CHAPTER 1

INTRODUCTION

RANDOMIZED AND OBSERVATIONAL STUDIES

Randomization is one of the most important attainments in the last century concerning research on the effect of treatment.[1,2] In medical research the randomized controlled trial is the gold standard for quantifying treatment effects. The major characteristic of this type of studies is the control over treatments by the researcher by means of randomization. Randomization can be defined as the random allocation of experimental units across treatment groups. An *observational study* on the other hand lacks such random allocation of subjects. William Cochran was the first to define an observational study:

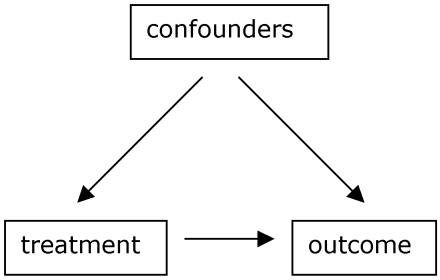
> "... the objective is to elucidate cause-and-effect relationships ... [in which] it is not feasible to use controlled experimentation, in the sense of being able to impose the procedures or treatments whose effects it is desired to discover or to assign subjects at random to different procedures."[3]

Barriers to random assignment are for instance ethical (one of the treatments is harmful), political (it is not possible for an individual researcher to influence political processes), personal (subjects do not want to change their habits) or economic (randomized control over treatments is too costly). Without such random assignment uncertainty about the true effect of treatment is in general greater and alternative explanations for the observed effect are easier to give. If such explanations are also plausible these should be subject to future investigations to either increase or decrease the evidence for the causal relationship between treatment and outcome. Principles on the *design and analysis* of studies are of utmost importance, such as the selection of covariates and the method of analysis.[4] Examples of major medical findings that came from observational studies are for instance the causal effect of smoking on lung cancer[5] and the causal effect of the use of DES on the presence of vaginal cancer.[6]

CONFOUNDING

The most important challenge in observational studies when treatment effect estimation is involved, is to combat *confounding*. Confounding is the phenomenon that an effect estimation (quantitative association between treatment and outcome) is distorted by prognostic factors of the outcome which are unequally distributed over treatment modalities. This is illustrated in Figure 1.1. While in randomized studies imbalances between known and unknown prognostic factors are largely suppressed by the randomization procedure, in observational studies these imbalances generally exist. Therefore, effort should be made to adjust the estimated treatment effect for these confounding factors as much as possible. Subject of this thesis are statistical methods that have the objective to adjust for the non-random assignment of individuals to treatments.

Figure 1.1: Illustration of the concept of confounding



OUTLINE OF THE THESIS

In Chapter 2 we give an overview of such methods, discuss their use, advantages and limitations. In the other chapters we focus on two of these methods, *propensity scores* and *instrumental variables*. Chapter 3 covers some specific advantages and limitations of these methods. An overlooked advantage of propensity scores is the subject of Sections 3.1 and 3.2, whereas the application, the assumptions and the limitations of instrumental variables are discussed in Section 3.3. In Chapter 4 we demonstrated how propensity scores and instrumental variables can be used with censored survival data. In Section 4.1 different propensity score methods were applied and in Section 4.2 tools are given for calculating survival probabilities based on an instrumental variable. In Chapter 5 we suggested improvements in propensity score applications, especially by proposing measures that quantify the balance reached in propensity score modelling. Chapter 6 contains the main results, the strengths and limitations of the chosen methods and implications and recommendations for future research.

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