Emulation of Target Trials to Study the Effectiveness and Safety of Medical Interventions

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EMULATION OF TARGET TRIALS TO STUDY THE EFFECTIVENESS
AND SAFETY OF MEDICAL INTERVENTIONS

ANDERS HUITFELDT

A Dissertation Submitted to the Faculty of
The Harvard T.H. Chan School of Public Health
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Science
in the Department of Epidemiology

Harvard University
Boston, Massachusetts.
November 2015
Ideally, clinical guidelines would be informed by well-designed randomized experiments. However, it is generally not possible to conduct a randomized trial for every clinically relevant decision. Decision makers therefore often have to rely on observational data. Guidelines that rely on observational data due to the absence of randomized trials benefit when the analysis mimics the analysis of a hypothetical target trial. This can be achieved by explicitly formulating the protocol of the target trial, and thoroughly discussing the feasibility of the conditions that must be met in order to validly emulate the target trial using observational data.

In chapter one, we discuss the emulation of trials that compare the effects of different timing strategies, that is, strategies that vary the frequency of delivery of a medical intervention or procedures, and provide an application to surveillance for colorectal cancer. In chapter two, we discuss a study design that attempts to avoid bias by comparing initiators of the treatment of interest with initiators of an “active comparator” that is believed to be inactive for the outcome, in order to emulate a randomized trial that compares the treatment of interest with an inactive comparator. In chapter three, we describe a new method that combines randomized trial data and external information to emulate a different target trial. We apply this
method to a randomized trial of postmenopausal hormone therapy in order to emulate a trial of a joint intervention on hormone therapy and statin therapy.
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At the time I first enrolled as an MPH student in August 2010, I did not even know the meaning of the word “Epidemiology”. Under ordinary circumstances, I very likely would have concluded that the word refers to a toolbox of methods for producing a never-ending stream of observational studies that always seem to contradict each other. Under ordinary circumstances, the thought of becoming an epidemiologist would not even have occurred to me.

But these were no ordinary circumstances. By a genuine stroke of inspiration, the department had assigned the introductory course to Miguel Hernán, perhaps the only professor in the world who would even have considered the idea of using it to teach a coherent framework for reasoning about the process whereby we obtain new knowledge about the consequences of decisions: What I now somewhat pretentiously refer to as the epistemology of medical decision making.

I was hooked from day 1, and after the course completed I was somehow able to talk my way into the doctoral program and into Miguel’s research group. I will never be able to repay my debt of gratitude to Miguel: For giving me a chance to take on this incredible challenge, for introducing me to a way of thinking about medical research that actually makes sense, for his unmatched ideas and suggestions about the direction of my projects, for all the incredibly hard work he did to tighten up my informal writing style, and most of all for believing in me.
I also want to thank my research committee member Jamie Robins. Jamie has an incredible ability to generate razor sharp insights that can completely change the direction of a research project, sometimes even changing how one conceptualizes the research question itself. Without his contributions, this thesis would certainly not have been possible. But above all, I am thankful to Jamie for what has been the true highlight of my five years at HSPH: The unique opportunity to be a teaching assistant for his groundbreaking course on advanced epidemiologic methods, and share a small part in helping the next generation of scientists absorb his core insights about causal inference in epidemiology. It is sometimes said that philosophers are “doomed to find Hegel waiting patiently at the end of whatever road they travel”.¹ While the truth value of this statement is questionable in the case of Hegel, I do not doubt that Epidemiologists will meet Jamie at the end of any path that they end up travelling.

My research committee would not have been complete without the invaluable contributions of Mette Kalager. Mette provided subject matter expertise in cancer screening and surveillance, and a much needed grounding in practical, clinical reasoning. I am deeply grateful to Mette for giving me the chance to collaborate with a fabulous and successful research group at the University of Oslo, where I hope to maintain deep connections for the duration of my research career, regardless of where it may take me. I also want to thank her for finding the time to videoconference in to committee meetings at arbitrary, often inconvenient times.

Funding for this research was provided in part by NIH grants P01 CA134294 and R01 AI102634 and in part by the Norwegian Research Council. I am grateful to everyone involved in obtaining these grants, in particular Miguel Hernán, Michael Bretthauer and Xihong Lin.

On a personal note, I want to thank my friends in the Boston area rationality and effective altruism community. You were there when I needed to believe that the world had not gone insane, that there really are smart people out there who genuinely believe in truth, in reason and in making a genuine attempt to build a world that is slightly less wrong.

Finally, I want to thank my parents for all their support throughout my 12 (!) years of higher education. I’m ready to get a job now – I promise.
If the causal effect is identified
I desire to believe that the causal effect is identified
If the causal effect is not identified
I desire to believe that the causal effect is not identified
Let me not become attached to beliefs I may not want
Methods to estimate the comparative effectiveness of clinical strategies that administer the same intervention at different times

Anders Huitfeldt, Mette Kalager, James M. Robins, Geir Hoff, Miguel A. Hernán
Abstract

Clinical guidelines that rely on observational data due to the absence of data from randomized trials benefit when the observational data or its analysis emulates trial data or its analysis. In this paper, we review a methodology for emulating trials that compare the effects of different timing strategies, that is, strategies that vary the frequency of delivery of a medical intervention or procedure. We review trial emulation for comparing (i) single applications of the procedure at different times, (ii) fixed schedules of application, and (iii) schedules adapted to the evolving clinical characteristics of the patients. For illustration, we describe an application in which we estimate the effect of surveillance colonoscopies in patients who had an adenoma detected during the NORCCAP trial.
1. Introduction

Clinical decisions are increasingly reliant on guidelines, but clinical guidelines are only as good as the available evidence on the comparative effectiveness of interventions. Ideally, such evidence would come from randomized controlled trials. When a randomized trial is not available, it may be possible to emulate it using observational data. This approach requires appropriate confounding adjustment, avoidance of selection bias in the definition of the groups to be compared, and formulation of a research question that is relevant for decision makers.

Prior explicit attempts to emulate trials using observational data have studied, for example, postmenopausal hormone therapy, statins, epoetin, and antiretroviral therapy. Here we review the emulation of trials to compare strategies that differ in the timing of the intervention of interest. As an example, we will consider post-polypectomy surveillance by colonoscopy. During this procedure, adenomas (benign tumors of the colon) are detected and removed. Most adenomas will not develop into colorectal cancer, but most cancers arise from adenomas. In patients with removed adenomas, surveillance colonoscopies are recommended to detect and remove future adenomas before they become malignant. The optimal interval between colonoscopies is not known. Current guidelines both in the US and the EU are mostly based on expert opinion due to the scarcity of available evidence.
Besides reviewing a methodology to emulate trials for the comparison of strategies that administer the same intervention at different times, we also review a classification of these strategies. First, we consider point interventions to study the effectiveness of a single application of the treatment. Second, we consider sustained interventions to study the effectiveness of a fixed treatment schedule (e.g., colonoscopy at 3 years after the initial procedure). Third, we consider sustained interventions to study the effectiveness of a personalized schedule of treatment (e.g., colonoscopy every year if the most recent procedure detected large adenomas, otherwise every 3 years). To fix ideas, we review the methodology in the context of its implementation to a cohort of Norwegian individuals. We start by describing this cohort.

2. Data

The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study was a randomized clinical trial of once-only sigmoidoscopy screening versus no sigmoidoscopy, conducted in Oslo and Telemark counties in Norway between 1999 and 2001. Our analysis includes participants in the sigmoidoscopy arm in whom at least one adenoma was detected (n=2190). As part of the trial, endoscopies were conducted in these individuals until the bowel was free from adenomas. We excluded patients with history of serious gastrointestinal disease, known genetic predisposition to colorectal cancer, and cancer detected as a result of screening in NORCCAP.
In addition to the available data (age, sex, county, smoking, family history of colorectal cancer, and findings at NORCCAP colonoscopies), we conducted a manual chart review at all hospitals in Oslo and Telemark—guided by claims data from the governmental single-payer agency HELFO—to collect data on the date, findings (e.g., size and type of adenomas) and indication of all subsequent colonoscopies and sigmoidoscopies. Of the post-screening endoscopies, 64% were for surveillance purposes (3% sigmoidoscopies and 61% colonoscopies), 30% were clinically indicated because of symptoms (27% colonoscopies, 3% sigmoidoscopies), and 6% were due to a recent incomplete endoscopy (4% colonoscopies, 2% sigmoidoscopies).

Our outcome of interest was incidence of colorectal cancer. For many surveillance interventions, the use of cancer incidence as an outcome is questionable because of potential lead time bias: cancer cases will be detected earlier in patients with more intensive surveillance, which will make surveillance appear less beneficial. In this case, however, the use of the outcome cancer incidence is justified because most of the beneficial effect of surveillance colonoscopy seems to be due to removing adenomas before they become malignant, with only a small component of the effect due to earlier detection of prevalent cancer. Death from colorectal cancer could not be studied as an outcome because there were too few cases.

We refer to the date of the last NORCCAP colonoscopy as time of “first eligibility” for our analyses. For each individual, follow-up ends at colorectal cancer, death, sigmoidoscopy,
emigration, or December 2011, whichever occurred first. Because we are trying to estimate the effects of post-baseline colonoscopies, which were not randomly assigned to the trial participants, ours is an analysis of observational data. The flow chart in Figure 1.1 describes the enrollment of participants in our study. Table 1.1 displays the characteristics of the eligible individuals.
Figure 1.1: Flowchart of selection of the 2190 eligible individuals from the intervention arm of the NORCCAP trial
Table 1.1: Characteristic of 2190 eligible individuals from the intervention arm of the NORCCAP trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Number of men</td>
<td>1322 (60%)</td>
</tr>
<tr>
<td>Average (SD) age at first eligibility, years</td>
<td>57.2 (3.8)</td>
</tr>
<tr>
<td>Median (IQR) duration of follow-up, months</td>
<td>134 (126-143)</td>
</tr>
<tr>
<td>Incident cases of colorectal cancer detected at surveillance colonoscopy</td>
<td>21</td>
</tr>
<tr>
<td>Deaths from colorectal cancer</td>
<td>187</td>
</tr>
<tr>
<td>Number of colonoscopies during follow-up</td>
<td>819</td>
</tr>
<tr>
<td>Number of sigmoidoscopies</td>
<td>75</td>
</tr>
<tr>
<td>Number of people with at least one colonoscopy after first eligibility</td>
<td>577</td>
</tr>
<tr>
<td>Number of people whose first follow-up colonoscopy was for surveillance</td>
<td>395</td>
</tr>
<tr>
<td>Median (IQR) time to first colonoscopy, months</td>
<td>68 (51-91)</td>
</tr>
<tr>
<td>Number of colonoscopies per individual</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1613 (74%)</td>
</tr>
<tr>
<td>1</td>
<td>389 (18%)</td>
</tr>
<tr>
<td>2</td>
<td>140 (6%)</td>
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<tr>
<td>3+</td>
<td>48 (2%)</td>
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</table>
3. **Three hypothetical randomized trials**

The design of any trial is determined by the causal question of interest, which in turn is determined by the population, the strategies being compared, and the outcome of interest to the decision makers. For surveillance tests, the strategies are defined by the timing of the test. Some strategies involve a point intervention at baseline, whereas other strategies involve interventions that are sustained over time according to either a fixed schedule (e.g., do not perform a colonoscopy for five years after baseline, then perform a colonoscopy at the end of year 5) or a schedule that depends on each individual’s time-evolving clinical characteristics (i.e., schedule the time of every colonoscopy according to the findings at the previous colonoscopy). We refer to sustained strategies with a fixed schedule as static and to those with a subject-specific schedule as dynamic.

Here we review 3 types of hypothetical trials that compare static and dynamic strategies and therefore address different questions regarding the effectiveness of surveillance colonoscopy. In all trials, eligible individuals are followed until death, loss to follow-up (i.e., emigration out of Norway), sigmoidoscopy, occurrence of the outcome (here, diagnosis of colorectal cancer), or Dec 31st 2011, whichever occurred earlier. In all trials, individuals receive a colonoscopy whenever it is clinically indicated (e.g., due to symptoms) but a surveillance colonoscopy only according to the trial protocol. A graphical representation of each trial is shown in Figure 1.2.
**Trial type #1: Point interventions assigned at a fixed time after first eligibility**

Individuals who survived 36 months since first eligibility are randomized to either 1) immediate surveillance colonoscopy, or 2) no surveillance colonoscopy. Additional eligibility criteria are no colorectal cancer, colonoscopy, or sigmoidoscopy during the 36 months before randomization. Individuals who reach age 70 or develop any invasive non-colorectal cancer before baseline also become ineligible (other comorbidities might be added to the exclusion criteria). For each individual, follow-up starts at the time of randomization, i.e., baseline is 36 months after first eligibility.

More generally, one can consider trials in which baseline is month $z$, where $z$ ranges between 36 and 84. The effect estimates from these trials will only apply to survivors without symptoms or cancer by $z$ months after first eligibility. These trials will help determine the effect of undergoing a colonoscopy among the survivors, but it does not directly inform the decision of when to undergo the colonoscopy. The next trial does so.

**Trial type #2: Sustained static strategies assigned at first eligibility**

Baseline is the time of first eligibility. Individuals are randomized to either 1) surveillance colonoscopy 36 months after baseline, or 2) surveillance colonoscopy 84 months after baseline. Individuals in both arms who reach age 70 or develop malignancies other than colorectal cancer may have surveillance colonoscopies at any time as determined by their physician. More generally, one can consider additional arms in which 36 is replaced by any value $x$ between 36
and 84. We could also consider similar trials in which baseline is any month after first eligibility.

For example, one could consider a trial in which individuals who have survived 36 months after first eligibility are randomized to either 1) immediate surveillance colonoscopy, or 2) surveillance colonoscopy at month 84 after first eligibility (48 months after baseline at 36 months). We will only consider trials with baseline at first eligibility.

Both trials type #1 and #2 compare fixed surveillance schedules, but they address different questions. Trial #1 helps individuals who have survived z months after adenoma removal decide whether they should undergo a surveillance colonoscopy at that time. Trial #2 helps individuals who just had their adenomas removed decide how long they should wait before having a surveillance colonoscopy (if they plan to have only one surveillance colonoscopy).

Neither trial type considers strategies that assign different surveillance schedules to different individuals (i.e., dynamic strategies). The next trial type does so.

**Trial type #3: Sustained dynamic strategies assigned at first eligibility**

Individuals at first eligibility are randomized to either 1) receive surveillance colonoscopies according to the following rules:

- First surveillance colonoscopy at 36 months if the adenomas detected at baseline sigmoidoscopy were low risk (1 or 2 small adenomas without villous features) and 12 months earlier (at month 24) otherwise.
• Follow-up surveillance colonoscopy 36 months after the previous colonoscopy (surveillance or clinical) if low-risk adenomas were detected, 12 months earlier (24 months after the previous colonoscopy) if high-risk adenomas (more than two, or large, or containing villous features) were detected, and 12 months later (48 months) if no adenomas were detected.

or 2) surveillance colonoscopies according to similar rules, but where 36 months is replaced by 84 months. During the follow-up, individuals in both arms of the trial may also receive a colonoscopy whenever it is clinically indicated due to symptoms. Individuals who reach age 70 or develop malignancies other than colorectal cancer after baseline may have surveillance colonoscopies at any time as determined by their physician. For each individual, follow-up starts at the time of randomization, i.e., baseline is the time of first eligibility.

More generally, one can consider additional arms in which 36 is replaced by \( x \) with \( x \) ranging from 36 to 84, or trials in which the time until the next surveillance colonoscopy is obtained by adding or subtracting \( y \) (rather than 12) months.
Figure 1.2: The three trial types considered in Chapter 1

Circles represent randomization, dotted lines represent periods when the strategy specifies all interventions (e.g., colonoscopy or no colonoscopy), solid lines represent periods when the strategy does not specify the intervention (e.g., anything goes, colonoscopy or no colonoscopy).
4. Emulating the design of the hypothetical trials

In this section we review how to emulate the design of each of the above hypothetical trials by setting up a database with the same structure as that of the trial. In the next section, we review how to mimic the analysis of the hypothetical trials.

Trial type #1: Point intervention assigned at a fixed time after first eligibility

We emulated 49 “trials,” one starting at each month \( z \) between months 36 and 84 after first eligibility. For the “trial” starting in month \( z \), we identified the individuals who met the eligibility criteria at baseline, i.e., all individuals with adenomas detected and removed at first eligibility who were alive and had not yet had a post-screening colonoscopy/sigmoidoscopy or been diagnosed with colorectal cancer by \( z \) months of follow-up. For each “trial,” individuals were classified into the colonoscopy arm if they received a colonoscopy during month \( z \) and into the control arm otherwise.

We identified 2028 eligible individuals. On average, each participated in 45 “trials,” of which at most 1 was in the colonoscopy arm. The number of eligible individuals who received a colonoscopy at baseline ranged between 0 (in several “trials”) and 16 (in “trial” \( z=61 \)). See Appendix Table 1 for details. Unfortunately, all “trials” had zero cancers among the exposed, which means the data from NORCCAP cannot be used for a meaningful emulation of Trial type #1.
Trial type #1 has the advantage of being easy to emulate and analyze when sufficient observational data are available. This approach has been used in observational studies to estimate the observational analog of the intention-to-treat effect of statin therapy\(^4\) and postmenopausal hormone therapy.\(^3\) Here we will not consider this trial type further.

**Trial type #2: Sustained static strategies assigned at first eligibility**

We emulated a randomized trial with 49 arms, in which the participants were assigned at first eligibility to colonoscopy at a randomly assigned time ranging from month 36 to 84 after first eligibility. Classifying the 2190 eligible individuals into a single arm is not possible because, at baseline, each individual’s data are consistent with all 49 arms. To overcome this problem we created an expanded dataset with 49 clones of each individual who did not receive a colonoscopy at baseline, and assigned each of them to a different arm.\(^4\) The 2190 eligible subjects contributed 107,309 clones to this “trial.” See Appendix Table 2 for details.

The clones in the expanded dataset were censored at the time their data deviated from the strategy to which they were assigned. For example, in arm 84, 12.9% of participants were censored for having a surveillance colonoscopy too early (before month 84), 73.5% of participants were censored for failing to have a surveillance colonoscopy in time (in month 84), and 0.5% were censored for having a sigmoidoscopy. Those who received a colonoscopy for clinical reasons or developed malignancies other than colorectal cancer were subsequently considered “immune” from censoring.
**Trial type #3: Sustained dynamic strategies assigned at first eligibility**

We emulated a trial with 49 arms, one for each value \( x \) in the dynamic strategies defined above. The 2190 individuals were classified into the arm that was consistent with their observed data. Like in the previous trial, individuals cannot be assigned to a single arm at baseline, so we created an expanded dataset with 49 clones of each individual and assigned each of them to a different arm. The clones were censored at the time they deviated from the strategy to which they were assigned. For example, in arm 84, 11.3% of participants were censored for having a surveillance colonoscopy too early, 79.7% of participants for failing to have a surveillance colonoscopy in time, and 1.3% for having a sigmoidoscopy. The 2190 eligible subjects contributed 107,309 clones to this “trial.” See Appendix Table 3 for details.

5. **Emulating the design of hypothetical trials with a grace period**

So far we have implicitly assumed that it is possible to administer a colonoscopy at a precisely specified time point, e.g., month 36. However, in many clinical settings, this may not be feasible. We may therefore be more interested in emulating trials with a grace period, that is, a window of \( m \) months during which the patient may undergo colonoscopy. For example, in Trial type #2, patients would be assigned to interventions of the form “surveillance colonoscopy between \( x \) and \( x+m \) months after baseline.” Trials with a grace period more accurately reflect clinical practice in which administrative delays and patient availability may prevent an immediate intervention.
Strategies with a grace period are emulated using “clones” as described above, but with different criteria for censoring. Suppose we use a grace period of $m=6$ months. An individual who received a surveillance colonoscopy in month 40 now has data consistent with arm 36 because subjects assigned to this arm are allowed to have a colonoscopy at any time between months 36 and 42. Therefore his clones assigned to arms 36 to 40 will not be censored whereas his clone assigned to arm 41 will be censored because he received a surveillance colonoscopy before the assigned time.

The addition of a grace period requires us to specify the distribution of the interventions during the grace period. For example, we might ask whether most colonoscopies are performed during the first two months of the grace period, or whether they are more equally distributed during the grace period. In our application, we will specify a uniform distribution of colonoscopies during the grace period.\textsuperscript{14}

In both Trials #2 and #3 with a 6-month grace period, each of the 2190 eligible individuals in the original dataset contributed 49 clones, for a total of 107,310 clones to the expanded dataset. In trial #2, the average censoring time ranged between 41.9 months for $x=36$ to 89.1 months for $x=84$. In arm 84, 12.9% of participants were censored for having a surveillance colonoscopy too early (before month 84), 71.5% of participants were censored at month 90 for failing to have a surveillance colonoscopy in time, 0.1% were censored after month 90 for having a second surveillance colonoscopy, and 0.6% were censored for having a
sigmoidoscopy. Across the 49 arms, there were 381 incident cases of colorectal cancer in the clones, which occurred in 12 unique individuals.

In Trial #3, the average censoring time ranged from 34.2 months for \( x=36 \) to 78.1 months for \( x=84 \). For arm 84, 11.3\% of participants were censored for having a surveillance colonoscopy too early, 77.6\% for failing to have a surveillance colonoscopy in time, and 1.4\% for having a sigmoidoscopy. In total, there were 254 incident cases of colorectal cancer in 13 unique individuals. See Appendix Tables 2 and 3 for details.

6. Emulating the analysis of the hypothetical trials

After reviewing how to create observational databases with the same structure as hypothetical randomized trials, we review how to use those databases to estimate the cumulative incidence curves (or their complement, the survival curves) that would have been observed under each strategy if all individuals had fully adhered to their original arm assignment. In a slight abuse of notation, we index the strategies by the variable \( x \), which was defined in the previous sections. For example, in Trial #2, \( x = 78 \) corresponds to the strategy “surveillance colonoscopy between 78 and 78+6 months after baseline.”

In a true randomized trial with many arms \( x \), we could estimate these curves nonparametrically (Kaplan-Meier curves) or parametrically by fitting a pooled logistic model of the form

\[
\text{logit } \Pr(Y_{t+1} = 0|Y_t = D_t = 0, x) = \alpha_{0,t} + \alpha_1 f(x) + \alpha_2 f(x) \times t, \text{ where } t \text{ denotes time (in months)},
\]

18
$Y_t$ is an indicator of colorectal cancer by $t$, $D_t$ an indicator of death by $t$, $\alpha_{0,t}$ is a time-varying intercept (estimated, for example, via restricted cubic splines for time with knots at 30, 60, 90 and 120 months), $f(x)$ is a function of $x$ (for example, a second degree polynomial), and $f(x) \times t$ is a product term to allow the hazard ratio to vary during the follow-up. For example, for the first 36 months of follow-up, the hazard is known to be identical under all strategies, but it may change after that if colonoscopy has a non-null effect on colorectal cancer incidence.

We would then calculate the predicted values for each value of $x$ and compute their product in order to estimate the survival curves. Pointwise 95% confidence intervals for the curves can be obtained via a non-parametric bootstrap. In our emulated trials, however, the above logistic model needs to be adjusted by both baseline and post-baseline (time-varying) confounders. The procedure then needs to be modified as we now describe.

Adjustment for covariates

In both trials #2 and #3, we need to adjust for covariates that jointly predict surveillance colonoscopy $A_t$ (and therefore censoring) and subsequent outcome. Some of these variables are fixed at the baseline of each trial; others vary during the follow-up. Let $L_0$ represent the vector of baseline covariates, which include age at baseline, sex, family history of colorectal cancer, history of smoking, and findings at NORCCAP colonoscopies (number of adenomas, size, histology and presence of villous elements). Let $L_t$ represent the vector of time-varying covariates, which include an indicator for incident non-colorectal malignancies, and a vector of
the findings from the most recent colonoscopy (number of adenomas, size of largest adenoma, histological grade and presence of villous elements).

To adjust for \( L_0 \), one could fit the pooled logistic model
\[
\logit \ Pr(Y_{t+1} = 0|Y_t = 0, x, L_0) = \alpha_{0,t} + \alpha_1 f(x) + \alpha_2 f(x) \times t + \alpha_3 L_0
\]
to the expanded dataset of each trial separately. To obtain the survival curves under each strategy \( x \), one would then calculate the predicted values for each value of \( x \), standardized them by \( L_0 \) and compute their product. However, the time-varying covariates \( L_t \) cannot be added to the logistic model because these variables may be affected by prior treatment\(^{10,11}\) (a colonoscopy may change the findings at future colonoscopies, for example by removing adenomas; see Appendix). We therefore need to use IP weighting to adjust for \( L_t \).

The subject-specific, time-varying IP weights are
\[
W_t = \prod_{j=0}^{t-1} \frac{1}{f(A_j | \bar{A}_{j-1}, \bar{L}_j, Y_j = D_j = 0)}.
\]
Informally, the denominator of the weights is each subject’s conditional probability of having, at each time \( t \), his or her own surveillance colonoscopy history. We use overbars to denote history, i.e., \( \bar{L}_t = (L_0, L_1, L_2, \ldots, L_t) \).

The factors in the denominator of the weights were set to 1 in months following age 70, a non-surveillance colonoscopy, or the diagnosis of malignancies other than colorectal cancer because the individual has a probability 1 of remaining uncensored during those months. The factors in the denominator were also set to 1 during the first 9 months after a colonoscopy is
received, because no surveillance colonoscopies were performed during this period (only colonoscopies due to symptoms or to incompleteness of the preceding colonoscopy). In previous applications of IP weighting for strategies with grace periods, the investigators were interested only in strategies that were not sustained beyond the initial decision to treat. Therefore, the contributions to the weights were set to 1 for all time periods after treatment was first received.

For all other months, we estimate the denominator by fitting a logistic model for the conditional probability of receiving a colonoscopy to the original, unexpanded study population. We fit the model

\[
\text{logit } \Pr(A_t = 1|\tilde{A}_{t-1}, \tilde{L}_t) = \beta_{0,t} + \beta_1 g(\tilde{A}_{t-1})P_t + \beta_2 L_t + \beta_3 L_t P_t
\]

where \(\beta_{0,t}\) is a time-varying intercept estimated via restricted cubic splines with knots at 30, 60, 90, and 120 months, \(g(\tilde{A}_{t-1})\) is the time since the most recent colonoscopy, and covariate history \(\tilde{L}_t\) is summarized via the time-varying covariates \(L_t\) and the baseline variables \(L_0\), which include age (restricted cubic splines with knots at 50, 55, 60, and 65 years), sex, family history of colorectal cancer (yes/no), history of smoking (yes/no), findings at the NORCCAP colonoscopies (indicators for 3 or more adenomas, adenoma greater than 10mm, adenoma with villous component, and histological grade (1 if high grade dysplasia, 0 otherwise). The variables \(g(\tilde{A}_{t-1})\) and \(L_t\) are entered to the model only in a product (“interaction”) term with \(P_t\), an indicator for prior colonoscopy (1 if the individual had a colonoscopy before \(t\), 0 otherwise),
such that the terms are zero in individuals who have not had a previous surveillance colonoscopy.

Because the IP weights already adjust for the baseline covariates $L_0$, we did not include them as covariates in the outcome model. That is, we fit the weighted pooled logistic model

\[ \text{logit } \Pr(Y_{t+1} = 0|Y_t = 0, x) = \alpha_{0,t} + \alpha_1 f(x) + \alpha_2 f(x) \times t. \]

To check the robustness of our estimates to different choices of functional form for time and $x$, we explored different parameterizations of the outcome model, including a quadratic functional form for time, cubic terms for $x$, and additional interaction terms between $f(x)$ and time.

**Grace Period**

Because our strategies of interest include grace periods, the above IP weights $W_t$ need to be modified. Specifically, the numerator of the factors corresponding to months included in the grace period need to change to ensure that surveillance colonoscopies will be uniformly distributed during the grace period. For trial #2, the numerator of factors corresponding to month $j$ of the grace period is replaced by $\frac{1}{m+1-j}$ with $j = 0, 1, \ldots, 5$ when $A_t = 1$, and replaced by $\frac{m-j}{m+1-j}$ when $A_t = 0$. For trial #3, where there can be multiple surveillance colonoscopies, we use the same approach during all grace periods.

*Estimates from NORCCAP data*
Table 1.2 shows the 5- and 10-year risks of colorectal cancer for arms 36 and 84 in Trials #2 and #3. For both static and dynamic strategies, earlier surveillance colonoscopy resulted in a lower risk. The estimated survival curves for selected arms of trials #2 and #3 are shown in Figure 1.3. As expected, the survival curves are essentially identical over the first three years, as the strategies are the same during this time period. Results were similar in sensitivity analyses using different functional forms for f(x) and time.

Note that, had the dataset included no cancer diagnoses after surveillance colonoscopy, the conclusion that delaying colonoscopy increases risk would be foregone. In our dataset, only one individual who has a surveillance colonoscopy between months 36 and 84 subsequently developed colorectal cancer, and he was censored before getting cancer under most clinically relevant strategies. Any changes to the strategies that led to him not being censored, would result in substantial changes to the estimates. Therefore our analysis needs to be replicated in a larger dataset.
Figure 1.3: Estimated survival curves for Trials #2 and #3
Table 1.2: Estimated risk of colorectal cancer at 5 and 10 years under selected surveillance strategies, intervention arm of the NORCCAP trial

<table>
<thead>
<tr>
<th></th>
<th>Risk, % (95% CI) x=36</th>
<th>Risk, % (95% CI) x=84</th>
<th>Risk difference, % (comparing x=36 with x=84) (95% CI)</th>
<th>Risk ratio (comparing x=36 with x=84) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Static Strategies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 years</td>
<td>0.15 (0.03-0.37)</td>
<td>0.30 (0.08-0.59)</td>
<td>-0.15 (-0.31 – 0.00)</td>
<td>0.47 (0.06-0.87)</td>
</tr>
<tr>
<td>At 10 years</td>
<td>0.31 (0.05-0.69)</td>
<td>0.63 (0.27-1.14)</td>
<td>-0.32 (-0.67 – 0.01)</td>
<td>0.49 (0.10-1.01)</td>
</tr>
<tr>
<td><strong>Dynamic Strategies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 years</td>
<td>0.12 (0.00-0.36)</td>
<td>0.25 (0.01-0.50)</td>
<td>-0.13 (-0.30 – 0.01)</td>
<td>0.49 (0.03-1.18)</td>
</tr>
<tr>
<td>At 10 years</td>
<td>0.30 (0.05-0.90)</td>
<td>0.44 (0.17-0.76)</td>
<td>-0.14 (-0.46 – 0.03)</td>
<td>0.67 (0.10-1.76)</td>
</tr>
</tbody>
</table>
7. Conclusions

After a medical procedure or medication has been shown to be effective, the next question is usually how often it should be administered. In this paper, we reviewed an approach that, when applied to a sufficiently large and rich dataset, helps decide among various timing strategies. Specifically, we outlined the design and analysis of hypothetical randomized trials to compare different strategies, and provided a methodology for emulating these trials using observational data.

As a motivating example, we compared the effectiveness of different strategies for scheduling surveillance colonoscopies in patients with adenomas, a clinical question for which the available evidence is sparse.\textsuperscript{9,15-20} Our analysis suggests that more frequent surveillance colonoscopies leads to a greater reduction in colorectal cancer risk; as expected, the analysis also suggests that dynamic strategies are more effective than static strategies. However, our analysis is more an example of implementation than an attempt at providing definite answers to the clinical question because the sample size of our study was small.

The application of the methods outlined in this review allowed us to specify a research question that is directly relevant to decision makers interested in timing questions. Though these methods allow adjustment for both baseline and time-varying covariates, the possibility of unmeasured confounding remains as in any observational study.
REFERENCES


Comparative effectiveness research using observational data:
Active comparators to emulate target trials with inactive comparators

Anders Huitfeldt, Miguel A. Hernán, Mette Kalager, James M. Robins
Abstract

Because non-initiators of treatment differ from initiators in terms of unmeasured variables including access to healthcare and health-seeking behavior, guidelines for the conduct of observational research often recommend using an “active” comparator group consisting of people who initiate a treatment other than the medication of interest. In this paper, we discuss the conditions under which this approach is valid if the goal is to emulate a trial with an inactive comparator. We provide four different conditions under which a target trial in a subpopulation can be validly emulated from observational data, using an active comparator that is known or believed to be inactive for the outcome of interest. The average treatment effect in the population as a whole is not identified, but under certain conditions this approach can be used to emulate a trial either in the subset of individuals who were treated with the treatment of interest, in the subset of individuals who were treated with the treatment of interest but not with the comparator, or in the subset of individuals who were treated with both the treatment of interest and the active comparator. We discuss whether the required conditions can be expected to hold in pharmacoepidemiologic research, with a particular focus on whether the conditions are plausible in situations where the standard analysis fails due to unmeasured confounding by access to health care or health seeking behaviors.
1. Introduction

Randomized trials to evaluate the effectiveness or safety of an active treatment can be classified into two groups: trials that compare the treatment of interest with an active treatment which is a clinical alternative to the treatment of interest (head-to-head trials), and trials that compare the treatment of interest with an inactive comparator such as placebo or usual care without treatment. Observational data are often used to try to emulate both types of randomized trials. Head-to-head trials may be emulated via comparisons of individuals initiating the treatment of interest versus initiating the active comparator. Trials with inactive comparators may be emulated via comparisons of individuals initiating versus not initiating the active treatment.

While all trial emulations using observational data are subject to bias, emulating trials with inactive comparators is especially challenging because people who initiate treatment may be different from non-initiators in ways that are difficult to assess: access to healthcare, health-seeking behaviors, time since and accuracy of the measurement of confounders, outcome and comorbidities. As a result, the observational estimates may be biased by unmeasured confounding and differential mismeasurement of key variables.\(^1\) This bias is of particular concern in studies that rely on administrative data.\(^2,3\)

A proposal to reduce these biases in observational research is the use of active comparators even when the goal of the research is to emulate a trial with inactive comparators. To do so,
investigators often choose an active comparator that is thought to be inactive for the outcome under consideration and therefore, generally, will not be a clinical alternative to the treatment of interest. It has been argued that using such active comparators may mitigate bias because initiators of the treatment of interest and of the active comparator are expected to have a similar health status\(^4\) and use of the health care system\(^5\), and comparable quality of information.

The use of active comparators has been endorsed in several guidelines for the conduct of observational research, including the GRACE principles,\(^1\) AHRQ’s “Protocol for Observational Comparative Effectiveness Research”,\(^2\) PCORI’s “Standards for Causal Inference in Analyses of Observational Studies”\(^3\) and the FDAs “Best practices for conducting and reporting pharmacoepidemiologic safety studies”.\(^6\) Table 2.1 summarizes several published examples of observational studies that used active comparators to emulate trials with inactive comparators.

However, these guidelines do not describe the method in detail. For example, none of these documents explicitly differentiate between the use of active comparators to emulate head-to-head trials or to emulate trials with inactive comparators. In addition, they do not provide a precise definition of the causal effect that is to be estimated when active comparators are used, and therefore cannot characterize the conditions that are necessary in order to identify this causal effect. Finally, the guidelines neither specify whether the treatment group should exclude individuals who also take the comparator drug nor whether the analysis should be
restricted to individuals with indications for both active treatments. As a result, different versions of active comparator approaches exist (see Table 2.1).

In this paper, we consider the possible designs of observational studies that use active comparators to emulate trials with inactive comparators. We characterize the causal effect that is targeted by each design and the comparability assumptions under which the design-specific causal effects are identified from the data. Since we are interested in identification and not inference we shall ignore sampling variability by supposing the study population is sufficiently large that sampling variability can be ignored.

As a running example, we will consider a target trial whose goal is to compare usual care plus initiation of statin therapy ($A=1$) vs. usual care without initiation of statin therapy ($A=0$) on the 5-year risk of coronary heart disease $Y$ (1: yes, 0: no) in some well-defined study population, say an insurance or medicare data base. We shall sometimes use “treated” as shorthand for “subjects who initiated treatment with statins.”
Table 2.1: Examples of observational studies that use active comparators to emulate randomized trials with inactive comparators

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment group</th>
<th>Comparator group</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glynn et al (2001)¹²</td>
<td>Initiators of several classes of cardiac drugs</td>
<td>Initiators of glaucoma drugs</td>
<td>Death</td>
</tr>
<tr>
<td>Glynn et al (2006)¹³</td>
<td>Initiators of lipid-lowering medications</td>
<td>Initiators of any other medications who do not use lipid-lowering medications</td>
<td>Death</td>
</tr>
<tr>
<td>Solomon et al (2006)⁵</td>
<td>Initiators of NSAIDS/Coxibs</td>
<td>Initiators of glaucoma/hypothyroidism therapy who do not take NSAIDs/Coxibs</td>
<td>Hospital admission for myocardial infarction or stroke</td>
</tr>
<tr>
<td>Schneeweiss et al (2007)¹⁴</td>
<td>Initiators of statins who do not use glaucoma therapy</td>
<td>Initiators of glaucoma therapy who do not use statins</td>
<td>Death</td>
</tr>
<tr>
<td>Setoguchi (2007)¹⁵</td>
<td>Initiators of statins who do not use glaucoma therapy</td>
<td>Initiators of glaucoma therapy who do not use statins</td>
<td>Lung, breast and colorectal cancer</td>
</tr>
</tbody>
</table>
2. Emulating a trial with inactive comparators in a subset of the study population

To fix ideas, we first review the counterfactual approach to causal inference. We shall let the counterfactuals $Y_{a=1}$ and $Y_{a=0}$ denote the outcome of interest $Y$ when treated and not treated with statins respectively. We make the consistency assumption that a subject’s observed outcome $Y$ is equal to $Y_{a=1}$ if the subject initiated statin treatment; otherwise $Y$ is equal to $Y_{a=0}$.

We first consider two causal effects that are often of interest. The first of these is the average treatment effect (ATE) in the entire study population $E[Y_{a=1}] - E[Y_{a=0}]$, i.e., the difference between the 5-year risk of coronary heart disease had everyone undergone usual care plus initiation of statin therapy ($E[Y_{a=1}]$), and the 5-year risk of coronary heart disease had everyone undergone usual care alone ($E[Y_{a=0}]$). To identify the average causal effect in the entire population we need to be able to identify both $E[Y_{a=0}]$ and $E[Y_{a=1}]$ from the observed data. If the ATE is identified, we are able to emulate a trial comparing initiation of statins with usual care in the entire study population.

The second is the average causal effect in the treated population $E[Y_{a=1} | A=1] - E[Y_{a=0} | A=1]$ which is often referred to as the effect of treatment on the treated (ETT). The ETT compares the five-year risk of coronary heart disease under statin therapy and usual care in the subgroup of the population who were observed to initiate treatment with statins. Since by consistency the average $Y_{a=1}$ among subjects observed to have $A=1$ is equal to the mean of $Y$ among these
subjects, we have that $E[Y^a=1 \mid A=1]$ is equal to $E[Y \mid A=1]$ and the ETT is $E[Y \mid A=1] - E[Y^a=0 \mid A=1]$. In other words, confounding by unmeasured factors is not an issue for $E[Y^a=1 \mid A=1]$ and thus to identify the ETT it is sufficient to identify the mean $E[Y^a=0 \mid A=1]$ of $Y^a=0$ from the observed data. If the ETT is identified, we will be able to emulate a trial in the subset of the study population who initiated statin treatment.

As discussed above, the observational difference in risk of coronary heart disease between statin initiators and non-initiators, $E[Y \mid A=1] - E[Y \mid A=0]$, may be biased for the ATE contrast $E[Y^a=1] - E[Y^a=0]$ and for the ETT $E[Y^a=1 \mid A=1] - E[Y^a=0 \mid A=1]$. The bias may persist even if the observational contrast were computed within levels of the measured confounders $L$ available in the data base, i.e., $E[Y \mid A=1, L=l] - E[Y \mid A=0, L=l]$, owing to within-stratum confounding by unmeasured factors and measurement error. For notational simplicity, in this paper we often suppress $L=l$ from the conditioning event, but consider that all observational contrasts are calculated in a subset of the population $L=l$.

3. Three Designs

In an attempt to eliminate the bias, we can consider three possible active comparator designs. In the following we let $B$ denote the active comparator drug so that subjects with $B=1$ initiate the active comparator and subjects with $B=0$ do not. Consider subjects who have yet to initiate either treatment at some fixed time from start of follow-up divided into 4 groups: Group (1)
consists of subjects who initiate A but not B, Group (2) consists of subjects who initiate B but not A, Group (3) consists of subjects who initiate both A and B and Group (4) consists of subjects who initiate neither A nor B. Note that if A and B are alternative therapies for the same illness then it may be that there exist no subjects initiating A and B at once. Since, as discussed in the introduction, we are considering the case in which A and B do not treat the same condition, we will assume there do exist simultaneous initiators.

In all designs we compare the observed mean of the outcome in some subset of the treated with the mean outcome among the untreated subjects who initiate the comparator drug. In design 1, we use the mean outcome in all subjects treated with statins. In design 2, we use the mean outcome in treated subjects who do not take the comparator drug. In design 3, we use the mean outcome in treated subjects who take the comparator drug. Thus we replace the usual observational contrast \( E[Y|A=1] - E[Y|A=0] \) by one of the following design specific observational contrasts:

Design 1: \( E[Y|A=1] - E[Y|A=0, B=1] \)

Design 2: \( E[Y|A=1, B=0] - E[Y|A=0, B=1] \)

We next discuss the causal effect targeted by each design. Recall that $B$ is an active treatment which is known or thought to be inactive for the outcome $Y$. In our running example we take $B$ to be an active therapy for glaucoma that is inactive for our outcome coronary heart disease.

The above observational contrasts do not generally identify the ATE, ie average causal effect of $A=1$ versus $A=0$ in the entire study population, $E[Y_{a=1}] - E[Y_{a=0}]$. However, under certain comparability conditions described below, each of these contrasts identifies the average causal effect of $A=1$ versus $A=0$ in a particular subset of the treated population that depends on the design: Under design 1, it is the entire population treated with treatment $A$ (groups 2 and 3); under design 2 it is the subset of treated population who do not initiate treatment $B$ (group 2), and under design 3 it is the subset of treated who initiate treatment $B$ (group 3). Figure 2.1 illustrates the groups compared and the trials that are emulated by each design.

We now describe the comparability conditions under which each of the above design specific observational contrasts identifies these effects. Let $p_{ab} \equiv E[Y_{a=0} | A=a, B=b]$. For example, $p_{01}$ is the mean of $Y_{a=0}$ among subjects who initiate glaucoma therapy (treatment $B$) but do not initiate statins (treatment $A$). Consider the four comparability conditions:

i. $p_{11} = p_{01}$

ii. $p_{10} = p_{01}$

iii. $p_{10} = p_{01} = p_{11}$

iv. $p_{10} = p_{01} = p_{11} = p_{00}$
We now show that certain of these conditions identity the subpopulation causal effects described earlier.

The effect of A among those initiating A and B

Condition (i) states that among subjects initiating B, those also initiating treatment A have the same mean of $Y^{a=0}$ as those not initiating A. Under comparability condition (i), the contrast $E[Y|A=1, B=1] - E[Y|A=0, B=1]$ of Design 3 identifies the effect of active treatment $A=1$ versus no treatment $A=0$ among the subset initiating both A and B. In our example, this is the average causal effect of statins versus no statins among subjects who initiated both statins and glaucoma therapy.

Lemma 1: If $p_{11}=p_{01}$ then $E[Y|A=1, B=1] - E[Y|A=0, B=1] = E[Y^{a=1} - Y^{a=0}|A=1, B=1]$.

Proof:

$E[Y|A=1, B=1] = E[Y^{a=1}|A=1, B=1]$ by consistency

$E[Y|A=0, B=1] = E[Y^{a=0}|A=0, B=1]$ by consistency

$= E[Y^{a=0}|A=1, B=1]$ by (i)
The effect of A among those treated with A but not B

Condition (ii) states that subjects initiating B but not A have the same mean of \( Y^{a=0} \) as those initiating A but not B. Under condition (ii), the contrast \( \text{E}[Y|A=1, B=0] - \text{E}[Y|A=0, B=1] \) identifies the effect of active treatment \( A=1 \) versus no treatment \( A=0 \) among those initiating A but not B. In our example, this effect is the average causal effect of statins versus no statins among initiators of statins who did not initiate glaucoma therapy.

Lemma 2: If \( p_{10}=p_{01} \) then \( \text{E}[Y|A=1, B=0] - \text{E}[Y|A=0, B=1] = \text{E}[Y^{a=1}-Y^{a=0}|A=1, B=0] \).

Proof:

\[
\text{E}[Y|A=1, B=0] = \text{E}[Y^{a=1}|A=1, B=0] \quad \text{by consistency}
\]

\[
\text{E}[Y|A=0, B=1] = \text{E}[Y^{a=0}|A=0, B=1] \quad \text{by consistency}
\]

\[
= \text{E}[Y^{a=0}|A=1, B=0] \quad \text{by (ii)}
\]

Lemma 2 is essentially due to Rosenbaum (2007).\textsuperscript{7,8}

The effect of A among those treated with A

Under condition (iii), we obtain the above results plus we identify the effect of treatment on the entire treated population (\( A=1 \)). Under this condition, the contrast \( \text{E}[Y|A=1] - \text{E}[Y|A=0, B=1] \) identifies the effect of active treatment \( A=1 \) versus no treatment \( A=0 \) among those who initiated A in the observational data. In our example, this is the average causal effect of statins
versus no statins among all initiators of statins. As noted earlier, this causal estimand is commonly referred to as ETT

Lemma 3: If \( p_{10} = p_{01} = p_{11} \) then not only are the results of Lemma 1 and 2 true but in addition

\[
E[Y|A=1] - E[Y|A=0, B=1] = E[Y_{a=1} - Y_{a=0}|A=1]
\]

Proof:

\[
E[Y|A=1] = E[Y_{a=1}|A=1] \quad \text{by consistency}
\]

\[
E[Y|A=0, B=1] = E[Y_{a=0}|A=0, B=1] \quad \text{by consistency}
\]

\[
= E[Y_{a=0}|A=1] \quad \text{by (iii)}
\]

It is easy to see that condition (iii) both implies and is implied by conditions (i) and (ii). If the even stronger condition (iv) holds, the observational contrast \( E[Y|A=1] - E[Y|A=0] \) identifies the effect of \( A \) in the treated. In other words, if condition (iv) holds we would not need to collect data on \( B \) to identify the ETT

Lemma 4: If \( p_{10} = p_{01} = p_{11} = p_{00} \) then \( E[Y|A=1] - E[Y|A=0] = E[Y_{a=1} - Y_{a=0}|A=1] \)

Proof:

\[
E[Y|A=1] = E[Y_{a=1}|A=1] \quad \text{by consistency}
\]
\[ E[Y|A=0] = E[Y_{=0} | A=0] \quad \text{by consistency} \]

\[ = E[Y_{=0} | A=1] \quad \text{by (iv)} \]
Figure 2.1: Venn diagrams showing the groups compared and the subpopulation to which the effect estimates apply
4. The comparability conditions

The results in the previous section depend on comparability conditions (i)-(iv). Since these conditions, like other comparability conditions, can be neither empirically verified nor refuted we should only adopt those that are plausible a priori. We now discuss the plausibility of these conditions.

We begin by showing that unless the comparator B has no direct effect on the outcome of interest we could not expect any of the above conditions except possibly (i) to hold. This should not be surprising, as the causal null hypothesis for the comparator is essential to the intuition behind most active comparator study designs. To proceed we need some further definitions. Let $Y^{a,b}$ be the counterfactual representing the joint effect of $A$ and $B$ on $Y$. The counterfactuals $Y^a$ discussed earlier are determined by the counterfactuals $Y^{a,b}$ via consistency. Specifically, $Y^a = Y^{a,b=1}$ for subjects treated with $B (B=1)$ in the observed data. For subjects with $B=0$ in the data, $Y^a = Y^{a,b=0}$.

By definition, $B$ has no direct effect on $Y$ if $Y^a = Y^{a,b=0} = Y^{a,b=1}$ for each subject. If $B$ had a direct effect, the condition $P_{10} = P_{01}$ becomes $E[Y^{0, b=1} | A=0, B=1] = E[Y^{0, b=0} | A=1, B=0]$. Since the counterfactuals $Y^{0, b=1}$ and $Y^{0, b=0}$ would differ, there is no a priori reason to expect the mean of $Y^{0, b=1}$ in a subgroup to equals that of $Y^{0, b=0}$ in a second subgroup. As conditions (iii) and (iv) hold only if condition (ii) does, they too are implausible if $B$ has a direct effect. Henceforth, we
will assume the investigators have chosen a comparator $B$ which has no direct effect on the outcome.

Next turn to condition (iv). This condition is implausible because it implies that subjects who initiated neither treatment $A$ nor treatment $B$ are comparable to those who did, which as discussed in the introduction cannot be assumed, an observation which indeed motivated the need for active comparators. We therefore proceed to discuss the weaker conditions (i), (ii) and (iii), focusing on describing hypothetical situations where the weaker conditions (i), (ii) or (iii) hold but (iv) does not. In such settings, an active comparators design may be required.

Consider two indistinguishable groups of subjects in the population with different means of $Y^{a=0}$, and hence non-comparable. We label these groups $G_1$ and $G_2$. Conditions (i), (ii) and (iii) but not (iv) would hold if all $G_1$ members refrain from initiating either $A$ or $B$, whereas comparability condition (iv) holds in $G_2$. Therefore, all subjects who initiated either $A$ or $B$ would be in $G_2$ while those who initiated neither would be an indistinguishable mixture of groups $G_1$ and $G_2$. As an example, we might suppose all subjects with health seeking behaviors were in $G_2$ and those without were in $G_1$. However, since covariates such as health seeking behavior are not truly binary, and since sicker individuals will tend seek health care preferentially, it is implausible that the division into such groups will ever hold precisely.
An alternative way to think about condition (iii) is in terms of a treatment choice model as discussed by Rosenbaum using ideas introduced by Tversky and Sattath (1979). In these models, a subject first decides whether to refrain from all treatment or not, and then decides which treatment to take. The probability of refraining from treatment can depend on $Y_{a=0}$, but after having decided to take a treatment the decision about whether to take $A$, $B$ or both cannot further depend on $Y_{a=0}$. Again, it is implausible that this model would hold exactly.

Such a mechanistic treatment model can also be used to describe a situation where condition (ii) but not (iii) would hold. For example, this would occur the subject first decides whether to take one, two or no treatments; with the decision depending on $Y_{a=0}$; and in the event that he decides to initiate one treatment proceeds to choose among $A$ and $B$ with a probability that does not depend on $Y_{a=0}$. As discussed by Rosenbaum, this scenario might be plausible if $A$ and $B$ were alternative therapies prescribed for the same indication. However, these models become implausible when, as in this paper, the indication for treatment with the comparator $B$ (e.g., glaucoma therapy) differs from that for active treatment $A$ (statins).

The requirements for condition (i) are less restrictive. This condition would hold if among initiators of treatment $B$, initiators and noninitiators of treatment $A$ are exchangeable with respect to the outcome $Y$, ie if $Y_{a=0} \perp A \mid B=1$. This condition will be true under the following scenario: Suppose that initiators and noninitiators of statins are not exchangeable because of
differences in health care access (an unmeasured variable). If all initiators of treatment $B$ have access to health care then, in the subset of initiators of $B$, initiators and noninitiators of $A$ do not differ with respect to health care access. Therefore, conditional on prognostic factors other than health care access, comparability condition (i) would hold among initiators of $B$ even if health care access remains unmeasured. Note in addition that $B$ having a direct effect on $Y$ has no bearing on the plausibility of condition (iv).

All conditions in this paper will be violated if there exist unmeasured common causes of $A$ and $Y$ other than those that can be controlled by conditioning on $B=1$. Moreover, conditions (ii), (iii) and (iv) will all be violated if there exist unmeasured common causes of $B$ and $Y$ other than those that can be controlled by conditioning on $A=1$. Therefore, to justify the use of designs (2) or (3), the investigators will have to control for all indications for treatment $A$ and all indications for the active comparator $B$. If medications $A$ and $B$ have different indications, this will usually produce a violation of the necessary positivity condition: Nobody will be treated with statins unless they have elevated cholesterol, and nobody will be treated with glaucoma therapy unless they have glaucoma. Investigators are therefore required either to limit the analysis to those individuals who have indications for both medications, or alternatively make the additional assumption that having glaucoma is independent of the outcome (such that it does not need to be controlled for).
Finally, we want to point out that all independence assumptions in this section are defined in terms of counterfactual variables that are specific for each outcome \( Y \) under consideration. It is often the case that a comparator will be independent of one outcome, but not another.

5. Using active comparators to reduce misclassification bias

Besides potentially making the treatment groups more comparable in terms of unobserved covariates, the second argument for using active comparators in observational studies is that it may protect against a certain form of differential misclassification bias. Specifically, people who have not started a drug recently may not have all their comorbidities entered in the database, for instance because they have not had a recent physical examination. In observational research using health care databases, such individuals are generally considered not to have the condition; this phenomenon will therefore usually result in misclassification of the variable rather than missing data.

Differential misclassification due to lack of access to healthcare will generally not affect measurement of the treatment: People who do not have access to healthcare will correctly be recorded as not being treated. In contrast, the outcome \( Y \) will often be measured with error for reasons related to access to health care.
Let $Y^*$ be the measured value of the outcome. The active comparators design can be used to eliminate differential misclassification of the outcome if condition (4) holds, i.e., $p_{10} = p_{01} = p_{11} = p_{00}$, and $Y$ is measured accurately if the patient has access to health care, such that $E[Y^* | A=a, B=b] = E[Y | A=a, B=b]$ for all strata except $a=0, b=0$ where $Y$ is measured with error.

An example of such a situation is as follows: Suppose non-initiators of statins are disproportionately more likely to be uninsured than initiators, and uninsured individuals with chest pain are less likely to seek medical attention. In such a situation, the non-initiator group will be less likely to be diagnosed if they have silent myocardial infarctions and $E[Y^* | A=0, B=0] < E[Y | A=0, B=0]$. In such a situation the standard analysis will have a bias that makes treatment appear falsely more effective at reducing the incidence. We may hope to eliminate this bias by using a comparator group consisting of glaucoma therapy initiators, as glaucoma therapy initiators are known to have adequate access to health care and will be diagnosed with the same accuracy as statin users if symptoms occur.

This type of bias does not occur when the outcome (e.g., death) is measured accurately in all individuals. In this setting, concern about misclassification is not a compelling reason to use an active comparator design.
It is also possible for the confounders to be misclassified for the same reasons discussed above for the outcome. However since doctors can only make treatment decisions based on the information that they have available, the measured value of the variable is usually the proximal cause of treatment initiation; controlling for the mismeasured version is therefore generally preferable to controlling for the true value. For this reason, mismeasurement of confounders due to lack of access to healthcare is not a concern for most uses of health care databases.

Finally, in situations where differential misclassification may be eliminated by the use of an active comparators design, it is usually the case that a similar objective can be achieved simply by restricting the study to individuals who had a certain level of health care utilization prior to baseline.

6. Discussion

Observational studies that compare two active drugs often have less confounding than studies that compare a drug to no treatment. However, these two types of studies estimate different effects. We encourage investigators to think closely about what effects they are estimating when using “active comparators” to emulate a target trial of treatment versus no treatment. In this paper, we have provided the conditions under which such a trial can be validly emulated using a comparator group that consists of initiators of an active treatment that is inactive for the outcome of interest.
We have discussed four different conditions that allow the identification of subtly different causal effects. In most settings, condition (i) will be the most plausible one (it holds under a standard exchangeability assumption, and it does not rely on the assumption that the comparator treatment has no effect on the outcome), but an approach based on condition (i) will reduce sample size considerably and will restrict the interpretation of the estimated effect to the small subset of the population who share characteristics with those subjects who initiated both treatment A and treatment B in the observational data. Conditions (ii), (iii) and (iv) will be difficult to justify in most settings. Condition (ii) is weaker than condition (iii), and therefore less likely to be violated, but condition (iii) identifies a potentially more relevant causal effect.

One potential way to test whether these conditions hold approximately would be to obtain observational data containing all relevant covariates including access to health care and health-seeking behavior, and see whether an analysis that strips the dataset of these variables is able to use the methods proposed in this paper to obtain the same results as the standard analysis for estimating the causal effect in the corresponding subgroup.

In any design that uses active comparators in observational data, it will be difficult to analyze multiple outcomes within the same study. This is because the active comparator has to be
chosen specifically in the context of subject-matter knowledge about the relationship between
the comparator and the outcome under study, and justifications for using an active comparator
comparator B for one outcome Y do not readily transfer to using the same comparator for a
different outcome.

In summary, investigators who employ an active comparators design to emulate a trial with
inactive comparators should exercise caution.
REFERENCES


Can the results of the WHI E+P trial be explained by differential statin initiation?

Anders Huitfeldt, Mette Kalager, Miguel A. Hernán, James M. Robins
Abstract:

In 2002, the Women’s Health Initiative clinical trial was stopped early after it became clear that hormone replacement therapy was associated with an increased risk of coronary heart disease (CHD). This result was contrary both to prior observational studies and expert beliefs about biological pathways, and several hypotheses have been proposed to explain the study. In this paper, we examine if the results from WHI can be explained by differences in statin initiation between the randomization arms. Because of unmeasured confounding for the statin-CHD relationship, standard methods are unable to answer this question. We therefore provide a new g-estimation-based methodology for estimating the controlled direct effect, which relies on incorporating external information on the effect of the mediator. Specifically, we are able to provide a valid estimate for the direct effect of hormone replacement therapy on CHD, even in the presence of unmeasured confounding for the statin-CHD relationship. Despite substantial differences in LDL-cholesterol and statin initiation between the randomization arms, we find that statins had little impact on the results of the trial.
1. Introduction:

The Women’s Health Initiative (WHI) clinical trial randomized 16,608 women with intact uterus to either hormone replacement therapy (HRT) with conjugated equine estrogens and medroxyprogesterone acetate (E+P), or placebo. In July 2002, this trial was stopped early, after finding a 29% greater incidence of coronary heart disease (CHD) among women in the E+P hormone therapy arm.\(^1\) As data collection for the intervention phase became more complete, the HRs were 1.24 (95% CI: 1.00 – 1.54)\(^2\) and 1.18 (95% CI, 0.95-1.45)\(^3\) in updated analyses.

Several hypotheses have been suggested to explain the findings from the WHI trial. Much interest has been on the timing of HRT initiation.\(^4,5\) An alternative hypothesis is that the results could be explained by differences in post-randomization initiation of HMG-CoA Reductase Inhibitors (statins). Hormone therapy is known to reduce serum levels of LDL cholesterol,\(^6\) and doctors are less likely to prescribe statins in patients with low LDL cholesterol. Statins are known to lower the risk of CHD.\(^7\) Women in the treatment arm of the WHI had lower post-randomization levels of LDL than those in the placebo group, presumably due to the LDL-lowering effect of oral estrogens; thus, they may have had a lower probability of initiating statin treatment. This could potentially explain the trial finding.

If the results from the WHI trial are explained by differential statin usage, this would not mean that the trial was somehow less valid. Indeed, any effect of HRT, even if it is due to its effects on statin initiation, is part of the causal effect that a randomized trial is designed to estimate.
However, a natural interpretation of such a conclusion would be that HRT makes it more difficult to identify those women who would benefit from Statin treatment. This would suggest either that the prognostic value of LDL is reduced or that the LDL threshold value for statin initiation needs to be adjusted in women receiving HRT. Moreover, if the results from the trial are explained by differential statin initiation, this may go some way towards rehabilitating the observational studies that preceded WHI, which in most cases were conducted before statins became widely available and therefore would not be expected to capture the hypothetical component of the effect that is mediated by statins.

To examine the hypothesis that the trial findings could be explained by differential use of statins, we estimated the direct effect of estrogen relative to statin usage. Because of unmeasured confounding for the statin-CHD relationship, the direct effect of estrogen is not identified from the WHI data alone. We therefore provide a new methodology based on incorporating external information about the effects of statins, which enables us to estimate the direct effect of estrogen even in the presence of mediator-outcome confounding. This external information was obtained from another large randomized trial, the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA), which compared Atorvastatin to Placebo. We considered 3 outcomes: CHD (defined as acute myocardial infarction requiring overnight hospitalization, silent myocardial infarction identified through serial electrocardiograms, or death due to CHD), stroke, and all-cause mortality.
2. **Study Setting, Intermediate Biomarkers and Statin Usage:**

From 1993 to 1998, 16,608 women aged 50-79 were randomized to HRT with E+P or Placebo as part of the Women’s Health Initiative. Of the participants, 1,115 used statins at baseline and were excluded from our analysis, leaving us with a sample size of 15,493. Participants were followed from randomization until the event of interest, death, loss to follow-up or July 2002, whichever occurs first. As part of follow-up, participants completed annual questionnaires on changes to their medical history including initiation of statins; therefore, if a woman started statins in the same year she had a heart attack it is difficult to tell what happened first. Some covariates, including post-baseline serum lipids and cholesterol, were only collected in a random subsample (the Core Analytes), consisting of 6.6% of the study participants.

Baseline characteristics of participants in the WHI trial are shown in Table 3.1. A summary of the key post-baseline biomarkers as measured in the Core Analytes subsample is shown in Table 3.2. On average, one year after baseline women in the E+P arm had 12.7 percentage points lower LDL-c (95% CI: 10.5%-14.6%), 7.3 percentage point higher HDL-c (95%CI: 5.5-9.0%), and 5.4 percentage points lower total cholesterol (95% CI: 2.5% - 11.5%) than women in the placebo arm. Results at year 3 were nearly identical to those at year 1. These intermediate biomarkers suggest a substantial beneficial effect of HRT on lipid profiles.

By the end of follow-up, 10.2% of the placebo arm and 15.9% of the HRT arm had initiated statin treatment. This implies a cumulative incidence difference for statin initiation of 5.7% (95%
CI: 4.6% - 6.8%). A Kaplan-Meier curve with statin initiation as the outcome is shown as figure 3.1; this graph shows that throughout the course of the trial, women in the placebo arm were more likely to initiate statins than women in the E+P arm. The difference between the arms is highly unlikely to be due to sampling variability; one hypothesis to explain the graph is that doctors were less likely to prescribe statins to users of HRT because their lipid profiles were improved.

These findings are all consistent with what one would expect to see if the effect of HRT is partly mediated by differential statin initiation, but there are multiple other explanations that are also consistent with the data. For example, statin initiation could be a marker for high cholesterol without being a significant mediator of the causal effect of HRT. The descriptive statistics alone are not sufficient to differentiate the statin hypothesis from other explanations, and we therefore turn to a formal mediation analysis in the next sections. In order to do so, we will incorporate external information on the causal effect of statins.

Based on a meta-analysis by the Cholesterol Treatment Trialists’ Collaboration, we assumed the causal Hazard Ratio associated with statin usage was 0.70 for CHD, and that this hazard ratio was relatively homogenous between different subgroups. We assumed hazard ratios of 0.76 and 0.91 for stroke and all-cause mortality, respectively.
For certain analyses, we were required to identify a trial on statin usage where the published results included separate Kaplan Meier curves for each outcome. Among trials that met this requirement was the ASCOT-LLA\textsuperscript{8}, from which we extracted information about the effect of statins. Briefly, ASCOT-LLA was a multicenter randomized controlled trial which randomized 10,305 hypertensive patients aged 40-79 years old to 10mg atorvastatin once daily, or placebo. This trial estimated that initiation of statin treatment was associated with an intention-to-treat hazard ratio of 0.64 for non-fatal myocardial infarction and fatal CHD (95% CI: 0.50-0.83). Adherence-adjusted effect estimates from ASCOT-LLA have not been published. A summary of baseline characteristics in this trial is shown in Table 3.3. Only 18.8% of participants were women, this represents a major difference between the ASCOT-LLA and WHI study populations; we were unable to find a statin trial that was limited to women.
Table 3.1: Characteristics of Participants in WHI E+P trial who did not take statins at baseline (n=15493)

<table>
<thead>
<tr>
<th>Variable</th>
<th>E+P (n=7926)</th>
<th>Placebo (n=7567)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Median</td>
<td>57-69</td>
<td>58-69</td>
</tr>
<tr>
<td>White</td>
<td>6659 (84.0%)</td>
<td>6659 (84.1%)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>28.5 (5.8)</td>
<td>28.5 (5.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>127.6 (17.6)</td>
<td>127.8 (17.5)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>75.6 (9.1)</td>
<td>75.8 (9.1)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>880 (10.5%)</td>
<td>838 (10.5%)</td>
</tr>
<tr>
<td>Statins</td>
<td>1188 (15.7%)</td>
<td>799 (10.1%)</td>
</tr>
<tr>
<td>By end of follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before baseline</td>
<td>504 (6.9%)</td>
<td>520 (6.4%)</td>
</tr>
<tr>
<td>During follow-up</td>
<td>165 (2.1%)</td>
<td>125 (1.7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before baseline</td>
<td>54 (0.7%)</td>
<td>66 (0.9%)</td>
</tr>
<tr>
<td>During follow-up</td>
<td>132 (1.7%)</td>
<td>96 (1.3%)</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By end of follow-up</td>
<td>210 (2.6%)</td>
<td>203 (2.6%)</td>
</tr>
</tbody>
</table>

Parenthesis are either percentages or standard deviations, depending on variable type.
Table 3.2: Laboratory results in Core Analytes subsample (N=1319)

<table>
<thead>
<tr>
<th></th>
<th>Mean at baseline (Pooled across randomization arms)</th>
<th>SD</th>
<th>Change Difference (Average percentage change in E-P arm, minus Average Percentage Change in Placebo arm)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>222</td>
<td>37.1</td>
<td>-5.4%</td>
<td>-4.0%, -7.0%</td>
</tr>
<tr>
<td>LDL-c (mg/dl)</td>
<td>134.7</td>
<td>32.9</td>
<td>-12.7%</td>
<td>-10.5%, -14.5%</td>
</tr>
<tr>
<td>HDL-c (mg/dl)</td>
<td>55.3</td>
<td>13.6</td>
<td>7.3%</td>
<td>5.5%, 9.0%</td>
</tr>
<tr>
<td>Serum Triglycerides (mg/dl)</td>
<td>130.9</td>
<td>59.4</td>
<td>-6.9%</td>
<td>-2.5%, -11.5%</td>
</tr>
</tbody>
</table>

Note: Direct access to data from the Core Analytes subsample was not obtained. Figures are from published results. For baseline measurements, the averages are pooled over randomization status.
Table 3.3: Baseline characteristics of participants in the ASCOT-LLA trial. Parenthesis are percentages or standard deviations, depending on variable type

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (n=5168)</th>
<th>Placebo (n=5137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>979 (18.9%)</td>
<td>963 (18.7%)</td>
</tr>
<tr>
<td>Age ≤60</td>
<td>1882 (36.4%)</td>
<td>1853 (36.1%)</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>3286 (63.6%)</td>
<td>3284 (63.9%)</td>
</tr>
<tr>
<td>White</td>
<td>4889 (94.9%)</td>
<td>4863 (94.7%)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>212.7 (30.9)</td>
<td>212.7 (30.9)</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>131.5 (27.1)</td>
<td>131.5 (27.1)</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>50.3 (15.5)</td>
<td>50.3 (15.5)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>28.6 (4.7)</td>
<td>28.7 (4.6)</td>
</tr>
<tr>
<td>Systolic blood pressure, (mmHg)</td>
<td>164.2 (17.7)</td>
<td>164.2 (18.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure, (mmHg)</td>
<td>95.0 (10.3)</td>
<td>95.0 (10.3)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1718 (33.2%)</td>
<td>1656% (32.2%)</td>
</tr>
</tbody>
</table>
Figure 3.1: Statin initiation over time in the WHI trial

Product-Limit Failure Curves
With 95% Hall-Wellner Bands

Probability of Using Statins

Logrank \( p < .0001 \)

Censored

0
1

0.0
0.1
0.2
0.3
0.4

0
20
40
60
80
100

time

0

3. **Standard Analysis**

Baron and Kenny (1986)\(^{11}\) described a method for estimation of the direct and mediated effects that has become widely utilized and cited. Briefly, they suggest using a series of regression models to check for mediation by assessing (1) whether the exposure is associated with the outcome, (2) whether exposure is associated with the suspected mediator and (3) whether the effect of the exposure is attenuated when conditioning on the mediator. In the WHI trial, this approach to mediation analysis is not valid; even if post-baseline cholesterol had been measured in all individuals the Baron-Kenny approach would have been invalid because LDL confounds the effect of statins but acts a mediator on the causal pathway from HRT to CHD.\(^{12}\)

In order to illustrate certain aspects of the data set, we conducted the analysis suggested by Baron-Kenny, both in the full WHI data set and in women not taking statins at baseline. Note that in the previous section, we have already determined that exposure to HRT causes increased incidence CHD, and that exposure to CHD causes reduced incidence of statin initiation, corresponding to the first two Baron-Kenny criteria for mediation. Regression parameters corresponding to the Baron-Kenny analysis are shown as Table 3.4. Survival curves predicted from the parameters of these models are shown as Figures 3.2-3.3.

These models show that history of statin usage is highly correlated with CHD among women in WHI: When the statin variable is used as originally coded in the dataset, the hazard ratios associated with statin use exceed 2.5. This is almost certainly an artifact of the previously
mentioned data collecting process, which makes it hard to sort out the temporal sequence of events if statin initiation and CHD occur during the same year. It is therefore very likely that this correlation is driven in large parts reverse causation, ie that women are initiating statin treatment because they have been diagnosed with CHD. For the remainder of our analyses, we therefore used a statin variable that was delayed by a year. Using this lagged version of the variable, the hazard ratio associated with statin usage remains above 1. Given that statins are known to be protective, this is a clear indication that women initiating statins are at higher risk than those who don’t, ie that the effect of statins is highly confounded.

After we deleted women taking statins at baseline, the unadjusted hazard ratio for HRT in our data set is 1.24 (0.98-1.56). We note that the coefficients for the effect HRT are not attenuated by conditioning on statin initiation; in fact, the effect of HRT is if anything slightly amplified in three of the models after conditioning on statin initiation. This must be seen in light of the known confounding for the effect of the mediator. The Baron-Kenny analysis therefore does not allow us to conclude either way, and we turn to a different approach to mediation analysis in the next section.

We also conducted an analysis in a dataset where people were censored at the time they initiated statin treatment. In this dataset, the Hazard Ratio associated with HRT was 1.28 (95% CI: 0.99 - 1.65) when using the original statin variable to determine censoring time, and 1.23 (95% CI: 0.97 – 1.56) when using the delayed variable.
For reference, we also provide the incidence rates for CHD, both overall and during person time on statins: In women not taking statins at baseline, the incidence rate of CHD during WHI was 0.0033 per person year. In women who initiated statins during WHI (based on the unaltered variable), the incidence rate after initiation was 0.0081 per person year. If we delay the statin variable by a year, the incidence rate after statin initiation is 0.0038 per person year.
Table 3.4: Hazard Ratios associated with HRT and Statins in different pooled logistic models in the WHI data set

<table>
<thead>
<tr>
<th></th>
<th>Outcome: CHD</th>
<th>Outcome: CHD</th>
<th>Outcome: Statins</th>
<th>Outcome: CHD</th>
<th>Outcome: CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predictors: HRT</td>
<td>Predictors: Statins</td>
<td>Predictors: HRT</td>
<td>Predictors: HRT and Statins</td>
<td>Predictors: HRT, Statins and Interaction Term</td>
</tr>
<tr>
<td>HRT</td>
<td>Statins</td>
<td>HRT</td>
<td>Statins</td>
<td>HRT</td>
<td>Statins</td>
</tr>
<tr>
<td>Full WHI dataset</td>
<td>Untransformed Statin variable</td>
<td>1.20 (0.96-1.49)</td>
<td>2.66 (2.08-3.39)</td>
<td>-</td>
<td>1.24 (1.01-1.55)</td>
</tr>
<tr>
<td></td>
<td>Lagged Statin variable</td>
<td>1.20 (0.96-1.49)</td>
<td>1.90 (1.43-2.52)</td>
<td>-</td>
<td>1.22 (0.98-1.45)</td>
</tr>
<tr>
<td>WHI excluding those on statins at baseline (n = 15493)</td>
<td>Untransformed Statin variable</td>
<td>1.24 (0.98-1.56)</td>
<td>2.69 (1.93-3.74)</td>
<td>0.62 (0.56-0.67)</td>
<td>1.30 (1.03-1.64)</td>
</tr>
<tr>
<td></td>
<td>Lagged Statin variable</td>
<td>1.24 (0.98-1.56)</td>
<td>1.11 (0.65-1.92)</td>
<td>0.61 (0.55-0.67)</td>
<td>1.24 (0.98-1.56)</td>
</tr>
</tbody>
</table>

1The statin variable was lagged by 12 month in all individuals except those taking statins at baseline, in whom initiation was known to occur before month 1 such that reverse causation cannot occur.
Figure 3.2: Survival curves predicted from standard models (with untransformed statin variable, model without interaction term)
Figure 3.3: Survival curves predicted from standard models (without interaction terms, with lagged statin variable)
Figure 3.4: Kaplan Meier curves for WHI E+P trial (showing both original data, and data where women are censored at the time of statin initiation, delayed by 12 months)
4. Identification of the Controlled Direct Effect

Let $T$ be the primary time scale of the WHI trial (time since randomization), and let $K$ be a secondary time scale for time since initiation of statin therapy. Let $A$ represent the baseline (intention-to-treat) treatment assignment with HRT and $M_t$ be a time-varying indicator for whether the woman has initiated statin treatment by time $T$. The counterfactual survival time under estrogen treatment is labelled $T_{a=1}$, and the counterfactual survival time under no estrogen treatment is labelled $T_{a=0}$. The variable $T^A$ refers to the counterfactual survival time when evaluated at the treatment value for HRT that the woman received (ie the value that was randomly assigned); under the consistency condition $T^A$ is equal to the observed survival time $T$. $T^A_{m=0}$ refers to a similar counterfactual survival time where the treatment value for hormone replacement therapy is evaluated at the observed value, and statins are not initiated.

In the ASCOT-LLA trial, time since statin initiation is equal to time since randomization; the primary time scale of the ASCOT-LLA trial therefore corresponds to the secondary time scale $K$ from the WHI trial. On the $K$ time scale, the intention-to-treat indicator for statin initiation is time-fixed and we can therefore drop the time subscript (ie, $M_t=M$ at all time points), otherwise all variables are identical between the trials. $K_{m=0}$ and $K_{m=1}$ are counterfactual variables for the survival times from statin initiation; sometimes we will be discussing the distribution of these survival times in terms of their equivalent causal survival functions under statin treatment and no statin treatment, $S_0(k)$ and $S_1(k)$ respectively. Let $H(k)= S_0^{-1}(S_1(k))$ be the quantile-quantile function that describes the relationship between these two survival time distributions. This
function takes a time point \( k \) as input, finds the quantile of people in the statin arm who failed at that time, and gives as output the time point at which the corresponding quantile has the event under no statin treatment.

Our aim is to estimate what the effect of HRT would have been in the WHI trial in the absence of post-randomization initiation of statin therapy, i.e., the “controlled direct effect”\(^\text{13}\) of hormone replacement therapy. In other words, we are interested in emulating a hypothetical “target trial” that is different from the one that was actually conducted, such that the protocol of the target trial specifies that participants cannot initiate statin treatment. This will require us to identify the counterfactual distribution of survival time under hormone replacement therapy and no statin treatment \( f(T^{a=1,m=0}) \), and the counterfactual distribution of survival time under no hormone replacement therapy and no statin treatment \( f(T^{a=0,m=0}) \), in terms of observed data.

The target trial can be emulated using WHI data alone if one has measured all joint predictors of hormone replacement therapy and CHD, and all joint predictors of statin initiation and CHD. Randomization of treatment assignment ensures that there is no confounding of the intention-to-treat effect of hormone replacement therapy. The primary confounders of the Statin-CHD relationship are the serum lipids and cholesterol measurements. Since these covariates were only measured in a subset of 6.6% of the WHI trial, the controlled direct effect is not identified from the WHI data, and methods such as marginal structural models cannot be used.
However, the controlled direct effect of hormone replacement therapy is identified from a combination of the WHI data and the ASCOT-LLA data under the following conditions:

- $T_{a,m=0} \perp A$ for all values $a$ (in the WHI trial),
- $K^{m=0} \perp M$ (in the ASCOT-LLA trial)
- Equal treatment effects for statins between the following three groups:
  - Participants in the ASCOT-LLA trial
  - Initiators of statins in the Estrogen arm of the WHI trial
  - Initiators of statins in the Placebo arm of the WHI trial

Conditions (1) and (2) are both expected to hold due to random treatment assignment in the respective trials. The viability of condition (3) will depend on the similarity of the two trial populations in terms of baseline effect modifiers, and on the similarity between the initiators of statins in the two arms of the WHI trial in terms of time-dependent effect modifiers. We discuss the plausibility of this condition in the appendix. We next provide an outline of how the target trial can be emulated under these three conditions.

First, observe that because of randomized treatment assignment in the ASCOT-LLA trial (Condition (2)), $H(k)$ is identified from the ASCOT-LLA data. Under an assumption of rank preservation, this will allow us to compute the counterfactual survival time under no statin
treatment for participants in the treatment arm of the ASCOT-LLA trial: For any individual who initiated statins and later had the event at time $K$, the survival time under no statin initiation is given by $K^{m=0} = H(K)$.

Our next step is to use this quantile-quantile function as a link between the WHI dataset and the ASCOT-LLA trial. Among women who initiate statin therapy during WHI, the counterfactual survival time $T^{A,m=0}$ is by definition equal to $N^A + K^{A,m=0}$. In words, this says that the time they would have survived without the event under no statin treatment is equal to the time they initiated statins, plus the time they would have survived under no treatment. If the treatment effect is the same in all subgroups defined in condition (3), the quantile-quantile function can be applied to compute the counterfactual survival time under no statin treatment among women in the WHI trial who initiated statins: $K^{A,m=0} = H(K^A)$. Therefore, we know that:

$$T^{A,m=0} = \begin{cases} N^A + H(K^A) & \text{if statins were initiated (by equal treatment effects)} \\ T^A & \text{if statins were not initiated (by consistency)} \end{cases}$$

In other words, when $H(k)$ is known, we can apply the G-estimation blip-down function to remove the effect of statins from all women in the WHI data set. To do this, we will need two pieces of information: The woman’s time of statin initiation $N$ (because $N^A = N$ under consistency) and her observed event time (because $T^A = T$ under consistency, and $K^A$ can be calculated as $T^A - N^A$). Note that $T^{A,m=0}$ cannot be calculated in participants who are censored. In these women, we can get a lower bound on $T^{A,m=0}$ by calculating what it would have been if
they failed immediately after they were censored; this therefore serves as their adjusted censoring time. We discuss bias due to censoring later in the paper.

In the data set where we have removed the effect of statins, we will observe the distribution \( f(T^{a=1,m=0} | A=1) \) in the stratum where \( A=1 \), and \( f(T^{a=0,m=0} | A=0) \) in the stratum where \( A=0 \). Under our exchangeability Condition (1) these distributions are equal to \( f(T^{a=1,m=0}) \) and \( f(T^{a=0,m=0}) \) respectively. Therefore, the randomized trial that compares these two counterfactual distributions can be emulated using any comparison between the groups \( A=1 \) and \( A=0 \) in the modified data set.

5. Estimation of the Controlled Direct Effect

We proceed to give the quantile-quantile function a parametric form by specifying a structural nested accelerated failure time model (SNAFTM) for the effect of statins. We specify the model

\[
H(k) = \int_0^k e^{\Psi_k * f(k)} \, dk,
\]

which can be equivalently stated as

\[
K^0 = \int_0^K e^{\Psi_k * M_k * f(k)} \, dk
\]

In this model, effects are measured as the multiplicative expansion of survival time due to treatment. \( \Psi_k \) is a vector parameter for the time-dependent effect of statins, and \( f(k) \) is the functional form for the interaction with time (we used indicator variables for time units of length
6 months). Because of randomized assignment of treatment (Condition 2), $\Psi_k$ is identified from the ASCOT-LLA data. Since we did not have access to the raw ASCOT-LLA data set, the published Kaplan-Meier curves were used to estimate $\Psi_k$. The procedure is explained in the appendix.

Turning to the WHI data, we then used the g-estimation step down procedure based on $\Psi_k$ to create a modified data set where failure times and censoring times were changed to remove the effect of statins. In this data set, we conducted both a non-parametric analyses in the form of Kaplan Meier estimators of the survival function, and fit the pooled logistic regression model

$$\text{logit} \ Pr(Y_t = 1|A, \bar{Y}_{t-1} = 0) = \beta_{0,t} + \beta_1A.$$  

Since $A$ was randomly assigned, the parameter $\beta_1$ in this model can be interpreted as the parameter $\gamma_1$ of the structural Cox model

$$\lambda_{a,m=0}(t) = \lambda_{o,m=0}(t)e^{\gamma_1x_a},$$

where $e^{\gamma_1}$ is the Hazard Ratio associated with the use of HRT when Statins are withheld. We also fit multivariate Cox models conditional on baseline covariates.

Our approach takes the effect of statins to be fixed at the point estimate of ASCOT-LLA, such that our estimators do not incorporate uncertainty due to sampling variability in that trial. A sensitivity analysis was conducted to determine the extent to which our conclusions depend on the assumed value for the effect of statins. We did this by increasing and decreasing the values of each parameter for the effect of statins in increments of 50% of the observed value, ranging from 0% (ie, statins have no effect) through 100% (the observed effect of statins in the randomized trial) to 200% (double the effect seen in the trial).
6. Administrative Censoring:

Since the WHI trial was stopped in July 2002, all surviving individuals are administratively censored at that calendar date. The vast majority of censoring in WHI was administrative. A Kaplan Meier curve with censoring as the outcome is shown as Figure 3.5. On the time scale of the study, the time of administrative censoring is a variable: A woman who enrolled in 1995 will have at most 8 years of follow-up, whereas one who enrolled in 1998 will have at most 5 years of follow-up. Let the variable $C_t$ indicate administrative censoring at time $t$, and $C_{t,a,m=0}$ be a counterfactual variable to denote whether the woman would have been administratively censored at time $t$ when we intervene to prevent statin usage.

If a woman is censored because of the end of the study (rather than being lost to follow-up), this is not expected to be correlated with cardiovascular risk unless one expects a secular trend in incidence. It is therefore commonly assumed that administrative censoring is non-informative, a convention we will adopt by assuming $C_t \perp Y$, ie that the probability of being censored at any time $t$ is independent of the cardiovascular risk. In our dataset, we tested the assumption of non-informative censoring by running an analysis where every individual is weighted by their probability of not being censored (estimated by a logistic model conditional on statin usage and baseline covariates). When using stabilized weights, the weighted outcome model was identical to the unweighted model to three decimal places, providing some support for the assumption of non-informative censoring.
However, even if administrative censoring in the actual trial is non-informative, censoring in the emulated target trial may be informative because women taking statins have their censoring time accelerated. In other words, in the emulated trial, $C_{t,a,m=0} \perp Y_{a,m=0}$ does not hold. Therefore, if doctors prescribed statins to women who were at higher cardiovascular risk, our procedure will lead to women at high risk being censored earlier than women at low risk.

Structurally, the only cause of informative censoring in the emulated trial is the procedure we performed to accelerate failure times. Since this process depended only on the history of statin usage, we know that $C_{t,a,m=0} \perp Y_{a,m=0} \mid A, M_t$. We can therefore eliminate the bias by weighting all uncensored observations by $w_t = \prod_t \frac{1}{\Pr(C_{t,a,m=0} = 0 \mid A, M_t)}$. Since the history of statin usage at time $t$ can be summarized by an indicator for ever having initiated and the time since initiation (if they have initiated by time $t$), these weights can be estimated by fitting the model

$$\text{logit} \Pr(C_t = 0 \mid A, M_t) = \beta_0 A + \beta_1 A + \beta_2 I(t > N) + \beta_3 \ast I(t > N) \ast (t - N)$$

in the modified data set.

Table 3.5 shows the parameter estimates from the model for the weight numerator. Tables 3.6 and 3.7 show the distribution of stabilized and unstabilized weights at time 60, 72 and 84 (along the transformed time scale), and at the last observation for any individual. Note that some of these weights are very large, potentially leading to unstable estimates.
Figure 3.5: Kaplan Meier curve for censoring
Table 3.5: Parameter estimates from weight models (Pooled logistic models, Odds ratios)

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>Ever use of statin (Lagged indicator)</th>
<th>Time since initiation (lagged)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numerator</td>
<td>0.858</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Denominator</td>
<td>0.896</td>
<td>2.898</td>
<td>1.022</td>
</tr>
</tbody>
</table>
Table 3.6: Distribution of stabilized weights over time

<table>
<thead>
<tr>
<th>Time</th>
<th>Observations</th>
<th>Mean</th>
<th>Median</th>
<th>90th Percentile</th>
<th>99th Percentile</th>
<th>Max observation</th>
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</thead>
<tbody>
<tr>
<td>60</td>
<td>10638</td>
<td>1.01</td>
<td>0.96</td>
<td>0.96</td>
<td>3.60</td>
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<td>72</td>
<td>5446</td>
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<td>0.91</td>
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<td>84</td>
<td>2182</td>
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<td>0.87</td>
<td>0.87</td>
<td>45.96</td>
<td>60.23</td>
</tr>
<tr>
<td>At last observation</td>
<td>15493</td>
<td>1.83</td>
<td>0.93</td>
<td>1.61</td>
<td>9.29</td>
<td>805.96</td>
</tr>
</tbody>
</table>
Table 3.7: Distribution of unstabilized weights over time

<table>
<thead>
<tr>
<th>Time</th>
<th>Observations</th>
<th>Mean</th>
<th>Median</th>
<th>90th Percentile</th>
<th>99th Percentile</th>
<th>Max observation</th>
</tr>
</thead>
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<tr>
<td>60</td>
<td>10638</td>
<td>1.47</td>
<td>1.36</td>
<td>1.41</td>
<td>5.10</td>
<td>23.63</td>
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<tr>
<td>72</td>
<td>5446</td>
<td>3.48</td>
<td>2.29</td>
<td>2.52</td>
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<td>345.94</td>
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<tr>
<td>84</td>
<td>2182</td>
<td>12.30</td>
<td>6.10</td>
<td>7.47</td>
<td>322.67</td>
<td>577.50</td>
</tr>
<tr>
<td>At last</td>
<td>15493</td>
<td>10.17</td>
<td>1.84</td>
<td>12.22</td>
<td>80.18</td>
<td>8699.39</td>
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<tr>
<td>observation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7. Structural Nested Cumulative Failure Time Models

Structural nested cumulative failure time models (SNCFTM) are an alternative to accelerated failure time models. These models are less sensitive to administrative censoring, but require a rare outcome assumption. In this section, we proceed to estimate the controlled direct effect of HRT using similar principles as above, but using a SNCFTM for the effect of statins in place of the SNAFTM. All variables are the same as in the previous section; in addition, we will further define the baseline covariates using the letter $L$. This is not because we are worried about confounding, but rather to discuss assumptions that have to be made about possible effect modification by $L$.

Picciotto et al (2012) describe the general form of a SNCFTM. In our case, since we are using a time-fixed intention to treat variable for the effect of statins, we will be able simplify the models considerable from those considered by Picciotto. Let $E[Y_{k}^{\text{IP}}|L, M]$ be the average counterfactual risk of developing the outcome by $Y$ time $k$, given the observed covariate and treatment history at the time of statin initiation, had everybody initiated treatment with statins. The general model for the intention-to-treat effect of statin initiation is then given by:

$$e^{\gamma_{k}(L,M; \psi^{\ast})} = \frac{E[Y_{k}^{\text{IP}}|L,M]}{E[Y_{k}^{0}|L,M]}$$

where $\gamma_{k}(L,M; \psi^{\ast})$ is a function of treatment and covariate history indexed by the
(possibly vector-valued) parameter $\psi$ whose unknown true value is $\psi^*$. An immediate
corollary of this model is that $H_k(\psi^*) = Y_k \times \frac{1}{e^{\gamma_k(L,M;\psi^*)}}$ has the same conditional mean
(given baseline covariates and treatment history) as the counterfactual probability of having the
event by time $k$, i.e. $E[Y_{k,m=0}^M | L, M]$. Picciotto et al refer to $\gamma_k(L,M; \psi^*)$ as the “blip down
function” and provide several different variations of functional forms. If we assume
$\frac{E[Y_k^M | L, M]}{E[Y_k^0 | L, M]}$ is
constant over time, $e^{\gamma_k(L,M; \psi^*)}$ is then equal to the hazard ratio, which can be estimated either
from a specific trial, or from a meta-analysis. If we further assume that the hazard ratio is
constant between levels of baseline covariates $L$, we can use the simple model $e^{\gamma_k(L,M; \psi^*)} =
e^{\psi \times M}$.

We next proceed to remove the effect of statins from the WHI data, by assuming that the blip-
down function $e^{\gamma_k(L,M; \psi^*)}$ is equal between the following three groups:

1. Women initiating statins in the HRT arm of WHI

2. Women initiating statins in the Placebo arm of WHI

3. Participants in the Statin trial

For any possible time of statin initiation in WHI (denoted $n$), we define the subset of the study
participants who are eligible to initiate statins, i.e. those who have not had the event and who
have not already initiated statins prior to $n$. Consider their probability of having the event by
time $k$ (where $k>n$), under the intervention where statins are not initiated at any time point after
conditional on whether they initiated treatment. Mathematically, this is written as
\[ E[Y_k^{A_{m_k=0}} | L = l, Y_n = 0, \overline{M}_{n-1} = \bar{0}, M_n = m]. \]

For those women who initiated statins, we can blip down their observed data \( E[Y_k^A | L = l, Y_n = 0, \overline{M}_{n-1} = \bar{0}, M_n = 1] \) to the counterfactual mean \( E[Y_k^{A_{\overline{m}=0}} | L = l, Y_n = 0, \overline{M}_{n-1} = \bar{0}, M_n = 1] \) by replacing the distribution of events at time \( k \) with \( H_k(\psi^*) \). Among women who did not initiate statins, the observed data \( E[Y_k^A | L = l, Y_n = 0, \overline{M}_{n-1} = \bar{0}, M_n = 0] \) is equal to the counterfactual mean \( E[Y_k^{A_{\overline{m}=0}} | L = l, Y_n = 0, \overline{M}_{n-1} = \bar{0}, M_n = 0] \) by consistency; therefore, the observed distribution does not need to be altered in these women.

In most applications of g-estimation, it is necessary to implement the blip-down procedure sequentially, working backwards from the last possible time of treatment. However, in our specific case, because treatment can only be initiated once, any individual will at most be blipped down at one time point. Therefore, the analysis can be pooled it over time \( n \).

We implemented this analysis as follows: first we fit a pooled logistic model for the probability of CHD in individuals taking statins (i.e., where \( t>n \)). We then used this model to predict the instantaneous risk at all time points \( t \), and multiplied this predicted risk by the reciprocal of the hazard ratio for statins. We next ran 10000 Monte Carlo simulations, where each individual had one Bernoulli trial at each time point, with the time-dependent failure probabilities were given
by the predicted risks. Follow-up ends at the time of the (simulated) event, or observed time of follow-up, whichever occurs first. The observed data was retained in individuals not taking statins. In each resulting data set we fit a Cox model with randomization arm as the predictor, averaging the parameter estimates over all simulations. 95% confidence intervals were obtained using a non-parametric bootstrap with 250 samples.

8. Results:

We first replicated the results from the WHI trial by fitting an unadjusted Cox model, with the randomized treatment assignment as the only predictor. This model showed a Hazard Ratio of 1.24 (95% CI: 0.98-1.56), corresponding to the published results

Table 3.8 shows the estimated direct effects of estrogen on CHD and on the secondary outcomes (stroke and all-cause mortality). In the unweighted SNAFTM analysis, adjusting the survival times to remove the effect of statins resulted in a minor reduction in the hazard ratio, to 1.22 (95% CI: 0.96-1.54). Including the baseline covariates in the outcome model had negligible impact. Note that when the weights are applied, the results change in unpredictable directions. This is likely due to a near-violation of positivity. In the case of the unstabilized weights, the change of the direction of the effect may be related to the fact that these weights, which do not use time in the numerator, giving more importance to the latter parts of the survival curve where HRT is protective. In light of the surprisingly large differences
between different weighted analyses, we advise that the results from the SNAFTM analysis should be interpreted with caution.

Figure 3.6 shows the unadjusted and adjusted Kaplan Meier curves for the analysis based on accelerated failure time models. In the SNCFTM analysis, the adjusted hazard ratio based on 10000 Monte Carlo simulations was 1.22 (95% CI: 0.97-1.50). The adjusted Kaplan Meyer curve based on the SNCFTM model is shown as Figure 3.7.

Tables 3.9 and 3.10 show sensitivity analysis where we varied the assumed effect of statins, to show how sensitive our estimates are to our assumption that we have reliable external information on the effect of statins. We note that both in the case of the SNCFTM and the unweighted SNAFTM, even large changes to the assumed effect of statins lead to qualitatively similar effect estimates.

Much of the impact of our adjustment is concentrated in the later years: When censoring all women at 5 years and 6 years, adjustment has negligible impact on the hazard ratio for CHD. Results at 5 years are shown as Table 3.11. This is reflected in the survival curves, where the adjusted survival curve is essentially superimposed on the unadjusted arm during the first years of the trial.
Because we sometimes cannot be sure that statin initiation happened before the heart attack (and because statin initiation sometimes happens because of a heart attack) we delayed the variable $M_t$ by a year in the primary analysis. In a sensitivity analysis, we used the originally recorded time of statin initiation; this had negligible impact on the SNAFTM analysis. In the case of the SNCFTM analysis, this led to substantially increased risks in both arms of the study, but had little impact on the hazard ratio. It is not surprising that the SNCFTM analysis is more affected by using the original statin variable, as the parameter $\alpha_2$ in the model

$$\text{logit } \Pr(Y_t | Y_{t-1} = 0, A, M) = \alpha_{0,t} + \alpha_1 * A + \alpha_2 * I(M_t \neq 0) * + \alpha_3 * I(M_t \neq 0) * (t - N)$$

will be seriously affected by “reverse causation bias”, whereas no similar parameter for the effect of statins is estimated from the WHI data in the accelerated failure time model.
### Table 3.8: Hazard Ratios for Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted Hazard Ratio (in subset who did not take statins at baseline, n=15493)</th>
<th>Adjusted Hazard Ratio (SNAFTM)</th>
<th>Adjusted Hazard Ratio (SNAFTM)</th>
<th>Adjusted Hazard Ratio (SNAFTM)</th>
<th>Adjusted Hazard Ratio (SNAFTM)</th>
<th>Adjusted Hazard Ratio (SNAFTM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unweighted</td>
<td>Weighted by stabilized weights</td>
<td>Weighted by unstabilized weights truncated at 40</td>
<td>Weighted by unstabilized weights truncated at 40</td>
<td>Weighted by unstabilized weights truncated at 40</td>
</tr>
<tr>
<td>CVD</td>
<td>1.24 (0.98-1.56)</td>
<td>1.22 (0.96-1.54)</td>
<td>1.25 (0.99-1.59)</td>
<td>1.23 (0.97-1.56)</td>
<td>0.95 (0.75-1.21)</td>
<td>0.96 (0.70-1.35)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.33 (1.03-1.73)</td>
<td>1.32 (1.02-1.72)</td>
<td>1.38 (1.06-1.80)</td>
<td>1.44 (0.94-2.22)</td>
<td>1.53 (0.99-2.02)</td>
<td>1.42 (1.02-2.36)</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>0.98 (0.82-1.18)</td>
<td>0.98 (0.81-1.18)</td>
<td>0.98 (0.81-1.18)</td>
<td>0.98 (0.75-1.29)</td>
<td>0.97 (0.73-1.27)</td>
<td>0.97 (0.81-1.14)</td>
</tr>
</tbody>
</table>
Table 3.9: Sensitivity Analysis for unweighted SNAFTM models

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted analysis</th>
<th>Adjusted to 50% of statin effect in trial</th>
<th>Adjusted to 100% of statin effect in trial</th>
<th>Adjusted to 150% of statin effect in trial</th>
<th>Adjusted to 200% of statin effect in trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.24 (0.98-1.56)</td>
<td>1.22 (0.97-1.55)</td>
<td>1.22 (0.96-1.54)</td>
<td>1.21 (0.96-1.53)</td>
<td>1.21 (0.96-1.53)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.33 (1.03 – 1.73)</td>
<td>1.33 (1.02-1.72)</td>
<td>1.32 (1.02-1.72)</td>
<td>1.32 (1.02-1.71)</td>
<td>1.32 (1.02-1.71)</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>0.98 (0.82-1.18)</td>
<td>0.98 (0.82-1.18)</td>
<td>0.97 (0.81-1.18)</td>
<td>0.97 (0.81-1.18)</td>
<td>0.97 (0.81-1.18)</td>
</tr>
</tbody>
</table>
Table 3.10: Sensitivity analysis for SNCFTM model

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted analysis</th>
<th>Adjusted to HR=0.85</th>
<th>Adjusted to HR=0.70 (result from meta-analysis)</th>
<th>Adjusted to HR= 0.55</th>
<th>Adjusted to HR=0.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.24 (0.98-1.56)</td>
<td>1.23 (0.94-1.51)</td>
<td>1.22 (0.97-1.50)</td>
<td>1.21 (0.92-1.44)</td>
<td>1.17 (0.93-1.41)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted analysis</th>
<th>Adjusted to HR=0.89</th>
<th>Adjusted to HR=0.76 (result from meta-analysis)</th>
<th>Adjusted to HR= 0.63</th>
<th>Adjusted to HR=0.50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1.33 (1.03 – 1.73)</td>
<td>1.33 (1.07 - 1.68)</td>
<td>1.33 (1.04-1.66)</td>
<td>1.32 (1.07-1.65)</td>
<td>1.31 (1.05 - 1.63)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted analysis</th>
<th>Adjusted to HR=0.94</th>
<th>Adjusted to HR=0.91 (result from meta-analysis)</th>
<th>Adjusted to HR= 0.87</th>
<th>Adjusted to HR=0.82</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>0.98 (0.82-1.18)</td>
<td>0.98 (0.88 - 1.10)</td>
<td>0.97 (0.81- 1.14)</td>
<td>0.97 (0.88 - 1.11)</td>
<td>0.97 (0.87 -1.09)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Unadjusted Hazard Ratio (in subset who did not take statins at baseline, n=15493)</td>
<td>Adjusted Hazard Ratio (SNAFTM) Unweighted</td>
<td>Adjusted Hazard Ratio (SNAFTM) Weighted by stabilized weights</td>
<td>Adjusted Hazard Ratio (SNAFTM) Weighted by stabilized weights truncated at 40</td>
<td>Adjusted Hazard Ratio (SNAFTM) Weighted by unstabilized weights</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>CVD</td>
<td>1.47 (1.13-1.92)</td>
<td>1.46 (1.12-1.91)</td>
<td>1.46 (1.12-1.91)</td>
<td>1.46 (1.12-1.91)</td>
<td>1.46 (1.12-1.91)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41 (1.05, 1.89)</td>
<td>1.39 (1.04-1.85)</td>
<td>1.39 (1.04-1.85)</td>
<td>1.37 (1.03-1.84)</td>
<td>1.37 (1.03-1.84)</td>
</tr>
</tbody>
</table>
Figure 3.6: Adjusted Kaplan-Meier curve from SNAFTM models (Unweighted)
Figure 3.7: Adjusted Kaplan Meier curve from SNCFTM model
9. Discussion:

We have provided a new method for determining whether the results of a randomized trial can be explained by post-baseline variation in a mediator variable. This method is valid regardless of whether there is unmeasured confounding of the mediator-outcome relationship as long as one has an unbiased external estimate of the effect of the mediator. We applied this new method to data from the WHI trial, to estimate the direct effect of HRT relative to statin initiation and thereby determine if the trial results could be explained by differences in statin usage between the randomization arms. This question is of interest not only for its clinical implications, but also as due to its implications for the interpretation of observational studies on HRT that preceded WHI.

In the WHI trial, women in the E+P arm were less likely to initiate statins than women randomized to placebo. This is plausibly explained by differences in lipid profiles, as women in the estrogen arm have significantly lower LDL cholesterol. In other words, doctors appear to withhold statins in women taking estrogen because their cholesterol levels are lower. However, our analysis suggests that differential initiation of statins cannot explain the trial findings: The minor reductions in the hazard ratios are unlikely to be clinically relevant, and must be seen in light of the wide confidence intervals.

This may seem counterintuitive in light of the substantial difference in utilization between the arms. In order to resolve this apparent paradox, we want to point out that most of the effect of
HRT in the WHI trial was seen during the first few years after baseline. During this time, few women had initiated statins in either arm of the study. This is reflected in our analysis by the finding that adjustment to remove the effect of statins had negligible impact during the first few years of follow-up.

As any analysis, our study has limitations. Our approach takes the effect of statins as being fixed at the point estimate of the trial in which it was estimated, we therefore do not incorporate sampling variability from that trial. However, our sensitivity analysis show that varying the assumed effect of statins had relatively little impact on the conclusions. Moreover, a large number of randomized trials have been conducted on statins, with relatively consistent findings, which suggest that the effect of statins is known with at least some degree of certainty.

A further limitation is that the SNAFTM blip-down procedure induces informative censoring in the resulting dataset, and the weights we estimated to adjust for this bias had inconsistent impact on the models, making it difficult to interpret the estimates. However, it is reassuring that the SNCFTM model, which is not subject to the same type of informative censoring bias, had relatively similar results.

The crucial assumption underlying this analysis is that the effect of statins is equal between initiators of statins in the WHI trial and the participants in the statin trial, on the effect measure
that was used to transport the effect. We note that meta-analyses of statin trials provide some
evidence that the effect of statins is relatively constant between different subgroups on the
hazard ratio scale.

Despite the limitations of the study, it seems unlikely that any of them would have caused a
bias that would substantially alter the interpretation of the results. We conclude that at least in
some subset of women, hormone replacement therapy with estrogen and progestin has a
direct effect on coronary heart disease, which is not explained by failure to initiate statin
treatment.
REFERENCES


The need for inverse probability weights

To see why inverse-probability weighting is required to adjust for previous findings at colonoscopy, consider the directed acyclic graph in Appendix Figure 1. $A_t$ is an indicator for colonoscopy at time $t$, $L_t$ is an indicator for the (possibly unknown to the investigator) presence of adenomas at time $t$, $L^*_t$ is an indicator for the presence of known adenomas at time $t$.

Adenomas only become known through colonoscopy: If $A_t=1$ then $L_{t+1}^*=L_t$, otherwise $L_{t+1}^*=L_t^*$. $U$ represents the common causes of adenomas and colorectal cancer, such as genetics. $Y$ is an indicator of colorectal cancer by the end of follow-up.

According to this causal diagram, $L_{t+1}^*$ is a confounder for the effect of $A_{t+1}$ on $Y$: Knowledge of adenomas at time $t+1$ predicts colonoscopy at time $t+1$, and is also a marker for actual adenomas $L_t$, which cause cancer at time $k>t$. However, confounding adjustment via conditioning on the collider $L_{t+1}^*$ would open the biasing path $A_t \rightarrow L_{t+1}^* \leftarrow L_t \rightarrow Y$. Note that, to avoid clutter, we chose not to include the direct arrow from $A_{t-1}$ (not shown on graph) to $L_t$, which would only increase the number of biasing paths.

Another possible problem is that conditioning on $L_{t+1}^*$ may partially block the effect of $A_t$ through the path $A_t \rightarrow L_{t+1}^* \rightarrow Y$. The arrow $L_{t+1}^* \rightarrow Y$ exists because the detection of polyps necessarily leads to polypectomy, which affects the risk of cancer at later times.
Figure A.1: Causal directed acyclic graph to represent the effect of $A_t$ (colonoscopy at time $t$ followed by polypectomy if necessary) on colorectal cancer $Y$.

In this graph, $L_t$ is an indicator for the presence of adenomas and $L_t^*$ is an indicator for the presence of known adenomas at time $t$. 
On The Homogeneity of the Causal Effect

The meta-analysis of Statin trials conducted by the Cholesterol Treatment Trialists collaboration (CTT)\textsuperscript{7} suggests that the effect of statins is relatively homogenous between different patient groups on the Hazard Ratio scale\textsuperscript{7}. However, this is not sufficient to establish the validity of our analysis, which requires the effect to be homogenous on the accelerated failure time scale. We next proceed to discuss the conditions under which homogenous effects on the Hazard Ratio scale implies homogenous effects on the accelerated failure time scale.

It is well established that if failure times follow an exponential or Weibull distribution, then the parameters of an accelerated failure time model will equal the parameters of a proportional hazards model\textsuperscript{1}. Therefore, if one assumes an exponential distribution, homogenous hazard ratios on the hazard ratio scale will necessarily lead to homogenous parameters in the accelerated failure time model. However, since hazards tend to increase with age, exponential failure times is an assumption which is difficult to justify. We therefore conducted a simulation study to determine the extent to which the parameter of the an accelerated failure time model will be non-homogenous between different risk groups, if the effects are homogenous on a hazard ratio scale.

In the WHI data set, the observed rate of CHD was 0.0032 per person year. We created a simulated randomized trial comparing statin usage to no statin usage in two groups of people: A high risk group with a baseline rate of 0.004 events per person year, and a low risk group with 0.002 events per person year. In both groups, we assumed that CHD incidence rate increases by 5% every year from baseline. In both statin arms, all hazards were multiplied by a hazard ratio of 0.70.

In this simulated data set, we then fit an accelerated failure time model in each subgroup. These two accelerated failure time models had very similar parameters for the expansion of survival time, both slightly below 0.7. This is consistent with the conjecture that if the effects are homogenous on the hazard ratio scale, they will also be relatively homogenous on the accelerated failure time scale.
Estimation of $\Psi_k$ using published Kaplan Meier Curves

The full specification of our model for the effect of statins is

$$K^0 = \int_0^K e^{\Psi_1 \cdot M_k \cdot I(0<k\leq6) + \Psi_2 \cdot M_k \cdot I(6<k\leq12) + \Psi_3 \cdot M_k \cdot I(12<k\leq18) + \cdots} \, dk$$

Here, each $\Psi$ parameter represents the contraction or expansion of survival time associated with statin treatment during a 6-month time interval since statin initiation.

Using graphical software with a ruler and a rectangular drawing tool applied to the published Kaplan Meier curves, we mapped each time point in the Estrogen arm to the time point where the corresponding quantile in the Placebo arm failed. Our assumption of rank preservation gives us license to interpret this as the failure time that would have been observed under no treatment.

For example, in order to estimate the parameter $\Psi_1$, which is the effect during the first 6 months, we begin by placing the corner of a rectangle on 6 months on the X-axis. We then draw a line segment perpendicular to the X-axis, and place the second corner of this rectangle where it intersects with the Kaplan Meier curve for the estrogen arm. We then draw another line segment parallel to the X-axis, and place the third corner at the point where it intersects with the Kaplan Meier curve for the Placebo arm. The fourth corner of this rectangle will be the failure time under no treatment.
If we imagine that the individual who failed at month 6 in the Statin arm was mapped to a counterfactual survival time under no treatment in month 3, we can now estimate the treatment effect $\Psi_k$ during the first 6 months by solving the equation $3 = \int_0^6 e^{\Psi_1} \, dk$. In this case, we will find that $\Psi_1 = -0.69$.

Knowing the value of $\Psi_1$, we can then go on to estimate $\Psi_2$. To do this, we repeat the process at the 1 year mark by solving $K^0 = \int_0^{12} e^{\Psi_1M_k*1(0<k\leq6) + \Psi_2M_k*1(6<k\leq12)}$ for $\Psi_2$, where $\Psi_1$ has been substituted by its estimate -0.69.