**Age-period-cohort methodology**

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Chapter 3.

Birth cohort appeared to confound effect estimates of guidelines changes on statin utilization

Abstract

Objective: To investigate how birth cohorts can confound population-based intervention effect estimates.

Study design & Setting: Interrupted time series design was applied to study the prevalence of statin use in Dutch diabetes patients over the period 1998 to 2011. Effects of guideline changes on the outcome were estimated using a Poisson regression model with and without the birth cohort dimension modelled through random intercepts.

Results: Both models estimated a stronger increase in prevalence of statin use after influential studies were published in 2003 for patients aged below 50 and above 70 years. The model which controlled for birth cohort also estimated an effect for patients aged 50 to 70 from 2003 onwards. The magnitude of the intervention effect for patients aged above 70 years when we controlled for birth cohort was reduced from 0.078, 95% Confidence Interval (CI) 0.065 to 0.091, to 0.027 (CI:0.013 to 0.041). Similarly, for patients aged below 50 years the estimated guideline effect was reduced from 0.070 (CI: 0.048 to 0.092) to 0.55 (CI:0.035 to 0.075).

Conclusions: In this case study, the birth cohort dimension appeared to confound population-level effect estimates of guideline changes on prevalence of statin use in patients with diabetes.

Introduction

The effects of interventions at population-level should preferably be measured through randomized controlled studies (RCTs) to control for the distorting influence of confounding factors [1, 2]. In an observational setting, unless investigators had the foresight, funding and expedition to take random samples before and after the intervention of interest, population-level (i.e. aggregated) data are most widely used to study population-level intervention effects. A challenge that arises from such studies, is that due to extraneous factors the composition of the population before and after the intervention may be different, which may bias intervention effect estimates. Population-level data commonly contains information on only a limited number of variables, making it difficult to control for these extraneous factors. An important extraneous factor which contains confounding information and which is widely available in both patient-level and population-level studies, is the birth cohort dimension [3-5]. To the best of our knowledge, this is the first study to investigate how the birth cohort dimension confounds effect estimates of guideline changes in population-level observational studies.

A birth cohort refers to a group of individuals born in the same period and who therefore share formative experiences and other events. Furthermore, birth cohort has been shown to contain physiological information, for example caused by in utero exposure to famine [6] or early life morbidity [7, 8]. Therefore, the birth cohort dimension is a population-level proxy of both the social and behavioral characteristics that develop during critical periods of development in the individuals that make up the cohort [9]. Because of its relation with lifestyle factors and physiology, birth cohort differences have frequently been found to be important determinants in health trends over time (e.g. [8, 10, 11]). This also indicates that the effect of interventions may be different for different birth cohorts because birth cohorts may differ in their perception of preventive measures, may differ physiologically, or may differ in prescription and adherence culture. Yet paradoxically, birth cohort has not been controlled for in population-level intervention studies. This is likely caused by the fact that including the birth cohort dimension as a predictor in conventional methods incurs an identification problem due to the linear dependency between age, calendar time and birth cohort. However, with sufficient modeling assumptions and the use of penalized regression methods, this identification problem becomes manageable [12].

The aim of this study is to investigate how the birth cohort dimension affects estimates of interventions in population-level observational studies. Statin use among Dutch
diabetes patients is a useful case to investigate this because of two reasons. Firstly, in previous research, birth cohort effects were shown to have a strong effect on the trend of statin utilization over time in the Netherlands [3]. Secondly, for the subgroup of Dutch diabetes patients, influential studies [13-16] and guideline changes [17] took place which affected the age groups being targeted and which resulted in more attention to statin utilization for primary prevention of cardiovascular disease in such patients, next to secondary prevention.

Methods

Setting
Outpatient pharmacy data were used from IADB.nl, which contains dispensing information from 55 community pharmacies in the Netherlands, covering on average 500,000 persons annually (www.IADB.nl) [18]. The database's pharmacy information includes, among others, name of the drug, anatomic–therapeutic–chemical (ATC) classification and date of prescription. With the exception of over-the-counter drugs and in-hospital prescriptions, all prescriptions are included regardless of prescriber, insurance, or reimbursement status. Medication records of patients are virtually complete because of high patient pharmacy commitment in the Netherlands [18]. The IADB ensures anonymity of patients by using anonymous identifiers. The database has been used in previous studies on statin use [3, 19].

Study population
The study population consisted of diabetic patients between ages 30 and 85 in the study period 1998 to 2011 (therefore belonging to birth cohorts 1913-1981). Diabetic patients were defined as having at least one prescription for blood glucose lowering drugs (ATC A10A or A10B). Patients who were only prescribed insulins (A10A) were excluded. From these patients we determined the number of diabetic patients ‘at risk’ by calendar year and age category by counting the number of unique patients with at least one prescription in the respective calendar year and age category.

Exposure
In the Netherlands, while at first prescription of statins was discouraged to patients aged older than 70 years, in 2002 and 2003 important studies showed the drug's effectiveness at older ages in preventing cardiovascular disease [13-16]. In 2006, age restrictions were
formally abolished [17]. Furthermore, the studies showed that patients with diabetes, who are at increased risk of cardiovascular events, benefited strongly from statins [14-16] and consequently guidelines indicated statin prescription to all diabetic patients [17]. Therefore, we will effectively investigate how birth cohort may confound age-specific intervention effect estimates.

**Outcome measure**

The primary outcome measure of this study is age and period-specific prevalence of statin use. We determined the number of statin users by calendar year and birth cohort by counting the number of patients in the risk set with at least one prescription for statins (C10AA or C10B) in that respective year and age category. Prevalence was calculated as the number of statin users by calendar year and birth cohort divided by the total number of diabetic patients at risk. Because calendar year – birth year = age, this can also be considered age-specific prevalence. Direct age standardization was applied to the overall annual trend to control for the changing age composition of the study population over time [20]. As the standard population, the study population in 2004 was used.

**Statistical analyses**

Prevalence of statin use in diabetic patients by year and age was modelled by taking the count of statin users as the response variable in a Poisson model, with the natural logarithm of the respective count of patients at risk of prescription as an offset variable. To correct for potentially correlated errors over time, we modelled a first order autoregressive covariance structure. We used R 3.0.1 and SAS 9.3 for our statistical analyses. The model which did not control for the birth cohort dimension was specified as follows:

\[
\ln(\text{count}) = \beta_0 + \beta_1 \cdot (\text{year} - 1998) + \beta_2 \cdot (\text{year} > 2003) \cdot (\text{year} - 2003) \\
+ \beta_3 \cdot (\text{age} < 50) \cdot (\text{year} > 2003) \cdot (\text{year} - 2003) \\
+ \beta_4 \cdot (\text{age} >= 70) \cdot (\text{year} > 2003) \cdot (\text{year} - 2003) \\
+ \beta_5 \cdot (\text{year} > 2006) \cdot (\text{year} - 2006) \\
+ \beta_6 \cdot (\text{age} < 50) \cdot (\text{year} > 2006) \cdot (\text{year} - 2006) \\
+ \beta_7 \cdot (\text{age} >= 70) \cdot (\text{year} > 2006) \cdot (\text{year} - 2006) \\
+ \beta_8 \cdot \text{sex} + \beta_{9\to63} \cdot \text{age group} + \ln(\text{diabetics})
\]

Where \( \ln \) refers to the natural logarithm, count to the count of statin users in some age group and calendar year. Year refers to calendar year and age to patient age in years.
I refers to an indicator variable which is 1 if the condition between its brackets is met and 0 otherwise. $\beta_0$ is the intercept, $\beta_1$ measures the general change in statin prescription over time. $\beta_2$ measures a potential effect of the studies in 2002-2003 on the change in statin prescription from 2003 onwards, $\beta_3$ and $\beta_4$ allow different effects for the studies in 2002-2003 for patients aged below 50 and above 70 respectively. $\beta_5$ measures a potential effect of the guideline changes from 2006 onwards and $\beta_6$ and $\beta_7$ again allow that effect to differ for persons aged below 50 and above 70 respectively. $\beta_8$ measures the effect of sex. $\beta$’s 9 to 63 measure the effects of each age year (30, 31 … to 85) as age group is entered categorically. Ln(diabetics) is an offset variable and refers to the natural logarithm of the number of diabetics at risk in each age and calendar year category.

In order to control for the birth cohort dimension, we added independent, normally distributed random intercepts for all birth cohorts to the model [12], thereby turning the fixed effects model into a mixed effects model. Our model is therefore effectively a modification of the Hierarchical APC model for rates as discussed by Yang & Land [12].

The significance of adding the birth cohort dimension was assessed using a restricted likelihood ratio test which contrasts the models with and without random intercepts. We compare intervention effect estimates between the two types of models by comparing parameter estimates and percentage annual change in prevalence. Model estimates were translated to percentage annual change in prevalence of statin use through the formula $((\exp(\gamma) - 1) \cdot 100\%$, where $\gamma$ refers to the sum of the relevant parameter estimates from the Poisson model.

Results

Prevalence of statin use
The number of diabetic patients with at least one statin prescription in a respective year ranged from 1707 in 1998 (when the study population consisted of 8112 diabetic patients) to 14341 in 2011 (when the study population consisted of 19364 diabetic patients). Overall, prevalence in the entire study period taken together was 568 users per 1000 patients with diabetes. Age-standardized prevalence increased from approximately 200 per 1000 patients in 1998 to 400 per 1000 patients in 2003, then increased stronger to 700 per 1000 patients in 2006 and then remained approximately constant (Figure 1). Approximately 48.4% of the diabetic patients in the study population were male.
Birth cohort appeared to confound effect estimates of guideline changes on statin utilization.

Figure 1. Age-standardized prevalence of statin use in the population of patients with diabetes aged 30-85 years in the Netherlands (1998-2011).

**Guideline effect estimates**

Both the model which did not control for the birth cohort dimension (AP model) and the model which did control for the birth cohort dimension (HAPC model) estimated an increase in prevalence of similar magnitude in the period 1998-2003 for all three age groups (Table 1 and Table 2). From 2003 onwards, for ages younger than 50 and older than 70 years, both models estimated a stronger increase in the prevalence of statin use over time. However, the magnitude of the estimate for the specific age 70 and older effect in 2003 in the HAPC model was only approximately one third that of the effect in the AP model. The specific estimate for ages younger than 50 years in the HAPC model was similar to that of the AP model. Nonetheless, the estimated slope for patients in this age category was higher. Importantly, based on the confidence intervals, under the AP model we did not find a statistically significant change of the slope for patients aged 50 to 70 from 2003 onwards, relative to the slope in the 1998-2003 period, while the HAPC model suggested a statistically significant small positive difference. The effects estimated in 2006 for both models bring the percentage of (age-specific) annual change in prevalence of statin use to near 0 percent for all age categories.
Table 1. Effect estimates for the model which does not control for birth cohort (AP model) and the model which does control for birth cohort (HAPC model) (sex and age effect estimates not shown) in the population of patients with diabetes aged 30 to 85 in the Netherlands (1998 to 2011).

Table 2. Estimated percentage annual change in prevalence of statin use among diabetic patients aged 30-85 in the Netherlands (1998-2011) according to the model which does not control for birth cohort (AP model) and the model which does control for birth cohort (HAPC model) with 95% confidence intervals.

Birth cohort effects

Figure 2 shows the birth cohort effects as estimated by the HAPC model. Controlling for age and time, we find effect estimates far below average for the oldest birth cohorts (born around 1913), which then steeply increase up to the peak in 1929, with birth cohorts born between 1920 and 1929 having above average estimated effects. From 1929 onwards there is a slow decline in the effect estimates up to approximately 1966, with cohorts born between...
Birth cohort appeared to confound effect estimates of guideline changes on statin utilization. For patients born in 1929 and 1950, estimates were above the average, while those born after 1950 had estimates below the average. After 1966, the pattern fluctuated strongly. The addition of the random intercepts by birth cohort resulted in a reduction in restricted -2 log likelihood of 295. On a mixture chi-squared distribution with 0 and 1 degrees of freedom, this results in $p < 0.001$, indicating a highly significant addition of the birth cohort dimension to the model.

![Figure 2](image)

Figure 2. Estimated birth cohort effects (random intercepts) for birth cohorts born in 1913-1981 in the population of patients with diabetes aged 30-85 years in the Netherlands (1998-2011). The estimates are relative to prevalence of statin use as predicted by using only age, time, sex, and the intervention effect estimates (the fixed effects).

Discussion

In the present case study, we found that the birth cohort dimension appeared to confound population-level effect estimates of guideline changes on prevalence of statin use in Dutch patients with diabetes. Although, both the AP and the HAPC model estimated a stronger increase in prevalence of statin use after influential studies were published in 2003 for patients aged below 50 and above 70 years, the HAPC model also estimated a significant effect for patients aged 50 to 70 from 2003 onwards. The magnitude of the effect for patients aged above 70 when we controlled for birth cohort was reduced to one-third of its originally estimated magnitude. Furthermore, effect estimates for patients aged below 70 were somewhat higher in the model which controlled for birth cohort.
Evaluation of data and methods

All of the data of the study came from the same source, a representative prescription database, and the data were gathered and coded in the same manner during the observation period. The shape of the overall prevalence trend (Fig. 1) was comparable to that of our previous study [3] and that of another study of statin use in the Netherlands [21], although absolute prevalence differed due to differences in the study population and age standardization.

We chose to follow the Yang & Land approach to APC modeling because this method makes the identification problem more manageable. Because no additional birth cohort references have to be chosen (such as in the Clayton & Schifflers approach [22]), this model is more easily applied as an extension of conventional (segmented) time series analysis. Furthermore, penalization through random intercepts is a useful method to prevent model overfitting because it avoids the assumption that parameters of two reference birth cohorts are identical. Constraining two birth cohort parameters to be identical was found to lead to biased estimates if incorrect [12]. However, critical forethought (leading to appropriate model constraints) remains necessary when APC models are applied [23]. Therefore, we modified the standard Yang & Land model by modelling period effects as fixed effects (instead of random effects) using continuous variables. In standard segmented regression analysis the period effect is also measured in this manner. There was no indication of overdispersion in our models, as the dispersion parameters were 1.03 and 0.66 for the AP and HAPC models respectively. There was some indication of autocorrelation in the random effects, but parameter estimates were virtually unchanged when we additionally modelled a first order autoregressive covariance structure in the random effects.

Due to the identification problem present in APC analysis, it cannot be distinguished from the data whether the birth cohort pattern found is an effect tied to birth cohort or the result of model misspecification (e.g. assuming linear period effects). However, the pattern of birth cohort effects found in this study is very similar to that found in another study of prevalence of statin use [3], despite the fact that the other study used the Clayton & Schifflers [22] approach instead of the Yang & Land [12] approach, and the study population ‘at risk’ differed and was calculated differently. This may add confidence that the pattern found is close to that of the true birth cohort effects, as opposed to being either an artifact in the data or the result of model misspecification. Furthermore, we additionally performed our analysis with birth cohort modelled through fixed effects (i.e. a model based on the Clayton & Schifflers approach). Though this affected the parameter estimates of the guideline effects, our conclusions remained the same.
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*Guideline effect estimates*

While a number of influential studies were published in 2002 and 2003, the official guideline change occurred in 2006. Therefore, we had expected the increase in prevalence of statin use in the diabetic population in 2006 to be stronger than the increase in 2003. Instead, the descriptive graph and both models indicated that the trend changed strongly from 2003 onwards, and became constant in 2006. Evidently, while other factors could have affected this trend, it appears that the studies in 2002 and 2003 were more influential than expected, and that the guideline change in 2006 was lagging behind the changes in prescribing practice and thereby merely a formality. The cause of the leveling off of the overall (age 30 to 85) prevalence of statin use after 2006 may be statin utilization reaching saturation level.

We expected an increase in prevalence of statin use in diabetic patients aged 70 and older due to the studies which showed the effectiveness of statins in this age category for patients in general, and in patients aged below 50 years due to this age category having a low prevalence while studies showed the efficacy of statins for all diabetic patients. This also indicates that young diabetic patients have an otherwise low risk of cardiovascular disease. Both hypotheses hold according to both models, but the magnitude of the effect estimates differed. Below we explain how the estimates of the AP model were confounded by the birth cohort dimension.

*Birth cohort and confounding*

In this case study, the birth cohort dimension contained confounding information because parameter estimates change notably due to the introduction of birth cohort into the model. However, it is noteworthy that changes in parameter estimates following the entry of an additional variable is not necessarily evidence for confounding. Such changes may also occur due to noncollapsibility; i.e. the phenomenon that the marginal effect of some variable does not equal the stratum specific effect [24]. In general, noncollapsibility can occur in the absence of confounding and vice versa [25], but noncollapsibility does not play a role in our study because of the use of a log link in our models [26]. Furthermore, our study is an empirical study; strictly speaking, confounding bias can only be determined by taking mathematical expectations. Since this is not possible in an empirical setting, more empirical studies are needed to corroborate the finding that birth cohort confounds effect estimates of guideline changes.

The mechanism by which the birth cohort dimension confounded the intervention effect estimates of the model which does not control for birth cohort can be explained
through the estimated pattern of birth cohort effects (Figure 2). We shall here interpret
the birth cohort effects as caused by extraneous factors, such as lifestyle differences or
physiological differences between birth cohorts. During the study period, patients
belonging to the birth cohorts 1928 to 1941 moved from the age category 50 to 70
years old to the 70 to 85 years old age category. The estimated birth cohort effects for
these birth cohorts were higher than for all other birth cohorts (Figure 2). Therefore, as
time progressed and this birth cohort aged into the age 70 to 85 years old category, the
prevalence in that age category would go up even if no true (age-specific) guideline effect
existed. This effect would then be attributed to the age-specific guideline effect if birth
cohort effects are not controlled. In our study, where there is some guideline effect, not
controlling for birth cohort therefore leads to a higher effect estimate of this guideline
effect for the highest age category. Through the same mechanism, the 1948 to 1961 birth
cohorts, which have some of the lowest birth cohort effect estimates relative to other birth
cohorts, are tied to the higher parameter estimate for patients aged 30 to 50 years in 2003,
and lower effect estimate for patients aged 50 to 70 in 2003 in the AP model.

In theory, birth cohort may also confound intervention effect estimates that are not
age-specific. In order to get unbiased estimates of intervention effects, ideally we compare a
group of individuals that has experienced the intervention with a group which has not, but
are otherwise similar in terms of relevant characteristics (e.g. age and health status). If we
compare individuals before and after an intervention, confounding will occur if birth cohort
differences in the outcome of interest are present; individuals of the same age at different
moments in time will, by definition, have different dates of birth and thereby different mean
levels in the outcome of interest even in the absence of an intervention effect.

**Observed cohort effect**

If we choose to interpret the observed birth cohort trends as extraneous factors, then in
particular, the observed trends of the 1928 to 1941 birth cohorts and the 1948 to 1961 birth
cohorts should be explained. The former birth cohort had relatively high prevalence of statin
use, whereas the latter had a relatively low prevalence. A possible cause for this difference is
nutritional status during childhood. In the Netherlands, like many other Western countries,
the 1930s and 1940s were characterized by economic depression and war, resulting in a
period of lower nutritional intake [27]. Lower nutritional status in childhood was found to
be related to more health problems later in life, including obesity [28]. An extreme example
of this is that of the Dutch Hunger Winter; patients that were in utero during the Dutch
Hunger Winter in 1946 experienced higher rates of cardiovascular mortality at older ages.
However, this effect is largely limited to urban agglomeration in the west of the Netherlands. In an earlier study, in which a pattern similar to the observed pattern in our case study was found, we excluded differences between birth cohorts in cardiovascular disease as the cause of the observed trend [3] Another explanation is that the observed cohort effects are caused by behavioral differences between the cohorts, but unfortunately data on such differences between these cohorts in the Netherlands is lacking.

**Population-level intervention studies**

Birth cohort effects can be relevant in studies using individual patient-level data, however they can be especially valuable in studies with population-level data. In population-level data, the degree of detail of the information that is available is commonly low; data from national statistics offices or other population-based registries are commonly stratified by age, sex and time. Additional information may be desired by the investigators for a multitude of reasons, one of them being the need to control for important confounders. The birth cohort dimension contains physiological and behavioral information and hence is a potential confounder. However, this confounding information can also be highly useful in population-level studies seeking to answer physiological and behavioral specific hypotheses (e.g. [27-34]).

**Conclusion**

Prevalence of statin use in Dutch diabetic patients increased more strongly from 2003 onwards as a result of influential studies published in 2002 and 2003. The magnitude of the age-specific intervention effects differed notably when we controlled for the birth cohort dimension. This indicates that the birth cohort dimension can confound the estimation of age-specific interventions in time series analysis. Clearly, if extraneous birth cohort effects are present, including the birth cohort dimension is merely a part of proper model specification and therefore important in preventing bias in effect estimation. Unbiased intervention effect estimates at population-level are needed by policy makers and others in taking informed measures for the future.

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Part 2.

Age-period-cohort approach to statin effectiveness