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

Maarten J. Bijlsma, Fanny Janssen, René Lub, Jens H.J. Bos, Folgerdiena M. De Vries, Stijn Vansteelandt, Eelko Hak

Abstract

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

Study Design and Setting: Interrupted time series design was applied to study the prevalence of statin use in Dutch diabetes patients over the period 1998–2011. Effects of guideline changes on the outcome were estimated using a Poisson regression model with and without the birth cohort dimension modeled 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 that controlled for birth cohort also estimated an effect for patients aged 50–70 years from 2003 onward. 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, 0.091] to 0.027 (95% CI: 0.013, 0.041). Similarly, for patients aged below 50 years, the estimated guideline effect was reduced from 0.070 (95% CI: 0.048, 0.092) to 0.055 (95% CI: 0.035, 0.075).

Conclusion: 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.

Keywords: Intervention; Effect estimation; Confounding; Birth cohort; Statins; Diabetes

1. Introduction

The effects of interventions at population level should preferably be measured through randomized controlled studies 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 (ie, aggregated) data are most widely used to study population-level intervention effects. A challenge that arises from such studies is that because of 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 contain information on only a limited number of variables, making it difficult to control for these extraneous factors. An important extraneous factor that contains confounding information and that 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
What is new?

Key findings

- Birth cohort can confound intervention effect estimates in population-level observational studies.

What this adds to what was known?

- We expand the limited amount of information available to control for confounding in population-level observational research by including the birth cohort dimension.

What is the implication and what should change now?

- Unbiased intervention effect estimates at population level are needed by policy makers and others in taking informed measures for the future.

differences have frequently been found to be important determinants in health trends over time (eg, [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 was 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.

2. Methods

2.1. 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].

2.2. Study population

The study population consisted of diabetic patients between ages 30 and 85 years in the study period 1998–2011 (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 insulin (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.

2.3. Exposure

In the Netherlands, although 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.

2.4. 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.

2.5. Statistical analyses

Prevalence of statin use in diabetic patients by year and age was modeled 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 modeled a first-order autoregressive covariance structure. We used R 3.0.1 and SAS 9.3 for our statistical analyses. The model that did not control for the birth cohort dimension was specified as follows:

$$\ln(\text{count}) = \beta_0 + \beta_1 \cdot (\text{year} - 1998) + \beta_2 \cdot I(\text{year} > 2003) \cdot (\text{year} - 2003) + \beta_3 \cdot I(\text{age} < 50) \cdot I(\text{year} > 2003) \cdot (\text{year} - 2003) + \beta_4 \cdot I(\text{age} \geq 70) \cdot I(\text{year} > 2003) \cdot (\text{year} - 2003) + \beta_5 \cdot I(\text{year} > 2006) \cdot (\text{year} - 2006) + \beta_6 \cdot I(\text{age} < 50) \cdot I(\text{year} > 2006) \cdot (\text{year} - 2006) + \beta_7 \cdot I(\text{age} \geq 70) \cdot I(\text{year} > 2006) \cdot (\text{year} - 2006) + \beta_8 \cdot \text{sex} + \beta_9 \ldots \beta_{63} \cdot \text{age group} + \ln(\text{diabetics})$$

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 onward, and $\beta_3$ and $\beta_4$ allow different effects for the studies in 2002–2003 for patients aged below 50 and above 70 years, respectively. $\beta_5$ measures a potential effect of the guideline changes from 2006 onward, and $\beta_6$ and $\beta_7$ again allow that effect to differ for persons aged below 50 and above 70 years, respectively. $\beta_8$ measures the effect of sex. $\beta_{9\ldots63}$ measure the effects of each age year (30, 31 … to 85) as age group is entered categorically. $\ln(\text{diabetics})$ is an offset variable and refers to the natural logarithm of the number of diabetics at risk in each age and calendar year category. This model was termed an age-period model (AP model).

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 (HAPC model) for rates as discussed by Yang and 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.

3. Results

3.1. Prevalence of statin use

The number of diabetic patients with at least one statin prescription in a respective year ranged from 1,707 in 1998 (when the study population consisted of 8,112 diabetic patients) to 14,341 in 2011 (when the study population consisted of 19,364 diabetic patients). Overall, prevalence in the entire study period taken together was 568 users per 1,000 patients with diabetes. Age-standardized prevalence increased from approximately 200 per 1,000 patients in 1998 to 400 per 1,000 patients in 2003, then increased stronger to 700 per 1,000 patients in 2006, and then remained approximately constant (Fig. 1). Approximately 48.4% of the diabetic patients in the study population were men.

3.2. Guideline effect estimates

Both the model that did not control for the birth cohort dimension (AP model) and the model that 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 (Tables 1 and 2). From 2003 onward, for ages younger than 50 years 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 years 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

![Fig. 1. Age-standardized prevalence of statin use in the population of patients with diabetes aged 30–85 years in the Netherlands (1998–2011).](image-url)
Table 1. Effect estimates for the model that does not control for birth cohort (AP model) and the model that does control for birth cohort (HAPC model) (sex and age effect estimates not shown) in the population of patients with diabetes aged 30–85 years in the Netherlands (1998–2011)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AP model</th>
<th>HAPC model</th>
</tr>
</thead>
<tbody>
<tr>
<td>General slope ($\beta_1$)</td>
<td>0.146</td>
<td>0.141</td>
</tr>
<tr>
<td>Slope change 2003 ($\beta_2$)</td>
<td>-0.011</td>
<td>0.024</td>
</tr>
<tr>
<td>Additional slope change ages 30–50 years 2003 ($\beta_3$)</td>
<td>0.070</td>
<td>0.055</td>
</tr>
<tr>
<td>Additional slope change ages 70–85 years 2003 ($\beta_4$)</td>
<td>0.078</td>
<td>0.055</td>
</tr>
<tr>
<td>Slope change 2006 ($\beta_5$)</td>
<td>-0.138</td>
<td>-0.155</td>
</tr>
<tr>
<td>Additional slope change ages 30–50 years 2006 ($\beta_6$)</td>
<td>-0.070</td>
<td>-0.071</td>
</tr>
<tr>
<td>Additional slope change ages 70–85 years 2006 ($\beta_7$)</td>
<td>-0.056</td>
<td>-0.012</td>
</tr>
</tbody>
</table>

**Abbreviations:** AP, age-period; CI, confidence interval; HAPC, Hierarchical APC.

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 in the slope for patients aged 50–70 years from 2003 onward, relative to the slope in the 1998–2003 period, whereas 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.

3.3. Birth cohort effects

Fig. 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 onward, there is a slow decline in the effect estimates up to approximately 1966, with cohorts born between 1929 and 1950 having estimates above the average, whereas born after 1950 have estimates below the average. After 1966, the pattern fluctuates strongly. The addition of the random intercepts by birth cohort resulted in a reduction in restricted –2log 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.

4. Discussion

In the present case study, we found that the birth cohort dimension appears 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 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 HAPC model also estimated an effect for patients aged 50–70 years from 2003 onward. The magnitude of the effect for patients aged above 70 years when we controlled for birth cohort was reduced to one-third of its originally estimated magnitude. Furthermore, effect estimates for patients aged below 70 years were somewhat higher in the model that controlled for birth cohort.

4.1. Evaluation of data and methods

All 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.

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

<table>
<thead>
<tr>
<th>Period and age category</th>
<th>AP model</th>
<th>HAPC model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Annual change</td>
<td>95% CI</td>
</tr>
<tr>
<td>1998–2003 ages 30–85 years</td>
<td>15.7</td>
<td>14.7%, 16.8%</td>
</tr>
<tr>
<td>2003–2006 ages 30–50 years</td>
<td>22.7</td>
<td>20.2%, 25.3%</td>
</tr>
<tr>
<td>2003–2006 ages 50–70 years</td>
<td>14.5</td>
<td>13.2%, 15.7%</td>
</tr>
<tr>
<td>2003–2006 ages 70–85 years</td>
<td>23.7</td>
<td>22.3%, 25.1%</td>
</tr>
<tr>
<td>2006–2011 ages 30–50 years</td>
<td>-0.3</td>
<td>-1.5%, 0.8%</td>
</tr>
<tr>
<td>2006–2011 ages 50–70 years</td>
<td>-0.3</td>
<td>-1%, 0.5%</td>
</tr>
<tr>
<td>2006–2011 ages 70–85 years</td>
<td>1.9</td>
<td>1.0%, 2.8%</td>
</tr>
</tbody>
</table>

**Abbreviations:** AP, age-period; CI, confidence interval; HAPC, Hierarchical APC.
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 modeled through fixed effects (ie, a model based on the Clayton and Schifflers approach). Although this affected the parameter estimates of the guideline effects, our conclusions remained the same (Online Supplementary Data).

4.2. Guideline effect estimates

Although 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 onward and became constant in 2006. Evidently, although 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 30–85 years) 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 years and older because of the studies that 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, although 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. In the following, we explain how the estimates of the AP model were confounded by the birth cohort dimension.

4.3. 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 after the entry of an additional variable are not necessarily evidence for confounding. Such changes may also occur due to noncollapsibility; that is, 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. Because this is not possible in an empirical setting, more empirical studies

![Image](image_url)
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 that does not control for birth cohort can be explained through the estimated pattern of birth cohort effects (Fig. 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—1941 moved from the age category 50- to 70-year-olds to the 70- to 85-year-olds. The estimated birth cohort effects for these birth cohorts were higher than for all other birth cohorts (Fig. 2). Therefore, as time progressed and this birth cohort aged into the age 70- to 85-year-olds 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—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—50 years in 2003 and lower effect estimate for patients aged 50—70 years in 2003 in the AP model.

In theory, birth cohort may also confound intervention effect estimates that are not age specific. 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 (eg, 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.

4.4. 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—1941 birth cohorts and the 1948—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 during the Dutch Hunger Winter in 1946 experienced higher rates of cardiovascular mortality at older ages. However, this effect is largely limited to the 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 effect is caused by behavioral differences between the cohorts, but unfortunately, data on such differences between these cohorts in the Netherlands are lacking.

4.5. 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 (eg, [29—36]).

5. Conclusion

Prevalence of statin use in Dutch diabetic patients increased more strongly from 2003 onward 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.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jclinepi.2014.10.010.

References

340


[2] Groenwold RHH, Hak E, Hoes AW. Quantitative assessment of unob-

served confounding is mandatory in nonrandomized intervention


1052–60.


204–26.


60:227–34.


[7] Finch CE, Crimmins EM. Inflammatory exposure and historical


34:1149–59.


3106–14.


[25] Gail MH, Wieand S, Piantadosi S. Biased estimates of treatment effec-

t in randomized experiments in randomized experiments with nonlinear regression and omitted covariates. Biometrika 1984;71:

431–44.

[26] Greenland S, Robins JM, Pearl J. Confounding and collapsibility in


[31] Krieger N, Strong EF, Makosky C, Weuve J. Breast cancer, birth co-


405–11.


demiol 2002;31:23–6.


[35] Steenfemserle D, Streifel C, Shihadeh ES. Cohort size and arrest rates over the life course: the Easterlin Hypothesis Reconsidered. Am So-


[36] Tarone RE, Chu KC. Implications of birth cohort patterns in inter-


1402–10.