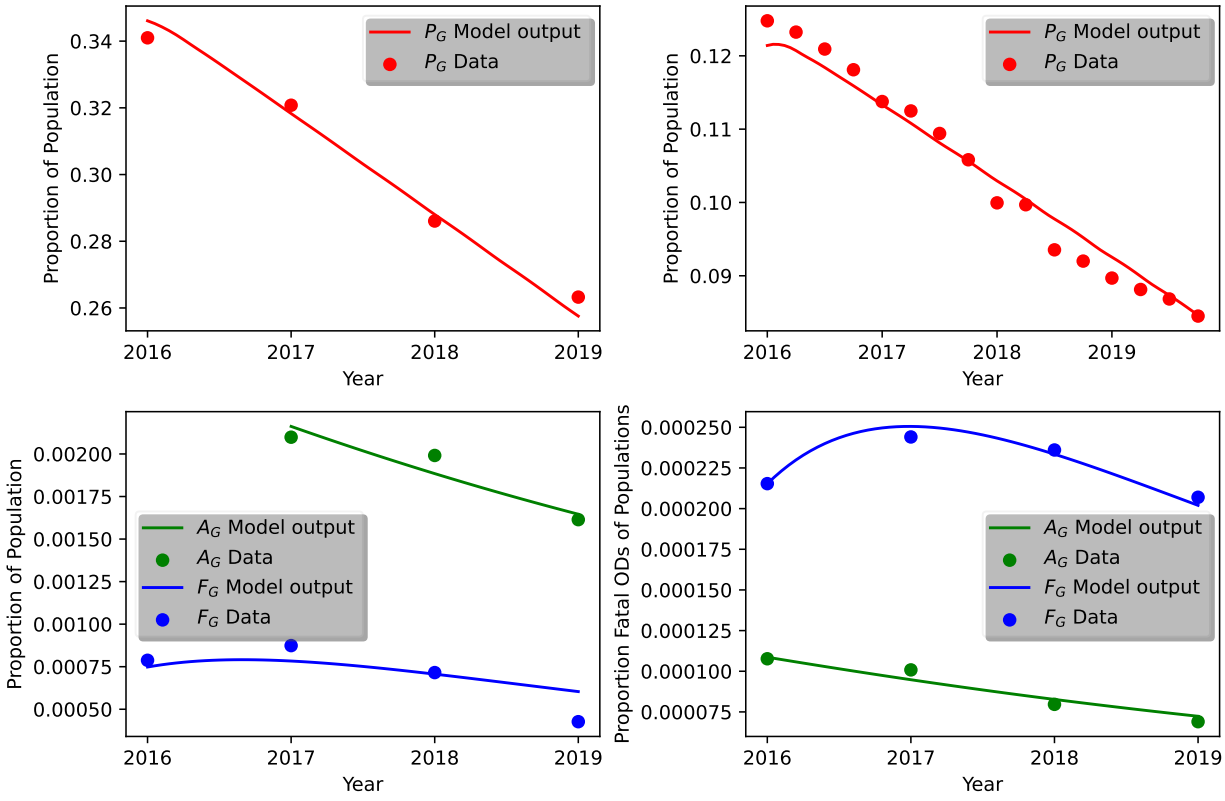


Figure 3: Model simulation results fit to data for Case 2 parameter estimation, where μ_A and μ_F are estimated parameters. This figure's data includes yearly prescription opioid data, quarterly prescription opioid data, yearly POUD data, yearly FHUD data, yearly POUD fatal overdose data, and yearly FHUD fatal overdose data.

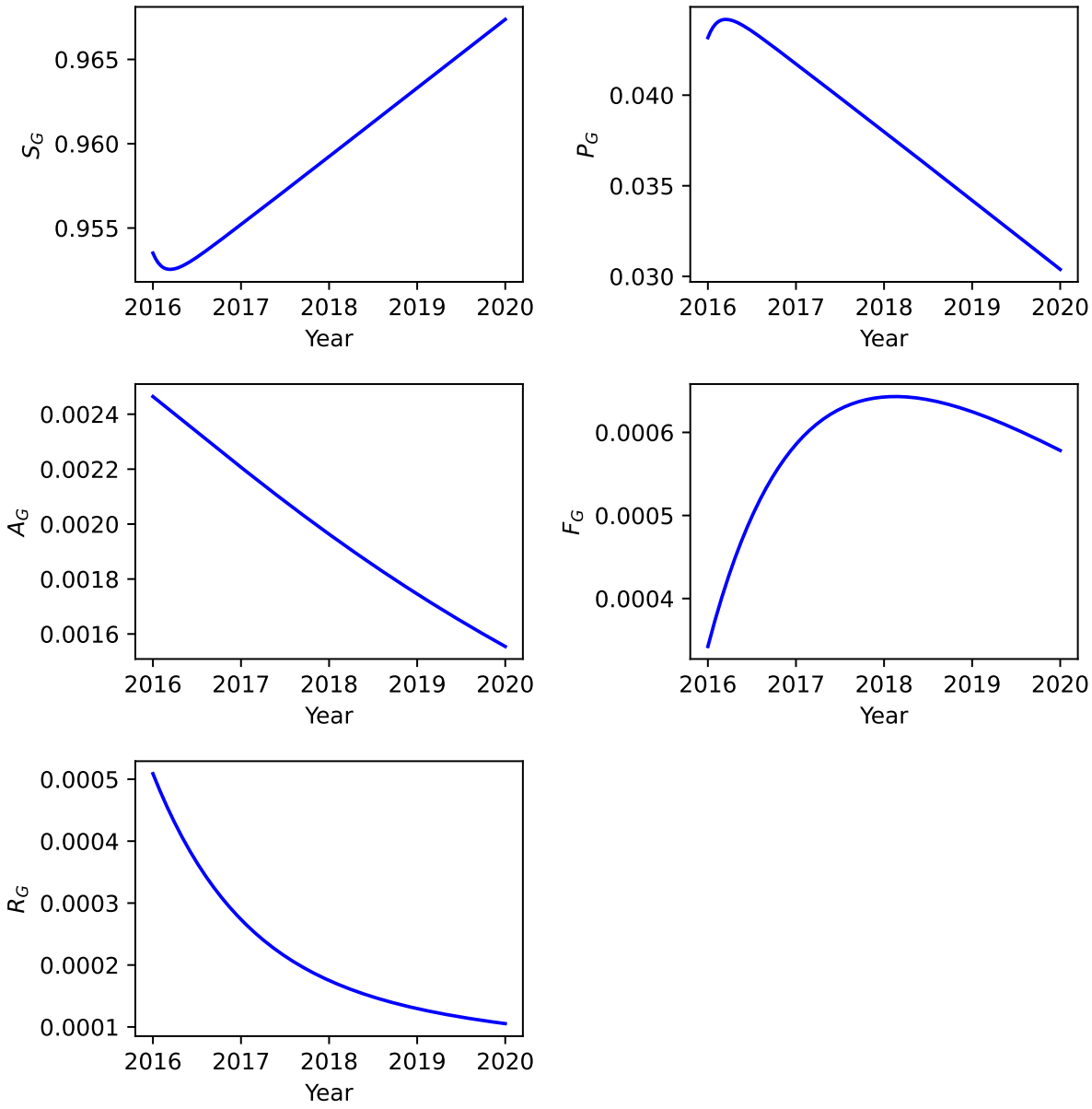


Figure 4: Solution curves using the parameter values from Table 7 from the Case 2 parameter estimation where μ_A and μ_F are estimated parameters.

When N is not at least 40 times larger than K (i.e., $N/K < 40$), it is recommended to use the correct or second order AIC, denoted $\mathrm{AIC_C}$, which has the form

$$\mathrm{AIC_C} = \mathrm{AIC} + \frac{2K(K+1)}{N-K-1}$$

[5]. In both of the cases, N is significantly less than 40 times that of K ($N/K_1 = 35/19 \approx 1.84$ and $N/K_2 = 35/21 \approx 1.67$), so we use $\mathrm{AIC_C}$ to compare the model cases.

In Case 1, we have that

$$\mathrm{AIC_{C1}} = 35 \ln\left(\frac{0.920}{35}\right) + 2(19) + \frac{2(19)(19+1)}{35-19-1} = -43.747,$$

and in Case 2, we have that

$$\mathrm{AIC_{C2}} = 35 \ln\left(\frac{0.276}{35}\right) + 2(21) + \frac{2(21)(21+1)}{35-21-1} = -62.929.$$

Thus, since $\mathrm{AIC_{C2}}$ is the lowest of the corrected AIC scores, we can say that, despite estimating two additional parameters, Case 2 is the better model. This confirms what we see upon visual inspection of Figure 1 and Figure 3.

4 Sensitivity Analysis

Sensitivity analysis (SA) is a method to identify critical inputs of a model and quantify how uncertainties in model inputs (parameters and initial conditions) affect model outputs (the classes at the final time). To determine the sensitivity of our classes to our model inputs, we use the Sobol method, a variance-based global SA method [37]. As a variance-based SA method, the Sobol method proportions the model's output variance into fractions attributed to the model inputs or combination of interacting inputs; these fractions are a measure of sensitivity [29]. Additionally, as a global SA method, the Sobol method measures sensitivity across the whole model input space and can be used on models with non-linear outputs [33].

The Sobol method offers three types of sensitivity indices: first-order, higher-order, and total-order, but our main focus is on the first- and total-order. The first-order sensitivity index describes the percent of model output variance contributed by a model input individually (i.e., the effect of varying that one model input alone) [29]. In other words, it is the proportion of the total model output variance that could be reduced if there was no uncertainty about this model input [32]. If a model input's first-order sensitivity index is one, then all the variance in the model output is entirely driven by this input [33]. The total-order sensitivity index describes the entire influence of a model input on the model output, including first-order and all of its interactions with other inputs; it describes the proportion of the total model output variance that remains when uncertainty is removed from all other inputs except this input [14, 32]. It is the best measure of sensitivity since it explains both the individual and interactive effects of the model input [29].

To implement this method in Python, we first use the Saltelli sampler from the SALib package to generate N(2D+2) samples where N is the number of sample points, and D is the number of inputs (parameters and initial conditions) in the model [15, 13]. All of these ranges are summarized in Table 8 and Table 9, and the reasoning for the ranges is outlined below. The model inputs are drawn uniformly from these ranges. We then evaluate the model using the generated inputs and save the model outputs, which are the population classes (S_G, P_G, A_G, F_G, R_G, S_C, S_H, P_C, A_C, F_C, and R_C), at the final time. Finally, we use the Sobol analyze function from the SALib package on the outputs to compute the first- and total-order sensitivity indices [15, 13].

Table 8: Range of values for each parameter used for the Sobol sensitivity analysis.

Parameter	**Range**
$\tilde{m}_G$	$[-0.0284, -0.0174]$
$\tilde{b}_G$	$[0.223, 0.396]$
$\log(\beta_{GA})$	$[-4.0, -2.0]$
$\log(\beta_{GP})$	$[-5.0, -3.0]$
$\log(\theta_{SC})$	$[-4.0, -2.0]$
$\log(\theta_P)$	$[-3.0, -1.0]$
θ_A	$[24.5, 73.4]$
ϵ_G	$[3.5, 10.5]$
$\log(\gamma)$	$[-5.9, -3.9]$
ζ	$[0.0268, 0.0805]$
$\log(\nu)$	$[-3.5, -1.5]$
σ	$[0.485, 1.46]$
λ_A	$[0.00317, 0.0095]$
λ_F	$[0.5, 1.0]$
μ	$[0.00715, 0.0215]$
μ_F	$[0.235, 0.706]$
μ_A	$[0.0235, 0.0706]$
$\tilde{m}_H$	$[-0.0393, -0.016]$
$\tilde{b}_H$	$[0.212, 0.444]$
$\tilde{m}_C$	$[-0.0393, -0.016]$
$\tilde{b}_C$	$[0.212, 0.444]$
ρ_C	$[0.001, 2.0]$
ρ_H	$[0.001, 2.0]$
$\log(\beta_{CA})$	$[-4.5, -1.5]$
$\log(\beta_{HA})$	$[-4.5, -1.5]$
$\log(\beta_{CP})$	$[-5.5, -2.5]$
$\log(\beta_{HP})$	$[-5.5, -2.5]$
ϵ_C	$[1.75, 12.3]$
ϵ_H	$[1.75, 12.3]$
$\log(\theta_{SH})$	$[-4.5, -1.5]$
$\log(\theta_{SV})$	$[-4.5, -1.5]$
k	$[1 * 10^{-10}, 1.0]$

The ranges for the general population parameters are set to $\pm 50\%$ of the parameter values estimated in Case 2 (as shown in Table 7), with the exception of $\tilde{m}_G$, $\tilde{b}_G$, and the parameters that were estimated on a logarithmic scale (β_{GA}, β_{GP}, θ_{S_G}, θ_P, γ, and ν).

For parameters that were estimated using a logarithmic scale in the least squares estimation, we continue to use a log scale and add ± 1 range to their log values and round to the first decimal, as these parameters are on a very small scale. For instance, the range for $\log(\beta_{GA})$ is $[-4, -2]$ since the estimated value for β_{GA} was $10^{-3} = 0.001$ from Table 7.

For $\tilde{m}_G$ and $\tilde{b}_G$, note that these parameters are part of the general population prescribing

Table 9: Range of values for each initial value used for the Sobol sensitivity analysis.

Parameter	Range
P_{C_0}	$[0.0216, 0.0647]$
A_{C_0}	$[0.00123, 0.00369]$
F_{C_0}	$[0.00017, 0.000509]$
R_{C_0}	$[0.000254, 0.000763]$
S_{H_0}	$[0.0, 0.5]$
P_{V_0}	$[0.0108, 0.0755]$
A_{V_0}	$[0.000616, 0.00431]$
F_{V_0}	$[8.48 * 10^{-05}, 0.000594]$
R_{V_0}	$[0.000127, 0.00089]$

rate α_G, where

$$\alpha_G(t) = \tilde{m}_G \cdot t + \tilde{b}_G.$$

We require that α_G remains non-negative at the final time (the start of 2020). The estimated parameter values for $\tilde{m}_G$ and $\tilde{b}_G$ from Table 7 are $\tilde{m}_G = -0.0288$ and $\tilde{b}_G = 0.332$, so the corresponding $\pm 50\%$ bounds of $\tilde{m}_G$ and $\tilde{b}_G$ are $[-0.0432, -0.0144]$ and $[0.166, 0.498]$, respectively. However, we wish to choose the bounds of $\tilde{m}_G$ and $\tilde{b}_G$ such that the value of α_G varies $\pm 50\%$ at the final time. The value of α_G at the final time is

$$\alpha_G(2020) = -0.0288(4) + 0.332 = 0.217.$$

The $\pm 50\%$ range for this value is $[0.109, 0.326]$. To achieve this range while staying in the $\pm 50\%$ range of $\tilde{m}_G$ and $\tilde{b}_G$, we choose the range of $\tilde{m}_G$ and $\tilde{b}_G$ to be $[-0.0284, -0.0174]$ and $[0.2226, 0.396]$, respectively.

Finally, if the upper bounds for λ_A or λ_F exceed one, they are truncated to one, as these parameters must lie between zero and one.

For the community parameters, we set the ranges to be $\pm 75\%$ of their corresponding general population parameter where applicable (e.g., the parameter ranges for ε_C and ε_H are $\pm 75\%$ of the parameter value estimated for ε_G), since we know even less about the parameter values of the community model, with the exception of $\tilde{m}_C$, $\tilde{b}_C$, $\tilde{m}_H$, $\tilde{b}_H$, S_{H_0} and the community parameters that correspond with a general population parameter that are using the logarithmic scale (β_{CA}, β_{HA}, β_{CP}, β_{HP}, θ_{S_C}, and θ_{S_H}).

We assume that it would be unreasonable for a community to have more than half of its susceptible population have chronic pain. Thus, we let S_{H_0} range from $[0, 0.5]$.

For the community parameters whose corresponding general population parameter uses the logarithmic scale, we also use a log scale for these parameters and add ± 1.5 to their corresponding general population log parameter for the range, rounding to the nearest decimal. For example, the range of $\log(\beta_{CA})$ is $[-4.5, -1.5]$ since the estimated value for β_{GA} was 10^{-3} from Table 7.

We wish to choose the bounds of $\tilde{m}_C$ and $\tilde{b}_C$ such that the range of α_C is $\pm 75\%$ of the estimated value of α_G at the final time. Thus, we wish the range of α_C to range from $[0.0543, 0.380]$. We choose the range of $\tilde{m}_C$ and $\tilde{b}_C$ to be $[-0.0393, -0.0160]$ and $[0.212, 0.444]$, respectively, to accomplish this. We also chose these ranges for $\tilde{m}_H$ and $\tilde{b}_H$, respectively.

Additionally, for k, the range is set as $[0, 1]$ (or $[1.0 \times 10^{-10}, 1]$ for computational reasons), and for ρ_H and ρ_C, the parameter ranges are set to $[0.001, 2.0]$.

We have $D = 41$ and use $N = 2^{15}$ for a total of 2,752,512 samples. The number of sample points N was chosen so that the results do not change with a slightly higher value. This was run over four years, and the sensitivities of the parameters were evaluated for the population classes at the final time. The first-order results can be seen in Figure 5a, and the total-order results can be seen in Figure 5b. The length of the colored bars represents the contribution of that parameter to the variance of that population class at the final time; the longer the colored bars, the higher the effect of that parameter on that class.

We are interested in the parameters that the OUD classes (A and F) are most sensitive to at the final time. We also take an interest in what parameters the stably recovered classes (R) are most sensitive to since these could be determining factors in the number of fatal ODs the population experiences. From the total-order index, we see that A_G is most sensitive to:

- A_{C_0}, the initial condition of the A_G class;
- ζ, the rate at which those with POUD stably recover; and
- μ_A, the overdose death rate for individuals with POUD.

F_G is most sensitive to:

- μ_F, the overdose death rate for individuals with FHUD;
- A_{C_0}, the initial condition of the A_G class; and
- R_{C_0}, the initial condition of the R_G class.

R_G is most sensitive to:

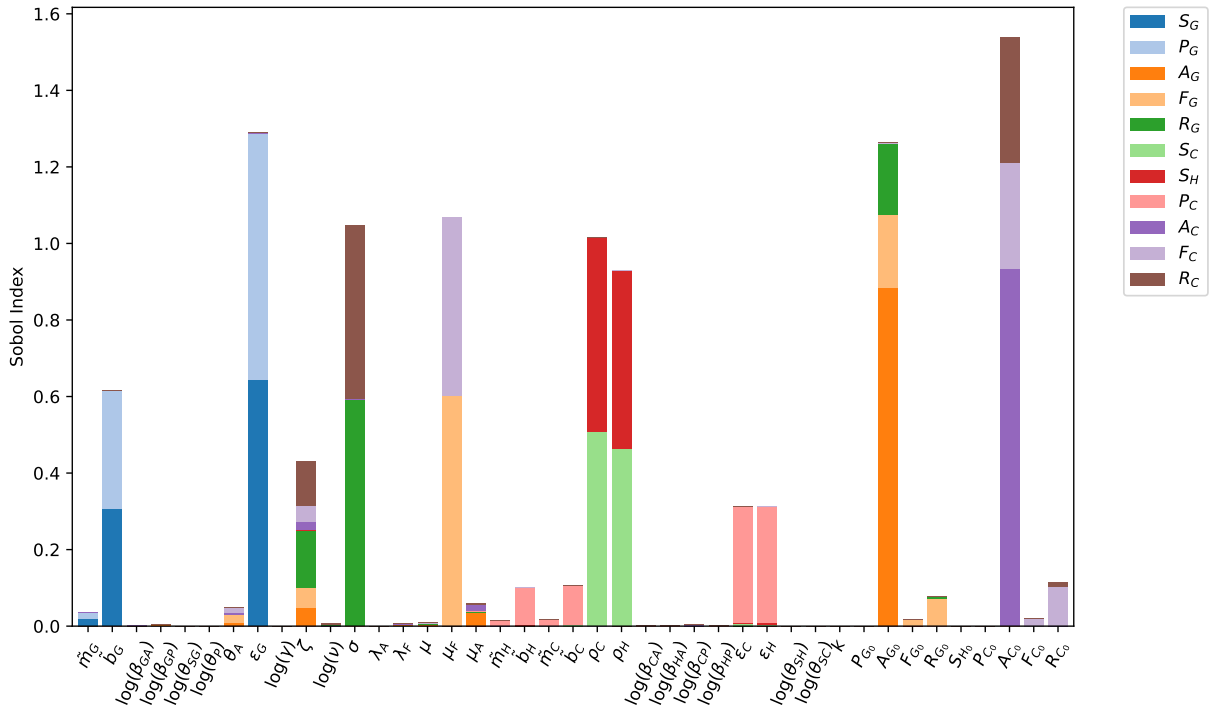
- σ, the rate at which stably recovered individuals relapse;
- A_{C_0}, the initial condition of the A_G class; and
- ζ, the rate at which those with POUD stably recover.

A_C is most sensitive to:

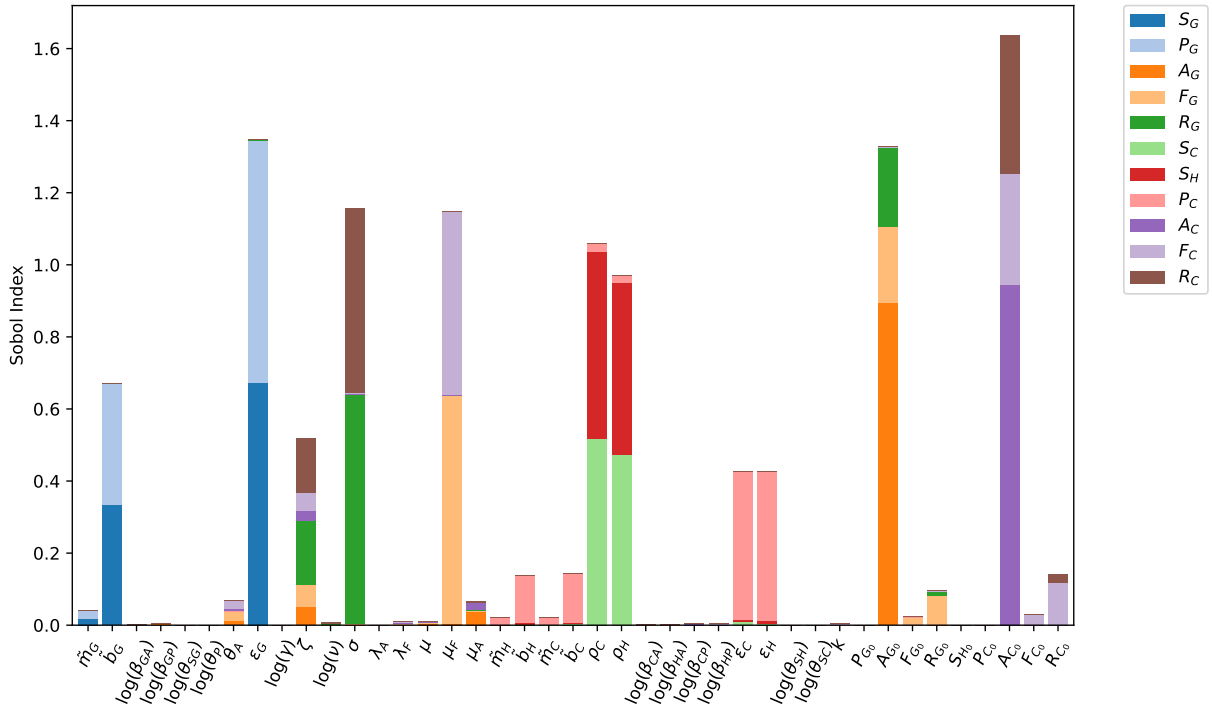
- A_{V_0}, the initial condition of the A_C class;
- ζ, the rate at which those with POUD stably recover; and
- μ_A, the overdose death rate for individuals with POUD.

F_C is most sensitive to:

- μ_F, the overdose death rate for individuals with FHUD;



(a) first-order indices



(b) total-order indices

Figure 5: Sobol sensitivity results for the size of each class at the beginning of 2020 run from 2016 to 2019 with 2,752,512 samples for the (a) first-order indices and (b) total-order indices.

- A_{V_0}, the initial condition of the A_C class; and
- R_{V_0}, the initial condition of the R_C class.

Finally, R_C is most sensitive to:

- σ, the rate at which stably recovered individuals relapse;
- A_{V_0}, the initial condition of the A_C class; and
- ζ, the rate at which those with POUD stably recover.

According to the first-order index, these parameters are also the ones to which these OUD and stably recovered classes are most sensitive. Note that the first-order index and the total-order index results are very similar, suggesting that not many higher-order interactions occur; this means most of the interactions are first-order.

5 Community Cases

Thus far, our focus has been on the general population as a whole, based on data that reflects the entire group. Moving forward, we aim to dive deeper into the community and explore various specific cases within it. First, we need to establish a baseline set of parameters for the community. We define these parameters and initial conditions to closely mirror the general population's overall output as accurately as possible, within reason, before making any adjustments to specific parameters. Doing this should more clearly demonstrate the effects of altering certain parameters.

To establish the initial conditions, we refer to estimates indicating that in 2016, approximately 20.4% of U.S. adults experienced chronic pain (defined as pain lasting three months or longer) [10], with a similar estimate of 20.9% in 2021 [30]. Since the community model divides the susceptible class into those with or without chronic pain, we set the initial condition of S_H to be 20% of the estimate of S_{C_0} from Table 7, and set S_C to be the remaining 80% of S_{C_0}. The remaining community initial conditions are set the same as their general population counterparts (e.g., P_{V_0} is the same as the estimate for P_{C_0}). A summary of these values can be seen in Table 10.

Since we want the community output to be similar to the general population output for the base case, we let $k = 1$ (i.e., there is no discrimination/preference between influencing interactions with those who are or are not in the community). The reasoning for choosing the remaining parameter values is described below, and a summary of the chosen values can be seen in Table 10.

The solution to the general population ODEs in Figure 4 shows that P_G initially increases before decreasing between 2016 and 2017. At the initial time, we want P_G and P_C to increase at approximately the same rate, so we want the differential equations for P_G and P_C at the

Table 10: The values of the parameters used in the community base case.

Parameter	**Value**	**Units**
$\tilde{m}_C$	-0.03456	$\frac{1}{\text{year}}$
$\tilde{b}_C$	0.3154	$\frac{1}{\text{year}}$
$\tilde{m}_H$	-0.00576	$\frac{1}{\text{year}}$
$\tilde{b}_H$	0.3984	$\frac{1}{\text{year}}$
ρ_C	0.1	$\frac{1}{\text{year}}$
ρ_H	0.4	$\frac{1}{\text{year}}$
β_{CA}	0.0008	$\frac{1}{\text{year}}$
β_{HA}	0.0002	$\frac{1}{\text{year}}$
β_{CP}	8.0×10^{-5}	$\frac{1}{\text{year}}$
β_{HP}	2.0×10^{-5}	$\frac{1}{\text{year}}$
θ_{S_C}	0.000891	$\frac{1}{\text{year}}$
θ_{S_H}	0.000223	$\frac{1}{\text{year}}$
ε_C	5.603	$\frac{1}{\text{year}}$
ε_H	1.401	$\frac{1}{\text{year}}$
k	1.0	dimensionless
S_{H_0}	0.191	dimensionless
P_{V_0}	0.0432	dimensionless
A_{V_0}	0.00246	dimensionless
F_{C_0}	0.000339	dimensionless
R_{C_0}	0.000508	dimensionless

initial time to be equal. If we chose ε_C and ε_H such that they sum to ε_G, then we want $\tilde{b}_C S_{V_0} + \tilde{b}_H S_{H_0}$ to equal $\tilde{b}_G S_{C_0}$. Thus we wish to chose choose $\tilde{b}_C$ such that

$$\begin{aligned}\tilde{b}_C &= \frac{\tilde{b}_G S_{C_0} - \tilde{b}_H S_{H_0}}{S_{V_0}} \\ &= \frac{\tilde{b}_G S_{C_0} - 0.2\tilde{b}_H S_{C_0}}{0.8 S_{C_0}} \\ &= 1.25\tilde{b}_G - 0.25\tilde{b}_H.\end{aligned}$$

It is also reasonable to assume that $\tilde{b}_H$ would be greater than $\tilde{b}_C$. Thus, if be chose $\tilde{b}_H = 1.2\tilde{b}_G$, then $\tilde{b}_C = 0.95\tilde{b}_G$.

By similar logic, we want $\tilde{m}_G$ to equal $0.8\tilde{m}_C + 0.2\tilde{m}_H$. It is also reasonable to assume that $\tilde{m}_C < \tilde{m}_H$. If we let $\tilde{m}_C = 1.2\tilde{m}_G$, then we get that $\tilde{m}_H = 0.2\tilde{m}_G$.

Recall that ρ_C is the transition rate from S_C to S_H (i.e., the rate at which susceptible individuals without pain develop pain), and ρ_H is the transition rate from S_H to S_C (i.e., the rate at which susceptible individuals with chronic pain no longer experience chronic pain without going through the route of taking prescription opioids). We want the rate from S_C into S_H to be approximately the same as the rate from S_H into S_C, at least at the initial time. Thus we want $\rho_C S_{C_0}$ to be approximately $\rho_H S_{H_0}$. We then choose ρ_H such that

$$\begin{aligned}\rho_H &= \frac{\rho_C S_{C_0}}{S_{H_0}} \\ &= \frac{\rho_C 0.8 S_{C_0}}{0.2 S_{C_0}} \\ &= 4\rho_v.\end{aligned}$$

If we let $\rho_C = 0.1$, then we choose ρ_H to be 0.4.

For the remaining parameters, we let the parameter corresponding with the S_C class be 80% of its corresponding S_G parameter and let the parameter corresponding with the S_H class be 20% of its corresponding S_G parameter. For example, $\varepsilon_C = 0.8\varepsilon_G$ and $\varepsilon_H = 0.2\varepsilon_G$.

Figure 6 illustrates the solution curves for the "baseline" community, using the parameter values specified in Table 10. In Figure 7, the solution curves of both the general population and community are compared, with the general population parameter values drawn from Table 7 and the "baseline" community parameters as outlined in Table 10.

References

[1] *Diagnostic and statistical manual of mental disorders : DSM-5-TR*, 5th edition, text revision. ed. American Psychiatric Association Publishing, Washington, DC, 2022.

[2] American Psychological Association. APA dictionary of psychology, 2023. accessed 12/18/23, `https://dictionary.apa.org/substance-use-disorder`.

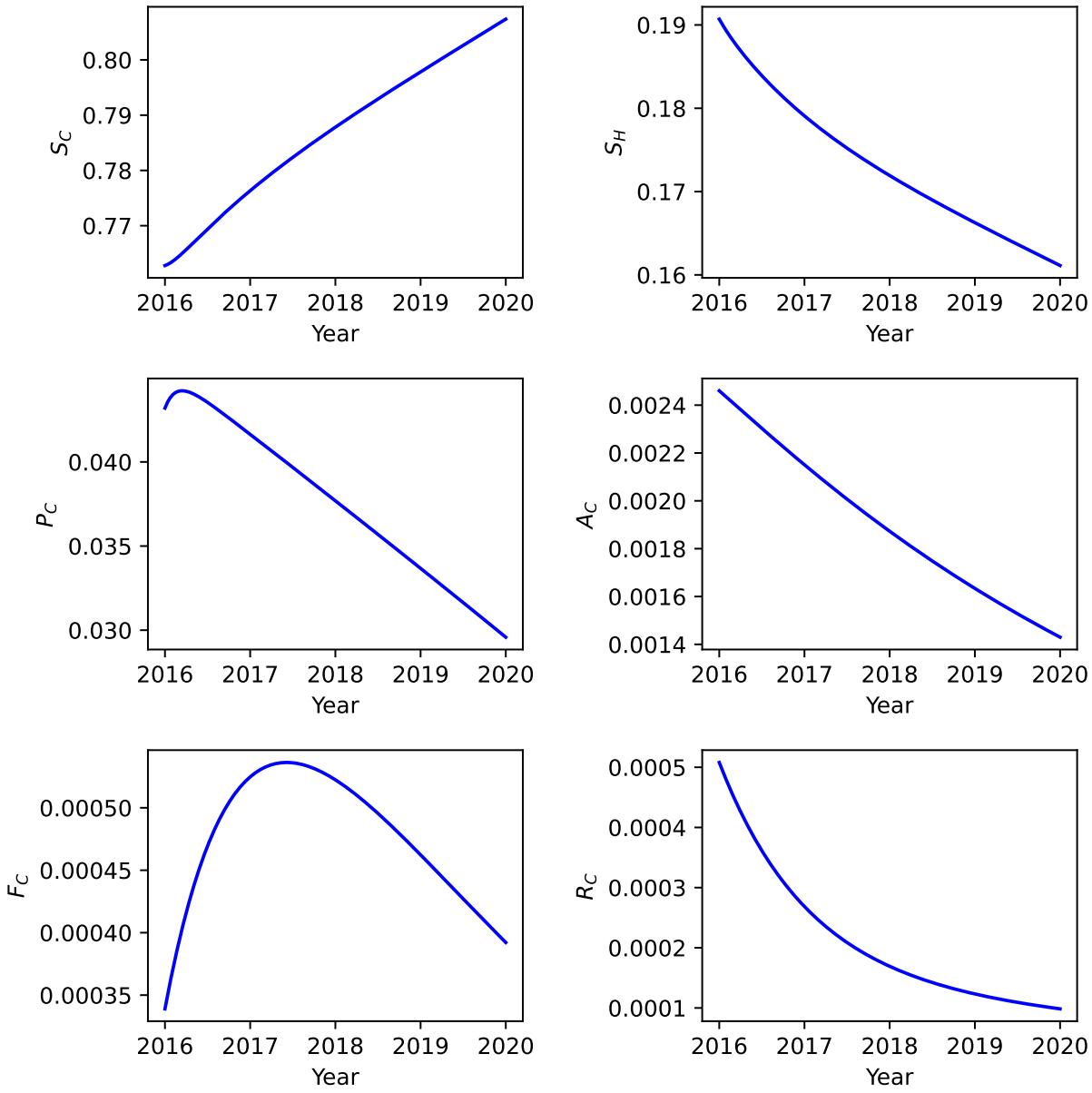


Figure 6: Community solution curves using the general population parameters values from Table 7 and the "baseline" community parameters values as seen in Table 10.

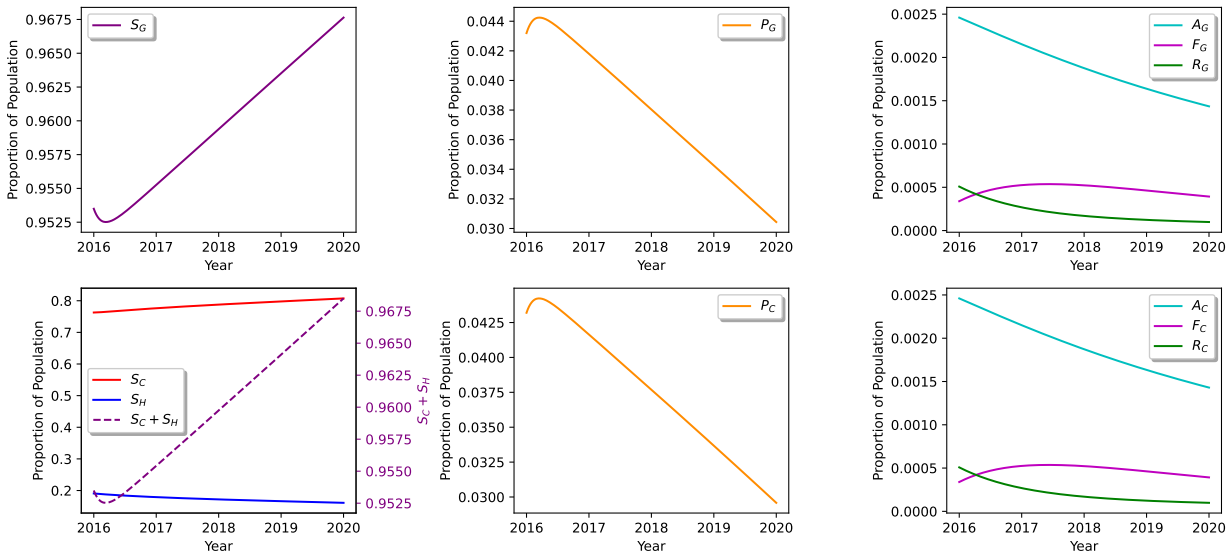


Figure 7: Solution curves using the general population parameters values from Table 7 and the "baseline" community parameters values as seen in Table 10. The general population solutions are shown in the top row, and the community solutions are shown in the bottom row. The bottom left graph features the solutions to S_C (red), S_H (blue), and the sum of S_C and S_H (dashed purple) to demonstrate its resemblance to the solution curve for S_G.

[3] Appalachian Regional Commission. Health disparities related to opioid misuse in appalachia, 2019. accessed 01/07/2025, https://www.arc.gov/wp-content/uploads/2020/06/HealthDisparitiesRelatedtoOpioidMisuseinAppalachiaApr2019.pdf.

[4] Banerjee, S., and Argáez, C. Multidisciplinary treatment programs for patients with acute or subacute pain: A review of clinical effectiveness, cost-effectiveness, and guidelines. Tech. rep., Canadian Agency for Drugs and Technologies in Health, Ottawa (ON), May 7 2019. Accessed: 02-07-25.

[5] Banks, H. T., and Joyner, M. L. AIC under the framework of least squares estimation. *Applied Mathematics Letters 74* (2017), 33–45.

[6] Battista, N. A., Pearcy, L. B., and Strickland, W. C. Modeling the prescription opioid epidemic. *Bulletin of mathematical biology 81* (2019), 2258–2289.

[7] Bell, C. C. Dsm-iv: diagnostic and statistical manual of mental disorders. *Jama 272*, 10 (1994), 828–829.

[8] Centers for Disease Control and Prevention. About prescription opioids, 2024. accessed 02/05/2025, https://www.cdc.gov/overdose-prevention/about/prescription-opioids.html#:~:text=Opioids%20should%20only%20be%20used,for%203%20days%20or%20less.

[9] Centers for Disease Control and Prevention. Understanding the opioid overdose epidemic, 2024. accessed 10/30/24, https://www.cdc.gov/overdose-prevention/about/understanding-the-opioid-overdose-epidemic.html.

[10] Dahlhamer, J. Prevalence of chronic pain and high-impact chronic pain among adults—united states, 2016. *MMWR. Morbidity and mortality weekly report 67* (2018).

[11] Han, B., Compton, W. M., Blanco, C., Crane, E., Lee, J., and Jones, C. M. Prescription opioid use, misuse, and use disorders in us adults: 2015 national survey on drug use and health. *Annals of internal medicine 167*, 5 (2017), 293–301.

[12] Hasin, D. S., O'brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., Compton, W. M., Crowley, T., Ling, W., Petry, N. M., et al. Dsm-5 criteria for substance use disorders: recommendations and rationale. *American Journal of Psychiatry 170*, 8 (2013), 834–851.

[13] Herman, J., and Usher, W. SALib: An open-source python library for sensitivity analysis. *The Journal of Open Source Software 2*, 9 (jan 2017).

[14] Homma, T., and Saltelli, A. Importance measures in global sensitivity analysis of nonlinear models. *Reliability Engineering & System Safety 52*, 1 (1996), 1–17.

[15] Iwanaga, T., Usher, W., and Herman, J. Toward SALib 2.0: Advancing the accessibility and interpretability of global sensitivity analyses. *Socio-Environmental Systems Modelling 4* (May 2022), 18155.

[16] Mauro, P. M., Gutkind, S., Annunziato, E. M., and Samples, H. Use of medication for opioid use disorder among us adolescents and adults with need for opioid treatment, 2019. *JAMA network open 5*, 3 (2022), e223821–e223821.

[17] Moody, L. N., Satterwhite, E., and Bickel, W. K. Substance use in rural central appalachia: Current status and treatment considerations. *Journal of Rural Mental Health 41*, 2 (2017), 123.

[18] Muhuri, P. K., Gfroerer, J., and Davies, C. Associations of nonmedical pain reliever use and initiation of heroin use in the united states. Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality (CBHSQ), 2013. https://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm.

[19] National Academies of Sciences, Engineering, and Medicine and others. Pain management and the opioid epidemic: balancing societal and individual benefits and risks of prescription opioid use. National Academies Press, 2017, ch. 4.

[20] National Institute of Mental Health. Substance use and co-occurring mental disorders, 2023. accessed 12/18/23, https://www.nimh.nih.gov/health/topics/substance-use-and-mental-health.

[21] National Institute on Drug Abuse. Drug misuse and addiction, 2011. accessed 12/10/24, https://nida.nih.gov/publications/drugs-brains-behavior-science-addiction/drug-misuse-addiction.

[22] National Institute on Drug Abuse. Drug overdose deaths: Facts and figures, 2024. accessed 11/05/24, https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates.

[23] National Survey on Drug Use and Health. State data tables and reports from the 2019-2020 nsduh, 2021. accessed 12/13/24, https://www.samhsa.gov/data/nsduh/state-reports-NSDUH-2020.

[24] National Survey on Drug Use and Health. 2021 national survey on drug use and health (nsduh) releases, 2022. accessed 12/13/24, https://www.samhsa.gov/data/release/2021-national-survey-drug-use-and-health-nsduh-releases.

[25] Office of Information and Analytics Tennessee Department of Health. Tennessee's annual overdose report 2021: Report on epidemiologic data and projects to address the overdose epidemic., 2021. accessed 11/17/23, https://www.tn.gov/content/dam/tn/health/documents/pdo/2021%20TN%20Annual%20Overdose%20Report.pdf.

[26] Office of Information and Analytics Tennessee Department of Health. Data dashboard, 2022. accessed 09/25/23, https://www.tn.gov/health/health-program-areas/pdo/pdo/data-dashboard.html.

[27] Office of Information and Analytics Tennessee Department of Health. Fatal drug overdose data dashboard information, 2022. accessed 09/25/23, https://www.tn.gov/content/dam/tn/health/documents/pdo/dashboard/Technical%20Notes%20-%20Fatal.pdf.

[28] Phillips, T., Lenhart, S., and Strickland, W. C. A data-driven mathematical model of the heroin and fentanyl epidemic in tennessee. *Bulletin of Mathematical Biology 83*, 10 (2021), 97.

[29] Reed, P. M., Hadjimichael, A., Malek, K., Karimi, T., Vernon, C. R., Srikrishnan, V., Gupta, R. S., Gold, D. F., Lee, B., Keller, K., et al. Addressing uncertainty in multisector dynamics research. *Zenodo* (2022).

[30] Rikard, S. M. Chronic pain among adults—united states, 2019–2021. *MMWR. Morbidity and Mortality Weekly Report 72* (2023).

[31] Rohatgi, A. Webplotdigitizer, 2022. accessed 01/15/24, https://automeris.io/WebPlotDigitizer/.

[32] Saltelli, A. Sensitivity analysis for importance assessment. *Risk analysis 22*, 3 (2002), 579–590.

[33] Saltelli, A., Aleksankina, K., Becker, W., Fennell, P., Ferretti, F., Holst, N., Li, S., and Wu, Q. Why so many published sensitivity analyses are false: A systematic review of sensitivity analysis practices. *Environmental modelling & software 114* (2019), 29–39.

[34] Shah, A. Characteristics of initial prescription episodes and likelihood of long-term opioid use—united states, 2006–2015. *MMWR. Morbidity and mortality weekly report 66* (2017).

[35] Smyth, B., Barry, J., and Keenan, E. K. D. Lapse and relapse following inpatient treatment of opiate dependence. *Irish Medical Journal 103*, 6 (2010), 176–179.

[36] Smyth, B. P., Barry, J., Keenan, E., and Ducray, K. Lapse and relapse following inpatient treatment of opiate dependence. *Ir Med J 103*, 6 (2010), 176–9.

[37] Sobol, I. M. Global sensitivity indices for nonlinear mathematical models and their monte carlo estimates. *Mathematics and computers in simulation 55*, 1-3 (2001), 271–280.

[38] Social Security Administration. Actuarial life table, 2019. accessed 10/30/23, https://www.ssa.gov/oact/STATS/table4c6_2016_TR2019.html.

[39] Social Security Administration. Actuarial life table, 2020. accessed 10/30/23, https://www.ssa.gov/oact/STATS/table4c6_2017_TR2020.html.

[40] Social Security Administration. Actuarial life table, 2022. accessed 10/30/23, https://www.ssa.gov/oact/STATS/table4c6_2019_TR2022.html.

[41] Social Security Administration. Actuarial life table, 2023. accessed 10/30/23, https://www.ssa.gov/oact/STATS/table4c6.html.

[42] Substance Abuse and Mental Health Services Administration. 2015-2016 national survey on drug use and health: Guide to state tables and summary of small area estimation methodology, 2017. accessed 11/13/23, https://www.samhsa.gov/data/sites/default/files/NSDUHsaeMethodology2016/NSDUHsaeMethodology2016.htm.

[43] Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the united states: Results from the 2016 national survey on drug use and health, 2017. accessed 12/12/23, https://www.samhsa.gov/data/report/key-substance-use-and-mental-health-indicators-united-states-results-2016-national-survey.

[44] Substance Abuse and Mental Health Services Administration. 2015-2016 NSDUH estimated totals by state: Table 9. heroin use in the past year, by age group and state: Estimated numbers (in thousands), annual averages based on 2015 and 2016 NSDUHs, 2018. accessed 10/27/23, https://www.samhsa.gov/data/report/2015-2016-nsduh-estimated-totals-state.

[45] Substance Abuse and Mental Health Services Administration. 2017 national survey on drug use and health (NSDUH) releases - table 1.1a – types of illicit drug use in lifetime, past year, and past month among persons aged 12 or older: Numbers in thousands, 2016 and 2017, 2018. accessed 10/27/23, https://www.samhsa.gov/data/report/2017-nsduh-detailed-tables.

[46] Substance Abuse and Mental Health Services Administration. 2017 national survey on drug use and health (NSDUH) releases - table 12.1a – numbers (in thousands) of persons aged 12 or older, by gender and detailed age category: 2016 and 2017, 2018. accessed 12/12/23, https://www.samhsa.gov/data/report/2017-nsduh-detailed-tables.

[47] Substance Abuse and Mental Health Services Administration. 2017 national survey on drug use and health (NSDUH) releases - table 4.4b – past year initiation of substance use among persons aged 12 or older, persons aged 12 or older at risk for initiation of substance use, and past year substance users aged 12 or older: Numbers in thousands and percentages, 2016 and 2017, 2018. accessed 12/12/23, https://www.samhsa.gov/data/report/2017-nsduh-detailed-tables.

[48] Substance Abuse and Mental Health Services Administration. 2017 national survey on drug use and health (NSDUH) releases - table 5.2a – substance use disorder for specific substances in past year among persons aged 12 or older, by age group: Numbers in thousands, 2016 and 2017, 2018. accessed 10/27/23, https://www.samhsa.gov/data/report/2017-nsduh-detailed-tables.

[49] Substance Abuse and Mental Health Services Administration. 2016-2017 NSDUH estimated totals by state: Table 9. heroin use in the past year, by age group

and state: Estimated numbers (in thousands), annual averages based on 2016 and 2017 NSDUHs, 2019. accessed 10/27/23, https://www.samhsa.gov/data/report/2016-2017-nsduh-state-specific-tables.

[50] Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the united states: Results from the 2018 national survey on drug use and health, 2019. accessed 12/12/23, https://www.samhsa.gov/data/report/2018-nsduh-annual-national-report.

[51] Substance Abuse and Mental Health Services Administration. 2017-2018 NSDUH estimated totals by state: Table 9. heroin use in the past year, by age group and state: Estimated numbers (in thousands), annual averages based on 2017 and 2018 NSDUHs, 2020. accessed 10/27/23, https://www.samhsa.gov/data/report/2017-2018-nsduh-state-specific-tables.

[52] Substance Abuse and Mental Health Services Administration. 2017 national survey on drug use and health (NSDUH) releases - table 1.1a – types of illicit drug use in lifetime, past year, and past month among persons aged 12 or older: Numbers in thousands, 2018 and 2019, 2020. accessed 10/27/23, https://www.samhsa.gov/data/report/2019-nsduh-detailed-tables.

[53] Substance Abuse and Mental Health Services Administration. 2017 national survey on drug use and health (NSDUH) releases - table 5.1a – substance use disorder for specific substances in past year among persons aged 12 or older, by age group: Numbers in thousands, 2018 and 2019, 2020. accessed 10/27/23, https://www.samhsa.gov/data/report/2019-nsduh-detailed-tables.

[54] Substance Abuse and Mental Health Services Administration. 2018-2019 NSDUH estimated totals by state: Table 9. heroin use in the past year, by age group and state: Estimated numbers (in thousands), annual averages based on 2018 and 2019 NSDUHs, 2021. accessed 10/27/23, https://www.samhsa.gov/data/report/2018-2019-nsduh-state-specific-tables.

[55] Substance Abuse and Mental Health Services Administration. State data tables and reports from the 2019-2020 NSDUH, 2021. accessed 10/27/23, https://www.samhsa.gov/data/nsduh/state-reports-NSDUH-2020.

[56] Substance Abuse and Mental Health Services Administration. 2021 NSDUH model-based estimated totals for states (in thousands): Table 9. heroin use in the past year: Among people aged 12 or older; by age group and state, estimated numbers (in thousands), 2021, 2023. accessed 02/09/24, https://www.samhsa.gov/data/report/2021-nsduh-estimated-totals-state.

[57] Tennessee Department of Health. All-cause death counts and mortality rates by demographic groups and geographic area.

[58] United States Census Bureau. County population by characteristics: 2010-2019, 2021. accessed 10/23/23, https://www.census.gov/data/tables/time-series/demo/popest/2010s-counties-detail.html.

[59] United States Census Bureau. County population totals and components of change: 2020-2022, 2023. accessed 10/23/23, https://www.census.gov/data/tables/time-series/demo/popest/2020s-counties-total.html.