CHAPTER 1

General introduction
Ideally, randomized controlled trials (RCTs) are used to evaluate both causal intended and unintended effects of interventions. If the intervention is allocated randomly, the trial has a large number of participants and there is no substantial loss to follow-up, groups of patients with and without the intervention will on average have similar risks of outcomes, except for the potential benefits and risks caused by the intervention itself. Unfortunately, it is often unethical or not feasible to perform a RCT [1]. For example, it would be unethical to design a RCT deliberately exposing patients to a potentially harmful exposure such as diethylstilboestrol (DES).

Moreover, RCTs are often too expensive or not feasible when studying the effect of exposures on rare outcomes or exposure-outcome relationships with long induction periods [1]. When it is unethical or not feasible to perform a RCT, non-randomized observational studies are essential to guide health care decision making [2]. Often, in absence of RCTs, the best available evidence for decision-making will come from observational studies.

However, in daily life, exposures are generally not allocated by a random process. By the art of medicine, drugs are prescribed to patients in need of treatment, persons who regularly exercise have a healthier life style in general than persons who rarely exercise, subjects that do not use alcohol may do this because of an underlying disease, etc. As a consequence, observational studies that study the effects of exposures are prone to confounding bias [3].

Although several empirical examples have shown that observational studies tend to find similar effect estimates as RCTs [4-7], such non-randomized designs have been criticized because of notorious examples in which observational studies found contrasting results with RCTs. For example, findings from large RCTs refuted observational studies that suggested a protective effect of hormone replacement therapy against coronary heart disease [8]. While several observational studies suggested a protective effect of beta-carotene consumption against lung cancer among smokers, large RCTs showed no beneficial effect [9]. Another textbook example is the case of vitamin E supplementation and the risk of cardiovascular events, where observational studies did find a protective effect whereas RCTs did not [10]. Differences in effect estimates between observational and randomized studies are often attributed to unmeasured or inadequately measured confounders. For example, consumption of vitamin E supplements may correlate with a healthy life style. Consequently, patients with a relatively healthy life style are compared with patients with a less healthy life style; hence effect estimates will be biased by difficult to measure differences in average prognosis between comparison groups. It is therefore essential to adequately measure, adjust for, and report about all relevant confounders. Unfortunately, information on important potential confounders is often lacking from routine health care databases. Even when the effect estimates are adjusted for measured...
potential confounders as in the examples mentioned above, biased effect estimates may be obtained, especially when difficult to measure patient characteristics or confounding domains are expected to bias the association of interest.

Given the vulnerability of observational studies to confounding, complete and transparent reporting about confounding is necessary to enable readers to assess the validity of study findings. Nevertheless, poor quality of reporting of confounding has previously been observed [11]. Acknowledging the widespread problem of inadequate reporting, the ‘STrengthening the Reporting of OBservational studies in Epidemiology’ (STROBE) guideline was developed and published in 2007 [12]. This guideline includes several items related to the reporting of confounding and is endorsed by a growing number of biomedical journals. In this thesis we aim to assess whether the reporting of confounding improved in articles published after the publication of the STROBE guideline compares with articles published before that guideline.

One of the more novel developments with regard to the control of confounding in observational studies is the application of a self-controlled or case-only design. Examples are self-controlled case-series [13, 14], case-crossover design [15] and sequence symmetry analysis [16] which have been developed to overcome the problem of confounding by difficult to measure patient characteristics. The underlying idea of these designs is that patients can serve as their own controls, which reduces confounding by factors that are stable over time. This may include characteristics that are often not available to researchers such as chronic use of nonprescription drugs, health behaviors, tendency to seek professional care, occupation, etcetera. Although self-controlled designs are increasingly being used in recent years [17], empirical comparisons of such designs with each other, with more traditional observational designs and with randomized controlled trials are scarce. In this thesis we aim to apply and empirically compare various available self-controlled designs to quantify and control for confounding with other designs and to apply novel techniques.

As study objects both acute and chronic drug therapies with unintended and intended outcomes will be researched in this thesis. First, the association between angiotensin-converting enzyme inhibitors and urinary tract infections will be evaluated, because we have access to data from both randomized trial and large routine health care databases. Another advantage of assessing this association to research the self-controlled designs is that angiotensin-converting enzyme inhibitors are prescribed to patients with risk-factors for urinary tract infections such as diabetes and renal impairment [18]. Consequently, there is a high potential for confounding by indication for this association in the absence of accurately measured information about potential renal problems.
Second, we aim to study the effect of concomitant use of selective serotonin reuptake inhibitors (SSRIs) and nonsteroidal anti-inflammatory drugs (NSAIDs) on the occurrence of peptic ulcer. Previously, a conventional cohort study compared concomitant use of SSRIs with NSAIDs with concomitant use of tri-cyclic antidepressants (TCAs) and NSAIDs without adjusting for potential differences between these two groups of patients [19]. It has been shown that heavy alcohol use is a very strong confounder when evaluating the association between SSRI use and gastrointestinal bleeding [20]. Since TCAs can potentiate the effects of alcohol due to their antihistaminic effects, while SSRIs have minimal effects on alcohol pharmacokinetics and pharmacodynamics [21, 22], heavy alcohol use is likely less common among TCA users than SSRI users due to channeling by the physician. Consequently, this association has strong potential for confounding and is an interesting study object.

A third empirical study will be focused on the association between antibiotic use during pregnancy and development of asthma among preschool children. There is an ongoing debate about whether the increased risk observed in several conventional observational studies is due to unmeasured confounding [23-25]. Two recent studies suggested that the increased risk was due to confounding [23, 24]. However, both studies were vulnerable to different biases. In the current thesis, different novel methods to quantify and minimize confounding will be applied in order to evaluate whether the increased risk is indeed largely due to confounding bias.

Although individual studies comparing different designs and single-study comparisons can identify and highlight different strengths and weaknesses of case-only designs, systematic comparisons are needed to obtain more insights into the merits of case-only designs and possible limitations. Therefore, the concordance between case-only and cohort or case-control studies in published empirical studies will also be evaluated in a systematic way. A secondary aim is to identify predictors of discrepancies between case-only designs and traditional designs, with specific focus on potentially important underlying assumptions of the self-controlled case-series and case-crossover design.

**Thesis objectives**

The studies presented in this thesis will focus on two main objectives: (1) to evaluate the reporting of confounding in observational cohort and case-control studies before and after the publication of an important reporting guideline for observational studies (STROBE) [26], and (2) to evaluate how self-controlled, or case-only, designs can be used to quantify and adjust for confounding. Various self-controlled designs will be
object of study: prescription sequence symmetry analysis [16], case-crossover [15], case-sibling [27], time-trend-control-sibling and self-controlled case-series [14].

Thesis outline

In chapter 2 the reporting of confounding in observational cohort and case-control studies on interventions for which a beneficial effect was hypothesized before and after the publication of an important reporting guideline for observational studies (STROBE) is presented. In chapter 3 the effect of pravastatin on recurrent urinary tract infections is evaluated in a post hoc analysis of a randomized controlled trial. In addition, the effect of fosinopril, an angiotensin-converting enzyme inhibitor, on acute urinary tract infections is assessed. In chapter 4 the association of angiotensin-converting enzyme inhibitors with the risk of acute urinary tract infections is assessed using a prescription sequence symmetry analysis. In chapter 5, the association between angiotensin-converting enzyme inhibitors and urinary tract infections is further evaluated using a case-crossover design. An empirical comparison with the prescription sequence symmetry analysis and the post-hoc analysis of the randomized controlled trial (chapter 3) is used to discuss some important differences between the sequence symmetry design and the case-crossover design. In chapter 6, the association of combined use of selective serotonin reuptake inhibitors and nonsteroidal anti-inflammatory drugs with the risk of starting peptic ulcer treatment is evaluated using a prescription sequence symmetry design. A comparison is made with a previously published cohort study that used the same database but did not adjust for potential confounders. In chapter 7 the association between antibiotic use during pregnancy and the development of asthma in preschool children is analysed using different confounding-minimizing designs, including a case-control and case-sibling design. In addition, we will develop a method that can address time-trend bias in case-sibling designs in this chapter. In chapter 8 the concordance between case-only and case-control or cohort studies in empirical studies is evaluated in a systematic way. In addition, predictors of discrepancies between both types of designs are identified. Chapter 9 provides a general discussion of our findings and future perspectives.
References


