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

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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

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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