

# Baseline risk in medical decision making

From outcome prediction to the assessment of treatment effect  
heterogeneity

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## Welcome

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This is the website for the PhD thesis titled “*Baseline risk in decision making: From outcome prediction to the assessment of treatment effect heterogeneity*”.  
Visit the github repository for more information.



# CHAPTER 1

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## Introduction

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## 1.1 Personalizing outcome risk

Baseline risk—the probability of a patient experiencing an outcome of interest without receiving the treatment under study based on a set of predefined baseline characteristics—is a crucial component of medical decision making. For example, in the European Society of Cardiology and the European Society of Hypertension guidelines of 2018 for the management of arterial hypertension, treatment initiation is based—among other things—on the patient’s baseline 10-year cardiovascular risk [<https://doi.org/10.1093/eurheartj/ehy339>]. Similarly, an algorithm for management of osteoporosis has been suggested, based on a patient’s osteoporotic fracture risk [<https://doi.org/10.1007/s00198-019-05176-3>].

Risk prediction models, i.e. mathematical functions relating the presence of the outcome of interest to a set of measured predictors (covariates) [<https://heart.bmj.com/content/98/9/683>], are important empirical tools for the assessment of a patient’s baseline risk. Adequate evaluation of the prediction models’ performance in new patients is crucial. In most cases, this mainly focuses on the prediction models’ discriminative performance, i.e. their ability to separate lower from higher risk patients, and their calibration, i.e. the agreement of predicted risk to observed event rates [Ewout book; TRIPOD]. Though measures of discrimination and calibration are useful for assessing the predictive performance of one or multiple prediction models, they do not provide insight on the added value of using these models for medical decision making. Baseline risk is only one of the crucial pieces required for predicting individual responses to treatment. Knowledge of the patients’ responsiveness to treatment, their vulnerability to side-effects and their utilities for other relevant outcomes is necessary information required for making truly informed clinical decisions [Kravitz, 2004].

## 1.2 Personalizing treatment effect

In order to provide the most optimal medical care, doctors are advised to align their clinical practice with the results of well-conducted clinical trials, or the aggregated results from multiple such trials [Greenfield 2007]. This approach implicitly assumes that all patients eligible for treatment experience the same effects (benefits and harms) of treatment as the reference trial population. However, the estimated treatment effect is often an average of heterogeneous treatment effects and, as such, may not be applicable to most patient subgroups, let alone individual patients. If a treatment causes a serious adverse event, then treating all patients on the basis of an observed overall positive treatment effect may be harmful for some [Rothwell, Lancet 1995; ...].

Conceptually, heterogeneity of treatment effect (HTE) is the variation of treatment effects on the individual level across the population [<https://doi.org/10.>



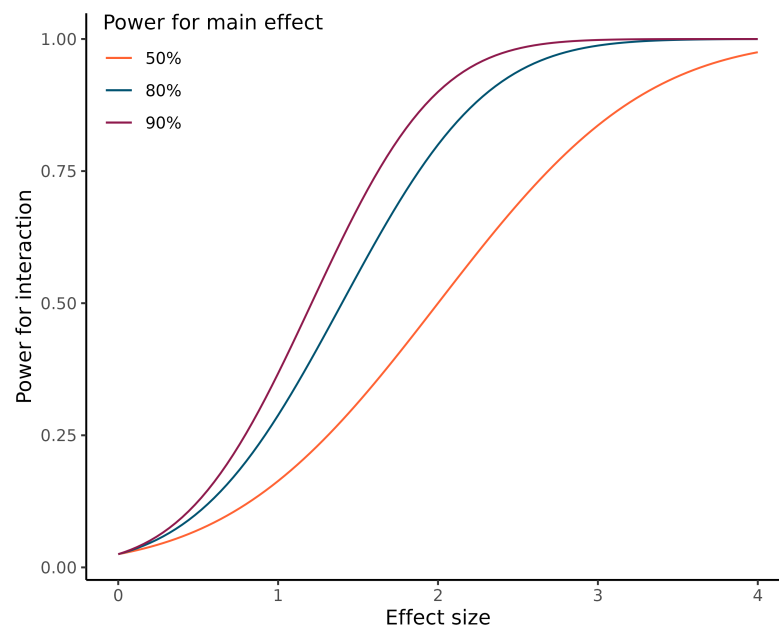
1111/j.0887-378X.2004.00327.x]. The identification and quantification of HTE is crucial for guiding medical decision making and lies at the core of patient-centered outcomes research. Despite HTE being widely anticipated, however, its evaluation is not straightforward. Individual treatment effects are—by their nature—unobservable: the moment a patient receives a specific treatment, their response under the alternatives becomes unmeasurable (fundamental problem of causal inference; [Holland, 1986]).

To “glimpse” at a specific individual’s response under alternative treatments, researchers usually observe the outcomes of other “similar” patients that actually received one of the other candidate treatments. More individualized treatment effects are derived from the average effects estimated within a subgroup of similar patients. However, patient similarity is not straightforward to assess. Patients differ in a vast number of characteristics which may or may not be relevant to modifying treatment responses. Identification of such patient characteristics can be quite complicated. In clinical trials it usually relies on the detection of statistically significant interactions of treatment with measured covariates (subgroup analyses).

As clinical trials are usually only adequately powered to detect overall effects of a certain size, this kind of analyses can be problematic. Existing guidance on carrying out subgroup analyses attempts to mitigate these issues [refs]. Lack of statistical power often results in falsely concluding “consistency” of the treatment effect across several subpopulations of interest or overestimating the effect size of a treatment-covariate interaction. The former because an existing interaction effect was smaller than the detectable effect size, the latter because of false positives introduced from multiple testing. In Figure 1.1 the statistical power for detecting an interaction effect of equal size to the main effect is below 30%, despite the clinical trial being powered at 80% for the detection of the overall effect.

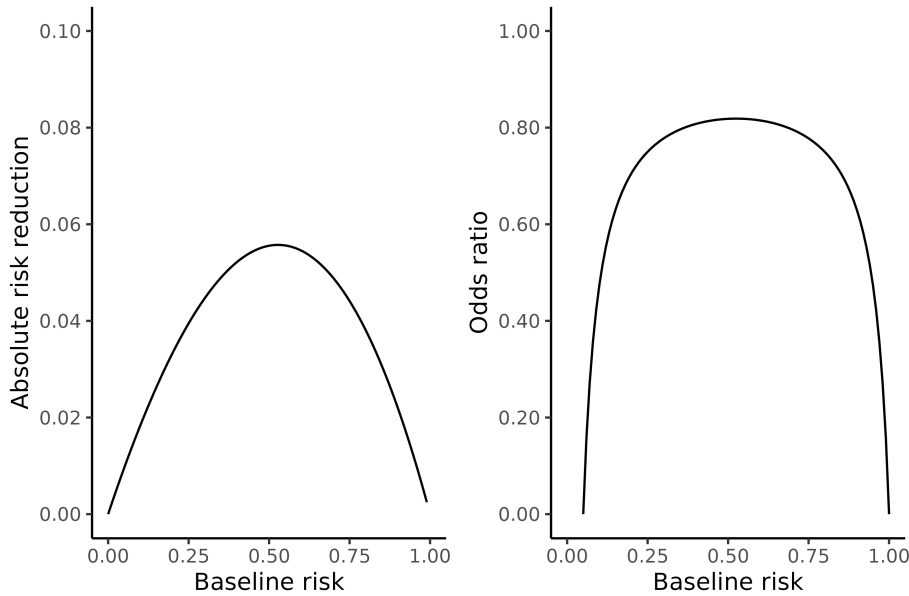
Baseline risk is an important determinant of treatment effect [refs]. It sets an upper bound on the treatment effect size. Low risk patients can only experience minimal treatment benefit before their risk is reduced to zero, while high risk patients can benefit much more. This means that baseline risk can be used as a subgrouping variable for assessing HTE. For many common settings prediction models of high quality for estimating baseline risk already exist and can be directly applied to the data at hand [refs]. If no such models exist, the researcher can develop one from the available dataset [refs].

Baseline risk can also be used for directly predicting individual treatment benefit [Califf; Dahabreh, IJE 2016]. For example Califf et al [ref] predicted individual benefits regarding mortality with tissue plasminogen activator (tPA) compared to streptokinase treatment in patients with acute myocardial infarction using baseline mortality risk and assuming a constant relative tPA treatment effect. However, relative treatment effect does not need to be assumed constant. Modeling more flexible interactions of treatment with baseline outcome risk may provide more informative absolute benefit predictions for individual patients.



**Figure 1.1:** Statistical power for the detection of an interaction when the interaction effect size is between 0 and 4 times the main effect size. For simplicity, we assume equal number of treated and untreated patients and that patients are equally separated between the subgroup levels

Depending on the scale treatment effect is measured, HTE may or may not be identified (Figure 1.2). For example, despite finding statistically significant subgroup effect evaluated on the relative scale, the absolute risk difference between the two groups may be so small that has no clinical relevance [<http://dx.doi.org/10.1016/j.jclinepi.2013.11.003>]. Therefore, in the presence of a truly effective treatment, effect heterogeneity should always be anticipated on some scale [Dahabreh, IJE 2016], as baseline risk is bound to vary across trial patients. If effect modifiers are known and the available sample size provides adequate statistical power for evaluating treatment-covariate interactions, modeling these interactions would be the optimal approach for assessing HTE. However, this approach may lead to overfitting and unstable estimates for the interaction effects [Balan, JCE].



**Figure 1.2:** Scale dependency of treatment effect heterogeneity. In the left panel a constant odds ratio of 0.8 is assumed. In the right panel a constant absolute risk reduction of 0.1 is assumed.

### 1.3 Observational data

Healthcare data is routinely collected by general practitioners, hospitals, insurance companies, and many other private or public bodies and is becoming increasingly available giving researchers access to massive amounts of patient data. Theoretically, the aforementioned statistical power challenges for the evaluation

of HTE would be largely mitigated if the analyses were performed on even a single such database. However, as this data is not being accumulated for research purposes, it suffers from many biases causing many commonly used methods to fail. Doctors prescribing a specific treatment expect—usually based on results from clinical trials—that it will be beneficial for the patient they are treating. This causes systematic differences in important characteristics among patients receiving different treatments and renders their comparison very challenging.

If all relevant patient characteristics on which the treating physician based their decision have been captured in the observational dataset, methods are available that can be used to account for these systematic differences [refs]. Among the more popular ones is limiting the analyses to the propensity score matched subpopulation. Propensity scores are the patient-specific probabilities of receiving the treatment under study and have been shown to have the balancing property, i.e. conditional on the propensity score treatment assignment is independent of the potential outcomes [refs]. This means that in a subset of patients with equal propensity scores there are no differences in covariate distributions between patients receiving the treatment under study and those who are not. Consequently, patients within this subset can be assumed to be randomized.

Unfortunately, not all the information that was used to decide on treatment is captured. As a consequence, propensity score adjustment will not suffice to evaluate treatment effects using the observational data, be it overall or subgroup effects. Sensitivity analyses searching for evidence of this systematic unmeasured imbalances have been proposed and can be of assistance in many situations [refs].

Another important problem with observational databases is that they use different architectures. As anyone gathering routinely observed healthcare data did so in a way that was more convenient to them, a plethora of structures for the resulting databases arose. Diseases, treatments, medical exams and many more aspects of healthcare are often coded differently in different observational databases. In addition, more fundamental disparities between databases also factor in database incompatibility: different types of information are recorded in different databases. Different patient characteristics are captured—at different levels of detail—in a general practitioner database, in a hospital medical record or in an administrative claims database. This means that combining results from multiple databases is not a simple task.

One of the solutions put forward for handling database incompatibility was the creation of the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) [refs]. This provided a standard for structuring an observational database while large effort was put into developing processes for mapping existing databases from their own specific structure to OMOP-CDM. A high level of standardization and scalability for observational studies was achieved. Common definitions of diseases, treatments, and outcomes can now be applied uniformly across a network of many databases containing information on hundreds of millions of patients. An analysis plan can be executed follow-

ing the exact same steps across the network providing effect estimates derived in different populations. The fragmented information scattered across multiple databases can now be summarized in a consistent way to give a fuller picture.

The power of the common database structure was demonstrated in a large-scale comparative effectiveness study of first-line treatment for hypertension [Suchard, Lancet 2019]. This study compared five different first-line drug classes prescribed for hypertension regarding three primary effectiveness, six secondary effectiveness, and 46 safety outcomes across a global network of 9 observational databases, all mapped to OMOP-CDM. A framework following best practices for carrying out such analyses was proposed and implemented on a large scale. The results complemented the already available evidence generated in clinical trials, confirming earlier findings and providing effect estimates on previously unexplored comparisons.

Observational databases provide access to massive numbers of “real-life” patients. This motivates the exploration of methods for the assessment of treatment effect heterogeneity in the observational setting despite the challenges inherent to this type of data. The statistical power problem related to multiple subgroup analyses can still be present, as observational data is high-dimensional, i.e. the number of measured patient characteristics increases with the number of patients. Attempting a treatment effect modeling approach, where treatment-covariate interactions are modeled for the prediction of individualized treatment benefits, suffers from the same statistical power issues and often results to highly variable estimates. Therefore, using baseline outcome risk as the subgrouping variable, can provide good insight of treatment effect heterogeneity in the observational setting. Modern libraries for developing risk prediction models and for correcting for confounding are available and—capitalizing on OMOP-CDM—can be easily applied across databases with millions of patients.

## 1.4 Aims

The overall aim of this thesis is to explore the use of baseline risk prediction models as the basis for medical decision making. We will study and apply methods for the evaluation of treatment effect heterogeneity in both clinical trial data and observational data. The specific research aims are:

1. *Systematically organize the current literature on predictive approaches to treatment effect heterogeneity.* We are going to focus on regression modeling approaches applied in clinical trial data. Methods will be categorized based on their definition of patient similarity.
2. *Develop risk-based predictive approaches to the assessment of treatment effect heterogeneity.* We are going to explore new subgrouping methods based on risk stratification along with more personalized approaches, fo-

cusing on both the observational and clinical trial setting. Scalability and reproducibility of the considered methods are crucial.

3. *Apply risk-based methods to better guide medical decisions.* We are going to develop baseline risk prediction models in several case studies easily applicable in clinical practice.

In **Chapter 2** we present the results of a scoping literature review of regression modeling approaches for the assessment of treatment effect heterogeneity in the clinical trial setting. The identified methods are divided into broader categories based on how they incorporate prognostic factors and treatment effect modifiers.

In **Chapter 3** we develop a standardized scalable framework for the assessment of treatment effect heterogeneity using a risk-stratified approach in the observational setting. We, also, develop the software for the execution of the framework in observational databases mapped to OMOP-CDM. We, finally, demonstrate the application of the framework, assessing treatment effect heterogeneity in first-line treatment for hypertension across three US claims databases.

In **Chapter 4** we compare different risk-based methods for predicting individualized treatment effects using an extensive simulation study. We only consider the clinical trial setting where treatment is administered at random.

In **Chapter 5** we develop a model for the prediction of 5-year recurrence risk in sentinel node positive melanoma patients, using data from nine European Organization for Research and Treatment of Cancer centers. We calibrate the recurrence model to predict 5-year risk of distant metastasis and overall mortality and develop a nomogram for graphical representation. The models are, then, externally validated.

In **Chapter 6** we develop a model for the prediction of 28-day mortality for patients presenting at the emergency department with suspected COVID-19 infection at four large Dutch hospitals between March and August, 2020. We predict 28-day admission to the intensive care unit by calibrating the mortality model. An easy to use web application is also supplied. We perform temporal validation to assess model performance using data between September and December, 2020.

In **Chapter 7** we apply the standardized framework to evaluate effect heterogeneity of teriparatide treatment compared to oral bisphosphonates in female patients above the age of 50 with established osteoporosis. We use different risk stratification approaches based on quantiles of predicted risk and externally derived risk thresholds for treatment. We evaluate the presence of residual confounding using sensitivity analyses.

Finally, in **Chapter 8** we present a general discussion along with perspectives on future work.

## CHAPTER 2

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### Predictive approaches to heterogeneous treatment effects: a scoping review

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## CHAPTER 3

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A standardized framework for risk-based  
assessment of treatment effect heterogeneity in  
observational healthcare databases

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## CHAPTER 4

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Individualized treatment effect was predicted  
best by modeling baseline risk in interaction  
with treatment assignment

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## CHAPTER 5

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### The EORTC-DeCOG nomogram

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## CHAPTER 6

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### COVID Outcome Prediction in the Emergency Department

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## CHAPTER 7

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Osteoporosis project

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## CHAPTER 8

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### General discussion

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## 8.1 Organization of predictive treatment effect heterogeneity literature

### 8.1.1 Main findings

We systematically organized the available methodological literature on the evaluation of treatment effect heterogeneity using the reference class each method used to define patient similarity. This resulted in the identification of three separate categories of methods.

Risk-based approaches define patient similarity based solely on risk factors. These methods can be further divided into risk stratification approaches that rely on the definition of risk-based subgroups of patients and risk magnification approaches that assume a constant relative treatment effect. The latter can be used to make personalized benefit predictions. In chapter 4 the strong assumption of constant relative treatment effects was relaxed, allowing for increasingly flexible (??) interactions of baseline risk with treatment. Of course, the assumption that treatment effect is a function of baseline risk remained intact.

Treatment effect modeling methods focus both on risk factors and treatment effect modifiers to make personalized absolute benefit predictions. These methods are more intuitive, in the sense that they attempt to account for all dimensions of treatment effect heterogeneity (**elaborate!!**). However, statistical power is an important constraint, as multiple treatment-covariate interaction effects need to be estimated. In the presence of well-documented and clinically supported effect modifiers statistical power may suffice as only a small pre-defined set of interaction effects will be evaluated. In more automated settings, staging or penalization approaches can be considered. The former rely on the “calibration” of first-stage “working” models including many treatment-covariate interactions. The latter rely on automated processes that shrink the estimated interaction effects towards 0.

Finally, optimal treatment rule methods focus on modeling treatment effect modifiers for the evaluation of treatment effect heterogeneity. Their aim is not to provide personalized treatment effect estimates or to separate patients into subgroups of similar expected treatment effect, but rather to separate them into two categories. Patients who benefit from treatment and patients who do not. If there are no major treatment-related harms, they can be used out of the box to guide medical decisions. However, in the presence of serious treatment adverse events, these methods may be more challenging to implement. That is because the effect of baseline risk factors is not taken into account. This means that the baseline risk of the main outcome of interest is not evaluated and, therefore, the absolute risk reduction achieved with treatment cannot be compared to the risk increase for the adverse event in question. Also, the clinical relevance of following the treatment assignment rule cannot be easily evaluated (**elaborate!!**).

### 8.1.2 Other categorization methods in the literature

The above categorization of methods for the assessment of treatment effect heterogeneity is not the only possible. When focusing on subgroup analyses Lipkovich et al identified two frameworks for personalized medicine: 1) methods that identify the right patient for a specific treatment and 2) methods that identify the right treatment for a specific patient. In the first case, a set of treatment effect modifiers is sought that quantitatively interact with treatment in an attempt to achieve the highest overall benefit across the entire population. In the second case, the objective is the identification of a set of effect modifiers that qualitatively interact with treatment.

The literature review proposed a general approach for categorizing methods evaluating treatment effect heterogeneity. However, more thorough separation of these methods can also be considered. For example in a more technical approach focusing mainly on tree-based methods, Kunzel separated existing staging methods into A and S-learners while also suggesting a new approach, the X-learners. The suggested methods differed in the way they used to recalibrate the initially derived estimates to estimate conditional average treatment effects. These suggested categories can be considered as further separation of treatment effect modeling methods. Assuming binary treatment assignment, A-learners fit treatment-arm specific models before estimating individualized treatment effects as their difference. S-learners include treatment assignment in the development of the tree-based model. They estimate conditional average treatment effect as the difference of between setting the treatment indicator to control and active treatment. Finally, their proposed X-learners, use first-stage outcome models separately fitted in each treatment arm to impute counterfactual outcomes, thus generating an “observed” treatment effect. Any regular modeling approach can then be used to estimate treatment effects.

### 8.1.3 Limitations

The analyzed literature was identified through a mix of systematic literature search and suggested literature identified by an expert panel. Though this may have resulted in a more targeted initial selection of reviewed publications, it is possible that not all of the targeted literature was captured. However, the main finding of the review, i.e. a systematic separation of the predictive methods in the evaluation of treatment effect heterogeneity, should be quite robust against missing citations. In any way, treatment effect heterogeneity being a focal point of current research, literature has been growing rapidly since the presented review was carried out (**need citations??**).

Evaluation of treatment effect heterogeneity is not a problem specific to healthcare research with important advances being made in economics, social sciences, and other fields, as well. In addition, the increasing availability of observational data from massive databases capturing a large proportion of patients’ interaction

with the healthcare system has provided additional challenges, with confounding, suboptimal data capture, local or temporal inconsistencies only being a few of them. All these have resulted on the suggestion of many different methods for the evaluation of treatment effect heterogeneity, many of which may have not been captured in the current literature review. Our focus was on the clinical trial setting and mainly regression modeling methods were considered.

#### 8.1.4 Future research

Several future research goals can be identified. Most importantly, a review of the fast-growing literature in the observational setting using the suggested categorization approach needs to be carried out. Due to the added complexity in this setting (large patient numbers, large number of captured covariates, data quality issues, and many more) focus has shifted from regression modeling methods to more automated machine-learning approaches. Therefore, it can be expected that treatment effect modeling and optimal treatment regime methods are more prominent in this setting.

In addition, literature search should expand to capture methods suggested in other research fields. In this way, similar methods developed under different settings can be unified and transferred among research fields. The categorization approach suggested can be used to guide this endeavor, while also it can be further generalized to account for the fundamental differences between settings.