Monotonicity assumptions in estimating the treatment effect for a principal stratum

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Abstract

In addition to the treatment effect for all randomized patients, sometimes it is of interest to understand the treatment effect for a principal stratum, a subset of patients defined by one or more post-baseline variables. For example, what is the treatment effect for those patients who could be compliant with the experimental treatment? One commonly used assumption for estimating such a treatment effect is deterministic monotonicity, which assumes that a patient with a stratum-defining event under one treatment would also have that event under the alternative treatment. Alternatively, a less widely used stochastic monotonicity condition assumes the probability of a patient in a stratum with a stratum-defining event under one treatment is no smaller (or no larger) than that under the alternative treatment. In this article, we discuss the lack of plausibility of the deterministic monotonicity assumption and the advantages of using the principal score for estimating principal strata effects in clinical trials through theoretic argument and a real data example from a 2x2 cross-over study. As we illustrate, in some cases, methods based on modeling the probability of strata membership using baseline covariates (the principal score) may lead to reliable inferences without the need for making monotonicity assumptions.

Key words: Counterfactual, principal ignorability, principal score, treatment ignorability.
1 Introduction

The concept of principal stratification was first introduced in the late 1990s and early 2000s, primarily in estimating the treatment effect for patients who cannot be compliant with the assigned treatment\textsuperscript{1–3}. A principal stratum is defined by one or more post-baseline potential variables, which generally cannot be observed for all patients in a parallel clinical trial where each patient is randomized only to one of several candidate treatments. The choice of the principal stratum variable can be treatment compliance, treatment adherence, occurrence of an adverse event, survivor’s status, or based on an efficacy variable. The estimation of the treatment effect for a principal stratum has attracted the interest of clinical trialists. For example, Permutt\textsuperscript{4,5} discusses uses of the principal stratum for treatment discontinuation and adherence in clinical trials. Recently, the newly published ICH E9(R1) Addendum\textsuperscript{6} listed principal stratification as one of the key strategies for defining estimands.

Many approaches have been proposed for constructing estimators of the treatment effect in a principal stratum, all requiring relatively strong assumptions. One stream of research focuses on estimating the bounds of a treatment effect in a principal stratum or estimating such a treatment effect via introducing some sensitivity parameters (not estimable from data alone)\textsuperscript{7–10}. Another line of research provides estimators based on the principal score, the probability of a subject belonging to the principal stratum as a function of baseline covariates\textsuperscript{11–15}. Louizos et al.\textsuperscript{16} propose methods for directly estimating potential outcomes of a response variable under the alternative treatment if the principal stratum can be observed in one treatment group. Qu et al.\textsuperscript{17} provide a more general framework by modeling the potential outcome of the response variable and/or the principal score via baseline covariates and potential post-baseline intermediate measurements.

Many existing approaches, however, rely on the \textit{monotonicity} assumption to identify strata-specific effects\textsuperscript{15,18–24}. Monotonicity basically assumes that a patient with a stratum-defining “event” under one treatment would also have the same type of event under the alternative treatment. For example, assume the stratum is defined by the presence of an adverse event (AE). One type of monotonicity assumption is that if the AE is present for a
patient assigned to placebo, the AE must be present if this same patient were assigned to
the experimental treatment.

Monotonicity provides a convenient way to construct an estimator for the estimand in a
principal stratum; however, it may be unrealistic to assume the deterministic relationship
for the stratum defined by random variables. Vanderweele and Robins\(^\text{25}\) discuss a general
stochastic counterfactual framework, which assumes there is a random distribution of poten-
tial response for a binary stratum variable (characterized by the mean function) in contrast
to the deterministic counterfactual framework that assumes each subject has one potential
outcome given a treatment. A great deal of research in causal inference is still being con-
ducted within the deterministic counterfactual framework. This is probably because most
applications of causal inference only deal with potential outcomes for the response variable,
not for the principal strata. For example, in the propensity score analysis of observational
studies, one only needs to consider the potential outcome for the response variable. In
this case, the same commonly used method (e.g., based on inverse probability weighting or
matching) can be derived whether assuming a deterministic or a stochastic counterfactual
framework. Methods assuming deterministic monotonicity for the stratum variable, however,
will not work under stochastic monotonicity that assumes the probability of being in one
stratum is a monotone function of the treatment indicator.

The validity of the (deterministic) monotonicity assumption is very difficult to verify,
especially in parallel clinical trials where each subject only has the opportunity to receive
one treatment. To understand the plausibility of the monotonicity assumption, we looked
into a 2 × 2 cross-over clinical trial where each patient sequentially received both candidate
treatments and therefore the principal strata could be naturally observed. In this article, we
share our findings, which we believe will provide insight and directions for research into the
estimation for the estimand in a principal stratum. As the purpose of this research is to gain
insight into the plausibility of the monotonicity assumption irrespective of the specifics of
particular estimation methods, we will not elaborate on the formulae for various estimators
of treatment effect in a principal stratum.
This article is organized as follows. In Section 2, we will discuss deterministic and stochastic monotonicity and other assumptions, and review the methods of estimating the treatment effect for a principal stratum via principal scores. In Section 3, we will evaluate the plausibility of the monotonicity assumption and the methods based on principal scores. Finally, Section 4 serves as the summary and discussion.

2 Methods

We start by introducing the notation based on the counterfactual framework. Let \( j = 1, 2, \ldots, n \) denote the index for \( n \) subjects. For subject \( j \), let \( T_j \) denote the treatment indicator (\( T_j = 0 \) for the control treatment and \( T_j = 1 \) for the experimental treatment), \( A_j \) be a post-baseline indicator variable to define the stratum of interest, \( X_j \) be the baseline covariate, \( Z_j \) be a post-randomization intermediate outcome on which the probability of \( A_j \) may depend, and \( Y_j \) denote the response variable. Note, \( A_j \) can be the treatment adherence indicator, or an indicator variable derived from an efficacy or safety variable. For simplicity, we consider \( X_j \) and \( Z_j \) scalar random variables, but all arguments and derivations in this article can be applied to multivariate baseline covariates and intermediate outcomes (e.g., for \( X_j \) and \( Z_j \) as vectors). The potential outcome under a treatment \( T = t \) is denoted by placing the treatment as an argument, \( (t) \), following the variable name. For example, \( Y_j(0) \) denotes the potential outcome for the response variable for subject \( j \) under the control treatment \( (T = 0) \). The principal strata are defined by the potential outcome \( A_j(0) \) and \( A_j(1) \). Similarly to Qu et al. (2019), we use \( S_{kl} \) \( (k = 0, 1, *, \ l = 0, 1, *) \) to denote the principal stratum defined by:

\[
S_{kl} = \{ j : A_j(0) = k, A_j(1) = l \},
\]

\[
S_{k*} = \{ j : A_j(0) = k \},
\]

\[
S_{*l} = \{ j : A_j(1) = l \}.\tag{1}
\]
Then, the estimand (the average treatment difference) for a principal stratum $S_{kl}$ is defined as:

$$\mu_{d,kl} = n^{-1} \sum_{j=1}^{n} E[Y_j(1) - Y_j(0)|S_{kl}].$$

(2)

For simplicity, we omit the summation sign and write the estimand as:

$$\mu_{d,kl} = E[Y_j(1) - Y_j(0)|S_{kl}].$$

(3)

The treatment effect for the principal strata $\{j : A_j(0) = 0\}$ or $\{j : A_j(1) = 0\}$ is often difficult to estimate because no outcome data are observed for stratum $\{j : A_j(t) = 0\}$ even for patients randomized to arm $T = t$ (e.g., $A = 1$ indicates survival or adherence status). However, such strata are generally of little clinical interest. Notable examples from causal literature and some recent contributions have been focusing on the treatment effect for the principal strata of $S_{*1}$ and $S_{11}$, including:

- Complier Average Causal Effect (CACE) for patients who can be compliant to a treatment.
- Survivor Average Causal Effect (SACE) for patients who can be survivors under one or both treatments.
- Potential viral loads for Always-Infected Principal Stratum.
- Adherence Causal Estimator (ACE) for patients who can adhere to one or both treatments.

2.1 Stable unit treatment value assumptions and monotonicity

The estimand in (3) is not easy to estimate since the principal stratum is generally not observed for all patients. Additional assumptions are therefore required. A set of basic assumptions that are used in most causal inference frameworks is the stable unit treatment
value assumptions (SUTVA) described in Rubin\textsuperscript{27}:

\begin{align*}
A1 : & \quad Y_j = Y_j(1)T_j + Y_j(0)(1 - T_j) \\
A2 : & \quad Z_j = Z_j(1)T_j + Z_j(0)(1 - T_j) \\
A3 : & \quad A_j = A_j(1)T_j + A_j(0)(1 - T_j).
\end{align*}

SUTVA implies the hypothetical outcome is the same as the observed outcome under the same treatment, known as “consistency”, implying “no interference” (treatment status of any patient does not affect the potential outcomes of other patients) and “no-multiple-versions-of-treatment” assumptions\textsuperscript{28}. SUTVA is only a very basic assumption, and more assumptions are required to estimate the $\mu_{d,s}$. One commonly used assumption is the monotonicity assumption, without loss of generality in terms of the monotonicity direction (i.e., “$\geq$” or “$\leq$”), defined as:

\[ M : \quad A_j(1) \geq A_j(0). \]

Since $A_j(t)$ is a random variable, even if the monotonicity holds in probability in that, for example, $\Pr(A_j(1) = 1) \geq \Pr(A_j(0) = 1)$, the monotonicity for the potential outcomes may be violated simply because of the inherent variability in $A_j(0)$ and $A_j(1)$. We call the above SUTVA and monotonicity as deterministic SUTVA and deterministic monotonicity.

Following the concept of stochastic counterfactuals\textsuperscript{25}, a more realistic modeling of the mean potential outcome $Y$, $Z$ and $A$ at subject (indexed by $j$) and population levels is given by:

\begin{align*}
Y_j(t) &= \mu_{y,j}(t) + \epsilon_{y,j}(t) \quad \text{and} \quad \mu_{y,j}(t) = \mu_y(t) + s_{y,j}(t) \quad (4) \\
Z_j(t) &= \mu_{z,j}(t) + \epsilon_{z,j}(t) \quad \text{and} \quad \mu_{z,j}(t) = \mu_z(t) + s_{z,j}(t) \quad (5) \\
A_j(t) &= \mu_{a,j}(t) + \epsilon_{a,j}(t) \quad \text{and} \quad \mu_{a,j}(t) = \mu_a(t) + s_{a,j}(t) \quad (6)
\end{align*}

where $\mu_y(t), \mu_z(t)$ and $\mu_a(t)$ are the population mean for $T = t$ for variable $Y, Z$ and $A$, respectively; and $\mu_{y,j}(t), \mu_{z,j}(t)$ and $\mu_{a,j}(t)$ are the subject-level mean for subject $j$ under treatment $T = t$ for variable $Y, Z$ and $A$, respectively; and $s_{y,j}(t), s_{z,j}(t)$ and $s_{a,j}(t)$ are subject-level errors and $\epsilon_{y,j}(t), \epsilon_{z,j}(t)$ and $\epsilon_{a,j}(t)$ are residual errors for variable $Y, Z$ and
Note $s_{y,j}$ reflects the inherent random effect associated with the patient that remains the same if the experiment were repeated multiple times. In contrast, $\epsilon_{y,j}$ is error regenerated for any new realization “experiment” with that same subject. As such, the stochastic SUTVA is defined as

$$A1^* : \mu_{y,j} = \mu_{y,j}(1)T_j + \mu_{y,j}(0)(1 - T_j)$$

$$A2^* : \mu_{z,j} = \mu_{z,j}(1)T_j + \mu_{z,j}(0)(1 - T_j)$$

$$A3^* : \mu_{a,j} = \mu_{a,j}(1)T_j + \mu_{a,j}(0)(1 - T_j)$$

and a stochastic monotonicity condition\(^{13}\) is given by

$$M^* : \mu_{a,j}(1) \geq \mu_{a,j}(0) \text{ or } \mu_{a,j}(1) \leq \mu_{a,j}(0).$$

The replacement of A1 with A1* has no impact on any causal inference estimator for the principal stratification-based estimands because adding an independent random error to the response variable will not change the biasedness of an estimator. The replacement of A2 with A2* and A3 with A3* does not impact the validity of the methods based on the principal score because because adding an independent random error to the response variable will not affect the expected value of an estimator and hence will not affect its bias or lack of such; however, most methods depending on the deterministic monotonicity assumption M do not work under the stochastic monotonicity M*. In Section 2.2, we will describe the role of stochastic monotonicity in the estimation of the principal score.

### 2.2 Principal score modeled by baseline covariates

For the principal strata defined in (1), conditional on the baseline covariate $X_i$, the corresponding principal scores are given by $Pr(S_{kl}|X_j), k = 0, 1, *; l = 0, 1, *$. For parallel clinical trials, the principal score $Pr(S_{kl}|X_j), k = 0, 1; l = 0, 1$ can not be estimated directly because each patient can only take one treatment; however, the “marginal” principal score can be modeled and estimated using observed data. Assuming the marginal principal score can be
modeled as a function of baseline covariate $X$:

$$
\mu_{a,j}(t) := \mu_a(X_j, t) = \Pr(A_j(t) = 1|X_j).
$$

(11)

The function $\mu_a(x, t)$ can be estimated from the observed data $(A_j, X_j)$ in treatment group $T = t$. For example, $\mu_a(x, t)$ can be modeled as a logistic regression model

$$
\log \left( \frac{\mu_a(x, t)}{1 - \mu_a(x, t)} \right) = \alpha_{0,t} + \alpha_{1,t}x
$$

(12)

and the parameters $a_{0,t}$ and $a_{1,t}$ can be estimated from observed data

$$
\{(A_j, X_j) : j \in \{l : T_l = t\}\}.
$$

With the stochastic monotonicity assumption, we may assume a more parsimonious model:

$$
\log \left( \frac{\mu_a(x, t)}{1 - \mu_a(x, t)} \right) = \alpha_0 + \alpha_1 x + \alpha_2 t.
$$

(13)

Additionally, we assume the treatment ignorability assumption (Assumption A4) and the principal ignorability assumption (Assumption A5):

$$
A4: \quad T \perp \{Y_j(0), Y_j(1), A_j(0), A_j(1)\}|X_j
$$

$$
A5: \quad A_j(t) \perp \{Y_j(1 - t), A_j(1 - t)\}|X_i. \quad \forall t = 0, 1.
$$

With Assumptions A4 and A5, an estimator of the average potential outcome for $Y$ in the principal stratum $S_{11}$ is provided by Hayden et al.\textsuperscript{11} and estimators for principal stratum $S_{s1}$ are provided in\textsuperscript{12,14,15}. Jo and Stuart\textsuperscript{12} first introduced the term “principal score” and “principal ignorability,” although this method and the underlying assumptions were used earlier in Hayden et al., under the name explainable nonrandom survival\textsuperscript{11}. Of note, in most references, the principal ignorability assumption only includes the independence of $A_j(t)$ and $Y_j(1 - t)$ given $X_j$. The additional assumption of independence of $A_j(t)$ and $A(1 - t)$ given $X_j$ is needed for the estimation of the mean potential outcome of $Y$ for strata $S_{00}, S_{01}, S_{10}$ and $S_{11}$, but not for $S_{0*}, S_{1*}, S_{s0}$ and $S_{s1}$. While potential outcomes evaluated on the same patient for alternative treatments $t$ and $1 - t$ are naturally correlated, it is not unreasonable
to assume that they are conditionally independent, given measured covariates. We briefly review the estimators in the Appendix using the notation of this article to make it easier for the readers to follow.

The estimators for the treatment effect within principal stratum $S_{*1}$ can also be constructed based on the estimation of $\mu_{y,j}(0)$ for each individual patient randomized to treatment $T = 1$, assuming the mean outcome $Y$ can be modelled through the baseline covariates. This is a special case described in Louizos et al.\textsuperscript{16} and Qu et al.\textsuperscript{17}. As this is not relevant for the principal score estimation, we do not discuss this approach in detail here.

### 2.3 Principal score that depends on post-baseline measurements

Sometimes the principal score may depend on post-baseline intermediate outcome $Z_j$. For example, when the principal strata is defined by the treatment adherence indicator $A_j$ for $j$-th patient, the probability of strata membership (treatment discontinuation) may be driven by the patient’s poor intermediate efficacy $Z_j$. Qu et al. propose the adherence causal estimators (ACEs) for the principal stratum such that the probability of strata membership is modeled by baseline and post-baseline (intermediate) outcomes. The required additional assumptions are:

- **A4**: $T_j \perp \{Y_j(0), Y_j(1), A_j(0), A_j(1), Z_j(0), Z_j(1)\}|X_j$
- **A5**: $A_j(t) \perp \{Y_j(1), Y_j(0), Z_j(1-t)\}|\{X_j, Z_j(t)\}, \quad \forall t = 0,1$
- **A6**: $Y_j(t) \perp Z_j(1-t)|\{X_j, Z_j(t)\}, \quad \forall t = 0,1$
- **A7**: $Z_j(0) \perp Z_j(1)|X_j$

The relationship between $X_j, Z_j, Y_j$ and $A_j$ is described in the diagram in Figure 1. Under Assumptions (A1*–A7*), the ACEs can be constructed. The formulae for the ACEs are rather complex and our purpose is to understand the role of the monotonicity assumption, so we will not provide more details for the estimators here. Based on Assumptions (A1*–A7*) or the diagram in Figure 1, the probability for the potential adherence indicator ($A_j$) conditional
on $X_j$ and $Z_j$ does not depend on $T_j$. Therefore, the principal score

$$
\mu_{a,j}(t) = \Pr\{A_j(t) = 1|X_j, Z_j(t)\}
$$

is a function of the baseline covariate $X_j$ and the potential outcome $Z_j(t)$. Since $Z_j(t)$ is a random variable, even the stochastic monotonicity may not be a realistic assumption in this case.

### 3 Evaluating the plausibility of monotonicity assumption using a real-life data example

In this section, we will explore the plausibility of the commonly used monotonicity assumption using a 2×2 cross-over study comparing two regimens of the basal insulin peglispro (BIL): a fixed-time regimen given daily in the evening ($T = 0$) vs. a variable-time regimen given in the morning on Mondays, Wednesdays and Fridays and in the evening on Tuesdays, Thursdays, Saturdays and Sundays ($T = 1$) for patients with Type 1 diabetes mellitus. The study consists of a lead-in period of a daily injection of BIL at a fixed time each day for 12 weeks, and then randomized to 2×2 cross-over treatment periods with the above 2 regimens with 12 weeks for each period. Since insulins are to control the glucose without modifying the underlying disease and their effect from the treatment in the first period can be washed out in a few weeks during the second period of treatment, there is no need for a
separate washout period. After the lead-in period, 182 patients were randomized to either the fixed/variable-time treatment sequence (N=92) or the variable/fixed treatment sequence (N=90). The baseline characteristics and the main study results were published in Garg et al.\textsuperscript{29}.

We consider 3 variables to define the principal strata:

1. The between-day fasting glucose variability measured by standard deviation (BGSD), which is considered to be related to the study medication and treatment regimen.

2. The occurrence of the adverse events of injection reactions, which is considered related to the study medication but not the treatment regimen.

3. The occurrence of any adverse events belonging to the system organ class of infections and infestations, which is considered unrelated to the study medication and the treatment regimen.

In the evaluation in the rest of this section, we assume there are no carry-over and period effect. The implication of the violation of such assumptions is discussed in Section 4.

### 3.1 Evaluation of deterministic monotonicity assumption

In the first analysis, we evaluate the principal stratum defined by BGSD. Since BGSD is a continuous variable, we consider using the indicator for whether the change in BGSD from baseline (randomization) is greater than zero to define the principal strata. For illustration purposes, we only include those patients who had non-missing values for the change in BGSD under both treatment regimens (n = 87 for the fixed/variable-time sequence and n = 76 for the variable/fixed-time sequence) so that we can understand the “true” principal strata. Overall, the mean (SD) baseline BGSD was 41.3 (22.4) mg/dL. The mean (SD) change in BGSD from baseline to 12 weeks was -3.4 (25.4) mg/dL for the fixed-time regimen and -1.7 (24.8) mg/dL for the variable-time regimen.

Table 1 shows the number (%) of patients in each principal stratum defined by the values of $A_j(0)$ and $A_j(1)$, where $A$ is the indicator of whether the BGSD was increased from
the measurement at randomization. Since both treatment regimens used the same medication except for the dosing time, the variable-time regimen theoretically should have larger between-day glucose variability than the fixed-time regimen. In this case, the (deterministic version of) the monotonicity assumption is

\[ A_j(1) \geq A_j(0) \quad \text{or} \quad \Pr\{A_j(0) = 1, A_j(1) = 0\} = 0, \quad j = 1, 2, \ldots, n, \]

which implies

\[ \Pr(S_{10}) = 0, \]

where \( S_{kl} = \{ j : A_j(0) = k, A_j(1) = l \} \). From Table 1, the probability \( \Pr(S_{10}) \) was estimated as 19.0\%, which was far from 0. Clearly, the deterministic monotonicity assumption for BGSD does not hold.

Table 2 shows the number (%) of patients in each stratum defined by the occurrence of treatment-emergent adverse events related to injection site reactions. Since the injection device and the drug are exactly the same in both treatment regimens, we expect the dosing time would not impact on those adverse events related to injection sites. Therefore, the deterministic monotonicity implies

\[ A_j(1) \geq A_j(0) \quad \text{and} \quad A_j(0) \geq A_j(1), \quad j = 1, 2, \ldots, n. \]

It follows that

\[ A_j(1) = A_j(0), \quad j = 1, 2, \ldots, n; \quad \text{and} \quad \Pr(S_{01}) = \Pr(S_{10}) = 0. \]

In Table 2, the observed percentages of patients in \( S_{01} \) and \( S_{10} \) were both 1.2\%. While 1.2\% might seem low by absolute value, it accounted for 50\% to the probabilities \( \Pr(S_{01}) \) and
Pr(S_{1*}). Therefore, this also suggests the deterministic monotonicity assumption may be violated.

Table 2: Number (%) of patients by principal stratum defined by the occurrence of treatment-emergent adverse events related to injection site reaction

| A(0) = 0 | A(0) = 1 |
|----------|----------|
| A(1) = 0 | 161 (96.4) | 2 (1.2) | 163 (97.6) |
| A(1) = 1 | 2 (1.2) | 2 (1.2) | 4 (2.4) |
| A(0) ∈ {0, 1} | 163 (97.6) | 4 (2.4) | 167 (100) |

Table 3: Number (%) of patients by principal stratum defined by the occurrence of treatment-emergent adverse events related to infections and infestations

| A(0) = 0 | A(0) = 1 |
|----------|----------|
| A(1) = 0 | 105 (62.8) | 22 (13.2) | 127 (76.0) |
| A(1) = 1 | 27 (16.2) | 13 (7.8) | 40 (24.0) |
| A(0) ∈ {0, 1} | 132 (79.0) | 35 (21.0) | 167 (100) |

Table 3 shows the number (%) of patients in each stratum defined by the occurrence of treatment-emergent adverse events related to infections and infestations. Since no evidence suggests BIL has an effect on infections (based on other clinical studies), we can consider the occurrence of infections and infestations were not related to the treatment regimen. Again, if the deterministic monotonicity assumption holds, we should have

\[ Pr(S_{01}) = Pr(S_{10}) = 0. \]

From Table 3, the observed proportion of patients belonging to \( S_{01} \) and \( S_{10} \) were 13.2% and 16.2%, respectively. Again, the deterministic monotonicity assumption was violated.
3.2 Evaluation of the stochastic monotonicity assumption via the principal score

In this section, we evaluate the assumptions for the principal score and the stochastic monotonicity assumption. For the principal stratum variable based on treatment-emergent adverse events related to the injection site reaction, the rate was very low, so modeling the principal score via logistic regression is not possible. For the principal stratum variable based on treatment-emergent adverse events related to infections and infestations, there is no known baseline variable that can predict those adverse events. For most efficacy outcomes, the baseline measurement is generally the most predictable variable for the post-baseline measurement. Therefore, we evaluate the modeling of the principal score for the indicator of BGSD increase via baseline BGSD.

First, we evaluate the plausibility of the stochastic monotonicity assumption. The stochastic monotonicity assumption is

\[ \mu_{a,j}(1) \geq \mu_{a,j}(0), \quad j = 1, 2, \ldots, n, \]  

where \( \mu_{a,j}(t) = \Pr\{A_j(t) = 1|X_j\} \) for \( t = 0, 1 \). With this assumption, we have

\[ \Pr(S_{*1}) = \frac{1}{n} \sum_{j=1}^{n} \mu_{a,j}(1) \geq \frac{1}{n} \sum_{j=1}^{n} \mu_{a,j}(0) = \Pr(S_{1*}). \]

From Table 1, we can see \( \hat{\Pr}(S_{*1}) = 49.1\% \) and \( \hat{\Pr}(S_{1*}) = 42.9\% \), which is in agreement with the stochastic monotonicity assumption (14).

We estimate the principal score function \( \mu_a(x, t) \) without monotonicity restriction using model (12) and with stochastic monotonicity restriction using model (13). With the principal ignorability assumption (A5), the probability of membership in each principal stratum \( S_{kl}(k = 0, 1; l = 0, 1) \) can be estimated via the marginal principal score as

\[ \hat{\Pr}(S_{kl}) = \frac{1}{n} \sum_{j=1}^{n} \{1 - \hat{\mu}_a(X_j, 0)\}^{1-k} \{\hat{\mu}_a(X_j, 0)\}^{k} \{1 - \hat{\mu}_a(X_j, 1)\}^{1-l} \{\hat{\mu}_a(X_j, 1)\}^{l}. \]

In this cross-over study, the percentage of patients in each principal stratum can be directly estimated by the number of patients in each stratum. We compared the estimated
Table 4: Probability (%) for each principal stratum defined by the indicator of increase in BGSD from baseline to 12 weeks

|                      | $S_{00}$ | $S_{01}$ | $S_{10}$ | $S_{11}$ |
|----------------------|----------|----------|----------|----------|
| Observed             | 31.9     | 25.2     | 19.0     | 23.9     |
| Estimated Without Stochastic Monotonicity Assumption | 31.2 | 25.9 | 19.7 | 23.2 |
| Estimated Under Stochastic Monotonicity Assumption | 32.4 | 26.0 | 18.9 | 22.7 |
| Estimated Without Conditioning on Covariates | 29.1 | 28.0 | 21.9 | 21.1 |

probability for each principal stratum with and without monotonicity restrictions with the percentage directly observed from the cross-over periods (Table 4). We can see that the estimated probability for each principal stratum was similar to the observed percentage, regardless of the monotonicity restriction. The coefficient for the baseline BGSD for the model (12) was significant for both $t = 0$ ($p = 0.005$) and $t = 1$ ($p < 0.001$). We also tested for the interaction between $X_j$ and $T_j$ using a generalized linear mixed effects model, and the interaction p-value was 0.10.

In Table 4, we also present the estimated probability without using baseline values, i.e., assuming each subject has the same probability belonging to each principal stratum. The estimated probabilities without baseline BGSD in the model for principal score were more different from the observed probabilities compared to those estimated when baseline BGSD was included in the model. This and the p-values reported above suggest that the baseline BGSD was correlated with the principal stratum variable defined by the change in BGSD, and the prediction seems reasonable, although the impact of other unmeasured predictors cannot be ruled out.

3.3 Estimating the mean response for principal strata

In this section, we estimate the mean change in BGSD for all 4 principal strata ($S_{00}, S_{01}, S_{10}, S_{11}$) using the principal score as a function of the baseline covariates without the restriction of stochastic monotonicity as described in (12), and without using the fact that the principal
strata \( S_{kl} (k = 0, 1; l = 0, 1) \) are observed. Baseline BGSD was used in the model (12) for the estimation of the principal score. We then compare these estimates with the mean responses directly estimated from the observed strata using the cross-over study feature.

Without using the data on paired strata under both treatments, \( A_j(t), A_j(1-t) \), available in the cross-over study, the mean response for principal stratum \( S_{kl} \) can be estimated as

\[
\hat{\mu}_{0,kl} = \frac{\sum_{j=1}^{n} A_{j0}^k \cdot (1 - A_{j0})^{(1-k)} \cdot \{\hat{\mu}_{a,j}(1)\}^l \{1 - \hat{\mu}_{a,j}(1)\}^{1-l} \cdot Y_{j0}}{\sum_{j=1}^{n} (A_{j0})^k \cdot (1 - A_{j0})^{(1-k)} \cdot \{\hat{\mu}_{a,j}(1)\}^l \{1 - \hat{\mu}_{a,j}(1)\}^{1-l}},
\]

and

\[
\hat{\mu}_{1,kl} = \frac{\sum_{j=1}^{n} A_{j1}^l \cdot (1 - A_{j1})^{(1-l)} \cdot \{\hat{\mu}_{a,j}(0)\}^k \{1 - \hat{\mu}_{a,j}(0)\}^{1-k} \cdot Y_{j1}}{\sum_{j=1}^{n} (A_{j1})^l \cdot (1 - A_{j1})^{(1-l)} \cdot \{\hat{\mu}_{a,j}(0)\}^k \{1 - \hat{\mu}_{a,j}(0)\}^{1-k}},
\]

for treatment \( T = 0 \) and \( 1 \), respectively, where \( A_{jt} \) is the indicator variable for whether subject \( j \) is in stratum \( \{A(t) = 1\} \) for \( T = t \), \( Y_{jt} \) is the observed outcome for the response variable \( Y \) under treatment \( T = t \), and \( \hat{\mu}_{a,j}(t) \) is the estimator for the principal score defined in (11) only using the data in the period on treatment \( T_j = t \). The derivation for estimators (15) and (16) is provided in Appendix-C. Although the principal stratum indicator \( A_{jt} \) used in the above estimators can be replaced with the principal score \( \hat{\mu}_{a,j}(t) \), the choice of \( A_{jt} \) over the principal score is to maximize the use of directly observed data and minimize the use of model-based quantities.

We emphasize that equations (15) and (16) do not use the information on principal strata under alternative treatments observable only in a cross-over study, although the principal score function is estimated using the principal strata variable for the \( 1 - t \) treatment period when estimating the mean response for treatment \( T = t \). Even though the principal score function is estimated using exactly the same patients, we do not use the paired data \( \{A_{j0}, A_{j1}\} \). Instead, we use \( A_{j0} \) and \( A_{j1} \) in a non-paired fashion, similar to what we would have done in a parallel study. Although in this example both \( Y_{j0} \) and \( Y_{j1} \) were observed for the same subject \( j \) (which obviously would not be the case in a parallel study), equations (15) and (16) do not require the \( Y_{j0} \) and \( Y_{j1} \) to be from the same subject as long as the corresponding principal scores can be estimated (which is true for parallel studies under Assumption A4). Although we could easily derive the variance estimators for estimated
principal strata effects in (15) and (16), we chose not to do so because the principal strata can be observed in a cross-over study and such a calculation has no practical use. For illustrative purposes, we calculate the 95% confidence interval using the percentile bootstrap method. For this cross-over study, both $A_{j0}$ and $A_{j1}$ are observed, so a direct estimator of the mean response for each treatment arm in a stratum $S_{kl}$, $k = 0, 1; l = 0, 1$ can be obtained as a simple average of the outcomes for patients in that stratum:

$$\hat{\mu}_{t,kl}^{dir} = \frac{1}{|S_{kl}|} \sum_{\{j: j \in S_{kl}\}} Y_{jt},$$

where $|S_{kl}|$ is the size of the set $S_{kl}$. Table 5 summarizes the mean response for each treatment regimen and the treatment difference via the principal score and the direct estimation exploiting the cross-over study feature. Firstly, we can see the mean responses for each treatment regimen and the treatment effect were very different across four principal strata, indicating the importance of considering the principal stratum. Secondly, the estimates (especially for the treatment difference) via the principal score were close to the direct estimates for all principal strata. This example suggests that the estimation of treatment effects in principal strata via the principal score under the principal ignorability assumption (A5) is a viable approach and could result in valid inferences in some situations. From this example, the estimator in (15) and (16) based on the principal ignorability assumption of (A5) is more plausible than the approach based on the assumption of $A(t) \perp Y(1 - t)|X$ and the monotonicity assumption in Ding et al. (2016).

4 Summary and Discussion

In this article, we discussed the commonly used deterministic SUTVA and monotonicity assumptions for estimating treatment effects within principal strata. We proposed stochastic versions of SUTVA and monotonicity assumptions. For the response variable $Y$, the deterministic and stochastic SUTVAs make no difference for almost all methods of estimating the estimand based on a principal stratum; therefore, the deterministic SUTVAs can continue to be used.
Table 5: Estimates for the mean change in BGSD on various principal strata by directly using the observed principal strata and by the principal score

| Stratum | Method | FTR         | VTR         | FTR vs. VTR |
|---------|--------|-------------|-------------|-------------|
| S_{00}(n = 52) | DIRECT | -22.2 (-27.4, -17.1) | -20.3 (-25.4, -15.1) | -2.0 (-6.5, 2.6) |
|         | PS     | -23.9 (-28.6, -19.4) | -21.3 (-26.2, -16.8) | -2.7 (-7.0, 1.7) |
| S_{01}(n = 41) | DIRECT | -15.6 (-20.7, -10.5) | 13.6 (8.9, 18.3) | -29.2 (-34.8, -23.7) |
|         | PS     | -13.8 (-17.4, -10.7) | 16.9 (13.3, 20.7) | -30.7 (-35.4, -26.2) |
| S_{10}(n = 31) | DIRECT | 15.4 (10.0, 20.8) | -18.2 (-24.5, -12.0) | 33.6 (25.6, 41.7) |
|         | PS     | 18.0 (13.7, 22.8) | -16.8 (-20.7, -13.5) | 34.8 (29.4, 40.5) |
| S_{11}(n = 39) | DIRECT | 19.7 (13.4, 26.0) | 20.1 (14.8, 25.5) | -0.4 (-8.4, 7.5) |
|         | PS     | 17.6 (13.7, 22.0) | 16.7 (13.3, 20.5) | 0.9 (-4.3, 6.5) |

Abbreviation: BGSD, between-day fasting glucose variability measured by standard deviation; DIRECT, estimator directly based on the observed principal stratum; FTR, fixed-time regimen; PS, estimator via the principal score; VTR, variable-time regimen.

We evaluated the monotonicity assumption through a 2x2 cross-over design where the membership of patients in each principal stratum was naturally observed. For all three stratum variables considered, the deterministic monotonicity assumption seemed not being supported by the data, which is consistent with the statistical principles that \( A_j(t) \) is a random variable and it is not plausible to impose a deterministic condition on potential outcomes \( A_j(0) \) and \( A_j(1) \) at an individual patient level. As methods that depend on the deterministic monotonicity assumption do not work under the weaker stochastic monotonicity assumption, statistical methods not requiring the deterministic monotonicity assumption should continue to be developed in the field of principal stratification.

In the example in Section 3, we assume there were no carry-over and period effects. Based on the study design, disease stage and treatments, minimal carry-over effect and period ef-
fects were expected. Generally, such a cross-over study is considered a gold standard that can identify the principal strata. As discussed in Section 2, the plausibility of stochastic monotonicity is also supported by the general agreement that the within-subject variability should be taken into account when imputing missing outcomes. This is analogous to the case of using baseline values to impute the post-baseline missing values. The baseline observation carried forward (BOCF) imputation method ignores the within-subject variability and uses the actual observed value at baseline to impute a future value. The return-to-baseline imputation considers the within-subject variability and is much more widely accepted than BOCF in the literature.

Although methods relying on the deterministic monotonicity assumption are not theoretically valid, in some cases the resulting estimators can serve as a good approximation. One example is when the stratum variable is an adverse event that is very rare under the control treatment and is not so rare under the experiment treatment. In this case, we can assume $\Pr(A_j(0) = 1) \approx 0$. Then,

$$\Pr(A_j(0) = 1, A_j(1) = 0) \leq \Pr(A_j(0) = 1) \approx 0.$$  

Methods using the monotonicity assumption of $\Pr(A_j(0) = 1, A_j(1) = 0) = 0$ can still provide a reasonable approximation, which may be useful as a sensitivity analysis.

The methods based on the principal score estimated via baseline covariates technically do not need the (deterministic or stochastic) monotonicity assumption under the principal ignorability assumption (A5). In the real data example from a cross-over study, we showed the method via the principal score provides reasonable estimates for the treatment difference for each principal stratum. The only benefit of using the deterministic monotonicity assumption in the principal score estimation is the elimination of one parameter in the model, which may not necessarily outweigh the risk of poor model fitting due to misspecification. Therefore, we recommend a more flexible model for the principal score without using the stochastic monotonicity assumption, e.g., using model (12).

When the principal score estimation depends on post-baseline (intermediate) outcomes, even the stochastic monotonicity assumption is not possible because the mean principal
score conditional on baseline covariates and post-baseline intermediate outcomes is also a random variable of potential outcomes, unless we also pose a deterministic “monotonicity” assumption on the intermediate outcome.

In practice, choosing which methods to use for the estimation of the treatment effect within a principal stratum depends on the situation. If $A$ is defined based on a post-baseline efficacy variable that can be predicted by baseline covariates with relatively good accuracy, the methods using the principal score via baseline covariates may be used. e.g., the example in Section 3. If $A$ is likely to depend on post-baseline intermediate outcomes ($Z$), the methods using principal scores estimated as a function of $X$ and $Z$ can be used. For example, consider the case that $A$ is the indicator for treatment adherence defined as not experiencing an intercurrent event. The reasons for non-adherence can be classified into 3 categories: due to adverse event, due to lack of efficacy, or due to administrative reasons. If the intermediate efficacy measurements and AEs are observed and collected before the occurrence of the intercurrent event, we can reasonably assume the principal score can be modeled through baseline covariates and the intermediate outcomes. In case when the principal score depends on the post-baseline variables, additional assumptions are needed for constructing the estimator for the treatment effect (Section 2.3). Methods that require sensitivity parameters may also be useful if the value (or range of plausible values) for the sensitivity parameters can be reasonably justified. It is unlikely that one method can fit all situations. In practice, we need to choose an appropriate method based on the nature of the data. Even when models for strata membership are far from perfect in terms of prediction, they may still produce reasonably accurate estimates of the average treatment effect in a principal stratum (which is our target here). One key assumption is the principal ignorability assumption. Of course, as always, model misspecification may be a problem. One specific form of misspecification is when conditional independence of strata membership requires adding an unobserved covariate or outcome (e.g., $Y$) in the model if $Y$ is not observed for patients in certain principal strata. This may be checked using a logistic model with a sensitivity parameter, as a coefficient $\beta$ associated with $Y$. 
In summary, in this article we argue that the deterministic monotonicity assumption is likely not to be satisfied based on both theoretical argument and analysis of real data from a cross-over study. Researchers seeking estimation of treatment effects in principal strata may avoid this assumption. In our real example, the method based on the principal score provided reasonable estimates when the key baseline predictors for the stratum variable can be identified and included in modeling. Therefore, methods utilizing principal score may be useful in some cases; however, the assessment of the assumptions for principal score estimation and relevant sensitivity analyses deserve further research.

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Appendix Derivation details

Appendix-A Construct the estimator for the mean response in $Y$ for stratum $S_{11}$

For the principal stratum of $S_{kl}(k = 0, 1; l = 0, 1)$, under assumptions (A1*, A2*, A3*, A4, A5), the average response for $Y(0)$ is given by

$$
\mu_{0,11} := E\{Y_j(0)|S_{11}\} = E\{Y_j(0)|A_j(0) = 1, A_j(1) = 1\} = \frac{E[Y_j(0) \cdot A_j(0) \cdot A_j(1)]}{\Pr\{A_j(0) = 1, A_j(1) = 1\}}
$$

$$
= \frac{E[E\{Y_j(0) \cdot A_j(0) \cdot A_j(1)|X_i\}]}{E\{\Pr(A_j(0) = 1, A_j(1) = 1|X_i)\}}
$$

$$
= \frac{E\{Y_j(0) \cdot A_j(0) \cdot \mu_a(X_i, 1)\}}{E\{A_j(0) \cdot \mu_a(X_i, 1)\}} \quad \text{ (Using Assumption A5)}
$$

$$
= \frac{E\{Y_j(0) \cdot A_j(0) \cdot \mu_a(X_i, 1)|T_j = 0\}}{E\{A_j(0) \cdot \mu_a(X_i, 1)|T_j = 0\}} \quad \text{ (Using Assumption A4)}
$$

Then, an estimator of $\mu_{0,11}$ is given by

$$
\hat{\mu}_{0,11} = \frac{\sum_{j=1}^{n} Y_j A_j(1 - T_j) \hat{\mu}_a(X_i, 1)}{\sum_{j=1}^{n} A_j(1 - T_j) \hat{\mu}_a(X_i, 1)} ,
$$

where the principal score function $\hat{\mu}_a(X_i, 1)$ can be obtained (e.g., via a logistic regression) using the observed data in treatment group $T_j = 1$. Similarly,

$$
\hat{\mu}_{1,11} = \frac{\sum_{j=1}^{n} Y_j A_j T_j \hat{\mu}_a(X_i, 0)}{\sum_{j=1}^{n} A_j T_j \hat{\mu}_a(X_i, 0)} ,
$$

where the principal score function $\hat{\mu}_a(X_i, 0)$ can be obtained (e.g., via a logistic regression) using the observed data in treatment group $T_j = 0$. 

Appendix-B  Construct the estimator for the mean response in $Y$ for stratum $S_{*1}$

For the principal stratum of $S_{*1}$, $Y_j(1)$'s can be observed for patients in this principal stratum and an estimator for $u_{1,*1} := E\{Y_j(1)|S_{*1}\}$ is

$$\hat{\mu}_{1,*1} = \frac{\sum_{i=1}^{n} Y_j A_j T_j}{\sum_{i=1}^{n} A_j T_j}. \quad (20)$$

We also have

$$\mu_{0,*1} = E\{Y_j(0)|S_{*1}\} = E\{Y_j(0)|A_j(1) = 1\}$$

$$= \frac{E\{Y_j(0) \cdot I\{A_j(1) = 1\}\}}{Pr\{A_j(1) = 1\}}$$

$$= \frac{E(E[Y_j(0) \cdot I\{A_j(1) = 1\}|X_i])}{Pr\{A_j(1) = 1\}}$$

$$= \frac{E((Pr\{A_j(0) = 1|X_i\})^{-1} E[Y_j(0) I\{A_j(0) = 1\}|X_i] \cdot Pr\{A_j(1) = 1|X_i\})}{Pr\{A_j(1) = 1\}} \quad (\text{Using Assumption A5})$$

$$= \frac{E(\mu_a^{-1}(X_i, 0) \cdot \mu_a(X_i, 1) \cdot Y_j(0) \cdot I\{A_j(0) = 1\})}{Pr\{A_j(1) = 1\}}$$

$$= \frac{E(\mu_a^{-1}(X_i, 0) \cdot \mu_a(X_i, 1) \cdot Y_j \cdot A_j|T_j = 0)}{Pr\{A_j = 1|T_j = 1\}}. \quad (\text{Using Assumption A4}) \quad (21)$$

Then, an estimator for $\mu_{0,*1}$ is

$$\hat{\mu}_{0,*1} = \frac{\sum_{i=1}^{n} \hat{\mu}_a^{-1}(X_i, 0) \hat{\mu}_a(X_i, 1) Y_j A_j(1 - T_j) \cdot (\sum_{i=1}^{n} T_j)}{(\sum_{i=1}^{n} A_j T_j) \cdot \{\sum_{i=1}^{n}(1 - T_j)\}}. \quad (22)$$
Appendix-C  Construct the estimator for the mean response in $Y$
for stratum $S_{kl}(k = 0, 1; l = 0, 1)$ if no missing data for $Y$

$$
\mu_{0,kl} = E\{Y_j(0)|S_{kl}\}
$$

$$
= E\{Y_j(0)|A_j(0) = k; A(1) = l\}
$$

$$
= \frac{E[Y_j(0) \cdot I\{A_j(0) = k\} \cdot I\{A_j(1) = l\}]}{Pr\{A_j(0) = k, A_j(1) = l\}}
$$

$$
= \frac{E(E[Y_j(0) \cdot I\{A_j(0) = k\} \cdot I\{A_j(1) = l\}|X_j])}{E[Pr\{A_j(0) = k, A_j(1) = l|X_j\}]}
$$

$$
= \frac{E(E[Y_j(0) \cdot I\{A_j(0) = k\}|X_j] \cdot E[I\{A_j(1) = l\}|X_j])}{E[Pr\{A_j(0) = k|X_j\} \cdot Pr\{A_j(1) = l|X_j\}]}
$$

$$
= \frac{E(Y_j(0) \cdot I\{A_j(0) = k\} \cdot \{\mu_{a,j}(1)\}^l \cdot \{1 - \mu_{a,j}(1)\}^{1-l})}{E[I\{A_j(0) = k\} \cdot \{\mu_{a,j}(1)\}^l \cdot \{1 - \mu_{a,j}(1)\}^{1-l}]}
$$

$$
= \frac{E[Pr\{A_j(0) = k|X_j\} \cdot \{\mu_{a,j}(1)\}^l \cdot \{1 - \mu_{a,j}(1)\}^{1-l}]}{E[I\{A_j(0) = k\} \cdot \{\mu_{a,j}(1)\}^l \cdot \{1 - \mu_{a,j}(1)\}^{1-l}]} \cdot (23)
$$

Therefore, a consistent estimator for $\mu_{0,kl}$ is given by (15). The estimator (16) can be derived in a similar fashion.