Is the birth cohort dimension associated with differences in statin therapy's effectiveness in reducing cardiovascular mortality? Evidence from aggregated time trend analyses.

Maarten J. Bijlsma [a], *Fanny Janssen* [b, a], *Jens Bos, Pieter W. Kamphuisen*[c], *Stijn Vansteelandt* [d], *Eelko Hak* [a]

[a] Unit PharmacoEpidemiology & PharmacoEconomics (PE^2), Department of Pharmacy, University of Groningen, Groningen, The Netherlands.

[b] Population Research Centre (PRC), Faculty of Spatial Sciences, University of Groningen, Groningen, The Netherlands.

[c] Department of Vascular Medicine, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands.

[d] Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium.

Introduction

Cardiovascular mortality is a major cause of death in both industrialized and developing countries (Kulasmaa et al. 2000, Capewell et al. 2000, Murray et al. 1997). In much of the Western world, age-specific cardiovascular mortality has been declining steadily since 1970 (Kesteloot et al. 2006). There is ongoing debate about the determinants of this decline. Lifestyle changes on a population-level such as changes in diet and smoking behaviour appear to be important determinants (Vartiainen et al. 2010). However, some lifestyle changes have adverse effects, resulting in an increase in prevalence of diabetes and obesity (Zimmet et al. 2001, Johnson et al. 2012). Therefore, another important cause of lowered cardiovascular mortality may be the increased use of medicinal drugs aimed at preventing or treating cardiovascular disease such as Statins, ACE-inhibitors and Angiotensin Receptor Blockers (Layte et al. 2010).

The effectiveness of drugs used in the treatment of cardiovascular disease, such as the aforementioned drugs, has been demonstrated in clinical trials (e.g. Shepherd et al. 2002; Van Vark et al. 2012). However, the demographic composition of individuals and important factors such as concomitant drug use and co-morbidity in a clinical trial setting commonly differ from those of a post-marketing setting (Martin et al. 2004; Critchley et al. 2002), i.e. end-users potentially differ demographically and behaviorally from clinical test subjects. Therefore, in

order to understand the impact of medicinal drugs on cardiovascular mortality in the population of end-users, observational studies are needed.

A potentially important factor affecting cardiovascular mortality on a population level, which has so far been acknowledged (e.g. Capewell et al. 1999, Janssen et al. 2005, Amiri et al. 2006) but often excluded from studies, are birth cohort effects. 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 a strong effect on cardiovascular mortality in later life (Schulz et al. 2010). However, birth cohort effects might also indirectly affect cardiovascular mortality through behaviour such as drug utilization and adherence. Recently, we found that individuals born before 1930 were less likely to utilize statin compared to individuals born after 1930 (Bijlsma et al. 2012). This 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, this study seeks to investigate whether the effectiveness of statin use in reducing cardiovascular and cerebrovascular mortality differs between birth cohorts.

Data & Methods

Setting

Cardiovascular (International Classification of Disease 9 (ICD9) 410-414, ICD10 I20-I25) and cerebrovascular (ICD9 430-438, ICD10 I60-I69) mortality data were received from Statistics Netherlands by five year age and half year period and by two year age and one year period. We tabulated this into two year age by half year period using linear interpolation. Information on the population at risk of mortality was also received from Statistics Netherland. 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) (Visser et al., 2013).

Study population

The study population consisted of individuals in the Netherlands between ages 50 and 83 years in the study period 1994 to 2011, belonging to birth cohorts 1916-1959).

Cardiovascular medications and diabetes

Individuals were considered a user of a drug in a half year period if they received at least one prescription for that drug in the respective half year period. In this way, we determined the number of users of statins, ACE inhibitors, antithrombotic agents, angiotensin receptor blockers, beta blockers, calcium channel blockers, diuretics, fibrates and nitrates. Statin use is our drug of primary interest. Individuals were considered to have diabetes in a half year period if they received at least one prescription for a blood glucose lowering drug (including insulins), and received a prescription for a blood glucose lowering drug (excluding insulins) at any point in time. We calculated the prevalence of users of each drug by dividing the number of users by the population at risk of prescription.

Outcome measure

The primary outcome measure of this study is age and birth cohort specific count of mortality due to acute myocardial infarction (ICD9 410). We also studied mortality due to other ischaemic heart diseases (ICD9 411-414) and cerebrovascular disease (ICD9 430-438).

Statistical analyses

We fitted a Poisson model with the count of cause-specific mortality as the outcome variable and the natural log of life years at risk of mortality as an offset variable, thereby effectively modeling the incidence of cause-specific mortality. Predictors in this model were age category (50-51, 52-53, …, 82-83), birth cohort (1916-1919, 1920-1924, …., 1956-1959), prevalence of statin use and prevalence of antithrombotic use. Prevalence of statin use was given a 2 year lag in age and calendar time, as the drug is expected to be efficacious on the longer term. Because the prevalence of these drugs increases steadily over time, to some degree they will serve as proxies of period time. Therefore, this model can be seen as an age-period-cohort characteristic model (APCC model) (O'Brien et al. 2000). We adjusted for prevalence of the other cardiovascular medications and diabetes. 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.

Results

Effectiveness of statins and cardiovascular medications

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.

Birth cohort effects

We found that in general, younger birth cohorts had lower relative incidence of acute myocardial infarction than older birth cohorts, with some apparent stagnation for cohorts born in the period 1920 to 1928 (Figure 1). Very similar patterns were found for other ischaemic heart diseases (ICD9 411-414) and cerebrovascular diseases (ICD9 430-438).

Effectiveness of statin use by birth cohort

Interactions by birth cohort added significantly to the models ($p < 0.01$). For the model with ICD9 410 as the outcome, the majority of point estimates were close 1 to and did not differ significantly from 1 (Figure 2). Significant estimates were close enough to 1 to be clinically irrelevant. Findings for the models with ICD9 411-414 and ICD9 430-438 were similar.

Conclusion

In our aggregated time-trend analysis we found differences between birth cohorts in cardiovascular mortality. However, despite a significant addition of the interaction between birth cohort and statin therapy, we did not find clinically relevant differences between birth cohorts in the effectiveness of statin therapy on the reduction in cardiovascular mortality.

References

Amiri M, Kunst AE, Janssen F, Mackenbach JP. Cohort-specific trends in stroke mortality in seven European countries were related to infant mortality rates. J Clin Epidemiol 2006;59:1295e302.

Bijlsma MJ, Hak E, Bos JH, de Jong-van den Berg LT, Janssen F. Inclusion of the birth cohort dimension improved description and explanation of trends in statin use. J Clin Epidemiol 2012 Oct;65(10):1052-1060.

Capewell S, Beaglehole R, Seddon M, McMurray J. Explanation for the decline in coronary heart disease mortality rates in Auckland, New Zealand, between 1982 and 1993. Circulation 2000 Sep 26;102(13):1511-1516.

Capewell S, Morrison CE, McMurray JJ. Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. Heart 1999 Apr;81(4):380-386.

Critchley JA, Capewell S. Why model coronary heart disease? Eur Heart J 2002 Jan;23(2):110-116.

Janssen F, Kunst AE. Cohort patterns in mortality trends among the elderly in seven European countries, 1950-99. Int J Epidemiol 2005;34:1149e59.

Johnson W, Chumlea WC, Czerwinski SA, Demerath EW. Secular trends in the fat and fat-free components of body mass index in children aged 8-18 years born 1958-1995. Ann Hum Biol 2012 Sep 26.

Kesteloot H, Sans S, Kromhout D. Dynamics of cardiovascular and all-cause mortality in Western and Eastern Europe between 1970 and 2000. Eur Heart J 2006 Jan;27(1):107-113.

Kuulasmaa K, Tunstall-Pedoe H, Dobson A, Fortmann S, Sans S, Tolonen H, et al. Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. Lancet 2000 Feb 26;355(9205):675-687.

Layte R, O'Hara S, Bennett K. Explaining structural change in cardiovascular mortality in Ireland 1995-2005: a time series analysis. Eur J Public Health 2011 Oct;21(5):597-602.

Martin K, Begaud B, Latry P, Miremont-Salame G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. Br J Clin Pharmacol 2004 Jan;57(1):86-92.

Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997 May 24;349(9064):1498-1504.

O'Brien. Age Period Cohort Characteristic Models. Social Science Research 2000; 29(1): 123-39.

Schulz LC. The Dutch Hunger Winter and the developmental origins of health and disease. *PNAS* September 28, 2010 vol. 107 no. 39 16757-16758.

Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002 Nov 23;360(9346):1623-1630.

Van Vark LC, Bertrand M, Akkerhuis KM, Brugts JJ, Fox K, Mourad JJ, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. Eur Heart J 2012 Aug;33(16):2088-2097.

Vartiainen E, Laatikainen T, Peltonen M, Juolevi A, Mannisto S, Sundvall J, et al. Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol 2010 Apr;39(2):504-518.

Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001 Dec 13;414(6865):782-787.

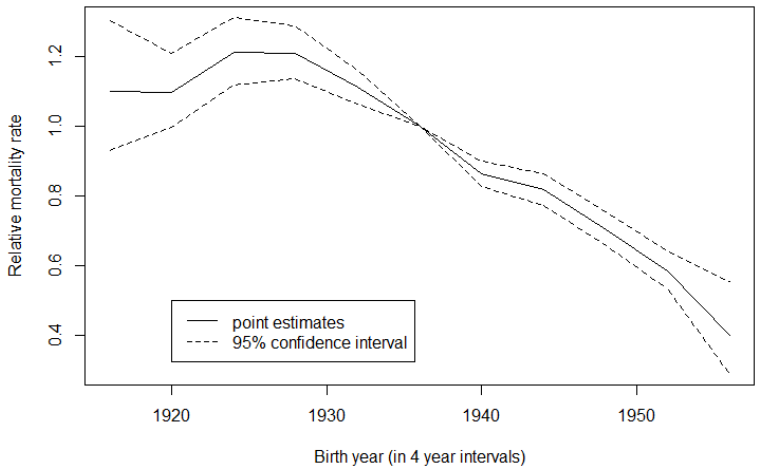

Figure 1: Estimated birth cohort effects in mortality due to acute myocardial infarction in the period 1994-2010, ages 50 to 83 in the Netherlands according to the age-period-cohort characteristic model.

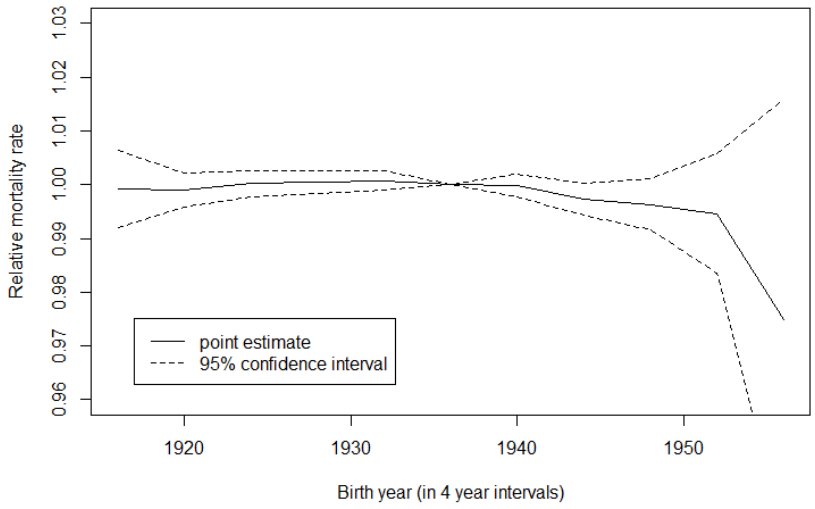

Figure 2: Estimates of the modification by birth cohort of the effect of statin use on mortality due to acute myocardial infarction in the period 1994-2010, ages 50 to 83 in the Netherlands.