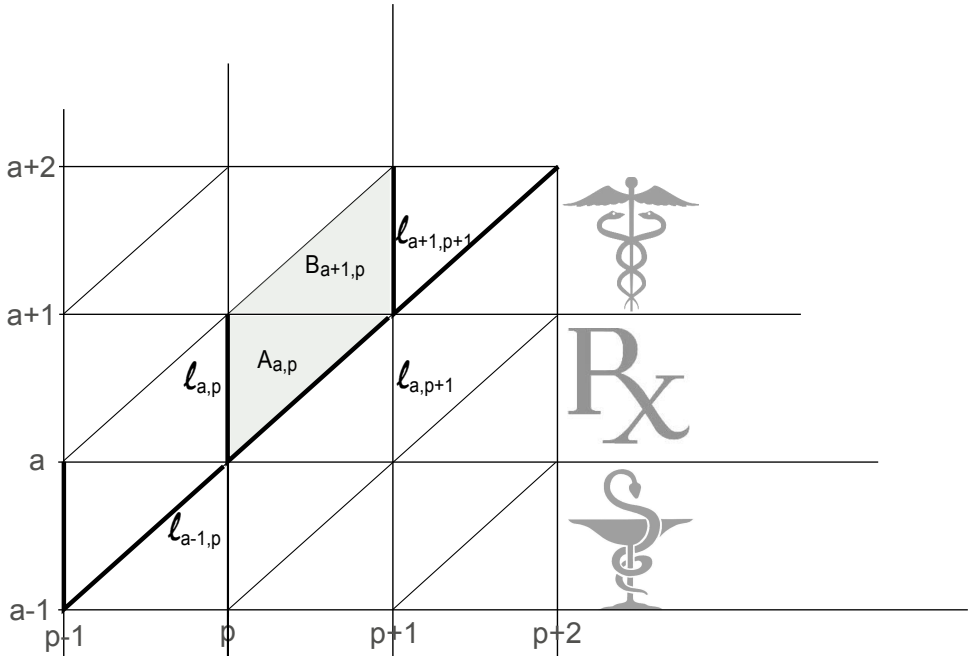


Age, period and cohort effects
in the prescription of benzodiazepine and statin in the Netherlands 1994 - 2008

Maarten J. Bijlsma

University of Groningen
Faculty of Spatial Sciences

Master´s thesis Research Master Regional Studies
Specialization: Population Studies
Supervised by dr. F. Janssen

Summary

Age, period and cohort effects in the prescription of benzodiazepine and statin in the Netherlands 1994 – 2008

Background
A large proportion of the Dutch population receives a prescription drug each year. The number of individuals receiving a prescription has continuously increased in the last twenty years. Prescription trends are partly tied to demographic trends but also to other effects, such as guideline and insight changes. Actors such as the government and insurance companies depend on current trend information and extrapolation because it provides insight into (future) expenditure and into the effects of policy. Demographic methods may help improve pharmacoepidemiological analyses such as time trend studies. This study intends to demonstrate this by studying the prescription trends of benzodiazepine and statin. Both drugs have a large number of users and underwent guideline changes in recent years to combat addiction and cardiovascular disease in the population respectively. Few studies on the trends of these drugs exist, yet these studies are needed. The studies that exist are cross-sectional, which is a design masks birth cohorts effects. Therefore, this study looks at age, period and cohort effects.

Primary research question
What are the effects of age, period and cohort on trends of users of benzodiazepine and statin in the Netherlands in the period 1994 - 2008?

Theory
Drug prescription is strongly tied to population health but also to socio-cultural factors such as the verbosity of patients. Age effects: prescription should increase with age because, at the population level, health deteriorates with age. Period effects: prescription is influenced by calendar time because, for example, new drugs are introduced or prescription guidelines are changed. Cohort effects: prescription should also relate to birth cohort because the historical economic and socio-cultural conditions that an individual grew up in affects their future health and behaviour. Benzodiazepine is an addictive drug used to alleviate pain. In 2001, efforts were made to prevent new chronic users in the population by limiting starters of the drug. Statin is a drug introduced in 1994 and shown to be effective at reducing cardiovascular disease at ages 40 to 70. In 2002 studies showed it to be effective also at age 70+.

Research approach
Literature on prescription drug use is used to build a framework in which age is a proxy for physiological age (health) and social age (behaviour associated with age), period is a proxy for policy change, cultural change, publicity and epidemiological changes that occur in calendar time, and cohort is a proxy for the socio-cultural and physical experiences of a generation. Sex represents the gender aspect of prescribing. On the basis of this framework hypotheses were formulated. A drug registration database (IADB.nl) containing information on 500,000 individuals annually is used as the data source. User prevalence (users per 1000 population) is used as the primary measure of this study. The study population consists of males and females between 18 and 85 years of age and born in the period 1911 and 1988. The primary methods of study are descriptive graphs and APC models. Graphs are made of age-standardized user prevalence trends, age-specific trends within each period (AP) and within each cohort (AC). In the latter, location within calendar time is also highlighted when relevant

(APC). APC models are built using the classical approach by Clayton & Schifflers in which age, non-linear period and non-linear cohort are modelled as categorical variables in addition to the common linear component of cohort and period (drift).

Hypotheses

Based on the literature, and during operationalization, hypotheses were formulated. General hypotheses are: a) The user prevalence will increase with age as health deterioriates with age; b) Cohorts born during the First and Second World War will have more users than neighbouring cohorts; c) Post-war cohorts (1946+) will have higher user prevalence than pre-war cohorts due to different formative experiences.

Benzodiazepine specific hypotheses are: a) female user prevalence is higher than male user prevalence; b) The user prevalence of cohorts increases over time as number of users within a cohort accumulate due to addiction; c) Due to policy change the increase in user prevalence within cohorts is curbed from 2001 onwards. This will result in a decline from 2001 onwards.

Statin specific hypotheses are: a) Male user prevalence is higher than female user prevalence; b) The increase of user prevalence should become stronger in 2000; c) Before 2002 there will be a low user prevalence at ages 70+, after 2002, due to insight change, this will increase and this effect will strengthen in 2006; d) There will be less growth in user prevalence in 2007 due to negative publicity.

Results

Benzodiazepine: prevalence is higher for women than for men. The prevalence increases with age and decreases over calendar time starting from 2001 onwards. The effect of an important guideline change in 2001 affects especially young cohorts. Some cohorts born during the two World Wars have lower prevalence than surrounding cohorts, especially for males. Older cohorts have higher prevalence at the same ages as younger cohorts. User incidence levels indicate accumulation of users within cohorts. The APC model shows an increase with age, a dip for the 1917-1919 cohort for males and a dip from 1932 (males) and 1941 (females) to 1964.

Statin: user prevalence is higher for men than for women. The user prevalence increases with age. Prevalence increases strongly over calendar time but stagnates from 2006 onwards. The effect of an important insight change on age 70+ around 2002 is not found. There is no clear effect of the World Wars on cohorts. The 1930 cohort represents a peak in prevalence and its becoming older dominates the trend of statin prevalence. The APC model shows similar trends: an increase of prevalence with age and period, and a peak in prevalence for the 1930 cohort which declines slowly towards younger cohorts.

Discussion and conclusion

The results of the age variable are very clear and largely fit the hypotheses. This is likely the case because age is a good proxy for population health: as age increases, health deteriorates and more persons start using drugs. The hypotheses regarding period effects are partially rejected: the guideline change for benzodiazepine only appears to affects young cohorts and the effect of the insight change on statin is possibly obscured by a much stronger cohort effect affecting the relevant age range. The hypotheses regarding non-linear cohort effects are also partially rejected: cohort effects for the World Wars are only partially found. There is little evidence of post and pre-war cohort effects. Another important cohort effect, namely that of the 1930 cohort of statin users, which was not expected, was found. An age-period-cohort framework is considered a useful framework for studying trends in drug prescription.

Age, period and cohort effects in the prescription of benzodiazepine and statin in the Netherlands 1994 – 2008.

Author:
M.J. Bijlsma (s1650564)

Supervisor:
dr. F. Janssen

Master's thesis Research Master Regional Studies
Graduate School of Spatial Sciences
Faculty of Spatial Sciences
University of Groningen

Groningen, August 2011

Foreword and acknowledgements

"Geographers map space,
demographers map time."
– prof. dr. L.J.G. van Wissen

A Master's thesis on trends in users of prescription drugs may seem like a strange way to finish a two-year Research Master's programme in which I specialized in Population Studies. What do demography and pharmacoepidemiology have in common? By using the above citation I hope to show that the chosen topic is not so strange after all: demographers study population dynamics, but by doing so they have developed a methodology in which time plays, implicitly and explicitly, a central role. The rest of my thesis will hopefully prove to the reader that the application of techniques from demography to pharmacoepidemiology can both be very interesting and very fruitful.

While the Master's thesis is officially half a year's work in terms of credits, working on the Master's thesis starts from day one of the Research Master programme. A lot of individuals have, in one way or another, helped me by providing input, data, ideas or criticism and should therefore be thanked. I will start by mentioning my parents because it seems chronologically appropriate: existence is, of course, a prerequisite to finishing a Master's thesis. More academically, I should start by thanking my supervisor dr. Fanny Janssen for providing me with essential input needed to shape this thesis. Also of the Population Research Centre should be thanked prof. dr. Inge Hutter for mentoring me in the first year of my Master's studies and prof. dr. Leo van Wissen for providing input such as citations with which to start a foreword. The coordinator of the Research Master prof. dr. Philip McCann should be thanked for being inspiring both professionally and personally. Of the Department of Pharmacy should be thanked prof. dr. Lolkje de Jong-van den Berg for her input and enthusiasm regarding my first ideas on this topic, prof. dr. Eelko Hak (more on him later) and of course the staff of IADB, Sipke, Jens, Bert and Marieke, for providing excellent data and helping me with my queries. I also visited the Centre for Population Change and the Department of Social Statistics and Demography in Southampton during the writing of my thesis. In particular, dr. Sabu Padmadas and dr. Andrew Hinde deserve my thanks for their great help during the analysis phase. Finally, in order to keep these acknowledgements chronologically appropriate, Fanny Janssen and Eelko Hak should be mentioned again for seeing potential in my research: they have supported my successful bid for an Ubbo Emmius grant at the Faculty of Mathematics and Natural Sciences. This thesis serves as the basis of the following four years of my PhD research.

Table of contents

Figures

Tables

Chapter 1. Introduction

Demography is the scientific study of human populations (Weeks, 2005). More specifically, demographers study the (change in) size, structure, characteristics and geographic distribution of populations. The structure of a population refers to its composition in terms of sex and age and is affected by just three processes: birth, death and migration. Together these processes are termed "population dynamics". In the early years of demography as a discipline, population dynamics were mostly studied quantitatively by a branch named formal or analytical demography. This tradition of quantitative analysis goes back at least as far as 1662, when John Graunt, the "father of demography", analyzed the Bills of Mortality (Weeks, 2005; Newell, 1988). While population dynamics are also studied using qualitative techniques, which have contributed to establishing demography as a scientific discipline, this thesis will look at the application of techniques from analytical demography to the field of pharmacoepidemiology.

Pharmacoepidemiology studies the use of drugs in large populations, in particular their beneficial or adverse effects (De Vries & De Jong-van den Berg, 2009; Strom, 2005a; Strom 2005b). Drugs are defined as chemical substances used to prevent, diagnose, cure or treat disease, or to enhance physical or mental well-being. Due to a series of international calamities during the twentieth century, such as birth defects as a result of the use of thalidomide by pregnant mothers (during the 1960s), drugs became subject to more strict pre-marketing study in many countries (Strom, 2005a; Strom, 2005b). Rigorous pre-marketing tests such as the randomized clinical trial now exist. However, it is considered important to monitor the effects of drugs after the introduction into the general population as well. For example because the demographic profiles of pre-marketing and post-marketing users may differ (De Vries & De Jong-van den Berg, 2009). Therefore, drugs are also studied after their introduction into the general population. Post-marketing drug surveillance is the primary purpose of pharmacoepidemiology (Strom, 2005a).

Pharmacoepidemiology is a relatively new discipline, merging clinical pharmacology with epidemiology. While existing in some form since at least the second half of the twentieth century, it can be said that pharmacoepidemiology has only recently become an independent discipline with its own journals (Strom, 2005b). In the study of populations, pharmacoepidemiology may benefit from demography by adopting some of its methodological tools and techniques. Demographers have studied open populations since the founding of the discipline, which means they should be able to add expertise on drug use in open populations as well. For example, through standardization methods the composition of a population can be controlled, making it easier to identify effects that are the subject of research. Demographic methods of indirect estimation or of assessing data quality are likely of use to pharmacoepidemiology as well. Furthermore, demographers practice population forecasting. As drug prescription is strongly related to population dynamics (e.g. population ageing), demographic theory and methodology may improve estimations of future use of, and expenditure on, prescription drugs. This list could be extended, but instead the author opts to demonstrate the usefulness of combining demography and pharmacoepidemiology through this study.

There is relevance to studying drug prescription in general and using a demographic perspective on drug prescription specifically. In the Netherlands, in 2009, 40% of the population had received at least one prescription drug (Statistics Netherlands, 2011). These drug utilization figures do not fluctuate much between years, but have increased every subsequent year since at least the 1990s (Statistics Netherlands, 2011). As drug prescription is strongly affected by age, and the population of the Netherlands is ageing, some of this increase is likely the result of the changing age structure of the Dutch population, and therefore highly related to demography. However, age-specific rates have also increased over the years (Statistics Netherlands, 2011) which means there is an increase independent of age composition as well. This effect could, in part, be attributed to changes in policy, such changes in the prescription criteria or changes in drug prices. Next to policy relevance, and in part tied to policies, there is economic relevance. For example, in the Netherlands in 2007, total expenditure on (non-illicit) drugs is estimated at 5.6 billion euro (Suykerbuyk & Tjoeng, 2005). Part of this expenditure is financed by government subsidies, part by (health) insurance companies, and part by the consumer. More accurate projection methods, as mentioned earlier, are a useful tool for such actors in estimating their future expenditure. In order to create reliable projections of future users in the Netherlands, current factors affecting trends in prescription drug use need to be found and explained first.

This study aims to investigate and subsequently demonstrate how techniques from demography can aid and improve pharmacoepidemiological investigation using a case study of trends in the use of two drug types, namely benzodiazepine and statin in the Netherlands over the period 1994-2008. Benzodiazepine is used to alleviate anxiety and pain, but it also has addictive qualities (Ashton, 2009; Gorgels et al., 2001). Statin is used to lower cholesterol levels in the blood and thereby lower the probability of cardiovascular incidents (SFK, 2010). Both drugs were chosen because they have a large number of users, because they have recently undergone guideline changes, and because there are few scientific studies into trends of users (including the effect of guideline changes) of these drugs. As will be detailed in the following chapter, the addictive qualities of benzodiazepine led to a large number of chronic users in the population (Gorgels et al., 2001). One in three users of benzodiazepine is a chronic user (three percent of the Dutch population). This is a substantial burden on the Dutch health care system (Van Eijk et al., 2009; Rooijmans et al., 1999). Through a guideline change, the number of chronic users should be reduced. How effective was this guideline change in reducing (chronic) use of the drug? If it is effective, how long will it remain so? Statin is a newly developed drug, having been introduced in the general population in the 1990's and its use has been increasing since then. Statin is an expensive drug (SFK, 2010), one type of statine, Atorvastatine (Lipitor), was in the top ten of drugs with the highest annual turnover in the Netherlands in the last five years. In 2009, for example, its turnover amounted to 146 million euro (SFK, 2010). In 2002 statin underwent a guideline change which should result in an increase of users at old age (NHG, 2010). However, some studies report that statin use is still low at older ages even after the guideline change (e.g. Ohlsson et al., 2005). This is problematic because at old age the benefits are possibly the greatest (Geleedst-De Vooght et al., 2010). How long will the increase in statin users continue? At what ages is statin used especially and does this age-pattern change over time? All of the previous questions are of

relevance to health authorities, pharmacists, health insurance companies, general practitioners and even the population of (potential) users. All of the previous questions require insight into trends of users of these drugs.

There are few studies of trends in statin use (e.g. Walley et al., 2005), and even less in a Dutch context (e.g. Geleedst-De Vooght et al., 2010), likely because it is a new drug. More trend studies exist on benzodiazepine (e.g. Magrini et al., 1996; Tu et al., 2001; Van Hulten et al., 2003), however it is a (much) older drug and not all studies are very recent. Furthermore, for both drugs, those studies that do exist are cross-sectional, which is the conventional method of trend studies in (pharmaco)epidemiology: trends over time are compared between different age groups. Such a design masks what are called birth cohort effects (Glenn, 2005). Individuals born in the same period (birth cohorts) have, at the population level, similar trajectories in life. In demography (e.g. Susser et al., 2001) but also in epidemiology (e.g. Janssen et al., 2005) such effects were shown to be of influence on (health) trends. Since drug prescription is a response to health (detailed in the following chapter), it is likely that cohort effects are of importance in drug prescription trends as well. Therefore, this study aims to explain trends of users of benzodiazepine and statin by looking at age, period *and* cohort; the study aims to apply an age-period-cohort (APC) framework. This means the study will attempt to attribute changes in trends to the effects of age, such as deteriorating health that comes with increasing age, to the effects of period, such as guideline or insight changes, and the effects of birth cohort, such as cultural or health differences between generations.

The main research question of this study is therefore:

What are the effects of age, period and cohort on trends of users of benzodiazepine and statin in the Netherlands in the period 1994 - 2008?

In order to answer this question and its implications, the following objectives are set:

1. Construct a theoretical and analytical framework using age, period and cohort effects, with which to study drug prescription.
2. Formulate hypotheses on trends of benzodiazepine and statin using the theoretical and analytical framework and the background literature as a basis.
3. Specify an APC model with which to study trends in drug prescription.
4. Describe the observed effect of age, period and cohort on drug prescription in the Dutch population, by sex.
5. Determine whether the observed effects of age, period and cohort correspond with the hypothesized effects in order to assess the usefulness of an APC-framework.

The following subquestions need to be answered to meet the objectives and thereby answer the main question:

1. What are the effects of age, period and cohort on the prescription and use of benzodiazepine and statin in the Netherlands in the period 1994-2008 according to the literature?
2. What methods are used to study age, period and cohort?

3. What are the effects of age, period and cohort for benzodiazepine and statin according to descriptive analysis?
4. What are the effects of age, period and cohort for benzodiazepine and statin according to APC models?
5. Do the observed effects of age, period and cohort correspond to the hypothesized effects of the literature?
6. Is an age-period-cohort framework a useful framework for studying trends in drug prescription?

The structure of the thesis is as follows. The literature review on drug prescription in general and benzodiazepine and statin specifically will be described in chapter 2. Chapter 3 details the research approach, moving from the epistemological position to conceptualization and operationalization and finally to the methods and the hypotheses. Chapter 4 provides in-depth information on the measures and methods used in this study. Chapter 5 shows the results of the study. Finally, in chapter 6 the study is discussed, which includes a summary of the most important results, a critical evaluation of the data and methods, an interpretation of the results, recommendations for further research and policy, and a conclusion.

Chapter 2. Literature review

This chapter describes the literature regarding drug prescription. First, the general factors affecting drug prescription are detailed and inventoried by age, period and cohort, but also by gender and socio-economic status, in section 2.1. Most of its subsections will also refer to the situation in the Netherlands. Secondly, section 2.2 details the literature on two specific drug types, namely benzodiazepine and statin. The general and specific effects detailed in this chapter will be ordered in an analytical framework in the next chapter.

2.1 General factors affecting drug prescription

Drugs are defined as chemical substances used to prevent, diagnose, cure or treat disease, or used to enhance physical or mental well-being. According to this definition, the physical or mental state of an individual is likely the most important predictor of drug prescription. For example, an individual may have certain risk factors for the development of a disease and is therefore prescribed a drug to prevent the disease (Midlöv et al., 2009), such as prescribing a drug to prevent cardiovascular incidents to persons with high cholesterol levels in the blood. This relates strongly to age effects as health commonly deteriorates with increasing age as described in subsection 2.2.1. It, however, also relates to calendar time: e.g. increasing time may bring new inventions to cure a disease, or a new strain of disease may emerge (Omran, 1998). A number of general period effects are described in subsection 2.2.2. In demography, 'cohort' refers to a group of units (commonly individuals) that experience a particular event (e.g. birth or marriage) during a specific time interval (Preston, 2008). In this study, cohort refers the aggregate of individuals born in the same period (a generation) as they move through time (as they age) (Pressat, 1993). Some cohorts are more or less healthy than others due to historical circumstances, others may be more pro-active and demanding to doctors. These 'cohort effects' will affect drug prescription trends. Cohort effects are described in subsection 2.2.3. In the literature some factors were found that could not be categorized as age, period or cohort effects. These are the effects of gender, described in subsection 2.2.4, and the effects of socio-economic status and ethnicity, described in subsection 2.2.5.

2.1.1 Age effects

Health and disease are strongly tied to age. For example, some diseases are more common at younger ages and some at older ages. This will affect age-specific prescription trends of drugs developed to detect, treat or cure specific diseases. Furthermore, while the health status of individuals may vary across life, health is strongly tied to age in populations (Hobcraft, 1982). Common diseases such as diabetes, cancer and cardiovascular disease are examples of diseases with a higher prevalence at older ages. This is reflected in drug prescription trends, with more persons at older ages getting drugs prescribed than those at younger ages (Midlöv et al., 2009).

The beliefs of individual doctors will also affect drug prescription. Denig & Haaijer-Ruskamp (2009) write that doctors are less likely to prescribe to younger persons, even if they have the same symptoms as older persons. This is the case as doctors often believe younger persons to have a better prognosis of recovery, therefore not needing the aid of drugs.

Regardless of the exact combination of factors that determine drug prescription as related to age, the Foundation for Pharmaceutical Statistics (SFK, 2008) writes that in the Netherlands persons older than 65 get three times as many prescriptions than average, and persons aged 75+ four times as many. The age group 65+ is also the group in which most drugs are prescribed chronically; four out of five prescriptions are repeat-prescriptions.

2.1.2 Period effects

Period effects are effects that can be attributed to changes in calendar-time. One of the most well-known theories on the relation between health (and thereby drug prescription) and time is the epidemiological transition theory (Omran, 1998). The types of diseases that are prevalent in a population can change over time. Infectious and parasitic diseases have strongly declined in Western countries in the 19th and 20th centuries. This has allowed more persons to survive to older ages where they are more likely to suffer from chronic, degenerative and man-made diseases. It is clear that this affects drug prescription: as explained earlier, the types of diseases that are prevalent will be influence the types of drugs used. However, drug use does not merely follow disease patterns. The underlying trend in disease is also determined by drug use itself: for example, advances in medicine, such as the discovery and subsequent availability of antibiotics (post-WWII), helped further reduce infectious disease in populations.

The prescribing behaviour of doctors will, of course, also affect drug prescription trends. An important factor affecting prescribing behaviour and that could be termed a period effect is government policy as it changes through time. In the Netherlands, the system of health insurance has recently changed. As an incentive for more competition between health insurance companies, the health insurance system was changed on January 1, 2006, with the passing of the 'Zorgverzekeringswet'. Before 2006, drug pricing had little effect on prescription behaviour in the Netherlands. Since 2006, patients will have to pay part of the costs of some drug types. Doctors have been shown to avoid prescription of these drugs if possible, preferably prescribing drugs for which the costs are covered (Denig & Haaijer-Ruskamp, 2009).

Another period effect would be the culture of a country as it changes over time (SCP, 2010). Dutch natives may attempt to persuade their doctor to get a drug treatment they want. In Western countries, from the 1970s onwards, the doctor has steadily lost authority, while the patient has become more demanding (Furedi, 2008; Mol & Van Lieshout, 2008). With the rise of the internet, patients can now diagnose themselves online. This has been used as a tool by pharmaceutical companies to actively affect the doctor-patient relationship: companies now market their products directly to the consumer through so-called 'disease awareness campaigns' (Woloshin & Schwartz, 2006). It is based on the active patient that demands the marketed product from their doctor (Woloshin & Schwartz, 2006; Moynihan et al., 2002). Note that while culture changes over time, culture is also partly a cohort effect, as values instilled in persons during childhood will be carried with a birth cohort as it ages (SCP, 2010). This is described in the following subsection.

Companies will send 'pharmaceutical consultants' to doctors to market their products (Denig & Haaijer-Ruskamp, 2009; De Jong-van den Berg & De Smit, 2009). Also,

pharmaceutical companies may finance education of doctors, in order to influence their prescription behaviour. Such strategies are found to be successful (Denig & Haaijer-Ruskamp, 2009). But publicity may also be negative. For example, the third generation oral contraceptive gained negative publicity when it became apparent that its use had more severe adverse side effects than the second generation oral contraceptive (De Jong-Van den Berg et al., 2003). This has affected trends in prescription of the third generation oral contraceptive.

2.1.3 Cohort effects

Persons are shaped by the socio-cultural environment and historic events of their childhood. For example, persons born in the 1920s had different formative experiences than persons born in the 1960s (SCP, 2010). Persons would be affected in their behaviour through, for example, the educational system of their time, but also in their health, for example through the nutritional customs prevalent in their childhood. Generational differences are more likely to be of a continuous than of a discrete nature, making it problematic to precisely mark the start and end points of a generation (SCP, 2010). Behavioural and health effects are believed to stay with a generation as it ages, influencing how they experience life at older ages, and affecting trends even at later points in time, until the members of the cohort have died. For this reason Kuh and Davey Smith (1990) write that some researchers consider year of birth to be a more important determinant of mortality risk than year of death. Finding cohort effects, then, becomes important for forecasting of future trends as well, as many members of cohorts alive today will also be alive in the future.

The Barker Hypothesis, also known as the fetal origins hypothesis, states that adult health can be influenced by factors originating during fetal development (Roseboom et al., 2000). Studies show that nutritional deficiency of mothers during pregnancy can adversely affect the health of the child in later life. For example, there is an increased risk of cardiovascular disease (Roseboom et al., 2000), congenital anomalies and schizophrenia spectrum disorders (Hoek et al., 1998). Among others, this was found to be the case for persons who had been *in utero* during the 'Dutch Hunger Winter' (Roseboom et al., 2000), born in 1945 and 1946. This may have affected trends in drug prescription as well. Authors from the Foundation for Pharmaceutical Statistics noted that there were clear spikes in prescriptions of persons born in 1946 and 1919 (SFK, 2004). In both cases this pertains to persons born directly after the end of the First and Second World Wars, whose mothers would have been pregnant with them during periods of famine. Mazumder et al. (2010) and Almond (2006), however, attribute the negative health effects that can be found in the 1918-1919 cohorts in various countries to *in utero* exposure to influenza during the influenza pandemic of that period. Van den Berg et al. (2006) also write about the impact of this pandemic on the Netherlands specifically.

Finch & Crimmins (2004) show a link between health in early life and health in later life. Persons that experienced major illness during early childhood have a greater risk of cardiovascular disease, cancer and chronic lung conditions later in life. These effects persist even if epidemiological conditions improve in later periods. Finch & Crimmins (2004) refer to such health effects that are rooted in health at early life and in turn rooted in the historical conditions in which a generation grew up as the 'cohort morbidity phenotype'. It is plausible

that the effect of the Dutch Hunger Winter would therefore not be limited to those cohorts that were *in utero*. Young children could have a greater risk of morbidity due to malnutrition in that period.

Individuals born after the Second World War benefit from medical advances, such as antiobiotics, and from protection provided by the Welfare state (Willets, 2004). Paes & Smit (2009) write that, due to the progression of medical knowledge and capabilities, persons in younger cohorts, who would have died at an early age due to medical complications, will now survive to become adults with chronic morbidity. This would result in younger cohorts having more prescriptions at the same ages as older cohorts, as each cohort would have a larger proportion of 'unhealthy' persons compared to the past. In contrast, but using similar reasoning, Willets (2004) writes that cohorts born after the Second World War are more healthy than pre-war cohorts. Pre-war cohorts experienced economic depression and war, whereas post-war cohorts benefitted from the Welfare state, a buoyant labour market and better education.

Finally, there may be differences in behaviour between cohorts due to growing up in a different socio-cultural environment. For example in the Western world, including the Netherlands, various time-periods have been characterized differently (SCP, 2010). This would result in a different worldview and consequently in different behaviour. Evandrou and Falkingham (2000) show evidence for behavioural and (consequent) health differences between cohorts due to growing up in a different political, economic and cultural historical context. The cohort growing up before the second world war experienced unemployment and eventually war. Those experiencing formative years after the war lived in economic prosperity and safety, thereby involving themselves more with non-material affairs such as personal development (the so-called 'post-materialist' orientation) (SCP, 2010). It may be of note that the first cohort of persons of a post-materialist orientation reached their young adulthood during the 1960's and 70's. This coincides with a period of cultural change, including the rise of anti-authoritarian attitudes also discussed in the subsection on period effects. Cultural differences between cohorts in their perception of medicine may lead to different trends in users between cohorts and may result in guideline changes affecting different cohorts differently. Cultural differences in other behaviours, for example exercise or smoking, may also cause cohort differences in drug prescriptions through its effect on health.

2.1.4 Gender

In the Netherlands, more women get drugs prescribed than men (Denig & Haaijer-Ruskamp, 2009). Paes and Smit (2009) write that women visit the general practitioner on average 1.3 times more than men do. Part of the higher prescriptions for women can be explained by female-specific issues; thirteen percent of all general practitioner consults are of gynaecological or obstetric nature (Paes & Smit, 2009). However, according to the Foundation for Pharmaceutical Statistics (SFK, 2007), difference in prescriptions can partly be explained through the higher life expectancy of females. When looking at specific drug-types on their own, the effects of sex become even stronger. Some types of drugs aimed at preventing or treating cardiovascular diseases are prescribed more to men than to women (Denig & Haaijer-Ruskamp, 2009). Women, on the other hand, are much more likely to

receive benzodiazepines (a pain killer, see also sub-section 2.5.1), even if symptoms do not justify prescription of this drug. This may be due to communication differences: women are more likely to present their symptoms in a social context, which results in a different diagnosis than men would (Denig & Haaijer-Ruskamp, 2009; Hall et al., 1994). Men are referred to a specialist while women receive a prescription.

2.1.5 Socio-economic status and ethnicity

The socio-economic status or ethnicity of a patient can influence drug prescription. According to Denig & Haaijer-Ruskamp (2009), Morrocans in the Netherlands have a different expectation of their general practitioner, and will more likely put pressure on their general practitioner to receive drugs, than would Dutch natives. Furthermore, due to cultural differences the number of general practitioner visits resulting in a prescription is lower than in surrounding countries (Denig & Haaijer-Ruskamp, 2009). Ailments that in the Netherlands are seen as a nuisance, therefore not requiring medical care, are reasons to visit a doctor -and receive a prescription- in surrounding countries. For example, Dutch natives are more likely to describe certain symptoms as the 'common cold' while Belgian persons would describe the same symptoms as bronchitis. Belgians would then be more likely to put pressure on their general practitioner to receive antibiotics, as that is the accepted treatment for bronchitis (Denig & Haaijer-Ruskamp, 2009).

The socio-economic status of patients was found to affect drug prescription even when the relation between (physical and mental) health and sex is controlled for (Denig & Haaijer-Ruskamp, 2009). Patients with a low socio-economic status are more likely to get drugs prescribed than others. Research also shows there is an almost linear relation between education and drug prescription when controlling for sex and age (RIVM, 2008).

2.2 Specific drug types

In this section, the literature regarding two specific drug types, benzodiazepine (subsection 2.2.1) and statin (subsection 2.2.2), is described.

2.2.1 Benzodiazepine

Benzodiazpine is a drug used to relieve anxiety, promote sleep and relax muscles (Ashton, 2009). It is a drug that acts on the nervous system, therefore it belongs to the anatomical group N of the ATC-classification (WHOCC, 2010). Specifically, the codes for benzodiazpine are N05BA (anxiolytics: benzodiazepine derivatives) and N05CD (hypnotics and sedatives: benzodiazepine derivatives). Benzodiazepine is among the highest used drugs in the Netherlands. In the period 2002 – 2006, the number of users was approximately 1.4 million (Geers et al., 2009).

One of the major problems of benzodiazepine is that its users may develop physical and mental dependence on the drug (Gorgels et al., 2001), resulting in chronic use. Both in the Netherlands and Sweden one in three users of benzodiazepine was a chronic user in the 1980s according to Van Hulten (2003). Near the change of the millennium the number of chronic users remained at one in three (Oude Voshaar, 2003). Geers et al. (2009) write that chronic use of benzodiazepine is one of the largest problems in prescription drug use in the

Netherlands. Chronic use leads patients to become insensitive to the drug, thereby reducing its effectiveness. The negative side-effects, however, remain. These include memory loss and an increased probability of falling due to drowsiness, especially in the elderly (Geers et al., 2009; Glass et al., 2005). Dependence syndrome can include symptoms such as of shakiness, insomnia, nausea, headaches and lethargy (King et al., 1992). Next to dependence, patients may request repeat prescriptions because the underlying cause of anxiety or insomnia is not removed but its symptoms merely suppressed by the drug. Van Hulten (2003), on the other hand, reports that dependence on benzodiazepine seems not to be affected by the underlying mental or physical state of a person. Patients commonly only require an initial prescription for benzodiazepine in order to receive repeat prescriptions (Van der Waals et al., 1993): repeat prescriptions are often issued by an assistant who does not re-evaluate the patient's continuing need for benzodiazepines (Niessen et al., 2005; Dijkers 1997). Guideline changes have occurred in order to curb dependence and chronic use. These are detailed below. A preferred method currently is to limit the number of first users and to prevent the development of dependence in new patients through guidance and education (Geffen et al., 2009).

There is a notable sex difference in the prescription of benzodiazepine: use among women is twice as high as it is among men (Rooijmans et al., 1999; Van der Waals, 1993). Men were also more likely to quit the use of benzodiazepine according to Niessen et al. (2005), though they report this conflicts with other studies. Rooijmans et al. (1999) also reports that women are more likely to be chronic users. Tu et al. (2001) suggest that women have a higher incidence of anxiety, insomnia and symptoms of depression. These are indications for which the drug is prescribed. Van der Waals et al. (1993), on the other hand, report that more women than men are given benzodiazepines for conditions other than anxiety, stress and insomnia; they conclude that general practitioners are less strict when initially prescribing benzodiazepine to women. The problem then persists as repeat prescriptions are continued by an assistant without a re-evaluation. Williams et al. (2003) writes that women are more likely given therapy to relieve symptoms (e.g. anxiety) while for men the underlying cause of the symptoms is researched. Bogunovic et al. (2004) report that women that have developed a dependence on benzodiazepine may not be diagnosed with dependence (a misdiagnosis). Therefore they continue with chronic use longer than men.

The use of benzodiazepine increases significantly with age (Bogunovic et al., 2004). An Italian study shows prevalence levels which increase roughly with age (Magrini et al., 1996). Elderly persons are also more likely to use benzodiazepine chronically (Bogunovic et al., 2004). Bogunovic et al. suggest this is likely caused by elderly suffering more from chronic pain, depression and isolation. However, they note that there have only been a few studies of the prevalence of benzodiazepine abuse in the geriatric outpatient population. Fitting the above, Niessen et al. (2005) report that younger patients are more likely to stop using benzodiazepine than older persons.

Prescription of benzodiazepine underwent changes over time. Benzodiazepines were introduced in the 1960's (Rooijmans et al., 1999). Originally they were seen mostly positively and as having few negative side effects. However, within the same decade as its introduction persons developing physical and mental dependence on the drugs occurred more often than originally thought (Rooijmans et al., 1999). Other negative effects, such as drowsiness, falling

and traffic accidents were also receiving more attention. While the dependence on benzodiazepines was found in the 1960s, it was not until the 1970s that warnings against overprescribing appeared and not until the 1980s that it became seen more and more as a serious concern (King et al., 1992). In industrialized countries the use of benzodiazepine peaked in 1979 according to King et al. (1992), after which a slow decline set in. In the 1980s and 1990s doctors warned their patients against taking benzodiazepines regularly and against using for longer than a few weeks, but many patients did not heed this advice (Rooijmans et al., 1999): in the 1990s 3% of the total adult population of the Netherlands used benzodiazepines chronically. King et al. (1993) writes that most decline occurred because the number of new users declined while a core of chronic users kept using the drug. In the Netherlands in the 1990s there was also a decline of benzodiazepine use (Rooijmans et al., 1999). Nevertheless, in this period benzodiazepine was still one of the most prescribed drugs (Niessen et al., 2005), and they still are. In the Netherlands, the debate and research on reducing chronic use of benzodiazepine was reinvigorated by a report of the National Health Council in 1998 (Rooijmans et al., 1999; Gezondheidsraad 1998). The report detailed the use of the drug and its adverse effects: the report advised to use benzodiazepine with short duration and educating patients about risks of use. Importantly the report suggested more research on preventing chronic benzodiazepine use (Rooijmans et al., 1999). The report did not go into detail on the development of dependence because, Rooijmans (1999) supposes, little was yet known about these mechanisms. A number of Dutch studies on preventing the development of addiction or dependence on benzodiazepine are done in the following years with important publications in 2001 (e.g. Gorgels et al., 2001). In 2001, doctors are advised to prescribe benzodiazepine sparsely and to keep the treatment period below two months (CVZ Farmacotherapeutisch Kompas, 2010). In order to increase patient adherence to these guidelines, computer programmes were written to aid pharmacists in detecting and guiding first and second users with their use (Blom et al., 2007). This is aimed at reducing the number of new users and in preventing first users from becoming chronic users (Geffen et al., 2009).

2.2.2 Statin

Statins are classified as C10AA (HMG CoA reductase inhibitors) of the ATC classification (WHOCC, 2010). Statins are drugs which lower cholesterol levels in the blood and are used in the primary prevention of cardiovascular disease (SFK, 2010). Individuals are prescribed statin if they meet certain criteria for being at risk of cardiovascular disease, such as having renal complications or cholesterol levels that are too high (Smulders et al., 2008). Since it is highly unlikely for individuals to leave the cardiovascular risk category, most individuals that start using statin become permanent users. Like benzodiazepine, statin is one of the highest prescribed drugs in the Netherlands (SFK, 2010).

In the Netherlands (Geleedst-De Vooght et al., 2010) but also in other countries (e.g. Williams et al., 2003) more men than women receive a prescription for statin. The primary cause is likely that men have a higher risk of cardiovascular disease (e.g. NHG, 2010). However, Williams et al. (2003) write that, in Ireland, there appears to be a social bias in prescribing as well. Chest pains and anxiety in women are less often believed to be related to cardiovascular disease than in men, more women than men therefore receive symptomatic

therapy, namely anxiolytic benzodiazepines to reduce anxiety, instead of statin therapy (Williams et al., 2003). It is possible that the same occurs in the Netherlands: Denig & Haaijer-Ruskamp (2009) report similar gender biases in prescription in the Netherlands in general.

The use of statin is increasing: in the past decade, its use has grown thirteen percent on average annually (SFK, 2009). Statin is a very new drug, having been introduced in the 1990s (Walley et al., 2005), which partly contributes to the growth of statin as the drug goes through the first stages of the marketing cycle. Another part of its growth can be attributed to population ageing: the 'babyboom' generation reaches older ages which results in an increased number of persons with a heightened risk of developing cardiovascular disease in the Dutch population (SFK, 2010). Another part of its growth can likely be attributed to guideline changes.

Statin was introduced in Western Europe in the first half of the 1990s (Walley et al., 2005). Since its introduction, the prescription trends of statin have increased strongly. In the past two decades a number of events have occurred which should have affected its prescription trend. The most important of these events regards the age range of its users. The initial studies that showed the effectiveness of the drug in reducing cardiovascular disease focused on the 40 to 70 year age range (Geleedst-De Vooght et al., 2010). In fact, in the Netherlands, the 1998 CBO (Dutch Institute for Healthcare Improvement) guideline 'Cholesterol' advised not to prescribe statins to persons aged over 70 because the protective qualities of the drug for this age group were not proven (NHG, 2010). Therefore, the initial users of the drug were especially within the 40 to 70 age range. However, in 2002 important studies showed that statins also reduced cardiovascular disease at ages older than 70 (Heart Protection Study Collaborative Group, 2002; Shepherd et al., 2002). Nevertheless, the increase in prescribing at older ages did not seem strongly affected by these studies: prescriptions remained low at older ages (Geleedst-De Vooght et al., 2010). A study by Ohlsson et al. (2005) reports a similar lack of effect in Sweden. Geleedst-De Vooght et al. (2010) reports this to be problematic: trial results show that elderly with the highest cardiovascular disease risk benefit the most from statin therapy and since the baseline mortality risk is higher at older ages the number needed to treat to get an effect is lower. Possible reasons for the lag in prescription at older ages are lingering doubts about benefits of the drug at older ages, cost effectiveness, negative side effects (for example, see Hippisley-Cox & Coupland, 2010) and polypharmacy (Geleedst-De Vooght et al., 2010). In 2006 the new guideline for prescribing statins named 'Cardiovasculair risicomanagement' (NHG, 2010) was formally released: the age restriction on prescribing statins was removed as the evidence for its effectiveness at older ages was found to be compelling. In order for this guideline change to be more effective, pharmacists and general practitioners participated in a kick-off meeting to discuss the importance of adherence to the guideline. In the new guideline it was also agreed to start prescribing to patients with diabetes, depending on their cholesterol level and life expectancy (Geleedst-De Vooght et al., 2010).

Next to the above studies and the related guideline changes, some other events may also affect the time trend of statin users. Firstly, in the year 2000, in an effort to increase the prescribing of statins to protect against cardiovascular disease, the Health Council of the

Netherlands advised the minister of Public Health to prescribe statin preventively to persons with a higher than average blood cholesterol level and persons suffering from cardiovascular disease or diabetes (SFK, 2003). Secondly, in March 2007, the programme 'Tros Radar' aired an episode with negative publicity on statin, in particular its side effects. This had a visible effect on the amount of quitters, which was increased by 35% (SFK, 2008). There was also a 33% decrease in the number of persons that started statin therapy in that year. This caused the number of statin users to decline for the first time in several years. However, the effect was only temporary, with an increase in prescriptions again in the second half of 2007 (SFK, 2008). Finally, Geleedst-De Vooght et al. (2010) reports a decline in prevalence in 2008, she attributes this, without absolute certainty, to the loss of a nursing home from the dataset and therefore does not provide an additional explanation.

Chapter 3. Research approach

This chapter describes the conceptual and operational parts of the study. The chapter starts with the foundation of scientific inquiry, namely the epistemological position from which the study is conducted, in section 3.1. Then the theoretical framework (section 3.2) and the analytical framework (section 3.3) are described. These frameworks direct the conceptualization in section 3.4. Moving to operationalization, the data source of the study is described in section 3.5. In section 3.6 the dependent variables of the study are chosen. With the background literature described, the frameworks constructed and the dependent variables determined, the hypotheses can be formulated in section 3.7. Finally, the methods used to test the hypotheses are described in section 3.8. In chapter 4 these methods are discussed in-depth.

3.1 Epistemological position

This study is conducted from the epistemological position of (post-)positivism. Scientists working from this paradigm look for universal laws through empirical observation. In social science this tends to mean statistical laws or 'general patterns' as the subject is less controllable than in the natural sciences. Additionally, researchers should seek to falsify hypotheses, as confirmation is impossible (Van den Bersselaar, 2003). Through falsification only strong theories will survive or become further specified. Falsification of hypotheses does not automatically lead to the rejection of an entire theory, as Kuhn has described (Kuhn, 1996). Instead, the process is slower. For social science, this is not a problem because social science hypotheses tested are of a probabilistic nature; it can be expected that deviations may occasionally test the rule. Note that positivism with amendments by Popper, Kuhn and others is sometimes referred to as post-positivism (Philips & Burbules, 2000).

While formally the epistemological position does not dictate the research subject or method (Flowerdew & Martin, 2005), in practice it appears that some epistemological positions fit better with some subjects and with some research methods. This fits the notion that methodology is applied epistemology (LPSG, 2005). As will be described in the following sections, quantitative data analysis is the method of choice in this research project. Data analysis is one of the research methods that fits a positivist-empiricist position in social science (Van den Bersselaar, 2003). While data analysis allows for less control than an experiment -especially an experiment in the natural sciences- it allows social scientists to find correlations and general patterns. This often includes the building and testing of statistical models. If a model fits the data well, it may be used for prediction (Van den Bersselaar, 2003). Furthermore, by interpreting a model using a theoretical and an analytical framework, the model can also contribute to understanding (explanation). Finally, the choice of a positivist paradigm is logical as it is likely that research findings coming from a positivist paradigm can most easily be communicated back to, and become accepted by, biomedical scientists (such as pharmacologists), as they work within the same paradigm.

3.2 Theoretical framework

The theoretical framework of this study is mostly informed by the epidemiological transition theory (Omran, 1998). The epidemiological transition theory describes changes in health patterns in societies over time: starting from 1) the stage of pestilence and famine, the theory describes how societies move to 2) the stage of receding pandemics then to 3) the stage of degenerative, stress, and man-made diseases followed by 4) the stage of declining cardiovascular disease, mortality, ageing and emerging diseases and finally 5) a prospective stage of aspired quality of life with persistent inequalities. Important for this study is that the epidemiological transition theory A) puts health changes in a historical explanatory framework and B) proposes macro-level sub-transitions as the main drivers of changing health patterns over time which emphasize the role of calendar time. Both of these aspects of the transition inform the age, period and cohort components of the research (and thereby the analytical framework).

In terms of the historical explanatory framework the research pertains to the second half of the third stage and the full fourth stage of the (Western) epidemiological transition. The third phase starts around 1850 and lasts approximately one hundred years (Omran, 1998), which means this phase is of relevance to the cohort component of this study. The fourth phase starts in approximately 1950, which means both the cohort and (entirely) the period component of this study take place within it. The relevant events that could affect drug prescription which occurred during these periods are described in the background literature and will be used to explain trends in the final chapter of this study.

The sub-transitions described by Omran (1998) are the lifestyle and educational transition, the health care transition and the technology transition, which in turn affect, among others, the demographic transition (for the latter see Kirk, 1996). Important is that these drivers contain both biomedical and socio-cultural explanations for changes in health patterns over time. These transitions and their explanations will also interact with one another. For example changing hygienic practices are part of a lifestyle transition and they are supported by technological transitions (e.g. increasing availability of soap and public sanitation). It is clear that drug prescription plays an important role in this theory as well: prescription drugs are a medical technology. Drug prescription can be a consequence of a (possibly unhealthy) lifestyle but drug prescription also affects lifestyles and (on a population level) health trends.

Through the subtransitions Omran (1998) implicitly mentions cultural change. As the literature review shows culture to be potentially an important determinant of drug prescription trends, cultural change should be placed more explicitly within the theoretical framework. While designed to explain demographic change, the Second Demographic Transition theory (Van de Kaa, 1988) describes cultural processes as a key driver for changes in society. In particular, it describes an increase of values such as individualism, self-actualization and rationalism in the 20th century. Other authors have shown that such values are related to drug prescription (or, more broadly, to seeking medical help) in particular to their increase (Furedi, 2008; Mol & Van Lieshout, 2008). Since these cultural changes can interact with technology and (certainly) lifestyle, as also described by Van de Kaa (1998) himself, it is unproblematic to add this component to the epidemiological transition theory. As with the historical context,

the relevant biomedical and socio-cultural effects on the drug prescription are described in the background literature and will be used to explain trends in the final chapter of this study.

Finally, the social theory by Coleman (1990) should be mentioned. Coleman describes how processes at the macro level can affect individual behaviour. Many individuals acting in a certain way will, in turn, affect macro level processes. The drivers of the epidemiological transition theory, the sub-transitions, are macro-level processes. For example, a guideline change in drug prescription (macro level) may cause doctors to prescribe less benzodiazepine to new patients (micro level) which in turns results in less chronic use of benzodiazepine in the population in the long term (macro level). While this study looks primarily at the effect of macro level drivers on macro level trends, the causal mechanisms work primarily on the micro level.

3.3 Analytical framework

Age, period and cohort can be used as proxy variables. In demography, age is sometimes used to measure physiological status (physical health) or exposure to social influences (Hobcraft et al., 1982). According to Hobcraft et al. (1982), age is a good measure of this. Although individuals age physiologically and socially at different rates, on a population level trends will become apparent. Period and cohort effects are further removed from the effects for which they serve as proxy. As described in the theoretical framework, the study is placed in a certain (historical) setting. Period is a proxy for influences that happen in a particular period. For example, the effects of periods of social unrest on migration. Cohort effects are a proxy for influences in the past: groups of people who went through the same event in the same period, such as being born or getting married, may respond differently to age or period effects than others. "Measured 'effects' of period and cohorts are thus measures of our ignorance: in particular, of whether the factors about which we are ignorant are more or less randomly distributed along chronologically measured dimensions" (Hobcraft et al., 1982, p.5). While age, period and cohort effects are measures of our ignorance, we are not entirely ignorant: there is information available on the effects which we aim to measure indirectly. For example, theory and background literature is available on the diseases a drug targets, and even at what ages such diseases are most common in the population. In an age-period-cohort framework, this could be measured by age effects. By describing the effects that are, according to theory and background literature, of effect on drug prescription, and defining them as age, period or cohort effects, an analytical framework is built. This framework, which shall be referred to as an APC-framework, will be used to formulate hypotheses.

3.4 Conceptualisation

The information from the background literature was ordered by categorizing it as age, period and cohort. In addition, gender and socio-economic status were considered because they cannot be categorized as age, period or cohort. In the stage of conceptualisation, age, period and cohort are used as proxies for underlying concepts that were most apparent in the literature review (see figure 3.1).

Age is a proxy for physiological age and social influences accumulated over time and for social effects that make their presence known in certain age ranges. Physiological age

refers to health conditions or symptoms that may warrant drug prescription. It may also refer to the side effects of drugs, which can be different at different ages or experienced differently at different ages, which can affect drug prescription (e.g. through ending drug therapy). In the literature regarding age, the physiological influences on drug prescription are much more pronounced than social influences.

Period is a proxy for effects that occur as calendar time elapses. This can be the enactment of policy (regulatory changes), the effects of publicity (positive or negative media attention), cultural change (e.g. the position of doctors, the attitude of patients), or epidemiological transitions (changes in health conditions on a population level).

Cohort, referring in this study specifically to birth cohort, is essentially a proxy for the accumulated social and physical experiences of a generation (a group of persons born within a certain time span). Examples are persons that were *in utero* or in early childhood during the Dutch Hunger Winter, but also different formative experiences due to growing up within different periods (e.g. the pre-war period of depression and post-war period of economic prosperity). These experiences may express themselves, among other ways, in different drug prescription trends even at older ages later in calendar time.

Gender has a physiological and a social component. The physiological component refers to the male or female division of the human species as differentiated with reference to the reproductive functions. This is related to drug prescription through health conditions that are specific to males or females. However, part of the prescription differences between males and females are social or behavioural. For example, women describe their symptoms differently than men, resulting in a different diagnosis.

Finally, socio-economic status refers to economic status (e.g. income) and social status (prestige, education). Persons with a certain level of purchasing power may be able to afford drug therapy. Or a certain level of knowledge may have protective benefits on health.

The relations between the concepts described above are visualized in a conceptual model (figure 3.1.). Note that SES (socio-economic status) is grey as this variable could not be included in the study. Gender will operationalized as sex. Note also that the different concepts may interact with one another. For example, as described in the literature, cohort are affected by culture and epidemiological effects during their upbringing (period effects). Such relations are excluded from the model in the interest of simplicity.

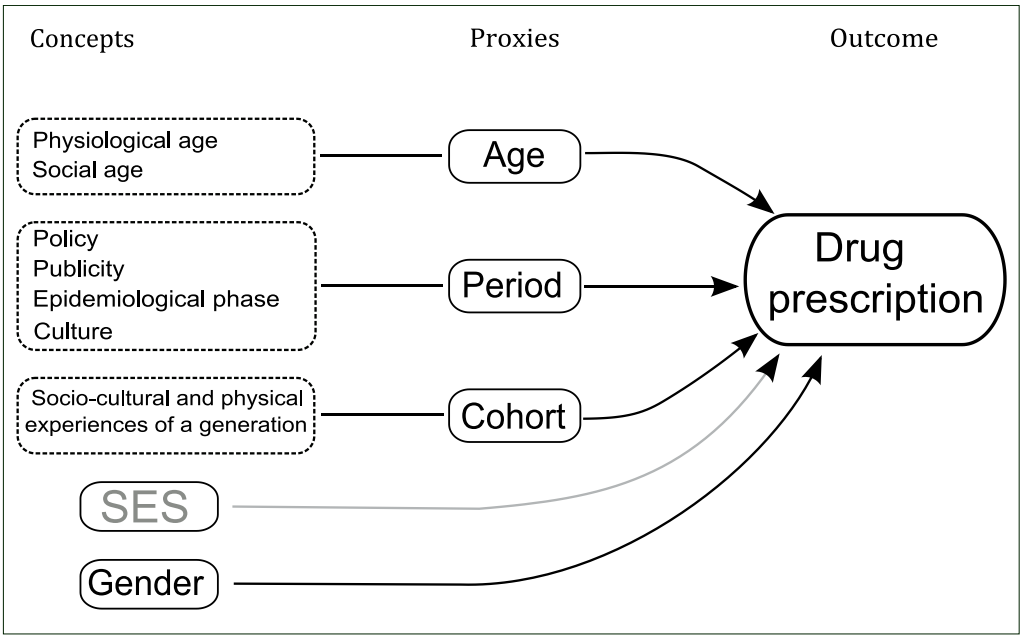


Figure 3.1. Conceptual model of the effect of age, period, cohort, socio-economic status and gender on drug prescription.

3.5 The data source: IADB

The database used for this study is called the IADB. IADB is an acronym for 'InterAction Database', referring to the interaction between the community pharmacies and the Department of Pharmacy, University of Groningen, that together have built and currently maintain the database. IADB contains anonymous prescription information received from community pharmacies in the north and east of the Netherlands and is still frequently updated. Currently, IADB receives information from approximately 50 community pharmacies, and covers a population of 500,000 individuals yearly. For most drug types, the IADB is considered to be representative for the Netherlands as a whole (Bos, personal communication March 3, 2011). The database has been active since 1994 with new pharmacies added every year until 1998, when the dataset became geographically constant.

All individuals that visit one of the IADB pharmacies receive a unique identifier code, so that they can be followed from then onwards. Information is stored on their date of birth, sex, general practitioner (also coded), the date of entering the dataset (commonly the date of the first prescription) and information on all of the prescriptions received. These include the exact dates of the received prescription, the number of units (e.g. syringes or pills), the dosage and a code used to identify the drug. This code is called an ATC-code (WHOCC, 2010). An ATC-code uses a series of letters and numbers for every type of drug, where the first letter denotes the body part or system that is targeted by the drug (*anatomy*), the following numbers denote the type of *therapy* and the following letter and number combination the specific *chemical* used (hence ATC) (WHOCC, 2010).

IADB only has micro data on persons that receive a prescription from an IADB pharmacy. In order to estimate user prevalence, the primary measure used in this study, information is required on the number of persons in the coverage area of IADB pharmacies: in other words, the number of persons estimated to go to an IADB pharmacy if they were to

receive a prescription. This total population information is estimated with the help of Statistics Netherlands. This is explained in subsection 4.2.4.

3.6 The dependent variables: user prevalence and incidence

The main research question of this study refers to users. For this reason a measure referred to as 'user prevalence' is chosen as the primary dependent variable of this study. User prevalence is based on the epidemiological measure 'prevalence'. User prevalence measures the number of users as a proportion of some total population in a defined period of time (e.g. Uchida et al., 2009; Valiyeva et al., 2008; Ding et al., 2007). A user is defined as a person with at least one prescription in the measurement interval (Valiyeva et al., 2008). Since it is not known whether an individual truly used the drug prescribed to him, Cosentino et al. (2000) emphasizes 'apparent' drug use. The measurement interval varies between studies. In this study, user prevalence is expressed as the number of users per 1000 population in a year. Note that some formulations of a measure called 'prescription rate' are synonymous with the above definition of user prevalence.

User prevalence does not provide information on whether an individual is a first user or a long-time user. Since the benzodiazepine literature describes a reduction in first users a measure called 'user incidence' will also be calculated. User incidence is based on the epidemiological measure 'incidence'. It measures the number of individuals that become a user as a proportion of some total population in a defined period of time (Meijer et al., 2004). This requires a definition of 'first user'. The number of users of a drug cannot be estimated properly if the drug in question is used infrequently (Truter et al. 1996); a person cannot be considered a new user every time there is a short gap in-between use of the drug. Drug utilization studies using the incidence measure solve this by considering a person a 'new user' only if he or she has not used the studied drug at any point in a defined time period prior to current use. For example, Meijer et al. (2004) consider a user a 'new user' if he or she did not use an anti-depressant within one year prior to current use. In this study, user incidence is expressed as the number of starters per 1000 population in a year.

Both user prevalence and user incidence can be expressed as age and sex standardized measures. By controlling for population composition, changes in the trends in drug prescription cannot be attributed to the size of cohorts and can therefore be attributed to another effect, such as guideline changes. Furthermore, both user prevalence and incidence can be used in APC-analysis because it is possible to calculate age, period and cohort-specific values or combinations of APC-specific values. For more information and backgrounds on the exact calculation of user prevalence and incidence see section 4.2.

There are a number of other measures in drug utilization studies, namely prescription rate and daily defined dose. Concisely put, some formulations of prescription rate measure the number of prescriptions rather than users, which is of no importance to this study. The daily defined dose can be used to indirectly measure the number of users, but this is not required for this study as direct information on users is available. A detailed explanation of the strengths and weaknesses of these measures, including user prevalence and user incidence in pharmacoepidemiological studies, is given in appendix A.

3.7 Hypotheses

3.7.1 Benzodiazepine use

1. Benzodiazepine is a drug used to relieve pain, anxiety and sleep problems. These problems are related to the physical state of a person, which deteriorates with age. Therefore, user prevalence will increase with age.
2. Persons that start using benzodiazepine have a high likelihood of becoming addicted. As first users become chronic users, the number of users accumulates within cohorts over time resulting in increasing user prevalence within cohorts over time.
3. Due to policy changes, the number of new users is curbed from 2001 onwards. This will end the increase of user prevalence within cohorts from 2001 onwards.
4. As the influx of new users ceases, user prevalence may decrease with calendar time due to attrition: some users will overcome addiction and become non-users, while others may die due to selection effects (the users of benzodiazepine represent a selection of the population with worse health than non-users).
5. Following the fetal origins and the cohort morbidity phenotype hypotheses, cohorts of whom the members were *in utero* or in early childhood during the famine and influenza following the First World War (1919), or during the famine of the Second World War (1945 and 1946) will have higher user prevalence than other cohorts.
6. Post-war cohorts (1946 and later) will have higher user prevalence than pre-war cohorts due to different formative experiences.
7. Female user prevalence is higher than male user prevalence.

The first four hypotheses are visualized in figure 3.2. The latter three would result in a shift of a cohort up or down, relative to other cohorts, in user prevalence.

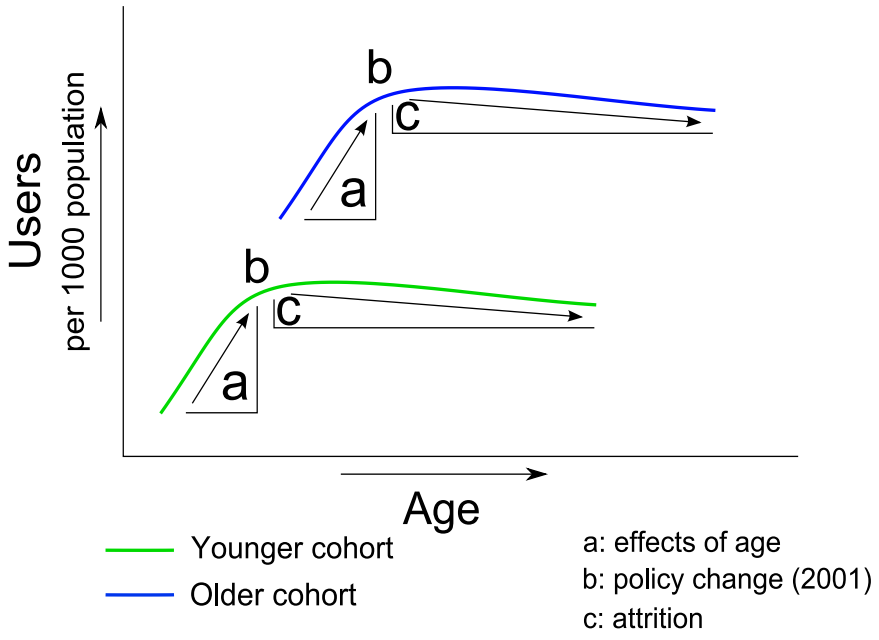


Figure 3.2.
Visual representation of the first four hypotheses on benzodiazepine use.

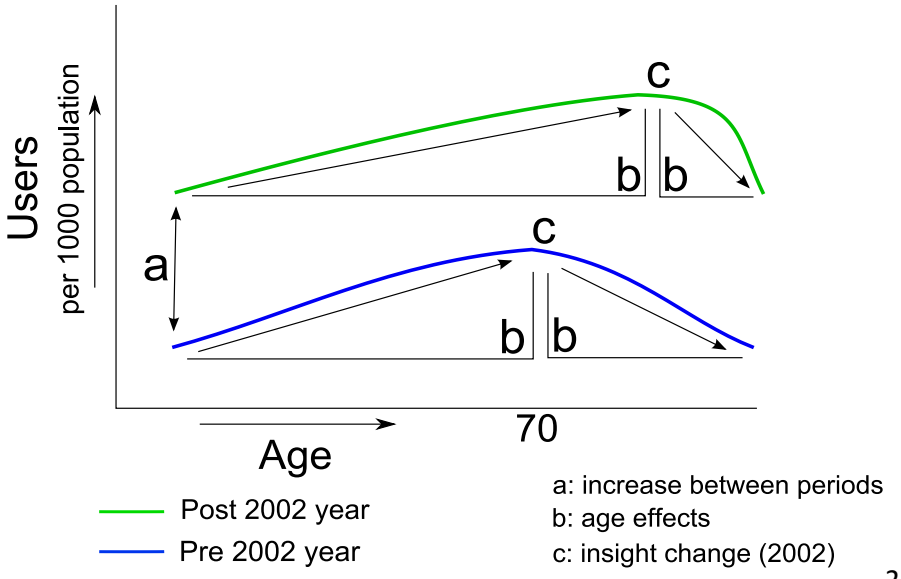
3.7.2 Statin use

1. Statin is a new drug, therefore user prevalence will increase with calendar time. The increase will be especially high after the year 2000, when the minister of health was advised to prescribe the drug preventively.
2. a. Statin is a drug used to prevent cardiovascular incidents. It is prescribed preventively for persons who have a higher risk for cardiovascular disease. The risk for cardiovascular disease increases with age. In 2002 important studies showed that the drug was effective for persons over 70.
   - Before 2002, the use prevalence of statin will increase with age up to age 70. It will decline after age 70.
   - After 2002, due to the findings of new studies, user prevalence at age 70 and higher will increase.

   b. This effect will strengthen in 2006 with the new guideline for statin prescribing.
3. Due to negative publicity, there will be less growth, or even decline, of user prevalence in 2007.
4. Following the fetal origins and the cohort morbidity phenotype hypotheses, cohorts of whom the members were *in utero* or in early childhood during the famine and influenza following the First World War (1919), or during the famine of the Second World War (1945 and 1946) will have higher user prevalence than other cohorts.
5. Post-war cohorts (1946 and later) will have higher user prevalence than pre-war cohorts due to different formative experiences.
6. Male user prevalence is higher than female user prevalence.

The first two hypotheses are visualized in figure 3.3. The third hypothesis would result in a decrease of user prevalence relative to 2006. The fourth and fifth hypotheses would be represented by an increase in the number of users in some age-range (which would shift with calendar time as the cohort ages). The sixth hypothesis will result in a lower user prevalence for females relative to male user prevalence in the same year. Note that the green and blue lines represent periods instead of cohorts, this differs from the previous figure.

Figure 3.3.
Visual representation of the first two hypotheses on statin use.



3.8 Methods of analysis

The study uses two methods to test the hypotheses: descriptive graphical analysis of user prevalence and incidence, and statistical age-period-cohort (APC) models of user prevalence.

3.8.1 Graphical analysis

Plotting of observations is an important part of APC-analysis. Carstensen (2007) writes that plotting should precede APC modeling. A number of different graphs are used in this study in order to explore trends in the prescription of benzodiazepine and statin from multiple perspectives. First, for both drug types a graph of age-standardized user prevalence is constructed for each year in the observation period (1994 – 2008). This gives insight into the overall prevalence trend over time while controlling for changes in population age composition which may occur over time (Preston, 2008). Secondly, for both drugs, graphs are constructed of age-specific user prevalence for each year in the observation period. This provides insight into the age-trend of user prevalence within each year and also allows for comparison between years as the age-trend possibly changes over time. Thirdly, graphs of age-specific user prevalence for cohorts are constructed. This provides insight into the user prevalence trend as cohorts age or as calendar time increases and allows for the comparison of user prevalence trends or users prevalence levels between cohorts. In the primary graph of this type the position of cohorts within calendar time is also marked in order to elucidate the possible period effects (e.g. guideline or insight changes) on the trends within cohorts. Finally, specifically for benzodiazepine a graph of age-specific user incidence for cohorts is constructed in which the position of cohorts within calendar time is also marked. This has been done in order to find whether the user incidence levels within cohorts decrease after a guideline change. More in-depth explanation of the construction of the graphs is given in section 4.3.

3.8.2 APC models

In the graphs discussed above the effects of age, period and cohort together shape the trends in user prevalence. Ideally, the effects of age, period and cohort are isolated from one another in order to properly test the hypotheses regarding age, period and cohort effects. APC models are statistical models used in the attempt to isolate each of the three effects. Unfortunately, this is not entirely possible: age, period and cohort are linearly related to each other (Glenn, 2005). Including all three variables in the same model results in overidentification (this is explained in-depth in section 4.4). Therefore, the linear component of period and cohort, termed ‘drift’, is commonly extracted. An APC model thus measures age, non-linear period, non-linear cohort, and drift (Clayton & Schifflers, 1987b). Depending on side-information (Glenn, 2005), such as the literature, drift can be attributed to either period or cohort. In order to assess the goodness of fit of the statistical model, the contribution of each component of the APC model to the reduction in scaled deviance are compared using a chi-squared distribution.

In this study APC models of user prevalence are constructed using the classical procedure by Clayton & Schifflers (1987b) for both benzodiazepine and statin. Concisely put, that means age, period and cohort are measured using categorical variables. The model is fit as a Poisson Rate model in which users of the drug are the dependent variable, the (log of) the

exposure is used as an offset variable and age, period and cohort are independent variables. For benzodiazepine, drift is split evenly between period and cohort as it is unclear from side-information where to attribute drift. For statin, drift is wholly contributed to period as it is known from literature that most of the growth in statin use is a period effect. A more in-depth explanation of APC models and their construction is given in section 4.5.

Chapter 4. Measures and methods

Since this study has a strong methodological component (the application of demographic techniques to pharmacoepidemiology), the measures and methods used should be elaborated upon. This chapter provides background information and elaborate explanations on the calculations used to produce user prevalence and incidence, the constructing of graphs and the constructing of APC models. The chapter starts with an explanation of the Lexis diagram in section 4.1. The calculations behind user prevalence and incidence in general and in this study specifically are discussed in section 4.2. In section 4.3 the construction of graphs is described. Finally, APC models are elaborated upon in section 4.4.

4.1 The Lexis diagram

The Lexis diagram is a useful tool for demographic and epidemiological analyses, and, because it is of particular relevance in studying age, period and cohort, it is used extensively in this chapter. The Lexis diagram, shown in figure 4.1, is a coordinate system in which age is represented by one dimension, the y-axis, and calendar time by the other, the x-axis (Pressat, 1993). The units of measurement on both axes are commonly of the same increment, such as years (Preston, 2008). Within the Lexis diagram, lifelines can be shown, representing individuals moving through time, or counts of events or individuals.

By using vertical, horizontal or diagonal lines, or combinations of the these, particular selections in age and period intervals can be displayed. Shown in figure 4.1, the blue column is a selection of individuals of all ages in period *p*, used for example when a crude period rate is calculated (Preston, 2008). The green row is a selection of all persons of age *a+2* (last birthday) in all periods. A period and age (AP) selection results in a square which is sometimes called a Lexis-square. Such a selection is used when calculating age-specific rates for a period. The diagonal orange line is used to represent a birth cohort. In Lexis diagrams, birth cohort selections are diagonals, because they are comprised of the lifelines of individuals born in a particular period. Because individuals become older (moving upwards in the diagram) as calendar time increases (moving rightward in the diagram), lifelines are diagonal. If *a-1* is 0, the individuals belonging to the orange birth cohort were born in period *p-1*. The intersection of a period selection and a cohort selection (PC) is parallelogram shaped. The intersection of a cohort selection and an age selection (AC) creates an age-cohort selection, which is also shaped like a parallelogram. A selection can also be specified on the basis of age, period *and* cohort, resulting in an APC selection. An APC selection has the shape of a (Lexis-)triangle (see the purple and dark red triangles in figure 4.1).

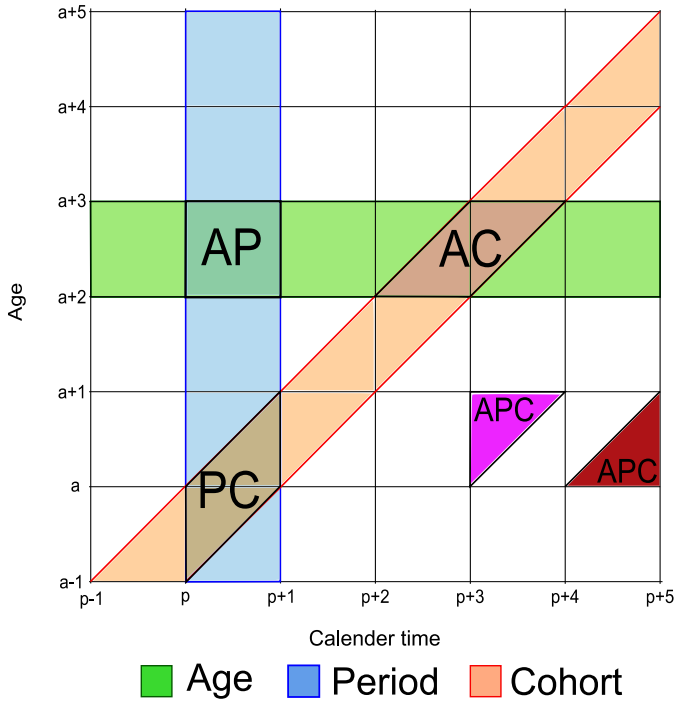


Figure 4.1. Lexis diagram showing age, period and cohort specific selections.
AP stands for age-period (a Lexis-square), PC for period-cohort (a Lexis-parallelogram), AC for age-cohort (a Lexis-parallelogram) and APC for age-period-cohort (a Lexis-triangle)

4.2 Calculation of user prevalence and incidence

This section describes the calculation of the dependent variables of the study. First, in subsection 4.2.1 the fundamentals of the calculation of rates in demography and epidemiology will be described. Secondly, subsection 4.2.2 describes prevalence and incidence. Thirdly, there is a problem in the calculation of age and period-specific user prevalence which will be discussed in subsection 4.2.3. Fourthly, the calculation of the denominator, known as person-time exposed, will be described in subsection 4.2.4. Finally, subsection 4.2.5 will summarize the exact calculation of user prevalence and user incidence used in this study, drawing upon the earlier subsections.

4.2.1 The calculation of rates

User prevalence and user incidence are based on the measures in epidemiology referred to as 'prevalence' and 'incidence'. Prevalence and incidence are occasionally referred to as 'rates' and, as described in the previous chapter, user prevalence is occasionally referred to as prescription rate. However, neither measure is necessarily a 'true' rate. Furthermore, both prevalence and incidence can be calculated in different ways.

A true rate measures how frequently some event, for example childbirth or death, occurs per unit of time (Rockett, 1999; Preston et al., 2008). In order to measure this, certain criteria need to be met regarding the correspondence between the numerator and the denominator used to calculate the rate. Firstly, the events counted in the numerator may only have occurred to persons in the denominator. Secondly, all of the persons counted in the denominator must have been 'at risk' of having the event (Jekel et al., 1996). The

denominator is further specified into 'person-time at risk'. This is the amount of time, during a time and age interval, in which persons are exposed to having the studied event. Person-time is often expressed as person-years. For example, if one person is at risk of developing a disease for ten years, he contributes ten person-years at risk to the denominator. However, the same number can also be contributed by five persons that are each at risk for two years (Rockett, 1999). Total person-time at risk should be calculated by summing the time that all non-cases (persons that never experienced the event) were at risk, plus the time that cases (persons that experienced the event) were at risk of experiencing the event (Rockett, 1999).

Deviations from the above rule are common. For example, in population-level research, persons may migrate into and out of the population making it difficult to track exact time that individuals are at risk. In these situations the mid-year population, rather than person-time at risk, is often chosen as the denominator. Rates calculated in this manner are actually pseudo-rates (Rockett, 1999).

Some demographic rates could also be considered non-true rates using the above definition of rate. This is especially clear for the rate of in-migration: the person already in the population cannot be 'at risk' of migration into the population, yet they do make up the denominator (Preston, 2008). Therefore, it is said that demographic rates measure the rate at which the population is changing as a result of their respective events (Preston, 2008).

4.2.2 Prevalence and incidence

Prevalence, including user prevalence, is calculated as

$$Prevalence = \frac{Cases}{Total\ population}$$

Prevalence is not a true rate because persons undergoing the event (cases), whether it be the use of a drug or some illness, contribute to the denominator. Furthermore, the denominator consists of the total population, rather than person-time at risk. This total population can be an estimate of the average population alive in the interval, and therefore can be seen as a measure of person-time, but it would not represent person-time at risk.

Incidence rate, including user incidence, is calculated as

$$Incidence\ rate = \frac{New\ Cases}{Person\ time\ at\ risk}$$

Incidence is a true rate if it is calculated using person-time in the denominator. If instead the number of persons at the start of the time interval is chosen as the denominator, incidence is referred to as cumulative incidence (Vandenbroucke et al., 1999). Finally, as described above, in population-level research the mid-year population is often used as a substitute, resulting in a pseudo-rate (Rockett, 1999).

Furthermore, some texts (for example Rockett, 1999; Jekel et al., 1996) will note that

$$Prevalence \approx Incidence\ rate \cdot (Average)\ Duration$$

However, even in standard epidemiological practice this estimation is only true under certain circumstances, and it is even less true in drug utilization studies. The latter is the case for two reasons. Firstly, in the calculation of user prevalence, a person is considered a user if they used in the time interval. This means that the duration of being a user is bounded by the interval. When the next interval starts, such as the next year, status as a user will be reassessed. Secondly, in the calculation of user incidence, a person is only considered a new user if they did not use the drug for some defined period of time. In other words, the relation between prevalence and incidence in drug utilization studies is not as direct as it is in etiological studies, and therefore the above equation is untrue in drug utilization studies using the definitions of user prevalence and user incidence as described above.

Finally, a distinction can be made between 'point prevalence' and 'period prevalence'. Point prevalence refers to the number of persons with a studied disease (the studied drug) at a specific point in time (Jekel et al., 1996). An example of this is the drug utilization study of Meijer et al., (2004), where the number of users of a drug at an exact point in time is measured. Period prevalence refers to the number of persons that had the studied disease at any time during an interval (Jekel et al., 1996). Examples of drug utilization studies using period prevalence are Ding et al. (2007) and Donoghue et al. (1996). Note that those studies refer to it as 'prescription rate'. In epidemiological studies, period prevalence is the prevalence at the beginning of the time interval plus incidence during this interval. It is therefore a mixed measure and discouraged for scientific work (Jekel et al., 1996). However, as explained in the previous paragraph, user prevalence and user incidence differ from standard prevalence and incidence. Importantly, there is no prevalence at the beginning of the interval as the number of users is reassessed in each interval. Furthermore, while point prevalence could be estimated, not all drugs are used continuously (Truter et al., 1996), resulting in an undercount of the number of users at any point in time for some drugs (including benzodiazepine; Truter et al., 1996). In other words, point prevalence measures 'using at *p*', while period prevalence measures 'being a user in the period *p, p+1*'. The latter is what this thesis aims to study. However, period prevalence can under some conditions result in an overestimation of the number of users. This will be considered in the next subsection.

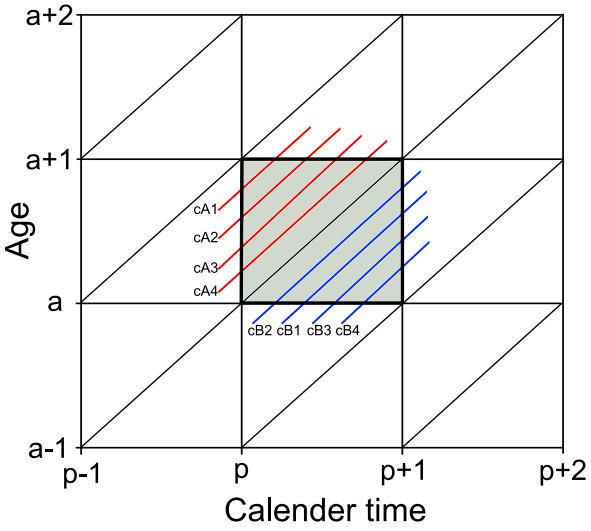
4.2.3 User prevalence and overestimation

According to the definition of user prevalence, all persons with at least one prescription in the time interval are counted and divided by the average total population. This can result in an overestimation of age-specific user prevalence. The cause of the problem is a mismatch between the numerator and the denominator. The denominator, the average total population, is an estimate of person-years in the interval. The numerator counts all individuals with a prescription once. When the denominator is in person-years, the numerator implicitly states that individuals spend one year in the interval on average. When individuals, on average, spend less time in the interval than the stated time, overestimation occurs.

Consider the example in figure 4.2. It shows a single year, single age interval (a period-age selection). Four individuals enter this interval at *p*, namely individuals cA1, cA2, cA3 and cA4. They are represented by the red lines. At the end of the interval, these

individuals have left the interval due to reaching age *a+1*. However, other individuals have entered during the interval due to reaching age *a*, namely cB1, cB2, cB3 and cB4. They are represented by the blue lines. Therefore, a total of eight individuals have been exposed to the event, getting a drug prescribed, in the interval. It is common for population-level studies to estimate the total population in the time interval by summing the total individuals at the January 1 and those at the December 31, and dividing this by two. In other studies the midyear population is chosen as the denominator. In the example (figure 4.2), both of these methods would result in an estimated total population of four. This is a reasonable estimate of the number of person-years in the population, as for example persons cA1 and cB4 spend very little time in the interval, but person cA4 and cB1 spend nearly a full year in the interval. However, when the event is common, such as with drug prescription, it is possible that all eight persons are able to experience the event, regardless of their time spent in the interval. In this situation the numerator is eight. When this number is divided by four, the resulting prevalence would be two, or 200% of the population is a user of the drug. Figure 4.2 shows that individuals from both cohorts are, on average, roughly half a year in the interval while they are counted as being in the interval an entire year. As 1 / 0.5 = 2, the estimate is twice as high as it should be.

Figure 4.2. Overestimation represented in a Lexis diagram.
The red and blue lines represent the 'lifelines' of individuals belonging to birth cohorts cA and cB respectively. The square with the grey background represents the time and age interval *a, p* (which is time interval *p* to *p+1* and age interval *a* to *a+1*).



This particular situation has likely gone unnoticed, or is considered irrelevant, in drug utilization studies due to the large age intervals chosen. In a single year, single age interval, two cohorts of individuals are exposed to having an event, while only one cohort (the average of two cohorts) of exposure is considered. However, if the age interval is increased, the exposure will increase accordingly, while the overestimation remains by one cohort. Therefore, the overestimation decreases as the age interval increases. When the time interval is a single year and all cohorts are of equal size

$$Overestimation\ (\%) = \frac{n+1}{n} \cdot 100\%$$

Where *n* is the size of the age interval in years (integers) and the resulting value is the percentage of overestimation (where 100% is the accurate estimation). The larger the age category, the smaller the overestimation. In this thesis, the age intervals are small, and thus a solution is required. It should be noted that in reality cohorts are not all of equal size. Therefore the overestimation formula is merely to demonstrate the mechanism of less overestimation with increasing size of the age interval.

Since the problem is caused by the numerator counting individuals as if they spend on average one full year in the interval when the true time spent in the interval is lower, a solution would be to weigh events by the true average time spent in the interval. However, this does not result in the optimal solution. A rule in demography (Preston, 2008) and epidemiology (Jekel, 1996) is that age specific rates, when weighed by the proportion of their denominator in the total sum of age-specific denominators, sum up to the crude rate

$$Crude\ rate = \sum_{a=0}^{\infty} {}_nM_a \cdot {}_nC_a$$

Where *n* is the size of the age interval, *a* is age, ${}_nM_a$ is an age-specific rate and ${}_nC_a$ is the proportion of the total population in age interval *a* to *a* + *n* (Preston 2008, p. 23). This rule does not necessarily hold when, in order to prevent overestimation, events are weighed by the average time spent in the interval. Consider the example in figure 4.3.

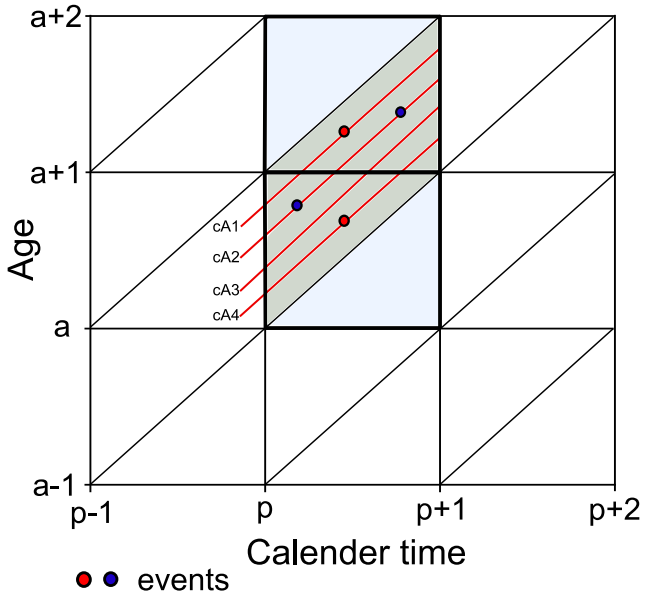


Figure 4.3. Lifelines in a Lexis diagram. The red lines represent the 'lifelines' of individuals belonging to cohort cA. The red and blue circles represent prescriptions (events), signifying whether a person is a user or a non-user.

In this example, the period-age interval *a, p* (lower of the two squares) and *a+1, p* are (upper of the two squares) are compared with a crude calculation (*a, p* and *a+1, p* taken together). The lifelines and events in the light-blue sections of each square are ignored. In an age-specific calculation, both Lexis-squares would have two events, and four individuals. As the individuals spend on average half a year in the interval, the denominator is two, but events will also be weighed by half in order to eliminate overestimation. This results in a user

prevalence 0.5 (50% of the population is a user). When the two age-specific user prevalences are added together, the result will be a user prevalence of 0.5. This *should* equal the crude prevalence as described by Preston (2008). However, it will not.

In the crude calculation, there are four individuals and three events. Neither the denominator nor the nominator need to be weighed, as users spend on average one full year in the interval. This results in a user prevalence of 0.75 (75% of the population is a user). The difference between the weighed sum of the age-specific calculations and the crude calculation is because person cA1 only has an event in the interval *a+1, p* and person cA4 only has an event in the interval *a, p*. If both individuals had an event in both intervals, the age-specific prevalences would also be 0.75. Since this will not necessarily be the case, the solution for the overestimation problem is to use the cohort-period (CP) shape as the basic shape for calculating prevalence in this study.

Note that, even with the above solution, some over or underestimation may still occur in population-level research due to mortality and migration. For example, it is possible that persons enter the study area halfway through the interval, experience the event (contribute to the numerator), and leave the study area (due to migration or death) before the end of the interval, resulting in no contribution to the denominator. While such situations cannot be ruled out, they are unlikely to happen on a large scale if the time and age intervals are of sufficiently small size and the study area is socio-politically stable. Estimation errors due to mortality are more likely to occur at higher ages due to higher mortality rates at those ages.

4.2.4 Estimation person-years of exposure

In order to calculate prevalence and incidence, next to users, also information on the number of person-years exposed must be known. First, the total population in the coverage of the IADB must be known. This total population is estimated. Statistics Netherlands possesses information on the total population for all postal code areas, but within each of these areas can be more than one pharmacy, some of which may not report to the IADB. Furthermore, persons can visit pharmacies in other postal codes than their residential postal code. The estimation goes as follows: for some administrative regions there is complete coverage (all pharmacies in the area report to the IADB). The total population of these areas by age and sex is known. Using this information, the age, sex and period year-specific proportions of the total population that visits the pharmacy can be calculated, this is called the 'population fraction' by the database managers.

The population fraction is used to calculate the age and sex structure of the total populations (at January 1 of each year) of the administrative regions that were not fully covered by IADB pharmacies. For example, if it is known that for a certain age and year the population fraction is 0.5 (50% of persons of that age and sex visit the pharmacy), and for a certain postal code we know that 20% of the total population visits an IADB-related pharmacy in the area, then the total population in the coverage of the IADB-pharmacy of that area is calculated as $2/5^{th}$ of the total population (the remaining $3/5^{th}$ would be in the coverage of another, non-IADB-related pharmacy).

The total population as estimated by the IADB can be used to estimate the person-years 'exposed' to being a prescription drug user (the denominator of the prevalence

measure). A common suggestion for the calculation of the exposure in an interval is to sum the population at the beginning of the time and age interval (often January 1) with the population alive at the end of the time and age interval (December 31), and to divide this by two, or

$$\frac{1}{2}l_{a,\,p} + \frac{1}{2}l_{a,\,p+1}$$

Where *a* refers to a single-year age category, *p* to a calendar year and $l_{a,\,p}$ to the population size in age class *a* at the beginning of year *p* (see also figure 4.4). Carstensen (2007) writes that it would be more accurate to calculate person-years lived in Lexis-triangles. Furthermore, the person-years between two triangles of the same birth cohort would differ, as individuals in Lexis-triangle B must first survive through Lexis-triangle A (figure 4.4) (Carstensen, 2007; Sverdrup, 1965; Rosenbauer & Strassburger, 2008). As this study uses as its basis a cohort-age interval (the grey parallelogram in figure 4.3) in order to prevent overestimation, calculating person-years for Lexis-triangles will not work. In this study, person-years lived in the interval will be calculated as:

$$\frac{1}{2}l_{a,\,p} + \frac{1}{2}l_{a+1,\,p+1}$$

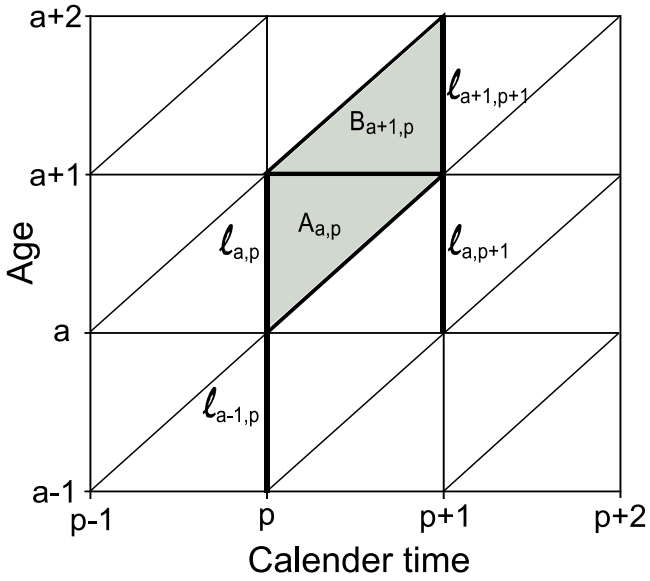


Figure 4.4. Person-years in a Lexis diagram.
The triangles with the grey background represent subsets $A_{a,p}$ and $B_{a+1,p.}$ *l* refers to the persons alive at some age category (*a*, *a+1*, etc.) and the beginning of a calendar year (*p*, *p+1*, etc.), represented by the bold vertical lines.
Source: adapted from Rosenbauer & Strassburger, 2008.

However, the estimate of the exposure of the first four years will deviate from the above formula. In the period 1994 – 1998, new pharmacies joined the IADB. This mean prescription and patients records were added. Consequently, the estimated total population in the IADB-pharmacies (the coverage) had to be adjusted (see figure 4.5 for the estimated total population in each year). The majority of the participating community pharmacies were added at the beginning of each year (January 1). This allows for better correspondence between the prescription information and exposure information, the latter of which is estimated for the first of January of every year. The exception are three pharmacies: one in 1996 and two in

1998, all added approximately halfway during the year (Bos, personal correspondence May 9, 2011). On a total of 50 pharmacies, these three pharmacies should not account for large fluctuations. However, the growth of database in the period 1994 to 1998 does have consequences for exposure estimation and the subsequent calculation of user prevalence. The method ½ $l_{a,p}$ + ½ $l_{a+1,p+1}$ to calculate exposure is not advisable for the first four years of the dataset, as *p+1* has a much larger exposure than *p*. Therefore, for the periods 1994, '95, '96 and '97, exposure is estimated with $l_{a,p}$.

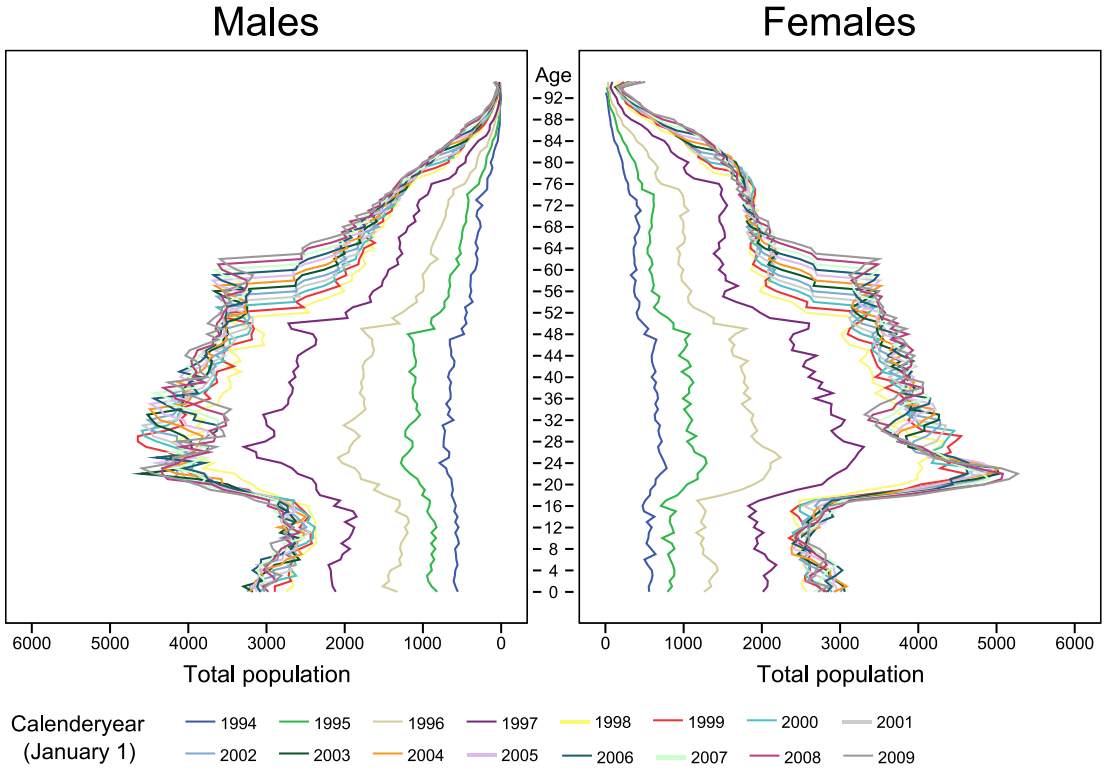


Figure 4.5. Total population estimated to be in the IADB coverage by sex, age and calendar year. Ages 0 to 95 and periods 1994 to 2009.

4.2.5 Calculation of user prevalence and incidence in this study

User prevalence is calculated for each single year period, single year birth-cohort interval (the shape of the grey parallelogram in figure 4.4). Users of benzodiazepine or statin are defined as persons with at least one prescription for benzodiazepine (identified by the ATC codes N05BA or N05CD) or statin (identified by ATC code C10AA) respectively. All users in an interval are counted. The result is divided by the estimated person-years lived (exposure) in the interval. Exposure is estimated as ½ $l_{a,p}$ + ½ $l_{a+1,p+1}$, except for the first four years when it is estimated as $l_{a,p}$. As explained in the beginning of this section, user prevalence is not a rate, but a ratio. The age of this cohort-period selection is taken as the age of that selection at *p+1*.

User incidence is also calculated for parallelograms. New users are defined as persons that have existed in the database for a full year and have not used the drug in question (benzodiazepine or statin) for a full year, as users may have 'gaps' in-between prescriptions (Truter et al., 1996). All new users in an interval are counted. The resulting value is divided

by the estimated person-years in the interval. Since individuals must exist in the database for a full year before they are assessed whether they are a user, there is a one-year lag: e.g. persons entering in 1994 will not be considered until 1995. This means that there is no data available for 1994. It also means that the number of new users in a year is influenced by the population size in the IADB coverage of the previous year. Therefore, the exposure as calculated for the previous year and age is taken rather than the exposure of the current year: $½\ l_{a-1,\,p-1} + ½\ l_{a,p}$, except for the first four years when it is estimated as $l_{a-1,p-1.}$ Finally, since the estimates of person-time do not take into account true person-time at risk, this calculation of user incidence results in a pseudo-rate, as explained in the beginning of this section.

4.3 Construction of graphs

This section describes how the plots used in the results chapter were created. Note that the basic one-year period by one-year birth cohort (PC) shape is used for all calculations (its calculation is explained in the previous section).

4.3.1 Age-standardized user prevalence for periods

Period specific (crude) user prevalence can give insight into the overall trend the number of users. However, changes in crude prevalence can be caused by changes in the age-composition of the population (Preston et al., 2008). Therefore, the prevalence is age-standardized using the formula by Preston et al. (2008)

$$Age\ standardized\ prevalence = \sum_{a=18}^{85} M_a^j . C_a^s$$

Where *a* is age, *j* is some population (here the population estimated to be in IADB coverage in any year in 1994-2008), *s* refers to the population chosen as standard (here the population estimated in IADB coverage in 2001). Therefore M_a^j is the prevalence at the a^{th} age interval in any year and C_a^s is the proportion of the population in the a^{th} age interval in 2001. Separate age-standardized user prevalences were calculated for males and females. User prevalence is expressed per 1000 population.

4.3.2 Age-specific user prevalence for periods

Age-specific cohort prevalence gives information on the number of users as a proportion of the total population in each age category. In order to create stable prevalences, three-year age groups were created, starting with age category 18-20, then 21-23, … etc. up to age category 84-86. Users within these categories are summed and divided by the sum of the age-specific exposures in that category. This was done for all years in the period 1994 to 2008. Separate user prevalences were calculated for males and females. User prevalence is expressed per 1000 population.

4.3.3 Age-specific user prevalence for cohorts

Age-specific period prevalence gives information on the number of users per 1000 population in each cohort. There are 78 birth cohorts in the study (1911 to 1988) when a cohort is defined by a single year of birth. Two different sets of plots were made: the first set consists of three-year period by three-year cohort categories. The second set consists of three-year age categories within single-year birth cohorts.

The first set, three-year period by three-year cohort categories takes into account all of the information available in the dataset and produces the most stable prevalences. Furthermore, it allows comparison of trends within cohorts (there are five data points for the majority of cohorts) and comparison of different cohorts in the same age-range. All users belonging to three adjacent birth cohorts in three adjacent years were summed and divided by the sum of the exposures in the same selection. Separate user prevalences were calculated for males and females. The age-range of each selection is defined as the age-range of the three cohorts in the final period year of the selection. The cohorts categories are: 1911-1913, 1913-1915, ..., 1986-1988. The age-ranges in each period are 20-22, 23-25, ..., 83-85. The periods are 1994-1996, 1997-1999, ..., 2006-2008. For example, in 1994-1996, the birth cohort 1974-1976 is aged 20 to 22. For purposes of clarification, this selection is also shown in figure 4.6. This selection is later also used for modeling (see section 4.5). Note that the same colours of each year will also be used later to denote the position of each cohort in calendar time in the plot.

In the second set of plots, three-year age categories within single-year birth cohorts take into account the fact that single-year birth cohorts may differ from others because of a particular experience that only occurred to that cohort (e.g. the *in utero* nutritional deficiency of the birth cohorts of 1945 and 1946). Such differences may not be apparent in three-year period by three-year cohort categories. All users in three adjacent single-year ages within a single-year birth cohort were summed and divided by the sum of the exposures in the same selection. Separate user prevalences were calculated for males and females. These calculations were done for all birth cohorts. However, due to the large number of cohorts, this would create a 'fuzzy' pattern that makes it difficult to discern one cohort from the other. Therefore, three plots were made for each sex. In each plot only every third cohort is shown. The first plot starts with cohort 1911, then 1914, 1917, etc. up to 1986 (thus omitting cohorts 1912 and 1913, 1915 and 1916, etc.). The second plot start with 1912, then 1915, 1918, etc. up to 1987. The third plot starts with 1913, then 1916, 1919, etc. up to 1988. By doing this, the information of each individual single-year birth cohort can be studied. Because cohorts are divided into three-year age groups, the majority of cohorts have five data points: one for each period (1994-1996, 1997-1999, …, 2006-2008).

4.3.4 Age-specific user incidence for cohorts

User incidence gives information on the number of new users within a timeframe. No information for 1994 is available, as individuals had to be in the database for one year prior to being considered a new user or not. Since fourteen years of information is available, two-year period by two-year cohort categories were created. All starters within two adjacent years and two adjacent birth cohorts were summed and divided by the summed exposure in the same

selection. Separate user incidence was calculated for males and females. Incidence is expressed per 1000 population. Since the resulting plot is 'cluttered', every second birth cohort was removed. Therefore, the graph will show the birth cohorts 1911-1912, 1915-1916, 1919-1920, etc. up to 1987-1988. User incidence is expressed per 1000 population.

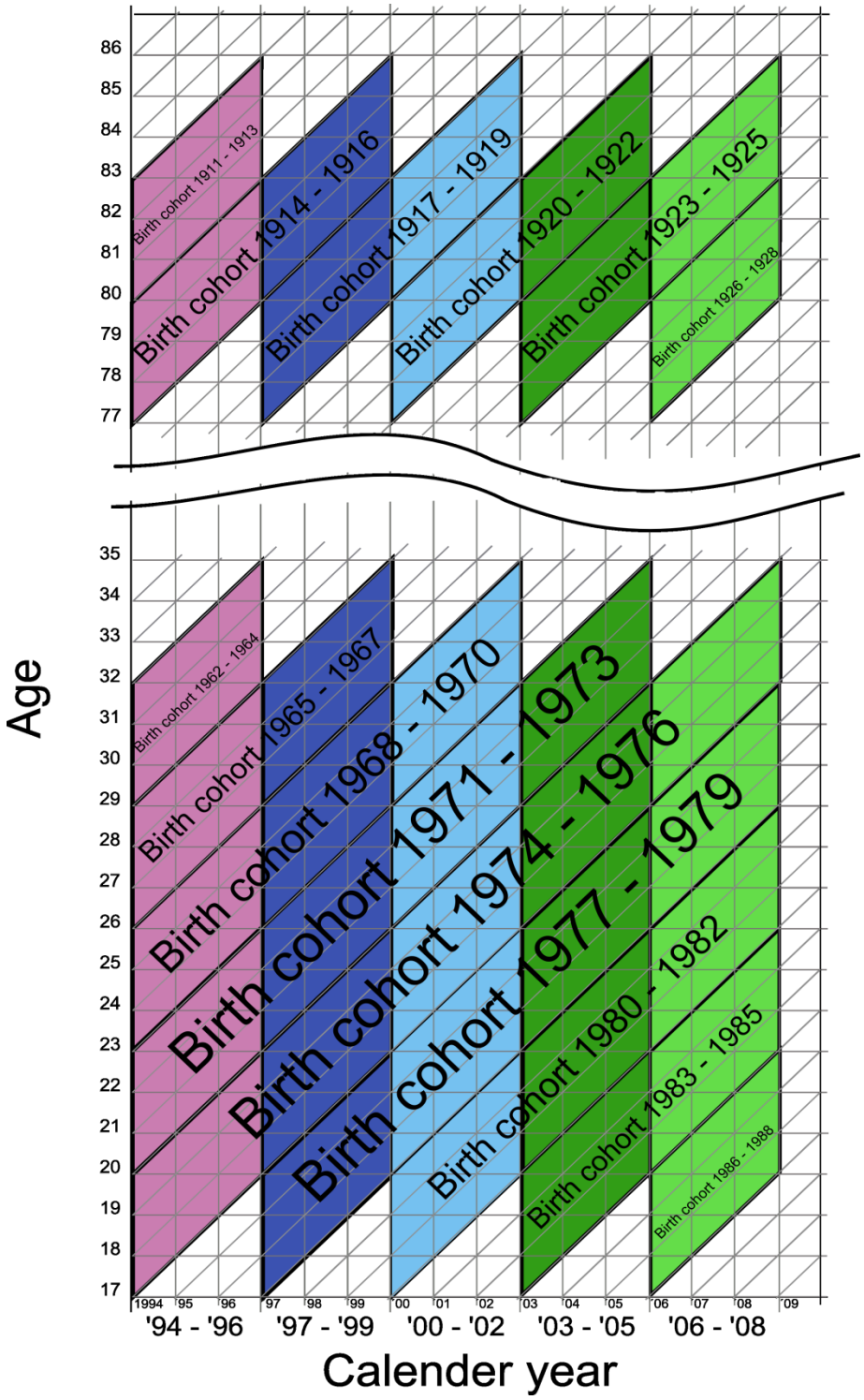


Figure 4.6. Lexis diagram showing the selection of three-year period by three-year cohort intervals.

4.4 Linear dependency

A fundamental problem in APC-analysis is called linear dependency. Linear dependency occurs when three (or more) independent variables are included in an analysis, and each of them is a linear function of the other two. This occurs in APC-analysis because

$$p - c = a$$
$$a + c = p$$
$$p - a = c$$

Linear dependency makes it impossible to statistically identify the linear effects of the variables involved because overidentification has occurred (Glenn, 2005). Therefore, it is also referred to as 'the identification problem'. In statistical terms, "the multiple correlation of each independent variable with the other ones is unity--the most extreme kind of collinearity that is possible" (Glenn, 2005, p. 6). In the case of descriptive analysis, the effect of each independent variable cannot be determined, even given apparently clear patterns, as any combination of the three variables could have produced the observed rates (Glenn, 2005). This should be kept in mind when studying the descriptive graphs produced by this study.

Because of the identification problem, the role of theory or other 'side information' becomes crucial in determining the effects of age, period and cohort (Glenn, 2005). If there is reason to believe that one of the three independent variables has no effect, the effects of the remaining two variables can be estimated easily (Glenn, 2005). If all three variables are believed to have an effect, the researcher has to use side information to determine what combination of magnitudes is chosen (Glenn, 2005).

If the effects of age, period and cohort are non-linear, they can be separated. This is done by isolating the 'linearity', thereby leaving non-linear effects to be estimated. However, some deviation from linearity does not necessarily mean that the effects of APC can be statistically separated (Glenn, 2005).

That it is logically impossible to separate the effects of age, period and cohort through statistical modeling or descriptive analysis only means that the quest to find the precise effects of APC should be abandoned (Glenn, 2005). Reasonable or plausible estimates of APC effects can still be made. However, there is no formal approach to making such estimates: the research objectives, and side information required to make estimates, differ per study (Glenn, 2005). In all cases, using information from a variety of sources is highly advisable. For this reason, descriptive statistics and statistical modeling are useful, as they provide additional insight into APC effects. (Glenn, 2005). This study, of course, combines theory with graphical analysis and statistical modeling.

4.5 APC models

This section describes APC models. Subsection 4.5.1 will describe the fundamentals of age-period-cohort models. Subsequently, subsection 4.5.2 will describe the classical approach as set out by Clayton & Schifflers (1987a; 1987b) and includes some criticism and amendments by Carstensen (2007). Finally, subsection 4.5.3 describes the construction of the models used in this study.

4.5.1 The fundamentals of APC models

Age-period-cohort models are an extension of age-period and age-cohort models. The latter two models were developed for the analysis of vital rates in descriptive epidemiology (Clayton & Schifflers, 1987a). As these two models can be considered components of a full APC model, they will each be shortly describes in this subsection. Afterwards, the fundamentals of the full APC model will be described.

An age-period model states that age-specific rates have the same shape in each period but possibly vary in level between periods (Carstensen & Keiding, 2005). It can be expressed as:

$$\lambda_{ap} = a_a \cdot b_p \quad \text{or} \quad ln[\lambda_{ap}] = \alpha_a + \beta_p \qquad \text{(adapted from Clayton \& Schifflers, 1987a)}$$

Where λ represents the rate at age a and period p, a_a measures the age effect (α_a the log of the age effect effect) and b_p the period effect (β_p the log of the period effect). It is common to constrain one period parameter to be 0, $\beta_{p0} = 0$. This period will then function as the reference (or baseline) period. The αs are the logs of age-specific rates for the reference period, and the age-specific rates for that period are $\exp(\alpha_a)$. The βs are (natural) log rate-ratios relative to period p_0 (Carstensen & Keiding, 2005). Therefore, the age-specific rates should be considered cross-sectional rates (as they refer to p_0): they have a demographic interpretation as opposed to a biological interpretation (Carstensen & Keiding, 2005).

The age-cohort model is very similar to the age-period model. Age-specific rates are stated to have the same shape in each cohort, but possibly vary in level between cohorts (Carstensen & Keiding, 2005. It can be expressed as:

$$\lambda_{ac} = a_a \cdot c_c \quad \text{or} \quad ln[\lambda_{ac}] = \alpha_a + \gamma_c \qquad \text{(adapted from Clayton \& Schifflers, 1987a)}$$

Where λ represents the rate at age a and cohort c. For age-cohort models it is common to constrain one cohort parameter to be 0, $\gamma_{c0} = 0$. Similar to age-period models, the αs are the logs of age-specific rates for the reference cohort, and the age-specific rates for that cohort are $\exp(\gamma_a)$. The γs are (natural) log rate-ratios relative to period c_0 (Carstensen & Keiding, 2005). As the produced age-specific rates are what would be expected for persons born in c_0, these rates lend themselves more readily to a biological interpretation (Carstensen & Keiding, 2005). It should be noted that the oldest and youngest cohorts in the analysis have less information (because they have less observations in the Lexis diagram), it is therefore advised not to choose these as the reference cohort (Carstensen & Keiding, 2005). Finally, it should be noted that age-cohort models often have a much better fit than age-period models: this is in part because it has greater complexity; there are more diagonals (and thus more cohort parameters) in a Lexis diagram than there are columns (period parameters) (Clayton & Schifflers, 1987a).

It is not uncommon for both the age-period and the age-cohort model to provide a good fit to the same data. The first model may show a highly significant period effect while the second model may show a highly significant cohort effect (Clayton & Schifflers, 1987a). This can be explained by the fact that some of the temporal variation of rates is

indistinguishable between period and cohort: both models take into account this temporal variation of the rates. This temporal component is referred to as 'drift' (Clayton & Schifflers, 1987a) and represents the common linear trend of age and period. While one can distinguish between period-drift and cohort-drift, both will have the same values:

$$ln[\lambda_{ap}] = \alpha_a + \delta_p (p - p_0)$$

$$ln[\lambda_{ac}] = \alpha_a + \delta_c (c - c_0)$$ (adapted from Clayton & Schifflers, 1987a)

Where p_0 is the reference period and c_0 the reference cohort. δ_p represents the constant change in log-rates from one period to the next (period-drift) and δ_c the constant change on log-rates from one cohort to the next (cohort-drift) (Clayton & Schifflers, 1987a). Carstensen & Keiding (2005) demonstrate that both of the previous models are the same, meaning there is only one age-drift model.

Carstensen and Keiding therefore conclude that, analytically, it makes no sense to attribute the constant annual change in rates to either period or cohort. However, similar to Glenn (2005), they add that the choice of the parameterization should be based on context ('side information' in Glenn's words) or additional data. It cannot be based on the data recorded in the Lexis diagram alone (Carstensen & Keiding, 2005). Because it is difficult to know whether drift should be attributed to either period or cohort, Clayton & Schifflers (1987b) suggest first fitting an age-drift model: only if this model does not adequately describe the data should age-period or age-cohort models be considered. Finally, it is not possible to formally compare whether the age-period or the age-cohort model describe the data more adequately (Clayton & Schifflers, 1987b).

Clayton & Schifflers (1987a; 1987b) write that if neither the age-period nor the age-cohort models adequately describe the data, the full age-period-cohort model should be considered. It can be expressed as:

$$ln[\lambda_{apc}] = \alpha_a + \beta_p + \gamma_c$$ (adapted from Clayton & Schifflers, 1987b)

Of course, as Clayton & Schifflers (1987b) describe, it is still impossible to let the model determine whether to ascribe drift to either period or cohort. This creates problems when interpreting the estimates of model parameters but also in using the model because including age, period *and* cohort leads to overidentification (as $p - a = c$). There is no unique solution to this problem; consequently, a variety of approaches to deal with the identification problem have been proposed, each with their own strengths and weaknesses (for example see Carstensen 2007, Glenn, 2005; Holford, 1991; Clayton & Schifflers 1987b; Sasaki & Suzuki, 1987; Boyle & Robertson, 1987; Osmond & Gardner, 1982; Mason et al., 1973). A common method in the classical approach to APC modelling is discussed in the following subsection, which will also be used in this study.

Finally, a note on age-period-cohort models and submodels (age-period, age-cohort, age-drift) is that it must be assumed that the rate is constant within each tabulation category of the Lexis diagram (Carstensen, 2007). Models for the rate (λ) can be fitted using a programme

for Poisson regression for independent observations and an offset term can be used to represent person-years of exposure in each tabulation category (Carstensen, 2007). Carstensen points out that this does not mean that the number of cases is Poisson distributed, instead the Poisson regression is used for making likelihood-based inference. Furthermore, most programmes produce a deviance statistic (a measure of unexplained variance), which can be used to derive the likelihood-ratio test for model reductions (Carstensen, 2007): as touched upon above, it has become customary to compare submodels with one another and with the full APC model in the either the sequence age › age-drift › age-period › age-period-cohort or age › age-drift › age-cohort › age-period-cohort, though some argue that such comparison is irrelevant as the models are descriptive (Carstensen, 2007).

4.5.2 The classical approach and criticism

The 'classical' approach to age-period-cohort modelling was developed by Clayton & Schifflers (1987a; 1987b). Age, period and cohort are modelled as categorical variables (termed 'factors' by Carstensen (2007) and therefore referred as a 'factorial model' by him): each level in the tabulation has one parameter. Events are often tabulated by age and period in coarse Lexis-squares (e.g. five-year age and period intervals), along with corresponding person-years of exposure. Tabulation is often coarse in the classical approach because it avoids an excess amount of parameters in the model and because the curves of the effects are more likely to be smooth (Carstensen, 2007). The Lexis-square is likely chosen because administrative data are often stored by age and period. However, even if data is also stored by birth cohort, Osmond & Gardner (1989) have demonstrated that models using data tabulated by age, period *and* cohort (Lexis-triangles) *de facto* split into a model for the upper triangles and a model for the lower triangles and are therefore unsatisfactory.

When specifying an age-period-cohort model using the classical approach (categorical variables), we may expect 1+(A-1)+(P-1)+(C-1) parameters, as this is normal for a model with three factors (Carstensen & Keiding, 2005). However, depending on the statistical programme used, the model may not run or we may find that either period or cohort has a second parameter less (either P-2 or C-2). This is caused by linear dependency between the three variables (Carstensen & Keiding, 2005). The method chosen to deal with linear dependency will strongly affect the effect estimates of the model. A common method is to constrain a second parameter of either period or cohort to 0. For period the first and the last period are often chosen as reference or for cohort the first and the last cohort with the most information (as the 'outermost' cohorts are observed for less time and are therefore less reliable). Two constraints for age is uncommon as this variable is considered the most important from an epidemiological point of view (Carstensen, 2007). The cohort or period variable with only a single parameter constrained to 0 will absorb drift (e.g. Janssen, 2005), while the variable with two parameters constraints to 0 will only show non-linear effects. A variation on this model, which is much less common, is to constrain two parameters to 0 for both period and cohort, allowing for an explicit drift parameter. In such a model, both period and cohort only show non-linear effects (Carstensen, 2007). Analytically, of course, both models are the same: in the first drift is implicit, in the second drift is explicit.

Carstensen (2007) and Carstensen & Keiding (2005) suggest a number of amendments to the classical approach. A major source of criticism is the (coarse) tabulation in Lexis-squares: the coarser the tabulation, the more information is lost. Instead, Carstensen (2007) suggests a tabulation by age, period *and* cohort (Lexis-triangles) of as small a size as possible with a correspondingly more accurate estimation of person-years (for the latter see Rozenbauer & Strassburger, 2008). In order to avoid a disjoint model (one for upper triangles and one for lower triangles), which occurs when Lexis-triangles are used in the classical approach, Carstensen proposes a parametric solution: age, period and cohort should be modelled as continuous variables. In order to allow the slope to change and thereby model non-linear effects, Carstensen (2007) suggests using parametric smoothing techniques such as splines with 1^{st}, 2^{nd} and 3^{rd} degree polynomials in predefined intervals and knots connecting those intervals, natural splines and combinations of polynomials of various (even non-integer) powers. As an added advantage, a parametric function for cohort will also allow the model to reflect more adequately the available information in cohorts (the outermost cohorts have less information), whereas the classical approach will generate a parameter even for cohorts with a single point of observation (Carstensen, 2007). Carstensen also suggests a number of other amendments regarding the parametrization of APC models, but these will not be considered here as they are less relevant to this study.

A final suggestion by Carstensen (2007) and Carstensen & Keiding (2005) regards the reporting of age-period-cohort model outcomes: it should be possible to reconstruct the fitted rates from the reported values. Often, graphs are presented with only the relative effects, making it impossible to reconstruct the fitted rates (Carstensen, 2007). Carstensen suggests plotting age on a rate-scale and period and cohort on a relative-risk scale (rate ratio). As one of the three effects is now on a rate-scale, the fitted rates can be reconstructed. Furthermore, Carstensen (2007) suggests displaying all three effects in one figure with the same equidistance on the horizontal scale (though age will have age on the x-axis, while cohort and period will have years on the x-axis). Displaying in this manner will allow the slopes of the three effects to be more easily compared. As is conventional, Carstensen also advises not to report tables with model outcomes.

4.5.3 Construction of APC models in this study

This section details the specifics of the models used in this study. An APC model is made for user prevalence of benzodiazepine and another for user prevalence of statin. Before describing the technical aspects of these specific models, it may be useful to consider that models for user prevalence of drugs differ somewhat from the standard application of APC models in epidemiology. Commonly, applications of APC model disease or mortality rates. Firstly, the models in this study have user prevalence instead of a rate as the dependent variable. As explained in section 4.2, prevalence is not a true rate. Nevertheless, prevalence and rate are very similar in their construction, making it possible to also use (user) prevalence as the dependent variable in an APC model. Secondly, the dependent variable is prevalence of users of a drug, rather than disease or mortality. This means that, in their interpretation, the models are (even) further removed from biological effects than APC models commonly are.

In this study, the classical approach as detailed by Clayton & Schifflers (1987a; 1987b) is followed, with some deviations detailed below. Taking into account the criticism by Carstensen & Keiding (2005), the classical approach should function properly as the chosen intervals are less coarse than is traditional (three-year rather than five-year) and therefore less information is lost, the chosen drug types have a large number of users and therefore modeling of statistical noise is less likely, and because it is not possible to use Lexis-triangles (without making additional assumptions). Regarding the latter point: parallelograms are used to overcome the problem of overestimation as detailed in subsection 4.2.3. This also means a disjoint model is avoided and therefore it is less necessary to use continuous variables. Furthermore, because it uses continuous variables, the Carstensen approach may smooth out dips or spikes that are relevant from a theoretical perspective. By using Clayton & Schifflers' approach, this is avoided.

The tabulation of data in the Lexis diagram for the models used in this study is identical to that used in the descriptive graph of age-specific user prevalence in cohorts (subsection 4.3.3), represented visually in figure 4.6. The same information is repeated here: information on the number of users and the exposure is tabulated in three-year period and three-year cohort intervals (parallelograms), with the age-range in the third period-year of this selection as the age-range of the entire selection. The cohorts categories are: 1911-1913, 1913-1915, ..., 1986-1988. The age-ranges in each period are 20-22, 23-25, ..., 83-85. The periods are 1994-1996, 1997-1999, ..., 2006-2008. The above tabulation is chosen because of the availability of the data: tabulation by single years would result in an excess of parameters, while five-year intervals would provide too few data points to properly model potential period effects (note the importance of period effects in this study: they represent guideline changes).

For both the models used in this study, the contributions of drift, non-linear period and non-linear cohort are measured by comparing the reductions in scaled deviance between submodels and the final APC model. The sequence followed is age ‹› age-drift ‹› age-period ‹› age-period-cohort. For statin, the last two models have implicit drift, whereas those for benzodiazepine have explicit drift: whether drift is explicit or implicit does not affect the reductions in scaled deviance. The statistical significance of the differences in scaled deviance between subsequent models is tested using a log-likelihood ratio test with one-sided *p*-values: the difference in scaled deviance between subsequent models is compared using a chi-squared distribution with degrees of freedom equal to the difference in degrees of freedom between the compared models. The scale for the deviance statistic is one because the deviance/df ratio of both full APC models are considered close enough to one not to suspect problems of overdispersion (the values of both are between one and two; Field, 2009).

Both APC models were built as Poisson loglinear models using the generalized linear model procedure in SPSS. The number of users of a drug is the dependent variable and the natural log of the exposure is entered as an offset variable. The log of the exposure is used as the procedure uses a log-link function for the left side of the model, but not for the right side which is where the offset is placed, e.g.

we achieve:

$$\ln\left(\frac{users_{apc}}{exposure_{apc}}\right) = constant + \alpha_a + \beta_p + \gamma_c$$

by defining the model as:

$$\ln(users_{apc}) = [\ln(exposure_{apc}) + constant] + \alpha_a + \beta_p + \gamma_c$$

Both the benzodiazepine and the statin model are very similar: the models are the same for age and cohort: age (a) has 22 categories and age category 20-22 (the first category) is chosen as the reference category, resulting in 21 parameter estimates. Cohort (c) has 26 categories and two cohort-categories are chosen as reference: 1925-27 and 1976-79 (the outermost cohorts with full information), resulting in 24 parameter estimates.

Period (p) has five categories, but the benzodiazepine and statin model differ when it comes to period: for statin an implicit drift parameter was used because it is known from side-information (literature) that the extremely strong rise in statin-use is a period effect. This means that the vast majority of drift is likely attributable to cohort. Period-category 1994-96 is chosen as the reference category, resulting in four parameter estimates for period.

For benzodiazepine, the literature is unclear as to where to attribute drift: guideline-changes are period effects, however *past* age effects (rising number of users with age) that are no longer of influence due to guideline change will result in *current* cohort differences. Therefore it was chosen to build a model with explicit drift, requiring two reference categories for period: 1994-96 and 2006-2008 (the outermost periods) were chosen as the reference periods, resulting in three parameter estimates for period. Subsequently, drift was split evenly between period and cohort.

Both the benzodiazepine and the statin models were run twice: once on data including only females and once on data including only males. This was chosen over entering a sex variable because the latter assumes the shape of the APC-effects for males and females is the same with merely different levels between the sexes, which is not necessarily true.

As advised by Carstensen & Keiding (2005), the models are represented visually in this report (full output can be found in appendix B). Age is reported on a rate-scale in order to allow reconstruction of the fitted rates. These figures were produced by taking the exponent of the sum of the coefficient of an age category and the constant. This value was subsequently multiplied by 1000 to find the number of users per 1000 population. For period and cohort the exponents of the coefficients of period and cohort respectively are used.

Chapter 5. Results

This chapter shows the results of the study. The chapter is divided into two sections: the first section (5.1) shows the descriptive graphs of the data on the use of benzodiazepine (5.1.1) and statin (5.1.2). The second section (5.2) shows the output of the APC models for benzodiazepine (5.2.1) and statin (5.2.2). The results are discussed in the following chapter.

5.1 Descriptive results

5.1.1 Descriptive results: benzodiazepine

Figure 5.1 displays the age-standardized user prevalence of benzodiazepine for males and females. It can be seen that user prevalence is higher for females than for males. We see a level prevalence between 1994 to 1997 (even a slight increase for males), then a strong decline between 1997 and 1998, followed again by a level period between 1998-2000. If the 1998-2000 trend is extrapolated, it becomes very clear that a steady decline has set in since 2001.

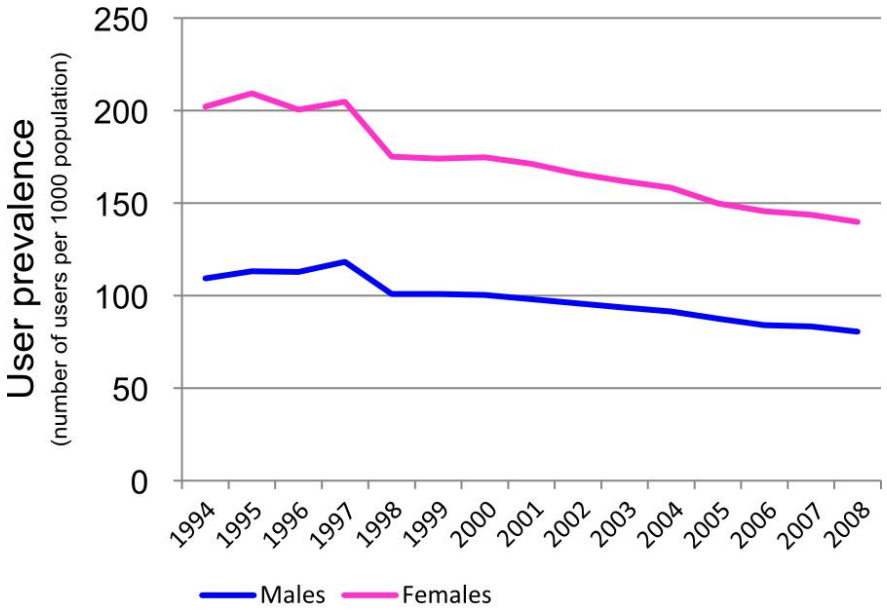


Figure 5.1. Age-standardized user prevalence of benzodiazepine by period and sex in the Netherlands 1994 to 2008.

Figure 5.2 displays the age-specific annual user prevalence of benzodiazepine for males and females. It can be seen that for both males and females the prevalence goes up with age. The increase appears to be linear with age for females, whereas for males there is a short level period between ages 45 to 60 in the most recent years. Similar to figure 5.1, a decline between subsequent years can be seen. For both males and females, the period lines are approximately parallel to each other.

Figure 5.3 shows the age-specific user prevalence of benzodiazepine for three-year for cohorts. It can be seen that the prevalence increases with age for the younger cohorts (1955 to

1983), but becomes more level over time. Older cohorts (< 1955 and > 1928) have undergone a decline since 1994-1996. For those cohorts born before 1928 the trend appears to be mostly level again. For both sexes, older cohorts have higher prevalence than younger cohorts at the same ages, indicating that in the past the number of users increased with calendar time. A notable exception to the apparent rule that older cohorts have higher prevalence than younger cohorts is the 1917-1919 cohort for males. Also of interest is the large gap in users between the 1938-1940 cohort and the 1941-1943 cohort for females. A similar gap seems to exist for males, but it is smaller. For both males and females, the cohort lines are approximately parallel to each other, though there is more deviation from this than among the period lines.

Figure 5.4 shows the age-specific user prevalence of benzodiazepine for single-year cohorts. For benzodiazepine, the differences between single-year birth cohorts are of note. Since the focus is on the difference between cohorts in prevalence levels, the position of cohorts within calendar time is not indicated in the figure. The overall patterns are largely similar to figure 5.3. Figure 5.4a shows that the 1917 cohort has lower prevalence than the 1920 cohort for males. Also for males, the 1932 cohort has higher prevalence than the 1929 cohort. In figure 8.4b, the 1918 cohort is below the 1921 for both males and females. The 1942 cohort has lower prevalence than the 1945 cohort for males. A gap between the 1942 cohort and the 1939 cohort can be seen for females in the same figure. Figure 5.4c shows approximately the same trends as figure 5.3. For males the 1949 cohort is below or equal to the 1952 cohort. For females, the 1949 cohort has higher prevalence than it should, putting it at approximately the same level as the 1946 cohort.

Figure 5.5 shows the two-year age-specific *incidence* for two-year cohorts. For both males and females, the incidence increase with age for the younger cohorts (approximately cohorts 1964 to 1984). For females, this increase is much steeper than for males. For males, this increase stops during 2003-2004 and seems to stabilise after that period. For the middle aged male cohorts (1930 to 1963), a decline sets in after 2003-2004. The older cohorts, 1915 to 1928, do show some increase with age. For females, the middle aged to oldest cohorts (< 1964) show a steep decline from 1995 – 1996.

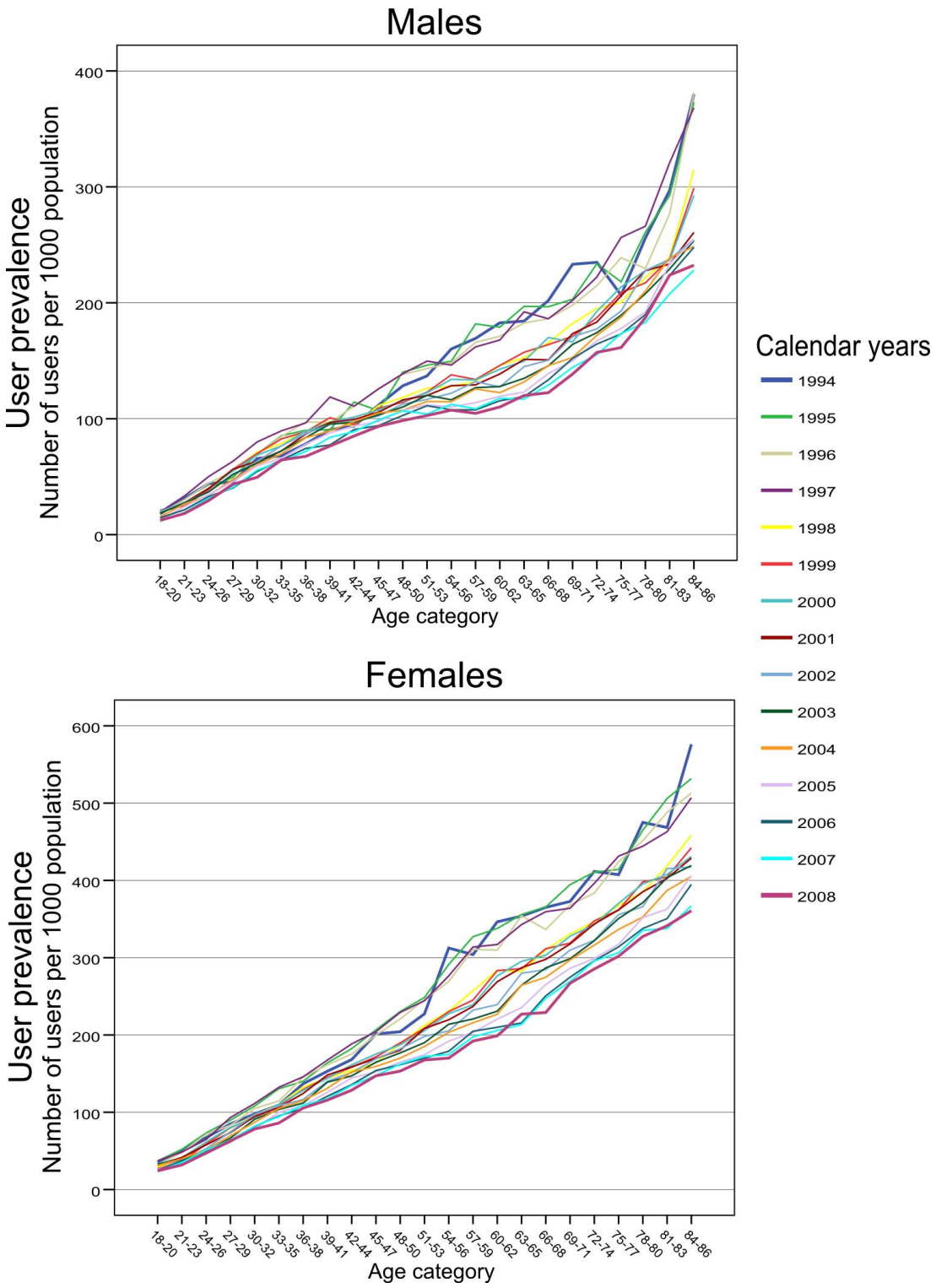


Figure 5.2. Three-year age-specific user prevalence of benzodiazepine by period and sex in the Netherlands. Ages 18-20 to 84-86 and periods 1994 to 2008.

N.B. The lines for 1994 and 2008 are thicker for easier comparison of the overall trend. The scales on the y-axes of males and females differ.

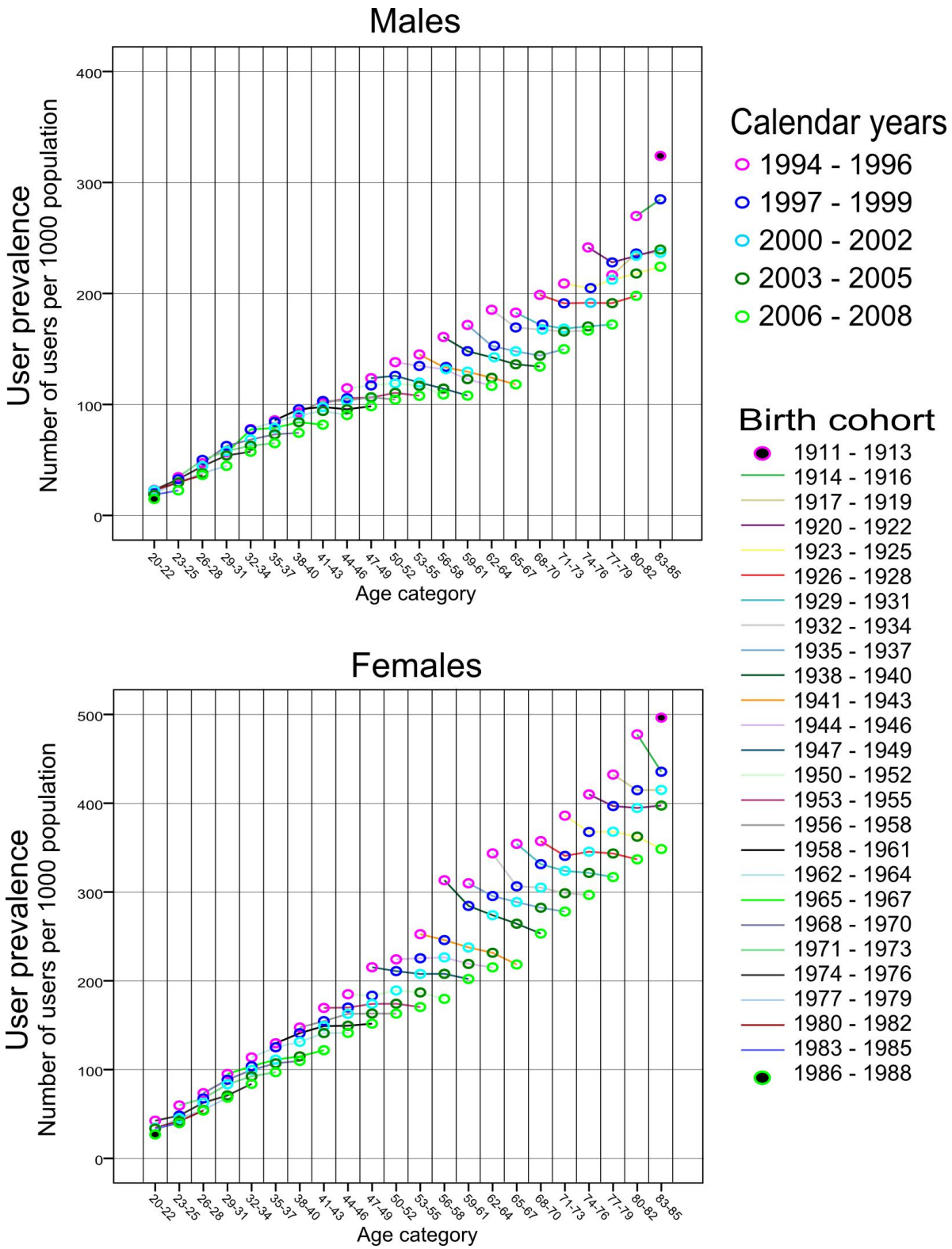


Figure 5.3. Three-year age-specific user prevalence of benzodiazepine by three year cohorts and sex in the Netherlands. Ages 20-22 to 83-85, periods 1994-1996 to 2006-2008, cohorts 1911-1913 to 1986-1988.

N.B. Comparison vertically (within an age range) makes it possible to compare prevalence between cohorts at the same ages whereas comparison within lines makes it possible to compare the age- and-time trend within a cohort. The scales on the y-axes of males and females differ.

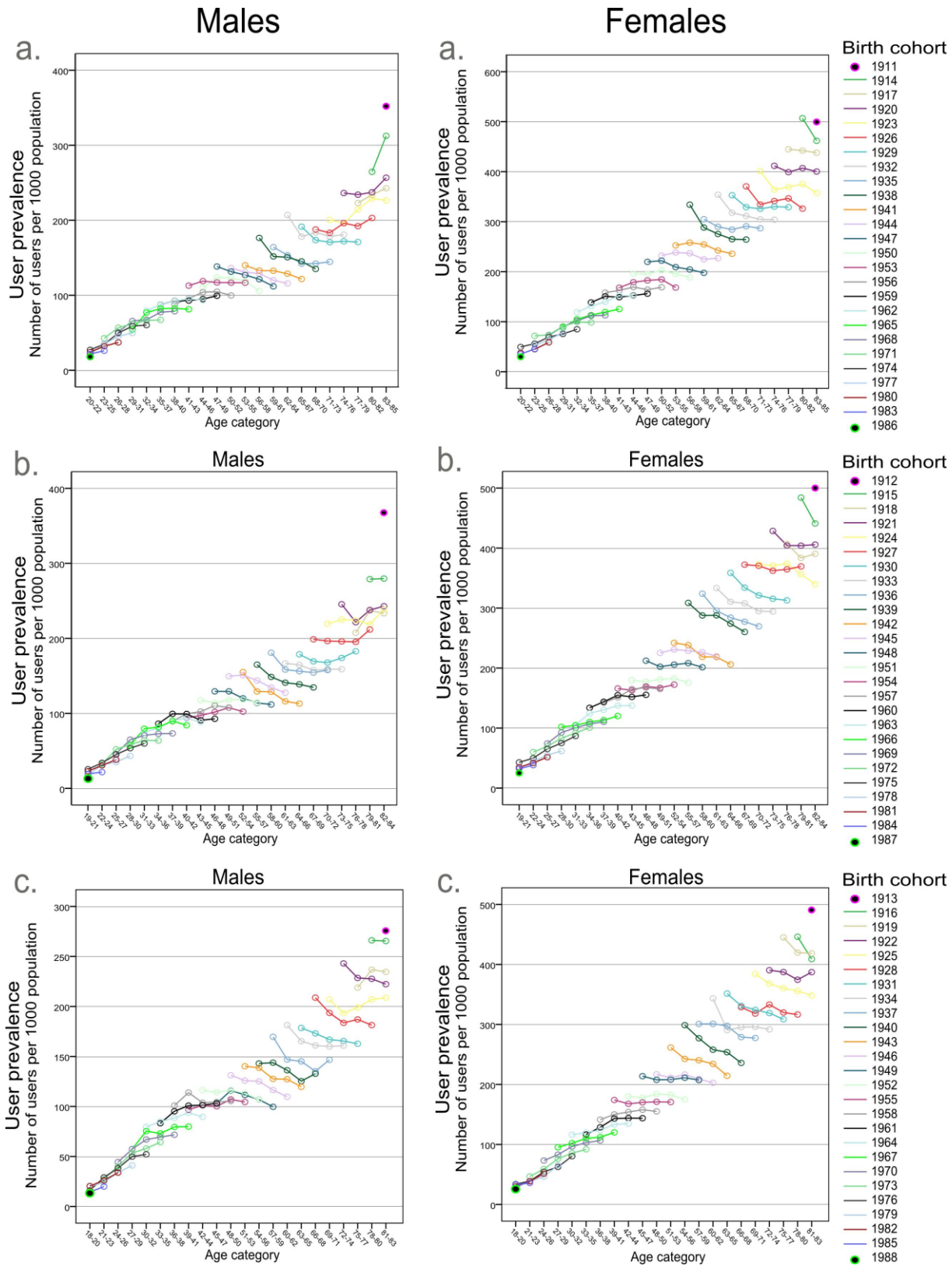


Figure 5.4. Three-year age-specific user prevalence of benzodiazepine by one-year cohorts and sex in the Netherlands. Ages 20-22 to 83-85. Figure 8.4a shows cohorts 1911, 1914, …., 1986. Figure 8.4b shows cohorts 1912, 1915, …., 1987. Figure 8.4c shows cohorts 1913, 1915, …., 1988.

N.B. The scales on the y-axes of males and females and between a, b and c differ.

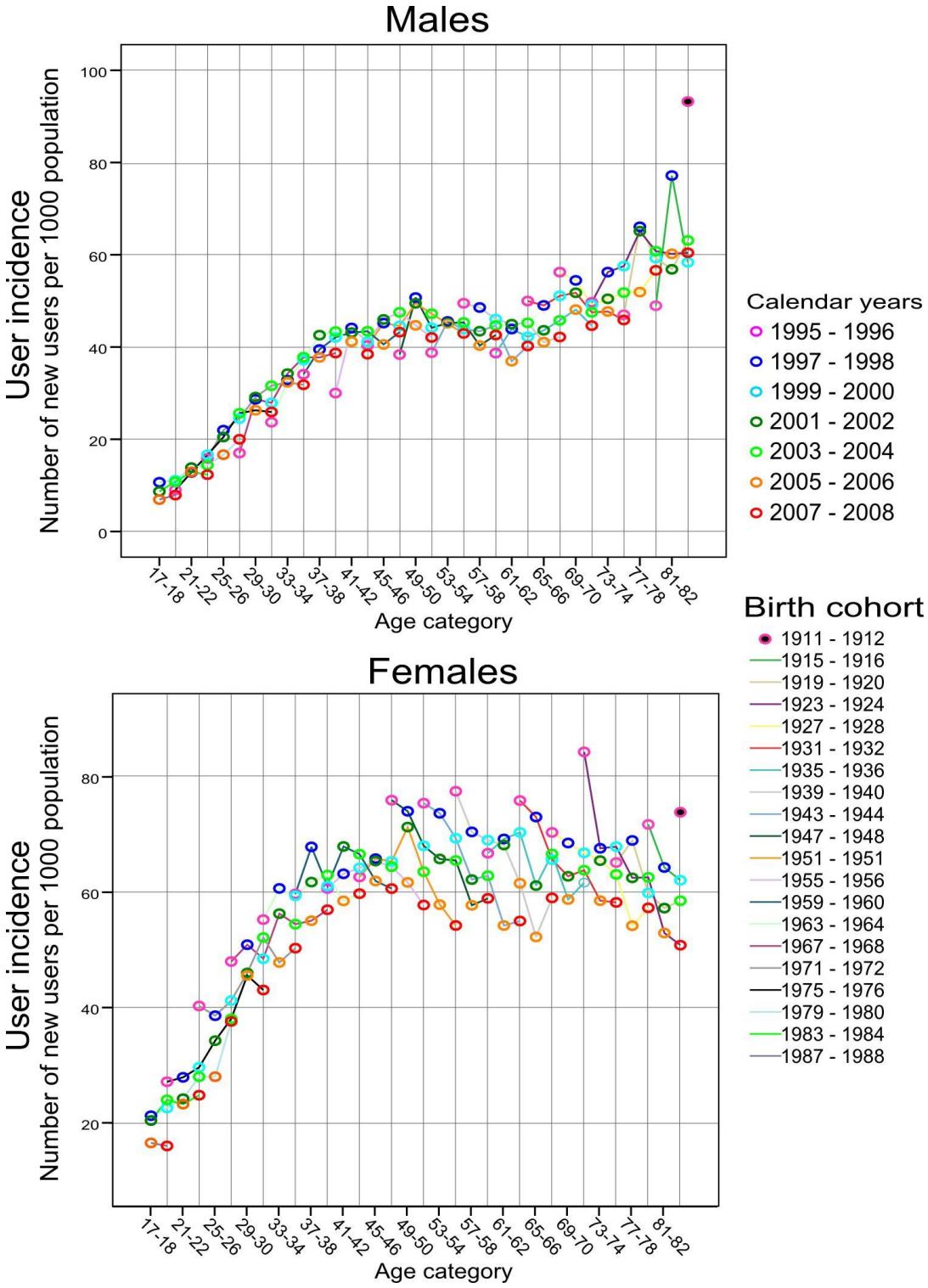


Figure 5.5. Two-year age-specific user incidence of benzodiazepine by two-year cohorts and sex in the Netherlands. Ages 17-18 to 83-84 and cohorts 1911-1912 to 1987-1988.
N.B. the scales on the y-axes of males and females differ.

5.1.2 Descriptive results: statin

Figure 8.6 displays the age-standardized user prevalence of statin for males and females. There are more users of statin among males than among females. For both sexes there is a strong increase in users over time, with a short level period between 1997 and 1998. The slope increases in the period 2003-2006 relative to the previous periods but then levels off in 2006.

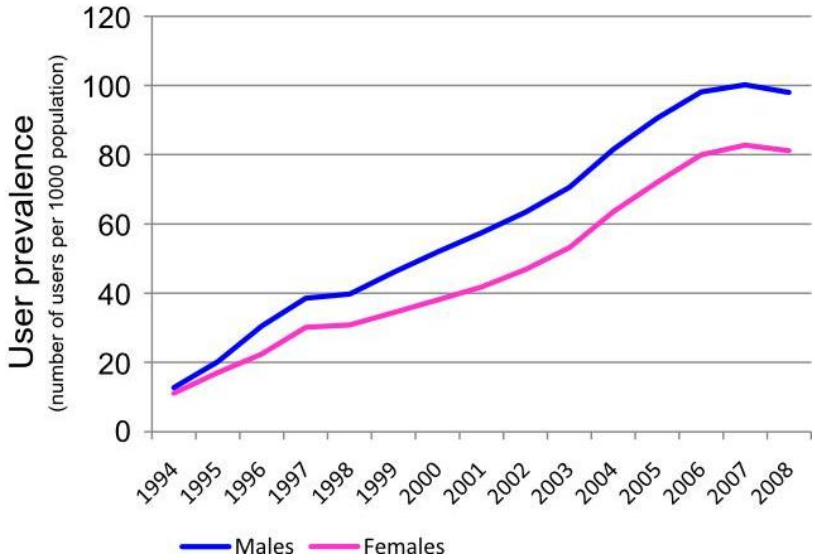


Figure 5.6. Age-standardized user prevalence of statin by period and sex in the Netherlands 1994-2008.

Figure 5.7 displays the age-specific annual user prevalence of statin for males and females. It can be seen that for both males and females the prevalence increases with age in each period: At age category 30-32, there are almost no users per 1000 population in any of the periods. In 1994, the peak of user prevalence can be found at age category 63-63. In 2001 the peak has shifted to age category 69-71, and in 2008 it can be found at age category 75-77. After each peak we see a strong decline in the prevalence with age. The upwards slope towards the peak and the downwards slope from the peak increase in steepness with increasing calendar time. Similar to figure 5.6, a strong increase between periods can be seen, with the exception being the most recent years (2006-2008).

Figure 5.8 shows the age-specific prevalence for cohorts. A strong increase with age or time can be seen for all cohorts, reflecting the findings of figures 5.6 and 5.7. The slope becomes more steep after the period 2002. The increase has a less steep slope at the oldest ages or for the oldest cohorts (ages 74 to 85 and correspondingly cohorts 1911 to 1920). The figure also shows that the cohort 1929-1931 is responsible for the shifting peak in statin use, as it always has the most statin users per 1000 population in any of the calendar years. Furthermore, younger cohorts have more users of statin at the same ages as older cohorts.

For statin, the differences between single-year birth cohorts are negligible. Therefore, the results are not reproduced here. See appendix C for these figures.

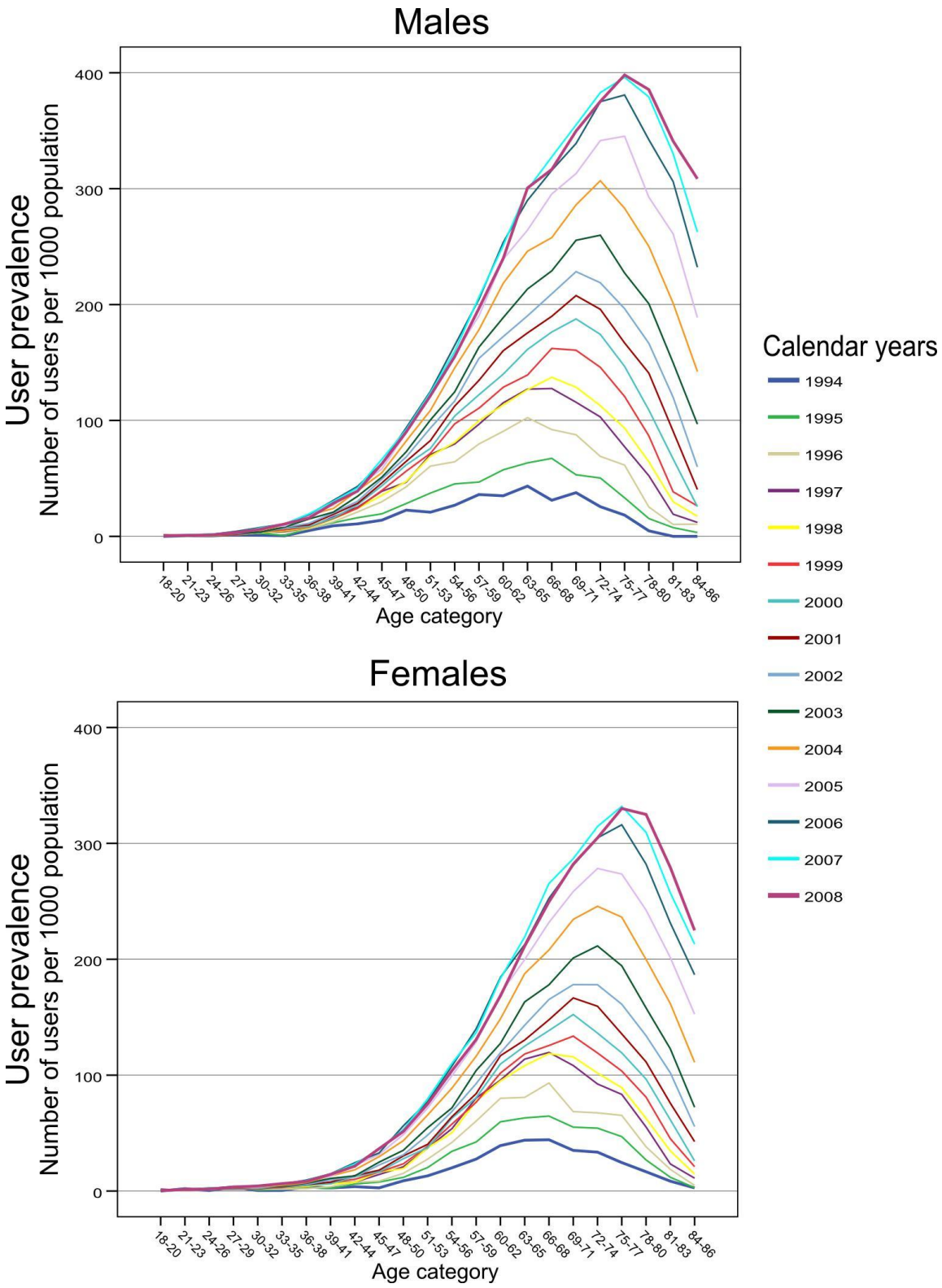


Figure 5.7. Three-year age-specific user prevalence of statin by period and sex in the Netherlands. Ages 18-20 to 84-86 and periods 1994 to 2008.

N.B. The lines for 1994 and 2008 are thicker for easier comparison of the overall trend.

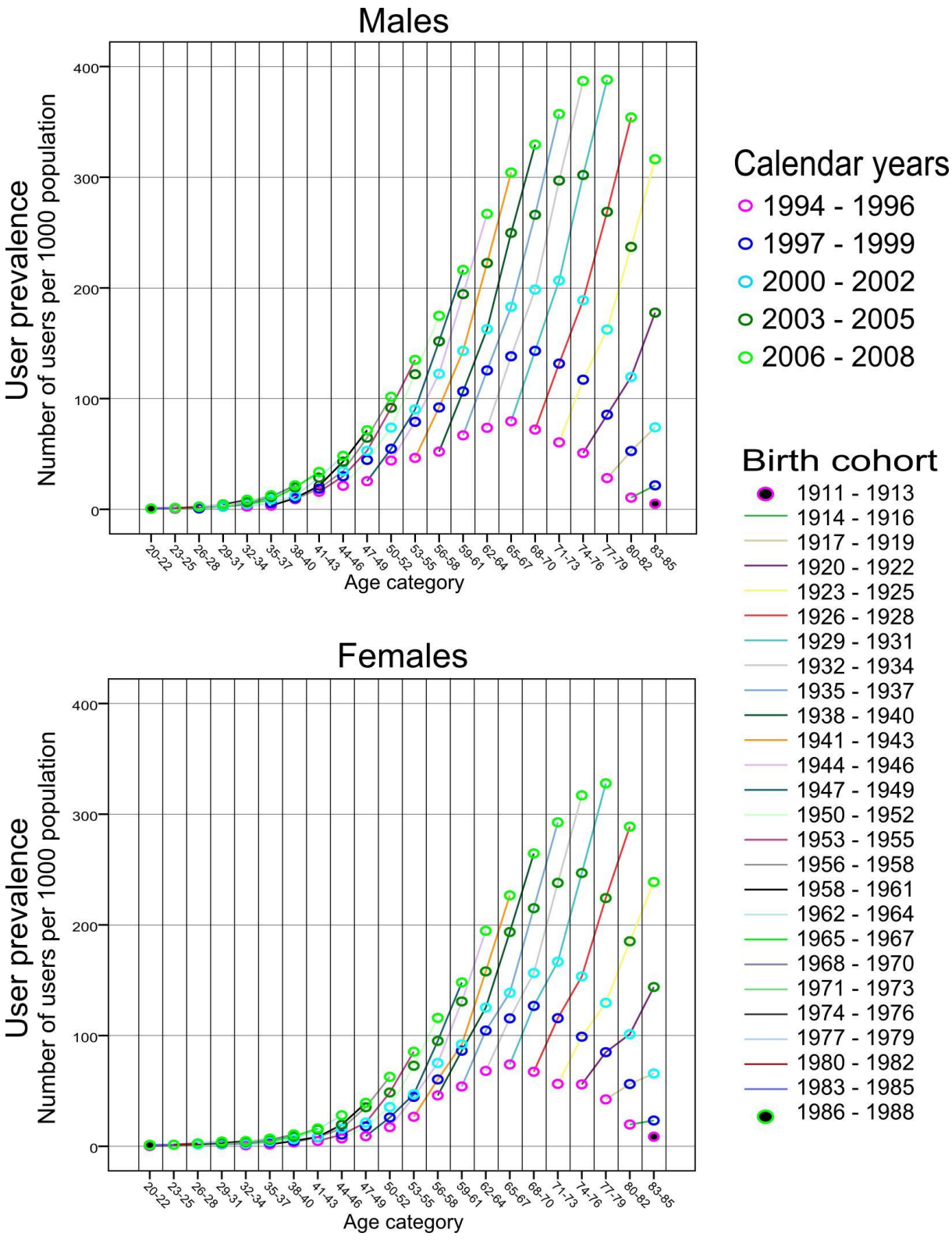


Figure 5.8. Three-year age-specific user prevalence of statin by three year cohorts and sex in the Netherlands. Ages 20-22 to 83-85, periods 1994-1996 to 2006-2008, cohorts 1911-1913 to 1986-1988.

N.B. Comparison vertically (within an age range) makes it possible to compare prevalence between cohorts at the same ages whereas comparison within lines makes it possible to compare the age- and-time trend within a cohort.

5.2 APC model output

5.2.1 APC model output: benzodiazepine

Figure 5.9 shows the output of the APC model for benzodiazepine (see appendix B for the remaining non-graphical output). For both sexes we see an increase in the number of users per 1000 population with age. For females this increase is somewhat more linear than for males, though for both sexes the strongest increase in user prevalence appears to be at 70-plus (the slope becomes steepest). Cohort and period effects are expressed as rate-ratio. Since drift was split evenly between cohort and period a decrease can be seen with increasing calendar time: older cohorts have a higher rate ratio than younger cohorts and the rate ratio decreases in each subsequent calendar year. For males, there are some notable deviations from the overall trend: there is a strong dip for the 1917-19 birth cohort, a smaller one for the 1929-31 cohort, then a long dip lasting for the 1932 to 1964 birth cohorts, and finally a smaller one again the 1977-79 cohort. For females, deviations from the overall trend are much less apparent: notable is the decline between the 1938-40 cohort and the 1941-43 cohort, returning to a higher level again around 1964. Finally, for the period effects no strong deviations from the overall trend can be discerned, the exception being a small dip in the 1997-99 period relative to the overall trend.

Figure 5.10 shows the reductions in scaled deviance as contributed to the overall model on benzodiazepine user prevalence by drift, non-linear period and non-linear cohort for males and females separately. Table 5.1 shows the associated non-graphical information. For both sexes, drift contributes most (91% for males and 94.5% for females). The non-linear cohort effect contributed more for males (8.6%) than for females (5%), corresponding with the above deviations from the overall trend being clearer for males. The non-linear period effect for males and females was minor for both males and females (both ca. 0.4%), though their addition still led to a significantly better model fit. The table also shows that the final model has a deviance/df between one and two, indicating no problems of overdispersion.

Table 5.1. Goodness of fit statistics of the models of benzodiazepine.

Goodness of fit

Males

	Sc. Dev.*	Reduction	df	Difference in df	*p*-value**	Deviance/df
Age	2629	-	88	-	-	29.88
Age-drift	322	2307	87	1	> 0.005	3.70
Age-period-drift	313	9	84	3	> 0.05	3.72
Age-period-cohort	93	219	60	24	> 0.005	1.56

Females

	Sc. Dev.*	Reduction	df	Difference in df	*p*-value**	Deviance/df
Age	5376	-	88	-	-	61.09
Age-drift	358	5019	87	1	> 0.005	4.11
Age-period-drift	334	23	84	3	> 0.005	3.98
Age-period-cohort	65	270	60	24	> 0.005	1.08

* Scaled deviance, ** One-tailed

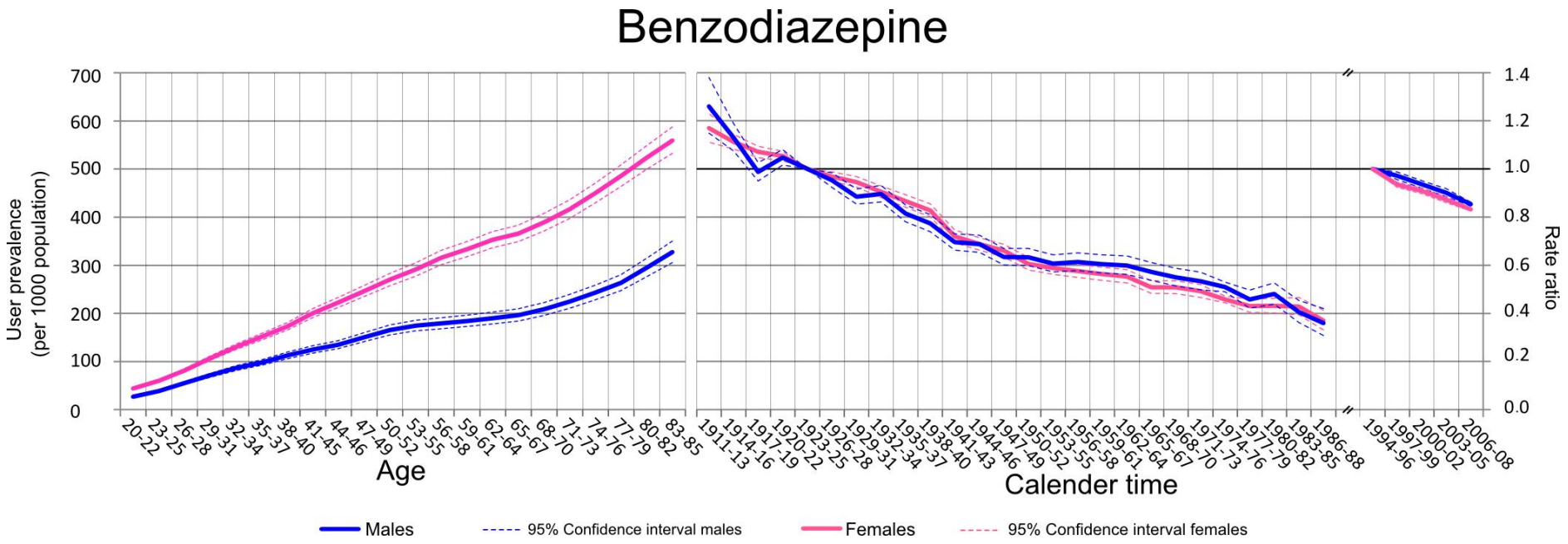


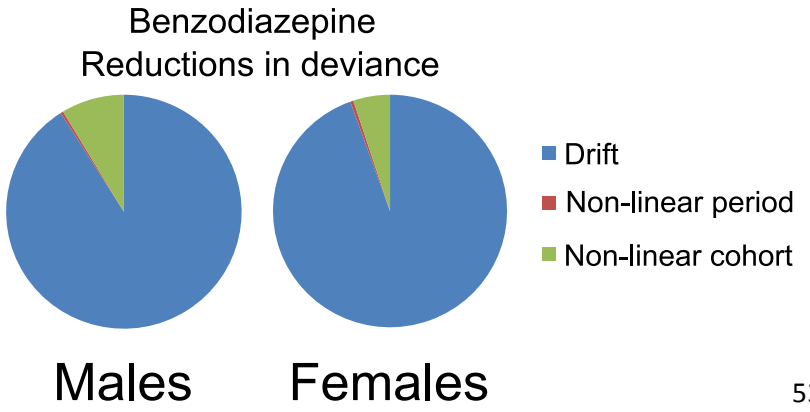
Figure 5.9. (above) Age, period and cohort trends in user prevalence of benzodiazepine.

The lines on the left represent age effects, the middle lines non-linear cohort effects and half of the drift while the lines on the right represent non-linear period effects with the remaining drift.

Non-graphical model output can be found in appendix B.

Figure 5.10. (right) Contribution to reductions in scaled deviance for benzodiazepine.

All effects are significant at $p < 0.01$ (one-tailed) level, with the exception of the non-linear period effect for males, which is significant at the $p < 0.05$ (one-tailed) level.



5.2.2 APC model output: statin

Figure 5.11 shows the output of the APC model for statin (see appendix B for the remaining non-graphical output). For males and females the number of users per 1000 population increases with age: for males this the increase starts at around age 30 and is mostly linear. The increase for females also starts at approximately age 30 but the overall shape appears more like an S-curve: the increase is especially strong between circa age 45 to 60 and the increase slows after that, leveling off at around age 75. Cohort and period effects are, again, expressed as rate-ratio. The cohort effects are strictly non-linear: very clear is the strong increase from oldest cohorts to ca. 1931 for both males and females. For males the rate ratio in 1931 to 1949 remains level, whereas for females it declines in the same period. For males, from 1949 onwards the trend declines, with fluctuations. For females, the trend remains mostly level from 1949 until 1974-76 (the second reference), with two spikes of note (1956-58 and 1962-64). Finally, for the period effect (which includes all of the drift) we see a strong rise with increasing calendar time. For both sexes the slope becomes most steep from the period 2000-02 onwards.

Figure 5.12 shows the reductions in scaled deviance as contributed to the overall model on statin user prevalence by drift, non-linear period and non-linear cohort for males and females separately and table 5.2 shows the associated non-graphical information. Again drift contributes most to the reduction in scaled deviance for both males (84.9%) and females (87.5%). Non-linear cohort is the second strongest contributor for both sexes, but slightly more for males (12.8%) than for females (11.3%). Finally, non-linear period also adds significantly to the model for both males (2.3%) and females (1.3%), which is considerably more than non-linear period did for benzodiazepine. The table also shows that the final model has a deviance/df between one and two, indicating no likely problems of overdispersion.

At the end of appendix B a χ^2 table can be found with degrees of freedom and associated *p*-values.

Table 5.2. Goodness of fit statistics of the models of statin.

Goodness of fit

Males

	Sc. Dev.*	Reduction	df	Difference in df	*p*-value**	Deviance/df
Age	25267		88	-	-	287.12
Age-drift	3891	21376	87	1	> 0.005	44.72
Age-period-drift	3304	587	84	3	> 0.005	39.34
Age-period-cohort	80	3225	60	24	> 0.005	1.33

Females

	Sc. Dev.*	Reduction	df	Difference in df	*p*-value**	Deviance/df
Age	23548		88	-	-	267.59
Age-drift	3039	20509	87	1	> 0.005	34.93
Age-period-drift	2735	304	84	3	> 0.005	32.56
Age-period-cohort	96	2640	60	24	> 0.005	1.59

* Scaled deviance, ** One-tailed

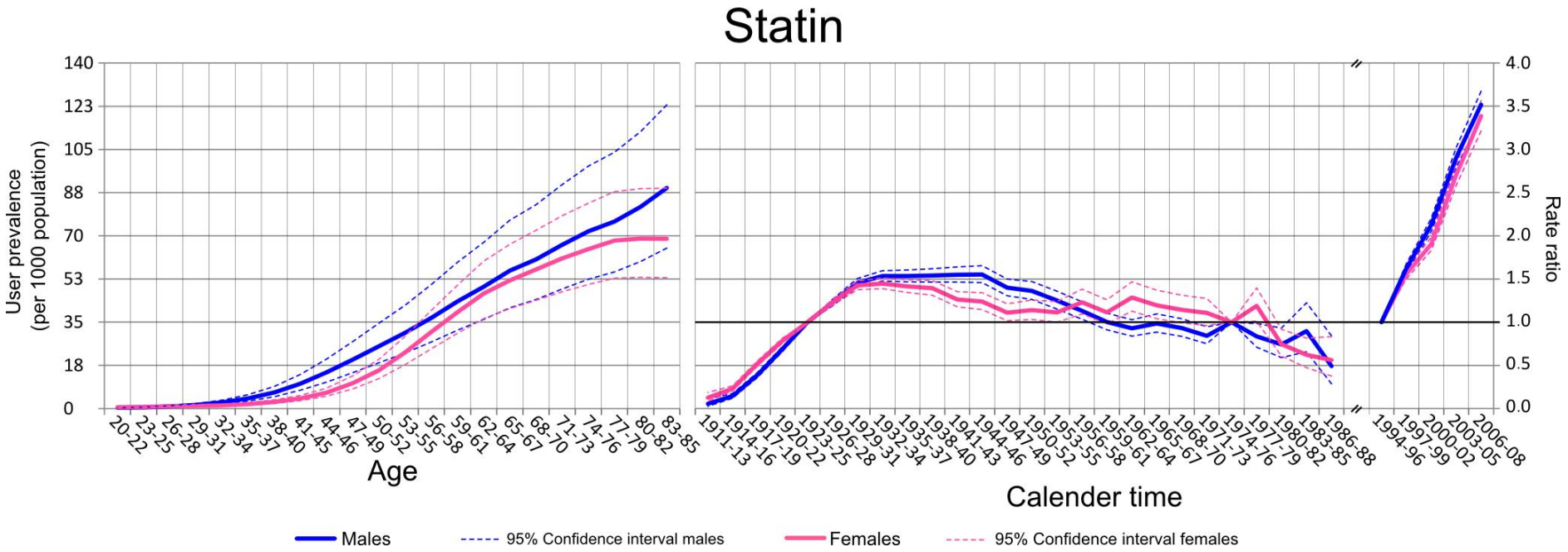


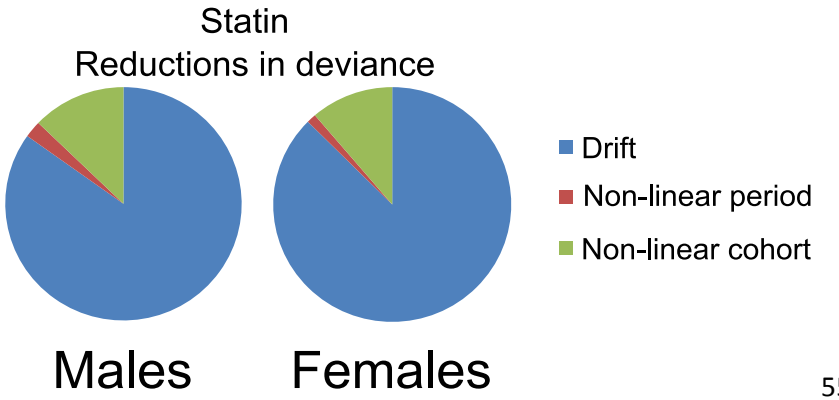
Figure 5.11. (above) Age, period and cohort trends in user prevalence of statin.

The lines on the left represent age effects, the middle lines non-linear cohort effects and the lines on the right show non-linear period effects and all of the drift.

Non-graphical model output can be found in appendix B.

Figure 5.12. (right) Contribution to reductions in scaled deviance for statin.

All effects are significant at $p < 0.005$ (one-tailed) level.



Chapter 6. Discussion

The primary research question of this study is:

'*What are the effects of age, period and cohort on trends of users of benzodiazepine and statin in the Netherlands in the period 1994 - 2008?'*

In this final chapter the primary research question will be answered. Section 6.1 summarizes the results of the study. Section 6.2 reviews the strengths and weaknesses of the data and methods used in the study, and their potential effects on the results. In section 6.3 the results of the study will be interpreted, taking into account the hypotheses that have been formulated for benzodiazepine and statin. Section 6.4 details recommendations and suggestions for policy and for further research. Finally, section 6.5 concludes the study.

6.1 Summary of the results

The age-standardized user prevalence of benzodiazepine of women is twice as high as that of men. The trend for both sexes is initially level, but there is a strong decline between 1997 and 1998 and from 2001 onwards there is a decline in prevalence. The age-specific annual prevalence within each year increase almost linearly with age. The age-trends of user prevalence within cohorts for the youngest cohorts (birthyear > 1955) increases with age but becomes more level around the year 2001. The cohorts born between 1928 and 1955 already undergo decline from 1994 onwards. For the oldest cohorts (birthyear < 1928) the trend is mostly level. In general, older cohorts have higher prevalence than younger cohorts at the same ages, though there are some deviations from this: for males, the 1917, 1918, 1942 and 1949 cohorts have lower prevalence relative to surrounding cohorts. For females, the 1917, 1942 and the 1949 cohorts have less users than surrounding cohorts. The overall pattern of user incidence of benzodiazepine is similar to that of prevalence, though the incidence levels are much lower than those of prevalence. For the young male cohorts the increase levels in 2003-2004, for middle male cohorts (birthyear 1930 – 1963) there is a decline after that point in time. For females, the middle and oldest cohorts (< 1964) show decline from 1994 onwards. The APC model of benzodiazepine shows a linearly increasing prevalence with age. For males, the 1917-19, the 1929-31, the 1935-64 and the 1977-79 birth cohorts all have lower prevalence when compared to the overall trend. For females, deviations from the overall trend are less apparent. Period effects show a decrease over calendar time, with a notable dip in 1997-99. All reductions in scaled deviance (addition of drift, then period, then cohort) are statistically significant.

The age-standardized user prevalence of statin is higher for men than for women. The prevalence increases with calendar time, though there is some stagnation between 1997 and 1998. The increase in prevalence becomes stronger after 2003 but becomes level around 2006, even showing minor decline between 2007 and 2008. The age-specific annual prevalence for statin increase starting at around age 40 and moves to a peak found in the range 63-75 and then decline again. This peak can be found at age 63-65 in 1994 and age 75-77 in 2008: it

moves to older ages with each passing year. User prevalence within cohorts shows that this shifting peak can be attributed to the 1929-1931 cohort; this cohort always has the highest number of users within a period-year. For both sexes the APC model shows an increase in user prevalence with age. The non-linear cohort effects show an increase in rate ratio from the oldest cohort (1911-13) to 1929-31. For males, the rate ratio then remains level until cohort 1944-46, after which a decline sets in. For females a slow decline sets in from 1929-31. The period trend (including drift) shows a strongly increasing rate ratio over time. All reductions in scaled deviance (addition of drift, then period, then cohort) are statistically significant.

6.2 Evaluation of data and methods

This section discusses the quality of the data and the adequacy of the methods used in the study. In particular, the manner in which the data and methods have shaped the outcomes of the study will be reviewed.

Drug registration databases are a common source of data for pharmacoepidemiological studies. This study used a drug registration database of high quality. All of the data comes from the same source (IADB.nl) and the data was gathered and coded in the same manner during the observation period. However, it is noteworthy that the database increased in size and coverage during the 1994-98 period as it may affect the results. The increase in size of the database was taken into account in the study when determining the calculation of exposure. For most age categories, exposure was estimated as $½\ l_{a,p} + ½\ l_{a+1,p+1,}$ this formula for exposure is common in demography and epidemiology. When this formula was used for the years 1994-97, it lead to findings that were discernibly erroneous. Because this was likely caused by $l_{a+1,p+1}$ being much higher than $l_{a,p}$, leading to exposure estimations that were far too high, the exposure was instead estimated using solely $l_{a,p}$ for the first four years. This lead to prevalence figures that were more likely to be accurate. However, it was found that there was a strong trend-break between 1997 and 1998: for benzodiazepine the number of users strongly declined (the trend was otherwise level), whereas for statin the number of users remains level (whereas it otherwise underwent growth). The author considers it quite likely that this is caused by an exposure estimation that is lower than it should be in the period 1994-97, making the number of users per 1000 population appear to be higher than is truthfully the case in that period.

The user prevalence of major drugs calculated using the IADB are considered to be representative for the Netherlands as a whole. However, the study population is found in the north and east of the Netherlands. This may have some effects on the results that should be considered. Firstly, most drug registration databases, including the IADB, store relatively little information on the individuals visiting pharmacies. This means the study cannot control for the ethnic composition of the population because information on ethnicity is not stored. The ethnic composition of the population can change over time as the study population is an open population. Studies have shown that ethnicity affects prescription behaviour. In this regard it is perhaps fortunate that the study population is found in the north and east of the Netherlands. The population in this area of the country is more homogeneous than in the western part of the country. Furthermore, the study period is fifteen years, leaving little time for large-scale ethnic compositional change. The author therefore considers it unlikely that

ethnic-compositional change has affected the time-trends in any discernable manner, though some minor effects cannot be ruled out. Secondly, it was expected that the cohorts born during the Second World War would deviate from surrounding cohorts due to having experienced the Dutch Hunger Winter *in utero* or as a young child. While the famine affected all of the Netherlands, the western part of the Netherlands was affected much more strongly than other parts. Individuals that were *in utero* in the Dutch Hunger Winter may have migrated since then and can therefore be found in other parts of the country. Nevertheless, it is possible that a famine-effect would be more pronounced if registration data of the western provinces was used.

The study population is an 'open cohort': individuals can leave and enter the study area at will. This means an individual could receive a prescription at an IADB pharmacy without being considered in the exposure. Fortunately, this situation is unlikely to occur on a large scale: Dutch patients are loyal to one pharmacy and one GP (Leufkens and Urquhart, 2005). However, an open cohort also means that the composition of the patients in the IADB can change. Glenn (2005) writes that compositional change is a fourth factor that, next to age, period and cohort, can affect trends. Population composition should therefore be taken into account where possible. As detailed in the literature review, age and ethnicity can affect prescription behaviour (Midlöv et al., 2009; Denig and Haaijer-Ruskamp, 2009). Age composition can be controlled for by calculating age-specific or age-standardized rates. In this study, ethnic composition cannot be controlled for, as information on the ethnic composition of the IADB population is not available. Furthermore, the database does not have information on socio-economic status, while this concept plays an important role in the literature on drug prescription. It is possible that socio-economic status may have affected trends in drug prescription, for example it is possible that socio-economic status differs between birth cohorts or through calendar time.

The study placed the literature on prescription drug use within an age-period-cohort framework. The advantage of this is that A) the framework orders the somewhat fragmented literature on drug use and B) it provides a clear way of analyzing trends in prescription drug use on the population level, namely by using age, period and cohort as proxies for underlying effects. The latter is useful because drug registration databases gather little other information. The consequence of using proxies is, of course, that it is unknown whether they truly measure the effects they were intended to measure. For this reason, as this study has done, it is important to formulate hypotheses in advance, because reasoning based on corroborated *a priori* statements has more strength than reasoning based on *a posteriori* statements. *A posteriori* statements carry less strength because a reason can often be found since the proxies are relatively broad categories. Nevertheless, as will be seen in the following section, this study cannot escape some *a posteriori* reasoning.

The study used prevalence as its primary measure. This measure controls for the different sizes of birth cohorts or age groups because it takes into account exposure. By using age-specific and age-standardized prevalence, the effect of changing age-composition is also controlled for. Nevertheless, the measure did require some improvement as its conventional calculation resulted in an overestimation of users. Part of this improvement meant that one-year age by one-year period by one-year cohort Lexis-triangles could not be used. Instead, a

one-year period by one-year cohort Lexis-parallelogram was used as the basic tabulation, which is a slightly less detailed form of tabulation. For some graphs and for the APC models, a three-year period by three-year cohort Lexis-parallelogram was used. It is noteworthy that this is still a more detailed form of tabulation than is commonly used in APC models (five-year age by five-year period is common).

The primary approaches to APC modelling are the classical approach by Clayton & Schifflers and the newly developed approach by Carstensen. Both approaches have their advantages and disadvantages. A major reason for using the Carstensen approach is that it allows greater detail in the tabulation (Lexis-triangles) while avoiding a disjoint model. Also, modeling age, period and cohort as continuous variables is considered more epidemiologically informed by Carstensen. However, as described in the previous paragraph, this study could not use Lexis-triangles. Furthermore, because the Carstensen approach uses continuous variables it will smooth out dips or spikes that occur in small intervals. In this study, such small effects were considered to be of interest and therefore such smoothing was avoided: e.g. it was hypothesized that the 1918-19 and the 1945-46 cohorts should have some spikes in users relative to neighbouring cohorts. It could be argued that adding splines specifically for these cohorts would allow these spikes to be measured, but this would be difficult to justify unless splines were added with knots at each three-year interval (which would make the Carstensen approach very similar to the Clayton & Schifflers approach). The author therefore considers the Clayton & Schifflers approach to be the most appropriate for this study. There is, however, one critical sidenote: the Carstensen approach lends itself better to the use of interaction terms because it uses continuous variables. In order to test one of the hypotheses for statin, it may have been of interest to create an interaction-term between the age-slope of age 70+ and the period variable (see Wilmoth, 1990, for a suggestion of an APC model with an interaction term between age and period). Currently, the effect of the 1930 cohort moving through the age-70 range during the observation period makes it difficult to find the effect of the guideline change that recommended prescribing to persons that are over 70. However, a full APC model controls for the effect of the 1930 cohort moving through this age-range. Therefore, if the guideline change was effective, the interaction term should indicate an increase in the number of users at age 70+ with increasing calendar time.

Another critical remark regarding APC models concerns the extraction and subsequent attribution of the common linear component of cohort and period (drift). As suggested by authors such as Glenn, side-information (namely the literature) was used to determine how to attribute drift. For statin the choice was clear: the extreme growth in users over time meant it was highly likely that most of the drift should be attributed to period. Therefore, the cohort variable measured only non-linear effects. For benzodiazepine, however, side-information was lacking. Therefore, drift was split evenly between period and cohort. However, without proper side-information it becomes difficult to test whether older cohorts have more users per 1000 population than younger cohorts (they would if drift is attributed to cohort) or if the number of users declines due to guideline changes (a decline occurs throughout the study period if drift is attributed to period).

The final remark regarding APC models in general concerns the reductions in scaled deviance. In the models the drift variable contributed most to the reductions in scaled

deviance, followed by cohort and finally period. All components contributed significantly to the full model. It should be clear that a full APC-analysis is a definite improvement over the more common age-period analysis (cross-sectional analysis). The cohort effect likely has a strong contribution to the reduction in scaled deviance because it has some (often overlooked) explanatory power. Nevertheless, it should be noted that the cohort effect is stronger than the period effect in part because it simply has more parameters than period does (as also noted by Clayton & Schifflers).

Finally two more specific remarks: one on benzodiazepine and one on statin. The (non-linear) period effect of the APC model for benzodiazepine does not show the decline in users which takes place after 2001, whereas such a decline is apparent in the age-standardized figure. There are two possible explanations. It is possible that the decline has been absorbed into the drift component (which is also negative). Another possibility is that the model does not show the decline because for the majority of the observations, namely all ages above 40 or all cohorts born before 1955, there simply is no clear period effect. The latter explanation is elaborated upon in the following section.

For both sexes, the APC model for statin shows an increase of the rate ratio from the oldest cohorts up to the 1930 cohort followed by a level trend and then a slow decline. The observation period of this study is relatively short (15 years). Since cohort effects are a proxy of biological effects, it is possible that some cohort effects are latent and are therefore not expressed until a point in time after of the observation period. Such effects would only be captured if the observation period were to be extended. E.g. the 1950 cohort could eventually reach the level of the 1930 cohort as it becomes older (in essence an interaction-effect between cohort and age). This is of note because it determines whether the 1930 cohort should be seen as a ‘forerunner’ or a ‘lone peak’, which is turn is of importance when making predictions about the future.

6.3 Interpretation and explanation

In this section the age, period and cohort effects that were found in the results will be compared to the hypotheses that were made for benzodiazepine and statin. By doing so, the trends in prescription drug use will be explained. Not all trends were predicted, therefore some additional interpretation is done. First benzodiazepine and secondly statin are discussed, thirdly a comparison between the two drugs is made.

6.3.1 Benzodiazepine

Benzodiazepine is a drug used to relieve pain, anxiety and sleep problems. These symptoms can stem from a variety of underlying causes. Since it is accepted that health, especially health on a population level, deteriorates with increasing age, it was hypothesized that the user prevalence of benzodiazepine would increase with age. This hypothesis is not rejected. Both the descriptive graphs and the APC model for benzodiazepine show an increasing prevalence with increasing age. It should be noted that the descriptive graphs of users within cohorts show, for all but the youngest cohorts, a level or decreasing trend with increasing age from the start of the study period (1994) onwards. However, older cohorts have higher prevalence than younger cohorts at the same ages, indicating that in the past the user prevalence did

increase with age for those cohorts. No hypothesis was formulated regarding the exact shape of the increase with age: it is noteworthy that this increase is nearly linear from age 20 onwards because the majority of physical health problems should manifest especially at older age. This shape is further discussed in the comparison between benzodiazepine and statin trends in subsection 6.3.3.

From the literature it is well-known that there are a large number of chronic users of benzodiazepine. Chronic use is problematic because the it lowers sensitivity to the drug. An important cause of chronic use is addiction to the drug. It was hypothesized that the number of users within a cohort would accumulate over time as some users become addicted, resulting in an increasing user prevalence within cohorts over time. This hypothesis is also not rejected. While we cannot know from the data whether chronic users are also addicted, accumulation appears to occur. The accumulation of users can be inferred by comparing the cohort figures on starters of benzodiazepine (user incidence) with the cohort figures on users of benzodiazepine (user prevalence): the incidence and prevalence levels are very similar at the youngest ages. However we see that with increasing age (even within some cohorts) the user prevalence rises from below 100 users per 1000 population to above this level, whereas the user incidence remains below 100 starters per 1000 population. The number of users being higher than the number of starters indicates accumulation. It should be noted that for some cohorts there is a decline in prevalence: these cohorts must have undergone accumulation in the past, unless user incidence levels were (much) higher before the observation period.

Policy changes were made in 2001 in order to curb chronic use of benzodiazepine. This was done by attempting to curb the number of starters of the drug. In the study it was hypothesized that this would end the increase of users within cohorts and instead lead to a reduction in starters and thereby a further (albeit slow) reduction in users (the latter due to attrition). This hypothesis is partially rejected. It is apparent that the 2001 guideline change had an effect on user prevalence: the age-standardized annual figures of user prevalence clearly show a slow decline starting in 2001. Also, for the youngest cohorts an increase of prevalence with age can be seen followed by a level trend after 2001, which was the expected shape of cohorts for benzodiazepine. It is, however, somewhat questionable whether the primary mechanism for the reduction in prevalence is the reduction in starters: for males the user incidence (starters) is indeed curbed in the youngest ages and reduced in the middle ages, however this appears to occur mostly from 2003-04 onwards, rather than from 2001-02. For females, the effects are even less clear. Furthermore, the assumption underlying the hypothesis appears to be incorrect. It was expected that the user prevalence within cohorts would increase with age up to 2001. This appears to be incorrect: for the oldest cohorts the user prevalence trend was level from 1994 onwards and for the middle cohorts there was a decline from 1994 onwards. While the 2001 guideline change may have had an effect on all cohorts, it only has a clear effect on the user prevalence trends of the youngest cohorts; the slopes of the older cohorts hardly change. It would appear then that the clear decline which can be seen in the age-standardized prevalence from 2001 onwards is strongly attributable to the changes in the youngest cohorts. In other words, the guideline change was likely most effective for the youngest cohorts or for the youngest age groups. This fits the literature as it is described that it is easier for younger persons to stop using.

The literature describes that individuals who were *in utero* during a famine or the influenza pandemic, or that were strongly weakened during early childhood due to morbidity, tend to have worse health at older age. It was hypothesized that such effects would in turn result in a higher user prevalence of benzodiazepine for cohorts born during or shortly after the First and Second World Wars. This hypothesis is rejected. Looking at the descriptive findings, it is noteworthy that the majority of deviating cohorts can be found in the 1917-19 and the 1940-46 period, which corroborates the hypothesis that being *in utero* or spending childhood in a period of famine or influenza pandemic may result in deviating drug prescription trends. The APC model for benzodiazepine also shows a cohort effect for the 1917-19 which deviates from the overall trend, further lending credence to the possible effect of the First World War. Firstly, however, those (war-)cohorts that deviated from neighbouring cohorts and the overall trend had lower rather than higher user prevalence. Since it is unlikely that war and famine would lead to a better health, it is proposed that these cohorts have undergone selection effects: the unhealthy member of this cohort have died, leaving the healthier members which do not require prescription drugs. Secondly, there are some differences between the sexes: while for both males and females the 1918 and the 1942 cohorts deviate in the descriptive statistics, the 1917 cohort only deviates for males. Furthermore, the APC model for females does not show any strong deviations, whereas for males the 1917-1919 cohort does deviate. Thirdly, it would be expected that especially the Second World War cohorts would deviate, as this is when the Dutch Hunger Winter took place. Instead, the First World War cohorts show stronger effects than the Second World War cohorts, both descriptively and in the APC model (the model does not show any effect of the Second World War). A possible explanation is that such cohort effects do not express themselves until even older ages; the First World War cohorts were older ages during the observation period (such a 'latent cohort effect' is discussed in the previous section on data and methods for statin). Also, rather than the 1944-46 cohorts deviating, which are the cohorts that were hypothetically most affected by the Dutch Hunger Winter, the 1942 cohort deviates for both males and females. It is possible that these persons were strongly weakened by the famine at a critical stage in their development, which lead to health complications at older age, but it does not explain why the other war cohorts do not deviate.

It was hypothesized that cultural change also brought about changes in drug prescriptions. Those cohorts growing up after the Second World War experienced economic prosperity and focused on non-material affairs such as personal development and mental and physical health (a so-called 'post-materialist' orientation). It was hypothesized that these cohorts would have a higher user prevalence of benzodiazepine, due to their focus on health and due to more demanding attitudes towards the general practitioner. This hypothesis is rejected. The period trend shows lower user prevalence with time. The non-linear period effect does show a notable decrease in prevalence for the 1932 to 1964 cohorts for males and the 1943 to ca. 1964 cohorts for females. However, this is a decrease rather than an increase. It is possible that this is an effect of growing up (or, reaching young-adulthood for the oldest cohorts) in a post-war Netherlands and experiencing economic revival: these generations reached adulthood after the Second World War and the effect lasts for many cohorts. The effect seems to end for cohorts born after the '60s, which is also the period that the

‘Wederopbouw’ (post-war rebuilding) officially ended. However, the youngest of these deviating cohorts were still born in the 60s, meaning they did not experience the rebuilding consciously (and therefore did not get instilled with the values of that period).

Finally, in the literature it was written that women were more likely to get benzodiazepine prescribed than men. The reason being communication differences: women are more likely to present their symptoms in a social context, which results in a prescription for benzodiazepine while men are referred to a specialist. This hypothesis is not rejected: the results clearly show that the user prevalence of women is about two times higher than the user prevalence of men.

6.3.2 Statin

Statin is a drug which lowers cholesterol levels in the blood and is used in the primary prevention of cardiovascular disease. It is a relatively new drug, being introduced in the 1990’s. Because it is a very successful new drug, it was hypothesized that the user prevalence of statin would increase over time. This increase was believed to be especially strong after the year 2000, when the minister of health was advised to prescribe the drug preventively. This hypothesis is partially rejected: the drug does indeed show a very strong rise in user prevalence over time. However, the age-standardized prevalence, the prevalence within cohorts and the APC model all show that the increase in users strengthens from approximately 2003 onwards, rather than from 2000. The following paragraph may explain the change in 2003.

It was hypothesized that the user prevalence of statin would increase with age because the risk of cardiovascular disease also increases with age. The user prevalence of statin should increase up to age 70, but after age 70 it should decline again because the guidelines discouraged prescription to persons over 70 for lack of evidence of its effectiveness at that age. However, important studies showed that the drug was effective for persons over 70 in 2002, possibly resulting in more users over age 70. This hypothesis is partially rejected. The results do show a clear relation with age: the APC model, which isolates age from the other two components, shows a linear relation for males and a more curved relation for females. The exact shape of this age-trend is discussed further in the comparison of the trends between benzodiazepine and statin in subsection 6.3.3. There is also a peak in prevalence, which shifts to older ages with calendar time, as predicted. However, the results clearly show that this shifting peak is a cohort effect rather than an attribute of period. In particular, the shifting peak is fully correlated with the 1930 birth cohort becoming older: both the descriptive graphs and the APC model show this. This does not mean that the insight change brought about by the studies had no effect on statin use: the increase of users strengthened in 2003 as described in the previous paragraph. It is possible that this is caused by these influential studies. The 1930 cohort likely obscures the effect of the insight change, as it moves through the 70+ age-range. The 1930 cohort effect is discussed later in this subsection and also in the following subsection. According to the literature, the effect of the studies should be strengthened in 2006 because of the release of a guideline which removed the age restriction on statin prescription. However, none of the results show an increase from 2006 onwards. In fact, there appears to be a decline from 2006 onwards. Therefore, this part of the hypothesis is rejected.

Statin received some negative publicity in 2007: it was reported that the negative side-effects might outweigh the benefits of using the drug. It was hypothesized that this would result in a stagnation or even a decline of user prevalence in 2007. This hypothesis is not rejected: the age-standardized trend shows a stagnating prevalence in 2007 and even a slight decline in 2008. The APC model does still show increase, but the slope is slightly less steep. While the hypothesis is therefore not rejected, it is questionable whether the stagnation and decline are fully attributable to negative publicity. The literature reports that the effect of the negative publicity only lasted shortly; it should not have lasted until 2008. One study did report a decline in 2008 but attributed it to the database used (the loss of a nursing home from the database). Since this study used a different database but had a similar result, some explanation for the 2008 decline should be sought. Perhaps the stagnation that is found is instead the result of the drug reaching the saturation level in the market.

Similar to benzodiazepine, it was hypothesized that cohorts born during the First and Second World War would have a higher user prevalence of statin compared to neighbouring cohorts. This hypothesis is rejected. The results did not show any deviations in prevalence between specific cohorts. This is remarkable because both the fetal origins hypothesis and the cohort morbidity phenotype hypothesis specifically report a higher risk of cardiovascular disease. A possible explanation is that statin is a drug that is prescribed preventively, and that the category of persons considered 'at risk' (and therefore prescribed the drug) is relatively broad. In essence, the difference between a cohort with very poor health (caused by the *in utero* nutritional deficiency during the famine or by strong morbidity during early childhood) and a cohort with 'normal' poor health is negligible, because both groups of persons fall within the risk category and therefore receive the drug. Of course, as explained in the previous section, it may also be a data issue.

Also similar to benzodiazepine, it was hypothesized that cultural change brought about changes in drug prescriptions. In particular, post-Second World War cohorts should have a higher user prevalence than pre-war cohorts because they are more demanding of their doctors. This hypothesis is partially rejected. The APC model results show very clearly that the rate ratio of user prevalence increases up to the 1930 cohort for both men and women. It is possible that this is a cultural effect: the 1930 cohort is among the first cohorts to reach adulthood after the Second World War. Furthermore, the level of use remains mostly stable for a period of time after 1930, meaning the 1930 cohort is potentially a forerunner. If this is the case, then the 1930 cohort and birth cohorts following it have a greater desire to be protected from cardiovascular disease and are more demanding of their doctors to receive statin therapy. However, the rate ratio of statin use does decline at some point after 1930 for both men and women. As discussed in the previous section the decline could be the result of a short observation period, but the decline does weaken the hypothesis. Furthermore, a post-war cohort effect was expected for cohorts born after the Second World War, whereas the 1930 cohort is born before the war. In fact, the decline for males starts at the 1946-48 cohort and for females it starts at the 1943-45 cohort, detracting from the post-war culture hypothesis further. A contesting explanation is that the 1930 cohort effects do not persist for cohorts born in later periods. If this is the case, the hypothesis regarding cultural effects would have to be rejected. In this 'lone peak' scenario it would have to be explained why the 1930 to

approximately 1950 cohorts have a higher prevalence than both the older and the younger surrounding cohorts. A possible explanation lies in socio-economic status (which the study could not control for): while the persons born in the 1930s and early 1940s faced hardship during childhood, they may have fared better in the labour market than preceding cohorts (whose employment status was disrupted by economic depression and war) and following cohorts (which faced more competition for resources due to the Baby Boom) once they had reached adulthood. Since cardiovascular disease is also a welfare disease (and thus positively related to SES), this could explain why statin prevalence peaks for the 1930 cohort and then declines again.

Men have a higher risk of cardiovascular disease than women. It was therefore hypothesized that more men would be prescribed statin than women. This hypothesis is not rejected. The results clearly show that the user prevalence of men is 1.3 times higher than the user prevalence of women.

6.3.3 Comparison of benzodiazepine and statin trends

Benzodiazepine and statin are two very different drugs. Statin is prescribed to prevent the onset of disease whereas benzodiazepine is used, among others, in treating pain that is caused by disease and disability. Nevertheless, the trends in users of benzodiazepine and statin show some interesting similarities and differences. The three most noteworthy are shortly discussed in this subsection.

Firstly the age-trends as produced by the APC models of both drugs are remarkably similar. For both drugs the age-trends are nearly linearly related to age, though the trend for statin seems to start about ten to fifteen years in age after the trend for benzodiazepine. An exception is of course the age-trend of statin for females, which is somewhat more curved. The similarity is remarkable because statin is prescribed for a very specific health condition whereas benzodiazepine is prescribed for a large variety of both mental and physical health conditions. Hobcraft wrote that age is a good proxy for health and that of all three variables in the APC-analysis, age is the most reliable. This appears to be the case for drug-prescription as well, which is one step further removed from health conditions than measuring disease directly (which is usually done in APC-analysis in epidemiology). The strong similarity between the age-trends of both drugs corroborate this.

Secondly, for both drug types it was hypothesized that the trends in user prevalence of both drugs in the war cohorts (1917-19 and 1940-46) would deviate because evidence from the literature shows deviating health trends for these cohorts. In particular, the effects should have been strongest for statin because evidence for the fetal origins hypothesis shows that especially the risk of cardiovascular disease increases. The evidence shows the contrary: benzodiazepine seems to show the strongest evidence, and in particular the effects of the First World War. A possible explanation is that statin is prescribed preventively, and the category for individuals ‘at risk’ is broad, whereas benzodiazepine is prescribed for alleviation of health problems that are already experienced.

Thirdly, while the cohort-trends for both drugs are mostly dissimilar, there are some similarities. Trends in male benzodiazepine prevalence show a long dip lasting from 1932 to 1964, whereas for females it is approximately 1941-64 (but much less pronounced). For

statin, there is, of course, the very clear peak in users from 1930 to approximately 1950. For males, which have the clearest deviations from the overall trends in both drugs, the overlap is about 20 years: namely the 1930s and the 1940s. For females, the overlap is about 10 years (the 1940s). While the specific hypotheses regarding the effect of the war were (partially) rejected, it is conceivable that this particular period of overlap is no coincidence, hinting at some prolonged effect of both the economic depression of the 1930s and the war in the 1940s.

6.4 Recommendations and suggestions

6.4.1 Policy

In the year 2001, medical doctors were advised to prescribe benzodiazepine sparsely and to keep the treatment period under two months in order to prevent addiction and thereby chronic use in the population. The study concludes that this was successful for the younger age groups or the younger cohorts. In order to reap the most benefits from this successful implementation of policy it is recommended to keep a strict prescribing regimen for the individuals in the younger cohorts: in this way, the 2001 guideline change will have the greatest long-term effects because accumulation within cohorts over time due to addiction is kept to a minimum. This prevents having to implement costly interventions in order to reduce the number of chronic users in the future. Of course, this is also most beneficial to the individuals who would otherwise become chronic users. The guideline change did not appear to have a strong effect for older ages or older cohorts. Nevertheless, for some older cohorts decline in prevalence was already occurring before the guideline change, which is a positive outcome. However, for many cohorts the decline is not very steep (and even for the youngest cohorts the increase merely becomes level). While preventing chronic users appears to be successful, it may be wise to target those individuals who have already become chronic users as well, even if this is more costly than preventing starters. Especially for the 'young old' this would be effective as it can still prevent many future person-years of addiction. Even for the older old persons this can be cost effective as benzodiazepine can result in falls which, at old age, may result in bone fractures (Geers et al., 2009; Glass et al., 2005). Next to cost effectiveness, of course, the use of benzodiazepine can decrease quality of life as some of the associated side-effects are insomnia, nausea, headaches and lethargy (King et al., 1992). Only for the very old may the temporary problems of withdrawal not be outweighed by the benefits of the non-dependent period afterwards. A number of studies have suggestions for effective methods of decreasing chronic use (e.g. Niessen et al., 2005)

In 2002 important studies showed the effect of statin in reducing cardiovascular disease at ages above 70. Whether these studies had an effect on the uptake of the drug at older ages is not entirely clear. The policy change in 2006, however, does not appear to have had any effect. If it is assumed that the 1930 cohort is a forerunner then two options are possible. The first option is that no policy action is taken because in approximately ten years the 1930 cohort will have reached the oldest ages resulting in a high user prevalence in those ages, which should remain constant afterwards. However, this would possibly result in cardiovascular death that could have been prevented in the highest ages in the coming ten years (before the 1930 cohort reaches those ages). As Geleedst-De Vooght et al. (2010) write, the oldest ages is likely where statin is most (cost-)effective. Therefore, a second option is to

intensify efforts of statin prescription to individuals in the oldest ages. A possible reason for low prescribing of statin at older ages is that doctors are concerned about negative side effects and polypharmacy at older ages (Geleedst-De Vooght et al., 2010). If these concerns are grounded in empirical reality then prescription at older ages should not be advised. If these concerns are not grounded in empirical reality then a campaign would likely be successful if it targeted such concerns. Regardless of the option chosen, it is likely that the coming ten years are important for the statin prescription trends after those ten years. In both options a larger number of older individuals will use statin. Their experience with the drug (both its beneficial and adverse effects) will likely influence the attitude of doctors towards prescription of statin in future years. If the 1930 cohort is currently a lone peak then it may become a forerunner if its experience with statin at older ages is positive whereas if it is currently a forerunner it may become a (quickly declining) lone peak if its experience with statin at older ages is negative.

6.4.2 Research

This research found that some simple measurements can be improved: the literature review of measurements used to study trends in drug prescription found that most studies use very broad age categories while other studies even excluded age as a variable. This is remarkable, considering that age is a good proxy for health status. It is therefore suggested to include age in pharmacoepidemiological studies and to tabulate it as finely as possible. The study also found that 'user prevalence', a basic measure, could result in overestimation. In future studies it is suggested to use the method developed by this study which prevents overestimation, or even to improve upon it if possible (e.g. develop a calculation that takes into account overestimation while still making the use of Lexis-triangles possible). Finally, the study has shown that cohort is a useful, even important, addition to the analysis of time trends. The addition of cohort can be useful for theoretical reasons, thereby adding new explanations to the literature, but it can also be useful for statistical reasons as it can improve the fit of predictive models. It is therefore recommended to include birth cohort in future studies as well.

In terms of concrete ideas for further research, it is firstly suggested to research the causal links between cohort effects and drug prescription. In the literature review it was found that there are very few studies which describe the link between drug prescription (or drug use) and cohort effects. It is likely that any cohort effects have, until now, largely been interpreted as age effects. The proposed research would likely be a combination of historical research, as cohort effects are rooted in past experiences, and contemporary research, as birth cohorts experience drug prescription in contemporary time. In particular, the effect of the 1930 cohort warrants attention: is this cohort a forerunner or a lone peak? This is crucial information when predicting future trends of statin use. Similarly, the long dip found for benzodiazepine cohorts should be explained.

Secondly, it is suggested to repeat the data analysis of this study while using the Carstensen approach to APC modeling rather than the Clayton & Schifflers' approach. This would allow the two methods to be compared. It would also provide the opportunity to try the suggestion described in section 6.2 to try and take into account the cohort effect in order to more accurately measure the guideline change. This may provide the insight necessary to

create a more general tool for holding one of the three variables of APC-analysis constant in order to measure the interrelation between the other two variables more clearly (which is problematic considering linear dependency between the three variables).

Thirdly, it is suggested to research the cause of the 2008 decline in statin use: the decline is found within this study but also in another Dutch study (which attributed it to data issues). Attributing the decline to the data is unlikely when multiple studies using different databases report the same finding. Therefore, the decline likely represents a real event for which a cause must exist.

Fourthly, it is suggested to combine information on uptake of drugs, such as user prevalence and incidence, with information on outcomes of drugs, such as cause-specific mortality and hospitalization. By combining such information the effects of drug use on a population level can possibly be estimated more accurately. It should be clear that this could be of major relevance to public health and is possibly another example of a fertile combination of demography and pharmacoepidemiology.

Finally, it is suggested to forecast APC-trends. Clayton & Schifflers (1987b) clearly write that APC-analysis should be considered an advanced descriptive method and warn against forecasting APC-trends. However, this study found that some cohort effects play a strong role in the overall trend, potentially justifying forecasting of future trends. Other authors have recently come to a similar conclusion: Shibuya et al. (2005) used APC-analysis in which the cohort parameter was projected using autoregressive moving averaging (ARIMA) while Bray (2002) applies a Bayesian variant of APC-analysis to project cancer incidence and mortality. It may also be of interest to compare these various methods of APC-analysis and trend projection.

6.5 Conclusion

The above sections explain the effects of age, period and cohort in the trends of benzodiazepine and statin in the period 1994 – 2008, thereby answering the primary research question. By describing the implications of these findings for policy and research, the social and academic relevance of the answer to this research question is also demonstrated. Therefore, an age-period-cohort framework can be considered a useful framework for studying trends in drug prescription. That leaves a short conclusion on the inspirational basis of the study: the application of demography to pharmacoepidemiology. While this study is largely limited to APC-analysis, enough of the outcomes show that demographic techniques and insight provide new ways of analyzing pharmacoepidemiological data and thereby provide new and relevant explanations. It is recommended to continue with the application of demographic methodology to pharmacoepidemiology. This does not have to be limited to APC-analysis. For example, topics such as the link between life expectancy and prescription drug use, or the effect of migration through ethnic compositional change on drug prescription trends, have hardly been studied so far. Therefore a world of research is to be done when combining demography and pharmacoepidemiology.

References

Almond D (2006), 'Is the 1918 influenza pandemic over? Long-term effects of in utero influenza exposure in the post-1940 U.S. Population'. *Journal of Political Economy* 114: pp. 672-712.

Ashton, H (2009), 'Benzodiazepines: how they work and how to withdraw'. Internet: http://www.benzo.org.uk/manual/bzcha01.htm Last visited August 31, 2010.

Berg GJ van den, Lindeboom M, Portrait F (2006), 'Economic Conditions Early in Life and Individual Mortality'. *American Economic Review* 96: pp. 290-302.

Bersselaar V van den (2003), *Wetenschapsfilosofie in veelvoud*. Bussum: Coutinho.

Blom ATG, Hugtenburg JG, Post CO (2007), 'Begeleiding tweede uitgifte nuttig voor de patiënt'. *PW Wetenschappelijk Platform*. 1(7): pp.156-9.

Bogunovic OJ, Greenfield SF (2004), 'Use of Benzodiazepines Among Elderly Patients'. *Psychiatric Services* 55(3): pp. 233-5.

Bos J (2010), 'Werken aan de database; de populatieschatting'. Internet: http://www.iadb.nl/news/2010/10dec.pdf Last visited July 26, 2011.

Boyle P, Robertson C (1987), 'Statistical modelling of lung cancer and laryngeal cancer incidence in Scotland, 1960-1979'. *American Journal of Epidemiology* 125(4): pp. 731-44.

Bray I (2002), 'Application of Markov chain Monte Carlo methods to projecting cancer incidence and mortality'. *Journal of Applied Statistics.* 51(2): pp. 151–64.

Carstensen B (2007), 'Age–period–cohort models for the Lexis diagram'. *Statistics in Medicine* 26: pp. 3018–45.

Carstensen B, Keiding N (2005), 'Age-Period-Cohort models: Statistical inference in the Lexis diagram'. Internet: http://staff.pubhealth.ku.dk/~bxc/Lexis/Lexis.pdf Last visited April 27, 2011.

Clayton D, Schifflers E (1987a), 'Models for temporal variation in cancer rates. I: Age–period and age–cohort models.' *Statistics in Medicine* 6: pp. 449–67.

Clayton D, Schifflers E (1987b), 'Models for temporal variation in cancer rates. II: Age–period–cohort models.' *Statistics in Medicine* 1987 6: pp. 469–81.

Coleman, J. (1990), *Foundations of Social Theory*, Cambridge: Harvard University Press.

Cosentino M, Leoni O, Banfi F, Lecchini S, Frigo G (2000), 'An approach for the estimation of drug prescribing using the defined daily dose methodology and drug dispensation data'. *European Journal of Clinical Pharmacology* 56: pp. 513-7.

CVZ Farmacotherapeutisch Kompas (2010), 'Benzodiazepinen'. Internet: http://www.fk.cvz.nl/default.asp?soort=inleidendetekst&naam=inl%20benzodiazepinen Last visited December 22, 2010.

Denig P, Haaijer-Ruskamp FM (2009), 'Hoofdstuk 7. Voorschrijven van geneesmiddelen'. In: Buurma H, Beudeker HJ, Jong-van den Berg de LTW, Leufkens HGM (eds.), *Het geneesmiddel*. Elsevier Gezondheidszorg: Maarssen.

Ding H, Yang Y, Wei J, Fan S, Yu S, Yao K, Wang A, Shen X (2008), 'Influencing the use of antibiotics in a Chinese pediatric intensive care unit'. *Pharmacy World & Science* 30: pp. 787-93.

Dijkers FW (1997), 'Repeat prescriptions; a study in general practice in the Netherlands'. *PhD thesis*. University of Groningen: Groningen.

Donoghue J, Tylee A, Wildgust H (1996), 'Cross sectional database analysis of antidepressant prescribing in general practice in the United Kingdom, 1993–5'. *British Medical Journal* 313: pp. 861-2.

Eijk JTM van, Bosma H, Jonkers CCM, Lamers F, Muijrers PEM (2009), 'Prescribing Antidepressants and Benzodiazepines in the Netherlands: Is Chronic Physical Illness Involved?'. *Depression Research and Treatment* DOI:10.1155/2010/105931 [Epub].

Evandrou E, Falkingham J (2000), 'Looking back to look forward: lessons from four birth cohorts for ageing in the 21st Century. *Population Trends* 99: pp. 27-36.

Field A (2009), *Discovering statistics using SPSS*. Sage Publications Inc.: London.

Finch C, Crimmins EM (2004), 'Inflammatory exposure and historical changes in human life-spans'. *Science* 305: pp. 1736–39.

Flowerdew R, Martin D (2005), *Methods in Human Geography: a guide for students doing a research project*. London: Pearson Education Limited.

Furedi F (2008), 'Medicalisation in a Therapy Culture', in: *A Sociology of Health*. London: Sage.

Geers H, Arents B, Bouvy ML (2009), 'Minimale interventie in een cohort van chronische benzodiazepinegebruikers'. *PW Wetenschappelijk platform* 3(4): pp. 62-6.

Geffen K, Bohemen C van, Dijk L van, Hulten R van, Bouvy M (2009), 'Slechts 1 op 10 stopt na benzomaatregel. Afschaffing vergoeding heeft beperkt effect'. *Pharmeutisch Weekblad* 144(49): pp. 28-31.

Geleedst-De Vooght M, Maitland-van der Zee A, Schalekamp T, Mantel-Teeuwisse A, Jansen P (2010), 'Statin Prescribing in the Elderly in the Netherlands: A pharmacy Database Time Trend Study'. *Drugs & Aging* 27(7): pp. 589-696.

Gezondheidsraad (1998), *Naar een doelmatig gebruik van benzodiazepines*. Gezondheidsraad: Den Haag.

Glass J, Lanctot KL, Herrmann N (2005), Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *British Medical Journal* 331: p. 1169.

Glenn ND (2005), *Cohort analysis*. Sage publications: Thousand Oaks.

Gorgels WJMJ, Oude Voshaar RC, Mol AJJ, Breteler MHM, Lisdonk EH van de, Zitman FG (2001). 'Het langdurig gebruik van benzodiazepines'. *Nederlands Tijdschrift voor Geneeskunde* 14: pp. 1342-6.

Hall J, Irish J, Roter D, Ehrlich C, Miller L (1994), 'Gender in medical encounters: an analysis of physician and patient communication in a primary care setting'. *Health Psychology* 13: pp. 384-92.

Heart Protection Study Collaborative Group (2002), 'MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial (HPS)'. *The Lancet* 360: pp. 7-22.

Hippisley-Cox J, Coupland C (2010), 'Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database'. *British Medical Journal* 340:c2197.

Hobcraft J, Menken J, Preston S (1982), 'Age, Period and Cohort Effects in Demography: A review'. *Population Index* 48(1): pp. 4-43.

Hoek HW, Brown AS, Susser E (1998), 'The Dutch Famine and schizophrenia spectrum disorders'. *Social Psychiatry and Psychiatric Epidemiology* 33: pp. 373-79.

Holford TR (1991), 'Understanding the effects of age, period, and cohort on incidence and mortality rates'. *Annual Review of Public Health* 12: pp. 425-57.

Hulten R van, Isacson D, Bakker A, Leufkens HB (2003), 'Comparing patterns of long-term benzodiazepine use between a Dutch and a Swedish community'. *Pharmacoepidemiology and drug safety* 12: pp. 49-53.

Janssen F, Kunst AE, Netherlands Epidemiology and Demography Compression of Morbidity research group (2005), 'Cohort patterns in mortality trends among the elderly in seven European countries, 1950-1999'. *International Journal of Epidemiology* 34(5): pp. 1149-59.

Jekel JF, Elmore JG, Katz DL (1996), *Epidemiology, biostatistics and preventive medicine*. Saunders: Philadelphia.

Jong-van den Berg LTW de, Smit DJ (2009), 'Hoofdstuk 10. Communicatie'. In: Buurma H, Beudeker HJ, Jong-van den Berg de LTW, Leufkens HGM (eds.), *Het geneesmiddel*. Elsevier Gezondheidszorg: Maarssen.

Jong-van den Berg LTW de, Tobi H, Bijker B, Berg P van den (2003), 'Influence of the third generation pill controversy on prescriptions for oral contraceptives among first time users: population based study'. *British Medical Jounral* 326: p. 254.

Kaa DJ van de (1988), 'The second demographic transition revisisted: theories and expectations'. Paper presented at the Conference on Population and European Society, December 7-9, 1988, Florence.

King B (1992), 'Is there still a role for benzodiazepines in general practice?'. *British Journal of General Practice* 42: pp. 202-5.

Kirk D (1996), 'Demographic Transition Theory'. *Population Studies* 50: pp. 361-87.

Kuhn TS (1996), *The structure of scientific revolutions (3rd edition).* Chicago: University of Chicago Press.

Leufkens HB, Urquhart J (2005), 'Automated Pharmacy Record Linkage in the Netherlands', in: Strom (ed.), *Pharmacoepidemiology*. Wiley: Chichester.

LPSG (2010) 'Epistemology and Methodology'. Internet: http://www.ucl.ac.uk/philosophy/LPSG/Ep&Meth.htm. Last visited February 7, 2011.

Magrini N, Vaccheri A, Parma E, D'Allesandro R, Bottoni A, Occhionero M, Montanaro N (1996), 'Use of benzodiazepines in the Italian general population: prevalence, pattern of use and risk factors for use'. *European Journal of Clinical Pharmacology* 50: pp. 19-25.

Mason KO, Mason WM, Winsborough HH, Poole KW (1973), 'Some methodological issues in cohort analysis of archival data'. *American Sociological Review* 38: pp. 242-58.

Mazumder B, Almond D, Park K, Crimmins EM, Finch CE (2010), 'Lingering prenatal effects of the 1918 influenza pandemic on cardiovascular disease. *Journal of Developmental Origins of Health and Disease* 1: pp. 26-34.

Meijer EEW, Heerdink ER, Leufkens HGM, Herings RMC, Egberts ACG, Nolen WA (2004), 'Incidence and determinants of long-term use of antidepressants'. *European Journal of Clinical Pharmacology* 60: pp. 57-61.

Midlöv P, Eriksson T, Kragh A (2009), *Drug-related problems in the elderly*. Springer: Dordrecht.

Mol A, Lieshout P van (2008), 'Hoofdstuk 2. Ziek en gezond', in: *Ziek is het woord niet*. Amsterdam: Amsteram University Press.

Moynihan R, Health I, Henry D (2002), 'Selling sickness: the pharmaceutical industry and disease mongering'. *British Medical Journal* 324(7342): pp. 886-91.

Newell C (1988), *Methods and models in demography*. Belhaven Press: London.

NHG (2010), NHG-Standaard Cardiovasculair risicomanagement. Internet: http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/NHGStandaard/M84_std.htm Last visited January 12, 2010.

Niessen WJM, Stewart RE, Broer J, Haaijer-Ruskamp FM (2005), 'Vermindering van gebruik van benzodiazepinen door een brief van de eigen huisarts aan chronische gebruikers'. *Nederlands Tijdschrift voor Geneeskunde* 149: pp. 356-61.

Ohlsson H, Lindblad U, Lithman T, Ericcson B, Gerdtham G, Melander A, Rastam L, Merlo J (2005), 'Understanding adherence to official guidelines on statin prescribing in primary health care—a multi-level methodological approach'. *European Journal of Clinical Pharmacology* 61: pp. 657-665.

Omran AR (1998), 'The epidemiologic transition theory revisited thirty years later'. *World Health Statistics Quarterly* 51: pp. 99-119.

Osmond C, Gardner MJ (1982), 'Age, period and cohort models applied to cancer mortality rates'. *Statistics in Medicine* 1: pp. 245-59.

Oude Voshaar RC (2003), 'Consecutive treatment strategies to discontinue long-term benzodiazepine use: a systematic evaluation in general practice'. *PhD thesis*. Nijmegen: Radboud University Nijmegen.

Paes AHP, Smit C (2009), 'Hoofdstuk 9. 'De patiënt, zijn ziekte en geneesmiddelengebruik'. In: Buurma H, Beudeker HJ, Jong-van den Berg de LTW, Leufkens HGM (eds.), *Het geneesmiddel*. Elsevier Gezondheidszorg: Maarssen.

Philips DC, Burbules NC (2000): *Postpositivism and Educational Research.* Lanham: Rowman and Littlefield.

Pressat R (1993), 'Location in time'. In Bogue DJ, Arriaga EE, Anderton DL, eds. *Readings in population research methodology Volume 1*. Chicago: Published for the United Nations Population Fund by Social Development Center: pp. 12-6.

Preston SH, Heuveline P, Guillot M (2008), *Demography*. Blackwell: Oxford.

RIVM (2008), 'Voorgeschreven medicijngebruik: verschillen naar geslacht, leeftijd en opleidingsniveau2003'. Internet: http://www.rivm.nl/vtv/object_document/o4982n25485.html Last visited December 20, 2010.

Rockett IRH (1999), *Population Bulletin: Population and Health: An Introduction to Epidemiology*. Population Reference Bureau: Washington DC.

Rooijmans HGM (1999), 'Gezondheidsraad-rapport over gebruik van benzodiazepinen'. *Nederlands Tijdschrift voor Geneeskunde* 143(11): 551-2.

Roseboom TJ, Meulen JHP van der, Ravelli ACJ, Bleker OP (2000), 'De samenhang tussen prenatale blootstelling aan de Hongerwinter en medische bevindingen op lange termijn'. *Nederlands Tijdschrift voor Geneeskunde* 144(52): pp. 2488-91.

Rosenbauer J, Strassburger K (2008), 'Comments on 'Age-period-cohort models for the Lexis diagram' by Carstensen B. Statistics in Medicine 2007; 26:3018-3045'. *Statistics in Medicine* 27 pp: 1557-60.

Sasaki M, Suzuki T (1987), 'Changes in religious commitment in the United States, Holland, and Japan. *American Journal of Sociology* 92: pp. 761-5.

SCP (2010), *Sociaal en Cultureel Rapport 2010: Wisseling van de wacht: generaties in Nederland.* Sociaal en Cultureel Planbureau: Den Haag.

SFK (2003, 2007, 2008, 2009, 2010), 'Data en Feiten'. Internet: http://www.sfk.nl/publicaties/data_en_feiten.html Last visited on 23-12-2010.

SFK (2004), 'Farmacie in cijfers: grijze golf geeft gestage groei geneesmiddelengebruik'. *Pharmaceutisch Weekblad* 139(16): p. 540.

Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM (2002), 'PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial.' *The Lancet* 360: pp. 1623-30.

Shibuya K, Inoue M, Lopez AD (2005), 'Statistical modeling and projections of lung cancer mortality in 4 industrialized countries'. *International Journal of Cancer* 117: pp. 476–485.

Smulders YM, Burgers JS, Scheltens T, Van Houts BA, Wiersma T, Simoons ML, on behalf of the guideline development group for the Dutch guideline for multidisciplinary cardiovascular risk management (2008), 'Clinical practice guideline for cardiovascular risk management in the Netherlands'. *The Netherlands Journal of Medicine* 66(4): pp. 169-74.

Statistics Netherlands (2011), 'Gebruik medische voorzieningen'. Internet: http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=7042MC&D1=360-361,366-369&D2=10-29&VW=T Last visited August 4, 2011.

Strom BL (2005a), 'Preface'. In: Strom (ed.), *Pharmacoepidemiology*. Wiley: Chichester.

Strom BL (2005b), 'Chapter 1. What is Pharmacoepidemiology?'. In: Strom (ed.), *Pharmacoepidemiology*. Wiley: Chichester.

Susser M (2001), 'The longitudinal perspective and cohort analysis'. *International Journal of Epidemiology*. 30 (4): pp. 684-7.

Suykerbuyk HAM, Tjoeng MM (2009), 'Hoofdstuk 6. Distributie van geneesmiddelen'. In: Buurma H, Beudeker HJ, Jong-van den Berg de LTW, Leufkens HGM (eds.), *Het geneesmiddel*. Elsevier Gezondheidszorg: Maarssen.

Sverdrup E (1967), *Statistiske metoder ved dødelikhetsundersøkelser*. Statistical Memoirs. Institute of Mathematics, University of Oslo.

Truter I, Wiseman IC, Kotze W van (1996), 'The defined daily dose as a measure of drug consumption in South Africa'. *South African Medical Journal* 86: pp. 675-9.

Tu K, Mamdani MM, Hux JE, Tu J (2001), 'Progressive Trends in the Prevalence of Benzodiazepine Prescribing in Older People in Ontario, Canada'. *Journal of the American Geriatrics Society* 49: pp. 1341- 5.

Uchida H, Suzuki T, Mamo DC, Mulsant BH, Tsunoda K, Takeuchi H, Kikuchi T, Nakajima S, Nomura K, Tomita M, Watanabe, Kashima H (2009), 'Survey of benzodiazepine and antidepressant use in outpatients with mood disorders in Japan'. *Psychiatry and Clinical Neurosciences* 63 pp. 244-46.

Valiyeva E, Herrman N, Rochon PA, Gill SS, Anderson GM (2008), 'Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis'. *Canadian Medical Association Journal* 179(5): pp. 438-46.

Vandenbroucke JP, Hofman A, Héléne WA, Stiphout van J (1999), *Grondslagen der epidemiologie*. Elsevier/Bunge: Maarssen.

Vries de CS, Jong-van den Berg LTW de (2009), 'Spontane rapportage en farmaco-epidemiologie.' In: H. Buurma, H.J. Beudeker, L.T.W. de Jong-van den Berg, H.G.M. Leufkens (eds.), *Het geneesmiddel*. Elsevier Gezondheidszorg: Maarssen.

Waals F van der, Mohrs J, Foets M (1993), 'Sex differences among recipients of benzodiazpines in Dutch general practice'. *British Medical Journal* 307: pp. 363-6.

Walley T, Folino-Gallo P, Stephens P, Van Ganse E, on behalf of the EuroMedStat group (2005), 'Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe 1997-2003'. *British Journal of Clinical Pharmacology* 60(5): pp. 543–51.

Weeks JR (2005), *Population. An introduction to concepts and issues.* Wadsworth Publishing: Belmont.

WHOCC (2010), 'ATC/DDD Index 2011'. Internet: http://www.whocc.no/atc_ddd_index/ Last visited February 9, 2011.

Willets RC (2004), 'The Cohort Effect: Insights and Explanations'. *British Actuarial Journal* 10(4): pp. 833-77.

Williams D, Bennet K, Freely J (2003), 'Evidence for an age and gender bias in the secondary prevention of ischaemic heart disease in primary care'. *British Journal of Clinical Pharmacology* 55: pp. 604-608.

Wilmoth JR (1990), 'Variation in vital rates by age, period & cohort'. *Sociological Methodology* 20: pp. 295-335.

Woloshin S, Schwartz LM (2006), 'Giving Legs to Restless Legs: A Case Study of How the Media Helps Make People Sick.' *PLoS Medicine* 3(4): e170.