Chapter 8.

General Discussion
Main findings

The objective of this dissertation “Age-period-cohort methodology: confounding by birth cohort in cardiovascular pharmacoepidemiology” was to assess the value of including the birth cohort dimension in causal analyses of statin utilization and statin effectiveness in reducing cardiovascular mortality, when age, calendar time, and potentially other relevant variables were also controlled. The research questions were:

- Part 1: Are birth cohort effects present in statin utilization, and can such effects confound effect estimates of interventions on statin utilization?
- Part 2: Is birth cohort a confounder or effect modifier of the relation between statin therapy and cardiovascular mortality?
- Part 3: Does a mechanism-based approach improve the identification of age, period and birth cohort effects?

Through the research approach, applied to drug dispensing data and cardiovascular mortality data from the Netherlands, and through a simulation study, a number of interesting findings were made. We found that birth cohort effects had a strong presence in statin utilization patterns at the population level in the Netherlands (Chapter 2). These patterns, when unaccounted for, confounded population-level effect estimates of an intervention on statin utilization (Chapter 3). Birth cohort effects were also present in cardiovascular mortality trends after adjusting for cardiovascular drug utilization (Chapter 4). While birth cohort appeared less clinically relevant in this assessment as it did not confound nor modify the clinical effect of statins on cardiovascular mortality, including birth cohort was useful because we used it as a proxy to account for some unmeasured confounders, which is essential to validly assess the effect of statins on cardiovascular mortality (Chapter 4).

To assess the presence or absence of similar findings at the individual-level, a method was developed for measuring time-varying adherence (Chapter 5). After applying the time-varying adherence measure on the individual-level, in contrast to the population-level findings, evidence of birth cohort effects in cardiovascular mortality was not found. In addition, there was also no evidence for effect modification or confounding by birth cohort of the effect of statins on cardiovascular mortality (Chapter 6). Throughout the dissertation, the APC linear identification problem was solved by measuring non-linear birth cohort effects. However, it was found that the mechanism-based approach to the identification of age-period-cohort effects, which is based on a causal inference approach,
may also be a good candidate for future APC studies on the individual-level (Chapter 7). Furthermore, the mechanism-based approach was extended to non-linear link functions and parametric forms of any level of complexity, thereby improving its utility for application in the social and health sciences.

Reflection on main findings

*Birth cohort effects in statin utilization*

It was demonstrated that including the birth cohort dimension improved drug utilization studies; it helped explain trends in statin utilization, and its inclusion reduced confounding of an intervention effect in a time series analysis. Both in chapters 2 and 3, we found substantial birth cohort effects. In chapter 2, we used a classical Clayton & Schifflers model and studied age-specific statin prevalence trends in the entire population of the Netherlands, whereas in chapter 3 we used a model with random intercepts for birth cohort and studied age-specific statin prevalence trends only in patients with diabetes [1, 2]. Patients with diabetes were chosen because they are at greater risk of cardiovascular disease, and studies in 2002 found that statin therapy was also efficacious for patients with this disease [3, 4]. Despite these differences in study population and modelling approach, we found clear birth cohort effects with overall very similar shapes; i.e. adjusted for age and calendar time, the birth cohorts born between roughly 1910 and 1925 had much lower relative prevalence of statin use, while those born around 1930 had relatively higher prevalence of statin use, even relative to younger birth cohorts. This moving peak was also evident in the descriptive graphs of chapter 2, which were not subject to modelling constraints. In chapter 3, it was furthermore shown that disregarding these birth cohort effects could result in confounding of intervention effect estimates. In 2002 and 2003, important studies were published which showed the efficacy of statins in patients aged above 70 years and in diabetic patients [3, 5, 6]. An effect of these studies was that the prevalence of statin use in the Netherlands increased, but this effect estimate was lower once we adjusted for birth cohort in the analysis. The analysis that produced this conclusion rests on the assumption that the birth cohort effects were extraneous, i.e. not caused by the guideline itself. This assumption is reasonable since the moving peak in statin utilization can be detected in descriptive graphs before the interventions of 2002 and 2003. Since we measured only non-linear birth cohort effects, the analysis further rests on the assumption that the birth cohort effects were entirely non-linear, i.e. that the ‘drift’ component (the
linear trend through time) is attributed to the period dimension. Different constraints could have been used which attribute part of the drift to birth cohort. Given that we measured the intervention effects through linear terms for period, this may have resulted in even stronger differences between the model that controlled for birth cohort, and the model that did not. This would be an adequate adjustment for confounding if indeed the additional drift belonged to the birth cohort dimension, but would result in bias if instead it belongs to the period dimension. Due to the APC linear identification problem, it cannot be known to which dimension drift should be attributed. Therefore, as in any APC analysis, the choice for constraints should be applied with caution.

Unfortunately, it is as of yet unknown what caused the shape of the birth cohort effects that was observed in chapters 2 and 3. There is evidence from the United Kingdom that cohorts born in the 1930s and 1940s experienced undernutrition, and had different adiposity trajectories compared to other cohorts [7]. Undernutrition, especially in utero, has also been shown to be associated with later life obesity [8]. Obesity is a well-known risk factor for cardiovascular disease, but undernutrition has also been shown to adversely affect metabolic function, including liver function [9]. Like many countries, the Netherlands also experienced the economic depression in that time period, leading to lower nutrition and hence it is possible that individuals belonging to these birth cohorts in the Netherlands had a similar experience [10]. This could have led to proportionally more dyslipidemia, leading to more indications for statin therapy. However, evidence of APC studies of cardiovascular mortality, even when controlling for statin therapy (as in chapter 4), do not clearly show the 1930 birth cohort effect, and hence this cohort effect is less likely caused by physiological differences between generations [11]. The descriptive graphs show that, even at ages above 70 years, before the influential studies in 2002 and 2003, there was a rise in the prevalence over time. Yet, it may be that physicians were somewhat more hesitant to prescribe a new drug to older patients, and hence the prevalence in older cohorts did not rise as steeply over time. The 1930 birth cohort may then simply represent a vanguard of relatively young patients for whom there was less hesitation. This does not mean that the birth cohort effect is not a confounder. Even if the influential studies had not been published in 2002 and 2003, this 1930 birth cohort effect would remain because by the time this cohort reached ages above 70 years, doctors would have become more familiar with the drug. However, for this explanation to hold, the decline in the birth cohort pattern seen for cohorts born after 1930 would have to be temporary. Furthermore, this does not mean that the studies of 2002 and 2003 were not influential: as evidenced from the models in chapter 3, the studies themselves also had an effect on age specific
prevalence, their impact was simply smaller once adjusted for birth cohort.

It is recommended to further investigate the 1930 birth cohort effect. Initially, an international comparison could determine if the effect is also found in other countries, which may help narrow down the possible causes of the effect. Based on these findings, an analysis with individual-level data may be necessary to further narrow down possible causes.

**Birth cohort effects in statin effectiveness**

The birth cohort dimension was of lesser value for the drug effectiveness studies. It was primarily valuable in chapter 4, where we studied the effect of statins on cardiovascular mortality at the population level in the Netherlands. In chapter 4, we found a birth cohort effect in cardiovascular and cerebrovascular mortality even after controlling for age and potential population-level confounders; younger birth cohorts had lower rates than older cohorts. These findings were similar to those found in other studies [11, 12]. It was hypothesized that the findings in chapter 4 indicate that younger birth cohorts have better cardiovascular health than older birth cohorts, even when relevant medication is taken into account. There are many possible causes for this, such as the earlier discussed differences in nutrition between generations, but most prominently smoking behavior [7, 10]. There are strong birth cohort effects in smoking behavior, and smoking is also a major determinant of cardiovascular disease [13-15]. Therefore, we also used birth cohort as a proxy for smoking behavior. This was necessary, because adequately tabulated smoking data was missing for that study, while smoking could have been a confounder.

The birth cohort dimension did not improve individual-level analyses of the effect of time-varying adherence to statin therapy on cardiovascular and cerebrovascular mortality in the Netherlands (Chapter 6). Birth cohort was neither an effect modifier, nor a confounder at the individual level. Since birth cohort can represent health behavior, and various covariates that were adjusted for in chapter 6 also represented behavior, the birth cohort effect may have been largely masked. In other words, birth cohort is more of a group-level variable; all members of a cohort have the same value for birth cohort, while other variables, for which cohort may be a proxy at the population level, can be directly measured and can vary within individuals in a birth cohort and thereby have more explanatory value at the individual-level. Furthermore, birth cohort also did not appear to be a confounder at the individual-level, which fits expectation. In the population-level analysis of statin utilization, birth cohort could be a confounder because intervention effect estimates were measured through terms for the period effect, as
explained previously. However, in the individual-level analysis, the primary exposure was statin adherence. While statin adherence and subsequent cardiovascular mortality may both be affected by birth cohort, the (potentially confounding) information contained in birth cohort is also contained in the combination of age and period through linear dependency. Therefore, it appears that birth cohort has more utility for population-level analyses than for individual-level analyses.

Based on these findings, it is recommended that birth cohort, next to age and calendar time, is investigated as a possible explanatory variable or confounder in population-level analyses. This is not recommended for individual-level analyses, unless there is a lack of explanatory variables and measured confounders. However, when a rich dataset with individual-level variables is available, it may be of interest to investigate which individual-level variables correlate with birth cohort, so as to generate more information about health risks associated with birth cohort in general.

In both chapter 4 and chapter 6, there was a lack of evidence of modification of the effect of statin therapy on cardiovascular and cerebrovascular mortality by birth cohort. The lack of evidence for effect modification was not caused by low statistical power, and therefore likely means that the relative clinical effect of statins does indeed not differ by generation. However, given that there are differences between generations in cardiovascular illness, and in statin utilization, absolute differences between generations in the effect of statins on cardiovascular mortality may exist. A possible explanation for the lack of relative differences between generations in the clinical effect of statins is that, while behavioral differences between generations may exist, the general practitioner and the pharmacist act as a filter by starting therapy in similar patients according to their prognosis, and thereby level out the differences in clinical effect between generations.

On the basis of these findings it is therefore not recommended, given also that both analyses found statins to be effective in reducing both cardiovascular and cerebrovascular mortality, that a change in prescribing guidelines of statins occurs, since statins appear to have the same clinical effect for different generations.

Furthermore, very little is known about effect modification by birth cohort in general. Even in demography, the field where birth cohort is traditionally more prominent than in epidemiology, investigators commonly do not go beyond specifying main terms for birth cohort in an APC model. An innovative aspect of this thesis was that both effect modification and confounding by birth cohort were investigated. It is recommended that in explanatory studies, also in demography, effect modification and confounding by birth cohort are studied more.
A causal inference approach to APC analysis

The mechanism-based approach developed by Winship & Harding can be used to validly separate birth cohort effects from age and period effects [16]. The approach works by first modelling the causal effect of one (or more) of the APC variables on a set of intermediate variables, and then modelling the causal effect of the intermediate variables and the other two APC variables on the outcome directly. By using Pearl’s front door criterion, the effect of the APC variable for which indirect estimation via mediators was used, can be found.

In this dissertation, it was found that this indeed works adequately if the causal path from APC variables to mediators, and from mediators to the outcome, are correctly modelled. Furthermore, in this dissertation it has been demonstrated how this approach can be extended to non-linear link functions and parametric forms of any level of complexity, using Monte Carlo integration [17]. Unfortunately, the approach also has weaknesses, such as requiring bootstrapping to produce standard errors, which means that individual-level data will be necessary in many applications of the method. The most important weakness of the approach is that the linear identification problem still exists, but has been moved to the mediator stage of the modelling procedure; a mediator may be causally affected by all three age, period and cohort variables, and hence the conventional APC problem remains. Therefore, like other approaches to age-period-cohort analysis, the approach relies on untestable assumptions. However, it can also be considered a strength of the method that it forces researchers to reflect on the meaning of age, period and cohort effects, and to think more critically about through which causal pathways APC effects arise in reality. This is important, because a major criticism of APC models is that they are often applied without being informed by substantive theory, such as theories of social mechanisms or disease etiology [18].

Therefore, if there is substantive interest in age, period and cohort effects themselves, instead of using them as proxy variables, it is recommended that the mechanism-based approach is applied in studies where individual-level data is available.

Reflection on research approach

The research approach applied in this dissertation was multidisciplinary, combining demography, clinical (pharmaco)epidemiology, and statistics. An important aspect of this approach was that effects were studied both at the population-level and the individual-level. With important exceptions, demographic analyses are still often done with
population-level data, whereas epidemiological analyses focus on the individual-level [19, 20]. The differences between a population-level effect and an individual-level effect can be very relevant. For example, while the use of antibiotics can improve individual health, widespread use of antibiotics can present threats at the population-level [21]. Because the relations at the different levels can be different, findings on the population-level should not be directly used to infer an individual-level effect, as this can incur an ecological fallacy (drawing incorrect conclusions about individuals from a study at the population-level), and vice versa an individual-level (conditional) effect can be different from the population-level effect. However, methods such as G-computation and the parametric G-formula [22, 23], can be used to estimate population-averaged effects from individual-level data. G-computation is a method of direct standardization, and is therefore mathematically identical to direct standardization as used in demography [24]. However, the implementation of G-computation is commonly different since demographers apply direct standardization to aggregated data. Since time-varying covariates were used in chapter 6, a generalization of G-computation called the parametric G-formula was used instead [23]. Since these methods allow us to control for confounders at the patient-level, and then provide an estimate of a population-level effect, they should be preferred over estimating population-level effects from population-level data directly, if these data are available.

An important part of the approach used in this dissertation was the application of APC models. APC models are controversial because APC decomposition incurs a linear identification problem which can only be solved by making untestable assumptions [25, 26]. Therefore, some authors have referred to the quest for a statistical method that can determine unbiased APC effects as an ‘unholy’ or ‘futile’ quest because the linear dependency problem is mathematically unsolvable (e.g. [26, 27]). However, independent effects of age, period, and cohort may in truth empirically exist, as discussed in chapter 7. Furthermore, if there are in reality independent effects from age, period and birth cohort on an outcome, and our estimation model contains less than all three APC variables, there will be misattribution of drift due to linear dependency. In other words, a model with just one or two of the three APC variables is already making untestable assumptions. This means that any model with at least age, period, or cohort as included covariates is a ‘hidden’ APC model; the linear dependency is less apparent because of the omitted APC variables, but the dependency nevertheless affects parameter estimation. Given that a large amount of studies in both the social and medical sciences will adjust for age, there are in fact many such hidden APC models. Fortunately, the biases in estimation that occur
due to this error will be limited to age, period and cohort, and hence this is only a problem if the age (or period, or cohort) parameter estimate is causally interpreted.

Given these considerations, it is important that discussion and theorizing about the APC problem has continued, and will continue. Recently it has been argued that APC analysis can only be better conceptualized if age, period and cohort effects are more grounded in social theory [18]. In line with this, it is recommended that APC analysts in (pharmaco)epidemiology attempt to ground their analyses in biomedical theory, ideally in combination with social theory, such as employed in life course epidemiology [28]. This is not an easy task in either the social or health sciences, and so exemplary empirical studies are needed.

Conclusion

In this dissertation, the value of the birth cohort dimension was investigated using APC models applied in a cardiovascular pharmacoepidemiological context using data from the Netherlands. The birth cohort dimension was shown to be valuable for the analysis of statin utilization at the population-level. However, the birth cohort dimension proved less valuable for analyses at the individual-level. Furthermore, it was determined that a mechanism-based approach to APC analysis provides a solution to the linear-identification problem, but while the method is a methodological step forward, it 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.
References


Summary

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List of publications

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