GPMatch: A Bayesian Doubly Robust Approach to Causal Inference with Gaussian Process Covariance Function As a Matching Tool

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Gaussian process (GP) covariance function is proposed as a matching tool in GPMatch within a full Bayesian framework under relatively weaker causal assumptions. The matching is accomplished by utilizing GP prior covariance function to define matching distance. We show that GPMatch provides a doubly robust estimate of the averaged treatment effect (ATE) much like the G-estimation, the ATE is correctly estimated when either conditions are satisfied: 1) the GP mean function correctly specifies potential outcome $Y^{(0)}$; or 2) the GP covariance function correctly specifies matching structure. Simulation studies were carried out without assuming any known matching structure nor functional form of the outcomes. The results demonstrate that GPMatch enjoys well calibrated frequentist properties, and outperforms many widely used methods including Bayesian Additive Regression Trees. The case study compares effectiveness of early aggressive use of biological medication in treating children with newly diagnosed Juvenile Idiopathic Arthritis, using data extracted from electronic medical records.

KEYWORDS
causal inference, matching, doubly robust (DR) estimator, marginal structural model, g-estimation, real world data (RWD)
1 | INTRODUCTION

Data from nonrandomized experiments, such as registry and electronic records, are becoming indispensable sources for answering causal inference questions in health, social, political, economics and many other disciplines. Under the assumptions of no unmeasured confounders, ignorable treatment assignment, and distinct model parameters governing the science and treatment assignment mechanisms, Rubin (1978) suggested Bayesian approach to the estimation of causal treatment effect can be accomplished by directly modeling the outcomes, treating it as a missing potential outcome problem. Direct modeling is able to utilize the many Bayesian regression modeling techniques to address complex data type and data structures, such as examples in Hirano et al. (2000), Zajonc (2012), Imbens and Rubin (1997) and Baccini et al. (2017).

Parameter rich Bayesian modeling techniques are particularly appealing as it does not presume an known functional form, thus may help mitigate potential model miss-specification issues. Hill (2011) suggested Bayesian additive regression tree (BART) can be used for causal inference, and showed it produced more accurate estimates of average treatment effects compared to propensity score matching, inverse propensity weighted estimators, and regression adjustment in the nonlinear setting, and performed as well under the linear setting. Others have used Gaussian Process in conjunction with Dirichlet Process priors, e.g. Roy et al. (2016) and Xu et al. (2016). Roy et al. (2017) devised enriched Dirichlet Process priors tackling missing covariate issues. However, naive use of regression techniques could lead to substantial bias in estimating causal effect as demonstrated in Hahn et al. (2018a).

The search for ways of incorporating propensity of treatment selection into the Bayesian causal inference has been long standing. Including propensity score (PS) as a covariate into the outcome model may be a natural way. However, joint modeling of outcome and treatment selection models leads to a “feedback” issue, and a two-stage approach was suggested by McCandless et al. (2010), Zigler et al. (2013) and many others. Discussion about whether the uncertainty of the first step propensity score modeling should be taken into account when obtaining the final result in the second step can be found in Hill and Reiter (2006), Ho et al. (2007), Rubin and Stuart (2006), Rubin and Thomas (1996) for details. Saarela et al. (2016) proposed an approximate Bayesian approach incorporating inverse probability treatment assignment probabilities as importance-sampling weights in Monte Carlo integration. It offers a Bayesian version to the augmented inverse probability treatment weighting (AIPTW). Hahn et al. (2017) suggested incorporating estimated treatment propensity into the regression to explicitly induce covariate dependent prior in regression model. These methods all require a separate step of treatment propensity modeling, thus may suffer if the propensity model is mis-specified.

Matching is one of the most sought-after method used for designing observational study to answer causal questions. Matching experimental units on their pre-treatment assignment characteristics helps to remove the bias by ensuring the similarity or balance between the experimental units of the two treatment groups. Matching methods impute the missing potential outcome with the value from the nearest match or the weighted average of the values within the nearby neighborhood defined by (a chosen value) caliper. Matching on multiple covariates could be challenging when the dimension of the covariates are large. For this reason, matching is often performed using the estimated propensity score (PS) or by the Mahalanobis distance (MD). The idea is, under the no unmeasured confounder setting, matching induces balance between the treated and untreated groups. Therefore, it serves to transform a nonrandomized study into a pseudo randomized study. There are many different matching techniques, a comprehensive review is provided in Stuart (2010). A recent study by King and Nielsen (Forthcoming) compared the PS matching with the MD matching and suggests that PS matching can result more biased and less accurate estimate of averaged causal treatment as the precision of matching improves, while the MD matching is showing improved accuracy. Common to matching methods, the data points without a match are discarded. Such a practice may lead to a sample no longer representative of the
target population. A user-specified caliper is often required, but different calipers could lead to very different results. Furthermore, matching on a miss-specified PS could lead to invalid causal inference results.

Rubin (1973) suggested that the combination of matching and regression is a better approach than using either of them alone. Ho et al. (2007) advocated matching as nonparametric preprocessing for reducing dependence on parametric modeling assumptions. Gutman and Rubin (2017) examined different strategies of combining the preprocessed matching with a regression modeling of the outcome through extensive simulation studies. They demonstrated that some commonly used causal inference methods have poor operating characteristics, and considered ways to correct for variance estimate for causal treatment effect obtained from regression modeling after preprocessed matching. To our knowledge, no existing method can accomplish matching and regression modeling in a single step.

Gaussian process (GP) prior has been widely used to describe biological, social, financial and physical phenomena, due to its ability to model highly complex dynamic system and its many desirable mathematical properties. Recent literature, e.g. Choi and Woo (2013) and Choi and Schervish (2007), has established posterior consistency for Bayesian partially linear GP regression models. Bayesian modeling with GP prior can be viewed as a marginal structural model where the potential outcome under the no treatment condition is modeled parametrically. It allows for predicting the missing response by a weighted sum of observed data, with larger weights assigned to those in closer proximity but smaller to those further away, much like a matching procedure. This motivated us to consider using GP prior covariance function as a matching tool for Bayesian causal inference.

The idea of utilizing GP prior in Bayesian approach to causal inference is not new. Examples can be found in Roy et al. (2016) for addressing heterogeneous treatment effect, in Xu et al. (2016) for handling dynamic treatment assignment, and in Roy et al. (2017) for tackling missing data. While these studies demonstrated GP prior could be used to achieve flexible modeling and tackle complex setting, no one has considered GP as a matching tool. This study adds to the literature in several ways. First, we offer a principled approach to Bayesian causal inference utilizing GP prior covariance function as a matching tool, which accomplishes matching and flexible outcome modeling in a single step. Second, we provide relaxed causal assumptions than the widely adopted assumptions from the landmark paper by Rosenbaum and Rubin (1983). By admitting additional random noise in outcome measure and in the treatment effect, these new assumptions fit more naturally within Bayesian framework. Under these weaker causal assumptions, GPMatch method offers a doubly robust approach in the sense that the averaged causal treatment effect is correctly estimated when either one of the conditions are met: 1) when the mean function correctly specifies the $Y^{(0)}$; or 2) the covariance function matrix correctly specifies the matching structure. At last, the proposed method has been implemented in an easy-to-use publicly available on-line application (https://pcats.research.cchmc.org/).

The rest of the presentation is organized as follows. Section 2 describes methods, where we present problem setup, causal assumptions, and the model specifications. The utility of GP covariance function as a matching tool is presented in Section 3, followed by discussions of its doubly robustness property. Simulation studies are presented in Section 4. Simulations are designed to represent the real world setting where the true functional form is unknown, including the well-known simulation design suggested by Kang and Schafer (2007). We compared the GPMatch approach with some commonly used causal inference methods, i.e. linear regression with PS adjustment, AIPTW, and BART, without assuming any knowledge of the true data generating models. The results demonstrate that the GPMatch enjoys well calibrated frequentist properties, and outperforms many widely used methods under the dual miss specification setting. Section 5 presents a case study, examining the comparative effectiveness of an early aggressive use of biological medication in treating children with recent diagnosed juvenile idiopathic arthritis (JIA). Section 6 presents summary, discussions and future directions.
2 | METHOD

2.1 | Notations and Parameters of Interests

We introduce the method by considering a simple yet commonly adopted problem setting, i.e. a single-time-assignment binary treatment and a fixed-time-point outcome measure. No post-treatment confounding exists. The more complex type of treatment, such multilevel or continuous treatment, multivariate outcomes, as well as the considerations of post-treatment factors, could be generalized without much difficulty. Let the treatment assignment \( A_i = 1/0 \), denotes the \( i^{th} \) individual is assigned to the experimental/control treatment, where the corresponding potential outcomes are \((Y_i^{(1)}, Y_i^{(0)})\). Since an individual could receive only one treatment at a given time, one of the potential outcomes is unobservable, i.e. \( Y_i^{(A_i)} \) is observed, but \( Y_i^{(1-A_i)} \) is missing. Let \( Y_i \) denotes the observed outcomes, \( X_i \) the p-dimensional prognostic variable, i.e. baseline covariates that are determinants of the potential outcomes, and \( V_i \) the q-dimensional baseline standardized confounders, which are the pre-treatment covariates related to the treatment assignment. The \( X_i \) and \( V_i \) could be overlapping. In this study, we assume all prognostic variables \( X_i \) and confounding variables \( V_i \) are observed, and that the potential outcomes are uniquely determined by the underlying science mechanisms:

\[
Y_i^{(0)} = f^{(0)}(x_i, v_i) \\
Y_i^{(1)} = f^{(1)}(x_i, v_i) = f^{(0)}(x_i, v_i) + \tau(x_i).
\]

In other words, given the prognostic variables \( X_i \) and confounding variables \( V_i \), such as a patient characteristics, such as age, gender, race, genetic make up, disease status, environmental exposures, past treatment histories, then the potential outcomes for this given patient are known if we could possess the knowledge of science mechanisms \( f^{(x)}(\cdot) \). Subsequently, the treatment effect \( f^{(1)}(\cdot) - f^{(0)}(\cdot) \) is also available. Thus, our goal is to uncover the science mechanisms.

Let the treatment assignment mechanism be \( A_i \sim Ber(\pi(v_i)) \), where the true propensity of treatment assignment \( \pi(\cdot) \) is usually not known in the observational studies. Under the given treatment assignment, the observed outcome may be measured with error; thus is a noisy version of the corresponding potential outcomes,

\[
Y_i = Y_i^{(0)}(1 - A_i) + Y_i^{(1)}A_i + \epsilon_i, \tag{1}
\]

where \( E(\epsilon_i) = 0 \). In other words, the observed outcome for the \( i^{th} \) individual, under the assigned treatment \( A_i \) has an expected mean of \( E(Y_i|A_i, X_i, V_i) = Y_i^{(0)}(1 - A_i) + Y_i^{(1)}A_i \). Thus, the observed outcome for the \( i^{th} \) individual is a realization of the joint actions between the science mechanisms and the treatment assignment.

The parameters of interests are individual level and group level causal treatment effect, as well as the science mechanisms \( (f^{(0)}, f^{(1)}) \). The individual level causal treatment effect \( \tau(x_i) \) may differs by some known individual characteristics, such as age, gender, race, disease subtypes, or genotype. The population level average causal treatment effect, \( PATE = E_X(\tau(x_i)) \), is another causal parameter of interests from the policy and community prospective. Because the sampling mechanism of the larger population is not generally available, the PATE cannot be estimated usually. Therefore, sample averaged treatment effect, \( \text{SATE} = \frac{1}{n} \sum_i \tau(x_i) \) is commonly used. While the method could be used for estimating heterogeneous treatment effect, here, we focus on estimating the SATE, which we will simply refer as ATE in the rest of the presentation.
2.2 | The Causal Assumptions

We allow for a version of relaxed causal assumptions than the widely adopted version from the landmark paper by Rosenbaum and Rubin (1983) (RR):

**CA1.** Stable Unit Treatment Value Expectation Assumption (SUTVEA). This is a relaxed version to the widely adopted stable unit treatment value assumption (SUTVA). Like SUTVA, it also contains two components.

   (i) The consistency assumption of RR requires the observed outcome is an exact copy of the potential outcome, i.e. $Y_i = Y_i^{(0)}(1 - A_i) + Y_i^{(1)}A_i$. Instead, we consider the observed outcome is a noisy version of the potential outcome where expectation of the observed outcome $E(Y_i) = Y_i^{(0)}(1 - A_i) + Y_i^{(1)}A_i$.

   (ii) The no interference assumption of RR requires the potential outcomes of one experiment unit is not influenced by the potential outcomes of another experiment unit, i.e. $Y_i^{(a)} \perp Y_j^{(b)}$. Instead, we assume $Y_i^{(a)} \perp Y_j^{(b)} | X, V$.

**CA2.** Ignorable Treatment Assignment Assumption. Similarly as in RR, we assume $(Y_i^{(0)}, Y_i^{(1)}) \perp A_i | (X_i, V_i)$. The assumption requires no unmeasured confounders.

**CA3.** Positivity Assumption. This is the same assumption as in RR, it requires every sample unit has nonzero probability of being assigned into either one of the treatment arms, i.e. $0 < Pr(A_i | V_i) < 1$.

The SUTVEA assumption represents a somewhat weaker assumption than SUTVA. It acknowledges existence of residual random error in the outcome measure. The observed outcomes may differ from the corresponding true potential outcomes due to some measurement errors. In addition, the observed outcomes could differ when treatment received deviates from its intended version of treatment. For example, outcomes could differ by the timing of the treatment, pre-surgery preparation procedure or the concomitant medication. In addition, we consider the potential outcomes from different experimental units may be correlated, where the correlations are determined by the covariates. Under the no unmeasured confounders assumption, we may model the correlation between two potential outcomes. Since only one outcome could be observed out of all potential outcomes, the causal inference presents a highly structured missing data setup where the correlations between $(Y_i^{(1)}, Y_i^{(0)})$ are not directly identifiable. Admitting residual random errors and allowing for explicit modeling of the covariance structure, the new assumptions could facilitate better statistics inference.

2.3 | Model Specifications

Marginal structural model (MSM) is a widely adopted modeling approach to causal inference, which serves as a natural framework for Bayesian causal inference. The MSM specifies

$$Y_i^{(1)} = Y_i^{(0)} + A_i \tau(x_i).$$

Without prior knowledge about the true functional form, we let $Y_i^{(0)} \sim GP(\mu_f, K)$, where the mean function $\mu_f$ maybe modeled by a parametric regression equation, and $K$ defines the covariance function of the GP prior. Specifically, GPMatch is proposed as a partially linear Gaussian process regression fitting to the observed outcomes,

$$Y_i = f_i(x_i, v_i) + A_i \tau(x_i) + \epsilon_i, \quad (2)$$
where
\[ f_i(x_i, v_i) = \mu_f(x_i) + \eta(v_i), \]
\[ \eta_i(v_i) \sim GP(0, K), \]
\[ \epsilon_i \sim N(0, \sigma_0), \]
\[ \epsilon_i \perp \eta_i. \]

Here, we may let \( \mu_f = ((1, X_i\beta)_{n\times1}), \) where \( \beta \) is a \((1 + p)\) dimension parameter vector of regression coefficients for the mean function. This is to allow for implementing any existing knowledge about the prognostic determinants to the outcome. Also, let \( \tau = ((1, X_i\alpha)_{n\times1}) \) to allow for potential heterogeneous treatment effect, where \( \alpha \) is a \((1 + p)\) dimension parameter vector of regression coefficients for the treatment effect.

Let \( Y_n = (Y_1, ..., Y_n) \), the model (2) can be re-expressed in a multivariate representation
\[ Y_n|A, X, V, \gamma \sim MVN(Z'\gamma, \Sigma). \]

where \( Z' = (1, X_1, A_1, A_1 \times X_1)_{n\times(2+2p)} \), \( \gamma = (\beta, \alpha) \), \( \Sigma = (\sigma_{ij})_{n\times n} \), with \( \sigma_{ij} = K(v_i, v_j) + \sigma_0^2 \delta_{ij} \). The \( \delta_{ij} \) is the Kronecker function, \( \delta_{ij} = 1 \) if \( i = j \), and 0 otherwise.

Gaussian process can be considered as distribution over function. The covariance function \( K \), where \( k_{ij} = Cov(\eta_i, \eta_j) \), plays a critical role in GP regression. It can be used to reflect the prior belief about the functional form, determining its shape and degree of smoothness. In the next section, we show for the data comes from an experimental design where the matching structure is known, GP covariance could be formulated to reflect the matching structure. Often, the exact matching structure is not available, a natural choice for the GP prior covariance function \( K \) is the squared-exponential (SE) function, where
\[ K(v_i, v_j) = \sigma_f^2 \exp \left( -\sum_{k=1}^{q} \frac{|v_{ki} - v_{kj}|^2}{\phi_k^2} \right), \]

for \( i, j = 1, ..., n \). The \( (\phi_1, \phi_2, ..., \phi_q) \) are the length scale parameters for each of the covariates \( V \).

There are several considerations in choosing the SE covariance function. The GP regression with SE covariance can be considered as a Bayesian linear regression model with infinite basis functions, which is able to fit a smoothed response surface. Because of the GP’s ability to choose the length-scale and covariance parameters using the training data, unlike other flexible models such as splines or the supporting vector machine (SVM), GP regression does not require cross-validation(Rasmussen et al. (2006)). Moreover, SE covariance function provides a distance metric that is similar to Mahalanobis distance, thus it could be served as a matching tool.

The model specification is completed by specification of the rest of priors.
\[ \gamma \sim MVN \left( 0, \omega \sigma_{im}^2 \left(ZZ^t\right)^{-1} \right), \]
\[ \sigma_0^2 \sim IG(a_0, b_0), \]
\[ \sigma_f^2 \sim IG(a_f, b_f), \]
\[ \phi_k \sim IG(a_\phi, b_\phi). \]

We set \( \omega = 10^6 \), \( a_\phi = b_\phi = 1 \), \( a_0 = a_f = 2 \), \( b_0 = b_f = \sigma_{im}^2/2 \), \( \sigma_{im}^2 \) is the estimated variance from a simple linear regression model of \( Y \) on \( A \) and \( X \) for computational efficiency.

The posterior of the parameters can be obtained by implementing a Gibbs sampling algorithm: first sample the
covariate function parameters from its posterior distribution \( \Sigma | Data, \alpha, \beta \); then sample the regression coefficient parameter associated with the mean function from its conditional posterior distribution \( [\alpha, \beta | Data, \Sigma] \), which is a multivariate normal distribution. The individual level treatment effect can be estimated by \( \hat{\tau}(x_i) = (1, X_i)' \hat{\alpha} \) and the averaged treatment effect is estimated by \( \hat{ATE} = \frac{1}{n} \sum_{i=1}^{n} \hat{\tau}(x_i) \).

### 3 | ESTIMATE ATE: RELATIONSHIP WITH MATCHING AND G-ESTIMATION

#### 3.1 | Design the GP Covariance Function as a Matching Tool

To demonstrate the utility of the GP covariance function as a matching tool, let us first first consider design a covariance function for the known matching data structure. In other words, we assume for any given sample unit, we know who are the matching units. For simplicity, us consider fitting the data with a simple nonparametric version of the GPMatch,

\[ Y_n \sim MVN(\mu 1_n + \tau A_n, \Sigma), \]

where \( \Sigma = K + \sigma_0^2 I_n \).

With known matching structure, the GP covariance function may present the matching structure by letting \( K = (k_{ij})_{n \times n} \), where \( k_{ij} = 1 \) indicates that the pair is completely matched, and \( k_{ij} = 0 \) if unmatched. A common setting of the matched data can be divided into several blocks of subsample within which the matched data points are grouped together. Subsequently, we may rewrite the covariance function of the nonparametric GP model (5) as a block diagonal matrix where the \( i^{th} \) block matrix takes the form

\[ \Sigma_i = \sigma^2 \left( (1 - \rho) I_{n_i} + \rho J_{n_i} \right), \]

where \( \sigma^2 = 1 + \sigma_0^2 / \rho = 1 / \sigma^2 \) and \( J_{n_i} \) denotes the matrix of ones. The parameter estimates of the regression parameters can be derived by

\[ \left( \begin{array}{c} \hat{\beta} \\ \hat{\tau} \end{array} \right) = \left( \begin{array}{cc} 1_n' & A_n' \\ A_n & \Sigma^{-1} \end{array} \right)^{-1} \left( \begin{array}{c} 1_n' \\ A_n' \end{array} \right) \Sigma^{-1} Y_n. \]

It follows that the estimated average treatment effect is,

\[ \hat{\tau} = \frac{1_n' \Sigma^{-1} 1_n A_n' \Sigma^{-1} Y_n - A_n' \Sigma^{-1} 1_n 1_n' \Sigma^{-1} Y_n}{1_n' \Sigma^{-1} 1_n A_n' \Sigma^{-1} A_n - A_n' \Sigma^{-1} 1_n 1_n' \Sigma^{-1} A_n}, \]

Applying the Woodbury, Sherman & Morrison formula, we see \( \Sigma^{-1} \) is a block diagonal matrix of

\[ \Sigma_i^{-1} = \frac{1}{\sigma^2 (1 - \rho)(1 - \rho + n_i)} \left( (1 + (n - 1)\rho) I_{n_i} - \rho J_{n_i} \right). \]

Let \( \bar{Y}_{i(a)} \) denote the sample mean of outcome and \( n_{i(a)} \) number of observations for the control \( (a = 0) \) and treatment group \( (a = 1) \) within the \( i^{th} \) subclass, \( i = 1, 2, ..., L \). The treatment effect can be expressed as a weighted sum of two
\[ \hat{\tau} = \lambda \hat{\tau}_1 + (1 - \lambda) \hat{\tau}_0, \]

where \( \lambda = \frac{\rho D_1}{\rho D_1 + (1 - \rho) D_2} \), \( \hat{\tau}_1 = \frac{C_1}{D_1} \) and \( \hat{\tau}_0 = \frac{C_2}{D_2} \).

\[
C_1 = \sum q_i n_i \times \sum q_j n_j \left( \bar{Y}_1 - \bar{Y}_0 \right),
\]
\[
C_2 = \sum q_i n_i \times \sum q_j n_j \bar{Y}_1 - \sum q_i n_i \times \sum q_j n_j \bar{Y}_0,
\]
\[
D_1 = \sum q_i n_i \times \sum q_j n_j, \quad D_2 = \sum q_i n_i \times \sum q_j n_j.
\]

\( q_i = (1 - \rho + \rho n_i)^{-1}, n_i = n_{i(0)} + n_{i(1)} \) and the summations are over \( l = 1, \ldots, L \). To gain better insight into this estimator, it should help to consider two special matching cases.

The first example is a matched twin experiment, where for each treated unit there is an untreated twin. Here, we have a \( 2n \times 2n \) block diagonal matrix \( \Sigma_{2n} = I_n \otimes J_n + \sigma_0 I_{2n} \). Thus, \( \sigma = 1 + \sigma_0^2, \rho = \frac{1}{1 + \sigma_0^2}, n_k = 2, n_{k(0)} = n_{k(1)} = 1 \). Substitute them into the treatment effect formula derived above, we have the same \( 1:1 \) matching estimator of treatment effect \( \hat{\tau} = \bar{Y}_1 - \bar{Y}_0 \).

The second example is a stratified randomized experiment, where the true propensity of treatment assignment is known. Suppose the strata are equal sized, \( \Sigma \) is a block diagonal matrix of \( I_L \otimes J_n + \sigma_0 I_n \), where \( L \) is total number of strata, the total sample size is \( N = Ln \). It is straightforward to derive \( \sigma = 1 + \sigma_0^2, \rho = \frac{1}{1 + \sigma_0^2}, n_l = n, \) for \( l = 1, \ldots, L \). Then the treatment effect is a weighted sum of \( \hat{\tau}_0 = \bar{Y}_1 - \bar{Y}_0, \) and \( \hat{\tau}_1 = \frac{\Sigma \sigma_{i(0)} \sigma_{i(1)} (\bar{Y}_{i(1)} - \bar{Y}_{i(0)})}{\Sigma \sigma_{i(0)} \sigma_{i(1)}} \). Where the weight \( \lambda = \frac{L \Sigma \sigma_{i(0)} \sigma_{i(1)}}{n_l \sigma_0^2 + L \Sigma \sigma_{i(0)} \sigma_{i(1)}} \) is a function of sample sizes and \( \sigma_0^2 \). We can see when \( \sigma_0^2 \rightarrow 0 \), then \( \lambda \rightarrow 1, \sigma \rightarrow \sigma_1 \). That is when the outcomes are measured without error, the treatment effect is a weighted average of \( \bar{Y}_{i(1)} - \bar{Y}_{i(0)} \), i.e. the group mean difference for each strata. As \( \sigma_0^2 \) increase, \( \lambda \) decrease, then the estimate of \( \sigma \) puts more weights on \( \hat{\tau}_0 \). In other words, GP estimate of treatment is a shrinkage estimator, where it shrinks the strata level treatment effect more towards the overall sample mean difference when outcome variance is larger.

More generally, instead of \( 0/1 \) match, the sample units may be matched in various degrees. By letting the covariance function takes a squared-exponential form, it offers a way to specify a distance matching, which closely resembles Mahalanobis distance matching. For a pair of "matched" individuals, i.e. sample units with the same set of confounding variables \( u_i = u_j \), the model specifies \( Corr(Y_j^{(0)}, Y_j^{(1)}) = 1 \). In other words, the "matched" individuals are expected to be exchangeable. As the data points move further apart in the covariate space of \( \Omega_* \), their correlation becomes smaller. When the distant is far part sufficiently, the model specifies \( Corr(Y_j^{(0)}, Y_j^{(1)}) \approx 0 \) or "unmatched". Distinct length scale parameters are used to allow for some confounder playing more important roles than others in matching. By manipulating the values of \( \nu_i \) and the corresponding length scale parameter, one could formulate the SE covariance matrix to reflect the known \( 0/1 \) or various degree of matching structure. However, the matching structure is usually unknown, and was left to be estimated in the GPMatch model informed by the observed data.

### 3.2 Doubly Robust Estimator of ATE

**Theorem 1** Let the true treatment effect be \( \tau^* \), the GPMatch estimator is an unbiased estimate of the average treatment effect, i.e. \( E(\hat{\tau}_i) = \tau^* \), for \( i = 1, \ldots, n \), when either one of the condition is true: i) the GP mean function is correctly specified, i.e. \( E(Z_i \hat{\tau}) = Y_i^{(0)} \); and ii) the GP covariance function is correctly specified, in the sense that, from the weight-space point of view of
GP regression, the weighted sum of treatment assignment $\tilde{A}_i$ correctly specifies the true treatment propensity $\pi_i = Pr(A_i = 1)$.

Proof It is relatively straight forward for the first part. From the GPMATCH model (3) $Y_{ni} \sim MVN(Z'\gamma, \Sigma)$, when the linear regression model fits the potential outcome correctly, i.e. $E(Z'_i \hat{\gamma}) = Y_i^{(0)}$, then $Z$ degenerate to a diagonal matrix, suggesting all units are exchangeable. It follows $E(\hat{\tau}) = \tau^*$, the treatment effect is correctly estimated.

The second part proceeds as the following. From the weight-space point of view, the GPMATCH model predicts the potential outcomes using a weighted sum of the observed outcomes,

$$
\hat{Y}_i^{(a)} = \sum_{j=1}^n w_{ij}(Y_j - \tilde{A}_j \hat{\tau}) + \alpha \hat{\tau} = \hat{Y}_i + (A_i - \tilde{A}_i) \hat{\tau},
$$

where $Y_i = \sum_{j=1}^n w_{ij} Y_j$ and $\tilde{A}_i = \sum_{j=1}^n w_{ij} A_j$, for $i = 1, ..., n$. The weight $w_{ij} = \frac{\kappa_{ij}}{\sum \kappa_{ij}}$ where $\kappa_{ij} = k(v_j, v_i) \Sigma^{-1}$, with $k(v_j, v_i) = (k(v_j, v_i))_{ij}$. Thus, the $\hat{Y}_i$ and $\tilde{A}_i$ could be considered as the Nadaraya-Watson estimator of the observed outcomes and treatment assignment for each of the $i$-th unit in the sample. The estimate of treatment effect could be obtained by solving

$$
\frac{\partial \sum_{i=1}^n (Y_i - \hat{Y}_i^{(a)})^2}{\partial \hat{\tau}} = 0.
$$

We can see that, given a known GP covariance function, the GPMATCH treatment effect $\hat{\tau}$ is an M-estimator that satisfies $\sum \Psi_i(\hat{\tau}) = 0$, where

$$
\Psi_i(\tau) = (Y_i - \hat{Y}_i - \tau(A_i - \tilde{A}_i))(A_i - \tilde{A}_i) = 0.
$$

Let the true propensity be $\pi_i = Pr(A_i)$, given the SUTVEA, we have $Y_i = A_i Y_i^{(1)} + (1 - A_i) Y_i^{(0)} + \epsilon_i$. Given the true treatment effect $\tau^*$, it can be derived that $Y_i^{(a)} = E(Y_i) + (a - \pi_i) \tau^*$. When $\tilde{A}_i = \pi_i$ is true, we have $\Psi_i(\tau) = \{E(Y_i) - \hat{Y}_i + (A_i - \pi_i)(\tau - \tau^*) + \epsilon_i\}(A_i - \pi_i)$. Thus, the GPMATCH estimator is an M-estimator of ATE, where the estimating function is conditionally unbiased, i.e. $E(\Psi_i(\tau^*)) = 0$, for $i = 1, ..., n$, when the GP covariance function is correctly specified in the sense $\tilde{A}_i = \pi_i$.

Remark There are several remarks worth noting. First, the equation (7) is the empirical correlation of the residuals from the outcome model and the residuals from the propensity of treatment assignment. Thus, GPMATCH method attempts to induce independence between the treatment selection process and the outcome modeling, just as the G-estimation equation suggested in Robins et al. (2000) and later in Vansteelandt et al. (2014). Unlike the moment based G-estimator, which requires fitting of two separate models for the outcome and propensity score, the GPMATCH approach estimates covariance parameters the same time as it estimates the treatment and mean function parameters. All within a full Bayesian likelihood framework.

Second, some data points may have treatment propensity close to 0 or 1. Those data usually are a cause of concern in causal inference. In the naive regression type of model such as BART, it may cause unstable estimation without added regularization. In the IPTW type of method, a few data points may put undue influence over the estimation of treatment effect. In matching methods, these data points often are discarded. Such practice could lead to sample no longer representative of the target population. Like the G-estimation, in the equation (7), these data points contribute very little or no information to the GPMATCH estimation of treatment effect. Thus GPMATCH share the same added robustness as the G-estimation.

At last, the GPMATCH model with a parametric mean function will be predicting the potential outcomes, for any new unit, by $\hat{Y}_i = Z_i' \hat{\gamma} + \Sigma_i \Sigma^{-1} (Y_n - Z' \hat{\gamma})$, where $\Sigma_i$ denotes the i-th row of $\Sigma$. Given the model setup, two regression surfaces are predicted, where the distance between the two regression surfaces represents the treatment effect. By including the treatment by covariate interactions, the model could offer conditional treatment effect as a function of the patient characteristics. Although the model specifications presented in section 2.3 suggest using a parametric
linear regression equation for modeling the treatment effect $\tau(x_i)$, it is always difficult to know if any higher order terms should be included in the model. One may consider introducing a few fixed basis functions instead, estimation of the regression coefficients could inform existence of any nonlinear or heterogeneous treatment effect.

4 | SIMULATION STUDIES

To empirically evaluate the performances of GPMatch in a real world setting where neither matching structure or functional form of the outcome model are known, we conducted three sets of simulation studies to evaluate the performances of the GPMatch approach to causal inference. The first set evaluated frequentist performance of GPMatch. The second set compared the performance of GPMatch against MD match, and the last set utilized the widely used Kang and Schafer design, comparing the performance of GPMatch against some commonly used methods.

In all simulation studies, the GPMatch approach used squared exponential covariate function, including only treatment indicator in the mean and all observed covariates into the covariate function, unless otherwise noted. The results were compared with the following widely used causal inference methods: sub-classification by PS quantile (QNT-PS); AIPTW, linear model with PS adjustment (LM-PS), linear model with spline fit PS adjustment (LM-sp(PS)) and BART. Cubic B-splines with knots based on quantiles of PS were used for LM-sp(PS). We also considered direct linear regression model (LM) as a comparison. The ATE estimates were obtained by averaging over 5000 posterior MCMC draws, after 5,000 burn in. For each scenario, three sample sizes were considered, $N = 100, 200, 400$. The standard error and the 95% symmetric interval estimate of ATE for each replicate were calculated from the 5,000 MCMC chain. For comparing performances of different methods, all results were summarized over $N=100$ replicates by the root mean square error $\text{RMSE} = \sqrt{\sum(\hat{\tau}_i - \tau)^2}/N$, median absolute error $\text{MAE} = \text{median} | \hat{\tau}_i - \tau |$, coverage rate $R_e = (\text{the number of intervals that include} \ \tau)/N$ of the 95% symmetric posterior interval, the averaged standard error estimate $SE_{ave} = \sum \hat{\sigma}_i/N$, where $\hat{\sigma}_i$ is the square root of the estimated standard deviation of $\hat{\tau}_i$, and the standard error of ATE was calculated from 100 replicates $SE_{emp} = \sqrt{\sum(\hat{\tau}_i - \bar{\tau}_i)^2/(N-1)}$.

4.1 | Well Calibrated Frequentist Performances

Let the single covariate $x \sim N(0, 1)$. The potential outcome was generated by $y^{(a)} = e^x + (1 + U) \times a + U_0$ for $a = 0, 1$, where the true treatment effect was $1 + U_i$ for the $i$-th individual unit. The $(U, U_0)$ are unobserved covariates. The treatment was selected for each individual following $\logit(P(A = 1 | X)) = -0.2 + (1.8 X)^1/3$. The observed outcome was generated by $y | x, a \sim N(y^{(a)}, \sigma^2_0)$. Two parameter settings were considered. First, we set $(U_i = 0, U_0 \sim N(0, 0.25), \sigma^2_0 = 0.75), i.e. all individual units had the same uniform treatment effect of 1, and outcomes were observed with measurement error. Second, we set $(U_i \sim N(0, 0.15), U_0 \sim N(0, 1), \sigma^2_0 = 0), i.e. the treatment effect varied from individual unit to unit, but the averaged treatment effect remained at 1.

The simulation results were summarized in the histogram of the posterior mean over the 100 replicates across three sample sizes in Figure 1. Table 1 presented the results of GPMatch and the gold standard. The gold standard was obtained by fitting the true outcome generating model. For both Table 1 and Figure 1, the upper panel presented results from the uniform treatment parameter setting; and the lower panel presented the results from the homogeneous treatment setting. Under both settings, GPMatch presented well calibrated frequentist properties with nominal coverage rate, and only slightly larger RMSE. The averaged bias, RMSE and MAE quickly improve as sample size increases, and perform as well as the gold standard with the sample size of 400. Comparison of the RMSE and MAE with the results using other causal inference methods were presented in Figures S1 and S2.
TABLE 1  Results of ATE Estimates under the Single Covariate Simulation Study Setting.

| Method   | Sample Size | RMSE  | MAE   | Bias | Rc  | $SE_{avg}$ | $SE_{emp}$ |
|----------|-------------|-------|-------|------|-----|------------|------------|
| Gold     | 100         | 0.243 | 0.165 | -0.066 | 0.930 | 0.216     | 0.235      |
|          | 200         | 0.149 | 0.109 | 0.027 | 0.940 | 0.150     | 0.147      |
|          | 400         | 0.123 | 0.087 | -0.007 | 0.930 | 0.107     | 0.123      |
| GPMatch  | 100         | 0.260 | 0.160 | -0.038 | 0.93  | 0.242     | 0.258      |
|          | 200         | 0.161 | 0.116 | 0.033 | 0.97  | 0.167     | 0.159      |
|          | 400         | 0.122 | 0.085 | -0.005 | 0.96  | 0.118     | 0.123      |
| Gold     | 100         | 0.220 | 0.134 | -0.011 | 0.92  | 0.213     | 0.221      |
|          | 200         | 0.159 | 0.098 | 0.001 | 0.94  | 0.151     | 0.159      |
|          | 400         | 0.107 | 0.077 | -0.003 | 0.95  | 0.107     | 0.108      |
| GPMatch  | 100         | 0.237 | 0.152 | 0.013 | 0.97  | 0.244     | 0.238      |
|          | 200         | 0.175 | 0.114 | 0.007 | 0.94  | 0.169     | 0.175      |
|          | 400         | 0.117 | 0.084 | 0.001 | 0.96  | 0.117     | 0.118      |

RMSE = root mean square error; MAE = median absolute error; Bias = Estimate-True; Rc = Rate of coverage by the 95% interval estimate; $SE_{avg}$ = average of standard error estimate from all replicate; $SE_{emp}$ = standard error of ATE estimates from all replicate; Gold: Using the true outcome generating model; GPMatch: Bayesian marginal structural model with Gaussian process prior, only treatment effect is included in the mean function; covariance function includes $X$.

4.2  Compared to Manhalanobis Distance Matching

To compare the performances between the MD matching and GPMatch, we considered a simulation study with two independent covariates $x_1, x_2$ from the uniform distribution $U(-2,2)$, treatment was assigned by letting $A_i \sim Ber(\pi_i)$, where

$$logit \pi_i = -x_1 - x_2.$$ 

The potential outcomes were generated by

$$y_i^{(a)} = 3 + 5a + x_1^2,$$

$$Y_i | X_i, A_i \sim N(y_i^{(A_i)}, 1).$$
The true treatment effect is 5. Three different sample sizes were considered N= 100, 200 and 400. For each setting, 100 replicates were performed and the results were summarized.

We estimated ATE by applying Mahalanobis distance matching and GPMatch. The MD matching considered caliper varied from 0.125 to 1 with step size 0.025, including both X1 and X2 in the matching using the function Match in R package Matching by Sekhon (2007). The averaged bias and its 95%-tile and 5%-tile were presented as vertical lines corresponding to different calipers in Figure 2. To be directly comparable to the matching approach, the GPMatch estimated the ATE by including treatment effect only in modeling the mean function, both X1 and X2 were considered in the covariance function modeling. The posterior results were generated with 5,000 MCMC sample after 5,000 burn-in. Its averaged bias (short dashed horizontal line) and 5% and 95%-tiles of the ATE estimate (long dashed horizontal lines) were presented on the Figure 2 for each the sample sizes. Also presented in the Figure were the bias, median absolute error (MAE), root mean square error (RMSE), and rate of coverage rate (Rc) summarized over 100 replicates of GPMatch. The bias from the matching method increases with caliper; the width of interval estimate varies by sample size and caliper. It reduces with increased caliper for the sample size of 100, but increases with increased caliper for sample size of 400. In contrast, GPMatch produced a much more accurate and efficient estimate of ATE for all sample sizes, with unbiased ATE estimate and nominal coverage rate. The 5% and 95%-tiles of ATE estimates are always smaller than those from the matching methods for all settings considered, suggesting better efficiency of GPMatch.

4.3 | Performance under Dual Misspecification

Following the well-known simulation design suggested by Kang and Schafer (2007), covariates z1, z2, z3, z4 were independently generated from the standard normal distribution N(0, 1). Treatment was assigned by $A_i \sim Ber(\pi_i)$, where

$$\logit \pi_i = -z_{i1} + 0.5z_{i2} - 0.25z_{i3} - 0.1z_{i4}.$$  

The potential outcomes were generated for $a = 0, 1$ by

$$Y_i^{(a)} = 210 + 5a + 27.4z_{i1} + 13.7z_{i2} + 13.7z_{i3} + 13.7z_{i4},$$

$$Y_i | A_i, X_i \sim N(y_i^{(A_i)}, 1).$$

The true treatment effect is 5. To assess the performances of the methods under the dual miss-specifications, the transformed covariates $x_1 = exp(z_{i1}/2)$, $x_2 = z_{i2}/(1 + exp(z_{i1})) + 10$, $x_3 = \left(\frac{z_{i1}z_{i3}}{25} + 0.6\right)^3$, and $x_4 = (z_{i2} + z_{i4} + 20)^2$ were used in the model instead of $z_i$.

Two GPMatch models were considered: GPMatch1 modeled the treatment effect only and GPMatch2 modeled all four covariates $X_1 \sim X_4$ in the mean function model. Both included $X_1 \sim X_4$ with four distinct length scale parameters. The PS was estimated using two approaches including the logistic regression model on $X_1 \sim X_4$ and the covariate balancing propensity score method (CBPS, Imai and Ratkovic (2014)) applied to $X_1 \sim X_4$. The results corresponding to both versions of PS were presented. Summaries over all replicates were presented in Table 2, and the RMSE and the MAE were plotted in Figure 3, for all methods considered. As a comparison, the gold standard which uses the true outcome generating model of $Y \sim Z_1 \sim Z_4$ was also presented. Both GPMatch1 and GPMatch2 clearly outperforms all the other causal inference methods in terms of bias, RMSE, MAE, Rc, and the $SE_{ave}$ is closely matched to $SE_{emp}$. The ATE and the corresponding SE estimates improve quickly as sample size increases for GPMatch. In contrast, the QNT_PS, AIP_T, LM_PS and LM_sp(PS) methods show little improvement over increased sample size, so is the simple
LM. Improvements in the performance of GPMatch over existing methods are clearly evident, with more than 5 times accuracy in RMSE and MAE compared to all the other methods except for BART. Even compared to the BART results, the improvement in MAE is nearly twice for GPMatch2, and about 1.5 times for the GPMatch1. Similar results are evident in RMSE and averaged bias. The lower than nominal coverage rate is mainly driven by the remaining bias, which quickly reduces as sample size increases. Additional results are presented in Figure S3.

**Table 2** Results of ATE Estimates using Different Methods under the Kang and Shafer Dual Misspecification setting.

| Method    | Sample Size | RMSE | MAE  | Bias  | Rc  | $SE_{avg}$ | $SE_{emp}$ |
|-----------|-------------|------|------|-------|-----|------------|------------|
| Gold      | 100         | 0.224| 0.150| 0.011 | 0.95| 0.225      | 0.225      |
|           | 200         | 0.171| 0.125| -0.015| 0.94| 0.163      | 0.171      |
|           | 400         | 0.102| 0.063| -0.015| 0.96| 0.112      | 0.102      |
| GPMatch1  | 100         | 2.400| 1.606| -1.254| 0.92| 2.158      | 2.057      |
|           | 200         | 1.663| 1.309| -1.051| 0.86| 1.213      | 1.295      |
|           | 400         | 0.897| 0.587| -0.564| 0.86| 0.673      | 0.701      |
| GPMatch2  | 100         | 1.977| 1.358| -0.940| 0.91| 1.672      | 1.748      |
|           | 200         | 1.375| 1.083| -0.809| 0.82| 0.980      | 1.117      |
|           | 400         | 0.761| 0.484| -0.432| 0.87| 0.567      | 0.629      |
| QNT_PSa   | 100         | 7.574| 6.483| -6.234| 0.970| 7.641      | 4.324      |
|           | 200         | 7.408| 6.559| -6.615| 0.860| 5.199      | 3.535      |
|           | 400         | 7.142| 6.907| -6.797| 0.500| 3.576      | 2.203      |
| QNT_PSb   | 100         | 8.589| 7.360| -7.177| 0.970| 7.541      | 4.744      |
|           | 200         | 8.713| 8.121| -7.964| 0.720| 5.214      | 3.550      |
|           | 400         | 8.909| 7.980| -8.399| 0.300| 3.607      | 2.987      |
| LM        | 100         | 6.442| 5.183| -5.556| 0.65| 3.571      | 3.277      |
|           | 200         | 6.906| 6.226| -6.375| 0.28| 2.547      | 2.668      |
|           | 400         | 7.005| 6.649| -6.702| 0.04| 1.796      | 2.048      |
| AIPTWa   | 100         | 5.927| 4.402| -4.330| 0.72| 3.736      | 4.067      |
|           | 200         | 19.226| 5.262| -7.270| 0.59| 4.874      | 17.888     |
|           | 400         | 29.405| 5.603| -7.676| 0.36| 6.115      | 27.908     |
| AIPTWb   | 100         | 5.410| 4.243| -3.659| 0.77| 3.780      | 4.005      |
|           | 200         | 5.780| 5.075| -4.950| 0.52| 2.712      | 2.999      |
|           | 400         | 6.204| 5.482| -5.652| 0.24| 2.105      | 2.569      |
| LM_PSa   | 100         | 5.103| 3.832| -4.091| 0.74| 3.420      | 3.066      |
|           | 200         | 5.392| 4.648| -4.793| 0.53| 2.452      | 2.483      |
|           | 400         | 5.091| 5.128| -4.787| 0.19| 1.706      | 1.741      |
| LM_Psb   | 100         | 5.103| 3.832| -4.091| 0.74| 3.420      | 3.066      |
|           | 200         | 5.392| 4.648| -4.793| 0.53| 2.452      | 2.483      |
|           | 400         | 5.091| 5.128| -4.787| 0.19| 1.706      | 1.741      |
| LM_sp(PS)a | 100     | 4.809| 3.161| -3.598| 0.79| 3.165      | 3.207      |
|           | 200         | 4.982| 4.152| -4.266| 0.52| 2.250      | 2.587      |
|           | 400         | 4.470| 4.038| -4.127| 0.23| 1.559      | 1.727      |
| LM_sp(PS)b | 100     | 4.984| 3.619| -3.806| 0.77| 3.095      | 3.233      |

*Continued on next page*
Table 2 – Continued from previous page

| Method  | Sample Size | RMSE | MAE  | Bias   | Rc  | $SE_{avg}$ | $SE_{emp}$ |
|---------|-------------|------|------|--------|-----|------------|------------|
|         | 200         | 5.237| 4.374| -4.507 | 0.51| 2.248      | 2.681      |
|         | 400         | 4.856| 4.484| -4.494 | 0.18| 1.585      | 1.851      |
| BART    | 100         | 3.148| 2.504| -2.491 | 0.79| 2.163      | 1.935      |
|         | 200         | 2.176| 1.870| -1.726 | 0.74| 1.308      | 1.332      |
|         | 400         | 1.283| 0.942| -0.997 | 0.71| 0.757      | 0.812      |

$^a$ Propensity score estimated using logistic regression on $X_1 - X_4$.

$^b$ Propensity score estimated using CBPS on $X_1 - X_4$.

RMSE = root mean square error; MAE = median absolute error; Bias = Estimate-True; Rc = Rate of coverage by the 95% interval estimate; $SE_{avg}$ = average of standard error estimate from all replicate; $SE_{emp}$ = standard error of ATE estimates from all replicate;

GPMatch1-2: Bayesian structural model with Gaussian process prior. GPMatch1 including only treatment effect, and GPMatch2 including both treatment effect and $X_1 - X_4$ in the mean function; both including $X_1 - X_4$ in the covariance function.

QNT_PS: Propensity score sub-classification by quintiles.

AIPTW: augmented inverse probability of treatment weighting;

LM: linear regression modeling $Y - X_1 - X_4$;

LM_PS: linear regression modeling with propensity score adjustment.

LM_splPS: linear regression modeling with spline fit propensity score adjustment.

BART: Bayesian additive regression tree.

5 | A CASE STUDY

JIA is a chronic inflammatory disease, the most common autoimmune disease affecting the musculoskeletal organ system, and a major cause of childhood disability. The disease is relatively rare, with an estimated incidence rate of 12 per 100,000 child-year (Harrold et al. (2013)). There are many treatment options. Currently, the two common approaches are the non-biologic disease modifying anti-rheumatic drugs (DMARDs) and the biologic DMARDs. Limited clinical evidence suggest that early aggressive use of biologic DMARDs may be more effective (Wallace et al. (2014)). Utilizing data collected from a completed prospectively followed up inception cohort research study (Seid et al. (2014)), a retrospective chart review collected medication prescription records for study participants captured in the electronic health record system. This comparative study is aimed at understanding whether therapy using early aggressive combination of non-biologic and biologic DMARDs is more effective than the more commonly adopted non-biologic DMARDs monotherapy in treating children with recently (<6 months) diagnosed polyarticular course of JIA. The study is approved by the investigator’s institutional IRB.

The GPMatch model included the baseline JADAS, CHAQ, time since diagnosis at baseline, and time interval between baseline and the six month follow-up visit in modelling the covariance function. These four covariates, along with the binary treatment indicator and an indicator of positive test of rheumatoid factor were used in the partially linear mean function part of the GPMatch. Applying the proposed method, GPMatch obtained the average treatment effect of -2.90 with standard error of 1.91, and the 95% credible interval of (-6.65, 0.79). Figure 5 presents the trace plot and histogram of the posterior distribution of the ATE estimate. The results suggest that, the early aggressive combination of non-biologic and biologic DMARDs as the first line of treatment is more effective, leading to a nearly 3 point of reduction in JADAS six months after treatment, compared to the non-biologic DMARDs treatment to children.
with a newly diagnosed disease. The results of ATE estimates by GPMatc
naive two group comparison and other exis
ting causal inference methods are presented in Table 3. The LM, LM_PS, LM_sp(PS) and AIP
tW include the same five covariates in the model along with the treatment indicator. BART used the treatment indicator and those covariates. While all results suggested effectiveness of an early aggressive use of biological DMARD, the naive, PS sub-classification by quintiles, and AIPTW suggested a much smaller ATE effect. The BART and PS adjusted linear regression produced results that were closer to the GPMatc results suggesting 2 or 3 points reduction in the JADAS score if treated by the early aggressive combination DMARDs therapy. None of the results were statistically significant at the 2-sided 0.05 level.

The primary outcome is the Juvenile Arthritis Disease Activity Score (JADAS) after 6 months of treatment, a disease severity score calculated as the sum of four core clinical measures: physician's global assessment of disease activity (0-10), patient's self-assessment of overall wellbeing (0-10), erythrocyte sedimentation rate (ESR, standardized to 0-10), and number of active joint counts (AJC, truncated to 0-10). It ranges from 0 to 40, with 0 indicating no disease activity. Out of the 75 patients receiving either non-biological or the early combination of biological and non-biological DMARDs at baseline, 52 patients were treated by the non-biologic DMARDs and 23 were treated by the early aggressive combination DMARDs. The patients with longer disease duration, positive rheumatoid factor (RF) presence, higher pain visual analog scale (VAS) and lower baseline functional ability as measured by the childhood health assessment questionnaire (CHAQ), higher lost range of motion (LROM) and JADAS score are more likely to receive the biologic DMARDs prescription. The propensity score was derived using the CBPS method applied to the 11 pre-determined

| Method   | Estimate | SD  | LL  | UL  |
|----------|----------|-----|-----|-----|
| Naive    | -0.338   | 1.973 | -4.205 | 3.529 |
| QNT_PS   | -0.265   | 0.792 | -1.817 | 1.286 |
| AIPTW    | -0.639   | 2.784 | -6.094 | 4.817 |
| LM       | -2.550   | 1.981 | -6.432 | 1.332 |
| LM_PS    | -2.844   | 2.002 | -6.767 | 1.079 |
| LM_sp(PS)| -1.664   | 2.159 | -5.896 | 2.568 |
| BART     | -2.092   | 1.629 | -5.282 | 1.155 |
| GPMatc   | -2.902   | 1.912 | -6.650 | 0.789 |

SD = standard deviation; LL = lower limit; UL = upper limit;
Naive: Student-T two group comparisons;
QNT_PS: Propensity score sub-classification by quintiles.
AIPTW: augmented inversed probability of treatment weighting;
LM: linear regression modeling $Y \sim X$;
LM_PS: linear regression modeling with propensity score adjust-
ment.
LM_sp(PS): linear regression modeling with spline fit propensity score adjustment;
BART: Bayesian additive regression tree;
GPMatc: Bayesian structural model with Gaussian process prior.

**Table 3** Results of Case Study ATE Estimates with None-Matching Methods
important baseline confounders. The derived PS were able to achieve a desired covariate balance within the 0.2 absolute standardized mean difference (Figure 4), and comparable distributions in important confounders (Figure S4).

We also applied the covariate matching method to the same dataset based on the same five baseline covariates. Table 4 presents the results from using different caliper. As expected, as calipers narrow, the number of observations being discarded increases. Since only 10 patients had RF positive, thus, when the calipers were set to 1 or smaller, we cannot matching on RF positive anymore. Thus, for calipers smaller than 1, all subjects with positive RF were being excluded. When calipers were set at 0.5, about 50% observations were discarded. When the calipers were set at 0.2, 62 out of 73 observations were discarded, rendering the results obtained from 11 observations only! The estimate of ATE was sensitive to the choices of calipers, ranged from -6.59 to -3.12, making it difficult to interpret the study results.

### 6 | CONCLUSIONS AND DISCUSSIONS

Bayesian approaches to causal inference commonly consider it as a missing data problem. However, as suggested in Ding and Li (2018), the causal inference presents additional challenges that are unique in itself than the missing data alone. Approaches not carefully address these unique challenges are vulnerable to model mis-specifications and could lead to seriously biased results. When not considering the treatment-by-indication confounding, naive regression approaches could suffer from "regularity induced bias" (Hahn et al. (2018a)). Because no more than one potential outcome could be observed for a given individual unit, the correlation of \(Y_i^{(1)}, Y_i^{(0)}\) is not directly identifiable, leading to "inferential quandary" as suggested in Dawid (2000). Extensive simulations presented in Kang and Schafer (2007); Gutman and Rubin (2017); Hahn et al. (2018b) suggested poor operational characteristics observed in many widely adopted causal inference methods.

The proposed GPMatch method offers a full Bayesian causal inference approach that can effectively address the unique challenges inherent in causal inference. First, utilizing GP prior covariance function to model covariance of observed data, GPMatch could estimate the missing potential outcomes much like the matching method. Yet, it avoids pitfalls of many matching methods. No data is discarded, and no arbitrary caliper is required. Instead, the model allows
the data to speak by itself via estimating length scale and variance parameters. The SE covariance function of GP prior offers an alternative distance metric, which closely resembles Mahalanobis distance. It matches data points by the degree of matching proportional to the SE distance, without requiring specification of caliper. For this reason, the GPMatch could utilize data information better than matching procedure. Different length scale parameters are considered for different covariates used in defining SE covariance function. This allows the data to select the most important covariates to be matched on, and acknowledge some variable is more important than others. While the idea of using GP prior for Bayesian causal inference is not new. Utilizing GP covariance function as a matching device is a unique contribution of this study. The matching utility of GP covariance function is presented analytically by considering a setting when matching structure is known. We show that GPMatch enjoys doubly robust properties, in the sense that it correctly estimate the averaged treatment effect when either one of the conditions is true: 1) the mean function of the GPMatch correctly specifies the prognostic function of the potential outcome $Y^{(0)}$; and 2) the GP prior covariance function correctly specifies matching structure. We show that GPMatch estimates the treatment effect by inducing independence between two residuals: the residual from treatment propensity estimate and the residual from the outcome estimate, much like the G-estimation method. Unlike the two-staged G-estimation, the estimations of the parameters in covariance function and the mean function for the GPMatch are performed simultaneously. Therefor, GPMatch regression approach can integrate the benefits of the regression model and matching method and offers a natural way for Bayesian causal inference to address challenges unique to the causal inference problems. The robust and efficient proprieties of GPMatch are well supported by the simulation results designed to reflect the most realistic settings, i.e. no knowledge of matching or functional form of outcome model is available.

The validity of the causal inference by GPMatch approach rests on three causal assumptions. In particular, we propose SUTVEA as a weak causal assumption than SUTVA. SUTVEA suggests that the potential outcomes and their difference are random variables. It can be considered as a version of the stochastic consistency advocated by Cole and Frangakis (2009) and VanderWeele (2009). The SUTVEA is proposed to reflect more realistic setting that outcome could be measured with error, and the treatment received by different individuals may vary, even though the treatment prescribed is identical. Despite the fact that Rubin (1978) has pointed out such treatment variations, no approach to our knowledge has explicitly acknowledged it as such. Rather, most of the methods consider the treatment from the real world as having the exactly same meaning as those from the randomized and strictly controlled experiments. Acknowledging existence of random error in outcome measures, the GPMatch method is more capable of defending against potential model misspecification in the challenging real world setting. Like others, the no unmeasured confounder is also required. Because no one has more than one potential outcome observed in the real world, the assumptions remain untestable. However, our SUTVEA implies the correlations among the potential outcomes have an inherent structure, which could be modeled when all confounders are observed. Therefore, potential outcomes from different individuals could be correlated. The correlation is null only when conditional on confounders. This new causal assumption allows for a direct and explicit way of describing the underlying data generating mechanisms, which may help relieve the "inferential quandary". By explicitly modeling the mean and covariance functions, the GPMatch can be considered as an extension of the widely adopted marginal structural mean model.

Full Bayesian modeling approach is particularly useful in comparative effectiveness research. It offers a coherent and flexible framework for incorporating prior knowledge and synthesizing information from different sources. As a full Bayesian causal inference model, the GPMatch offers a very flexible and general approach to address more complex data types and structures natural to many causal inference problem settings. It can be directly extended to consider multilevel or cluster data structure, and to accommodate complex type of treatment such as multiple level treatment, continuous or composite type of treatment. The model could be extend to time-varying treatment setting without much difficulty by following the g-formula framework. The post-treatment confounding can be addressed by incorporate
the confounding variables into the modeling of mean function. We are already implementing these extensions in an ongoing case study. Although we focused on presenting GPMatch for estimating the average treatment effect in this study, it can be readily used for modeling treatment effect as a function of pre-specified treatment modifying factors. Sivaganesan et al. (2017) suggested a Bayesian decision theory based approach for identifying subgroup treatment effect in a randomized trial setting. With GPMatch, the same idea could be applied to identify subgroup treatment analyzing real world data. Studies are ongoing to evaluate its performances for estimating heterogeneous treatment effect. The GP regression has been extended to general types of outcomes including binary and count data (Rasmussen (2004)). Future studies may further investigate its performance under the general types of outcome and data structures. Our simulation focused on comparing with the commonly used causal inference method. Future studies may consider comparisons of our method with other advanced Bayesian methods such as those proposed by Roy et al. (2017) and Saarela et al. (2016), as well as other advanced non-Bayesian approaches like Targeted MLE (Van Der Laan and Rubin (2006)). At last, while our discussion has been focused on estimation averaged treatment effect of the sample (ATE), the approach is directly applicable to estimation of averaged treatment effect in treated (ATT) and averaged treatment effect in control (ATC).

The GP regression is a very flexible modeling technique, but it is computationally expensive. The time cost associated with GP regression increases at $n^3$ rate, thus it can be challenging with large sample sizes. The Bayesian Gibbs Sampling algorithm we have used makes it even more demanding in computational resources. Some literature has offered solutions by applying GP to large data, such as Banerjee et al. (2008). Alternatively, one may consider using Bayesian Kernel regression as an approximation. Further studies are needed to improve the computational efficiency and to consider variable selection. It is well known the length scale parameter is hard to estimate. Researchers derived different kinds of priors for GP, for example the objective prior in Berger et al. (2001), Kazianka and Pilz (2012), and Ren et al. (2013). Gelfand et al. (2005) suggested using uniform prior for the inverse of the scale parameter in a spatial analysis, but we found that using a prior with preference to smooth surface was more suitable for our purpose. Researchers could also blend their knowledge in the prior to obtain a more efficient estimate. Here we considered squared exponential covariance function but different covariance function such as Matérn could also be considered. Simple block compound symmetry with one correlation coefficient parameter could be used as an alternative covariance matrix. Such blocked covariance set up could be useful particularly for a large sample size and where the data has a reasonable clustering structure, such as in the case of a multi-site study. Future study will explore along this direction.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.
REFERENCES

Baccini, M., Mattei, A. and Mealli, F. (2017) Bayesian inference for causal mechanisms with application to a randomized study for postoperative pain control. Biostatistics, 18, 605–617.

Banerjee, S., Gelfand, A. E., Finley, A. O. and Sang, H. (2008) Gaussian predictive process models for large spatial data sets. Journal of the Royal Statistical Society. Series B. Statistical methodology, 70, 825–848.

Berger, J. O., De Oliveira, V. and Sanso, B. (2001) Objective Bayesian analysis of spatially correlated data. Journal of the American Statistical Association, 96, 1361–1374.

Choi, T. and Schervish, M. J. (2007) On posterior consistency in nonparametric regression problems. Journal of Multivariate Analysis, 98, 1969–1987.

Choi, T. and Woo, Y. (2013) On asymptotic properties of Bayesian partially linear models. Journal of the Korean Statistical Society, 42, 529–541.

Cole, S. R. and Frangakis, C. E. (2009) The Consistency Statement in Causal Inference: A Definition or an Assumption? Epidemiology, 20.

Dawid, A. P. (2000) Causal inference without counterfactuals (with Discussion). Journal of the American Statistical Association, 95, 407–424.

Ding, P. and Li, F. (2018) Causal Inference: A Missing Data Perspective. Statistical Science, 33, 214–237. URL: https://projecteuclid.org/euclid.ss/1525313143.

Gelfand, A. E., Kottas, A. and MacEachern, S. N. (2005) Bayesian nonparametric spatial modeling with Dirichlet process mixing. Journal of the American Statistical Association, 100, 1021–1035.

Gutman, R. and Rubin, D. B. (2017) Estimation of causal effects of binary treatments in unconfounded studies. Statistical Methods in Medical Research, 26, 1199–1215.

Hahn, P. R., Carvalho, C. M., Puelz, D. and He, J. (2018a) Regularization and confounding in linear regression for treatment effect estimation. Bayesian Analysis.

Hahn, P. R., Dorie, V. and Murray, J. S. (2018b) Atlantic Causal Inference Conference (ACIC) Data Analysis Challenge 2017. Tech. rep., math.la.asu.edu. URL: https://math.la.asu.edu/~prhahn/debrief.pdf.

Hahn, P. R., Murray, J. and Carvalho, C. M. (2017) Bayesian Regression Tree Models for Causal Inference: Regularization, Confounding, and Heterogeneous Effects. SSRN. URL: https://arxiv.org/pdf/1706.09523.pdf http://arxiv.org/abs/1706.09523.

Harrold, L. R., Salmon, C., Shoor, S., Curtis, J. R., Asgari, M. M., Gelfand, J. M., Wu, J. J. and Herrinton, L. J. (2013) Incidence and prevalence of juvenile idiopathic arthritis among children in a managed care population, 1996-2009. The Journal of Rheumatology, 40, 1218–25.

Hill, J. and Reiter, J. P. (2006) Interval estimation for treatment effects using propensity score matching. Statistics in Medicine, 25, 2230–2256.

Hill, J. L. (2011) Bayesian nonparametric modeling for causal inference. Journal of Computational and Graphical Statistics, 20, 217–240.

Hirano, K., Imbens, G. W., Rubin, D. B. and Zhou, X.-H. (2000) Assessing the effect of an influenza vaccine in an encouragement design. Biostatistics, 1, 69–88.

Ho, D. E., Imai, K., King, G. and Stuart, E. A. (2007) Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. Political Analysis, 15, 199–236.
Imai, K. and Ratkovic, M. (2014) Covariate balancing propensity score. *Journal of the Royal Statistical Society: Series B (Statistical Methodology),* **76**, 243–263.

Imbens, G. W. and Rubin, D. B. (1997) Bayesian inference for causal effects in randomized experiments with noncompliance. *The Annals of Statistics,*** **25**, 305–327.

Kang, J. D. Y. and Schafer, J. L. (2007) Demystifying double robustness: A comparison of alternative strategies for estimating a population mean from incomplete data. *Statistical Science,*** **22**, 523–539.

Kazianka, H. and Pilz, J. (2012) Objective Bayesian analysis of spatial data with uncertain nugget and range parameters. *The Canadian Journal of Statistics,*** **40**, 304–327.

King, G. and Nielsen, R. (Forthcoming) Why propensity scores should not be used for matching. *Political Analysis.*

McCandless, L. C., Douglas, I. J., Evans, S. J. and Smeeth, L. (2010) Cutting feedback in bayesian regression adjustment for the propensity score. *The International Journal of Biostatistics,*** **6**.

Rasmussen, C. E. (2004) Gaussian processes in machine learning. In *Advanced lectures on machine learning,*** 63–71. Springer.

Rasmussen, C. E., Williams, C. K. I., Sutton, R. S., Barto, A. G., Spirtes, P., Glymour, C., Scheines, R., Schölkopf, B. and Smola, A. J. (2006) *Gaussian Processes for Machine Learning.* Cambridge, Massachusetts, London, England: MIT Press MIT Press. URL: http://www.gaussianprocess.org/gpml/chapters/RW.pdf.

Ren, C., Sun, D. and Sahu, S. K. (2013) Objective bayesian analysis of spatial models with separable correlation functions. *Canadian Journal of Statistics,*** **41**, 488–507.

Robins, J. M., Hernan, M. A. and Brumback, B. (2000) Marginal structural models and causal inference in epidemiology.

Rosenbaum, P. R. and Rubin, D. B. (1983) The central role of the propensity score in observational studies for causal effects. *Biometrika,*** **70**, 41–55.

Roy, J., Lum, K. J. and Daniels, M. J. (2016) A bayesian nonparametric approach to marginal structural models for point treatments and a continuous or survival outcome. *Biostatistics,*** **18**, 32–47.

Roy, J., Lum, K. J., Zeldow, B., Dworkin, J. D., Re III, V. L. and Daniels, M. J. (2017) Bayesian nonparametric generative models for causal inference with missing at random covariates. *Biometrics.*

Rubin, D. B. (1973) The use of matched sampling and regression adjustment to remove bias in observational studies. *Biometrics,* 185–203.

— (1978) Bayesian inference for causal effects: The role of randomization. *The Annals of Statistics,* **34**, 34–58.

Rubin, D. B. and Stuart, E. A. (2006) Affinely invariant matching methods with discriminant mixtures of proportional ellipsoidally symmetric distributions. *The Annals of Statistics,*** **34**, 1814–1826.

Rubin, D. B. and Thomas, N. (1996) Matching using estimated propensity scores: relating theory to practice. *Biometrics,*** **52**, 249.

Saarela, O., Belzile, L. R. and Stephens, D. A. (2016) A Bayesian view of doubly robust causal inference. *Biometrika,* **66**, 667–681.

Seid, M., Huang, B., Niehaus, S., Brunner, H. I. and Lovell, D. J. (2014) Determinants of health-related quality of life in children newly diagnosed with juvenile idiopathic arthritis. *Arthritis Care & Research,*** **66**, 263–269.

Sekhon, J. S. (2007) Multivariate and propensity score matching with balance optimization. *Retrieved June.*

Sivaganesan, S., Müller, P. and Huang, B. (2017) Subgroup finding via bayesian additive regression trees. *Statistics in medicine,*** **36**, 2391–2403.
Stuart, E. A. (2010) Matching methods for causal inference: A review and a look forward. *Statistical Science, 25*, 1–21.

Van Der Laan, M. J. and Rubin, D. (2006) Targeted maximum likelihood learning. *The International Journal of Biostatistics, 2*.

VanderWeele, T. J. (2009) Concerning the Consistency Assumption in Causal Inference. *Epidemiology, 20*.

Vansteelandt, S., Joffe, M. et al. (2014) Structural nested models and g-estimation: The partially realized promise. *Statistical Science, 29*, 707–731.

Wallace, C. A., Ringold, S., Bohnsack, J., Spalding, S. J., Brunner, H. I., Milojevic, D., Schanberg, L. E., Higgins, G. C., O’Neil, K. M., Gottlieb, B. S. et al. (2014) Extension study of participants from the trial of early aggressive therapy in juvenile idiopathic arthritis. *The Journal of Rheumatology, jrheum–140347*.

Xu, Y., Müller, P., Wahed, A. S. and Thall, P. F. (2016) Bayesian Nonparametric Estimation for Dynamic Treatment Regimes With Sequential Transition Times. https://doi.org/10.1080/01621459.2015.1086353.

Zajonc, T. (2012) Bayesian inference for dynamic treatment regimes: Mobility, equity, and efficiency in student tracking. *Journal of the American Statistical Association, 107*, 80–92.

Zigler, C. M., Watts, K., Yeh, R. W., Wang, Y., Coull, B. A. and Dominici, F. (2013) Model feedback in bayesian propensity score estimation. *Biometrics, 69*, 263–273.
FIGURE 1  Distribution of the GPMatch Estimate of ATE, by Different Sample Sizes under the Single Covariate Simulation Study Setting
FIGURE 2  Simulation Study Results of comparing GPMatch with Manhalanobis Distance Matching Methods. The circles are the averaged biases of estimates of ATE using Mahalanobis matching with corresponding calipers. The corresponding vertical lines indicate the ranges between 5th and 95th percentiles of the biases. The horizontal lines are the averaged ATE (short dashed line), and the 5th percentile and 95th percentile (long dashed line) of the biases of the estimates from GPMatch.
FIGURE 3  The RMSE and MAE of ATE Estimates using Different Methods under the Kang and Shafer Simulation Study Setting. GPMatch1-2: Bayesian structural model with Gaussian Process prior. GPMatch1 including only treatment effect, and GPMatch2 including both treatment effect and $X_1 - X_4$ in the mean function; and $X_1 - X_4$ are included in the covariance function. QNT_PS: Propensity score sub-classification by quintiles. AIPTW: augmented inverse probability of treatment weighting; LM: linear regression modeling $Y \sim X_1 - X_4$; LM_PS: linear regression modeling with propensity score adjustment. LM_spl(PS): linear regression modeling with spline fit propensity score adjustment.
**FIGURE 4**  Balance Check Results for the Cases Study

**FIGURE 5**  Case Study Trace Plot and Histogram
### TABLE S1 Results of ATE Estimates from the Single Covariate Simulation Study Setting 1a: $U_i = 0, U_{0i} \sim N(0, 0.25), \sigma_0^2 = 0.75.$

| Method     | Sample Size | RMSE  | MAE   | Bias  | Rc    | $SE_{avg}$ | $SE_{emp}$ |
|------------|-------------|-------|-------|-------|-------|------------|------------|
| GPMatch    | 100         | 0.26  | 0.16  | -0.038| 0.93  | 0.241      | 0.258      |
|            | 200         | 0.161 | 0.116 | 0.033 | 0.97  | 0.166      | 0.159      |
|            | 400         | 0.122 | 0.085 | -0.005| 0.96  | 0.118      | 0.123      |
| QNT_PS     | 100         | 0.376 | 0.244 | 0.052 | 0.950 | 0.392      | 0.216      |
|            | 200         | 0.309 | 0.220 | 0.127 | 0.940 | 0.275      | 0.283      |
|            | 400         | 0.238 | 0.159 | 0.096 | 0.920 | 0.201      | 0.197      |
| LM         | 100         | 0.409 | 0.216 | -0.179| 0.93  | 0.347      | 0.37       |
|            | 200         | 0.291 | 0.183 | -0.119| 0.89  | 0.25       | 0.266      |
|            | 400         | 0.28  | 0.169 | -0.171| 0.84  | 0.185      | 0.223      |
| AIPTW1     | 100         | 0.82  | 0.341 | -0.176| 0.96  | 0.554      | 0.805      |
|            | 200         | 0.765 | 0.294 | -0.209| 0.98  | 0.504      | 0.74       |
|            | 400         | 0.753 | 0.251 | -0.231| 0.96  | 0.426      | 0.721      |
| AIPTW2     | 100         | 0.411 | 0.236 | -0.045| 0.91  | 0.349      | 0.41       |
|            | 200         | 0.288 | 0.203 | 0.029 | 0.93  | 0.268      | 0.288      |
|            | 400         | 0.225 | 0.146 | 0.002 | 0.93  | 0.197      | 0.226      |
| LM_PS1     | 100         | 0.367 | 0.239 | -0.109| 0.91  | 0.332      | 0.352      |
|            | 200         | 0.272 | 0.161 | -0.051| 0.91  | 0.246      | 0.268      |
|            | 400         | 0.198 | 0.13  | -0.064| 0.95  | 0.181      | 0.189      |
| LM_PS2     | 100         | 0.366 | 0.201 | -0.054| 0.93  | 0.349      | 0.364      |
|            | 200         | 0.256 | 0.181 | 0.031 | 0.99  | 0.253      | 0.255      |
|            | 400         | 0.185 | 0.136 | -0.004| 0.95  | 0.186      | 0.186      |
| LM_sp(PS1) | 100         | 0.264 | 0.186 | -0.054| 0.91  | 0.241      | 0.26       |
|            | 200         | 0.156 | 0.102 | 0.023 | 0.97  | 0.167      | 0.155      |
|            | 400         | 0.127 | 0.086 | -0.008| 0.94  | 0.118      | 0.128      |
| LM_sp(PS2) | 100         | 0.267 | 0.175 | -0.057| 0.9   | 0.24       | 0.262      |
|            | 200         | 0.155 | 0.11  | 0.02  | 0.98  | 0.167      | 0.154      |
|            | 400         | 0.126 | 0.089 | -0.01 | 0.94  | 0.118      | 0.126      |
| BART       | 100         | 0.27  | 0.156 | -0.026| 0.95  | 0.257      | 0.27       |
|            | 200         | 0.185 | 0.145 | 0.048 | 0.95  | 0.178      | 0.18       |
|            | 400         | 0.133 | 0.084 | 0.016 | 0.97  | 0.125      | 0.133      |

RMSE = root mean square error; MAE = median absolute error; Bias = Estimate-True; Rc = Rate of coverage by the 95% interval estimate; $SE_{avg}$ = average of standard error estimate from all replicate; $SE_{emp}$ = standard error of ATE estimates from all replicate; GPMatch: Bayesian structural model with Gaussian process prior, only treatment effect is included in the mean function; covariance function includes X.

QNT_PS: Propensity score sub-classification by quintiles.
AIPTW1 & AIPTW2: augmented inversed probability of treatment weighting.
LM_PS1 & LM_PS2: linear regression modeling with propensity score adjustment;
LM_sp(PS1) & LM_sp(PS2): linear regression modeling with spline fit propensity score adjustment;
BART: Bayesian additive regression tree.
Propensity scores are estimated using different logistic models, with AIPTW1, LM_PS1 & LM_sp(PS1) use PS estimated using logistic model
\( \logit A \sim X \); and AIPTW2, LM_PS2 & LM_sp(PS2) use PS estimated using logistic model \( \logit A \sim X^{1/2} \). QNT_PS using either PS estimates produces identical results.

**TABLE S2** Results of ATE Estimates from the Single Covariate Simulation Study Setting 1b:
\( U_i \sim N(0, 0.15), U_{0i} \sim N(0, 1), \sigma_0^2 = 0 \).

| Method     | Sample Size | RMSE  | MAE   | Bias   | Rc    | \( SE_{avg} \) | \( SE_{emp} \) |
|------------|-------------|-------|-------|--------|-------|----------------|----------------|
| GPMatch    | 100         | 0.237 | 0.152 | 0.013  | 0.97  | 0.243          | 0.238          |
|            | 200         | 0.175 | 0.114 | 0.007  | 0.94  | 0.169          | 0.175          |
|            | 400         | 0.117 | 0.084 | 0.001  | 0.96  | 0.117          | 0.118          |
| QNT_PS     | 100         | 0.436 | 0.271 | 0.089  | 0.950 | 0.466          | 0.429          |
|            | 200         | 0.301 | 0.210 | 0.103  | 0.980 | 0.287          | 0.284          |
|            | 400         | 0.254 | 0.171 | 0.096  | 0.880 | 0.209          | 0.236          |
| LM         | 100         | 0.427 | 0.255 | -0.214 | 0.93  | 0.399          | 0.371          |
|            | 200         | 0.348 | 0.174 | -0.164 | 0.93  | 0.263          | 0.309          |
|            | 400         | 0.318 | 0.166 | -0.198 | 0.81  | 0.191          | 0.25           |
| AIPTW1     | 100         | 0.933 | 0.378 | -0.226 | 0.96  | 0.671          | 0.91           |
|            | 200         | 3.853 | 0.246 | -0.478 | 0.95  | 0.861          | 3.842          |
|            | 400         | 1.25  | 0.213 | -0.396 | 0.98  | 0.565          | 1.192          |
| AIPTW2     | 100         | 0.413 | 0.306 | -0.029 | 0.96  | 0.411          | 0.414          |
|            | 200         | 0.345 | 0.156 | -0.001 | 0.96  | 0.281          | 0.346          |
|            | 400         | 0.244 | 0.124 | -0.021 | 0.97  | 0.221          | 0.244          |
| LM_PS1     | 100         | 0.352 | 0.265 | -0.087 | 0.97  | 0.368          | 0.343          |
|            | 200         | 0.273 | 0.181 | -0.055 | 0.93  | 0.251          | 0.269          |
|            | 400         | 0.192 | 0.11  | -0.082 | 0.92  | 0.188          | 0.174          |
| LM_PS2     | 100         | 0.337 | 0.251 | -0.018 | 0.98  | 0.397          | 0.339          |
|            | 200         | 0.252 | 0.154 | -0.004 | 0.97  | 0.262          | 0.253          |
|            | 400         | 0.175 | 0.101 | -0.004 | 0.98  | 0.192          | 0.176          |
| LM_sp(PS1) | 100         | 0.237 | 0.158 | -0.006 | 0.97  | 0.242          | 0.238          |
|            | 200         | 0.171 | 0.109 | -0.004 | 0.94  | 0.169          | 0.172          |
|            | 400         | 0.118 | 0.083 | -0.003 | 0.96  | 0.118          | 0.118          |
| LM_sp(PS2) | 100         | 0.248 | 0.163 | 0.002  | 0.96  | 0.243          | 0.249          |
|            | 200         | 0.171 | 0.103 | 0.001  | 0.95  | 0.169          | 0.172          |
|            | 400         | 0.116 | 0.087 | -0.006 | 0.96  | 0.118          | 0.117          |
| Bart       | 100         | 0.286 | 0.176 | 0.054  | 0.95  | 0.266          | 0.283          |
|            | 200         | 0.182 | 0.115 | 0.034  | 0.96  | 0.18           | 0.18           |
|            | 400         | 0.161 | 0.085 | 0.01   | 0.93  | 0.127          | 0.161          |

RMSE = root mean square error; MAE = median absolute error; Bias = Estimate-True; Rc = Rate of coverage by the 95% interval estimate;
\( SE_{avg} \) = average of standard error estimate from all replicate; \( SE_{emp} \) = standard error of ATE estimates from all replicate;
GPMatch: Bayesian structural model with Gaussian process prior; only treatment effect is included in the mean function; covariance function includes \( X \).
QNT_PS: Propensity score sub-classification by quintiles.
AIPTW1 & AIPTW2: augmented inversed probability of treatment weighting.
LM_PS1 & LM_PS2: linear regression modeling with propensity score adjustment;
LM_sp(PS1) & LM_sp(PS2): linear regression modeling with spline fit propensity score adjustment;
BART: Bayesian additive regression tree.
Propensity scores are estimated using different logistic models, with AIPTW1, LM_PS1 & LM_sp(PS1) use PS estimated using logistic model \( \text{logit} A \sim X \); and AIPTW2, LM_PS2 & LM_sp(PS2) use PS estimated using logistic model \( \text{logit} A \sim X^{1/3} \). QNT_PS using either PS estimates produces identical results.
**FIGURE S1** Comparisons of root mean square error (RMSE), and median absolute error (MAE) of the ATE Estimates by Different Methods Across Different Sample Sizes under the Simulation Setting 1a:

\[ U_i = 0, \ U_{0i} \sim N(0, 0.25), \ \sigma_0^2 = 0.75 \]

1 Propensity score estimated using logistic regression on \( \logit A \sim X \). 2 Propensity score estimated using logistic regression on \( \logit A \sim X^{1/3} \). GPMatch: Bayesian structural model with Gaussian process prior. QNT_PS: Propensity score sub-classification by quintiles. AIPTW: augmented inverted probability of treatment weighting; LM: linear regression modeling \( Y \sim X \); LM_PS: linear regression modeling with propensity score adjustment. LM_sp(PS): linear regression modeling with spline fit propensity score adjustment. BART: Bayesian additive regression tree.
FIGURE S2  Comparisons of root mean square error (RMSE), and median absolute error (MAE) of the ATE Estimates by Different Methods Across Different Sample Sizes under the Simulation Setting 1b:

\( U_i \sim N(0, 0.15), U_{0i} \sim N(0, 1), \sigma_0^2 = 0 \)

1 Propensity score estimated using logistic regression on \( \logit A \sim X \). 2 Propensity score estimated using logistic regression on \( \logit A \sim X^{1/3} \). GPM: Bayesian structural model with Gaussian process prior. QNT_PS: Propensity score sub-classification by quintiles. AIPTW: augmented inversed probability of treatment weighting; LM: linear regression modeling \( Y \sim X \); LM_PS: linear regression modeling with propensity score adjustment. LM_sp(PS): linear regression modeling with spline fit propensity score adjustment. BART: Bayesian additive regression tree.
**FIGURE S3** Distribution of the Estimated by Different Sample Sizes ATE from GPMatch under the Kang and Shafer Dual Misspecification Setting. Upper panel presents the results of GPMatch with the treatment effect only in the mean function model; lower panel presents the results of GPMatch with the treatment effect and the $X_1 - X_4$ in the mean function model. Both included $X_1 - X_4$ in the covariate function.
FIGURE S4  Distributions of key covariates in unweighted and weighted samples using inverse probability weighting of propensity scores for the case study.
Boxplot in unweighted sample

Non-biologic  Early combination
JADAS at baseline

Boxplot in weighted sample

Non-biologic  Early combination
JADAS at baseline

Cumulative distribution in unweighted sample

Proportion <= x

Non-biologic  Early combination
JADAS at baseline

Cumulative distribution in weighted sample

Proportion <= x

Non-biologic  Early combination
JADAS at baseline

Boxplot in unweighted sample

Non-biologic  Early combination
CHAQ

Boxplot in weighted sample

Non-biologic  Early combination
CHAQ

Cumulative distribution in unweighted sample

Proportion <= x

Non-biologic  Early combination
CHAQ

Cumulative distribution in weighted sample

Proportion <= x

Non-biologic  Early combination
CHAQ