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Uncertainty in Propensity Score Estimation: Bayesian Methods for Variable Selection and Model Averaged Causal Effects

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Abstract

Causal inference with observational data frequently relies on the notion of the propensity score (PS) to adjust treatment comparisons for observed confounding factors. As decisions in the era of "big data" are increasingly reliant on large and complex collections of digital data, researchers are frequently confronted with decisions regarding which of a high-dimensional covariate set to include in the PS model in order to satisfy the assumptions necessary for estimating average causal effects. Typically, simple or ad-hoc methods are employed to arrive at a single PS model, without acknowledging the uncertainty associated with the model selection. We propose three Bayesian methods for PS variable selection and model averaging that 1) select relevant variables from a set of candidate variables to include in the PS model and 2) estimate causal treatment effects as weighted averages of estimates under different PS models. The associated weight for each PS model reflects the data-driven support for that model's ability to adjust for the necessary variables. We illustrate features of our proposed approaches with a simulation study, and ultimately use our methods to compare the effectiveness of surgical vs. nonsurgical treatment for brain tumors among 2,606 Medicare beneficiaries. Supplementary materials are available online.

Keywords

Bayesian statistics; causal inference; comparative effectiveness; model averaging; propensity score

1 INTRODUCTION

Causal inference with observational data frequently relies on methods based on the propensity score (PS) (Rosenbaum and Rubin, 1983), as these methods are designed to estimate causal treatment effects by adjusting for observed confounding factors. PS methods typically unfold in two stages; first, a model is fit to estimate the probability of assignment to treatment (the estimated PS), and then outcomes of interest are compared between treated and untreated units having similar values of the estimated PS. As with all methods for making causal inferences with observational data, PS methods require that the researcher specify the confounders necessary to satisfy the assumption of strong ignorability (i.e., the "no unmeasured confounding" assumption), rendering correct specification of the PS model

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SUPPLEMENTARY MATERIALS

Web Appendix: A supplementary appendix with additional simulation studies, a complement to the analysis of Medicare data of Section 5, and a detailed account of the MCMC algorithm for the SSVS approach of Section 3.3.

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of vital importance. However, the correct set of variables to include in the PS model is rarely known, and researchers in the modern era of "big data" are increasingly confronted with decisions regarding which of many covariates to include in the PS. Such is often the case when, for example, large administrative data bases are used to compare the effectiveness of medical therapies as they are employed in routine clinical practice.

One recommendation for choosing a PS model is to simply include every available covariate. Aside from the efficiency sacrificed by the inclusion of possibly extraneous variables, this "kitchen sink" approach is becoming increasingly untenable as PS methods are deployed in high-dimensional data settings. In attempt to include only a subset of relevant variables in the PS model, researchers often combine expert knowledge with traditional or ad-hoc procedures to select variables that are predictive of treatment assignment (Austin, 2008). Methods targeting the subset of variables that best predicts treatment assignment have noted drawbacks in terms of efficiency and finite-sample bias. In fact, the target set of variables to include in the PS model should also take into account how covariates are related the outcome (Rubin and Thomas, 1996; Rubin, 1997; Brookhart et al., 2006). Despite disagreement about whether data-driven approaches to select the PS model should incorporate information in the outcome (Rubin, 2008), the purported benefit of including important outcome predictors has spawned data-driven methods to do so, such as the reasoned algorithmic approach of Schneeweiss et al. (2009).

Regardless of the exact procedure used, current methods for selecting PS models fail to account for the uncertainty in the selection, and have never been considered within a Bayesian framework. Once a researcher arrives at a particular PS model, all subsequent inference conditions on this single model. The lack of methods to formally acknowledge the uncertainty in PS model selection is an important barrier to tailoring PS methods to modern research priorities such as the Big Data Research and Development Initiative put forth by the United States government. To acknowledge the inherent uncertainty in the specification of the PS model, we propose three Bayesian procedures for PS models that 1) select relevant variables from a (potentially large) set of candidate variables to include in the PS and 2) estimate causal treatment effects as weighted averages of estimates under different PS models. One vital feature of our approach is that the associated weight for each PS model reflects the data-driven support for that model's ability to adjust for the desired variables. Thus, our methods account for the uncertainty associated with what is arguably the most important choice in a PS analysis: the choice of which variables to include in the PS.

Our proposed methodology has important points of contact with the recently proposed method for "Bayesian Adjustment for Confounding" (BAC), which Wang et al. (2012) introduce as a means for selecting variables to include in a regression model based on associations with both an exposure and an outcome. Although Wang et al. (2012) do not explicitly consider the PS, discussions of that work pointed towards similar notions of Bayesian confounder selection in PS models (McCandless, 2012; Vansteelandt, 2012), which we explore in detail here. In founding our approach from a Bayesian perspective, our methodology is a continuation of recent work investigating Bayesian PS estimation based on a single joint likelihood representing both the PS and outcome models simultaneously (McCandless et al., 2009; Zigler et al., 2013), which is distinct from traditional sequential PS approaches that first estimate the PS model to obtain the estimated PS, then treat these estimated quantities as fixed and known for estimation of the outcome model.

Section 2 of this paper reviews PS methods and draws distinctions between traditional sequential and joint Bayesian estimation. Section 3 outlines three related approaches for Bayesian variable selection and model averaging for PS methods. Section 4 presents a simulation study to illustrate the key features of our proposed approaches. Section 5

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compares the effectiveness of surgical vs. nonsurgical treatment for malignant brain tumors among 2,606 Medicare beneficiaries. We conclude with a discussion.

2 BAYESIAN PROPENSITY SCORE ESTIMATION

In this section, we briefly review the motivation for PS methods and summarize joint Bayesian PS estimation as distinct from traditional sequential procedures. We consider likelihood-based methods that estimate causal effects with a model for the outcome that adjusts for the PS.

2.1 Estimating Causal Effects with Propensity Scores

For the ith observational unit, denote the binary treatment with $X_i = 0, 1$, the outcome of interest with Y_i, and a vector of p measured pre-treatment covariates with $U_i = (U_{i1}, U_{i2}, \ldots, U_{ip})$. Rosenbaum and Rubin (1983) defined the PS as the conditional probability of assignment to treatment $X = 1$, given U, and illustrated that the PS enjoys the properties of a *balancing score* in that, conditional on the PS, the individual covariates are orthogonal to the treatment indicator: $X \perp\!\!\!\perp U|PS$. The balancing property of the PS combined with the assumption of strongly ignorable treatment assignment (i.e., that there are no unmeasured confounders) implies that outcome comparisons between treated and untreated units with the same value of the PS represent estimates of average causal effects (Rosenbaum and Rubin, 1983). One salient benefit of estimating causal effects in this manner is that it does not necessarily rely on a detailed parametric model for the outcome. Rather, covariate information is condensed into a scalar quantity (the PS), adjustment for which can recover causal estimates without strong parametric assumptions pertaining to how covariates relate to Y.

2.2 Models for Propensity Score Estimation and the Average Causal Effect

Typically, the PS, defined as $E[X|U]$, is estimated with a model for the relationship between X and U, which we represent with the generalized linear model:

$$g_x(E[X_i|U_i]) = \sum_{k=0}^{p} \alpha_k \gamma_k U_{ik}, \quad (1)$$

where we define $U_{i0} \equiv 1$ for all i to denote a model intercept. Here, γ_k ($k \geq 1$) represents the coefficient describing the association between U_k and the probability of treatment assignment to $X = 1$, and $g_x(\cdot)$ is a link function. An individual PS model is denoted with a particular value of the vector α, denoted $\alpha^m = (\alpha_0^m, \alpha_1^m, \alpha_2^m, \ldots, \alpha_p^m)$, where each $\alpha_k^m = 1, 0$ represents whether U_k is or is not included in the mth PS model. Throughout, we fix $\alpha_0 = 1$ to force the inclusion of a model intercept. For brevity, we refer to a particular α^m as a particular model, and say that U_k with $\alpha_k^m = 1$ are variables included in model α^m. In general, a particular U_k could represent a derived function such as an interaction or higher order polynomial term.

Estimating causal effects with the PS often relies on a model for the outcome, conditional on the PS. While models for general outcome types are permitted, we simplify notation by considering only generalized linear models for binary outcomes of the form:

$$g_y(E[Y_i|X_i, U]) = \beta_0 + \beta_X X_i + h(PS(\gamma, \alpha, U_i); \xi) + \sum_{k=1}^{p} \alpha_k \delta_k U_{ik}, \quad (2)$$

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where $Y_i = 0, 1$, $g_y(\cdot)$ is a link function, and the notation $PS(\gamma,\alpha,U_i)$ explicates that the PS for the ith unit is a deterministic function of (γ,α,U_i), that is, $PS(\gamma,\alpha,U_i)=g_x^{-1}(\Sigma\alpha_k\gamma_k U_{ik})$. For this outcome model, β_X represents the conditional treatment effect at a given value of the PS, and treatment-by-PS interactions could be included. The function $h(PS(\gamma,\alpha,U_i);\xi)$ denotes how the PS enters the outcome model depending on unknown parameters ξ, and the $\Sigma\alpha_k\delta_k U_{ik}$ represents residual adjustment for individual covariates in addition to the PS. Note that the $PS(\gamma,\alpha,U)$ and the residual adjustment term $\Sigma\alpha_k\delta_k U_{ik}$ depend on the same α, implying that, for a given α^m, the PS is comprised of the variables in α^m, and residual adjustment for an individual U_k is conducted in the outcome model if and only if that variable is included in α_m. For example, $h(PS(\gamma,\alpha,U_i);\xi)$ could denote dummy variables indicating membership in subclasses defined by quantiles of the PS, with $\Sigma\alpha_k\delta_k U_{ik}$ denoting linear adjustment for each covariate included in the PS. We detail the rationale for including the residual adjustment $\Sigma\alpha_k\delta_k U_{ik}$ in subsequent sections, but note here that this strategy is akin to doubly robust procedures that will estimate causal effects if either the PS model or the residual adjustment is correctly specified (Little and An, 2004; Bang and Robins, 2005).

Upon specification of the U required to satisfy the assumption of strongly ignorable treatment assignment, the average causal effect (ACE) is defined as $\Delta = E_U\{E[Y|X = 1,U] - E[Y|X = 0,U]\}$, which, provided that α contains the necessary U, can be obtained by calculating the average differences between the predicted values from model (2) with X set to 1 and the analogous predicted values with X set to 0. We revisit the implications of estimating the ACE under different values of α in Section 3.

2.3 Joint Bayesian PS Estimation

Traditional PS estimation is carried out sequentially in the sense that the researcher first specifies the variables to include in the PS (i.e., sets $\alpha = \alpha^0$) and estimates γ from (1). Then, the selected α^0, the estimated $\hat{\gamma}$, and implied estimated PS are used for estimation of (2), that is, estimation of causal effects is based on $g_y(E[Y_i|X_i,U_i])=\beta_0+\beta_X X_i+h(PS(\hat{\gamma},\alpha^0,U_i);\xi)+\Sigma\alpha_k^0\delta_k U_{ik}$. Several limitations of this sequential approach have been noted, including the misstatement of uncertainty due to treating $\hat{\gamma}$ (and hence, the estimated PS) as fixed and known in the outcome model, when these quantities are in fact estimated with error (Gelman and Hill, 2007). More pertinent to model uncertainty, the decision regarding which variables to include in the PS (i.e., setting $\alpha = \alpha^0$) is made in the first stage and also treated as fixed in the second stage.

In contrast to sequential methods, joint Bayesian methods have been recently introduced to estimate causal effects with a pre-specified $\alpha = \alpha^0$ (McCandless et al., 2009; Zigler et al., 2013). Extending these methods to settings with unknown α, joint Bayesian inference relies on the following likelihood that simultaneously considers quantities in the PS and outcome models:

$$L(\boldsymbol{Y},\mathbf{X}|\mathbf{U},\gamma,\alpha,\beta,\delta)=\prod_{i=1}^{n}\left\{[g_x^{-1}(\sum_{k=0}^{p}\alpha_k\gamma_k U_{ik})]^{X_i}[1-g_x^{-1}(\sum_{k=0}^{p}\alpha_k\gamma_k U_{ik})]^{1-X_i}\right. \quad (3)$$

$$\times[g_y^{-1}(\beta_0+\beta_X X_i+h(PS(\gamma,\alpha,U_i);\xi)+\sum_{k=1}^{p}\alpha_k\delta_k U_{ik})]^{Y_i}[1-g_y^{-1}(\beta_0+\beta_X X_i+h(PS(\gamma,\alpha,U_i);\xi)+\sum_{k=1}^{p}\alpha_k\delta_k U_{ik})]^{1-Y_i}, \quad (4)$$

where, here and throughout, boldface represents vectors and matrices for the entire sample of n units. This likelihood, coupled with a prior distribution $p(\gamma,\alpha,\beta,\xi,\delta)$ serves as the basis for joint Bayesian estimation of causal effects. One key feature of joint Bayesian estimation

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with the likelihood in (3)–(4) is that the α and γ determining the PS are treated as unknown quantities, uncertainty about which is integrated out of posterior distributions of causal effects. Not only does this propagate uncertainty regarding the variables contained in the PS model and the estimates of the PS themselves, but it also allows information from the outcome model to contribute to the PS model.

2.4 Model Feedback

Note that some parameters (namely, γ and α) appear in both term (3) and term (4) of the above likelihood. As a result, posterior distributions of these parameters depend on both the PS and outcome models, a phenomenon referred to as "feedback" because quantities in the outcome model will indirectly inform quantities in the PS model. With the likelihood in (3)–(4), there are two distinct sources of feedback. The first relates to the appearance of γ in both terms of the likelihood, meaning that Y and other quantities in the outcome model inform estimation of γ and hence, the PS. This type of feedback, which we refer to here as γ-feedback, has been previously considered when α is fixed and known, and was shown to be potentially detrimental to PS estimation (Zigler et al., 2013). Specifically, Zigler et al. (2013) show that, conditional on any model α, γ-feedback from the outcome model into the PS model can distort the balancing-score property of the PS and yield biased estimates of causal effects. Zigler et al. (2013) also show that one way to prevent distortion of the PS is to conduct residual adjustment for every covariate that appears in the PS model. In other words, when conducting joint Bayesian PS estimation, we specify the outcome model (2) to include residual adjustment via $\Sigma\alpha_k\delta_k U_{ik}$.

The inclusion of the parameter α in terms (3) and (4) of the likelihood leads to another source of feedback. We refer to this feedback as α-feedback which, in principle, will allow variable selection to be conducted based jointly on covariate associations with X and with Y. The use of α-feedback to select variables based on associations with both X and Y is an important departure from traditional PS approaches. Note here that α feedback would occur even without residual adjustment with $\Sigma\alpha_k\delta_k U_{ik}$ because α implicitly appears in the outcome model via $h(PS(\gamma,\alpha,U_i);\xi)$.

Either source of feedback could also be "cut" by conducting an approximately-Bayesian analysis that still uses the likelihood in (3)–(4), but updates some parameters from conditional posterior distributions that exclude some terms of the likelihood and prior distributions (Lunn et al., 2009; Liu et al., 2009). For example, updating α from $p(\alpha|X,U,\gamma)$ would "cut the feedback" between the outcome model and the selection of variables. We detail one such approximately-Bayesian approach in Section 3.2.

3 BAYESIAN VARIABLE SELECTION AND MODEL AVERAGING FOR PROPENSITY SCORES

As alluded to in Section 2.2, the introduction of the parameter α denoting whether each variable is included in the PS model reflects the model uncertainty. Essentially, by adding the parameter α, we can estimate the causal treatment effect as a weighted average over different PS and outcome models, with weights corresponding to data-driven support of whether each variable should or should not be included for adjustment (Hoeting et al., 1999).

More formally, let $\mathscr{M}$ denote the set of all models being considered, which, for our purposes, will consist of the $M = 2^p$ possible values of $\alpha^m = (1, \alpha_1^m, \alpha_2^m, \ldots, \alpha_p^m)$ (recall α_0 is fixed to 1). With prior probability of model m denoted as $p(\alpha^m)$, the posterior probability

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of model m is $p(\alpha^m|Data)=\frac{p(\alpha^m)p(Data|\alpha^m)}{\Sigma_{\alpha^i\in\mathscr{M}}p(\alpha^i)p(Data|\alpha^i)}$. Our goal is estimation of the average causal effect of treatment with $X = 1$ vs. treatment with $X = 0$, making our target for inference the posterior distribution of the ACE, which will be a weighted average of estimates of Δ under each model in $\mathscr{M}$, with weights corresponding to the posterior probability of each model:

$$p(\Delta|Data) \approx \sum_{\alpha^m\in\mathscr{M}} p(\Delta^{\alpha^m}|\alpha^m, Data)p(\alpha^m|Data), \quad (5)$$

where $\Delta^{\alpha^m} = E_{U_{\alpha^m}}\{E[Y|X = 1,U_{\alpha^m}]-E[Y|X = 0,U_{\alpha^m}]\}$ and U_{α^m} denotes the subset of U in α^m. Note that Δ^{α^m} will not necessarily share the same interpretation as the causal effect Δ, resulting in the approximation in (5). The key issue for interpreting Δ^{α^m} as an estimate of the causal effect pertains to whether α^m contains the confounders necessary to satisfy the assumption of strong ignorability; failure to include even one confounder would result in a Δ^{α^m} that does not share the causal interpretation of Δ. In theory, there exists some minimal model, α^*, that is sufficient for satisfying the assumption of strong ignorability and interpreting Δ^{α^*}as the causal estimate. Adding variables to α^* will not alter this causal interpretation. We treat α^* as unknown, assuming only that it is comprised of a subset of the p variables available for analysis. The motivation for using (5) for estimating causal effects is that the procedures outlined below assign posterior weights, $p(\alpha^m|Data)$, based jointly on covariate associations with X and Y or on covariate associations with X only. This approximates the true posterior distribution of Δ by distributing most posterior weight to models containing α^*. Similar reasoning motivates the BAC method of Wang et al. (2012).

In practice, evaluation of each model's posterior probability may be infeasible for all M models under consideration (e.g., $p = 20$ implies over 1 million models). In such cases, Markov chain Monte Carlo (MCMC) algorithms that sample from the joint posterior of $p(\alpha,\Delta|Data)$ have been developed to estimate quantities such as that in (5) by visiting only the models with non negligible posterior support from the data (Hoeting et al., 1999; George and McCulloch, 1997). We explore two such methods in this article: the MCMC Model Composition (MC^3) approach of Madigan et al. (1995) and the stochastic search variable selection (SSVS) method of George and McCulloch (1997). Throughout, we assume equal prior probability for all M models.

3.1 Bayesian PS Model-Averaged Causal Effects with MC^3

Given a current value for α^m, the MC^3 method constructs an MCMC chain that iteratively visits "neighboring" models by either adding or removing a single variable from α^m to obtain α', then moving the chain by setting $\alpha = \alpha'$ with probability $min\{1, \frac{p(\alpha'|Data)}{p(\alpha^m|Data)}\}$ and estimating Δ^α (Madigan et al., 1995; Raftery et al., 1997). One key necessity for this approach is an available expression for $p(\alpha^m|Data)$, which requires an analytically-tractable expression for the integrated likelihood: $p(Data|\alpha^m) = \int p(Data|\alpha^m,\theta)p(\theta|\alpha^m)d\theta$, where θ here represents the collection of all parameters for which presence or absence in the model depends on α (e.g., $\theta = (\gamma,\delta)$ in (3)–(4)). While the integrated likelihood is readily available for some standard problems (e.g., linear regression), it will only be available in closed form for the PS likelihood in (3)–(4) under specific parametric assumptions, which is illustrated in Appendix A.2. In particular, for fully-Bayesian estimation with MC^3, we assume:

- **i.** $g_x(\cdot)$ and $g_y(\cdot)$ are both Φ^{-1} representing Probit regression in both the PS and the outcome models.

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ii. $h(PS(\gamma,\alpha,U_i);\xi) = \xi \times \Sigma\alpha_k\gamma_k U_{ik}$, that is, the outcome model in (2) adjusts for $\Phi^{-1}(PS)$ as a linear covariate.

iii. Residual adjustment via $\Sigma\alpha_k\delta_k U_{ik}$ is included with one variable having $\alpha_k = 1$ removed to prevent perfect colinearity with the PS.

Incorporating these assumptions into the likelihood as expressed in (3)–(4) essentially negates one integral feature using the PS to adjust for confounding. Specifically, assumptions (ii) and (iii) yield an outcome model that is a simple reparameterization of a model containing a linear main effect term for every variable in α but *not the propensity score*. This is shown in Appendix A, along with details of the prior specification and complete MCMC algorithm.

Conducting the above MC^3 procedure is operationally a PS approach in that it relies on specification of a PS model and outcome model with (3)–(4), but the restrictive parametric model implied by assumptions (i) – (iii) is a Probit regression with only main effect terms for each covariate; precisely the type of model that PS methods are typically used to avoid. Nonetheless, this strategy will be useful for illustrating (via simulation studies in Section 4) the salient issues involved in selecting variables for PS models.

3.2 Approximately-Bayesian PS Model-Averaged Causal Effects with MC^3

Altering the MC^3 approach of Section 3.1 to allow more flexible model specifications can be accomplished with an approximately-Bayesian analysis of the likelihood in (3) – (4) by "cutting the feedback" (or modularizing) the PS and outcome models (Lunn et al., 2009; Liu et al., 2009). Specifically, we propose an approximately-Bayesian MC^3 approach, where, at each MCMC iteration, the ratio $\frac{p(\alpha'|Data)}{p(\alpha^m|Data)}$ governing acceptance of a move between models is obtained without regard to Y, as are updates of γ and the PS. Then, (β,ξ,δ) are simulated conditional on α and the PS, which only involves term (4) of the likelihood and the relevant prior distributions. Full details of the approximately-Bayesian method appear in the Appendix A.4. The key benefit of this approach is that the integrated likelihood used to calculate $\frac{p(\alpha'|Data)}{p(\alpha^m|Data)}$ only involves integration over quantities in the PS model, and, for Probit regression, this integration can be easily evaluated without assumptions (ii) and (iii) that were required for the fully-Bayesian MC^3 approach in Section 3.1. The absence of γ-feedback in the approximately-Bayesian method also allows omission of residual adjustment term $\Sigma\alpha_k\delta_k U_{ik}$ from (2), if desired. However, the flexibility gained by cutting feedback between the PS and outcome model comes at the cost of foregoing the use of Y to inform the selection of α, meaning that inclusion of variables in the PS model is only informed by associations with X.

3.3 Bayesian PS Model-Averaged Causal Effects with SSVS

In contrast to the fully-Bayesian method of Section 3.1 that entails restrictive parametric assumptions and the approximately-Bayesian approach in Section 3.2 that precludes Y from informing the PS model, we also propose a fully-Bayesian SSVS approach with so-called "spike-and-slab" hierarchical mixture priors for the coefficients in the PS and outcome models (George and McCulloch, 1997). This strategy reformulates the expressions in (1) and (2) to yield the following:

$$g_x(E[X_i|U_i]) = \sum_{k=0}^{p} \gamma_k U_{ik}, \quad (6)$$

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$$g_y(E[Y_i|X_i,U])=\beta_0+\beta_X X_i+h(PS(\gamma,U_i);\xi)+\sum_{k=1}^{p}\delta_k U_{ik}, \quad (7)$$

$$p(\gamma_k|\alpha_k)=N(0,\tau_\gamma^2)\times\alpha_k+N(0,c_\gamma^{-2}\tau_\gamma^2)\times(1-\alpha_k), \quad (8)$$

$$p(\delta_k|\alpha_k)=N(0,\tau_\delta^2)\times\alpha_k+N(0,c_\delta^{-2}\tau_\delta^2)\times(1-\alpha_k), \quad (9)$$

for $k = 0,1, \ldots, p$, where $\tau_\gamma^2, \tau_\delta^2$are hyperparameters chosen to reflect proper but noninformative prior distributions for (γ_k,δ_k) with $\alpha_k = 1$ (the "slab"), and (c_γ,c_δ) are hyperparameters chosen to concentrate prior mass very tightly around zero for (γ_k,δ_k) with $\alpha_k = 0$ (the "spike"). Rather than completely remove variables from the model when $\alpha_k = 0$, the SSVS approach shrinks coefficients very close to zero. Note that the PS setting involves the unique feature that the mixture priors are specified for two sets of parameters (γ and δ) but, for a given k, both γ_k and δ_k are constrained to belong to the same mixture component because there is only one model indicator, namely, α.

As compared to the MC^3 approaches in Sections 3.1 and 3.2, the SSVS approach does not require any additional parametric assumption. Model selection proceeds by iteratively sampling γ_k,δ_k,β, and ξ from their appropriate conditional posterior distributions, then updating each α_k from a binomial distribution that depends on the current values of γ_k and δ_k and on the prior distributions in (8) and (9). Note that while the inclusion of the residual adjustment term $\Sigma\alpha_k\delta_k U_{ik}$ is primarily motivated by the discussion of γ-feedback in Section 2.4, this residual adjustment is required for α feedback in the SSVS approach so that $p(\alpha_k = 1|Data)$ will be closer to one for variables with $\gamma_k^2+\delta_k^2$ large. Thus, unlike the MC^3 approaches in Sections 3.1 and 3.2, the SSVS approach incorporates outcome information into the PS model selection while also allowing flexible parametric specification. These benefits come at the cost of some practical difficulties in implementation. Specifically, the choice of hyperparameters for the mixture priors in (8) and (9) will affect which variables are selected to have $\alpha_k = 1$, and SSVS with the likelihood in (3)–(4) can be computationally expensive for large values of p. Full details appear in Web Appendix A. To simplify presentation, we henceforth fix $\tau_\gamma = \tau_\delta = \tau$ and $c_\gamma = c_\delta = c$.

4 SIMULATIONS TO ILLUSTRATE PROPENSITY SCORE VARIABLE SELECTION AND MODEL AVERAGING

Here we use simulated data to illustrate the approaches for Bayesian variable selection and model averaging in Section 3. For all illustrations, data are generated as follows: For $i = 1,2, \ldots, n$, we simulate p covariates $U_i = (U_{i1},U_{i2}, \ldots, U_{ip})$ from $MVN(0, I)$, where I is the identity matrix, and U_{0i} is set to 1 to denote a model intercept. X_i is simulated from a Bernoulli distribution with probability $X_i = 1$ specified with (1), with $g_x(\cdot)$ set to $\Phi^{-1}(\cdot)$. We set $\gamma = (0.6, -0.6,0.6, -0.6,0,0, \ldots, 0)$ to denote four covariates (U_1,U_2,U_3,U_4) associated with assignment to treatment. Y_i are simulated from Bernoulli distributions with probability $Y_i = 1$ specified with $\Phi(\Sigma_{k=1}^{p}\phi_k U_{ik})$, with $\phi= (0.6, -0.6,0,0,0.6, -0.6,0,0, \ldots, 0)$ to denote four covariates (U_1,U_2,U_5,U_6) associated with Y. This implies a true value of $\Delta = 0$ and that the minimal model required to satisfy the assumption of strong ignorability is $\alpha^* = (1,1,0,0, \ldots, 0)$. All scenarios entail $p - 6$ extraneous covariates that are not associated with X or Y.

We simulate 1000 replicated data sets under each of several simulation scenarios. We analyze the simulated data with the three methods proposed in Section 3 and with three

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comparator methods: 1) a traditional sequential "kitchen sink" approach that includes all p variables in the PS model; 2) a forward "stepwise on X" procedure that selects variables according to a BIC criterion applied to the PS model only, without acknowledging uncertainty in the variable selection; and 3) a "gold standard" approach that directly estimates the correct data-generating mechanism without making use of the PS. All Bayesian and approximately-Bayesian inferences are based on MCMC chains run for 10,000 iterations, with the first 2,000 discarded as burn in and every 10th sample saved for posterior inference. MC^3 analyses are run using R software (R Core Team, 2013), SSVS analyses are programmed in C++, and all stated computing times are from a desktop computer running Mac OS X with a 2.66GHz Intel Core i5 processor and 4GB RAM. The gold standard, kitchen sink, and stepwise on X methods are fit using maximum likelihood, with the latter methods treating the estimated PS as fixed in the outcome stage. Careful analysis with the PS should generally involve checks of whether covariates are balanced between treated and untreated observations. We forego balance checks until the data analysis of Section 5.

4.1 Bayesian PS model averaging when large *p* requires model selection

We first consider scenarios where the kitchen sink approach is unavailable because p is too large relative to n, rendering some form of model selection necessary to estimate Δ with PS methods. We simulate two such scenarios; one with $n = 200$, $p = 100$ and another with $n = 500$, $p = 200$. Recall that the fully-Bayesian MC^3 approach requires the parametric assumptions outlined in Section 3.1, namely, that $h(PS(\gamma,\alpha,U_i);\xi)$ denotes linear adjustment for $\Phi^{-1}(PS)$ and that residual adjustment is included for all except one variable having $\alpha_k = 1$ to prevent perfect colinearity. Also recall that these parametric assumptions reduce to a Probit regression model that includes only main effects for selected variables and no PS, which, in this case, corresponds to the true data-generating mechanism. For the approximately-Bayesian MC^3, SSVS, kitchen sink, and stepwise on X approaches, we specify $h(PS(\gamma,U_i);\xi)$ to adjust for five subclasses defined by quintiles of the PS, and conduct residual adjustment for every variable included in the PS. We set ($\tau = 5, c = 200$) for the prior specification in (8) and (9) for the SSVS approach. Computing time for the analysis of a single simulated dataset for the approximately-Bayesian MC^3 (SSVS) approach with $n = 200$, $p = 100$ was 58.7 (302.4) seconds. Analogous values for the $n = 500$, $p = 200$ scenario were 102.9 (2169.7) seconds. The computing time for the fully-Bayesian MC^3 approach was similar to that of the approximately-Bayesian MC^3 approach. The computational demand of the SSVS approach precluded the ability to analyze all 1000 replicated data sets for the $n = 500$, $p = 200$ scenario; results for the SSVS analysis of this scenario are based on analysis of 340 data sets.

Out of the 1000 data sets simulated under the scenario with $n = 200$, $p = 100$ ($n = 500$, $p = 200$), PS model estimates in 997 (916) were so unstable that estimated PS values were equal to 0 for all observations with $X_i = 0$ and equal to 1 for all observations with $X_i = 1$, meaning that any PS adjusted comparison is completely confounded and not interpretable as an estimate of the causal effect. Thus, in these settings, model selection is necessary to estimate causal effects with the PS. For the three proposed methods, Table 1 summarizes the average marginal probability that variable k is included in the PS model ($p(\alpha_k = 1|Data)$) across the simulated data sets, along with the frequency with which each variable is included in the comparator methods. Figure 1 displays box plots of posterior mean estimates from the Bayesian methods as well as point estimates from the comparator methods, along with bias and mean squared error (MSE) for estimates from each method. Recall that the salient issue for estimating a causal effect is whether the method averages estimates across models including the variables that comprise α^*, here, (U_1,U_2). From Table 1, we see that, in both scenarios, all three proposed methods average causal estimates across models that virtually always contain (U_1,U_2), the notable exception coming for the SSVS approach with $n = 200$,

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p = 100, which produces average values of $p(\alpha_k = 1|Data) \approx 0.80$ for k = 1, 2. This implies that SSVS in this scenario (and with these values of τ,c) estimates Δ with weighted averages over models that frequently do not include all confounders, leading to the bias depicted in Figure 1(a). For the n = 500, p = 200 scenario, all procedures always include (U_1,U_2), and exhibit negligible bias. In both scenarios, all methods tend to average estimates across models that include (U_3,U_4) that are only associated with X, with the SSVS analysis of the n = 200, p = 100 scenario including these variables substantially less often than the other methods. The distinction between the fully-Bayesian approaches and the approximately Bayesian approach is highlighted in Table 1 by the average values of $p(\alpha_k = 1|Data)$ for the variables only associated with Y (U_5,U_6); the SSVS and fully-Bayesian MC^3 approaches average causal estimates across models that tend to include these variables, whereas the approximately-Bayesian MC^3 approach does not. The variables (U_5,U_6) are included in the PS model least often with the stepwise on X procedure. The efficiency gain associated with the inclusion of (U_5,U_6) is highlighted in Figure 1, where the SSVS and fully-Bayesian MC^3 approach produce estimates with lower MSE than the approximately-Bayesian or stepwise on X approaches, although recall that the fully-Bayesian MC^3 approach requires very restrictive parametric assumptions that happen to correspond to this simulated data generation. The fully-Bayesian MC^3 approach should not be expected to perform as well in practice. In summary, in a setting where the kitchen sink approach is unavailable and a choice regarding the PS model is required, the proposed methods can reliably select the variables in α^* and estimate the causal effect Δ with improved performance over a stepwise on X procedure that selects a single PS model without acknowledging the associated uncertainty.

4.2 Bayesian PS model averaging with moderate *p*

In settings with more moderate p relative to n, the kitchen sink approach can be used to circumvent variable selection altogether. Here we simulate three such settings to investigate whether our proposed methods can improve over the kitchen sink by averaging causal estimates across models that include only relevant variables. Towards this end, we simulate data with sample sizes n = 1000,500, and 200, while holding p fixed at 20. For these simulations, we forego the restrictive fully-Bayesian MC^3 approach and analyze the simulated data with the approximately-Bayesian MC^3 approach of Section 3.2 and with the SSVS approach of Section 3.3, with (τ= 5,c = 200). For all methods in this section, we specify $h(PS(\gamma,U_i);\xi)$ to adjust for five subclasses defined by quintiles of the PS, and conduct residual adjustment with $\Sigma\alpha_k\delta_k U_{ik}$. Computing time for the analysis of a single simulated dataset for the approximately-Bayesian MC^3 (SSVS) approach was 100.6 (237.3), 69.3 (122.2), 51.2 (51.3) seconds for the n = 1000,500,200 scenarios, respectively.

Figure 2 displays the average marginal inclusion probabilities, $p(\alpha_k = 1|Data)$ for k = 1,2, …, 20, from the fully-Bayesian SSVS analysis and the approximately-Bayesian MC^3 analysis across the 1000 replicated data sets with n = 200, 500, and 1000, compared with the proportion of times each variable was selected with the stepwise on X procedure. The Bayesian methods average causal estimates across models that always contain α^*, with $p(\alpha_k = 1|Data) = 1.0$ for k = 1,2 for all three scenarios, and the stepwise on X procedure always selects these variables. All methods virtually always include (U_3,U_4) associated with X only, with minimum average $p(\alpha_k = 1|Data) = 0.95$ for k = 3,4 from the Bayesian methods across the three scenarios. The major departure between the methods comes in the omission of the variables only associated with Y from PS models estimated with the approximately-Bayesian MC^3 approach and the stepwise on X approach, as compared to the SSVS approach that exhibits minimum average $p(\alpha_k = 1|Data) = 0.96$ for k = 5,6 across all there scenarios.

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Figure 3 displays the relative MSE of posterior-mean estimates of Δ and estimates from the stepwise on X and kitchen sink procedures, relative to estimates from the gold standard approach. All methods exhibit negligible bias (results not shown). Figure 3 illustrates that the SSVS approach produces estimates with MSE closest to the gold standard, and that the stepwise on X procedure yields the largest MSE. While the efficiency loss associated with including extraneous variables in the kitchen sink approach becomes more pronounced as the sample size decreases, the kitchen sink estimates still exhibit lower MSE than the approximately-Bayesian MC^3 approach that averages causal estimates across models that rarely include the variables associated with Y only (U_5,U_6).

Web Appendix D illustrates a simulation study with $n = 200$, $p = 20$ for which the U_k are correlated. Again, the SSVS approach produces estimates with MSE closest to the gold standard, and the stepwise on X approach exhibits the largest MSE. Unlike the uncorrelated data setting depicted in Figure 3, the approximately-Bayesian approach produces estimates with lower MSE than the kitchen sink approach in the correlated data setting of Web Appendix D, and failure to always select the variables in α* leads to small bias in estimates from from the SSVS, approximately-Bayesian MC^3, and stepwise on X approaches.

These simulations illustrate that when p is moderate relative to n, the SSVS and approximately-Bayesian MC^3 methods for variable selection and model averaging can outperform (in terms of MSE) a stepwise on X selection procedure and a kitchen sink approach that circumvents variable selection entirely. Thus, we have shown that, in certain situations, the additional uncertainty associated with variable selection and model averaging can outweigh the drawbacks of a stepwise procedure or the inefficiency of extraneous adjustment that comes as a consequence of automatically including every potential confounder in the PS model.

5 COMPARING THE EFFECTIVENESS OF TREATMENTS FOR MALIGNANT BRAIN TUMORS

Standard treatment for malignant brain tumors (most commonly malignant astocytomas such as glioblastoma) often involves surgical excision of the tumor, but recent evidence suggests that surgery is often foregone in elderly patients, especially those with poor preoperative status and of particularly advanced age (Iwamoto et al., 2008). Due in part to the relatively low incidence of these tumors, evidence as to whether elderly patients benefit from surgical treatment is unclear, and large administrative databases have emerged as a key tool for comparing the effectiveness of treatments for malignant brain tumors. We use data on 2,606 Medicare beneficiaries residing in the Northeastern United States (Massachusetts, Connecticut, New Hampshire, Maine, Rhode Island, and Vermont) who were hospitalized with a primary diagnosis of malignant brain neoplasm during 2000–2009 to compare the effectiveness of surgical excision $X = 1$ vs. no surgery $X = 0$ for lowering the risk of mortality within 1 year of diagnosis. To ensure that our study population did not include patients with brain metastases of other cancers, this patient sample excludes patients with a previous cancer diagnosis.

Table 2 summarizes the characteristics of patients who were treated with surgical excision ($n = 1118$) and those who did not receive surgery ($n = 1488$). As expected, patients aged over 85 years were much less likely to receive surgery, and patient characteristics measured by Hierarchical Condition Categories (Pope et al., 2004) capturing current or previous comorbidities were different in the two groups, with surgical patients exhibiting fewer comorbidities overall. An unadjusted comparison indicates that the rate of death within 1 year of hospitalization is 15.2% lower in surgical patients. We estimate the average causal effect of surgery (vs. no surgery) with the approximately-Bayesian MC^3 approach from

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Section 3.2, as well as with the fully-Bayesian SSVS approach from Section 3.3 (with $\tau = 5, c = 1000$). For both methods, we specify $h(PS(\gamma, U_i); \xi)$ to adjust for five subclasses defined by quintiles of the PS, and conduct residual adjustment within PS subclass for every covariate included in the PS. As in our simulations, we specify Probit regression in the PS and outcome models. For both methods, MCMC chains were run for 150,000 iterations, discarding the first 50,000 as burn in and saving every remaining 10th sample for posterior inference. Computing times were 2965.9, 11712.4 seconds for the approximately-Bayesian MC^3, SSVS procedure, respectively.

Covariate balance was assessed at each MCMC iteration by comparing covariate prevalence between surgical and nonsurgical patients within PS subclass, using only the covariates in the model at that iteration. Both methods similarly balanced all the covariates in Table 2 within PS subclass, with some age group imbalances persisting in the lowest PS subclass. Detailed balance checks appear in Web Appendix B.

The approximately-Bayesian MC^3 approach produced a posterior mean estimate of $\hat{\Delta} = -0.119$ and a 95% posterior interval $(-0.151, -0.087)$. Table 3 displays the 10 models with highest posterior support from this approach. Together, these 10 models comprise 34% of the total posterior model support, meaning that 66% is spread across models not appearing in Table 3. Every individual model not in Table 3 receives < 2% posterior support. Table 2 displays the marginal $p(\alpha_k = 1|Data)$ for $k = 1, \ldots, 28$, across all 2^{28} models. These tables indicate that the posterior estimate of Δ is a weighted average of estimates from models that virtually always include patient age group, but also commonly involve presence of stroke, dementia, functional disability, psychological disorder, and seizure disorder.

The fully-Bayesian SSVS analysis produced a similar causal estimate, with a posterior mean $\hat{\Delta} = -0.122$, with 95% posterior probability interval $(-0.154, -0.090)$. Table 4 displays the 10 models with highest posterior support from the SSVS analysis. These 10 models comprise 97% of the posterior model support, and Table 2 displays the marginal $p(\alpha_k = 1|Data)$ for $k = 1, \ldots, 28$. For the SSVS analysis, the posterior distribution of Δ is a weighted average of estimates from models that always include patient age group and seizure disorder, with substantial posterior support also distributed across models including renal failure, diabetes, dementia, and chronic fibrosis.

Recall that these two methods differ in two important ways and do not converge to the same stationary distribution. First, the approximately-Bayesian MC^3 approach builds PS models based only on covariate associations with X, whereas the fully-Bayesian SSVS approach uses associations with both X and Y. Second, the approximately-Bayesian MC^3 approach includes variables on the basis of increases in the integrated likelihood term for the PS model, whereas SSVS includes variables based on the estimated magnitude of $(\gamma_k^2 + \delta_k^2)$ from (7) and the specification of hyperparameters (τ, c). These differences are evident when comparing the results from these two methods. For example, estimates of Δ from the approximately-Bayesian MC^3 method virtually never rely on a model that includes diabetes, whereas diabetes appears in 68% of the models constructed with the fully-Bayesian SSVS approach (see Tables 2 – 4). This likely occurs because diabetes is not predictive of having a surgical excision, but is strongly related to death within 1 year of hospitalization. However, comparison between the approximately and fully-Bayesian procedures does not always follow so clearly. For example, history of stroke appears frequently in models estimated with the approximately-Bayesian MC^3 procedure ($p(\alpha_k = 1|Data) = 0.28$), but does not appear in any model receiving posterior support from the SSVS procedure. Such an apparent discrepancy could arise for several reasons. It is possible that, after adjusting for variables that tend to appear in the SSVS analysis (e.g., chronic fibrosis), stroke is no longer related to X or Y. As a rough guide from which to judge variable associations with Y, Web Appendix C

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augments Table 2 with point estimates, standard errors, and p-values from a Probit regression model that does not include the PS but includes main effects for each of the 28 variables. Finally, it is important to note that the differences in implementation lead the MC^3 approach to distribute support across a large set of models compared to the SSVS approach, which concentrates 79% of the posterior mass at the top 3 models in Table 4. The concentration of posterior mass on relatively few models with the SSVS approach is due to the feature that SSVS uses more information in the data (e.g., information pertaining to Y), and also to the specification of the hyper parameters (τ,c), which will generally affect which variables are selected and how often; for a fixed value of τ, larger values of c distribute more posterior support to models containing more covariates. The need to decide an appropriate value of c highlights one practical difficulty for implementing the SSVS approach, although results from analyses of these data with different values of c are not reported because causal estimates remained virtually unchanged.

For comparison, a standard sequential kitchen sink approach produced a point estimate of $\hat{\Delta} = -0.115$, with a 95% confidence interval of $(-0.146, -0.084)$ based on 1000 parametric bootstrap samples. In summary, all methods estimate a similar beneficial ACE of surgical treatment for preventing death within 1 year of hospitalization that is attenuated as compared to the simple unadjusted comparison.

6 DISCUSSION

For causal inference methods based on the PS, we have introduced Bayesian methods for variable selection and model averaging to estimate causal treatment effects that can offer improvement over standard PS approaches, especially when p is large and some form of variable selection is required. Rather than condition inference on a single PS model, our approaches average causal estimates across many different models that are supported by the observed data.

Aside from notions of model averaging and model uncertainty, our proposed fully-Bayesian procedures entail another important distinction with traditional approaches that select variables based only on covariate associations with treatment assignment (X). The fully-Bayesian approaches build PS models based in part on covariate associations with the outcome (Y) as well, which is important in light of the well-documented result that including outcome predictors in PS models can improve causal estimates (Rubin and Thomas, 1996; Rubin, 1997; Brookhart et al., 2006). This feature of our approach also relates to the notion of the “prognostic score” that balances covariates between treated and untreated units based *only* on associations with Y (Hansen, 2008), although it remains unclear whether models for the prognostic score and the outcome, conditional on the score, could be combined in a joint likelihood for the type of Bayesian analysis pursued here.

Data-driven approaches to select important outcome predictors could be construed as in violation of one philosophical motivation of the PS. Specifically, Rubin (2008) argues that the PS is meant to approximate the design stage of a randomized study, and as such should be constructed without any access to the outcome to ensure objective design decisions that are completely separate from analysis decisions. It should be noted that the use of outcome information in our fully-Bayesian approaches is completely automated, thus precluding the selection of variables based on post-hoc knowledge of the estimated treatment effect. The approximately-Bayesian strategy of Section 3.2 selects variables based only strength of association with X, without regard to Y, and as such cannot be construed as violating the separation of design and analysis decisions. However, at least in our simulation studies, the approximately-Bayesian approach did not perform as well (in terms of MSE) as the fully-Bayesian approaches, nor did it perform as well as the kitchen sink approach when p was

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moderate and the covariates were uncorrelated. This highlights the potential benefit of including predictors of *Y*. One important limitation that our proposed methods share with nearly all methods for selecting variables to include in the PS is that they will include those that are strongly associated with *X* even if they are not at all associated with *Y*, and such variables have been shown to reduce efficiency of causal estimates (Rubin, 1997; Brookhart et al., 2006). Rubin (1997) argues that the efficiency loss of including such variables should be relatively inconsequential if the variable is even weakly associated with *Y*. In general, relative performance of the proposed and traditional methods will depend on the nature of associations between covariates, treatment, and outcome.

One general feature of the proposed approaches is their reliance on parametric model specifications for the PS and outcome models. This was most pronounced in the fully-Bayesian MC^3 approach of Section 3.1, which motivated the more flexible approaches of Sections 3.2 and 3.3. Nonetheless, our proposed methods necessarily rely on model specification more than modern machine-learning approaches to building PS models, such as generalized boosted models (McCaffrey et al., 2004), that can model the relationships between covariates and treatment assignment in a very flexible manner. In exchange for parametric specification, our methods have the benefit of selecting variables based in part on their association with *Y*, and also preclude the need to condition on a single PS model for inference. Efforts to improve the parametric flexibility of our methods are warranted, including exploration of approximations to the integrated likelihood that can circumvent the restrictive parametric assumptions required for a fully-Bayesian MC^3 analysis, possibly along the lines of the Bayes factor approximations commonly used for generalized linear models (Hoeting et al., 1999). Alternatively, the methods described here could serve as a precursor step to define a reasonably-sized set of candidate variables for use in model-averaged estimates that make use of more flexible parametric specifications.

We made use of two distinct computational strategies for Bayesian variable selection and model averaging, both having relative merits and limitations. The MC^3 approach is computationally appealing because it relies on an expression of the likelihood with the (possibly high dimensional) vector of model-specific coefficients integrated out, but required restrictive parametric assumptions for a fully-Bayesian approach. In contrast, the SSVS approach accommodates general likelihood expressions, but shrinks variables close to zero rather than remove them from the model, entailing a heavy computational burden for large *p*. Furthermore, the shrinkage is governed by hyperparameters that must be specified, and different specifications can produce different results.

Modern decision-making in the health sciences and other fields increasingly relies on very large observational data bases containing a wealth of covariate information, highlighting the importance of issues regarding model uncertainty in PS methods. This is especially true in comparative effectiveness investigations leveraging information in administrative data bases, but could also prove integral in other “big data” applications that routinely deal will very large numbers of potential confounding factors. However, we stress that our data-driven approaches for variable selection and model averaging cannot replace careful scientific thought. For example, we considered situations where all *U* were known to be pre-treatment covariates, but, in general, particular attention should be paid to whether some available variables are affected by treatment, leaving them inappropriate for PS adjustment. Finally, our methods do not provide a means for adjusting for unmeasured confounding; we assume that all confounders necessary to satisfy the assumption of ignorable treatment assignment are an unknown subset of those available for analysis. This is especially relevant in the results of our data analysis, where the Medicare data lacks disease-specific information, thus presenting the possibility of unmeasured confounding.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

A DETAILS OF THE *MC*³ APPROACHES FOR PROPENSITY SCORE VARIABLE SELECTION AND MODEL AVERAGING

A.1 Prior distributions

The MC^3 approaches of Sections 3.1 and 3.2 rely on prior specification for $p(\beta,\xi,\gamma,\delta,\alpha)$, which we factorize as $p(\alpha)p(\gamma_\alpha|\alpha)p(\delta_\alpha|\alpha)p(\beta,\xi)$, where $(\gamma_\alpha,\delta_\alpha)$ denotes the components of (γ,δ) included in model α. As noted in Section 3, we assume equal prior probability for all possible α, $p(\alpha)=\frac{1}{M}$. For $p(\gamma_\alpha|\alpha)$, we assume a Normal distribution with mean 0 and variance $\lambda_\gamma(\mathbf{U}_\alpha'\mathbf{U}_\alpha)^{-1}$. For $p(\delta_\alpha|\alpha)$ we use a Normal distribution with mean 0 and variance $\lambda_\delta(\mathbf{U}_{\alpha,\boldsymbol{Y}}'\mathbf{U}_{\alpha,\boldsymbol{Y}})^{-1}$ for the fully-Bayesian MC^3 approach, and a Normal distribution with mean 0 and variance $10^2\mathbf{I}$ for the approximately-Bayesian approach, where $\mathbf{I}$ is the identity matrix. Here $\mathbf{U}_\alpha$ represents the subset of $\mathbf{U}$ contained in α (with dimension $n \times p_\alpha$), and $\mathbf{U}_{\alpha,\mathbf{Y}}$ denotes the subset of $\mathbf{U}_\alpha$ included for residual adjustment in the outcome model (with dimension $n \times p_{\alpha,Y}$). We henceforth consider $\lambda_\gamma = \lambda_\delta = \lambda$. All analyses of simulated and Medicare data assume $\lambda = 4n$. Furthermore, we assume $p(\beta,\xi)$ follows a Normal distribution with mean 0 and variance $10^2\mathbf{I}$.

A.2 *MCMC* algorithm for the fully-Bayesian *MC*³ approach

Variable selection with MC^3 relies on an expression for $\frac{p(\alpha'|Data)}{p(\alpha|Data)}$ that governs the probability of the MCMC chain transitioning from α to a neighboring model α'. For the fully-Bayesian approach of Section 3.1, the integrated likelihood can be expressed as $\int\int L(\mathbf{Y},\mathbf{X}|\mathbf{U},\gamma,\alpha,\beta,\delta)p(\gamma|\alpha)p(\delta|\alpha)p(\alpha)p(\beta,\xi)d\gamma d\delta$, with $L(\mathbf{Y},\mathbf{X}|\mathbf{U},\gamma,\alpha,\beta,\delta)$ as in (3)–(4). Note that the resulting expression will also depend on ξ and β, as the appearance of these parameters does not depend on α, but we omit this conditioning to simplify notation. Similarly, we omit the prior distribution $p(\beta,\xi)$ from the following expressions.

We follow Albert and Chib (1993) and specify a Probit link for both $g_x(\cdot)$ and $g_y(\cdot)$, which allows allows an MCMC data-augmentation procedure that iteratively samples Normally-distributed latent continuous data with unit variance such that the latent X^* (Y^*) are > 0 when $X = 1$($Y = 1$), and < 0 otherwise. This is Assumption (i) of Section 3.1. Conditional on simulated $(\mathbf{X}^*,\mathbf{Y}^*)$, the integrated likelihood can be expressed as

$$\int\int (2\pi)^{-.5(n+p_\alpha+n+p_{\alpha,Y})}\det[\lambda(\mathbf{U}_\alpha'\mathbf{U}_\alpha)^{-\mathbf{1}}]^{-.\mathbf{5}}\det[\lambda(\mathbf{U}_{\alpha,\boldsymbol{Y}}'\mathbf{U}_{\alpha,\boldsymbol{Y}})^{-\mathbf{1}}]^{-.\mathbf{5}} \times\exp\{-.\mathbf{5}[(\tilde{\mathbf{X}}^{*\prime}\tilde{\mathbf{X}}^*)+(\tilde{\mathbf{Y}}^{*\prime}\tilde{\mathbf{Y}})+\gamma_\alpha'(\frac{1}{\lambda}\mathbf{U}_\alpha'\mathbf{U}_\alpha)\gamma_\alpha+\delta_\alpha'(\frac{1}{\lambda}\mathbf{U}_{\alpha,\boldsymbol{Y}}'\mathbf{U}_{\alpha,\boldsymbol{Y}})\delta_\alpha]\}\mathbf{d}\gamma\mathbf{d}\delta \quad (10)$$

where $\tilde{\mathbf{X}^*} = (\mathbf{X}^* - \mathbf{U}_\alpha\gamma_\alpha)$ and $\tilde{\mathbf{Y}}^* = (\mathbf{Y}^* - \beta_\mathbf{0}\mathbf{1} - \beta_\mathbf{X}\mathbf{X} - \mathbf{h}(\mathbf{PS}(\gamma,\alpha,,\mathbf{U});\xi) - \mathbf{U}_{\alpha,\mathbf{Y}}\delta)$. Note that integration with respect to γ in (10) is relatively straightforward if $\mathbf{h}(\mathbf{PS}(\gamma,\alpha,\mathbf{U}))$ is chosen such that the term in exp $\{\cdot\}$ remains quadratic in γ, because this will allow simplifications relying on the Normal probability distribution function. If the term in exp $\{\cdot\}$ is not quadratic in γ, closed-form integration in (10) will prove problematic. This motivates Assumptions (ii) and (iii) in Section 3.1; specifying $h(PS(\gamma,\alpha,U_i);\xi) = \xi \times \Sigma\alpha_k\gamma_k U_{ik}$ to denote an outcome model that adjusts for $\Phi^{-1}(PS(\gamma,\alpha,U_i)) = \Sigma\alpha_k\gamma_k U_{ik}$ as a linear covariate facilitates closed-form evaluation of (10) with respect to γ, and one covariate in α must be removed from the residual adjustment term $\Sigma\alpha_k\delta_k U_{ik}$ to prevent perfect colinearity with the $\Sigma\alpha_k\gamma_k U_{ik}$. This strategy implies that if $\mathbf{U}_\alpha$ is of dimension $n \times p_\alpha$, then $\mathbf{U}_{\alpha,\mathbf{Y}}$ will be the same except for the removal of the intercept term and one covariate, resulting in $p_{\alpha,Y} = p_\alpha - 2$.

Accordingly, substituting $\mathbf{h}(\mathbf{PS}(\gamma,\alpha,\mathbf{U}))$ with $\xi \times (\mathbf{U}_\alpha\gamma_\alpha)$ in (10) and integrating over γ and δ yields:

$$p(\alpha|Data) \propto (2\pi)^{-n}(1+\lambda\xi^2+\lambda)^{\frac{-p_\alpha}{2}}\lambda^{\frac{-p_{\alpha,Y}}{2}}\det[V_\delta]^{\frac{1}{2}}\det[\mathbf{U}_{\alpha,\boldsymbol{Y}}'\mathbf{U}_{\alpha,\boldsymbol{Y}}]^{\frac{\mathbf{1}}{\mathbf{2}}} \times\exp\{-.5[\mathbf{X}^{*\prime}\mathbf{X}^*+\tilde{\mathbf{W}}'\tilde{\mathbf{W}}-(\mathbf{X}^*+\xi\tilde{\mathbf{W}})'\mathbf{U}_\alpha\mathbf{V}_\gamma\mathbf{U}_\alpha'(\mathbf{X}^*+\xi\tilde{\mathbf{W}})-\tilde{\mathbf{D}}'\mathbf{U}_\alpha\mathbf{V}_\delta\mathbf{U}_\alpha'\tilde{\mathbf{D}}]\}, \quad (11)$$

where

$\tilde{\mathbf{W}}=(\boldsymbol{Y}^*-\beta_\mathbf{0}\mathbf{1}-\beta_\mathbf{X}\mathbf{X}), \tilde{\mathbf{D}}=(\mathbf{U}_{\alpha,\boldsymbol{Y}}'\tilde{\mathbf{W}}-\xi\mathbf{U}_{\alpha,\boldsymbol{Y}}'\mathbf{U}_\alpha\mathbf{V}_\gamma\mathbf{U}_\alpha'(\mathbf{X}^*+\xi\tilde{\mathbf{W}})), \mathbf{V}_\gamma^{-\mathbf{1}}=(\mathbf{U}_\alpha'\mathbf{U}_\alpha(\frac{1}{\lambda}+\xi^2+1))$, and $\mathbf{V}_\delta^{-\mathbf{1}}=(\mathbf{U}_{\alpha,\boldsymbol{Y}}'\mathbf{U}_{\alpha,\boldsymbol{Y}}(1+\frac{1}{\lambda}) - \mathbf{U}_{\alpha,\boldsymbol{Y}}'\mathbf{U}_\alpha\mathbf{V}_\gamma\mathbf{U}_\alpha'\mathbf{U}_{\alpha,\boldsymbol{Y}}\xi^2)$.

The MC^3 algorithm described in Section 3.1 is outlined as follows for iteration $(t + 1)$, considering current values of $\alpha^{(t)}$, $\gamma^{(t)}$,$\delta^{(t)}$,$\beta^{(t)}$,$\xi^{(t)}$,$\mathbf{X}^{*(t)}$,$\mathbf{Y}^{*(t)}$:

1. Propose α' by adding or removing one term from $\alpha^{(t)}$.
2. Set $\alpha^{(t+1)} = \alpha'$ with probability $min\{1, \frac{p(\alpha'|Data)}{p(\alpha^{(t)}|Data)}\}$, where $p(\alpha|Data)$ is as in (11). Set all elements of γ and δ not included in $\alpha^{(t+1)}$ to 0.
3. Update $(\beta^{(t+1)},\xi^{(t+1)})$ from random-walk Metropolis step with values proposed from a Normal distribution with mean $(\beta^{(t)},\xi^{(t)})$ and proposal variance $0.1\mathbf{I}$.
4. Update $\delta_\alpha^{(t+1)}$ from $N(\mathbf{M}_\delta,\mathbf{V}_\delta)$, where $\mathbf{M}_\delta = \mathbf{V}_\delta\tilde{\mathbf{D}}$.
5. Update $\gamma_\alpha^{(t+1)}$ from $N(\mathbf{M}_\gamma,\mathbf{V}_\gamma)$, where $\mathrm{M}_\gamma=\mathbf{V}_\gamma(\mathbf{U}_\alpha'(\mathbf{X}^*+\xi\tilde{\mathbf{W}} - \xi\mathbf{U}_{\alpha,\boldsymbol{Y}}\delta))$ and recalculate the corresponding propensity score, $\mathbf{U}_\alpha\gamma_\alpha$.
6. Simulate new $\mathbf{X}^*$ from a truncated Normal distribution with mean $\mathbf{U}_\alpha\gamma_\alpha$ and variance 1, and simulate new $\mathbf{Y}^*$ from a truncated normal distribution with mean $\beta_\mathbf{0}\mathbf{1} + \beta_\mathbf{X}\mathbf{X} + \xi\mathbf{U}_\alpha\gamma_\alpha + \mathbf{U}_{\alpha,\mathbf{Y}}\delta$ and variance 1, as in Albert and Chib (1993).

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A.3 Implied parameterization of outcome surface for the fully-Bayesian *MC*^{3} approach

Without loss of generality, consider α = (1,1, …, 1) to denote inclusion all *p* available covariates. With assumptions (ii)–(iii), the linear term in the outcome model (2) can be expressed as:

$$\beta_0+\beta_X X+\xi(\gamma_0+\gamma_1 U_1+\gamma_2 U_2+\ldots+\gamma_p X_p)+\delta_2 U_2+\delta_3 U_3+\ldots\delta_p U_p \quad (12)$$

where, again without loss of generality, U_1 is removed from the residual adjustment in accordance with assumption (iii). Expression (12) can be rewritten as $\beta_0^*+\beta_X X+\xi\gamma_1 U_1+\beta_2^* U_2+\beta_3^* U_3+\ldots+\beta_p^* U_p$, where $\beta_0^*=(\beta_0+\xi\gamma_0)$, and $\beta_k^*=(\xi\gamma_k+\delta_k)$ for *k* = 2,3, …, *p*. This corresponds to an outcome model that is simply a reparameterization of a model entailing an additive main effect term for every covariate, which is precisely the type of parametric outcome model PS methods are meant to avoid.

A.4 MCMC Algorithm for the approximately-Bayesian *MC*^{3} approach

As laid out in Section 3.2, an approximately-Bayesian approach follows from adapting the above strategy to update (α,γ) conditional on quantities that appear only in the PS model, then update parameters (β,ξ,δ) conditional on (α,γ). This simplifies the expression for $\frac{p(\alpha'|Data)}{p(\alpha|Data)}$ because of the simplified form of the integrated likelihood:

$$\begin{aligned}\int (2\pi)^{\frac{-(n+p\alpha)}{2}}\det[\lambda(\mathbf{U}_\alpha'\mathbf{U}_\alpha)^{-1}]^{\frac{-1}{2}}\exp\{ \\ -.5[\tilde{\mathbf{X}}^{*\prime}\tilde{\mathbf{X}}^*) \\ +\gamma_\alpha'(\frac{1}{\lambda}\mathbf{U}_\alpha'\mathbf{U}_\alpha)\gamma_\alpha]\}\mathbf{d}\gamma, =(2\pi)^{\frac{-n}{2}}(\lambda+1)^{\frac{-p\alpha}{2}}\exp\{-.5[\mathbf{X}^{*\prime}\mathbf{X}-\mathbf{X}^{*\prime}\mathbf{U}_\alpha((1+\frac{1}{\lambda})\mathbf{U}_\alpha'\mathbf{U}_\alpha)^{-1}\mathbf{U}_\alpha'\mathbf{X}^*)]\}\end{aligned} \quad (13)$$

evaluation of which does not depend on *h*(*PS*(γ,α,U_i);ξ), β,δ or *Y*. Thus, the approximately-Bayesian *MC*^{3} approach is outlined as follws:

1. Propose α′ by adding or removing one term from $\alpha^{(t)}$.
2. Set $\alpha^{(t+1)}$ = α′ with probability $min\{1, \frac{p(\alpha'|Data)}{p(\alpha^{(t)}|Data)}\}$, where *p*(α|*Data*) is as in (A. 4). Set all elements of γ and δ not included in $\alpha^{(t+1)}$ to 0.
3. Update $\gamma_\alpha^{(t+1)}$ from $N(\frac{\lambda}{1+\lambda}(\mathbf{U}_\alpha'\mathbf{U}_\alpha)^{-1}\mathbf{U}_\alpha'\mathbf{X}^*, \frac{\lambda}{1+\lambda}(\mathbf{U}_\alpha'\mathbf{U}_\alpha)^{-1})$.
4. Update $(\beta,\xi,\delta_\alpha)^{(t+1)}$ from $N((\tilde{\mathbf{Z}'\mathbf{Z}}+(.1)^2\mathbf{I})^{-1}(\tilde{\mathbf{Z}'\mathbf{Y}}*), (\tilde{\mathbf{Z}'\mathbf{Z}}+(.1)^2\mathbf{I})^{-1})$, where $\tilde{\mathbf{Z}}$ is the design matrix with columns representing an intercept, **X**,**h**(**PS**(γ,α,**U**)), and $\mathbf{U}_{\alpha,\mathbf{Y}}$.
5. Simulate new **X*** from a truncated Normal distribution with mean $\mathbf{U}_\alpha\gamma_\alpha$ and variance 1, and simulate new **Y*** from a truncated normal distribution with mean $\beta_0\mathbf{1}+\beta_{\mathbf{X}}\mathbf{X}+\xi\mathbf{h}(\mathbf{PS}(\gamma,\alpha,\mathbf{U}))+\mathbf{U}_{\alpha,\mathbf{Y}}\delta$ and variance 1, as in Albert and Chib (1993).

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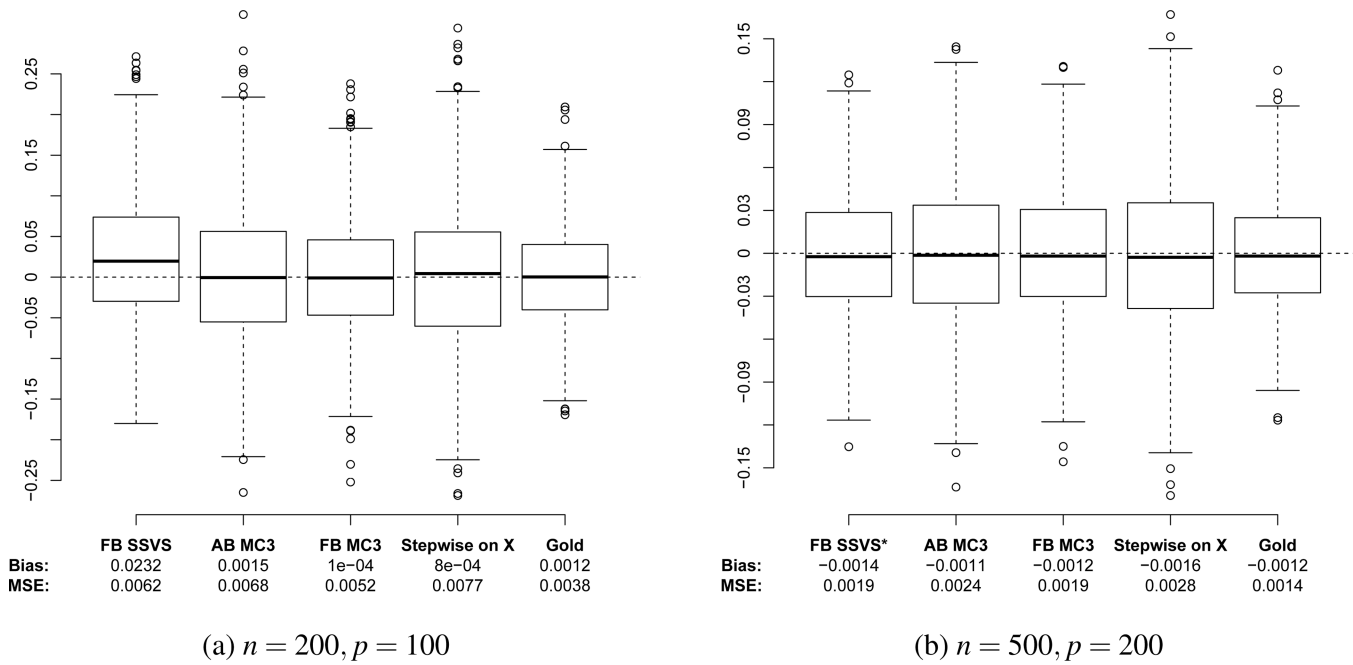

(a) $n = 200, p = 100$ (b) $n = 500, p = 200$

Figure 1.

Simulated scenarios where p is large relative to n: Boxplots of point estimates of Δ across 1000 simulated data sets with n = 500, p = 200 or n = 200, p = 100. "FB MC3" refers to the fully-Bayesian MC^3 approach of Section 3.1, "AB MC3" refers to the approximately-Bayesian MC^3 approach of Section 3.2, and "FB SSVS" refers to the fully-Bayesian SSVS approach of Section 3.3. . *SSVS analysis of n = 500, p = 200 scenario based on analysis of 340 data sets.

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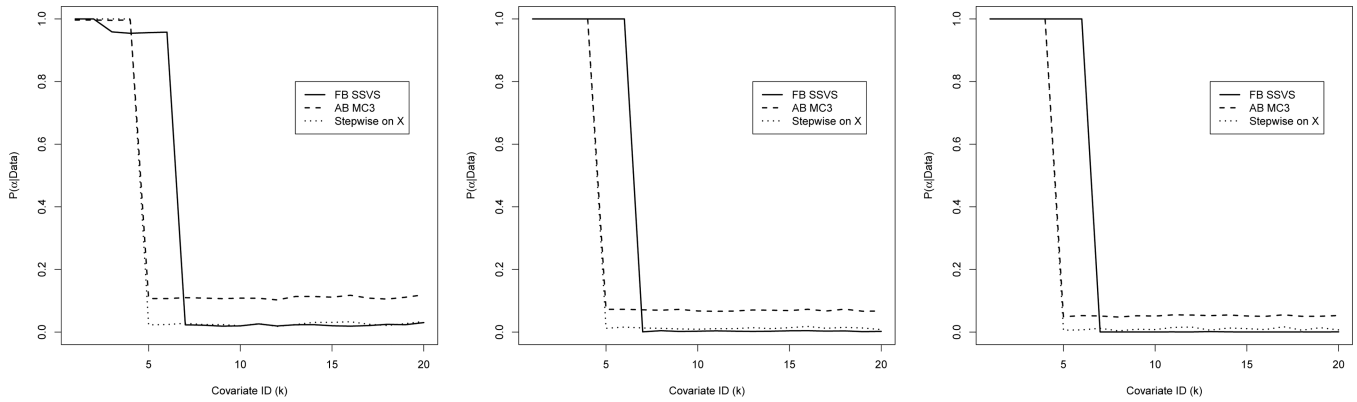

(a) $n = 200$ (b) $n = 500$ (c) $n = 1000$

Figure 2.

Simulated scenarios where p = 20 and n = 200, 500, or 1000. Average values of $p(\alpha_k = 1|$ *Data*) for k = 1,2, …, 20, averaged across 1000 simulated datasets. "FB SSVS" refers to the SSVS approach of Section 3.3, "AB MC3" refers to the approximately-Bayesian approach of Section 3.2, and "Stepwise on X" refers to proportion of times each variable was selected with the forward BIC procedure described in Section 4.

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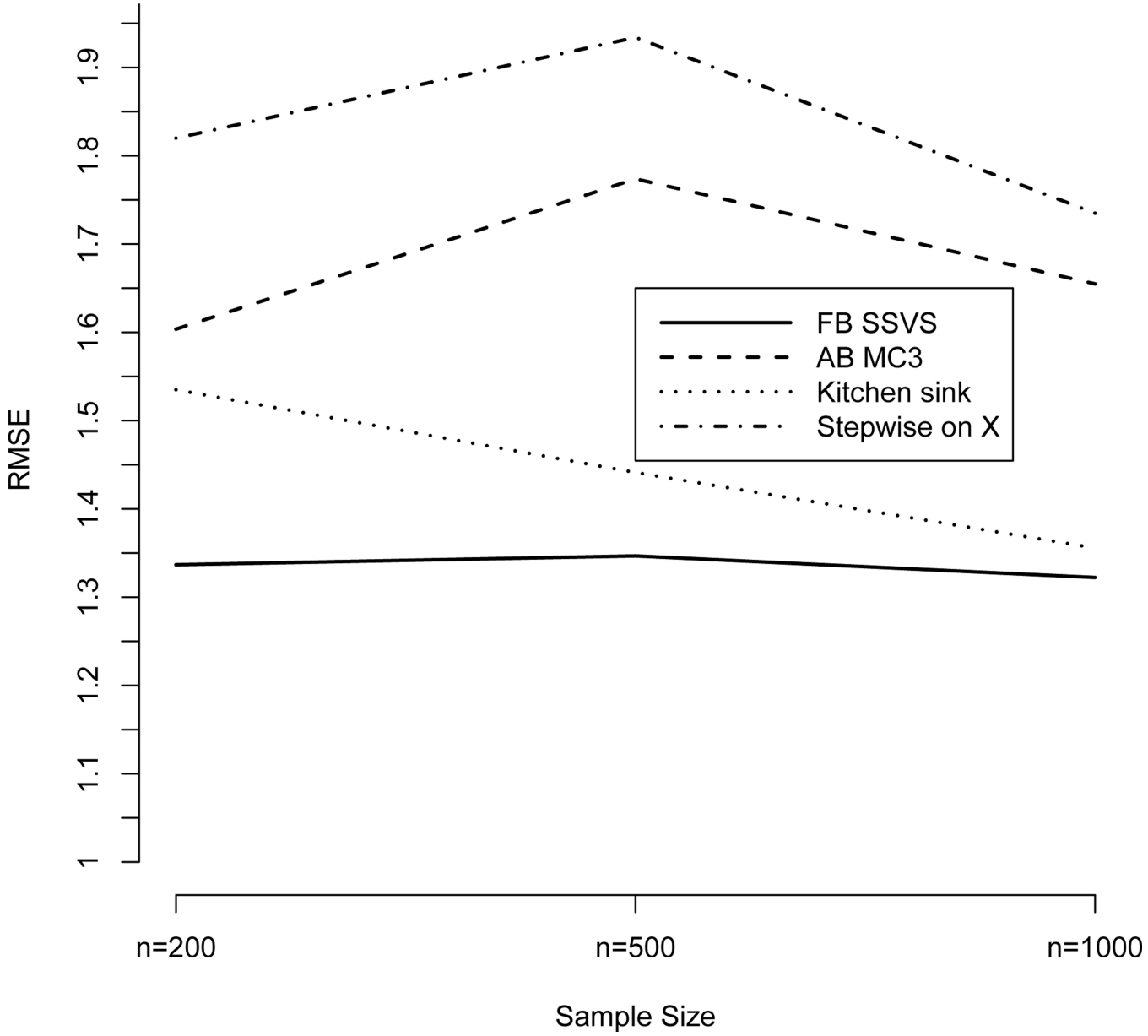

Figure 3.

Simulated scenarios where $p = 20$ and $n = 200,500$, or 1000: Relative mean squared error (MSE) of estimates of Δ (relative to the "gold standard" approach), averaged across 1000 simulated datasets. "FB SSVS" refers to the SSVS approach of Section 3.3 and "AB MC3" refers to the approximately-Bayesian approach of Section 3.2.

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Table 1

Simulated scenarios where p is large relative to n. "FB MC3" refers to the fully-Bayesian MC^3 approach of Section 3.1, "AB MC3" refers to the approximately-Bayesian MC^3 approach of Section 3.2, and "FB SSVS" refers to the fully-Bayesian SSVS approach of Section 3.3. Table entries for the Bayesian procedures denote estimates of the posterior probability that U_k is included in the model ($p(\alpha_k = 1|Data)$), averaged across replicated data sets with $n = 500$, $p = 200$ or $n = 200$, $p = 100$. Entries for the other approaches denote the proportion of 1000 replicated data sets for which U_k was selected. Values listed for $k > 6$ are the minimum and maximum value.

	Covariate ID (k)							
	Assoc. with X and Y (α^*)		Assoc. with X Only		Assoc. with Y Only		Not Associated	
	$k = 1$	2	3	4	5	6	$k > 6$ (min)	$k > 6$ (max)
n=200, p=100								
n=200 FB MC3	1.000	1.000	0.982	0.984	0.985	0.983	0.021	0.057
n=200 AB MC3	0.995	0.998	0.997	0.996	0.233	0.247	0.229	0.260
n=200 FB SSVS	0.811	0.818	0.297	0.306	0.716	0.702	0.003	0.008
n=200 Stepwise on X	1.000	1.000	0.999	0.999	0.023	0.030	0.020	0.049
n=200 Kitchen Sink	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
n=200 Gold	1.000	1.000	0.000	0.000	1.000	1.000	0.000	0.000
n=500, p=200								
n=500 FB MC3	1.000	1.000	1.000	1.000	1.000	1.000	0.006	0.049
n=500 AB MC3	1.000	1.000	1.000	1.000	0.084	0.087	0.073	0.093
n=500 FB SSVS[+]	1.000	1.000	0.992	0.992	1.000	1.000	0.001	0.006
n=500 Stepwise on X	1.000	1.000	1.000	1.000	0.018	0.019	0.008	0.025
n=500 Kitchen Sink	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
n=500 Gold	1.000	1.000	0.000	0.000	1.000	1.000	0.000	0.000

[+] Based on analysis of 340 data sets

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Table 2

Baseline characteristics (% experiencing) and 1-year mortality rate for patients with and without surgery for brain tumor removal, along with estimated $p(\alpha_k = 1|Data)$ for the fully-Bayesian SSVS and approximately-Bayesian MC^3 analyses of the Medicare data from the North-eastern US in 2000–2009

			$p(\alpha_k = 1\|Data)$	
	No Surgery (n = 1488)	**Surgery (n = 1118)**	**SSVS**	**AB MC^3**
Female	51.0	44.6	0.00	0.06
White	97.2	97.9	0.00	0.04
Congestive Heart Failure	5.0	2.6	0.00	0.10
Myocardial Inarction	1.3	0.9	0.00	0.01
Chronic Atherosclerosis	22.8	18.2	0.00	0.08
Respiratory Failure	1.1	1.2	0.00	0.01
Valvular Disease	6.5	5.4	0.00	0.01
Arrhythmia	7.2	4.7	0.03	0.02
Hypertension	63.2	60.5	0.00	0.01
Stroke	5.4	2.6	0.00	0.28
Cerebrovascular Disease	4.0	2.5	0.00	0.04
Renal Failure	2.7	1.2	0.11	0.05
COPD	10.0	10.7	0.00	0.02
Pneumonia	3.8	4.1	0.00	0.04
Diabetes	19.3	17.4	0.62	0.02
Dementia	15.2	9.5	0.33	0.68
Functional Disability	4.0	1.8	0.00	0.25
Peripheral Vascular Disease	2.0	1.3	0.00	0.02
Trauma in the Past Year	5.0	3.6	0.00	0.02
Substance Abuse	6.7	6.6	0.00	0.02
Major Psychiatric Disorder	5.4	3.2	0.00	0.35
Depression	8.5	7.2	0.00	0.02
Parkinsons/Huntingtons	2.2	1.4	0.08	0.03
Seizure Disorder	22.7	18.9	1.00	0.27
Chronic Fibrosis	1.5	0.8	0.58	0.05
Asthma	2.9	3.3	0.01	0.02
Age 65–74	37.1	52.3	(reference)	
Age 75–84	43.1	41.9	1.00	0.99
Age 85+	19.8	5.8	1.00	1.00
Death within 1 Year	85.6	70.4		

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Table 3

Ten models with highest posterior support from the approximately-Bayesian MC^3 analysis of the Medicare data.

	α_k								
Model m	**Stroke**	**Dementia**	**Functional Disability**	**Psych. Disorder**	**Seizure**	**Age 75–84**	**Age 85+**	$p(\alpha^m \mid Data)$	$\Delta^{\hat{\alpha}^m}$
1	0	1	0	0	0	1	1	0.08	−0.118
2	1	1	0	0	0	1	1	0.05	−0.119
3	0	1	1	0	0	1	1	0.05	−0.117
4	0	1	0	0	1	1	1	0.03	−0.122
5	0	1	0	1	0	1	1	0.03	−0.116
6	1	1	0	1	0	1	1	0.02	−0.117
7	0	0	1	0	0	1	1	0.02	−0.118
8	0	1	1	1	0	1	1	0.02	−0.118
9	0	1	0	1	1	1	1	0.02	−0.123
10	1	0	0	1	0	1	1	0.02	−0.116
					Posterior mass of top 10 models:			0.34	

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Table 4

Ten models with highest posterior support from the fully-Bayesian SSVS analysis of the Medicare data.

	α_k											
Model m	**Arrhythm.**	**Renal Fail**	**Diabetes**	**Dementia**	**Parkinsons/ Huntingtons**	**Seizure**	**Chronic Fibrosis**	**Asthma**	**Age 75–84**	**Age 85+**	$p(\alpha^m \mid Data)$	$\Delta^{\hat{\alpha}^m}$
1	0	0	1	0	0	1	0	0	1	1	0.27	−0.122
2	0	0	0	1	0	1	1	0	1	1	0.24	−0.123
3	0	0	1	0	0	1	1	0	1	1	0.18	−0.122
4	0	0	1	0	1	1	1	0	1	1	0.08	−0.12
5	0	0	0	1	0	1	0	0	1	1	0.08	−0.124
6	0	1	0	0	0	1	1	0	1	1	0.05	−0.123
7	0	1	1	0	0	1	0	0	1	1	0.03	−0.121
8	1	0	1	0	0	1	0	0	1	1	0.02	−0.119
9	1	1	1	0	0	1	0	0	1	1	0.01	−0.12
10	0	1	0	0	0	1	1	1	1	1	0.01	−0.118
							Posterior mass of top 10 models:				0.97	