Principal Stratification for Causal Inference With Extended Partial Compliance

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Principal Stratification for Causal Inference With Extended Partial Compliance

Hui JIN and Donald B. RUBIN

Many double-blind placebo-controlled randomized experiments with active drugs suffer from complications beyond simple noncompliance. First, the compliance with assigned dose is often partial, with patients taking only part of the assigned dose, whether active or placebo. Second, the blinding may be imperfect in the sense that there may be detectable positive or negative side effects of the active drug, and consequently, simple compliance has to be extended to allow different compliances to active drug and placebo. Efron and Feldman presented an analysis of such a situation and discussed inference for dose–response from the nonrandomized data in the active treatment arm, which stimulated active discussion, including on the role of the intention-to-treat principle in such studies. Here, we formulate the problem within the principal stratification framework of Frangakis and Rubin, which adheres to the intention-to-treat principle, and we present a new analysis of the Efron–Feldman data within this framework. Moreover, we describe precise assumptions under which dose–response can be inferred from such nonrandomized data, which seem debatable in the setting of this example. Although this article only deals in detail with the specific Efron–Feldman data, the same framework can be applied to various circumstances in both natural science and social science.

KEY WORDS: Causal inference; Missing data; Rubin Causal Model.

1. EFRON–FELDMAN AND THE LRC–CPPT DATA

Efron and Feldman (1991; hereafter EF) was among the earliest statistical articles to address noncompliance in randomized experiments. It analyzed a subset of the data from the Lipid Research Clinics Coronary Primary Prevention Trial (LRC–CPPT), which was a placebo-controlled dou1ble-blind randomized clinical trial designed to study the effectiveness of cholestyramine for lowering cholesterol levels. In the trial reported in EF, 164 men were randomized to the treatment group and assigned active pills of the drug, whereas 171 men were randomized to the control group and assigned placebo pills. Each man's cholesterol level was measured before the trial and at the end of the trial, which lasted for about 7 years; the outcome variable was his decrease in cholesterol level. The complication in this trial is that most of the patients in the experiment took only part of their assigned dose, which is typical partial-compliance behavior. The only data available to us are the treatment assignment, the proportion of the assigned drug or placebo taken, and the observed cholesterol reduction.

Figure 1 displays the LRC–CPPT data used in EF with EF's regression curves of outcome on compliance, after the removal of outliers. Figure 1(a) exhibits the association in the treatment group between the observed outcome of cholesterol reduction and the observed compliance to drug, defined as the proportion of active drug taken, which both EF and we assume is measured without error. Figure 1(b) shows the association in the control group between the observed outcome of cholesterol reduction and the observed compliance to placebo, defined as the proportion of placebo taken. Considering that the drug is designed to reduce cholesterol, it is not surprising that there is an apparent increasing trend in Figure 1(a): Better compliance to drug is associated with larger reductions in cholesterol levels. However, a similar but less dramatic association also exists in Figure 1(b): Better compliance to placebo also seems to be associated with larger reductions in cholesterol levels. As noted by EF, "...compliance has a different meaning in the Treatment and Control groups. Compliance determines the amount of active drug taken for Treatment group patients and also indicates something about the patient's psychological status. In the Control group, only the psychological component of compliance applies." Thus, compliance to drug and compliance to placebo are both explanatory variables in the experiment, but may have different roles to play.

In particular, how much of the greater cholesterol reduction in the treatment group is caused by taking more drug, and how should we formulate this intuitive question? In some intuitive sense, in Figure 1, we would like to subtract the control panel from the treatment panel. Consistent with EF (1991, pp. 9, 10), we believe a correct way to formulate it is in terms of the "true dose–response relationship" that would have been observed if dose had been randomly assigned and 100% compliance had been enforced. We present two analyses, both different from EF's analysis: The first regards both placebo compliance and cholestyramine compliance in this study as characteristics of patients and therefore does not address causal (i.e., true) dose–response; the second analysis explicitly imposes assumptions in the form of a hypothetical dose–response randomized trial, which led to the observed data, and allows us to estimate the true dose–response curves.

By randomization, the distribution of unobserved drug compliance in the control group is, in expectation, the same as the distribution of observed drug compliance in the treatment group, and analogously for unobserved placebo compliance in the treatment group. If the placebo were perfect in a sense formalized in Section 2.3, the observed treatment and control compliance distributions would differ only randomly.

Figure 2 shows the distribution of the drug and placebo compliances in the two random halves of the experiment. The histogram of compliance to drug differs from that of compliance to placebo, with a greater proportion at the lower compliance levels for those assigned drug and a greater proportion at the higher compliance levels for those assigned placebo. This difference is possibly due to the adverse side effects of the drug, which include increased colonic gas, and may induce some people to stop taking it. The difference is also revealed by the quantile–quantile plot in Figure 3.

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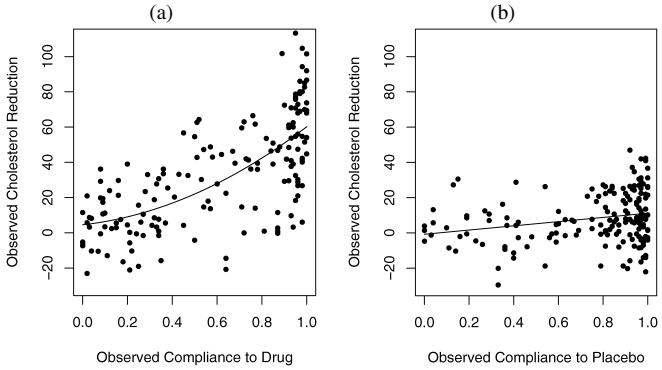

Figure 1. LRC–CPPT data. (a) Treatment group; (b) control group.

To handle this obvious violation of the "perfect blind assumption" (EF), which asserts that compliance to placebo is identical, unit by unit, to compliance to drug, EF assumed a monotonely increasing deterministic function relating the compliances in the two groups and, therefore, deterministically imputed "adjusted compliances" for the control group used in their inferences. That is, the imputed drug compliance for each control group member is a deterministic function of his placebo compliance. We believe that the EF assumption of a deterministic relation between drug and placebo compliances is overly restrictive and can be replaced with weaker and more plausible assumptions. Moreover, we estimate the true dose–response relation under explicit additional assumptions, which we view as necessary for a causal interpretation of the association between dose and response.

2. THE PRINCIPAL STRATIFICATION FRAMEWORK APPLIED TO EXTENDED PARTIAL COMPLIANCE

2.1 General Notation

The principal stratification framework in causal inference was proposed in Frangakis and Rubin (2002), but its implicit application for simple noncompliance phenomena in randomized experiments had received considerable attention previously (e.g., Angrist, Imbens, and Rubin 1996; Imbens and Rubin 1997; Frangakis, Rubin, and Zhou 2002; Greevy, Silber, Cnaan, and Rosenbaum 2004). Specifically, because compliance was not controlled by the experimenter, we should not hypothesize what the outcomes would have been if compliance had been enforced, as in a different experiment, without being explicit about this other hypothetical experiment. Therefore, how a patient would comply under *both* treatment *and* control in the actual experiment should, at least initially, be viewed as a bivariate pretreatment covariate consisting of a pair of potential compliances. Doing so, we can classify the patients into different principal strata according to this bivariate characteristic and study the average causal effects in each principal stratum, which collectively are called principal causal effects. In the simplest binary compliance case with only assignment to take or not take a drug, we have four principal strata: compliers, never-takers, always-takers, and defiers. The key idea with principal stratification is that the strata are created based on the values of one or more intermediate outcome variables, which are generally only partially observed. For example, compliance to drug is only observed when the person is actually assigned to take the drug. This approach forms the basis for our analyses.

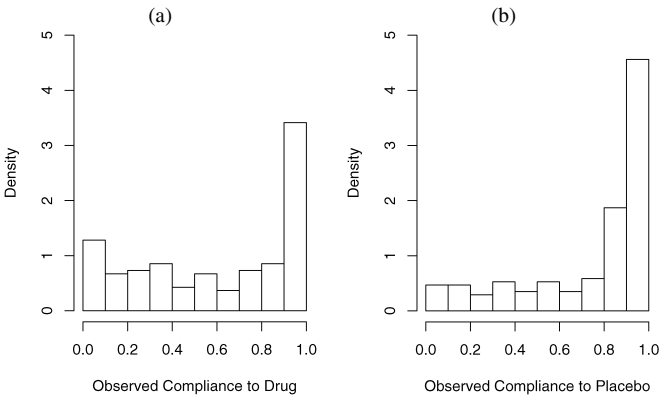

Figure 2. Histograms of observed drug compliance and placebo compliance in LRC–CPPT. (a) Treatment group; (b) control group.

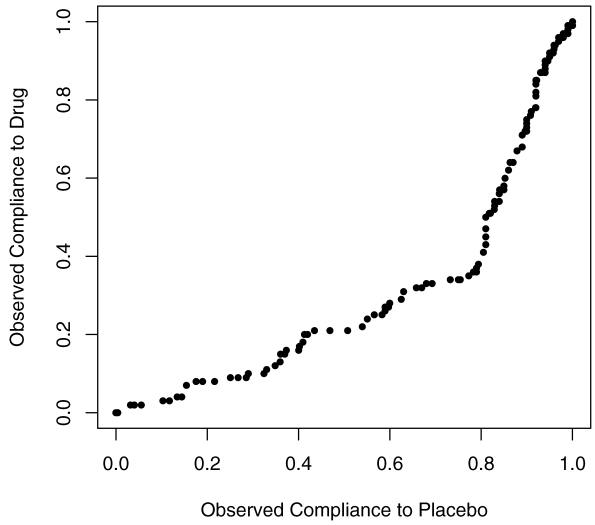

Figure 3. Q–Q plot of observed drug compliance and placebo compliance in LRC–CPPT.

To start, we use notation basically consistent with the applications in the previously mentioned articles. Let n be the number of patients in the LRC–CPPT experiment. Let Z_i represent the treatment assignment for patient i, $i = 1, 2, \ldots, n$: $Z_i = T$ if patient i is assigned treatment, and $Z_i = C$ if patient i is assigned control. Then $Y_i(Z_i = T)$ is the potential outcome giving the cholesterol reduction of patient i if assigned treatment, and $Y_i(Z_i = C)$ is the potential outcome giving the cholesterol reduction if assigned control. The causal effect of treatment assignment on cholesterol reduction for patient i is $E_i = Y_i(T) - Y_i(C)$, and the average causal effect across all the n patients is $\overline{E} = \overline{Y}(T) - \overline{Y}(C)$. These are standard primitives in the Rubin Causal Model (e.g., Holland 1986; Rubin 2005). For some questions, it is helpful to think of these n patients as a random sample from a much larger population of patients who are not in this experiment, but in this article we focus on the n patients in the experiment.

Let $D_i(Z_i = T)$ denote the level of active treatment received by patient i if assigned treatment, and let $D_i(Z_i = C)$ denote the level of active treatment received by patient i if assigned control, where the amount of drug taken is defined as the proportion of that assigned in accordance with Figure 1. Likewise,

let $d_i(Z_i = T)$ denote the actual level of placebo received by patient i if assigned treatment and let $d_i(Z_i = C)$ denote the level of placebo received by patient i if assigned control.

The principal stratum patient i belongs to is the combination of potential compliance pairs $S_i = [D_i(T), D_i(C), d_i(T), d_i(C)]$. We define the principal causal effect in stratum S as $\overline{E}_s = \mathrm{AV}E_{i\in S}[Y_i(T) - Y_i(C)]$, the average causal effect in the principal stratum, where the number of patients in S_i is n_i, $\sum_i n_i = n$. In previous binary compliance applications, $S_i = [D_i(T), D_i(C), 0, 0]$ with $D_i(T)$ and $D_i(C)$ taking values of 1 or 0 only, thereby implying at most four principal strata. For a specific example, Greevy et al. (2004) considered the case with $S_i = [D_i(T), 0, 0, 0]$ and response directly proportional to dose. We describe the new framework as handling "extended partial compliance" in the sense of extending $[D_i(T), D_i(C)]$ to $[D_i(T), D_i(C), d_i(T), d_i(C)]$ and allowing the four components to be "partial" in the sense of being between 0 and 1.

We illustrate the general structure of this framework with the toy example in Table 1 with eight patients evenly randomized into treatment and control, where X_i represents any pretreatment covariates, such as age and sex. The "⋆" denotes observed data, and the "?" denotes unobserved, or missing, data. For units 1–4 assigned to the treatment group, the potential compliances and outcomes in the treatment arm, $D_i(T)$, $d_i(T)$, and $Y_i(T)$, are observed, whereas the corresponding values in the control arm, $D_i(C)$, $d_i(C)$, and $Y_i(C)$, are missing. The exact opposite is true for units 5–8 assigned to the control group.

2.2 Standard Assumptions

Two assumptions are standard in the setting we consider and need no modification.

1. *Stable unit treatment value assumption* (SUTVA; Rubin 1980). For unit i assigned treatment, there is only one possible value of $[Y_i(T), D_i(T), d_i(T)]$, and analogously, for unit i assigned control, there is only one possible value of $[Y_i(C), D_i(C), d_i(C)]$. This assumption has implications, such as that there is no interference between units (Cox 1958); that is, one patient's treatment assignment will not affect another patient's potential outcomes (e.g., whether patient 1 is assigned drug or placebo does not affect patient 2's potential cholesterol reductions or compliance behaviors). Also, SUTVA asserts that there are "no hidden versions of treatments." SUTVA is widely assumed in clinical research, and the representation of the potential outcomes in Table 1 would not be adequate without it.

Table 1. Principal stratification structure of extended partial compliance

i	X_i	Z_i	$D_i(T)$	$D_i(C)$	$d_i(T)$	$d_i(C)$	$Y_i(T)$	$Y_i(C)$
1	⋆	T	⋆	?	⋆	?	⋆	?
2	⋆	T	⋆	?	⋆	?	⋆	?
3	⋆	T	⋆	?	⋆	?	⋆	?
4	⋆	T	⋆	?	⋆	?	⋆	?
5	⋆	C	?	⋆	?	⋆	?	⋆
6	⋆	C	?	⋆	?	⋆	?	⋆
7	⋆	C	?	⋆	?	⋆	?	⋆
8	⋆	C	?	⋆	?	⋆	?	⋆

NOTE: "⋆" represents observed data; "?" represents missing data.

2. *Ignorable treatment assignment* (Rubin 1978). Formally, $P(Z|Y(T), Y(C), D(T), D(C), d(T), d(C), X) = P(Z|Y_{\mathrm{obs}}, D_{\mathrm{obs}}, d_{\mathrm{obs}}, X)$, where Y_{obs}, D_{obs}, and d_{obs} represent the observed outcome and compliance values, respectively. This assumption basically states that the treatment assignment is a known probabilistic function of observed values, which is true in the randomized LRC–CPPT experiment, because, by the complete randomization of Z, $P(Z|Y(T), Y(C), D(T), D(C), d(T), d(C), X) = P(Z)$. Under ignorability, we do not need to model the assignment mechanism for Bayesian or likelihood inference.

2.3 Assumptions With Extended Partial Compliance

Other assumptions are extensions of those made with simple problems of noncompliance at the unit level.

1. *Access monotonicity*. In the expanded framework, we differentiate two levels of access monotonicity.

1.A. *General access monotonicity*. This assumption has two parts: treatment access monotonicity, $D_i(T) \geq D_i(C)$; and placebo access monotonicity, $d_i(T) \leq d_i(C)$. Treatment access monotonicity means that for every patient, the amount of active drug he takes if assigned treatment will be greater than or equal to the amount of active drug he takes if assigned control, because he has more convenient access to drug under treatment than he does under control. Analogously for placebo access monotonicity: For each patient, the amount of placebo he takes under control will be greater than or equal to the amount of placebo he takes under treatment, because he has more convenient access to placebo under control. Note that in the binary compliance case, we only have treatment access monotonicity because we only consider compliance to drug. It is often safe to assume both access monotonicity assumptions.

1.B. *Strong access monotonicity*. This assumption also has two parts: strong treatment access monotonicity, $D_i(C) = 0$; and strong placebo access monotonicity, $d_i(T) = 0$. That is, first, no member of the treatment group has access to placebo, and, second, no member of the control group has access to drug. In tightly controlled experiments, it is often reasonable to assume both of these.

2. *Side-effect monotonicity*. There are two versions of this assumption: negative side-effect monotonicity, $D_i(T) \leq d_i(C)$; and positive side-effect monotonicity, $D_i(T) \geq d_i(C)$. If the drug has more negative side effects than the placebo, the amount of drug patient i takes under treatment will be at most the amount of placebo he takes under control, and vice versa for positive side-effect monotonicity. Often, one or the other of these assumptions will be reasonable, but certainly not always. In fact, in some cases the sample could be realistically viewed as a mixture of two subgroups, one susceptible to positive side effects and the other susceptible to negative side effects.

3. *Perfect blind*. This assumption asserts $D_i(T) = d_i(C)$; that is, the amount of drug taken by a patient under treatment is exactly equal to the amount of placebo he takes under control, which requires the active drug to be perceived identically as the placebo, with identical side effects for instance. Under this strong assumption, everyone's principal

stratum is known, because, for each person, either $D_i(T)$ or $d_i(C)$ is observed. Thus, under the perfect-blind assumption, the principal strata can be further simplified into $S_i = D_i(T) = d_i(C)$, and we can directly group patients based on their observed $D_i(T)$ or $d_i(C)$ and, thereby, directly estimate principal causal effects for each principal stratum. The whole problem can then be reduced to a relatively simple one with a fully observed covariate. However, the perfect-blind assumption can be contradicted by the observed data, as with the EF compliance data of displayed in Figures 2 and 3.

4. *Equipercentile equating of compliances*. This assumption is a weakening of the perfect-blind assumption so that it cannot be contradicted by the observed data. It states that $D_i(T) = f[d_i(C)] = F_D^{-1}\{F_d[d_i(C)]\}$, where $F_D(\cdot)$ and $F_d(\cdot)$ are the cumulative distribution functions (CDFs) of $D(T)$ and $d(C)$, respectively. In practice, under this assumption, the "equating function" $f(\cdot)$ is estimated by the relationship between the empirical CDFs of observed $D(T)$ and observed $d(C)$ as illustrated in Figure 3. For the EF data, EF used $\hat{f}[d_i(C)]$, which has essentially the identical observed distribution in the control group as $D_i(T)$ does in the treatment group. This transformation is known in the educational testing world as "equipercentile test equating" (see the discussion in Rubin 1991). The analysis becomes straightforward again due to the resulting fully observed principal strata. Nonetheless, this one-to-one mapping function $f(\cdot)$ denies the possibility that two patients who take the same amount of placebo under control may take different amounts of drug under treatment, possibly because of different tolerances to the drug's side effects. The side-effect monotonicity assumptions allow for this possibility and are, therefore, less restrictive than the equipercentile equating assumption.

2.4 Application of Assumptions to LRT–CPPT Data

The EF analysis assumes SUTVA, ignorable treatment assignment, strong access monotonicity, and equipercentile equating of compliances. We agree that all of these are reasonable for the EF data except for the equipercentile equating of compliances. We replace this assumption with negative side-effect monotonicity because of the obvious negative side effects of the drug. Of course, it is possible that some patients do not experience these negative side effects and may even realize positive side effects from their reported cholesterol reductions after periodic blood tests, but the analyses presented here do not address this possibility. Our first analysis estimates principal causal effects with principal strata defined by (D_i, d_i); our second analysis will add more assumptions and estimate true dose–response relationships between cholesterol reduction and dose of active drug with principal strata defined only by d_i, the psychological compliance behavior, where we assume dose is randomly assigned in a particular hypothetical experiment described in Section 4.

More explicitly, our first analysis uses a Bayesian parametric model to draw inferences for causal effects within each principal stratum defined by $S_i = [D_i(T), 0, 0, d_i(C)]$, or, more simply, $S_i = [D_i(T), d_i(C)] = [D_i, d_i]$. As a result, we have the structure for the LRC–CPPT data presented in Table 2.

Table 2. Principal stratification structure of LRC–CPPT data

i	Z_i	$D_i(T)$	$D_i(C)$	$d_i(T)$	$d_i(C)$	$Y_i(T)$	$Y_i(C)$
1	T	⋆	0	0	?	⋆	?
2	T	⋆	0	0	?	⋆	?
⋮	T	⋆	0	0	?	⋆	?
n_T	T	⋆	0	0	?	⋆	?
n_T+1	C	?	0	0	⋆	?	⋆
n_T+2	C	?	0	0	⋆	?	⋆
⋮	C	?	0	0	⋆	?	⋆
n	C	?	0	0	⋆	?	⋆

NOTE: "⋆" represents observed data; "?" represents missing data.

3. MODEL, COMPUTATION, AND RESULTS BASED ON PRINCIPAL STRATIFICATION ON (D_i, d_i)

3.1 Bayesian Inference Framework

For Bayesian inference, the quantities for each patient in Table 2, Z_i, D_i, d_i, $Y_i(T)$, and $Y_i(C)$, are regarded as a joint realization of random variables from the following general model:

$$f\big[Z, (D, d), (Y(T), Y(C))\big] = f(Z, S, Y) = f(S, Y|Z) f(Z) = f(S, Y) f(Z),$$

where Z is the $n \times 1$ vector indicating treatment assignment, $S = (D, d)$ is the $n \times 2$ matrix of principal strata, and $Y = (Y(T), Y(C))$ is the $n \times 2$ matrix of potential outcomes. The last equality follows from the randomization of Z, which enables us to separate the "science," the joint distribution of (S, Y), from the treatment assignment mechanism $f(Z)$. With essentially no loss of generality (Rubin 1978), we can rewrite the joint distribution of (S, Y) as

$$f(S, Y) = \int \prod_i f(S_i, Y_i|\theta) p(\theta)\, d\theta = \int \prod_i f(S_{\text{obs},i}, S_{\text{mis},i}, Y_{\text{obs},i}, Y_{\text{mis},i}|\theta) p(\theta)\, d\theta,$$

where θ is a generic parameter with prior distribution $p(\theta)$, and $(Z_i, S_{\text{obs},i}, S_{\text{mis},i}, Y_{\text{obs},i}, Y_{\text{mis},i})$ represents the data, both observed and missing for patient i, using standard self-explanatory notation. The posterior distribution of θ can be written as

$$\begin{aligned} p(\theta|Z, S_{\text{obs}}, Y_{\text{obs}}) &\propto p(\theta) \times \int\int \prod_i f(S_{\text{obs},i}, S_{\text{mis},i}, Y_{\text{obs},i}, Y_{\text{mis},i}|\theta)\, dY_{\text{mis},i}\, dS_{\text{mis},i} \\ &= p(\theta) \int \prod_i f(S_{\text{obs},i}, S_{\text{mis},i}, Y_{\text{obs},i}|\theta)\, dS_{\text{mis},i}. \end{aligned} \quad (1)$$

Direct inference from (1) is computationally difficult in general, because of the integral over $S_{\text{mis},i}$. However, inference from the following posterior joint distribution of (θ, S_{mis}),

$$p(\theta, S_{\text{mis}}|Z, S_{\text{obs}}, Y_{\text{obs}}) \propto p(\theta) \prod_i f(S_{\text{obs},i}, S_{\text{mis},i}, Y_{\text{obs},i}|\theta), \quad (2)$$

is easier. The right side of (2) is proportional to the standard posterior distribution of θ with $S_{\text{mis},i}$ observed in a randomized experiment. It is typically easy to compute using (2) because of the simplicity of the "complete-data likelihood" given the $S_{\text{mis},i}$, as well as the availability of missing data algorithms such as the expectation–maximization (EM) algorithm (Dempster, Laird, and Rubin 1977), data augmentation (Tanner and Wong 1987), and the Gibbs sampler (Geman and Geman 1984). For example, in each iteration of the Gibbs sampler, we draw the parameter θ given the missing principal strata components S_{mis}, and then draw the missing S_{mis} given θ, and continue until the process converges. This method of inference is relatively easy because the two conditional posterior distributions are readily written once we specify the prior distribution $p(\theta)$ and the complete-data likelihood $\prod_i f(S_{\text{obs},i}, S_{\text{mis},i}, Y_{\text{obs},i}|\theta)$. Here we define "complete data" as $(S_{\text{obs}}, S_{\text{mis}}, Y_{\text{obs}})$ and exclude Y_{mis}, because missing potential outcomes in each principal stratum can be easily dealt with using standard complete-data tools.

3.2 Our Parametric Model

Our parametric model consists of one model for the distribution of the principal strata and one model for the conditional distribution of potential outcomes given the principal strata. Consistent with Figure 1, EF proposed a linear model for $Y(C)$ as a function of compliance and a quadratic model for $Y(T)$ as a function of compliance, but, as mentioned earlier, they did not employ the concept of principal strata and effectively set $D_i = \hat{f}(d_i)$ in both models.

We first specify a Beta distribution for the psychological component of compliance, that is, placebo compliance d_i:

$$d_i|\theta \sim \text{Beta}(\alpha_1, \alpha_2), \tag{3}$$

and then consistent with negative side-effect monotonicity, we specify another Beta distribution for relative drug compliance D_i/d_i given placebo compliance; specifically,

$$\frac{D_i}{d_i}\Big| d_i, \theta \sim \text{Beta}(\alpha_3, \alpha_4). \tag{4}$$

Consistent with EF, we assume a normal distribution for $Y_i(C)$ given S_i with mean linear in D_i and d_i:

$$Y_i(C)|D_i, d_i, \theta \sim \text{N}(\beta_0 + \beta_1 D_i + \beta_2 d_i, \sigma_C^2), \tag{5}$$

and a normal distribution for $Y(T)$ given S_i with a quadratic regression on D_i and a linear regression on d_i:

$$Y_i(T)|D_i, d_i, \theta \sim \text{N}(\gamma_0 + \gamma_1 D_i + \gamma_2 D_i^2 + \gamma_3 d_i, \sigma_T^2). \tag{6}$$

For simplicity, we initially assume $Y_i(T)$ and $Y_i(C)$ are independent given S_i, because only one of them can be observed for each patient and the observed data have no information about their partial correlation. The partial correlation, ρ, between $Y_i(T)$ and $Y_i(C)$ given D_i, d_i, and θ can be viewed as a sensitivity parameter, as in Rubin (1990) and as is done here in Section 3.4. The complete-data likelihood for $\theta = (\alpha_1, \alpha_2, \alpha_3, \alpha_4, \beta_0, \beta_1, \beta_2, \gamma_0, \gamma_1, \gamma_2, \gamma_3, \sigma_C, \sigma_T, \rho = 0)$ is

$$\begin{aligned}
&\prod_i f(S_{\text{obs},i}, S_{\text{mis},i}, Y_{\text{obs},i}|\theta) \\
&\quad = \prod_i \frac{\Gamma(\alpha_1+\alpha_2)}{\Gamma(\alpha_1)\Gamma(\alpha_2)} d_i^{\alpha_1-1}(1-d_i)^{\alpha_2-1} \frac{\Gamma(\alpha_3+\alpha_4)}{\Gamma(\alpha_3)\Gamma(\alpha_4)} \\
&\qquad \times \left(\frac{D_i}{d_i}\right)^{\alpha_3-1}\left(1-\frac{D_i}{d_i}\right)^{\alpha_4-1}\frac{1}{d_i} \\
&\qquad \times \prod_{i\in\{Z_i=T\}} \frac{1}{\sqrt{2\pi}\sigma_T} \\
&\qquad \times \exp\left[-\frac{(Y_i(T)-\gamma_0-\gamma_1 D_i-\gamma_2 D_i^2-\gamma_3 d_i)^2}{2\sigma_T^2}\right] \\
&\qquad \times \prod_{i\in\{Z_i=C\}} \frac{1}{\sqrt{2\pi}\sigma_C} \\
&\qquad \times \exp\left[-\frac{(Y_i(C)-\beta_0-\beta_1 D_i-\beta_2 d_i)^2}{2\sigma_C^2}\right].
\end{aligned}$$

We use a prior distribution on $(\alpha_1, \alpha_2, \alpha_3, \alpha_4)$, roughly analogous to that in Hirano, Imbens, Rubin, and Zhou (2000), which specifies a prior distribution through hypothetical data points. This corresponds to adding to the observed-data likelihood function six extra observations of (D, d) selected in the following way: First, we construct a dataset of (D, d) values for all the patients in the experiment according to EF's equipercentile equating assumption; second,we select the 1st, 21st, 41st, 61st, 81st, and 100th percentiles in this dataset and add these six prior data points [with complete (D, d) values, but missing all Y values] to the actual data; see Table 3 for the six data points to be added to the EF data in Table 2. We believe this prior is reasonable because it weakly pulls the posterior distribution of $(\alpha_1, \alpha_2, \alpha_3, \alpha_4)$ toward the equipercentile equating assumption displayed in Figure 3. After the addition of these six prior data observations to the observed data, the prior distribution for the parameters is a standard improper diffuse prior proportional to $(\sigma_C\sigma_T)^{-2}$. The Appendix provides details of the computation.

3.3 Results—Principal Causal Effects in Strata Defined by (D_i, d_i) With $\rho = 0$

Figure 4 displays the posterior medians of all the principal causal effects, that is, the posterior median of $\overline{E}_s$ for each (D, d); the median at four specific values of (D, d) is displayed at the bottom. Given any principal stratum (D, d) in the defined triangular area $D \le d$ of the horizontal plane, we plot in the vertical direction the posterior median of the corresponding principal causal effect of assignment to drug versus assignment to placebo. The surface of these posterior medians for the principal causal effects is smooth, rising from its lowest point -13 at principal stratum (0, 1) to its highest point 50 at principal stratum (1, 1). Thus, given the value of d, the type of compliance under control, the estimated principal causal effect increases as

Table 3. Structure of prior data observations to be added to data of Table 2

i	Z_i	$D_i(T)$	$D_i(C)$	$d_i(T)$	$d_i(C)$	$Y_i(T)$	$Y_i(C)$
(1)	?	⋆	0	0	⋆	?	?
(2)	?	⋆	0	0	⋆	?	?
⋮	?	⋆	0	0	⋆	?	?
(6)	?	⋆	0	0	⋆	?	?

NOTE: "⋆" represents observed data; "?" represents missing data.

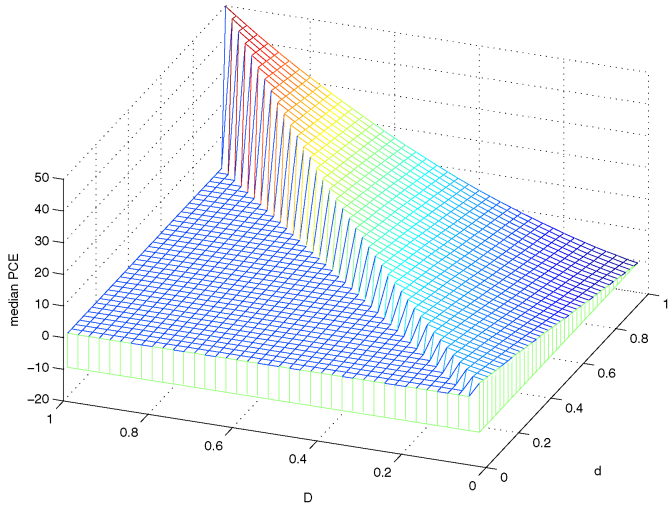

Figure 4. Posterior medians of principal causal effects with $\rho = 0$.

D increases, that is, as the strata represent men with better compliance under treatment. Numerically, the increase in the estimated causal effect is mainly due to the rapid increase in $Y(T)$ and the relatively stable increase in $Y(C)$ as D increases with fixed d. Table 4 displays the 2.5, 50.0, and 97.5 percentiles of the posterior distribution of the principal causal effects for principal start with D and d values at zero, their respective first quartile, medians, third quartile and one. The widest interval is $(-42, 27)$ at the principal stratum $(0, 1)$, whereas the intervals become narrower as the principal strata move toward the "median complier" who has $D = .70$ and $d = .89$ in this experiment. The posterior median and 95% interval for the principal causal effect for the median complier are 24 and (17, 30), which are comparable with those of the estimated intention-to-treat effect of 25 and (20, 30). Given that the median cholesterol reduction for good compliers in the treatment group is about 60, and the median cholesterol reduction for good compliers in the control group is about 10 (see the right ends of the two regression lines in Fig. 1), it is not surprising that the largest principal causal effect is 50 (39, 59) in the perfect-complier stratum $(1, 1)$.

The first column of Figure 5 assesses whether EF's deterministic equipercentile equating of d and D is a reasonable assumption within the context of our model with $\rho = 0$, wherein each panel represents one draw of the principal strata. Each dot represents the principal stratum $S_i = (D_i, d_i)$ for patient i in this draw. If the dots were distributed closely around the solid curve, then EF's equipercentile equating assumption would be reasonable in the context of our more general negative side-effect monotonicity assumption. However, this does not seem to be the case. The second column of Figure 5 displays the corresponding distributions for D_i/d_i. The first two columns reveal that, under our model, the perfect-blind assumption might be true or close to being true for many patients, because D_i/d_i is concentrated near 1 in the histograms, and most points are on or close to the 45° line in the scatterplots. However, under our model, some patients appear to suffer from negative side effects of the drug, and they would take less drug under treatment than they would take placebo under control. The existence of these two kinds of patients explains the quantile–quantile plot of the observed D and observed d in Figure 3.

The third and fourth columns of Figure 5 assess our model with $\rho = 0$ by comparing the distribution of simulated missing D (and missing d) with that of the observed D (and observed d) in the same two posterior draws of principal strata. As mentioned previously, the distribution of unobserved drug compliance in the control group (missing D) is, in expectation, the same as the distribution of observed drug compliance in the treatment group (observed D) due to the randomization, and analogously for the distribution of unobserved placebo compliance in the treatment group (missing d) and the distribution of observed placebo compliance in the control group (observed d). Therefore, the simulated missing D or missing d from an appropriate model should satisfy this expectation. The quantile–quantile plots support the propriety of our model in this regard.

3.4 Sensitivity Analysis to ρ

We now conduct a sensitivity analysis to ρ, the partial correlation between $Y_i(T)$ and $Y_i(C)$ given the principal strata. Because we never observe the two potential outcomes for any patient, the data contain no information about ρ. When ρ is not zero, we modify the distribution of $Y_i(T)$ in (6) as follows:

$$\begin{aligned} &Y_i(T)|Y_i(C), D_i, d_i, \theta \\ &\quad \sim \mathrm{N}\Big[(\gamma_0 + \gamma_1 D_i + \gamma_2 D_i^2 + \gamma_3 d_i) \\ &\qquad + \rho\frac{\sigma_T}{\sigma_C}\big(Y_i(C) - \beta_0 - \beta_1 D_i - \beta_2 d_i\big), (1-\rho^2)\sigma_T^2\Big]. \end{aligned} \quad (7)$$

We let ρ be $-.2$, .2, .4, .6, .8, and .9, and reestimate the principal causal effects. Table 5 reports the results for principal causal effects in four representative strata. We see that different values of ρ change the results only slightly.

Table 4. Posterior 2.5, 50.0, and 97.5 percentiles of representative principal causal effects with $\rho = 0$

		d				
		0	.6	.89	.97	1
D	1					39, 50, 59
	.95				36, 45, 53	36, 45, 53
	.7			17, 24, 30	16, 24, 32	15, 24, 32
	.27		−5, 5, 15	−19, 0, 21	−23, −1, 23	−24, −2, 23
	0	−6, 5, 16	−23, −4, 17	−37, −9, 24	−41, −10, 25	−42, −13, 27

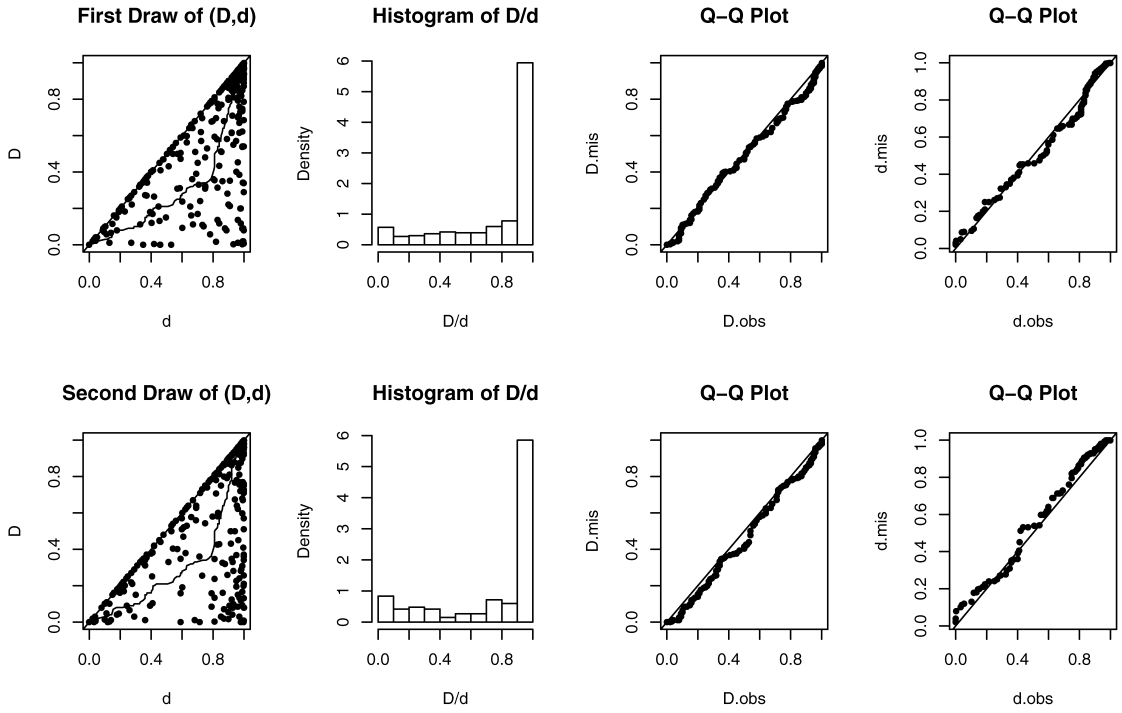

Figure 5. Two draws of principal strata (D, d) in the sample with $\rho = 0$.

4. ESTIMATION OF DOSE–RESPONSE WITHIN PRINCIPAL STRATA DEFINED BY d_i

4.1 General Formulation and Hypothetical Underlying Randomized Experiment

To estimate dose–response causal effects as if the doses were assigned and enforced in a hypothetical randomized experiment, we have to make an additional critical assumption and use a modified framework. Specifically, imagine that the EF data arose from the following hypothetical experiment: First, we measured d_i^*, the psychological or baseline compliance to placebo for each patient (e.g., as measured in a pilot study); second, we randomly divided the patients into treatment and control. Then, in the treatment group, we stochastically assigned dose $Z_{Di} \le d_i^*$ according to a certain "rule" that depended only on d_i^*, where we enforced compliance to this assigned dose; in the control group, we assigned a full dose of placebo and measured d_i. After the experiment was over, we noticed that $d_i = d_i^*$ in the control group, and we were so pleased with this finding that we made two mistakes: First, because $d_i = d_i^*$ in the control group, we discarded d_i^* in both the control group and the treatment group; second, because we had measured Z_{Di}, we "forgot" the exact stochastic rule for the assignment of Z_{Di}.

Table 5. Posterior median and 95% interval of representative principal causal effects for different values of ρ

(D, d)	(1, 1)	(.68, .89)	(0, 1)	(0, 0)
$\rho = -.2$	49 (39, 59)	24 (18, 30)	−10 (−40, 25)	4 (−6, 14)
$\rho = 0$	50 (39, 59)	24 (17, 30)	−13 (−42, 27)	5 (−6, 16)
$\rho = .2$	50 (39, 59)	23 (16, 29)	−11 (−47, 27)	5 (−7, 18)
$\rho = .4$	50 (40, 59)	23 (16, 29)	−6 (−43, 34)	6 (−7, 20)
$\rho = .6$	51 (39, 62)	22 (15, 30)	−10 (−43, 30)	7 (−8, 23)
$\rho = .8$	52 (38, 63)	22 (11, 33)	−8 (−62, 68)	6 (−11, 28)
$\rho = .9$	51 (37, 66)	22 (6, 36)	−1 (−74, 79)	9 (−25, 41)

Accordingly, Table 2 is modified into Table 6 as follows: First, we add a column for the fully missing d_i^*. Second, the columns involving $D_i(T)$ and $D_i(C)$ are no longer present because D is no longer viewed as an outcome variable. Third, we use Z_{Di} to denote the assigned dose of active drug under treatment, which can be $T_0, \ldots, T_D, \ldots, T_1$, where $T_D \in [0, 1]$. Fourth, because we still assume strong access monotonicity, there is just one column of d_i that is relevant, that is, $d_i(C)$. Finally, there are now many Y columns, one for $Y_i(C)$ and one for each $Y_i(T_D)$, where, for notational simplicity, we set $\{Y_i\} = \{Y_i(T_0), \ldots, Y_i(T_D), \ldots, Y_i(T_1), Y_i(C)\}$ and $\{Y\} = \{\{Y_i\} | i = 1, \ldots, n\}$. See Table 6 for the results.

In this hypothetical experiment, the assignment of Z_{Di} is no longer ignorable, because the dosage assignment mechanism in the treatment arm, $P(Z_{Di}|\{Y\}, d_i^*) = P(Z_{Di}|d_i^*)$, depends explicitly on d_i^*, which is missing; however, it would be ignorable if d_i^* were fully observed in the treatment arm. Therefore, the dosage assignment mechanism can be called "latently ignorable" given d_i^* (Frangakis and Rubin 1999). Consequently, we accept a version of SUTVA appropriate to Table 6, strong access monotonicity, and a dose assignment mechanism that has $Z_{Di} \le d_i^*$; that is, the experimenter never attempts to enforce a dose of the active drug that is larger than the self-selected dose of placebo in the pilot study. However, we supplement the ignorable treatment assignment assumption for the assignment of T versus C with a critical assumption in the treatment group, the latent ignorable assignment of dose of active drug Z_D given d^*; furthermore, we assume that d_i^* is equal to the observed d_i in the control group, whereas both d_i and d_i^* are unobserved in the treatment group.

Table 6. Dose–response structure of LRC–CPPT data

i	d_i^*	Z_i	Z_{Di}	$d_i(T)$	$d_i(C)$	$Y_i(T_0)$	$\cdots$	$Y_i(T_D)$	$\cdots$	$Y_i(T_1)$	$Y_i(C)$
1	?	T	T_0	0	?	⋆	?	?	?	?	?
$\cdots$	?	T	$\cdots$	0	?	$\cdots$	$\cdots$	$\cdots$	$\cdots$	$\cdots$	?
$\cdots$	?	T	T_D	0	?	?	?	⋆	?	?	?
$\cdots$	?	T	$\cdots$	0	?	$\cdots$	$\cdots$	$\cdots$	$\cdots$	$\cdots$	?
n_T	?	T	T_1	0	?	?	?	?	?	⋆	?
$n_T + 1$	?	C	?	0	⋆	?	?	?	?	?	⋆
$\cdots$	?	C	?	0	⋆	?	?	?	?	?	⋆
$\cdots$	?	C	?	0	⋆	?	?	?	?	?	⋆
n	?	C	?	0	⋆	?	?	?	?	?	⋆

NOTE: "⋆" represents observed data; "?" represents missing data.

4.2 Dose–Response With Principal Strata Defined by d_i

All the random variables in this case are Z, Z_D, d, and $\{Y\}$, with joint distribution

$$f(Z, Z_D, d, \{Y\}) = f(Z_D, d, \{Y\}) f(Z),$$

because of the randomized assignment of Z, and

$$f(Z_D, d, \{Y\}) = f(\{Y\}|d) f(Z_D|d) f(d)$$

due to the latent ignorable assignment of Z_D given d. Thus, given d, the analysis for dose–response is a standard complete-data Bayesian causal analysis (e.g., see Rubin 1978; or for more details, see Rubin 2007).

Our specific model for the distribution of the baseline compliance d_i, $f(d_i|\theta)$, is the same as in (3). Our model for the latent ignorable assignment mechanism of Z_{Di}, $f(Z_{Di}|d_i, \theta)$, is analogous to (4):

$$\frac{Z_{Di}}{d_i} \Big| d_i, \theta \sim \text{Beta}(\alpha_3, \alpha_4). \tag{8}$$

For the model specified by (3) and (8), we use the analogous prior distribution as in Section 3.2, which includes the six extra data points for the prior distribution of $p(\alpha_1, \alpha_2, \alpha_3, \alpha_4)$.

The joint distribution of the Y potential outcomes given principal strata, $f(Y_i(Z_{Di}), Y_i(C)|d_i, \theta)$, is specified in two parts. First, (5) is modified to be

$$Y_i(C)|d_i, \theta \sim \text{N}(\beta_0 + \beta_2 d_i, \sigma_C^2),$$

where the distribution of $Y_i(C)$ is now only a function of d_i, because it cannot depend on Z_{Di}, the randomly assigned treatment dose. Second, (6) [or more generally (7)] is modified to be

$$Y_i(Z_{Di})|Y_i(C), d_i, \theta \sim \text{N}[Y_i(C) + \gamma_1 Z_{Di} + \gamma_2 Z_{Di}^2 + \gamma_3 d_i Z_{Di}, \sigma_{T.C}^2], \tag{9}$$

where $\gamma_1 \geq 0$, $\gamma_2 \geq 0$, and $\gamma_1 + \gamma_3 \geq 0$. The form of the regression (9) having intercept $Y_i(C)$ derives from the science of dose–response. First, when dose Z_{Di} is zero, the outcome $Y_i(Z_{Di})$ is, as expected, the same as if assigned placebo, that is, $Y_i(C)$; EF made a similar assumption in their equation (2.1), but without the benefit of different variables Z_{Di} and d_i. Second, the constraints on γ_1, γ_2, and γ_3 are invoked because the dose–response curve, that is, the expectation of $Y(Z_{Di}) - Y_i(C)$, has to be monotonically increasing in Z_{Di} for all values of $d_i \in [0, 1]$, and because, from Figure 1, we expect any quadratic aspects in these curves to be increasing. The effect of being in different principal strata defined by placebo compliance (i.e., d_i) is to change the shape of the quadratic dose–response. This question of changing the dose–response as a function of placebo compliance cannot be addressed within the EF framework because Z_{Di} is a deterministic function of d_i, so conditioning on d_i automatically conditions on D_i and, thus, Z_{Di}. We assume, as before, the standard improper diffuse prior distribution for the parameters of the Y potential outcomes proportional to $(\sigma_C \sigma_{T.C})^{-2}$.

Within each cohort of patients with the same baseline compliance d, we calculate the posterior distribution of the mean of the individual responses, $E_i = Y_i(Z_{Di}) - Y(C)$, for those assigned dose Z_{Di}, where $Z_{Di} \leq d$. Figure 6 displays the estimated true dose–response relationship within four principal strata: perfect placebo complier ($d_i = 1.00$), 75th percentile placebo complier ($d_i = .97$), median placebo complier ($d_i = .89$), and 25th percentile placebo complier ($d_i = .60$). Plotted are the posterior medians (the thick curves) and the 95% intervals (the thin curves) of dose–response. The dotted lines indicate the differing responses at dose .60. Notice that the poorer placebo compliers appear to benefit more from the drug than do the better placebo compliers, possibly because the better compliers are doing other things to lower their cholesterol in any case, as seen in Figure 1(b). In fact, the plot suggests that the 25th percentile placebo compliers benefit almost twice as much as the perfect compliers from an assigned dose of .60: an estimated 48-point causal reduction in the $d_i = .60$ group relative to a 26-point causal reduction for the perfect placebo compliers.

5. DISCUSSION OF DOSE–RESPONSE AND THE ROLE OF COVARIATES

The methods and analyses of Sections 2 and 3 were based on principal stratification on (D, d). That is, we treated both compliance to drug and compliance to placebo as psychological characteristics of patients and then estimated the expected effect of assignment to treatment versus assignment to control for each type of person jointly defined by D and d. But it is difficult to look at such results without thinking that the resulting dose, D, causally affects response (cholesterol reduction relative to placebo) for each type of person defined by their compliance to placebo, d. That is, we should be able to encourage people to move to higher levels of D compliance and, thereby, to shift principal strata. To make this leap formally, however, required

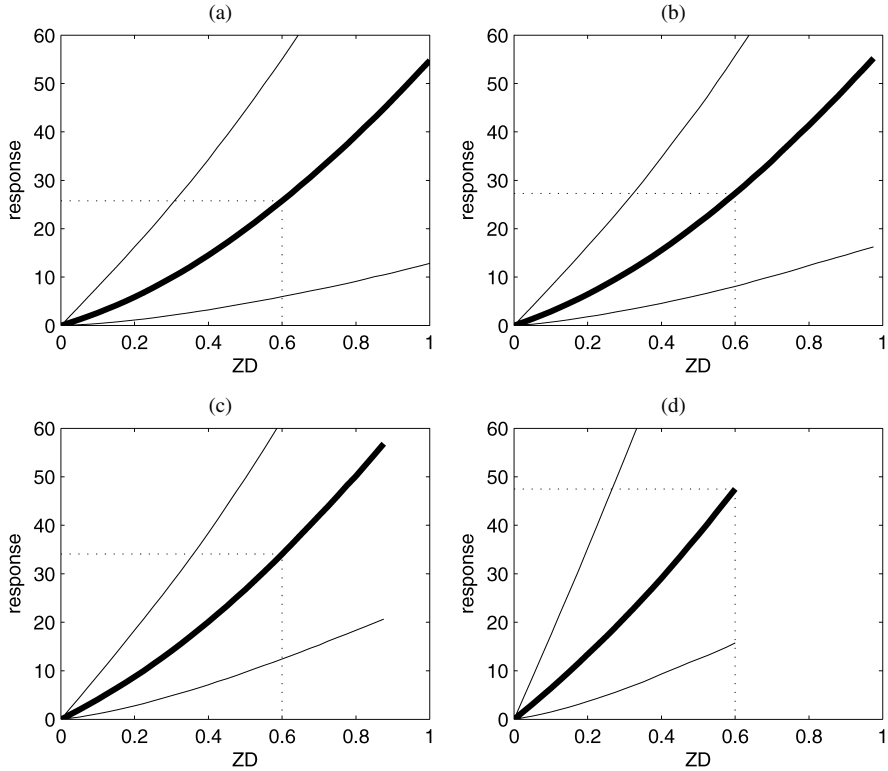

Figure 6. Dose–response. The thick curves are posterior medians of dose–response at $d = 1.00$ (a), .97 (b), .89 (c), and .60 (d), where the d values are the 100th, 75th, 50th, and 25th percentiles of compliance in the control group. The thin curves provide the corresponding 95% posterior intervals. The dotted curves represent the median dose–response for $Z_D = .60$ at these d levels.

more structure, which was described in Section 4. In particular, estimating true dose–response required an assignment mechanism for dose, which we assumed was latent ignorable given d. Under these assumptions, we estimated a quadratically increasing positive dose–response curve for each type of placebo complier, using a dose–response model with scientific assumptions formalized. We find evidence that poorer placebo compliers benefited more from the same dose of drug, presumably because they do not do other things to help reduce their cholesterol.

Despite these provocative dose–response results, they are causal only under a debatable assumption, namely, "nature's" latently ignorable assignment of Z_D given d, that is, $f(Z_D|\{Y\}, d) = f(Z_D|d)$. A more plausible assumption for this assignment mechanism would involve covariates, such as some true pre-experimental measures of sensitivity to the side-effects of the drug, which could play a key role in the patients' compliance behavior to the drug. Letting X indicate such side-effect covariate measurements, we believe $f(Z_D|\{Y\}, X, d) = f(Z_D|X, d)$ would be more plausible than our current assumption. In general, the role of covariates in randomized experiments with complications, such as noncompliance or missing data, seems to be underappreciated.

If a covariate vector $\tilde{X}_i = [1, X_{1i}, \ldots, X_{mi}]^T$ were observed, we could, for example, specify a model such as

$$d_i|\tilde{X}_i, \theta \sim \text{Beta}\big(e^{\tilde{\alpha}_1^T \tilde{X}_i}, e^{\tilde{\alpha}_2^T \tilde{X}_i}\big),$$

$$\frac{Z_{Di}}{d_i}\Big|\tilde{X}_i, d_i, \theta \sim \text{Beta}\big(e^{\tilde{\alpha}_3^T \tilde{X}_i}, e^{\tilde{\alpha}_4^T \tilde{X}_i}\big),$$

$$Y_i(C)|\tilde{X}_i, d_i, \theta \sim \text{N}(\tilde{\beta}_0^T \tilde{X}_i + \beta_2 d_i, \sigma_C^2),$$

$$Y_i(Z_{Di})|\tilde{X}_i, Y_i(C), d_i, \theta \sim \text{N}\big[Y_i(C) + e^{\tilde{\gamma}_1^T \tilde{X}_i} Z_{Di} + e^{\tilde{\gamma}_2^T \tilde{X}_i} Z_{Di}^2 + \big(e^{\tilde{\gamma}_3^T \tilde{X}_i} - e^{\tilde{\gamma}_1^T \tilde{X}_i}\big) Z_{Di} d_i, \sigma_{T.C}^2\big],$$

where $\tilde{\alpha}_1$, $\tilde{\alpha}_2$, $\tilde{\alpha}_3$, $\tilde{\alpha}_4$, $\tilde{\beta}_0$, $\tilde{\gamma}_1$, $\tilde{\gamma}_2$, and $\tilde{\gamma}_3$ are the corresponding $(m + 1)$-dimensional column vectors of parameters. Obviously, other specifications with covariates are also possible. The computation would be adjusted accordingly to incorporate these parameters and their prior distributions, but the basic methodology of Bayesian inference would remain the same. We could also use this formulation to test the sensitivity of our dose–response results to an unmeasured covariate X, but this too is a topic for future work.

APPENDIX: COMPUTATION

We apply Markov chain Monte Carlo (MCMC) to the first analysis using the basic idea of the Gibbs sampler. Specifically, in each iteration, we carry out the following computations.

1. Given the parameter θ and observed data, draw the missing data d_i or D_i.

For the control group members, we need to draw the missing $D_i^{(t)}$ from the distribution

$$D_i|\theta, d_i, Y_i(C) \propto D_i^{\alpha_3 - 1}(d_i - D_i)^{\alpha_4 - 1} \exp\Big[-\frac{(Y_i(C) - \beta_0 - \beta_1 D_i - \beta_2 d_i)^2}{2\sigma_C^2}\Big].$$

We use a Metropolis–Hastings method to draw the new $D_i^{(t)}$ at iteration t: First, draw D_i^* from the beta distribution $D_i^*/d_i \sim$

Beta(α_3, α_4), and then accept it with probability

$$p_D = \exp\Bigg[-\frac{(Y_i(C) - \beta_0 - \beta_1 D_i^* - \beta_2 d_i)^2}{2\sigma_C^2} + \frac{(Y_i(C) - \beta_0 - \beta_1 D_i^{(t-1)} - \beta_2 d_i)^2}{2\sigma_C^2}\Bigg],$$

where $D_i^{(t-1)}$ is the value in the last iteration $t-1$.

For the treatment group members, we need to draw the missing d_i from the following distribution:

$$d_i|\theta, D_i, Y_i(T) \propto d_i^{\alpha_1-\alpha_3-\alpha_4}(1-d_i)^{\alpha_2-1}(d_i - D_i)^{\alpha_4-1} \times \exp\Bigg[-\frac{(Y_i(T) - \gamma_0 - \gamma_1 D_i - \gamma_2 D_i^2 - \gamma_3 d_i)^2}{2\sigma_T^2}\Bigg].$$

We draw d_i^* from the beta distribution $\frac{1-d_i^*}{1-D_i} \sim \text{Beta}(\alpha_2, \alpha_4)$ and then accept it with probability

$$p_d = \left(\frac{d_i^*}{d_i^{(t-1)}}\right)^{\alpha_1-\alpha_3-\alpha_4} \times \exp\Bigg[-\frac{(Y_i(T) - \gamma_0 - \gamma_1 D_i - \gamma_2 D_i^2 - \gamma_3 d_i^*)^2}{2\sigma_T^2} + \frac{(Y_i(T) - \gamma_0 - \gamma_1 D_i - \gamma_2 D_i^2 - \gamma_3 d_i^{(t-1)})^2}{2\sigma_T^2}\Bigg].$$

2. Given the $D_i, d_i, Y_{\text{obs},i}$, and other parameters, draw the parameters $\alpha_1, \alpha_2, \alpha_3$, and α_4.

The methods for α_1, α_2, α_3, and α_4 are similar; therefore, we only describe in detail how to draw α_1 from the distribution $\alpha_1|D_i, d_i, Y_{\text{obs},i}, \alpha_2 \propto \prod \frac{\Gamma(\alpha_1+\alpha_2)}{\Gamma(\alpha_1)} d_i^{\alpha_1-1}$. Because it is not a standard distribution, we also use the Metropolis–Hastings method with a truncated normal distribution centered at the value of the last draw as the jumping distribution. First, draw α_1^* from $\alpha_1^* \sim \text{N}(\alpha_1^{(t-1)}, 1), \alpha_1^* > 0$, with normalizing constant $c_1 = \int_0^\infty \phi(x - \alpha_1^{(t-1)})\,dx$. Then calculate the normalizing constant for the left-truncated normal distribution $\text{N}(\alpha_1^*, 1)$ of "jumping back": $c_1^* = \int_0^\infty \phi(x - \alpha_1^*)\,dx$. Second, accept α_1^* with probability

$$p_1 = \frac{c_1}{c_1^*} \prod \frac{\Gamma(\alpha_1^* + \alpha_2)\Gamma(\alpha_1^{(t-1)})}{\Gamma(\alpha_1^{(t-1)} + \alpha_2)\Gamma(\alpha_1^*)} d_i^{\alpha_1^* - \alpha_1^{(t-1)}}.$$

Similarly, we can draw new values of α_2 and α_3 with acceptance rates

$$p_2 = \frac{c_2}{c_2^*} \prod \frac{\Gamma(\alpha_1 + \alpha_2^*)\Gamma(\alpha_2^{(t-1)})}{\Gamma(\alpha_1 + \alpha_2^{(t-1)})\Gamma(\alpha_2^*)} (1-d_i)^{\alpha_2^* - \alpha_2^{(t-1)}},$$

$$p_3 = \frac{c_3}{c_3^*} \prod \frac{\Gamma(\alpha_3^* + \alpha_4)\Gamma(\alpha_3^{(t-1)})}{\Gamma(\alpha_3^{(t-1)} + \alpha_4)\Gamma(\alpha_3^*)} \left(\frac{D_i}{d_i}\right)^{\alpha_3^* - \alpha_3^{(t-1)}},$$

and

$$p_4 = \frac{c_4}{c_4^*} \prod \frac{\Gamma(\alpha_3 + \alpha_4^*)\Gamma(\alpha_4^{(t-1)})}{\Gamma(\alpha_3 + \alpha_4^{(t-1)})\Gamma(\alpha_4^*)} \left(1 - \frac{D_i}{d_i}\right)^{\alpha_4^* - \alpha_4^{(t-1)}},$$

respectively.

3. Given the $D_i, d_i, Y_{\text{obs},i}$, and other parameters, draw the parameters β, γ, and σ.

This step comprises two standard Bayesian regressions (Gelman, Carlin, Stern, and Rubin 2004); specifically, we draw samples of β, σ_C, γ, and σ_T from the two Bayesian regression models in Section 3.2.

4. Iterate until approximate convergence.

After convergence, continue the previous steps, drawing the missing potential outcome $Y_i(T)$ or $Y_i(C)$, and thereby drawing $E_i = Y_i(T) - Y_i(C)$ for each patient, as well as any other estimands of interest.

For the sensitivity analysis to ρ, the only modification to the preceding computation is that we now can simulate $Y_{\text{mis},i}$ given D_i, d_i, $Y_{\text{obs},i}$, and a specific value of ρ; then we use both $Y_{\text{obs},i}$ and $Y_{\text{mis},i}$ in the two Bayesian regressions which draw the parameters β, γ, and σ.

We checked the computer program and the results in two ways. First, to examine convergence, we ran parallel Markov chains with different starting values, to ensure that they all converge to the same posterior distribution. Second, to ensure there are no coding errors in our program, we repeatedly drew θ from a proper but diffuse prior distribution, simulated datasets given each drawn parameter θ, made inferences with our program, and calculated the Bayesian posterior quantiles for θ. See Cook, Gelman, and Rubin (2006) for details of the general method. The z scores were all insignificant, as expected with a correctly written program.

The computation for the dose–response is the same as before, except that we do not have missing Z_D and the regression for $Y(Z_D)$ and $Y(C)$ is slightly different. We also checked the computer program using the Bayesian posterior quantile method, which indicated that the program was written correctly.

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