Accounting for Unmeasured Confounding in Cost-Effectiveness Analyses

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Overview

- Unmeasured confounding in epidemiology and pharmaco-epidemiology
- Cost effectiveness models
- Bayesian inference for the model
- Simulation Study
- Extensions
- Conclusion

Unmeasured Confounding

- Problem in epidemiologic/observational studies
- For example, interest is in effect of a drug on occurrence and frequency of some adverse event
- Variables such as smoking, BMI, etc. are often not available for all subjects in the study
- Greenland (2005) and references therein provide a good review of unmeasured confounding in observational studies
- Schneeweiss (2006) notes that unmeasured confounding is a problem in epidemiologic studies of drug effects

- We focus on a single binary unmeasured confounder
- Wang and Krieger prove this is the "worst case scenario" for the case of matched pairs and is the most commonly assumed situation (Gustafson and McCandless, 2010)
- Methods to correct for unmeasured confounding
    - External validation data
        - Information on unmeasured confounder from previous studies is used. Generally does not contain information about disease/confounder relationship
    - Internal validation data
        - Extra effort is undertaken to ascertain the unmeasured confounder for a randomly selected subset of the main study data
    - Sensitivity analysis
        - Assumed values of the "bias" parameters are plugged in to determine potential effect of the unmeasured confounding
    - Informative priors (Bayesian/Monte Carlo sensitivity)
        - Probability distributions are used in place of the assumed fixed values

Cost Effectiveness

- Cost-effectiveness studies are an important part of an overall analysis for decision making in health policy issues
- There has been considerable interest in the joint modeling of cost and effectiveness
- Applications in clinical trials include
  - O'Hagan et al. (2001) - assume both cost and effectiveness are normally distributed
  - Negrin and Vazquez-Polo – assume both cost and effectiveness are normally distributed, perform Bayesian model averaging
- Applications in multi-center clinical trials include
  - Bachmann et al. (2007) – assume Bernoulli effectiveness and test for whether gamma or normal is better fit for costs
  - Grieve et al. (2010) – assume gamma distribution for costs and normal distribution for effectiveness
- Applications in non-randomized studies
  - Nixon and Thompson (2005) – use covariates to adjust for non-randomness, assume gamma distribution for costs, normal effectiveness

Bayesian inference for cost/effectiveness data with unmeasured confounding

- We will consider both binary and continuous effectiveness
- We will use a gamma distribution for costs since they are often skewed.
- We focus on Bayesian estimation procedures
- All models are straightforward to fit in the freely available package WinBUGS

Binomial effectiveness

- Let e_i, $i = 1, \ldots, n$ denote effectiveness for the i^{th} subject, $e_i = 1$ if effective, 0 otherwise
- Probability of effectiveness is related to covariates via

$$\text{logit}(p_{e_i}) = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \lambda_E u_i$$

  - x_1 is a binary treatment/exposure variable
  - x_2 is a measured confounder
  - u is an unmeasured binary confounder
- The parameter β_1 is of primary interest as it represents the impact of the treatment on the probability of effectiveness.
- The parameter λ_E represents the impact of the unmeasured confounder on the probability of effectiveness.
- Since u is (in general) unmeasured, λ_E is referred to as a bias parameter

Gamma distributed cost

- Assume continuous cost variable is gamma distributed with mean μ_{ci} and shape ρ.
- For this parameterization of the gamma, the variance is $\mu_{C_i}^2 / \rho$.
- The mean costs is related to the covariates and effectiveness via

$$\log(\mu_{C_i}) = \alpha_0 + \alpha_1 x_{1i} + \alpha_2 x_{2i} + \gamma e_i + \lambda_C u_i$$

  - x_1, x_2 and u are as defined before

- The parameter α_1 is of primary interest as it represents the impact of the treatment on the costs.
- The parameter λ_C represents the impact of the unmeasured confounder on the costs and is another bias parameter.
- The parameter γ accounts for the relationship between costs and effectiveness.

Normally distributed effectiveness

- Though we focus on binary effectiveness, we also consider the case of continuous effectiveness.
- Assume e_i has a normal distribution with mean μ_{ei} and variance σ^2. The mean is related to covariates via

$$\mu_{e_i} = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \lambda_E u_i$$

- The parameter β_1 is of primary interest as it represents the impact of the treatment on the mean effectiveness.
- The parameter λ_E represents the impact of the unmeasured confounder on the probability of effectiveness.

Unmeasured Confounder

- Ignoring the unmeasured confounder, U, can result in biased estimation
- We consider the case of a binary unmeasured confounder, $u_i \sim \text{Bernoulli}(\pi_i)$
- We make the standard assumption that the unmeasured confounder is related to the exposure

$$\text{logit}(\pi_{u_i}) = \delta_0 + \delta_1 X_{1i}$$

- The parameters modeling the unmeasured confounding, δ_0 and δ_1 are also "bias" parameters
- The parameters λ_E, λ_C, δ_0 and δ_1 are not directly estimable from the data and require either validation data or expert opinion in order to obtain an identifiable model.

Bayesian approach

- Bayesian methods are often used to model scenarios with over-parameteriziation
  - Gustafson (2003) provides textbook length treatment of misclassification and measurement error in covariates
  - Paulino et al. (2003) and McInturff et al. (2004) provide Bayesian approaches for binomial responses with misclassification
  - Greenland (2009) has noted, “The absence of identification renders all analyses part of a sensitivity analysis”
- Provides operational way to combine validation data (if available) and expert opinion in order to estimate parameters

Validation data

- For a subsample of subjects the “unmeasured” confounder is available
- If the data is a random sample from the current “main study”, the data is referred to as internal validation
    - Expensive
    - Provides information on all parameters of interest
- If the subsample is from a previous study or database, it is referred to as external validation
    - Generally provides information on reporting probabilities and the unmeasured confounder/exposure relationship
    - Requires the assumption of transportability

Likelihood and prior distributions

- We assume a validation sample of size n_0, total sample size of n, thus "main study" sample of size $n - n_0$
- The likelihood for the model with internal validation data is

$$L(\theta, \boldsymbol{y}, \boldsymbol{u} \mid \boldsymbol{y}^*, \boldsymbol{u}_0, \boldsymbol{y}_0) \propto \prod_{i=1}^{n-n_0} \left(\frac{\rho}{\mu_i} \right)^{\rho} \frac{c_i^{\rho-1} \exp\left(-\rho / \mu_i c_i\right)}{\Gamma(\rho)} p_{e_i}^{e_i} (1 - p_{e_i})^{1-e_i} \times \pi_{u_i}^{u_i} (1 - \pi_{u_i})^{1-u_i} \times \prod_{j=1}^{n_0} \left(\frac{\rho}{\mu_j} \right)^{\rho} \frac{c_{j0}^{\rho-1} \exp\left(-\rho / \mu_j c_{j0}\right)}{\Gamma(\rho)} p_{e_j}^{e_{j0}} (1 - p_{e_j})^{1-e_{j0}} \times \pi_{u_j}^{u_{j0}} (1 - \pi_{u_j})^{1-u_{j0}}$$

$$\text{logit}(p_{e_i}) = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \lambda_E u_i$$

$$\log(\mu_{C_i}) = \alpha_0 + \alpha_1 x_{1i} + \alpha_2 x_{2i} \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \gamma e_i + \lambda_C u_i$$

$$\text{logit}(\pi_{u_i}) = \delta_0 + \delta_1 X_{1i}$$

- u_{j0} is the value of the unmeasured confounder for the j^{th} observation in the validation sample
- If validation data is available, relatively diffuse priors can be used for the parameters, for instance Normal(0, 10)
- Default prior in software packages such as WinBUGS is N(0, 10^6) priors
- For moderate validation data the model exhibits problems converging for some data sets if too large of a variance is chosen
- Informative priors can be elicited via conditional-means prior (CMP) procedure

Computation

- No closed form for posterior distributions of interest
- MCMC methods
- WinBUGS program available upon request
  - With validation data and/or informative priors, chains converge
  - Computation does take time
- PROC MCMC provides an alternative, but the current version appears limited in its ability to handle missing data problems

Simulation Study 1

- Assume main study sample of 350 observations and an additional 50 observations where all variables are fully observed
- Parameter values are provided in table
- Simulations are based on 500 generated data sets
- For each data set, a burn-in of 5,000 iterations was used followed by 30,000 iterations keeping every 5^{th} for inference

Simulation Results

	True value	Mean	Coverage Probability	Interval Width
α_0	5	4.99	0.946	0.301
		4.88	0.254	0.174
α_1	0.5	0.486	0.930	0.270
		0.427	0.676	0.192
α_2	0.25	0.247	0.948	0.187
		0.249	0.958	0.186
γ	–0.3	–0.298	0.948	0.248
		–0.273	0.906	0.200
β_0	0	0.000	0.934	1.457
		–0.226	0.752	0.664
β_1	1.5	1.579	0.944	1.400
		1.380	0.914	0.889
β_2	0.4	0.409	0.958	0.949
		0.391	0.946	0.893
ρ	5	5.143	0.952	1.758
		4.737	0.872	1.270
δ_0	–0.2	–0.189	0.922	1.541
		N/A	N/A	N/A
δ_1	1.1	1.097	0.936	2.348
		N/A	N/A	N/A
λ_E	–0.5	–0.615	0.940	2.766
		N/A	N/A	N/A
λ_C	–0.25	–0.237	0.952	0.463
		N/A	N/A	N/A

Comments on simulation study 1

- For the naïve model, largest impact of unmeasured confounding is in the intercepts and the treatment effects.

- The treatment effect for the efficacy variable is somewhat biased but coverage is close to nominal

- Repeated the simulation with $\lambda_c = 0.25$ and $\lambda_e = 0.5$. Bias for naïve model is not as drastic, but still present.

- As λ_c and λ_e move away from 0, naïve model performance significantly worsens.

Simulation Study 2

- Observational cost/effectiveness studies often have large sample sizes.
- Simulations were performed to determine what degree of validation data is required for large samples.
- Parameter values are same as first study, n = 2000 and with validation data n_0 = 50, 100, 150, 200, 250, 300.
- Monitored posterior means and coverage of 95% intervals of primary parameters of interest, α_1 and β_1.
- For comparison purposes, for the naïve model with n = 2000, for α_1 the average posterior mean was 0.426 and the coverage is 0.088 while for β_1 the average was 1.352 with coverage probability of 0.69.

Simulation 2 Results

n/n_1	Mean	Coverage	Width
1950/50	0.507	0.956	0.18
1900/100	0.503	0.932	0.142
1850/150	0.504	0.94	0.127
1800/200	0.5	0.956	0.117
1750/250	**0.501**	**0.967**	**0.111**

n/n_1	Mean	Coverage	Width
1950/50	1.549	0.97	1.031
1900/100	1.519	0.944	0.722
1850/150	1.527	0.953	0.617
1800/200	1.513	0.96	0.579
1750/250	**1.519**	**0.933**	**0.553**

Extensions

- Many sources of bias in observational studies
  - Response misclassification
  - Covariate misclassification
  - Covariate measurement error
  - Selection bias
- Greenland (2009, 2010) and Gustafson and McCandless (2010) overview Bayesian and Monte Carlo sensitivity analysis procedures to address these issues.
- We extend the model to address the issue of response misclassification for the binary efficacy variable.

Misclassification of binary response

- Instead of observing true effectiveness, e, we observe "contaminated" value e^*.
- $P(e_i^* = 1 | e_i = 1) = p_{e_i} Se + (1 - p_{e_i})(1 - Sp)$ where Se is the sensitivity and Sp is the specificity.
- We assume Se and Sp are constant regardless of other individual characteristics.
- Se and Sp add two more bias parameters to be estimated using the validation data, assuming the true effectiveness status can be ascertained for these subjects.
- Informative priors can be used from previous studies as well.
- We consider a single example with $n = 800$ and $n_1 = 200$.

Misclassification example

	True value	Mean	95% Interval
α_0	5	5.00	(4.92, 5.08)
		4.84	(4.78, 4.91)
α_1	0.5	0.552	(0.479, 0.635)
		0.407	(0.347, 0.467)
α_2	0.25	0.216	(0.157, 0.278)
		0.211	(0.150, 0.273)
γ	–0.3	–0.259	(–0.345, –0.172)
		–0.143	(–0.209, –0.078)
β_0	0	0.169	(–0.227, 0.555)
		0.127	(–0.081, 0.337)
β_1	1.5	1.514	(1.071, 1.999)
		0.989	(0.720, 1.259)
β_2	0.4	0.209	(–0.147, 0.572)
		0.103	(–0.170, 0.375)
ρ	5	5.19	(4.645, 5.784)
		4.561	(4.180, 4.955)
δ_0	–0.2	–0.546	(–0.941, –0.156)
		N/A	NA
δ_1	1.1	1.397	(0.846, 1.978)
		N/A	NA
λ_E	–0.5	–0.544	(–1.187, 0.096)
		N/A	NA
λ_C	–0.25	–0.316	(–0.423, –0.197)
		N/A	NA
Se	0.9	0.908	(0.866, 0.947)
		NA	NA
Sp	0.8	0.836	(0.752, 0.909)
		NA	NA

Conclusions

- Failing to count for uncontrolled confounding can result in biased estimates in cost-effectiveness studies
- A Bayesian approach with internal validation data appropriately corrects estimates in simulations considered
- Internal validation may not be available
- More simulation is needed to demonstrate performance of external validation and informative prior approaches