Age-period-cohort methodology
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Chapter 4.

Association between statin use and cardiovascular mortality at the population level: an ecological study

Abstract

Background: We assessed the contribution of statin use to the decline in cardiovascular mortality for the Netherlands over the period 1994-2010.
Methods: Aggregated mortality data from Statistics Netherlands were combined with dispensing data from a representative drug dispensing database. We estimated mortality if prevalence of statin use had remained at its observed 1994 levels throughout the period 1994-2010 for acute myocardial infarction (AMI), other ischemic heart disease (other IHD) and cerebrovascular disease using Poisson models adjusted for various confounders.
Results: We estimated that keeping prevalence of statin use at observed 1994 levels would have resulted in 0.06 (95% CI: 0.049 to 0.080), 0.02 (95% CI: 0.012 to 0.023) and 0.04 (95% CI: 0.023 to 0.044) more AMI, IHD and cerebrovascular deaths per 100 person-years respectively.
Conclusion: The findings indicate that statin therapy may have played an important role in decreasing national cardiovascular mortality rates in the period 1994 to 2010.

Introduction

Cardiovascular disease is a major cause of death in both industrialized and developing countries and threatening healthy ageing of citizens [1-3]. In much of the Western world, nationwide age-specific cardiovascular mortality has been declining steadily since 1970 [4]. There is ongoing debate about the role of several determinants of this decline. Lifestyle changes at the population level, such as changes in diet and smoking behavior, are important contributors [5]. Improvements in, and wider application of, surgical procedures such as percutaneous coronary intervention and coronary artery bypass grafting can be of importance [2, 6]. Finally, improved cardiovascular care with a wide arsenal of medicines aimed at preventing or treating cardiovascular disease such as statins, ace-inhibitors and angiotensin-receptor blockers may also have a major impact [7].

The clinical effectiveness of preventive and therapeutic cardiovascular drugs was demonstrated in various clinical trials (e.g. [8, 9]). However, the demographic composition of clinical trial populations as well as important risk factors such as concomitant drug use and co-morbidity in a clinical trial setting commonly differ from those of clinical practice [10, 11]. This means that end-users potentially differ demographically and behaviorally from trial participants. Therefore, in order to understand the impact of pharmaceutical measures at population level, observational studies are needed. Observational studies may combine population level drug dispensing data with (cause-specific) mortality data, and can thereby provide insights into their nationwide role of drug utilization on population level mortality trends.

A potentially important risk factor affecting cardiovascular mortality at the population level, which has so far been acknowledged (e.g. [12-14]) but often ignored, is birth cohort. A birth cohort refers to a group of individuals born in the same period and who therefore share formative experiences and other events. For example, the effect of famine on fetal development during the Dutch Hunger Winter was shown to have a strong effect on cardiovascular mortality in later life [15]. However, birth cohort effects might also indirectly affect cardiovascular mortality through behavior such as drug utilization and adherence. Recently, we found that individuals born before 1930 were less likely to utilize statin therapy compared to individuals born after 1930, which makes birth cohort a potential confounder [16]. The potential importance of birth cohort effects warrants an investigation which explicitly takes into account the birth cohort dimension in both drug uptake and mortality outcome.

Through the use of aggregate data, the primary objective of this study is to investigate the association between statin use and cardiovascular mortality in the Netherlands during
the period 1994 to 2010. Furthermore, we explored whether population level effects were different for different birth cohorts.

Methods

Study population
The study population in this ecological study consisted of an annual average of ~5 million individuals in the Netherlands aged 50 to 83 years during the study period 1994 to 2010, belonging to birth cohorts 1916 to 1959. These ages were chosen as prevalence of statin use is very low before age 50, and information from the drug-dispensing database that we used (see below) becomes less reliable above age 84.

Primary exposure: aggregated at the population level
Statin use is our primary exposure. Individuals were considered to be a user of statins in a half year period if they received at least one prescription for statins (anatomic-therapeutic-chemical (ATC)-code C10AA). We tabulated by half year period, instead of by year, because it allows for more time intervals at which comparisons can be made. We calculated prevalence of statin use by dividing the number of users of statin by the person-years at risk of prescription, which was received from Statistics Netherlands. Data on statin use were received from the Dutch drug dispensing data base IADB.nl which contains dispensing information from 55 community pharmacies in the Netherlands, covering on average 500,000 persons annually [17]. With the exception of over-the-counter drugs and in-hospital prescriptions, all prescriptions are included in the IADB regardless of prescriber, insurance, or reimbursement status. Medication records of patients are virtually complete because of high patient pharmacy commitment in the Netherlands [17]. The database is representative for the Netherlands as a whole and has been used in previous studies on statin use [16, 18]. In the Netherlands, statin therapy first started around 1994 and cannot be received over the counter.

Outcome measure
The primary outcome measure of this study is the count of mortality due to acute myocardial infarction (AMI) (ICD9-code 410; ICD10-code I21) [19,20]. We also studied mortality due to other ischaemic heart diseases (Other IHD) (ICD9-codes 411-414; ICD10-codes I20, I22-I25) and cerebrovascular disease (ICD9-codes 430-438; ICD10-
Association between statin use and cardiovascular mortality at the population level in the Netherlands 1994-2010: an ecological study

These data were received from Statistics Netherlands by five year age and half year period and by two year age and one year period [21]. We tabulated this into two year age by half year period using linear interpolation. Cause-specific mortality rates were obtained by dividing these numbers of deaths by person-years at risk.

**Covariates**

Based on the literature, we predefined potential confounders for the association between prevalence of statin use and cardiovascular mortality. These were prevalence of other cardiovascular drug use, diabetes, birth cohort, age and sex. Other cardiovascular drugs we included were ACE inhibitors (ATC-codes C09AA, C09BA and C09BB), antithrombotic agents (ATC-code B01), angiotensin receptor blockers (ATC-codes C09C and C09D), beta blockers (ATC-code C07), calcium channel blockers (ATC-code C08), diuretics (ATC-code C03; this category includes important antihypertensives), fibrates (ATC-code C10AB) and nitrates (ATC-code C01AD). Individuals were considered users of a drug in a half-year period if they received at least one prescription for that drug in that period. Patients who received at least one prescription for blood glucose lowering drugs (ATC codes A10A or A10B) were considered diabetic patients. As also nondiabetic patients may receive insulins (ATC code A10A), patients who were only prescribed insulins were not considered diabetic patients. As with our primary exposure measure, we calculated the prevalence of users of each drug by dividing the number of users by the person-years at risk of prescription.

**Descriptive analysis**

Age and sex-standardized rates and age-specific rates were depicted in graphs by calendar year. Direct age standardization was applied to the overall trend to control for the changing age composition of the study population over time [22]. As the standard population, we used the age- and sex-specific population of the Netherlands in 2001.

**Statistical analyses**

We applied time series analysis to determine the association between prevalence of statin use and the cardiovascular mortality rate. To do so, we fitted a Poisson regression model with the half year count of cause-specific mortality (AMI, other IHD or cerebrovascular disease) as the outcome variable and the natural log of person-years at risk of mortality as an offset variable. Covariates in this model were prevalence of statin use, two year age-category (50-51, 52-53, ..., 82-83), 4-year birth cohort (1916-1919, 1920-1924, ..., 1956-
1959), sex, prevalence of diabetes and other cardiovascular drug use. An interaction term between prevalence of statin use and birth cohort was used to assess whether the association of statin use with the cause-specific mortality rate is modified by birth cohort. Because the prevalence of many of the drugs listed above changed over time, they served as proxies of calendar time. Therefore, this model is a type of age-period-cohort characteristic model (APCC) [23]. Because prevalence of statin use may also have long-term effects, we also applied this model with a two-year lag between cause-specific mortality and prevalence of statin use as a sensitivity analysis.

We also fitted a model with a linear time trend as an additional covariate. This enables the estimation of the association between prevalence of statin use and cardiovascular mortality rate while adjusting for the linear decline in cardiovascular mortality in the Netherlands since at least 1980, and thus before the introduction of statins [4, 24]. In this model, we had to further constrain the birth cohort dimension due to its linear dependency with age and time, by setting the coefficients of the adjacent middle birth cohorts (1932-1935 and 1936-1939) to be equal [25].

Finally, in order to determine the association of statin use with decline in cardiovascular mortality in the Netherlands in the period 1994-2010, we calculated excess mortality [26]. That is, for each half year, while allowing other covariates to change, we predicted mortality if prevalence of statin use had remained at its 1994 level and compared it with mortality predicted using observed levels of prevalence of statin. These predictions were obtained from the regression models without lag and without adjustment for the linear decline over time in cardiovascular mortality. Excess mortality was divided by person-years at risk so as to make the results more readily interpretable.

Results

Decline in cardiovascular mortality

The overall age-standardized mortality rate due to acute myocardial infarction (AMI) (ICD9-code 410) in 1994 was 0.28 deaths per 100 person-years. This rate declined almost linearly to 0.08 deaths per 100 person-years in 2010, representing a relative decrease in cardiovascular mortality rate of 71% over the whole study period or 3.7% per half year (Figure 1). The overall age-standardized mortality rate of other IHD in 1994 was 0.08 deaths per 100 person-years and declined steadily to 0.04 deaths per 100 person-years in 2010, a 50% decline over the period. Finally, in 1994 0.18 deaths per 100 person-years
occurred due to cerebrovascular disease, which declined to 0.08 deaths per 100 person-years in 2010, corresponding with a 56% decline over that period. For each of the three causes of death, the decline was also approximately linear in each of the different age groups (Appendix 1 eFigures 1-3), with older age categories having a higher mortality rate than younger age categories.

**Figure 1.** Age standardized mortality rate of acute myocardial infarction (ICD9-code 410), other ischemic heart disease (ICD9-codes 411-414), and cerebrovascular disease (ICD9-codes 430-438) in the Netherlands by half year period in 1994 to 2010, ages 50 to 83.

**Prevalence of statin use**

Overall, age-standardized prevalence of statin use in 1994 was 5 users per 100 person-years in the population. This increased to 40 users per 100 person-years in 2010 (Figure 2). Prevalence of statin use increased over time in most age groups, but the prevalence became constant from 2006 to 2010, except in ages above 70 where prevalence of statin use increased (Appendix 1 eFigure 4).
Association between statin use and cardiovascular mortality decline

Adjusting for age, sex, birth cohort, other drug use and diabetes, an increase of one statin user per 100 person-years in a half year period was associated with a 1.23% decrease in the number of individuals that would die of AMI in the same half year period (95% confidence interval (CI) 0.93 to 1.53%). This was 0.93% (CI: 0.42 to 1.43%) for mortality due to other IHD and 1.06% (CI: 0.70 to 1.42%) for cerebrovascular mortality. The association between prevalence of statin use and mortality after two years was stronger; an increase of one statin user per 100 person-years in a half year period was associated with a 1.61% decrease in the number of individuals that would die of AMI two years later (CI: 1.33 to 1.88%). This was 1.06% (CI: 0.60 to 1.51%) for other IHD and 1.14% (CI: 0.82 to 1.46%) for cerebrovascular mortality.

Taking into account the linear decline in cardiovascular mortality lowered the association of other cardiovascular medications with mortality decline, especially that of ARBs, ACE inhibitors and, to a lesser extent, antithrombotic drugs. The association between cardiovascular mortality and statins increased; we found that an increase of one statin user per 100 person-years in a half year period was associated with a decrease of 1.51% (CI: 1.25 to 1.77%) in mortality due to AMI in the same period. Similarly, an increase of one statin user per 100 person-years was associated with a 1.05% (CI: 0.63 to 1.47%) decrease in other IHD mortality, and a 1.26% (CI: 0.97 to 1.55) reduction in cerebrovascular mortality.
Statin use and mortality decline

Figure 3 shows the predicted AMI mortality rate if prevalence of statin use had remained constant at observed 1994 levels throughout the study period (see appendix 1 eFigures 5 and 6 for corresponding figures for other IHD and cerebrovascular mortality). We found that keeping prevalence of statin use at the observed 1994 levels, the AMI mortality rate over the study period was predicted to have been on average 0.064 deaths per 100 person-years higher (95% CI: 0.049 to 0.080). For other IHD and cerebrovascular mortality this was 0.017 (95% CI: 0.012 to 0.023) and 0.033 (95% CI: 0.023 to 0.044) per 100 person-years higher, respectively.

Figure 3. Observed acute myocardial infarction mortality (ICD9 410) and predicted acute myocardial infarction mortality if prevalence of statin use had remained constant in the Netherlands in the period 1994-2010, ages 50 to 83.

Effect modification by birth cohort

We found that, in general, younger birth cohorts had a lower AMI mortality rate than older birth cohorts, with a slight rise and stagnation for cohorts born in the period 1920 to 1928 (Figure 4). Similar patterns were found for other IHD and cerebrovascular disease. Interaction terms between statin use and birth cohort did not add significantly to the models (p = 0.61). For the model with AMI as the outcome, all interaction effects were close to 1, and did not differ significantly from 1 (Figure 5), which also indicates no effect. Findings for the models with other IHD and cerebrovascular mortality were similar.
Figure 4. Estimated birth cohort effects in mortality due to acute myocardial infarction in the period 1994-2010, ages 50 to 83 in the Netherlands according to the APCC model.

Figure 5. Estimates of the modification by birth cohort of the effect of statin use on mortality due to acute myocardial infarction (ICD9 410) in the period 1994-2010, ages 50 to 83 in the Netherlands.
Discussion

In this Dutch population-level time series analysis, cardiovascular mortality declined throughout the 1994 to 2010 study period, while prevalence of statin use increased from 1994 to 2006 and stabilized afterwards except for those aged 70 years and older. Controlling for various important risk factors, we estimated that keeping prevalence of statin use at observed 1994 levels resulted in 0.06 more AMI deaths per 100 person-years, 0.02 more IHD deaths per 100 person-years and 0.04 more cerebrovascular deaths per 100 person-years during the study period. Differences between birth cohorts in the effectiveness of statin use were not observed.

Evaluation of data and methods

Using aggregate data to analyze the effect of prevalence of statin use on cardiovascular mortality has both strengths and weaknesses. The main strength of using aggregated data is that we were able to achieve a large sample size. This resulted in high precision and thereby very high statistical power to detect even small effect sizes. The large sample size kept standard errors small, despite collinearity between some covariates in the model. The most important weakness of using aggregate data is the risk of ecological fallacy. Furthermore, we could not take into account dosage or duration of use. However, the majority of patients using statins are chronic users and, on the population level, dosage does not change over time. Other important factors that affect cardiovascular mortality over time may be changes in cardiac interventions, aspirin use and smoking. While cardiac interventions are effective for individuals, their impact on the population level is limited because it is only performed on a small group of patients [7]. A limitation of the study is that we could not control for trends in aspirin use in the Netherlands, because this drug does not require a prescription. Furthermore, research indicates that smoking behavior is strongly tied to birth cohort [28-30]. Therefore, we believe to have captured significant lifestyle effects over time by including birth cohort. We included cardiovascular medications other than statins, such as ace inhibitors, antihypertensive and antithrombotic medication, to control for potential confounding by these medications. However, we found that the effect estimate of prevalence of statin use on cardiovascular mortality did not change strongly if these drugs were excluded from the model. Furthermore, in a sensitivity analysis, we included a linear time trend in the model in order to capture other potential confounders such as changes in health behavior over time. However, even after this addition, the estimate of statin effectiveness remained robust. Therefore, with the possible exception of the effect...
of aspirin use, we believe our estimate of statin prevalence on cardiovascular mortality to be controlled for the most important confounders. Finally, it is unlikely that our findings are distorted by competing risks because there is no evidence in the literature that statins strongly increase mortality due to non-cardiovascular causes.

Another strength of the study is that all of the drug dispensing data of the study came from the same source, a database representative for the Netherlands (IADB.nl), and the data were gathered and coded in the same manner during the observation period. Mortality and life years at risk data also came from the same source throughout the study period, but mortality data underwent a coding change in 1996, when ICD-9 was changed to ICD-10. From previous research it showed that for the causes of death under study (and the codes used), no apparent discontinuities in mortality trends due to this ICD change occurred [20].

**Effectiveness of statin use**

A Cochrane review of trial evidence indicated that statins are protective against fatal cardiovascular events (RR: 0.83, 95% CI: 0.72 to 0.96), though not against fatal stroke (RR: 0.61, 95% CI: 0.18 to 2.23) [27]. However, in our study, the percentage reduction in mortality that we found associated with an increase in statin prevalence cannot be directly compared to results from clinical trials. This is because of the nature of the data used and the consequent difference in explanatory variables. Where clinical trials and some observational studies compare the hazard of mortality between users and non-users of statin, we investigated the relation between a prevalence of statin use in a group of patients and the rate of cardiovascular mortality in that group.

Mortality due to acute myocardial infarction in the Netherlands declined by approximately 3.7% per half year. Many factors are believed to contribute to this decline. Nevertheless, it is noteworthy that our model predicts that keeping prevalence of statin use at its observed 1994 levels resulted in 0.06 more AMI deaths per 100 person-years during the study period. This is quite considerable, given that the observed AMI mortality rate in the study period was between 0.08 and 0.28 deaths per 100 person-years. The excess mortality of other IHD and cerebrovascular mortality were of lower magnitude, but relative to observed mortality rates are also considerable. Furthermore, we also adjusted for linear decline. This was done to adjusts for certain unmeasured (confounding) factors, such as population-level changes in diet, exercise or (utilization of) surgical procedures that together would have produced linear decline of cardiovascular mortality over time. The effect estimate of prevalence of statin use on cardiovascular mortality was not strongly
affected by adjusting for linear decline, while it did strongly change the effect estimates of other cardiovascular medications. These findings indicate that, on the population level, statins appear to have played a strong role in the reduction of cardiovascular mortality in the period 1994 to 2010.

**Birth cohort differences**

Controlling for age, sex, diabetes and prevalence of cardiovascular drugs, we found that, relative to the 1936-1939 birth cohort, younger birth cohorts have lower cardiovascular mortality rates. Other studies have also found similar differences between birth cohorts in cardiovascular mortality (e.g.[13, 14]). This indicates that, at the population level, younger birth cohorts have better cardiovascular health than older birth cohorts, even when relevant medication and calendar time (by proxy) are taken into account. These differences may be related to behavioral differences between birth cohorts that impact cardiovascular mortality such as birth cohort differences in smoking behavior [28, 29]. Since we could not adjust for such underlying factors directly, this demonstrates the utility of adjusting for birth cohort.

There were no differences in the effectiveness of statins in reducing cardiovascular mortality between birth cohorts on the population level. Differences between birth cohorts could be due to differences in biological efficacy or clinical efficacy. While biological differences between birth cohorts have been found (e.g. [15]), these are rare and furthermore it is unknown if such differences would also change drug efficacy (e.g. through changes in drug metabolism). Birth cohort differences in behavior have been shown to exist (e.g. [30, 31]). It is as of yet unknown if such behavioral differences may lead to differences in clinical effectiveness between birth cohorts. Because we did not find differences between birth cohorts in effectiveness, our study can be seen as generating preliminary evidence that such differences between birth cohorts in behavior also do not exist. However, a study with patient level data would be needed to test this hypothesis.

**Conclusion**

Statin use appeared strongly associated with a decrease in mortality due to acute myocardial infarction, other ischemic heart diseases and cerebrovascular diseases. The study indicates that lipid-lowering drugs play an important role in decreasing national cardiovascular mortality rates. The effect of statins did not differ by birth cohort, providing a first indication that the clinical effectiveness of statins in reducing cardiovascular mortality is not affected by behavioral differences between birth cohorts.
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Conflicts of interest

None declared.
References


Appendix 1

**eFigure 1.** Age-specific mortality rate of acute myocardial infarction (ICD9 410), in the Netherlands by half year period 1994 to 2010, ages 50 to 83.

**eFigure 2.** Age specific mortality rate of other ischemic heart disease (ICD9 411-414), in the Netherlands by half year period 1994 to 2010, ages 50 to 83.
eFigure 3. Age specific mortality rate of cerebrovascular disease (ICD9 430-438), in the Netherlands by half year period 1994 to 2010, ages 50 to 83.

eFigure 4. Age specific prevalence of statin use (ATC C10AA) in the Netherlands by half year period 1994 to 2010, ages 50 to 83.
eFigure 5. Observed other ischemic heart disease mortality (ICD9 411-414) and predicted other ischemic heart disease mortality if prevalence of statin use had remained constant in the Netherlands in the period 1994-2010, ages 50 to 83.

eFigure 6. Observed cerebrovascular disease mortality (ICD9 430-438) and cerebrovascular disease mortality if prevalence of statin use had remained constant in the Netherlands in the period 1994-2010, ages 50 to 83.