Chapter 3. Estimation and Reporting of Heterogeneity of Treatment Effects

Abstract

Patient populations within a research study are heterogeneous in terms of characteristics that vary between individuals such as age, sex, disease etiology and severity, presence of comorbidities, concomitant exposures, and genetic variants. These patient characteristics can potentially modify the effect of a treatment on outcomes. Despite this heterogeneity, many studies estimate an average treatment effect (ATE). The treatment effect within subgroups may vary considerably from the ATE, however, as differences may arise from an underlying causal mechanism or may be due to artifacts of measurements or methods (e.g., chance, bias, or confounding). Heterogeneity of treatment effect (HTE) is the non-random, explainable variability in the direction and magnitude of treatment effects for individuals within a population. The main goals of HTE analysis are to estimate treatment effects in clinically relevant subgroups and to predict whether an individual might benefit from a treatment. Subgroup analysis is the most common analytic approach for examining HTE. Selection of subgroups should be based on mechanism and plausibility, taking into account prior knowledge on treatment effect modifiers. This chapter focuses on defining and describing HTE and how to evaluate and report such heterogeneous effects using subgroup analysis. Understanding HTE is critical for decisions that are based on knowing how well a treatment is likely to work for an individual or group of similar individuals, and is relevant to most stakeholders, including patients, clinicians, and policy makers. The chapter concludes with a checklist of key considerations for discussion of HTE and addressing planned subgroup analysis in an observational CER protocol or proposal.

"If it were not for the great variability between individuals, medicine might as well be a science, not an art" (William Osler, 1892).

Introduction

Randomized controlled trials (RCTs) and observational studies of comparative effectiveness usually report an average treatment effect (ATE), even though experience suggests that the same treatment can have varying impacts in different people. The clinical experience and expectation that differences in patient prognostic characteristics will lead to heterogeneous responses to therapy is mainly why medicine is as much an art as it is science. Yet, studies tend to emphasize a single measure of the impact of treatment, the ATE, which is a summary of individual treatment effects (which cannot be examined directly). Variation is often undesirable in studies and is reduced by excluding people with characteristics that are thought to cause variations in responses to treatment. This intentional restriction in patient heterogeneity within RCTs contributes to their limited generalizability. Determining whether a treatment works for people in a target population that differs from the study population requires additional information and methods.[1]

Heterogeneity of Treatment Effect

All studies have variability in the data. Random variability is generally not concerning because it is uncorrelated with explanatory variables, and can be handled well with statistical approaches for quantifying uncertainty. We focus on the non-random variability in treatment effects that can be attributed to patient factors. We define HTE as non-random variability in the direction or magnitude of a treatment effect, where the effect is measured using clinical outcomes (either a clinical event such as myocardial infarction or a change in a continuous clinical measure such as level of pain).[2]

Understanding HTE is critical for decisions that are based on knowing how well a treatment is likely to

work for an individual or group of similar individuals and is relevant to stakeholders including patients, clinicians, and policy makers. It also has implications for applicability of findings from pragmatic trials and observational comparative effectiveness research (CER) to individual patients (personalized medicine). Pragmatic trials are large and simple experiments of treatments with broad eligibility criteria from which evidence is expected to be generalizable. While these designs incorporate heterogeneity in the risk of outcome among subjects, they might also lead to HTE for treatments that are applied. These studies may be more likely to yield null ATE than efficacy trials, where stricter inclusion criteria produce relatively homogeneous study populations. Therefore, understanding major sources of variations in treatment response is essential.

For a formal general definition of HTE, see Box 3.1.

Box 3.1. Formal Definition of HTE

Let an individual or a targeted subgroup with specific levels of characteristics be denoted by i. Let z stand for treatment at two levels {1, 2}, for example, being given aspirin (z=1) or not (z=2). The potential outcomes $\{Y_i(z=1), Y_i(z=2)\}$, are assumed to be binary, 0 or 1, for example, experiencing a heart attack within 1 year: Y=0, if a heart attack does not occur and, Y=1, if a heart attack occurs. The individual treatment effects can be measured using an absolute or relative risk model. For the absolute risk model the individual treatment effect, $\theta_i = \text{Prob}(Y_i(2)=1) - \text{Prob}(Y_i(1)=1)$. For the relative risk model, $\theta_i = \log [\text{Prob}(Y_i(2)=1)/\text{Prob}(Y_i(1)=1)]$. Individual variability of treatment effect occurs if the variance $(\theta_i) > 0$. Group variability (HTE) occurs if the variance of individual treatment effect is non-random (i.e. correlated with explanatory variables) so that $\theta_{subgroup1}$ (average θ_i for a subgroup defined by level 1 of an explanatory variable) $\neq \theta_{subgroup2}$ (average θ_i for a subgroup defined by level 2 of an explanatory variable). When this variability encompasses treatment effects of different directions, i.e., both benefit and harm, this is sometimes called a qualitative treatment interaction, whereas differences in the magnitude of treatment effect in the same direction are called quantitative interactions.

There are numerous cases where the effectiveness of specific therapies may be heterogeneous. For example, children may respond differently to therapy via different response to treatment or to aspects of dosing that are not realized. Older adults may have worse outcomes from surgeries and devices as well as more drug side effects or drug-drug interactions so that therapies might be less effective. Individuals with multiple conditions may be on several therapies that interfere with the new treatment (or each other), resulting in a different treatment effect in these patients. Genes may also influence response to therapy; since genetic differences (differences in allele frequencies) might cluster by race or ethnicity, these characteristics might represent proxies for genetic differences that are more difficult to measure directly.

Treatment Effect Modification

If two or more exposure variables act in concert to cause disease, we will observe that the effect of exposure on outcome (treatment effect) differs according to the level of the other factor(s). A number of terms have been used to describe this phenomenon, including "joint" effects, "synergism", "antagonism", "interaction", "effect modification", and "effect measure modification." Where effect modification exists, sound inferences will require accounting for factors that modify the effect of the exposure of primary interest. Accounting for this HTE may be required even when the variable that modifies treatment effect is not a risk factor for the outcome in the untreated group (e.g., a receptor that determines how a drug is metabolized).

Four perspectives have been advanced on the concept of interaction and the relevance of the effect modification in terms of its implication:[3]

Biological perspective: This perspective is that the interaction elucidates how factors act at the biological (mechanistic) level. The implications of this perspective are that the interaction is a representation of an underlying causal structure. Example: The finding that hypertension and smoking have a greater than additive effect on heart attack risk is a representation of some underlying biological processes that may enhance our understanding of heart attack etiology.

Statistical perspective: This perspective is that the interactions represent non-random variability in data unaccounted for by a model that contains only first-order terms (main effects). Implication is that the model needs to be reformulated to more accurately reflect the data. Example: A differently structured model will appropriately account for the underlying variability in the data on hypertension, smoking, and heart attack risk).

Public health perspective: This perspective is that the interactions represent a departure from additivity and highlight populations (subgroups) where an intervention can be expected to have particularly beneficial effects. Example: the finding that hypertension and smoking have a greater than additive effect on heart attack risk suggests that limited public health resources might be most efficiently directed at patients who have hypertension and who are also smokers.

The individual decision-making perspective: This perspective is that the interactions represent a departure from additivity so that combined effects in an individual are greater than their sum. Example: Someone with hypertension can reduce heart attack risk even more by quitting smoking than someone with normal blood pressure.

Since an effect modifier changes the magnitude or direction of the association under study, different study populations may yield different results concerning the association of interest. As such, HTE is often suggested as a reason for differences in findings across studies. If two studies included people with different characteristics and the effect of the treatment is different in the portion of the population that differs between the studies, then HTE is a plausible explanation for the difference. Further, HTE can be an explanation for differences in treatment effect from interventional and observational studies, since observational studies often include patients with different characteristics than interventional studies. Such a hypothesis might be addressed through reweighting subgroup effects according to prevalence (standardization) across studies.

Unlike potential confounders, modifying variables cannot create the appearance of an association (for exposed versus unexposed) where none exists. But the proportion of the study population that has a greater susceptibility will influence the strength of the association. Therefore, to achieve comparability across studies, it is necessary to control for the effect of the modifying variables, generally by carrying out a separate analysis at each level of the modifier.

Additionally, the different strength of association between the exposure and outcome within strata of the effect modifier may lead to a need to be more precise in the measurement and specification of the exposure variable (such as more clearly within strata of the effect modifier).

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Goals of HTE Analysis

There are two main goals of HTE analyses: (1) to estimate treatment effects in clinically relevant subgroups (subgroup analysis), and (2) to predict whether an individual might benefit from a treatment (predictive learning).[2] The first goal of HTE is highlighted in the definition of comparative effectiveness research (CER) proposed by the Congressional Budget Office: "an analysis of comparative effectiveness is simply a rigorous evaluation of the impact of different treatment options that are available for treating a given medical condition *for a particular set of patients"*.[1] The second goal of HTE analysis is individual-level prediction. Predicting beneficial and adverse responses of individuals to different treatments in terms of multiple endpoints is essential for informing individualized treatment decisions. One version of this goal has been described as answering the question: "Who will benefit most from Treatment A and who will benefit most from Treatment B?"[4] Creating such a narrowly-defined subgroup (the individual patient) leads to an extremely challenging problem, which has not been adequately studied, and one for which there are few reliable methods that provide protection against spurious findings.[5] Subgroup analysis, on the other hand, has been extensively studied.[6] Hence, we will focus on the subgroup analysis.

Subgroup Analysis

Subgroup analysis is the most popular analytic approach for examining HTE. This method usually evaluates the treatment effect for a number of subgroups, one variable at a time, usually a baseline or pre-treatment variable. A test for interaction is conducted to evaluate if a subgroup variable has a statistically significant interaction with the treatment indicator. If the interaction is significant, then the treatment effect is estimated separately at each level of the categorical variable used to define mutually exclusive subgroups (e.g., men and women).

It should be cautioned, however, that the interaction test generally has low power to detect differences in subgroup effects.[7] For example, when compared to the sample size required for detecting ATE of a particular size, a roughly four times larger sample size is required for detecting a difference in subgroup effects of the same magnitude as ATE for a 50:50 subgroup split; and approximately 16 times larger sample size is required for detecting a difference that is half of ATE (at significance level 0.05).

Even though the interaction test has low power to detect a true difference in subgroup effects, there is a danger of falsely detecting a difference in subgroup effects if we perform separate interaction tests for multiple subgrouping variables. That is, suppose we perform separate interaction tests for 100 subgroup variables. The interaction test will be statistically significant (at a significance level of 0.05), on average, for about 5 subgroup variables, when in truth the treatment effect is homogeneous. Now, if we make a Bonferroni correction for multiple testing in order to maintain the correct Type-I error probability, we would be further increasing the Type-II error probability, which increases the likelihood of not identifying true heterogeneity in subgroup effects.

It should also be noted that a statistical test of interaction does not correspond to an assessment of biological interaction. The presence or absence of statistical interaction depends on various mathematical aspects of the regression model (e.g., scale of dependent variable, covariates present in the model, distributional assumptions). These considerations are largely irrelevant for biological interactions.3

An important lesson in the use and potential for misuse of subgroup analyses (and implied HTE) came in the form of a large randomized trial of therapies for myocardial infarction. In 1988, the results of the Second International Study of Infarct Survival (ISIS-2) study, a randomized 2x2 factorial study of the effect of streptokinase and aspirin for treatment of myocardial infarction, were published.[8] This study provided evidence indicating that either streptokinase or aspirin reduced mortality during follow-up, and that the combination of streptokinase and aspirin improved survival over either treatment alone. In the aspirin-treated subjects, there was a reduction in mortality (804 deaths among 8,587 people, 9.4%) relative to subjects not treated with aspirin (1,016 deaths among 8,600 people, 11.8%, $p<0.05$). Numerous subgroup analyses were conducted, most of which indicated relatively consistent effects within subgroups. However, one particular subgroup analysis, astrological birth sign, suggested heterogeneity of effect. In the subgroup of patients born under the astrological sign Gemini or Libra, there were more deaths (150 of 1,357, 11.1%) among the aspirin-treated patients than there were among the non-aspirin-treated patients (147 of 1,442, 10.2%) (p not significant).

This apparent heterogeneity in the effect of aspirin served as a caution. Rather than inferring that aspirin should not be used in the treatment of myocardial infarction if the patient is a Gemini or a Libra, the authors strongly caution against drawing strong inferences from subgroup analyses. When the ATE is clearly positive (both aspirin and streptokinase reduce mortality in patients with myocardial infarction) and many subgroup analyses are conducted, false positive or negative findings are to be expected. Findings from such subgroup analyses should be interpreted with caution even if a plausible biologic mechanism exists. Indeed, the ISIS-2 subgroup analysis results found a mortality benefit for streptokinase among persons >65 years, those with a previous infarct, and in those presenting more than 6 hours from onset of pain, subgroups that an earlier randomized trial of streptokinase (GISSI) had suggested would not benefit from streptokinase therapy on the basis of subgroup analyses, even though the average effect of streptokinase was beneficial. When there are plausible a priori reasons that a treatment may not be effective (such as in patients with contraindications to the therapy) and subgroup analyses find no benefit in that subgroup, stronger inferences might be drawn.

Types of Subgroup Analysis

Three different types of subgroup analyses may be distinguished: (a) confirmatory, (b) descriptive, and (c) exploratory.[9] See Table 3.1 for a summary of the essential characteristics of these three types of subgroup analyses.

Confirmatory Subgroup Analysis

The main goal is to test and confirm hypotheses on subgroup effects. The essential elements of this type of analysis are: clear definition and pre-specification of subgroups; clear definition and pre-specification of endpoints related to outcomes; pre-specification of a small number of hypotheses on subgroup effects, including the direction in which the effects are expected to vary in subgroups; availability of strong a priori biological & epidemiological evidence; detailed description of statistical analysis plan on how testing will be done; and adequate power to test subgroup hypotheses. Essentially, the study intent, design, and analysis are all focused on the subgroup hypotheses to be tested. Due to these stringent requirements, the findings from a confirmatory analysis are potentially actionable.

Table 3.1. Essential Characteristics of Three Types of Subgroup Analyses[9]

Properties	Confirmatory	Descriptive	Exploratory

Goal	To test hypotheses related to subgroup effects	To report treatment effects for future synthesis	To generate hypotheses for further study
Number of hypotheses examined	A small number, typically one or two	Moderate and pre-specified	Not made explicit, but may be large, and not pre-specified
Prior epidemiological or mechanistic evidence for hypothesis	Strong	Weak or none	Weak or none
Pre-specification of data analytic strategy	Pre-specified in complete detail	Pre-specified	Not pre-specified
Control of familywise type I error probability	Necessary	Possible, but not essential since the goal is not to test hypotheses	Not essential
Characterization of sampling error of the statistical estimator	Easy to achieve	Possible	Difficult to characterize sampling properties (e.g., confidence intervals)
Power of testing hypothesis	Study may be explicitly designed to have adequate power	Likely to be inadequately powered	Inadequate power to examine several hypotheses

Descriptive Subgroup Analysis

The main goal of descriptive subgroup analysis is to describe the subgroup effects for future evaluation and synthesis. The essential elements of this type of analysis are: clear definition and pre-specification of subgroups, clear definition and pre-specification of endpoints related to outcomes, pre-specification of hypotheses relating to subgroup effects, and detailed description of statistical analysis plan on how testing will be done. The results of these subgroup analyses may be presented as a table in the main report and as forest plot, with a vertical line representing the overall treatment effect (ATE). See Antman (2006) for a good example of such a forest plot.[10] Alternatively, they may be made available as an appendix or as electronic supplemental material in order to facilitate future evaluation and for synthesis and meta-analysis by systematic reviewers.

Exploratory Subgroup Analysis

Exploratory subgroup analyses are mainly done to identify subgroup hypotheses for future evaluation. Typically, exploratory subgroups are not pre-specified. Compared to confirmatory and descriptive HTE analyses, exploratory analyses enjoy more flexibility for identifying baseline characteristics that interact with treatment. Definition of subgroups, endpoints, hypotheses, and modeling parameters are usually derived in response to the data. An example of this would be the use of a stepwise model selection approach to identify treatment by covariate interactions. A major problem with these analyses is that it is extremely difficult to obtain the sampling properties of subgroup effect estimators (e.g., standard errors). Often, it is not clear how many hypotheses were tested (e.g., using stepwise model selection to identify HTE). Post-hoc exploratory subgroup analyses may, sometimes, identify promising hypotheses that could be subject to more rigorous future examination. The results of these subgroup analyses, while potentially important, should be clearly labeled as exploratory.

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Potentially Important Subgroup Variables

Important subgroups are ones for which limited data is typically available, such as the AHRQ priority populations (e.g., women, men, children, minorities, elderly, rural populations, individuals with disabilities, etc.).[11]

Subgroup variables must be true covariates, i.e., variables that are defined before an individual is exposed to the treatment or variables that are known to be unaffected by the treatment. Variables that change in response to treatment and post-randomization variables are not covariates. Some additional important types of subgroup variables are: 1) demographic (e.g., age); 2) pathophysiologic variables (e.g., timing after stroke, stable or unstable angina); 3) comorbidities (e.g., presence of renal disease when treating hypertension); 4) concomitant exposures (e.g., beta-blockers, aspirin); and 5) genetic markers (e.g., interaction between K-ras gene mutation and cetuximab for colorectal cancer). Sex and age should always be evaluated for interaction with treatment, although it is not obvious how to define the age categories. Notwithstanding, the definition of age categories should be pre-specified. The other subgroup variables should be considered when there is prior epidemiological or mechanistic evidence suggesting some potential for interaction with the treatment.

Subgroup Analyses: Special Considerations for Observational Studies

General Considerations

Randomized trials generally have broad exclusion criteria that serve several purposes. These criteria reduce the heterogeneity of the study population so that there is less variability with respect to outcome measures, thereby improving statistical power for a given sample size. Exclusion criteria also serve to protect patients who might be harmed by a treatment (such as those with a contraindication to the treatment). Since the aim of many observational studies is to describe the effect of treatment as actually used, fewer exclusions are typically applied, and those that are often applied are for the purpose of improved confounder control. As a result, observational studies often include patients for whom no randomized data of treatment effect exists. For example, a patient with a relative contraindication for a treatment might be excluded from a randomized trial, but a treating clinician may decide that the benefits outweigh the risks for this patient and apply the therapy.

The study of treatment effects can be challenging in observational studies. Observational studies are susceptible to confounding by indication, ascertainment biases in exposure to treatment, measurement error in assessment of health outcomes, and lack information on important prognostic variables (in studies using existing data). These biases and measurement errors can introduce apparent HTE when in fact none is present, or conversely, obscure true HTE. Because heterogeneity in observational studies can be due to chance or bias, investigators must evaluate the observed HTE to determine whether a finding is indicative of true heterogeneity. To do this, chance findings should be evaluated by testing for interaction; biases should be avoided via adherence to sound study design principles and by evaluating balance on covariates within subgroups to assess the potential for confounding.

There are several potential sources of heterogeneity in observational studies, and these tend to mirror the potential explanations for a finding of an overall effect (ATE). As such, many of the approaches for reducing the potential for an incorrect inference are the same. Careful attention to study design principles is an important starting point for avoiding incorrect inferences with respect to overall findings and also benefits the identification of potential HTE. The use of the incident (new) user design reduces the potential for inclusion of immortal person-time (i.e., person-time during which a study outcome

cannot occur; see chapter 4 for a detailed discussion).[12] Contemporaneous follow-up of exposed and unexposed subjects (parallel group design) avoids calendar time differences in exposure/covariate/outcome identification. Measures of exposure, outcome, and covariates should address misclassification and seek to limit potential for information bias (exposure measure, outcome measure, covariate measures).

Despite the challenges in using observational data for HTE analysis, randomized experiments cannot be performed to answer all clinically important questions regarding HTE attributable to patient characteristics. Therefore, a huge demand will be placed on observational studies to produce evidence to inform decisions. Hence, procedures must be put in place to ensure that the results from observational studies are trustworthy. A key principle here is that the observational studies should be designed and analyzed in the same manner as randomized controlled experiments. Some potential steps include registering observational CER studies prospectively, publishing the study protocol (including clear definitions of subgroups and outcomes, pre-specified hypotheses, and power calculations), and developing a detailed analytic plan (including how confounding, missing data, and loss-to-follow-up will be handled). Sox has called for registration of observational studies, along the lines of National Institutes of Health's clinical trials registry.[13] Rubin has put forth an interesting proposal for "objective causal inference," where a greater emphasis is placed on understanding treatment selection. The modeler is blinded to outcomes until the treatment assignment modeling is completed and made available to scrutiny.[14] This places the emphasis on study design and treatment assignment, and the investigator only observes outcomes at the end, as in randomized experiments. This ensures some degree of objectivity in the outcome modeling.

Value of Stratification on the Propensity Score

A study by Kurth and colleagues illustrates the use of summary score stratification as a means to assess HTE in observational studies.[15] Since many strokes are the result of thrombosis in cerebral or precerebral arteries, a highly specific thrombolytic therapy became available in the form of recombinant tissue plasminogen activator (TPA). Three randomized studies showed that TPA neither decreased nor increased mortality substantially in people who had recently experienced a stroke. However, observational studies of the same question consistently indicated that TPA therapy increased mortality, and the discrepancy in results between observational and interventional studies was not readily apparent. With data sourced from a German stroke registry, Kurth and colleagues were able to reproduce the observational effect of an increase in mortality with TPA with careful attention to study design and regardless of adjustment for measured covariates. However, different analytic approaches (particularly matching on the propensity score) provided results more comparable to the randomized trials than was obtainable from adjusted analyses. By stratifying patients according to propensity to receive TPA and conducting analyses of TPA effect within strata, this study found that much of the observational result was being driven by a few subjects with low propensity to receive TPA who were highly influential in analyses that included them (the covariate-adjusted, propensity score adjusted, propensity score stratified, and the inverse probability weighted analyses). However, the propensity score matched analyses excluded these influential subjects, and the standardized mortality ratio weighted results downweighted their influence so that these results were similar to the randomized controlled trials. As a summary of propensity to receive a medication or strength of indication, propensity score identifies clinically relevant subgroups. If heterogeneity is observed in the propensity score, further investigation is warranted.

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Conclusion

RCTs often exclude individuals with characteristics that may cause variation in response to treatment, limiting the generalizability of findings from these studies. Observational studies often have broad inclusion/exclusion criteria, allowing for the assessment of comparative effectiveness in large, diverse populations in "real-world" settings. With the increase in generalizability comes the potential for HTE. Investigators should understand the potential for HTE prior to conducting an observational CER study, and clearly state if and how subgroups will be defined and analyzed. If subgroup analysis is intended to be confirmatory, investigators should ensure adequate statistical power to detect proposed subgroup effects, and adjust for multiple testing as appropriate. When an interaction test is significant, subgroup effects should be reported, and a discussion of the potential clinical importance of the findings should be included. When an interaction test is not significant, the investigator should report the ATE and discuss plausible reasons for null findings in relation to other studies. . Exploratory analyses should be clearly labeled as such, and the corresponding results should not be emphasized in the abstract of the study report. Reporting of results from descriptive analysis of subgroups defined by priority populations using an informative forest plot is encouraged.

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Checklist: Guidance and Key Considerations for the Development of the HTE/Subgroup Analysis Section of an Observational CER Protocol or Proposal

Guidance	Key Considerations	Check
Summarize prior knowledge on treatment effect modifiers and reference sources		☐
Pre-specify subgroups to be evaluated	- Note if priority populations with limited effectiveness data will be included in the study and evaluated as subgroups - Subgroups should be defined by variables measured at baseline or variables known to be unaffected by exposure	☐
Specify the hypothesized direction of effect within subgroups and the significance levels that will be used to assess statistical significance	- If confirmatory analyses, do power calculations - Describe methods to adjust for multiple testing, if applicable	☐
Describe how confounding will be addressed	- Assess covariate balance between the treatment groups within each stratum of the subgrouping variable	
Describe statistical approaches that will be used to test for interactions for pre-specified covariates	If the interaction test is not significant: - Report ATE - Discuss plausible reasons for null findings in relation to other studies and plausible biological mechanism	☐
Describe how overall (ATE) and subgroup effects will be reported if interaction test is or is not significant	- Clearly distinguish subgroup results as confirmatory, descriptive, or exploratory analyses - Report subgroup effects in a table and/or a Forest plot with a vertical line representing the overall treatment effect (ATE)	☐

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