Self-controlled designs to control confounding
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 23-02-2019
Summary

In the absence of randomized controlled trials, the best available evidence for decision-making on interventions will often come from observational studies. However, observational studies that evaluate the effects of interventions are prone to confounding bias. Given the vulnerability of observational studies to confounding, complete and transparent reporting on confounding is necessary to enable readers to assess the validity of study findings. Therefore, the first aim of this thesis is to assess whether the reporting of confounding improved in articles published after the publication of the STROBE guideline compared with articles published before the guideline was introduced.

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. Empirical comparisons of such study designs with each other, with more traditional observational designs and with randomized controlled trials are scarce. Hence, the second aim of this thesis is to apply and empirically compare various available self-controlled designs to quantify and control for confounding with other designs.

In chapter 2 the reporting of confounding in observational cohort and case-control studies on interventions before and after the publication of a widely endorsed guideline for observational studies (STROBE) is presented. The median of reported number of items (range 1-8) was similar before and after the publication of the STROBE statement (median 4, interquartile range [IQR] 3-5 vs median 4, IQR 4-5), although the distribution shifted somewhat to the right (p<0.001). Results were similar for journals that published the STROBE statement, endorsed the guideline in their author instructions or required the submission of a completed STROBE checklist. Our study showed that although the quality of reporting about confounding improved in certain aspects, the overall quality remains suboptimal. Research is needed into the development and evaluation of strategies to improve the quality of reporting and adherence to reporting guidelines.

In chapter 3 the effect of pravastatin on recurrent urinary tract infections is evaluated in a post-hoc analysis of a randomized controlled trial (PREVEND-IT). In addition, the effect of fosinopril, an angiotensin-converting enzyme inhibitor (ACEi), on acute urinary tract infections is assessed. Intention-to-treat analyses showed that pravastatin was associated with a reduced total number of urinary tract infection antibiotic prescriptions (relative risk, 0.43; 95% CI: 0.21–0.88) and occurrence of second urinary tract infection antibiotic prescriptions [hazard ratio (HR) 0.25; 95% CI: 0.08–0.77]. No significant effect on occurrence of first urinary tract infection antibiotic prescriptions was found (HR 0.83; 95% CI: 0.57–1.20). Fosinopril was associated with an increased
occurrence of first urinary tract infection antibiotic prescriptions (HR 1.82; 95% CI: 1.16–2.88). Combination therapy with fosinopril and pravastatin did not significantly influence the number of urinary tract infection antibiotic prescriptions. This study suggests that pravastatin can reduce the occurrence of recurrent urinary tract infections and fosinopril may induce first urinary tract infections. Larger studies are needed to confirm these findings.

In chapter 4 the association of ACEi with the risk of acute urinary tract infections is assessed using a prescription sequence symmetry analysis. A total of 101 (63%) patients started ACEi therapy first followed by nitrofurantoin treatment (a proxy for urinary tract infections), while 60 (37%) patients started nitrofurantoin treatment first, which corresponds to an adjusted sequence ratio (ASR) of 1.68 (95% CI: 1.21-2.36). No association was found between β-blockers and nitrofurantoin treatment (ASR 1.01, 95%CI: 0.74-1.38). To conclude, a significant excess of patients received urinary tract infection antibiotic prescriptions following the first month after ACEi initiation. This prescription sequence asymmetry agrees with the trial findings and suggests that ACEi initiation increases the risk of developing urinary tract infections.

In chapter 5 the association between ACEi and urinary tract infections is further evaluated using a case-crossover design. Of included patients, 276 patients were only exposed to ACEi during the risk window and 150 patients only during the control window (adjusted OR 1.74; 95% CI 1.42-2.13). When using similar criteria as in the prescription sequence symmetry analysis, the case-crossover estimates were slightly higher (adjusted OR 2.09, 95% CI 1.68-2.61). These findings suggest that ACEi use increases the risk of developing first urinary tract infections. Despite the similarities between the case-crossover design and the PSSA, the PSSA led to slightly lower effect estimates than the case-crossover design and the post-hoc analysis of the randomized trial.

In chapter 6 the association of combined use of selective serotonin reuptake inhibitors (SSRIs) and nonsteroidal anti-inflammatory drugs (NSAIDs) 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 contrast to the previous cohort study (RR 12.4; 95% CI: 3.2-48.0), combined use of SSRIs with NSAIDs was not associated with a higher risk of peptic ulcer treatment than NSAIDs alone (ASR 1.48; 95% CI: 0.90-2.49 vs ASR 2.50; 95% CI: 2.27-2.76). Our findings indicate that at least part of the previously reported association between combined use of SSRIs with NSAIDs and peptic ulcer initiation might be attributed to unmeasured or residual confounding.
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. Both the case-sibling and case-control analysis yielded similar increased risks of asthma in preschool children when antibiotics were used in the third trimester of pregnancy (aOR 1.37; 95%CI: 1.02-1.83 and aOR 1.40; 95%CI: 1.15-1.47). Time trend analyses showed that results were not influenced by a time trend in antibiotic exposure. Significant increased risks of asthma in preschool children after exposure to antibiotics in any trimester of pregnancy was observed in the conventional case-control analysis only (aOR 1.46; 95%CI 1.34-1.59). In conclusion, exposure to antibiotics in the third trimester of pregnancy appeared to be associated with a small increased risk of asthma in preschool children. This association appeared not to be influenced by time-invariant confounders or time trends in antibiotic exposure.

In **chapter 8** the concordance between case-only and parallel group designs in empirical studies is evaluated in a systematic way. In addition, predictors of discrepancies between both types of designs are identified. The correlation coefficient between the intervention effect in case-only versus parallel group designs was mediocre 0.64 (p<.001). In 221 of the 519 comparisons (43%) the difference between both study designs was beyond what would be expected by chance alone. The following predictors of discrepancy were found: intermittent exposure, rare event, acute outcome, length of hazard period, type of case-only design and sample size of the traditional study design. We found that the concordance between effect estimates of case-only and cohort or case-control design is moderate, and discrepancies beyond chance are very common. Such discrepancies could be predicted by failure to meet important assumptions of case-only designs.

To conclude, this thesis evaluated whether the reporting of confounding improved in articles published after the publication of the STROBE guideline compared with articles published before that guideline. In addition we applied and empirically compared various available self-controlled designs with other designs that were used to control for confounding. Based on the conclusions of the studies we recommend to focus on development and evaluation of strategies to improve the quality of reporting and adherence to reporting guidelines rather than adding another guideline to the steadily increasing pile of reporting guidelines; to apply self-controlled designs when there are concerns about unmeasured confounders and the research question seems appropriate for such a design; to verify whether assumptions are likely met when applying a study design and in case of uncertainty about this to apply sensitivity analyses. Finally, self-controlled methods should be empirically tested and modified to overcome their main limitations such as vulnerability for time trends and to develop new methodologies that further reduce or better quantify confounding in observational intervention research.