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Abstract

Adjusting for several unmeasured confounders is a challenging problem in the analysis of observational data. Information about unmeasured confounders is sometimes available from external validation data, such as surveys or secondary samples drawn from the same source population. In principal, the validation permits us to recover information about the missing data, but the difficulty is in eliciting a valid model for nuisance distribution of the unmeasured confounders. Motivated by a British study of the effects of trihalomethane exposure on full-term low birthweight, we describe a flexible Bayesian procedure for adjusting for a vector of unmeasured confounders using external validation data. We summarize the unmeasured confounders with a scalar summary score using the propensity score methodology of Rosenbaum and Rubin. The score has the property that it breaks the dependence between the exposure and unmeasured confounders within levels of measured confounders. To adjust for unmeasured confounding in a Bayesian analysis, we need only update and adjust for the summary score during Markov chain Monte Carlo simulation. We demonstrate that trihalomethane exposure is associated with increased risk of full-term low birthweight, and this association persists even after adjusting for eight unmeasured confounders. Empirical results from simulation illustrate that our proposed method eliminates bias from several unmeasured confounders, even in small samples.

Keywords: Confounding; Bias; Observational studies; propensity scores, causal inference

Running title: Adjustment for Unmeasured Confounders.

1. Introduction

Statistical methods for adjusting for unmeasured confounding in observational studies have been studied extensively in recent years [1–6]. A popular strategy is to work from the assumption that there is a single binary unmeasured confounder. In regression analysis, this gives a parametric model for the observed data, averaging over the distribution of the unmeasured confounder. The resulting model is nonidentifiable and indexed by so-called *bias parameters* that characteristic the confounding effect of the missing covariate. To adjust for unmeasured confounding, the investigator uses sensitivity analysis and computes inferences over a range of possible values for the bias parameters. A Bayesian approach is also possible where uncertainty about bias parameters is incorporated into the analysis as prior information [1, 7, 8]. The posterior distribution for the exposure effect summarizes uncertainty from unmeasured confounding in addition to random error.

In practice we may have complicated patterns of missing confounders, and the assumption of a binary unmeasured confounder may be simplistic. One estimation strategy is to model the unmeasured confounders as missing data within a Bayesian framework [1, 9]. We model the joint distribution of the data and unmeasured confounders. Inference proceed via posterior updating of the unmeasured confounders using Markov chain Monte Carlo (MCMC) in a manner akin to multiple imputation. But the difficulty with this approach is in eliciting a satisfactory model for the distribution of the unmeasured confounders. They may be high dimensional, correlated and either continuous or categorical. Parametric models may give inadequate representations of complex patterns of missing data.

In this article, we consider the case where supplementary information on unmeasured confounding is available from external validation data. Examples include survey data or secondary

samples from the population under study. Thus our setting is observational studies where there is bias from missing data, which we alleviate by synthesising different sources of empirical evidence. We distinguish between the *primary data* which denotes the original dataset and the *validation data* which denotes a smaller sample of units drawn from the same source population and with complete information about missing variables. The motivation for this work is the intuitive idea that it should be possible to develop a flexible procedure for using the validation data in order to recover information about the confounding effect of missing covariates.

The problem of combining inference for primary and validation data for control of unmeasured confounding has been studied in the context of two-stage sampling designs. Schill et al. [10], Breslow et al. [11] review two stage sampling methods for control of confounding and other biases in observational studies. Fully parametric methods for adjusting for multiple unmeasured confounders from validation data are available [12–16]. These approaches can be somewhat restrictive because they require that the unmeasured confounders follow a specific family of multivariate distributions. Alternatively, Chatterjee et al. [17] reviews techniques which use density estimates of the distribution of the unmeasured confounders in the validation data. There is also a large literature on adjusting for missing covariates via design-based estimators derived from estimating equations. These circumvent the need for a parametric model for missing covariates by calculating inferences using sampling weights. See Schill et al. [10] and Breslow et al. [11] for details.

In this article we describe a Bayesian method for adjusting for multiple unmeasured confounders using external validation data. We use the idea of propensity scores, originally introduced by Rosenbaum and Rubin [18]. The method can be a used in settings where the confounders are either continuous and categorical with correlated components. We summarize

the unmeasured confounders using a scalar summary score, which can be interpreted as the propensity score *adjusted for measured confounders*. The score has the property that it breaks the association between the exposure and unmeasured confounders, within levels of measured confounders. To adjust for unmeasured confounding using Bayesian techniques, we need only update and adjust for the summary score during Markov chain Monte Carlo simulation. Modelling variation in the outcome variable within levels of the unmeasured confounders is unnecessary.

To illustrate the problem of unmeasured confounding, Section 2 begins by describing a large epidemiological investigation of the effect of trihalomethanes, a water disinfection by-product, on risk of low birthweight in England. The primary data are obtained from United Kingdom Birth Registry which benefits from a large sample size but has only limited information on factors influencing birthweight such as maternal smoking and ethnicity. Rich covariate information on eight unmeasured confounders is taken from validation data from the Millennium cohort study. In Section 3, we describe a method for adjusting for unmeasured confounding using propensity score techniques. We outline the model, prior distributions and an algorithm for posterior simulation. Technical details concerning the propensity score and confounder control are given in the Appendix. We apply the method in Section 4 and show that trihalomethane exposure is associated with increased risk of low birthweight even after adjusting unmeasured confounding. Furthermore, uncertainty from unmeasured confounding accounts for nearly 30% of the total posterior uncertainty of the exposure effect. A brief simulation study in Section 5 illustrates that interval estimates which ignore this uncertainty will give inferences which are falsely precise. Section 6 concludes with a discussion.

2. Example: Estimating the Effect of Trihalomethanes on Low

Birth Weight

To illustrate the problem of unmeasured confounding, we consider the example of an observational study of the relationship between trihalomethanes, a water disinfection by-product, and risk of full-term low birth weight in the United Kingdom [19]. Pregnant mothers are be exposed to trihalomethanes in a variety of different ways including bathing, drinking water or swimming. Published investigations of adverse birth outcomes related to trihalomethane exposure have yielded contradictory findings with some studies reporting increased risk of low birthweight, while others showing no association [19]. Low birth weight is rare and any increased risk due with trihalomethane exposure it is likely to be small. Furthermore, exposure assessment is prone to measurement error and published studies are often missing information on important confounders []. These study characteristics are likely to mask any true association.

In the present investigation, we consider the data from a previous study by Toledano et al. [19, 20]. Information was collected for 9060 births between 2000 and 2001 in the region of North West England serviced by a single water utility company. Birth records from the United Kingdom National Births Registry were linked to estimates of trihalomethane water concentrations using maternal residence at birth. Following the terminology given in the introduction, we call this dataset the *primary data*. The National Births Registry data have the advantage of capturing information on all births in the population under study. But it contains only limited information on mother and infant characteristics which may impact birth weight. Complete details on the data are given by [19, 20].

Let Y be an indicator variable for the outcome under study, taking value one if an infant has full term low birth weight, and zero otherwise. Full term low birthweight is defined as a gestational age greater than 37 weeks in combination with a birthweight less than 2.5kg. In

this investigation, the quantity Y for each of the 9060 subjects is obtained is obtained from the data and model of Molitor et al. [16] as a single imputation of the outcome variable. To model exposure to trihalomethanes, we let X be an indicator variable taking value one for a concentration greater than $\geq 60\mu$mol/L and zero otherwise. Let C denote a vector of $p = 5$ confounding variables that are contained in the primary data. These include indicator variables for mother's age ($\leq$ 20, 20-24, 25-29, 30-34, $\geq$ 35), and an indicator variable if the baby gender is male.

To explore the association between X and Y in the primary data, we fit a logistic regression of Y on X while adjusting for C. The results are presented in Table 1 under the heading "NAIVE". We see a an odds ratio of 2.27 with 95% CI (1.68, 3.06) indicating that trihalomethane exposure is associated with a sizeable increase in risk of full term low birth weight.

A difficulty with this analysis is that the effect estimate is likely to be biased from unmeasured confounding. Owing to the limited number of variables in the primary data, there is limited information on factors that influence birth weight, including maternal smoking, ethnicity or income. Trihalomethane concentrations may vary by neighbourhood income level. Without appropriate adjustment for confounding, the risk patterns between exposure groups may be an artifact of systematic differences in characteristics between populations.

In this investigation, information about unmeasured confounders is available from external validation data. The United Kingdom Millennium Cohort Study [20] contains survey information on mothers and infants born during the period 2000-2001 when the primary data were collected. The data are a disproportionately stratified sample based on ethnicity and income of place of residence. Following Molitor et al. [20] we link the survey data with that of the National Birth Registry to obtain partial information about unmeasured confounders for 1115 out of a possible

9060 births. Thus the primary data have sample size $m = 7945$, while the validation data have sample size $m = 1115$. We let U be a $q = 8$ vector of eight unmeasured confounders including; indicator for lone parent family, number of live children for mother, maternal smoking, alcohol consumption , body mass index prior to pregnancy, ethnicity (three categories), income (ordinal with three levels calculated from tertiles in the population), and indicator variable for the mother having high school diploma.

Denote the primary data as $\{(Y_i, X_i, C_i, U_i)|$ for $i \in 1 : m = 7945\}$ and the validation data as $\{(Y_j, X_j, C_j, U_j)|$ for $j \in 1 : m = 1115\}$. The quantity U_i is completely unobserved. To study the impact of unmeasured confounding, Table 2 presents odds ratios for the association between Y_j and X_j when adjusting for C_j alone, versus adjusting for C_j and U_j. In the first column of Table 2, we fit weighted logistic regression of Y_j on X_j and C_j using the survey weights supplied in the documentation of the validation data in order to correct for non-random sampling. The odds ratio is equal to 2.52 with 95% CI (1.03, 6.15). In the second column we fit the same regression, but adjust for both C_j and U_j and obtain 2.43 (0.95, 6.24). The exposure effect estimates are similar, but the interval estimate in the fully adjusted analysis is wider and crosses zero. Furthermore, smoking and ethnicity are important predictors of low birth weight.

Thus Table 2 indicates that the components of U play an important role in explaining variation in the outcome. Valid inference from the primary data may require adjustment for unmeasured confounding. As discussed in the introduction, a standard analytic approach is to model the unmeasured confounders as missing data. But this is challenging because the components of U_j are correlated binary variables which depend on X_j and possibly C_j. In Section 3, we present Bayesian procedure for summarizing and adjusting for the confounding effect of U_i using propensity scores.

3. Bayesian Adjustment for Unmeasured Confounding (BAYES).

We present a method for Bayesian adjustment for unmeasured confounding using external validation data, which we henceforth call by the acronym BAYES. The BAYES method uses the idea of propensity scores, described by Rosenbaum and Rubin [18], in order to build a scalar summary of U_i which is included as a covariate in a regression model for the outcome. In Section 3.1 that follows, we describe a model for unmeasured confounding. We model the density function $P(Y, X, U|C)$ and integrate over the unmeasured U. This gives likelihood functions for the primary data and validation data that can be used for Bayesian inference. A family of prior distributions for model parameters is given in Section 3.2. Section 3.3 describes an algorithm for sampling from the posterior distribution using MCMC. This permits us to calculate estimates of the exposure effect which adjusts unmeasured confounders.

3.1 Models

3.1.1 A Model When There Is No Unmeasured Confounding

Suppose that (Y_i, X_i, C_i, U_i) and (Y_j, X_j, C_j, U_j) for $i \in 1:n$ and $j \in 1:m$ are identically distributed observations drawn from the same population with probability density function $P(Y, X, C, U)$. Building on the Bayesian propensity score analysis of McCandless et al [21], we model the conditional density $P(Y, X|C, U)$ using a pair of logistic regression models:

$$\text{Logit}[P(Y = 1|X, C, U)] = \beta X + \xi^T C + \tilde{\xi}^T g\{Z(U)\} \quad (1)$$

$$\text{Logit}[P(X = 1|C, U)] = \gamma^T C + Z(U), \quad (2)$$

where $Z(U) = \tilde{\gamma}^T U$.

Equation (1) is a model for the outcome and includes a exposure effect parameter β and a linear term for the covariates C with regression coefficients $\xi = (\xi_0, \ldots, \xi_p)$. Equation (2) models

the probability of exposure, which depends on the measured and unmeasured confounders via the regression coefficients $\gamma = (\gamma_0, \ldots, \gamma_p)$ and $\tilde{\gamma} = (\tilde{\gamma}_1, \ldots, \tilde{\gamma}_q)$. To ease modelling of regression intercept terms, we set the first component of C equal to one, so that C is a $(p+1) \times 1$ vector.

In equations (1) and (2), the quantity $Z(U) = \tilde{\gamma}^T U$ is a scalar summary of U, which can be interpreted as the propensity score adjusted for C. To illustrate, the propensity score on the log odds scale is defined as $\text{Logit}[P(X = 1|C, U)]$, according to the original definition of Rosenbaum and Rubin [18]. From equation (2), this quantity follows a regression model and is given by $\gamma^T C + \tilde{\gamma}^T U$. If we condition on C, then quantity $\gamma^T C$ is a constant intercept term. In the Appendix, we prove that $Z(U)$ has the property that

$$X \perp\!\!\!\perp U|C, Z(U). \tag{3}$$

This result is analogous to Theorem 1 of Rosenbaum and Rubin [18]. It says that within levels of C, conditioning on $Z(U)$ forces independence between X and U. Variability in X due to U is mediated entirely through $Z(U)$. The summary score $Z(U)$ breaks the association between the unmeasured confounders and exposure.

In Theorem 2 of the Appendix, we prove that if there is no unmeasured confounding conditional on (C, U), then equation (3) implies that there is no unmeasured confounding conditional on $(C, Z(U))$. This means that exposure effect measures computed from the marginal density $P(Y|X, C, Z(U))$ have a causal interpretation. To control for confounding bias due to U, it suffices to stratify on $(C, Z(U))$. We can estimate the exposure effect by using models which assume that $Y \perp\!\!\!\perp U|X, C, Z(U)$.

Accordingly, equation (1) includes the quantity $Z(U)$ as a covariate in a regression model for the outcome via a linear predictor $g\{.\}$. For the trihalomethane data example, we let $g\{a\} = \sum_{j=0}^{l} \tilde{\xi}_j g_j\{a\}$ where the quantities $g_j\{.\}$ are natural cubic spline basis functions with

$l = 3$ knots (q_1, q_2, q_3) and regression coefficients $\tilde{\xi} = (\tilde{\xi}_0, \tilde{\xi}_1, \tilde{\xi}_2, \tilde{\xi}_3)$ [22]. This gives a smooth yet flexible relationship between $Z(U)$ and outcome within levels of X and C. The choice of $l = 3$ knots reflects a trade off between smoothness and complexity. See Austin and Mamdani [22] for a detailed discussion of regression modelling strategies which use the propensity score as a regression covariate.

We could alternatively control confounding from C and U by fitting the outcome model

$$\text{Logit}[P(Y = 1|X, C, U)] \quad = \quad \beta X + \tilde{\xi}^T g\{Z(U, C)\} \tag{4}$$

where $Z(U, C) = \text{Logit}[P(X = 1|U, C)] = \gamma^T C + \tilde{\gamma}^T U$. This is a standard approach to controlling confounding, and it does not distinguish between measured and unmeasured confounders in calculating the propensity score. However, an advantage of using equation (1) rather than equation (4) is that it allows direct modelling of variability in Y arising from C. We include a linear term "... $+ \xi^T C +$ .." while summarizing the contribution of U using the $Z(U)$. This is appropriate in the present context because C is measured while U is not. Furthermore, the summary score $Z(U)$ has the appealing property that in the special case when $\gamma = 0$ in equation (2), then $Z(U)$ is equal to the log odds of the propensity score. In this case, U is the only confounder for the effect of X on Y, and equation (1) reduces to standard regression adjustment for the propensity score, as advocated by Rosenbaum and Rubin [18].

3.1.2 A Model for Unmeasured Confounding

In the primary data, the quantities Y_i, X_i and C_i are observed in the registry data while U_i is not. Equations (1) and (2) define the density $P(Y, X|C, U)$, and we can use it to calculate

the marginal model for $P(Y, X|C)$ integrating over U. We have

$$\begin{aligned} P(Y, X|C) &= E\{P(Y, U, X|C)\} \\ &= \int P(Y|X, C, U)P(X|C, U)P(U|C)dU, \end{aligned} \tag{5}$$

where $P(Y|X, C, U)$ and $P(X|U, C)$ are given in equations (1) and (2). To complete the specification, we require a model for U given C.

One simplification is to assume that C and U are marginally independent, meaning that $P(U|C) = P(U)$. In this case, we can model $P(U)$ using the empirical distribution of $U_1, \ldots, U_m$ from the validation data alone. We may approximate

$$P(Y, X|C) \approx \frac{1}{m}\sum_{j=1}^{m} P(Y|X, C, U_j)P(X|U_j, C). \tag{6}$$

Using this approach, we model $P(Y, X|C) = E\{P(Y, U, X|C)\}$ as the empirical average of $P(Y|X, C, U_j)P(X|U_j, C)$ over replicates U_j. An advantage of this representation is that it requires no parametric model for the distribution of U_j. It can be used regardless of whether the components of U_j are correlated and contain both continuous and categorical variables.

In practice, measured and unmeasured confounders are likely to be correlated, and the assumption that $P(U|C) = P(U)$ will be implausible. Because the components of U are categorical in the trihalomethane data, it would be possible to assign a parametric model for $P(U|C)$. Nonetheless, previous authors have argued that ignoring these correlations leads to inferences which are *conservative* under fairly general settings. Fewell et al. [23] study the impact of confounding from multiple unmeasured variables using simulations. The authors show that when measured and unmeasured variables are correlated this tends to reduced unmeasured confounding. Adjusting for measured variables has the secondary effect of partially adjusting for unmeasured variables. This reasoning is also discussed by Schneeweiss [2].

In contrast to equation (5), previously proposed methods of sensitivity analysis for unmeasured confounding favour models of the form

$$P(Y|X,C) \;\; = \;\; \int P(Y|X,C,U)P(U|X,C)dU,$$

which require models for $P(U|X,C)$ [6–8, 24, 25]. The approach of equation (5) applies Bayes rule to $P(U|X,C)$ in order to switch the conditional dependence. The advantage is that the model for $P(X|C,U)$ comes "for free" in a propensity score analysis controlling for C and U. Thus propensity score methods offer unique advantages in settings with unmeasured confounding. Dimension reduction of covariates in regression modelling, simplifies missing data modelling when some covariates are partially observed.

3.1.3 Bias Parameters and Nonidentifiability.

In equations (1) and (2), the parameters $\tilde{\xi}$, $\tilde{\gamma}$ model the relationship between the unmeasured confounder U and the data Y, X, C. We call these quantities *bias parameters* in the sense that they model bias from unmeasured confounding. If the parameters $\tilde{\gamma}$ or $\tilde{\xi}$ are large in magnitude then this means that U contains powerful confounders [26].

The model for the primary data given in equation (6) is nonidentifiable. To illustrate, suppose that that validation data has sample size $m = 1$. Then equation (6) is becomes

$$P(Y,X|C) \;\; \approx \;\; \left[\frac{\exp(Y(\beta X + \xi^T C + \tilde{\xi}^T g\{Z(U^*)\}))}{1+\exp(\beta X + \xi^T C + \tilde{\xi}^T g\{Z(U^*)\})}\right]\left[\frac{\exp(X(\gamma^T C + \tilde{\gamma}^T U^*\}))}{1+\exp(\gamma^T C + \tilde{\gamma}^T U^*)}\right],$$

where U^* is a known fixed quantity taken from the validation data. The conditional distribution of Y given X and C cannot distinguish between the quantity ξ_0 and $\tilde{\xi}^T g\{Z(U)\}$ because they both serve as regression intercept terms. We can only estimate the sum $\xi_0 + \tilde{\xi}^T g\{Z(U)\}$. Similarly, we cannot distinguish between γ_0 and $\tilde{\gamma}^T U$. When U is unobserved, the density $P(Y,X|C)$

can arise from different and indistinguishable patters of unmeasured confounding and baseline prevalences of Y and X.

If the bias parameters $\tilde{\xi}$ and $\tilde{\gamma}$ are known a priori, then the model for the primary data in equation (6) is identifiable. The quantities $\tilde{\xi}^T g\{Z(U)\}$ and $\tilde{\gamma}^T U$ are known offsets in the density $P(Y, X|C)$. We can calculate the maximum likelihood estimate for (β, ξ, γ) from the likelihood function for the primary data, given by

$$\prod_{i=1}^{n} P(Y_i, X_i|C_i). \tag{7}$$

Consequently, an alternative frequentist approach to adjusting for unmeasured confounding would be to plug in estimates for the bias parameters $\tilde{\xi}$ and $\tilde{\gamma}$ into the model for $P(Y, X|C)$ in equation (6) and then maximize the resulting likelihood to estimate (β, ξ, γ). This approach to external adjustment forms the basis of sensitivity analysis and is conceptually similar to the procedure described by Rosenbaum and Rubin [3]. We revisit this maximum likelihood approach in Section 4 and compare it to the BAYES method.

3.2 Prior Distributions

We assign proper independent normal priors to $\beta, \xi, \tilde{\xi}, \gamma, \tilde{\gamma}$.

$$\alpha,\ \beta,\ \xi_1, \ldots, \xi_p,\ \tilde{\xi}_i, \ldots, \tilde{\xi}_p,\ \gamma_1, \ldots, \gamma_p,\ \tilde{\gamma}_i, \ldots, \tilde{\gamma}_p \sim N\left\{0, \left(\frac{\log(15)}{2}\right)\right\}$$

The priors models the belief that the odds ratio for the exposure effect β is not overly large and lies between 1/15 and 15 with probability 95%. Similarly, the priors make analagous modelling assumptions about the prior magnitude for the association between Y and C, $Z(U)$ given X, and also the association between C, U and X.

3.3 Posterior Simulation

Let *data* denote the both the primary and validation data $\{(Y_i, X_i, C_i);\ \text{for } n = 1 : n\}$ and $\{(Y_i, X_i, C_i);\ \text{for } n = 1 : n \text{ and }\}$, respectively. Inferences from BAYES are obtained from the posterior density $P(\beta, \xi, \tilde{\xi}, \gamma, \tilde{\gamma}|data)$, which we sample from using MCMC simulation techniques. We have

$$\begin{aligned} P(\beta, \xi, \tilde{\xi}, \gamma, \tilde{\gamma}|data) \ &\propto \ \Big\{\prod_{i=1}^{n} P(Y_i, X_i|C_i)\Big\} \times \Big\{\prod_{j=1}^{m} P(Y_j, X_j|C_j, U_j)\Big\} \\ &\quad \times P(\beta, \xi, \tilde{\xi}, \gamma, \tilde{\gamma}) \end{aligned}$$

where the products over i and j are the likelihood functions for the primary and validation data, respectively, and $P(\beta, \xi, \tilde{\xi}, \gamma, \tilde{\gamma})$ is the prior density for $\beta, \xi, \tilde{\xi}, \gamma$ and $\tilde{\gamma}$.

We sample from $P(\alpha, \beta, \xi, \tilde{\xi}, \gamma, \tilde{\gamma}|data)$ by updating from the conditional distributions for $[\beta, \xi, \tilde{\xi}|\gamma, \tilde{\gamma}, data]$ and $[\gamma, \tilde{\gamma}|\beta, \xi, \tilde{\xi}, data]$ using the Metropolis Hastings algorithm. To update from $[\beta, \xi, \tilde{\xi}|\gamma, \tilde{\gamma}, data]$, we use a proposal distribution based on a random walk which updates each component $\beta, \xi_0, \ldots, \xi_p, \tilde{\xi}_1, \ldots \tilde{\xi}_k$ one at a time using a mean zero normal disturbance. Multivariate updating from $[\gamma, \tilde{\gamma}|\beta, \xi, \tilde{\xi}, data]$ is accomplished using the algorithm described in McCandless et al [21].

A difficulty with this sampling scheme is that the likelihood for the primary data is expensive to compute. It requires calculating $P(Y_i, X_i|C_i, U_j)$ over all combinations of i and j. Alternatively, we can recognise that the expression for $P(Y, X|C)$ in (6) is a sample mean estimate of $E\{P(Y, U, X|C)\}$. We can use a quadrature estimate

$$P(Y, X|C) \ = \ \sum_{k=1}^{M} \omega_k \left[\frac{\exp\{Y(\beta X + \xi^T C + \tilde{\xi}^T g\{\hat{Z}_k\})\}}{1 + \exp\{\beta X + \xi^T C + \tilde{\xi}^T g\{\hat{Z}_k\}\}}\right] \left[\frac{\exp\{X(\gamma^T C + \hat{Z}_k)\}}{1 + \exp\{\gamma^T C + \hat{Z}_k\}}\right] \qquad (8)$$

based on a histogram of $\tilde{\gamma}^T U_1, \ldots \tilde{\gamma}^T U_m$. The quantities $\hat{Z}_k$ are the interval midpoints in the histogram and ω_k are the bin frequencies. In applications we find this summation much faster

to calculate compared to equation (6) because it requires far fewer evaluations of $P(Y, X|C, U)$.

4. Analysis Results for the Trihalomethane Data

4.1 Bayesian Adjustment for Unmeasured Confounding (BAYES).

Before applying the BAYES method to the trihalomethane data, we set a priori values for the knots used define the linear predictor $g\{.\}$ in equation (1). Following McCandless et al [21], we fit the logistic regression model given in equation (2) to the validation using maximum likelihood to estimate the bias parameter $\tilde{\gamma}$. The estimated CPS, computed by evaluating $\{\tilde{\gamma}^T U_j, \text{ for } j \in 1:m\}$, range from -0.1 to 2.0 with median equal 0.35 and interquartile range $(0.41, 0.67)$. Three knots are chosen as $0.41, 0.51$ and 0.67 to define approximate quartiles for the true distribution of the CPS.

We then apply BAYES to the data by sampling from the posterior density $P(\beta, \xi, \tilde{\xi}, \gamma, \tilde{\gamma}|data)$. As discussed in Section 2, the validation data in the Millennium Cohort Study are collected through disproportionately stratified sampling, with survey weights supplied with the accompanying documentation. We calculate the quantities in equations (6) and (8) by weighting the U_j using the survey weights. We then obtain a single MCMC chain of length 100 000 after suitable burn-in and thin the chain to retain 10 000 sample.

Figures 2 and 3 illustrate MCMC chains for model parameters and indicate that convergence is not ideal. Interestingly, convergence of the parameters β, ξ, γ is much better than for the bias parameters $\tilde{\xi}$ and $\tilde{\gamma}$. These results are somewhat expected because the model for unmeasured confounding is only weakly identifiable. As argued in Section 3.1.3, because U is unmeasured in the primary data, there is little information to distinguish between the intercept ξ_0 and linear predictor $\tilde{\xi}^T g\{Z(U)\}$. Similarly, the MCMC sampler cannot distinguish between γ_0 and $\tilde{\gamma}^T U$.

Sampler convergence problems are also reported in other contexts using non-identifiable models [27, 28].

We argue that the mixing of β, ξ and γ is satisfactory for computing posterior summaries, and that poor convergence of $\tilde{\xi}$ and $\tilde{\gamma}$ is not a serious concern. The reason is because the overall model fit for the primary and validation data is unaffected by poor mixing. To illustrate, Figure 3 presents the mixing of the deviance, given by

$$-2\log\left[\prod_{i=1}^{n} P(Y_i, X_i|C_i)\right] \times \left[\prod_{j=1}^{m} P(Y_j, X_j|C_j, U_j)\right],$$

calculated at each MCMC iteration. The deviance is a measure of overall model fit [9], with low values correspond to better fitting. We see in Figure 3 that the deviance values are stable across MCMC iterations. Poor convergence of the bias parameters has a modest impact on model fit. Because the convergence the MCMC chain for β, ξ and γ is satisfactory, we can use it to calculate valid posterior summaries.

Table 2 presents the results of the analysis under the heading "BAYES", which contain posterior means and 95% credible intervals for the exposure effect and covariate effects. We see that adjustment for unmeasured confounding has a sizable impact on estimation of the exposure effect. Trihalomethane exposure is associated with increased risk of low birthweight, with odds ratio 1.96, 95% CI (1.32,2.92), and these inferences are robust to adjustment for eight unmeasured confounders. The BAYES point estimate for β is shifted towards zero relative to the NAIVE analysis which ignores unmeasured confounding. This results make sense because, in Table 1, we see that when analyzing the validation data alone, adjustment for C_j and U_j drives the estimate of β towards zero compared an analysis ignoring U_j.

The interval estimate for the exposure effect calculated from BAYES is longer than for NAIVE, with length 1.60 versus 1.37. This result seems puzzling at first because an analysis of

the primary and validation data combined intuitively ought to yield less posterior uncertainty compared to a NAIVE analysis of the primary data alone. Nonetheless, the NAIVE analysis ignores bias uncertainty about unmeasured confounding. If there is bias in the registry data, then the NAIVE interval estimates will be falsely precise without nominal 95% coverage levels. McCandless et al. [21] investigate the frequentist performance of Bayesian credible interval which model bias from unmeasured confounding.

4.2 Maximum Likelihood Estimation to Adjust for Unmeasured Confounding

For comparison, we also apply a method for adjusting for unmeasured confounding which does not use Bayesian techniques. We call the method FREQ, meaning frequentist adjustment for unmeasured confounding, and we define the method as follows. First, fit the regression models in equations (1) and (2) in the validation data alone and compute maximum likelihood estimates of the bias parameters $\tilde{\xi}$ and $\tilde{\gamma}$. This is straightforward because U_j is observed. Next, we substitute the point estimates into the likelihood function for the primary data, given in equations (6) and (7), and maximize it with respect to (β, ξ, γ) using a Newton Raphson algorithm. Estimated standard errors for are (β, ξ, γ) obtained from the observed information matrix.

FREQ is as a fast analogue of BAYES. The validation data is used as a source of information about bias parameter, but there is no simultaneous analysis of multiple datasets. There is no propagation of uncertainty in the bias parameters through the analysis. We expect that interval estimates for the exposure effect calculated from FREQ may be falsely precise. FREQ can also be used as a diagnostic procedure to determine if BAYES is worthwhile. If FREQ and NAIVE

give markedly different inferences, then this indicates that unmeasured confounding is important and BAYES is worthwhile. Both methods use the same knots (q_1, q_2, q_3) in the linear predictor $g\{.\}$.

The results of applying FREQ to the trihalomethane data are given in the third column of Table 2. Comparing FREQ and BAYES, we can see that inferences are similar in the sense that both estimates of the exposure effect are driven towards zero relative the NAIVE analysis. Trihalomethane exposure is associated with risk of full term low birthweight. The association is robust even after having adjusted for the eight unmeasured confounders in the validation data.

BAYES interval estimate for β are wider than for FREQ. Additionally, the FREQ interval estimate for β has exactly the same length as the NAIVE estimate on the log odds scale. While FREQ corrects for unmeasured confounding using the same models as BAYES, the method ignores uncertainty in the bias parameters. It assumes that the bias parameters $\tilde{\xi}$ and $\tilde{\gamma}$ are known exactly. In contrast, BAYES models and propagates uncertainty through the analysis. This has a large impact on the length of interval estimates.

One strategy for reconciling the difference between BAYES and FREQ is to study the effect of admitting uncertainty in the bias parameters the posterior variance of β. Using the relation $Var[A] = E\{Var[A|B]\} + Var\{E[A|B]\}$, we can write

$$Var[\beta] = E\{Var[\beta, \xi, \gamma|\tilde{\xi}, \tilde{\gamma}]\} + Var\{E[\beta, \xi, \gamma|\tilde{\xi}, \tilde{\gamma}]\}, \tag{9}$$

where expectations and variances are over posterior uncertainty in model parameters. This gives an ANOVA type decomposition where the first term models uncertainty in β *within* bias parameters, while the second term models uncertainty *between* bias parameters [29]. Denote $V_{between} = Var\{E[\beta, \xi, \gamma|\tilde{\xi}, \tilde{\gamma}]\}$ and $V_{within} = E\{Var[\beta, \xi, \gamma|\tilde{\xi}, \tilde{\gamma}]\}$. When the quantities $\tilde{\xi}$ and $\tilde{\gamma}$ are known a priori, as is assume in FREQ, then $V_{between}$ is equal to zero and the posterior

variance of β reduces to V_{within}. Conversely, when we admit uncertainty in the bias parameters, then $V_{between}$ is non-zero.

The ratio

$$\frac{V_{between}}{V_{between} + V_{within}}$$

models the proportion of uncertainty in β that is attributable to bias. As the sample size n increase, the quantity V_{within} will tend to zero, while $V_{between}$ remains constant. Thus the ratio illustrates how bias uncertainty tends to dominate total uncertainty asymptotically in observational studies with bias from unmeasured confounding. Further discussion is given by Gustafson [29]) and Greenland [1]. We can get a rough estimate of the ratio by comparing the width of the 95% interval estimates for the exposure effect on the log odds scale. For BAYES the width is 0.79 versus 0.60 for FREQ. Thus in the trihalomethane data, uncertainty from unmeasured confounding accounts for nearly one third of the total posterior uncertainty for the exposure effect. FREQ and NAIVE substantially under report the this uncertainty.

5. The Performance of BAYES and FREQ in Synthetic Data

The preceding analysis motivates questions about the performance of the BAYES in more general settings. For example, is the scalar $Z(U)$ from equation (1) an adequate summary of U, giving unconfounded exposure effect estimates? Does modelling uncertainty in the bias parameters give meaningful improvement in the coverage probability of interval estimates? A further issue is the sample size m of the validation data. If m is small, then we might expect that BAYES and FREQ will break down because they fail to recover the marginal distribution of propensity scores in the source population. We explore these issues using simulations by analyzing synthetic datasets which contain confounding from multiple unmeasured variables.

5.1 Simulation Design

We generate and analyze ensembles of 100 pairs of synthetic datasets, where each pair consists of primary data with $n = 1000$ and validation data with $m = 100, 250, 500$ or 1000. We consider the case where there are four measured confounders and four additional unmeasured confounders (thus C is a 5×1 vector and U is 4×1). Primary data ($n = 1000$) and validation data (m =75, 100, 250, 500 and 1000) are generated using the following algorithm:

1. Simulate $\{C_i, C_j\}$ for $i \in 1:n, j \in 1:m$, and also $\{U_i, U_j\}$ for $i \in 1:n, j \in 1:m$, where each component of C_i, C_j, U_i, U_j is independent and identically distributed as a N(0,1) random variable.

2. For fixed $\gamma_0, \ldots, \gamma_4 = 0.1$, and $\tilde{\gamma}_1, \ldots, \tilde{\gamma}_4 = 0.2$, simulate $\{X_i, X_j\}$ for $i \in 1:n, j \in 1:m$ for using the logistic regression model of equation (2).

3. For fixed $\beta = 0$, $\xi_0, \ldots, \xi_4 = 0.1$ and $\tilde{\xi}_1, \ldots, \tilde{\xi}_4 = 0.2$, simulate $\{Y_i, Y_j\}$ for $i \in 1:n, j \in 1:m$ for using the model

$$\text{Logit}[P(Y = 1|X, C, U)] \;\; = \;\; \beta X + \xi^T C + \tilde{\xi}^T U.$$

Note that the first component of C_i and C_j is equal to one so that γ_0 and ξ_0 are regression intercept terms.

We fix $\beta = 0$ to model the setting where there is no exposure effect. The choice for $\xi, \tilde{\xi}, \gamma, \tilde{\gamma}$ models moderate but realistic log odds ratios that are encountered in epidemiologic investigations [30]. The bias parameters $\tilde{\gamma}$ and $\tilde{\xi}$ govern the association between the unmeasured confounder and the treatment and outcome respectively. Setting $\tilde{\gamma}$ and $\tilde{\xi}$ to be large in magnitude induces bias from unmeasured confounding.

We analyze the 100 pairs of datasets across for each combination of n and m using BAYES, FREQ and NAIVE to obtain point and 80% interval estimates of the exposure effect β. Sampler convergence is assessed using separate trial MCMC runs.

5.2 Results

Figure 4 summarizes the performance of BAYES, FREQ and NAIVE analyses of 100 synthetic datasets. The upper three panels quantify bias and efficiency of point estimates for the exposure effect $\beta = 0$, as a function of m the sample size in the validation data. The lower three panels quantify coverage probability and average length of 80% interval estimates for β.

For the NAIVE analysis, estimates of β should perform poorly because the method ignores unmeasured confounding. This is apparent in Figure 3. In the top right panel, the blue curve lies far from zero indicating that NAIVE estimates are badly biased. The blue curve is flat and does not depend on m because the NAIVE analysis ignores the validation completely. Similarly, in the lower right panel, the blue curve hovers below 60%, indicating that the coverage probability of NAIVE interval estimates is far below the nominal level of 80%.

In contrast, BAYES and FREQ eliminate unmeasured confounding over a wide range of values for m. In the upper panels, we see that the blue curves hover near zero. BAYES and FREQ are essentially unbiased for all m under consideration. Summarizing the four unmeasured confounders using the summary score $Z(U)$ appears to reduce confounding. We do not consider the case where $m < 100$ corresponding to validation data which is less than 10% the size of the primary data with $n = 1000$. The reason is because the validation data contain little information about the bias parameters. The model for the primary data given in equation (6) is only weakly identifiable. Sampler convergence deteriorates and point estimates of $\tilde{\xi}, \tilde{\gamma}$ are highly variable.

There is little information available for adjustment for unmeasured confounding.

The lower panels of Figure 3 summarize the performance of interval estimates for the exposure effect β. BAYES interval estimates have improved coverage probability compared to FREQ or NAIVE. As m tends to zero, the coverage probability of FREQ drops off more sharply compared to BAYES. Ignoring uncertainty in the bias parameters appears to adversely affects interval estimation when the validation data is small. We note that the difference in coverage estimates for BAYES versus FREQ is modest compared to the simulation standard errors. However, reducing the standard errors by one half requires a fourfold increase in the number of simulations, which is prohibitively expensive.

Somewhat surprisingly, inferences from BAYES may actually be more efficient than FREQ or NAIVE. As expected, when the validation data is small BAYES interval estimates are wider. This is consistent with intuition and the analysis of the trihalomethane data. Modelling uncertainty in the bias parameters gives an increase in uncertainty in the exposure effect. But for large m BAYES intervals are actually shorter than FREQ or NAIVE. Furthermore, BAYES point estimates of β have smaller variance. Intuitively, the validation data contain information about β which is ignored by FREQ. In equation (9), the quantity V_{within} tends to decrease while the bias uncertainty V_{bias} increases. The resulting posterior variance for β is smaller than the large sample variance from either FREQ or NAIVE. This reinforces the notion that a joint analysis of the primary and validation data may be preferable. In Figure 3, there appears to be little reason to choose FREQ over BAYES. When the validation data is small, FREQ will under report uncertainty, and when the validation data is large FREQ will suffer on efficiency.

6. Discussion

In this article, we describe a flexible procedure for adjusting for a vector of unmeasured confounders using validation data. We summarize the unmeasured variables using a scalar summary score $Z(U)$, which can be interpreted as the propensity score adjusted for measured confounders. As discussed in Section 3, conditioning on $Z(U)$ breaks association between X and U, within levels of C. To adjust for unmeasured confounding in the trihalomethane data example, we need only update and adjust for $Z(U)$. This approach is similar to the sensitivity analysis methodology of Brumback et al. [31]. It overcomes the challenge of model-based adjustment for a large number of variables by estimating marginal exposure effects, which are averaged over the distribution of unmeasured confounders.

Our case-study reveals that Trihalomethane exposure is associated with increased risk of full-term low birthweight, and this association persists even after adjustment for eight unmeasured confounders. Furthermore, analyses which ignore uncertainty from unmeasured confounding yield interval estimates which are too narrow. Despite the large sample sizes in the primary and validation data, fully one third of the posterior uncertainty in the exposure effect is attributable to unmeasured confounding.

Simulations illustrate that ignoring bias uncertainty can adversely affect the coverage probability of interval estimates. Additionally, a joint analysis of the primary and validation data sometimes improves the efficiency of exposure effects estimates relative to an analysis which handle the datasets separately. The reason is because the validation data may contain information about other population quantities that can be used to improve estimation. If it is reasonable to assume that all data are drawn from the same source population, then the validation data should not be used simply as a source of prior information about unmeasured confounders.

A limitation of our method is that it ignores variability in the empirical estimate of equation (6). While this quantity is unbiased for $P(Y, X|C)$ in equation (5), it may have high variance. Supplying more validation data will alleviate this problem, but also at issue is the dimension of U and the nature of the dependence of $P(Y|X, C, U)P(X|C, U)$ on U. If the bias parameters $\tilde{\xi}$ and $\tilde{\gamma}$ are large in magnitude, meaning that U contains powerful confounders, then the variability of $P(Y|X, C, U)P(X|C, U)$ will increase. To capture this variability, one extension of our method would be to model uncertainty in the quantity in equation using a Bayesian bootstrap [9].

Appendix

Parallelling arguments by Rosenbaum and Rubin [18], we detail the theoretical behind using the summary score $Z(U)$ in equations (1) and (2) for control of unmeasured confounders. For the trihalomethane data, let $Y_{\{1\}}$ and $Y_{\{0\}}$ denote potential outcomes for birth weight for an infant [32]. The quantity $Y_{\{1\}}$ models the birth weight when the mother is exposed to trihalomethane $\geq 60\mu/L$, and takes value one if the infant has full term low birth weight and zero otherwise. The quantity $Y_{\{0\}}$ models the corresponding potential outcome for birth weight assuming the mother has trihalomethane less than $60\mu/L$. Let

$$Y = Y_{\{X\}} = \begin{cases} Y_{\{1\}} \text{ if } X = 1 \\ \\ Y_{\{0\}} \text{ if } X = 0 \end{cases}$$

denote the observed potential outcome. Following convention for causal inference in observational data, we assume that there is no interference between units and that conditional on (C, U), there is no unmeasured confounding, meaning that $(Y_{\{1\}}, Y_{\{0\}}) \perp\!\!\!\perp X|(C, U)$ [32]. This implies that

$$P(Y|X, C, U) = P(Y_{\{X\}}|X, C, U) = P(Y_{\{X\}}|C, U)$$

for $X = 0, 1$. Effect measures computed from $P(Y|X, C, U)$ have a causal interpretation.

Theorem 1: Assume that the model in equation (2) is correct, where $Z(U) = \tilde{\gamma}^T U$. Then $X \perp\!\!\!\perp U|C, Z(U)$.

Proof: Following Rosenbaum and Rubin [18] Theorem 1, it suffices to show that $P(X = 1|U, C, Z(U)) = P(X = 1|C, Z(U))$. We have $E\{P(X = 1|U, C, Z(U))|Z(U), C\} = E\{(1 + \exp(\gamma^T C + Z(U))^{-1}|Z(U), C\} = (1 + \exp(\gamma^T C + Z(U))^{-1}$. When $Z(U)$ is fixed, then the right hand side does not depend on U, proving the identity. ∎

In principle, this result could be generalized to exposure models other than that given in equation (2). Any function of U, denoted $Z(U)$, will satisfy equation (3) provided that $P(X = 1|C, U)$ depends on U only through $Z(U)$.

The following theorem shows that effect measures computed from the conditional distribution $P(Y|X, C, Z(U))$ have a causal interpretation. To control for confounding bias due to U, it suffices to stratify on $(C, Z(U))$. We can estimate the exposure effect by using models which assume that $Y \perp\!\!\!\perp U|X, C, Z(U)$.

Theorem 2: Assume that $(Y_{\{1\}}, Y_{\{0\}}) \perp\!\!\!\perp X|(C, U)$ and that $X \perp\!\!\!\perp U|C, Z(U)$, then $(Y_{\{1\}}, Y_{\{0\}}) \perp\!\!\!\perp X|(C, Z(U))$.

Proof: Again, following Theorem 3 of Rosenbaum and Rubin [18], we show that

$$P(X = 1|Y_0, Y_1, C, Z(U)) = P(X = 1|C, Z(U)) = P(X = 1|C, U).$$

We have

$$\begin{aligned} P(X=1|Y_0,Y_1,C,Z(U)) &= E\{P(X=1|Y_0,Y_1,C,Z(U),U)|Y_0,Y_1,C,Z(U)\} \\ &= E\{P(X=1|Y_0,Y_1,C,U)|Y_0,Y_1,C,Z(U)\} \quad (10) \\ &= E\{P(X=1|C,U)|Y_0,Y_1,C,Z(U)\} \quad (11) \\ &= E\{(1+\exp(\gamma^T C+Z(U))^{-1}|Y_0,Y_1,C,Z(U)\} \\ &= (1+\exp(\gamma^T C+Z(U))^{-1} \\ &= P(X=1|C,U). \end{aligned}$$

Equation (10) holds because $Z(U)$ is a function of U, while equation (11) holds because $(Y_{\{1\}}, Y_{\{0\}}) \perp\!\!\!\perp X|(C,U)$. ∎

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noindent

Table 1: Odds ratios (95% interval estimates) for the association between covariates and risk of full-term low birthweight.

Description		Odds ratio (95% interval estimate)		
		NAIVE	BAYES	FREQ
Trihalomethanes $> 60\mu g/L$	$\exp(\beta)$	2.27 (1.68, 3.06)	2.03 (1.37, 2.93)	2.08 (1.54, 2.81)
Mother's age				
≤ 20	$\exp(\xi_1)$	0.35 (0.16, 0.77)	0.32 (0.15, 0.66)	0.34 (0.16, 0.76)
20 - 24	$\exp(\xi_2)$	1.86 (1.29, 2.66)	1.76 (1.24, 2.47)	1.88 (1.30 , 2.68)
25 - 29*	.	1.0	1.0	1.0
30 - 34	$\exp(\xi_3)$	0.67 (0.42, 1.05)	0.61 (0.40, 0.95)	0.66 (0.42, 1.05)
≥ 35	$\exp(\xi_4)$	0.89 (0.53, 1.47)	0.87 (0.53, 1.40)	0.89 (0.53, 1.47)
Male baby	$\exp(\xi_5)$	0.87 (0.65, 1.16)	0.84 (0.64, 1.12)	0.86 (0.64, 1.15)

* Reference group

Table 2: Odds ratios (95% interval estimates) for the association between covariates and risk of full-term low birthweight in the MCS data alone ($m = 1333$).

Description	Odds ratio (95% interval estimate)	
	Adjusting for C_j only	Adjusting for C_j and U_j
Trihalomethane $> 60\mu g/L$	2.52 (1.03, 6.15)	2.39 (0.94, 6.11)
Mother's age		
≤ 20	0.54 (0.08, 3.47)	0.27 (0.04, 1.88)
20 - 24	1.81 (0.66, 4.97)	0.99 (0.33, 2.98)
25 - 29*	1.0	1.0
30 - 34	0.37 (0.09, 1.48)	0.52 (0.12, 2.18)
≥ 35	0.79 (0.19, 3.19)	1.31 (0.30, 5.73)
Male baby	0.92 (0.39, 2.13)	0.80 (0.33, 1.92)
Lone parent family	.	1.20 (0.38, 3.80)
Number of live children	.	0.86 (0.69, 1.07)
Smoking during pregancy	.	4.08 (1.34, 12.40)
Non-white etnicity	.	3.88 (1.00, 15.11)
Alcohol during pregancy	.	1.77 (0.97, 3.22)
Body mass index† (Kg/m^2)	.	0.75 (0.38, 1.49)
Income (1=Low, 2=Med, 3=High)	.	0.44 (0.17, 1.18)
High school diploma	.	1.07 (0.43, 2.68)

* Reference group

† Measured prior to pregnancy

Figure 1: Sampler convergence for the treatment effect β, and the covariate effects ξ and γ.

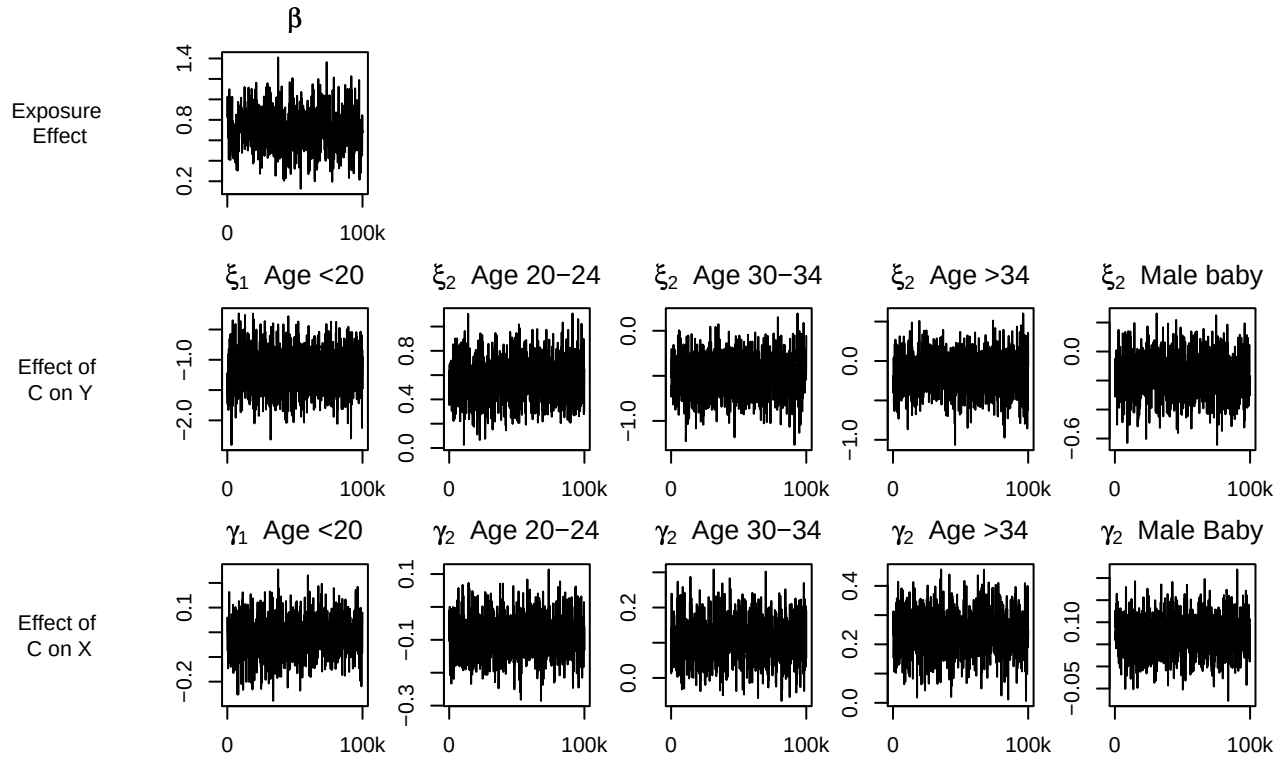


Figure 2: Sampler convergence for bias parameters $(\tilde{\xi}, \tilde{\gamma})$ and regression intercept terms (ξ_0, γ_0).

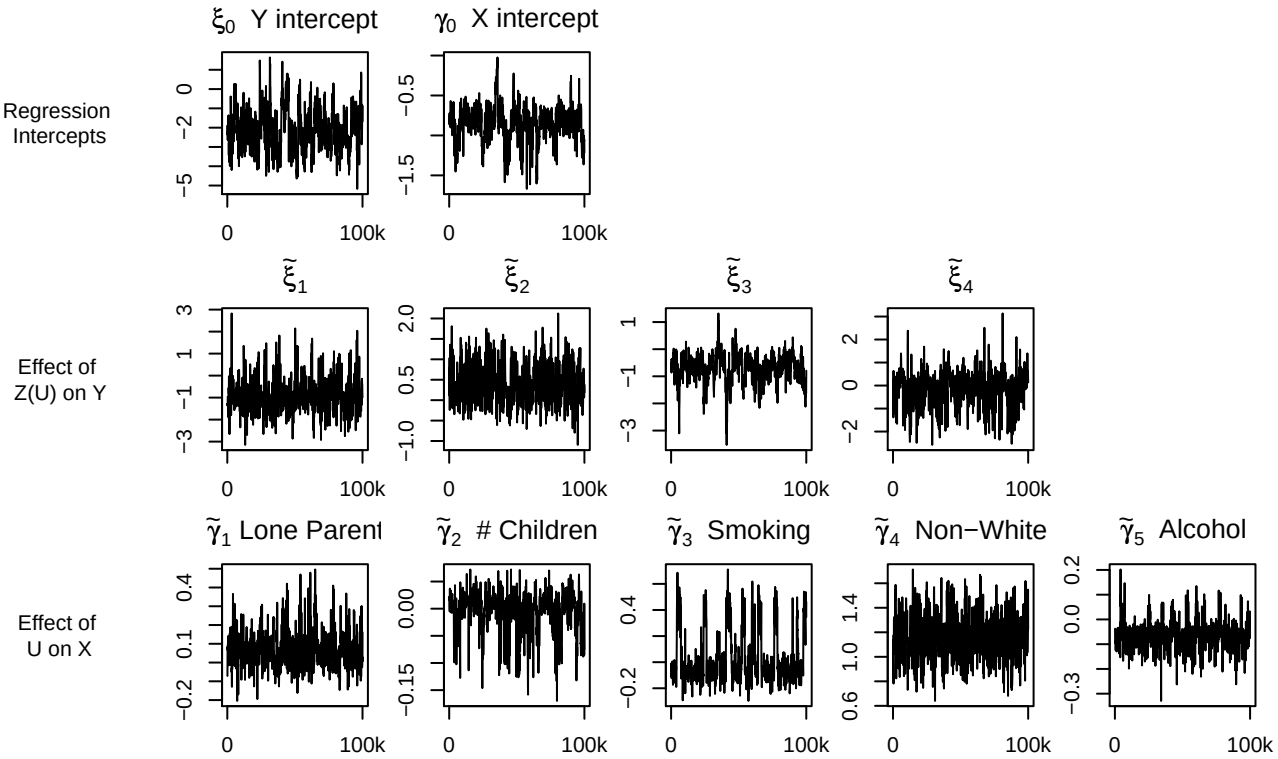


Figure 3: Sampler convergence the deviance evaluated over MCMC iterations of $(\beta, \xi, \tilde{\xi}, \gamma, \tilde{\gamma})$.

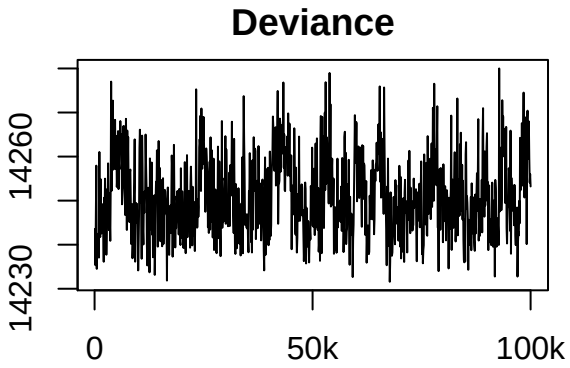
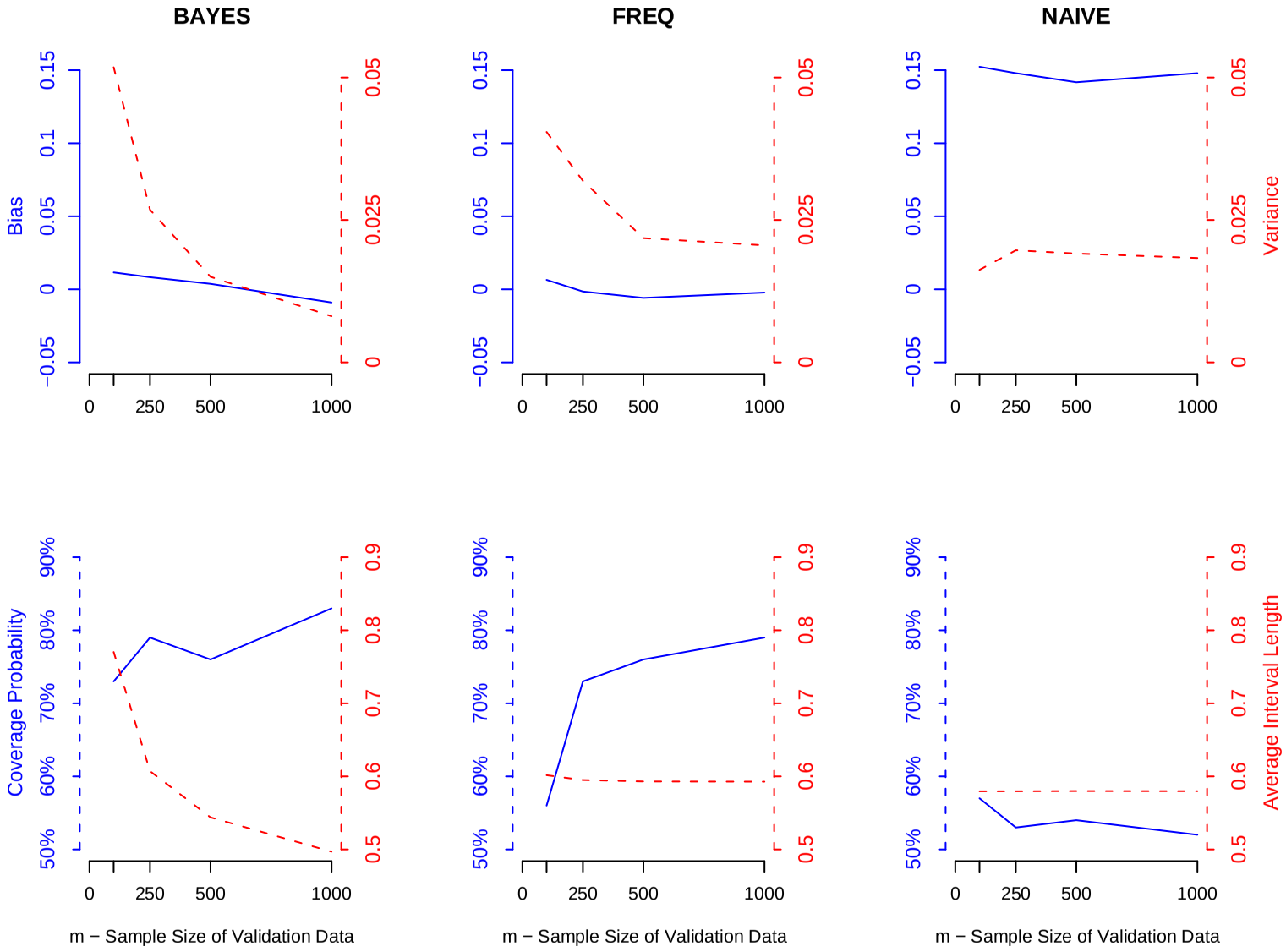


Figure 4: Performance of point and interval estimates for the exposure effect β calculated using either BAYES, FREQ or NAIVE. The top panels describe the bias (simulation standard error (SE) < 0.02) and variance (SE <0.006) of point estimates. The bottom panels describe the coverage probability (SE $<4\%$) and length (SE <0.007) of 80% interval estimates.



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