Abstract

In this paper we present a data-adaptive estimation procedure for estimation of average treatment effects in a time-to-event setting based on generalized random forests. In these kinds of settings, the definition of causal effect parameters are complicated by competing risks; here we distinguish between treatment effects on the crude and the net probabilities, respectively. To handle right-censoring, and to switch between crude and net probabilities, we propose a two-step procedure for estimation, applying inverse probability weighting to construct time-point specific weighted outcomes as input for the forest. The forest adaptively handles confounding of the treatment assigned by applying a splitting rule that targets a causal parameter. We demonstrate that our method is effective for a causal search through a list of treatments to be ranked according to the magnitude of their effect. We further apply our method to a dataset from the Danish health registries where it is of interest to discover drugs with an unexpected protective effect against relapse of severe depression.

Ranking of average treatment effects with generalized random forests for time-to-event outcomes

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1 Introduction

Drug repurposing is an important low-cost method for drug discovery which is typically based on a data-driven experimental approach. In this paper, our general aim is the ability to rank a list of treatment variables according to their effect on a time-to-event outcome. We consider average treatment effect estimation based on generalized random forests in a time-to-event setting with competing risks. We find two aspects particularly important when having to search through a potentially large list of treatments. First, the search algorithm should be as flexible as possible: In drug repurposing studies, in particular, one may have expert knowledge of the outcome process being studied but not the treatments, and if one has many treatments to search through it will be impossible to correctly specify parametric models for all treatment propensities with main effects and interactions. Second, we need a real-valued measure to be used for ranking that should have a sensible interpretation. Compared to other methods for average treatment effect estimation in right-censored and competing risks settings (see, e.g., Ozenne et al., 2020), the methods presented in this paper do not require specification of models for treatment propensity and outcome distribution. Further, we discuss the choice between different causal parameters in the competing risks setting when the aim is to identify new active substances.

A random forest (Breiman, 2001) is a popular data-driven algorithm that can be used for variable importance analysis, i.e., to rank variables according to their association with the outcome of interest (Ishwaran et al., 2007; Strobl et al., 2008). Mostly, these variable importance measures are based on prediction performance (Breiman, 2001; Ishwaran et al., 2007) or based on the tree building process of the forests (Ishwaran et al., 2010, 2011). Our approach in this paper is different in that we consider the use of causal treatment effect parameters as a variable importance measure. Similar approaches have also been considered in the context of high-dimensional biomarker discovery, see, for example, Tuglus and van der Laan (2008); Bembom et al. (2009); Wang and van der Laan (2011). In a counterfactual framework (Neyman, 1923; Rubin, 1974), treatment effect parameters are formally defined as a difference between expected counterfactual outcomes. Under a set of structural and distributional assumptions the parameters are linked to the observed data. We formulate causal parameters in terms of average differences of event probabilities at pre-specified time horizons of interest, allowing us to report a time-point specific measure of the effect of a particular treatment.

Generalized random forests (GRFs) (Wager and Athey, 2018; Athey et al., 2019) are a recent extension of Breiman's random forests that have been applied to provide nonparametric inference for heterogeneous treatment effects in settings with real-valued and uncensored outcomes of interest. The GRF algorithm is implemented to optimize estimation of the causal treatment effect specifically. Here we implement GRFs for time-to-event outcomes by using inverse probability weighting to make the GRF implementation directly applicable to our setting with right-censoring and competing risks. In the competing risks setting, we further discuss the distinction between treatment effects on crude and net probabilities. These considerations are closely related to the work of Young et al. (2020).

Our motivation comes specifically from a large-scale observational registry study on drug purchases and development of psychiatic disorders. Here the goal is to discover if drugs that are already in clinical use may have a protective effect against depression. Psychiatric disorders is a field where the pharmaceutical industry has substantially withdrawn from developing new drugs; thus, in the absence of new randomized clinical trials, and to supplement the expensive and time-consuming generation of data from clinical trials, a systematic search through all drug purchases in the registry data is a cost-efficient way to identify new treatments as well as to discover adverse side-effects. Specific findings can then subsequently be further investigated in randomized trials. For proof of concept and illustration, we analyze Danish registry data on all Danish citizens who have a first time diagnosis with depression registered. We follow these patients until depression relapse, onset of other mental disorders, death without relapse, or right-censoring, and apply our proposed method to rank drug treatments according to the magnitude of their effect on depression relapse.

The article is organized as follows. In Section 2 we introduce the setting and notation for survival and competing risks data. We define our target parameters in terms of counterfactual outcomes, and we discuss the distributional assumptions under which we can identify the parameters from the observed data. In Section 3 we review the generalized random forest methodology and present our weighting approach for making the methodology applicable to time-to-event data. In Section 4 we introduce and discuss the use of average treatment effects specifically for the purpose of variable importance analysis. In Section 5 we study the performance using simulated data. In Section 6 we analyze Danish registry data. We close with a discussion in Section 7.

2 Setting and notation

In time-to-event settings subjects are observed from study entry to the occurrence of an event of interest or a competing event. If no event of any kind is observed within the subject-specific follow-up time, the subject is right-censored. Specifically, we consider a competing risks situation with $J \geq 2$ mutually exclusive types of events. For sake of presentation, we assume throughout that $J = 2$. We denote by T_i the uncensored event time, by $\Delta_i \in \{1, 2\}$ the event type and by C_i the censoring time, such that the observed data are $\tilde{T}_i = \min(T_i, C_i)$ and $\tilde{\Delta}_i = \mathbb{1}\{T_i \leq C_i\}\Delta_i$. Moreover, $\boldsymbol{X}_i \in \mathcal{X} \subseteq \mathbb{R}^p$ is a vector of baseline covariates and $\boldsymbol{A}_i = (A_{1,i}, \ldots, A_{K,i}) \in \{0,1\}^K$ is a vector of $K \in \mathbb{N}$ binary treatment variables with $A_k = 1$ indicating treatment and $A_k = 0$ no treatment, $k = 1, \ldots, K$. The data consist of $n \in \mathbb{N}$ independent samples, $\{(\boldsymbol{X}_1, \boldsymbol{A}_1, \tilde{T}_1, \tilde{\Delta}_1), \ldots, (\boldsymbol{X}_n, \boldsymbol{A}_n, \tilde{T}_n, \tilde{\Delta}_n)\}$. We are interested in estimating the effect of the treatment variable $A_k \in \{0, 1\}$ on the probability of events of type $j = 1$. We refer to the other type of events ($j = 2$) as competing events, or competing risks. We define our target parameter in terms of counterfactuals, using a notation with superscripts to define interventions. In particular, we define T^a as the uncensored counterfactual event time and Δ^a as the corresponding event indicator that would result from setting treatment A_k to a. Further, for $j = 1, 2$, we use $T^{j,a}$ to denote the uncensored counterfactual event time of type j that would result if treatment A_k had been set to a in a hypothetical world where cause j is the only cause. Note that we distinguish between the counterfactual event time variable T^a with a single superscript and the counterfactual event time variable $T^{j,a}$ with double superscript. Note also that when studying the treatment A_k, the other treatments can enter the vector of baseline covariates.

2.1 Treatment effects in presence of competing risks

2.1.1 The competing risks problem revisited

As a motivation for our later discussions on causal parameters for treatment effect ranking, we here briefly revisit the problems with causal inference in competing risks settings. In particular, in presence of competing risks, the one-to-one correspondence between the cause-specific hazard and the absolute risk is lost (Andersen et al., 2012), and the effect of variables on the cause-specific hazard may be quite different from their effect on the absolute risk (Gray, 1988). Specifically, variables may have an indirect effect on the absolute risk only through its effect on the cause-specific hazard of the competing event. Consider the following example.

Example 2.1 *Suppose that it is of interest to rank two treatments, A_1 and A_2, according to their effect on the event of interest. Assume that the cause-specific hazard rates are given as follows for the event of interest (λ_1) and the*

competing event (λ_2):

$$\lambda_1(t \mid A_1, A_2) = e^{-0.2A_1 - 0.2A_2}, \quad and, \quad \lambda_2(t \mid A_1, A_2) = e^{-0.2A_1}.$$

Clearly, A_1 and A_2 have the same effect on the hazard of the event of interest. Nonetheless, the cause-specific cumulative incidence of the event of interest also depends on the hazard rate of the competing event. Now, assume that A_1 and A_2 are both Bernoulli variables with $P(A_k = 1) = 0.5$, $k = 1, 2$. The average effects at time $t = 0.1$ are very similar, $\mathbb{E}[F_1(0.1 \mid 0.1, A_2) - F_1(0.1 \mid 0, A_2)] = -0.0138$ and $\mathbb{E}[F_1(0.1 \mid A_1, 1) - F_1(0.1 \mid A_1, 0)] = -0.0145$, whereas for increasing t they get very different: At time $t = 1$, for example, we have $\mathbb{E}[F_1(1 \mid 1, A_2) - F_1(1 \mid 0, A_2)] = -0.0290$ and $\mathbb{E}[F_1(1 \mid A_1, 1) - F_1(1 \mid A_1, 0)] = -0.0547$, i.e., a considerably larger effect of A_2. Thus, in this example, due solely to the effect that A_1 has on the competing cause-specific hazard rate, we would conclude very different effects of the two treatments on the cumulative risk of cause 1.

Our goal is variable importance and the ability to rank a list of treatment variables according to their effect on a specific time-to-event outcome. Example 2.1 illustrates the interpretational issues with absolute risks in the presence of competing risks, and the question is if we would like to conclude different effects for the two treatments A_1 and A_2. This problem is not solved by analyzing the cause-specific hazard rates alone. Specifically, these are defined conditional on post-treatment mechanisms and therefore cannot be ascribed an interpretation as a measure of a causal treatment effect (Hernán, 2010; Martinussen et al., 2020).

In the following, we discuss the distinction between effects on *crude* and *net* probabilities, respectively, to characterize the effect of a treatment variable A_k on the occurrence of events of type $j = 1$. We emphasize that the choice between crude and net effects corresponds to the choice between different causal parameters, and altogether depends upon the goal of the analysis. In summary, we argue that:

1. Causal effects on **crude probabilities** are used for describing the real world; crude probabilities allow us to infer on treatment effects that would actually occur in a given population.

2. Causal effects on **net probabilities** are defined in hypothetical worlds without competing risks and reflect effects of etiological nature. They allow us to infer treatment effects directly on the event type of interest without interference from indirect effects on the competing event time.

Different assumptions on the underlying data-generating mechanisms are necessary when focus is on crude or on net probabilities as we describe in Section 2.4. Importantly, the assumptions needed to identify net probabilities are considerably more ambitious and net probabilities have thereby been criticized (Andersen and Keiding, 2012). In this work we argue that in a variable importance analysis (Section 4), the subject matter interest may not in the treatment effects on the crude probability scale but rather to assess treatment effects only directly on the occurrence of type $j = 1$ events. In Section 2.2, we start by discussing treatment effects on crude probabilities. In Section 2.3, we present treatment effects on net probabilities.

2.2 Effects on crude probabilities

Recall that the random variables T^0 and T^1 denote the uncensored counterfactual event times that would result if treatment had been set to $A_k = 0$ or $A_k = 1$, respectively. The average treatment effect (ATE) of A_k on the crude risk of events of type 1 before a fixed time horizon $t_0 > 0$ is defined as follows

$$\bar{\theta}_{\text{crude}} = P(T^1 \leq t_0, \Delta^1 = 1) - P(T^0 \leq t_0, \Delta^0 = 1). \tag{1}$$

The quantities $P(T^a \leq t_0, \Delta^a = 1)$, $a = 0, 1$, in (1), referred to as the crude probabilities, are the cumulative incidence functions (Gray, 1988) of the event of interest for a hypothetical treated and a hypothetical untreated population, respectively. These crude probabilities also depend on the hazard rate of the competing event, since, at any time, the event of interest can only occur for subjects who have survived all risks so far. A treatment which reduces the hazard rate of the competing risk increases the event-free survival probability and thereby indirectly increases the crude risk of the event of interest, and vice versa. Particularly, a treatment effect reflected in a non-zero value of $\bar{\theta}_{\text{crude}}$ will occur also if there is only an indirect effect via the hazard rate of the competing event.

2.3 Effects on net probabilities

Recall that the counterfactual random variables $T^{1,0}$ and $T^{1,1}$ are the (uncensored) counterfactual event times that would have been observed in a hypothetical world in which cause $j = 1$ is the only cause and where treatment had been set to $A_k = 0$ and $A_k = 1$, respectively. Particularly, $T^{1,0}$ and $T^{1,1}$ are latent times that are not always observed in the real world due to cause $j = 2$ events and due to right-censoring. The average treatment effect of A_k on the net risk of events of type 1 is defined as follows

$$\bar{\theta}_{\text{net}} = P(T^{1,1} \leq t_0) - P(T^{1,0} \leq t_0). \tag{2}$$

We emphasize that, opposed to the crude risks $P(T^a \leq t_0, \Delta^a = 1)$, $a = 0, 1$, in Equation (1), the net risks $P(T^{1,a} \leq t_0)$, $a = 0, 1$, are not affected by the (indirect) effect that a treatment may have on the hazard rate of the competing risk. They are interpreted as net probabilities for the event of interest in a hypothetical world where the competing event cannot happen. A treatment effect reflected in a non-zero value $\bar{\theta}_{\text{net}}$ will only occur if the studied treatment has a direct effect on the event of interest.

2.4 Identifiability of treatment effects on crude and net probabilities

The average treatment effects on crude probabilities $\bar{\theta}_{\text{crude}}$ and net probabilities $\bar{\theta}_{\text{net}}$ are defined in terms of counterfactual random variables, and are identified from the observed data only under causal assumptions (Hernan and Robins, 2020). We review these assumptions in the supplementary material (Appendix A) separately for $\bar{\theta}_{\text{crude}}$ and $\bar{\theta}_{\text{net}}$. We here point out the assumption of *no unmeasured confounding* only, to really contrast the choice between the two parameters. Particularly, for identifiability of the crude effects, this is an assumption of conditional independence between the counterfactuals and the treatment and censoring mechanisms, as follows, $(T^a, \Delta^a) \perp\!\!\!\perp A_k \mid \boldsymbol{X}$, for $a = 0, 1$, and $(T, \Delta) \perp\!\!\!\perp C \mid A_k, \boldsymbol{X}$. To move from crude to net effects, one needs additionally that $T^{1,A_k} \perp\!\!\!\perp T^{2,A_k} \mid A_k, \boldsymbol{X}$. As previously mentioned, we stress that this is a very strong assumption: Whether A_k and $\boldsymbol{X}$ together include all factors that we believe to be predictive of both event types depends very much on the nature of the competing events and how rich the measured set of covariates is.

3 Generalized random forests with inverse probability weighted outcomes

Generalized random forests (GRFs) (Athey et al., 2019) are a recent generalization of the original random forest algorithm (Breiman, 2001), a machine learning tool that adaptively searches the covariate space by recursive sample splitting. Generally, a forest consists of $B \in \mathbb{N}$ randomized trees, where the bth tree of the forest is grown by recursively splitting the covariate space according to some split criterion. GRFs provide a data-adaptive approach to estimation of conditional treatment effects for uncensored data, particularly, for a generic outcome variable $Y \in \mathbb{R}$, $\theta(\boldsymbol{x}) = \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}]$. A key part of the generalized random forest algorithm is the splitting rule that targets specifically the estimation of the quantity $\theta(\boldsymbol{x})$ of interest; particularly, each tree applies a splitting rule that adaptively makes binary partitions of the covariate space such as to maximize heterogeneity in $\theta(\boldsymbol{x})$. By averaging over neighborhoods defined by the trees, the forest produces a neighborhood function that is used as a kernel for estimation of $\theta(\boldsymbol{x})$. In the supplementary material (Appendix C) we describe the local gradient-based criterion for making splits and the kernel-based estimator for average treatment effects for uncensored data as proposed by Athey et al. (2019). We further review the structural model formulation of treatment effects of Athey et al. (2019, Section 6) and its relation to our setting with the counterfactual formulation.

The problem in our setting is that we do not observe the actual outcomes of interest. For the parameter $\bar{\theta}_{\text{crude}}$, for example, we do not observe $Y := \mathbb{1}\{T \leq t_0, \Delta = 1\}$ due to right-censoring. In this section we assume that we are given a conditional distribution function G such that $G(t \mid A_k, \boldsymbol{X}) = P(C > t \mid A_k, \boldsymbol{X})$. Based on G, we define the inverse probability weighted outcome:

$$\tilde{Y} := \frac{\mathbb{1}\{\tilde{T} \leq t_0, \tilde{\Delta} = 1\}}{G(\tilde{T}- \mid A_k, \boldsymbol{X})}. \tag{3}$$

For this outcome, we show in Section 3.1 below that

$$\theta_{\text{crude}} = \mathbb{E}\big[\mathbb{E}[\tilde{Y} \mid \boldsymbol{X} = \boldsymbol{x}, A_k = 1] - \mathbb{E}[\tilde{Y} \mid \boldsymbol{X} = \boldsymbol{x}, A_k = 0]\big].$$

The idea is that we can apply GRFs directly to our weighted outcome $\tilde{Y}$. This provides an estimator $\hat{\theta}_{\text{crude}}(\boldsymbol{x})$ for the conditional effect $\theta_{\text{crude}}(\boldsymbol{x}) = P(T^1 \leq t_0, \Delta^1 = 1 \mid \boldsymbol{X} = \boldsymbol{x}) - P(T^0 \leq t_0, \Delta^0 = 1 \mid \boldsymbol{X} = \boldsymbol{x})$ and thereby an estimator for the corresponding average effect $\hat{\bar{\theta}}_{\text{crude}} = \frac{1}{n} \sum_{i=1}^{n} \hat{\theta}_{\text{crude}}(\boldsymbol{X}_i)$. This leads to the following two-step approach:

Step 1. The conditional distribution function G is estimated based on the full dataset and is used to construct the weighted outcome $\tilde{Y}$ as defined by Equation (3).

Step 2. A generalized random forest is applied with $\tilde{Y}$ as outcome, yielding estimates $\hat{\theta}_{\text{crude}}(\boldsymbol{x})$, $\boldsymbol{x} \in \mathcal{X}$, and the ATE is then estimated simply by averaging.

An equivalent two-step approach is utilized to estimate the effect on net probabilities. We note that this requires, in addition to an estimator for the conditional distribution G, an estimator for the conditional distribution function G_2 such that $G_2(t \mid A_k, \boldsymbol{X}) = P(T^{2,a} > t \mid A_k, \boldsymbol{X})$, and construction of the inverse probability weighted outcome

$$\tilde{Y}' := \frac{\mathbb{1}\{\tilde{T} \leq t_0, \tilde{\Delta} = 1\}}{G(\tilde{T}- \mid A_k, \boldsymbol{X}) G_2(\tilde{T}- \mid A_k, \boldsymbol{X})}. \tag{4}$$

Thus, to construct the weights, we need to model the survival functions of both the latent time to a competing risk event and the censoring time.

3.1 Identifiability by inverse probability weighting

The causal assumptions (see Section 2.4) allow us to link the distribution of the counterfactual variables to the observed data distribution. Since,

$$\mathbb{E}\big[\tilde{Y} \mid \boldsymbol{X}, A_k\big] = \mathbb{E}\left[\frac{\mathbb{1}\{\tilde{T} \leq t_0, \tilde{\Delta} = 1\}}{G(\tilde{T}- \mid A_k, \boldsymbol{X})} \,\bigg|\, \boldsymbol{X}, A_k \right] = \mathbb{E}\big[\mathbb{1}\{T \leq t_0, \Delta = 1\} \mid A_k, \boldsymbol{X}\big],$$

it follows that,

$$
\begin{aligned}
\bar{\theta}_{\text{crude}} &= \mathbb{E}\big[P(T^1 \leq t_0, \Delta^1 = 1 \mid \boldsymbol{X} = \boldsymbol{x}) - P(T^0 \leq t_0, \Delta^0 = 1 \mid \boldsymbol{X} = \boldsymbol{x})\big] \\
&= \mathbb{E}\big[P(T \leq t_0, \Delta = 1 \mid \boldsymbol{X} = \boldsymbol{x}, A_k = 1) - P(T \leq t_0, \Delta = 1 \mid \boldsymbol{X} = \boldsymbol{x}, A_k = 0)\big] \\
&= \mathbb{E}\big[\mathbb{E}[\tilde{Y} \mid \boldsymbol{X} = \boldsymbol{x}, A_k = 1] - \mathbb{E}[\tilde{Y} \mid \boldsymbol{X} = \boldsymbol{x}, A_k = 0]\big].
\end{aligned}
$$

Similarly, we identify $\theta_{\text{net}}(\boldsymbol{x})$. More details can be found in the supplementary material (Appendix B).

3.2 Estimation of inverse probability weights

To implement our two-step approach, we need consistent estimators for the nuisance parameters G and G_2 on $[0, t_0]$. We here describe an approach based on the reverse Kaplan-Meier estimator stratified on a subset of categorical covariates $\boldsymbol{Z} \subset \{A_k, \boldsymbol{X}\}$. With this method, we estimate the censoring survival distribution function G, conditional on $\boldsymbol{Z}$, as follows

$$\hat{G}(t \mid \boldsymbol{z}) = \prod_{t_k \leq t} \left(1 - \frac{\sum_{i=1}^{n} \mathbb{1}\{T_i = t_k, \Delta_i = 0, \boldsymbol{Z}_i = \boldsymbol{z}\}}{\sum_{i=1}^{n} \big(\mathbb{1}\{T_i \geq t_k\} - \mathbb{1}\{T_i = t_k, \Delta_i > 0, \boldsymbol{Z}_i = \boldsymbol{z}\}\big)} \right).$$

Ties in the event times are handled with the usual convention that the event of interest happens before competing events and censoring events. Similarly, we estimate G_2 with Kaplan-Meier estimator for the competing event time conditional on $\boldsymbol{Z}$,

$$\hat{G}_2(t \mid \boldsymbol{z}) = \prod_{t_k \leq t} \left(1 - \frac{\sum_{i=1}^{n} \mathbb{1}\{T_i = t_k, \Delta_i = 2, \boldsymbol{Z}_i = \boldsymbol{z}\}}{\sum_{i=1}^{n} \big(\mathbb{1}\{T_i \geq t_k\} - \mathbb{1}\{T_i = t_k, \Delta_i \neq 2, \boldsymbol{Z}_i = \boldsymbol{z}\}\big)} \right).$$

Under the working assumption that $G(t \mid A_k, \boldsymbol{X}) = P(C > t \mid A_k, \boldsymbol{X}) = P(C > t \mid \boldsymbol{Z})$, standard arguments (Andersen et al., 1993) lead to $\hat{G}(t|\boldsymbol{Z}) \to G(t|\boldsymbol{Z})$ a.s. as $n \to \infty$ for all $t \le t_0$, and likewise for $\hat{G}_2(t|\boldsymbol{Z})$. However, violation of the working assumption may lead to asymptotic bias in Step 1 of our two-step approach which may also lead to bias in the ranking of the treatment variables. We note that these working assumptions are appropriate in our illustrative data example (Section 6), whereas other settings may require a different approach; in Section 7, we discuss the bias-variance trade-off and how one may relax the working assumptions.

4   Variable importance

Suppose we have a list of treatments, $A_1, A_2, \ldots, A_K$, $K \in \mathbb{N}$, that we would like to rank according to their effect on a time-to-event outcome. Specifically for the purpose of ranking, we continue our discussion from Section 2.1.1 to distinguish between crude and net probabilities. The problem with crude probabilities is that they reflect a mixture of effects on the hazard rate of the event of interest and effects on the hazard rate of the competing risks. Net effects, on the other hand, are defined in a hypothetical world where all competing causes are eliminated and allow us to study the effect of a particular drug in a way that is independent of the effect that this drug may have on the hazard rate of the competing events. We argue that, for the purpose of drug discovery, it may be desirable to restrict the search to drugs that have net effects.

To obtain a ranking of the treatments, we apply the two-step approach of Section 3 which yields estimates $\hat{\bar{\theta}}_{\mathrm{net},k}$ for the treatment effects on the net probability scale for all drugs A_k, $k = 1, \ldots, K$. For comparison and illustration, we also compute estimates $\hat{\bar{\theta}}_{\mathrm{crude},k}$ for the treatment effect on the crude probability scale. A standard delta method argument using the standard errors $\hat{\sigma}_n(\boldsymbol{x})$ for the conditional estimates (as provided by Athey et al., 2019, Theorem 5 and Section 6) yields asymptotic normality of the forest estimators $\hat{\bar{\theta}}_{\mathrm{net},k}$, $\hat{\bar{\theta}}_{\mathrm{crude},k}$ for the average treatment effects, based on which we construct confidence intervals. Albeit the asymptotic standard errors also contain a contribution from the uncertainty of the weights constructed in Step 1 of our procedure, these contributions are in our experience often very small in real data applications. In our simulations and illustrative data analysis, we only show confidence intervals which ignore the statistical uncertainty due to Step 1. Despite these shortcomings, we note that in our simulation studies (Section 5) the coverage of the confidence intervals lies nicely around 95%.

5   Simulation study

To evaluate the performance of our proposed methodology, and as a proof of concept, we test our algorithm on simulated data. Our simulations further illustrate the difference between treatment effects on the crude and net probability scales. We here explain the design of the simulations. Further details in the form of R-code can be found on github, see Section 8.

We start by simulating covariates, $\boldsymbol{X} = (X_1, \ldots, X_6)$. We let X_1, X_4, X_5, X_6 be uniformly distributed on the unit interval $(0, 1)$, X_2 be categorical with three ordered categories, and X_4 be categorical with four ordered categories. We consider a setting where we compare $K = 10$ treatment variables drawn from Bernoulli distributions that are all dependent on one of the covariates, $\mathbb{E}[A_k \mid \boldsymbol{X}] = \mathrm{expit}(\beta_0^k + \beta_1^k X_{l_k})$, with $l_k \in \{1, \ldots, 6\}$. Given treatments and covariates, three latent event times T^1, T^2, C are simulated according to Weibull distributions. The Weibull distribution of the latent censoring time is specified independently of covariate and treatment variables. The Weibull distribution of the latent time to the event of interest is specified with a shape parameter dependent on X_1, X_3 and A_1. The Weibull distribution of the latent competing event time is specified with a shape parameter dependent on X_1, X_2 and A_2. Our simulation design is summarized in Table 1.

Event of interest:	$T^1 \sim A_1 + X_1 + X_3$
Competing event:	$T^2 \sim A_2 + X_1 + X_2$
Censoring:	$C \sim 1$

Table 1: Summary of simulation design.

The parameters $\bar{\theta}_{\text{net}}$ and $\bar{\theta}_{\text{crude}}$ are defined with time horizon $t_0 = 0.5$. Generally, we say that a treatment A_k has a protective effect on the net (crude) probability scale if $\bar{\theta}_{\text{net},A_k} < 0$ ($\bar{\theta}_{\text{crude},A_k} < 0$), a harmful effect if $\bar{\theta}_{\text{net},A_k} > 0$ ($\bar{\theta}_{\text{crude},A_k} > 0$), and a neutral effect if $\bar{\theta}_{\text{net},A_k} = 0$ ($\bar{\theta}_{\text{crude},A_k} = 0$). Throughout this section, we focus on three of the treatment variables: A_1 that has a direct effect on the event of interest, A_2 that has a effect only on the competing event, and A_3 that has no effect at all. The values of $\bar{\theta}_{\text{net},A_k}, \bar{\theta}_{\text{crude},A_k}$, $k = 1, 2, 3$, can be found in Table 2. Note that A_2 has no net effect but a protective crude effect since A_2 increases the rate of the competing event.

Effects on net probabilities:	$\bar{\theta}_{\text{net},A_1} = -0.113$	$\bar{\theta}_{\text{net},A_2} = 0$	$\bar{\theta}_{\text{net},A_3} = 0$
Effects on crude probabilities:	$\bar{\theta}_{\text{crude},A_1} = -0.083$	$\bar{\theta}_{\text{crude},A_2} = -0.047$	$\bar{\theta}_{\text{crude},A_3} = 0$

Table 2: Values of $\bar{\theta}_{\text{net},A_k}, \bar{\theta}_{\text{crude},A_k}$, $k = 1, 2, 3$, for the simulation study.

Our aim is to show that weighting yields unbiased estimation of the ATEs and further to explore the effect of confounding and sample size. Our simulations consist of the following two parts:

1. *Effect estimation and coverage.* We simulate $M = 500$ datasets with sample size $n = 500$ from the data-generating distribution. We look at effect estimates and coverage of the confidence intervals based on the standard error estimates provided by the forest.

2. *Ranking effectiveness.* For sample sizes $n \in \{100, 200, 500, 1000, 1500, 2000\}$, we simulate $M = 500$ datasets from the data-generating distribution. For each dataset, we use our algorithm to estimate the variable importance of the treatments, in form of estimates $\hat{\bar{\theta}}^m_{\text{net},A_k}$, and $\hat{\bar{\theta}}^m_{\text{crude},A_k}$ for $k = 1, \ldots, 10$ and $m = 1, \ldots, M$. For $k = 1, \ldots, 10$, we define

$$\mathcal{R}^M_{\text{net}}(A_k) := \frac{1}{M} \sum_{m=1}^{M} \prod_{k' \neq k} \mathbb{1}\{\hat{\bar{\theta}}^m_{\text{net},A_k} \leq \hat{\bar{\theta}}^m_{\text{net},A_{k'}}\}, \tag{5}$$

$$\mathcal{R}^M_{\text{crude}}(A_k) := \frac{1}{M} \sum_{m=1}^{M} \prod_{k' \neq k} \mathbb{1}\{\hat{\bar{\theta}}^m_{\text{crude},A_k} \leq \hat{\bar{\theta}}^m_{\text{crude},A_{k'}}\}, \tag{6}$$

as the fraction of simulation repetitions (out of $M = 500$) where the treatment variable A_k is ranked "most important" among $A_1, \ldots, A_{10}$ in terms of the protective effect on net and crude probabilities, respectively. We report the ability of our method to, for instance, detect treatment A_1 as the "most important" variable among $A_1, \ldots, A_{10}$.

We consider three different adjustment schemes for the inverse probability weight estimation:

(a) Weight estimators $\hat{G}, \hat{G}_2$ that are adjusted for A_2, X_1 and X_2, i.e., $\boldsymbol{Z} = \{A_2, X_1, X_2\}$.

(b) Weight estimators $\hat{G}, \hat{G}_2$ that are adjusted only for A_2, i.e., $\boldsymbol{Z} = \{A_2\}$.

(c) Weight estimators $\hat{G}, \hat{G}_2$ that are unadjusted, i.e., $\boldsymbol{Z} = \{1\}$.

The weight estimators are constructed outside the forest in Step 1 of our two-step procedure as described in Section 4. Based on the weights, a separate (GRF) forest is applied for each treatment variable A_k to estimate $\bar{\theta}_{\text{net},A_k}$ and $\bar{\theta}_{\text{crude},A_k}$, for $k = 1, \ldots, 10$.

5.1 Simulation results

5.1.1 Effect estimation and coverage

Figure 2 shows mean estimates across $M = 500$ simulated datasets using adjustment schemes (a)–(c) for estimation of inverse probability weights. Using adjustment scheme (a), treatment A_1 is correctly shown to have a protective effect both on the scale of net probabilities and on the scale of crude probabilities. Furthermore,

treatment A_2 is correctly shown to have a protective effect on the crude probabilities and no effect on the net probabilities and treatment A_3 is correctly shown to have no effect on both scales. Confidence intervals all have a coverage around 95% despite the fact that the standard errors do not take the uncertainty of the weight estimation into account. Using adjustment scheme (b) the weights are only adjusted for A_2, but Figure 2 shows that we still achieve 95% coverage with our confidence intervals. A comparison of the results for adjustment schemes (b) and (c) in Figure 2, on the other hand, reveals that it is crucial to include treatment A_2 in $\boldsymbol{Z}$ in the weight estimation for estimating $\bar{\theta}_{\text{net}}$: Adjustment scheme (c) uses unadjusted estimators for the inverse probability weights leading to an incorrect conclusion of a protective effect of treatment A_2 on the net probabilities.

Estimation of $\bar{\theta}_{\text{crude}}$ is hardly affected across the weighting schemes (a)–(c) since the censoring times were generated independent of all treatment and covariate variables. Of course, we can produce biased results for $\bar{\theta}_{\text{crude}}$ with the unadjusted weighting scheme if we let the censoring mechanism depend on treatment variables and covariates.
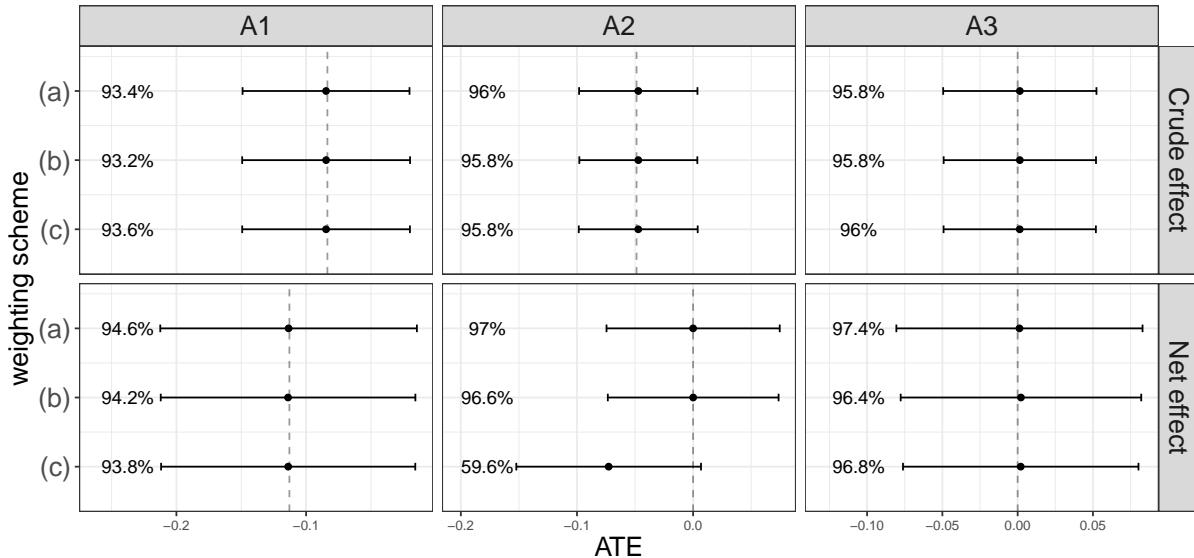

Figure 1: Results of the simulation studies. Shown are the results from estimation of $\bar{\theta}_{\text{net},A_k}$ and $\bar{\theta}_{\text{crude},A_k}$, $k = 1, 2, 3$, across $M = 500$ repetitions (all with sample size $n = 500$). The true values are marked by the dashed gray lines. Note that A_2 has an effect on the difference in crude probabilities (true effect $\bar{\theta}_{\text{crude},A_2} = -0.047$) through the effect on the competing risk event whereas it has no effect on the difference in net probabilities (true effect $\bar{\theta}_{\text{net},A_2} = 0$). The right column shows the coverage, i.e, the fraction of simulations where the confidence interval constructed based on the forest estimate of the standard error contains the true value. In weighting schemes (a) and (b), we used weights that were adjusted for $\boldsymbol{Z} = \{A_2, X_1, X_2\}$ and $\boldsymbol{Z} = \{A_2\}$, respectively, both resulting in unbiased estimators. In weighting scheme (c) we used unadjusted weights ($\boldsymbol{Z} = \{1\}$), inducing severe bias in the estimate of $\bar{\theta}_{\text{net},A_2}$. We do not show the results for $A_4, \ldots, A_{10}$ as these are similar to those for A_3.

5.1.2 Ranking effectiveness

Figure 2 shows the fractions $\mathcal{R}^M_{\text{net}}(A_1)$ and $\mathcal{R}^M_{\text{crude}}(A_1)$ defined in Equations (5) and (6) across different sample sizes. We show only the results from using adjustment scheme (b) and adjustment scheme (c) for estimating the inverse probability weights, as the results for weighting scheme (a) and (b) are similar.

Figure 2 shows $\mathcal{R}^M_{\text{net}}(A_k)$ and $\mathcal{R}^M_{\text{crude}}(A_k)$ for each of the three treatment variables A_1, A_2 and A_3. Recall that these are the fractions of simulation repetitions where A_k is ranked most important among $A_1, \ldots, A_{10}$ in terms of their effects on the net and crude probabilities, respectively. We would like $\mathcal{R}^M_{\text{net}}(A_1), \mathcal{R}^M_{\text{crude}}(A_1)$ to be close to one, and $\mathcal{R}^M_{\text{net}}(A_2), \mathcal{R}^M_{\text{crude}}(A_2), \mathcal{R}^M_{\text{net}}(A_3), \mathcal{R}^M_{\text{crude}}(A_3)$ to be close to zero. We further expect $\mathcal{R}^M_{\text{crude}}(A_2)$ to

be larger than $\mathcal{R}_{\text{net}}^M(A_2)$, due to the effect of A_2 on the competing risk event.

Figure 2 shows that both $\mathcal{R}_{\text{net}}^M(A_1)$ and $\mathcal{R}_{\text{crude}}^M(A_1)$ approach one as the sample size n increases: The larger the sample size, the more certain we are to detect the important variable A_1. On the other hand, it also shows that $\mathcal{R}_{\text{net}}^M(A_1)$ and $\mathcal{R}_{\text{crude}}^M(A_1)$ are both rather small for $n = 100$ and $n = 200$. Evidently, we need a certain sample size to be able to detect important variables with high probability. Across all sample sizes we have that $\mathcal{R}_{\text{net}}^M(A_3), \mathcal{R}_{\text{crude}}^M(A_3)$ are both very small, consistent with the fact that A_3 has no effect at all ($\bar{\theta}_{\text{net},A_3} = \bar{\theta}_{\text{crude},A_3} = 0$). The same is seen for $\mathcal{R}_{\text{net}}^M(A_2)$, except in the scenario where we fail to adjust for A_2 in the estimation of inverse probability weights. At last we note that $\mathcal{R}_{\text{crude}}^M(A_2)$ is overall larger than $\mathcal{R}_{\text{net}}^M(A_2)$, as we would expect.

6 Registry study

We apply our method to our motivating example in which it is of interest to study whether the use of any particular drug decreases the risk of relapse of depression resulting in psychiatric hospitalization. We here report estimates of effects on the net probabilities as well as those on the crude probabilities. Our aim is to discover new active substances; for this purpose, net probabilities will allow us to rank drugs according to their direct effect on depression, isolating this effect from what effect that drug may have on competing events.

The data we work with are obtained by linking Danish population-based registers that contain data on all prescribed medical purchases at pharmacies since 1995 and data on all patients treated at hospitals since 1977. A total of 78,700 patients were included who all had a first-time admission with depression after 2005. Figure 3 illustrates our design. The date of first contact with depression was defined as the index date. Patients with a psychiatric hospitalization in the eight weeks window following the index date were excluded. ATC drug codes were grouped after their first three digits to define binary exposure variables A_k with the value 1 if there was at least one prescribed purchase within the ATC group in the eight weeks window. Information on comorbidity was collected during a ten year period before the index date and included as covariates in the analysis, along with sex and age at the index date. Subjects were followed for five years from the end of the exposure window until depression relapse ($\Delta = 1$), a competing event ($\Delta = 2$), or loss to follow-up ($\Delta = 0$). Summary statistics on comorbidities, exposure and number of events can be found in the supplementary material (Appendix D).

To estimate the treatment effect of each considered drug group A_k on the net and crude probabilities, $\bar{\theta}_{\text{net},A_k}$ and $\bar{\theta}_{\text{crude},A_k}$, the inverse probability weights were adjusted for sex, age group and the treatment A_k itself. In the forest we used $B = 200$ trees, and we included sex, age group and all comorbidities as covariates.

6.1 Results

Figure 4 shows the causal forest estimates of the effect on net probabilities, $\bar{\theta}_{\text{net}}$, and of the effect on crude probabilities, $\bar{\theta}_{\text{crude}}$, for each drug group. We distinguish between a protective effect (if the upper confidence limit is below zero), a harmful effect (if the lower confidence limit is above zero), and a neutral effect (if zero is contained in the confidence interval). The size of the estimates allows us to rank the treatment groups according to their effect on relapse with depression. As we saw in the simulation study, there can be a substantial difference between $\bar{\theta}_{\text{net}}$ and $\bar{\theta}_{\text{crude}}$. Here we see in Figure 4, as well, that the estimates of the two parameters lead to slightly differing conclusions. Consider, for example, the drug group 'A12' (mineral supplements). This drug group is ranked higher in terms of net probabilities than in terms of crude probabilities (although the effect remains insignificant in both cases). On the other end of the spectrum, some drug groups are deemed harmful in terms of their effect on crude probabilities and neutral in terms of their effect on net probabilities: 'A10' (antidiabetics) and 'C10' (lipid modifying agents). Recall that net effects, if we believe in the assumptions required to go from a crude to a net interpretation (Section 2.4), allow us to rank drugs according to their direct effect on the depression relapse without interference from indirect effects on the competing events. Thus, we can avoid pitfalls like reporting, as we saw in our simulation study, a large treatment effect simply if that treatment increases the rate of a competing event, or, as we saw in Example 2.1, concluding smaller effects of treatments that also have protective effects on the rate of competing events.

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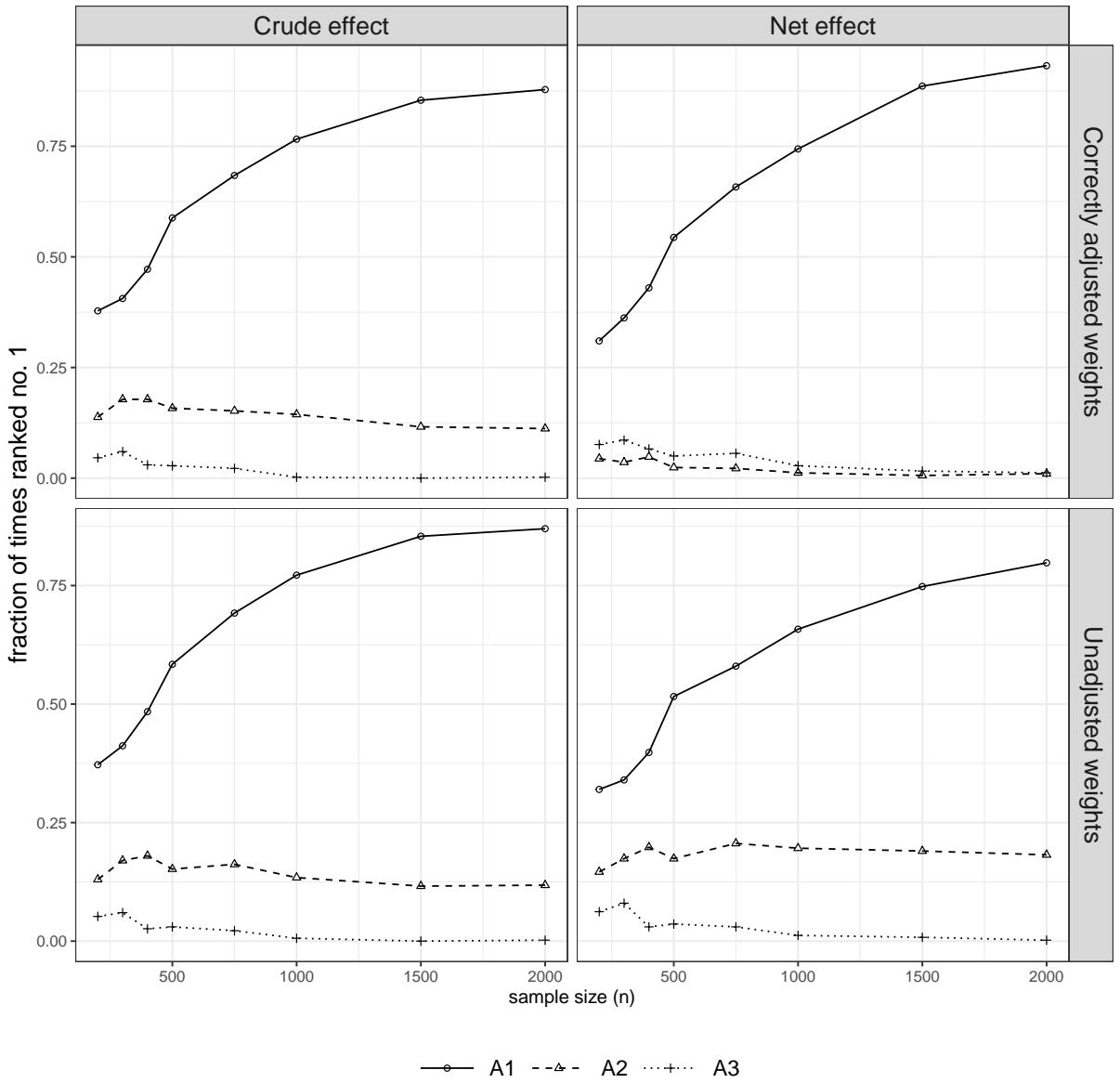
Figure 2: Results of the simulation studies. Shown are the fraction of times that each the three treatment variables A_1, A_2, A_3 was ranked most important (across $M = 500$ simulation repetitions) in terms of either the effect on the difference in net probabilities ($\bar{\theta}_{\mathrm{net}}$) or the effect on the difference in crude probabilities ($\bar{\theta}_{\mathrm{crude}}$). In the left plot, estimation of the inverse probability weights were adjusted for A_2 (weighting scheme (b)). In the right plot, we used unadjusted estimators (weighting scheme (c)) for the inverse probability weights.

7   Discussion

In this paper we have considered average treatment effect estimation for the purpose of ranking treatments according to their effect on a specific time-to-event outcome of interest. We have implemented a data-adaptive estimation method based on generalized random forests, where inverse probability weights are constructed to make the forest implementation directly applicable to the time-to-event setting. Our method makes no parametric model restrictions and really benefits from the flexibility of the generalized random forest which adaptively adjusts the propen-
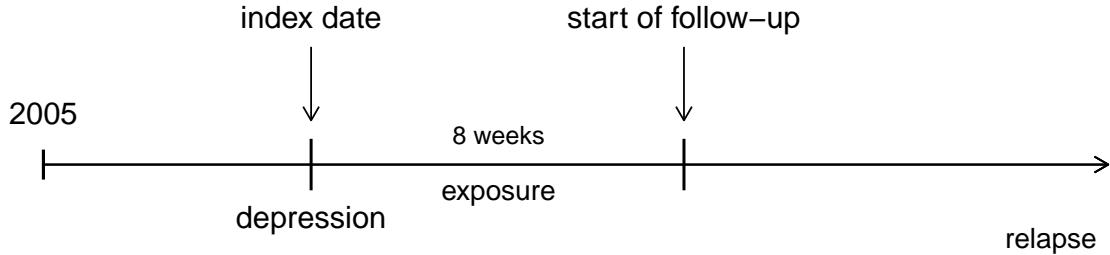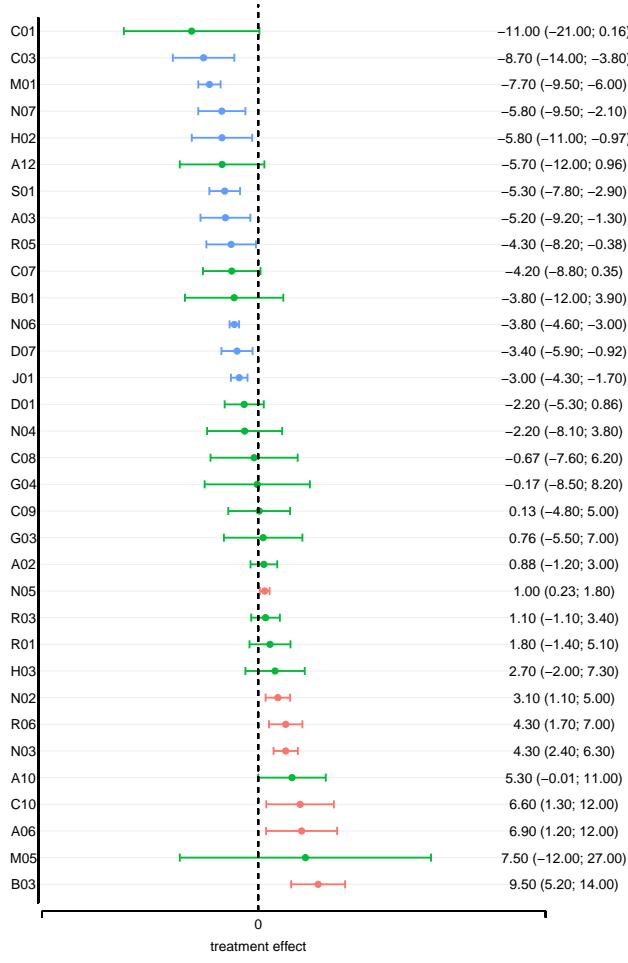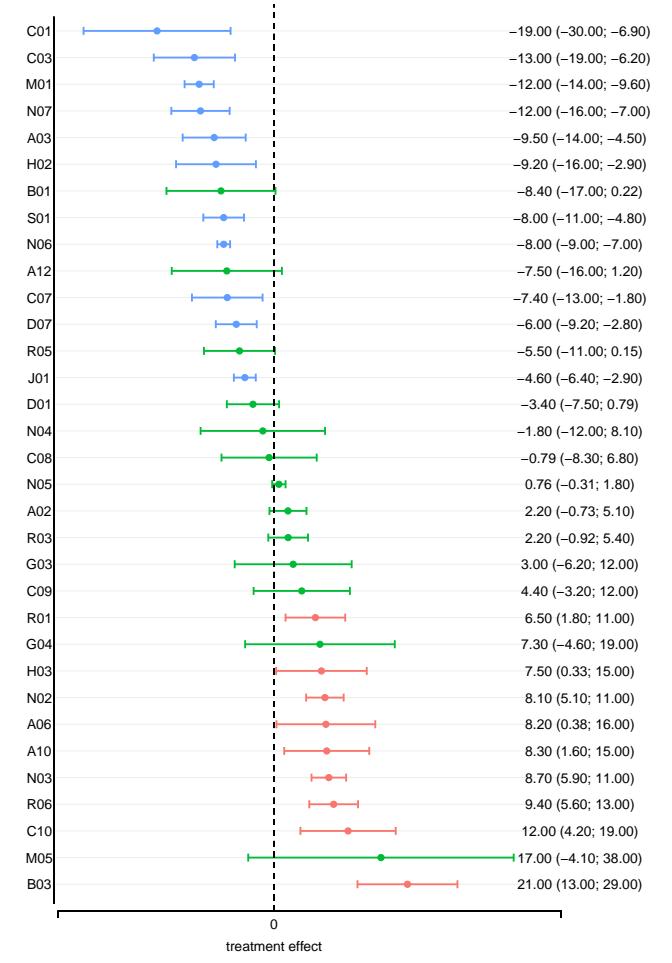
Figure 3: Illustration of our study design. The date of first contact with depression is defined as the index date. Patients with a psychiatric hospitalization in the eight weeks window following the index date are excluded. ATC drug codes are grouped after their first three digits to define binary exposure variables with the value 1 if there was at least one prescribed purchase within the ATC group in the eight weeks window. Information on comorbidity is collected during a ten year period before the index date and included as covariates in the analysis, along with sex and age at the index date.

sity of treatment for covariates. This altogether makes it highly applicable to drug discovery studies with many candidate drug treatments and not much prior subject matter knowledge. As an illustration, we have considered a particular application where it was of interest to rank a list of treatments according to their effect on depression.

To handle competing risks, we have discussed the use of two different average treatment effect parameters in the presence of competing risks, defined in terms of net and crude probabilities, respectively, with different interpretations. Particularly, net probabilities allow us to make inference for treatment directly on the outcome of interest, irrespective of that treatment's effect on competing risks. We argue for the utility of net probabilities when looking for new active substances as part of a drug discovery study, but emphasize, in accordance with earlier criticism, that they are not sensible interpreting the size of the effect, e.g., when counseling a patient. Crude probabilities should always be considered if interest is in the real world and the aim is to predict for a given patient. The methods proposed recently by Stensrud et al. (2020) provide an alternative route for isolating direct effects on the event of interest, but their methods require other untestable assumptions on the biological nature of the treatment mechanism.

A weakness of our presented analysis is the use of the Kaplan-Meier method for constructing the inverse probability weights. This may work in large scale registry data where most variables are categorical and a large amount of data are available to estimate the weights separately in all strata defined by the covariates. However, in other applications it may be necessary to allow that several continuous covariates affect the distributions G and G_2. Semiparametric theory tells us to use a flexible model and to include all covariates that affect the event time to improve robustness and efficiency (van der Laan and Robins, 2003). However, to achieve proper bias-variance trade-off for the target parameter in the second step, a data-adaptive method used for the weights must be undersmoothed. Another idea is to handle the weight estimation inside the forest in a one-step approach. Indeed, we may improve upon the current setting by implementing the splitting rule based on the efficient influence function (Robins and Rotnitzky, 1992; van der Laan and Robins, 2003), extending the methods of Rytgaard (2019) to the competing risks setting. In future work we follow this route and revise the implementation of GRFs to adapt it to the event history analysis setting as proposed by Rytgaard (2019).

Figure 4: *Left:* Causal forest estimates of $\bar{\theta}_{\text{net}}$ (using adjusted weights to construct weighted outcomes). *Right:* Causal forest estimates of $\bar{\theta}_{\text{crude}}$ (using adjusted weights to construct weighted outcomes). For each ATC group (marked on the x-axis) the plot shows the estimates and the estimated confidence intervals (numbers written on the right). The colors indicate the direction of the effect.

8 Supplementary Material

R code is available on github (https://github.com/helenecharlotte/grfCausalSearch). The supplementary material consists of Appendices A–D.

Appendix A

We here detail the identifiability assumptions for the effect on net probabilities and the effect on crude probabilities, respectively.

A.1 Identifiability assumptions for the effect on net probabilities, $\theta_{\mathrm{net}}(\boldsymbol{x})$

Identification of $\theta_{\mathrm{net}}(\boldsymbol{x})$ in terms of the observed data distribution depends on three untestable causal assumptions: Consistency, coarsening at random and positivity.

First, the assumption of consistency entails that the counterfactual event time $T^{1,a}$ corresponds to the observed event time for those subjects who were actually uncensored, free of event type $j = 2$ and were exposed to the treatment level $A_k = a$. Particularly, consistency provides the counterfactual variables as follows:

$$T = \min(T^{1,A_k}, T^{2,A_k}), \text{ and that, } T^{1,a} = T^{1,A_k} \text{ on the event that } A_k = a \text{ for } a = 0, 1. \tag{1a}$$

Here T^{2,A_k} is the uncensored counterfactual event time of type $j = 2$ under the observed treatment.

The second assumption of coarsening at random is characterized as follows. The full data we would have liked to observe are $(\boldsymbol{X}, T^{1,0}, T^{1,1})$. These are not fully observed due to censoring, the competing event and the treatment decision A_k, and we observe only the coarsened data $(\boldsymbol{X}, A_k, \tilde{T}, \tilde{\Delta})$ (Gill et al., 1997; van der Laan and Robins, 2003; Tsiatis, 2007). To identify $(\boldsymbol{X}, T^{1,0}, T^{1,1})$ from the data, we need coarsening at random (CAR) (Gill et al., 1997; van der Laan and Robins, 2003, Section 1.2.3), i.e., that the coarsening mechanism only depends on the full data structure $(\boldsymbol{X}, T^{1,0}, T^{1,1})$ through the observed data structure $(\boldsymbol{X}, A_k, \tilde{T}, \tilde{\Delta})$. Coarsening at random is implied by the following conditional independence conditions:

$$\begin{aligned} T^{1,a} &\perp\!\!\!\perp A_k \mid \boldsymbol{X}, \\ T^{1,A_k} &\perp\!\!\!\perp (C, T^{2,A_k}) \mid A_k, \boldsymbol{X}, \end{aligned} \tag{1b}$$

for $a = 0, 1$, also refer to as "no unmeasured confounding".

The last assumption of positivity requires for the coarsening mechanism that

$$P(\min(C, T^{2,A_k}) \geq t_0 \mid A_k, \boldsymbol{X}) \left(\pi_k(\boldsymbol{X})\right)^{A_k} (1 - \pi_k(\boldsymbol{X}))^{1-A_k} > \eta > 0, \tag{1c}$$

almost surely.

Under Assumptions 1a, 1b and 1c, we can link the distribution of the counterfactual variables to the observed data distribution as follows:

$$\begin{aligned} P(\tilde{T} &\in dt, \tilde{\Delta} = 1, A_k = a, \boldsymbol{X} \in d\boldsymbol{x}) \\ &= P(\tilde{\Delta} = 1 \mid T^{1,A_k} = t, A_k = a, \boldsymbol{X} = \boldsymbol{x}) P(T^{1,A_k} \in dt, A_k = a, \boldsymbol{X} \in d\boldsymbol{x}) \\ &= P(\min(C, T^{2,A_k}) \geq t \mid T^{1,A_k} = t, A_k = a, \boldsymbol{X} = \boldsymbol{x}) P(T^{1,A_k} \in dt \mid A_k = a, \boldsymbol{X} = \boldsymbol{x}) \\ &\hspace{5cm} P(A_k = a \mid \boldsymbol{X} = \boldsymbol{x}) P(\boldsymbol{X} \in d\boldsymbol{x}) \\ &= P(\min(C, T^{2,A_k}) \geq t \mid A_k = a, \boldsymbol{X} = \boldsymbol{x}) P(T^{1,a} \in dt \mid \boldsymbol{X} = \boldsymbol{x}) P(A_k = a \mid \boldsymbol{X} = \boldsymbol{x}) P(\boldsymbol{X} \in d\boldsymbol{x}). \end{aligned} \tag{7}$$

Particularly, the first line of Assumption 1b together with the Assumption 1a of consistency implies that

$$\begin{aligned} P(T^{1,A_k} \in dt \mid A_k = a, \boldsymbol{X} \in d\boldsymbol{x}) &\overset{1b}{=} P(T^{1,a} \in dt \mid A_k = a, \boldsymbol{X} = \boldsymbol{x}) \\ &\overset{1a}{=} P(T^{1,a} \in dt \mid \boldsymbol{X} = \boldsymbol{x}), \end{aligned}$$

whereas the second line of Assumption 2a yields that

$$P(\min(C, T^{2,A_k}) \geq t \mid T = t, \Delta = 1, A_k = a, \boldsymbol{X} = \boldsymbol{x}) = P(\min(C, T^{2,A_k}) \geq t \mid A_k = a, \boldsymbol{X} = \boldsymbol{x}).$$

Assumption 1c ensures that the right hand side of (8) is non-zero and well-defined.

A.2   Identifiability assumptions for the effect on crude probabilities, $\theta_{\mathrm{crude}}(\boldsymbol{x})$

The assumptions needed to identify $\theta_{\mathrm{crude}}(\boldsymbol{x})$ are less restrictive than those needed for $\theta_{\mathrm{net}}(\boldsymbol{x})$ and correspond to the standard setting for right-censored survival times. The consistency assumption for $\theta_{\mathrm{crude}}(\boldsymbol{x})$ can be expressed as

$$T = T^a \text{ and } \Delta = \Delta^a \text{ on the event that } A = a, \text{ for } a = 0, 1. \tag{2a}$$

The full data we would have liked to observe are $(\boldsymbol{X}, T^0, T^1, \Delta^0, \Delta^1)$, but we observe only the coarsened data $(\boldsymbol{X}, A_k, \tilde{T}, \tilde{\Delta})$ due to censoring C and treatment decision A_k. The equivalent of Assumption 1b,

$$\begin{aligned}
(T^a, \Delta^a) &\perp\!\!\!\perp A_k \,|\, \boldsymbol{X}, \quad \text{for } a = 0, 1, \\
(T, \Delta) &\perp\!\!\!\perp C \,|\, A_k, \boldsymbol{X},
\end{aligned} \tag{2b}$$

yields coarsening at random. We further make the positivity assumption that,

$$P(C \ge t_0 \,|\, A_k = a, \boldsymbol{X}) \,(\pi_k(\boldsymbol{X}))^a (1 - \pi_k(\boldsymbol{X}))^{1-a} > \eta > 0, \tag{2c}$$

almost surely, for $a = 0, 1$.

We can now express the observed data distribution as,

$$\begin{aligned}
P(\tilde{T} &\in dt, \tilde{\Delta} = 1, A_k = a, \boldsymbol{X} \in d\boldsymbol{x}) \\
&= P(\tilde{\Delta} \ge 1 \,|\, T = t, \Delta = 1, A_k = a, \boldsymbol{X} = \boldsymbol{x}) P(T \in dt, \Delta = 1, A_k = a, \boldsymbol{X} \in d\boldsymbol{x}) \\
&= P(C \ge t \,|\, T = t, \Delta = 1, A_k = a, \boldsymbol{X} = \boldsymbol{x}) P(T \in dt, \Delta = 1 \,|\, A_k = a, \boldsymbol{X} \in d\boldsymbol{x}) \\
&\qquad\qquad\qquad\qquad\qquad\qquad\qquad P(A_k = a \,|\, \boldsymbol{X} = \boldsymbol{x}) P(\boldsymbol{X} \in d\boldsymbol{x}) \\
&= P(C \ge t \,|\, A_k = a, \boldsymbol{X} = \boldsymbol{x}) P(T^a \in dt, \Delta^a = 1 \,|\, \boldsymbol{X} = \boldsymbol{x}) P(A_k = a \,|\, \boldsymbol{X} = \boldsymbol{x}) P(\boldsymbol{X} \in d\boldsymbol{x}),
\end{aligned} \tag{8}$$

relying on Assumptions 2a, 2b and 2c. Particularly, the first line of Assumption 2b together with the Assumption 2a of consistency implies that

$$\begin{aligned}
P(T \in dt, \Delta = 1 \,|\, A_k = a, \boldsymbol{X} \in d\boldsymbol{x}) &\overset{2b}{=} P(T^a \in dt, \Delta^a = 1 \,|\, A_k = a, \boldsymbol{X} = \boldsymbol{x}) \\
&\overset{2a}{=} P(T^a \in dt, \Delta^a = 1 \,|\, \boldsymbol{X} = \boldsymbol{x}),
\end{aligned}$$

whereas the second line of Assumption 2a yields that

$$P(C \ge t \,|\, T = t, \Delta = 1, A_k = a, \boldsymbol{X} = \boldsymbol{x}) = P(C \ge t \,|\, A_k = a, \boldsymbol{X} = \boldsymbol{x}).$$

Assumption 2c ensures that the right hand side of (8) is non-zero and well-defined.

Appendix B

B.3   Weighted outcome for net probabilities

Define the weighted outcome:

$$\tilde{Y}' = \frac{\mathbb{1}\{\tilde{T} \le t_0, \tilde{\Delta} = 1\}}{G'(\tilde{T}- \,|\, A_k, \boldsymbol{X})},$$

with weights given by

$$G'(\tilde{T}- \,|\, A_k, \boldsymbol{X}) = P(\min(T^{2, A_k}, C) \ge t \,|\, A_k, \boldsymbol{X}).$$

For this weighted outcome we have that,

$$\begin{aligned}
\theta_{\mathrm{net}}(\boldsymbol{x}) &= P(T^{1,1} \le t_0 \,|\, \boldsymbol{X} = \boldsymbol{x}) - P(T^{1,0} \le t_0 \,|\, \boldsymbol{X} = \boldsymbol{x}) \\
&= \mathbb{E}\big[\tilde{Y}' \,|\, \boldsymbol{X} = \boldsymbol{x}, A_k = 1\big] - \mathbb{E}\big[\tilde{Y}' \,|\, \boldsymbol{X} = \boldsymbol{x}, A_k = 0\big].
\end{aligned} \tag{9}$$

This follows straightforwardly by the identification in, and just after, Equation (7); indeed, we note that

$$
\begin{aligned}
\mathbb{E}[\tilde{Y}' \mid \boldsymbol{X}, A_k] &= \mathbb{E}\left[\frac{\mathbb{1}\{\tilde{T} \leq t_0, \tilde{\Delta} = 1\}}{G'(\tilde{T}- \mid \boldsymbol{X}, A_k)} \,\middle|\, \boldsymbol{X}, A_k \right] \\
&= \mathbb{E}\left[\mathbb{E}\left[\frac{\mathbb{1}\{T^{1,A_k} \leq t_0\}\mathbb{1}\{\tilde{\Delta} = 1\}}{G'(\tilde{T}- \mid \boldsymbol{X}, A_k)} \,\middle|\, T^{1,A_k}, \boldsymbol{X}, A_k \right] \,\middle|\, \boldsymbol{X}, A_k \right] \\
&= \mathbb{E}\left[\mathbb{1}\{T^{1,A_k} \leq t_0\} \mid \boldsymbol{X}, A_k \right] \mathbb{E}\left[\frac{\mathbb{E}[\mathbb{1}\{\tilde{\Delta} = 1\} \mid T^{1,A_k}, \boldsymbol{X}, A_k]}{G'(T^{1,A_k}- \mid \boldsymbol{X}, A_k)} \right] \\
&= \mathbb{E}\left[\mathbb{1}\{T^{1,A_k} \leq t_0\} \mid \boldsymbol{X}, A_k \right] \mathbb{E}\left[\frac{G'(T^{1,A_k}- \mid \boldsymbol{X}, A_k)}{G'(T^{1,A_k}- \mid \boldsymbol{X}, A_k)} \right] \\
&= \mathbb{E}[\mathbb{1}\{T^{1,A_k} \leq t_0 \mid \boldsymbol{X}, A_k],
\end{aligned}
$$

and

$$
\mathbb{E}[\mathbb{1}\{T^{1,A_k} \leq t_0 \mid \boldsymbol{X}, A_k = a] = \mathbb{E}[\mathbb{1}\{T^{1,a} \leq t_0\} \mid \boldsymbol{X}, A_k = a] = \mathbb{E}[\mathbb{1}\{T^{1,a} \leq t_0\} \mid \boldsymbol{X}],
$$

for $a = 0, 1$, which yields (9).

B.4 Weighted outcome for crude probabilities

For the weighted outcome,

$$
\tilde{Y} = \frac{\mathbb{1}\{\tilde{T} \leq t_0, \tilde{\Delta} = 1\}}{G(\tilde{T}- \mid A_k, \boldsymbol{X})},
$$

we have that,

$$
\begin{aligned}
\theta_{\mathrm{crude}}(\boldsymbol{x}) &= P(T^1 \leq t_0, \Delta^1 = 1 \mid \boldsymbol{X} = \boldsymbol{x}) - P(T^0 \leq t_0, \Delta^0 = 1 \mid \boldsymbol{X} = \boldsymbol{x}) \\
&= \mathbb{E}\big[\tilde{Y} \mid \boldsymbol{X} = \boldsymbol{x}, A_k = 1\big] - \mathbb{E}\big[\tilde{Y} \mid \boldsymbol{X} = \boldsymbol{x}, A_k = 0\big].
\end{aligned}
\tag{10}
$$

This follows straightforwardly by the identification in, and just after, Equation (8); indeed, we note that

$$
\begin{aligned}
\mathbb{E}[\tilde{Y} \mid \boldsymbol{X}, A_k] &= \mathbb{E}\left[\frac{\mathbb{1}\{\tilde{T} \leq t_0, \tilde{\Delta} = 1\}}{G(\tilde{T}- \mid \boldsymbol{X}, A_k)} \,\middle|\, \boldsymbol{X}, A_k \right] \\
&= \mathbb{E}\left[\mathbb{E}\left[\frac{\mathbb{1}\{T \leq t_0, \Delta = 1\}\mathbb{1}\{\tilde{\Delta} \geq 1\}}{G(T- \mid \boldsymbol{X}, A_k)} \,\middle|\, T, \Delta, \boldsymbol{X}, A_k \right] \,\middle|\, \boldsymbol{X}, A_k \right] \\
&= \mathbb{E}\left[\mathbb{1}\{T \leq t_0, \Delta = 1\} \frac{\mathbb{E}\big[\mathbb{1}\{\tilde{\Delta} \geq 1\} \mid T, \Delta, \boldsymbol{X}, A_k\big]}{G(T- \mid \boldsymbol{X}, A_k)} \,\middle|\, \boldsymbol{X}, A_k \right] \\
&= \mathbb{E}\left[\mathbb{1}\{T \leq t_0, \Delta = 1\} \frac{G(T- \mid \boldsymbol{X}, A_k)}{G(T- \mid \boldsymbol{X}, A_k)} \,\middle|\, \boldsymbol{X}, A_k \right] \\
&= \mathbb{E}\big[\mathbb{1}\{T \leq t_0, \Delta = 1\} \mid \boldsymbol{X}, A_k\big]
\end{aligned}
$$

and

$$
\begin{aligned}
\mathbb{E}[\mathbb{1}\{T \leq t_0, \Delta = 1\} \mid \boldsymbol{X}, A_k = a] &= \mathbb{E}[\mathbb{1}\{T^a \leq t_0, \Delta^a = 1\} \mid \boldsymbol{X}, A_k = a] \\
&= \mathbb{E}[\mathbb{1}\{T^a \leq t_0, \Delta^a = 1\} \mid \boldsymbol{X}],
\end{aligned}
$$

for $a = 0, 1$, which yields (10).

Appendix C

To explain the general idea of GRFs, we use a generic (uncensored) random variable $Y \in \mathbb{R}$ and a corresponding generic parameter of interest,

$$\theta(\boldsymbol{x}) = \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}],$$

representing the treatment effect of A_k on Y conditional on $\boldsymbol{X} = \boldsymbol{x}$. Athey et al. (2019, Section 6) consider a conditional average partial effect estimation problem which they formulate in terms of a structural model. Below we demonstrate the equivalence of their setting with the counterfactual formulation and show that the conditional average treatment effect estimation problem considered here is a special case. In particular, we show that the parameter $\theta(\boldsymbol{x})$ can be identified in terms of

$$\theta(\boldsymbol{x}) = \frac{\operatorname{cov}(A_k, Y \mid \boldsymbol{X} = \boldsymbol{x})}{\operatorname{Var}(A_k \mid \boldsymbol{X} = \boldsymbol{x})}. \tag{11}$$

This means that $\theta(\boldsymbol{x})$ can be estimated by providing estimators for $\operatorname{cov}(A_k, Y \mid \boldsymbol{X} = \boldsymbol{x})$ and $\operatorname{Var}(A_k \mid \boldsymbol{X} = \boldsymbol{x})$, respectively. The forest outputs weights that can be used to define such estimators as follows. First, forest weights are obtained by averaging over the neighborhoods $L_b(\boldsymbol{x})$ defined by the trees, $b = 1, \ldots, B$,

$$\alpha_i(\boldsymbol{x}) = \frac{1}{B} \sum_{b=1}^{B} \alpha_{b,i}(\boldsymbol{x}), \qquad \text{where,} \quad \alpha_{b,i}(\boldsymbol{x}) = \frac{\mathbb{1}\{\boldsymbol{X}_i \in L_b(\boldsymbol{x})\}}{\sum_{k=1}^{n} \mathbb{1}\{\boldsymbol{X}_k \in L_b(\boldsymbol{x})\}}. \tag{12}$$

Then, the forest estimator $\hat{\theta}_\alpha(\boldsymbol{x})$ is given by,

$$\hat{\theta}_\alpha(\boldsymbol{x}) = \left(\sum_{i=1}^{n} \alpha_i(\boldsymbol{x}) \left(A_i - \bar{A}_{k,\alpha} \right)^2 \right)^{-1} \left(\sum_{i=1}^{n} \alpha_i(\boldsymbol{x}) \left(A_i - \bar{A}_{k,\alpha} \right) \left(Y_i - \bar{Y}_\alpha \right) \right). \tag{13}$$

Here, $\bar{A}_{k,\alpha} = \sum_{i=1}^{n} \alpha_i(\boldsymbol{x}) A_i$ and $\bar{Y}_\alpha = \sum_{i=1}^{n} \alpha_i(\boldsymbol{x}) Y_i$ are estimators for the propensity score $\pi_k(\boldsymbol{x}) = \mathbb{E}[A_k \mid \boldsymbol{X} = \boldsymbol{x}]$ and for $\mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}]$, respectively. Athey et al. (2019, Theorem 5 and Section 6) provide conditions under which $\hat{\theta}_\alpha$ converges in distribution to a normal distribution centered around the true $\theta(\boldsymbol{x})$. They further propose an estimator $\hat{\sigma}_n(\boldsymbol{x})$ for the standard deviation of the asymptotic distribution.

A key part of the generalized random forest algorithm is the splitting rule that targets specifically the estimation of the quantity of interest $\theta(\boldsymbol{x})$. Each split starts with a mother node $M \subset \mathcal{X}$, corresponding to a subset of $\mathcal{X}$, that is to be split into two daughter nodes $D_1 \uplus D_2 = M$. For $l = 1, 2$, let $\hat{\theta}_{D_l}$ be the daughter node local estimate of $\theta(\boldsymbol{x})$ given by (13) with $\alpha_i(\boldsymbol{x}) = \mathbb{1}\{\boldsymbol{X}_i \in D_l\}$ that simply gives weight one to all samples falling in the respective daughter node. To derive their approximate criterion for picking good splits, Athey et al. (2019) use a gradient-based approximation of the mother node estimator $\hat{\theta}_M$. In the setting without censoring and competing risks, as we demonstrate below, it can be seen that the "pseudo-outcomes" used in the "labeling step" of the splitting rule correspond to mother node specific estimates of the efficient influence function for the target parameter. Specifically, the split criterion is based on,

$$\rho_i = W_M^{-1}(A_{k,i} - \bar{A}_M)\left(Y_i - \bar{Y}_M - \left(A_{k,i} - \bar{A}_M \right) \hat{\theta}_M \right), \tag{14}$$

where,

$$W_M = \frac{1}{\#\{i \,:\, \boldsymbol{X}_i \in M\}} \sum_{\{i \,:\, X_i \in M\}} (A_{k,i} - \bar{A}_M)^2,$$

and $\bar{A}_M, \bar{Y}_M$ are mother node averages. Each split of a mother node M into daughter nodes D_1, D_2 is carried out such as to maximize,

$$\tilde{\mathcal{L}}(D_1, D_2) = \sum_{l=1}^{2} \frac{1}{\#\{i \,:\, \boldsymbol{X}_i \in D_l\}} \left(\sum_{i \in \{i \,:\, X_i \in D_l\}} \rho_i \right)^2,$$

with ρ_i as defined in (14).

C.5 Equivalence between counterfactual formulation and structural model formulation

We demonstrate the equivalence of the setting of Athey et al. (2019, Section 6) with the counterfactual formulation and show that the conditional average treatment effect estimation problem considered in the main paper (Section 4) is a special case hereof.

Accordingly, we here consider observed data $O = (\boldsymbol{X}, A_k, Y)$, $\boldsymbol{X} \in \mathcal{X}$, $A_k \in \{0, 1\}$ and $Y \in \mathbb{R}$ (uncensored). Further, let Y^1 be the counterfactual outcome that would have been observed under $A_k = 1$, and Y^0 be the counterfactual outcome that would have been observed under $A_k = 0$. The consistency assumption states that

$$Y = A_k Y^1 + (1 - A_k) Y^0, \tag{15}$$

and the exogeneity assumption (no unmeasured confounding) that $(Y^1, Y^0) \perp\!\!\!\perp A_k \mid \boldsymbol{X}$. The conditional treatment effect is defined as,

$$\theta(\boldsymbol{x}) = \mathbb{E}[Y^1 - Y^0 \mid \boldsymbol{X} = \boldsymbol{x}] = \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}].$$

The second equality follows under the exogeneity assumption together with the consistency assumption.

Assume on the other hand that,

$$Y_i = a_i + b_i A_k + \varepsilon_i, \tag{16}$$

equivalent to (Athey et al., 2019, Section 6) with our $a_i + \varepsilon_i$ collapsed into just ε_i.

We show that (16) imposes no restriction when A_k is binary. Under consistency, we can express Y as,

$$
\begin{aligned}
Y &= A_k Y^1 + (1 - A_k) Y^0 \\
&= A_k Y^1 + (1 - A_k) Y^0 + A_k \big(\mathbb{E}[Y^1 \mid \boldsymbol{X}] - \mathbb{E}[Y^0 \mid \boldsymbol{X}]\big) - A_k \mathbb{E}[Y^1 \mid \boldsymbol{X}] - (1 - A_k) \mathbb{E}[Y^0 \mid \boldsymbol{X}] \\
&\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad + \mathbb{E}[Y^0 \mid \boldsymbol{X}] \\
&= \mathbb{E}[Y^0 \mid \boldsymbol{X}] + A_k \big(\mathbb{E}[Y^1 \mid \boldsymbol{X}] - \mathbb{E}[Y^0 \mid \boldsymbol{X}]\big) + A_k \big(Y^1 - \mathbb{E}[Y^1 \mid \boldsymbol{X}]\big) + (1 - A_k)\big(Y^0 - \mathbb{E}[Y^0 \mid \boldsymbol{X}]\big).
\end{aligned}
$$

So if we let,

$$
\begin{aligned}
a_i &:= \mathbb{E}[Y^0 \mid \boldsymbol{X}_i], \\
b_i &:= \mathbb{E}[Y^1 \mid \boldsymbol{X}_i] - \mathbb{E}[Y^0 \mid \boldsymbol{X}_i], \quad \text{and,} \\
\varepsilon_i &:= (1 - A_{k,i})\big(Y^0 - \mathbb{E}[Y^0 \mid \boldsymbol{X}_i]\big) + A_{k,i}\big(Y^1 - \mathbb{E}[Y^1 \mid \boldsymbol{X}_i]\big),
\end{aligned}
$$

we are back on the form in (16).

Further note that,

$$\mathbb{E}[\varepsilon_i \mid A_k, \boldsymbol{X}] = (1 - A_{k,i})\big(\mathbb{E}[Y^0 \mid \boldsymbol{X}_i] - \mathbb{E}[Y^0 \mid \boldsymbol{X}_i]\big) + A_{k,i}\big(\mathbb{E}[Y^1 \mid \boldsymbol{X}_i] - \mathbb{E}[Y^1 \mid \boldsymbol{X}_i]\big) = 0,$$

so that,

$$\mathbb{E}[Y_i \mid A_k, \boldsymbol{X}] = \mathbb{E}[Y^0 \mid \boldsymbol{X}_i] + \theta(\boldsymbol{x}) A_k.$$

C.6 Identification of the target parameter

We demonstrate that,

$$\theta(\boldsymbol{x}) = \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] = \frac{\operatorname{cov}(A_k, Y \mid \boldsymbol{X} = \boldsymbol{x})}{\operatorname{Var}(A_k \mid \boldsymbol{X} = \boldsymbol{x})}. \tag{17}$$

This follows since $A_k \in \{0, 1\}$, so that we have:

$$\begin{aligned}
\text{cov}(A_k, Y \mid \boldsymbol{X} = \boldsymbol{x}) &= \mathbb{E}[A_k Y \mid \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[A_k \mid \boldsymbol{X} = \boldsymbol{x}] \, \mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] \\
&= \mathbb{E}[A_k Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] \, \pi_k(\boldsymbol{x}) \\
&\qquad + \mathbb{E}[A_k Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] \, (1 - \pi_k(\boldsymbol{x})) - \pi_k(\boldsymbol{x}) \, \mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] \\
&= \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] \, \pi_k(\boldsymbol{x}) - \pi_k(\boldsymbol{x}) \left(\mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] \, \pi_k(\boldsymbol{x}) \right. \\
&\qquad \left. + \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] \, (1 - \pi_k(\boldsymbol{x})) \right) \\
&= \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] \, \pi_k(\boldsymbol{x})(1 - \pi_k(\boldsymbol{x})) \\
&\qquad - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] \, \pi_k(\boldsymbol{x})(1 - \pi_k(\boldsymbol{x})) \\
&= \left(\mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] \right) \pi_k(\boldsymbol{x})(1 - \pi_k(\boldsymbol{x})), \\
&= \left(\mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] \right) \text{Var}(A_k \mid \boldsymbol{X} = \boldsymbol{x}),
\end{aligned}$$

which yields (17).

C.7   Influence function used for splitting

The influence function used to split in the GRF algorithm for estimation of treatment effects (Athey et al., 2019, Section 6) is,

$$\rho_i = W_M^{-1}(A_{k,i} - \bar{A}_M)\Big(Y_i - \bar{Y}_M - \big(A_{k,i} - \bar{A}_M\big)\hat{\theta}_M\Big), \tag{18}$$

where,

$$W_M = \frac{1}{\#\{i \,:\, \boldsymbol{X}_i \in M\}} \sum_{\{i \,:\, X_i \in M\}} (A_{k,i} - \bar{A}_M)^2,$$

and $\bar{A}_M, \bar{Y}_M$ are mother node averages. Note that ρ_i in (18) is a mother node specific estimator for,

$$\phi(Y, A_k) = \big(\text{Var}(A_k \mid \boldsymbol{x})\big)^{-1}\big(A_k - \pi_k(\boldsymbol{x})\big)\big(Y - \mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] - \big(A_k - \pi_k(\boldsymbol{x})\big)\theta(\boldsymbol{x})\big). \tag{19}$$

We here demonstrate that $\phi(Y, A_k)$ in (19) can also be written,

$$\phi(Y, A_k) = \left(\frac{A_k}{\pi_k(\boldsymbol{x})} - \frac{1 - A_k}{1 - \pi_k(\boldsymbol{x})} \right) \Big(Y - \mathbb{E}[Y \mid A_k, \boldsymbol{X} = \boldsymbol{x}]\Big), \tag{20}$$

which we recognize as the efficient influence function for estimation of the parameter $\theta(\boldsymbol{x}) = \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}]$ (Scharfstein et al., 1999; Rosenblum and van der Laan, 2011).

First note that $\text{Var}(A_k \mid \boldsymbol{x}) = (1 - \pi_k(\boldsymbol{x}))\pi_k(\boldsymbol{x})$ since A_k is binary. Next, by iterated expectations, we have that,

$$\mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] = \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] \, \pi_k(\boldsymbol{x}) + \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] \, (1 - \pi_k(\boldsymbol{x})).$$

Moreover, we can write $(A_k - \pi_k) = A_k \, (1 - \pi_k) + (1 - A_k) \, \pi_k$. Also recall that $\theta_{\text{net}}(\boldsymbol{x}) = \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}]$.

Now rewrite,

$$\begin{aligned}
\frac{A_k}{\pi_k(\boldsymbol{x})} - \frac{(1 - A_k)}{1 - \pi_k(\boldsymbol{x})} &= \frac{A_k(1 - \pi_k(\boldsymbol{x}))}{\pi_k(\boldsymbol{x})(1 - \pi_k(\boldsymbol{x}))} - \frac{(1 - A_k)\pi_k(\boldsymbol{x})}{(1 - \pi_k(\boldsymbol{x}))\pi_k(\boldsymbol{x})} \\
&= \big(A_k - \pi_k(\boldsymbol{x})\big)\big(\text{Var}(A_k \mid \boldsymbol{x})\big)^{-1},
\end{aligned}$$

and,

$$\begin{aligned}
\mathbb{E}[Y \mid A_k &= 1, \boldsymbol{X} = \boldsymbol{x}] \\
&= \pi_k(\boldsymbol{x})\,\mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] + (1 - \pi_k(\boldsymbol{x}))\,\mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] \\
&= \mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}](1 - \pi_k(\boldsymbol{x})) + (1 - \pi_k(\boldsymbol{x}))\,\mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] \\
&= \mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] - (1 - \pi_k(\boldsymbol{x}))\big(\mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}]\big) \\
&= \mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] + (1 - \pi_k(\boldsymbol{x}))\big(\mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}]\big),
\end{aligned}$$

and likewise,

$$\begin{aligned}
\mathbb{E}[Y \mid A_k &= 0, \boldsymbol{X} = \boldsymbol{x}] \\
&= \pi_k(\boldsymbol{x})\,\mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] + (1 - \pi_k(\boldsymbol{x}))\,\mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] \\
&= \mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] + \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}]\,\pi_k(\boldsymbol{x}) - \pi_k(\boldsymbol{x})\,\mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] \\
&= \mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] - \pi_k(\boldsymbol{x})\big(\mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}]\big) \\
&= \mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] + (0 - \pi_k(\boldsymbol{x}))\big(\mathbb{E}[Y \mid A_k = 1, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y \mid A_k = 0, \boldsymbol{X} = \boldsymbol{x}]\big).
\end{aligned}$$

Collecting the above, we rewrite (20) as,

$$\begin{aligned}
\phi(Y, A_k) &= \left(\frac{A_k}{\pi_k(\boldsymbol{x})} - \frac{1 - A_k}{1 - \pi_k(\boldsymbol{x})}\right)\left(Y - \mathbb{E}[Y \mid A_k, \boldsymbol{X} = \boldsymbol{x}]\right) \\
&= (A_k - \pi_k(\boldsymbol{x}))\left(\mathrm{Var}(A_k \mid \boldsymbol{x})\right)^{-1}\left(Y - \mathbb{E}[Y \mid \boldsymbol{X} = \boldsymbol{x}] - (A_k - \pi_k(\boldsymbol{x}))\,\theta(\boldsymbol{x})\right),
\end{aligned}$$

which yields (19).

Appendix D

We here collect descriptive statistics for our data analysis.

Figure 5 shows unadjusted Aalen-Johansen estimators (Aalen and Johansen, 1978) for the risk of readmission with depression and risk of death without relapse, respectively.

Table 3 shows the number of subjects in each age group and in each comorbidity group. Table 4 shows the number of subjects exposed to the different drug groups in the exposure window. Table 5 shows the number of relapse with depression within five years, along with number of subjects who die without depression.

To illustrate the effects of covariates for the estimation of our target parameters, we compare our forest estimates of $\bar{\theta}_{\mathrm{crude}}$ to the naive Aalen-Johansen estimates of crude probabilities stratified on each treatment variable (that leaves out all covariate information), i.e., the nonparametric and unadjusted estimator of,

$$P(T \leq t_0, \Delta = 1 \mid A_k = 1) - P(T \leq t_0, \Delta = 1 \mid A_k = 0).$$

The naive Aalen-Johansen estimates along with confidence intervals and the corresponding causal forest estimates of the treatment effect on the crude probabilities, $\bar{\theta}_{\mathrm{crude}}$, are shown in Figure 6. We see that the treatment effect estimates for some drug groups differ quite a lot for the two methods. Considering these differences, we deduce that there is a covariate effect to be taken into account.

	Male (n=28748)	Female (n=49952)	Total (n=78700)
Infections	6429 (22.4)	14183 (28.4)	20612 (26.2)
Neoplasms	3775 (13.1)	9419 (18.9)	13194 (16.8)
Diseases of blood	674 (2.3)	1403 (2.8)	2077 (2.6)
Diseases of the nervous system	6560 (22.8)	11836 (23.7)	18396 (23.4)
Diseases of the circulatory or respiratory system	9446 (32.9)	16408 (32.8)	25854 (32.9)
Nutritional and metabolic diseases	6863 (23.9)	11752 (23.5)	18615 (23.7)
Diseases of the skin and subcutaneous tissue	2040 (7.1)	3752 (7.5)	5792 (7.4)
Diseases of the musculoskeletal system	7856 (27.3)	15212 (30.5)	23068 (29.3)
Diseases of the genitourinary system and pregnancy, childbirth and the puerperium	4002 (13.9)	21003 (42.0)	25005 (31.8)
age in (0,18]	1900 (6.6)	4595 (9.2)	6495 (8.3)
age in (18,25]	3437 (12.0)	7466 (14.9)	10903 (13.9)
age in (25,30]	2213 (7.7)	4347 (8.7)	6560 (8.3)
age in (30,40]	4668 (16.2)	8457 (16.9)	13125 (16.7)
age in (40,50]	5216 (18.1)	7360 (14.7)	12576 (16.0)
age in (50,60]	4349 (15.1)	5321 (10.7)	9670 (12.3)
age in (60,70]	2689 (9.4)	3486 (7.0)	6175 (7.8)
age in (70,80]	2308 (8.0)	4054 (8.1)	6362 (8.1)
age > 80	1968 (6.8)	4866 (9.7)	6834 (8.7)

Table 3: Comorbidities and demographics of the Danish population-based registry study. Shown are counts (%).

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	Male (n=28748)	Female (n=49952)	Total (n=78700)
N06	18740 (65.2)	33327 (66.7)	52067 (66.2)
N05	10049 (35.0)	16784 (33.6)	26833 (34.1)
N02	3384 (11.8)	7467 (14.9)	10851 (13.8)
A02	2509 (8.7)	4486 (9.0)	6995 (8.9)
J01	2118 (7.4)	5739 (11.5)	7857 (10.0)
B01	2687 (9.3)	3484 (7.0)	6171 (7.8)
N03	1713 (6.0)	2965 (5.9)	4678 (5.9)
C03	1610 (5.6)	3450 (6.9)	5060 (6.4)
G03	42 (0.1)	7352 (14.7)	7394 (9.4)
R03	1254 (4.4)	2381 (4.8)	3635 (4.6)
C09	2219 (7.7)	3079 (6.2)	5298 (6.7)
M01	1503 (5.2)	3082 (6.2)	4585 (5.8)
C10	1822 (6.3)	2356 (4.7)	4178 (5.3)
A10	1236 (4.3)	1339 (2.7)	2575 (3.3)
C07	1401 (4.9)	2075 (4.2)	3476 (4.4)
S01	866 (3.0)	2149 (4.3)	3015 (3.8)
C08	1170 (4.1)	1897 (3.8)	3067 (3.9)
A12	815 (2.8)	1907 (3.8)	2722 (3.5)
A06	756 (2.6)	1503 (3.0)	2259 (2.9)
C01	695 (2.4)	1082 (2.2)	1777 (2.3)
G04	1107 (3.9)	328 (0.7)	1435 (1.8)
H03	235 (0.8)	1390 (2.8)	1625 (2.1)
D07	633 (2.2)	1234 (2.5)	1867 (2.4)
N07	897 (3.1)	666 (1.3)	1563 (2.0)
B03	485 (1.7)	1076 (2.2)	1561 (2.0)
R05	370 (1.3)	951 (1.9)	1321 (1.7)
R06	442 (1.5)	1143 (2.3)	1585 (2.0)
A03	334 (1.2)	1010 (2.0)	1344 (1.7)
M05	158 (0.5)	1011 (2.0)	1169 (1.5)
H02	374 (1.3)	755 (1.5)	1129 (1.4)
N04	261 (0.9)	431 (0.9)	692 (0.9)
D01	458 (1.6)	708 (1.4)	1166 (1.5)
R01	357 (1.2)	672 (1.3)	1029 (1.3)

Table 4: Number (%) of subjects purchasing treatments in the Danish population-based registry study.

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Δ	event type	number of subjects	percent of total
0	censoring	67794	86.14 %
1	depression relapse	4613	5.861 %
2	competing event	6293	7.996 %

Table 5: Number of relapse events, censoring and competing events after five years.

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Risk of relapse


Risk of death without relapse
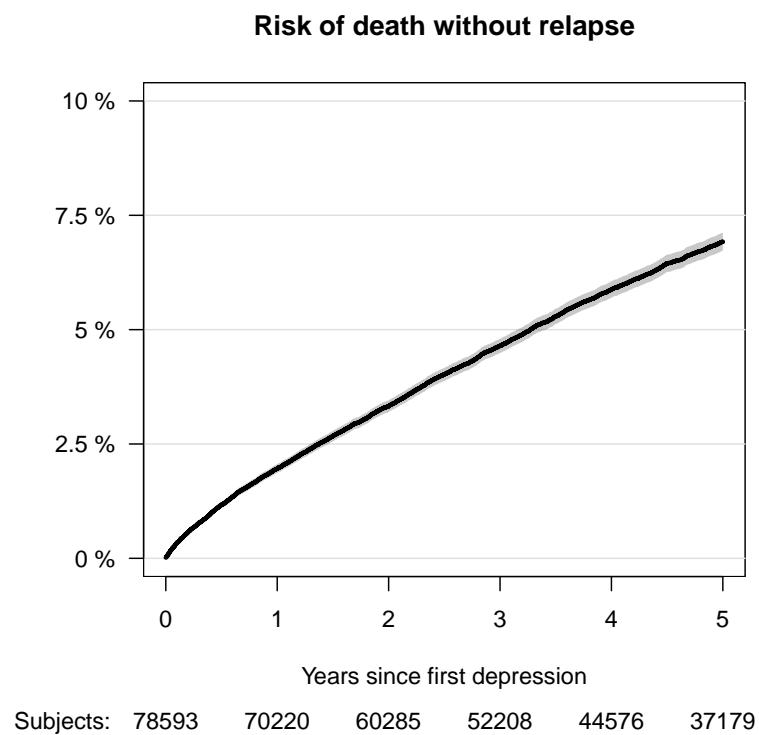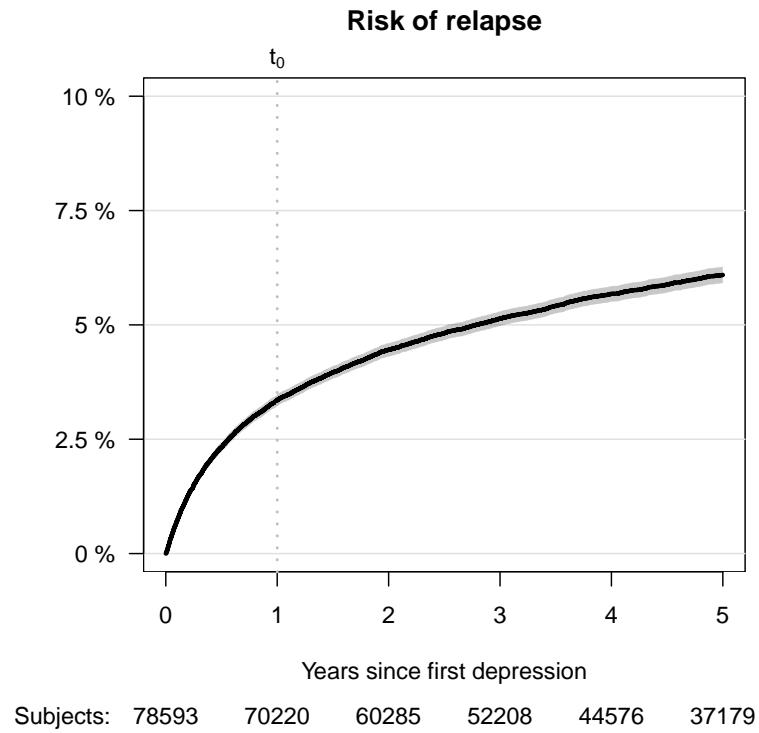
Figure 5: Aalen-Johansen estimators for the risk of readmission with depression (top) and risk of death without relapse (bottom), respectively. We are interested in readmissions within 1 year which is marked on the upper plot. The number of subjects at risk is shown below the plots.
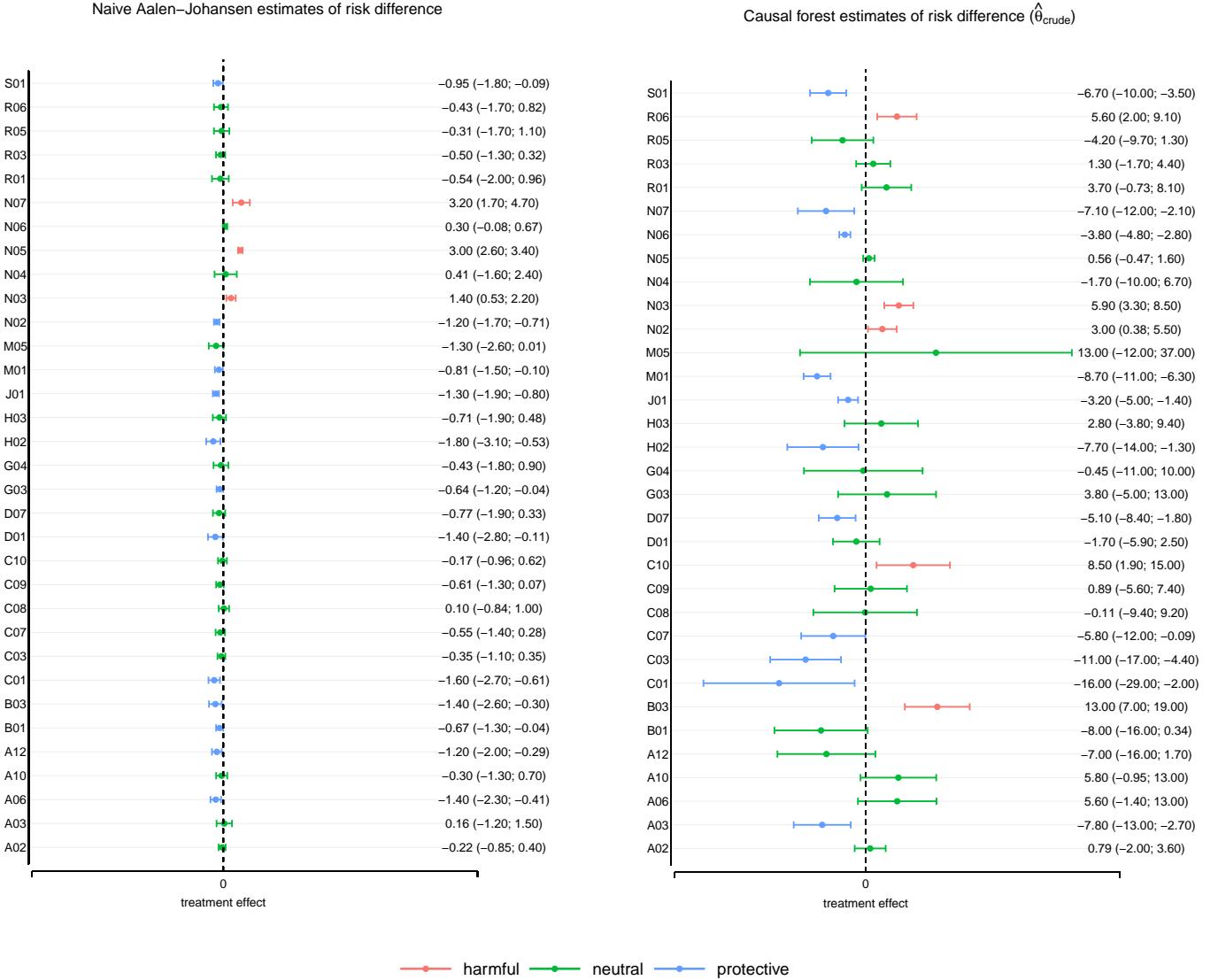
Figure 6: *Left:* Naive Aalen-Johansen estimates of the risk difference, i.e., the difference in crude probabilities stratified on the respective treatment. *Right:* Causal forest estimates of the effect on crude probabilities, $\bar{\theta}_{\text{crude}}$ (using unadjusted weights to construct weighted outcomes). For each ATC group (marked on the y-axis) the plot shows the estimates and the estimated confidence intervals (numbers written on the right). The colors indicate the direction of the effect.