Regression Analysis of Dependent Binary Data for Estimating Disease Etiology from Case-Control Studies
(“Small-Area Estimation” of Disease Etiology)

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R package “baker”: `https://github.com/zhenkewu/baker`

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- **Statistical problem**: estimate cause-specific case fractions, or **"population etiologic fractions" (PEFs)**; Think "Pie chart"
- **Motivation for this talk**: PEFs may vary by season, a child's age, HIV status, disease severity

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- Continuous covariates: the first p_1 and q_1 elements of $\boldsymbol{X}_i$ and $\boldsymbol{W}_i$, respectively.

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Model :

- $J = 7$: noisy presence/absence of 2 bacteria and 5 viruses in the nose
- Causes: seven single-pathogen causes plus an "Not Specified" (NoS) cause; So $L = J + 1$
- $\boldsymbol{X}_i$: enrollment date, age ($<$ or $>$ 1 year), disease severity for cases (severe or very severe), HIV status ($+$/-)
- $\boldsymbol{W}_i$: $\boldsymbol{X}_i$ minus "disease severity".

PERCH Data: Sparsely-Populated Strata☹

Table: The observed count (frequency) of cases and controls by age, disease severity and HIV status (1: yes; 0: no). The marginal fractions among cases and controls for each covariate are shown at the bottom. Regression results will be shown for the first two strata.

age ≥ 1	very severe (VS)	HIV positive	# cases (%)	# controls (%)
	(case-only)		total: 524 (100)	total: 964 (100)
0	0	0	208 (39.7)	545 (56.5)
1	0	0	72 (13.7)	278 (28.8)
0	1	0	116 (22.1)	0
1	1	0	33 (6.3)	0
0	0	1	37 (7.1)	85 (8.8)
1	0	1	24 (4.5)	51 (5.3)
0	1	1	25 (4.8)	0
1	1	1	3 (0.6)	0
case: 25.2%	34.5%	17.0%		
control: 34.3%	-	14.1%		

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4. Fitted in a Bayesian framework; can also estimate the posterior probability of the cause of disease for an **individual** case given her measurements.
5. Related to restricted latent class models (RLCM, Xu, 2017, AOS); Major differences: multiple sets of responses probabilities ("nested"); use control data ("partially-latent")

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Gap 1a Unstable PEF estimates due to sparsely-populated strata.

Gap 1b Informative TPR priors are often elicited for a case population and rarely for each stratum; Reusing independent prior distributions of the TPRs across all the strata will lead to overly-optimistic posterior uncertainty in $\boldsymbol{\pi}^*$, hampering policy decisions.

This talk☺

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(a) incorporates controls to estimate the PEFs ($\boldsymbol{\pi}$),

(b) specifies parsimonious functional dependence of $\boldsymbol{\pi}$ upon covariates such as additivity, and

(c) correctly assesses the posterior uncertainty of the PEF functions and the overall PEFs $\boldsymbol{\pi}^*$ by applying the TPR priors just once.

Okay, what is npLCM?

Quick Technical Review: Nested Partially Latent Class Models (npLCM)

For simplicity, we assume "single-pathogen causes"

npLCM Framework (no Covariates)

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The likelihood:

$$L = L_1 \cdot L_0 = \left\{ \prod_{i: Y_i = 1} \sum_{\ell=1}^{L} \pi_\ell \cdot \boldsymbol{P}_{1\ell}(\boldsymbol{M}_i; \boldsymbol{\Theta}, \boldsymbol{\Psi}, \boldsymbol{\eta}) \right\} \times \prod_{i': Y_{i'} = 0} \boldsymbol{P}_0(\boldsymbol{M}_{i'}; \boldsymbol{\Psi}, \boldsymbol{\nu})$$

Special Case: pLCM (Wu et al., 2016)

Setting $\eta_1 = 1$ and $\nu_1 = 1$

Control model for multivariate binary data $\{\boldsymbol{M}_i : where\ Y_i = 0\}$:

1. $\boldsymbol{P}_0(\boldsymbol{m}) = \prod_{j=1}^{J} \{\psi_j\}^{m_j} \{1 - \psi_j\}^{1-m_j} = \Pi(\boldsymbol{m}; \boldsymbol{\psi})$

   1a. $\Pi(\boldsymbol{m}; \boldsymbol{s}) = \prod_{j=1}^{J} \{s_j\}^{m_{ij}} \{1 - s_j\}^{1-m_{ij}}$ is the probability mass function for a product Bernoulli distribution given the success probabilities $\boldsymbol{s} = (s_1, \ldots, s_J)^\top$, $0 \leq s_j \leq 1$

   1b. Parameters $\boldsymbol{\psi} = (\psi_1, \ldots, \psi_J)^\top$ represent the positive rates absent disease, referred to as “false positive rates” (FPRs).

Local Independence: $M_{ij} \perp M_{ij'} \mid I = 0$

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2a-2b. Non-interference: disease-causing pathogen(s) are more frequently detected among cases than controls ($\theta_\ell > \psi_\ell$) and the non-causative pathogens are observed with the same rates among cases as in controls

"nested" pLCM

Relax the LI and Non-interference Assumption

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- Log-linear parametrization
- Generalized linear mixed-effect models (GLMM)
- Simplex factor model; similar to mixed-membership model (Cf. Bhattacharya and Dunson, 2012, *JASA*)

“nested” pLCM

Relax the LI and Non-interference Assumption

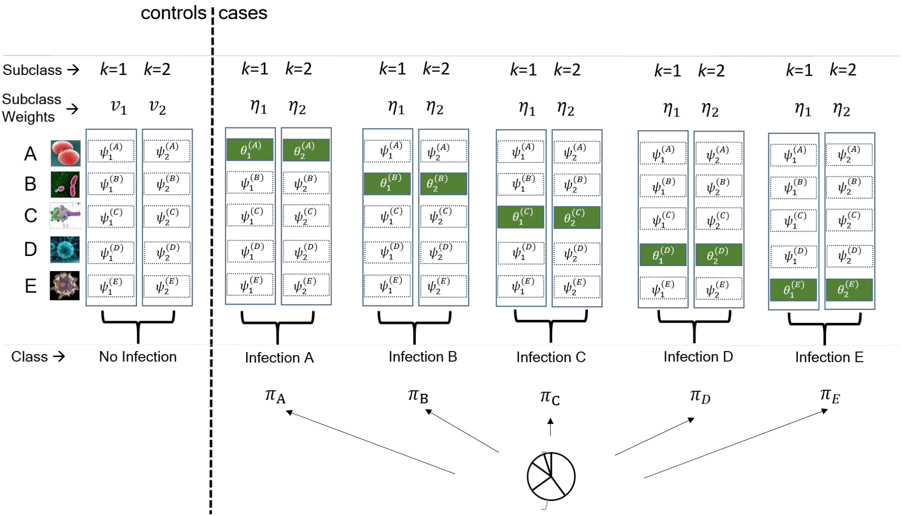
- Direct evidence: control measurements $(M_{i1},\ldots,M_{iJ})'$
    - test cross-reactions (prevented in PERCH assays)
    - lab technicians effect
    - heterogeneity in subjects’ immunity level
- Deviations from independence impacts inference (Cf. Pepe and Janes, 2007, *Biostatistics*; Albert et al., 2001, *Biometrics*)
- Modeling Deviation from LI Modeling a cross-classified probability contingency table

$$\mathbb{P}[M_{i1}=m_1,\ldots,M_{iJ}=m_J],\ \forall \boldsymbol{m}=(m_1,\ldots,m_J)'$$

- Log-linear parametrization
- Generalized linear mixed-effect models (GLMM)
- Simplex factor model; similar to mixed-membership model (Cf. Bhattacharya and Dunson, 2012, *JASA*)
- PARAFAC decomposition (Cf. Dunson and Xing, 2009, *JASA*)

Nested Partially-Latent Class Models (npLCM; Wu and Zeger, 2016)

Example: 5 Pathogens, 2 Subclasses; BrS Data Only



controls | cases

Subclass → k=1 k=2 (repeated for each class)

Subclass Weights → ν_1 ν_2 (controls); η_1 η_2 (cases)

A, B, C, D, E

No Infection: $\psi_1^{(A)}$ $\psi_2^{(A)}$, $\psi_1^{(B)}$ $\psi_2^{(B)}$, $\psi_1^{(C)}$ $\psi_2^{(C)}$, $\psi_1^{(D)}$ $\psi_2^{(D)}$, $\psi_1^{(E)}$ $\psi_2^{(E)}$

Infection A: $\theta_1^{(A)}$ $\theta_2^{(A)}$, $\psi_1^{(B)}$ $\psi_2^{(B)}$, $\psi_1^{(C)}$ $\psi_2^{(C)}$, $\psi_1^{(D)}$ $\psi_2^{(D)}$, $\psi_1^{(E)}$ $\psi_2^{(E)}$

Infection B: $\psi_1^{(A)}$ $\psi_2^{(A)}$, $\theta_1^{(B)}$ $\theta_2^{(B)}$, $\psi_1^{(C)}$ $\psi_2^{(C)}$, $\psi_1^{(D)}$ $\psi_2^{(D)}$, $\psi_1^{(E)}$ $\psi_2^{(E)}$

Infection C: $\psi_1^{(A)}$ $\psi_2^{(A)}$, $\psi_1^{(B)}$ $\psi_2^{(B)}$, $\theta_1^{(C)}$ $\theta_2^{(C)}$, $\psi_1^{(D)}$ $\psi_2^{(D)}$, $\psi_1^{(E)}$ $\psi_2^{(E)}$

Infection D: $\psi_1^{(A)}$ $\psi_2^{(A)}$, $\psi_1^{(B)}$ $\psi_2^{(B)}$, $\psi_1^{(C)}$ $\psi_2^{(C)}$, $\theta_1^{(D)}$ $\theta_2^{(D)}$, $\psi_1^{(E)}$ $\psi_2^{(E)}$

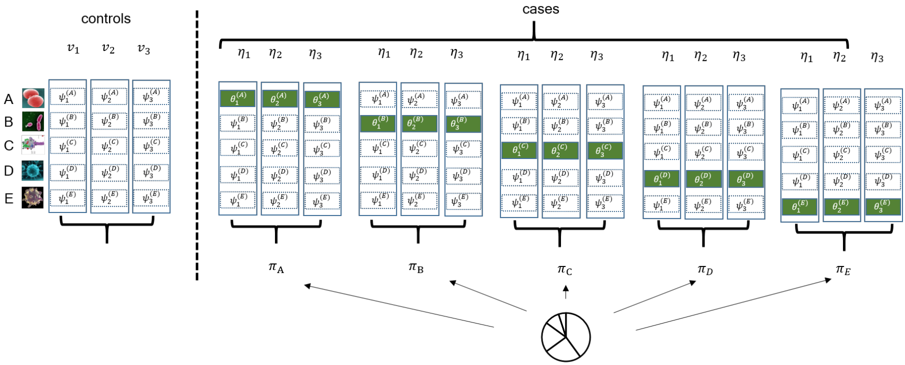
Infection E: $\psi_1^{(A)}$ $\psi_2^{(A)}$, $\psi_1^{(B)}$ $\psi_2^{(B)}$, $\psi_1^{(C)}$ $\psi_2^{(C)}$, $\psi_1^{(D)}$ $\psi_2^{(D)}$, $\theta_1^{(E)}$ $\theta_2^{(E)}$

Class → No Infection, Infection A, Infection B, Infection C, Infection D, Infection E

π_A π_B π_C π_D π_E

Nested Partially-Latent Class Models (npLCM; Wu and Zeger, 2016)

Example: 5 Pathogens, 3 Subclasses; BrS Data Only


controls
cases
ν_1 ν_2 ν_3
A
B
C
D
E
$\psi_1^{(A)}$ $\psi_2^{(A)}$ $\psi_3^{(A)}$
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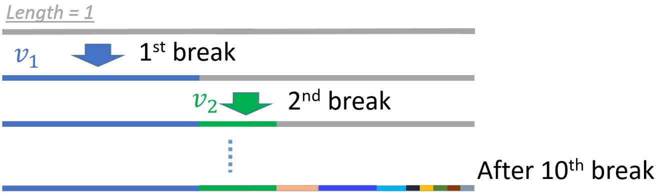
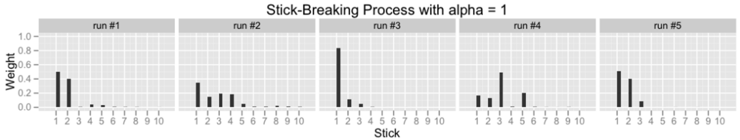
$\theta_1^{(E)}$ $\theta_2^{(E)}$ $\theta_3^{(E)}$
π_A
π_B
π_C
π_D
π_E

Encourage Few Subclasses: Stick-Breaking Prior

$V_j \sim \text{Beta}(1, \alpha)$; Example: $K = 10$, $\alpha = 1$





- On average, the first several segments receive most weights

npLCM: Likelihood and Prior

BrS Data Only

- Likelihood

$$
\begin{aligned}
\boldsymbol{P}_0(\boldsymbol{M}_i=\boldsymbol{m}) &= \sum_{k=1}^{K}\nu_k\prod_{j=1}^{J}\left\{\psi_k^{(j)}\right\}^{m_j}\left\{1-\psi_k^{(j)}\right\}^{1-m_j},\\
\boldsymbol{P}_1(\boldsymbol{M}_i=\boldsymbol{m}) &= \sum_{j=1}^{J}\pi_j\sum_{k=1}^{K}\left[\eta_k\left\{\theta_k^{(j)}\right\}^{m_j}\left\{1-\theta_k^{(j)}\right\}^{1-m_j}\prod_{\ell\neq j}\left\{\psi_k^{(j)}\right\}^{m_\ell}\left\{1-\psi_k^{(j)}\right\}^{1-m_\ell}\right],
\end{aligned}
$$

- Prior:

$$
\begin{aligned}
\boldsymbol{\pi} &\sim \text{Dirichlet}(.5,\ldots,.5),\\
\psi_k^{(j)} &\sim \text{Beta}(1,1),\ \ \theta_k\sim\text{Beta}(c_{1kj},c_{2kj}), j=1,...,J; k=1,...,\infty,\\
Z_{i'}\mid I_{i'}^{L}=j &\sim \sum_{k=1}^{\infty}U_k\prod_{\ell<k}\left[1-U_\ell\right]\delta_k,\qquad U_k\sim\text{Beta}(1,\alpha_0),\ \text{for all cases},\\
Z_i &\sim \sum_{k=1}^{\infty}V_k\prod_{\ell<k}[1-V_\ell]\delta_k,\qquad V_k\sim\text{Beta}(1,\alpha_0),\ \text{for all controls},\\
\alpha_0 &\sim \text{Gamma}(0.25,0.25),
\end{aligned}
$$

Now, how to incorporate covariates, to which quantities?

Regression Extension for P_0 and P_1: letting π_ℓ, ν_k, η_k depend on covariates

Roadmap

Let three sets of parameters in an npLCM (pg.17) depend on the observed covariates

1x. Etiology regression function among cases, $\{\pi_\ell(\boldsymbol{x}), \ell \neq 0\}$, which is of primary scientific interest

2x. Conditional probability of measurements $\boldsymbol{m}$ given covariates $\boldsymbol{w}$ in controls: $\boldsymbol{P}_0(\boldsymbol{m}; \boldsymbol{w}) = [\boldsymbol{M} = \boldsymbol{m} \mid \boldsymbol{W} = \boldsymbol{w}, I = 0]$,

3x. 2x above, but in the case class ℓ: $\boldsymbol{P}_{1\ell}(\boldsymbol{m}; \boldsymbol{w}) = [\boldsymbol{M} = \boldsymbol{m} \mid \boldsymbol{W} = \boldsymbol{w}, I = \ell]$, $\ell = 1, \ldots, L$

note Keep the specifications for the TPRs and FPRs ($\boldsymbol{\Theta}$, $\boldsymbol{\Psi}$) as in the original npLCM.

Etiology Regression $\boldsymbol{\pi}_\ell(\boldsymbol{X})$

$\pi_\ell(\boldsymbol{X})$ is the primary target of inference.

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3. Over-parameterized multinomial logistic regression: $\pi_{i\ell} = \pi_\ell(\boldsymbol{X}_i) = \exp\{\phi_\ell(\boldsymbol{X}_i)\}/\sum_{\ell'=1}^{L}\exp\{\phi_{\ell'}(\boldsymbol{X}_i)\}$, $\ell = 1, ..., L$, where $\phi_\ell(\boldsymbol{X}_i) - \phi_L(\boldsymbol{X}_i)$ is the log odds of case i in disease class ℓ relative to L: $\log \pi_{i\ell}/\pi_{iL}$.

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5a. Use B-spline basis expansion to approximate $f_{\ell j}^\pi(\cdot)$ and use P-spline for estimating smooth functions.

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5b. $\widetilde{\boldsymbol{x}}$ is the subvector of the predictors $\boldsymbol{x}$; $\boldsymbol{\Gamma}_\ell^\pi = (\boldsymbol{\beta}_{\ell j}^\pi, \boldsymbol{\gamma}_\ell^\pi)$.

$\boldsymbol{P}_0$: Multivariate binary regression for controls

Desirable properties

Model Specification:

- Model space large enough for complex conditional dependence of $\boldsymbol{M}$ given covariates $\boldsymbol{W}$
- Upward compatibility, or reproducibility (invariant parameter interpretation with increasing dimensions or complex patterns of missing responses)

Estimation:

- Consistency and Efficiency
- Adaptivity: regularization to adapt to the difficulty of the problem, e.g., model residual dependence $[\boldsymbol{M} \mid \boldsymbol{W}, I = 0]$ only if necessary; model the effect of covariates only if necessary

Let $\boldsymbol{P}_0$ depend on $\boldsymbol{W}_i$

Regression model for controls

- The pmf for controls' measurements: $Pr(\boldsymbol{M}_i = \boldsymbol{m} \mid \boldsymbol{W}_i, I_i = 0) = \sum_{k=1}^{K} \nu_k(\boldsymbol{W}_i)\Pi(\boldsymbol{m}; \Psi_k)$, $\Psi_k = (\psi_k^{(1)}, \ldots, \psi_k^{(J)})'$

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  - The vector $(\nu_1(\boldsymbol{W}_i), \ldots, \nu_K(\boldsymbol{W}_i))$ lies in a $(K-1)$-simplex

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  - $\Pi(\boldsymbol{m}; s) = \prod_{j=1}^{J}\{s_j\}^{m_{ij}}(1-s_j)^{1-m_{ij}}$

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- An equivalent generative process:

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- An equivalent generative process:

$$
\begin{aligned}
\text{sample subclass indicator}: &\quad Z_i \mid \boldsymbol{W}_i \sim \text{Categorical}_K(\boldsymbol{\nu}(\boldsymbol{W}_i))\\
\text{generate measurements}: &\quad M_{ij} \mid Z_i = k \sim \text{Bernoulli}(\psi_k^{(j)}),\\
&\quad \text{independently for } j = 1, ..., J.
\end{aligned}
$$

Let $\boldsymbol{P}_0$ depend on $\boldsymbol{W}_i$

Regression model for controls Stick-breaking parametrization of weight functions $\nu_k(\boldsymbol{W}_i) = P(Z_i = k \mid \boldsymbol{W}_i)$ by

$$\underbrace{h_k(\boldsymbol{W}_i; \boldsymbol{\Gamma}_k^{\nu})}_{stick\ \ k} = \begin{cases} g(\alpha_{ik}^{\nu}) \prod_{s<k} \left\{1 - g(\alpha_{is}^{\nu})\right\}, & \text{if } k < K, \\ \prod_{s<k} \left\{1 - g(\alpha_{is}^{\nu})\right\}, & \text{if } k = K, \end{cases}$$

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We specify α_{ik}^ν via additive models at g^{-1} scale $(g(\cdot) = 1/(1 + \exp\{-(\cdot)\}))$:

$$\alpha_{ik}^\nu = \mu_{k0} + \sum_{j=1}^{q_1} f_{kj}(\boldsymbol{W}_{ij}; \beta_{kj}^\nu) + \widetilde{\boldsymbol{W}}_i^\top \gamma_k^\nu,\ \ k = 1, \ldots, K-1.$$

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Expand the smooth functions by B-spline bases with coefficients $\boldsymbol{\beta}_{kj}^{\nu}$; $\widetilde{\boldsymbol{w}}$ is a subvector of covariates $\boldsymbol{w}$

Adaptivity Considerations☺

Proposed Model

- Prevent overfitting when the regression is easy, and improve interpretability
- We *a priori* place substantial probabilities on models with the following two features:
  a) Few subclasses with effective weights (in the sense that $\nu_k(\cdot)$ is bounded away from 0 and 1): a novel additive half-Cauchy prior for μ_{k0}.
  b) Smooth weight regression curves $\nu_k(\cdot)$: by Bayesian Penalized-Splines (P-Splines) combined with mixture priors on spline coefficients to sensitively distinguish constant $\alpha_k^\nu(\cdot)$ from flexible smooth curves

On Consideration a) Selective Stopping, or “Uniform Shrinkage over Simplex” for $\nu_k(\boldsymbol{W})$

Proposed Model

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- We let $\mu_{k0} = \sum_{j=1}^{k} u_{kj}\mu^{*}_{k0}$ where $u_{kj}, 1 \leq j \leq k$ are pre-specified trangular array of positive values. a large k has a large intercept: increasing burden only when justified

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- We specify the prior distributions for μ^*_{k0} to be heavy-tailed:

$$\mu^*_{k0} \sim Cauchy^{+}(0, s_k),\ k = 1, \ldots, K,$$

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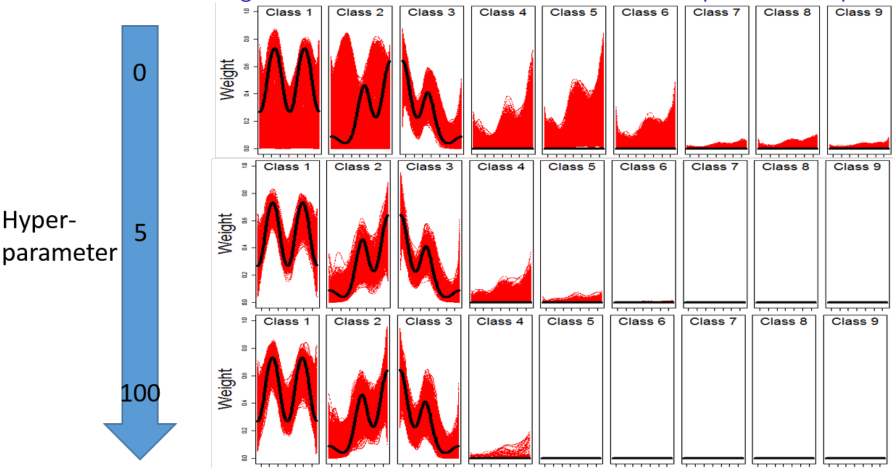
- A large s_k produce large μ^*_{k0} and help stop stick-breaking at class k, while small values let the stick-breaking continue to Step $k + 1$.
- Encourages using a small number of effective classes ($< K$) to approximate the observed 2^J probability contingency table in finite samples

Inference of $\nu_k(x)$ at three hyperparameter values s_k

Simulation: with a single continuous covariate; "—": truth, "—": posterior samples



Hyper-
parameter

X-axis: covariate values

Y-axis: weight; 0 to 1.

Let P_1 depend on X and W

Subclass Weight Regression: For Cases

Let $\boldsymbol{P}_1$ depend on $\boldsymbol{X}$ and $\boldsymbol{W}$

Subclass Weight Regression: For Cases

The pmf for cases' measurements:

$$Pr(\boldsymbol{M}_i = \boldsymbol{m}) = \sum_{\ell=1}^{L} \pi_{i\ell} \sum_{k=1}^{K} \eta_{ik} \Pi(\boldsymbol{M}_i; \boldsymbol{p}_{k\ell})$$

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- $\boldsymbol{p}_{k\ell} = \{p_{k\ell}^{(j)}, j = 1, \ldots, J\}$ are positive rates for J measurements in subclass k of disease class ℓ:
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- Equals the TPR $\theta_k^{(j)}$ for a causative pathogen and the FPR $\psi_k^{(j)}$ otherwise

Let P_1 depend on $\boldsymbol{X}$ and $\boldsymbol{W}$

Subclass Weight Regression: For Cases

The pmf for cases' measurements:

$Pr(\boldsymbol{M}_i = \boldsymbol{m}) = \sum_{\ell=1}^{L} \pi_{i\ell} \sum_{k=1}^{K} \eta_{ik} \Pi(\boldsymbol{M}_i; \boldsymbol{p}_{k\ell})$

- $\boldsymbol{p}_{k\ell} = \{p_{k\ell}^{(j)}, j = 1, \ldots, J\}$ are positive rates for J measurements in subclass k of disease class ℓ:
  $p_{k\ell}^{(j)} = \left\{\theta_k^{(j)}\right\}^{\mathbb{I}\{j=\ell\}} \cdot \left\{\psi_k^{(j)}\right\}^{1-\mathbb{I}\{j=\ell\}}$
- Equals the TPR $\theta_k^{(j)}$ for a causative pathogen and the FPR $\psi_k^{(j)}$ otherwise
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Let $\boldsymbol{P}_1$ depend on $\boldsymbol{X}$ and $\boldsymbol{W}$

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- we use μ_{k0} from the controls (why?)

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$$L_1^{\text{reg}} = \prod_{i:Y_i=1} \left\{ \sum_{\ell=1}^{L} \left[\underbrace{\pi_\ell(\boldsymbol{X}_i; \boldsymbol{\Gamma}_\ell^\pi)}_{PEF\ \ell} \sum_{k=1}^{K} \{\eta_{ik} \cdot \Pi(\boldsymbol{M}_i; \boldsymbol{p}_{k\ell})\} \right] \right\} \quad (2)$$

- $\nu_{ik} = h_k(\boldsymbol{W}_i; \boldsymbol{\Gamma}_k^\nu)$: The S$\underline{????}$-B$\underline{????}$ parameterization
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The joint likelihood for the regression model can be written as:
$L^{\text{reg}} = L_1^{\text{reg}} \times L_0^{\text{reg}}$.

Prior Specifications

Unknown parameters:

- etiology regression coefficients ($\{\mathbf{\Gamma}_\ell^\pi\}$),
- subclass mixing weight parameters for cases ($\{\mathbf{\Gamma}_k^\eta\}$) and controls ($\{\mathbf{\Gamma}_k^\nu\}$),
- true and false positive rates ($\mathbf{\Theta} = \{\theta_k^{(j)}\}, \mathbf{\Psi} = \{\psi_k^{(j)}\}$).

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To avoid potential overfitting, we *a priori* introduce:

- (a) few non-trivial subclasses via novel additive half-Cauchy prior for the intercepts $\{\mu_{k0}\}$
- (b) for continuous variable: smooth regression curves $\pi_{\ell}(\cdot)$, $\nu_k(\cdot)$ and $\eta_k(\cdot)$ by Bayesian Penalized-splines (Lang, 2004) combined with shrinkage priors on spline coefficients (Ni et.al, 2015) (to encourage towards constant values)

Posterior Inference

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Fit npLCMs (w/ or w/out covariates using R package baker (`https://github.com/zhenkewu/baker`)

- calls Bayesian model fitting software JAGS 4.2.0 (Plummer et al., 2003) from within R
- provides functions to visualize the posterior distributions of the unknowns
- also performs posterior predictive model checking

Simulation Results

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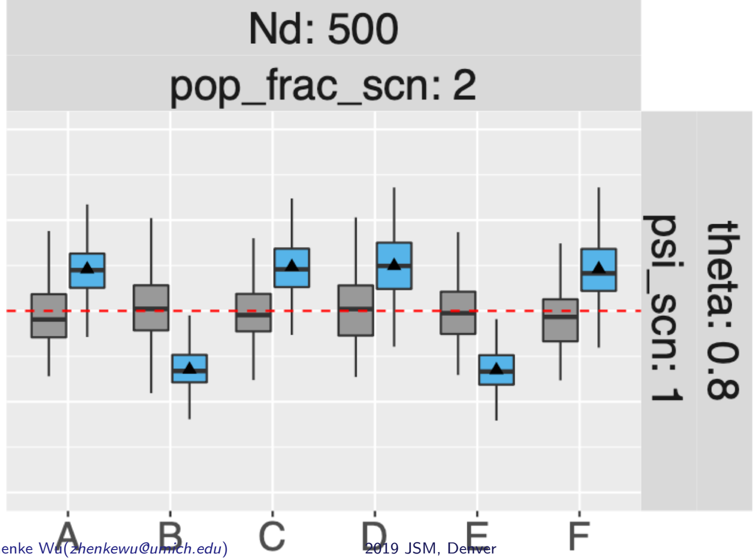
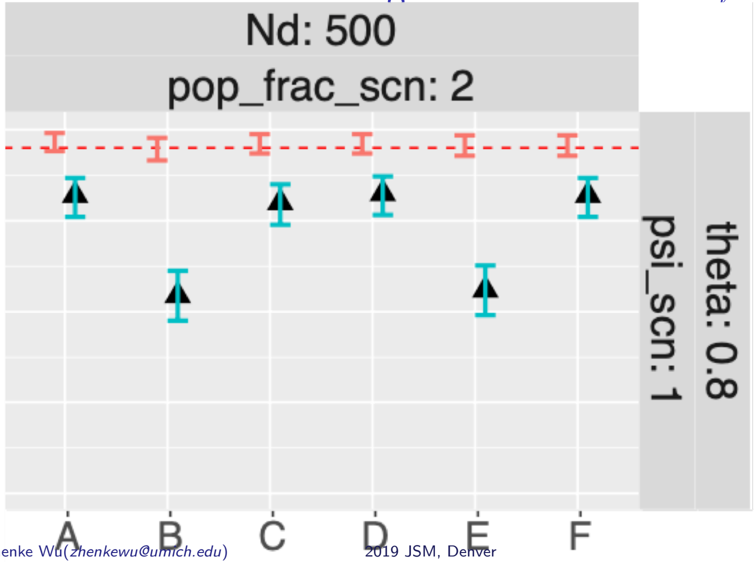
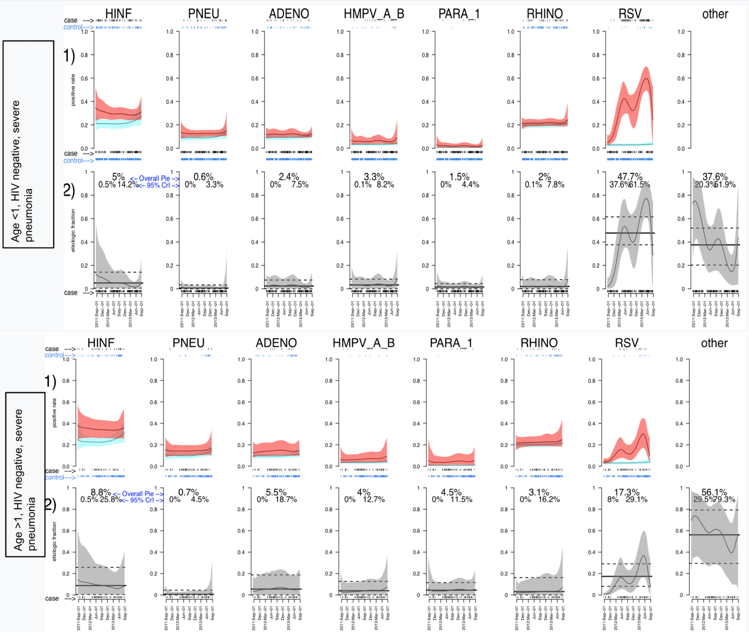
- Simulation I: demonstrate flexible statistical inferences about the PEF functions $\{\pi_\ell(\cdot)\}$ (not shown in this talk; check paper)
- Simulation II: determining overall PEF π_ℓ^* (empirical average) to quantify disease burdens in a population (potential policy interest)

Simulation II: Regression Model Reduces the Percent Relative Bias in Recovering the Overall PEFs π_ℓ^*



Simulation II: Regression Model Produces More Valid 95% CrIs in Recovering the Overall PEFs π^*_ℓ




Age <1, HIV negative, severe pneumonia
1)
2)
HINF
PNEU
ADENO
HMPV_A_B
PARA_1
RHINO
RSV
other
case -->
control-->
positive rate
etiologic fraction
5%
0.5% 14.2%
<- Overall Pie ->
<- 95% CrI ->
0.6%
0% 3.3%
2.4%
0% 7.5%
3.3%
0.1% 8.2%
1.5%
0% 4.4%
2%
0.1% 7.8%
47.7%
37.6% 61.5%
37.6%
20.3% 51.9%
Age >1, HIV negative, severe pneumonia
8.8%
0.5% 25.8%
0.7%
0% 4.5%
5.5%
0% 18.7%
4%
0% 12.7%
4.5%
0% 11.5%
3.1%
0% 16.2%
17.3%
8% 29.1%
56.1%
29.5% 79.3%
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2011:Sep-01
Dec-01
2012:Mar-01
Jun-01
Sep-01
Dec-01
2013:Mar-01
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Main Points Once Again

Context: Modern large-scale etiology studies generate complex measurements of unobserved causes of disease, and have raised the analytic needs of estimating cause-specific case fractions, or "Population Etiologic Fractions" (PEFs)

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Gap: Despite recent methodological advances, the need of describing the relationship between covariates and PEFs, remains unmet

Contribution: A general etiology regression framework building on npLCM that is broadly applicable to case-control studies

A general framework for a class of statistical problems that can be formulated as estimating covariate-dependent class-mixing weights.

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- 2) produces covariate-dependent reference distribution for controls, which is critical for assigning cause-specific probabilities to a given case ☺
    - because we can compare control measurements to case measurements with similar covariate values
- 3) TPR priors are only used once; avoids overly-optimistic etiology uncertainty estimates. ☺

Thank You!

Student
Irena Chen

Collaborators
Scott Zeger
Katherine O'Brien
Maria Deloria-Knoll
Laura Hammitt

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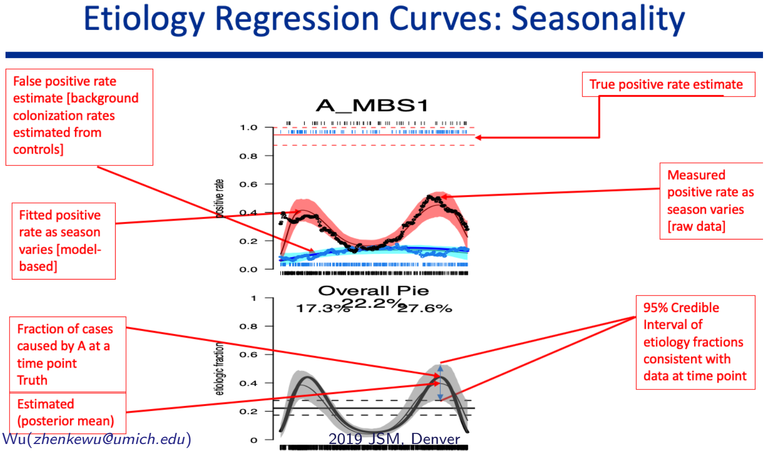
Bill & Melinda Gates Foundation [48968]
Michigan Precision Health Investigator Award
National Cancer Institute (P30CA046592, U01CA229437)

Some References (More at: `zhenkewu.com`)

1. **Wu Z** and Chen I (2019+).
   Regression Analysis of Dependent Binary Data: Estimating Disease Etiology from Case-Control Studies.
   Submitted. https://arxiv.org/abs/1906.08436
2. PERCH Study Group (2019+).
   Causes of severe pneumonia re- quiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi- country case-control study.
   The Lancet. https://doi.org/10.1016/S0140-6736(19)30721-4
3. **Wu Z**, Deloria-Knoll M and Zeger SL (2019+).
   A Bayesian Approach to Restricted Latent Class Mod- els for Scientifically-Structured Clustering of Multivariate Binary Outcomes.
   Submitted. https://doi.org/10.1101/400192
4. **Wu Z**, Deloria-Knoll M and Zeger SL (2017).
   Nested Partially-Latent Class Models for Estimating Disease Etiology from Case-Control Data.
   Biostatistics. 18 (2): 200-213.
5. **Wu Z**, Deloria-Knoll M, Hammitt LL, and Zeger SL, for the PERCH Core Team (2015).
   Partially Latent Class Models (pLCM) for Case-Control Studies of Childhood Pneumonia Etiology.
   Journal of the Royal Statistical Society: Series C (Applied Statistics). 65:97-114.

Simulation I Results

- $N_d = 500$ cases and $N_u = 500$ controls for each of two levels of S (discrete covariate); Uniformly sample the subjects' enrollment dates over a period of 300 days.



Etiology Regression Curves: Seasonality

False positive rate estimate [background colonization rates estimated from controls]

True positive rate estimate

Measured positive rate as season varies [raw data]

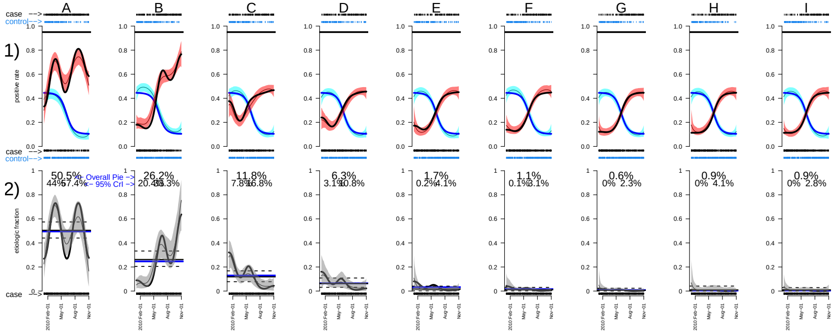
Fitted positive rate as season varies [model-based]

Fraction of cases caused by A at a time point Truth

Estimated (posterior mean)

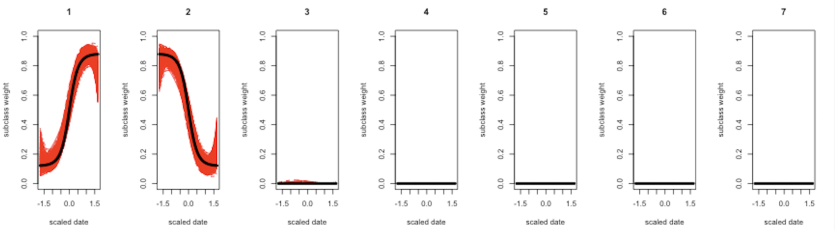
95% Credible Interval of etiology fractions consistent with data at time point

Simulation I: Recovery of Truth $\pi_\ell^0(t, S = s)$

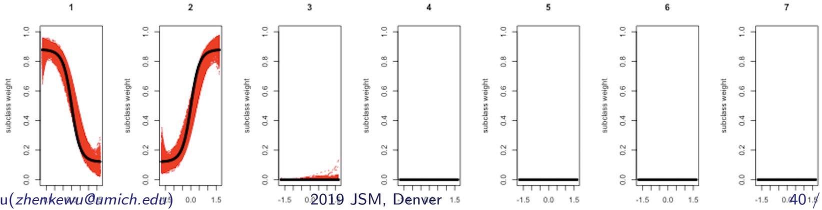


Simulation I: Recovery of $\nu_k(t)$ and $\eta_k(t)$

True $K^0 = 2$; Model fitted using a working number $K = 7$



(a) case



Appendix: Simulation II Setup

- npLCM regression analysis with $K^* = 3$, $R = 200$ replication data sets simulated under 48 different scenarios
- $L = J = 3, 6, 9$ causes, under single-pathogen-cause assumption, BrS measurements made on N_d cases and N_u controls for each level of X where $N_d = N_u = 250$ or 500.
- $\phi_\ell(X) = \beta_{0\ell} + \beta_{1\ell}\,\mathbb{I}\{X = 2\}$ take two sets of values to reflect PEF variability across X: i) $\boldsymbol{\beta}_0^{\text{i}} = (0, 0, 0, 0, 0, 0)$, $\boldsymbol{\beta}_1^{\text{i}} = (-1.5, 0, -1.5, -1.5, 0, -1.5)$; ii) $\boldsymbol{\beta}_0^{\text{ii}} = (1, 0, 1, 1, 0, 1)$ and $\boldsymbol{\beta}_1^{\text{ii}} = (-1.5, 1, -1.5, -1.5, 1, -1.5)$
- TPRs $\theta_k^{(j)} = 0.95$ or 0.8 and FPRs $(\psi_1^{(j)}, \psi_2^{(j)}) \in \{(0.5, 0.05), (0.5, 0.15)\}$, for $j = 1, \ldots, J$.
- $\nu_k(W) = \eta_k(W) = logit^{-1}\left(\gamma_{k0} + \gamma_{k1}\,\mathbb{I}\{W = 2\}\right)$ where $(\gamma_{10}, \gamma_{11}) = (-0.5, 1.5)$ and $(\gamma_{20}, \gamma_{21}) = (1, -1.5)$.

Appendix

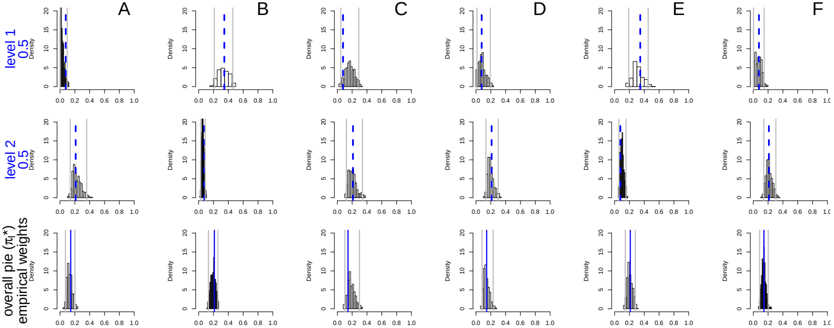


Figure: Posterior distributions of the stratum-specific (Row 1 and 2) and the overall (Bottom Row) PEFs based on a simulation with a two-level discrete covariate and $L = J = 6$ causes. The vertical gray lines indicate the 2.5% and 97.5% posterior quantiles, respectively; The truths are indicated by vertical blue dashed lines. *Row 1-2*) PEFs by stratum (level = 1,2) and cause (A-F); *Bottom*) π_ℓ^*: overall population etiologic fraction for cause A-F (empirical average of the two PEFs above).

Appendix

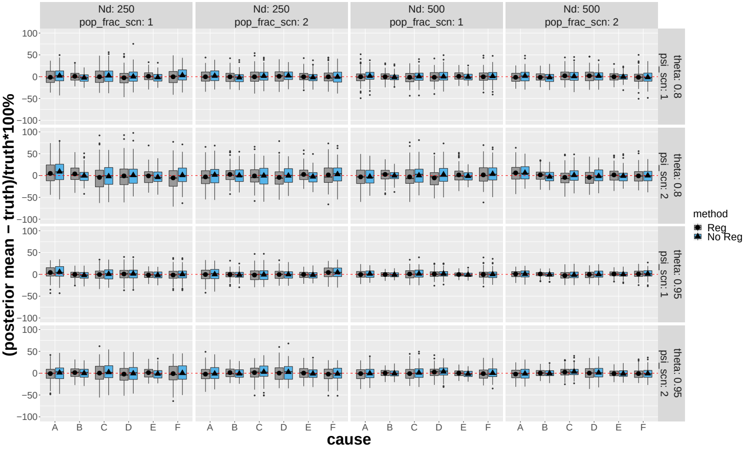
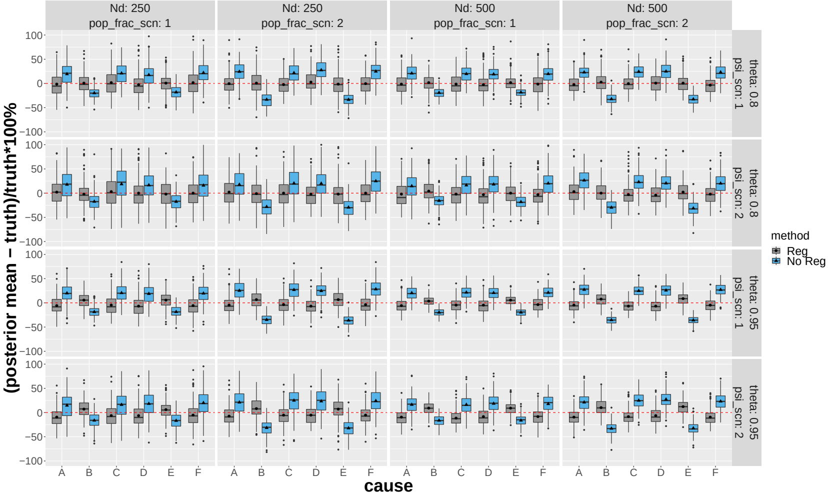


Figure: NPLCM analyses with or without regression perform similarly in terms of percent relative bias (top) and empirical coverage rates (bottom) over $R = 100$ replications in simulations where the case and control subclass weights *do not* vary by covariates. Each panel corresponds to one of 16 combinations of true parameter values and sample sizes.

Simulation II: Regression Model Reduces the Percent Relative Bias in Recovering the Overall PEFs π_ℓ^*



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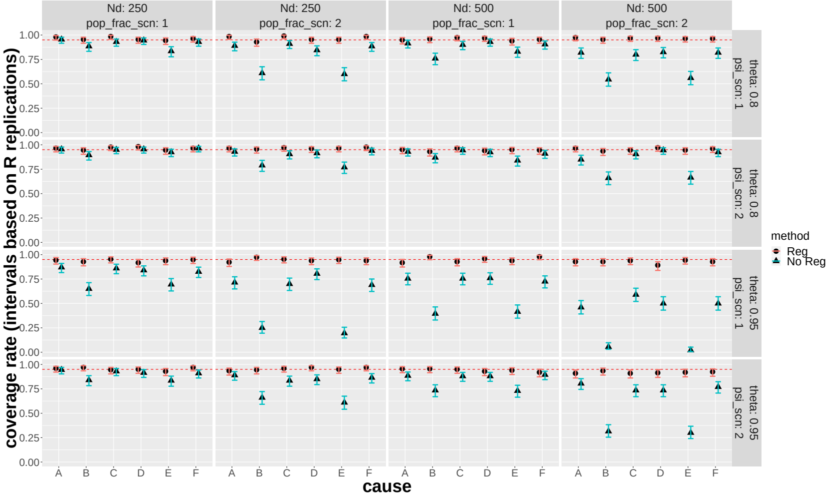

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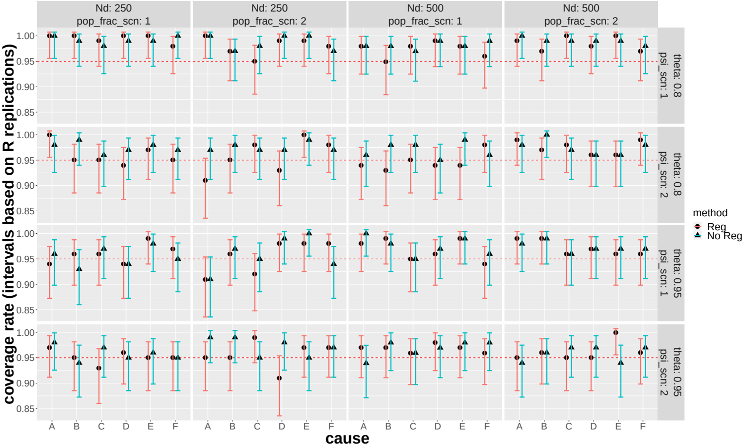

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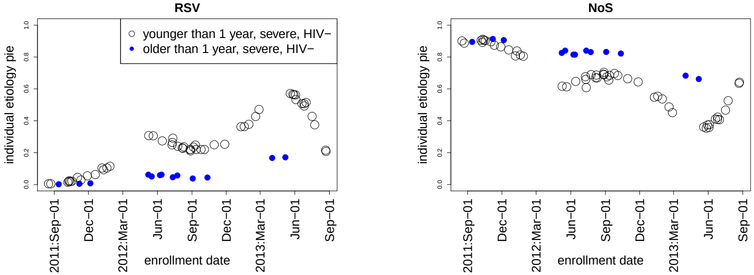

(a) Cause: RSV

(b) Cause: NoS

Figure: Individual etiology fraction estimates for RSV (left) and NoS (right) differ by age and season among HIV negative and severe pneumonia cases for whom the seven pathogens were *all tested negative* in the nasopharyngeal specimens.