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ORIGINAL ARTICLES

# Inclusion of the birth cohort dimension improved description and explanation of trends in statin use

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## Abstract

**Objective:** Including the birth cohort dimension improves trend studies of mortality and health. We investigated the effect of including the birth cohort dimension in trend studies of prescription drug use by studying prevalence of statin use among adults.

**Study Design and Setting:** Data from a drug prescription database in the Netherlands (IADB.nl) were used to obtain the number of users of statin per 1,000 population (prevalence) in the age range 18–85 years from 1994 to 2008. We applied descriptive graphs and standard age-period-cohort (APC) models.

**Results:** From 1994 to 2008, the prevalence increased from ~10 to ~90 users per 1,000 population, with the peak in prevalence shifting from age 63 to 78 years. The APC model shows patterns that were masked in the age-period (AP) model. The prevalence rate ratio increased from the 1911 birth cohort to the 1930 birth cohort and then declined. Similar for both sexes, adding nonlinear period effects contributed ~4.4% to reductions in deviance, whereas adding nonlinear birth cohort effects contributed ~12.9%.

**Conclusion:** Adding the birth cohort dimension to AP analysis is valuable for academic and professional practice as trends can be more accurately described and explained and it can help improve projections of future trends. © 2012 Elsevier Inc. All rights reserved.

**Keywords:** Age-period-cohort; Trend; Drug utilization; Statin; Pharmacoepidemiology; Generalized linear model

## 1. Introduction

Current studies of prescription drug use at the population level are less accurate than they could potentially be. Such studies commonly use a cross-sectional design (e.g., [1,2]). This is a standard design in epidemiology because changes in (age-specific) trends in each year can be attributed to some event that occurred in that year. However, a cross-sectional design masks the birth cohort dimension [3]. Individuals born in the same period, referred to as birth cohorts, share formative experiences and other events, which affects their behavior and health. Especially for population-level drug utilization studies, ignoring differences between birth cohorts might lead to distorted outcomes.

Since the 1980s, there has been a renewed interest in methods incorporating the (birth) cohort dimension, next to age and period, with important methodological contributions

by Clayton and Schiffers [4]. Birth cohort effects can have theoretical explanatory value; that is, they can capture long-lasting effects, the determinants of which may be found earlier in life, such as in utero exposure to famine [5], early life morbidity [6,7], or cultural effects [8,9]. Birth cohort effects can also have predictive value; that is, modeling trends by age, period, and birth cohort improves the accuracy of models. The birth cohort dimension added significantly to trend studies in demography (e.g., [10]) and epidemiology (e.g., [7,11]). Because members of birth cohorts alive today will also be alive in the future, current information about birth cohorts can also improve predictions of future trends [12].

In pharmacoepidemiology, cross-sectional trends can additionally lead to distorted outcomes because interventions might have a different uptake and impact for different birth cohorts because of differences between birth cohorts in perception of preventive measures, differences between birth cohorts in prescription and adherence culture, or guideline changes that affect different birth cohorts differently.

The aim of the present study was to analyze the added value of the birth cohort dimension in population-level trend studies of prescription drug use by comparing an

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**What is new?****Key finding**

- Extending a conventional cross-sectional analysis of prevalence of statin use with the birth cohort dimension provides additional information on trends and significantly improves the accuracy of the model.

**What this adds to what was known?**

- Age-period-cohort (APC) analysis revealed patterns that were masked by age-period analysis. For statin use, the moving peak in prevalence toward increasing age over time could be attributed to the 1930 birth cohort.

**What is the implication?**

- APC models help in the description and explanation of trends and can improve predictions of future trends. This is needed to aid policy makers and others in taking informed measures for the future.

age-period (AP) analysis to a full age-period-cohort (APC) analysis, taking statin use as an example. We studied trends for males and females separately to compare whether the pattern of their birth cohort effects were similar, in light of possible gender differences in health and prescription drug use. Statins are lipid-lowering drugs. Indications for statin are hypercholesterolemia and dyslipidemia (ICD-10 E78), diabetes mellitus (E10, E14), ischemic heart disease (I20–I25), and atherosclerosis (I70) [13]. Statin use was chosen as the object of study because statins were introduced fairly recently [2] and underwent changes in insight and guidelines. In our country of study, the Netherlands, prescription of statins was at first discouraged to persons aged older than 70 years. In 2002, important studies showed the drug's effectiveness at older ages [14,15], and in 2006 the age restrictions were formally abolished [16]. These changes are likely to have affected different birth cohorts differently, thereby providing a relevant case for the study of birth cohort effects.

## 2. Methods

### 2.1. Data

Outpatient pharmacy data were used from IADB.nl, which contains pharmacy prescription information in the Netherlands, covering on average 500,000 persons annually [17] ([www.IADB.nl](http://www.IADB.nl)), with a period of growth in 1994–1998 from approximately 100,000 to 500,000. 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. Patients have a unique but anonymous identifier. Because of high patient pharmacy commitment in the Netherlands and advanced pharmacy software, the medication records for each patient are virtually complete [18,19]. The database is representative of prescribing practice in the Netherlands. The prevalence of drug use information from the IADB is routinely compared with the national Drug Information System of the Health Care Insurance Board [20]. Prevalence matches for nearly all drugs, including statin. The database has been used in previous studies on statin use [21,22].

### 2.2. Study population

Individuals of both sexes between ages 18 and 85 years in the period 1994–2008, belonging to the birth cohorts 1911–1987, were included in the study. Total population covered by the IADB pharmacies specified by age, sex, and period was estimated with data from Statistics Netherlands. Age- and period-specific person-years at risk of drug prescription was calculated by taking the average of the population at the beginning of the year  $p$  in age  $a-1$  and the population at the end of the year  $p$  and age  $a$ .

### 2.3. Statin use

Individuals who received at least one prescription for statin in a calendar year were considered a user of statin in that respective year. This is considered accurate because statin continuance within 1 year is high [23]. Statins are coded as C10AA in the ATC classification of the WHO [24].

### 2.4. Outcome measures

The primary outcome measures of this study are age- and sex-specific prevalence of statin use, expressed per 1,000 population, and prevalence rate ratio (Box 1).

### 2.5. Graphical descriptive analysis

Age-standardized and age-specific prevalence by sex was depicted in graphs by both period and birth cohort. To improve visual clarity, prevalence was aggregated in 3-year age groups for the period graph and 3-year age and birth cohort groups for the birth cohort graph.

Direct age standardization was applied to the overall annual trend to control for the changing age composition of the study population over time [25]. As the standard population, the age- and sex-specific IADB population in 2001 was used.

### 2.6. APC modeling

We modeled prevalence as a function of age, period, and birth cohort. The formulation of our full APC model was

$$\ln[\lambda_{ap}] = \mu + \alpha_a + \beta_p + \gamma_c$$

## Box 1 Outcome measures

### Prevalence of statin use

Prevalence of statin use can be interpreted as the number of users of statin per 1,000 individuals in the population. It is calculated as

$$\frac{\text{Users by sex in period } p \text{ and birth cohort } c}{\text{Person years at risk by sex in period } p \text{ and birth cohort } c} \cdot 1,000$$

Age, or actually age at December 31, was automatically assigned as it results from subtracting birth cohort from period.

### Prevalence rate ratio

In this study, the prevalence rate ratio is the proportion of the observed prevalence compared with the prevalence of a baseline category. A prevalence rate ratio higher than 1 represents an increase relative to the baseline prevalence and a prevalence rate ratio lower than 1 represents a decrease relative to the baseline prevalence. The prevalence rate ratio was calculated by taking the exponent of the parameter estimates of the AP and APC models.

where  $\lambda$  represents prevalence;  $\mu$  represents the intercept; and  $a$ ,  $p$ , and  $c$  represent age, period, and birth cohort, respectively. The APC model was fitted using a program for Poisson regression and an offset term was used to represent person-years at risk of statin prescription for each period and birth cohort-specific category. Age, period, and birth cohort were measured as categorical variables. The model was run separately for males and females.

There is a linear dependency between age, period, and birth cohort ( $a = p - c$ ), resulting in overidentification if all three variables are included in the analysis [3,26]. We dealt with this problem by applying the standard Clayton and Schifflers approach [4]; we decomposed the prevalence as the effect of age, the effect of the shared linearity of period and birth cohort (referred to as drift), and nonlinear period effects and nonlinear birth cohort effects. Drift can be seen as the “overall slope” (e.g., prevalence increases or decreases linearly over time) and nonlinear period and nonlinear birth cohort effects represent deviations from this slope.

To assess the difference in the age and period patterns with and without controlling for the cohort dimension, we compared the fitted patterns of the AP model with those of the APC model. We show the resulting fitted patterns by age, period, and birth cohort, expressed as prevalence rate ratios with 95% confidence intervals (95% CIs). The prevalence rate ratio was calculated by taking the exponent of the parameter estimates. For the age parameter, age 18 years was taken as the baseline category. For the period parameter, one estimate was constrained to zero (1994), thereby setting it as the baseline for period and thereby drift is included in the period effect. This was considered reasonable because of the strong growth of prevalence by period. For birth cohort, two baseline categories (1923 and 1976)

had to be chosen on statistical grounds, thereby producing only nonlinear birth cohort effects.

To assess the contribution of adding the birth cohort dimension to the model, we compared the goodness of fit of age (A), age-drift (AD), AP, and APC for the different models (see Box 2). The deviance statistic, a measure of goodness of fit, was used to derive the likelihood ratio test for model reductions. The primary comparison was APC with AP, but we also compared AD with A and AP with AD. Each reduction in deviance is expressed as a percentage reduction in deviance between the age-only model and the full APC model, along with  $P$ -values. We display one-sided  $P$ -values because adding variables to the model can only result in a decrease of deviance. Finally, the fit of the AP and the APC models to the data was also tested using a log-likelihood ratio test.

## Box 2 Age, period, and cohort modeling

Model parameters	Statistical notation
Age (A)	$\ln[\lambda_a] = \mu + \alpha_a$
Age + drift (AD)	$\ln[\lambda_{ad}] = \mu + \alpha_a + \delta$
Age + period (AP)	$\ln[\lambda_{ap}] = \mu + \alpha_a + \beta_p + \delta$
Age + period + cohort (APC)	$\ln[\lambda_{ap}] = \mu + \alpha_a + \beta_p + \gamma_c$

$\ln[\lambda]$  is the natural log of user prevalence, with the number of users being Poisson distributed.  $\mu$  is the intercept and  $\alpha$ ,  $\delta$ ,  $\beta$ , and  $\gamma$  are the age, drift, period, and cohort effect, respectively. The variables for age ( $a$ ) and period ( $p$ ) had one baseline class. The variable for cohort ( $c$ ) had two baseline classes. The variables were indexes  $a = 1, 2 \dots 67, 68$ ,  $p = 1, 2 \dots 14, 15$ , and  $c = 1, 2 \dots 76, 77$ .

### 3. Results

#### 3.1. Prevalence of statin use

The number of patients with at least one statin prescription in a respective year ranges from 789 in 1994 (when 64,379 persons were in the study population aged 18–85 years) to 22,360 in 2008 (when 417,539 individuals were in the study population aged 18–85 years). Overall, prevalence in the entire study period taken together was 63 users per 1,000 population. There was a strong increase in age-standardized prevalence over time from ~10 users per 1,000 population in 1994 to about ~90 users per 1,000 in 2008, with a short level period between 1997 and 1998 (Fig. 1). The slope increased in the period 2003–2006 relative to the previous periods but then leveled off in 2006. Approximately, 48.5% of users were male. Overall, the prevalence of males was about 30% higher than the prevalence of females.

#### 3.2. Age-specific prevalence of statin use by period

The age-specific annual prevalence for both males and females increased with age up to a certain point, and thereafter declined with age, in each period (Fig. 2). At ages 20–40 years, the number of users per 1,000 population was close to zero. In 1994, the peak of the prevalence (~40 per 1,000 users) was found at about age 63 years. In 2001, the peak moved to about age 69 years and also reached a higher level of ~200 per 1,000 users for males and ~170 per 1,000 users for females. In 2008, prevalence peaked at age category 78 years at ~400 users per 1,000 for males and ~340 users per 1,000 for females. After the peak, there was a strong decline in the prevalence with age. Overall, the slope became more steep over time.

#### 3.3. Age-specific prevalence of statin use by birth cohort

An increase in prevalence with age could be seen for all birth cohorts (Fig. 3), but was especially strong for those

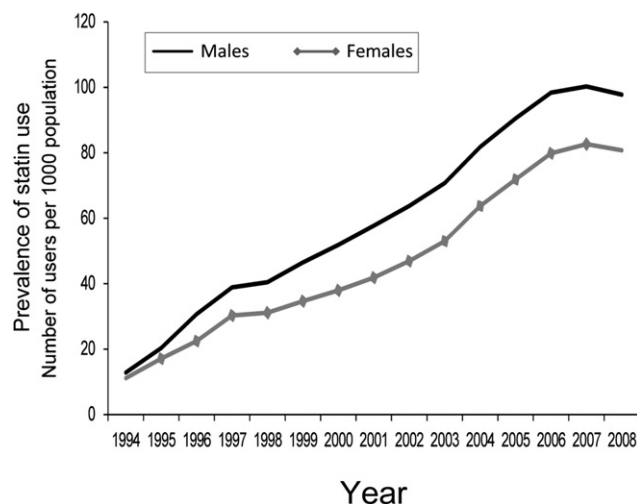


Fig. 1. Age-standardized prevalence of statin use by period and sex in the Netherlands, 1994–2008, ages 18–85 yr.

born between 1923 and 1946. Birth cohort 1929–1931 exhibited the most statin users per 1,000 population when compared with the other birth cohorts, and was responsible for the moving age peak over time in prevalence as seen in the age-specific cross-sectional figures. Furthermore, when comparing the birth cohorts within an age group, it showed that younger birth cohorts had a higher prevalence at the same ages as older birth cohorts. These differences became stronger with increasing age.

#### 3.4. Comparing age and period patterns with and without including the cohort dimension

When applying an AP model, the fitted patterns by age show that, for both sexes, the prevalence rate ratio increased from age 18 years (baseline) up to approximately age 70 years and then declined, reaching higher levels for males (400) than for females (200) (Fig. 4). The fitted patterns by period of the AP model revealed a strong increase in the prevalence rate ratios over time from 1994 (1) to 2006 (7.6 for males and 7 for females), and then became approximately level to 2008.

When applying an APC model, thereby additionally controlling for birth cohort, the prevalence rate ratio continuously increased with age; it did not start to decline at age 70 years (Fig. 5). Additionally, controlling for age and birth cohort, the period pattern (which included the drift) was similar to the period pattern of the AP model but the prevalence rate ratios were smaller (6.7 in 2006 for males and 5.4 for females).

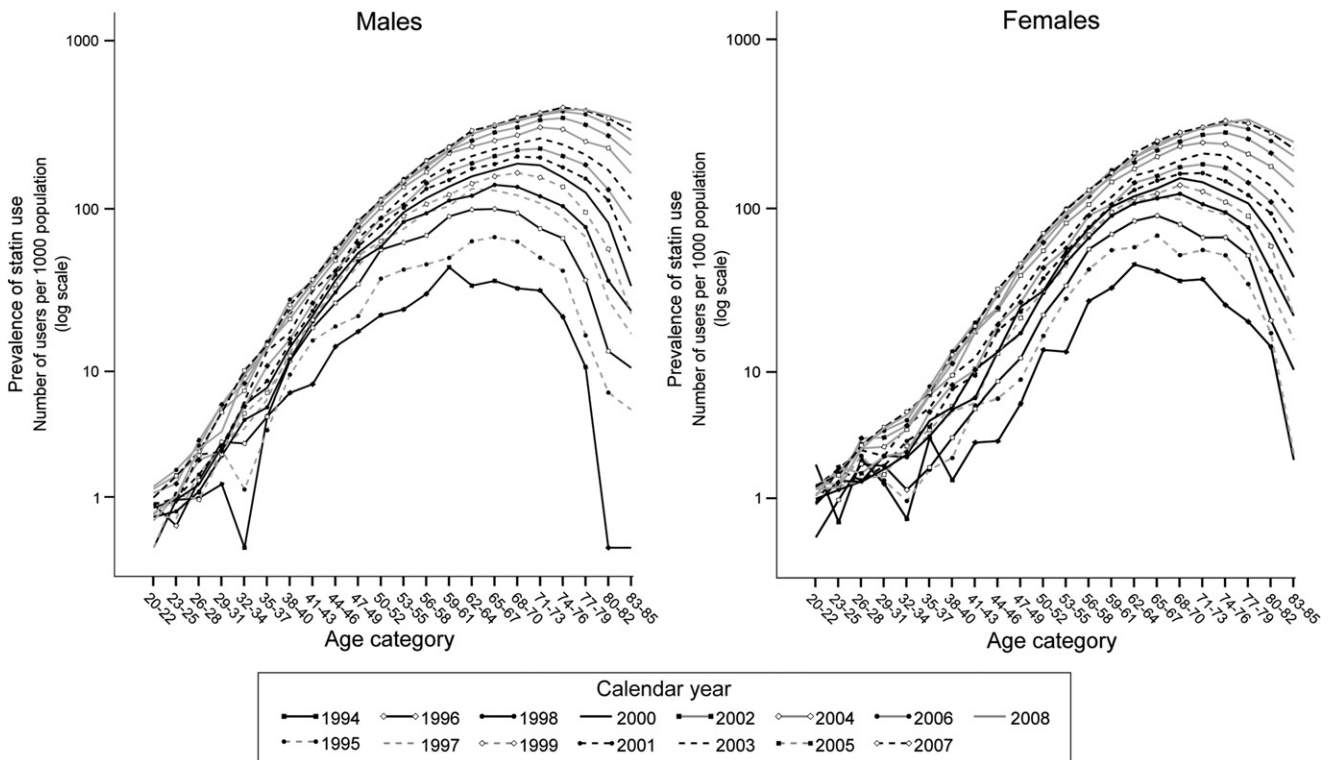
#### 3.5. The fitted birth cohort patterns

Controlled for age and period, the nonlinear birth cohort pattern showed very clearly the strong increase from the 1911 birth cohort (prevalence rate ratio of ~0.1, 95% CI: ~0.02, ~0.25) to about the 1930 birth cohort (prevalence rate ratio of ~1.5, 95% CI: ~1.4, ~1.6) for both males and females separately (third panel of Fig. 5). For males, the prevalence rate ratio in 1930–1946 remained level and then declined with fluctuations to a prevalence rate ratio of 0.35 (95% CI: 0.16, 0.79) for the 1987 birth cohort. For females, the prevalence rate ratio gradually declined from 1930 onward to about 1.13 (95% CI: 0.99, 1.29) for the 1950 birth cohort, then showed strong fluctuations until birth cohort 1980 and then declined until the 1987 birth cohort, where the prevalence rate ratio was 0.53 (95% CI: 0.30, 0.97).

#### 3.6. Contribution of age, period, and birth cohort to the model fit

All components of the APC model were significant at the  $P < 0.005$  (one-tailed) level (Table 1). Drift, the linear component of both period and birth cohort, contributed 81.6% for males and 84.0% for females to the reduction in deviance (a measure similar to residual variance). Non-linear period effects contributed 5.1% for males and 3.6%

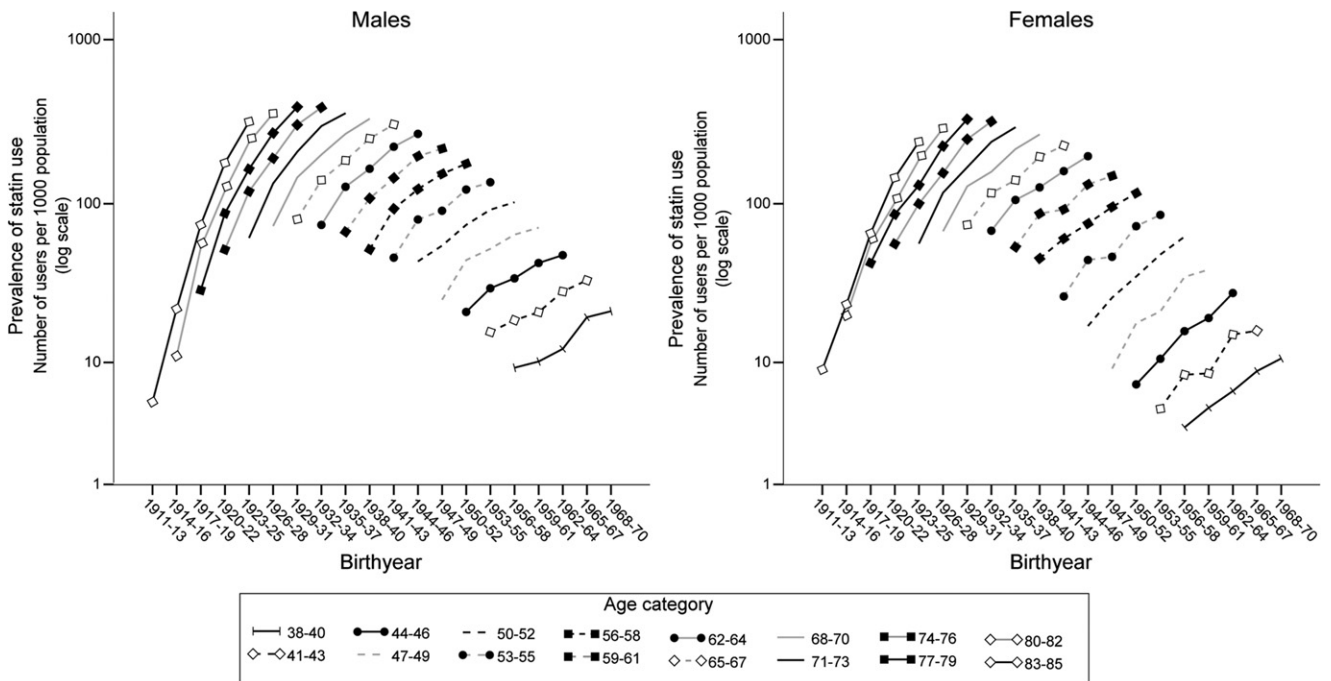




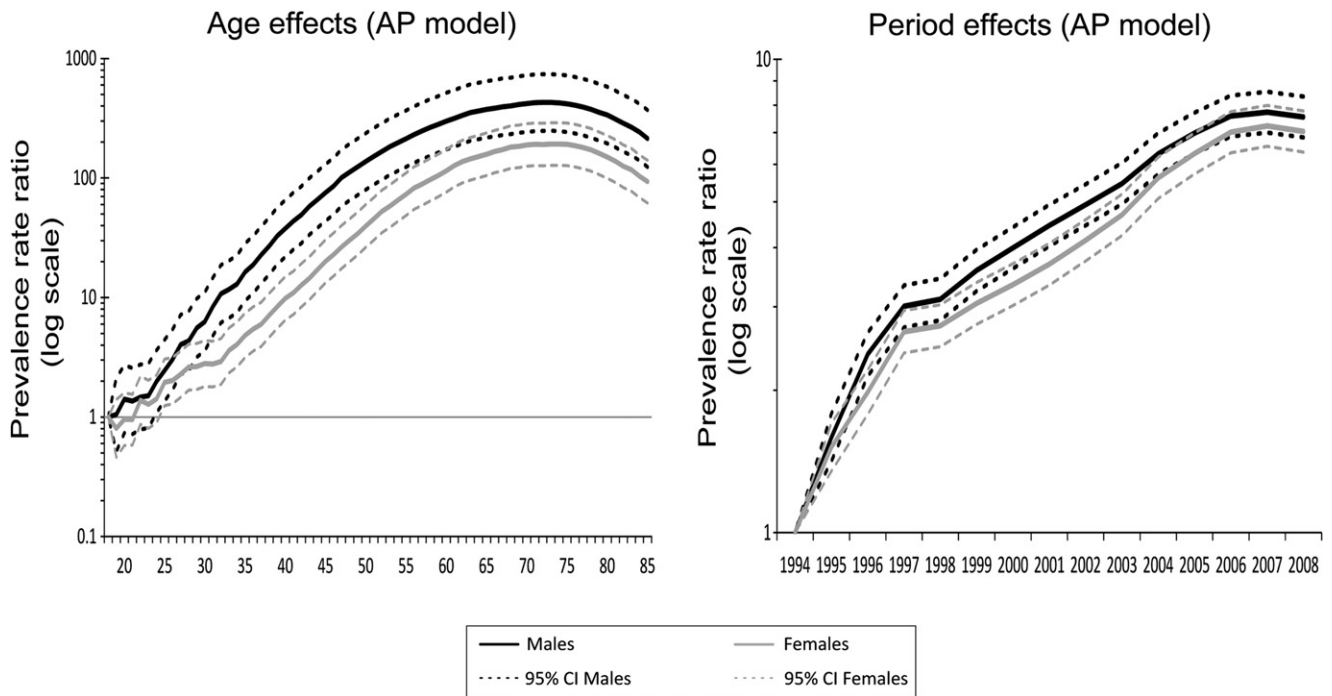
**Fig. 2.** Three-year age-specific prevalence of statin use by period and sex in the Netherlands, 1994–2008, ages 20–85 yr. To improve visual clarity, prevalence of statin use is displayed in 3-yr age groups.

for females. Nonlinear birth cohort effects were the second strongest contributor for both sexes, contributing 13.3% for males and 12.4% for females. The log-likelihood ratio test of the AP model against the data resulted in a *P*-value

of <0.005 for both males and females, whereas the log-likelihood ratio test of the APC model against the data resulted in a *P*-value of >0.99 for both males and females. The *P*-value of the Pearson chi-squared test for goodness



**Fig. 3.** Three-year age-specific prevalence of statin use by 3-yr birth cohort (1911–1913 to 1968–1970) and sex in the Netherlands, 1994–2008, ages 38–85 yr. To improve visual clarity, prevalence is displayed in 3-yr age by 3-yr birth cohort groups and the youngest birth cohorts were excluded.



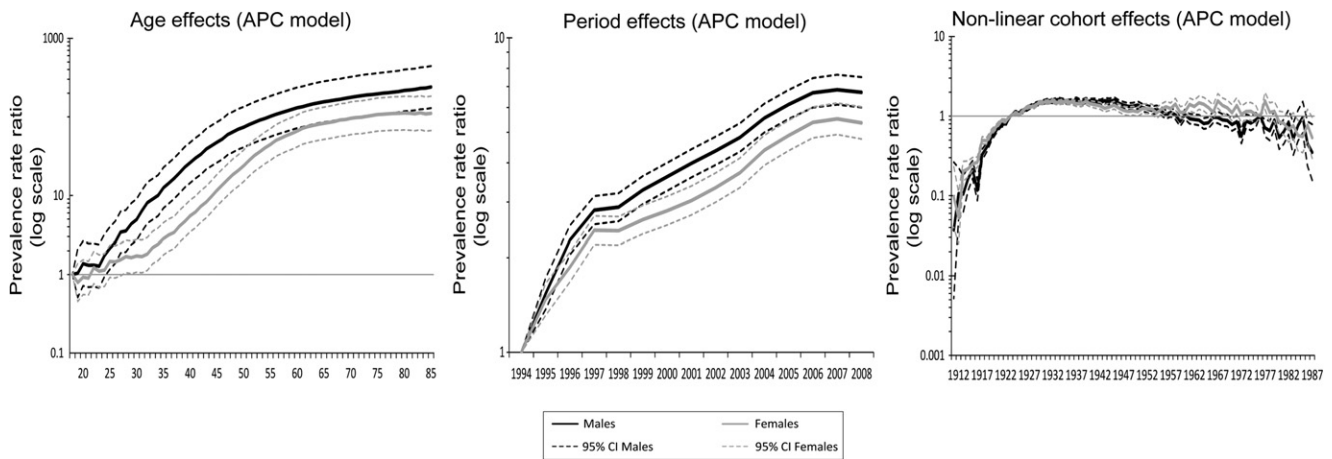
**Fig. 4.** Age-period model: fitted age and period effects in prevalence of statin use 1994–2008, ages 18–85 yr. The intercept is not included in the above visualization of age and period for clearer interpretation of the prevalence rate ratios.

of fit of the full APC model was also  $P > 0.99$  for both males and females.

**4. Discussion**

For statin use, we found that birth cohorts are, next to age and period, of importance in describing and explaining trends in drug prescription. Examining the trends from an age-cohort perspective, next to the standard AP perspective, showed that the shifting peak in prevalence to older ages over time could be attributed to the 1930 birth cohort.

Furthermore, the APC model showed patterns that were masked in the AP model; the prevalence rate ratio continuously increased with age, instead of declining after age 70 years. In statistical terms, the full APC model is an improvement over an AP model: there was a stronger decrease in deviance because of the addition of nonlinear birth cohort (~12.9%) than because of the addition of non-linear period (~4.4%). These additions were highly significant and similar for males and females. Finally, the outcome of the log-likelihood ratio test for model fit indicated that the full APC model provided a good fit to the data, whereas the AP model did not.



**Fig. 5.** Age-period-cohort model: fitted age, period, and cohort effects in prevalence of statin use 1994–2008, ages 18–85 yr. The intercept is not included in the above visualization of age, period, and cohort for clearer interpretation of the prevalence rate ratios.

**Table 1.** Goodness-of-fit statistics of the models of statin by sex, the Netherlands, 1994–2008, ages 18–85 yr

Goodness of fit						
Model	Deviance	Reduction	Percentage reduction <sup>a</sup> (%)	df	Model reduction test (one-tailed <i>P</i> -value) <sup>b</sup>	Model fit to data test (one-tailed <i>P</i> -value) <sup>c</sup>
Males						
Age	27,331	—	—	943	—	<0.005
Age-drift	5,467	21,864	81.6	942	<0.005	<0.005
Age-period	4,104	1,363	5.1	929	<0.005	<0.005
Age-period-cohort	528	3,575	13.3	854	<0.005	>0.99
Females						
Age	25,859	—	—	943	—	<0.005
Age-drift	4,561	21,298	84.0	942	<0.005	<0.005
Age-period	3,649	912	3.6	929	<0.005	<0.005
Age-period-cohort	518	3,132	12.4	854	<0.005	>0.99

<sup>a</sup> Reduction in deviance as a percentage of the difference between the age-only model and the full age-period-cohort model.

<sup>b</sup> Log-likelihood ratio test of model reductions in deviance comparing this model to the previous.

<sup>c</sup> Log-likelihood ratio test comparing the model to the data.

#### 4.1. Evaluation of data and methods

The study has several strengths. All of the data of the study came from the same source, a representative 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 another study of statin use in the Netherlands [1], although exact levels differed because of age standardization and different operationalizations of the prevalence of statin use. Because of the large sample size, the study had enough power to detect even small effects if they existed. We chose to use the standard Clayton and Schifflers approach to APC modeling so as not to lose potentially relevant trend fluctuations to parametric smoothing, which may occur in other approaches (e.g., [27]). By taking single-year period by single-year birth cohort intervals, we also had a more fine selection of data than is commonly the case in studies using the Clayton and Schifflers approach. Finally, we chose prevalence as our primary outcome measure because it better captures the total burden of statin use in the population than other population measures, such as incidence.

Statin use as defined in this study represents count data. Because cell counts were 0 for 2.2% of the cells and were low for approximately 30% of the cells, we applied a model with a Poisson distribution. The log-likelihood ratio tests and the Pearson chi-squared tests showed that the full APC model with the Poisson distribution fit the data adequately. Furthermore, the dispersion parameter (deviance divided by degrees of freedom) (Table 1) indicated that overdispersion was unlikely.

As we followed birth cohorts for 15 years, caution is warranted in interpreting the birth cohort pattern as different birth cohorts also represent different age groups; birth cohorts born further in the past were at older ages during the study period than younger birth cohorts. This can potentially result in an overestimation of the differences between birth cohorts. Conversely, for the same reason, birth cohort effects can be underestimated as some birth cohort effects

may be latent; different birth cohorts may have different trajectories in life.

#### 4.2. Explanation of observed trends

In our study of statin use, including a birth cohort dimension in the analysis provided additional insight into the structure of trends. The age-specific graph for birth cohorts indicated that the peak in prevalence was tied to the 1930 birth cohort. The APC model confirmed this by isolating the (nonlinear) birth cohort effects from the age and period effects. Furthermore, the APC model showed a continuous increase of prevalence with age, unlike the age pattern in the AP model where the increase turned into a decline at the older ages. A continuous increase is, however, more in line with the increasing risk of cardiovascular disease with increasing age [16]. Both the AP and APC models showed a strong increase in prevalence with period, which was expected as the drug underwent strong growth since its introduction. However, the growth was less in the APC model. Thus, in cross-sectional analysis, what was now attributed to birth cohort would either have been attributed to period or to age, or would be overlooked: in our AP model the birth cohort effects were partly attributed to age (the shape of the age patterns differ) and partly to period (the prevalence rate ratios of the period effect are larger for the AP model). This shows that in cross-sectional analysis the long-term consequences of a particular trend would not be recognized; the AP model does not show that the peak of the prevalence moves to older ages with time. Furthermore, trends may be incorrectly explained if birth cohort effects are not recognized as such.

The observed birth cohort pattern should be explained: overall, we observed a steep positive slope from the 1911 to the 1930 birth cohort and then a decline, with strong fluctuations for females, toward the 1987 birth cohort. This pattern may be caused by the guideline change. The international studies which showed the effectiveness of statins above age 70 years were published in 2002 (the guidelines were formally



changed in 2006). The 1930 birth cohort was approximately age 70 years when these studies were published and therefore had the right age at the right time. This birth cohort was aged approximately 60 years when statins were introduced in the Netherlands. Individuals in this age group had a higher risk of cardiovascular disease than younger ages, while they were in the age range for which evidence of the drug effectiveness existed [28]. By the time this birth cohort reached age 70 years, evidence for the effectiveness above age 70 years was about to be published. When older birth cohorts reached this age, prescription of statins would have been discouraged by the guidelines as the guidelines were still in effect at that time. In line with this explanation, we expect that younger birth cohorts will eventually—as they age—also show higher prevalence relative to the birth cohorts born before 1930.

We performed additional descriptive analyses to find out the potential role of birth cohort—specific cardiovascular problems for the observed birth cohort pattern. Descriptive graphs of prevalence trends of other cardiovascular medications (ACE inhibitors, angiotensin II receptor antagonists, and  $\beta$ -adrenoreceptor blockers) were studied (data on file). Their trends did not have the same overall shape, making it unlikely that the birth cohort pattern is related to birth cohort—specific cardiovascular problems. Also, the effect of contraindications on statin prescription was considered. The primary contraindication is liver disease [13]. Currently, no evidence exists to show that individuals born around 1930 have a lower prevalence of liver disease (when controlling for age) than other birth cohorts. The specific shape of the prevalence trend may therefore indeed be caused by the guideline changes. This is further supported by the nearly identical birth cohort patterns for both sexes although males and females generally have different health trends and behaviors.

#### 4.3. APC methodology in drug utilization studies

APC methodology is commonly used in studies of mortality or disease incidence trends (e.g., [11,29,30]) and in social research (e.g., [31–33]). As drug prescription should be strongly related to mortality and disease trends, it is perhaps surprising that there are few (or no) studies of drug prescription using APC methods or that otherwise include a birth cohort dimension. Some papers on illicit drug use that use APC methodology do exist (e.g., [34]). The “Monitoring the Future” series of studies on drug abuse by secondary school students, conducted by the National Institutes of Health and the National Institute of Drug Abuse, have used APC methodology for describing current trends and anticipating future trends since at least 1988 and consider it a particular important contribution of the series [35].

Statin use in the Netherlands is a good case for the investigation of birth cohort effects because of the introduction of age-specific guidelines, the effects of which remain with each birth cohort as it ages. Applying APC analysis to other drug types is likely to result in either stronger or weaker

birth cohort effects and different patterns, depending on the drug.

We would expect especially strong cohort effects as a result of policy changes, such as the implementation or abolishment of large-scale preventive intervention programs. For example, there may be differences between birth cohorts in vaccine coverage, especially as such programs can have age-specific risk criteria [36]. For vaccines with long-lasting protective effect (e.g., persistence of antibody titers), differences in coverage can have effects long after a policy change took place.

Specific underlying health or behavioral differences between birth cohorts may also result in clear birth cohort effects in drug prescription trends as well. For example, studies have found differences between birth cohorts in smoking-related causes of disease and mortality such as chronic obstructive pulmonary disease [37,38]. Trends of drugs used in the treatment of this disease may therefore have clear birth cohort effects as well. The underlying cause of this is differences between birth cohorts in prevalence of smokers in the population.

Behavioral differences between birth cohorts in prescription behavior, regardless of underlying health differences, may also result in clear birth cohort effects. However, such differences are more difficult to hypothesize, as research on this topic is lacking.

#### 4.4. Implications

The inclusion of the birth cohort dimension contributes to (scientific) practice primarily in two ways. Firstly, as demonstrated, birth cohort patterns provide additional insight into the structure of trends. By proposing explanations for the birth cohort effects and patterns that we have found, the APC analysis also provides an incentive for further research into the causes of trends. Secondly, birth cohort effects can be used to improve trend projections [12]. Because members of birth cohorts alive currently may also be alive in the future, current birth cohort patterns may persist in the future. This is the information that can be used in the prediction of future trends. If birth cohort effects are found to contribute more to trend explanation than period effects, a cohort-wise projection will lead to more accurate information about the future than a period-wise projection. In particular, due to population aging and its associated problems, accurate drug utilization projections are needed. Drug utilization impacts quality of life, morbidity, and mortality. Accurate information about future drug utilization in populations allows policy makers and others to take informed measures for the future.

#### 4.5. Overall conclusion

This study demonstrated the usefulness of incorporating a birth cohort dimension, next to age and period, in population-level drug utilization studies. The birth cohort

dimension is valuable for academic and professional practice as trends can be more accurately described and explained and as it can improve projections of future trends.

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