Differences Between Birth Cohorts in the Prevalence of Benzodiazepine Use

Name: Joren Melis
Student number: S3981088
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Supervisor: Dr. M.J. Bijlsma

Abstract

Objective: This study was performed to research the differences between birth cohorts in the prevalence of benzodiazepine use, to see if there are differences between men and women, and to see if there are differences between different ages.
Design: From the IADB.nl database the data was used, this covered people aged 18-85 over the years 1994-2000 from the database in the Netherlands. The database covers data from 120 community pharmacists containing data of 1.120.000 anonymous patients.
Methods: The prevalence of benzodiazepine use was calculated per 1000 population from the users in the database. To display the prevalence descriptive graphs were used and an APC model was applied.
Results: The prevalence of benzodiazepine use showed to decrease after the year 2008/2009, when changes to reimbursements were made in the Netherlands. The birth cohorts showed a decrease in benzodiazepine prevalence as they became younger. Within the birth cohorts themselves it showed that after the first period containing the year 2009, the prevalence of benzodiazepine use decreased. Women used approximately twice as many benzodiazepines than men, and the prevalence of benzodiazepines increased with an increasing age. The age, period, and cohort dimensions showed the same trends as the before mentioned results, and through the Akaike Information Criterion it was found that each dimension that was added adds predictive potential to the APC model.
Conclusion: The differences between birth cohorts in benzodiazepine prevalence was shown to be present. The historical trends of increasing prevalence with age and twice as many women using benzodiazepines than men, were found again. The decrease of benzodiazepine prevalence in 2009 can be connected to the changes in reimbursements in that year.

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Introduction

Benzodiazepines are drugs that are used in the treatment of several indications. These indications mainly include anxiety and insomnia [1]. The first benzodiazepine was discovered in 1955 by a Hoffmann-La Roche chemist and first marketed in 1960, with diazepam following shortly after in 1963 [2]. The prescription of benzodiazepines differs between age-groups. Benzodiazepines are more often prescribed for the elderly for the treatment of anxiety and insomnia, along with various non-specific symptoms [3]. In 2008 the total use of benzodiazepines in the Netherlands was studies using two databases. This resulted in finding that about 40.000 benzodiazepine prescriptions were found in a population of about 490.000 [4]. The SFK reported that in 2019 around 1,4 million people were prescribed benzodiazepines [5].

Benzodiazepines act on the GABA receptor, which in one of the most common neurotransmitters in the body. GABA has an inhibitory effect on the excitable neurons, this causes a calming or dampening effect of the cerebral activity. The intentional use of benzodiazepines is to use them only on short-term. However, it was found that the usage of benzodiazepines is often done over long-term [6]. The European guidelines of benzodiazepines recommend that the usage of benzodiazepines is done over a short period of time (less than 4 weeks). The usage of benzodiazepines is not recommended over a long period of time, because of the side effects and the risk of tolerance and dependence [7].

The long-term usage of benzodiazepines may lead to addiction problems with withdrawal symptoms. A diminishing effect and difficulty in discontinuation of the usage of benzodiazepines is also considered with the long-term usage of benzodiazepines. In elderly, benzodiazepines have serious adverse effects. The long-term use of benzodiazepines is still high in the elderly, but also in middle-aged people, even with the knowledge of the adverse effects. In a study performed in the Netherlands, that investigated the usage of benzodiazepines between 1992-2002 in the population aged 55-64, it was found that the use of benzodiazepines did not change. During this period no change in the use of benzodiazepines was observed, despite the more awareness mental health was gaining during the time and the change in guidelines for the use of benzodiazepines. The long-term users of benzodiazepines accounted for a high proportion of users [8].

The guidelines for benzodiazepine use vary between the indicated use for them. For insomnia it is recommended that the use of benzodiazepines is only done for a short period, 2-4 weeks, and only in exceptional cases. The usual benzodiazepines that are prescribed in insomnia are the short acting benzodiazepines, such as temazepam or zolpidem. For anxiety the use of benzodiazepines is only prescribed when SSRI's, SNRI's and psychological treatment were ineffective. In anxiety the use of benzodiazepines is recommended to be done for a maximum of 4-6 weeks. The maximum usage of only a few weeks for both insomnia and anxiety are recommended, as after a longer period of using benzodiazepines the effect of dependence acts up. There are also some general guidelines for benzodiazepine use that apply to both insomnia and anxiety. This includes only using benzodiazepines in low dosages, as a dosage equivalent to 30 mg/day of diazepam can inflict damage. Another general guideline for the use of benzodiazepine is that it is recommended that they are not

used every day, the recommendation is to only use it when necessary or with breaks. [9, 10, 11].

On the 1st of January 2009 in the Netherlands, a change was made by the health care insurance for the reimbursement of benzodiazepines to be stopped. This regulation was implemented to achieve less use of benzodiazepines in the Netherlands, mainly due to the negative effects, such as long-term use and addictive effects, of the benzodiazepines but also to reduce the costs that were involved in the supply of the benzodiazepines. The change in regulation was focused on reducing the long-term users of benzodiazepines, however it also affected first time users and short-term users. The reimbursement changes did not affect all benzodiazepine users, the patients who were dependent on benzodiazepines because no alternative treatment was available kept their funding of benzodiazepines. This includes people with anxiety disorders who had 2 anti-depressants fail to ameliorate the symptoms. Palliative sedation that is used in terminal care was also excepted from the reimbursement changes, along with patients who receive benzodiazepines for muscular spasms derived from neurological disorders. The change of the regulations has led to a moderate decrease in the use of benzodiazepines, however the prevalence over a longer time remains unknown [12].

In a 10-year follow-up study conducted during 1983-1992 on the usage patterns of benzodiazepines, it was found that twice as many women use benzodiazepines compared to men. The women in the study were not prescribed more DDDs per prescription than men. The same study also concluded that the use of benzodiazepines increases with age [13]. More current data still support this, as data from 2015 still shows the same ratio of women versus men. This data still shows that the use of benzodiazepines is approximately twice as high in women than in men [14].

In this study, we are going to investigate the differences between birth cohorts in the use of benzodiazepines using the data of the IADB.nl database. In this study we will investigate the differences between men and women and make a difference between the different generations (birth cohorts). With the benzodiazepines being available for such a long period of time, it allows for differences in the regulations and usage of benzodiazepines throughout the years to be investigated. Birth cohort studies can be used to study the usage of benzodiazepines in different generations.

Over the past few years more attention has been generated for mental health disorders. Along with advancements in drug discovery, which contributed to other treatment options for the indications for which benzodiazepines are originally used, it can account for less usage of benzodiazepines over the years. Finally, the new guidelines for the prescriptions of benzodiazepines usage and the changes to reimbursement, resulting from the increasing knowledge of adverse effects, can contribute to a lower usage of benzodiazepines. These factors would contribute to a lower usage of benzodiazepines throughout the years, which would be the expected trend that would follow from this study. Another result that would be expected is the distribution between men and women, in which women historically are prescribed twice as much benzodiazepines as men. This result would be expected to be seen again, as this distribution also did not change over the years and there is no suggestion that would allow for a specific decrease in benzodiazepine use between men and women.

Methods & Data

Data

The data from the patients that was used came from the IADB.nl database. This database contains data from more than 120 public pharmacies, which corresponds to more than 1.120.000 patients from the north of the Netherlands. This covers about 20% of the inhabitants of the north of the Netherlands. The database however is representative for the whole of the Netherlands. The prevalence of drug use matches that of the whole of the Netherlands. In the database the drugs are noted with their Anatomical Therapeutic Chemical (ATC) code, date of prescription and name of the drug. Patients are anonymously registered in the database and received a unique patient code to identify them. The patients are registered with their date of birth and sex. Every patient is included, independent of their health insurance status. The database excludes over the counter drugs or drugs prescribed in the hospital [15].

Study population

The study population is defined by persons between the ages of 18-85 and of both sexes in the time period of 1994-2020. These persons belong to the birth cohort of 1909-2002.

Benzodiazepine use

Patients who received at least one prescription of benzodiazepines in a calendar year were classified as a benzodiazepine user. This is because the guidelines for benzodiazepine prescription only recommends its usage for no more than 6 weeks [16]. Benzodiazepines are classified by the ATC classification: N03AE, N05BA, N05CD, N05CF [17].

Outcome measures

The outcome measures from the study are mainly age-specific and gender-specific use of benzodiazepines. This prevalence of benzodiazepines is expressed per 1.000 population. The prevalence of the benzodiazepines will be calculated according to equation 1.

Equation 1:

$$\frac{Users\ by\ classification\ in\ period\ p\ and\ birth\ cohort\ c}{Person\ years\ at\ risk\ by\ classification\ in\ period\ p\ and\ birth\ cohort\ c} * 1000$$ [18].

Definition of birth cohorts and age categories

The ages 18-85 have been divided into age categories of 4 years. The birth cohorts have been categorized accordingly into groups of 4 birth years. The birth cohorts can be seen in the figure below (figure 1). The gray highlighted years did not fit into a birth cohort but as these are only found in the early data years, they were deemed unreliable.

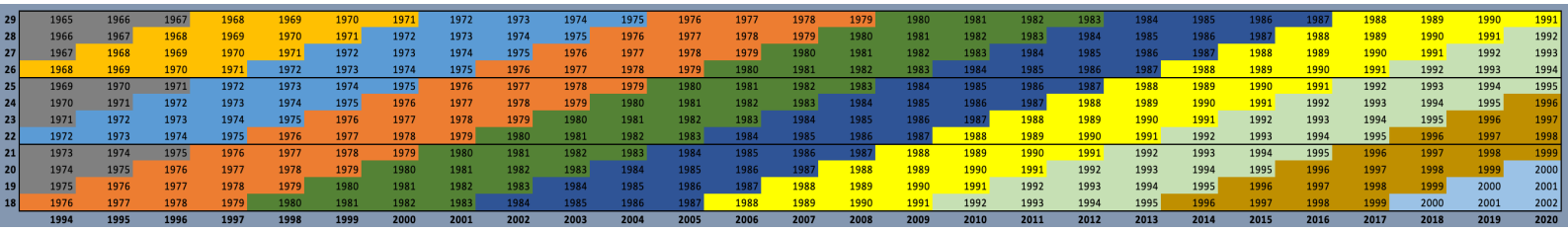

Figure 1: 4-year birth cohorts per 6-year periods displayed in a Lexis diagram. Gray birth years are not used in this study.

Graphical descriptive analysis

The data will be analyzed and depicted in graphs by birth cohort and by period and stratified by sex. The graphs depicting the prevalence by birth cohort and by period will be done in 4-year birth year groups.

APC model

The APC model that is used in this study, is used to model the prevalence. This is done as a function of age, period, and birth cohort, which leaves us with the following formula.

$$\ln[\lambda] = \mu + \alpha_a + \beta_p + \gamma_c$$

In the formula λ signifies the prevalence, the μ signifies the intercept. The a, p and c signify the age, period, and birth cohort. The model used a program for Poisson regression to be fitted and there was an offset term introduced to signify the person-years at risk of benzodiazepine prescription. The categories age, period and birth cohort were measured as a categorical variable. Men and women were separately run in the model. The age, period and birth cohort have a linear dependency, if all three are included in the analysis. This problem was dealt with by using the Clayton and Schifflers approach [18]. For each model the Akaike Information Criterion (AIC) is calculated, this is done to see whether an addition of another dimension adds to the predictive potential. In other words, to check if an addition of the period dimension adds predictive potential to the model only consisting of the age dimension, and if the cohort dimension adds predictive potential to the model consisting of the age and period dimensions.

Results

General trend of the prevalence of benzodiazepine use

The prevalence of benzodiazepine use shows a steady trend in both males and females, with a drop in the year 2009. From the year 1994 the trend follows a strong drop until 1999, whereafter it has a small increase until the trend stabilizes in the year 2001. After 2001 the prevalence of benzodiazepine use is stable for a few years until the year 2007, in which a gradual drop in prevalence can be observed (figure 2). The drop in prevalence ends in 2009, after this year the prevalence of benzodiazepine remains stable to 2020. The overall prevalence of benzodiazepine users after 2009 is 92 users per 1000 persons. The prevalence of benzodiazepine use, after 2009, is 66 users per 1000 men and 116 users per 1000 women. Between 2001 and 2008 the overall prevalence of benzodiazepine users is 125 users per 1000 population. In the same period, a prevalence of 91 users per 1000 men and 157 users per 1000 women. In the unstable years, between 1994 and 2000, an overall prevalence of 148 users per 1000 persons was calculated. The prevalence for men in this period is 105 users per 1000 men and for women the prevalence is 188 users per 1000 women. The distribution between men and women, shows that women use twice as many benzodiazepines than men.

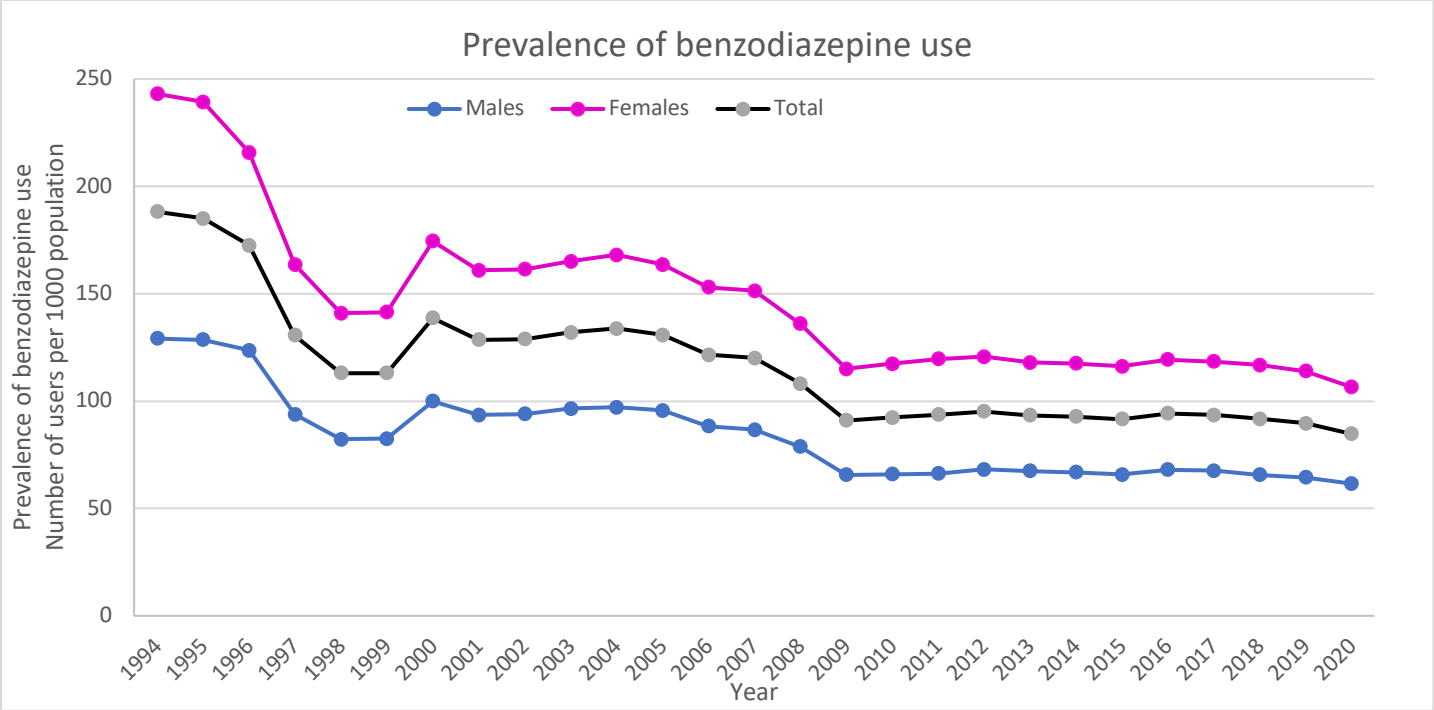

Figure 2: General trend of benzodiazepine use by year and sex, 1994-2020, ages 18-85.

Prevalence of benzodiazepine use per age-group

When divided into age-groups of 4-years, it shows that the prevalence of benzodiazepine users increases with each age-group in each year (figure 3 & figure 4). There are 3 bundles of years that can be found, those being the years 1994-1996, 1997-2007 and 2009-2020. The prevalence of benzodiazepine use drops as the years increase. The year 2008 stands out in these bundles, as this year lies a bit in between the bundle of 1997-2008 and 2009-2020. The bundles all start off at around the same prevalence of 32 users per 1000 men and 49

users per 1000 women, between the age-groups 18-21, 22-25 and 26-29. From age-group 30-33 onwards it shows that the 3 bundles start to split from each other. The prevalence of benzodiazepine use peaks in the age-group 82-85, where the number of 254 users per 1000 men are present and 411 users per 1000 women. The bundle of 1994-1996 has an overall number of 192 users per 1000 men and 332 users per 1000 women, with the peaks lying at 458 users per 1000 men in the age-group 82-85 in the year 1996 and the other peak at 726 users per 1000 women in the age-group 78-81 in the year 1994. The bundle of 1997-2007 has an overall number of 128 users per 1000 men and 221 users per 1000 women, the peaks lie at 341 users per 1000 men in the age-group 82-85 in the year 1997 and 505 users per 1000 women in the age-group 82-85 in the year 2003. In 2008 the overall prevalence lies at 106 users per 1000 men and 181 users per 1000 women, with the peaks in the age-group 82-85 at 239 users per 1000 men and 361 users per 1000 women. The bundle of 2009-2020 has an overall prevalence of 82 users per 1000 men and 147 users per 1000 women, the peaks lie in the age-group 82-85 with 208 users per 1000 men in 2009 and 330 users per 1000 women in 2012.

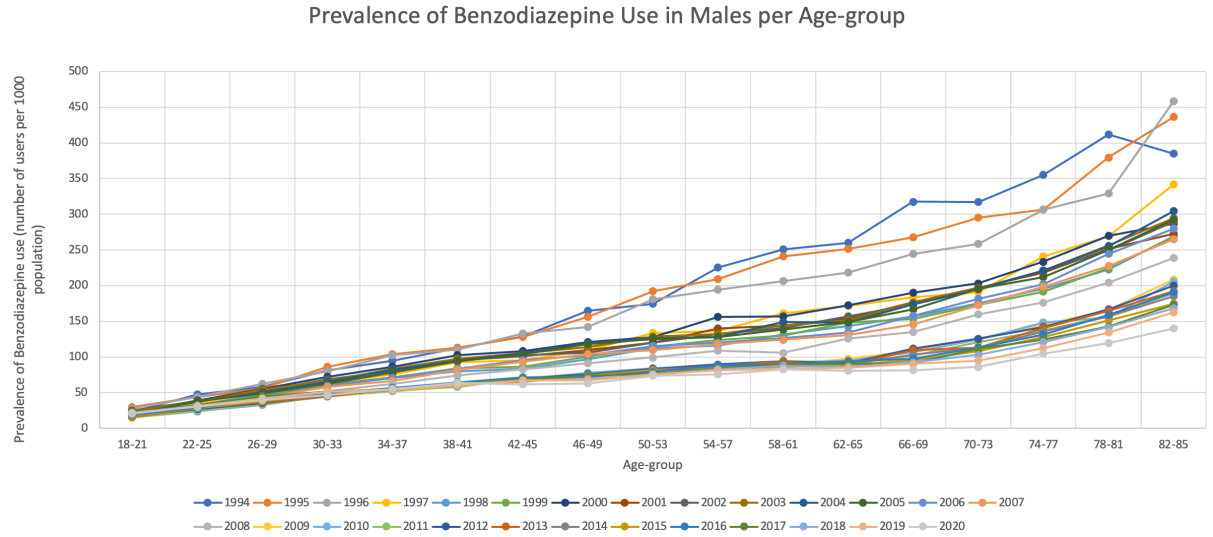

Figure 3: 4-year age-group-specific prevalence of benzodiazepine use in males by year, 1994-2020, ages 18-85.

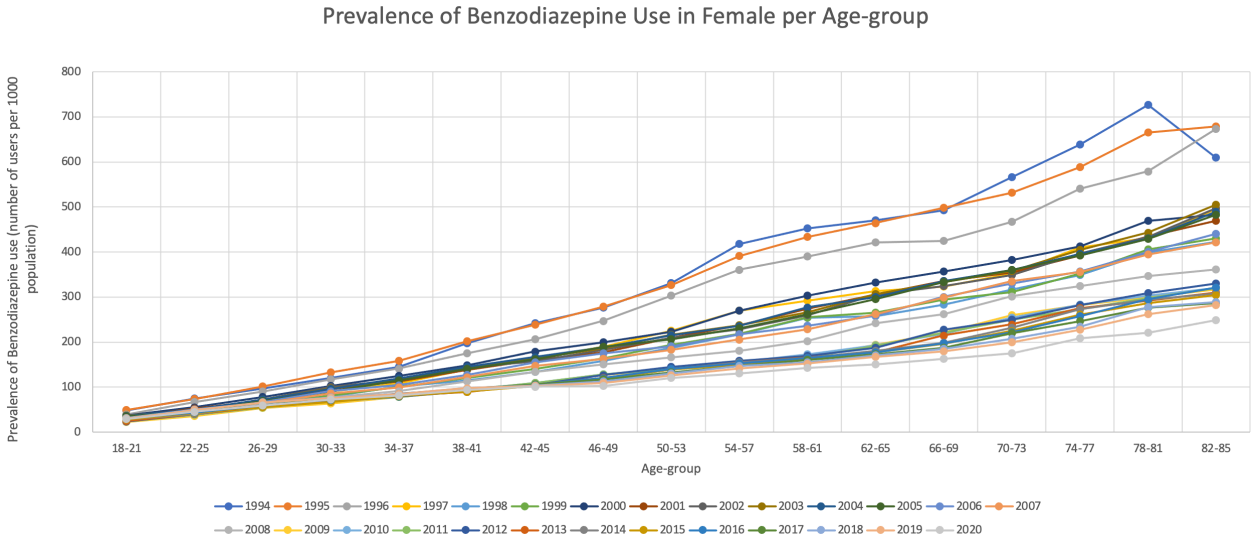

Figure 4: 4-year age-group-specific prevalence of benzodiazepine use in females by year, 1994-2020, ages 18-85.

Prevalence of benzodiazepine use per birth cohort

The prevalence of benzodiazepine use in the different birth cohorts shows that the prevalence increases with the older birth cohorts (figure 5 & figure 6). In most birth cohorts it is seen that the prevalence stays quite stable for the first periods and then decreases from the fourth period, 2006-2012, onward. The older birth cohorts show a more unstable pattern of prevalence, specifically the four oldest birth cohorts, 1912-1915 to 1924-1927, show an increasing prevalence throughout every period. In both men and women, the birth cohort 1912-1915 has the highest prevalence at a number of 637 users per 1000 men and 755 users per 1000 women. When comparing the prevalence within each age-group, it shows that in both men and women the older birth cohorts most of the times show a higher prevalence compared to the younger birth cohorts. In the birth cohort of 2000-2002 up an until the birth cohort of 1936-1939 it could be seen that the final point, correlating to the latest period of data, has the lowest prevalence in both men and women.

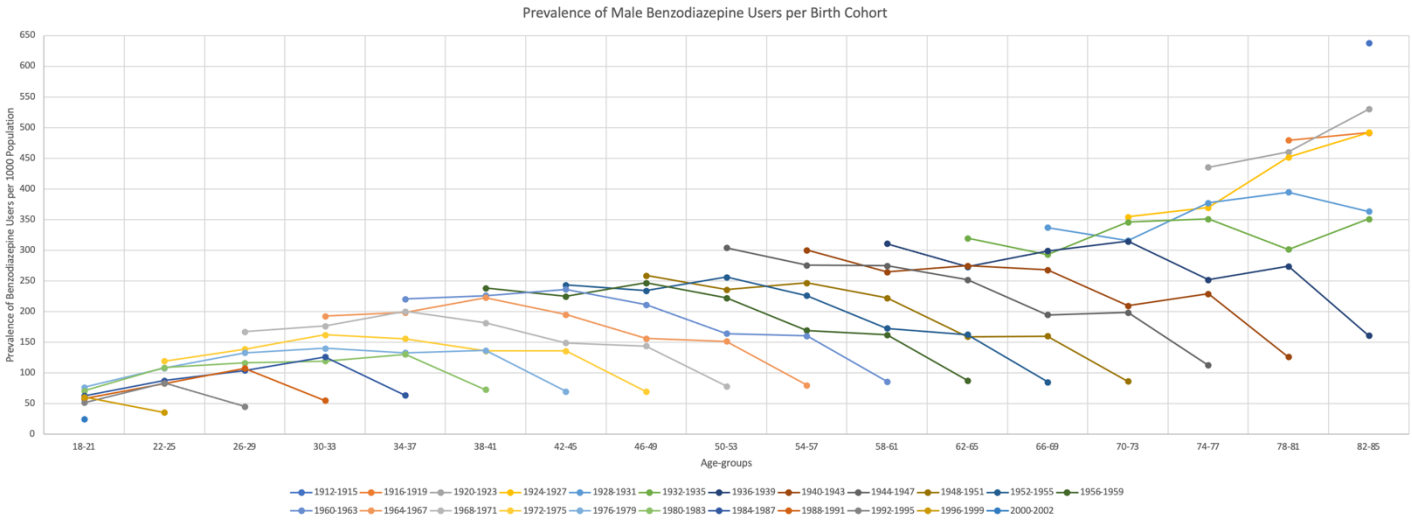

Figure 5: 4-year age-group-specific prevalence of benzodiazepine use by 4-year birth cohorts (1912-1915 to 2000-2002) in males. 1994-2020, ages 18-85.

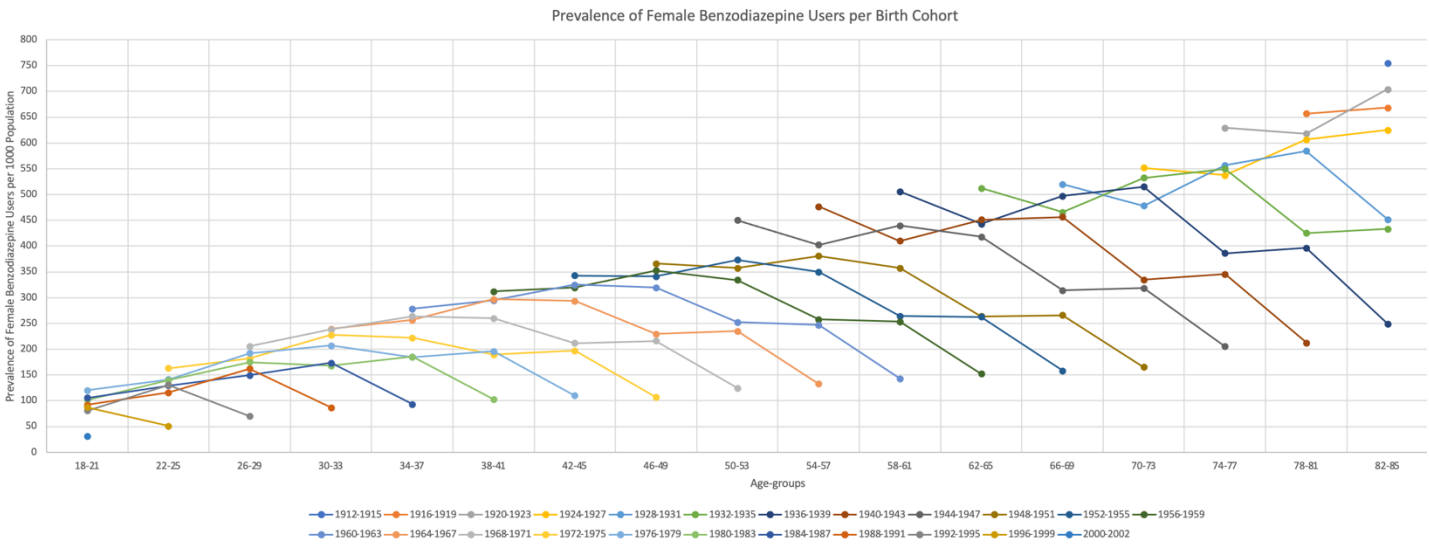

Figure 6: 4-year age-group-specific prevalence of benzodiazepine use by 4-year birth cohorts (1912-1915 to 2000-2002) in females. 1994-2020, ages 18-85.

APC model

The results from the APC model resulted in 3 graphs for men and women, the graphs include the effect of age on the prevalence, the effect of the period on the prevalence and the non-linear effect of the birth cohorts on the prevalence. The effect of age on the prevalence of the benzodiazepine use shows for both men and women to have an increasing odds ratio after the reference age and a decreasing odds ratio before the reference age, in women it shows that the increase and decrease are less steep than in men (figure 7 & figure 8).
The reference value selected for the age effects is selected to be 50, on this age the odds ratio is 1.

The next dimension in the APC model is the period dimension, these graphs have the reference value on the period 2006-2012 with its value being 1. In the graphs for both men and women it shows that the periods before the reference value have a higher odds ratio and after the reference value the odds ratio is seen to decrease (figure 9 & figure 10). Last, the birth cohort dimension is introduced to the APC model, this gives a graph for the non-linear birth cohort effects. The reference value for these graphs is different to the other dimensions, as for the birth cohort effect graphs there are 2 reference values selected. The reference values are selected to be the birth cohorts of 1952-1955 and 1956-1959, these cohorts were valued at an odds ratio of 1.

The birth cohort effects graphs show a higher odds ratio in the older birth cohorts, before the reference values, but with the birth cohorts coming closer to the reference values the odds ratio's come closer to an odds ratio of 1, with the last birth cohort before the reference values even dropping below 1. After the reference values it shows that the odds ratio's keep decreasing, however once the birth cohort of 1972-1975 is reached the odds ratio increases again. Only the last birth cohort has a decreasing trend in birth cohort, with the decrease in odds ratio being a lot bigger in women than in men (figure 11 & figure 12). Finally, the Akaike Information Criterion was calculated for the APC model, these values can be found in figure 13. It shows that the AIC decreases with each added dimension, for both men and women.

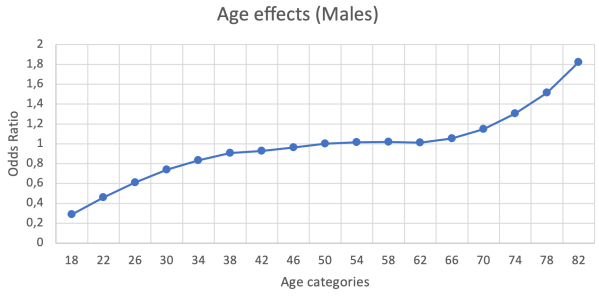

Figure 7: Fitted age effects for males in prevalence of benzodiazepine use 1994-2020. Ages 18-85. Reference value at 50-53 years old.

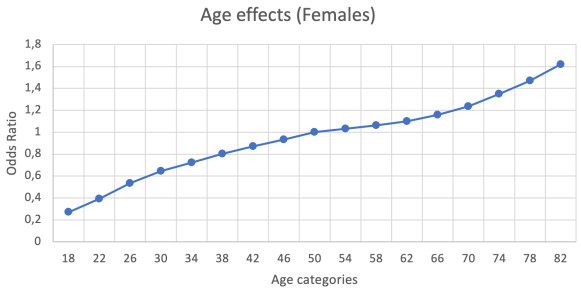

Figure 8: Fitted age effects for females in prevalence of benzodiazepine use 1994-2020. Ages 18-85. Reference value at 50-53 years old.

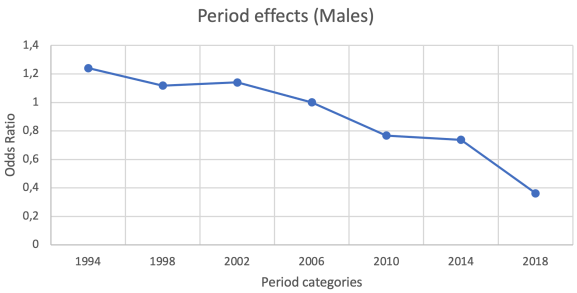

Figure 9: Fitted period effects for males in prevalence of benzodiazepine use 1994-2020. Ages 18-85. Reference value at period of

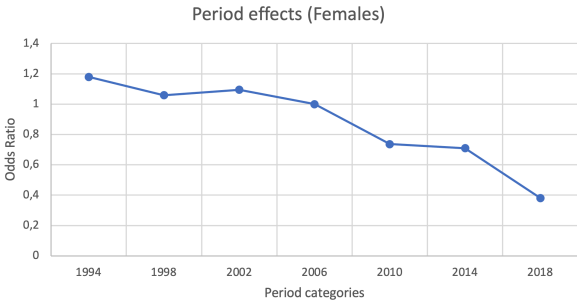

Figure 10: Fitted period effects for females in prevalence of benzodiazepine use 1994-2020. Ages 18-85. Reference value at period of

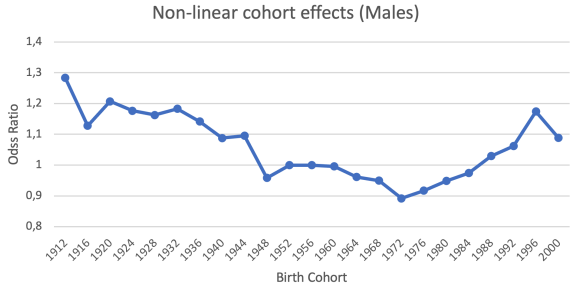

Figure 11: Fitted Non-linear cohort effects for males in prevalence of benzodiazepine use 1994-2020. Ages 18-85. Reference value at cohorts 1952-1955 and 1956-1959.

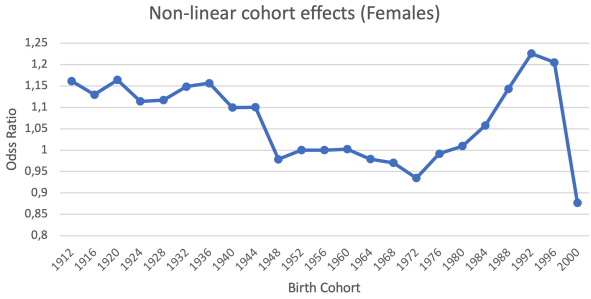

Figure 12: Fitted Non-linear cohort effects for females in prevalence of benzodiazepine use 1994-2020. Ages 18-85. Reference value at cohorts 1952-1955 and 1956-1959.

Figure 13: Table containing the Akaike Information Criterion values for the dimensions in the APC model. Where a signifies the age, p signifies the period and c signifies the cohort.

	A	A+P	A+P+C
Male	43727	2255	1650
Female	61294	3089	1975

Discussion

Main findings

This study was conducted to research if there was any difference in the prevalence between different birth cohorts, and to see if there was any difference between men and women. This was study gave the results in four different graphs, those being the general trend, prevalence per age-group, prevalence per birth cohort and an APC model. The most important results from those graphs are the seen decrease in prevalence after the years 2008/2009 in the general trend and in the prevalence per age-group, the older birth cohorts having a higher prevalence than the younger ones and that within a birth cohort that the prevalence decreases after the fourth period. The distribution between men and women showed that women use approximately twice as many benzodiazepines than men. And that the prevalence of benzodiazepine use increase with age. The APC model showed that the odds ratio of the age effects increased with age, the odds ratio of the period effects decreased after the period of 2006-2012, and the non-linear cohort effects showed that the odds ratio decreased until the cohort of 1972-1975 after which the odds ratio increased again.

Strengths and limitations

This study has several strengths, one of them is that this study used the IADB database, which contains a great amount of data from patients. The data found in this database is representative for the whole of the Netherlands. Another strength of this study is the large sample size used for the study. The data used in this study has an overall good reliability, however the data from the first years is more unreliable than the other years. This includes the years 1994-1998, as these years shows great fluctuation in the general trend of the benzodiazepine use prevalence. The years 1994-1998 also show a generally lower total population, which creates a more unstable calculation of the prevalence of benzodiazepine use. This can be related to another limitation of this study, that being a poor estimation of the total population. The users in this study are defined as a person who has at least one prescription of benzodiazepines. This definition can be a limitation of the study, as there is a risk that a pharmacist registers a wrong ATC-code which ends up in the IADB database. This would create an overestimation, because a patient who receives a few prescriptions of benzodiazepines can be registered wrong once but with the next prescription they would be registered correctly. However, someone who does not receive a benzodiazepine prescription can be registered incorrectly and is then registered as a benzodiazepine user to our used definition.

General trend of the prevalence of benzodiazepine use

The general trend of the prevalence shows an unstable first years in the graph. This can be explained by the unstableness of the first years of the database. Another explanation for this can be the poor estimation of the total population. After the unstable first years the trend levels out and has a stable level. This level remains stable until the year 2008/2009, after those years the level drops to a lower level that remains until 2020. The drop after the years 2008/2009 can be explained by the change in reimbursement made in 2009. The change in reimbursements included that benzodiazepine users did not receive any reimbursement for their benzodiazepine prescription. This change in reimbursement was implemented to reduce the use of benzodiazepines, the expected result from this would be a decrease in

benzodiazepine prevalence after the year 2008 [12]. The decrease in benzodiazepine prevalence after the year 2008 can thus be explained by this change in reimbursement. The drop of prevalence in benzodiazepine in the year 2008 cannot be explained by the change in reimbursement. However, the drop in prevalence in 2008 could be related to the change in reimbursement in the following year, as it could have led to anticipation on the new reimbursement policies in the following year.

Furthermore, a more significant decrease in prevalence can be observed in the year 2020. With 2020 being the last year from which data is available, it is hard to say whether this decrease in prevalence is due to a reason or related to fluctuations is left to be further explored. The final thing we can observe in the general trend, is the distribution between men and women. As expected, beforehand, it can be seen that the distribution between men and women follows the same pattern. This being that around twice the number of women use benzodiazepines than men [13,14]. The possibility of more mental health awareness being a reason for a drop in benzodiazepine prevalence is hard to tell from the results because of the fluctuations in the prevalence throughout the years, as no significant drop in prevalence can be observed that can be linked with the gaining awareness for mental health over the years.

Prevalence of benzodiazepine use per age-group

When looking into the prevalence of benzodiazepine use on different age-groups, a few things can be noticed. The most important being the increase of prevalence with increasing age. The increase of prevalence in benzodiazepine use along with increasing age is a known outcome of an already performed study [3,13]. A possible explanation is also given in the same article as elderly have a worse health, are faster to seek health care and there is a different interaction between the patient and physician [13]. With this research being performed in the period of 1983-1992, which bring forward the question whether this would still apply in this research. With the increasing elderly population in the Netherlands the properties mentioned by the other study are still relevant. As these properties mentioned are not specific to a certain time, there is a good possibility that the same reasons still apply in this study. The distribution between men and women also shows to be approximately twice as high in women than in men, this result was expected prior to the study and follows the same result as the general trend of benzodiazepine use prevalence [13,14].

The 3 bundles that show in the graph for men and in the graph for women require a same explanation as the general trend, as for these bundles it is necessary to look at the years in the database. The bundle with the highest prevalence resulted from the first 3 years in the database, 1994-1996, as previously discussed these years suffer from an unstable database and thus created more untrustworthy results. The high prevalence of this bundle can be deemed unreliable by the unstableness of the first years in the database. The results from the first bundle should lie more towards the prevalence of the second bundle as these years don't differ in benzodiazepine prescription and reimbursement.

The second bundle of prevalence lies in between the highest bundle and lowest bundle, this bundle spans over the years 1997-2007. In this bundle it still includes some unstable database years, however when these years have been calculated per age-group in a certain year they seem to fit better with the rest of the data. These years represent the benzodiazepine use prevalence before the changes in reimbursement [12]. In comparison to the general trend, these years show the same stable level of fluctuation between the

prevalence in the separate years. Before reaching the third bundle, with the lowest prevalence, the year 2008 can be seen to lie between the second bundle and third bundle. This could be explained by the changes in reimbursements the year later, as in the year 2008 it could already have had some effect on the benzodiazepine prevalence [12]. The third bundle ranges from the years 2009-2020, this bundle has the lowest prevalence. The lower prevalence can be explained by the changes in reimbursement, which were intended to lower the prevalence of benzodiazepine use by no longer reimbursing the costs for benzodiazepines [12]. As previously mentioned for the general trend, the drop in prevalence can be nicely seen in the year 2009 whereafter the prevalence stays lower. It is also seen that the year 2020 lies a bit lower than the other years from the third bundle, however the reason for this is still up for debate. As it can either be a fluctuation in prevalence or it is the start of a downwards trend, but this should be investigated in further research.

Prevalence of benzodiazepine use per birth cohort

In the birth cohorts there are two results that are important for this study. The first one being the increasing overall prevalence of benzodiazepine use with the older birth cohorts. This is an expected result, as the prevalence of the older birth cohorts corresponds with the older age-groups [3,13]. The other result that is of importance is the prevalence in the birth cohorts themselves. In the birth cohorts it shows that the prevalence drops in the fourth period inside each birth cohort, except for a few of the older birth cohorts. The drop in the fourth period inside each birth cohort, can be explained by the change in reimbursements. As the fourth period ranges from 2006-2012, it includes the year 2009 in which the reimbursement changes were introduced [12]. These changes in reimbursement make it that the prevalence drops in the birth cohorts themselves and not between birth cohorts. After the fourth period in a birth cohort the prevalence stays lower than before as all periods since then all include the year 2009 or fall after the year 2009, making them affected by the change in reimbursement [12]. The change in reimbursement is the most likely cause for the lower prevalence.

Another thing that can be seen in most of the birth cohorts, is the drop in prevalence in the final period. This drop is probably not entirely trustworthy, due to the definition of the birth cohorts. When the birth cohorts were defined, they were split into 4 birth years starting in 1994. This led to the data of the final period of the birth cohorts only consisting of data from 2018-2020. The smaller last period of each birth cohort could thus be the reason for its lower prevalence; however, it should be considered that these final periods in each birth cohort is quite unstable. The distribution between men and women in the birth cohorts is not the same as the earlier results, with twice as many women using benzodiazepines than men. The distribution does shows that women use more than men but with the birth cohorts it does not show that it is in the range of twice as much. When calculating the prevalence for the general trend and in the separate age-groups it did show a distribution in the range of twice as many women using benzodiazepines than men. The difference could have an origin in the way the prevalence is calculated because the total population calculation is performed in a different way than for the other two sections. With the total population of the birth cohort being calculated from the total population of the middle year in each period.

APC model

The first result coming from the APC model are the Akaike Information Criterion, AIC, values. These values say something about the dimension that is added to the model. When the AIC value decreases when another dimension is added to the model, it adds predictive potential to the model. With each value decreasing when a new dimension is added to the model, for men and women, it suggests that each dimension adds quality to the model.

The APC model gave results for 3 different dimensions, the age, the period, and the birth cohort. The age effects showed that the odds ratio was lower before the reference value and higher after the reference value. This would suggest that the prevalence of the benzodiazepine use would increase with age. This is supported by the knowledge that increase benzodiazepine usage with age is a known effect [3,13].

The period effects showed that the odds ratios are higher before the reference value at the period of 2006-2012 and the odds ratios are lower after that period. This suggests that the prevalence of benzodiazepine use is higher before the reference value and has a lower prevalence after the reference value. In other words, the early periods have a higher prevalence than the later periods. The turnover point lies at the reference value, which happens to include the year 2009. In 2009 the changes to reimbursement of benzodiazepines took place and have led to a reduction in benzodiazepine prescription [12]. The drop in odds ratio in the period effects support this effect of changes in reimbursements, with the decrease odds ratio in the periods after and including 2009.

The non-linear cohort effects show that there is a higher odds ratio in the older birth cohorts compared to the two reference values. As the cohorts get younger and more towards the reference values the odds ratio drop. This supports to the known trend of benzodiazepine usage to be correlating with an increasing age, because the overall age decreases with younger cohorts it supports this trend [3,13]. After the reference values it shows that this trend continues to be supported by the cohort effects graph, until the birth cohort of 1972-1975. After this birth cohort the odds ratios start to increase, this would suggest that the prevalence of the next cohorts would also increase. This effect is unwanted as an increase in benzodiazepine usage is not wanted, because of all the unwanted side effects and dependence issues benzodiazepines brings with them [7,8]. An explanation for this trend is something that would need to be studied in a later drug utilization study to see if the same trend is observed. After the increasing trend of odds ratios after the cohort of 1972-1975 it shows that in the cohort of 2000-2002 there is a drop in odds ratio. This drop is larger in women than in men and would suggest that the prevalence decreases in this birth cohort. However, this birth cohort only consists of 3 years and would therefore need to be considered more carefully than other birth cohorts. Because of the 3 years birth cohort the calculation of the prevalence is more unstable than the other birth cohorts, and thus making the result less reliable.

Overall conclusion

In this study it showed that there have been changes in the prevalence of benzodiazepine usage overtime and that some already known trends are still present. The decrease of benzodiazepine usage after the year 2009 supports the hypothesis that a decrease is expected after the changes in reimbursement of benzodiazepines. The historical trends of increasing benzodiazepine use with increasing age and twice as many women using benzodiazepines than men, which were expected to be a result of this study, did indeed show up in the results and thus supporting that hypothesis.

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