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THE PERFORMANCE OF MARGINAL MODELING METHODS FOR RARE EVENTS WITH APPLICATION TO OPIOID OVERDOSE MORTALITY AND MORBIDITY

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THE PERFORMANCE OF MARGINAL MODELING METHODS FOR RARE EVENTS WITH APPLICATION TO OPIOID OVERDOSE MORTALITY AND MORBIDITY

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Public Health
at the University of Kentucky

By
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ABSTRACT OF DISSERTATION

THE PERFORMANCE OF MARGINAL MODELING METHODS FOR RARE EVENTS WITH APPLICATION TO OPIOID OVERDOSE MORTALITY AND MORBIDITY

Opioid misuse is a nationwide epidemic, with Kentucky having one of the highest opioid overdose-related fatality rates across all US states. These rates have increased significantly over the past decade, with particularly large increases during the COVID-19 pandemic. This dissertation aims to study the behavior of these increases and the methods for the marginal modeling of count outcomes related to opioid overdose.

Opioid overdose-related fatality rates in Kentucky increased significantly during the COVID-19 pandemic. In this chapter, we characterize the changes in opioid overdose fatality rates in Kentucky and identify associations between potential factors and fatality rates. County-level opioid overdose fatality data were used to fit a marginal negative binomial model to determine which factors were associated with opioid overdose fatality rates in 2019 (before the COVID-19 pandemic) and 2021 (2nd COVID-19 pandemic). Results show that adjacent-to-metropolitan county status was associated with opioid overdose fatalities in 2021, indicating a differential effect of COVID-19 on suburban communities.

Rare cluster-level count outcomes are often found in epidemiological settings, such as cluster-randomized trials (CRTs) and observational studies. The goal of this chapter is to compare marginal modeling methods for rare events, with a particular focus on opioid overdose fatalities. For both CRT and observational study settings, simulation studies were conducted to compare the validity of inference and power of the three regression methods. Conditional on a valid standard error estimator, power was similar between the regression methods when the event of interest was very rare, but differed between the methods as the marginal probability of the event increased. Careful consideration is required when choosing a regression method for modeling rare cluster-level count outcomes in the settings studied in this chapter.

Events that can occur more than once are often of interest in epidemiology research. One such event is opioid-related poisonings, which is the focus of the third chapter. Using opioid poisoning data from Kentucky Emergency Medical Services (EMS) records, simulated data sets were used to compare the validity of inference and power of the three marginal modeling methods used in the previous chapter for modeling rare events that can occur more than once per person. Based on the results from the simulation studies, all three regression methods produced test sizes that were close to nominal, although slightly inflated. In terms of power, modified negative binomial and modified overdispersed binomial regression performed similarly, and were more powerful than modified Poisson regression.

KEYWORDS: Opioid Overdose, Marginal Model, Count Outcome, Cluster Randomized Trials

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Chapter 1 - Introduction

Both cluster randomized trials (CRTs) and observational studies involving clustered data are common in epidemiological settings. [1] [2] [3] [4] [5] Count outcomes of events collected at the cluster level, such as diseases, are often of interest in these settings. In these settings, researchers may aim to model the population-averaged, or marginal, probabilities or rates of these events. The focus of this dissertation is on the application of marginal modeling methods for rare events in clusters large enough to observe a sufficient amount of events. First, we apply a marginal negative binomial regression model to an observational study of opioid overdose-related fatalities in Kentucky. Next, we compare the validity of inference and power of marginal modeling methods in both cluster randomized trial and observational study settings, with a specific focus on rare events that can occur at most once per person, such as opioid overdose-related fatalities. Finally, we compare the performance of the previously studied methods for rare events that can occur more than once per person, and apply these methods to the study of opioid poisonings in Kentucky.

The primary motivation for this dissertation is the study of opioid overdose in Kentucky. Kentucky has one of the highest rates of opioid overdose-related fatalities among US states, and it is crucial that appropriate treatment and prevention strategies are developed to curb this epidemic. [6] [7] The second chapter of this dissertation serves as an application of negative binomial regression to modeling opioid overdose-related fatality rates in Kentucky. In this application, we identify county-level factors, such as metropolitan status and age, that were associated with opioid overdose-related fatalities in 2019 (before the COVID-19 pandemic) and 2021 (2nd COVID-19 pandemic).

Additionally, using the marginal negative binomial model, we were able to characterize the changes in opioid overdose-related fatality rates in Kentucky from 2019 to 2021.

Next, in the third chapter of this dissertation, we aim to compare the validity of inference, power, and practicality of several methods for the marginal modeling of rare cluster-level count outcomes. In this chapter, which focuses on rare events which can occur at most once per person, both cluster randomized trial and observational study settings will be studied. We conduct simulation studies across a variety of settings in order to compare the validity of inference and power of modified regression approaches, which incorporate empirical sandwich standard error estimates to allow for the possibility of valid inference even when the overdispersion structure is misspecified. [8] [9] [10] An application example based on the study of county-level factors associated with opioid overdose-related fatalities in Kentucky, as conducted in the second chapter, is used to support the results from the simulation studies. In the simulation studies, we show that when the event of interest is very rare, conditional on a valid bias-corrected standard error estimator, the three methods - modified overdispersed binomial regression, modified negative binomial regression, and modified Poisson regression - performed similarly in terms of power, although with slight differences depending on the true overdispersion structure of the data. However, as the marginal probability of the event increased, the difference in power between the methods increased as well.

Finally, in the fourth chapter of the dissertation, we extend the study of the modified regression approaches compared in the third chapter to their applications in modeling cluster-level count outcomes of rare events that can occur more than once per person. Because of the additional level of clustering that results from the event of interest

being able to occur more than once per person, the working overdispersion structure of the three modified regression approaches may not correspond to the true overdispersion structure of the data. The applied focus of this chapter is an observational study of community-level opioid poisoning rates. As in the third chapter, simulation studies are conducted to compare the validity of inference and power of the three modified regression approaches. In general, the three modified regression approaches resulted in inference that was slightly liberal. Modified negative binomial regression and modified overdispersed binomial regression resulted in higher power than modified Poisson regression.

Chapter 2 - Community-Level Factors and Their Associations with Opioid Overdose Mortality in Kentucky from 2019 to 2021

Overview of Chapter 2

Kentucky has one of the highest opioid overdose-related fatality rates among US states. [6] With opioid overdose-related fatality rates in Kentucky, particularly those attributed to fentanyl misuse, increasing over the past decade, it is imperative to identify factors related to these trends in order to improve treatment and prevention. [7] This increase in fatality rates was particularly large during the early stages of the COVID-19 pandemic and has been linked to several societal changes due to the pandemic. [11] [12] In this chapter, we aim to characterize changes in opioid overdose-related fatality rates in Kentucky from 2019 (before the COVID-19 pandemic) to 2021 (during the COVID-19 pandemic). Another goal of this chapter is to identify associations between community-level factors and opioid overdose-related fatality rates in 2019 and 2021, as well as how these associations may have changed. By understanding the changes in opioid overdose-related fatality rates and how pandemic-related factors are related to these increased rates, policymakers can construct targeted interventions that properly address opioid misuse given the unique characteristics of communities in Kentucky.

Introduction

Overview

In this section, we will provide background information on the landscape of opioid overdose in Kentucky and the potential COVID-19-related factors that play a role in opioid overdose-related fatalities. First, we will describe recent trends in drug and opioid overdose in both the US and Kentucky. Next, we will highlight several potential factors related to the COVID-19 pandemic that may be associated with opioid overdose-related fatalities in Kentucky. Finally, we will describe the overall goals of this chapter, which include characterizing the changes in opioid overdose-related fatality rates in Kentucky and identifying factors related to these fatality rates and their changes from 2019 to 2021.

Drug and Opioid Overdose in Kentucky

Drug overdose remains a leading cause of death in the United States, with over 107,000 deaths in 2021. [13] Of these deaths, almost three-quarters can be attributed to opioids. [14] Opioid overdose deaths have increased dramatically, with nationwide rates doubling from 2010 to 2019. [15] Initially, the majority of these deaths were a result of prescription opioid overdose. Due to a number of initiatives on reducing prescription opioid overprescribing, misuse and diversion at state and national levels (e.g. reformulation of OxyContin as an abuse deterrent formulation, strengthening state prescription drug monitoring program laws, closure of pill mill clinics, improved prescriber education, mandated reduction in prescription opioid production by the Drug Enforcement Administration), prescription opioid overdose deaths decreased significantly

in 2012-2013. [16] [17] However, without adequate capacity for treatment for people with opioid use disorder, the demand for opioids continued, and heroin became cheaper and more accessible, reflected in the increase in heroin-related overdose deaths after 2011. In 2014-2015, illicitly produced fentanyl and fentanyl analogs became more widely available, and have proven to be much deadlier than prescription opioids because of their potency. [18] In a study by Gladden et al. conducted in 27 states, drug products obtained by law enforcement that tested positive for fentanyl increased by 426% from 2013 to 2014. [19] Since 2016, fentanyl, either mixed with other opioids or marketed as heroin, has been the largest contributor to opioid-related deaths, being responsible for almost 50% of them. [20] Because of this, in addition to those who willingly seek out fentanyl, there are many who overdose due to consuming fentanyl unknowingly. In summary, the propagation of illicit fentanyl has been a contributing factor towards the increase in opioid overdose deaths in recent years.

Kentucky is especially affected by the opioid overdose epidemic, as it had the 5th highest opioid overdose fatality rate among US states in 2020. [6] Drug overdose has long been an issue in Kentucky, as prescription opioids such as oxycodone have been prevalent in rural areas due to aggressive marketing and lack of access to alternative pain treatment. [21] In addition, there is a relatively high prevalence of physical labor occupation in Appalachian Kentucky, which are frequently associated with acute and chronic pain. The overprescribing of opioid analgesics is a contributing factor towards the high rate of opioid use in Kentucky. [22] Prior prescription opioid misuse is linked to the use of heroin and illicit fentanyl, and the decrease in the availability of diverted prescription opioids has caused much of the opioid misuse in Kentucky to transition

towards these forms of opioids. [19] [23] [24] Despite legislation in the mid-2010s aimed at increasing the availability of the opioid antagonist naloxone, as well as substance use disorder treatment services, fentanyl overdose death rates have increased significantly in recent years. [7] [23] [25] Factors such as poverty, unemployment, and family stressors have been linked to opioid overdose in Kentucky communities, especially rural communities. [26] [27] Opioid misuse in remote rural communities poses additional risk, as offering help in these areas is much harder due to lack of cellular phone service and long distances from healthcare services. These socioeconomic root factors make tackling the opioid overdose problem in Kentucky much more complex.

Opioid overdose has become an alarming issue in recent years. Nationwide, synthetic opioid overdose deaths increased by 39% from the 12-month period ending in May 2020 to the 12-month period ending in May 2021. [13] From 2019 to 2020, opioid overdose death rates among Kentucky residents increased from 23.10 to 35.74 per 100,000 residents, a 55% increase, with fentanyl overdose deaths increasing from 17.08 to 30.10 per 100,000 residents, a 76% increase. [7] There was a large increase in opioid overdoses in Kentucky during the early stages of the pandemic; emergency medical service calls for opioid overdose in Kentucky rose by 17% from the 2-month period prior to COVID-19 to the first two months of COVID-19 (March and April 2020). [11] However, it is still unclear which factors have been the most impactful in increasing opioid overdose fatalities after the onset of COVID-19.

There have been several societal changes that have occurred due to COVID-19 that have been identified as potential links to this recent increase. [12] Of these changes, there are two main factors - mental health and unemployment - that we aim to investigate.

First, stay-at-home orders at the beginning of the COVID-19 pandemic have been linked with increased psychological stress, which has been associated with economic instability and social isolation. [28] Of all US adults, 13.9% reported symptoms of psychological distress during the early stages of the COVID-19 pandemic (April 2020) compared to 3.9% in 2018. [29] An increase in substance use during the COVID-19 pandemic may also be indicative of stressors causing individuals to turn to substances such as opioids as relief, thus increasing their risk of substance use-related harm. [30] In addition, access to mental health care was stymied during the pandemic, largely due to closures in clinician offices and concerns about in-person care due to the virus. [28] The lack of mental health care is uniquely concerning in the wake of COVID-19 due to the increased need of treatment in an environment with intensified psychological stressors. [31]

The COVID-19 pandemic has caused drastic changes in unemployment in the United States, especially during the initial stages. The unemployment rate tripled from February to April 2020 and did not return to pre-COVID-19 levels until September 2021. [32] Increases in unemployment rates have been found to be associated with increased levels of opioid overdose. [33] [34] More generally, unemployment has been found to be associated with adverse health behaviors, such as substance misuse. [35] Unemployment introduces economic stressors that can limit access to health care as well as inhibit the ability to adhere to substance misuse treatment regimens. [36] [37] In short, the rapid and severe increase in unemployment during the COVID-19 pandemic has introduced economic stressors that may cause individuals to turn to opioid misuse, often resulting in harmful situations that may lead to overdose deaths.

Several demographic factors have been found relevant to changes in opioid overdose mortality trends. Age, for example, is important to account for, as opioid overdose is generally more common in younger populations. [38] Race is another demographic factor that has been found to be associated with disparity in drug overdose deaths. [39] Specifically, the average annual percentage change of opioid overdose fatalities between 2013 and 2020 was nearly twice as high among African Americans compared to White individuals (26.16 vs. 13.19). [40] In addition, there is evidence that African American communities were uniquely affected by COVID-19 due to factors such as access to health care. [41] Disparity in socioeconomic status and poverty within communities have been linked to increased risk of opioid overdose due to lack of access to health care as well as the prevalence of manual labor. [34] [42] [43] Another factor related to socioeconomic status as well as the COVID-19 pandemic is access to health insurance. During the initial stages of the COVID-19 pandemic, the percentage of uninsured individuals increased by 1.4% during the three-month period in 2020 between April to July. [44] Access to health insurance is crucial for opioid use disorder treatment, as services such as Medicaid cover medication for opioid use disorder (MOUD). [45]

In addition to access to health insurance, availability of MOUD for opioid overdose is crucial. Both methadone and buprenorphine have been shown to be effective at treating OUD compared to other OUD treatment pathways. [46] Methadone is an opioid agonist that must be administered at certified opioid treatment programs (OTPs). [47] Because of geographic and policy limitations, access to methadone treatment from OTPs is often difficult, which was exacerbated during COVID-19. [48] [49] Access to methadone treatment is more difficult in rural areas, where distance to OTPs is much

greater, on average. [50] Buprenorphine is a partial opioid agonist that can be prescribed or administered by certain trained healthcare practitioners. [51] Access to buprenorphine is disproportionately limited in rural areas, with many rural counties not having access to a provider. [52] During the initial months of the COVID-19 pandemic, both overall buprenorphine prescriptions and Kentucky transmucosal (TM) buprenorphine reception rates decreased significantly. [53] [54] Recent initiatives, such as allowing prescription without an in-person physician meeting, have been introduced to counteract this disruption to buprenorphine access. [28] [55]

Naloxone is a life-saving opioid antagonist that is available in community pharmacies. The U.S. Surgeon General called naloxone a key part of the public health response to the opioid epidemic. [56] While there have been recent efforts to expand naloxone distribution in Kentucky through legislation and pharmacist training programs, naloxone access still remains an issue in rural communities due to scarcity of accessible community pharmacies as well as a lack of knowledge of the availability of naloxone. [57] [58] Finally, although the majority of opioid overdose fatalities can be attributed to the use of synthetic opioids such as fentanyl, high-risk opioid prescribing, including extended duration or high dosage opioid prescription, is a factor that can contribute to increased risk of opioid misuse and overdose.

Much of the disparity in access to health insurance and MOUD can be attributed to differences in rural and urban environments. The discrepancy between rural and urban socioeconomic stressors is well understood, access to health care and opioid use disorder treatment programs are more scarce in rural areas. [33] Furthermore, suburban communities, compared to rural communities, have experienced higher opioid-related

mortality rates since 2016. [59] In addition, rural communities may be more affected by social and economic stressors caused by COVID-19. Understanding the dynamics of opioid misuse between communities with different levels of urbanicity during COVID-19 is key to constructing appropriate targeted interventions in Kentucky. Highlighting Appalachian counties in the context of opioid overdose in Kentucky is crucial – opioid overdose rates in Appalachia are significantly higher due to various factors specific to the region. Specifically, lack of transportation and health services limiting access to OUD and overdose treatment, as well as economic deprivation, make the opioid overdose situation in Appalachia uniquely severe compared to the rest of Kentucky. [60] [61]

Goals

Because of the massive societal changes due to the COVID-19 pandemic, as well as their demographic and geographical discrepancies within the state of Kentucky, it is crucial to understand the pandemic's effects on opioid overdose. While we have highlighted many other potential factors that can be associated with the increase in opioid overdose during COVID-19, COVID-19-related factors are of particular interest due to the pandemic's unique effects.

We aim to characterize the changes in opioid overdose fatality rates in Kentucky from 2019 to 2021, with a specific focus on changes among Appalachian vs non-Appalachian Kentucky residents. We will also determine which factors were associated with opioid overdose fatalities in 2019 and 2021 and how these associations may have changed. We hope that our findings will inform targeted interventions that improve both opioid overdose prevention and treatment of OUD.

Methods

Overview

In this section, we will describe the data and methods used in the analyses. We will provide details on the structure and data sources for the outcome, county-level yearly opioid overdose-related fatalities, as well as for each of the county-level factors included in the analyses. Next, we will describe the descriptive analyses conducted. These descriptive analyses include opioid overdose-related fatality counts and rates, which are stratified by Appalachian and metropolitan county statuses. Finally, we describe the statistical analysis, which involves a marginal negative binomial regression model that is used to determine the associations between potential county-level factors and opioid overdose-related fatalities in 2019 and 2021.

Measures and Data Sources

The main outcome of interest was county-level yearly opioid overdose fatalities in Kentucky per 100,000 residents. Opioid overdose fatality counts were calculated using death certificates of Kentucky residents, extracted from the Kentucky Office of Vital Statistics. Opioid-involved overdose deaths for Kentucky residents over the age of 18 were identified by an underlying cause-of-death ICD-10 code in the range X40-X44, X60-X64, X85, Y10-Y14 and a supplementary ICD-10 cause-of-death code in the range T40.0-T40.4, or T40.6. To calculate fatality rates, estimates for Kentucky population over the age of 18 were obtained from the United States Census Bureau American Communities Survey (ACS) in 2019. [62]

Based on proposed links to opioid overdose presented in the literature, a variety of potential factors related to opioid overdose in Kentucky, including COVID-19-related factors, demographics, county metropolitan and Appalachian status, and factors related to MOUD, were analyzed.

For the COVID-19-related factors of interest, county-level variables related to unemployment and mental health were investigated. Monthly unemployment rates from both 2019 and 2021 were obtained from the National Bureau of Labor Statistics (BLS). [33] The number of mental health providers per 100,000 residents, which was obtained from National Provider Information (NPI) data from 2019 provided by the Centers for Medicare & Medicaid Services (CMS), was used to account for the availability of mental health care in each county. [63]

A county was defined as Appalachian following the designation described by the Appalachian Regional Commission. [64] To account for disparities between rural and urban communities, county metropolitan status was defined using Rural-Urban Continuum Codes from the US Department of Agriculture's Economic Research Service. [65] County metropolitan status was divided into metropolitan (continuum codes 1-3), adjacent-to-metropolitan (continuum codes 4-6), and non-metropolitan groups (continuum codes 7-9).

Data on percentage non-White, percentage residents over the age of 65, and percentage residents in poverty were obtained from the US Census Bureau American Communities Study in 2019. [62] The percentage of residents in each county who were uninsured was obtained from the US Census Bureau's Small Area Health Insurance Estimates (SAHIE) program. [66]

Prevalence of OUD estimates in 2019 were calculated for each Kentucky county by Thompson et al., using Multiple Systems Estimation and were shared for this study. [67] This method linked data from multiple Kentucky healthcare data sources, and the number of individuals with OUD on each combination of lists was used to estimate the number of individuals with OUD that were unobserved. [68]

Number of naloxone units distributed in Kentucky communities for both 2019 and 2021 was obtained from the Kentucky Pharmacists Association (KPhA). [69] The Kentucky All Schedule Prescription Electronic Reporting (KASPER) program monitors all controlled substance prescriptions dispensed in Kentucky. Using KASPER data, the number of individuals 18 years of age or older receiving buprenorphine treatment for OUD was used to calculate the monthly rate of buprenorphine receipt in 2019. [70] Methadone for treatment of OUD is dispensed at OTPs and not reported to the KASPER program. Thus, we could not account for availability of methadone MOUD. Finally, KASPER data were used to calculate measures for high-risk opioid prescribing in 2019. [70]

Statistical Analysis

Analyses were performed at the county level. Yearly opioid overdose fatality rates and 95% confidence intervals per 100,000 residents over the age of 18 for 2019 and 2021, as well as the rate ratios comparing rates between the two years, were calculated. Opioid fatality counts and rates, with 95% confidence intervals, for 2019 and 2021 are presented in Table 2.1, and are stratified by Appalachian county status and metropolitan classification. County-level summary statistics for 2019 variables are presented in Table

2.2. Unemployment rates, naloxone distribution rates, as well as rate ratios for these variables over the two years are presented in Table 2.3. Monthly opioid overdose rates for 2019 and 2021 are presented in Figure 2.1, and are stratified by metropolitan and Appalachian county status for each year in Figures 2.2-2.5.

To determine which county-level factors were associated with opioid overdose fatality rates in 2019 and 2021, as well as if these associations changed, an adjusted marginal generalized estimating equation (GEE)-type negative binomial model was fit. [71] [72] The outcome for each county in a given year was defined as the number of opioid overdose fatalities, and the statistical correlation among count outcomes from the same county was modeled using working unstructured covariance matrices. Due to variation in county population, the model's offset was the natural log of the number of residents in a given county. Yearly rates are directly modeled, and rate ratios are used as the basis for comparisons between years. Results for the associations for each year as well as whether the changes in association between 2019 and 2021 are statistically significant are presented Table 2.3. Estimates for the changes in associations are presented in Table 2.4, and can be interpreted as the ratio of the rate ratios for associations in 2021 vs. 2019. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). [73] [74] Statistical significance was defined as $p < 0.05$.

Results

Overview

In this section, we will provide results for both the descriptive and statistical analyses. Opioid overdose-related fatality rates in 2019 and 2021 and the rate ratios for the change between the two years will be presented for Kentucky overall, as well as stratified by Appalachian and metropolitan county status. Descriptive statistics for other variables included in the model will be presented as well. For the statistical analysis, adjusted rate ratios for each of the county-level factors in 2019 and 2021, as well as how these rate ratios changed, will be presented. By evaluating whether the adjusted rate ratios are statistically significant, we can identify factors that are associated with opioid overdose-related fatalities.

Descriptive Results

As presented in Table 2.1, opioid overdose fatalities increased from 976 in 2019 to 1780 in 2021 (RR: 1.82). Appalachian counties had a lower fatality rate than non-Appalachian counties in 2019 (22.01 vs. 33.06 per 100,000 residents), but experienced a larger increase (RR: 2.38 vs. 1.68) in fatality rate from 2019 to 2021. The fatality rate in Appalachian counties was higher than that of non-Appalachian counties in 2021 (52.26 vs. 51.56 per 100,000 residents).

Among the three metropolitan status categories, adjacent-to-metropolitan counties experienced the largest increase in opioid overdose fatality rates from 2019 to 2021, with a rate ratio of 2.54. In contrast, metropolitan had the highest fatality rate in 2019, with

35.19 fatalities per 100,000 residents but experienced the lowest increase in fatalities from 2019 to 2021, with a rate ratio of 1.59.

The county-level average for unemployment rate increased from 4.82% to 5.16% (RR: 1.07) from 2019 to 2021 (Table 2.2). The naloxone distribution rate per 1,000 residents increased

drastically from 2019 to 2021 (RR: 3.01).

In 2019, the average county percentage of residents older than 65 years of age was 17.44%; the average county percentage of non-White residents was 6.93%, and the percentage living in poverty was 19.73% (Table 2.2). The baseline assessment of opioid use disorder prevalence was 53.53 per 1,000 residents. In 2019, on average, every month 1.72 per 1,000 residents had dispensed buprenorphine prescription(s) for treatment of opioid use disorder; 1.86 per 1,000 residents met the criteria for high-risk opioid prescribing.

Modeling Results

Regression results for 2019 and 2021 are displayed in Table 2.3, and results for the change in rates are displayed in Table 2.4. After accounting for other variables in the model, we found no significant difference in the opioid overdose fatality rate between Appalachian and non- Appalachian counties in 2019 (RR: 1.12, 95% CI: (0.72, 1.77)) and in 2021 (RR: 1.55, 95% CI: (1.04, 2.32)) (Table 2.3). The change in association between Appalachian status and opioid overdose mortality from 2019 to 2021 was not statistically significant (p-value: 0.136).

In 2019, metropolitan county status, compared to non-metropolitan county status, was associated with an increase in opioid overdose fatalities (RR: 1.96, 95% CI: (1.25, 3.07), p-value: 0.003).This association had a statistically significant decrease from 2019 to 2021 (RR: 0.61, 95% CI: (0.40, 0.94), p-value: 0.023), showing shrinking differences in mortality between metropolitan and non-metropolitan counties. Metropolitan county status did not have a statistically significant association with opioid overdose fatalities in 2021. On the other hand, in 2021, adjacent-to-metropolitan counties had an opioid overdose mortality rate almost two times that of non-metropolitan counties (RR: 1.94, 95% CI: (1.30, 2.89), p-value: 0.001), while in 2019 the difference in their rates was not significant (RR 1.48, 95% CI: (0.85, 2.59)).

Neither of the COVID-19-related variables – unemployment or mental health providers – had clinically or statistically significant associations in either year, nor were the changes in associations from 2019 to 2021 statistically significant. As for the medication-related variables, the associations between estimated opioid use disorder prevalence in 2019 and overdose fatalities in both years were statistically significant (2019 – RR: 1.01, 95% CI: (1.00, 1.02), p-value: 0.002
/ 2021 – RR: 1.01, 95% CI: (1.00, 1.02), p-value: 0.008), but the change in associations between the years was not statistically significant (p-value: 0.626). None of the other medication-related variables were associated with opioid overdose fatalities in either year.

Of the demographic variables, the 2019 percentage residents over 65 was statistically significantly associated with opioid overdose fatalities in both 2019 (RR:

0.94, 95% CI: (0.91, 0.98), p-value: 0.002) and 2021 (RR: 0.88, 95% CI: (0.85, 0.92), p-value: <0.001). In addition,

the change in association from 2019 to 2021 was statistically significant (RR: 0.94, 95% CI: (0.91, 0.97), p-value: <0.001). None of the other demographic variables were statistically significantly associated with opioid overdose in either year.

Discussion

Overview

In this section, we will highlight the conclusions of our results and evaluate how these results may be used to inform policy and construct treatment and prevention strategies for curbing opioid overdose-related fatalities in Kentucky. Next, we will identify some strengths and limitations of this study. Finally, we will highlight potential future work that could expand on this chapter, such as the subject of the third chapter of this dissertation.

Summary of Results

Our analysis showed an increased gap in opioid overdose mortality between Appalachian and non-Appalachian counties from 2019 to 2021 (adjusted rate ratios 1.12 vs. 1.55), potentially indicating that the pressures brought by the COVID-19 pandemic affected Appalachian counties disparately. Appalachian counties are vulnerable to opioid overdose due to issues such as economic deprivation and lack of access to health care, which became more prevalent during the pandemic. [28] [31] Proliferation of alternative solutions to tackling opioid overdose treatment in Appalachia, such as telehealth, is crucial even in the post-COVID-19 world due to barriers such as spatial access to health care. [75] The increase in naloxone distribution rate from 2019 to 2021 (RR: 3.01) may be attributed to recent efforts to expand naloxone distribution in Kentucky, such as a Kentucky General Assembly Amendment in June 2019, which expanded the ability of pharmacies to distribute naloxone, likely contributed to this increase. [76]

Metropolitan county status, compared to non-metropolitan status, had its adjusted rate ratio decrease from 2019 to 2021 (1.96 vs. 1.21). This may be due to the societal changes brought about by COVID-19 disproportionately affecting non-metropolitan counties. Increased psychological distress combined with the lack of access to appropriate health care could have been a contributor to an increased rate of opioid overdose in rural communities. [28] [33] However, adjacent-to-metropolitan county status, compared to non-metropolitan status, had its adjusted rate ratio increase from 2019 to 2021 (1.48 vs. 1.94). One possible explanation for this result is that due to occupations commonly found among suburban residents transitioning to telework during the pandemic, time spent in isolation may have increased, resulting in poorer mental health over the course of COVID-19. Further investigation into the environment of suburban Kentucky during the COVID-19 pandemic is necessary for clarification on this result.

Percentage residents over 65 was associated with a decrease in opioid overdose fatality rates for both 2019 and 2021. Notably, this association was stronger in 2021 than in 2019. Since opioid overdose is generally more common among younger populations, it is possible that younger communities' vulnerability to the societal pressures caused by COVID-19 increased their susceptibility to opioid overdose. Kentucky residents aged 15-24 experienced the highest increase (81%) in drug overdose fatality rates from 2019 to 2021. [7]

Strengths and Limitations

There are several strengths of this study. There exist previous studies that have examined the association between demographic and socioeconomic factors and opioid

overdose as well as ones that have investigated opioid overdose during COVID-19. However, this study is unique in that factors involved in societal changes during the COVID-19 pandemic, as well as how these associations changed during the pandemic, are examined. In addition, there is a lack of research regarding long-term opioid overdose trends after the COVID-19 pandemic. While there exists some literature examining the short-term implications of COVID-19 on opioid overdose, 2021 data have not been extensively studied, and can provide insights on the lasting effects of the pandemic. Being able to construct interventions and programs in a post-COVID-19 world is crucial to improving treatment and preventative measures in the current landscape.

Despite the strengths of this study, there exist key limitations. Social isolation became more prevalent during the onset of the COVID-19 pandemic due to government-imposed measures to enforce social distancing. Although social isolation has been linked to opioid overdose, we were not able to account for it in our analysis. Social isolation also presents a unique roadblock in traditional forms of opioid overdose reversal, as unconscious individuals experiencing an overdose event will not be able to administer naloxone. Social isolation has been linked to poor mental health and psychological stress, which are both factors linked to increased risk of opioid overdose. [77] [78] Isolation may also increase sensitivity to chronic pain, which may lead individuals to seek opioids as pain treatment. [79] It would be fruitful for future studies to analyze social isolation as a factor associated with opioid overdose fatalities. Social isolation caused by unemployment could have also contributed to unemployment's lack of statistically significant associations with overdose fatalities in either year.

In addition, we were not able to account for the changes in several of the factors during the pandemic, as 2021 data was not available for all examined factors. For example, county-level data describing the proliferation of telehealth in Kentucky and loosening of buprenorphine prescription restrictions was not included in the models. [80] This may have contributed to the lack of detected change in associations from 2019 to 2021. Incorporating 2021 data into the analysis would allow us to investigate associations in 2021, as well as the changes in associations between the two years, more precisely. Also, factors that contribute to a county's vulnerability to COVID-19, such as population density and social distancing measures, were unable to be accounted for. These factors may have been associated with opioid overdose, as vulnerability to COVID-19 may be representative of vulnerability to other adverse health events, such as opioid overdose. The COVID-19 Pandemic Vulnerability Index (PVI) is a measure developed by the National Institute of Environmental Health Sciences (NIEHS) to represent each county's vulnerability to COVID-19. [81] However, since this score is composite and contains factors already accounted for in our model, such as demographic information, it was not included.

Future studies could investigate variables similar to those that compose the PVI to understand how factors that contribute to a county's vulnerability to COVID-19 affected opioid overdose rates. Finally, the opioid use disorder prevalence variable used in our analysis was an estimate as opposed to the true, unknown value, and hence estimated associations may be biased.

A lack of variability in community-level covariates can imply a lack of power. This lack of sufficient variability manifests itself as two major limitations to our analysis.

First, because certain demographic variables that could be confounders, such as gender, do not vary significantly between counties, they were not included in our analysis. In addition, several of the factors which have been previously linked to opioid overdose were not found to be associated with overdose fatalities in our analysis. For example, unemployment rate has been found to be associated with opioid overdose and substance misuse in general. [33] [34] However, we did not find unemployment rate to be associated with opioid overdose fatalities in either 2019 or 2021.

Unemployment rate's relatively small range among counties in both years (7.4% for 2019 and 9.1% in 2021) is indicative of low variability. Thus, our ability to detect a statistically significant association between unemployment rate and opioid overdose fatalities was not as high as if we were able to use individual-level data.

Finally, there are some limitations to the measures chosen to be included in the model.

Many of the measures may not be accurate representations of the factor in question. For example, while mental health providers per 1,000 residents provides a picture of the available resources to treat mental health, it does not elucidate the entirety of the mental health situation for each county. Despite these limitations, however, this study provides salient information on how various factors could be associated with opioid overdose before and during the COVID-19 pandemic.

Conclusion

In conclusion, opioid overdose fatality rates increased in Kentucky from 2019 to 2021, with the largest increases occurring in adjacent-to-metropolitan and Appalachian

regions. We found several variables, such as metropolitan status and Appalachian status, as well as age, to be associated with opioid overdose fatality rates in one or both of the years. In addition, we found metropolitan status and age to have observed associations that changed from 2019 to 2021.

These findings can be used to construct targeted interventions that improve treatment and prevention in adjacent-to-metropolitan areas as well as amongst younger populations. Future studies should aim to investigate other COVID-19-related variables as well as which factors are associated with overdose fatality rates in other regions of the United States. Additionally, in this study, we used marginal negative binomial regression to model opioid overdose-related fatalities. However, other methods for marginal modeling of count outcomes, such as overdispersed binomial regression and modified Poisson regression, may result in higher power. The comparison of these methods will be the focus of the third chapter of this dissertation.

Supplemental Materials

Figure 2.1 Opioid Overdose Fatality Rates per 100,000 Residents in Kentucky in 2019 and 2021

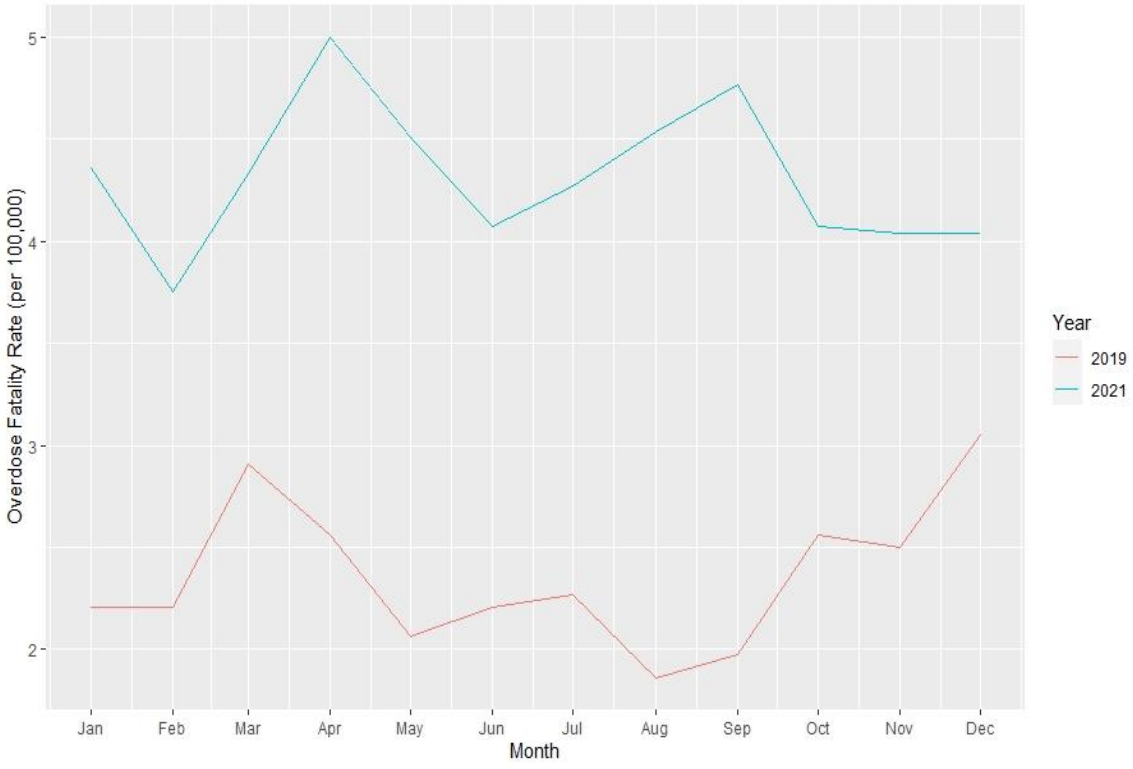

Figure 2.2 Opioid Overdose Fatality Rates in Kentucky by Metropolitan County Status, 2019

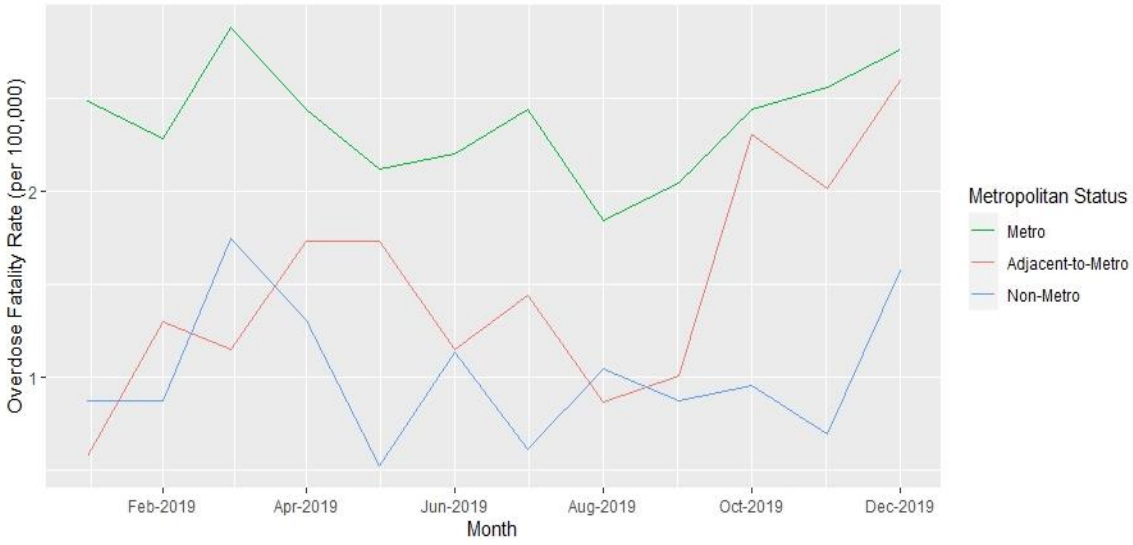

Figure 2.3 Opioid Overdose Fatality Rates in Kentucky by Metropolitan County Status, 2021

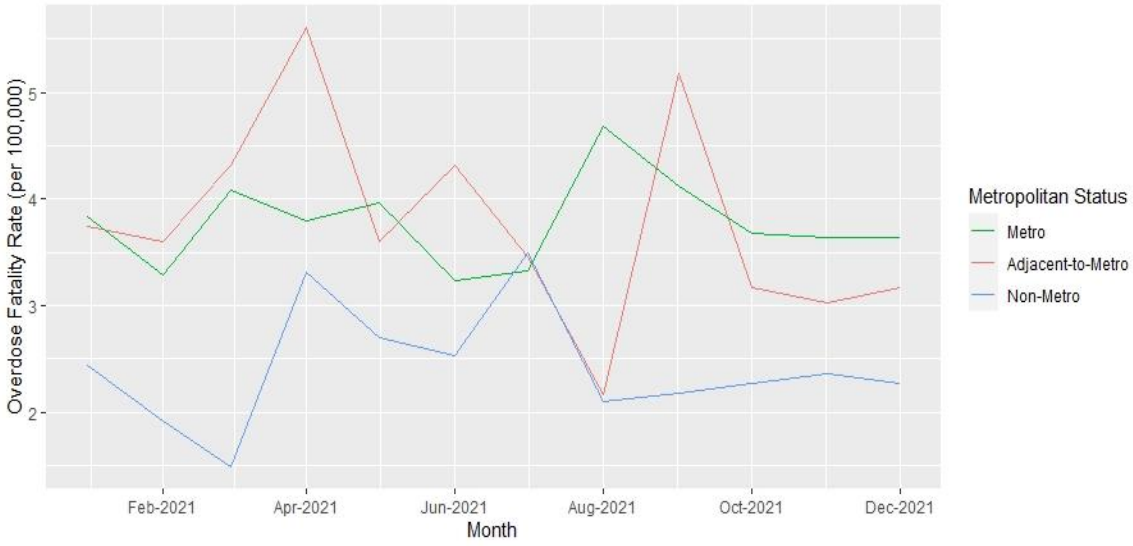

Figure 2.4 Opioid Overdose Fatality Rates in Kentucky by Appalachian Status, 2019

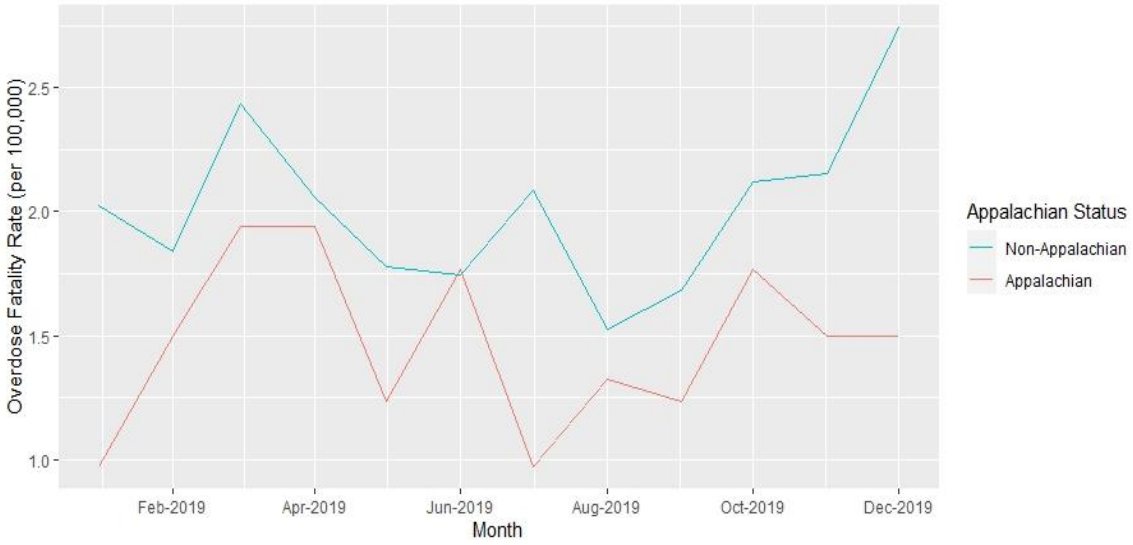

Figure 2.5 Opioid Overdose Fatality Rates in Kentucky by Appalachian Status, 2021

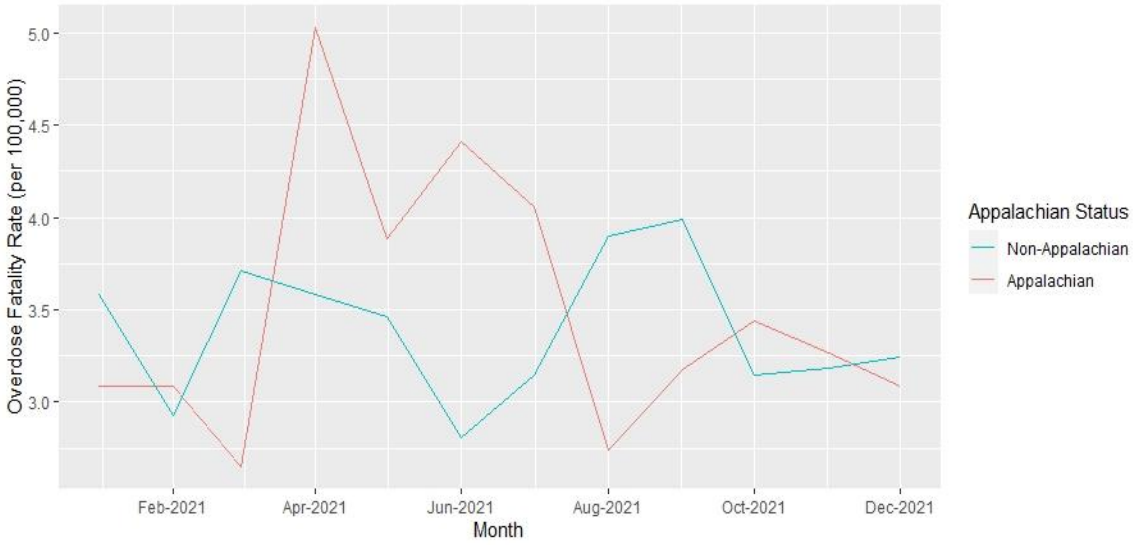

Table 2.1 Opioid Overdose Fatality Counts and Rates per 100,000 Residents in Kentucky in 2019 and 2021

	Fatality Counts (Rates per 100,000 Residents)		
	2019	2021	RR* (95% CI†)
Overall	976 (28.37)	1780 (51.75)	1.82 (1.68, 1.97)
Metropolitan Status			
Metropolitan	712 (35.19)	1132 (55.96)	1.59 (1.45, 1.75)
Adjacent-to-Metropolitan	124 (23.51)	315 (59.73)	2.54 (2.06, 3.13)
Non-Metropolitan	164 (18.78)	348 (45.88)	2.44 (2.12, 2.81)
Appalachian Status			
Appalachian	200 (22.01)	475 (52.26)	2.38 (2.02, 2.81)
Non-Appalachian	776 (30.66)	1305 (51.56)	1.68 (1.54, 1.84)

*RR = Rate Ratio

†CI = Confidence Interval

Table 2.2 County-Level Means of Variables from 2019 and 2021

	2019		2021		
	Mean (SD*)	95% CI†	Mean (SD)	95% CI	RR§ - 2021 vs. 2019
Mental Health Providers (per 1,000 Residents)	1.67 (2.70)	(1.19, 2.16)	-	-	-
Demographic Variables					
% Age > 65	17.44 (3.36)	(16.84, 18.05)	-	-	-
% Non-White	6.93 (5.49)	(5.94, 7.91)	-	-	-
% Poverty	19.73 (6.63)	(18.55, 20.92)	-	-	-
Uninsured % (% of population under 65 without health insurance)	6.01 (0.91)	(5.89, 6.13)	-	-	-
Medication-Related Variables					
Monthly Buprenorphine Reception Rate (per 1,000 Residents)	1.72 (1.35)	(1.55, 1.89)	-	-	-
Monthly High-Risk Opioid Prescribing Rate (per 1,000 Residents)	1.86 (0.53)	(1.80, 1.93)	-	-	-
Opioid Use Disorder Prevalence (per 1,000 Residents)	53.53 (32.52)	(49.40, 59.35)	-	-	-
Unemployment Rate (%)	4.82 (1.31)	(4.59, 5.05)	5.16 (1.41)	(4.91, 5.41)	1.07 (1.06, 1.08)
Naloxone Distribution Rate (per 1,000 Residents)	4.98 (9.49)	(4.82, 5.13)	14.99 (22.19)	(14.63, 15.36)	3.01 (2.96, 3.06)

*SD = Standard Deviation
†CI = Confidence Interval
§RR = Rate Ratio

Table 2.3 Model Estimates (Adjusted Rate Ratios) for Yearly Opioid Overdose Fatalities per 100,000 Residents.

Variable	2019	2021
	RR* (95% CI†)	**RR (95% CI)**
COVID-19-Related Variables		
Unemployment Rate	0.99 (0.87, 1.14)	0.97 (0.89, 1.06)
Mental Health Providers per 1,000 Residents	0.99 (0.96, 1.03)	1.02 (0.99, 1.05)
Geographical Variables		
Metropolitan Status		
Metropolitan vs. Non-Metropolitan¶	1.96 (1.25, 3.07) §	1.21 (0.78, 1.86)
Adjacent-to-Metropolitan vs. Non-Metropolitan	1.48 (0.85, 2.59)	1.94 (1.30, 2.89) §
Metropolitan vs. Adjacent-to-Metropolitan¶	1.33 (0.75, 2.35)	0.62 (0.42, 0.92) §
Appalachian Status		
Appalachian vs. Non-Appalachian	1.12 (0.72, 1.77)	1.55 (1.04, 2.32) §
Demographic Variables		
Non-White %	0.99 (0.96, 1.03)	1.00 (0.98, 1.03)
Age > 65 %¶	0.94 (0.91, 0.98) §	0.88 (0.85, 0.92) §
Poverty %	0.98 (0.95, 1.02)	0.99 (0.96, 1.01)
Uninsured % (% of population under 65 without health insurance)	0.98 (0.83, 1.16)	0.96 (0.85, 1.09)
Medication-Related Variables		
Monthly Naloxone Distribution per 1,000 Residents	1.01 (0.99, 1.02)	1.00 (1.00, 1.01)
Monthly Buprenorphine Reception Rate per 1,000 Residents	1.05 (0.83, 1.33)	1.04 (0.86, 1.27)
Monthly High-Risk Opioid Prescribing Rate per 1,000 Residents	0.88 (0.54, 1.45)	0.72 (0.49, 1.06)
Opioid Use Disorder Prevalence per 1,000 Residents	1.01 (1.00, 1.02) §	1.01 (1.00, 1.02) §

*RR = Rate Ratio
†CI = Confidence Interval
§$p<0.05$
¶Change in association between 2019 and 2021 is statistically significant. Results are presented in Table 2.4.

Table 2.4 Model Estimates (Adjusted Rate Ratios) for the Interactions Between Factors of Interest and Year for Yearly Opioid Overdose Fatalities per 100,000 Residents.

Variable	Change from 2019 to 2021 RR* (95% CI†)	p-value
COVID-19-Related Variables		
Unemployment Rate	0.98 (0.87, 1.10)	0.675
Mental Health Providers per 1,000 Residents	1.03 (0.99, 1.07)	0.211
Geographical Variables		
Metropolitan Status		
Metropolitan vs. Non-Metropolitan	0.61 (0.40, 0.94)	0.023§
Adjacent-to-Metropolitan vs. Non-Metropolitan	1.31 (0.85, 2.02)	0.218
Metropolitan vs. Adjacent-to-Metropolitan	0.47 (0.31, 0.71)	<0.001§
Appalachian Status		
Appalachian vs. Non-Appalachian	1.38 (0.90, 2.11)	0.136
Demographic Variables		
Non-White %	1.01 (0.99, 1.03)	0.291
Age > 65 %	0.94 (0.91, 0.97)	<0.001§
Poverty %	1.00 (0.97, 1.04)	0.814
Uninsured % (% of population under 65 without health insurance)	0.98 (0.85, 1.13)	0.751
Medication-Related Variables		
Monthly Naloxone Distribution per 1,000 Residents	1.00 (0.99, 1.01)	0.501
Monthly Buprenorphine Reception Rate per 1,000 Residents	0.99 (0.83, 1.18)	0.900
Monthly High-Risk Opioid Prescribing Rate per 1,000 Residents	0.82 (0.55, 1.21)	0.311
Opioid Use Prevalence per 1,000 Residents	1.00 (1.00, 1.01)	0.626

*RR = Rate Ratio
†CI = Confidence Interval
§$p<0.05$

Chapter 3 - The Performance of Marginal Modeling Methods for Rare Cluster-Level Count Outcomes with Application to Opioid Overdose Mortality

Overview of Chapter 3

Clustered or correlated outcomes in study settings where people are nested within groups or clusters occur in a variety of epidemiological settings. [1] [2] [3] [4] [5] [82] Such clustered data can arise in observational studies where people are grouped into naturally formed clusters. In addition to observational studies, in cluster-randomized trials (CRTs), subjects are organized into clusters, and these clusters of subjects are randomized to being either an intervention or control group. Examples of clusters for both types of studies may include, but are not limited to, subjects' county of residence or the hospital they are attending. Our focus will be on observational and CRT studies at the community level in order to ensure clusters are large enough to observe a sufficient number of rare events. Motivating examples are based on real-life data, including a salient count outcome in opioid overdose fatalities per county, that can be modeled using various regression approaches. A cross-sectional study of opioid overdose fatalities in Kentucky will serve as a motivating example of an observational study. The HEALing (Helping to End Addiction Long-term^{SM}) Communities Study (HCS) will serve as a motivating example of a CRT. [90] In either situation, and regardless of how clustering arises, the goal of this chapter is to describe and compare regression approaches to modeling rare cluster-level count outcomes in terms of practicality, validity of inference, and power, with a specific focus on modeling population-averaged probabilities or rates of rare events.

Introduction

Overview

The introduction that follows will describe cluster-level observational studies and CRTs in more detail. First, cluster-level observational studies will be addressed with an overview and description of our motivating example. CRTs will be addressed with a similar overview and motivating example. Descriptions of the concept of relative risk and the nature of the count data of interest will follow. Finally, the methods used for comparison of power, validity of inference, and practicality will be outlined along with the goals of this chapter.

Cluster-Level Observational Studies Overview

In certain observational studies, especially in epidemiological settings, researchers might obtain data from naturally formed clusters. For instance, subjects can be grouped by physical distance from each other, such as residents within a state being grouped based on county of residence. A specific example is a 2021 observational study conducted by Marks et al. aimed to predict county-level opioid overdose fatality rates in the United States. [83] In this example, because the interest of the study was to identify counties at greater risk of opioid overdose fatalities, subject-level fatality data were grouped into clusters based on county. Although opioid overdose fatalities occur at the subject level and can occur only once per subject, where each observation represents a fatality, the data were obtained as county level counts. In this study, it was not feasible to obtain subject-level data for factors of interest such as socioeconomic and health care access indicators. Additionally, the goal of the research was to identify counties at greater

risk of opioid overdose fatalities. For these reasons, the data were analyzed at the county level.

In addition to observations being grouped into naturally formed clusters based on physical location, retrospective observational studies examining the effect of an intervention may find it useful to group observations into clusters. For example, a study examining the effectiveness of a policy implemented in hospitals throughout a state may gather data from patients that are naturally grouped by the hospital they are attending. One such example is an observational study of hospital readmission rates in Maryland by Jencks et al. [84] In this study, subjects from the same hospital formed a cluster, and researchers aimed to estimate a variety of cluster-level factors' associations with hospital readmission. Since the main outcome of interest, hospital readmission, came from patients clustered within hospitals, other factors obtained from patients, such as the area disadvantage index (ADI) of the neighborhood of residence, were grouped at the cluster level as well. In either example, the observational study was conducted at the cluster level due to a natural grouping of subjects, and the associated cluster-level analysis aligned with the goals of the research and the nature of the data.

Cluster-Level Observational Studies Motivating Example

Our motivating example is an observational, cross-sectional study of community-level associations with opioid overdose-related fatalities across the state of Kentucky. Opioid overdose fatalities in the United States have doubled from 2010 to 2019. [15] Since the start of the COVID-19 pandemic, this number has only continued to increase, potentially due to structural and societal changes, such as social isolation, increase in

unemployment, and barriers restricting access to medications for opioid use disorder (MOUD). [12] [28] [34] Kentucky had the 5th highest opioid overdose fatality rate among US states in 2020, and experienced a drastic increase in fatalities from 2019 to 2020, going from 29.5 to 42.6 fatalities per 100,000 residents. [6] [7] A sizable portion of Kentucky is part of the Appalachian region, a socioeconomically distressed region with a lack of adequate transportation and access to health services. [33] [60] These factors were magnified during the COVID-19 pandemic, which stymied many paths to access appropriate treatment for opioid overdose in a region that already lacked adequate resources. In this scenario, a researcher may be interested in whether a county being part of Appalachia is associated with opioid overdose fatalities in 2021, which was during the second COVID-19 pandemic. In this example, our goal should be to use the most powerful, practical, and valid approach possible to model opioid overdose fatalities, and specifically the marginal probabilities of opioid overdose fatalities.

Cluster Randomized Trials Overview

CRTs are often employed by researchers to study the effects of an intervention on a group of individuals within already existing clusters. [1] [2] [3] [85] [86] There are several reasons a CRT may be optimal or necessary. [4] One such reason might be that the intervention that is being studied cannot be implemented feasibly at an individual level, so treating each community as a cluster may be the only feasible approach. For example, a public awareness campaign of opioid overdose prevention was conducted in bars and nightclubs in New York. [87] The effects of such a campaign on outcomes would not be able to be measured at the subject level, as anyone entering venues with the

campaign messages would be exposed to the intervention. Because of this, each venue must be treated as a cluster, and data collection and analysis must be conducted at the cluster level.

Similarly, implementing interventions at the cluster level may simply be more practical. For example, a CRT aimed at determining whether naloxone co-dispensing affected opioid risk behavior randomized pharmacies to either the intervention (early co-dispensing) or control (co-dispensing after 10 months) group. [88] Because the goal of the study was to examine the effect of pharmacy-based naloxone dispensing, it was more feasible to instruct the intervention group to begin co-dispensing naloxone to all eligible patients within each pharmacy than to randomize patients within a pharmacy and selectively co-dispense early.

Another reason a CRT may be used is to prevent contamination. [4] [89] In vaccine intervention trials, CRTs are commonly used because clustering reduces the likelihood of contamination between the vaccinated and control groups. Contamination between groups can compromise the ability of the researchers to analyze the impact of the vaccine treatment by making potential immunity conferred by the vaccine indistinguishable from herd immunity developed amongst subjects assigned to a control group. For example, in the study of infectious diseases, CRTs are often the only feasible method of implementing an intervention and analyzing its effects at the population level. Issues of sharing medication and contamination between treatment and control groups are more easily avoided if clusters, rather than individuals, are assigned to groups. Ensuring proper implementation of treatment is also easier when done at the cluster level.

Providing each subject with the correct treatment is more feasible and can result in fewer errors if all subjects within a cluster are assigned a specific treatment.

Because of the different reasons for conducting a CRT, the types of clusters can vary greatly across studies in terms of cluster size, number of clusters, and the way the clusters are formed. For any given situation where a CRT is deemed optimal due to practicality or feasibility concerns, researchers must design a CRT that is most suitable given the research goals and availability of resources. Additionally, the types of clusters that may be created in a CRT may also correspond to naturally formed clusters that could also be used in observational studies. Despite this variety, however, the focus of this chapter is on observational studies and CRTs involving clusters large enough when the subject-level outcome is a rare binary indicator, such as an opioid overdose fatality.

Cluster Randomized Trials Motivating Example

The HEALing (Helping to End Addiction Long-term^{SM}) Communities Study (HCS), a CRT aimed at addressing the opioid epidemic in the United States, serves as a motivating example for this chapter. [90] [91] [92] [93] The increase in opioid overdose fatalities in the US, primarily due to illicit fentanyl and its analogs, has highlighted the need for interventions in at-risk communities. [94] The HCS aims to examine the Communities That HEAL (CTH) intervention, which supports the implementation of evidence-based practices (EBP) in 67 communities across four states - Kentucky, Massachusetts, New York, and Ohio. These communities are of particular interest to the HCS, as the average opioid overdose fatality rate in these communities was twice that of the national average from 2016 through 2017. The CTH intervention is composed of

three components that work together to help effectively implement EBPs in the 67 communities: 1) a communication engagement strategy to support the adoption of EBPs, 2) the Opioid-overdose Reduction Continuum of Care Approach (ORCCA), a compendium of EBPs and associated technical assistance guides, and 3) community-based communication campaigns aimed at improving awareness of EBPs. Covariate-constrained randomization, which aimed to balance opioid overdose fatality rate, population size, and urban/rural status, was used to assign each of the 67 communities to either the CTH intervention or waitlist comparison arm. In this chapter, our focus is motivated by the 16 counties in Kentucky that participated in the HCS. Of the 16 counties, 8 were assigned to the intervention arm, and the other 8 were assigned to the waitlist comparison arm. This study is a relevant motivating example because it involves large communities and very rare events that can occur at most once for each subject. [92]

Risk and Rarity of Event

In epidemiology, rare events are common, and it is often the goal of researchers to estimate the association between an intervention and the relative risk of the event. The focus of the work in this chapter is on rare events in large clusters, as is the case in our motivating examples. Specifically, we focus on large communities where enough rare events may be observed that a meaningful study can be conducted.

Risk refers to the probability of an event occurring given all possible outcomes, whereas odds refers to the probability of an event occurring compared to the probability of the event not occurring. [95] Relative risk of the associated count outcome, which is defined as the ratio of the risk of an event occurring in one group versus the risk of the

event in another group, is often of interest, and several approaches have been proposed, as well as used in practice, in order to estimate relative risk. Relative risk is often confused with odds ratio, and cannot be interpreted the same way. Discrepancies between the measures can result in incorrect reporting. [96] [97] Despite this, when events are rare, risk and odds are approximately equal. [98] When an event's marginal probability is less than or equal to 0.1, the event is considered to be rare, and relative risk and odds ratio can be used interchangeably under the "rare disease assumption". [99] The focus of this chapter will be restricted to events that fall under this assumption.

Description of Count Data and Overdispersion

Because count data caused by clustering appear so frequently in epidemiological settings, both in CRTs and in observational studies, it is crucial that researchers understand how to most effectively model the prevalence or incidence rate of an outcome, such as a disease or disorder. The outcome of interest in both motivating examples is a community-level count of the number of opioid overdose fatalities. In general, in this Chapter, we are interested in rare subject-level events that can occur at most once per person that are collected at the community level and are treated as count outcomes. This resulting community-level count outcome is the sum of person-level binary event indicators. Thus, conditional on each community or cluster, this count outcome can be considered to follow a binomial distribution, where the number of trials is equal to the number of residents in the community. Because of the binomial nature of the outcome variable, binomial regression using a logit link function, hence logistic regression, is a natural approach to utilize. [100] [101] The focus of this chapter is on rare

events, and a binomial outcome with a large number of residents within a community will behave like a Poisson outcome when events are rare. [102] Because of this, Poisson regression would also make sense as an alternative approach to modeling the relative risk. Although Poisson regression technically models the rate, it is approximately equivalent to risk when events are rare.

Unfortunately, these models do not allow the potential for overdispersion to be considered while estimating regression parameters. Due to the variability of community-specific probabilities or rates, which average out to marginal or population-averaged probabilities that are conditional on community-specific covariate values, count outcomes will have variances that are larger than what is assumed by a binomial or Poisson distribution. [103] [104] Thus, this count outcome is considered to be overdispersed.

Modeling Methods for Comparison

To account for this overdispersion when modeling the overall population average, we can extend the aforementioned approaches to construct marginal models. In these marginal models, we will be incorporating modified regression, which refers to the use of empirical standard error estimates, which allows for the possibility of valid inference in cases where the overdispersion structure is misspecified. [8] [9] Hence, inference will be based on quasi-likelihood. [109]

Modified overdispersed binomial regression can be used as an extension of binomial regression using either a logit or a log link function. This is the most natural approach since the data being analyzed follow an unknown overdispersed binomial distribution. In general, the use of the SAS commands PROC GENMOD or PROC

GLIMMIX is appropriate for modeling cluster-level count outcomes. [73] However, this regression approach assumes a common intra-cluster correlation coefficient (ICC), which measures the degree of similarity between individual responses within a cluster. [103] Coding an overdispersed binomial regression model in SAS could be done through the use of, for example, PROC LOGISTIC, in order to estimate the ICC through Williams' method. [105] However, in order to incorporate empirical standard error estimates, the additional use of PROC GENMOD or PROC GLIMMIX is required. [40] Despite this method's drawbacks in terms of ease of coding, it is an important method to include due to its theoretical properties and its traditional use.

Modified negative binomial regression is an extension of Poisson regression that uses a different functional form for the overdispersion and hence ICC. [72] Negative binomial regression has been proposed as an alternative to overdispersed binomial regression to model rare outcomes in large communities, and assumes a common overdispersion parameter k in the overdispersion structure. [72] Like Poisson regression, negative binomial regression is a method that is familiar to epidemiologists, making it an ideal choice if it can perform similarly or better in terms of validity of inference and power compared to the other methods. Additionally, negative binomial regression, unlike overdispersed binomial regression, can be coded using just SAS GLIMMIX or GENMOD.

Finally, modified Poisson regression is another feasible method of modeling the data that assumes no overdispersion. [10] [106] However, modified Poisson regression inherently accounts for the overdispersion present in the data, and is analogous to assuming a specific overdispersion structure, such that the ICC and cluster size are

inversely related. Modified Poisson regression, like negative binomial regression, can be coded using only SAS GLIMMIX or GENMOD. If the modified Poisson model can be shown to perform similarly or better compared to the other regression models in terms of validity of inference and outperform other regression methods, the familiarity of Poisson regression and its ability to directly estimate relative risk are aspects of the model that epidemiologists may find appealing. These three methods are the main approaches to modeling the count outcome of interest that will be compared.

Goals: Valid Inference, Optimal Power, and Practicality

We hope to elucidate the potential of each of the three described methods in modeling cluster-level overdispersed binomial count data through simulation studies for both CRT and observational study settings, as well as an application example for the observational study setting. Each of the three methods models the overdispersion structure of the data differently, but can all yield valid inference, given an appropriate standard error estimator. More accurately modeling the overdispersion structure can, in theory, result in greater efficiency of regression parameter estimates and thus improved power. [102] [107] This theoretical power increase drives our study of the regression approaches under their assumed overdispersion structures in order to identify relative power advantages and limitations.

First, in order to properly compare power across the approaches, we must verify that these regression methods are able to ensure valid inference, ideally at the nominal level. To account for potentially inflated test sizes due to small numbers of clusters, multiple bias corrections will be studied in order to determine the preferred empirical

standard error estimator. If inference is valid, power comparisons are appropriate, as power will not be artificially inflated by a test with size that is too liberal. Simulations will be conducted for both CRT and observational study settings, and test sizes will be compared across various bias correction methods. Next, the power of the three regression methods will be compared across a variety of settings. We expect, given the use of appropriate bias-corrected empirical standard error estimates, all three regression approaches to result in valid inference. Additionally, we expect the regression approach that corresponds to the given true overdispersion structure to be the most powerful, as correctly modeling the overdispersion structure should reduce true standard errors and improve power. [102] [107]

Methods

Overview

In the first part of this section, we will begin by describing the concept of overdispersion, as this is a key statistical concept in terms of power, and possibly validity of inference, that is differently addressed by the regression methods we will compare. Next, the three regression methods used will be described in detail. Modifications to the models used, including bias correction methods, are presented next.

The second part of this section will focus on the simulation studies and application example. First, a description of the methods used to construct and execute the simulation studies for both the CRT and observational study settings will be provided. Additionally, the process used to compare validity of inference and power across the various settings will be detailed. Finally, a description of the application example based on a cross-sectional observational study of opioid overdose fatalities in Kentucky will be given. The HCS example data will not be analyzed.

Overdispersion

As noted above in this chapter, probabilities can vary across clusters, even though they may have the same covariates in the statistical model. Thus, the variance of the count outcome can be higher than those assumed by either binomial or Poisson regression models, which are approximately equivalent in the rare event settings of focus. [103] The modeled variance should try to accurately account for this inflation, as this can potentially increase power through reduced standard errors.

Let □ denote the number of clusters. Given $\theta_{□}$, the unknown community-specific probability, the count outcome Y_i for each cluster $□ = 1, \ldots, □$ can be considered to arise from a binomial distribution - $□(□_{□}, □_{□})$ – where $□_{□}$ is the cluster size, e.g. the number of residents in cluster □. The marginal probability of the outcome, which is the population average of community-specific probabilities, or $E(\theta_i)$, can be expressed as $\pi_{□}$, and thus the marginal mean of the count outcome conditional on cluster-level covariate values is equal to $□_{□}□_{□}$. [36] The ICC for cluster □, $\rho_{□}$, is defined as the ratio of the variance of the community-specific probabilities to the marginal variance of a subject-level binary outcome: $\rho_{□} = □□□(□_{□})/[□_{□}(1 - □_{□})]$. [2] [103] [104] [108] When data are analyzed at the subject level, $\rho_{□}$ represents the exchangeable correlation among binary subject-level outcomes from any two subjects in cluster □. [103] In general, the variance of the count outcome can be expressed as $□□□(□_{□}) = □_{□}□_{□}(1 - □_{□})[1 - (□_{□} + 1)□_{□}]$, where the multiplicative factor of the variance, $[1 - (□_{□} + 1)□_{□}]$, is referred to as the variance inflation factor (VIF), and is the true but unknown form for the overdispersion. [108]

In reality, it is impossible to know the true values of $\rho_{□}$. Because of this, the VIF is unknown. The three regression methods compared below use different working forms for the VIF, and are described in the next subsection. By choosing a method whose working form is closer to the true VIF, the estimation of the regression parameters can be more efficient, thus reducing the standard errors and increasing power. [102] [108] Therefore, theoretically, if one of our three methods correctly models the true VIF, it should be equally or more powerful than the other methods.

A quasi-likelihood approach to fitting these models is suitable because the true likelihood or distribution is unknown. [109] When using the quasi-likelihood approach, only working forms for the marginal mean and variance must be specified in order to potentially attain valid inference. By specifying a working form for the variance, the quasi-likelihood approach is able to account for overdispersion present in the data through a multiplicative overdispersion factor, as described above. The details of the working forms of each of the regression methods are presented in Table 3.1. We note that empirical standard errors, described below, are used as the working form for the overdispersion or VIF and may not be the true form.

Regression Models

Overdispersed Binomial Model

One possible overdispersion structure in the overdispersed binomial model assumes a common ICC, denoted by ρ, which is an assumption that is generally taken due to limitations in statistical software. [102] The marginal mean for the modeled mean for Y_i, which is the number of events in cluster i and is based on a logistic regression model, is given by

$$\mu_i = n_i \frac{e^{\boldsymbol{x_i\beta}}}{1 + e^{\boldsymbol{x_i\beta}}}, i = 1, \dots, N$$

The modeled variance is given by

$$Var(Y_i) = n_i\pi_i(1 - \pi_i)[1 + (n_i - 1)\rho], i = 1, \dots, N$$

Where π_i represents the marginal probability of the event for a person in cluster i and n_i represents the number of individuals in cluster i.

When assuming a common ICC, ρ, the working or assumed form for the VIF is given by $1 + (n_i - 1)\rho$. With this assumption, the VIF, and thus regression parameter estimates, can be influenced by cluster size. [108] If the true overdispersion structure of the count data being modeled follows a common ICC, the overdispersed binomial regression approach assuming a common ICC should be the most powerful.

Alternatively, a traditional assumption for how the overdispersion is modeled is to assume the VIF, ϕ, is common amongst all clusters. [110] While this assumption may not reflect the true nature of the overdispersion, the VIF and resulting parameter estimates generated by this approach are not influenced by the variation in cluster size, unlike the assumption of a common ICC. [107] [111] This overdispersion structure will be the focus of modified Poisson regression, which will be discussed below, and results for overdispersed binomial regression using this overdispersion structure will not be presented.

Traditionally, an overdispersed binomial regression approach uses a logit link function, as described above, which estimates the odds ratio for the count outcome. When events are rare, the log link function, which estimates relative risk, can be used as an approximation, and will result in regression parameter estimates that are similar to those when a logit link function is used. [72] In addition, log binomial regression models have been found to have convergence issues in some settings, especially when additional continuous covariates are included, so other methods must be used in these scenarios. [106] [112] [113] Despite these drawbacks, the modified overdispersed binomial regression model is an important approach to compare, and if it can be shown to perform similarly to modified negative binomial regression and modified Poisson regression in

terms of validity of inference, and outperform them in terms of power, it would be a reasonable choice for researchers aiming to model overdispersed binomial count data.

Modified Poisson Model

To estimate relative risk directly, in addition to log binomial regression, Poisson regression is a common approach. [114] When dealing with overdispersed binomial count data, there exist issues with these two approaches as they are normally used. Log binomial regression models often result in convergence issues, even when applied to clustered data, which can result in a failure to estimate relative risk. [106] [112] [113] Poisson regression does not experience these convergence issues. However, Poisson regression, just like log binomial regression, does not account for the overdispersion present in overdispersed binomial count data, which makes it an inappropriate approach in this situation.

A proposed solution to this issue is the modified Poisson regression approach. In modified Poisson regression, the modeled mean for Y_i, which is the number of events in cluster i, is given by

$$\mu_i = n_i e^{\boldsymbol{x_i \beta}}, i = 1, \dots, N$$

And the modeled variance is given by

$$Var(Y_i) = n_i \lambda_i, \ i = 1, \dots, N$$

Where λ_i represents the marginal rate per person in cluster i and n_i represents the number of individuals in cluster i. The offset in the model is $\ln(n_i)$.

Modified Poisson regression was initially proposed as an alternative to binomial regression in scenarios with independent binary outcomes. However, it has also seen use

in the analysis of clustered data, and has been shown to experience fewer convergence issues than binomial regression, even when the data are clustered. [106] [115] [116] In modified Poisson regression, a Poisson model is fit using empirical sandwich standard errors to account for the overestimated variance that results when Poisson regression is normally applied to binomial data. [10] Using empirical sandwich standard errors results in consistent parameter estimation, and thus valid inference, even when the overdispersion structure is misspecified. Because the event of interest is rare, modified Poisson regression's overdispersion structure corresponds to that of overdispersed binomial regression assuming a common VIF.

In addition to the lack of convergence issues and improved estimation, modified Poisson regression has the advantage of being an extension of Poisson regression. For those who are familiar with using Poisson regression for modeling relative risk of a count outcome, which can be approximated to rate per person for rare events, modified Poisson regression serves as a similar approach. Modified Poisson regression, like negative binomial regression, can also be coded easily in a variety of statistical software. If modified Poisson regression can be shown to perform similarly to other methods in terms of validity of inference, and outperform other methods in terms of power when its assumed overdispersion structure matches the true overdispersion structure, it can potentially be a useful tool for researchers who are familiar with Poisson regression. For these reasons, modified Poisson regression is an important alternative method to explore in the context of epidemiological studies.

Negative Binomial Model

In the negative binomial regression model, the modeled mean for Y_i, which is the number of events in cluster i, is given by

$$\mu_i = n_i e^{\boldsymbol{x_i \beta}}, i = 1, \dots, N$$

And the modeled variance is given by

$$Var(Y_i) = n_i \lambda_i (1 + k n_i \lambda_i), i = 1, \dots, N \text{ [72] [117]}$$

Where λ_i represents the marginal rate per person in cluster i and n_i represents the number of individuals in cluster i. The offset in the model is $\ln(n_i)$.

Epidemiological studies are often interested in relative risk, which negative binomial regression is naturally tailored to. While Poisson regression is also used with community-level count data that are commonly found in epidemiological studies, and can directly estimate relative risk, negative binomial regression has the ability to account for the overdispersion that may be present in the data. Westgate et al. proposed the use of negative binomial regression as a practical approach to modeling rare count outcomes in large communities. [72] Compared to overdispersed binomial regression, negative binomial regression has some advantages. First, it is already a commonly used method for modeling relative risk in epidemiological settings. [118] [119] The second advantage of negative binomial regression, compared to overdispersed binomial regression, is that it can be performed easily in any type of statistical software, including the use of empirical standard errors. A less tedious approach that performs similarly to other approaches is preferable for accessibility. If negative binomial regression can be shown to have similar or greater power and validity of inference compared to other regression approaches in our study settings, researchers who use this method due to familiarity can be confident in its

ability to properly model the count outcome of interest in scenarios where its use is appropriate.

Modifications for Valid Inference

Through unbiased estimating equations and empirical sandwich standard error estimators, sometimes referred to as Huber-White standard errors, we can retain valid inference even when the covariance structure is not correctly specified. [8] [9] However, when the number of clusters is small, the robust empirical sandwich estimator is negatively biased due to residuals being too small on average. [120] This can result in inflated test size, which can impact valid inference for any approach using these empirical standard errors.

To correct for this, several bias corrections are commonly used in CRT settings. Both Kauermann and Carroll as well as Mancl and DeRouen have proposed bias corrections to the covariance estimator that reduce bias in small sample scenarios. [120] [121] Westgate and Ford found that using the average of the Kauermann and Carroll and Mancl and DeRouen corrections with degrees of freedom equal to the number of clusters minus the number of regression parameter estimates results in close to nominal test sizes, even when the number of clusters is few or cluster size varies greatly. [122] [123]

We will denote modeling methods that use empirical sandwich standard errors as "modified". Because of the utility of modified regression approaches in producing valid inference in small-sample settings, the three primary approaches of interest - negative binomial, overdispersed binomial, and Poisson - will be compared using their modified versions. This way, researchers interested in analyzing count data will find results from

these comparisons applicable, even when the number of clusters is small and the overdispersion structure is not correctly specified.

Simulation Studies

The goal of this paper is to evaluate regression approaches used in both CRT and observational study settings. To do this, we will conduct simulation studies to compare the validity of inference and power of modified negative binomial, modified overdispersed binomial, and modified Poisson regression approaches within the context of our motivating examples. These simulation studies will consist of a series of 10,000 replications per studied setting (described below) motivated by the setup of the HCS in Kentucky or the cross-sectional observational study of opioid overdose fatalities in Kentucky in 2021 across a variety of settings. These settings vary in parameters such as number of clusters, the true structure of the overdispersion in the count outcome, and marginal probability of the count outcome. For each setting, modified Poisson regression, modified overdispersed binomial regression, and modified negative binomial regression will be compared in terms of empirical size and power.

Cluster Randomized Trial Settings

The simulated data sets for the CRT settings will be motivated by opioid overdose fatalities based on the setup of the HCS in Kentucky. [90] [91] For each simulation, half of the clusters will be assigned to the intervention arm and the other half will be assigned to the control arm. To compare the effect of the number of clusters on size and power, simulations with 5, 8, and 20 clusters per arm will be conducted. Trial arm, the main

independent variable of interest, will be represented by an indicator variable in the statistical model. Simulations will also be conducted using an additional continuous covariate. This covariate will be generated from a uniform distribution whose parameters mirror the unemployment rates of the 16 HCS counties. The linear predictor for the models used in these simulations to determine power and size can be written as follows:

$$\beta_0 + \beta_1 Intervention_i + \beta_2 Unemployment_i, i = 1, \dots, N$$

where $Intervention_i$ refers to the trial arm assignment, where 1 is the intervention arm and 0 is the control arm, of county □. 〖$Unemployment$〗_i refers to the unemployment rate of county □, and will be included in the data sets with the simulated unemployment rates.

The size of each cluster will be generated from a negative binomial distribution with a mean cluster size of 89600 and a dispersion parameter of 0.385, which mirror the county-level populations in the HCS counties in Kentucky. The count outcome for each county will be generated from a beta-binomial distribution. In the beta-binomial distribution, the probability used to sample from the binomial distribution is based on a beta distribution. [124] In this distribution, the true overdispersion structure of the data dictate the scale and shape parameters of the beta distribution. The marginal probability of the event and the ICC are used to generate the scale and shape parameters for each setting, and are described below.

The marginal probability of the event will range from 0.0004, which is based on the average opioid overdose fatality rate in the HCS counties in Kentucky, to 0.1, which is considered the upper threshold for what is considered a rare event. Since the overdispersion of the count outcome is unknown, we will consider three possible true

structures, and simulated data sets will be generated for all settings for each of the three structures. The first structure is one where the ICC is common across all clusters, corresponding to the structure assumed by the overdispersed binomial regression model. Simulations will be conducted using ICC values that are 5% and 10% of the marginal probability. The second overdispersion structure of interest utilizes a common overdispersion parameter, k, which corresponds to the overdispersion structure assumed by the negative binomial distribution. In these simulations, the overdispersion parameter, k, will be generated such that the mean of the ICC will be equal to either 5% or 10% of the marginal probability. Finally, the third overdispersion structure assumes a common VIF, which corresponds to the structure assumed by modified Poisson regression. In these simulations, the VIF will be generated such that the mean of the ICC across all clusters will be equal to either 5% or 10% of the marginal probability.

For the simulations used to calculate test size, marginal probabilities will be equal in both arms. For the power calculations, simulated data sets where the marginal probability of the intervention arm is 20% and 40% lower than that of the control arm will be generated. For all settings, we will use degrees of freedom equal to the number of clusters minus the number of regression parameter estimates. [123] We study three bias correction methods - Kauermann and Carroll, Mancl and DeRouen, and the average of these two bias correction methods – which will be compared to determine which works best in terms of validity of inference in our study settings. By choosing the bias correction that results in the test size that is closest to the nominal size of 0.05 for each regression method, we can potentially ensure fair and valid power comparisons among the three regression methods.

Observational Study Settings

For the simulation study based on a cross-sectional observational study of opioid overdose fatalities across the 120 counties of Kentucky, we will be using metropolitan status as the main independent variable of interest, and unemployment rate as an additional covariate included in the models. In each simulation, there will be 120 clusters, corresponding to the 120 Kentucky counties. Of these 120 counties, based on the 2013 Rural-Urban Continuum Codes, 35 are considered metropolitan, with the remaining 85 being non-metropolitan, and the 120 clusters in the simulations will mirror this distribution. [65]

The cluster size for each county will be generated from a negative binomial distribution with parameters corresponding to those of counties with the corresponding metropolitan status in Kentucky – a mean cluster size of 57802 and a dispersion parameter of 0.302 for metropolitan counties and a mean cluster size of 16667 and a dispersion parameter of 1.793 for non-metropolitan counties. Similarly, the parameters for the uniform distribution generating unemployment rate will depend on whether the cluster is considered metropolitan or non-metropolitan. These parameters will be based on the minimum and maximum county-level unemployment rates in Kentucky in 2021, which range from 3.5% to 12.5% for metropolitan counties and 3.4% to 6.8% for non-metropolitan counties. The marginal probabilities and overdispersion structures used for the CRT settings will also be used for the observational study settings, with power calculations being conducted using simulated data sets where the marginal probability of the non-metropolitan counties being 20% or 40% lower than that of the metropolitan

counties. As with the simulation studies for the CRT settings, we will be utilizing degrees of freedom equal to the number of clusters minus the number of regression parameter estimates, along with empirical standard error estimates incorporating the three bias correction methods previously outlined in order to determine which bias correction method most effectively ensures valid inference in our settings.

Comparing Test Size and Power for Simulations

We will compare test sizes produced by each of the three regression methods of interest and choose the bias correction method that results in test sizes closest to the nominal test size of 0.05 for power calculations. For both the CRT and observational study simulations, we will be choosing a bias correction method suitable for each regression method. Although the performance of each of the bias corrections may differ depending on the true overdispersion structure of the data, each regression method will use a single bias correction for all power calculations, regardless of the overdispersion structure. Once the bias corrections are chosen, they will be used to compare power across the three regression methods.

For each regression method, the bias correction method with the highest percentage of test sizes with corresponding 95% confidence intervals covering 0.05 (between 0.046 and 0.054) will be chosen for power comparisons. This range will be referred to as the nominal target range, and the bias correction method with the most test size calculations within this range will be preferred. It is also important to avoid bias corrections that result in test sizes that are too large, which can compromise valid inference. Because of this, a second range corresponding to all test sizes equal to or

below 0.054, which will be referred to as the valid target range, will be used to compare bias corrections to ensure valid inference. We will prioritize choosing a bias correction method with the highest percentage of test sizes within the nominal target range, but if multiple bias correction methods produce similar or equal proportions within the nominal range, the bias correction method with the highest percentage within the valid target range will be chosen. Although bias correction methods with a higher percentage of test sizes within the valid target range may result in a power reduction, using this range to select a bias correction method may be necessary to ensure valid inference. Test size results are presented in Table Series 3.1 and Table Series 3.3, with test sizes within the nominal target range in bold, and test sizes within the valid target range underlined. The proportions of test sizes within the nominal and valid target ranges are presented in Tables 3.2 and 3.3. Power calculations using the chosen bias correction for all settings will be presented in Table Series 3.2 and Table Series 3.4.

Observational Study Application Example

In addition to the simulation study, we will be comparing the three regression methods of interest in a practical setting by using cross-sectional opioid overdose fatality data across the 120 counties in Kentucky in 2021. Similar to the simulation study based on this example, the regression models used will utilize community-level covariates based on metropolitan status and unemployment rate. The linear predictor for the models used in this application example can be written as follows

$$\beta_0 + \beta_1 Metropolitan_i + \beta_2 Unemployment_i, i = 1, \dots, 120$$

where $Metropolitan_i$ refers to the metropolitan status, where 1 is urban and 0 is rural, of county □, and $Unemployment_i$ refers to the unemployment rate of county □. For each regression model, parameter estimates and standard error estimates for the intercept and the two community-level covariates will be reported and compared. Results for all three bias correction methods will be presented in order to compare results. By conducting this example based on existing data, we hope to support the results offered by the simulation study and provide researchers with a practical application of the various regression methods discussed in this paper.

Results

CRT Simulations

Test Size

The proportion of test sizes within the valid and nominal target ranges for the CRT simulations are presented in Table 3.2. All test size results are presented in Table Series 3.1.

Overdispersed Binomial Regression

When the true overdispersion structure involved a common ICC or a common overdispersion parameter k, test sizes were close to nominal most often when the average of the KC and MD bias corrections were utilized, as 60% of test sizes across all settings were within the nominal target range. However, utilizing the KC bias correction resulted in test sizes closest to 0.05 when the overdispersion structure utilized a common VIF, as 48% of test sizes were within the nominal target range, as opposed to 8% when the average of the KC and MD bias corrections was used. None of the test sizes were within the nominal target range when the MD bias correction was used. In general, using the KC bias correction resulted in inflated test sizes when the true overdispersion structure involved a common ICC or a common overdispersion parameter k. Additionally, for all true overdispersion structures, test size calculations were within the valid target range when the MD or the average of the KC and MD bias corrections were used. Thus, the average of the KC and MD bias corrections will be used for power calculations for the overdispersed binomial regression simulations to ensure valid inference.

Negative Binomial Regression

Across all settings, the average of the KC and MD bias corrections resulted in test sizes within the nominal target range 38% of the time, compared to 22% and 23% for the KC and MD bias corrections, respectively. Additionally, the percentage of test sizes within the nominal target range was higher for all three overdispersion structures when the average of the KC and MD bias corrections was used. However, it is important to note that, when marginal probabilities were low (0.0004 and 0.001), test sizes were slightly inflated. When the true overdispersion structure was that of a common ICC or a common overdispersion parameter k, using the average of the KC and MD bias correction resulted in only 58% of test sizes falling within the valid target range. Comparatively, 100% of test sizes were within the valid target range when using the MD bias correction. Although using the MD bias correction may result in a small power loss due to it being a more conservative method, it will be used to ensure valid inference.

Poisson Regression

The MD bias correction produced test sizes closest to 0.05, with 27% of test sizes across all settings falling within the nominal target range, as opposed to 0% and 11% for the KC and average of KC and MD bias corrections, respectively. However, test sizes were liberal when the true overdispersion involved a common ICC or overdispersion parameter k, as none of the test sizes were within the nominal target range when the KC or average of KC and MD bias corrections were used. When the true overdispersion structure involved a common VIF, however, both the MD and the average of the KC and MD bias corrections produced test sizes within the 95% confidence interval in 35% of

settings. However, 100% of settings utilizing the MD bias correction resulted in test sizes within the valid target range, compared to 0% and 45% for the KC and average of KC and MD bias corrections, respectively. Thus, in order to ensure valid inference, the MD bias correction must be used for modified Poisson regression.

Summary

In summary, for the purposes of comparing power while ensuring valid inference, the MD bias correction will be used for modified Poisson regression and modified negative binomial regression, and the average of the KC and MD corrections will be used for modified overdispersed binomial regression. However, as mentioned above, using the MD bias correction for modified negative binomial regression may result in conservative power calculations when the true overdispersion structure involves a common ICC or a common overdispersion parameter k. Also, despite the MD bias correction being the most conservative, power calculations for modified Poisson regression may still be slightly inflated. These bias correction methods, based on our test size results, will ensure valid inference in most settings.

Power

Power calculations corresponding to bias corrections that result in the most valid inference are presented in Table Series 3.2. Similar trends in power were observed across settings whether or not an additional covariate was included in the model.

When the true overdispersion structure involved a common ICC or common overdispersion parameter k, modified overdispersed binomial regression was the most

powerful approach, although the difference in power compared to modified negative binomial regression was small. Additionally, for all three methods, as marginal probability increased, so did power. Both modified negative binomial and modified overdispersed binomial regression were, in general, slightly more powerful than modified Poisson regression when marginal probability was low, especially as the number of clusters increased. The power difference between the former two models and modified Poisson regression increased as marginal probability increased.

When the true overdispersion structure involved a common VIF, power for modified Poisson regression was consistently higher than for the other two regression methods, and the power increased as marginal probability increased. Additionally, the difference in power between modified Poisson regression and the other two regression methods increased as marginal probability increased. For example, in the setting with 8 clusters per arm, no covariate adjustment, a 20% difference in marginal probability between the two groups, and a mean ICC equal to 10% of the marginal probability, modified Poisson regression has a power of 0.353, which is 0.040 higher than that of modified negative binomial regression (0.313) and 0.055 higher than that of modified overdispersed binomial regression (0.298) when the marginal probability is 0.0004. However, when the marginal probability is 0.1, modified Poisson regression has a power of 0.874, which is 0.554 higher than that of modified negative binomial regression (0.320) and 0.534 higher than that of modified overdispersed binomial regression (0.340). Although the differences in power between modified negative binomial regression and modified overdispersed binomial regression are small, it is important to note that modified overdispersed binomial regression was more powerful than modified negative

binomial regression when the marginal probability was 0.1, but was less powerful when the marginal probability was lower.

Observational Study Simulations

Test Size

The proportion of test sizes within the valid and nominal target ranges for the observational study simulations are presented in Table 3.3. All test size results are presented in Table Series 3.3.

Overdispersed Binomial Regression

In general, for overdispersed binomial regression, the MD bias correction produced test sizes closest to 0.05, as 50% of test sizes across all settings were within the nominal target range. When the overdispersion structure involved a common ICC, the MD bias correction outperformed the other two bias correction methods, with all test sizes falling within the nominal and valid target range, as opposed to 38% and 13% for KC and the average of the KC and MD bias corrections, respectively. When the overdispersion structure involved a common overdispersion parameter k, the MD bias correction resulted in a test size calculation within the nominal target range for just one setting, whereas the other two bias corrections did not result in any test size calculations within the nominal target range. When the overdispersion structure involved a common VIF, the average of the KC and MD bias corrections performed the best, as 88% of the test size calculations fell within the nominal target range, compared to 63% for the KC bias correction and 38% for the MD bias correction. However, the MD bias correction

resulted in 100% of test sizes within the valid target range, compared to 38% for the KC bias correction. Since test sizes were generally inflated for the other two overdispersion structures when the average of the KC and MD bias corrections was used, the MD bias correction must be used to ensure valid inference.

Negative Binomial Regression

For modified negative binomial regression, the MD bias correction produces test sizes closest to 0.05, with 54% of test sizes across all assumed overdispersion structures falling within the nominal target range, as opposed to 13% for the KC bias correction and 25% for the average of the KC and MD bias corrections. However, these test sizes are slightly liberal, as when the overdispersion structure is that of a common ICC or common k, the KC bias correction method produces no test sizes within the valid target range, and the MD and the average of the KC and MD bias corrections produce only 38% and 13% of test sizes within the valid target range, respectively. When the overdispersion structure is that of a common VIF, 100% of the test sizes fall within the valid target range when using the MD bias correction, as opposed to 38% and 63% for the other two bias correction methods. To ensure valid inference, the MD bias correction will be used for modified negative binomial regression when comparing power.

Poisson Regression

For modified Poisson regression, when the overdispersion structure assumed a common VIF, which corresponds to the overdispersion structure assumed by modified Poisson regression, all test sizes were within the nominal target range when using the MD

bias correction. However, test sizes were liberal (ranging from 0.070 to 0.087) when the overdispersion structure was assumed to have a common ICC or overdispersion parameter k, meaning none of the test sizes for these two overdispersion structures were within the nominal or valid target ranges. Thus, the MD bias correction will be used with modified Poisson regression. However, it is important to note that if the true overdispersion structure involves a common ICC or a common overdispersion parameter k, the empirical powers will likely be inflated.

Summary

In summary, for all three methods, the MD bias correction will be used to calculate power. However, it is important to highlight that if the true overdispersion structure follows a common overdispersion parameter k or a common ICC, power will likely be inflated for all three methods. Regardless, the MD bias correction is one that is the most likely to ensure valid inference and fair comparison of power across the three methods.

Power

Power calculations corresponding to bias corrections that result in the most valid inference are presented in Table Series 3.4. In all settings, modified negative binomial regression was slightly more powerful than modified overdispersed binomial regression, with power differences ranging from 0.010 to 0.055. This difference was most pronounced when marginal probabilities were low, and as marginal probabilities increased, the difference in power between the methods decreased.

When the true overdispersion structure assumed a common ICC or overdispersion parameter k, both regression methods resulted in power that was significantly higher than that of modified Poisson regression. The difference in power also increased as marginal probability increased. For example, in the setting with a true overdispersion structure involving a common ICC, when the marginal probability difference between the groups was 20%, and the ICC was 5% of the marginal probability, the difference in power between modified negative binomial regression and modified Poisson regression ranged from 0.064 (0.475 vs. 0.411) when the marginal probability was 0.0004 to 0.361 (0.954 vs. 0.593) when the marginal probability was 0.1.

However, when the true overdispersion structure assumed a common VIF, modified Poisson regression was more powerful than modified negative binomial or modified overdispersed binomial regression. This difference in power increased as marginal probability increased. Additionally, as marginal probability increased, power for modified negative binomial and modified overdispersed binomial regression increased at low marginal probabilities before decreasing as marginal probabilities approached 0.1, whereas modified Poisson regression increased in power as marginal probabilities increased. For example, when the marginal probability difference between the groups was 20%, and the ICC was 10% of the marginal probability, modified Poisson regression resulted in a power of 0.704, which was 0.022 higher than that of modified negative binomial regression (0.683) when the marginal probability was 0.0004. However, when the marginal probability was 0.1, the power of modified Poisson regression was 0.997, which was 0.295 higher than that of modified negative binomial regression (0.702). These trends were consistent across all settings.

Application Example

Parameter estimates and standard error estimates for all three models and bias correction methods are presented in Table 3.4. In general, consistent with the results from the simulation study, results from the modified negative binomial and modified overdispersed binomial regression models are similar in terms of parameter estimates and standard error estimates. However, results from the modified Poisson model are quite different from these two. Specifically, regression estimates for both metropolitan status and unemployment rate experienced an increase in the modified Poisson regression model compared to those from the other two models. The estimate for unemployment rate was 0.141 for modified Poisson regression, compared to 0.097 for modified negative binomial regression and 0.089 for modified overdispersed binomial regression. For metropolitan status, this disparity was even larger, as the estimate was 0.334 for modified Poisson regression compared to 0.068 and 0.057 for the other two approaches. Additionally, standard error estimates for modified Poisson regression are larger, especially that of metropolitan status, where it is nearly double those of the other two regression approaches.

The differences in parameter and standard error estimates are due to the way the overdispersion is modeled for each of the regression methods. For modified Poisson regression, the working overdispersion structure is a common VIF among all clusters, with estimated ICC varying based on cluster size. Thus, the higher standard errors produced as a result of modified Poisson regression suggest that the true overdispersion structure of the data does not correspond to the working overdispersion structure,

compared to the other two regression methods. Thus, it is likely that the true overdispersion structure is more accurately modeled by modified negative binomial regression and modified overdispersed binomial regression.

Discussion

Overview

In this section, we will highlight the main conclusions of our results and how these results can be used to help researchers choose a method for analyzing overdispersed binomial count data corresponding to rare events. Next, we will highlight some limitations of this work. Finally, we will highlight some potential future studies that can help address some of the limitations or expand upon findings from this chapter. One area of focus for future studies is the application of the methods studied in this chapter to rare events that can occur more than once per person, which is the focus of the fourth chapter of this dissertation.

Discussion of Results

Simulation Studies

In this chapter, we compared the validity of inference and power of modified negative binomial regression, modified Poisson regression, and modified overdispersed binomial regression in modeling rare overdispersed binomial count data. In our simulation studies, we found that all three methods could result in valid inference. In the CRT settings, the MD bias correction resulted in valid inference most often for modified negative binomial regression, and the average of the KC and MD bias corrections performed well for modified overdispersed binomial regression. However, none of the bias correction methods resulted in consistent valid inference for modified Poisson regression, although the MD bias correction worked well when the true overdispersion structure of the data corresponded to its working overdispersion structure. In the

observational study settings, the MD bias correction resulted in valid inference for modified negative binomial regression and modified overdispersed binomial regression across most settings. None of the bias correction methods resulted in valid inference for modified Poisson regression.

In terms of power, for both the CRT and observational study simulations, we found that when the assumed overdispersion structure was that of a common ICC or common overdispersion parameter k, both modified negative binomial and modified overdispersed binomial outperformed modified Poisson regression. Additionally, the power difference between the former two methods was not very large across all settings. We would expect modified negative binomial regression to be the most powerful when the overdispersion structure assumes a common overdispersion parameter k, and modified overdispersed binomial regression to be the most powerful when the overdispersion structure assumes a common ICC, as these overdispersion structures correspond to those assumed by each of the models. However, the results imply that the performance of these methods does not differ greatly in these settings.

When the working overdispersion structure was a common VIF, modified Poisson outperformed the other two regression methods, and the difference in power increased as marginal probability increased. Our hypothesis that modified Poisson regression would be the most powerful when the true overdispersion structure matched that which is assumed was confirmed. Additionally, the performance of modified negative binomial and modified overdispersed binomial regression did not differ greatly across such settings.

Application Example

For the application example, in terms of parameter and standard error estimates, modified negative binomial regression and modified overdispersed binomial regression were very similar. However, the standard error estimates were higher when modified Poisson regression was used. This could indicate that the true overdispersion structure did not correspond to the working overdispersion structure of Poisson regression. Theoretically, using a regression method whose working overdispersion structure matches the true overdispersion structure should result in lower standard error estimates.

Considerations for Research

In general, because modified negative binomial regression and modified overdispersed binomial regression performed similarly across our researched settings, researchers can choose to use either method interchangeably without a significant loss in power. However, the use of simulation studies to ensure these methods are applicable to the data and outcome of interest is encouraged. Because the true overdispersion structure of the data cannot be known, it is possible that, if there is reason to believe that the true ICC is inversely related to cluster size, modified Poisson regression may be appropriate. In order to assist with the selection of an appropriate working overdispersion structure, several criteria, such as the trace of the empirical covariance matrix (TECM) and the correlation information criterion (CIC) have been proposed. [125] [126] Further work is necessary to evaluate the performance of such criteria in different settings.

One potential drawback for the general use of negative binomial regression is that the assumption of large cluster size and rare events may not apply to all CRTs or

observational studies of overdispersed binomial count outcomes. When this assumption is violated, it is unclear whether negative binomial regression will be an appropriate modeling approach because the marginal variance will not be modeled correctly. Although the focus of this chapter is on rare events, it is important for the power and validity of inference to be compared in these situations in future studies, as researchers who are interested in modeling count outcomes where events are not rare must understand which approach is more applicable in these circumstances.

Another important consideration when comparing methods is practicality. Because modified negative binomial and modified overdispersed binomial regression performed similarly in terms of power across most settings, ease of coding may be an important consideration for a researcher looking to choose between the methods. While neither approach is exceptionally computationally intensive, the benefit of modified negative binomial regression is its ability to be coded using solely PROC GLIMMIX or GENMOD in SAS. Modeling using modified overdispersed binomial regression requires the additional use of PROC LOGISTIC to estimate the ICC. Another facet to practicality is the application of these methods to different kinds of data, such as events that can occur more than once per person. Modified negative binomial regression and modified Poisson regression, due to their ability to model the marginal relative rate of the event, may be more appropriate than modified overdispersed binomial regression in cases where the outcome does not correspond to a binomial distribution. Further limitations of this chapter's results are detailed below, and future study is required in order to evaluate these methods under different settings. It is important for researchers to carefully consider the data set in question before proceeding with a given approach.

Limitations and Further Work

The focus of this chapter was on rare count outcomes of events that could occur only once. However, there are several extensions of this chapter that could contribute to future studies. One limitation of our focus is that the data are cross-sectional. In many situations, count data may be collected longitudinally. Clustered longitudinal data can be analyzed retrospectively in observational studies, and the focus of the researcher may be to analyze how factors associated with the data change over time. For example, a researcher may be interested in how the association between unemployment and opioid overdose fatality rate changed from one year to the next. The results of this chapter do not focus on these types of research questions, and further studies can evaluate the performance of methods similar to those studied in this chapter, such as negative binomial and overdispersed binomial GEE regression, when applied to longitudinal data.

Another limitation of this chapter is that the applicability and performance of these methods may be worse when applied to data of events that are not rare. With respect to rare events, in the simulations, we found regression methods to perform differently as marginal probability changed. When the marginal probability of the event was exceptionally rare (less than 0.01), all three methods performed more similarly than when the marginal probability of the event was not as rare. Specifically, modified negative binomial regression and modified overdispersed binomial regression had a power advantage over modified Poisson regression when the assumed overdispersion structure involved a common k or common ICC, and this power advantage increased as marginal probability increased. Additionally, when the assumed overdispersion structure

involved a common VIF, modified Poisson regression was more powerful than the other two regression methods, and this discrepancy increased as marginal probability increased. Further studies of non-rare events and the performance of these regression methods in terms of power are necessary.

Another potential approach to modeling cluster-level count data is the generalized linear mixed-effects model (GLMM). There are several key points to note about the GLMM approach. In contrast to marginal modeling, meaning the estimates are interpreted at the population level, GLMM approaches result in cluster-specific interpretations. In the GLMM setup, the within-cluster correlation is accounted for by a random intercept for each cluster, which assumes a uniform correlation. The true correlation structure, however, may not be uniform; this misspecification may result in invalid inference, especially when the number of clusters is small. In contrast to this, GEE modeling has the ability to use empirical standard error estimates and is thus robust to misspecification of the correlation structure, meaning regression parameter estimation is consistent even when the correlation structure is misspecified. [127] Although GLMM approaches were not of particular interest in this chapter, they are important to note as a commonly used alternative to modeling cluster-level count data, and future studies can explore the viability of these approaches for modeling data similar to what was studied here.

Additionally, cluster-summary approaches, which have historically been used in CRTs due to their simplicity and robustness, even when the number of clusters is small, may be explored in their efficacy when applied to the settings studied in this chapter. [1] [128] One cluster-summary approach uses a two-sample t-test with the observed

proportions as the cluster-level outcomes. [129] [130] The unweighted version of this approach has been shown to produce nominal test sizes, but weights corresponding to cluster size are commonly used, and other weighting methods have been proposed. [1] [107] [129] In a second cluster-summary approach, a logistic regression model is fit, and inference with respect to the intervention effect is done using a two-sample t-test. [131] The unweighted version of this approach has been shown to produce nominal test sizes, whereas the weighted versions result in inflated test sizes and intervention effect estimates with larger variances. [109] Although test size produced by the weighted and unweighted versions of cluster-level summary approaches have been compared in the literature, there is less existing research on how these methods compare in terms of statistical power. [132] [133]

With respect to the event of interest in our motivating examples, opioid overdose fatalities, it is an event that can occur at most once for a given subject. However, there exist other types of events in epidemiology that can occur more than once for a given subject. For example, non-fatal opioid overdose poisonings are a key outcome of interest for the HCS, as they represent opportunities to improve treatment and prevention amongst those who misuse opioids. In this scenario, the event of interest can happen more than once for any given subject within a cluster. Thus, the assumption of the models used in this chapter that the subject-level outcome is binary no longer applies. Future studies, including the following chapter, can aim to compare the performance of models for count data where people can have the event more than once.

Supplemental Materials

Table 3.1 Details of Regression Methods Being Compared

Regression method, working overdispersion structure	Negative Binomial, common k	Overdispersed Binomial, common ICC	Poisson, common VIF
Regression Model Including Link Function	$ln(\lambda_i) = \boldsymbol{x_i\beta}$	$logit(\pi_i) = \boldsymbol{x_i\beta}$	$ln(\lambda_i) = \boldsymbol{x_i\beta}$
Mean	$n_i e^{\boldsymbol{x_i\beta}}$	$n_i \frac{e^{\boldsymbol{x_i\beta}}}{1+e^{\boldsymbol{x_i\beta}}} \approx n_i e^{\boldsymbol{x_i\beta}}$	$n_i e^{\boldsymbol{x_i\beta}}$
Variance of Y_i	$n_i\pi_i(1+kn_i\pi_i)$	$n_i\pi_i(1-\pi_i)[1-(n_i+1)\rho]$	$n_i\pi_i\phi$
VIF	$1+kn_i\pi_i$	$1-(n_i+1)\rho$	ϕ
ICC	$\rho_i \approx k\pi_i$	$\rho_i = \rho$	$\rho_i = \frac{1}{n_i-1}$
Estimating Equations	$\sum_{i=1}^{N} x_i{}^T \frac{Y_i - n_i\pi_i}{1+kn_i\pi_i}$	$\sum_{i=1}^{N} x_i{}^T \frac{Y_i - n_i\pi_i}{1-(n_i+1)\rho}$	$\sum_{i=1}^{N} x_i{}^T \frac{Y_i - n_i\pi_i}{\phi}$

Y_i: Number of events out of n_i subjects in cluster i

π_i: Marginal probability of event for a given subject in cluster i

λ_i: Marginal rate per subject in cluster i

$x_i\beta = \beta_0 + \beta_1 x_{1i} + \cdots + \beta_p x_{pi}$ is the linear predictor for cluster i

Due to the rarity of events and large cluster sizes, the following approximations are used:

$1-\pi_i \approx 1$, $\pi_i = \lambda_i$, and $1 + e^{\boldsymbol{x_i\beta}} \approx 1$

[72]

Table 3.2 Proportions of Test Sizes within Valid and Nominal Target Ranges, CRT Settings

Regression Model	True Overdispersion Form	Bias Correction Used for SE Estimation	% of Test Sizes Corresponding to Valid Inference (<0.054)	% of Test Sizes Corresponding to Nominal Inference (between 0.046 and 0.054)
Modified Negative Binomial	Common ICC	KC	29%	25%
		MD	100%	35%
		Average of KC/MD	58%	42%
	Common k	KC	21%	21%
		MD	100%	29%
		Average of KC/MD	58%	44%
	Common VIF	KC	52%	19%
		MD	100%	4%
		Average of KC/MD	85%	27%
Modified Poisson	Common ICC	KC	0%	0%
		MD	29%	17%
		Average of KC/MD	0%	0%
	Common k	KC	0%	0%
		MD	33%	29%
		Average of KC/MD	0%	0%
	Common VIF	KC	0%	0%
		MD	100%	35%
		Average of KC/MD	45%	35%
Modified Overdispersed Binomial	Common ICC	KC	40%	40%
		MD	100%	6%
		Average of KC/MD	100%	60%
	Common k	KC	35%	35%
		MD	100%	8%
		Average of KC/MD	100%	60%
	Common VIF	KC	94%	48%
		MD	100%	0%
		Average of KC/MD	100%	8%

Table 3.3 Proportions of Test Sizes within Valid and Nominal Target Ranges, Observational Study Settings

Regression Model	True Overdispersion Form	Bias Correction Used for SE Estimation	% of Test Sizes Corresponding to Valid Inference (<0.054)	% of Test Sizes Corresponding to Nominal Inference (between 0.046 and 0.054)
Modified Negative Binomial	Common ICC	KC	0%	0%
		MD	63%	63%
		Average of KC/MD	25%	25%
	Common k	KC	0%	0%
		MD	13%	13%
		Average of KC/MD	0%	0%
	Common VIF	KC	38%	38%
		MD	100%	88%
		Average of KC/MD	63%	50%
Modified Poisson	Common ICC	KC	0%	0%
		MD	0%	0%
		Average of KC/MD	0%	0%
	Common k	KC	0%	0%
		MD	0%	0%
		Average of KC/MD	0%	0%
	Common VIF	KC	0%	0%
		MD	100%	100%
		Average of KC/MD	13%	13%
Modified Overdispersed Binomial	Common ICC	KC	13%	13%
		MD	100%	100%
		Average of KC/MD	38%	38%
	Common k	KC	0%	0%
		MD	13%	13%
		Average of KC/MD	0%	0%
	Common VIF	KC	63%	63%
		MD	100%	38%
		Average of KC/MD	100%	88%

Table 3.4 Parameter Estimates from Application Example

Regression Method	Modified Overdispersed Binomial Regression	Modified Negative Binomial Regression	Modified Poisson Regression
Regression Parameter Estimates (KC SE, MD SE, Average KC/MD SE)			
β_0	-8.207 (0.262, 0.275, 0.269)	-8.255 (0.271, 0.278, 0.275)	-8.456 (0.368, 0.394, 0.381)
β_1	0.057 (0.163, 0.165, 0.164)	0.068 (0.162, 0.164, 0.163)	0.334 (0.255, 0.289, 0.272)
β_2	0.089 (0.041, 0.044, 0.043)	0.097 (0.043, 0.044, 0.044)	0.141 (0.054, 0.060, 0.057)
Estimated Overdispersion Parameter	$\hat{\rho} = 2.31 \times e^{-4}$	$\hat{k} = 0.559$ $\hat{\rho}_{min}, \hat{\rho}_{max} = 0, 4.74 \times e^{-4}$	$\hat{\phi} = 1$ $\hat{\rho}_{min}, \hat{\rho}_{max} = 1.68 \times e^{-6}, 6.15 \times e^{-4}$

Table Series 3.1 Size Calculations for CRT Settings

5 clusters per arm

Without Covariate Adjustment

Size - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.106	**0.046**	0.068	0.142	0.059	0.089	0.074	0.035	**0.052**
0.001	0.099	0.044	0.064	0.146	0.057	0.087	0.065	0.032	0.044
0.01	0.067	0.043	**0.053**	0.167	0.064	0.096	0.057	0.036	0.045
0.1	**0.051**	0.031	0.040	0.174	0.063	0.098	**0.051**	0.029	0.039

Size - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.094	0.045	0.061	0.143	0.059	0.084	0.066	0.033	**0.046**
0.001	0.089	**0.047**	0.063	0.159	0.064	0.093	0.065	0.037	**0.047**
0.01	0.058	0.040	**0.048**	0.172	0.068	0.102	**0.053**	0.036	0.044
0.1	**0.053**	0.033	0.042	0.168	0.060	0.094	**0.052**	0.032	0.040

Table Series 3.1, Continued

Size - Common k - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.103	0.043	0.065	0.135	0.056	0.083	0.065	0.028	0.040
0.001	0.096	0.043	0.061	0.151	0.055	0.086	0.063	0.031	0.042
0.01	0.068	0.042	0.055	0.162	0.058	0.092	0.056	0.036	**0.047**
0.1	0.055	0.034	0.043	0.168	0.063	0.095	**0.053**	0.034	0.042

Size - Common k - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.099	0.045	0.064	0.149	0.059	0.087	0.066	0.032	0.045
0.001	0.090	0.045	0.060	0.154	0.057	0.087	0.066	0.036	**0.049**
0.01	0.060	0.038	**0.047**	0.176	0.065	0.099	0.056	0.035	0.044
0.01	**0.052**	0.034	0.043	0.167	0.061	0.093	**0.052**	0.034	0.043

Table Series 3.1, Continued

Size - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.076	0.033	**0.046**	0.092	0.042	0.058	**0.051**	0.016	0.025
0.001	0.084	0.035	**0.053**	0.098	0.041	0.062	**0.049**	0.017	0.029
0.01	0.055	0.027	0.037	0.090	0.037	**0.054**	0.027	0.013	0.019
0.1	0.028	0.015	0.019	0.095	0.042	0.058	0.027	0.014	0.019

Size - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.079	0.032	**0.048**	0.093	0.039	0.057	**0.050**	0.027	**0.046**
0.001	0.079	0.036	**0.050**	0.095	0.044	0.061	**0.046**	0.019	0.028
0.01	**0.046**	0.024	0.032	0.098	0.044	0.060	0.024	0.012	0.018
0.1	0.027	0.014	0.020	0.092	0.041	0.057	0.027	0.014	0.019

Table Series 3.1, Continued

With Covariate Adjustment

Size - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.113	0.034	0.057	0.139	0.042	0.071	0.063	0.019	0.034
0.001	0.104	0.033	0.057	0.144	0.040	0.073	0.070	0.024	0.039
0.01	0.086	0.041	0.057	0.171	**0.051**	0.087	0.068	0.034	0.048
0.1	0.065	0.032	0.044	0.174	**0.047**	0.082	0.062	0.032	0.044

Size - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.110	0.038	0.061	0.150	0.045	0.079	0.074	0.027	0.043
0.001	0.103	0.038	0.061	0.156	0.045	0.076	0.072	0.030	0.045
0.01	0.072	0.035	**0.048**	0.168	**0.049**	0.081	0.065	0.031	0.044
0.1	0.062	0.031	0.042	0.167	**0.048**	0.084	0.061	0.030	0.041

Table Series 3.1, Continued

Size - Common k - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.104	0.029	**0.051**	0.139	0.039	0.067	0.063	0.019	0.031
0.001	0.113	0.041	0.062	0.153	**0.050**	0.079	0.072	0.029	0.043
0.01	0.085	0.040	0.057	0.172	**0.049**	0.083	0.069	0.035	**0.048**
0.1	0.063	0.032	0.044	0.167	**0.049**	0.081	0.061	0.031	0.043

Size - Common k - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.108	0.035	0.057	0.145	0.043	0.070	0.066	0.024	0.037
0.001	0.098	0.034	0.056	0.152	0.041	0.073	0.066	0.025	0.039
0.01	0.072	**0.051**	0.063	0.170	**0.048**	0.082	0.064	0.033	**0.047**
0.01	0.063	0.031	0.043	0.169	**0.049**	0.083	0.062	0.030	0.041

Table Series 3.1, Continued

Size - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.082	0.027	0.042	0.099	0.031	**0.050**	**0.048**	0.010	0.020
0.001	0.078	0.023	0.038	0.095	0.029	**0.047**	0.042	0.011	0.019
0.01	0.068	0.019	0.033	0.097	0.028	0.044	0.034	0.012	0.019
0.1	0.036	0.015	0.023	0.093	0.031	**0.049**	0.036	0.015	0.024

Size - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.076	0.023	0.037	0.092	0.028	0.045	0.040	0.008	0.017
0.001	0.078	0.027	0.042	0.095	0.030	**0.049**	0.040	0.012	0.021
0.01	**0.052**	0.020	0.029	0.094	0.029	**0.046**	0.032	0.012	0.020
0.1	0.036	0.015	0.021	0.097	0.031	**0.049**	0.036	0.014	0.022

Table Series 3.1, Continued

8 clusters per arm

Without Covariate Adjustment

Size - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.088	**0.052**	0.067	0.124	0.065	0.089	0.067	0.041	**0.052**
0.001	0.079	**0.052**	0.062	0.132	0.067	0.090	0.061	0.043	**0.052**
0.01	**0.050**	0.036	0.042	0.125	0.060	0.085	**0.048**	0.035	0.041
0.1	**0.052**	0.041	**0.047**	0.128	0.061	0.089	**0.052**	0.041	**0.046**

Size - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.081	**0.051**	0.063	0.123	0.062	0.086	0.065	0.044	**0.054**
0.001	0.068	**0.047**	0.055	0.133	0.067	0.092	0.057	0.039	**0.046**
0.01	0.056	0.041	**0.047**	0.140	0.067	0.092	0.055	0.040	**0.047**
0.1	**0.053**	0.039	**0.046**	0.134	0.066	0.091	**0.052**	0.039	0.045

Table Series 3.1, Continued

Size - Common k - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.085	**0.048**	0.062	0.118	0.058	0.082	0.061	0.038	**0.048**
0.001	0.078	**0.050**	0.061	0.129	0.068	0.090	0.061	0.041	**0.049**
0.01	0.060	0.043	**0.051**	0.139	0.068	0.092	0.056	0.041	**0.048**
0.1	**0.051**	0.039	0.045	0.140	0.068	0.095	**0.051**	0.040	0.044

Size - Common k - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.082	**0.051**	0.064	0.124	0.065	0.086	0.062	0.041	**0.050**
0.001	0.069	**0.049**	0.059	0.125	0.061	0.084	0.058	0.043	**0.050**
0.01	0.057	0.042	**0.049**	0.134	0.063	0.087	0.056	0.041	**0.047**
0.1	**0.052**	0.040	**0.046**	0.137	0.068	0.093	**0.052**	0.040	**0.046**

Table Series 3.1, Continued

Size - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.082	0.042	**0.056**	0.089	**0.047**	0.063	0.063	0.027	0.040
0.001	0.083	**0.046**	0.060	0.088	**0.051**	0.066	**0.052**	0.027	0.037
0.01	**0.054**	0.035	0.042	0.086	**0.047**	0.060	0.034	0.025	0.029
0.1	0.035	0.024	0.029	0.090	**0.050**	0.065	0.035	0.024	0.028

Size - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.083	0.045	**0.060**	0.091	**0.049**	0.065	0.058	0.029	0.040
0.001	0.072	0.039	**0.052**	0.082	0.045	0.059	0.044	0.025	0.031
0.01	0.041	0.026	0.033	0.084	**0.046**	0.062	0.034	0.021	0.028
0.1	0.038	0.027	0.032	0.083	**0.046**	0.059	0.038	0.027	0.032

Table Series 3.1, Continued

With Covariate Adjustment

Size - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.095	0.042	0.061	0.124	**0.052**	0.078	0.069	0.034	**0.048**
0.001	0.088	0.044	0.062	0.133	**0.052**	0.082	0.067	0.036	**0.050**
0.01	0.064	0.039	**0.049**	0.135	0.055	0.082	0.059	0.036	**0.046**
0.1	0.054	0.036	0.043	0.139	0.055	0.083	**0.054**	0.035	0.043

Size - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.093	**0.048**	0.067	0.135	0.057	0.085	0.071	0.039	**0.053**
0.001	0.083	**0.046**	0.062	0.140	0.056	0.082	0.065	0.039	**0.049**
0.01	0.061	0.038	**0.048**	0.144	0.056	0.089	0.058	0.036	**0.046**
0.1	0.055	0.035	0.045	0.135	**0.053**	0.081	0.055	0.033	0.042

Table Series 3.1, Continued

Size - Common k - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.089	0.041	0.060	0.119	**0.050**	0.074	0.069	0.032	**0.046**
0.001	0.090	0.044	0.064	0.131	**0.051**	0.080	0.066	0.036	**0.049**
0.01	0.061	0.038	**0.048**	0.137	**0.054**	0.083	0.058	0.035	0.045
0.1	0.059	0.039	**0.047**	0.140	**0.053**	0.082	0.057	0.038	**0.047**

Size - Common k - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.084	0.042	0.057	0.124	**0.052**	0.076	0.062	0.033	0.045
0.001	0.083	0.042	0.058	0.134	**0.050**	0.079	0.065	0.034	**0.049**
0.01	0.059	0.038	**0.047**	0.143	0.056	0.086	0.057	0.034	0.044
0.01	0.056	0.034	0.043	0.143	0.055	0.087	**0.053**	0.033	0.042

Table Series 3.1, Continued

Size - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.073	0.028	0.043	0.086	0.036	**0.053**	**0.048**	0.016	0.028
0.001	0.075	0.035	**0.046**	0.087	0.040	**0.054**	**0.049**	0.020	0.029
0.01	0.055	0.029	0.039	0.083	0.037	**0.052**	0.033	0.018	0.024
0.1	0.036	0.019	0.025	0.092	0.038	0.056	0.034	0.019	0.025

Size - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.074	0.029	0.045	0.086	0.038	0.055	**0.053**	0.022	0.031
0.001	0.079	0.032	**0.048**	0.089	0.039	0.057	**0.047**	0.022	0.030
0.01	0.045	0.025	0.034	0.085	0.036	**0.054**	0.036	0.021	0.027
0.1	0.039	0.021	0.030	0.089	0.040	0.058	0.039	0.021	0.028

Table Series 3.1, Continued

20 clusters per arm

Without Covariate Adjustment

Size - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.060	**0.051**	0.056	0.087	0.062	0.074	0.055	0.045	**0.051**
0.001	0.055	**0.047**	**0.050**	0.087	0.059	0.071	**0.051**	0.043	**0.047**
0.01	**0.048**	0.043	**0.046**	0.089	0.061	0.074	**0.047**	0.043	0.044
0.1	**0.053**	**0.047**	**0.050**	0.093	0.066	0.078	**0.052**	**0.047**	**0.050**

Size - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.059	**0.050**	0.055	0.087	0.062	0.073	**0.053**	**0.046**	**0.049**
0.001	**0.053**	**0.048**	**0.051**	0.091	0.061	0.075	**0.052**	**0.046**	**0.049**
0.01	**0.050**	0.044	**0.047**	0.085	0.058	0.070	**0.050**	0.044	**0.047**
0.1	**0.050**	0.045	**0.048**	0.087	0.058	0.071	**0.050**	0.045	**0.048**

Table Series 3.1, Continued

Size - Common k - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.065	**0.054**	0.059	0.091	0.067	0.077	0.058	**0.047**	**0.053**
0.001	0.056	**0.047**	**0.052**	0.090	0.062	0.073	**0.052**	0.044	**0.048**
0.01	**0.047**	0.042	**0.045**	0.092	0.063	0.074	**0.046**	0.040	0.043
0.1	**0.049**	0.045	**0.047**	0.088	0.061	0.074	**0.049**	0.045	**0.047**

Size - Common k - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.058	**0.049**	0.053	0.085	0.058	0.071	**0.054**	0.045	**0.049**
0.001	0.059	**0.050**	**0.054**	0.097	0.065	0.080	0.056	**0.049**	**0.053**
0.01	**0.054**	**0.048**	**0.051**	0.094	0.064	0.077	**0.054**	**0.047**	**0.051**
0.1	**0.051**	0.045	**0.047**	0.092	0.065	0.076	**0.050**	0.045	**0.047**

Table Series 3.1, Continued

Size - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	**0.046**	0.033	0.039	0.065	**0.047**	0.055	0.055	0.038	**0.047**
0.001	0.042	0.030	0.035	0.064	**0.049**	0.057	**0.049**	0.037	0.042
0.01	**0.048**	0.042	**0.046**	0.066	**0.051**	0.059	0.043	0.038	0.041
0.1	**0.046**	0.040	0.043	0.068	**0.051**	0.059	**0.046**	0.040	0.043

Size - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	**0.045**	0.033	0.039	0.064	**0.048**	0.054	**0.054**	0.042	**0.048**
0.001	0.041	0.030	0.034	0.064	**0.046**	0.055	**0.048**	0.040	0.044
0.01	0.042	0.038	0.040	0.060	**0.045**	0.051	0.042	0.037	0.040
0.1	**0.048**	0.044	**0.046**	0.073	**0.053**	0.062	**0.048**	0.043	**0.046**

Table Series 3.1, Continued

With Covariate Adjustment

Size - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.065	**0.048**	0.056	0.094	0.055	0.072	0.057	0.043	**0.051**
0.001	0.061	**0.048**	**0.054**	0.090	**0.054**	0.070	0.057	0.047	**0.052**
0.01	0.055	0.045	**0.050**	0.090	**0.054**	0.068	**0.053**	0.043	**0.049**
0.1	**0.051**	0.043	**0.047**	0.096	0.056	0.073	**0.050**	0.043	**0.047**

Size - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.059	**0.046**	**0.052**	0.093	**0.056**	0.072	**0.054**	0.042	**0.047**
0.001	0.059	**0.048**	**0.053**	0.096	**0.054**	0.072	0.056	0.045	**0.051**
0.01	**0.047**	0.040	0.044	0.095	0.056	0.074	**0.047**	0.039	0.043
0.1	0.049	0.042	**0.046**	0.100	0.059	0.076	**0.049**	0.042	**0.046**

Table Series 3.1, Continued

Size - Common k - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.067	**0.050**	0.058	0.088	0.055	0.069	0.062	0.045	**0.054**
0.001	0.055	0.044	**0.049**	0.089	**0.054**	0.069	**0.051**	0.040	0.044
0.01	0.055	**0.046**	**0.051**	0.095	0.055	0.071	**0.053**	**0.046**	**0.049**
0.1	**0.051**	0.043	**0.047**	0.099	0.058	0.074	**0.051**	0.043	**0.047**

Size - Common k - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.059	**0.047**	**0.053**	0.089	**0.052**	0.067	0.055	0.043	**0.050**
0.001	0.059	**0.047**	**0.053**	0.099	0.058	0.075	**0.053**	0.044	**0.049**
0.01	**0.053**	0.044	**0.048**	0.094	0.053	0.069	**0.051**	0.043	**0.047**
0.01	**0.053**	0.044	**0.049**	0.093	0.055	0.070	**0.052**	0.043	**0.047**

Table Series 3.1, Continued

Size - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.074	0.044	0.058	0.058	0.043	0.055	**0.054**	0.031	0.042
0.001	0.071	**0.047**	0.058	0.067	0.044	**0.053**	**0.047**	0.033	0.039
0.01	0.053	0.042	**0.047**	0.069	0.043	0.055	**0.047**	0.039	0.043
0.1	0.045	0.036	0.041	0.063	0.042	**0.051**	**0.046**	0.036	0.041

Size - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.069	0.044	0.055	0.069	0.044	**0.054**	**0.051**	0.035	0.043
0.001	0.068	0.045	0.056	0.070	**0.047**	0.057	**0.049**	0.038	0.043
0.01	**0.050**	0.042	**0.046**	0.070	**0.048**	0.058	**0.049**	0.040	0.044
0.1	0.044	0.036	0.040	0.065	0.040	**0.052**	**0.044**	0.035	0.039

Table Series 3.2 Power Calculations for CRT Settings

Without Covariate Adjustment

5 clusters per arm

Power, 20% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.098	0.112	0.101
0.001	0.126	0.136	0.135
0.01	0.186	0.165	0.206
0.1	0.211	0.162	0.239

Power, 20% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.077	0.090	0.082
0.001	0.095	0.105	0.103
0.01	0.116	0.110	0.132
0.1	0.122	0.114	0.142

Table Series 3.2, Continued

Power, 40% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.272	0.289	0.316
0.001	0.395	0.357	0.434
0.01	0.632	0.422	0.677
0.1	0.733	0.446	0.775

Power, 40% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.206	0.210	0.230
0.001	0.273	0.246	0.299
0.01	0.390	0.271	0.432
0.1	0.446	0.283	0.491

Power, 20% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.096	0.117	0.106
0.001	0.127	0.136	0.136
0.01	0.195	0.166	0.218
0.1	0.238	0.179	0.271

Table Series 3.2, Continued

Power, 20% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.079	0.095	0.091
0.001	0.096	0.105	0.107
0.01	0.118	0.121	0.137
0.1	0.133	0.123	0.154

Power, 40% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.313	0.330	0.354
0.001	0.452	0.409	0.499
0.01	0.727	0.498	0.765
0.1	0.852	0.541	0.878

Power, 40% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.233	0.239	0.265
0.001	0.321	0.286	0.351
0.01	0.478	0.318	0.519
0.1	0.562	0.340	0.605

Table Series 3.2, Continued

Power, 20% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.165	0.196	0.147
0.001	0.288	0.331	0.279
0.01	0.533	0.639	0.443
0.1	0.359	0.743	0.380

Power, 20% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.143	0.172	0.136
0.001	0.236	0.276	0.225
0.01	0.303	0.471	0.247
0.1	0.191	0.528	0.214

Power, 40% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.479	0.544	0.518
0.001	0.723	0.771	0.750
0.01	0.929	0.967	0.902
0.1	0.870	0.985	0.881

Table Series 3.2, Continued

Power, 40% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.451	0.513	0.473
0.001	0.633	0.714	0.670
0.01	0.771	0.896	0.737
0.1	0.657	0.937	0.682

8 clusters per arm

Power, 20% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.164	0.170	0.171
0.001	0.215	0.198	0.225
0.01	0.317	0.221	0.339
0.1	0.387	0.230	0.414

Power, 20% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.129	0.131	0.137
0.001	0.149	0.133	0.156
0.01	0.194	0.148	0.208
0.1	0.216	0.156	0.235

Table Series 3.2, Continued

Power, 40% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.539	0.473	0.565
0.001	0.695	0.543	0.711
0.01	0.895	0.597	0.898
0.1	0.953	0.620	0.961

Power, 40% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.402	0.340	0.421
0.001	0.501	0.362	0.519
0.01	0.674	0.392	0.697
0.1	0.725	0.408	0.749

Power, 20% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.171	0.174	0.180
0.001	0.220	0.199	0.228
0.01	0.312	0.217	0.331
0.1	0.397	0.240	0.420

Table Series 3.2, Continued

Power, 20% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.126	0.125	0.132
0.001	0.149	0.137	0.158
0.01	0.192	0.146	0.207
0.1	0.222	0.154	0.241

Power, 40% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.541	0.478	0.566
0.001	0.819	0.538	0.711
0.01	0.899	0.597	0.911
0.1	0.957	0.615	0.964

Power, 40% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.400	0.341	0.421
0.001	0.501	0.369	0.519
0.01	0.656	0.388	0.681
0.1	0.734	0.405	0.757

Table Series 3.2, Continued

Power, 20% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.346	0.383	0.338
0.001	0.583	0.625	0.555
0.01	0.764	0.925	0.641
0.1	0.514	0.961	0.525

Power, 20% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.313	0.353	0.298
0.001	0.513	0.548	0.452
0.01	0.496	0.820	0.415
0.1	0.320	0.874	0.340

Power, 40% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.828	0.857	0.810
0.001	0.959	0.969	0.943
0.01	0.979	1.000	0.960
0.1	0.946	1.000	0.949

Table Series 3.2, Continued

Power, 40% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.794	0.828	0.765
0.001	0.928	0.949	0.870
0.01	0.871	0.994	0.844
0.1	0.793	0.996	0.805

<u>20 clusters per arm</u>

Power, 20% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.436	0.336	0.436
0.001	0.545	0.368	0.549
0.01	0.745	0.405	0.751
0.1	0.846	0.431	0.852

Power, 20% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.304	0.230	0.305
0.001	0.366	0.241	0.372
0.01	0.477	0.249	0.487
0.1	0.546	0.261	0.557

Table Series 3.2, Continued

Power, 40% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.960	0.845	0.957
0.001	0.992	0.869	0.991
0.01	1.000	0.888	1.000
0.1	1.000	0.907	1.000

Power, 40% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.844	0.640	0.845
0.001	0.918	0.672	0.921
0.01	0.983	0.684	0.984
0.1	0.993	0.715	0.994

Power, 20% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.466	0.361	0.462
0.001	0.588	0.407	0.590
0.01	0.786	0.439	0.791
0.1	0.876	0.467	0.882

Table Series 3.2, Continued

Power, 20% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.317	0.245	0.317
0.001	0.391	0.248	0.396
0.01	0.514	0.266	0.523
0.1	0.604	0.284	0.614

Power, 40% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.981	0.906	0.977
0.001	0.997	0.923	0.997
0.01	1.000	0.942	1.000
0.1	1.000	0.954	1.000

Power, 40% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.906	0.727	0.904
0.001	0.961	0.760	0.961
0.01	0.996	0.771	0.996
0.1	0.999	0.802	0.999

Table Series 3.2, Continued

Power, 20% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.793	0.881	0.838
0.001	0.977	0.991	0.959
0.01	0.990	1.000	0.957
0.1	0.908	1.000	0.906

Power, 20% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.827	0.853	0.773
0.001	0.964	0.974	0.890
0.01	0.823	1.000	0.745
0.1	0.667	1.000	0.671

Power, 40% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.999	1.000	0.996
0.001	1.000	1.000	0.999
0.01	1.000	1.000	1.000
0.1	1.000	1.000	1.000

Table Series 3.2, Continued

Power, 40% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.998	0.999	0.993
0.001	1.000	1.000	0.998
0.01	0.999	1.000	0.998
0.1	0.997	1.000	0.997

With Covariate Adjustment

5 clusters per arm

Power, 20% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.062	0.077	0.074
0.001	0.090	0.101	0.106
0.01	0.131	0.113	0.164
0.1	0.168	0.126	0.213

Table Series 3.2, Continued

Power, 20% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.059	0.067	0.066
0.001	0.070	0.077	0.083
0.01	0.086	0.083	0.107
0.1	0.096	0.084	0.119

Power, 40% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.184	0.205	0.231
0.001	0.271	0.261	0.336
0.01	0.488	0.326	0.563
0.1	0.598	0.343	0.672

Power, 40% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.135	0.150	0.173
0.001	0.191	0.178	0.228
0.01	0.305	0.203	0.358
0.1	0.347	0.222	0.411

Table Series 3.2, Continued

Power, 20% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.063	0.077	0.072
0.001	0.088	0.096	0.099
0.01	0.146	0.121	0.179
0.1	0.183	0.134	0.227

Power, 20% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.056	0.068	0.065
0.001	0.069	0.077	0.086
0.01	0.093	0.084	0.116
0.1	0.102	0.088	0.125

Power, 40% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.188	0.214	0.230
0.001	0.288	0.282	0.372
0.01	0.568	0.377	0.647
0.1	0.699	0.416	0.764

Table Series 3.2, Continued

Power, 40% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.146	0.163	0.186
0.001	0.208	0.198	0.260
0.01	0.354	0.235	0.419
0.1	0.434	0.255	0.500

Power, 20% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.090	0.111	0.080
0.001	0.164	0.198	0.165
0.01	0.338	0.418	0.308
0.1	0.237	0.504	0.278

Power, 20% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.084	0.106	0.081
0.001	0.128	0.154	0.131
0.01	0.182	0.265	0.168
0.1	0.115	0.318	0.150

Table Series 3.2, Continued

Power, 40% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.293	0.354	0.326
0.001	0.493	0.558	0.547
0.01	0.766	0.837	0.755
0.1	0.685	0.899	0.736

Power, 40% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.272	0.323	0.300
0.001	0.422	0.479	0.462
0.01	0.552	0.689	0.546
0.1	0.447	0.738	0.512

<u>8 clusters per arm</u>

Power, 20% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.132	0.142	0.152
0.001	0.187	0.166	0.208
0.01	0.272	0.183	0.301
0.1	0.344	0.197	0.381

Table Series 3.2, Continued

Power, 20% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.106	0.107	0.121
0.001	0.132	0.117	0.146
0.01	0.168	0.118	0.188
0.1	0.194	0.130	0.219

Power, 40% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.434	0.396	0.489
0.001	0.596	0.466	0.644
0.01	0.836	0.524	0.865
0.1	0.908	0.555	0.927

Power, 40% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.320	0.268	0.355
0.001	0.423	0.304	0.460
0.01	0.588	0.327	0.626
0.1	0.670	0.352	0.709

Table Series 3.2, Continued

Power, 20% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.136	0.142	0.155
0.001	0.189	0.173	0.209
0.01	0.294	0.185	0.329
0.1	0.381	0.216	0.419

Power, 20% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.111	0.115	0.119
0.001	0.128	0.121	0.145
0.01	0.186	0.130	0.211
0.1	0.202	0.135	0.227

Power, 40% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.474	0.441	0.537
0.001	0.662	0.532	0.710
0.01	0.904	0.609	0.924
0.1	0.962	0.637	0.971

Table Series 3.2, Continued

Power, 40% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.350	0.307	0.403
0.001	0.488	0.362	0.529
0.01	0.689	0.386	0.724
0.1	0.765	0.413	0.797

Power, 20% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.246	0.288	0.263
0.001	0.437	0.482	0.444
0.01	0.692	0.834	0.575
0.1	0.457	0.902	0.485

Power, 20% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.217	0.256	0.222
0.001	0.364	0.403	0.359
0.01	0.389	0.652	0.337
0.1	0.252	0.716	0.287

Table Series 3.2, Continued

Power, 40% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.682	0.754	0.721
0.001	0.881	0.916	0.887
0.01	0.964	0.994	0.940
0.1	0.915	0.998	0.924

Power, 40% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.661	0.715	0.675
0.001	0.848	0.877	0.816
0.01	0.828	0.972	0.802
0.1	0.745	0.984	0.765

<u>20 clusters per arm</u>

Power, 20% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.402	0.311	0.412
0.001	0.497	0.343	0.515
0.01	0.768	0.383	0.729
0.1	0.860	0.404	0.828

Table Series 3.2, Continued

Power, 20% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.277	0.211	0.286
0.001	0.349	0.222	0.358
0.01	0.470	0.226	0.483
0.1	0.536	0.249	0.549

Power, 40% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.943	0.820	0.946
0.001	0.984	0.856	0.985
0.01	1.000	0.875	1.000
0.1	1.000	0.895	1.000

Power, 40% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.826	0.619	0.831
0.001	0.904	0.646	0.907
0.01	0.978	0.667	0.981
0.1	0.991	0.688	0.992

Table Series 3.2, Continued

Power, 20% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.418	0.336	0.430
0.001	0.544	0.377	0.559
0.01	0.768	0.421	0.779
0.1	0.860	0.443	0.870

Power, 20% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.292	0.217	0.304
0.001	0.367	0.236	0.380
0.01	0.500	0.246	0.515
0.1	0.578	0.264	0.595

Power, 40% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.967	0.883	0.965
0.001	0.994	0.911	0.995
0.01	1.000	0.931	1.000
0.1	1.000	0.946	1.000

Table Series 3.2, Continued

Power, 40% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.884	0.693	0.887
0.001	0.953	0.735	0.954
0.01	0.994	0.752	0.995
0.1	0.998	0.778	0.998

Power, 20% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.794	0.825	0.793
0.001	0.969	0.975	0.942
0.01	0.977	1.000	0.925
0.1	0.856	1.000	0.855

Power, 20% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.761	0.783	0.721
0.001	0.931	0.946	0.840
0.01	0.766	0.998	0.694
0.1	0.603	0.999	0.611

Table Series 3.2, Continued

Power, 40% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.998	0.999	0.993
0.001	1.000	1.000	0.999
0.01	1.000	1.000	0.999
0.1	0.998	1.000	0.998

Power, 40% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (Average KC/MD)
0.0004	0.998	0.999	0.981
0.001	1.000	1.000	0.991
0.01	0.992	1.000	0.984
0.1	0.981	1.000	0.980

Table Series 3.3 Size Calculations for Observational Study Settings

Size - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.067	0.056	0.061	0.095	0.070	0.080	0.064	**0.053**	0.058
0.001	0.061	**0.054**	0.058	0.101	0.072	0.085	0.059	**0.052**	0.057
0.01	0.056	**0.052**	**0.054**	0.107	0.074	0.088	**0.056**	**0.050**	**0.053**
0.1	0.060	0.055	0.058	0.114	0.077	0.093	0.058	**0.053**	0.056

Size - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.061	**0.053**	0.057	0.100	0.072	0.084	0.057	**0.049**	**0.052**
0.001	0.064	0.056	0.060	0.110	0.078	0.094	0.060	**0.053**	0.056
0.01	0.058	**0.051**	**0.054**	0.118	0.084	0.098	0.056	**0.050**	**0.053**
0.1	0.058	**0.052**	0.055	0.106	0.074	0.088	0.057	**0.053**	0.055

Table Series 3.3, Continued

Size - Common k - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.073	0.064	0.068	0.115	0.083	0.095	0.070	0.060	0.066
0.001	0.071	0.062	0.066	0.121	0.084	0.102	0.068	0.060	0.064
0.01	0.066	0.059	0.062	0.120	0.083	0.099	0.063	0.059	0.061
0.1	0.060	**0.054**	0.057	0.124	0.087	0.103	0.058	**0.053**	0.055

Size - Common k - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.072	0.063	0.067	0.122	0.087	0.102	0.069	0.060	0.064
0.001	0.068	0.060	0.064	0.120	0.084	0.099	0.062	0.057	0.059
0.01	0.069	0.063	0.066	0.121	0.087	0.101	0.066	0.060	0.064
0.1	0.065	0.060	0.063	0.125	0.086	0.101	0.064	0.058	0.060

Table Series 3.3, Continued

Size - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.070	**0.055**	0.062	0.063	**0.051**	0.056	0.055	0.045	**0.048**
0.001	0.063	**0.053**	0.057	0.060	**0.047**	**0.054**	**0.049**	0.043	**0.046**
0.01	**0.047**	0.042	0.044	0.065	**0.053**	0.059	**0.047**	0.043	0.045
0.1	0.056	**0.051**	**0.053**	0.062	**0.048**	0.055	0.056	**0.051**	**0.053**

Size - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Modified Negative Binomial KC	Modified Negative Binomial MD	Modified Negative Binomial Avg KC/MD	Modified Poisson KC	Modified Poisson MD	Modified Poisson Avg KC/MD	Modified OD Binomial KC	Modified OD Binomial MD	Modified OD Binomial Avg KC/MD
0.0004	0.063	**0.051**	0.057	0.063	**0.051**	0.057	**0.053**	0.044	**0.048**
0.001	**0.054**	**0.047**	**0.051**	0.065	**0.050**	0.057	**0.049**	0.044	**0.046**
0.01	**0.050**	**0.046**	**0.048**	0.065	**0.053**	0.058	**0.052**	**0.047**	**0.050**
0.1	0.057	**0.051**	**0.054**	0.065	**0.053**	0.059	0.056	**0.050**	**0.053**

Table Series 3.4 Power Calculations for Observational Study Settings

Power, 20% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.475	0.411	0.471
0.001	0.639	0.492	0.638
0.01	0.887	0.556`	0.887
0.1	0.954	0.593	0.953

Power, 20% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.362	0.295	0.358
0.001	0.473	0.326	0.470
0.01	0.661	0.348	0.660
0.1	0.755	0.382	0.752

Power, 40% reduction - Common ICC - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.971	0.906	0.970
0.001	0.997	0.942	0.997
0.01	1.000	0.954	1.000
0.1	1.000	0.966	1.000

Table Series 3.4, Continued

Power, 40% reduction - Common ICC - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.913	0.769	0.912
0.001	0.971	0.819	0.971
0.01	0.998	0.842	0.998
0.1	1.000	0.863	1.000

Power, 20% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.338	0.258	0.330
0.001	0.435	0.281	0.428
0.01	0.599	0.302	0.593
0.1	0.691	0.339	0.683

Power, 20% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.236	0.174	0.230
0.001	0.285	0.183	0.279
0.01	0.373	0.195	0.366
0.1	0.422	0.206	0.408

Table Series 3.4, Continued

Power, 40% reduction - Common k - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.920	0.788	0.916
0.001	0.979	0.824	0.978
0.01	0.999	0.843	0.999
0.1	1.000	0.869	1.000

Power, 40% reduction - Common k - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.802	0.583	0.798
0.001	0.894	0.614	0.891
0.01	0.969	0.628	0.968
0.1	0.984	0.666	0.983

Power, 20% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.726	0.752	0.719
0.001	0.932	0.946	0.909
0.01	0.975	0.999	0.965
0.1	0.931	1.000	0.928

Table Series 3.4, Continued

Power, 20% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.683	0.705	0.640
0.001	0.854	0.904	0.799
0.01	0.756	0.992	0.743
0.1	0.702	0.997	0.696

Power, 40% reduction - Common VIF - ICC = 5% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.996	0.997	0.996
0.001	1.000	1.000	1.000
0.01	1.000	1.000	1.000
0.1	1.000	1.000	1.000

Power, 40% reduction - Common VIF - ICC = 10% of marginal probability

Marginal Probability	Negative Binomial (MD)	Poisson (MD)	Overdispersed Binomial (MD)
0.0004	0.994	0.997	0.992
0.001	1.000	1.000	0.999
0.01	0.999	1.000	0.999
0.1	0.998	1.000	0.998

Chapter 4 - The Performance of Marginal Modeling Methods for Rare Cluster-Level Count Outcomes with Application to Opioid Overdose Morbidity

Overview of Chapter 4

In the previous chapter, we compared the methods of marginal modeling of rare cluster-level count outcomes for events that can occur at most once per person. In this chapter, we will return to the cross-sectional observational study settings and methods studied in the previous chapter to focus on rare events that can occur more than once per person. The motivating example will be an observational study of opioid poisonings in Kentucky. Opioid poisonings are rare at the population level, but can occur more than once per person, unlike opioid overdose-related fatalities. The goal of this chapter is to compare approaches to modeling rare cluster-level count outcomes in terms of validity of inference and power, with a specific focus on modeling rates of rare events that can occur more than once.

Introduction

Overview

In this section, we will recapitulate the goals and results of the previous chapter, which focused modeling probabilities and rates of events that can occur at most once per person. Next, we will provide details on the motivating example for this chapter, which is a cross-sectional observational study of opioid poisoning rates in Kentucky. Finally, we will shift focus to the goal of this chapter, which is to compare the approaches studied in the previous chapter for modeling rates of rare events that can occur more than once per person, as well as the challenges associated with modeling this type of outcome.

Background

In the previous chapter, we studied the performance of regression approaches to modeling rare cluster-level count outcomes in terms of practicality, validity of inference, and power, with a specific focus on modeling population-averaged probabilities or rates per resident of rare events. The event studied in our motivating examples was opioid overdose-related fatalities, which can occur at most once per person. Modified negative binomial regression, modified overdispersed binomial regression, and modified Poisson regression were compared using simulation studies based on cluster randomized trial (CRT) and observational study settings. Additionally, an application example using county-level data of opioid overdose-related fatalities in Kentucky in 2021 was used to provide a practical example of how the regression methods may be used for modeling real-life data.

All three methods could produce valid inference, conditional on a bias-corrected empirical standard error estimator. In general, modified overdispersed binomial

regression and modified negative binomial regression performed similarly in terms of power. Modified Poisson regression outperformed the other two methods when the true overdispersion structure corresponded to its working overdispersion structure, which assumes a common variance inflation factor (VIF) across all clusters, and the intra-cluster correlation coefficient and cluster size are inversely related. [10] However, modified Poisson regression was less powerful compared to the other two methods when the true overdispersion structure did not correspond to its working overdispersion structure. Researchers who choose one method over another must carefully consider the nature of their data in order to make an informed decision that both preserves validity of inference and maximizes power.

In this chapter, we focus on events that can occur more than once per subject, which are commonly found in epidemiological settings, both in CRTs and observational studies. Unlike the outcome studied in the previous chapter, opioid overdose-related fatalities, opioid overdose poisonings are events that can occur more than once per person and are collected and analyzed as cluster-level count outcomes. Thus, the findings from the previous chapter may not apply to this type of outcome.

Motivating Example

Our motivating example is a cross-sectional observational study of community-level associations with opioid poisonings across the state of Kentucky. As opioid overdose-related fatality rates in Kentucky remain one of the highest among US states, it is important to study the factors that are associated with not only fatalities, but instances of opioid poisonings. [7] Not only is opioid poisoning associated with opioid overdose-

related fatalities, but an increase in the number of non-fatal opioid poisonings has been found to be associated with subsequent opioid overdose-related fatalities. [134] [135] Despite this relationship, it is often the case that those who experience an opioid poisoning do not receive medications for opioid use disorder (MOUDs), such as buprenorphine and methadone. [136] Because MOUDs have been shown to be effective at preventing further opioid misuse and overdose mortality, it is crucial to understand the factors behind opioid poisoning in order to prevent and reduce resulting adverse health effects and subsequent overdose-related fatalities. [137] By understanding the factors that contribute to opioid poisonings, and thus potential cases of opioid overdose-related fatalities, intervention and policy that targets specific demographic groups or sectors of the healthcare system can be more effectively designed.

This motivating example will be used to provide a basis for a simulation study that will compare the validity of inference and power of the three regression methods across multiple settings. Additionally, we will apply the regression methods studied in this chapter to the data from the motivating example. Through this application, we hope to support the results of the simulation study and provide researchers with a practical scenario of how these regression methods can be applied to real-life data.

Challenges and Goals

Because the results from the previous chapter may not apply to the outcomes studied in this chapter, it is important to highlight the challenges that using the regression approaches presented in the previous chapter may pose. First, modified overdispersed binomial regression, which was a method that corresponded to the distribution of the

outcome in the third chapter, may not be appropriate for the outcome studied in this chapter. Additionally, because of the multiple levels of clustering, the working overdispersion structures for the methods studied may not correspond to the true overdispersion structure, and thus may not be able to correctly model the data.

In the case of rare person-level events that are collected at the cluster level, if the event can occur once per person, the resulting community-level count outcome is treated as the sum of person-level binary event indicators. [2] [103] This outcome, conditional on the cluster, corresponds to a binomial distribution. However, in the case of events that can occur more than once per person, such as opioid poisonings, as in our motivating example, the community-level count outcome will be the sum of person-level counts. This outcome is different because it no longer corresponds to a binomial distribution, and the true distribution will not be known. For ease of interpretability, we will choose to view this outcome as a population-averaged rate per resident, which is averaged across both communities and the residents within communities. Because the outcome does not correspond to a binomial distribution, it is theoretically unlikely for modified overdispersed binomial regression to be able to correctly model it. In contrast to modified overdispersed binomial regression, which models the odds ratio, both modified negative binomial regression and modified Poisson regression model the marginal rate of the outcome, which corresponds to the outcome we are attempting to model. Due to this, it is possible that these two methods perform better compared to modified overdispersed binomial regression.

This difference in the distribution of the outcome, compared to that of the outcome studied in the previous chapter, contributes to an extra level of clustering.

Because of this, the true distribution of the count outcome, including the overdispersion structure, can be very complex. In the simulation studies in the previous chapter, we were able to generate data sets with true overdispersion structures that corresponded with the working forms used by each of the regression methods. By choosing a method whose working form for the variance inflation factor (VIF) is closer to the true VIF, we should expect an increase in power resulting from improved efficiency. [102] [107] However, because of the additional level of clustering present in the data studied in this chapter, the true VIF of the data cannot be assumed to correspond to the working forms of any of the regression methods, and we do not expect any of the methods studied in this chapter to perfectly model the outcome.

Despite the challenges with respect to precisely modeling the outcome, the marginal methods presented in the third chapter have been shown to be appropriate for modeling rare count outcomes under the previously studied settings, and we would like to evaluate their performance when applied to the settings in our motivating example. We expect modified negative binomial regression and modified Poisson regression to perform better than modified overdispersed binomial regression in terms of power due to their ability to model rates. Overall, the goal of this chapter is to compare the three regression approaches presented in the third chapter - modified negative binomial regression, modified overdispersed binomial regression, and modified Poisson regression - in terms of validity of inference and power when applied to rare count outcomes of events that can occur more than once per person.

Methods

Overview

In this section, we will describe the nature of the outcome studied in this chapter and how the regression approaches introduced in the previous chapter may be used for modeling it. Next, we will introduce the opioid poisoning data that will be used as a basis for the simulation study and application example. Finally, we will outline the details of the simulation study and application example, and how they will be used to compare the approaches of interest.

Nature of the Event of Interest and Regression Approaches for Comparison

Despite the potential complexity of the true distribution of the count outcome, our goal with quasi-likelihood approaches, as in the previous chapter, is to specify working forms for the mean and variance. Through correctly specifying the mean and using bias-corrected standard error estimates, this approach has been shown to result in consistent parameter estimation, and thus valid inference, even when the overdispersion is misspecified. [109] The three approaches outlined in the third chapter - modified negative binomial regression, modified overdispersed binomial regression, and modified Poisson regression - use different working forms for the VIF.

Because our goal is to model the marginal rate of the outcome of interest, modified negative binomial regression and modified Poisson regression may be appropriate. In both methods, the marginal relative rate of the event per subject is modeled. For both of these regression approaches, the modeled marginal rate per person for cluster □ is given by

$$\lambda_i = e^{x_i\beta}, i = 1, \ldots, N$$

□□ and β refer to the cluster-level covariates and regression parameters, respectively. The offset in the model is ln (n_i). The working form for the VIF of modified negative binomial regression is given by $1 + kn_i\lambda_i$, where k is a common overdispersion parameter. [107] For modified Poisson regression, the overdispersion is common across all clusters, and its working form corresponds to that of overdispersed binomial regression assuming a common VIF.

In contrast, modified overdispersed binomial regression does not directly model the marginal rate of the event per person, and instead models the odds ratio, which assumes at most one event per person. The modeled mean number of events in cluster □ is given by

$$\mu_□ = □_□ \frac{□^{□_□□}}{1 + □^{□_□□}}, □ = 1, \ldots, □$$

and the working form for the VIF is given by $1 - (n_i + 1)\rho, i = 1, \ldots, N$, where ρ is common across all clusters. [103] [107]

Despite the issues with respect to how the modeled VIF of the regression methods does not correspond to the true VIF of the data, practicality is an important consideration for researchers. As described in the third chapter, both modified negative binomial regression and modified Poisson regression can be coded using solely PROC GLIMMIX or GENMOD in SAS, unlike overdispersed binomial regression, which requires the additional use of PROC LOGISTIC to estimate the intra-cluster correlation coefficient (ICC). [73] [105] Thus, if there is not a large difference in terms of validity of inference and power, researchers may choose to use modified negative binomial regression or modified Poisson regression for ease of coding.

Motivating Example Data and Application Example

The opioid poisoning data used for this study is obtained from the Kentucky Emergency Medical Services (EMS) system. [138] The Kentucky EMS system records all unique emergency medical service encounters, and all records are reported to the National Emergency Medical Services Information System (NEMSIS), which compiles EMS records for every US state. [139] For the purposes of this study, we will be focusing on records of opioid poisoning, which will be defined using the Rhode Island Enhanced State Opioid Overdose Surveillance (ESOOS) Case Definition for EMS. [140] The data set upon which the simulation study settings will be based encompasses all recorded EMS encounters involving an opioid poisoning that occurred in the state of Kentucky in 2023, and are grouped by county of incidence. In this data set, 119 of the 120 Kentucky counties contributed EMS records, and thus the settings for the simulation studies will be based on the data from these counties.

In addition to the simulation study described below, we will be comparing the regression approaches by using the cross-sectional opioid poisoning data from EMS runs across 119 Kentucky counties in 2023. In this example, we will consider community-level factors and their associations with opioid poisonings in Kentucky. In the regression models used for this application example, we will utilize community-level covariates based on metropolitan status and unemployment rate. The linear predictor for the models used in this application example can be written as follows:

$$\beta_0 + \beta_1 Metropolitan_i + \beta_2 Unemployment_i, i = 1, \dots, 119$$

$Metropolitan_i$ refers to the metropolitan status, where 1 is metropolitan and 0 is non-metropolitan, of county i, and $Unemployment_i$ refers to the percent unemployment rate of county i. We will present results for all three bias correction methods in order to compare results. For each regression model, parameter estimates and standard error estimates for the intercept and the two covariates will be reported and compared.

Simulation Studies

To compare the validity of inference and power of the three regression approaches, we will conduct simulation studies motivated by the cross-sectional observational study of opioid poisonings in Kentucky in 2023 across a variety of settings. These simulation studies will consist of a series of 10,000 replications per studied setting. For each data set, modified negative binomial regression, modified overdispersed binomial regression, and modified Poisson regression will be compared in terms of empirical size and power.

In each simulation, there will be 119 clusters, corresponding to the 119 Kentucky counties that contributed EMS records for opioid poisonings. For the purposes of these simulation studies, we will be using metropolitan status as the main variable of interest, which will be represented by an indicator variable in the statistical model. Based on the 2013 Rural-Urban Continuum Codes, 35 are considered metropolitan, with the remaining 84 being non-metropolitan. [65] Thus, in our simulated data sets, 35 of the clusters will be considered metropolitan, with the remaining 84 being considered non-metropolitan. The cluster size for each county will be generated from a negative binomial distribution.

The mean and dispersion parameters used for generating the cluster sizes for each county will depend on whether the given county is considered metropolitan or non-metropolitan, and will be based on the mean and variance of the populations of metropolitan and non-metropolitan counties in Kentucky. For metropolitan counties, we used a mean of 57802 and a dispersion parameter of 0.302, and for non-metropolitan counties, a mean of 16629 and a dispersion parameter of 1.764. We will also include settings with an additional covariate based on unemployment rate. This variable will be generated from a uniform distribution based on the county-level unemployment rates for metropolitan and non-metropolitan counties, which range from 3.5% to 12.5% and 3.4% to 6.8%, respectively.

In order to generate the count outcome for each subject within each county, which will be summed to produce the county-level count outcome, we will be sampling from a Poisson distribution. The count for each subject j in cluster i, represented by y_{ij} will be generated based on a Poisson distribution with random effects corresponding to communities and subjects within communities:

$$y_{ij} \sim Pois(e^{\beta_0+\beta_1 x_i+\alpha_i+\epsilon_{ij}})$$

These subject counts will be summed for each cluster i in order to obtain the count for each cluster, Y_i. β_0 is a fixed intercept equal to 1.31×10^{-3}, which was selected such that the marginal rate per person under the null hypothesis corresponds to the marginal opioid poisoning rate per resident in our data set. x_i is an indicator variable referring to the metropolitan status of cluster i, and will equal 1 if the county is designated metropolitan, and 0 if the county is designated non-metropolitan. β_1 corresponds to the 20% or 40% decrease, conditional on the random effects, in opioid poisonings in non-metropolitan counties for settings in which we compare empirical powers, and will thus be equal to -

0.22 or -0.51, respectively. α_i is the cluster-specific random effect for cluster i, and will be sampled from a standard normal distribution. Similarly, ϵ_{ij} is the subject-specific random effect for subject j in cluster i, and will be sampled from a standard normal distribution.

The linear predictor for the models fit by our three regression approaches can be written as follows:

$$\beta_0 + \beta_1 Metropolitan_i, i = 1, \dots, 119$$

$Metropolitan_i$ refers to the metropolitan status, where 1 is metropolitan and 0 is non-metropolitan, of county i. In settings where the additional covariate for unemployment rate is included, the linear predictor is given by:

$$\beta_0 + \beta_1 Metropolitan_i + \beta_2 Unemployment_i, i = 1, \dots, 119$$

where $Unemployment_i$ refers to the percent unemployment rate of county i.

We will compare empirical test sizes produced by the regression approaches studied in order to ensure valid inference. Specifically, for the purposes of comparing test size in order to ensure valid inference, we will be using three bias correction methods, as in the previous chapter - Kauermann and Carroll, Mancl and DeRouen, and the average of these two bias correction methods. [120] [121] [122] We aim to choose the bias correction method that results in test sizes closest to the nominal test size of 0.05 for power calculations. Choosing the bias correction that results in empirical test sizes closest to the nominal size of 0.05 for each regression method can ensure fair and valid power comparisons among the regression methods. For all settings, we will be using degrees of freedom equal to the number of clusters minus the number of regression parameter estimates. [123]

Results

Overview

In this section, we will present results for the empirical test size and power calculations from our simulation studies. Additionally, we will provide interpretations of results from the application example and connect it to the simulation study results.

Simulation Studies

Test Size

Test size results for settings with and without an additional covariate are presented in Table 4.1. For all three approaches across all settings, the MD bias correction method resulted in test size closest to the nominal test size of 0.05. Notably, however, all test sizes were inflated. While modified overdispersed binomial and modified negative binomial regression had similar test sizes, modified Poisson regression resulted in test sizes that were, in the case of no covariate adjustment, more inflated than those of the other two methods. In settings with covariate adjustment, however, modified negative binomial regression resulted in the most inflated test size. Thus, for all three methods, for the purposes of power comparison, we will be using the MD bias correction to ensure inference that is closest to valid.

Power

Power calculations are presented in Tables 4.2 and 4.3. For all settings, power was similar for both modified overdispersed binomial regression and negative binomial regression, and these two methods were more powerful than modified Poisson regression. Additionally, this power difference increased when the difference in opioid poisonings

between metropolitan and non-metropolitan communities increased from 20% to 40%. For settings with a 40% reduction, modified overdispersed binomial regression and modified negative binomial regression had power that was nearly double that of modified Poisson regression.

Application Example

Regression parameter estimates and standard error estimates for all three regression approaches and bias correction methods are presented in Table 4.4. Results from this application example are consistent with those from the simulation studies, as modified overdispersed binomial and modified negative binomial regression performed similarly in terms of parameter and standard error estimates. Parameter estimates resulting from the use of the modified Poisson regression are notably different from the other two methods. For example, the parameter estimate for unemployment rate was 0.040 for modified Poisson regression, compared to 0.008 for modified overdispersed binomial regression and 0.007 for modified negative binomial regression. Additionally, for metropolitan status, the parameter estimates for modified overdispersed binomial regression and modified negative binomial regression were both positive, being 0.42 and 0.63, respectively. In contrast, the parameter estimate for modified Poisson regression was negative, being -0.036. Standard error estimates for modified Poisson regression were slightly different compared to those from the other two methods. However, these differences varied based on the parameter. For metropolitan status, the standard error estimates were higher for modified Poisson regression compared to the estimates from the other two methods, but were relatively similar for unemployment rate.

As discussed in the previous chapter, the differences in parameter estimates and standard error estimates are due to the way the overdispersion structure is modeled for each of the three methods. As the standard error estimate for metropolitan status in modified Poisson regression was higher than those of the other two regression approaches, it can be implied that the working overdispersion structures for modified negative binomial regression and modified overdispersed binomial regression, compared to the working overdispersion structure for modified Poisson regression, are closer to the true overdispersion structure of the data.

Discussion

Overview

In this section, we will provide a summary and conclusion of the results presented in the previous section. Next, we will discuss limitations of the study and its settings, as well as future work that could expand and improve upon on our findings.

Summary of Results

In this chapter, we compared the validity of inference and power of modified negative binomial regression, modified Poisson regression, and modified overdispersed binomial regression in modeling overdispersed binomial count data for events that can occur more than once per person. In our simulation studies, we found that test size was generally inflated for all three methods across our settings, although the Mancl and Derouen bias-corrected empirical standard error produced test sizes closest to the nominal test size of 0.05. In terms of power, modified negative binomial regression and modified overdispersed binomial regression performed similarly, and were more powerful than modified Poisson regression across all settings.

Because none of the regression approaches resulted in valid inference, their use for modeling rare cluster-level count outcomes for events that can occur more than once per person should be studied further. However, given that, in general, modified negative binomial regression and modified overdispersed binomial regression were more powerful than modified Poisson regression across all studied settings, researchers may be more inclined to use either of the former two methods. Despite modified overdispersed binomial regression not being theoretically appropriate, given the theoretical distribution

of the outcome of interest, it may be potentially usable in the settings studied in this chapter. Researchers can additionally use criteria such as the trace of the empirical covariance matrix (TECM) or the correlation information criterion (CIC) to assist in choosing a regression approach. [125] [126]

Limitations and Future Work

There are several limitations to the data set used as the basis for the simulation study and application example. First, there are limitations in terms of the settings studied in this chapter. Our focus is limited to rare events, and the models used to simulate the data are limited as well. Because of this, results may not be applicable to other types of data. Another limitation with the data used is that the same adverse health event may be recorded twice by EMS due to changing departments. Despite the use of unique IDs to track individuals through the EMS pipeline, the true number of opioid poisonings may be overestimated due to duplicate records. The structure for recording EMS events is also not rigorous and can lead to inconsistencies from regional departments in how opioid poisoning events are recorded. Finally, certain departments may not choose to record every EMS event, which can result in the true number of opioid poisonings being underestimated in certain counties. For example, data from Rowan County was suppressed due to data quality, and was thus not included in this study. To assist with proper estimation of opioid poisonings across all counties, Multiple Systems Estimation used by Thompson et al. to estimate the prevalence of opioid use disorder may be helpful. [67] In this method, data from multiple Kentucky healthcare sources were used to estimate the number of individuals with opioid use disorder that were unobserved. This

method may be applied to opioid poisonings in order to obtain a more robust picture of the opioid poisoning rate in each county. [68]

Future work can extend the comparisons of the regression methods studied in this chapter to other settings. For example, in many CRTs, rare events that can occur more than once per person may be of interest. Thus, further investigation into the applications of the regression methods studied here for CRT settings would be helpful for assisting researchers in choosing the most appropriate regression approach. Additionally, the performance of these methods when the event of interest is very rare or not rare can be useful, as both types of events are found in epidemiological studies. As the scope of this chapter is limited to the study settings examined above, more thorough study is necessary to evaluate the performance of marginal modeling methods when applied to data sets with different true overdispersion structures. Finally, as mentioned in the future work of the third chapter, further study into the performance of generalized linear mixed models (GLMM) in comparison to the marginal approaches studied here may be useful, given GLMM's use as an alternative to modeling cluster-level count data.

Supplemental Materials

Table 4.1 Size Calculations for Simulation Study

Regression Approach	Modified Overdispersed Binomial			Modified Negative Binomial			Modified Poisson		
Bias Correction Method	KC	MD	Average	KC	MD	Average	KC	MD	Average
Test Size (Without Additional Covariate)	0.070	0.067	0.068	0.070	0.068	0.069	0.120	0.095	0.107
Test Size (Including Additional Covariate)	0.069	0.064	0.067	0.091	0.085	0.088	0.109	0.072	0.090

Table 4.2 Power Calculations for Simulation Study, 20% Reduction

Regression Approach	Modified Overdispersed Binomial			Modified Negative Binomial			Modified Poisson		
Bias Correction Method	KC	MD	Average	KC	MD	Average	KC	MD	Average
Test Size (Without Additional Covariate)	0.147	0.139	0.143	0.146	0.139	0.143	0.121	0.097	0.108
Test Size (Including Additional Covariate)	0.116	0.107	0.111	0.134	0.125	0.130	0.130	0.090	0.108

Table 4.3 Power Calculations for Simulation Study, 40% Reduction

Regression Approach	Modified Overdispersed Binomial			Modified Negative Binomial			Modified Poisson		
Bias Correction Method	KC	MD	Average	KC	MD	Average	KC	MD	Average
Test Size (Without Additional Covariate)	0.533	0.521	0.527	0.531	0.522	0.527	0.301	0.265	0.283
Test Size (Including Additional Covariate)	0.374	0.355	0.364	0.386	0.372	0.379	0.236	0.179	0.206

Table 4.4 Parameter Estimates from Application Example

Regression Method	Modified Overdispersed Binomial Regression	Modified Negative Binomial Regression	Modified Poisson Regression
Regression Parameter Estimates (KC SE, MD SE, Average KC/MD SE)			
β_0	-6.018 (0.121, 0.124, 0.122)	-6.009 (0.122, 0.125, 0.123)	-6.220 (0.114, 0.145, 0.129)
β_1	0.042 (0.131, 0.134, 0.133)	0.063 (0.131, 0.134, 0.132)	-0.036 (0.153, 0.158, 0.156)
β_2	0.008 (0.013, 0.014, 0.014)	0.007 (0.014, 0.014, 0.014)	0.040 (0.010, 0.016, 0.013)

Chapter 5 – Summary and Conclusions

In this dissertation, we explored the performance and applications of marginal modeling methods for rare cluster-level count outcomes. As this type of count data is common in epidemiological settings, it is crucial that researchers understand the consequences of choosing a specific approach given their data set and outcome of interest. Thus, one goal of this dissertation is to guide researchers on choosing the most powerful, practical, and valid approach possible for modeling count outcomes for rare events. Another goal of this dissertation is to provide practical examples of how these methods can be used, with a focus on applications to opioid overdose mortality and morbidity.

In the second chapter, we fit a marginal negative binomial regression model in order to characterize the changes in opioid overdose-related fatality rates in Kentucky from 2019 to 2021, and found that adjacent-to-metropolitan and Appalachian counties experienced the largest increases in fatality rates. Additionally, we used the regression model to determine which county-level factors were associated with opioid overdose-related fatalities in 2019 and 2021 and how these associations may have changed. Both metropolitan county status and age were found to be associated with opioid overdose-related fatalities in both years.

In the third chapter, we compared the performance of methods for the marginal modeling of rare events that can occur at most once per person. Motivated by the study of opioid overdose-related fatality rates in Kentucky, we conducted simulation studies for both cluster randomized trial and observational study settings in order to compare the validity of inference, power, and practicality of modified regression approaches. We

found that modified negative binomial regression and modified overdispersed binomial regression performed similarly in terms of power. Depending on the true overdispersion structure of the data, modified Poisson regression's power was either lower or higher than those of the other two methods.

In the fourth chapter, we compare the performance of the modified regression methods explored in the previous chapter for rare events that can occur more than once per person. Through simulation studies and an application example based on county-level opioid poisoning data in Kentucky, we found that, across the studied settings, modified negative binomial regression and modified overdispersed binomial regression were more powerful than modified Poisson regression.

This dissertation focused on cluster randomized trial and observational study settings for rare cluster-level count outcomes. Future work can expand on this dissertation to explore other settings that are found in epidemiological studies. For example, cross-sectional data was used as the basis for the simulation studies in the third and fourth chapters. Comparing the performance of methods for marginal modeling of longitudinal data, such as what was studied in the second chapter, is also important, as this kind of data is also common in epidemiological settings. Future studies can also focus on the performance of commonly used methods for modeling clustered data, such as generalized linear mixed models, in comparison to the marginal methods studied in this dissertation.

Example Code

Chapter 2 – Adjusted Marginal Negative Binomial Model

```
/*Model Using All Data*/
proc import datafile="combineddata.csv"
      out=combined
      dbms=csv
      replace;
run;

/*Set Offset*/
data combined2;
set combined;
rate='Overdose Rate'n * 100000;
Buprenorphine = Buprenorphine/2;
Prescription = Prescription/2;
log_n = log(Denom);
Prevalence = Prevalence*1000;
run;


/*Fit negative binomial model*/
proc genmod data=combined2;
class County Period(ref='0') Metro(ref='0') App(ref='0');
model 'OD Count'n = Period Unemployment Naloxone App Prevalence
Metro Ethnic Age Poverty Uninsured Buprenorphine Prescription
Mental Mental*Period Unemployment*Period Naloxone*Period
Buprenorphine*Period Prescription*Period Prevalence*Period
Age*Period Poverty*Period Uninsured*Period Ethnic*Period
App*Period Metro*Period/ dist=nb offset=log_n;
repeated subject=County / type=un corrw;
estimate "Time Period" Naloxone 0 Mental 0 Unemployment 0 Period
1 -1;
estimate "Unemployment 2021" Unemployment 1 Unemployment*Period 1
0;
estimate "Unemployment 2019" Unemployment 1 Unemployment*Period 0
1;
estimate "Unemployment 2021 vs 2019" Unemployment 0
Unemployment*Period 1 -1;
estimate "Mental Health Providers 2021" Mental 1 Mental*Period 1
0;
estimate "Mental Health Providers 2019" Mental 1 Mental*Period 0
1;
estimate "Mental Health Providers 2021 vs 2019" Mental 0
Mental*Period 1 -1;
estimate "Naloxone Distribution 2021" Naloxone 1 Naloxone*Period
1 0;
```

```
estimate "Naloxone Distribution 2019" Naloxone 1 Naloxone*Period
0 1;
estimate "Naloxone Distribution 2021 vs 2019" Naloxone 0
Naloxone*Period 1 -1;
estimate "Buprenorphine Reception 2021" Buprenorphine 1
Buprenorphine*Period 1 0;
estimate "Buprenorphine Reception 2019" Buprenorphine 1
Buprenorphine*Period 0 1;
estimate "Buprenorphine Reception 2021 vs 2019" Buprenorphine 0
Buprenorphine*Period 1 -1;
estimate "High-Risk Opioid Prescribing 2021" Prescription 1
Prescription*Period 1 0;
estimate "High-Risk Opioid Prescribing 2019" Prescription 1
Prescription*Period 0 1;
estimate "High-Risk Opioid Prescribing 2021 vs 2019" Prescription
0 Prescription*Period 1 -1;
estimate "Percent Over 65 2021" Age 1 Age*Period 1 0;
estimate "Percent Over 65 2019" Age 1 Age*Period 0 1;
estimate "Percent Over 65 2021 vs 2019" Age 0 Age*Period 1 -1;
estimate "Poverty Rate 2021" Poverty 1 Poverty*Period 1 0;
estimate "Poverty Rate 2019" Poverty 1 Poverty*Period 0 1;
estimate "Poverty Rate 2021 vs 2019" Poverty 0 Poverty*Period 1 -
1;
estimate "Percent Uninsured 2021" Uninsured 1 Uninsured*Period 1
0;
estimate "Percent Uninsured 2019" Uninsured 1 Uninsured*Period 0
1;
estimate "Percent Uninsured 2021 vs 2019" Uninsured 0
Uninsured*Period 1 -1;
estimate "Percent Non-White 2021" Ethnic 1 Ethnic*Period 1 0;
estimate "Percent Non-White 2019" Ethnic 1 Ethnic*Period 0 1;
estimate "Percent Non-White 2021 vs 2019" Ethnic 0 Ethnic*Period
1 -1;
estimate "Appalachian Status 2021" App 1 -1 App*Period 1 -1 0 0;
estimate "Appalachian Status 2019" App 1 -1 App*Period 0 0 1 -1;
estimate "Appalachian Status 2021 vs 2019" App 0 0 App*Period 1 -
1 -1 1;
estimate "Metro vs Non-Metro 2021" Metro 0 1 -1 Metro*Period 0 1
-1 0 0 0;
estimate "Metro vs Non-Metro 2019" Metro 0 1 -1 Metro*Period 0 0
0 0 1 -1;
estimate "Adjacent vs Non-Metro 2021" Metro 1 0 -1 Metro*Period 1
0 -1 0 0 0;
estimate "Adjacent vs Non-Metro 2019" Metro 1 0 -1 Metro*Period 0
0 0 1 0 -1;
estimate "Metro vs Adjacent 2021" Metro -1 1 0 Metro*Period -1 1
0 0 0 0;
estimate "Metro vs Adjacent 2019" Metro -1 1 0 Metro*Period 0 0 0
-1 1 0;
estimate "Metro vs Non-Metro 2021 vs 2019" Period 0 0 Metro 0 0 0
Metro*Period 0 1 -1 0 -1 1;
```

```
estimate "Adjacent vs Non-Metro 2021 vs 2019" Period 0 0 Metro 0
0 0 Metro*Period 1 0 -1 -1 0 1;
estimate "Metro vs Adjacent 2021 vs 2019" Period 0 0 Metro 0 0 0
Metro*Period -1 1 0 1 -1 0;
estimate "Prevalence Rate 2021" Prevalence 1 Prevalence*Period 1
0;
estimate "Prevalence Rate 2019" Prevalence 1 Prevalence*Period 0
1;
estimate "Prevalence Rate 2021 vs 2019" Prevalence 0
Prevalence*Period 1 -1;
ods output estimates=adjresults GEEEmpPEst=adjstats;
run;
```

Chapter 3 – Simulate CRT Data for Power Calculations, No Additional Covariate, 20% Reduction in Marginal Probability for Intervention Arm, Common ICC Overdispersion Structure

```
simulations=10000 # Number of simulations
clustersize=89600.31 #mean cluster size
disp=0.385 #dispersion parameter

n=16    #total number of clusters
cg=n/2   #clusters in each group
mu = c(0.0004, 0.001, 0.01, 0.1) # marginal probability
powermu = 0.8*mu #20% reduction in marginal probability for
intervention group
ICC = 0.05*mu #ICC
pcl=rep(NA,cg)
powerpcl=rep(NA,cg)
y=rep(NA,cg)
y2=rep(NA,cg)

#simulate data
for(j in 1:4){
  a = (1/ICC[j] - 1) * mu[j]
  b = (1 - mu[j]) * (1/ICC[j] - 1)
  powera = (1/ICC[j] - 1) * powermu[j]
  powerb = (1 - powermu[j]) * (1/ICC[j] - 1)
  npertotal=as.data.frame(matrix(NA,nrow=(n*simulations),ncol=4))
  #Now performing simulations
  for(k in 1:simulations){

    nper = rep(NA,cg)
    nper2 = rep(NA,cg)
    for(i in 1:cg){
      #control arm
      nper[i] =
as.matrix(max(c(round(rnbinom(1,size=disp,mu=clustersize),0),2000)))
#Generate cluster size per cluster
      pcl[i] = rbeta(1,a,b) #generate probability from beta
distribution
      y[i]=rbinom(1,nper[i],pcl[i]) #sample from binomial distribution

      #intervention arm
      nper2[i] =
as.matrix(max(c(round(rnbinom(1,size=disp,mu=clustersize),0),2000)))
      powerpcl[i] = rbeta(1,powera,powerb)
      y2[i]=rbinom(1,nper2[i],powerpcl[i])
    }

    npertotal[((n*(k-1))+1):(cg+(n*(k-1))),1]=nper
    npertotal[((cg+1)+n*(k-1)):(n*k),1]=nper2
    npertotal[((n*(k-1))+1):(cg+(n*(k-1))),2]=y
    npertotal[((cg+1)+n*(k-1)):(n*k),2]=y2
    npertotal[((n*(k-1))+1):(n*k),3]=c(rep(1,(n/2)),rep(0,(n/2)))
    npertotal[((n*(k-1))+1):(n*k),4]=k
```

```
  }

  colnames(npertotal)=c("clustersize","y","inter","sim")
  write.csv(npertotal,paste("filename",j,".csv"))

}
```

Chapter 4 – Simulate Observational Study Data for Power Calculations, No Additional Covariate, 40% Reduction in Rate for Rural Counties

```
n = 119 #number of clusters
clustersize=57801.69 #mean cluster size (urban)
disp=0.302 #dispersion parameter (urban)
clustersize2=16666.91 #mean cluster size (rural)
disp2=1.793 #dispersion parameter (rural)
rate = (12144/3419869)/exp(1) #fixed rate
rate2 = 0.6*rate #40% reduction in marginal probability for rural
counties
simulations = 10000 #number of simulations
npertotal=as.data.frame(matrix(NA,nrow=(n*simulations),ncol=4))
colnames(npertotal)=c("sim","group","count","pop")

#conduct simulations
for(k in 1:simulations){
  c1=rep(NA,35)
  c2=rep(NA,84)
  nper = rep(NA,n)
  #generate urban/rural county cluster size
  c1 = round(rnbinom(35,size=disp,mu=clustersize),0)
  c2 = round(rnbinom(84,size=disp2,mu=clustersize2),0)
  nper = c(pmax(c1,2000),pmax(c2,2000))

  #calculate population for each of the groups
  pop1=sum(nper[1:35])
  pop2=sum(nper[36:119])
  pop=sum(pop1,pop2) #total population

  dat = as.data.frame(matrix(nrow=pop, ncol = 4))
  colnames(dat) = c("Cluster","Count","cluster.error","subject.error")
  dat$Cluster = rep(seq(1,n),nper)

  cluster.error = rnorm(n) #generate cluster-level random intercept
  dat$cluster.error = rep(cluster.error,times=nper)

  dat$subject.error = rnorm(pop) #generate subject-level random
intercept

  #generate counts for each subject
  dat$Count = c(rpois(pop1, rate*exp(dat$cluster.error[1:pop1] +
dat$subject.error[1:pop1])),rpois(pop2,rate2*exp(dat$cluster.error[(pop
1+1):pop] + dat$subject.error[(pop1+1):pop])))

  #calculate number of events per cluster by summing counts within each
cluster
  clustercount = aggregate(dat$Count ~ dat$Cluster, FUN=sum)

  npertotal[((n*(k-1))+1):(n*k),1]=k
  npertotal[((n*(k-1))+1):(n*k),2]=seq(1,n)
  npertotal[((n*(k-1))+1):(n*k),3]=clustercount$`dat$Count`
  npertotal[((n*(k-1))+1):(n*k),4]=nper
  print(k)
}
```

```
#generate metropolitan status variable
npertotal$inter = rep(c(rep(1,35),rep(0,84)),simulations)
write.csv(npertotal,paste("filename.csv"))
```

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Vita

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Publications

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Chemical Science. 2017 Jul 1;8(7):5078-5086. https://pubs.rsc.org/en/content/articlelanding/2017/sc/c7sc00496f

2. Lawrence KA, Vogt D, Dugan AJ, **Nigam S**, Slade E, Smith BN. Mental Health and Psychosocial Functioning in Recently Separated U.S. Women Veterans: Trajectories and Bi-Directional Relationships. *International Journal of Environmental Research and Public Health*. 2021 Jan 22;18(3):935. https://pubmed.ncbi.nlm.nih.gov/33498982/
3. Lawrence KA, Vogt D, **Nigam S**, Dugan AJ, Slade E, Smith BN. Temporal Sequencing of Mental Health Symptom Severity and Suicidal Ideation in Post-9/11 Men and Women Veterans Who Recently Separated from the Military. *Chronic Stress*. 2021 Nov 24;5:24705470211061347. https://pubmed.ncbi.nlm.nih.gov/34870056/
4. Lawrence KA, Vogt D, Dugan AJ, **Nigam S**, Slade E, Smith BN. Psychosocial functioning deficits impact and are impacted by suicidal ideation in post-9/11 women veterans. *Journal of Affective Disorders Reports*. 2022 Jul;9:100361. https://pubmed.ncbi.nlm.nih.gov/35874166/
5. Oyler DR, Knudsen HK, Oser CB, Walsh SL, Roberts M, **Nigam SR**, Westgate PM, Watson J, Freeman PR. Equity of Overdose Education and Naloxone Distribution Provided in the Kentucky HEALing Communities Study. *Drug and Alcohol Dependence Reports*. 2024;10:100207. https://www.sciencedirect.com/science/article/pii/S277272462300077X?via%3Dihub
6. Westgate PM, Nigam SR, Shoben AB. Reconsidering stepped wedge cluster randomized trial designs with implementation periods: Fewer sequences or the parallel-group design with baseline and implementation periods are potentially more efficient. *Clin Trials*. 2024

Apr 22:17407745241244790. doi: 10.1177/17407745241244790. Epub ahead of print. PMID: 38650332. https://pubmed.ncbi.nlm.nih.gov/38650332/

Awards

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Contributed Presentations

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