Technical Appendix: Methods and results for complier average causal effect analysis

Supplement to: The specific effect of systematic exposure in irritable bowel syndrome: Complier average causal effect analysis using growth mixture modeling

Hugo Hesser, Erik Hedman, Perjohan Lindfors, Erik Andersson, and Brjánn Ljótsson

Ad hoc methods for the analysis of randomized trials with non-compliance, such per-protocol and as-treated analyses, break randomization and may hence result in bias (Little & Yau 1998; Jo 2002b). Recent advances in statistics have, however, made it possible to obtain unbiased causal estimates in randomized trials where not all individuals comply or receive treatment, commonly known as complier average causal effect (CACE) estimation (Angrist *et al.* 1996). The present appendix describes in detail the CACE analysis used to determine the effect of systematic exposure in irritable bowel syndrome (IBS) as evaluated in a previously published randomized component trial of an internet-delivered cognitive behavioral treatment (ICBT) for IBS (Ljótsson *et al.* 2014). In this study, 309 patients with IBS were randomized to the treatment protocol or to the same protocol without systematic exposure (but including psychoeducation, mindfulness training, and instructions to reduce avoidant and symptom control behaviors). All aspects were held equal with the only exception that patients randomized to the full protocol were also instructed to perform exposure exercises.

Brief background to CACE estimation

The basic idea of CACE estimation is to identify compliance status among control group participants and to compare outcomes between conditions as is normally done in ITT analysis. That is, CACE analysis aims to compare outcomes for individuals in the

intervention who complied with the treatment with individuals in the control group who *would* have complied with the treatment had they been offered the treatment (i.e., "potential" compliers). CACE is defined as

$$CACE = \mu 1c - \mu 0c,$$

where $\mu 1c$ is the population mean potential outcome for compliers when assigned to the treatment condition and $\mu 0c$ when assigned to the control condition. Using an instrument variable approach, Angrist *et al.* (1996) identified three different kinds of non-compliers in the case of binary compliance status: *Never-takers* (individuals who will never take the treatment regardless of assignment), *Always-takers* (individuals who will always take the treatment regardless of assignment) and *Defiers* (individuals who will do the opposite of what they are assigned to do). In a randomized trial that carefully restricts treatment access, the number of non-compliance classes can be reduced to one: Never-takers (Jo 2002b). In this context, Never-takers are those who would not receive the exposure intervention even if they were assigned to the experimental condition. In contrast, compliers are those who would receive the exposure intervention, but only if they were assigned to the experimental condition. In our trial, participants in the control (i.e., treatment without exposure) had no access to the treatment module (i.e., self-help text) that contained information about systematic exposure and we had high degree of control over which patients received the intervention in the experimental condition and when. This simplifies the identification of CACE, although some challenges remain.

One of the key challenges in CACE estimation is that the outcome for potential compliers in the control condition cannot be directly estimated from the sample statistics because only the overall mean for both compliers and non-compliers is observed (Jo 2002b). Similarly, compliance rate is only observed among those who were randomly allocated to the intervention, whereas this proportion is not known in the

control because patients did not receive the intervention. Hence, the key challenge in CACE estimation can be thought of as a missing data problem (Little & Yau 1998; Jo & Muthén 2001), where compliance rate and outcomes are observed in the intervention condition, but missing in the control. Angrist *et al.* (1996) addressed the assumptions that allow CACE to be identified and estimated. In addition to the requirements assumed in standard ITT analysis for causal inference in the potential outcomes framework – for example, random assignment, stable unit treatment value assumption (Holland 1986; Rubin 2004) – the so-called exclusion restriction assumption plays a critical role for identifying CACE (Jo 2002a). In our trial, this assumption holds if there is no effect of treatment assignment for Never-takers. In other words, effects of assignment to experimental (full-treatment protocol) and control condition (treatment protocol without exposure) on IBS symptoms are allowed for compliers, but disallowed for non-compliers. In the presence of auxiliary information (e.g., covariates), the assumption can be relaxed and violations to the exclusion restriction assumption can be tested (Jo 2002a).

Growth model used in both intention-to-treat (ITT) analysis and CACE analysis

To be able to compare results from CACE analysis with those obtained from standard ITT analysis, we used the same overall growth model in both models. The change in IBS symptoms was modeled in 309 individuals who had been randomly allocated to either the full treatment protocol (experimental condition) or the same protocol without systematic exposure (control condition). Dependent variables were the Gastrointestinal Symptom Rating Scale – IBS version (GSRS-IBS) at baseline (an average score for four measurements taken prior to randomization), ten weekly follow-up assessments over the active treatment phase, and at post-treatment assessment (an average score for four

measurements taken following the treatment period). We fitted a piecewise growth model in the structural equation model framework (Bollen & Curran 2006) to capture change and treatment effects in qualitatively distinct phases of the trial, before and after experimental manipulation,

$$Y_{ti} = \beta_0 + \beta_1(TIME1_{ti}) + \beta_2(TIME2_{ti}) + \beta_3(TX_i)(TIME2_{ti}) + b_{0i} + b_{1i}(TIME1_{ti}) + b_{2i}(TIME2_{ti}) + \varepsilon_{ti}$$

where β_0, β_1, β_2, and β_3 are fixed effects; b_{0i}, b_{1i}, and b_{2i} are random effects; and ε_{ti} is a time-specific residual. The decision to model nonlinear change with two linear slopes was based on the design of the study, i.e., both experimental and control conditions were identical up to study week 4. Thus, the first piece (β_1) captured the change in GSRS-IBS symptoms from pre-assessment to study week 4, and the second piece captured the change from study week 4 to post-assessment (β_2). Time scores were coded to reflect that first intercept represented the first measurement point (pre-assessment). Treatment condition (*TX*) was included as a binary variable (0.5 = experimental condition, -0.5 = control) in the model. The intercept and the slope in pieces 1 and 2 were regressed on patient characteristics measured at baseline (not shown in the equation above). Based on the study design, the effect of treatment on intercept and slope in piece 1 were constrained to zero (similar to the CACE analysis). A mean difference (with associated standard error) between conditions was estimated at post-treatment based on the slope difference in the second phase in which exposure was implemented in the experimental condition (i.e., β_3 multiplied by the time factor loading, 0.9, at post-assessment). A standardized mean difference effect size (*d*) was computed as the difference in model-implied means at post-treatment divided by the standard deviation pooled across the conditions at pre-treatment assessment (Feingold 2009).

CACE estimation using growth mixture modeling

CACE estimation was based on latent trajectories over time in a growth mixture modeling framework (Jo & Muthén 2003). In this framework, continuous latent variables are used to capture growth (and heterogeneity in growth) over time and a categorical latent variable is used to capture compliance status. Compliance status information is observed in the intervention group and latent (missing) in the control group. Thus, latent class membership (compliance status) is based on both known membership in the intervention and auxiliary information from covariates and growth trajectories included in the model. This modeling strategy allowed us to examine the effect of treatment assignment on the slope among different subgroups (e.g., compliers, non-compliers). To incorporate trajectory information with growth modeling, the precision of CACE can be improved and statistical power to detect intervention effects can be increased (Jo & Muthén 2001, 2003). All analyses were carried out in Mplus vs. 7.4 (Muthén & Muthén 2015) using full information maximum likelihood and EM algorithm to handle missing data under ignorable missing data assumption (i.e., MAR) (Little & Yau 1998; Jo 2002b; Jo & Muthén 2003).

Compliance status was treated as a categorical latent variable with observed values for the intervention group and missing for the control group (using the TRAINING option in Mplus) with two levels: Compliers and Never-takers (non-compliers). The effect of treatment assignment on the slope in piece two (change that had occurred following manipulation, after study week 4) was freely estimated in the compliers class, but were fixed at zero in the Never-takers class (as per the exclusion restriction assumption). Based on randomization and the design of the study, the slope of the first piece and the intercept (pre-treatment assessment) was fixed at zero in both classes. As in the conventional growth model (i.e., ITT analysis), intercept and slope in

pieces 1 and 2 were regressed on a set of covariates (i.e., patient characteristics measured at baseline). The effects of covariates were allowed to vary across classes (i.e., compliance status) as were means, variances and covariances of random effects. **Supplementary Figure S1** depicts the CACE model. To examine the impact of violations on the exclusion restriction assumption we also reran the growth mixture CACE model assuming an additive effect of treatment assignment; a model which is identified with auxiliary information such as covariates (Jo 2002a). In this model, the effect of treatment assignment on slope in piece 2 was allowed for both compliers and non-compliers.

Results

Descriptions of the fitted models are presented in **Supplementary Table S1**. The piecewise growth model (Model 1.1) fitted the data adequately according to commonly used model fit measures used in structural equation modeling (Bollen & Curran 2006): Chi-square (df = 141) = 305.10, $p<.001$, Comparative Fit Index (CFI) = .94, Tucker-Lewis Index (TLI) = .93, and root mean square error of approximation (RMSEA) = .061, 90% CI [.052, .071]. Constraining the effect of treatment assignment on the intercept and slope in the first piece to zero (model 1.2) did not worsen model fit, chi-2 (df = 2) = 0.87, p = .65. The estimated mean difference at endpoint of -4.15 (SE = 1.04) and corresponding standardized effect size of d = 0.43 were similar to the estimates obtained in the model in which the effects of treatment on intercept and slope in piece 1 were free parameters (-4.24 and d = 0.44, respectively; model 1.1; results presented in the main text).

Sensitivity analysis: relaxing the exclusion restriction assumption

An alternative growth mixture model was run as a sensitivity analysis to explore violations of the exclusion restriction assumption (i.e., no direct effect of treatment

assignment) in estimating CACE (model 2.2). Relaxing the exclusion restriction assumption revealed a small, non-significant negative treatment effect among non-compliers on the slope in piece 2 (estimate = -0.72, SE = 3.32, p = .83). The difference at endpoint was -0.66 (SE = 2.99), which corresponded to a trivial effect size of d = .07. The effect of treatment assignment on the slope in piece 2 remained statistically significant among compliers (estimate = -8.20, SE = 3.20, p = .01). The estimated mean difference at post-treatment was -7.38 (SE = 2.88), which corresponded to a standardized effect size of d = 0.77. Although the magnitude of the CACE effect was slightly lower than the one observed in the model assuming the exclusion restriction assumption, these findings suggested that potential violations to the exclusion restriction assumption did not bias the estimate in any substantial way (model 2.1; results presented in the main text).

References

Angrist JD, Imbens GW, & Rubin DB (1996). Identification of causal effects using instrumental variables. *Journal of the American Statistical Association* **91**, 444–455.

Bollen KA, & Curran PJ (2006). *Latent Curve Models: A Structural Equation Perspective*. Wiley: Hoboken, NJ.

Feingold A (2009). Effect sizes for growth-modeling analysis for controlled clinical trials in the same metric as for classical analysis. *Psychological Methods* **14**, 43–53.

Holland PW (1986). Statistics and causal inference. *Journal of the American Statistical Association* **81**, 945–960.

Jo B (2002a). Estimation of intervention effects with noncompliance: Alternative model specifications. *Journal of Educational and Behavioral Statistics* **27**, 385–409.

Jo B (2002b). Statistical power in randomized intervention studies with noncompliance. *Psychological Methods* **7**, 178–193.

Jo B, & Muthén BO (2001). Modeling of intervention effects with noncompliance: A latent variable approach for randomized trials. In *New Developments and Techniques in Structural Equation Modeling* Eds. GA Marcoulides & RE Schumacker, pp57–87. Lawrence Erlbaum Associates, Inc., Publishers: Mahwah, New Jersey.

Jo B, & Muthén BO (2003). Longitudinal studies with intervention and noncompliance: Estimation of causal effects in growth mixture modeling. In *Multilevel Modeling: Methodological Advances, Issues, and Applications.* Eds. SP Reise & N Duan, pp112–139. Lawrence Erlbaum Associates, Inc., Publishers: Mahwah, New Jersey.

Little RJ, & Yau LHY (1998). Statistical techniques for analyzing data from prevention trials: Treatment of no-shows using Rubin's causal model. *Psychological Methods* **3**, 147–159.

Ljótsson B, Hesser H, Andersson E, Lackner JM, El Alaoui S, Falk L, Aspvall K, Fransson J, Hammarlund K, Lofstrom A, Nowinski S, Lindfors P, & Hedman E (2014). Provoking symptoms to relieve symptoms: a randomized controlled dismantling study of exposure therapy in irritable bowel syndrome. *Behaviour Research and Therapy* **55**, 27–39.

Muthén L, & Muthén B (2015). *Mplus user's guide*. Seventh ed. Muthen & Muthen: Los Angeles, CA.

Rubin DB (2004). Teaching statistical inference for causal effects in experiments and observational studies. *Journal of Educational and Behavioral Statistics* **29**, 343–367.

Supplementary Table S1: Description of fitted models.

Model nr.	Description
1.1	ITT analysis: Piecewise growth model with random intercept (initial status) and random slope in pieces 1 and 2 regressed on a set of covariates and the treatment variable.
1.2	ITT analysis: Same as model 1.1, but the effect of treatment on initial status and slope 1 constrained to zero due to study design.
2.1	CACE analysis: Piecewise growth mixture model with covariates. Same growth model as 1.2, but also including a categorical latent variable representing compliance class. Effect of treatment on random slope in piece 2 are disallowed for subsample of non-compliers (as per the exclusion restriction assumption), but allowed for compliers. Growth factor means, variances and covariances were allowed to vary across classes.[1]
2.2	CACE analysis: The same model as 2.1, but effect of treatment on random slope in piece 2 is also allowed for the subsample of non-compliers.[1]

Note. [1] = small, nonsignificant negative residual variance constrained to zero at first measument point.

Supplementary Figure S1: Complier Average Effect model with covariates and weekly outcomes for IBS symptoms (GSRS-IBS).

Slope 1 = slope change between pre-assessment and study week 4 (gsrsw3); Slope 2 = slope change between week 5 (gsrsw4) and post-assessment. C = compliance class; Icept = intercept; Cov = a set of covariates; Tx = treatment variable.