# Multiply robust estimation of causal effects with noncompliance and time-to-event outcomes

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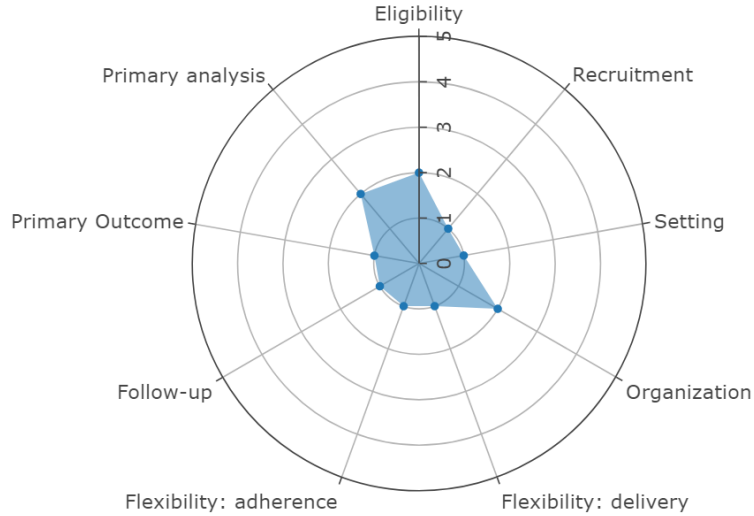
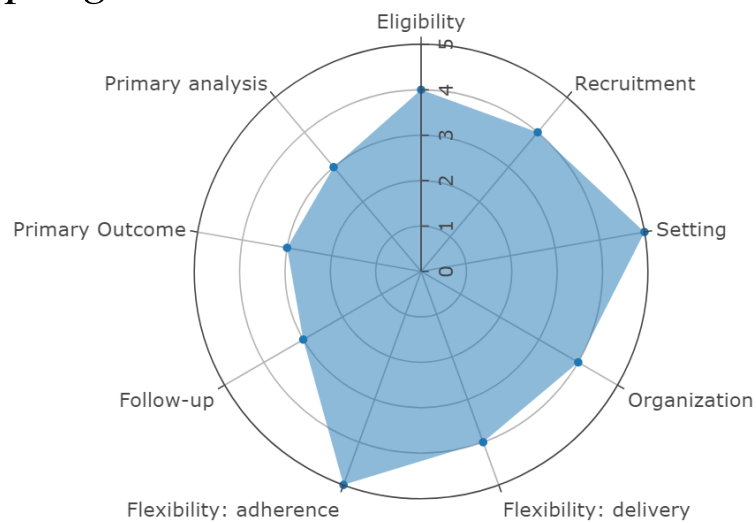
# Background: pragmatic trials

- Pragmatic trials often compare interventions or alternative delivery approaches to evaluate impact on outcomes under routine practice conditions
- Challenges arise as we move toward pragmatism
  - PRECIS-II
  - treatment effect estimands as increasingly important concept[1]
- Many pragmatic trials report null intention-to-treat (ITT) effect
- Provide an example to go beyond ITT estimand in a recent pragmatic trial with survival outcome

(a) *traditional RCT*



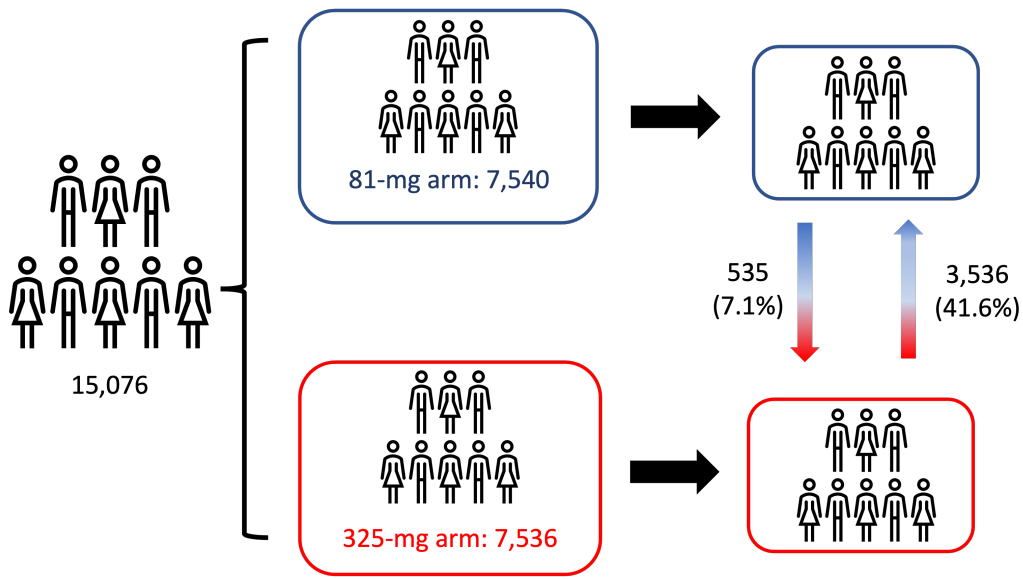

(b) *pragmatic trial*




[1]Kahan, B. C., Cro, S., Li, F., & Harhay, M. O. (2023). Eliminating ambiguous treatment effects using estimands. American Journal of Epidemiology, kwad036.

# An example: ADAPTABLE pragmatic trial

- ADAPTABLE (*Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness*) is a pragmatic trial to study the effectivenss of two aspirin dosing strategies for patients with established cardiovascular diseases[2].
- **Treatment assignment:** 81-mg v.s. 325-mg aspirin dosage
- **Outcome:** a composite outcome of death from any cause and hospitalization for stroke or myocardial infraction (time-to-event)
- **Complication:** not all patients take the assigned aspirin dosage.




[2]Jones, W., Mulder, H., and others (2021). Comparative effectiveness of aspirin dosing in cardiovascular disease. *New England Journal of Medicine*, 384(21), 1981-1990.

# Average treatment effect

- **Baseline covariates:** age, gender, race, ethnicity, medical and diseases history, aspirin dosage use prior to the trial, *etc*.
- Up until the maximum follow-up time (38 months after randomization), the outcome occurred in 7.5% and 7.4% of participants in the 81-mg arm and the 325-mg arm, respectively.
  - relatively rare events
- As expected, the primary analysis found a null average treatment effect
- To confirm no overall effect, we applied a covariate-adjusted approach to report the ITT effect
  - augmented estimator for the causal survival curves (Bai et al, 2013; Zhang and Schaubel, 2012)

# ITT effect estimates

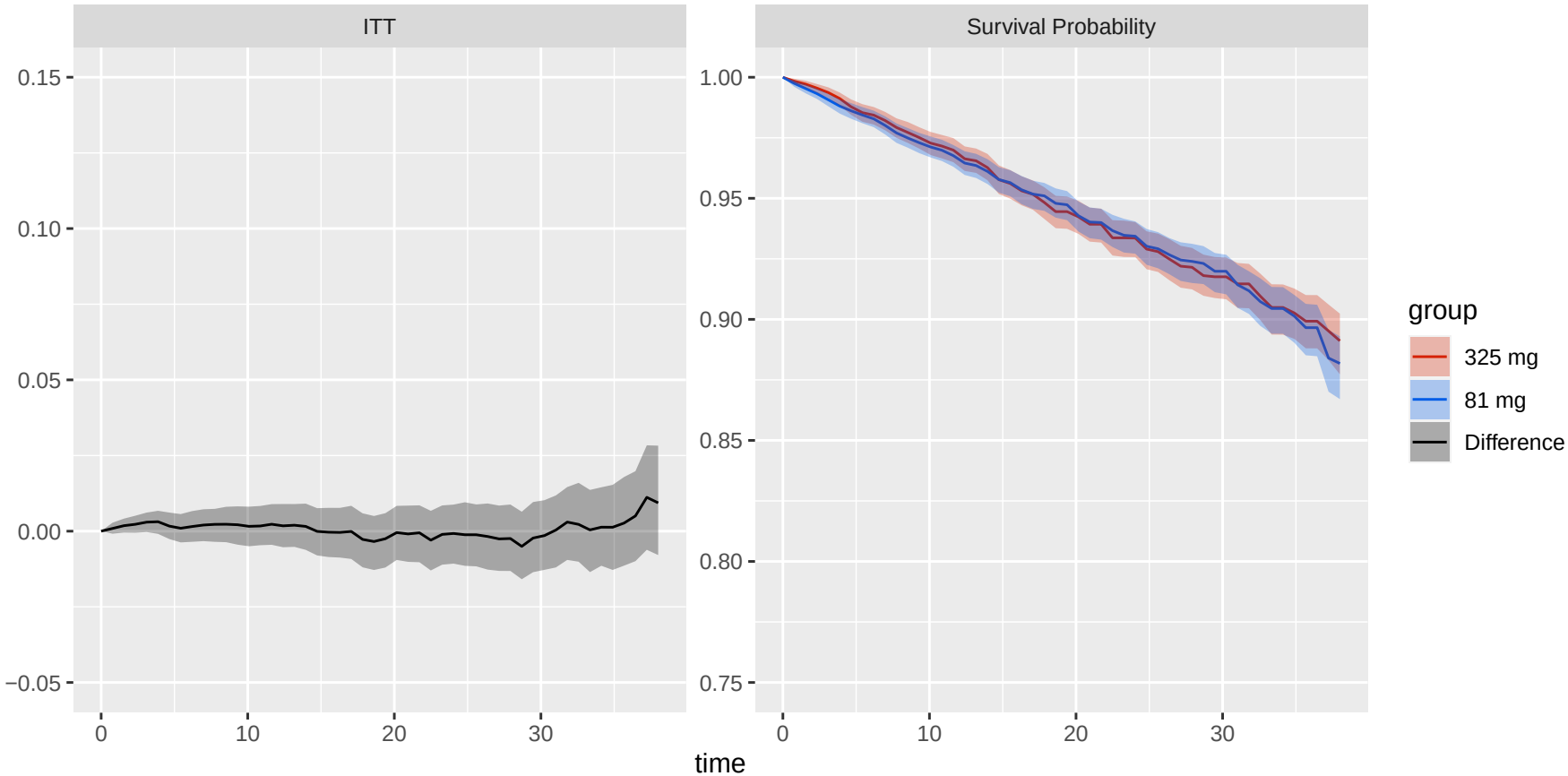



Figure: The ITT effects and corresponding survival probability curve, ADAPTABLE trial, 2016–2020. The ITT effects are obtained based on the doubly robust estimator by Bai et al. (2013)[3].

[3]Bai, X., Tsiatis, A. A., & O'Brien, S. M. (2013). Doubly-robust estimators of treatment-specific survival distributions in observational studies with stratified sampling. *Biometrics*, 69(4), 830-839.

# Motivating questions

Recognizing the potential impact of noncompliance

- Is one specific aspirin dosage more effective than the other among compliers?
  - the treatment efficacy
- Is there treatment effect heterogeneity among patients with different compliance behaviour types that contribute to the null ITT effect?
  - 'direct effect' of treatment assignment (possibly due to other mechanisms that are unmeasured)
- To what extent the study results are sensitive to unverifiable assumptions?

**Goal**: seek model-robust methods and sensitivity strategies to address noncompliance with a survival outcome

# Notation

- Data structure
  - $\boldsymbol{X}$: pre-treatment covariates
  - $Z$: treatment assignment (1 if 325-mg aspirin and 0 if 81-mg aspirin)
  - $S$: actual treatment received
  - $T$: survival time of interest—partially observed due to right censoring. Instead, we only observe $(U, \delta) = \Big( \min(T, C), \mathbb{I}(T \leq C) \Big)$, where $C$ is the censoring time
- Pursue potential outcomes framework and define
  - $S(z)$: the potential value of $S$ when setting the assignment to $z \in \{0, 1\}$.
  - $T(z)$ & $C(z)$: the potential value of $T$ and $C$ when setting the assignment to $z \in \{0, 1\}$.

# Estimands

- Under the principal stratification framework, we partition the study population into 4 principal strata, based on the joint potential values $G = \{S(1), S(0)\}$:
  - $G = \{1, 1\}$: always high-dose (325-mg) takers
  - $G = \{0, 0\}$: always low-dose (81-mg) takers
  - $G = \{1, 0\}$: compliers
  - $G = \{0, 1\}$: defiers
- abbreviate the above four principal strata as $\{a, n, c, d\}$, respectively.
- Define the **Principal Survival Causal Effect (PSCE)**:

$$\Delta_g(u) = \mathcal{S}_{1,g}(u) - \mathcal{S}_{0,g}(u)$$

where $\mathcal{S}_{z,g} = \mathbb{P}(T(z) > u | G = g)$ and $g \in \{a, n, c, d\}$.

  - $\Delta_c(u)$: 'efficacy' of the treatment in the ideal compliance condition.
  - $\Delta_a(u)$ and $\Delta_n(u)$: 'direct effect' due to treatment assignment
  - do not pursue strata-specific HR as estimands

# Assumptions

Five structural assumptions to identify the PSCE.

**Set I: standard assumptions in causal survival analysis** (Chen et al, 2001; Zhang and Schaubel, 2012; Bai et al. 2013)

A1. (SUTVA) For all $i$, we have $S_i(z) = S_i$, $T_i(z) = T_i$, and $C_i(z) = C_i$ if patient $i$ was assigned to treatment $Z_i = z$.

A2. (Conditional randomization) $\{T(1), T(0), S(1), S(0)\} \perp Z|\boldsymbol{X}$.

- in ADAPTABLE, a stronger version, $\{T(1), T(0), S(1), S(0), \boldsymbol{X}\} \perp Z$, is satisfied by study design.
- use a more general assumption to allow considerations of conditional randomized trials and observational studies.

A3. (Covariate-dependent censoring) $T(z) \perp C(z)|\{Z = z, S, \boldsymbol{X}\}$.

# Assumptions - cont'd

**Set II: additional assumptions**

A4. (Monotonicity) $S_i(1) \geq S_i(0)$ for all $i$.

- excludes defiers and can be plausible for ADAPTABLE

A5. (Prinicipal ignorability) For all $u \geq 0$, we have

$$\mathbb{P}\left(T(1) \geq u | G = a, \boldsymbol{X}\right) = \mathbb{P}\left(T(1) \geq u | G = c, \boldsymbol{X}\right),$$
$$\mathbb{P}\left(T(0) \geq u | G = c, \boldsymbol{X}\right) = \mathbb{P}\left(T(0) \geq u | G = n, \boldsymbol{X}\right).$$

- assumes sufficient baseline information to capture characteristics influencing both the noncompliance behavior and the potential outcomes
- extension of Ding and Lu. (2016); Jiang et al. (2022) to causal survival analysis
- a stronger version: $G \perp T(z) | \boldsymbol{X}$ for $z = 0, 1$

Both unverifiable from observed data and sensitivity analysis can help.

# Possible working models

1. **Assignment mechanism**:

   $\mathcal{M}_\pi$: $\pi(\boldsymbol{X}) = \mathbb{P}(Z = 1|\boldsymbol{X})$, the propensity score (Rosenbaum and Rubin, 1983).

   - in ADAPTABLE, $\pi(\boldsymbol{X}) = 0.5$ by randomization, but modeling this process may gain efficiency (Zeng et al, 2021; Li, Buchanan, Cole, 2022)

2. **Noncompliance**:

   $\mathcal{M}_e$: $e_g(\boldsymbol{X}) = \mathbb{P}(G = g|\boldsymbol{X})$ for $g \in \{a, c, n\}$ the principal scores (Ding and Lu, 2016).

   - define $e_g = E[e_g(\boldsymbol{X})]$ as strata proportion
   - by monotonicity, we have $e_c(\boldsymbol{X}) = p_1(\boldsymbol{X}) - p_0(\boldsymbol{X})$, $e_a(\boldsymbol{X}) = p_0(\boldsymbol{X})$, and $e_n(\boldsymbol{X}) = 1 - p_1(\boldsymbol{X})$, where $p_z(\boldsymbol{X}) = \mathbb{P}(S = 1|Z = z, \boldsymbol{X})$ is the observed probability for receiving the 325-mg dosage.

- Can fit logistic regressions to obtain $\widehat{\pi}(\boldsymbol{X})$ and $\widehat{p}_z(\boldsymbol{X})$.

# Possible working models - cont'd

3. **Censoring**:

   $\mathcal{M}_C$: $\mathcal{S}^C_{zs}(u|\boldsymbol{X}) = \mathbb{P}(C \geq u|Z = z, S = s, \boldsymbol{X})$

   - survival function of the censoring time within observed cell $(Z = z, S = s)$.

4. **Survival outcome (of interest)**:

   $\mathcal{M}_T$: $\mathcal{S}_{zs}(u|\boldsymbol{X}) = \mathbb{P}(T \geq u|Z = z, S = s, \boldsymbol{X})$

   - survival function of the time-to-event outcome of interest within observed cell $(Z = z, S = s)$

- Can fit Cox proportional hazards models to obtain $\widehat{\mathcal{S}}^C_{zs}(u|\boldsymbol{X})$ and $\widehat{\mathcal{S}}_{zs}(u|\boldsymbol{X})$

  - working models and no attempt to interpret HR as causal parameter

# Moment estimators

- We do not need all models to point identify PSCEs
- We characterized 3 moment-type estimators of $\Delta_g(u)$, each depending on part of, but not all of, the 4 working models $\mathcal{M}_\pi$, $\mathcal{M}_e$, $\mathcal{M}_C$, and $\mathcal{M}_T$.

| | $\mathcal{M}_\pi$ (IPTW) | $\mathcal{M}_e$ (PSW) | $\mathcal{M}_C$ (IPCW) | $\mathcal{M}_T$ (OM) |
|---|---|---|---|---|
| $\widehat{\Delta}_g^{(1)}(u)$ | ✓ | ✓ | ✓ | |
| $\widehat{\Delta}_g^{(2)}(u)$ | | ✓ | | ✓ |
| $\widehat{\Delta}_g^{(3)}(u)$ | ✓ | | | ✓ |

- $\widehat{\Delta}_g^{(1)}(u)$, $\widehat{\Delta}_g^{(2)}(u)$, and $\widehat{\Delta}_g^{(3)}(u)$ consistent to $\Delta_g(u)$ if $\mathcal{M}_{\pi+e+C}$, $\mathcal{M}_{e+T}$, and $\mathcal{M}_{\pi+T}$ is correctly specified, respectively
  - $\mathcal{M}_{a+b}$ is the intersection model, hence all 3 estimators are only singly robust

# Combing multiple working models with complete data

- Ideal to leverage all working models to improve robustness and efficiency
- Suppose the true failure time can be observed (no censoring) with the complete data $\mathcal{A} = \{\boldsymbol{X}, Z, S, T\}$.
- Adapted from Jiang et al. (2022)[4], a multiply robust estimator of $S_{1,c}(u)$ can be obtained by solving the following estimating equation,

$$\mathbb{P}_n \left[ \psi_{1,c}^{mr}(\mathcal{A}) \right] = 0,$$

where

$$\begin{aligned}\psi_{1,c}^{mr}(\mathcal{A}) = & \frac{e_c(\boldsymbol{X})}{\widetilde{p}_1 - \widetilde{p}_0} \frac{S}{p_1(\boldsymbol{X})} \frac{Z}{\pi(\boldsymbol{X})} \mathbb{I}(T \geq u) - S_{1,c}(u) \\ & + \frac{e_c(\boldsymbol{X})}{\widetilde{p}_1 - \widetilde{p}_0} \left(1 - \frac{Z}{\pi(\boldsymbol{X})}\right) S_{11}(u|\boldsymbol{X}) \\ & + \frac{S_{11}(u|\mathbf{X})}{\widetilde{p}_1 - \widetilde{p}_0} \left[ \frac{1-Z}{1-\pi(\boldsymbol{X})} (S - p_0(\boldsymbol{X})) + \frac{p_0(\boldsymbol{X})}{p_1(\boldsymbol{X})} \frac{Z}{\pi(\boldsymbol{X})} (p_1(\boldsymbol{X}) - S) \right],\end{aligned}$$

- The first row: a weighting-based estimating equation of $S_{1,c}(u)$; the last two rows: augmented zero-mean terms based on outcome modeling.

[4] Jiang, Z., Yang, S., & Ding, P. (2022). Multiply robust estimation of causal effects under principal ignorability. *JRSSB*, 84(4), 1423-1445.

# Accommodate right-censoring

- Observed data subject to censoring: $O = \{X, Z, S, U, \delta\}$
- Key idea: identify a set of unbiased estimating functions that depend only on the observed data $O$:

$$\psi_{1,c}(O) = \frac{\delta \psi_{1,c}^{mr}(\mathcal{A})}{S_{ZS}^{C}(U|X)} + \int h(r, Z, S, X) dM_{ZS}^{C}(r|X),$$

where $h(t, Z, S, X)$ can be arbitrary function and $dM_{ZS}^{C}(t|X)$ is the censoring process martingale (within in cell defined by $(Z, S)$).

  - The resulting estimator is an *augmented inverse probability of weighted complete-case* (AIPWCC) estimator (Tsiatis, 2006)

- The optimal choice of $h(t, Z, S, X)$ to maximize efficiency is

$$h(t, Z, S, X) = \frac{\mathbb{E}[\psi_{1,c}^{mr}(\mathcal{A})|T \geq t, Z, S, X]}{S_{ZS}^{C}(t|X)}$$

# The proposed estimator

- After some algebra, the proposed estimator has the following explicit form

$$\begin{aligned}\widehat{\mathcal{S}}^{mr}_{1,c}(u) = \mathbb{P}_n \Bigg\{ & \frac{\widehat{e}_c(\boldsymbol{X})}{\widehat{p}_1 - \widehat{p}_0} \frac{S}{\widehat{p}_1(\boldsymbol{X})} \frac{Z}{\widehat{\pi}(\boldsymbol{X})} \left[ \frac{\mathbb{I}(U \geq u)}{\widehat{\mathcal{S}}^C_{11}(u|\boldsymbol{X})} + \widehat{\mathcal{S}}_{11}(u|\boldsymbol{X}) \int_0^u \frac{d\widehat{M}^C_{11}(r|\boldsymbol{X})}{\widehat{\mathcal{S}}_{11}(r|\boldsymbol{X}) \widehat{\mathcal{S}}^C_{11}(r|\boldsymbol{X})} \right] \\ & + \frac{\widehat{\mathcal{S}}_{11}(u|\boldsymbol{X})}{\widehat{p}_1 - \widehat{p}_0} \left[ \frac{1 - Z}{1 - \widehat{\pi}(\boldsymbol{X})} (S - \widehat{p}_0(\boldsymbol{X})) + \frac{\widehat{p}_0(\boldsymbol{X})}{\widehat{p}_1(\boldsymbol{X})} \frac{Z}{\widehat{\pi}(\boldsymbol{X})} (\widehat{p}_1(\boldsymbol{X}) - S) \right] \\ & + \frac{\widehat{e}_c(\boldsymbol{X})}{\widehat{p}_1 - \widehat{p}_0} \left( 1 - \frac{Z}{\widehat{\pi}(\boldsymbol{X})} \right) \widehat{\mathcal{S}}_{11}(u|\boldsymbol{X}) \Bigg\},\end{aligned}$$

where $\mathbb{P}_n[V] = \frac{1}{n} \sum_{i=1}^n V_i$ is the empirical average operator

- Similar ideas to estimate counterfactual survival functions in other strata

- Bootstrap variance

# Multiple robustness

- **Result**. (Multiple robustness)

  *Suppose that Assumptions 1–5 hold. For all* $z \in \{0, 1\}$ *and* $g \in \{c, n, a\}$, $\widehat{\mathcal{S}}^{mr}_{z,g}(u)$ *is consistent to* $\mathcal{S}_{z,g}(u)$ *under the union model* $\mathcal{M}_{\pi+e+C} \cup \mathcal{M}_{\pi+T} \cup \mathcal{M}_{e+T}$. *As a consequence,* $\widehat{\Delta}^{mr}_{g}(u)$ *is also consistent to* $\Delta_g(u)$ *under* $\mathcal{M}_{\pi+e+C} \cup \mathcal{M}_{\pi+T} \cup \mathcal{M}_{e+T}$ *for all* $g \in \{c, n, a\}$.

- **remark 1**: the result is general and can be applied to observational study (where modeling assignment $\mathcal{M}_\pi$ is necessary for removing confounding bias)

- **remark 2**: in ADAPTABLE, because $\mathcal{M}_\pi$ is known under randomization, $\widehat{\Delta}^{mr}_{g}(u)$ becomes a doubly robust estimator, in that consistency holds under the union model $\mathcal{M}_{e+C} \cup \mathcal{M}_T$
  - correct weighting or correct outcome modeling, but not necessarily both

- simulations confirm the robustness property

# Application to ADAPTABLE

- Working models (all models adjusting for all baseline characteristics)
  - $\mathcal{M}_\pi$: logistic regression
  - $\mathcal{M}_e$: logistic regression
  - $\mathcal{M}_C$: Cox regression
  - $\mathcal{M}_T$: Cox regression
- Proportion of each principal strata estimated from principal scores (Figure)
- For any $V \in \boldsymbol{X}$, we calculate its estimated mean and variance within each strata
  - $\widehat{\mathbb{E}}[V|G=g] = \mathbb{P}_n\left[\frac{\widehat{e}_g(\boldsymbol{X})}{\widehat{e}_g}V\right]$
  - $\widehat{\text{Var}}[V|G=g] := s_g^2$ given by the principal score weighted variance
  - useful in describing and comparing demographic and clinical characteristics among different compliance strata.

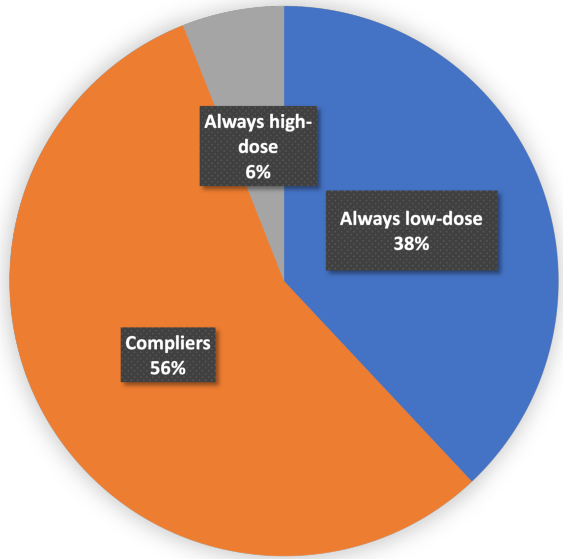



**Figure**:The estimated proportions of each strata (i.e., $\widehat{e}_g$)

# Strata characteristics

- **Always low-dose:** older, higher prevalence of cardiovascular diseases and worse medical history, more 81-mg aspirin users
- **Compliers:** less non-internet users, more white patients
- **Always high-dose:** youngest, less medical conditions, more 325-mg aspirin users

Table 3: Mean and standard deviation of baseline characteristics among always low-dose takers, compliers, and always high-dose takers, ADAPTABLE trial, 2016–2020.

| Variable | Always low-dose takers | Compliers | Always high-dose takers | Max ASD* |
|---|---|---|---|---|
| Age (years) | 67.70 (9.34) | 66.44 (9.36) | 66.02 (9.56) | 0.18 |
| Female sex | 0.32 (0.47) | 0.29 (0.45) | 0.28 (0.45) | 0.09 |
| White race | 0.78 (0.41) | 0.89 (0.31) | 0.80 (0.40) | 0.29 |
| Hispanic ethnicity | 0.04 (0.20) | 0.03 (0.16) | 0.04 (0.19) | 0.08 |
| Non-internet users | 0.21 (0.41) | 0.09 (0.28) | 0.24 (0.42) | 0.41 |
| Current smokers | 0.10 (0.31) | 0.08 (0.28) | 0.14 (0.35) | 0.18 |
| P2Y12 inhibitor | 0.25 (0.43) | 0.22 (0.41) | 0.22 (0.42) | 0.07 |
| **Medical History** | | | | |
| Myocardial infarction | 0.39 (0.49) | 0.35 (0.48) | 0.38 (0.49) | 0.09 |
| Atrial fibrillation | 0.09 (0.28) | 0.08 (0.27) | 0.10 (0.30) | 0.09 |
| Percutaneous coronary intervention | 0.46 (0.50) | 0.40 (0.49) | 0.39 (0.49) | 0.15 |
| Coronary artery disease | 0.96 (0.19) | 0.95 (0.21) | 0.94 (0.24) | 0.12 |
| Coronary-artery bypass grafting | 0.26 (0.44) | 0.25 (0.43) | 0.25 (0.43) | 0.02 |
| Hypertension | 0.89 (0.32) | 0.85 (0.35) | 0.90 (0.30) | 0.13 |
| Hyperlipidemia | 0.91 (0.28) | 0.90 (0.30) | 0.88 (0.32) | 0.10 |
| Peripheral artery disease | 0.29 (0.45) | 0.22 (0.41) | 0.25 (0.44) | 0.16 |
| Congestive heart failure | 0.27 (0.44) | 0.22 (0.41) | 0.26 (0.44) | 0.12 |
| History of bleeding | 0.11 (0.31) | 0.07 (0.26) | 0.10 (0.30) | 0.12 |
| **Aspirin use before trial** | | | | |
| Prior dose: 81 mg | 0.90 (0.30) | 0.87 (0.34) | 0.45 (0.50) | 1.11 |
| Prior dose: 325 mg | 0.08 (0.27) | 0.11 (0.32) | 0.47 (0.50) | 0.97 |

*Max ASD is the maximum pairwise absolute standardized difference across the three principal strata.

# Balance check

- Why balance check? To empirically check evidence for principal score model adequacy

- Balance metrics: The *weighted standardized mean differences* (SMDs) of a given covariate $V$ across the four observed $(Z, S)$-strata, $(Z = 1, S = 1)$, $(Z = 0, S = 1)$, $(Z = 1, S = 0)$, and $(Z = 0, S = 0)$:

$$\text{SMD}_c = \frac{1}{s_c}\left|\mathbb{P}_n\left[\frac{ZS\mathcal{W}_{1,c}(\boldsymbol{X})V}{\mathbb{P}_n[ZS]} - \frac{(1-Z)(1-S)\mathcal{W}_{0,c}(\boldsymbol{X})V}{\mathbb{P}_n[(1-Z)(1-S)]}\right]\right|,$$

$$\text{SMD}_n = \frac{1}{s_n}\left|\mathbb{P}_n\left[\frac{Z(1-S)\mathcal{W}_{1,n}(\boldsymbol{X})V}{\mathbb{P}_n[Z(1-S)]} - \frac{(1-Z)(1-S)\mathcal{W}_{0,n}(\boldsymbol{X})V}{\mathbb{P}_n[(1-Z)(1-S)]}\right]\right|,$$

$$\text{SMD}_a = \frac{1}{s_a}\left|\mathbb{P}_n\left[\frac{ZS\mathcal{W}_{1,a}(\boldsymbol{X})V}{\mathbb{P}_n[ZS]} - \frac{(1-Z)S\mathcal{W}_{0,a}(\boldsymbol{X})V}{\mathbb{P}_n[(1-Z)S]}\right]\right|,$$

  where $\mathcal{W}_{z,g}(\boldsymbol{X})$ for $z \in \{0, 1\}$ and $g \in \{c, a, n\}$ are specified weights.

- When $\mathcal{W}_{z,g}(\boldsymbol{X}) = 1$, the SMDs measure the systematic difference of $X$ across different $(Z, S)$-strata, and therefore reflects heterogeneity of $X$ due to patients' noncompliance behavior
- When $\mathcal{W}_{z,g}(\boldsymbol{X})$ is set to the (true) principal score weight, SMDs should be 0

# Balance check - cont'd

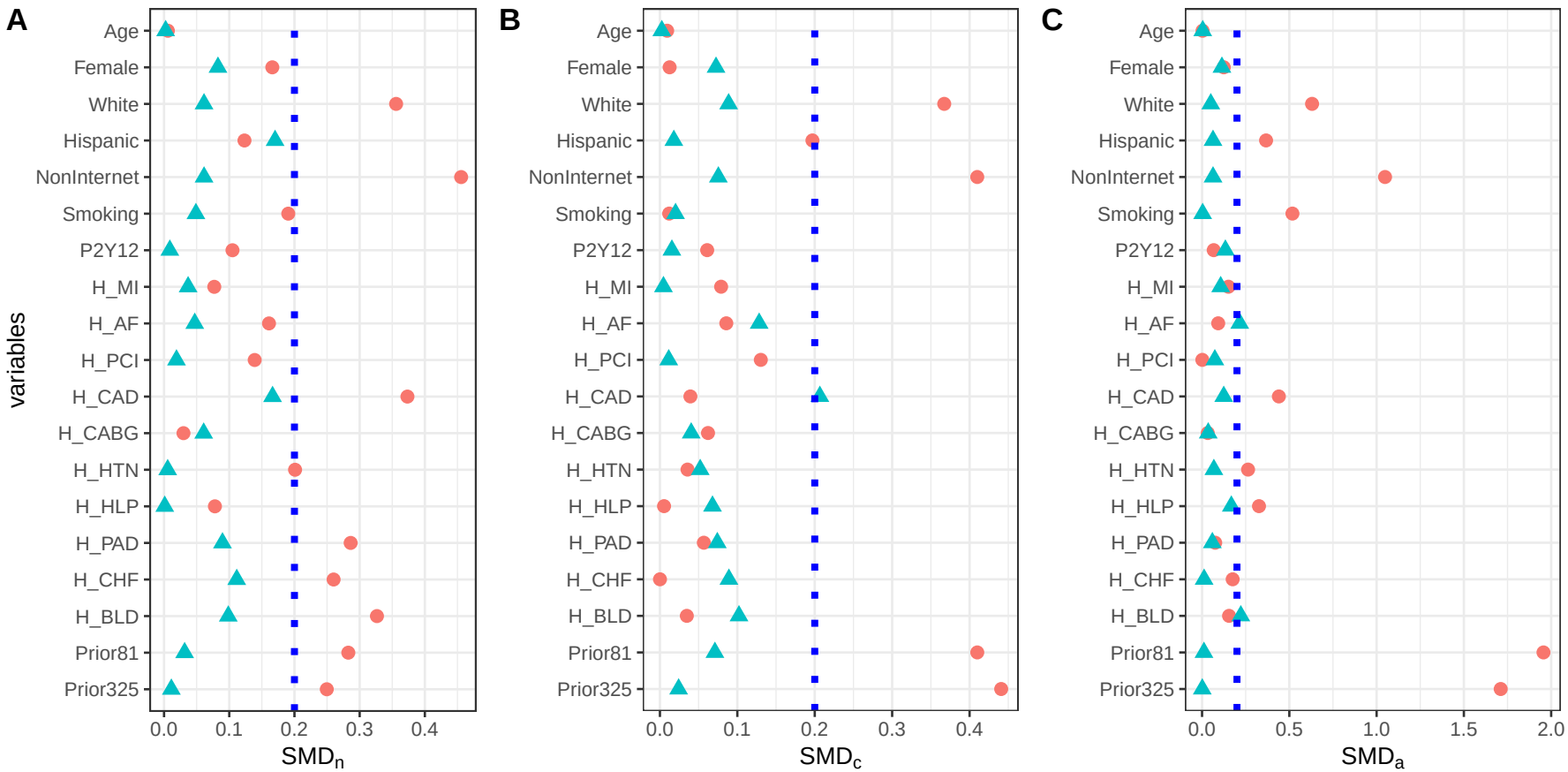



Figure: Balance check for baseline characteristics. The red '●' symbol indicates the unweighted SMDs and the blue '▲' symbol indicates the weighted SMDs by the principal score weighting.

# Principal causal effect estimates

- Implement the proposed estimator of the PSCEs among the always low-dose, compliers, and always high-dose

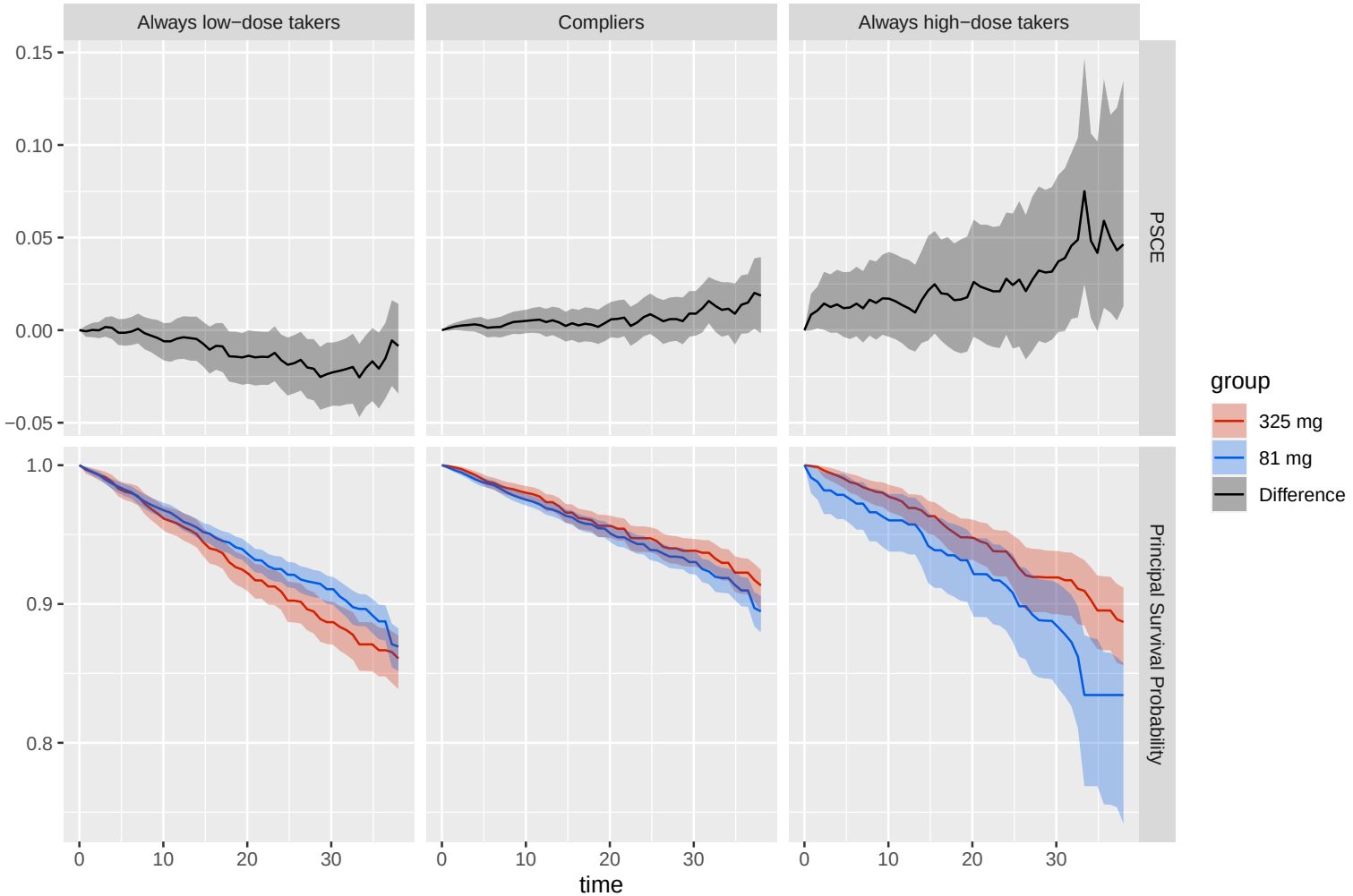



Figure: The principal survival causal effects (PSCEs) and the principal survival probability curves

# Sensitivity analysis for principal ignorability (PI)

- PI holds if there is no residual confounding between $G$ and $T$ contional on $\boldsymbol{X}$
  - PI violated if there exists unmeasured confounding ($U$) between $G$ and $T$
  - One potential $U$: digestive disease, which may increase the risk of death. Moreover, people with digestive diseases may prefer not to take high aspirin dosage due to its risk on bleeding.
- Consider sensitivity functions to measure departure from PI:

$$\varepsilon_1(t, \boldsymbol{X}) = \frac{\mathbb{P}(T(1) \geq t | G = c, \boldsymbol{X})}{\mathbb{P}(T(1) \geq t | G = a, \boldsymbol{X})} = \exp\left\{\xi_1 \times \left(\frac{t}{t_{\max}}\right)\right\}$$

$$\varepsilon_0(t, \boldsymbol{X}) = \frac{\mathbb{P}(T(0) \geq t | G = c, \boldsymbol{X})}{\mathbb{P}(T(0) \geq t | G = n, \boldsymbol{X})} = \exp\left\{\xi_0 \times \left(\frac{t}{t_{\max}}\right)\right\},$$

- We use $\{\xi_1, \xi_0\}$ to control the pattern of the two sensitivity functions

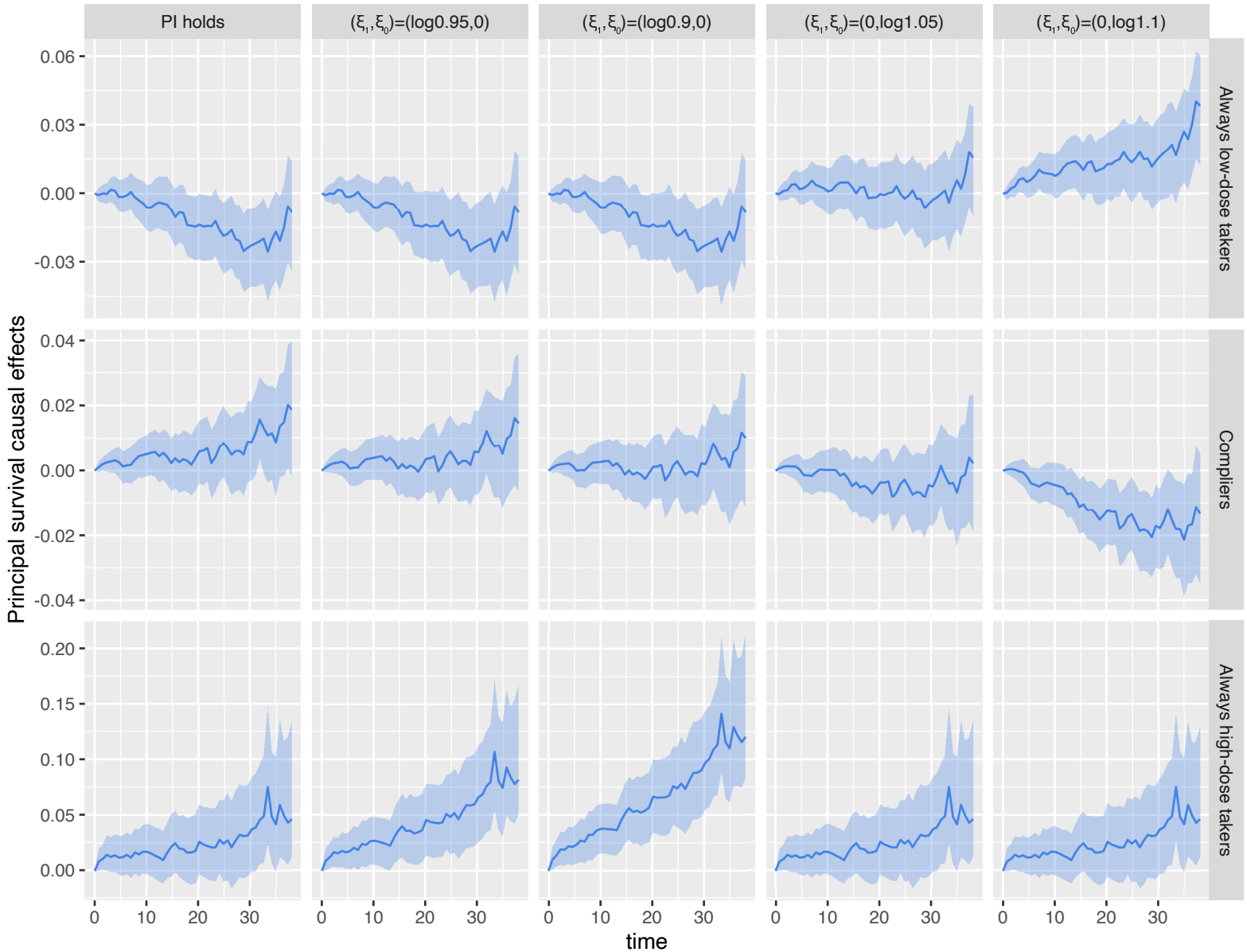
| Scenario | $\xi_1$ | $\xi_0$ | Interpretation |
|---|---|---|---|
| Benchmark | 0 | 0 | PI holds |
| I | − | + | always low-dose takers < compliers < always high-dose takers |
| II | + | − | always high-dose < compliers < always low-dose takers |
| III | − | − | compliers < {always high-dose, always low-dose takers} |
| IV | + | + | {always high-dose, always low-dose takers} < compliers |

Note: 'A<B' means that A is less healthier than B due to unobserved confounders (i.e., $U$).

# Choice of sensitivity parameter

- For fixed $\{\xi_1, \xi_0\}$, we develop a bias-corrected estimator for PSCE, $\widehat{\Delta}_g^{bc}(u)$, which is consistent under $\mathcal{M}_{\pi+e+C} \cup \mathcal{M}_{\pi+T}$.
  - Under randomization, doubly robust ($\mathcal{M}_{e+C} \cup \mathcal{M}_T$)
- A plausible scenario: always low-dose takers often less healthier than compilers; always high-dose taker often the healthiest.
- We choose $\xi_1 \in [\log(0.9), 0]$ and $\xi_0 \in [0, \log(1.1)]$, corresponding to Scenario I in previous table
  - since $\xi_1$ and $\xi_0$ defined based on conditional causal survival function, there is a bound on these values
  - a simple choice but can extend to $\xi_1(\boldsymbol{X})$ and $\xi_0(\boldsymbol{X})$

# Sensitivity analysis: results



# Discussion

- Carried out sensitivity analysis for monotonicity (A4) – results robust to this assumption in ADAPTABLE (back-up slides)
- **Some conclusions under PI**:
  - (1) always high-dose takers appear to benefit
  - (2) compliers slightly benefit
  - (3) always low-dose takers appear not to benefit
- (2) and (3) may change if PI does not hold (depending on how rich the collected baseline covariates are)
  - mechanisms of these effects require further studies
- **Limitations**:
  - composite outcomes
  - complete case analysis without addressing treatment discontinuation

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  - Lisa Wruck (Duke/DCRI)
  - Fan Li (Duke)
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# Simulation study (ignorable assignment)

- Scenario 1–4: the union model $\mathcal{M}_{\pi+e+C} \cup \mathcal{M}_{\pi+T} \cup \mathcal{M}_{e+T}$ is correctly specified.
- Scenario 5: all models are misspecified.

Table 1: Simulation results of $\widehat{\mathcal{S}}^{mr}_{0,c}(u)$, where $\mathcal{M}_e, \mathcal{M}_\pi, \mathcal{M}_T$ and $\mathcal{M}_C$ indicate whether the working model for principal score, propensity score, time-to-event and time-to-censoring is correctly specified (denoted by a 'T' label) or misspecified (denoted by a 'F' label).

| | $u$ | $\mathcal{S}_{0,c}(u)$ | $\widehat{\mathcal{S}}^{mr}_{0,c}(u)$ | Bias | Monte Carlo SE | Coverage Rate |
|---|---|---|---|---|---|---|
| Scenario 1 | 1 | 0.695 | 0.695 | 0.000 | 0.050 | 0.946 |
| $\mathcal{M}_e$ T | 2 | 0.517 | 0.518 | 0.000 | 0.048 | 0.960 |
| $\mathcal{M}_\pi$ T | 3 | 0.397 | 0.395 | -0.002 | 0.046 | 0.960 |
| $\mathcal{M}_T$ T | 4 | 0.309 | 0.306 | -0.003 | 0.039 | 0.968 |
| $\mathcal{M}_C$ T | 5 | 0.245 | 0.242 | -0.003 | 0.036 | 0.964 |
| Scenario 2 | 1 | 0.695 | 0.693 | -0.002 | 0.048 | 0.960 |
| $\mathcal{M}_e$ T | 2 | 0.517 | 0.517 | 0.000 | 0.048 | 0.972 |
| $\mathcal{M}_\pi$ T | 3 | 0.397 | 0.394 | -0.002 | 0.046 | 0.970 |
| $\mathcal{M}_T$ F | 4 | 0.309 | 0.307 | -0.003 | 0.041 | 0.960 |
| $\mathcal{M}_C$ T | 5 | 0.245 | 0.243 | -0.002 | 0.037 | 0.970 |
| Scenario 3 | 1 | 0.695 | 0.693 | -0.002 | 0.172 | 0.936 |
| $\mathcal{M}_e$ F | 2 | 0.517 | 0.517 | -0.001 | 0.133 | 0.946 |
| $\mathcal{M}_\pi$ T | 3 | 0.397 | 0.394 | -0.003 | 0.108 | 0.956 |
| $\mathcal{M}_T$ T | 4 | 0.309 | 0.306 | -0.004 | 0.084 | 0.966 |
| $\mathcal{M}_C$ F | 5 | 0.245 | 0.241 | -0.003 | 0.068 | 0.960 |
| Scenario 4 | 1 | 0.695 | 0.692 | -0.003 | 0.042 | 0.962 |
| $\mathcal{M}_e$ T | 2 | 0.517 | 0.517 | 0.000 | 0.044 | 0.954 |
| $\mathcal{M}_\pi$ F | 3 | 0.397 | 0.395 | -0.002 | 0.043 | 0.962 |
| $\mathcal{M}_T$ T | 4 | 0.309 | 0.308 | -0.002 | 0.038 | 0.968 |
| $\mathcal{M}_C$ F | 5 | 0.245 | 0.244 | -0.001 | 0.035 | 0.976 |
| Scenario 5 | 1 | 0.695 | 0.761 | 0.066 | 0.024 | 0.246 |
| $\mathcal{M}_e$ F | 2 | 0.517 | 0.600 | 0.083 | 0.029 | 0.228 |
| $\mathcal{M}_\pi$ F | 3 | 0.397 | 0.479 | 0.082 | 0.029 | 0.234 |
| $\mathcal{M}_T$ F | 4 | 0.309 | 0.387 | 0.078 | 0.029 | 0.264 |
| $\mathcal{M}_C$ F | 5 | 0.245 | 0.318 | 0.073 | 0.029 | 0.328 |

# Back-up: Basline table

- Balance check for baseline characteristics in each treatment arm

Table 2: Mean and standard deviation of baseline characteristics stratified by the treatment assignment group, ADAPTABLE trial, 2016–2020.

| Variable | 81-mg Group ($N = 5239$) | 325-mg Group ($N = 4791$) | ASD* |
|---|---|---|---|
| Age (years) | 67.00 (9.45) | 66.77 (9.32) | 0.02 |
| Female sex | 0.29 (0.46) | 0.31 (0.46) | 0.04 |
| White race | 0.84 (0.37) | 0.85 (0.36) | 0.02 |
| Hispanic ethnicity | 0.03 (0.18) | 0.03 (0.17) | 0.01 |
| Non-internet users | 0.15 (0.35) | 0.14 (0.35) | 0.02 |
| Current smokers | 0.09 (0.29) | 0.10 (0.30) | 0.01 |
| P2Y12 inhibitor | 0.23 (0.42) | 0.23 (0.42) | 0.00 |
| **Medical History** | | | |
| Myocardial infarction | 0.37 (0.48) | 0.36 (0.48) | 0.01 |
| Atrial fibrillation | 0.08 (0.27) | 0.09 (0.28) | 0.03 |
| Percutaneous coronary intervention | 0.42 (0.49) | 0.42 (0.49) | 0.01 |
| Coronary artery disease | 0.95 (0.21) | 0.96 (0.20) | 0.04 |
| Coronary-artery bypass grafting | 0.25 (0.44) | 0.25 (0.43) | 0.02 |
| Hypertension | 0.87 (0.34) | 0.87 (0.33) | 0.01 |
| Hyperlipidemia | 0.90 (0.30) | 0.91 (0.29) | 0.01 |
| Peripheral artery disease | 0.24 (0.43) | 0.25 (0.44) | 0.03 |
| Congestive heart failure | 0.23 (0.42) | 0.25 (0.43) | 0.04 |
| History of bleeding | 0.08 (0.28) | 0.09 (0.29) | 0.03 |
| **Aspirin use before trial** | | | |
| Prior dose: 81 mg | 0.85 (0.36) | 0.86 (0.35) | 0.02 |
| Prior dose: 325 mg | 0.12 (0.33) | 0.12 (0.33) | 0.01 |

*ASD: the absolute standardized difference.

# Back-up: Sensitivity for monotonicity

- If monotonicity does not hold, defiers exist and we have four strata $G \in \{c, n, a, d\}$.
- The following sensitivity parameter captures the deviation from monotonicity:

$$\zeta = \frac{\mathbb{P}(G = d|\boldsymbol{X})}{\mathbb{P}(G = c|\boldsymbol{X})},$$

  —ratio between the probability of defiers and compliers given $\boldsymbol{X}$.

- $\zeta$ takes values from 0 to $\infty$, and monotonicity holds with $\zeta = 0$.
  - if we further assume that the treatment assignment has a positive effect on the treatment receipt (i.e., $\mathbb{E}[S(1) - S(0)] \geq 0$), then $\zeta$ is bounded by

$$0 \leq \zeta \leq 1 - \frac{p_1 - p_0}{\min(p_1, 1 - p_0)},$$

    where $p_z = \mathbb{E}[p_z(\boldsymbol{X})]$.
  - in ADAPTABLE, the estimated bound is $\zeta \in [0, 0.103]$.
- For a fixed value $\zeta$, we developed a modified estimator, which is consistent under $\mathcal{M}_{\pi+e+C} \cup \mathcal{M}_{\pi+T} \cup \mathcal{M}_{e+T}$ for any $g \in \{c, n, a, d\}$.

# Back-up: Sensitivity for monotonicity