Two-stage Estimation for Causal Inference Involving a Semi-continuous Exposure

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Abstract

Methods for causal inference are well developed for binary and continuous exposures, but in many settings, the exposure has a substantial mass at zero—such exposures are called semi-continuous. We propose a general causal framework for such semi-continuous exposures, together with a novel two-stage estimation strategy. A two-part propensity structure is introduced for the semi-continuous exposure, with one component for exposure status (exposed vs unexposed) and another for the exposure level among those exposed, and incorporates both into a marginal structural model that disentangles the effects of exposure status and dose. The two-stage procedure sequentially targets the causal dose–response among exposed individuals and the causal effect of exposure status at a reference dose, allowing flexibility in the choice of propensity score methods in the second stage. We establish consistency and asymptotic normality for the resulting estimators, and characterise their limiting values under misspecification of the propensity score models. Simulation studies evaluate finite sample performance and robustness, and an application to a study of prenatal alcohol exposure and child cognition demonstrates how the proposed methods can be used to address a range of scientific questions about both exposure status and exposure intensity.

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1   Introduction

In many areas of public health research, the goal is to estimate causal effects of exposures on outcomes using observational data subject to confounding. Propensity scores summarise measured confounders for a binary exposure and can be used to mitigate bias in estimation of causal effects [Rubin, 1974, Rosenbaum and Rubin, 1983, 1984]. For continuous exposures, the generalised propensity score is defined as the conditional density of the exposure given covariates, evaluated at the observed exposure [Hirano and Imbens, 2004, Imai and Van Dyk, 2004]. Inverse density weighting can be used to estimate dose–response relationships, but the resulting estimators may be unstable when outliers are present and weights are highly variable [Naimi et al., 2014], and correctly modelling the exposure distribution can be challenging.

In many applications, however, the exposure is neither purely binary nor fully continuous. Samples often consist of both unexposed individuals and exposed individuals receiving varying doses, yielding a semi-continuous exposure with a point mass at zero and a continuous component among the exposed. Such structures arise, for example, in environmental health studies where pollutants may be absent at some locations but vary in concentration where present [Begu et al., 2016], and in studies of behaviours such as smoking or alcohol consumption where many individuals abstain but usage among those who do not can vary considerably. Yet despite their prevalence, semi-continuous exposures have received relatively little attention in causal inference using propensity score methods.

As a motivating example, we consider the challenge of assessing the effect of prenatal alcohol exposure (PAE) on child cognition. We analyse data from a Detroit longitudinal cohort of African-American children in which maternal alcohol use during pregnancy was measured as average daily ounces of absolute alcohol, yielding a semi-continuous exposure with a point mass at zero among non-drinkers and a continuous right-skewed distribution among drinkers [Jacobson et al., 2002]. Although epidemiological studies have reported associations between PAE and children's cognitive outcomes [Jacobson et al., 2004, 2011, Lewis et al., 2015, 2016], the precise nature of the dose–response effect remains unclear. Scientific and public health inquiries focus on the potential adverse effects of any alcohol consumption during pregnancy, as well as how those risks escalate with increased consumption. To address such semi-continuous exposures, Akkaya Hocagil et al. [2021] construct a two-part propensity score, modelling exposure status via logistic regression and the dose component among the exposed via log linear regression. In related work, Li et al. [2023] outline a two-stage analysis for semi-continuous exposures with continuous outcomes, focusing on the modelling strategy and empirical illustration rather than on a formal counterfactual causal framework or asymptotic and robustness properties. We return to this study in Section 6.

In this article, we develop and evaluate a two-stage procedure for assessing the causal effect of a semi-continuous exposure on a continuous outcome. In Stage I, we use propensity score regression adjustment among the exposed to estimate the effect of the continuous exposure level. In Stage II, we assess the effect of exposure at a specified reference dose compared with no exposure, using a second propensity score defined for the binary exposure indicator. This two-stage structure enables a doubly robust procedure in Stage II through augmented inverse probability weighted (AIPW) estimating equations [Bang and Robins, 2005, Robins et al., 2007]. We allow three distinct sets of confounders: one affecting exposure status (exposed versus unexposed), a second affecting the exposure dose among those exposed, and a third affecting both exposure status and dose. Within the potential outcomes framework, we define causal estimands for both status and dose, specify the assumptions required for identification, and derive the large sample properties of the resulting estimators. Extensive simulation studies are used to assess finite sample performance and to examine the impact of various forms of propensity score misspecification. Finally, we illustrate the methods using data from a study of PAE and child cognition.

The remainder of this article is organised as follows. In Section 2, we introduce notation, models, and assumptions for causal analysis with a semi-continuous exposure, and describe regression adjustment based on two propensity scores for the causal estimands of interest. In Section 3, we present the two-stage estimators for the binary status and continuous dose effects, and derive their asymptotic properties. In Section 4, we study the impact of propensity score misspecification by evaluating the limiting values of the estimators. Simulation studies are reported in Section 5, and in Section 6 we apply the methods to data from a study by Jacobson et al. [2002] on the effect of PAE on child cognition. Conclusions and future directions are discussed in Section 7.
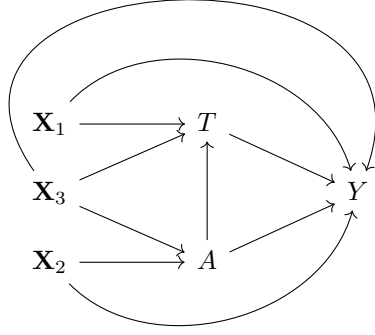
Figure 1: A directed acyclic graph for a two-part exposure model

2 Causal Analysis in a Two-part Model

2.1 Notation and Assumptions

Let Y denote a continuous response variable, T denote a non-negative random variable which represents the exposure (e.g. the ounces of absolute alcohol per day) of an individual, and let $A = I(T > 0)$ indicate the exposure status. A $k_1 \times 1$ vector of confounding variables $\mathbf{X}_1 = (X_{11}, ..., X_{1k_1})'$ has effects on T and Y, a $k_2 \times 1$ vector of $\mathbf{X}_2 = (X_{21}, ..., X_{2k_2})'$ confounds the relationship between the binary indicator A and Y among those with $A = 1$, and a $k_3 \times 1$ vector of confounders $\mathbf{X}_3 = (X_{31}, ..., X_{3k_3})'$ affects on (A, T), and Y; see the directed acyclic graph in Figure 1. We then let $\mathbf{X} = (\mathbf{X}_1', \mathbf{X}_2', \mathbf{X}_3')'$ be the $k \times 1$ full vector of confounders with $k = k_1 + k_2 + k_3$, $\mathbf{Z}_1 = (\mathbf{X}_1', \mathbf{X}_3')'$ be a $(k_1 + k_3) \times 1$ vector of confounders associated with the continuous exposure T and Y given $A = 1$, and $\mathbf{Z}_2 = (\mathbf{X}_2', \mathbf{X}_3')'$ be a $(k_2 + k_3) \times 1$ vector of confounders associated with the binary exposure A and the response. For a sample of n independent individuals, the observed data is $\{(Y_i, T_i, A_i, \mathbf{X}_i'), i = 1, \ldots, n\}$.

As is common in dose-response modelling, we consider a log transformation of the continuous positive exposure T to define the dose $D = \log T$, with d its realized value. We then let $Y_i(1, d)$ represent the potential outcome for the i-th individual exposed at dose d [Rubin, 1974, Splawa-Neyman et al., 1990]; if the i-th individual is unexposed, then the dose is undefined, but we denote the potential outcome as $Y_i(0, d)$ for consistency of notation, taking it as understood that d is undefined. For a semi-continuous exposure among those exposed, the average causal effect of a one-unit increase in dose from d to $d + 1$ is

$$E\{Y(1, d+1)\} - E\{Y(1, d)\};$$

we refer to this as the causal dose-response effect. To define the average causal effect of the binary exposure status we must specify a reference dose c for the exposed individuals. We then let

$$E\{Y(1, c)\} - E\{Y(0, d)\}$$

denote the average causal effect of exposure at level c corresponds to those that are unexposed. In a sample, we often use the sample average of the log volume among the exposed group for c, but any reference value can of course be set.

To identify the causal effects we extend the standard causal inference assumptions [Rubin, 1980, 1990, Rosenbaum and Rubin, 1983, Cole and Hernán, 2008] to the setting of a semi-continuous exposure; Web Appendix A provides a detailed discussion.

Assumption 1 (Stable Unit Treatment Value Assumption) *This assumption states that the potential outcome for one individual is independent of the exposure of another individual.*

Assumption 2 (Consistency) $Y_i(1, d) = Y_i$ *if the i-th individual is exposed at dose $D_i = d$ and $Y_i(0, d) = Y_i$ if unexposed for all d and $i = 1, \ldots, n$.*

Assumption 3 (Ignorability) $Y_i(1, d) \perp D_i | A_i = 1, \mathbf{X}_i = \mathbf{x}$ *and* $Y_i(1, d), Y_i(0, 0) \perp A_i | \mathbf{X}_i$ *for all d and $i = 1, \ldots, n$.*

Assumption 4 (Positivity) $f(D_i = d | A_i = 1, \mathbf{Z}_{i1}) > 0$ *for all d, and* $P(A_i = a | \mathbf{Z}_{i2}) > 0$ *for $a = 0, 1$ and $i = 1, \ldots, n$.*

2.2 Model Settings

Suppressing the index i for individuals, we assume the data generation model for Y:

$$Y = \theta_0 + \theta_{11}A + \theta_{12}A(D - c) + \mathbf{X}_1'\boldsymbol{\theta}_{21} + \mathbf{X}_2'\boldsymbol{\theta}_{22} + \mathbf{X}_3'\boldsymbol{\theta}_{23} + E, \tag{1}$$

with the error $E \sim N(0, \tau^2)$ and $E \perp (A, AD, \mathbf{X})$, c a specified reference dose, $\boldsymbol{\theta} = (\theta_0, \theta_{11}, \theta_{12}, \boldsymbol{\theta}_2')'$ is a $(k+3) \times 1$ vector of parameters with $\boldsymbol{\theta}_{21} = (\theta_{211}, ..., \theta_{21k_1})'$, $\boldsymbol{\theta}_{22} = (\theta_{221}, ..., \theta_{22k_2})'$, $\boldsymbol{\theta}_{23} = (\theta_{231}, ..., \theta_{23k_3})'$, and $\boldsymbol{\theta}_2 = (\boldsymbol{\theta}_{21}', \boldsymbol{\theta}_{22}', \boldsymbol{\theta}_{23}')'$; see the DAG of Figure 1. Note θ_{11} and θ_{12} in (1) represent the causal effects of the exposure at the reference dose (comparing to those who are unexposed) and the causal dose-response effect respectively. Since the mean response varies as a function of dose, a reference dose c is required to define the parameter θ_{11}; any value can be specified but values near the center of the distribution of doses among those exposed will often be appealing.

Here we consider a two-part model for the semi-continuous exposure with one for the exposure status and one for the dose [Smith et al., 2017]. The exposure model for the dose among those exposed has the form

$$E(D|A = 1, \mathbf{Z}_1; \boldsymbol{\alpha}_1) = \bar{\mathbf{Z}}_1'\boldsymbol{\alpha}_1 \tag{2}$$

where $\bar{\mathbf{Z}}_1 = (1, \mathbf{Z}_1')'$ and $\boldsymbol{\alpha}_1 = (\alpha_{10}, \boldsymbol{\alpha}_{11}', \boldsymbol{\alpha}_{12}')'$ where $\boldsymbol{\alpha}_{11} = (\alpha_{111}, ..., \alpha_{11k_1})'$ and $\boldsymbol{\alpha}_{12} = (\alpha_{121}, ..., \alpha_{12k_3})'$. For the data generating process we let $W = D - \bar{\mathbf{Z}}_1'\boldsymbol{\alpha}_1$ and assume $W|A = 1 \sim N(0, \sigma_W^2)$. We define the exposure model for A as

$$\log\left\{\frac{P(A = 1|\mathbf{Z}_2; \boldsymbol{\alpha}_2)}{1 - P(A = 1|\mathbf{Z}_2; \boldsymbol{\alpha}_2)}\right\} = \bar{\mathbf{Z}}_2'\boldsymbol{\alpha}_2 \tag{3}$$

with $\bar{\mathbf{Z}}_2 = (1, \mathbf{Z}_2')'$ and $\boldsymbol{\alpha}_2 = (\alpha_{20}, \boldsymbol{\alpha}_{21}', \boldsymbol{\alpha}_{22}')'$ where $\boldsymbol{\alpha}_{21} = (\alpha_{211}, ..., \alpha_{21k_2})'$ and $\boldsymbol{\alpha}_{22} = (\alpha_{221}, ..., \alpha_{22k_3})'$.

2.3 A New Marginal Structural Model (MSM)

MSMs relate potential outcomes to exposures after marginalising over baseline covariates [Robins, 2000]. We describe the effects of exposure status and dose through the MSM

$$Y(A, D) = \psi_0 + \psi_{11}A + \psi_{12}A(D - c) + Q \tag{4}$$

where $Y(A, D)$ is the potential outcome, $(A, D) \perp Q$, Q has a mean of zero, and $\boldsymbol{\psi} = (\psi_0, \psi_{11}, \psi_{12})'$. Based on Assumption 3, the potential outcomes $Y(A, D)$ are independent of observed exposures (A, D) given covariates $\mathbf{X}$ [Rosenbaum and Rubin, 1983] which implies Q is conditionally independent of A and D. Under Assumptions 1-4, ψ_{11} and ψ_{12} represent the causal effects of the exposure at the mean dose and the causal dose-response effect; see Web Appendix B for more derivation details.

2.4 Regression Adjustment with Two Propensity Scores

For binary exposures the propensity score (PS) is the conditional probability of exposure given covariates [Rosenbaum and Rubin, 1983], while for continuous exposures the generalised PS is the conditional exposure density given covariates [Imai and Van Dyk, 2004]. As noted by Imai and Van Dyk [2004], any function of the confounders that indexes the exposure distribution can serve as a PS. In our setting with a binary exposure A and a continuous dose D among the exposed, we therefore define two propensity scores $\mathbf{S}(\mathbf{X}; \boldsymbol{\alpha}) = \{S_1(\mathbf{Z}_1; \boldsymbol{\alpha}_1), S_2(\mathbf{Z}_2; \boldsymbol{\alpha}_2)\}'$ with $\boldsymbol{\alpha} = (\boldsymbol{\alpha}_1', \boldsymbol{\alpha}_2')'$ where $S_1(\mathbf{Z}_1; \boldsymbol{\alpha}_1) = E(D|A = 1, \mathbf{Z}_1; \boldsymbol{\alpha}_1)$ and $S_2(\mathbf{Z}_2; \boldsymbol{\alpha}_2) = E(A|\mathbf{Z}_2; \boldsymbol{\alpha}_2)$.

To adjust for confounding, we consider the regression model

$$E\{Y|A, D, \mathbf{S}(\mathbf{X}; \boldsymbol{\alpha}); \boldsymbol{\eta}\} = \eta_0 + \eta_{11}A + \eta_{12}A(D - c) + \eta_{21}S_1(\mathbf{Z}_1; \boldsymbol{\alpha}_1) + \eta_{22}S_2(\mathbf{Z}_2; \boldsymbol{\alpha}_2), \tag{5}$$

where $\boldsymbol{\eta} = (\eta_0, \boldsymbol{\eta}_1', \boldsymbol{\eta}_2')'$ with $\boldsymbol{\eta}_1 = (\eta_{11}, \eta_{12})'$ and $\boldsymbol{\eta}_2 = (\eta_{21}, \eta_{22})'$. Under Assumptions 1–4 and correct specification of the exposure models, conditioning on $\mathbf{S}(\mathbf{X}; \boldsymbol{\alpha})$ balances covariates, and η_{11} and η_{12} identify the causal effect of exposure at the reference dose and the causal dose–response effect, respectively. Detailed derivations are given in Web Appendix C.

3 Two-stage Causal Analyses

While attractive in its simplicity, the regression adjustment strategy in Section 2.4 hinges on the correct specification of both propensity score models. This reliance on joint specification motivates a two-stage formulation that separates estimation of the dose–response from the contrast between exposure and no exposure at a reference dose. In Stage I we estimate the causal dose–response effect among exposed individuals, and in Stage II we estimate the effect of exposure

at a reference dose. We use PS regression adjustment in Stage I, and PS regression adjustment, IPW, or AIPW in Stage II, and derive the corresponding estimating equations and asymptotic properties.

Let n denote the sample size and index individuals by $i = 1, \ldots, n$. The observed data are $\mathcal{D}_i = (Y_i, \mathbf{X}_i, A_i, D_i)$, $i = 1, \ldots, n$. We write $S_{iq} = S_q(\mathbf{Z}_{iq}; \boldsymbol{\alpha}_q)$, $q = 1, 2$, for the propensity scores based on covariates $\mathbf{Z}_{i1}$ for $D \mid A = 1$ and $\mathbf{Z}_{i2}$ for A, with parameters $\boldsymbol{\alpha}_q$.

3.1 Stage I: The Causal Dose-response Effect

Among exposed individuals ($A = 1$), we consider a PS regression adjustment to assess the causal dose–response effect by fitting the model

$$E\{Y_i | A_i = 1, D_i, S_1(\mathbf{Z}_{i1}; \boldsymbol{\alpha}_1); \boldsymbol{\gamma}_1\} = \gamma_{10} + \gamma_{11}D_i + \gamma_{12}S_1(\mathbf{Z}_{i1}; \boldsymbol{\alpha}_1) = \mu_{i11}(\boldsymbol{\phi}_1), \tag{6}$$

by least squares where $S_1(\mathbf{Z}_{i1}; \boldsymbol{\alpha}_1) = E(D_i | A_i = 1, \mathbf{Z}_{i1}; \boldsymbol{\alpha}_1)$, $\boldsymbol{\gamma}_1 = (\gamma_{10}, \gamma_{11}, \gamma_{12})'$, and $\boldsymbol{\phi}_1 = (\boldsymbol{\gamma}_1', \boldsymbol{\alpha}_1')'$. The estimating equation for $\boldsymbol{\gamma}_1$ is

$$\mathbf{U}_{11}(\mathcal{D}; \boldsymbol{\phi}_1) = \sum_{i=1}^{n} \mathbf{U}_{i11}(\mathcal{D}_i; \boldsymbol{\phi}_1) = \mathbf{0}, \tag{7}$$

where

$$\mathbf{U}_{i11}(\mathcal{D}_i; \boldsymbol{\phi}_1) = A_i \frac{\partial \mu_{i11}(\boldsymbol{\phi}_1)}{\partial \boldsymbol{\gamma}_1}\{Y_i - \mu_{i11}(\boldsymbol{\phi}_1)\}.$$

The parameter $\boldsymbol{\alpha}_1$ can be estimated by solving

$$\mathbf{U}_{12}(\mathcal{D}; \boldsymbol{\alpha}_1) = \sum_{i=1}^{n} \mathbf{U}_{i12}(\mathcal{D}_i; \boldsymbol{\alpha}_1) = \mathbf{0} \tag{8}$$

where

$$\mathbf{U}_{i12}(\mathcal{D}_i; \boldsymbol{\alpha}_1) = A_i \frac{\partial \mu_{i12}(\boldsymbol{\alpha}_1)}{\partial \boldsymbol{\alpha}_1}\{D_i - \mu_{i12}(\boldsymbol{\alpha}_1)\}$$

with $\mu_{i12}(\boldsymbol{\alpha}_1) = \bar{\mathbf{Z}}_{i1}'\boldsymbol{\alpha}_1$. Considering (7) and (8) jointly, the Stage I estimating equation is

$$\mathbf{U}_1(\mathcal{D}_i; \boldsymbol{\phi}_1) = \sum_{i=1}^{n} \mathbf{U}_{i1}(\mathcal{D}_i; \boldsymbol{\phi}_1) = \mathbf{0} \tag{9}$$

with $\mathbf{U}_{i1}(\mathcal{D}_i; \boldsymbol{\phi}_1) = \{\mathbf{U}_{i11}'(\mathcal{D}_i; \boldsymbol{\phi}_1), \mathbf{U}_{i12}'(\mathcal{D}_i; \boldsymbol{\alpha}_1)\}'$. Under Assumptions 1–4, the causal dose–response effect is represented by γ_{11}, which corresponds to ψ_{12} in (4).

3.2 Stage II: The Effect of Exposure Status

In Stage II, we assess the causal effect of exposure at a pre-specified reference dose c compared to no exposure, with γ_{11} obtained from Stage I and incorporated through the offset term $\gamma_{11}A_i(D_i - c)$. We use the term "offset" because in practice γ_{11} will be estimated in Stage I and $\hat{\gamma}_{11}A_i(D_i - c)$ will be treated as a fixed quantity in what follows. We represent it as the scaled parameter $\gamma_{11}A_i(D_i - c)$ here to unify the discussion of the estimation. We consider three alternative approaches to estimation: (i) PS regression adjustment [Vansteelandt and Daniel, 2014], (ii) IPW [Robins, 2000], and (iii) AIPW [Bang and Robins, 2005, Robins et al., 2007].

3.2.1 Propensity score (PS) regression adjustment

To assess the effect of $A = 1$ at dose $D = c$ via a PS regression adjustment, we consider a Stage II linear predictor of the form

$$E\{Y_i | D_i, A_i, S_2(\mathbf{Z}_{i2}; \boldsymbol{\alpha}_2); \boldsymbol{\gamma}_2\} = \mu_{i21}(\boldsymbol{\phi}_2) + \text{offset}\{\gamma_{11}A_i(D_i - c)\}$$

where $\mu_{i21}(\boldsymbol{\phi}_2) = \gamma_{20} + \gamma_{21}A_i + \gamma_{22}S_2(\mathbf{Z}_{i2}; \boldsymbol{\alpha}_2)$ with PS $S_2(\mathbf{Z}_{i2}; \boldsymbol{\alpha}_2) = E(A_i | \mathbf{Z}_{i2}; \boldsymbol{\alpha}_2)$, and $\boldsymbol{\gamma}_2 = (\gamma_{20}, \gamma_{21}, \gamma_{22})'$ with $\boldsymbol{\phi}_2 = (\boldsymbol{\gamma}_2', \boldsymbol{\alpha}_2')'$.

The regression parameter $\boldsymbol{\gamma}_2$ can be estimated for specified $(\boldsymbol{\gamma}_1', \boldsymbol{\alpha}_2')'$ by the estimating equation

$$\tilde{\mathbf{U}}_{21}(\mathcal{D}; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \sum_{i=1}^{n} \tilde{\mathbf{U}}_{i21}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \mathbf{0} \tag{10}$$

where

$$\tilde{\mathbf{U}}_{i21}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \frac{\partial \mu_{i21}(\boldsymbol{\phi}_2)}{\partial \boldsymbol{\gamma}_2} \left[Y_i - [\mu_{i21}(\boldsymbol{\phi}_2) + \text{offset} \{\gamma_{11} A_i (D_i - c)\}] \right].$$

The parameter $\boldsymbol{\alpha}_2$ can be estimated by solving

$$\mathbf{U}_{22}(\mathcal{D}; \boldsymbol{\alpha}_2) = \sum_{i=1}^{n} \mathbf{U}_{i22}(\mathcal{D}_i; \boldsymbol{\alpha}_2) = \mathbf{0} \tag{11}$$

where

$$\mathbf{U}_{i22}(\mathcal{D}_i; \boldsymbol{\alpha}_2) = \frac{\partial S_2(\mathbf{Z}_{i2}; \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_2} \frac{1}{S_2(\mathbf{Z}_{i2}; \boldsymbol{\alpha}_2) \{1 - S_2(\mathbf{Z}_{i2}; \boldsymbol{\alpha}_2)\}} \{A_i - S_2(\mathbf{Z}_{i2}; \boldsymbol{\alpha}_2)\}.$$

Any binary regression model can be used; we employ a logistic link. Let

$$\tilde{\mathbf{U}}_2(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \sum_{i=1}^{n} \tilde{\mathbf{U}}_{i2}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \mathbf{0}$$

denote the joint Stage II estimating equation under PS regression adjustment with $\tilde{\mathbf{U}}_{i2}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \left\{ \tilde{\mathbf{U}}'_{i21}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2), \mathbf{U}'_{i22}(\mathcal{D}_i; \boldsymbol{\alpha}_2) \right\}'$. Then taken together with the estimating equation of Stage I, the joint estimating equation for the two-stage analysis under PS regression adjustment is

$$\tilde{\mathbf{U}}(\mathcal{D}; \boldsymbol{\Omega}) = \left\{ \begin{array}{c} \mathbf{U}_1(\mathcal{D}; \boldsymbol{\phi}_1) \\ \tilde{\mathbf{U}}_2(\mathcal{D}; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) \end{array} \right\} = \mathbf{0} \tag{12}$$

for $\boldsymbol{\Omega} = (\boldsymbol{\phi}'_1, \boldsymbol{\phi}'_2)'$. Under Assumptions 1 to 4, γ_{21} represents the causal effect of exposure at the reference dose compared to no exposure. and this holds likewise for the IPW and AIPW approaches described in Sections 3.2.2 and 3.2.3.

3.2.2 Inverse Probability Weighting (IPW)

We construct inverse probability weights based on $S_2(\mathbf{Z}_{i2}; \boldsymbol{\alpha}_2)$ to fit the Stage II marginal structural model

$$E\{Y_i(A_i, D_i); \boldsymbol{\gamma}_1, \boldsymbol{\gamma}_2\} = \gamma_{20} + \gamma_{21} A_i + \text{offset} \{\gamma_{11} A_i (D_i - c)\}.$$

An IPW estimating equation [Hernán et al., 2000, Robins, 2000] is

$$\bar{\mathbf{U}}_{21}(\mathcal{D}; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \sum_{i=1}^{n} \bar{\mathbf{U}}_{i21}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \mathbf{0} \tag{13}$$

where

$$\bar{\mathbf{U}}_{i21}(\mathcal{D}; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \sum_{a=0}^{1} w_i(a; \boldsymbol{\alpha}_2) \frac{\partial \mu_{21}(a; \boldsymbol{\gamma}_2)}{\partial \boldsymbol{\gamma}_2} \left[Y_i - [\mu_{21}(a; \boldsymbol{\gamma}_2) + \text{offset} \{\gamma_{11} A_i (D_i - c)\}] \right]$$

where

$$\mu_{21}(a; \boldsymbol{\gamma}_2) = \gamma_{20} + \gamma_{21} a, \tag{14}$$

and

$$w_i(a; \boldsymbol{\alpha}_2) = \frac{I(A_i = a)}{S_2(\mathbf{Z}_{i2}; \boldsymbol{\alpha}_2)^a \{1 - S_2(\mathbf{Z}_{i2}; \boldsymbol{\alpha}_2)\}^{1-a}} \tag{15}$$

for $a = 0, 1$. The joint Stage II estimating equation under IPW is

$$\bar{\mathbf{U}}_2(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \sum_{i=1}^{n} \bar{\mathbf{U}}_{i2}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \mathbf{0}$$

where $\bar{\mathbf{U}}_{i2}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \left\{ \bar{\mathbf{U}}'_{i21}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2), \mathbf{U}'_{i22}(\mathcal{D}_i; \boldsymbol{\alpha}_2) \right\}'$. The two-stage estimating equations with IPW are therefore given by

$$\bar{\mathbf{U}}(\boldsymbol{\Omega}) = \left\{ \begin{array}{c} \mathbf{U}_1(\mathcal{D}; \boldsymbol{\phi}_1) \\ \bar{\mathbf{U}}_2(\mathcal{D}; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) \end{array} \right\} = \mathbf{0}. \tag{16}$$

3.2.3 Augmented Inverse Probability Weighting (AIPW)

An AIPW estimating function is introduced by Bang and Robins [2005] to obtain consistent estimators of causal effects when at least one of the PS model and the imputation model is correctly specified [Funk et al., 2011]; the augmentation term we describe ensures this double robustness property. We again estimate $\boldsymbol{\gamma}_2$ via an augmented estimating equation

$$\bar{\bar{\mathbf{U}}}_{21}(\mathcal{D}; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \sum_{i=1}^{n} \bar{\bar{\mathbf{U}}}_{i21}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \mathbf{0}, \tag{17}$$

and $\bar{\bar{\mathbf{U}}}_{i21}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2)$ is given by

$$\sum_{a=0}^{1} w_i(a; \boldsymbol{\alpha}_2) \frac{\partial \mu_{12}(a; \boldsymbol{\gamma}_2)}{\partial \boldsymbol{\gamma}_2} \big[Y_i - [\mu_{12}(a; \boldsymbol{\gamma}_2) + \text{offset}\{\gamma_{11} A_i(D_i - c)\}] \big] - \{w_i(a; \boldsymbol{\alpha}_2) - 1\} \boldsymbol{g}_i(a; \boldsymbol{\theta}, \boldsymbol{\gamma}_2)$$

where $\boldsymbol{\phi}_2 = (\boldsymbol{\gamma}_2', \boldsymbol{\alpha}_2', \boldsymbol{\theta}')'$ with $\boldsymbol{\theta} = (\boldsymbol{\theta}_1', \boldsymbol{\theta}_0')'$, and $\mu_{12}(a; \boldsymbol{\gamma}_2)$ is defined in (14). Here $w_i(a; \boldsymbol{\alpha}_2)$ is given in (15), and

$$\boldsymbol{g}_i(a; \boldsymbol{\theta}, \boldsymbol{\gamma}_2) = \frac{\partial \mu_{12}(a; \boldsymbol{\gamma}_2)}{\partial \boldsymbol{\gamma}_2} \{m_{ia}(\boldsymbol{\theta}) - \mu_{12}(a; \boldsymbol{\gamma}_2)\}$$

where $m_{ia}(\boldsymbol{\theta})$ denotes the imputed model based expression for the expected response under treatment $a \in 0, 1$; from (1). The imputed values are specified as

$$m_{ia}(\boldsymbol{\theta}_a) = E\{Y_i - \gamma_{11} a(D_i - c) | A_i = a, \mathbf{X}_i; \boldsymbol{\theta}_a\} = \theta_{a0} + \boldsymbol{\theta}_{a1}' \mathbf{X}_{i1} + \boldsymbol{\theta}_{a2}' \mathbf{X}_{i2} + \boldsymbol{\theta}_{a3}' \mathbf{X}_{i3},$$

where $\boldsymbol{\theta}_{ap}$ is k_p-dimensional, $p = 1, 2, 3$ for $a = 0, 1$. The estimating equation for $\boldsymbol{\theta}$ with specified $\boldsymbol{\gamma}_1$ is

$$\mathbf{U}_{23}(\mathcal{D}; \boldsymbol{\gamma}_1, \boldsymbol{\theta}) = \sum_{i=1}^{n} \mathbf{U}_{i23}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\theta}) = \mathbf{0} \tag{18}$$

where $\mathbf{U}_{i23}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\theta}) = \{\mathbf{U}_{i231}'(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\theta}_1), \mathbf{U}_{i232}'(\mathcal{D}_i; \boldsymbol{\theta}_0)\}'$ with

$$\mathbf{U}_{i231}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\theta}_1) = A_i \frac{\partial m_{i1}(\boldsymbol{\theta}_1)}{\partial \boldsymbol{\theta}_1} \{Y_i - \gamma_{11}(D_i - c) - m_{i1}(\boldsymbol{\theta}_1)\},$$

and

$$\mathbf{U}_{i232}(\mathcal{D}_i; \boldsymbol{\theta}_0) = (1 - A_i) \frac{\partial m_{i0}(\boldsymbol{\theta}_0)}{\partial \boldsymbol{\theta}_0} \{Y_i - m_{i0}(\boldsymbol{\theta}_0)\}.$$

By combining (17), (11), and (18), let $\bar{\bar{\mathbf{U}}}_{i2}(\mathcal{D}_i; \boldsymbol{\phi}_2) = \{\bar{\bar{\mathbf{U}}}_{i21}'(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2), \mathbf{U}_{i22}'(\mathcal{D}_i; \boldsymbol{\alpha}_2), \mathbf{U}_{i23}'(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\theta})\}'$ and consider the joint Stage II AIPW estimating equation

$$\bar{\bar{\mathbf{U}}}_2(\mathcal{D}; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \sum_{i=1}^{n} \bar{\bar{\mathbf{U}}}_{i2}(\mathcal{D}_i; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) = \mathbf{0}. \tag{19}$$

By combining (9) and (19), the joint estimating equation is

$$\bar{\bar{\mathbf{U}}}(\boldsymbol{\Omega}) = \left\{ \begin{array}{c} \mathbf{U}_1(\mathcal{D}; \boldsymbol{\phi}_1) \\ \bar{\bar{\mathbf{U}}}_2(\mathcal{D}; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) \end{array} \right\} = \mathbf{0}. \tag{20}$$

3.3 Estimation and Statistical Inference

3.3.1 Estimation in Two-stage Analysis

The two-stage analysis can be characterised by

$$\mathbf{U}(\mathcal{D}; \boldsymbol{\Omega}) = \left\{ \begin{array}{c} \mathbf{U}_1(\mathcal{D}; \boldsymbol{\phi}_1) \\ \mathbf{U}_2(\mathcal{D}; \boldsymbol{\gamma}_1, \boldsymbol{\phi}_2) \end{array} \right\} = \mathbf{0}, \tag{21}$$

where $\mathbf{U}_1(\cdot)$ is defined in (9) and $\mathbf{U}_2(\cdot)$ denotes the Stage II estimating equations under regression adjustment, IPW, or AIPW, as given in (12), (16), and (20), respectively. From a theoretical perspective, treating (21) as a unified system is convenient for deriving the large sample properties of the resulting estimators, and the estimates $\hat{\boldsymbol{\Omega}} = (\hat{\boldsymbol{\phi}}_1', \hat{\boldsymbol{\phi}}_2')'$ can be obtained by solving (21) directly. In practice, however, estimation proceeds sequentially: the Stage I estimating equation (9) is solved to obtain $\hat{\boldsymbol{\phi}}_1$ and hence $\hat{\gamma}_{11}$, which is then substituted into the Stage II estimating equation. Solving the latter yields $\hat{\boldsymbol{\phi}}_2$ which includes $\hat{\gamma}_{21}$, the estimator of the causal effect of exposure at the reference dose.

3.3.2 Large Sample Theory

We now establish the large sample properties of the two-stage estimator with AIPW in Stage II; results for regression adjustment and IPW follow analogously. Let $\hat{\boldsymbol{\Omega}}$ denote the solution to the joint estimating equation (21), where $\mathbf{U}_i(\cdot)$ is the stacked vector of estimating functions contributions from individual i from Stages I and II, $i = 1, \ldots, n$.

Theorem 1 *Suppose Assumptions 1–4 hold, and the PS $S_1(\mathbf{Z}_1; \boldsymbol{\alpha}_1) = E(D|A = 1, \mathbf{Z}_1; \boldsymbol{\alpha}_1)$ is correctly specified. Then the solution $\hat{\boldsymbol{\phi}}_1 = (\hat{\boldsymbol{\gamma}}_1', \hat{\boldsymbol{\alpha}}_1')'$ to (9) is consistent for $\boldsymbol{\phi}_1$. In particular, $\hat{\gamma}_{11}$ is a consistent estimator of ψ_{12}, the causal dose–response effect in the marginal structural model (4).*

Theorem 2 *Suppose Assumptions 1–4 hold, and that at least one of the PS $S_2(\mathbf{Z}_2; \boldsymbol{\alpha}_2)$ or the imputation model $m_a(\boldsymbol{\theta})$ is correctly specified. If $\hat{\gamma}_{11}$ is a consistent estimator of ψ_{12}, then the solution $\hat{\boldsymbol{\gamma}}_2 = (\hat{\gamma}_{20}, \hat{\gamma}_{21}, \hat{\gamma}_{22})'$ to the estimating equation (17) is consistent for $\boldsymbol{\gamma}_2$. In particular, $\hat{\gamma}_{21}$ is a consistent estimator of ψ_{11}, the causal effect of exposure at the reference dose in the marginal structural model (4).*

Theorem 3 *Suppose Assumptions 1–4 hold and standard regularity conditions [Van der Vaart, 2000] are satisfied. Then the joint estimator $\hat{\boldsymbol{\Omega}}$ is consistent for $\boldsymbol{\Omega}$, and $\sqrt{n}(\hat{\boldsymbol{\Omega}} - \boldsymbol{\Omega})$ converges in distribution to a mean-zero multivariate normal vector with covariance matrix*

$$\boldsymbol{\Sigma}(\boldsymbol{\Omega}) = \mathcal{A}^{-1}(\boldsymbol{\Omega}) \, \mathcal{B}(\boldsymbol{\Omega}) \, \{\mathcal{A}^{-1}(\boldsymbol{\Omega})\}',$$

where $\mathcal{A}(\boldsymbol{\Omega}) = E\left(-\partial \mathbf{U}(\boldsymbol{\Omega})/\partial \boldsymbol{\Omega}'\right)$ and $\mathcal{B}(\boldsymbol{\Omega}) = E\{\mathbf{U}_i(\boldsymbol{\Omega})\mathbf{U}_i'(\boldsymbol{\Omega})\}$.

Proofs of Theorems 1–3 and explicit expressions for the sandwich covariance estimator and Wald statistics are given in Web Appendix D. We use the resulting sandwich covariance matrix for $\hat{\boldsymbol{\Omega}}$ to compute standard errors and construct Wald tests and confidence intervals.

4 Implication of Misspecified Propensity Scores in Two-stage Approaches

The consistency of the causal effect estimators introduced above relies on correct specification of the PS models. Akkaya Hocagil et al. [2021] derive the explicit form of the possibly biased estimator obtained by PS regression adjustment based on a possibly misspecified PS model for a semi-continuous exposure in one stage. Here we derive limiting values under misspecified propensity scores for the two-stage approach with PS regression adjustment in both stages.

4.1 Misspecification of the Stage I Propensity Score

We work with expectations of the estimating functions to characterise limiting values under misspecification [White, 1982]. Since the data are i.i.d., we suppress the subscript i and use $(Y, A, D, \mathbf{X})$ to denote a generic observation.

Let $\tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1)$ denote the Stage I PS under misspecification parameterized by $\tilde{\boldsymbol{\alpha}}_1$. A regression adjustment based on $\tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1)$ involves fitting

$$E(Y|A = 1, D, \tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1); \tilde{\boldsymbol{\gamma}}_1) = \tilde{\gamma}_{10} + \tilde{\gamma}_{11}D + \tilde{\gamma}_{12}\tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1) = \mu_{11}(\tilde{\boldsymbol{\phi}}_1),$$

where $\tilde{\boldsymbol{\gamma}}_1 = (\tilde{\gamma}_{10}, \tilde{\gamma}_{11}, \tilde{\gamma}_{12})'$ and $\tilde{\boldsymbol{\phi}}_1 = (\tilde{\boldsymbol{\gamma}}_1', \tilde{\boldsymbol{\alpha}}_1')'$. Let $\mathcal{U}(\cdot)$ denote the corresponding estimating functions under misspecification. The limiting value of the estimator for $\boldsymbol{\gamma}_1$ is the solution to

$$E\left\{\mathcal{U}_{11}(\mathcal{D}; \tilde{\boldsymbol{\phi}}_1)\right\} = \mathbf{0}, \tag{22}$$

with

$$\mathcal{U}_{11}(\mathcal{D}; \tilde{\boldsymbol{\phi}}_1) = A \frac{\partial \mu_{11}(\tilde{\boldsymbol{\phi}}_1)}{\partial \tilde{\boldsymbol{\gamma}}_1} \{Y - \mu_{11}(\tilde{\boldsymbol{\phi}}_1)\},$$

where the expectation is taken with respect to the true distribution of $(Y, A, D, \mathbf{X})$. Solving (22) yields $\boldsymbol{\gamma}_1^* = (\gamma_{10}^*, \gamma_{11}^*, \gamma_{12}^*)'$ with

$$\gamma_{11}^* = \theta_{12} + \frac{\boldsymbol{\theta}_2'\left[\boldsymbol{\zeta}_1(\mathbf{X}|A = 1) - \boldsymbol{\beta}_1(\mathbf{X}|A = 1)\rho_1\sqrt{\frac{\text{var}\{E(D|\mathbf{X}, A=1)\}}{\text{var}\{\tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1)\}}}\right]}{\text{var}(D|A = 1) - \text{var}\{E(D|\mathbf{X}, A = 1)\}\rho_1^2}, \tag{23}$$

where $\rho_1 = \text{corr}\{E(D|\mathbf{X}, A = 1), \tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1)\}$, $\boldsymbol{\zeta}_1(\mathbf{X}|A = 1) = \{\zeta_{11}(\mathbf{X}|A = 1), \ldots, \zeta_{1k}(\mathbf{X}|A = 1)\}'$, and $\boldsymbol{\beta}_1(\mathbf{X}|A = 1) = \{\beta_{11}(\mathbf{X}|A = 1), \ldots, \beta_{1k}(\mathbf{X}|A = 1)\}'$, with $\zeta_{1j}(\mathbf{X}|A = 1) = \text{cov}\{E(D|\mathbf{X}, A = 1), \mathbf{X}_j|A = 1\}$ and $\beta_{1j}(\mathbf{X}|A = 1) = \text{cov}\{\tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1), \mathbf{X}_j|A = 1\}$ for $j = 1, \ldots, k$. Further details are provided in Web Appendix E.1.

When the PS model for the continuous exposure is correctly specified, $\tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1) = E(D|\mathbf{X}, A = 1)$. In this case $\rho_1 = 1$, $\boldsymbol{\zeta}_1(\mathbf{X}|A = 1) = \boldsymbol{\beta}_1(\mathbf{X}|A = 1)$, and $\text{var}\{E(D|\mathbf{X}, A = 1)\} = \text{var}\{\tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1)\}$. Substituting these equalities into (23) eliminates the second term, yielding $\gamma_{11}^* = \theta_{12}$. Otherwise, when $\tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1)$ is misspecified, the asymptotic bias of $\hat{\gamma}_{11}$ depends on the covariance structure among $E(D|\mathbf{X}, A = 1)$, $\mathbf{X}$ given $A = 1$, and $\tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1)$.

4.2 Biased Estimator in Stage II

We now derive the limiting value of the exposure effect at the reference dose compared to no exposure. Let $\tilde{S}_2(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_2)$ be the Stage II PS under misspecification, and then fit the regression model by treating $\tilde{\gamma}_{11} A(D - c)$ as an offset term in

$$E\left\{Y|D, A, \tilde{S}_2(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_2); \tilde{\boldsymbol{\gamma}}_1, \tilde{\boldsymbol{\gamma}}_2\right\} = \tilde{\gamma}_{20} + \tilde{\gamma}_{21} A + \tilde{\gamma}_{22} \tilde{S}_2(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_2) + \text{offset}\left\{\tilde{\gamma}_{11} A(D - c)\right\}$$

where $\tilde{\boldsymbol{\gamma}}_2 = (\tilde{\gamma}_{21}, \tilde{\gamma}_{22}, \tilde{\gamma}_{23})'$. The estimating equation for $\tilde{\boldsymbol{\gamma}}_2$ is

$$E\left\{\mathcal{U}_{21}(D; \tilde{\boldsymbol{\gamma}}_1, \tilde{\boldsymbol{\phi}}_2)\right\} = \mathbf{0} \tag{24}$$

where

$$\mathcal{U}_{21}(D; \tilde{\boldsymbol{\gamma}}_1, \tilde{\boldsymbol{\phi}}_2) = \frac{\partial \mu_{21}(\tilde{\boldsymbol{\phi}}_2)}{\partial \tilde{\boldsymbol{\phi}}_2} \left[Y - \left\{\mu_{21}(\tilde{\boldsymbol{\phi}}_2) + \tilde{\gamma}_{11} A(D - c)\right\}\right]$$

with $\mu_{21}(\tilde{\boldsymbol{\phi}}_2) = \tilde{\gamma}_{20} + \tilde{\gamma}_{21} A + \tilde{\gamma}_{22} \tilde{S}_2(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_2)$ again; the expectation in (24) is taken with respect to the true distribution of $(Y, D, A, \mathbf{X})$. Solving (24) with γ_{11}^* given by (23) yields $\boldsymbol{\gamma}_2^* = (\gamma_{20}^*, \gamma_{21}^*, \gamma_{22}^*)'$. Here we let $\rho_{21} = \text{corr}\{E(A|\mathbf{X}), \tilde{S}_1(\mathbf{X})\}$, $\rho_{22} = \text{corr}\{E(AD|\mathbf{X}), \tilde{S}_1(\mathbf{X})\}$, $\boldsymbol{\zeta}_2(\mathbf{X}) = \{\zeta_{21}(\mathbf{X}), ..., \zeta_{2k}(\mathbf{X})\}'$, $\boldsymbol{\beta}_2(\mathbf{X}) = \{\beta_{21}(\mathbf{X}), ..., \beta_{2k}(\mathbf{X})\}'$, and $\delta_1 = \text{cov}\{E(A|\mathbf{X}), \tilde{S}_1(\mathbf{X})\}$ where $\zeta_{2j}(\mathbf{X}) = \text{cov}\{E(A|\mathbf{X}), \mathbf{X}_j\}$ and $\beta_{2j}(\mathbf{X}) = \text{cov}\{\tilde{S}_1(\mathbf{X}), \mathbf{X}_j\}$ for $j = 1, 2, ..., k$. Then γ_{21}^* corresponding to the limiting value of the causal effect of the exposure at the reference dose c compared to no exposure under misspecification is

$$\gamma_{21}^* = \theta_{11} + \frac{\boldsymbol{\theta}_2' \left[\boldsymbol{\zeta}_2(\mathbf{X}) - \boldsymbol{\beta}_2(\mathbf{X}) \rho_{21} \sqrt{\frac{\text{var}\{E(A|\mathbf{X})\}}{\text{var}\{\tilde{S}_2(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_2)\}}}\right]}{\text{var}(A) - \text{var}\{E(A|\mathbf{X})\} \rho_{21}^2}$$

$$+ \frac{(\theta_{12} - \gamma_{11}^*) \left[\text{cov}(AD, A) - cE\{\text{var}(A|\mathbf{X})\} - \delta_1 \rho_{22} \sqrt{\text{var}\{E(A|\mathbf{X})\} \text{var}\{E(AD|\mathbf{X})\}}\right]}{\text{var}(A) - \text{var}\{E(A|\mathbf{X})\} \rho_{21}^2}. \tag{25}$$

Further details are provided in Web Appendix E.2.

Note that $\gamma_{21}^* = \theta_{11}$ when the second and third terms in (25) are zero. If $\tilde{S}_2(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_2)$ is correctly specified so that $\tilde{S}_2(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_2) = E(A \mid \mathbf{X})$, and the Stage I estimator is consistent (implying $\gamma_{11}^* = \theta_{12}$), these terms vanish and $\gamma_{21}^* = \theta_{11}$. More generally, the asymptotic bias in the Stage II estimator depends on the covariance and variance structure of $E(A \mid \mathbf{X})$, $\mathbf{X}$ and $\tilde{S}_2(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_2)$, as well as any misspecification of $\tilde{S}_1(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_1)$ in Stage I. The bias decreases as $\tilde{S}_2(\mathbf{X}; \tilde{\boldsymbol{\alpha}}_2)$ approaches $E(A \mid \mathbf{X})$ and as $\tilde{\gamma}_{11}$ approaches θ_{12}.

5 Simulation Studies

5.1 Data Generation and Simulation Design

We consider two data generation processes.

5.1.1 Data Generation Model 1

Let $\mathbf{X} = (X_1, \ldots, X_6)'$ follow a multivariate normal distribution with mean zero, unit variances and pairwise correlation 0.2 with $\mathbf{X}_1 = (X_{11}, X_{12})'$, $\mathbf{X}_2 = (X_{21}, X_{22})'$, and $\mathbf{X}_3 = (X_{31}, X_{32})'$. The binary exposure $A|\mathbf{Z}$ is generated from model (3) with $\bar{\mathbf{Z}}_2 = (1, \mathbf{X}_2', \mathbf{X}_3')'$, $\boldsymbol{\alpha}_{21} = (\log 1.2, \log 2)'$ and $\boldsymbol{\alpha}_{22} = (\log 0.8, \log 1.3)'$. We solve for α_{20} such that $P(A = 1) = E_{\mathbf{Z}_2}\{P(A = 1|\mathbf{Z}_2)\} = 0.25, 0.5$ or 0.75 which give values $\alpha_{20} = -1.249, 0.0008$ and 1.249. For those

exposed, the continuous exposure D is generated from model (2) with $\bar{\mathbf{Z}}_1 = (1, \mathbf{X}_1', \mathbf{X}_3')'$, $\alpha_{10} = 0$, $\boldsymbol{\alpha}_{11} = (1, 0.5)'$, $\boldsymbol{\alpha}_{12} = (0.6, 0.8)'$, and $W \sim N(0, 1)$. If $A_i = 0$ for each individual D_i undefined. Finally, we generate the response variable Y from model (1) with $\theta_0 = 0$, $\theta_{11} = 4$, $\theta_{12} = 0.5$, $\boldsymbol{\theta}_{21} = (0.6, 0.8)'$, $\boldsymbol{\theta}_{22} = (0.8, 0.4)'$, $\boldsymbol{\theta}_{23} = (0.3, 0.7)'$, and $E_i \sim N(0, 1)$.

5.1.2 Data Generation Model 2

Let $\mathbf{X} = (X_1, X_2)'$ follow a bivariate normal distribution with mean zero, unit variances and correlation 0.2. We generate A based on

$$\log \left\{ \frac{\pi(\mathbf{X})}{1 - \pi(\mathbf{X})} \right\} = \alpha_{10} + \boldsymbol{\alpha}_{11}' \mathbf{X} \tag{26}$$

with $\boldsymbol{\alpha}_{11} = (\log 1.2, \log 2)'$; we find α_{10} to give marginal probabilities of $A = 1$ as $0.25, 0.5$ and 0.75 yielding $\alpha_{10} = -1.224, 0.005$ and 1.236. If $A = 1$, the continuous exposure D is generated from

$$D = \alpha_{20} + \boldsymbol{\alpha}_{21}' \mathbf{X} + W, \tag{27}$$

where $\alpha_{20} = 0$, $\boldsymbol{\alpha}_{21} = (1, 0.5)'$, $W \perp \mathbf{X}$, and $W \sim N(0, 1)$. The second data generation model is the special case of (1)

$$Y = \theta_0 + \theta_{11} A + \theta_{12} A (D - c) + \mathbf{X}' \boldsymbol{\theta}_2 + E, \tag{28}$$

with $\theta_0 = 0$, $\theta_{11} = 4$, $\theta_{12} = 0.5$, $\boldsymbol{\theta}_2 = (0.8, 0.4)'$, and $E \sim N(0, 1)$.

5.2 Methods

For each data generation model, we generate 2000 replicated datasets of size $n = 1000$ and estimate the causal parameters using six methods: (i) a naive least-squares fit of the MSM (4); (ii) the correctly specified response model; (iii) two–PS regression adjustment in a single stage; (iv) two-stage approach with PS regression; (v) two-stage approach with IPW; and (vi) two-stage approach with AIPW.

Brookhart et al. [2006] note that including covariates unrelated to the exposure but related to the outcome can reduce the variance of causal effect estimators without introducing bias. Accordingly, we consider two propensity score specifications: (i) including only exposure-related covariates and (ii) including all outcome-related covariates. In data-generation model 2 these sets coincide, so the two specifications are identical.

To examine robustness, we consider five misspecification scenarios: (i) misspecified Stage I PS S_1; (ii) misspecified Stage II PS S_2; (iii) misspecified imputation model $m_a(\mathbf{X}; \boldsymbol{\theta})$; (iv) misspecification of S_1 and $m_a(\mathbf{X}; \boldsymbol{\theta})$; and (v) misspecification of S_2 and $m_a(\mathbf{X}; \boldsymbol{\theta})$. In all cases we focus on the setting with minimal propensity scores $\mathbf{S} = \{S_1(\mathbf{Z}_1), S_2(\mathbf{Z}_2)\}'$. Full details of how each model is misspecified are given in Web Appendix F.1.

5.3 Finite Sample Performance

Table 1 presents the empirical bias (EBias), empirical standard error (ESE), average robust standard error (RSE), and empirical coverage probability (ECP) for estimators with $P(A = 1) = 0.5$ under correctly specified models. The naive method yields poor estimates for both parts across both data-generation models. In contrast, all other methods show small biases and ECPs close to the nominal 95% level. Including all covariates in the PS models reduces empirical variance without inflating bias, in line with the variance reduction principle of Brookhart et al. [2006]. The ESEs closely match the mean RSE, supporting the validity of the sandwich variance estimator in Section 3.3.2.

Table 2 reports empirical results under misspecified S_1 and S_2 for the two-dimensional PS regression adjustment, PS regression in both stages, and PS regression in Stage I with IPW in Stage II with $\pi^* = 0.5$. Misspecification of S_1 induces bias in the Stage I estimator and consequently poor Stage II performance. Similarly, misspecification of S_2 yields large empirical bias in the Stage II estimator.

Table 3 summarises the performance of the Stage II AIPW estimators under model misspecification with $P(A = 1) = 0.5$. When either the imputation model or the S_2 model is misspecified, the estimator remains consistent by double robustness. In contrast, misspecified S_1 induces bias in both stages, and simultaneously misspecifying the imputation and S_2 models leads to biased Stage II estimates and loss of nominal coverage.

Web Tables 1–3 and 4–6 in Web Appendix F.2 present results for $P(A = 1) = 0.25$ and 0.75 respectively, and show patterns consistent with those for $P(A = 1) = 0.5$.

Table 1: Empirical properties of estimators of causal effects with $P(A = 1) = 0.5$ under six methods of analysis based on correctly specified models.

| Method | Exposure | Effect | Minimal PS: $\mathbf{S} = \{S_1(\mathbf{Z}_1), S_2(\mathbf{Z}_2)\}'$ | | | | Expanded PS: $\mathbf{S} = \{S_1(\mathbf{X}), S_2(\mathbf{X})\}'$ | | | |
			Ebias	ESE	RSE	ECP(%)	Ebias	ESE	RSE	ECP(%)
			Data Generation Model 1							
Naive	D	θ_{12}	0.760	0.036	0.035	0.0	-	-	-	-
	A	θ_{11}	0.952	0.128	0.126	0.0	-	-	-	-
DG model	D	θ_{12}	-0.001	0.028	0.027	94.2	-	-	-	-
	A	θ_{11}	< 0.001	0.067	0.068	95.2	-	-	-	-
Two PS Reg	D	θ_{12}	-0.002	0.034	0.034	94.3	-0.002	0.033	0.032	95.0
	A	θ_{11}	< 0.001	0.073	0.074	95.4	< 0.001	0.067	0.068	95.0
$\text{PS}_\text{I} + \text{PS}_\text{II}$	D	θ_{12}	-0.002	0.060	0.059	94.4	-0.002	0.046	0.045	94.2
	A	θ_{11}	-0.002	0.096	0.098	95.2	< 0.001	0.068	0.069	95.6
$\text{PS}_\text{I} + \text{IPW}_\text{II}$	D	θ_{12}	-0.002	0.060	0.059	94.4	-0.002	0.046	0.045	94.2
	A	θ_{11}	-0.002	0.107	0.107	94.5	< 0.001	0.082	0.083	95.5
$\text{PS}_\text{I} + \text{AIPW}_\text{II}$	D	θ_{12}	-0.002	0.060	0.059	94.4	-0.002	0.046	0.045	94.2
	A	θ_{11}	0.001	0.070	0.071	95.5	< 0.001	0.069	0.070	95.4
			Data Generation Model 2							
Naive	D	θ_{12}	0.462	0.034	0.034	0.0	-	-	-	-
	A	θ_{11}	0.486	0.080	0.080	0.0	-	-	-	-
DG model	D	θ_{12}	0.001	0.035	0.034	94.4	-	-	-	-
	A	θ_{11}	< 0.001	0.068	0.068	95.4	-	-	-	-
Two PS Reg	D	θ_{12}	0.001	0.035	0.037	95.4	-	-	-	-
	A	θ_{11}	< 0.001	0.068	0.068	95.3	-	-	-	-
$\text{PS}_\text{I} + \text{PS}_\text{II}$	D	θ_{12}	0.002	0.046	0.045	93.9	-	-	-	-
	A	θ_{11}	< 0.001	0.069	0.069	95.1	-	-	-	-
$\text{PS}_\text{I} + \text{IPW}_\text{II}$	D	θ_{12}	0.002	0.046	0.045	93.9	-	-	-	-
	A	θ_{11}	< 0.001	0.072	0.072	94.9	-	-	-	-
$\text{PS}_\text{I} + \text{AIPW}_\text{II}$	D	θ_{12}	0.002	0.046	0.045	93.9	-	-	-	-
	A	θ_{11}	< 0.001	0.070	0.070	94.4	-	-	-	-

DG model: Data generation model; Two PS Reg: Two-dimensional PS regression adjustment; $\text{PS}_\text{I} + \text{PS}_\text{II}$: Using PS regression adjustment in Stage I and II; $\text{PS}_\text{I} + \text{IPW}_\text{II}$: Using PS regression adjustment in Stage I and IPW in Stage II; $\text{PS}_\text{I} + \text{AIPW}_\text{II}$: Using PS regression adjustment in Stage I and AIPW in Stage II.

Table 2: Empirical results for estimators of causal effects with $P(A = 1) = 0.5$ for two-propensity-score regression adjustment and two-stage analysis under model misspecification.

| Method | Exposure | Effect | Misspecified S_1 | | | | Misspecified S_2 | | | |
			Ebias	ESE	RSE	ECP(%)	Ebias	ESE	RSE	ECP(%)
			Data Generation Model 1							
Two PS Reg	D	θ_{12}	0.135	0.039	0.039	6.9	-0.002	0.035	0.036	96.0
	A	θ_{11}	0.034	0.084	0.086	93.6	0.245	0.074	0.075	9.7
$\text{PS}_\text{I}+\text{PS}_\text{II}$	D	θ_{12}	0.348	0.062	0.062	0.1	-0.002	0.060	0.059	94.4
	A	θ_{11}	0.089	0.093	0.094	84.1	0.331	0.095	0.099	7.5
$\text{PS}_\text{I}+\text{IPW}_\text{II}$	D	θ_{12}	0.348	0.062	0.062	0.1	-0.002	0.060	0.059	94.4
	A	θ_{11}	0.089	0.103	0.102	84.3	0.330	0.097	0.100	7.8
			Data Generation Model 2							
Two PS Reg	D	θ_{12}	-0.053	0.045	0.044	75.9	0.002	0.046	0.045	93.9
	A	θ_{11}	-0.016	0.073	0.072	94.3	0.208	0.070	0.070	15.8
$\text{PS}_\text{I}+\text{PS}_\text{II}$	D	θ_{12}	0.144	0.044	0.043	8.4	0.002	0.046	0.045	93.9
	A	θ_{11}	0.044	0.068	0.068	90.5	0.241	0.069	0.069	6.9
$\text{PS}_\text{I}+\text{IPW}_\text{II}$	D	θ_{12}	0.144	0.044	0.043	8.4	0.002	0.046	0.045	93.9
	A	θ_{11}	0.043	0.072	0.071	90.3	0.241	0.070	0.069	6.8

S_1 represents the PS model for the continuous exposure D conditioned on $A = 1$, given by $S_1 = E(D|A = 1, \mathbf{Z}_1)$; S_2 represents the PS model for the binary exposure A, given by $S_2 = E(A|\mathbf{Z}_2)$.

Table 3: Empirical results for estimators of effects for both parts with $P(A = 1) = 0.5$ for applying PS regression adjustment in Stage I and AIPW in Stage II under model misspecification.

Misspecified Model	Exposure	Effect	Ebias	ESE	RSE	ECP(%)
			Data Generation Model 1			
S_1	D	θ_{12}	0.348	0.063	0.062	0.1
	A	θ_{11}	0.091	0.077	0.077	79.0
S_2	D	θ_{12}	-0.002	0.060	0.059	94.4
	A	θ_{11}	-0.015	0.071	0.072	95.0
$m_a(\mathbf{X}; \boldsymbol{\theta})$	D	θ_{12}	-0.002	0.060	0.059	94.4
	A	θ_{11}	-0.003	0.071	0.074	95.7
$S_1 + m_a(\mathbf{X}; \boldsymbol{\theta})$	D	θ_{12}	0.348	0.062	0.062	0.1
	A	θ_{11}	0.093	0.078	0.079	79.1
$S_2 + m_a(\mathbf{X}; \boldsymbol{\theta})$	D	θ_{12}	-0.002	0.060	0.059	94.4
	A	θ_{11}	0.225	0.069	0.071	11.0
			Data Generation Model 2			
S_1	D	θ_{12}	0.144	0.044	0.043	8.4
	A	θ_{11}	0.044	0.070	0.069	90.8
S_2	D	θ_{12}	0.002	0.046	0.045	93.9
	A	θ_{11}	< 0.001	0.069	0.069	95.0
$m_a(\mathbf{X}; \boldsymbol{\theta})$	D	θ_{12}	0.002	0.046	0.045	93.9
	A	θ_{11}	< 0.001	0.070	0.072	95.2
$S_1 + m_a(\mathbf{X}; \boldsymbol{\theta})$	D	θ_{12}	0.144	0.044	0.043	8.4
	A	θ_{11}	0.044	0.070	0.070	91.0
$S_2 + m_a(\mathbf{X}; \boldsymbol{\theta})$	D	θ_{12}	0.002	0.046	0.045	93.9
	A	θ_{11}	0.241	0.070	0.069	6.8

S_1 represents the PS model for the continuous exposure D conditioned on $A = 1$, given by $S_1 = E(D|A = 1, \mathbf{Z}_1)$; S_2 represents the PS model for the binary exposure A, given by $S_2 = E(A|\mathbf{Z}_2)$; $m_a(\mathbf{X}; \boldsymbol{\theta})$ represents the imputation models for $a = 0, 1$.

6 Application to the prenatal alcohol exposure study

6.1 Description of the data

The Detroit Longitudinal Cohort is a prospective study of 480 pregnant African-American women from inner-city Detroit and their children, followed from birth to age 19 to investigate the effects of PAE [Jacobson et al., 2004, 2002]. Prenatal alcohol intake was assessed at each visit using a timeline follow-back interview [Jacobson et al., 2002] and summarised as average daily consumption over pregnancy; let T denote the average ounces of absolute alcohol (AA) per day. We treat PAE as a semi-continuous exposure: $A = I(T > 0)$ is a binary indicator of any drinking, and $D = \log T$ is the log daily dose among drinkers. The reference dose is set to -2.31, the sample mean of D among exposed mothers. The outcome is the Freedom from Distractibility Index of the Wechsler Intelligence Scales for Children, 3rd edition (WISC-III), measured at age 7 years for 377 children.

We adjust for baseline maternal sociodemographic characteristics, smoking and other substance use during pregnancy, reproductive history, gestational age at screening, and measures of the home environment and maternal cognition (listed in Web Table 7 in Web Appendix G.1). To address missingness, we generate 20 multiply imputed datasets using an imputation model including all variables; further details are given in Web Appendix G.2. Point estimates and standard errors are combined using Rubin's rules under a missing-at-random assumption [Rubin, 1976, Little and Rubin, 2019].

6.2 Application and findings

We estimate the causal effects of prenatal drinking status and continuous dose using five approaches: (i) conventional covariate regression adjustment; (ii) two–propensity-score regression adjustment; (iii) a two-stage analysis with PS regression adjustment in Stage II; (iv) a two-stage analysis with IPW in Stage II; and (v) a two-stage analysis with AIPW in Stage II. Implementation details are provided in Web Appendix G.3.

Web Table 7 summarises the fitted models for the continuous and binary exposure components, $E(D|A = 1, \mathbf{X})$ and $P(A = 1|\mathbf{X})$. Both models include all candidate covariates, following the recommendation of Brookhart et al. [2006] that including variables related to the outcome can improve precision of causal effect estimates.

Table 4: Estimated effects of drinking status and log prenatal absolute alcohol consumption per day

Method	$D\|A=1$		A	
	Estimate	Standard error	Estimate	Standard error
Covariate adjustment	-0.125	0.515	0.253	1.655
Two–PS regression	-0.189	0.572	-0.128	1.621
$PS_I + PS_{II}$	-0.011	0.518	-0.013	1.634
$PS_I + IPW_{II}$	–	–	-0.268	2.128
$PS_I + AIPW_{II}$	–	–	-0.176	1.965

Two–PS regression: two-dimensional PS regression adjustment; $PS_I + PS_{II}$: PS regression adjustment in Stages I and II; $PS_I + IPW_{II}$: PS regression in Stage I and IPW in Stage II; $PS_I + AIPW_{II}$: PS regression in Stage I and AIPW in Stage II.

Table 4 reports the estimated causal effects under the five approaches. For all PS–based methods, the estimated effects of both $\log(\text{AA/day})$ and drinking status are negative, with the magnitude of the drinking status effect larger than that of the dose effect. By contrast, the conventional covariate adjustment model yields a small positive estimate (0.253) for drinking status and a slightly negative estimate (-0.125) for log dose. Given the reliance of covariate adjustment on correct specification of the outcome model [Greenland et al., 1999, Brookhart et al., 2006], these estimates may be more vulnerable to bias than those from the PS–based procedures.

For the log-dose effect among drinkers, PS–based point estimates are small and similar across methods, with standard errors around 0.5. For the drinking status effect, the PS–based estimates range from approximately -0.013 to -0.268, whereas the conventional covariate adjustment estimate is slightly positive. The two-stage AIPW estimator provides a negative point estimate (-0.176) and benefits from its double-robustness property, but, as in our simulations, weighting-based methods yield larger standard errors than regression-based approaches (approximately 2.0 versus 1.6). Taken together, the PS–based results are compatible with modest harmful causal effects of both increased prenatal alcohol dose among drinkers and drinking status at the reference dose on WISC-III distractibility scores, although none of the estimated effects is statistically significant at the 5% level.

7 Discussion

We propose a causal framework involving a semi-continuous exposure with two-stage estimation. In Stage I, propensity score regression adjustment is used to estimate the continuous exposure effect, and Stage II focuses on the binary exposure via an AIPW estimator. We establish large sample properties for these estimators, characterise their limiting values under PS misspecification, and examine their finite sample performance. Together, these developments provide an interpretable framework that separates the consequences of any exposure from those of increasing dose, while allowing the use of doubly robust methods for the status effect. Theoretical results and simulations indicate that the proposed estimators perform well in finite samples and that the bias expressions under misspecification offer practical guidance for propensity score modelling with semi-continuous exposures.

A main limitation is that we do not pursue doubly robust estimation of the continuous exposure effect in Stage I. Doubly robust estimators for continuous treatments based on kernel smoothing and flexible generalised PS models [e.g. Zhu et al., 2015, Kennedy et al., 2017, Zhao et al., 2020] could be used to strengthen Stage I and reduce sensitivity to model misspecification.

Children's cognition in the wider PAE literature is often assessed through multidimensional neurological outcomes across several U.S. cohort studies, including analyses based on hierarchical and structural equation models with PS adjustment [Akkaya Hocagil et al., 2022, Dang et al., 2023]. Extending our semi-continuous two-stage framework to multivariate neurological outcomes, and to settings that pool information across cohorts, is a natural next step.

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