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Zero-inflated count models for longitudinal measurements with heterogeneous random effects

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Abstract

Longitudinal zero-inflated count data arise frequently in substance use research when assessing the effects of behavioral and pharmacological interventions. Zero-inflated count models (e.g., zero-inflated Poisson or zero-inflated negative binomial) with random effects have been developed to analyze this type of data. In these random effects zero-inflated count models, the random effects covariance matrix is typically assumed to be homogeneous (constant across subjects). However, in many situations this matrix may be heterogeneous (differ by measured covariates). In this paper, we extend zero-inflated count models to account for random effects heterogeneity by modeling their variance as a function of covariates. We show via simulation that ignoring intervention and covariate-specific heterogeneity can produce biased estimates of covariate effects and random effect estimates. Moreover, those biased estimates can be rectified by correctly modeling the random effects covariance structure. The methodological development is motivated by and applied to the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study, the largest clinical trial of alcohol dependence in United States with 1,383 individuals.

Keywords

Zero-inflation model; Count data; Heterogeneity; Random effects modeling; Negative Binomial

1 Introduction

Longitudinal counts with excess zeros arise frequently in clinical and public health studies. Examples include skin cancers¹, units of blood product after surgery², the number of complications experienced after a procedure³, and alcohol or tobacco consumption in substance use studies^{4,5}. These count measurements provide useful information for observing the course of the target disease and evaluating the long-term effects of

interventions. In recent years, zero-inflated count models, e.g., the zero-inflated Poisson (ZIP)⁶ or zero-inflated negative binomial (ZINB)⁷, have been adopted for modeling longitudinal count measurements with excess zeros. Those models distinguish the sources of zeros and count components using a two-parts mixture of a point mass at zero and Poisson or negative binomial (NB) distribution.

To account for the correlation between repeated measures for each subject, zero-inflated count models with random effects have been developed. For example, Hall⁸ used a random effect to account for the within subject dependence in Poisson part of the ZIP model. Others have included separate random effects in the zero and Poisson parts. Min and Agresti⁹ proposed a two-part zero-inflated random effects model to handle the zero and positive count separately; Lee *et al.*¹⁰ incorporated shared subject-specific random effects in each zero-inflated model part to account for zero inflation and over-dispersion within longitudinal count measurements. Buu⁴ also employed such models to analyze longitudinal count measurements in the field of substance abuse. Other authors have presented such models under a Bayesian framework^{11,12}.

However, all the aforementioned approaches assume that the random effects covariance matrix is homogeneous (constant across subjects). However, in some cases, this covariance matrix may be heterogeneous (differ by subject-specific characteristics)^{13,14}. For example, in substance use studies, cognitive versus pharmacological interventions may give rise to different substance use patterns; this may also be true for demographic variables; for example, men and women are known to have different patterns, trajectories, and variance in drinking behavior^{15,16}. Statistically speaking, when fitting zero-inflated models to substance use outcomes, this may translate to random effects heterogeneity in either (or both) zero or count parts of the model, which, if ignored, can result in the biased estimates of the fixed and random effects and therefore, erroneous conclusions^{14,17}.

Random effects covariance heterogeneity has been discussed in generalized linear mixed effects models (GLMM)^{13,18–25}. For example, Daniels and Zhao¹⁴ modeled the random effects covariance matrix by using a special Cholesky decomposition of the matrix, Lin *et al.*²⁰ explicitly modeled heterogeneous, within-cluster variances in linear mixed model using logarithm of the mean as a linear function of the covariates, and Huang²⁶ proposed an approach incorporating for a heterogeneous random effects covariance matrix in joint analysis of longitudinal measurements and competing risks failure time data. The goal of this paper is to extend the current ZIP and ZINB models to a class capable of accommodating between-subject heterogeneity through modeling parameters of random effects covariance with a function of meaningful covariates; from this point on these are called *heterogeneous (ZIP or ZINB) models*. We illustrate the proposed heterogeneous models and compare their performance with the corresponding homogeneous counterparts via an extensive simulation study that mimics important data features of the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study²⁷.

The paper is organized as follows. In Section 2 we present the motivation from the COMBINE study. In Section 3, we present ZIP and ZINB models for longitudinal data with

heterogeneous random effects structure. In Section 4, we conduct an extensive simulation study to assess the performance of the proposed model. In Section 5, we assess competing models applied to the COMBINE study, and in Section 6 we conclude with remarks and future work.

2 Motivating Data

The methodological development of this paper is motivated by the COMBINE study, the largest study to assess the benefits of combining behavioral and pharmacological interventions in the treatment of alcohol dependence. We refer the reader to the original study for more details²⁷. Briefly, a total of 1,383 eligible alcohol dependent individuals were randomly assigned in a $2 \times 2 \times 2$ factorial design to receive either active/placebo naltrexone or active/placebo acamprostate yielding 4 medication groups within each level of counseling (CBI/no CBI). For the current analysis, the individuals who did not receive naltrexone (769 individuals) are combined and referred to as the reference group while the individuals who receive naltrexone treatment are combined and referred as the naltrexone treatment group. The decision to collapse these groups for our secondary analysis is based on primary reports of longitudinal drinking process, as well as meta-analyses of randomized controlled trials that show limited to no effect of acamprostate or CBI on consumption of alcohol^{27,28}. Additionally, as naltrexone is the only FDA approved treatment for alcohol dependence, it is sensible to focus on this comparison in this paper.

In the COMBINE study, daily drinking was collected at 9 medical management visits (weeks 0, 1, 2, 4, 6, 8, 10, 12 and 16) during the 16 weeks of treatment period. Time line follow-back (TLFB) was used to assess daily drinking. TLFB is a calendar recall method that is completed at each visit, or every 30 days. It has been well validated and has high internal validity when compared to biomarkers or drug screens. It exhibits high concordance with drinking behavior even when given monthly and has therefore become the most commonly used method for reporting and assessing drinking in clinical trials in the US^{29,30}.

To establish a longitudinal count drinking outcome variable of reasonable dimension, we summarize the TLFB into “mean number of drinks per day for each week”. We round this mean to the nearest whole number, resulting in a zero-inflated outcome since 50% of patients did not drink (were abstinent) during the treatment period. As per prior studies, covariates include treatment, age, gender, prior drinking, and the time of repeated measures for patients. As in the primary report²⁷, we confine analysis to the 16 weeks treatment periods and evaluate how naltrexone affects abstinence from alcohol, as well as the amount of drinking over the course of treatment.

We first fit the random effects ZIP model with covariance structure specified as in Min and Agresti⁹ to the COMBINE data including the covariates listed above (SAS Version 9.3 procedure NLMIXED). To assess goodness-of-fit, we obtain the estimated random effects for each individual using empirical Bayes approach. Figure 1 displays four Q–Q plots of the random effects in the Poisson and zero part of the model, by gender groups. In a well-fitted model, the distribution of estimated random effects (in each model part) should lie along the line, $y = x$. Figure 1 shows violations of homogeneous random effects assumption may exist

for gender, thus indicating covariate-specific heterogeneity in the random effects distribution. This along with the fact that men and women have different drinking variances, histories, trajectories, patterns, and reasons for drinking^{31–33}, is an important clinical motivator for the current development. From a practical model-fitting perspective, a heterogeneous ZIP model might better cope with the heterogeneity exemplified here, and is likely to be relevant to other zero-inflated problems in biomedical research.

3 Methods

3.1 Zero-inflated Poisson model

Under the longitudinal setting and assuming independence between subjects, let Y_{ij} denote the longitudinal response (such as the drinking count) for subject $i = 1, \dots, n$ at time j where $j = 1, \dots, J_i$. The distribution of Y_{ij} is

$$Y_{ij} \sim \begin{cases} 0 & \text{with probability } \phi_{ij} \\ \text{Poisson}(\lambda_{ij}) & \text{with probability } 1 - \phi_{ij}, \end{cases}$$

where ϕ_{ij} denotes the probability of the observation arising from the degenerated distribution at zero and λ_{ij} represents the mean of the Poisson distribution. This formulation incorporates more zeros than permitted under the Poisson assumption (i.e., where $\phi_{ij} = 0$).

The probability distribution function of the longitudinal ZIP model can be written as

$$P(Y_{ij}=0|\mathbf{Z}_{ij}) = \phi_{ij} + (1 - \phi_{ij})e^{-\lambda_{ij}} \quad (1)$$

$$P(Y_{ij}=y_{ij}|\mathbf{X}_{ij}) = (1 - \phi_{ij}) \frac{\lambda_{ij}^{y_{ij}} e^{-\lambda_{ij}}}{y_{ij}!}, y_{ij}=1, 2, \dots, \quad (2)$$

where $0 < \phi_{ij} < 1$ and $0 < \lambda_{ij} < \infty$. The matrix $\mathbf{Z}_{ij}$ is a set of covariates related to ϕ_{ij} (i.e., the probability of being abstinent in this context) and $\mathbf{X}_{ij}$ is a set of covariates related to λ_{ij} (i.e., the severity of drinking in this context). The $\mathbf{X}_{ij}$ and $\mathbf{Z}_{ij}$ can be mutually exclusive, partially, or completely overlapping to achieve modeling flexibility.

3.2 Zero-inflated negative binomial model

The alternative zero-inflated negative binomial model is appealing due to an additional parameter that captures variability due to over-dispersion³⁴. The probability distribution function of the ZINB is,

$$P(Y_{ij}=0|\mathbf{Z}_{ij}) = \phi_{ij} + (1 - \phi_{ij}) \left(\frac{\nu}{\lambda_{ij} + \nu} \right)^\nu \quad (3)$$

$$P(Y_{ij}=y_{ij}|\mathbf{X}_{ij})=(1-\phi_{ij})\left\{\frac{\Gamma(y_{ij}+\nu)}{\Gamma(\nu)\Gamma(y_{ij}+1)}\left(\frac{\nu}{\nu+\lambda_{ij}}\right)^{\nu}\left(\frac{\lambda_{ij}}{\nu+\lambda_{ij}}\right)^{y_{ij}}\right\}, \text{ if } y_{ij}=1, 2, \dots, \quad (4)$$

where $\Gamma(\cdot)$ denotes the gamma function and λ_{ij} is the mean of the underlying negative binomial distribution. The parameters ϕ_{ij} and λ_{ij} in ZINB model have similar meanings as those in the ZIP model. The $\mathbf{X}_{ij}$ and $\mathbf{Z}_{ij}$ are corresponding covariates or risk factors for each part of the ZINB model.

Let $k = 1/\nu$ be a measure of over-dispersion with range $k \geq 0$, the mean and variance for y_{ij} are $(1 - \phi_{ij})\lambda_{ij}$ and $(1 - \phi_{ij})\lambda_{ij}(1 + \lambda_{ij}(\phi_{ij} + k))$ respectively. It is obvious that Equations (3) and (4) reduces to Equations (1) and (2) when k approaches 0³⁵. In practice, we can test the null hypothesis $H_0: k = 0$ to ascertain the necessity of the overdispersion parameter.

3.3 Model specification for heterogeneity

For both the ZIP and ZINB models, $\text{logit}(\phi_{ij})$ and $\log(\lambda_{ij})$ are the natural link functions for the Bernoulli probability of success and the mean of the Poisson/NB. The covariates and subject-specific random effects, denoted u_i and v_i , enter the zero and Poisson/NB of the model as follows,

$$\text{logit}(\phi_{ij}) = \boldsymbol{\alpha}\mathbf{Z}_{ij} + u_i \quad (5)$$

$$\log(\lambda_{ij}) = \boldsymbol{\beta}\mathbf{X}_{ij} + v_i, \quad (6)$$

where $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ are fixed coefficient vectors and u_i and v_i are subject-specific random effects accounting for within-subject correlation in each model part. We assume the random effects follow a bivariate normal distribution due to its flexibility and straightforward mathematical properties. In the homogeneous random effects model, the variance matrix is identical for all subjects $i = 1, \dots, n$ and the distribution of random effects is:

$$\begin{pmatrix} u_i \\ v_i \end{pmatrix} \sim N(\mathbf{0}, \begin{bmatrix} \sigma_u^2 & \rho\sigma_u\sigma_v \\ \rho\sigma_u\sigma_v & \sigma_v^2 \end{bmatrix}), \quad (7)$$

where σ_u^2 and σ_v^2 are variance components in the Bernoulli and Poisson/NB part of the model, respectively; ρ captures their correlation, allowing dependency between the model regressions. We refer to the ZIP or ZINB models with random effects distribution of Equation (7) as homogeneous ZIP or ZINB models.

This model may be restrictive in the sense that it forces a model fit that is inconsistent with the data (e.g., Figure 1) and can be relaxed by allowing random effects to follow a bivariate normal distribution with covariate-specific covariance matrix,

$$\begin{pmatrix} u_i \\ v_i \end{pmatrix} \sim N(\mathbf{0}, \begin{bmatrix} \sigma_{u_i}^2 & \rho\sigma_{u_i}\sigma_{v_i} \\ \rho\sigma_{u_i}\sigma_{v_i} & \sigma_{v_i}^2 \end{bmatrix}), \quad (8)$$

where σ_{u_i} and σ_{v_i} are related to the covariates $\mathbf{W}_i$ and $\mathbf{G}_i$ through the following models.

$$\log(\sigma_{u_i}^2) = \zeta_u \mathbf{W}_i \quad (9)$$

$$\log(\sigma_{v_i}^2) = \zeta_v \mathbf{G}_i. \quad (10)$$

In models (7) and (8), $-1 \leq \rho \leq 1$ is a continuous parameter to be estimated, and in models (9) and (10), parameters ζ_u and ζ_v are coefficients resulting from the regression on the random effects variances in the zero and count parts of the model, respectively. The log linear form of Equations (9) and (10) ensures that the estimation of σ_u^2 and σ_v^2 are positive, and help to shrink the random effects covariance matrix toward a particular structure through modeling covariance elements using influential covariates. Covariate vectors $\mathbf{W}_i$ and $\mathbf{G}_i$ are the covariates impacting the variability of the bivariate random variable (u_i, v_i) and they can be different or identical to $\mathbf{X}_{ij}$ and $\mathbf{Z}_{ij}$. We refer to the ZIP or ZINB models with random effects distribution of Equation (8) as heterogeneous.

3.4 Model estimation

By assuming the Y_{ij} in each model part are conditionally independent given the random effects u_i and v_i , the full likelihood function for subject i can be written as

$$L_i(\boldsymbol{\theta}) = \prod_j P(Y_{ij}=0|\boldsymbol{\theta})^{I(Y_{ij}=0)} P(Y_{ij}=y_{ij}|\boldsymbol{\theta})^{I(Y_{ij}>0)}, \quad (11)$$

where $I(\cdot)$ is an indicator function and the parameters $\boldsymbol{\theta} = (\boldsymbol{\theta}_1, \boldsymbol{\theta}_{\sum_i})$, where $\boldsymbol{\theta}_1$ is $(\boldsymbol{\alpha}, \boldsymbol{\beta})$ for ZIP model and $(\boldsymbol{\alpha}, \boldsymbol{\beta}, \nu)$ for ZINB, and $\boldsymbol{\theta}_{\sum_i} = (\zeta_u, \zeta_v, \rho)$. The marginal likelihood is

$$L_i = \int L_i(\boldsymbol{\theta}_1 | u_i, v_i) f(u_i, v_i | \boldsymbol{\theta}_{\sum_i}) du_i dv_i, \quad (12)$$

where $f(u_i, v_i) = N_2(0, \Sigma_i)$ and Σ_i are specified in model (8). To obtain the maximum likelihood estimate of parameter vector $\boldsymbol{\theta}$, we optimize the likelihood function, $L = \prod_i L_i$.

Parameter estimation can be challenging as the likelihood cannot be evaluated analytically (since Equation (12) depends on the integral of a complicated non-linear function with respect to a multivariate normal probability density function for random effects). Usually,

numerical integration techniques, such as first-order method, Hardy-quadrature, Gauss-quadrature, and adaptive importance sampling, are practical approaches to approximate the estimation. Among all those approaches, adaptive Gaussian-quadrature method is more efficient and can provide a better approximation by accounting for the shape of the likelihood when replacing quadrature points³⁶.

When implementing the adaptive Gaussian quadrature method, we approximate L_i by weighting the average of the integrand assessed through the centered and scaled abscissas μ_q at Q pre-specified quadrature points ($q = 1; 2, \dots, Q$) over the random effects u_i and v_i

$$L_i(\theta) \approx \sum_{q=1}^Q L_i(\theta|\mu_q) f(\mu_q) w_q, \quad (13)$$

where $\mu_q = \sqrt{2}z_q$ and z_q are standard Gauss-Hermite quadrature abscissas, and $w_q = \sqrt{2}\eta_q$ denotes the weight with z_q and η_q obtained from tables or algorithms^{37,38}. The adaptive Gaussian quadrature method has been incorporated in SAS procedure NLMIXED, which can be easily implemented to estimate non-linear mixed models³⁹.

In this study, all models are fitted using SAS procedure NLMIXED under the maximum likelihood framework using the adaptive Gaussian quadrature as integration approximations. The Newton-Raphson method with line search and trust region method are used for optimization. Given that the resulting estimators follow asymptotically normal distributions, we compute the standard errors using the inverse of the Fisher information matrix. The initial values for all parameters are obtained from fitting corresponding zero-inflated Poisson or negative binomial model without random effects.

3.5 Model selection

To inform model selection, we use the Akaike Information Criterion (AIC)⁴⁰ and Bayesian Information Criterion (BIC)⁴¹ and Likelihood ratio test (LRT). AIC and BIC are defined as $AIC = D + 2p$, $BIC = D + p \ln(n)$, where p is the number of parameters in the model, n is number of observations, D is the deviance defined as twice of negative log likelihood either in the ZIP model (1) and (2) or the ZINB model (3) and (4). Specially, $D = \sum_{i=1}^n \sum_{j=1}^{J_i} d_{ij}$ and for ZIP model,

$$d_{ij} = -2 \begin{cases} \log[\phi_{ij} + (1 - \phi_{ij})e^{-\lambda_{ij}}] & y_{ij}=0 \\ \log[(1 - \phi_{ij}) \frac{\lambda_{ij}^{y_{ij}} e^{-\lambda_{ij}}}{y_{ij}!}] & y_{ij}>0, \end{cases}$$

and for ZINB model,

$$d_{ij} = -2 \begin{cases} \log[\phi_{ij} + (1 - \phi_{ij})(\frac{\nu}{\lambda_{ij} + \nu})^\nu] & y_{ij}=0 \\ \log[(1 - \phi_{ij}) \left\{ \frac{\Gamma(y_{ij} + \nu)}{\Gamma(\nu)\Gamma(y_{ij} + 1)} (\frac{\nu}{\nu + \lambda_{ij}})^\nu (\frac{\lambda_{ij}}{\nu + \lambda_{ij}})^{y_{ij}} \right\}] & y_{ij}>0. \end{cases}$$

The model with lower AIC and BIC values is preferred.

In Section 3.4, the numerical integration method provides a likelihood function from the original data for optimization. Based on those results, Likelihood ratio tests can be applied to compare the nested models⁴², as the homogeneous random effects model is nested within the heterogeneous random effects model under either the ZIP or ZINB framework. Moreover, since the negative binomial distribution converges to the Poisson distribution as k converges to 0, the Poisson models are also nested within their negative binomial counterparts. Therefore, we set up two sets of LRTs for models comparison in this study. The first set is a LRT to compare the homogeneous and heterogeneous random effect models under either the ZIP or ZINB framework. If we only include a single covariate in models (9) and (10) and the corresponding coefficients are ζ_{u1} and ζ_{v1} respectively, this LRT is equivalent to testing whether $\zeta_{u1} = \zeta_{v1} = 0$ and the hypothesis can be written as

$$H_0: \zeta_{u1} = \zeta_{v1} = 0 \quad \text{versus} \quad H_a: \text{Otherwise.} \quad (14)$$

and the corresponding statistics is: $\lambda = -2\log_{H_0}(L(\boldsymbol{\theta})) + 2\log_{H_a}(L(\boldsymbol{\theta})) \sim \chi^2_2(n)$, where the twice of negative log likelihood is equal to the deviance.

Another set of LRTs compares homogeneous and heterogeneous ZIP models with their ZINB counterparts. The LRT in this case is equivalent to testing $k = 0$, using the following hypothesis:

$$H_0: k = 0 \quad \text{versus} \quad H_a: k > 0. \quad (15)$$

The asymptotic distribution of this LRT statistic is not a standard statistical distribution k lies on the boundary of the parameter space ($k = 0$). According to the non-standard asymptotic theory developed by Self and Liang⁴³, the LRT statistic asymptotically has a mixture distribution with probability mass of half at zero and a half chi-square(1) distribution above zero. Finally, to facilitate the application of our proposed method, we have included SAS code in Appendix.

4 Simulation Study

In this section, we design and report results from a simulation study to compare the performance of the proposed heterogeneous ZIP or ZINB models with their homogeneous counterparts. In each setting, we generate 500 datasets with sample size $N = 1000$ each. The sample size, covariate structure, and true parameter values are chosen to mirror clinically relevant sizes. Specifically, the longitudinal count outcomes are simulated from Equations (16) and (17) with either the homogeneous structure as in Equation (7) or the heterogeneous structure as in Equation (8). We assume the two part model to be

$$\text{logit}(\phi_{ij}) = \alpha_0 + \alpha_1 I(trt_i) + \alpha_2 \text{Time}_j + u_i \quad (16)$$

$$\log(\lambda_{ij}) = \beta_0 + \beta_1 I(trt_i) + \beta_2 \text{Time}_j + v_i, \quad (17)$$

where $I(trt_i)$ is a binary treatment indicator for subject i and $j = 1, \dots, 6$ time points.

For the heterogeneous ZIP or ZINB models, we allow the random effects distribution to differ by a covariate illustratively labeled “treatment (trt),” i.e.,

$$\log(\sigma_{u_i}^2) = \zeta_{u0} + \zeta_{u1} I(trt_i) \quad (18)$$

$$\log(\sigma_{v_i}^2) = \zeta_{v0} + \zeta_{v1} I(trt_i). \quad (19)$$

We choose coefficients that reflect a clinically meaningful direction and magnitude. Specifically, the magnitude of the intercepts are chosen to reflect a baseline abstinence and drinking rate of 0.5. Coefficients α_1 and β_1 are chosen to be 0.6 and -0.4, respectively, reflecting moderate clinical impact on drinking, as expected in the COMBINE study. Time coefficients α_2 and β_2 are chosen to be -0.3 and 0.05, respectively, to reflect the fact that the probability of abstinence decreases over time and the drinking risk increases over time. Finally, $\rho = -0.5$ allows a moderate negative correlation between the random effects in the two model parts. The specific steps of the data generation are detailed below, first from the heterogeneous ZIP model.

1. Set $\zeta_u = (-0.69; 1.38)$, $\zeta_v = (-0.69; 1.792)$ and $\rho = -0.5$ to compute Σ_i in model (8) and simulate the random effects vectors $(u_i, v_i) \sim N_2(0, \Sigma_i)$ from models (18) and (19).
2. Set $\alpha = (1.3; 0.6, -0.3)'$, $\beta = (1.8, -0.4, 0.05)'$, and generate ϕ_{ij} and λ_{ij} for $j = 1, \dots, 6$ from models (16) and (17).
3. Generate a random variable, $t \sim \text{Unif}(0, 1)$. If $t > \phi_{ij}$ then simulate y_{ij} from $\text{Poisson}(\lambda_{ij})$. Otherwise, set $y_{ij} = 0$.
4. Repeat steps 1 to 4 until all individuals' outcomes are generated.

We generate data from the heterogeneous ZINB model using a similar steps except in Step 3, we simulate y_{ij} from the negative binomial(λ_{ij}, v) with $v = 0.5$. We generate data from the homogeneous ZIP and ZINB models allowing the random effects vector (u_i, v_i) to be simulated from Equation (7) with $\sigma_u^2 = 0.5$, $\sigma_v^2 = 2$, and $\rho = -0.5$.

The goals of the simulation study are to demonstrate the inference of both the homogeneous and heterogeneous ZIP and ZINB models using SAS procedure NLMIXED, and to determine how parameter estimates, standard errors, and coverage probabilities are affected by ignoring random effects heterogeneity (i.e., robustness of the ZIP and ZINB to model misspecification). To this end, we present the bias (the mean of the estimated parameter minus the true value), standard errors (SE, the square root of the average of the estimated

variance) and the coverage probabilities (CP) of 95% confidence intervals. All results are displayed in Tables 1 and 2.

Table 1 reports the results from homogeneous and heterogeneous ZIP (upper table) and ZINB (lower table) models for data simulated under heterogeneous random effects. In general, the heterogeneous ZIP and ZINB models result in negligibly small bias than their homogeneous counterparts, with CPs very close to the nominal value of 0.95. In contrast, fitting the misspecified homogeneous model to the heterogeneous data results in severely biased parameter estimates and CPs far from the nominal value, especially for the parameters in the Poisson and negative binomial parts of the models. Specifically, the treatment effects α_1 and β_1 have the largest bias, although there is also non-negligible bias in the intercepts. The results of this simulation setting suggests that when the treatment effect sizes are small to moderate, ignoring the heterogeneity results in biased estimates and maybe even invalid inference. In general, the results suggest that both heterogeneous ZIP and ZINB models can recover the true values in the presence of heterogeneous, covariate-dependent random effects.

Table 2 reports the results from homogeneous and heterogeneous ZIP and ZINB models for data simulated under homogeneous random effects model (i.e., $\zeta_{u1} = \zeta_{v1} = 0$ in Equations (18) and (19)). Table 2 shows that both the heterogeneous and homogeneous models provide estimates of all parameters with negligible bias, small SE, and with nominal coverage probabilities reasonably close to 95%. Since heterogeneous models provide unbiased and efficient regression parameter estimates as well as 0 estimates of the random effect covariance parameters, ζ_{u1} and ζ_{v1} , it appears overparameterization has negligible effects on inference.

Per the suggestions of an anonymous reviewer, we consider an additional simulation study to examine the influence of ignoring heterogeneity on estimation of interaction terms between treatment and time in the study. The outcome and covariates in this simulation study are similar to those presented in Equations (16) – (19) under ZINB framework, but with an interaction term of time and treatment. We simulate 300 datasets with the sample size of $N=1000$. Results are presented in Web supplement Tables 1 and 2. Results suggest that when there are interaction terms in both parts of the model (zero and negative binomial), the heterogeneous ZINB model results in a better coverage probability for these estimates than the homogeneous ZINB model, especially for the zero part (which makes sense since this part is usually harder to estimate) in the presence of covariate-dependent random effects. Both heterogeneous and homogeneous ZINB models provide comparable results under homogeneous random effects.

We conclude that the proposed heterogeneous models provide results comparable with the homogeneous models under homogeneous data generation. However, under heterogeneous data generation, heterogeneous models result in unbiased and efficient estimation while the homogeneous models give severely biased estimates with lower CPs. In general, the parameters in the Poisson/NB model parts are more sensitive to random effects covariance matrix assumptions.

5 Data Analysis

In this section, we apply the proposed models to the COMBINE study described in Section 2 and determine the best fit. The goal of the analysis is to quantify correctly how treatment and covariates affect abstinence from alcohol and risk of drinking throughout the 16 weeks treatment period. The models we fit are as follows,

$$\begin{aligned}\text{logit}(\phi_{ij}) &= \alpha_0 + \alpha_1 I(\text{NAL}_i) + \alpha_2 I(\text{Male}_i) + \alpha_3 \text{Priordrink}_i + \alpha_4 \text{Week}_j + u_i \\ \log(\lambda_{ij}) &= \beta_0 + \beta_1 I(\text{NAL}_i) + \beta_2 I(\text{Male}_i) + \beta_3 \text{Priordrink}_i + \beta_4 \text{Week}_j + v_i.\end{aligned}\quad (20)$$

The covariates included in the regression on the covariance matrix are

$$\begin{aligned}\log(\sigma_{u_i}^2) &= \zeta_{u0} + \zeta_{u1} I(\text{Male}_i) \\ \log(\sigma_{v_i}^2) &= \zeta_{v0} + \zeta_{v1} I(\text{Male}_i),\end{aligned}\quad (21)$$

where $I(\text{Male}_i) = 1$ is an indicator denoting the male group (versus female). The covariates include treatment variable (NAL) indicating receiving naltrexone or not, gender, prior drink (average number of drinks per day in the prior month), and week (1 – 16). We also consider the possibility that NAL and prior drinking might influence the random effect variances; however that exploratory analysis suggests that the corresponding coefficients are not significant. Hence, we only include gender for the variance. Moreover, the design of the COMBINE study was focused on main effects at a single follow up time point rather than interaction between treatment and time; thus the study was not powered to detect this interaction^{27,44}.

We fit both homogeneous and heterogeneous ZIP and ZINB models based on the methodology developed in Section 3. Table 3 presents various model fit criteria for models fit with increasing levels of complexity with respect to random effects covariance structure. The column entitled “Formula” provides the model details. The AIC, BIC and deviance are reported in Table 3 for model comparison and selection and smaller values of these criteria indicate a better fit.

We also compute the likelihood ratio test to compare the fit of the models in Table 3. To compare the heterogeneous ZIP and ZINB models with their homogenous counterparts, we obtain LRT statistics of 161 and 220 for ZIP and ZINB for the hypothesis test given in (14) with $H_0: \zeta_{u1} = \zeta_{v1} = 0$. Both are larger than the critical value $\chi_2^2(0.95) = 5.99$; the corresponding small p-values provide strong evidence in favor of the heterogeneous random effect models.

To determine whether overdispersion exists, we obtain an LRT statistics 501 for the test of $H_0: k = 0$. Here, the parameter k is on the boundary of the parameter space and the asymptotic distribution of the likelihood ratio statistics follows $0.5\chi_0^2:0.5\chi_1^2$ mixed distribution. However, the size of the test statistic provides a strong evidence against the null hypotheses indicating the heterogeneous ZINB provides a better fit to the data. The

heterogeneous ZINB model also has the smallest AIC and BIC among all the other models in Table 3. In general, all criteria indicate that the heterogeneous ZINB model provides the best fit to COMBINE data among the candidates considered. This fact is consistent with the finding that the effect of gender on the random variance components in the drinking abstinence part is highly significant, indicating that females have more variability in drinking behavior than males. It is clinically plausible that males have higher expected number of drinks and more nonzero drinking, but less variability in drinking behavior in general.

The detailed results of the heterogeneous ZINB model are summarized in Table 4. The main effects in this final model indicate that naltrexone increases the odds of abstinence ($OR = 1.898$; $[1.044; 3.449]$), and reduces the expected number of alcoholic drinks ($RR = 0.847$, $[0.734, 0.979]$). Further, the expected number of alcoholic drinks slightly increases with each week further from baseline ($RR = 1.014$; $[1.012; 1.017]$), and also in those who report more prior drinking. For inferential comparison purposes, we also include the homogeneous random effects ZINB model in Table 4.

6 Discussion

Our simulation study shows that when excess random effects heterogeneity exists in longitudinal count data, modeling ZIP and ZINB random effects as covariate-dependent provides unbiased and accurate estimates of parameters while typical homogeneous random effects assumptions result in biased estimates, and can lead to incorrect inference for covariate effects. Further, when random effects heterogeneity does not exist, overparameterized the heterogeneous random effects models still provide correct results and inference. Importantly, the proposed heterogeneous models can be conveniently fitted using the SAS procedure NLMIXED and therefore are easily accessible to, and modifiable by applied researchers.

Alcohol researchers are often interested in understanding how interventions affect the abstinence from alcohol and the amount of drinking in those at risk of relapsing over the course of treatment. The proposed models help to examine and address the function of interventions across these two drinking domains. Results from the present study both complement and augment previous clinical findings. Naltrexone significantly decreases the risk of drinking, which is consistent with the original COMBINE report (where naltrexone reduced the number of drinks per day). The original report did not find an effect of naltrexone on abstinence; however, this was detected in the current paper (and in other reports that consider the longitudinal vector of drinking) because of the way abstinence is operationalized in the zero-inflated model⁴⁵.

The data analysis demonstrates a large degree of heterogeneity in drinking by gender. By fitting a series of increasingly complex models using NLMIXED, the proposed approach is able to account for this heterogeneity, in addition to (1) providing correct statistical inference for fixed covariate effects in both parts of the zero-inflated models; (2) identifying and quantifying covariates associated with random effects heterogeneity, which is of direct clinical significance; and (3) providing valuable information about variability in treatment

effects which can be used to inform future studies. In summary, the proposed modeling approach approach has merit in distinguishing the indirect effects of relevant covariates through the random effects and direct effects of covariates on the response counts.

In this paper, we use the bivariate normal assumption for the random effects distribution, which is routinely used due to mathematical convenience and robustness to violations. In similar settings, McCulloch and Neuhaus⁴⁶ show that when shapes of random effects is misspecified, only intercepts are estimated with modest bias; they also demonstrate that the estimates of the random effects variance are relatively robust to misspecification⁴⁷. However, further investigation, such as use of flexible parametric distributions such as the t distribution, mixtures of normals, or semiparametric approaches could be considered in our model framework^{48–50}.

In this paper, we use the variance of each random effects to parameterize the heterogeneous random effects variance matrix directly. This would pose no problems in positive definiteness of the covariance matrix and would provide easily interpretable parameters¹⁴. Further work could also include linear or quadratic trends in the random effects and allow ρ to be subject-specific. In this case, generalized autoregressive parameters and innovative variance parametrization methods would be required to model the random covariance matrix. In the longitudinal and joint modeling framework, such methods have shown the advantage of computational attractiveness with a logical interpretation of parameters^{13,14,26}.

Finally, one could extend the ZIP mixed regression model to zero-inflated generalized Poisson (ZIGP) “mixed” regression model, where the baseline discrete distribution is generalized Poisson (GP) distribution⁵¹. A ZIGP model with correlated, heterogeneous random effects would be more computationally challenging but would also enhance flexibility and applicability since this distribution handles any type of under or over dispersion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The QQ plots for random effects in different model parts and different gender groups ((a): random effects in zero-part within men; (b): random effects in zero-part within women; (c): random effects in Poisson-part within men; (d): random effect in Poisson-part within women).

Table 1

Simulation results from fitting the heterogeneous and homogeneous ZIP and ZINB models to the heterogeneous datasets.

	Parameter	True	Heterogeneous			Homogeneous		
			Bias	SE	CP	Bias	SE	CP
ZIP model	Zero part							
	α_0	1.300	0.002	0.078	0.942	-0.009	0.086	0.956
	α_1	0.600	0.003	0.097	0.956	0.043	0.087	0.916
	α_2	-0.300	0.000	0.017	0.940	0.000	0.017	0.940
	Poisson part							
	β_0	1.800	0.000	0.035	0.964	-0.085	0.054	0.780
	β_1	-0.400	0.000	0.106	0.944	0.373	0.081	0.012
	β_2	0.050	0.000	0.003	0.972	0.000	0.003	0.972
	Random effects in Zero part							
	$\zeta_{\omega 0}$	-0.690	-0.009	0.179	0.952			
	$\zeta_{\omega 1}$	1.380	0.002	0.117	0.950			
	Random effects in Poisson part							
$\zeta_{\omega 0}$	-0.690	-0.005	0.074	0.932				
$\zeta_{\omega 1}$	1.792	-0.006	0.051	0.938				
Random effects correlation								
ρ	-0.500	0.001	0.035	0.952				
ZINB model	Zero part							
	α_0	1.300	0.001	0.082	0.950	-0.036	0.097	0.948
	α_1	0.600	-0.002	0.102	0.956	0.078	0.096	0.882
	α_2	-0.300	0.000	0.018	0.952	-0.001	0.020	0.954
	Negative Binomial part							
	β_0	1.800	-0.001	0.061	0.952	-0.117	0.080	0.744
	β_1	-0.400	-0.007	0.120	0.952	0.423	0.099	0.018
	β_2	0.050	0.000	0.011	0.952	0.000	0.012	0.952
	Random effects in zero part							

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Parameter	Heterogeneous				Homogeneous			
	True	Bias	SE	CP	Bias	SE	CP	CP
ζ_{u0}	-0.690	-0.022	0.193	0.966				
ζ_{u1}	1.380	0.009	0.150	0.958				
Random effects in negative Binomial part								
ζ_{v0}	-0.690	-0.006	0.107	0.970				
ζ_{v1}	1.792	0.003	0.061	0.958				
Random effects correlation								
ρ	-0.500	-0.003	0.024	0.948				
Overdispersion								
ν	0.500	-0.002	0.061	0.920				

Table 2

Simulation results from fitting the heterogeneous and homogeneous ZIP and ZINB models to the homogeneous datasets.

	Parameter	True	Heterogeneous			Homogeneous		
			Bias	SE	CP	Bias	SE	CP
ZIP model	Zero part							
	α_0	1.300	-0.004	0.079	0.960	-0.003	0.082	0.954
	α_1	0.600	-0.007	0.075	0.944	0.002	0.074	0.954
	α_2	-0.300	0.001	0.017	0.974	0.001	0.018	0.970
	Poisson part							
	β_0	1.800	-0.006	0.066	0.940	-0.005	0.068	0.928
	β_1	-0.400	-0.008	0.096	0.938	0.003	0.096	0.956
	β_2	0.050	0.000	0.003	0.958	0.000	0.003	0.954
	Random effects in Zero part							
	ζ_{i0}	-0.690	-0.021	0.193	0.969			
	ζ_{i1}	0.000	-0.041	0.107	0.969			
	Random effects in Poisson part							
ζ_{i0}	0.690	-0.008	0.071	0.950				
ζ_{i1}	0.000	0.017	0.063	0.962				
Random effects correlation								
ρ	-0.500	-0.010	0.064	0.944				
ZINB model	Zero part							
	α_0	1.300	-0.003	0.080	0.956	-0.003	0.085	0.960
	α_1	0.600	-0.003	0.074	0.962	-0.005	0.076	0.962
	α_2	-0.300	0.001	0.017	0.954	0.001	0.019	0.954
	Negative Binomial part							
	β_0	1.800	0.002	0.062	0.950	0.001	0.065	0.954
	β_1	-0.400	-0.001	0.064	0.950	-0.001	0.063	0.946
	β_2	0.050	0.000	0.011	0.930	-0.000	0.012	0.930
	Random effects in Zero part							

Parameter	Heterogeneous				Homogeneous			
	True	Bias	SE	CP	Bias	SE	CP	CP
ζ_{u0}	-0.690	-0.003	0.107	0.972				
ζ_{u1}	0.000	-0.008	0.080	0.948				
Random effects in negative Binomial part								
ζ_{v0}	0.690	-0.016	0.195	0.960				
ζ_{v1}	0.000	0.008	0.169	0.960				
Random effects correlation								
ρ	-0.500	-0.002	0.028	0.938				
Overdispersion								
ν	0.500	-0.001	0.062	0.956				

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Table 3

Model fit comparison: Akaike information criteria (AIC), Bayesian information criteria (BIC), deviance (Dev, -2Log-Likelihood).

		ZIP Model			ZINB Model		
	Formula	AIC	BIC	Dev	AIC	BIC	Dev
Homogeneous	$(20) + (7)$	53949	54017	53923	53509	53582	53481
Heterogeneous	$(20) + (21) + (8)$	53792	53870	53762	53293	53377	53261

Table 4

Parameter estimates resulting from both the ZINB heterogeneous and homogeneous models applied to the COMBINE study with weeks 1–16. NAL=naltrexone, Prior drink=average number of drinks per day for the month prior to the 30-day abstinence period.

Variables	Heterogeneous				Homogeneous			
	MLE	SE	P-value	95% CI	MLE	SE	P-value	95% CI
Probability of drinking abstinence								
Intercept	-3.069	0.465	<.001	[-3.982, -2.156]	-2.418	0.336	<.001	[-3.078, -1.759]
NAL	0.641	0.305	0.036	[0.043, 1.238]	0.634	0.260	0.015	[0.121, 1.141]
Male	2.139	0.451	<.001	[1.255, 3.023]	1.673	0.302	<.001	[1.080, 2.266]
Prior drink#	0.054	0.025	0.034	[0.004, 0.103]	0.052	0.022	0.018	[0.009, 0.095]
Weeks	-0.007	0.008	0.383	[-0.024, 0.009]	-0.005	0.008	0.517	[-0.021, 0.011]
Expected number of drinks per week								
Intercept	-0.056	0.085	0.513	[-0.223, 0.111]	-0.174	0.088	0.049	[-0.348, -0.001]
NAL	-0.165	0.074	0.025	[-0.309, -0.021]	-0.201	0.074	0.007	[-0.346, -0.0545]
Male	0.157	0.086	0.069	[-0.013, 0.326]	0.226	0.081	0.006	[0.0665, 0.385]
Prior drink#	0.060	0.007	<.001	[0.047, 0.073]	0.058	0.007	<.001	[0.045, 0.071]
Weeks	0.014	0.002	<.001	[0.011, 0.017]	0.014	0.002	<.001	[0.012, 0.017]
Overdispersion								
ν	0.063	0.004	<.001	[0.055, 0.071]	0.062	0.001	<.001	[0.054, 0.069]
Random effects for probability of drinking abstinence								
Intercept	3.592	0.165	<.001	[3.268, 3.917]				
Male	-0.617	0.190	0.001	[-0.991, -0.244]				
Random effects for expected number of drinks per week								
Intercept	-0.011	0.110	0.921	[-0.226, 0.204]				
Male	0.156	0.135	0.245	[-0.107, 0.420]				
ρ	-0.170	0.057	0.003	[-0.282, -0.058]				