The compliance score as a regressor in randomized trials

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SUMMARY
The compliance score in randomized trials is a measure of the effect of randomization on treatment received. It is in principle a group-level pretreatment variable and so can be used where individual-level measures of treatment received can produce misleading inferences. The interpretation of models with the compliance score as a regressor of interest depends on the link function. Using the identity link can lead to valid inference about the effects of treatment received even in the presence of nonrandom noncompliance; such inference is more problematic for nonlinear links. We illustrate these points with data from two randomized trials.

Keywords: Causal inference; Instrumental variables; Noncompliance; Potential outcomes; Randomized trials.

1. INTRODUCTION
Many randomized trials are plagued with noncompliance. Until recently, analysts have been loathe to use information on compliance in estimating treatment efficacy; the most obvious ways to use this information on compliance, through ‘as treated’ analysis and its variants, are justly regarded as subject to bias (Lee et al., 1991). There have been a number of recent proposals on how to use compliance information; several of them involve a useful quantity known as the ‘compliance score’ (Follmann, 2000). In this paper, we discuss the compliance score, its properties, and its proposed use as a regressor in standard regression models. As we shall see, some of its usefulness in estimating treatment effects depends on the measure of effect. We illustrate our points with data from two randomized trials.

2. OBSERVED AND LATENT DATA
Consider the data in a randomized trial. Let $R$ be a randomization indicator: $R = 1$ for subjects randomized to the experimental treatment, 0 if randomized to placebo. Let $A$ refer to treatment received. For a binary treatment, $A = 1$ indicates taking the study medication, 0 not taking it. More generally, $A$ indicates the dose of the active drug received, as a proportion of the medication prescribed to subjects randomized to treatment; for subjects in the treatment arm, $A = 1$ indicates full compliance. Finally, let $X$ refer to pretreatment covariates, and $Y$ refer to the outcome.

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2.1 The compliance score

The compliance score $\delta_X$ is $E(A|R = 1, X) - E(A|R = 0, X)$. It is the effect of randomization on treatment received on a difference scale. For a binary treatment $A$, it will sometimes also refer to the proportion of compliers in the subset of the population with covariate level $X$. Let $A'$ denote the level of treatment a subject would receive were he or she to be randomized to group $r$. $A'$ is a 'potential receipt' (Frangakis and Rubin, 1999) observed only if the observed $R = r$. A complier is defined here as a subject who would follow whichever treatment to which he/she is randomized: i.e. for whom $A^1 = 1$ and $A^0 = 0$. In a population with no defiers (i.e. subjects for whom $A^1 = 0$ and $A^0 = 1$), $\delta_X$ is the proportion of compliers among subjects with covariate level $X$. In a population which also has no always-takers (i.e. subjects for whom $A^1 = 1$ and $A^0 = 1$), we can identify compliers in the treatment or experimental arm as those who comply with their observed treatment (i.e. subjects for whom $A = 1$ and $R = 1$); compliers in the control arm cannot be identified. When subjects randomized to the control or placebo arm have no access to the active treatment, there are no defiers or always-takers, and $E(A|R = 0, X) = 0$; thus, the compliance score $\delta_X$ is $E(A|R = 1, X)$ in this setting.

The compliance score is a function solely of pre-randomization covariates and may be calculated for all subjects in a study, regardless of what treatment they are assigned. Thus, its use in analysis of data from randomized trials does not run afoul of the injunction against using post-randomization variables in estimating treatment effects. The compliance score, as the average effect of randomization on treatment received in the subgroup with covariates $X$, can also be viewed as a group-level or aggregate variable. Such variables are often included in regression models. Nonetheless, as in the analysis of ecologic data, using such group-level variables to learn about individual-level effects has pitfalls (Morgenstern, 1982).

2.2 The potential outcomes model

We use the potential outcomes model (Neyman, 1990; Rubin, 1974) to define the effects of a treatment. Let $Y^{r,a}$ denote the outcome that would be observed in an individual were he or she to be randomized to group $r$ and to receive treatment level $a$. The outcome $Y^{r,a}$ is only observed for subjects randomized to group $r$ who receive treatment level $a$, otherwise it is unobserved or counterfactual. Treatment effects are defined in terms of comparisons of the potential outcomes $Y^{r,a}$.

It is common to assume that randomization does not directly affect the outcome (Robins and Greenland, 1992); i.e. that all of its effect is mediated by treatment received. Mathematically, this can be written as

$$Y^{r,a} = Y^{r',a} = Y^{a}$$

for any $r, r'$. This assumption is sometimes called an exclusion restriction (Angrist, Imbens and Rubin, 1996).

Because the distribution of individual treatment effects is not generally estimable (Greenland and Robins, 1986), we concentrate on aggregate causal effects, which are comparisons of the distributions of different potential outcomes in the same population subgroups. Let $\mu_C \equiv E(Y|C)$ denote the mean outcome in the subgroup characterized by variables $C$, and let $\mu^{r,a}_C \equiv E(Y^{r,a}|C)$ denote the expected value of the potential outcome $Y^{r,a}$ in that subgroup; subscripts denote subsets of the data, and superscripts specify which potential outcomes are referenced. Comparisons of $\mu^{R,A}_{X,R,A}$ and $\mu^{R,0}_{X,R,A}$ are measures of the effect of treatment received among subjects who received level $A$ of treatment, and comparisons of $\mu^{1,a}_{X,R,A}$ and $\mu^{0,a}_{X,R,A}$ are measures of the direct effect of randomization. When randomization has no direct effect (1), the potential outcomes need be indexed only by treatment received $a$, and so we sometimes write the singly superscripted $\mu^{a}_{X,R,A}$ for $\mu^{r,a}_{X,R,A}$.
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There have been two general approaches to estimating these effects for this setting. One, which we call ‘estimation first’, posits a model for the observed outcome given observable quantities. The approach then proposes a causal interpretation for the parameters in these models. The second approach, which we call ‘estimands first’, starts with the potential outcomes and their comparisons, as above. It then specifies assumptions which identify the causal estimands and valid procedures for their estimation. These principled approaches are sometimes difficult to apply and software may be unavailable. Thus, it is of interest to know when the ‘estimation first’ approach provides an adequate basis for inference for causal effects.

Methods using the compliance score are among the more promising of ‘estimation first’ methods, because they have been proposed formally for this setting (Follmann, 2000), are sometimes valid even in the presence of nonignorable noncompliance, and do not use post-randomization variables as predictors in the regression. We will formally consider models of the following form:

\[
g(E(Y|\delta_X, R)) = \beta_0 + \delta_X\beta_1 + R\beta_2 + R\delta_X\beta_3, \tag{2}
\]

where \(g(\cdot)\) is a monotonic 1–1 link function (McCullagh and Nelder, 1989). One might view \(\beta_2\) as the direct effect of randomization and \(\beta_3\) as the indirect effect: i.e. that part mediated by treatment received. Further, some might regard \(\beta_2 + \beta_3\) as the intent-to-treat comparison among compliers (Follmann, 2000). Especially for nonlinear models (i.e. link functions \(g(\cdot)\) other than the identity function), these interpretations are often unwarranted. When there is no variation in the compliance score \(\delta_X\), as would be the case if there is only a single stratum \(X\) or a trial with perfect compliance, \(\beta_0\) and \(\beta_1\), and \(\beta_2\) and \(\beta_3\) are not separately identified; we consider appropriate simpler models for this situation below.

One could also consider as an alternate model the somewhat more complicated

\[
g(E(Y|X, \delta_X, R)) = \beta_0 + \delta_X\beta_1 + R\beta_2 + R\delta_X\beta_3 + X\beta_4. \tag{3}
\]

We concentrate on (2) because of its simplicity. In the development, it will emerge that the linearity implied by \(\delta_X\beta_1\) in either equation and the absence of \(X\beta_4\) in either model are convenient simplifications which may or may not be justified in particular applications; little should be read into them. The linearity implied by \(R\delta_X\beta_3\) plays a more central role.

3. MODELS FOR THE OUTCOME

We consider the interpretation of model (2) in several settings. We first consider all-or-none compliance, then settings in which compliance may take on multiple levels. For all-or-none compliance, we consider the identity link, then the logit link.

We begin with some preliminaries. We can express some observed regressions like (2) in terms of the compliance score and other variables: the effect of treatment received on outcome, the direct effect of randomization, and selection bias. Let \(\Phi_X = \mu_{x,1,1}^{1,1} - \mu_{x,1,1}^{1,0} = \mu_{x,1,1} - \mu_{x,1,1}^{1,0}\) measure, on a linear scale, the effect of treatment received among subjects randomized to treatment who take their assigned treatment and who have covariate level \(X\). Let \(\Delta_{X,R,A} = \mu_{X,R,A}^{1,0} - \mu_{X,R,A}^{0,0}\) measure the direct effect of randomization on outcome among subjects with observed variables \(\{X, R, A\}\); note that \(\mu_{X,R,A}^{1,1} - \mu_{X,R,A}^{0,1}\) is an alternative measure of direct effects (Joffe and Colditz, 1998; Robins and Greenland, 1992). Let \(\sigma_{X,R,A} = \mu_{X,R,A}^{0,0} - \mu_{X,R,A}^{0,0}\) indicate the difference in prognosis, among subjects with covariates \(X\), between people in group \(R, A\) and the control group; \(\sigma_{X,R,A}\) is a measure of selection bias (see Robins et al. (2000)). The effects and bias terms may also be defined for other links; nonetheless, there is particular advantage to considering the identity link, as will be explained.
3.1 All-or-none compliance

This section considers a simple but important setting, in which compliance is all-or-none, and in which all subjects randomized to control have no access to the active treatment. To examine the proposed interpretations of the coefficients in (2), we write the marginal (with respect to $A$) expectation of the outcome in terms of expectations of variables known by the time of randomization. In this setting, there is a simple expression corresponding to the expectations modeled in (2) (see the Appendix for derivation):

$$E(Y|X, R) = \mu_{X,R} = \mu_{X,0,0} + R\Delta_{X,1,0} + R\delta_X(\Phi_X + \Delta_{X,1,1} - \Delta_{X,1,0}). \tag{4}$$

Each term in (4) corresponds to particular terms in (2): to $\mu_{X,0,0}$ to $\beta_0 + \delta_X\beta_1$, $R\Delta_{X,1,0}$ to $R\beta_2$, and $R\delta_X(\Phi_X + \Delta_{X,1,1} - \Delta_{X,1,0})$ to $R\delta_X\beta_3$; this will aid interpretation of (2). The selection bias term $\sigma_{X,R,A}$ does not play a role in (4), because of a cancellation which occurs on the linear scale. We consider interpretation of our observed regression (2) in light of (4) first for a single stratum with constant $X$, then for multiple strata.

3.1.1 All-or-none compliance, single stratum. For a single covariate level $X$, there are two design points in regression (2) (we do not use treatment received $A$ in the regression except through the compliance score $\delta_X$): the group randomized to control, and that randomized to treatment. Because there are two design points but four unknown parameters, model (2) is overparametrized for this setting; one can set to 0 either $\beta_0$ or $\beta_1$ and either $\beta_2$ or $\beta_3$. For the identity link function $g(y) = y$, we have (fixing $\beta_3 = 0$) that $\beta_2 = \Delta_{X,1,0} + \delta_X(\Phi_X + \Delta_{X,1,1} - \Delta_{X,1,0})$.

If randomization has no direct effect (1), (4) simplifies to (5)

$$E(Y|X, R) = \mu_{X,0,0} + \delta_X R\Phi_X. \tag{5}$$

Under (5), it is useful to set $\beta_2 = 0$ in the observed regression (2); then, $\beta_3$ equals the effect $\Phi_X$ of treatment received. This interpretability of $\beta_2$ under the assumption of no direct effects derives from the fact that the expectation in (5) is linear in $\delta_X R$ on an untransformed scale, and so depends on the use of the identity link for the observed regression (2). Note that treatment effects on the untransformed scale are identified without knowing the degree of selection bias $\sigma_{X,R,A}$. We note that (5) can be rearranged to give the usual Wald version of the instrumental variables formula (Angrist et al., 1996); i.e.

$$\beta_3 = \Phi_X = (E(Y|X, R = 1) - E(Y|X, R = 0))/\delta_X.$$

3.1.2 All-or-non compliance, identity link, multiple strata. When, as in the last section, one does not account for covariates, the observed regression (2) can be used to identify the effect of treatment received only under the assumption that randomization has no direct effect (1). We might think to use the distribution of outcomes in different strata defined by baseline covariates $X$ to disentangle the direct and indirect effects of randomization. When compliance is associated with covariates $X$, the variation in compliance with $X$ can be used to disentangle these effects, but other assumptions must be substituted for (1). Suppose that the direct effect of randomization on treatment received is the same for all $X$ and $A$, so that we can substitute a common $\Delta$ for $\Delta_{X,1,a}$ and a common $\Phi$ for $\Phi_X$. These assumptions state, for example, that both the direct effect of randomization and the effect of treatment received are the same for men and women. The plausibility of these strong assumptions should be assessed in practical applications. Under these assumptions, (4) becomes

$$E(Y|X, R) = \mu_{X,0,0} + R\Delta + R\delta_X\Phi. \tag{6}$$
When (6) holds on the basis of the above assumptions, we can provide causal interpretation to the coefficients in the observed regression (2) using the identity link \(g(y) = y\). If the model \(\mu_{X,0,0}\) for the mean response in the control group is correctly specified (e.g. as \(\beta_0 + \delta_X\beta_1\), as in (2)), the coefficient \(\beta_2\) is the direct effect \(\Delta\) of randomization on response, and the coefficient \(\beta_3\) is the effect \(\Phi\) of treatment received. If the direct effects \(\Delta_{X,1,a}\) are different among subjects who do and do not receive their assigned treatment, the coefficient \(\beta_3\) does not equal the effect of treatment received \(\Phi_X\); the assumption of equal effects \(\Delta_{X,1,a}\) is not testable in these data. Even if \(\beta_3\) is not the effect of treatment received, \(\bar{\beta}_2\) and \(\beta_2 + \beta_3\) are the intent-to-treat effects (i.e. the overall effect of randomization, both direct and mediated through treatment received) among noncompliers \((\mu_{X,1,0} - \mu_{X,1,0})\) and compliers \((\mu_{X,1,1} - \mu_{X,1,1})\), respectively.

A heuristic view (Follmann, 2000) would look at extrapolating the expected outcomes \(E[Y|X, \delta_X, R]\) to a group in which everyone is a complier: i.e. to look at \(E[Y|X, \delta_X = 1, R]\). The difference between treatment and control in this group is then the overall effect of treatment \(\beta_2 + \beta_3\). This extrapolation is, in principle, of little interest if there are no groups of subjects identifiable by pretreatment characteristics with nearly perfect compliance, because we are extrapolating to groups which do not exist. Note that, from (4), the difference between treatment and control groups in expected outcomes is

\[
E(Y|X, \delta_X, R = 1) - E(Y|X, \delta_X, R = 0) = \Delta + \delta_X\Phi.
\]

Thus, \(\Phi\) may be recovered from by taking the difference between the treated and control groups in slopes in the regression of \(Y\) on \(\delta_X\), even when those regressions are not linear; there is no need to extrapolate the expected outcomes beyond the range of the compliance scores \(\delta_X\). Under the assumption that randomization has no direct effect, we can restrict \(\beta_2\) to equal 0; this is a model with common intercepts in the treatment and control arms.

Alternatively, one can examine the fit of models (2) for the observed data. Departures from the model for the observed data can indicate departures from causal assumptions (e.g. that the effect \(\Phi_X\) of treatment received and the direct effect \(\Delta_{X,1,a}\) of randomization are the same across strata).

3.1.3 Nonlinear links, all-or-none compliance. With other links \(g(x) \neq x\), interpretation of coefficients \(\beta\) in the regression model is more complicated; we illustrate this for the logit link, where the model for the observed data (2) is

\[
\logit(E(Y|X, \delta_X, R)) = \beta_0 + \delta_X\beta_1 + R\beta_2 + R\delta_X\beta_3.
\]

In our illustrations, treatment has no direct effect (1), compliance is all-or-none, people in the control group have no access to the study treatment, and there is no selection bias (i.e. \(\sigma_{X,R,A} = 0\)). Let \(\Psi_X \equiv (\mu_{X,1,1}/(1-\mu_{X,1,1}))/((\mu_{X,1,1}/(1-\mu_{X,1,1}))\) be the effect of treatment on the odds ratio scale for compliers with covariates \(X\).

Figure 1 illustrates regressions on the logit scale using the compliance score in two settings. In both settings, the control group risk is derived from the linear logistic regression \(\logit(E(Y|\delta_X, R)) = \beta_0 + \delta_X\beta_1\). The treatment group risk at a given compliance score is derived from the control group risk, the assumed treatment effect \(\Psi_X = \exp(\beta_3)\), the assumptions stated in the previous paragraph, and (5). In the first setting, depicted in the left-hand panels, the compliance score is unassociated with risk in the control group, \(\mu_{X,0,0}\), which is also the prognosis if unexposed for people in the treatment group \(\mu_{X,R=1,1}\). In the second setting, depicted in the right-hand panels, the compliance score is positively and linearly associated with the logit of risk if unexposed, \(\mu_{X,0,0}\). The upper panels plot the observed risk \(E(Y|R, X)\) in each treatment arm as a function of the compliance score \(\delta_X\). Even though the plots of the logit of the control risk (‘control group’ line in the upper panels) are linear in \(\delta_X\), the logit of the treatment risk (‘treatment group’ lines) is not.
Fig. 1.

The lower panels show the regression difference $\text{logit}(E(Y|X, R = 1)) - \text{logit}(E(Y|X, R = 0))$ as a function of the compliance score. In both lower panels, the true regression difference is not linear in $\delta_X$. This is most easily explained for the left-hand panels, where the control group risk does not vary with compliance score, and so the risk difference $E(Y|X, R = 1) - E(Y|X, R = 0)$ and the treated group risk $E(Y|X, R = 1)$ are linear in $\delta_X$. Transformation of the linear treated-group risk function to the logit scale results in a nonlinear regression function $\text{logit}(E(Y|X, R = 1))$ and a nonlinear regression difference.

If the range of compliance scores is restricted, these regressions may appear linear. Suppose that there are only two values of $\delta_X$, 0.5 and 0.7; a regression approximation (‘treatment group-regression approximation’ in the top panels) is obtained by connecting the values of $g(E(Y|X, R = 1))$ for the two values of $\delta_X$. Nonetheless, there may appear to be a main effects term $\beta_2$ for randomization even though there is no direct effect, especially if there are no strata with compliance scores close to 0. Further, the slope $\beta_3$ of the regression difference (‘regression approximation’ slopes in the lower panel of Figure 1) will not generally equal the log odds ratio $\ln(\Psi_X)$ (‘true’ in the lower panel of Figure 1 at $\delta_X = 1$), whether or not the main effect of randomization $\beta_2$ is restricted to equal 0.

In both examples, we also considered a model with a common intercept, which might be thought to represent the effect of treatment received under an assumption of no direct effects. The slope of the regression difference is again an overestimate of the common causal log odds ratio $\ln(\Psi_X)$. 
3.2 Multiple treatment levels, identity link

For treatments $A$ with many levels, the situation is more complicated; because of difficulties with nonlinear links $g(\cdot)$, we restrict attention to the identity link. It is less relevant to concentrate solely on the effect of treatment on the compliers, since there are degrees of compliance and perhaps few if any subjects will comply perfectly. We concentrate on the effect of treatment received and will consider models relating dose of treatment to outcome. Let $\Phi_{X,R,A} = \mu_{X,R,A} - \mu_{X,R,A}^0$ be the mean effect of treatment received $A$ on the outcome in the subgroup defined by the subscripted variables; we again assume that randomization has no direct effect. We no longer assume that access to active treatment is limited to subjects randomized to active treatment, but suppose that the effect of treatment received is linear in $A$, so that $\Phi_{X,R,A} = \eta_X A$.

Under these assumptions, it can be shown that

$$E(Y|X, R) = \mu_{X,0} + \delta_X R \eta_X,$$

(9)

where $\mu_{X,0} \equiv E(Y|X, R = 0)$. Again, if the proportional effect $\eta_X$ of treatment received is the same for all $X$, and $A = 1$ indicates full compliance, $\beta_3$ in the observed regression will equal the effect of treatment in the fully compliant, and a regression of outcome on observable variables (the left-hand side of (9)) can be used to learn about treatment effects defined through the potential outcomes approach (the right-hand side of (9)). As with (5), (9) can be rearranged to give the usual instrumental variables estimator

$$\hat{\beta}_3 = \hat{\eta}_X = (E(Y|X, R = 1) - E(Y|X, R = 0))/\delta_X$$

for stratum $X$.

4. Applications

4.1 Cholestyramine and cholesterol

We use data from two studies to illustrate the use of the compliance score. To illustrate continuous outcomes, we use data from the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), a randomized placebo-controlled double-blind trial of cholestyramine (CLT), a drug used to lower cholesterol levels and, thereby, the risk of coronary events and death (Lipid Research Clinic Program, 1984a, 1984b). Efron and Feldman (1991) used a subset of this study to examine the effect of compliance; we apply different methods towards the same end.

In the LRC-CPPT, serum cholesterol was measured at several pre-randomization and at bimonthly post-randomization clinic visits for the duration of follow-up, which averaged 7.4 years. These clinic visits were also used to dispense packets of their assigned medication; patients returned unused packets at each clinic visit. The proportion of packets used is a measure of compliance.

As above, our endpoint is the serum cholesterol at the end of a fixed follow-up period, here one year (400 days). We use as a scalar measure of the treatment received over the year $A$ the proportion of the total potential number of packets (number of days $\times$ 6 packets/day) used; for subjects who were prescribed reduced doses because they could not tolerate the drug, this variable is not identical to percentage compliance, such as used by Efron and Feldman (1991). Our model implicitly assumes that the actual dose taken, not the relation of the dose taken to the prescribed dose, determines treatment response. This would be reasonable if reasons for dose reduction are unrelated to the effect of CLT on serum cholesterol.

The distribution of compliance in the LRC-CPPT is skewed (Figure 2) and (essentially) has an upper limit of 1. To model the data, we divided compliance into several ordered categories $j, j = 0, \ldots, J$. We used the continuation ratio model (Greenland, 1994) (instead of the more commonly used ordinal logit or proportional odds model (McCullagh et al., 1989), which we had trouble fitting to these data) to model compliance with CLT (divided into several ordered categories) and so derive the compliance score $\delta_X$. We derived the compliance score from the fitted probabilities $\hat{\pi}_j$ of falling in each category, and estimated $\delta_X$ as $\sum_j \hat{\pi}_j \tau_j$, where $\tau_j$ is the midpoint of the compliance values in each category; thus, for the lowest
We modeled compliance $A$ in this way in the treatment arm as a function of pretreatment covariates $X$, which included age, race, sex, and center (Table 1); center was the most potent predictor of compliance.

We next relate compliance scores to outcome. The top panel of Figure 3 plots the mean log cholesterol against categorized compliance scores. Higher compliance scores are associated with lower cholesterol levels, especially in the active treatment group.

We next fit regression models to the uncategorized data; Table 2 presents coefficients from regression models for log cholesterol, using the compliance score as a regressor; some included a main effects term $\beta_2$ for treatment group $R$, and some restricted $\beta_2$ to 0. Figure 3 plots the corresponding linear regression lines. There is not much indication of departure from the assumption that randomization has no direct
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Table 1. Continuation ratio model regression coefficients for compliance outcome in treatment arm

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Point estimate</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline log HDL cholesterol</td>
<td>-1.05</td>
<td>0.37</td>
</tr>
<tr>
<td>Standard deviation baseline log cholesterol</td>
<td>-4.90</td>
<td>2.54</td>
</tr>
<tr>
<td>Baseline age</td>
<td>-0.010</td>
<td>0.005</td>
</tr>
<tr>
<td>Clinic (vs clinic 12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.33</td>
<td>0.15</td>
</tr>
<tr>
<td>2</td>
<td>0.56</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>-0.69</td>
<td>0.16</td>
</tr>
<tr>
<td>4</td>
<td>-0.31</td>
<td>0.14</td>
</tr>
<tr>
<td>5</td>
<td>0.03</td>
<td>0.15</td>
</tr>
<tr>
<td>6</td>
<td>-0.11</td>
<td>0.15</td>
</tr>
<tr>
<td>7</td>
<td>-0.09</td>
<td>0.14</td>
</tr>
<tr>
<td>8</td>
<td>0.21</td>
<td>0.15</td>
</tr>
<tr>
<td>9</td>
<td>-0.20</td>
<td>0.14</td>
</tr>
<tr>
<td>10</td>
<td>0.39</td>
<td>0.14</td>
</tr>
<tr>
<td>11</td>
<td>0.03</td>
<td>0.15</td>
</tr>
</tbody>
</table>

The model coefficients are for the model logit\(\{pA^* < j \mid X, A^* \leq j\} = \alpha_j + X\beta\), where \(A^*\), the categorized compliance variable, has the following categories: 0: \(A \in [0, 0.2)\); 1: \(A \in [0.2, 0.4)\); 2: \(A \in [0.4, 0.6)\); 3: \(A \in [0.6, 0.8)\); 4: \(A \in [0.8, 0.9)\); 5: \(A \in [0.9, 0.95)\); 6: \(A \in [0.95, 1.0]\). The cholesterol predictors refer to the average or standard deviation of the predictors over the five initial visits to the study, before randomization. The likelihood ratio chi-squared statistic for clinic as a predictor was 104.5 with 11 degrees of freedom.

effect on cholesterol (1). Under (1), we estimate that the effect of full compliance on log cholesterol is to reduce it by about 0.08 units; this corresponds to a decrease of about 17% in cholesterol. As in the derivation of (9), this interpretation depends on the assumption that the effect of treatment does not vary with age, race, sex, and center. The results are similar to results from G-estimation for the same data (Joffe and Brensinger, 2001). The intent-to-treat effect is a decline of 0.057 units; as-treated analyses yield a larger association, about 0.088 units.

The bottom panel of Figure 3 plots the difference in log cholesterol between treatment and placebo groups as a function of the compliance score. Under (1), the extrapolation of the second line (i.e. common intercept model) to a compliance score \(\hat{\delta}_X\) of 1 estimates the effect of CLT on outcome. One can also estimate CLT’s efficacy by extrapolating estimates of the cholesterol difference in the different compliance-score strata to \(\hat{\delta}_X = 1\); Figure 3 also plots these estimates of efficacy. Despite visual appearances, there is insufficient evidence to conclude that there is a downward trend in these efficacy estimates.

Because in this and any application the compliance scores are estimated, variance estimates for the effect of treatment received may be incorrect. To deal with this, we used a nonparametric bootstrap (Efron and Tibshirani, 1993), in which we sampled subjects with replacement from the cohort and used the bootstrap samples to recalculate the compliance score before regressing the outcome on the compliance score and other regressors. Table 2 provides bootstrap standard errors as well as the nominal standard errors obtained from the regression program.
An educational intervention and cholesterol change

The second example data come from a study of an audio tape-based educational program to modify diet and thereby cholesterol levels. This study comprised 266 African American adults, aged 40 to 70, with high cholesterol and/or hypertension. Subjects were randomized to one of two arms. Both arms received the same conventional printed nutritional materials for a general population of adults; subjects in the experimental arm also received home-based audio tapes tailored to African Americans. Non-compliance in the randomized-to-treatment group entailed non-use of the home-based audio equipment so that those in the treatment arm were exposed to only the conventional print materials as those in the usual care group were. Thus, treatment received \((A)\) is binary. One of the primary outcomes in the study and which is of interest in this paper is positive (i.e. beneficial) change in cholesterol according to established criteria determined by NIH-sponsored panels (National Cholesterol Education Program (NCEP), 1993); the outcome \(Y\) as used in the study was binary (improvement in cholesterol).
Table 2. Regression models for log cholesterol

<table>
<thead>
<tr>
<th></th>
<th>Point estimate</th>
<th>Standard error</th>
<th>Point estimate</th>
<th>Standard error</th>
<th>Point estimate</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nominal</td>
<td>Bootstrap</td>
<td>Nominal</td>
<td>Bootstrap</td>
<td>Nominal</td>
<td>Bootstrap</td>
</tr>
<tr>
<td>Intercept</td>
<td>2.45435</td>
<td>0.01192</td>
<td>0.01479</td>
<td>2.44321</td>
<td>0.01695</td>
<td>0.01493</td>
</tr>
<tr>
<td>Compliance score * randomization assignment ($\delta^*_X R$)</td>
<td>-0.07951</td>
<td>0.00306</td>
<td>0.00291</td>
<td>-0.10953</td>
<td>0.03263</td>
<td>0.03280</td>
</tr>
<tr>
<td>Compliance score ($\delta_X$)</td>
<td>-0.02310</td>
<td>0.01638</td>
<td>0.02020</td>
<td>-0.00793</td>
<td>0.02320</td>
<td>0.02038</td>
</tr>
<tr>
<td>Randomization assignment ($R$)</td>
<td>0.02203</td>
<td>0.02384</td>
<td>0.02395</td>
<td>0.02203</td>
<td>0.02384</td>
<td>0.02395</td>
</tr>
<tr>
<td>Baseline log cholesterol ($X$)</td>
<td>0.94317</td>
<td>0.02301</td>
<td>0.02239</td>
<td>0.94317</td>
<td>0.02301</td>
<td>0.02239</td>
</tr>
</tbody>
</table>

Bootstrap standard errors were based on 1000 bootstrap samples.
We fit the regression models (2) to the data using both the identity and logit links. Most (78.36%) subjects in the intervention group adhered. The compliance score \( \delta_X \) scarcely varied with covariates \( X \). Thus, the coefficient for the compliance score (\( \beta_1 \)) is highly collinear with the intercept (\( \beta_0 \)), and the coefficient for the compliance score-randomization interaction (\( \beta_3 \)) is collinear with the randomization main effect (\( \beta_2 \)), and so we set \( \beta_1 = \beta_2 = 0 \), and take \( \delta_X = 0.7836 \) for all subjects. One-quarter of subjects randomized to control improved, while a higher proportion in the active treatment group (0.366) did so.

Under the linear model, the effect of treatment received (\( \beta_3 \)) on a risk difference scale is 0.148\( = (0.366 - 0.25)/0.7836 \). Translating this into the odds ratio for compliers \( \Psi_X \) requires knowledge of the selection bias \( \sigma_{X,1,1} \), which is not identified only from regression (2). In cases such as this study, where controls have no access to the active treatment, under the assumption that randomization has no direct effects, we have \( \sigma_{X,1,1} = -\sigma_{X,1,0}(1 - \delta_X)/\delta_X \), which is identified from the data as \(- (0.3103 - 0.2500) * (1 - 0.7836)/0.7836 = -0.017 \). The expected outcome in compliers in the treatment group is \( \mu_{X,1,1} = \mu_{X,0,0} + \Phi_X + \sigma_{X,1,1} = 0.25 + 0.148 - 0.017 = 0.381; \) to obtain the expected outcome in compliers had they not complied, we subtract the effect of treatment \( \Psi_X \) to obtain \( \mu_{X,1,1} = \mu_{X,0,0} + \sigma_{X,1,1} = 0.381 - 0.148 = 0.233 \). Thus, the causal odds ratio \( \Psi_X \) for compliers is \( 0.381/(1 - 0.381)/(0.233/(1 - 0.233)) = 2.02 \). On the logit scale, we obtain a coefficient \( \beta_3 \) for the randomization-compliance score interaction of 2.01. The closeness of the compliance-score regression estimator of the odds ratio to the better justified estimate may be explained by the high proportion of compliers, requiring linear extrapolation only from \( \delta_X = 0.78 \) to 1.0, and by the relatively small treatment effect; under these conditions, the two estimates tend to differ little.

5. DISCUSSION

Methods using the compliance score as a regressor are closely related to other methods of analysis, in particular methods (Angrist et al., 1996; Baker, 1998; Permutt and Hebel, 1989; Robins et al., 1992; Robins et al., 2000) familiar to econometricians as instrumental variables methods. Some of these methods (e.g. two-stage least squares) have been automated in commercial statistical software. Explicit consideration of the compliance score has two advantages for data analysis. First, it forces the analyst to consider explicitly the models for treatment received \( A \), rather than using the default linear least squares approach. One can use nonlinear models, as we have in our example, and take the requisite care in examining such issues as interpretation of these models and goodness of fit. Second, using an explicitly calculated variable \( \delta_X \) enables application of familiar regression methods and readily available plots and diagnostics.

As we have seen, the causal interpretation of models using the compliance score with nonidentity links can be problematic; these problems result from the familiar finding that the expectation of a nonlinear function is not the nonlinear function of the expectation. Similar issues exist with proportional hazards models, for which these methods have been suggested (Follmann, 2000). Estimating the effect of treatment received in the presence of noncompliance in this setting may require using less familiar methods not easily implemented using standard statistical software (Robins, 1994; Ten Have and Joffe, 2001).

The compliance score has other possible uses in randomized trials with noncompliance. Joffe and Brensinger (2001) show that it can be used as a weight to improve efficiency in G-estimation. Further, the compliance score is closely related to the propensity score (Follmann, 2000). In trials in which the control group cannot obtain the active treatment, the compliance score of subjects in the treatment group is these subjects’ propensity score. As such, standard methods for adjustment using the propensity score may be used (Joffe and Rosenbaum, 1999; Robins et al., 1992; Rosenbaum and Rubin, 1983). The validity of such adjustments relies on assumptions about the ignorability of noncompliance in the treatment group (Rosenbaum et al., 1983), or, equivalently, of the comparability of subjects with the same compliance scores but different levels of compliance (Greenland et al., 1986). Such analyses are essentially ‘as treated’
analyses, which make no use of the fact of randomization and are widely and justly distrusted (Lee et al., 1991). The methods proposed here avoid these problems.

**APPENDIX. DERIVATION OF (4)**

Let \( \sigma_{X,R,A} \equiv \mu_{X,R,A} - \mu_{X,0,0} \) indicate the difference in prognosis between people in group \( R, A \) and the control group (here not having access to the study treatment); \( \sigma_{X,R,A} \) is a measure of selection bias. Because of randomization, we have \( \mu_{X,1,0} = \mu_{X,0,0} \delta_X \mu_{X,0,0} = \mu_{X,0,0}(1 - \delta_X) + \mu_{X,0,0} \delta_X \); this in turn implies \( \delta_X \sigma_{X,1,1} = -(1 - \delta_X)\sigma_{X,0,0} \).

We then have

\[
\]

\[
= R[\delta_X\mu_{X,1,1} + (1 - \delta_X)\mu_{X,1,0}] + (1 - R)\mu_{X,0,0} = \mu_{X,0,0} + R(\mu_{X,1,0} - \mu_{X,0,0})
\]

\[
+ \delta_X R(\mu_{X,1,1} - \mu_{X,1,0})
\]

\[
= \mu_{X,0,0} + R(\delta_X R\Delta_{X,1,1} - \delta_X R\Delta_{X,1,0} + \delta_X R\Phi_X + R(1 - \delta_X)\sigma_{X,1,0} + \delta_X R\sigma_{X,1,1}
\]

\[
= \mu_{X,0,0} + R\Delta_{X,1,0} + \delta_X R(\Delta_{X,1,1} - \Delta_{X,1,0}) + \delta_X R\Phi_X.
\]

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**REFERENCES**


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