

Certain Lifestyle Adjustments as an Alternative Remedy to Reduce the Trends in Preventive Cardiovascular Drug-prescriptions and Thereby Their Arising Ecotoxic Drug-Waste.

Bachelor research Project

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Abstract.

Background: The frequent use of blood pressure and cardiac muscle regulating agents has led to an increase in their retained hazardous drug-waste found within water treatment plants in the Netherlands. Since then, more nature friendly alternatives have emerged to replace preventive cardiovascular agents, and by that to reduce their chemical waste. A set of lifestyle alterations such as smoking cessation and an improved physical activity have been studied in research trials to investigate their ability to reduce cardiovascular risk factors.

Objective: The goal of this thesis is to investigate whether certain interventive lifestyle improvements would present a new therapy to reduce the frequent use of preventive cardiovascular drugs through cardiovascular health promotion. The ultimate goal by this replacement is to lower the retained drug-waste of these chemical agents, which would be environmentally and economically beneficial.

Methods: The database (IADB) was used to display the volume of the annual prescriptions of ACEIs and ARBs for both men and women aged 40 years and higher from 2010 until 2020. To investigate the gender and age association with the occurrence and the pathogenesis of cardiovascular abnormalities, the tested population was subdivided into four groups; those aged from 40 to 65 years, those who are older than 65, and men and women aged 40 or above separately. However, the groups were not divided based on the class of used medication. For each trend, the prevalence and incidence with the 95% confidence interval (CI), and their relative risks, were determined with 2020 as the indicator and 2010 as the reference year.

Results: The prevalence of ACEIs and ARBs increased for individuals aged 40 years and older between 2010 and 2020 with about 1.2%. The incidence of ACEIs and ARBs decreased for individuals aged 40 years and older between 2010 and 2020. The increase in the prevalence was the most substantial in men and patients older than 65 years of age. The opposite applies for women and individuals aged from 40 to 65 years. The incidence of ACEIs and ARBs decreased in all the risk groups but males. The prevalence and incidence differed immensely in all cases, and all the decreases and increases were significant according to Chi-square testing.

Conclusion: The disposal of ecotoxic drug-waste into water treatment plants has been on the rise since 2010 in the Netherlands. This reality can be altered and the drug-waste can be reduced if people with no cardiovascular abnormalities, but at high risk of developing them, would follow lifestyle intervention programs presented in the conducted and discussed systematic review of this report.

Introduction.

Lifestyle association with cardiovascular health and disease.

The cardiovascular system (CVS) is one of the most crucial physiological apparatuses within our bodies, it ensures sufficient supplementation of the blood, and thus oxygen and nutrients, to the whole human body [1]. Its improper functioning, or failure, would lead to life threatening events and even death. Arrhythmias, brady- or tachycardia, heart fibrillation and heart failure are examples of frequently occurring cardiovascular disorders [1]. They can be genetically related or, in most cases, lifestyle-related [1]. Factors such as the individual's age, genetic predisposition and gender can be considered as cardiovascular risk factors with a linkage to various cardiovascular abnormalities, these factors are however beyond our control as species. On the other hand, besides environmental factors, daily habits and different lifestyle activities may substantially influence cardiovascular health. For example, cigarette smoking, unhealthy dietary intakes (e.g., fast food), low physical activity and alcoholism, has been found in various clinical research trials to be heavy contributors to the progression of cardiovascular pathology [1].

The use of preventive cardiovascular agents.

Additionally, various pharmaceuticals have been introduced to treat most of these cardiovascular abnormalities, they operate as preventive substances that, for instance, block certain blood pressure and cardiomyocyte regulatory mechanisms and pathways. Scientific studies have demonstrated that certain unhealthy daily routines would negatively affect the cardiovascular function, and thus elevate the use of preventive cardiovascular agents (CVAs). This would result in an increase in their retained hazardous waste from water treatment plants. The elevation in CVD waste suggests that the dependence of humans on chemical pharmaceuticals has grown in favour of natural, and healthy lifestyle programs, leading to an ever-growing pollution of mother nature. Certain interventional lifestyle adjustments may reduce this resulting chemical drug waste, offer financial benefits and decrease adverse drug reactions. In this thesis, a set of interventional lifestyle improvements that promote cardiovascular health will be discussed and reviewed. Examples of frequently used CVAs are beta-blockers, angiotensin converting enzyme inhibitors (ACEIs), anti-platelets such as aspirin and angiotensin II receptors blockers (ARBs). CVAs can be divided into multiple classes; this would present a burden during the conduction of this suggested research project. Therefore, only the two CVA classes ARBs and ACEIs will be researched in this bachelor project, otherwise the research would be too broad, and thus, more time consuming.

Aim.

In this thesis we aim to uncover how and to what degree would certain lifestyle promotions and improvements prevent or lower the use of the cardiovascular drugs, and thereby reduce their ecotoxic drug-waste. The aim of this thesis appears to be too general, but CVDs as a whole do include our drugs of interest. However, information regarding the properties, pharmacokinetic profile, pharmacological action and importance of ACEIs and ARBs are firstly discussed in the following sections. And to clarify the importance and the reason for the frequent use of these two classes, indications of both classes are presented in the next segment below.

Indications of ACEIs and ARBs.

Both classes, while operating via separate mechanisms, inhibit the renin-angiotensin system (RAAS) through either the allosteric inhibition of the angiotensin converting enzyme (ACE inhibitor) that converts angiotensin I to its II active form, which reduces the amount and production of angiotensin II, a hormone that elevates blood pressure, or by blocking the receptor of angiotensin II (ARBs) [2]. Both classes are mostly prescribed to treat heart failure, left ventricular dysfunction, post myocardial infarction, established coronary heart disease and hypertension [2]. The classes are also used to reduce the burden of cardiovascular diseases and prevent secondary stroke events in combination with thiazide-like diuretics [2]. Specific natural compounds which are provided as food supplements may serve as “green alternatives” to replace these drugs, which goes along with the goal of this thesis. The next segment showcases the most effective green replacements to ACEIs and ARBs.

Natural substances as green alternatives to replace ACEIs or ARBs.

Garlic can be regarded as a natural ACEI because it may operate as a natural gamma-glutamyl cysteine, a natural ACE inhibitor. The compound is completely natural and it helps by dilating the arteries in combination with allicin [3].

Many studies evaluated pomegranate juice as a possible ACE inhibitor, in most conducted studies, the juice was found to be an effective ACEI, it is also advised not to drink it if you use certain anti-hypertensives, such as Warfarin [4].

Grapes are highly beneficial when it comes to cardiovascular health, they can block the working of the ACE and the angiotensin II receptor, and for this reason they exist as dietary supplements of grape seed extracts. From the trial assessing the benefits of the grape-seed extract, scientists concluded that the seed extract of red grapes remarkably reduced systolic and diastolic blood pressure within five to six weeks of the experimental follow-up [3].

Indian Gooseberry is known as a highly potent RAAS inhibitor. A research trial that involved an 8 weeks follow-up proved that Indian Gooseberry can enhance anti-hypertensive drug therapy. The study added: “The herb is rich in vitamin C and E, and it may support healthy cholesterol ratios” [3].

More natural ARBs:

Direct vasodilators: coenzyme Q10 and Omega 3 fatty acids, and diuretics: Vitamin B6, taurine, and magnesium [4].

For a deeper understanding of the two classes, their pharmacokinetic profile is presented below.

Pharmacokinetics and ADME Criteria of ACEIs and ARBs [2].

PHARMACOKINETICS	ARBs	ACEIs
Absorption	Depends on dosage form. Generally, oral bioavailability reaches beyond 90% (depends on the drug)	Depends on dosage form. Generally, oral bioavailability reaches beyond 90% (depends on the drug)
Distribution	Depends on dosage form	Depends on dosage form
Metabolism	Hepatic, CYP enzyme family metabolism	Hepatic hydrolysis
Elimination	Renal and biliary	Predominantly renal
Serum half-life	9-12 hours	5-6 hours
Administration	Mostly oral	Mostly oral
Protein binding	Nearly 99%	Above 95%
Dosage form (mostly)	Rapid acting	Inactive prodrug

Table 1, depicting a brief summary about the most important points of the pharmacokinetic profile of our drugs of interest

ACEIs and ARBs bind to tissue and plasma proteins; drug binding ensures that the plasma concentration-time profile has a prolonged elimination phase. The free drug and its metabolites are mostly eliminated by renal clearance, ARBs have an additional biliary elimination route of about 60%. Most ACEIs function as inactive prodrugs (e.g., Enalapril). These prodrugs require hepatic hydrolysis to reach their acidic active forms. This means that the dosage form and certain physio-chemical properties may alter the ADME profile of the class, especially the absorption and distribution. ARBs are mostly rapidly acting agents. Their absorption, and thus distribution, is relatively fast. Both classes are mostly orally administered with a few exceptions to overcome acute hypertensive crises. It is widely known that producing a drug suitable for a specific single patient, or a small group of, is immensely beneficial, because it reduces the occurrences of adverse drug responses, and thereby increases patient's compliance [6]. These are typically called 'tailor-made agents', factors such as the patient's age, weight, medical use and the genetic predisposition of a population are taken into account when synthesising these agents [7]. Therefore, a brief review on drug-personalisation of ACEIs and ARBs is presented in the following segment for a better understanding of the two classes.

Personalising ACEIs and ARBs.

The complex pathology of common cardiovascular diseases makes the development of personalised medicine difficult [5]. This problem is further confounded by classification of cardiovascular diseases based on the observed clinical phenotype rather than on the underlying mechanisms of the disease [5]. As the mechanistic understanding of complex cardiovascular diseases grows with the ability to identify causative factors at the individual patient level, opportunities for personalised medicine would occur [6]. Personalised cardiovascular medicine allows more effective treatment with fewer adverse effects [7]. Example of a personalised medicine is a tailor-made drug with respect to the individual's age, body weight, medication, health (diseases), patient's renal and hepatic functions (metabolic activity) [7]. In most cases, the dose and administration routes are adjusted in order to personalise CDAs [6]. In the next segment lies the objective of this research.

Objective.

To what extent would certain lifestyle improvements lower the use of preventive cardiovascular agents, and thereby reduce their ecotoxic drug-waste.

The goal of this thesis is to investigate whether certain interventional lifestyle alterations would present an alternative remedy to replace the use of preventive cardiovascular drugs by promoting cardiovascular health and proper functioning. The ultimate goal by this replacement, and thus this research project, is to reduce the annual drug-waste of these preventive drugs, which would be environmentally and economically beneficial. In this thesis, articles that discuss our subject of interest will be presented and reviewed to illustrate, and prove the importance, or legitimacy, of this thesis and its objective. A set of lifestyle alterations that have the biggest impact on the health of the CVS are showcased in the results section, the presented studies are either randomised controlled trials, cohort studies or clinical trials. The methods section shows how the scientific literature of interest was found.

Methods and Protocols.

Search strategy and data source.

Systematic research strategy was done using PubMed advanced Mesh database searching to find clinical and randomised controlled trials that share the aim of this thesis. The searches were conducted using the Mesh terms: "CARDIOVASCULAR", "HYPERTENSION", "LIFE STYLE", "DIET" and "SMOKING". Examples: search #1: ("Cardiovascular System"[Mesh]) AND "Life Style"[Mesh]. Search #2: ("Cardiovascular System"[Mesh]) AND "Diet"[Mesh]. The results of the used literature were read, and then individually and effectively formatted as conclusive, short summaries. Each article was linked with its results using: "according to". "According to" does not mean that the results were copied, this is just to showcase where the results were derived from, and whether they are legitimate. The IADB is a growing database. The data from the IADB is a good reflection of the general population in the Netherlands. The database gives information about the recipe and the patient [17]. This research made use of the following patient's data: patient ID (anopat), date of birth and gender. Information on given recipes included: patient's ID, date of prescriptions, number of daily doses and the ATC codes of drugs of interest. The data on preventive cardiovascular drug-use were researched on IADB according to the following protocol.

Study period and population.

This study consisted of men and women aged 40 and higher, this group is the most susceptible to cardiovascular events and the most frequent user of CVAs [8-16]. Any new drug user must exist in the database 365 days before the new prescription of a C09 drug. The underlying population of the database is used to determine the dominator of this research group. The population of the database is representative for the Netherlands [17]. The study period was from 1 January 2010 until 31 December 2020.

In- and exclusion criteria.

Inclusion of ACEIs and ARBs.

The prescription-trends of fixed doses of ACEIs and ARBs in different age groups and both genders were investigated separately, which was conducted using the anatomical therapeutic chemical code (ATC-code) of the two CVA classes of interest. These were the ATC-codes that begin with C09 followed by AA or DA. Therefore, the CVAs were divided into two groups according to the obtained data; ACEIs, which begin with C09A, and ARBs, which begin with C09DA. Both anti-RAAS classes start with C09, and all of their prescribed ATC codes in the study period are presented in the **table**. The risk factors were defined by distinguishing and comparing the trends of prescriptions in the two age groups: 40 to 65, and 65 or older. And between men and women.

Prevalence and incidence.

For all groups, the prevalence and incidence were determined. A participant is regarded as a prevalent user of CVAs if she or he had more than 1 prescription in the observed year. An incident CVA-user is a starter of either class. This is defined as a first-time user, or a user after a long time of non-CVA-use, which has to be at least 365 days. In short, these individuals are present in the database 365 days before their newest CVA prescription. These individuals must also be prevalent users; they should be registered to more than one prescription in the observed year.

Participants' information and data trends.

The trends were researched in the total enrolled population of men and women aged 40 years and higher from 2010 until 2020, where each year is regarded as a calendar year. The trends were distinguished in the two separate age groups, where the age of each participant was determined on the first of January of each year. The trends in the prescription of the two CVA classes, ACEIs and ARBs, were studied in four groups. The two age-groups for both genders, and each of the two genders separately. These characteristics were already set in the databases by the service provider

Obtaining the data.

All information on patient prescription trends were determined using IADB's structured query language (SQL). First, a dominator table for both incidence and prevalence was made. Afterwards, prevalence and incidence nominators were created using the patient and starter tables combined with the table of recipes. Finally, the obtained tables were used to determine the effect measurements of incidence and prevalence, incidence and prevalence in all comparable risk group presented in the study protocol, and the 95% CI of the prevalence, incidence and relative risk. The Chi square test was used to compare the prevalence or incidence of 2020 and 2010 with the corresponding 95% CI to test whether there is a significant difference. All the queries used to obtain the data of interest are appended and marked in the appendices section. The numerical data resulting from queries on SQL were brought to excel to create graphs and conduct calculations.

Descriptive statistics.

The yearly prevalence was calculated through determining the total number of patients aged 40 and higher who either used ACEIs or ARBs in the observed year. The obtained numbers were divided by the total number of individuals of the same age category who were recorded from the population of the database. Incidence nominators included all patients aged 40 years and above who were a starter of either class. This was also done in the same way for the two separate age groups (40-65, 65 or > 65), and both gender groups. In addition, the prevalence and the incidence of the four risk groups were calculated. The denominator for both, the prevalence and incidence, was the total number of persons aged 40 years and higher with the mentioned medication use. The nominator of the prevalence was the total number of persons aged 40 years and older who also used the pharmaceuticals of interest. The nominator of the incidence was the total number of starters of ACEIs and/ or ARBs users. All previous queries were then performed where the characteristics of each of the four separate risk groups (40-65, 65 or > 65, and both genders) were taken into account for the sake of comparison and in order to uncover the most impactful risk factors contributing to the use of preventive CVAs. As mentioned, the 95% confidence interval (CI) was determined for both the prevalence and the incidence. The formula $P \pm 1,96\sqrt{P(1-P)/N}$ was used to determine the prevalent 95% CI, where P is the prevalence and N is the denominator [18]. The formula $CI \pm 1,96\sqrt{CI(1-CI)/N}$ was then used to calculate the incidental 95% CI, where CI is the de-cumulative incidence [18].

Statistical analysis of the data.

The relative risk (RR), with its 95% CI and the p-value were derived to investigate the significance of the decrease or increase in the trends. If the p-value is <0,05 and the 95% CI did not include 1, the decrease or increase is then significant. The RR was determined using the prevalences of 2010 and 2020, where that of 2010 was the reference year and 2020 the indicator year. This was performed on all risk groups as well. Rothman K.'s Excel sheet was used to calculate the mentioned parameters. Finally, the formula $(1-RR)*100\%$ is used to express the decreases or increases in the trends as percentages.

Results.

The obtained IADB results demonstrated that the number of 'C09AA and 'C09DA' users was never constant throughout the study period. Within this dynamic cohort, the denominator for all individuals aged 40 years or above was 1145414 in 2020, 77969 of which used the mentioned drugs, and 2961 individuals were new starters after at least 365 days of non-preventive CVD use. For the group aged between 40 and 65 years, and in 2020, 29248 individuals used the medication (users divided by the total population was 0.0255), with an incidental use of 0.0016 (new users divided by the population). The second age group, aged 65 and higher, displayed a prevalent use of 50563 (users/ total population = 0.0441) in 2020, with an incidental use of 0.0005. In the same year, there were 43337 (55.85%) male and 34632 (44.42%) female users of the medication who were all 40 years of age or higher. In the year 2020, the male population displayed an incidental drug use of 1657 (55.96%), and the female population displayed an incidental drug use of 1304 (44.04%).

Prescription trends found throughout the study period in all patients aged 40 years or higher.

The trends in the prevalence and the incidence of C09AA and C09DA use are displayed in figures 1 and 2 below. The data for the prevalence was derived using the appendices 2.2, 3.4 and table 5.2. The data for the incidence was derived using the appendices 2.3, 3.5 and table 5.3.

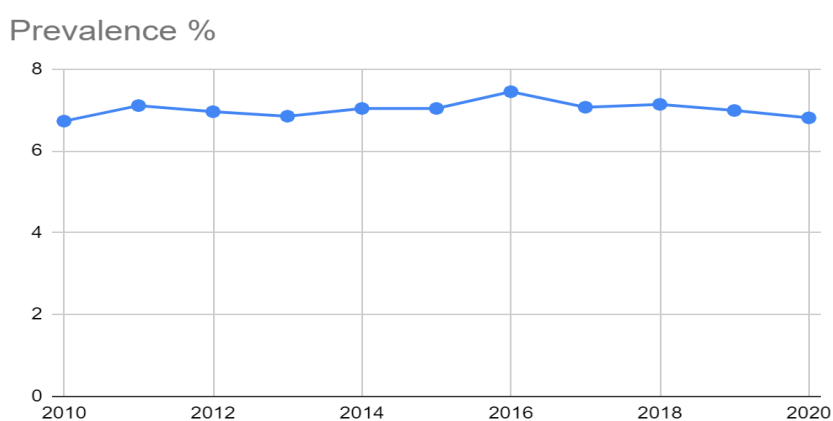


Figure 1, The prevalence of the prescriptions of C09AA and C09DA medications within the study period for all individuals aged 40 or above. The prevalence is expressed as percentages on the y-axis.

In figure 1, the prevalence is 6.73% in 2010 (95% CI: 0.06789509708 - 0.06670490292), followed by a small increase in 2011 to 7.11%. The trends are then fairly stable, until 2016, where the highest prevalent drug use emerges, displaying a percentage of 7.5%. The prevalence starts to relatively decrease after that, reaching 6.81% in 2020 (95% CI: 0.06856135267 - 0.06763864733). The prevalence increases with about 0.4% from the start of the follow up until 2016, then a decrease of nearly 0.7% in 2020. These numbers are not high when compared to other frequently used preventive cardiovascular medication and anti-hypertensives. Also, the differences between the prevalent trends in each calendar year are not substantial. Lastly, the general RR is 1.012 (95% CI: 0.99 - 1.015), with a RD of 0.0449 between the start and the end of the study.

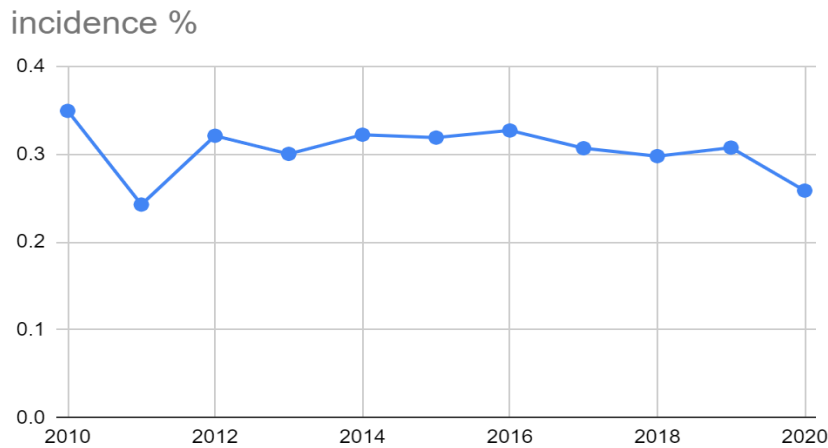


Figure 2, The incidence of the prescriptions of C09AA and C09DA medications within the study period for all individuals aged 40 or above. The incidence is expressed as percentages on the y-axis.

In figure 2, the incidental drug use of C09AA and C09DA reaches its highest peak in the year 2010, then it relatively decreases from that point, but the decrease is accompanied with visible fluctuations in the trends. In 2010 the incidental medication use was 0.3492% (95% CI: 0.003640275548 - 0.003359724452), then it substantially decreased to its lowest point in 2011 to become 0.2426%, followed by an increase in 2012 to become 0.3209%. The rest of the study period demonstrates a near stable percentile incidence-rate at about 0.3%, only to decrease in 2020 to become 0.2585% (95% CI: 0.002693260166 - 0.002506739834). In total, the incidence has decreased with 0.09071% throughout the study period.

Prescription trends found per age group.

The trends in the prevalence and the incidence of C09AA and C09DA drug use in the two separate age groups are displayed in figures 3 and 4 below. The data for the prevalence was derived using the appendices 4.1, 4.2 and tables 5.4 and 5.6. The data for the incidence was derived using the appendices 4.3, 4.4 tables 5.5 and 5.7.

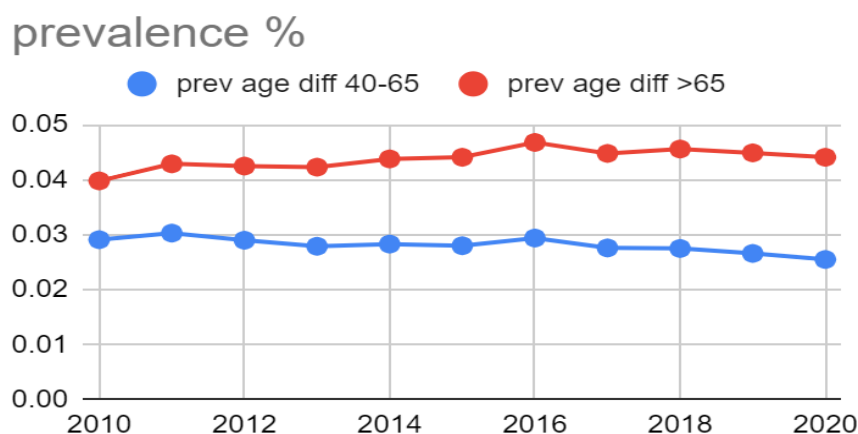


Figure 3, the prevalence of the prescriptions of C09AA and C09DA medications within the study period for all individuals aged 40-65 (blue), and 65 or above (red) separately. The prevalence is expressed as percentages on the y-axis.

From figure 3, throughout the entire study period, and in each year, the prevalent use of the preventive cardiovascular medication was the highest among the older patients (aged 65 or >). The

trends in the prescriptions for the older age group are displayed as the red bars. The percentages ranged from 4 to 4.6% in the older age group, while in the younger group the percentage varied between 3 to 2.5%. The most substantial difference between both groups is found in the year 2016 and the years thereafter. In 2010, the younger group was at 2.91% (95% CI: 0.02949924827 - 0.02870075173), and the older group at 3.98% (95% CI: 0.04026433529 - 0.03933566471). The percentile difference in 2010 between the two groups was 1.07% and in 2011, this became 1.26%. The differences then varied from 1.4% to 1.8% in the following period. The younger group had a prevalence of 2.55% (95% CI: 0.02578869272 - 0.02521130728) in 2020, and the older had a prevalence of 4.41% (95% CI: 0.04447601083 - 0.04372398917) in 2020. The older group had a percentile increase of 0.7% from the beginning of the study until 2016, followed by a decrease of 0.3% in 2020. However, the younger group only displayed a decrease at the last 4 or so years, while the older relatively remained stable after its most substantial increase in 2016. Additionally, the younger group's elevations in the prevalence were lower than its counterpart. The last three years displayed the highest percentile difference between the two groups. For the younger group, the RR is 0.88 (95% CI: 0.76 - 0.91), with a RD of 0.0101 between the start and the end of the study. And for the older group, the RR is 1.12, (95% CI: 1.08 - 1.16), with a RD of 0.0357 between the start and the end of the study.

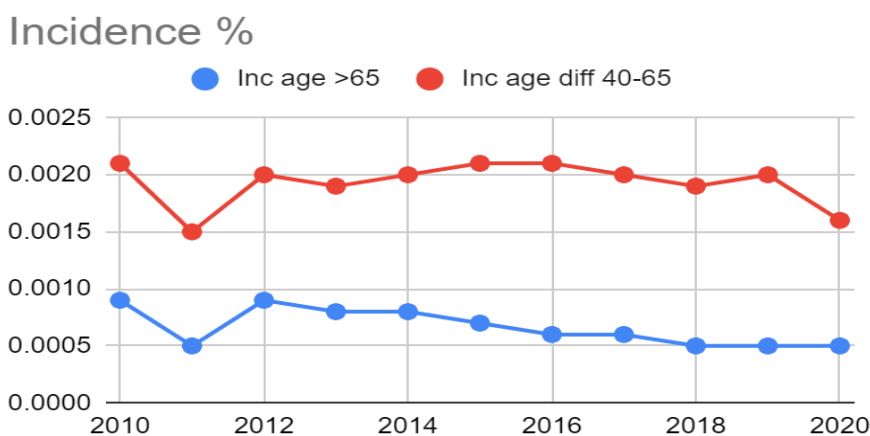


Figure 4, the incidence of the prescriptions of C09AA and C09DA medications within the study period for all individuals aged 40-65 (blue), and 65 or above (red) separately. The incidence is expressed as percentages on the y-axis.

Figure 4 illustrates the incidental trends of the prescriptions of the study medications per year throughout the study period, the red bars are indicative of the younger age group and the blue are indicative of the older one. The incidence in general displays a similar trend to that in figure 2, with seemingly close values at each year accordingly. Surprisingly, incidental prescriptions for the younger age group are generally higher than the older one, which differentiates this comparison from the previous one. Additionally, the differences showcased in figure 4 are more substantial than the ones present in figure 3. In 2010, the younger group had an incidence of 0.21% (95% CI: 0.002208733273 - 0.001991266727), and in the same year, the recorded incidence of the older group was 0.09% (95% CI: 0.0009712254228 - 0.0008287745772). The percentile difference between the two groups in 2010 was 0.12%, this reached its lowest value in the year 2011, to result in an only 0.1% difference. While the incidental trends in figure 4 for the older group would start decreasing after 2012, the younger group had an opposite outcome until the year of 2017, and demonstrated a percentile difference of 0.11% to 0.15%. This is a seemingly stable trend, yet it is distinctive of both groups. The incidence would keep on decreasing after 2012 from 0.096% to less than 0.05%. The younger group had an opposite outcome as mentioned, but this was short-lived as in the year 2017 a decrease was

observable. In 2020, the younger group displayed an incidence at 0.16% (95% CI: 0.001673195959 - 0.001526804041), and the older one displayed 0.05% (95% CI: 0.0005409403197 - 0.0004590596803). The general increase in the incidence within the younger patients was 0.15% to 0.21%. The reached percentage in 2019 would drop again in 2020 to reach nearly 0.15%, where, in this exact period, the most substantial difference was found in the incidental prescription trends between the two groups.

Prescription trends found per gender.

The trends in the prevalence and the incidence of C09AA and C09DA drug use in the two gender groups are displayed in figures 5 and 6 below. The data for the prevalence was derived using the appendices 4.5 and table 5.8. The data for the incidence was derived using the appendices 5.6 and table 5.9.

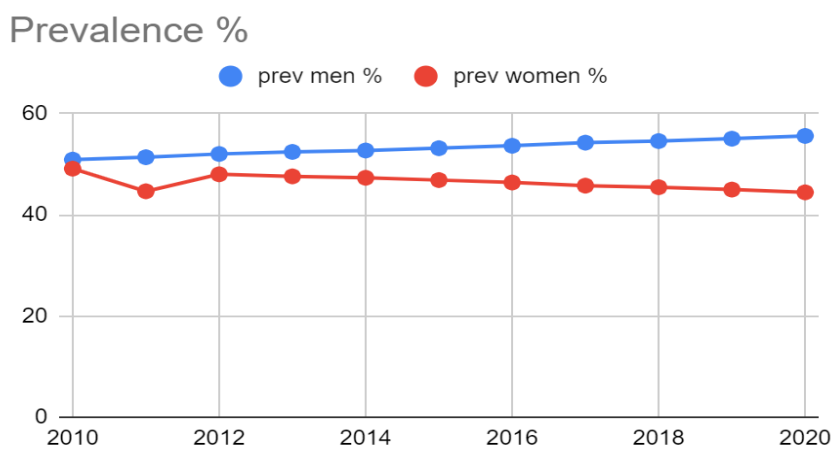


Figure 5, the prevalence of the prescriptions of C09AA and C09DA medications within the study period for men (blue) and women (red) separately, who are 40 years of age and higher. The prevalence is expressed as percentages on the y-axis.

In figure 5, the trends in prevalent drug use per year and per gender are presented as percentages, where men are depicted in blue and women in red. It's clear that both genders had nearly the same amount of prescriptions in the year 2010, with men being slightly higher (50.89%, 95% CI: 0.5100874368 - 0.5077125632, women's 95% CI: 0.4922874368 - 0.4899125632). However, the difference became higher in the year 2011, where men displayed a percentile prevalence of 51.37%. The prescription trends for women steadily decreased throughout the study period after the year 2012 (47.99%) to reach a prevalence of 44.42% by 2020 (95% CI: 0.4451099623 - 0.4432900377, men's 95% CI: 0.5567099623 - 0.5548900377). The prevalence of women never became higher than 50%, and the mentioned decrease was 47% to about 44%. These data help to understand the prescription trends for men, which are the inverse to those of women. The trends of men never decreased during the period, it demonstrated a steady increase of the drug prescriptions as showcased in figure 5. The prevalence for men was 50.89% in 2010 and 55.78% in 2020, thus displaying a near 6% increase in the prescriptions of C09AA and C09DA drugs for men in a period of 10 years. The highest difference between the trends of both genders is recorded in 2020 (11.36%), and the lowest one being in 2010 (1.78%). For men, the RR is 1.19 (95% CI: 1.17 - 1.22), with a RD of 0.0437 between the start and the end of the study. And for women, the RR is 0.95 (95% CI: 0.89 - 1.01), with a RD of 0.0203 between the start and the end of the study.

Incidence %

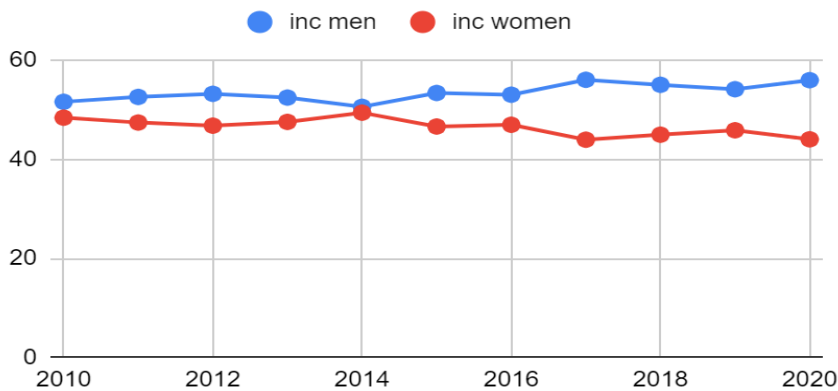


Figure 6, the incidence of the prescriptions of C09AA and C09DA medications within the study period for men (blue) and women (red) separately, who are 40 years of age and higher. The incidence is expressed as percentages on the y-axis.

In figure 5, the trends in incidental drug use per year, and per gender, are presented as percentages, where men are depicted in blue and women in red. Again, men have a higher incidence of C09 than women in all years. The incidence trend for women showcases a nearly constant trend from 2010 until 2013, with a mean incidence of nearly 47%, where the trend started at 47.4% (95% CI: 0.4851870167 - 0.4828129833, men's 95% CI: 0.5171870167 - 0.5148129833). This is followed by an increase in 2014 to become 49.41%, which is the highest recorded incidental drug use within this study period for females. The female group would display another decrease that went on from 2014 until 2020 with minor fluctuations to reach 43% in 2017 and 44% in 2020 (95% CI: 0.4413091538 - 0.4394908462, men's 95% CI: 0.5605091538 - 0.5586908462). Similar to the prevalent data, men had an increase in their drug use that went on from 2010 until 2020, but the incidence did display a lag in 2014, followed by an increase of 5.5% by 2017. Two minor reductions occurred in the incidence for men in 2018 and 2019 (55.03% and 54.14%), but it elevated again to reach 56% in 2020, which is the highest recorded increase in the male group. The differences between both genders in incidental drug use are throughout the years lower than in the prevalent one, at least in the first five years, where those differences varied between 3% to 6%. Those differences nearly doubled up in the next half of the study. The two biggest differences were in 2017 (nearly 11%) and 2020 (nearly 12%).

The flow chart illustrating literature selection.

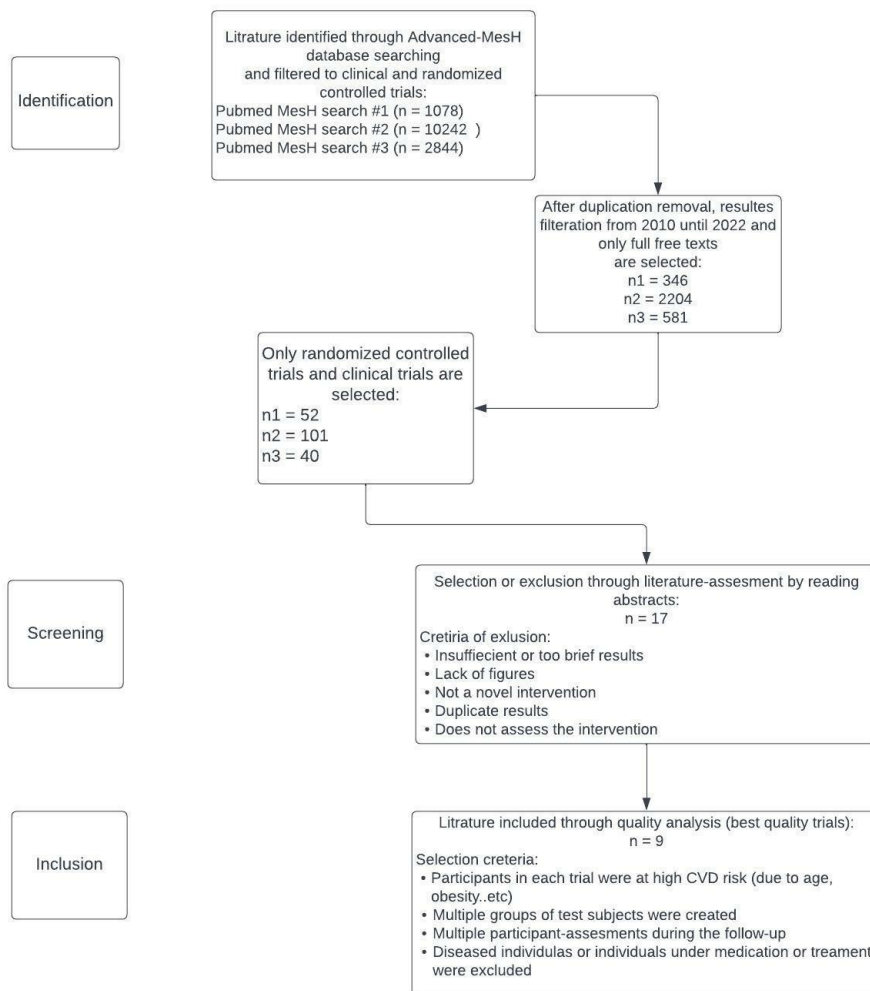


Figure 7, flowchart depicting the literature selection from the MesH database from PubMed

Lifestyle as an alternative remedy to decrease the risk factors of cardiovascular abnormalities.

According to Slavíček et al., 2010. In a controlled clinical trial that consisted of 1349 Czech volunteers (1029 women and 320 men) with a mean age of 51 +/- 14.5 (SD) years, parameters of risk factors of cardiovascular disease were measured before and after a single week of rehabilitative program. The study included 30 rehabilitative programs between 1999-2006 in the Czech Republic, the programs were identical and involved light physical exercise, disruption of alcohol, coffee and tea, a high daily water intake, regular social activities and a low-fat-vegetarian diet in a relaxing environment within a natural terrain. The measured parameters were the BMI, blood pressure, body weight, serum cholesterol and heart rate.

A table illustrating the change in the risk factor parameters resulting from 30 weeks of the program that consisted of 30 different participant groups. Controls vs treatment, where both genders are evaluated [8]:

	Number		Parameter	p
Weight (kg)	1,046	before	71.0±14.26	****
		after	70.3±13.90	
BMI (kg/m ²)	878	before	25.1±4.60	****
		after	24.8±4.49	
Blood pressure systolic (mmHg)	1,037	before	130.0±23.33	****
		after	123.9±21.62	
Blood pressure diasolic (mmHg)	1,029	before	80.0±12.85	****
		after	77.6±11.24	
Heart rate/min	983	before	72.2±11.8	n.s.
		after	72.5±11.54	
Serum cholesterol (mM/l)	834	before	4.82±0.97	****
		after	4.31±0.78	
Blood glucose (mM/l)	409	before	4.23±1.62	****
		after	3.82±1.37	

Table 3, the table showcases changes in the most important risk factors(due to the program; Groeneveld et al, a study following lifestyle alteration in multiple groups. (* p< 0.05, **p<0.01, ***p<0.001, ****p<0.0001)

According to Groeneveld et al., 2011. A short clinical trial consisted of eight weeks follow-up of 25 obese men aged between 30 to 70 years who had a BMI ranged from 31 to 39 kg/m². The subjects were divided into two groups, one group aged between 30 and 40 years, and the other between 50 and 70 years. Both groups underwent a restrictive dietary program and an intensive training program. Scientists measured participants' body composition using "dual energy X-ray absorptiometry". Additionally, their cardiometabolic rate was deduced from various blood analyses. On the other hand, their fat and muscle biopsies were evaluated using ex-vivo. Two-way repeated-measure ANOVA and linear mixed models were used to assess and compare the outcomes of the two groups. Post-interventive data demonstrated that the bone mass remained identical while the fat mass was lowered for both groups, this lowering was more significant in the older group. Lastly, plasma cholesterol and triglyceride levels were reduced, and the degree of insulin sensitivity was substantially greater post-intervention. The figure below displays the main findings:

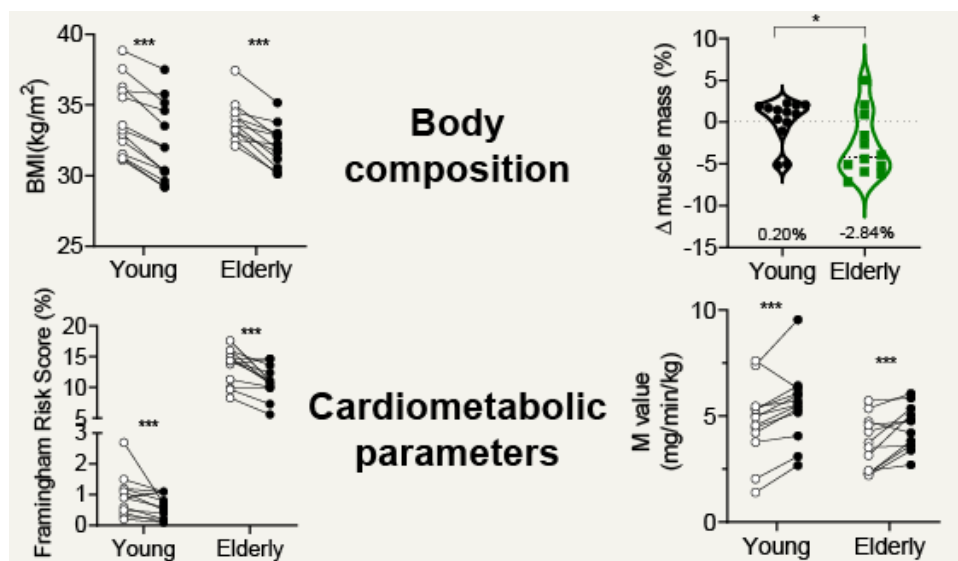


Figure 8 [9], depicts the changes in body compositions BMI (up left) and changes in muscle mass (up right), and the changes in the cardiometabolic parameters rate of metabolism (down right and Framingham risk scores (down left). The graphs are showing comparisons between elderly and young groups of men.

Dietary adjustments to improve cardiac health and lower CVS risk factors.

According to Davis et al., 2017. A randomised controlled trial investigated the effects of Mediterranean dietary intake on endothelial function and blood pressure which were evaluated in 166 men and women above 64 years of age. The participants were divided into a follow-up and a control group (their regular diet). The Mediterranean diet consisted of greens, fresh vegetables, nuts and extra-virgin olive oil. The endothelial function was monitored in 82 participants using flow-mediated dilatation starting from the baseline at $t = 0$ until $t = 6$ months. In addition, the blood pressure was assessed in 149 participants for starting from the baseline at $t = 0$ until $t = 3$ months and $t = 6$ months. The Mediterranean diet, compared to the control group, resulted in lower systolic blood pressure mean: -1.3 mm Hg (95% CI: $-2.2, -0.3$ mm Hg; $P = 0.008$) at 3 months and -1.1 mm Hg (95% CI: $-2.0, -0.1$ mm Hg; $P = 0.03$) at 6 months [10]. At 6 months, the percentage of flow-mediated dilatation was higher by 1.3% (95% CI: 0.2%, 2.4%; $P = 0.026$) in the Mediterranean Diet group [10].

According to Estruch et al., 2013. From a randomised controlled trial, a total of 7447 Spanish individuals at high cardiovascular risk and with similar dietary intakes between 55-80 years old (57% women) were chosen and divided into three groups supplemented with different diets; no individual suffered from a cardiovascular abnormality at the moment of registration. The first group received a Mediterranean diet consisting of various types of nuts, the second received a Mediterranean diet involving large intakes of extra-virgin olive oil, and a third control group (their regular diet). The study was halted after a follow-up of 4.8 years. The end point measurements were the rates of major cardiovascular abnormalities (stroke, fibrillation, myocardial infarction and mortality rates). According to biomarker analysis, both groups had good acceptance to the treatment [11]. Abnormal cardiovascular events were registered for all groups and were as follows: control group had 109 events, group supplemented with Mediterranean diet of extra-virgin olive oil had 96 events and group supplemented with Mediterranean diet of various nuts had 83 events.

According to Razavi et al., 2020. In a randomized clinical trial, 80 metabolic syndrome patients were enrolled randomly into two separate groups; an alternate-day fasting diet and calorie restriction groups. Risk factor parameters were assessed for 4 months. The parameters included BMI, body weight, levels of coagulation factors, tumour necrosis factor alpha and the high sensitivity C-reactive protein (hs-CRP) in both groups before and after commencing the dietary program. An alternate-day fasting diet (FD) led to higher reductions in cardiovascular risk factors than the calorie restriction diet (RD); body weight (kg) (FD: -6.43 ± 4.34 vs RD: -4.11 ± 4.27 ; $P = 0.02$), fat mass (kg) (FD: -4.88 ± 2.09 vs RD: -3.72 ± 2.43 ; $P = 0.03$), BMI (FD: -3.19 ± 2.90 vs RD: -1.43 ± 2.72 ; $P = 0.01$), hs-CRP levels (mg/L) (FD: -2.06 ± 1.18 vs RD: -0.97 ± 0.82 ; $P = 0.03$) and prothrombin time (s) (FD: 1.41 ± 2.34 vs RD: -0.41 ± 2.17 ; $P < 0.001$) [12]. Finally, there was no difference in the levels of IL-6 or TNF- α between the two groups [12].

How an elevation in physical activity affects cardiovascular health.

According to Stewart et al., 2017. A randomised controlled trial that involved 15,486 individuals from various ethnicities diagnosed with stable coronary heart disease, evaluated the patients' time spent on exercise. The patients had different exercise profiles ranging from low (normal physical activity), moderate or vigorous. The study was based on a follow up of 3.7 years where levels of exercise's length and intensity, and general habitual physical activity, were measured as metabolic equivalents in hours per week, and were linked with the outcomes. As a result, rates of morbidity and mortality occurring with an elevated daily exercise was substantially lowered. The reduction was higher at moderate levels of exercise. Doubling exercise volume was associated with lower all-cause mortality (unadjusted hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.79 to 0.85; adjusting for

covariates, HR: 0.90; 95% CI: 0.87 to 0.93) [13]. These associations were similar for the cardiovascular mortality rates (unadjusted HR: 0.83; 95% CI: 0.80 to 0.87; adjusted HR: 0.92; 95% CI: 0.88 to 0.96) [13]. Finally, myocardial infarction and stroke were not associated with exercise volume after adjusting for covariates [13].

According to Folta et al., 2019. Obese and overweight women who were 40 years of age or older were enrolled into a randomized controlled trial of 6 months. The women had no cardiovascular abnormalities at the moment of registration. The trial was an intervention program that consisted of special exercise and healthy nutrition activities. The control group was subjected to the mentioned lifestyle promotion program once per month. Detailed information on the daily physical activity and nutrition were deduced starting from the baseline until post-trial. The data was collected by self-reporting and question assays. Compared to the control group, the intervention group experienced a greater increase in weekly walking-minutes (difference: 113.5 minutes per week, 95% CI 12.8 to 214.2, $p = .027$) [14]. For physical activity, the BMI was significantly reduced in the intervention group compared to the baseline (27.5 ± 4.3 vs. 29.7 ± 5.1 kg/m²) [14].

The effect of smoking and smoking cessation on cardiovascular health.

According to Kamimura et al., 2018. A clinical trial involved 4129 middle aged test subjects from different ethnicities in the US, they were divided into three groups; 503 who were smoking at the time of the study, 742 who stopped smoking and 2884 who never smoked before. None of the participants had cardiovascular abnormalities at the moment of enrolment. In the trial, the relationships between smoking and the structure and the function of the left ventricle were determined using cardiac magnetic resonance imaging in 1092 subjects and incident heart failure hospitalisation in 3633 subjects. According to the study, current smokers had lower mean left ventricular circumferential strain than never-smokers, and higher mean left ventricular mass index than never-smokers. During about 8 years of median follow-up, there were 147 incidents of incidental heart failure hospitalizations. Following an adjustment for cardiovascular risk factors and incident heart failure or coronary heart disease, smoking intensity among current smokers (≥ 20 cigarettes/d: hazard ratio, 3.48; 95% confidence interval, 1.65-7.32) and smoking burden among participants who were smokers (≥ 15 pack-years: hazard ratio, 2.06; 95% confidence interval, 1.29-3.3) were significantly associated with incident heart failure hospitalisation in comparison with never-smokers.

According to Kondo et al., 2011. A cohort study involved a median follow-up of about 8 years of 25,464 healthy Japanese male test subjects aged between 20 to 60 years old. The subjects were split into four groups; a control group of never-smokers, light smokers, moderate smokers and heavy smokers (LS, MS, HS). Smoked-doses (cigarettes per day) were respectively: 1 to 10 for LS, 11 to 20 for MS and more than 20 for HS. The adjusted hazard ratios with a 95% confidence interval for all-cause death for the smoking groups were respectively: 1.51 (0.73, 2.94), 1.68 (1.07, 2.70), 1.30 (0.70, 2.34). And those for the total CVD events were: 1.91 (0.72, 4.67) for LS, 2.94 (1.65, 5.63) for MS and 3.25 (1.69, 6.54) for HS. All outcomes were compared to the control group of never-smokers. Occurrence of myocardial infarctions was present in all smoking-groups, and was in higher percentage in comparison with the control group. Stroke was increased at a moderate level of smoking (compared to light smokers). Compared with continued-smokers, those who quit smoking for four years or more had decreased hazard ratios for all-cause death to 0.64, and the total of CVD events to 0.34.

Discussion.

Interpreting the research data.

In summary, the prevalent C09-use is at an increasing trend for the underlying population aged 40 years or higher, the total increase is around 1.2% at the end of the study period, and according to Chi-square testing, this increase is significant. The opposite applies for the incidental trends in the same population and during the same study period, but the effect of the decrease is insignificant when compared to the increase in the prevalence. The incidence is less stable than the prevalence, more fluctuating and demonstrates a total decrease of 0.8% at the end of the study period. Keep in mind that the population under the incidence (starters after at least 365 days of non-use) is far smaller than the one underlying the trends in prevalence. In total, the increase in the prevalence is 110000+ users, and the decrease in the incidence is 2347 users from the start until the end of the study. Men are at a higher incidental and prevalent risk than women, and these risks have been increasing by men since the year 2010, the exact opposite applies for women. The incidence plotted separately for each gender is unstable and fluctuating, suggesting that it would highly be susceptible to changes in the future. The prevalence of both genders, while increasing in men and decreasing in women, is near-linear, suggesting that a change in both trends is less likely to happen in the future years. In general, being born as male automatically elevates the risk (in incidence and in prevalence) for the preventive cardiovascular drug-use. The older population (>65) has higher prevalence and a lower incidence than the younger one (40-65), possibly because the starters are mostly individuals younger than 65 years of age. Based on the observations, the older the individual, the more likely that he or she is using the C09-drugs, especially due to the fact that the prevalence in the older population is steadily increasing. Therefore, it is less likely that the trend is going to change in the upcoming years. Again, the incidental decreases are insignificant compared to the prevalent increases throughout the study period, meaning that they are unable to equalise or compensate for the elevation in ecotoxic wastes. All changes between the start and the end of the study are significant. A more detailed and broader discussion of the trends, the statistics and the outcomes is written below.

The prevalent drug use showcased in figure 1 demonstrates a nearly stable trend, with insignificant fluctuations. However, as the results suggested, there is a clear increase in the prevalence during the 10-year study period (6.73% in 2010 to 6.81% in 2020), while hardly observable, the numbers do prove that the frequency of prescriptions among the dutch population aged 40 years or higher has remarkably increased. This increase would reflect ecotoxic damage on the dutch society. The highest increase in the general prevalence was in 2011, when it reached 7.11%, a small percentage, but enough to cause major ecotoxic damage (more than 50000 recorded prescriptions). Additionally, the RR was greater than 1, meaning that the events of C09AA and C09DA drug use are more likely to occur when the subjects are exposed to risk factors. The RR displayed an increase of 1.2% in the general prevalent trends from the start until the end of the study, this does not seem significant, but this is an increase in the use of a total of 35 to 40 different drugs (drugs that start with C09 in their ATC-code), which might very well result in ecotoxic outcomes. Also, the Chi-square testing demonstrated that the difference in prevalence between the start and the end of study is significant (p -value <0.05). On the other hand, the general population incidence was neither stable nor constant (figure 2), but the trend was positive, because it followed a near-linear decrease in the last four years of the study period. Estimatively, the decrease was about 0.1%, with other sighted decreases of around 0.02 to 0.08%, which were higher than the small recorded increases. These numbers might appear low and insignificant, but we keep in mind that the incidental drug users (population) were

already present in low numbers. Finally, the Chi-square test showed that the difference in the incidence between the start and the end of study is significant (p -value <0.05).

Figure 3 displayed substantial differences between the prevalences of the two age groups, the older group had an increase in its prevalence (from 3.98% to 4.41%). This increase during the 10 years period is relatively not high, and only faced very minor changes, which means that increase is more likely to keep on going after the year 2020, with an increase-rate of 0.04% per year. This represents a huge concern, as there will be an increase of 2500+ of C09AA and C09DA users per year. This might not become alarming with the fact that the younger group displayed a remarkable decrease during the same 10-year period (2.91% to 2.55%), this decrease however is not substantial enough to compensate for the increase, especially with the fact the the older group is generally larger (more old patients than young patients), and it has the ability to grow more rapidly in size than the younger one [20]. Although, the rate of annual prevalent decrease from the younger group is about 0.04%, close enough to that of the annual prevalent increase found in the older group. However, the relative risk ratios suggest that in the upcoming years the older group is at a higher risk ($RR = 1.12$) than the younger one ($RR = 0.88$), with a higher risk difference of 0.0360 (younger group's $RD = 0.0101$) between the start and the end of the study. But these findings also demonstrate that the increase in the prevalent drug use is equal to the decrease (12%) in both groups, but the older group is logically bigger than the younger one, therefore, the prevalent increase of 12% is still impactful on the levels of ecotoxicity. The older population would also be less interested in lifestyle promotion programs and healthy exercises due to their lack of motivation, psychological interest, weakened bones and low muscle mass [20]. Additionally, older smokers have more difficulty quitting smoking than young smokers [15]. This suggests that decrease in the prevalent use in the younger population would not be able to compensate for the increase in the older one, this eventually leads to a relatively more frequent use of the preventive cardiovascular medications C09AA and C09DA in the upcoming years, which is economically and environmentally harmful. In general, the older population is at a higher cardiovascular risk than the younger one (figure 3). Seemingly, the prevalent increase would keep on going for the older population, while the opposite applies for the younger one. In both cases, the Chi-square testing led to p -values lower than 0.05, meaning that the increases (>65) and decreases (40-65) in the prevalence are significant, at least in this 10-year study period. In figure 4, the incidence differs largely between both age groups, with the younger one being the more frequent incidental drug-user. This outcome can be due to the fact that most new users are younger than 65, while those who are older than 65 are current users in most cases. The incidence however has a more positive trend than the prevalence, it is represented as a general decrease in both groups in figure 4. The incidence is displayed at significantly lower values than the prevalence. For the younger group, the decrease was from 0.21% to 0.15%, and the older one had a decrease from 0.9% to 0.5% from the start until the end of the follow-up. These reductions are not very beneficial, because they are insignificant compared to the annual increases that were found in the prevalence. Again, the younger group is at a higher incidental risk, and the differences in the incidental trends between the two age groups are bigger than the ones found within the prevalent trends, proving that there are, and there will be more current C09AA and C09DA drug-users emerging from the older population. Compared to the incidental decrease in the older group, the younger group demonstrated an incidental decrease at slower and smaller rates, and the decrease found in 2020 might be a recurring fluctuation, suggesting that the younger group might still actually be under a high incidental risk. Finally, the Chi-square test demonstrated that the differences in the incidence between the start and the end of study are significant in both age groups (p -value <0.05).

In figure 5, the prescription trends per gender group of patients aged 40 or older demonstrated that the male population is at a higher incidental and prevalent risk than the female population. The men

had a near-linearly increasing prevalence during the 10-year study period, the male-prevalence went from 50.89% in 2010 to 55.78% in 2020, this is a steady increase of 4.89% (about 0.5% per year). These results suggest that the prevalence of the trends of preventive cardiovascular drug-prescription is more likely to increase in the dutch male population that is 40 years of age or older in the upcoming years. The opposite applies for the dutch female population, and since this is a percentage, we may assume that the decreasing rate for women would be 0.4-0.5%, which is indeed the case when examining the results presented under figure 5. The RR of the male population is 1.19 (95% CI: 1.17 - 1.22), and that of the female population is 0.95 (95% CI: 0.89 - 1.01), meaning that the males had an increase of 19% in their prevalence since 2010 until 2020, which might still be increasing, and the females had small decrease of 5% in the same period. Since the increase found within the male population is almost four times bigger than the decrease found within the female population, it is possible to assume that the prevalent trend was environmentally hazardous and contributed to ecotoxicity. Again, these values are indicative of a more frequent use of the preventive cardiovascular medications C09AA and C09DA in the dutch male population in the upcoming years, which will eventually be economically and environmentally harmful in the future. The RD of the males is 0.0437 and that of the females is 0.0203, another evidence that the males have been at an increasingly higher risk than the females since the start of the study. In addition, the Chi-square test demonstrated that the increase in the prevalence of males and the decrease of the prevalence of females between the start and the end of study are significant (p-value <0.05). The incidence in figure 6 did demonstrate men to be at higher incidental risk as well, it increases more substantially than the incidence for women throughout the years. In this case, the incidence and the prevalence of both genders at the last 3 or 4 years are not far from each other when describing them as values and not as population estimates (figures 5 and 6). For the males, the increase was from 51.6% in 2010 to 55.96% in 2020. Again, the males are at a higher incidental risk than the females, and the differences in the incidental trends between the two groups are substantial, which proves that there will be more C09AA and C09DA drug-users in the upcoming years who underwent at least 365 days of non-use of the medications. Compared to the incidental increase between males, the females demonstrated an incidental decrease at smaller rates, suggesting once more that the males are under a higher incidental risk in the dutch population. Finally, the Chi-square test demonstrated that the increase in the incidence of males and the decrease in the incidence of females between the start and the end of study are significant (p-value <0.05).

The limitation of this research is the lack of highly contributing risk factors for cardiovascular events, and thereby the use of preventive cardiovascular medication (ATC = C09). It is therefore of a great benefit to incorporate them into the research. The risk factors include obesity (BMI-value), familial history of cardiovascular abnormalities, cholesterol levels and diabetes. Unfortunately, the IADB-database is unable to reveal such information. The research was therefore limited to only two risk factors; age and gender.

Systematic review.

The RCT-articles which investigated the benefits of altered dietary intakes displayed in their results a reduction of common CVD risk factors such as high blood pressure and blood cholesterol. Groups subjected to Mediterranean diet were at lower risk of morbidity and mortality resulting from cardiovascular events. Compared to restrictive diets, fasting and Mediterranean diets have proven to be more efficient methods to reduce CVD risk factors as seen in the results. Compared to the controls, the groups that followed the interventive diet programs had improved cardiovascular health in all studies.

Preventive exercise programs decreased all-cause mortality risk factors and hazard ratios associated with cardiovascular diseases. As the selected groups in both trials were at an extreme risk of developing any cardiovascular disease. However, the programs did not cure a diseased individual, they simply lowered the prevalence of cardiovascular abnormalities. This can be seen in groups that did not follow the programs, which were diseased at higher rates than people who did follow them. Even habitual exercise routines of different programs proved that the level of activity may impact the hazard ratios for all-cause mortality. At the baseline, all exercise groups failed at meeting many recommendations for the proper cardiovascular health, this was not the case at the end of the trial.

Trials that studied the effect of smoking and smoking cessation on the cardiovascular system demonstrated that the CVD events elevated significantly as the number cigarettes increased. The negative effects on the cardiovascular function resulting from cigarette smoking are well known and demonstrated in numerous studies and trials, in the presented trials, the adjusted hazard ratios and incidences of hospitalisation due to smoking addiction prove this as well. The presented results provide concrete evidence that smoking cessation decreases these hazard ratios and the prevalence of CVDs in comparison groups that did not stop. The smoking-dosage (number of cigarettes) displayed a clear difference in the degree of severity between smokers at different doses seen in levels of incidence heart failure and cardiac disorders, proving the fact that smoking cessation is an essential lifestyle adjustment.

General lifestyle alterations displayed significant drops in mean heart rate, blood pressure, BMI and serum cholesterol. These were the first results that were deduced from a research trial which consisted of healthy sleeping routines, motivative daily activities in a relaxing environment and substances that elevate the heart activity such as tea, coffee and cigarette smoke were prohibited. Additionally, participants were supplemented with vegetarian diets. As a result, parameters for CVDs events were remarkably reduced among the humans under the highest cardiovascular risks. The next clinical trial-results demonstrated that lifestyle interventive program consisting of fat and calorie restriction, and a balanced exercise program will improve the cardiometabolic function and decrease CVD risk factors in obese men.

The mentioned indications of our drugs of interest, ACEIs and ARBs, demonstrate them as preventive cardiovascular drugs of substantial benefits and high patient's tolerance. This means that these two drug-classes are one of the most used preventive cardiovascular agents, replacing them with some natural compounds will certainly be of a great environmental advantage because of their excreted toxic metabolites within the human urine that eventually reaches water treatment plants. These natural compounds may serve as green alternatives to replace CVAs and become a part of our daily diet as green and natural food supplements such as garlic, pomegranate juice, royal jelly...etc. As mentioned, many studies have demonstrated these green alternatives as natural ACEIs and ARBs, this can be used to replace these two drug-classes which in turn would lower the resulting ecotoxic drug-waste. The previously showcased pharmacokinetic profile of ACEIs and ARBs illustrated the

safety and mostly good distribution (depends on the drug itself, some for example are shorter-acting than others, i.e., Captopril), generally all ACEIs and ARBs have great distribution kinetics and an effective ADME profile with their clearance predominantly occurring via the kidneys. Not many attempts took place to personalise ACEIs and ARBs, but generally speaking, drug-personalization is highly dependent on a patient's attributes and health. Also, personalising cardiovascular agents is immensely complex and costly due to the classification of cardiovascular diseases based on the observed clinical phenotype only and general complexity of heart diseases.

The presented literature consisted of trials that were conducted on individuals diagnosed with the most common and impactful CVD risk factors. These CVD risk factors included obesity, high blood pressure, high levels of cholesterol and the activity of prothrombin. Reducing these risk factors using interventional dietary programs via commencing campaigns to raise awareness within the populations will most likely decrease the prevalence of cardiovascular abnormalities, and thus the use of preventive cardiovascular drugs, which is environmentally and economically beneficial since a reduction of drug-use means a decrease of the resulting toxic, and nature harming drug-waste. Three RCT-articles illustrated the benefits of dietary promotion that mainly included a reduction of common CVD risk factors such as high blood pressure and blood cholesterol. Groups subjected to Mediterranean diet were at lower risk of morbidity and mortality resulting from cardiovascular disorders. Compared to restrictive diets, fasting and Mediterranean diets have proven to be more efficient methods to reduce CVD risk factors. Compared to the controls, the groups that followed the interventional diet programs had improved cardiovascular health in all presented studies. Thus, interventional diet programs that were intended to reduce the common contributors for CVDs proved to be successful, which means that they can be introduced into societies through awareness campaigns, this would most definitely lower the use of preventive cardiovascular agents, and thereby, their resulting ecotoxic waste.

Similar to dietary intervention, certain exercise programs reduced all-cause mortality risk factors and hazard ratios associated with cardiovascular diseases. None of the programs healed a diseased individual, but prevented the occurrences of cardiovascular abnormalities as groups that did not follow the programs were diseased at higher rates than people who did follow them in all presented studies. Even habitual exercise profiles of different programs showcased that the degree of physical activity may impact the rate at which the morbidity and hazard ratios for all-cause mortality are reduced. At the baseline, all exercise groups failed at meeting many recommendations for the proper cardiovascular health, this was changed after the end of the research trial. It is also important to be reminded that the selected groups in both trials were at an extreme risk of developing any cardiovascular disease as stated by the researchers. Both cohort and clinical trials that investigated the effect of smoking and smoking cessation on cardiovascular health demonstrated that the CVD events elevated immensely as the number of daily-doses of smoked cigarettes increased. The negative effects on the cardiovascular function resulting from cigarette smoking are well known and demonstrated in numerous studies and trials, in the presented trials, the adjusted hazard ratios and incidences of hospitalisation due to smoking addiction prove this as well. The presented results provide concrete evidence that smoking cessation decreases these hazard ratios and the prevalence of CVDs in comparison with proceeded smoking. The level of smoking-dosage (cigarettes/day) resulted in an obvious difference in the burden and the severity seen in levels of incidence heart failure and hazard ratios, and prevalence of the sustained cardiac disorders, proving the fact that smoking cessation is a crucial lifestyle improvement to overcome CVDs. Smoking may lead to substantial heart defects, such consequences are normally treated by using chemical pharmaceuticals, smoking-cessation would prevent heart diseases and therefore the use of these chemical agents, which lowers their discarded environmentally-toxic wastes found within water

treatment plants. The same can be said when using physical interventive exercises as an alternative for CVAs.

The first presented study-results under general lifestyle alterations, displayed significant drops in body weight, mean heart rate, blood pressure, BMI, serum cholesterol and glucose concentration. The study consisted of a one-week follow-up program, that included healthy sleeping routine, motivative daily activities, resourceful social interactions and substances that elevate the heart activity such as tea, coffee and cigarette smoke were prohibited. Conclusively, all participants undertook a diet + exercise intervention program within a vacation-like setting. As presented, common contributing parameters for CVDs were remarkably reduced. This was a general lifestyle alternating-trial, that did not involve the administration or prevention of single lifestyle habit, but multiple, and indeed proved to be the most effective to reduce chance of the occurrence of cardiovascular abnormalities among the age-group under the highest cardiovascular risks, namely the middle-aged individuals. These rehabilitative programs are probably influenced by the gender and the genetic predisposition of the test subjects, as not all individuals had similar outcomes, some became at lower cardiovascular risks than others. This applies to the previously discussed results. Afterwards, the brief clinical trial on lifestyle intervention demonstrated that lifestyle interventive program consisting of fat and calorie restriction, and regulated physical activity will improve the cardiometabolic function, decrease CVD risk factors and enhance insulin sensitivity in younger and older obese men. Any cardiovascular risk-reduction means a less frequent use of many ecotoxic pharmacological agents, leading to advancements in the favour of environmental protection.

All trials consisted of a follow-up of mostly middle-aged, completely disease-free groups from certain populations, diagnosed with the most impactful CVD risk factors. The chosen test subjects were in all cases the most susceptible to cardiovascular abnormalities within their societies. In all trials, there were many dropouts between participants, or participants who failed to obey the rules, which meant that some trials ended with less participants and thus less results. Therefore, there might be some false positives. The mentioned lifestyle alterations are mostly not therapeutic in the case of an already-diseased person, and the risk reductions were in many cases not significant enough to prevent a cardiovascular event. This means that even after following the promotion programs, participants might still be in the need of a pharmacological agent (CDA). As seen in the results section, some of the presented trials were conducted on only one gender, or a single population, this is disadvantageous as some ethnic groups might benefit more from the conducted programs than others (genetically related), and the two genders may react differently to the same program. Also, some trials (5th, 4th, 3rd) did not specify on which population they were conducted. Dietary trials depended on self-reporting and answers given by patients, these could be false and misleading (false positives). The limitation of this thesis is that there are no negative studies or literature that were discussed or presented, this is simply because they were not found within the performed research. Another limitation of this thesis is the lack of figures that illustrate the results and findings of the presented studies.

Combining the systematic review with the drug-utilisation research

Generally, there is an elevation in the use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers since 2010. This is concerning, because this forms a threat to the eco-environmental state of the globe. On the other hand, the conducted systematic research showcased and reviewed eight trials performed between 2010 and 2020. All the discussed trials consisted of lifestyle-promotion and -intervention programs that combined multiple healthy activities and daily habits such as regulated exercise and low-calorie diets. The outcomes were then recorded by the researchers through comparing control groups that were not subjected to any program, and others that did. From the comparison, and as demonstrated above, after the follow-up of many years of individuals at high cardiovascular risk, those who were subjected to the lifestyle-intervention programs had lower morbidity rates, lower hospitalisation rates and less registered cases of cardiovascular events. When the risk factors for CVD are reduced, so would the exotoxic cardiovascular drug-use, reflecting reduced hazardous drug-wastes retained from water treatment plants. In short, certain lifestyle adjustments have proven to be successful in reducing cardiovascular risk factors and the chance of occurring cardiovascular abnormalities, which would thus reduce the recently elevated ecotoxic CO₉-drug-waste.

Conclusion.

This thesis aimed to investigate whether lifestyle promotions that enhance the functionality of the cardiovascular system and decrease the chances of its pathological events and morbidity would thereby be able to reduce the use of preventive cardiovascular drugs in order to lower their retained hazardous drug-waste. The drug-waste this research wants to address is the waste caused by angiotensin II receptor blockers and inhibitors of angiotensin converting enzyme. These two drug-classes inhibit the renin-angiotensin system and are used to prevent heart failure, myocardial infarctions and strokes, but also to reduce blood pressure and maintain stable cardiovascular activity. The pharmacokinetic profile of ACEIs and ARBs is both effective and safe, and has encountered high patient's compliance and satisfaction throughout the years. Some natural compounds and food supplements are able to mimic the working of ACEIs and ARBs (e.g., pomegranate juice), and can be therefore used as alternatives. This is of a huge benefit, because unlike the medicinal metabolites, the urinary excreted fractions of these green compounds are nature friendly. Personalisation of preventive CVAs is troubling, costly and suffers from insufficient insight into the underlying cardiovascular diseases. Yet it would be of great benefit due to the fact that the function of the cardiovascular system is heavily affected by personal characteristics and attributes (e.g., age, weight). This is indeed possible as the discussed results from nine different randomised controlled and clinical trials have demonstrated that certain interventive lifestyle adjustments such as a well-regulated physical activity, and restrictive and vegan diets are able to reduce many CVD risk factors such as systolic blood pressure, heart rate, BMI, fat disposition, levels of cholesterol, events of hospitalisation and all-cause ratios of morbidity. Conclusively, a lower risk at developing a disease would mean a less frequent use of medicines, which in turn would reduce the ecotoxic drug-wastes. To gain an insight into the extent of the disposed ecotoxic drug-wastes of ACEIs (ATC = C09AA) and ARBs (ATC = C09DA), the prescription-volumes of both classes were investigated among the dutch population aged 40 years or older. The findings demonstrated a general, and significant increase in the prevalent uses of these drugs since the year 2010, with old and male individuals being at higher risk of using these medications. The major risk factors are thus ageing and being born as male. The trends of the incidence were more positive, in general, it showcased a significant decrease since the year 2010 with the male population being an exception. The differences between the prevalence and the incidence were substantial in all cases. Thus, a decrease in the incidence will merely compensate for the increase in the prevalence. As a result, the disposal of ecotoxic drug-waste into water treatment plants has been on the rise since 2010 in the Netherlands. This reality can be altered and the drug-waste can be reduced if people with no cardiovascular abnormalities, but at high risk of developing them, would follow the lifestyle intervention programs presented in the conducted and discussed systematic review of this report. Unfortunately, the elderly tend to be less interested in such programs than the younger population. Adding to that is the need for campaigns to raise awareness, not only for individual's physiological, cardiovascular and financial safety, but also the safety of the planet and nature.

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Appendices

Appendix 1: ATC-code of ACEIs and ARBS [19].

Drug type	ATC-code	Commercial name
ACEIS		
	C09AA01	captopril
	C09AA02	enalapril
	C09AA03	lisinopril
	C09AA04	perindopril
	C09AA05	ramipril
	C09AA06	quinapril
	C09AA07	benazepril
	C09AA08	cilazapril
	C09AA09	fosinopril
	C09AA10	trandolapril
	C09AA11	spirapril
	C09AA12	delapril
	C09AA13	moexipril
	C09AA14	temocapril
	C09AA15	zofenopril
	C09AA16	imidapril
ARBs		
	C09DA01	Losartan and diuretics
	C09DA02	Eprosartan and diuretics
	C09DA03	Valsartan and diuretics
	C09DA04	Irbesartan and diuretics
	C09DA06	Candesartan and diuretics
	C09DA07	Telmisartan and diuretics
	C09DA08	Olmesartan medoxomil and diuretics
	C09DA09	Azilsartan medoxomil and diuretics
	C09DA10	Fimasartan and diuretics

Table 3, depicting the ATC codes of interest [19].

Appendix 2: Queries used in IADB to obtain general population data.

2.1. Denominator

```
CREATE TABLE denom(index(jaar))
SELECT
jaar,
SUM(pop_man + pop_vrouw) pop
FROM pop_schat
WHERE lftd >= 40
GROUP BY jaar
```

2.2. Prevalent Nominator:

```
SELECT
jaar,
count(distinct anopat) n
FROM recent INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C09%"
AND TIMEDIFF(YEAR, gebdat, afldat) >= 40
GROUP BY jaar
```

2.3. Incident Nominator:

```
SELECT
YEAR(startdat) jaar,
SUM(start_ATCs LIKE "C09%") C09,
SUM(start_ATCs LIKE "C08%") C08,
SUM(start_ATCs LIKE "C07%") C07
FROM starters
WHERE nr_start_atcs = 1
GROUP BY jaar
```

Appendix 3: queries to obtain trends of drug use within the study period

3.4. Prevalent effect measures

```
SELECT
jaar,
n,
n/pop
FROM (
SELECT
jaar,
count(distinct anopat) n
FROM recent INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C09%"
AND TIMESTAMPDIFF(YEAR, gebdat, afdat) >= 40
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

3.5. Incident effect measures

```
SELECT
jaar,
C09 / pop,
C08 / pop,
C07 / pop
FROM (
SELECT
YEAR(startdat) jaar,
SUM(start_ATCs LIKE "C09%") C09,
SUM(start_ATCs LIKE "C08%") C08,
SUM(start_ATCs LIKE "C07%") C07
FROM starters
WHERE nr_start_atcs = 1
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

3.6. Incident effect measures in percentages

```
SELECT
jaar,
(C09 / pop) * 100,
(C08 / pop) * 100,
(C07 / pop) * 100
FROM (
SELECT
YEAR(startdat) jaar,
SUM(start_ATCs LIKE "C09%") C09,
SUM(start_ATCs LIKE "C08%") C08,
SUM(start_ATCs LIKE "C07%") C07
FROM starters
WHERE nr_start_atcs = 1
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

Appendix 4: queries to obtain differences in trends of drug use between the risk groups within the study period

4.1. Prevalent age difference 65 y.o and above

```
SELECT
jaar,
n,
n/pop
FROM (
SELECT
jaar,
count(distinct anopat) n
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C09%"
AND TIMESTAMPDIFF(YEAR, gebdat, afl-dat) >=65
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

4.2. Prevalent age difference 40-65 y.o

```
SELECT
jaar,
n,
n/pop
FROM (
SELECT
jaar,
count(distinct anopat) n
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C09%"
AND TIMESTAMPDIFF(YEAR, gebdat, afl-dat) >= 40
AND TIMESTAMPDIFF(YEAR, gebdat, afl-dat) < 65
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

4.3. Incident age difference 65 y.o and above

```
SELECT
jaar,
C09 / pop,
C08 / pop,
C07 / pop
FROM (
SELECT
YEAR(startdat) jaar,
SUM(start_ATCs LIKE "C09%") C09,
SUM(start_ATCs LIKE "C08%") C08,
SUM(start_ATCs LIKE "C07%") C07
FROM starters
WHERE nr_start_atcs = 1
AND TIMESTAMPDIFF(YEAR, gebdat, edat) >=65
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

4.4. Incident age difference 40-65 y.o

```
SELECT
jaar,
C09 / pop,
C08 / pop,
C07 / pop
FROM (
SELECT
YEAR(startdat) jaar,
SUM(start_ATCs LIKE "C09%") C09,
SUM(start_ATCs LIKE "C08%") C08,
SUM(start_ATCs LIKE "C07%") C07
FROM starters
WHERE nr_start_atcs = 1
AND TIMESTAMPDIFF(YEAR, gebdat, edat) >=40
AND TIMESTAMPDIFF(YEAR, gebdat, edat) <65
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

4.5. Prevalent gender difference

```
SELECT
jaar,
count(*) n,
SUM(mv = 1) nman,
SUM(mv = 2) nvrouw,
ROUND((SUM(mv = 1) / count(*)) * 100,2) perc_nman,
ROUND((SUM(mv = 2) / count(*)) * 100,2) perc_nvrouw
FROM (
SELECT
jaar,
anopat,
mv
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C09%"
AND TIMESTAMPDIFF(YEAR, gebdat, aflidat) >= 40
GROUP BY jaar, anopat
) a
GROUP BY jaar
```

4.6. Incident gender difference

```
SELECT
jaar,
count(*) n,
SUM(mv = 1) nman,
SUM(mv = 2) nvrouw,
ROUND((SUM(mv = 1) / count(*)) * 100,2) perc_nman,
ROUND((SUM(mv = 2) / count(*)) * 100,2) perc_nvrouw
FROM (
SELECT
anopat,
mv,
YEAR(startdat)jaar
FROM starters
WHERE nr_start_atcs = 1 AND start_atcs LIKE "C09%"
GROUP BY jaar, anopat
) a
GROUP BY jaar
```

4.7. Denominator table with gender distinction

```
CREATE TABLE denom_mv(index(jaar))
SELECT
jaar,
SUM(mv = 1) nman,
SUM(mv = 2) nvrouw
FROM (
SELECT
jaar,
anopat,
mv
FROM patient inner join recept USING(anopat)
WHERE ATC LIKE "C09%"
GROUP BY (anopat)
) a GROUP BY jaar
```

Appendix 5: tables obtained from IADB

5.1. Denominator

```
Dinom
Jaar population
2010 680916
2011 1013714
2012 1088266
2013 1092638
2014 1105268
2015 1109432
2016 1064962
2017 1114670
2018 1124384
2019 1134984
2020 1145414
```

5.2. The prevalence

Jaar	users	users/ population
2010	45855	0.0673
2011	72048	0.0711
2012	75750	0.0696
2013	74809	0.0685
2014	77858	0.0704
2015	78089	0.0704
2016	79357	0.0745
2017	78782	0.0707
2018	80264	0.0714
2019	79334	0.0699
2020	77969	0.0681

5.3. The incidence

jaar	C09 users / population
2010	0.0035
2011	0.0024
2012	0.0032
2013	0.0030
2014	0.0032
2015	0.0032
2016	0.0033
2017	0.0031
2018	0.0030
2019	0.0031
2020	0.0026

5.4. Prevalence of population aged between 40-65

Jaar	users	users/pop
2010	19834	0.0291
2011	30669	0.0303
2012	31536	0.0290
2013	30538	0.0279
2014	31329	0.0283
2015	31023	0.0280
2016	31273	0.0294
2017	30750	0.0276
2018	30959	0.0275
2019	30140	0.0266
2020	29248	0.0255

5.5. Incidence of population aged between 40-65

jaar	C09 users / population
2010	0.0021
2011	0.0015
2012	0.0020
2013	0.0019
2014	0.0020
2015	0.0021
2016	0.0021
2017	0.0020
2018	0.0019
2019	0.0020
2020	0.0016

5.6. Prevalence of population aged >65

jaar	users	users/population
2010	27093	0.0398
2011	43494	0.0429
2012	46292	0.0425
2013	46229	0.0423
2014	48404	0.0438
2015	48885	0.0441
2016	49884	0.0468
2017	49940	0.0448
2018	51264	0.0456
2019	50962	0.0449
2020	50563	0.0441

5.7. Incidence of population aged >65

jaar	C09 users / population
2010	0.0009
2011	0.0005
2012	0.0009
2013	0.0008
2014	0.0008
2015	0.0007
2016	0.0006
2017	0.0006
2018	0.0005
2019	0.0005
2020	0.0005

5.8. Prevalence in both genders

Jaar	users	man	vrouw	%_nman	%_nvrouw
2010	45855	23336	22519	50.89	49.11
2011	72048	37013	35035	51.37	48.63
2012	75750	39397	36353	52.01	47.99
2013	74809	39217	35592	52.42	47.58
2014	77858	41029	36829	52.70	47.30
2015	78089	41029	36587	53.15	46.85
2016	79357	42556	35801	53.63	46.37
2017	78782	42741	36041	54.25	45.75
2018	80264	43794	36470	54.56	45.44
2019	79334	43657	35677	55.03	44.97
2020	77969	43337	34632	55.58	44.42

5.9. Incidence in both genders

jaar	n	nman	nvrouw	perc_nman	perc_nvrouw
2010	2378	1227	1151	51.60	48.40
2011	2459	1293	1166	52.58	47.42
2012	3492	1858	1634	53.21	46.79
2013	3281	1721	1560	52.45	47.55
2014	3560	1801	1759	50.59	49.41
2015	3537	1888	1649	53.38	46.62
2016	3481	1846	1635	53.03	46.97
2017	3419	1916	1503	56.04	43.96
2018	3347	1842	1505	55.03	44.97
2019	3489	1889	1600	54.14	45.86
2020	2961	1657	1304	55.96	44.04

NOTE: the tables look different because some tables could not be copied from IADB.nl