Summary

The importance of cardiovascular pharmaceutical interventions is increasing in high income countries due to population ageing. Among the pharmaceutical interventions available, statin therapy is one of the most prominent for reducing cardiovascular mortality risk. Trial evidence shows strong efficacy of statins in trial subjects, but population-level studies of its effect are lacking. Observational studies are urgently needed, but the challenge in these studies is adequate control for factors which create spurious relations between statin therapy and cardiovascular mortality, also known as confounders. A potentially relevant confounder in the study of statin utilization and statin effectiveness is birth cohort. A birth cohort refers to a group of people born in the same calendar period, and who therefore share formative events, potentially leading them to exhibit similar physical health problems and health behavior. Furthermore, the effect of statin therapy on cardiovascular mortality may be different for different birth cohorts, also known as effect modification. However, despite these potential qualities of birth cohort, epidemiological studies on the impact of pharmaceutical interventions commonly ignore the birth cohort dimension. The objective of this dissertation was to assess the value of including the birth cohort dimension in causal analyses of statin utilization, and its effectiveness in reducing cardiovascular mortality, when age, calendar time, and potentially other relevant variables are also controlled. The study population in the empirical studies in this thesis consisted of individuals in the Netherlands, aged 18 to 100 years in the period 1994 to 2012.

In chapter 2 of this dissertation, the trend of prevalence of statin utilization in the Netherlands is studied. Statin therapy was introduced in the Netherlands around 1994, and the prevalence of statin use has since strongly increased over time. Around 2002, important studies showed that statins were also effective for patients aged more than 70 years, and that it was effective for diabetic patients. Since the publishing of these studies, there was an even stronger increase in the prevalence of statin utilization. Around 2006, the growth of the prevalence halted. The study shows that the birth cohort dimension improves the description and explanation of trends in statin use. Controlling for age and calendar time, it is found that the birth cohort born around 1930 has a higher prevalence of statin use compared to cohort born in earlier time periods. This explains how the ‘peak’ in statin prevalence moved to older ages over time, an important characteristic of statin prevalence that is not captured by an ordinary age-period model.
In chapter 3 of this dissertation, it is shown that the 1930 birth cohort effect, found in chapter 2, also exists among the subgroup of diabetic patients in the Netherlands. In the 2002-2003 period, studies showed that statins were effective for diabetic patients and for individuals aged 70+ years, which affected the uptake of statin therapy. It is demonstrated that estimation of the effect of these studies on the uptake of statin therapy is confounded when the birth cohort dimension is omitted from the estimation model. When adjustment for birth cohort takes place, the parameter estimate of the ‘intervention’ effect is 0.027 (95% CI: 0.013 to 0.041), whereas this is 0.078 (95% CI: 0.065 to 0.091) when such an adjustment does not take place. Using the estimated pattern of birth cohort effects, it is also explained how this confounding takes place.

In chapter 4, the population-level association between prevalence of statin therapy and cardiovascular mortality in the Netherlands is investigated. It is found that if levels of statin prevalence had been kept at 1994 levels (i.e. if they had not increased over time), the average number of deaths during the study period due to acute myocardial infarction, due to other ischemic heart diseases, and due to cerebrovascular causes would have been 0.06 (95% CI: 0.049 to 0.080), 0.02 (95% CI: 0.012 to 0.023) and 0.04 (95% CI: 0.023 to 0.044) higher per 100 person-years respectively. This indicates a considerable contribution of statin utilization to the reduction of cardiovascular mortality in the Netherlands in the period 1994 to 2010. Furthermore, a birth cohort effect on cardiovascular mortality was found, but this did not modify or confound the relation between statin prevalence and cardiovascular mortality.

In order to determine if birth cohort was a confounder or effect modifier of the relation between statin therapy and cardiovascular mortality on the individual-level, a method for measuring time-varying adherence had to be developed. Therefore, in chapter 5, a new method is developed, based on the proportion of days covered method, to measure time-varying drug adherence. Through examples, it is demonstrated how this new method better distinguishes an irregularly dosing patient from a stably dosing patient, and demonstrates how the time-fixed method can result in a biased estimate of drug adherence. Furthermore, it is described how the method can be used to reduce certain types of confounding and misclassification of exposure.

In chapter 6, using the method that was developed in chapter 5, the clinical effect of adherence to statin therapy on cardiovascular mortality and falsification end-points at
the individual-level in the Netherlands is determined. The falsification end-points are outcomes that should, according to biomedical theory, not be affected by statin therapy. In a Cox regression model with few adjustments (statin adherence and statin drug exposure level, age, and calendar year), the hazard ratio associated with the effect of statin adherence is 0.70 (95% CI 0.61 to 0.81): this means that the hazard of cardiovascular death is reduced by 30% when a patient is fully adherent to statins, compared to when that patient is fully non-adherent. This estimate is similar to those from some other studies of statin therapy. However, when the model is expanded (adjusting for demographic factors, socio-economic factors, birth cohort, adherence to other cardiovascular medications, and diabetes), the hazard ratio becomes 0.53 (95% CI 0.46 to 0.61). A similar change occurs for the falsification end-points, indicating that the larger model is likely biased. It is postulated that this is caused by competing risks. In either case, both models indicate statins are protective against cardiovascular mortality. Furthermore, both models in chapter 6 indicated no confounding or effect modification by birth cohort.

A central problem in the analysis of age, period and cohort effects is that age, period and cohort are linearly dependent (age = period – cohort). The result of this problem is that linear models cannot determine the effects of age, period and cohort on an outcome, unless additional constraints are put on the model. Many possible constraints have been proposed, but it remains a topic of much debate. In chapter 7, a new approach to solving the age-period-cohort identification problem, called the ‘mechanism-based approach’, is assessed and extended. The method was largely limited to linear and probit regression. Therefore, in chapter 7, it is demonstrated how the mechanism-based approach can be extended to incorporate all generalized linear models, as well as non-linearities in these models linear predictors. This is highly useful, as the approach can now be applied, for example, with commonly used regression techniques in medical and social science, such as logistic and Poisson regression. Furthermore, the mechanism-based approach functions under ideal circumstances, but such circumstances are difficult (and perhaps impossible) to find in real applications of the method. Therefore, using simulations, it is investigated how well the approach performs under realistic circumstances, such as when 1) the set of available intermediate variables is incomplete; 2) intermediate variables are affected by two or more of the APC variables, but this feature is not acknowledged in the analysis, and 3) unaccounted confounding is present between intermediate variables and the outcome. It is found that that the mechanism-based approach (extended or not) is only slightly affected by bias when the departures from underlying assumptions are small.
In conclusion, the birth cohort dimension is shown to be valuable for the analysis of statin utilization at the population level. However, the birth cohort dimension is found to be less valuable for analyses at the individual level. Furthermore, it is determined that a mechanism-based approach to APC analysis provides a solution to the linear-identification problem but still relies on untestable assumptions. Better conceptualization of age, period and birth cohort effects is required, grounded in stronger social and biomedical theories, in order to advance the validity of research that seeks to disentangle age, period and birth cohort effects. Furthermore, in terms of statin’s effectiveness, the findings from chapter 4 and chapter 6 corroborate each other; there is no evidence of effect modification or confounding by birth cohort, and in both chapters statins were found to strongly reduce the risk of cardiovascular mortality. The implication of these findings for clinical practice is that changes to existing clinical statin prescription guidelines are not advocated, since the evidence of statin’s effectiveness in this thesis does not conflict with the evidence from clinical trials.