Drug use in population screening. Pharmacoepidemiological and pharmacoeconomical aspects
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CHAPTER 3

The effect of screening for cardio-renal risk factors on drug use in the general population

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ABSTRACT

Introduction
A screening procedure is aimed to select people at high-risk for an unfavorable health outcome for further investigation and treatment. It however, might increase medical consumption and drug use. The aim of this study is to evaluate the effect of a cardiovascular and renal screening program on desired-, and on undue drug use. We will evaluate the impact of screening of an aselect, but also of a targeted cohort, that is a cohort enriched for the presence of cardiovascular and renal risk factors.

Methods
We used data from PREVEND (Prevention of REnal and Vascular ENd-stage Disease) cohort study. For this analysis, the drug use of a random sample of screened subjects (the aselect cohort, n=2650) is compared with drug use in subjects not participating in the screening program, matched on age and sex (the unscreened reference group, n=10,434). The drug use in the overall PREVEND cohort, that was enriched for the presence of an elevated albuminuria (enriched cohort , n=6751), was also studied. The main outcome was incidence of drug use following the screening. We selected screening-related drugs e.g. antihypertensive, antilipidemic, antidiabetic and antithrombotic agents, as well as screening-unrelated drugs e.g. benzodiazepines, drugs for acid related disorders, and pain killers. Time to first prescription after screening is presented as Kaplan Meier curves.

Results
After 6.5 years of follow up the cumulative incidence of drug use was not significantly different between the screened aselect and the unscreened cohort. Antihypertensives were used by 21.5 and 20.8% of the screened and unscreened subjects, respectively, antilipidemic drugs by 12.8 and 10.2%, antidiabetics by 4.0 and 3.9%, and antithrombotic drugs by 11.4 and 12.0%. Screening-unrelated drugs were also used in comparable frequencies. As compared to the unscreened cohort screening related drugs had been prescribed more frequently to the subjects of the enriched PREVEND cohort (25.8, 15.5, 5.5, and 13.5% for the antihypertensive, antilipidemic, antidiabetic and antithrombotic drugs, respectively), while screening unrelated drugs were used in comparable frequencies.
**Conclusions.**

The incidence of drug use is not different in a screened aselect cohort as compared to an unscreened cohort. Our data thus show that screening does not lead to more drug prescriptions, and thus argues against the fear of undue medicalisation after a screening. The data also show that, for a screening to be successful, it should be performed in a targeted population, such as for example in a population enriched for having elevated albuminuria.
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INTRODUCTION

A population screening is meant to detect people at risk of an unfavorable health outcome for further investigation and subsequent advice and treatment. The most important benefit from detecting disease at an earlier stage is that treatment can be started earlier and may therefore be more effective. Screening and treatment of cardiovascular and renal risk factors such as hypertension, diabetes, hyperlipidemia and proteinuria can reduce the incidence and progression of cardiovascular and renal disease [1-5].

Whereas only a small proportion of the people screened will benefit from the screening program, some participants may also experience harm [6-7]. It is for example known that participants may experience psychological distress, including anxiety provoked by the screening procedure itself, the time waiting for the result and treatment of the disease for which is screened [7-10]. It has also been argued that screening may result in medicalisation [6,11-12] and thus may lead to increased drug use [13-15]. Indeed, hypertension and vascular disease screening programs have been found to result in an increased use of antihypertensive and lipid lowering drugs [16-17]. This may be undue use of these agents in asymptomatic patients and may also relate to an excessive use of drugs in general. The studies done thus far, however, did not compare the use of cardio- and renoprotective drugs in the screened population with the use in the unscreened population. These studies also did not test whether the awareness of being at risk for cardiovascular and renal disease may already result in an increased use of other drugs, not directly related to the diseases tested for.

We therefore evaluated in this study the effect of screening for cardiovascular and renal risk factors on drug use in a screened population as compared with a non-screened reference population. We looked for the use of drug groups that are related to the purpose of the screening, as well as for the use of drugs unrelated to the screening purpose. We similarly evaluated the drug use in a cohort that is enriched for the presence of cardiovascular and renal risk factors.
METHODS

Design
For this study we used data from the PREVEND screening program (Prevention of REnal and Vascular ENd-stage Disease), running in the city of Groningen, the Netherlands. In this report we studied drug use in a random sample of 3432 subjects of the Groningen population in the age of 28-75 years [18] for description of the cohort. Drug use in this screened aselect cohort was compared with the drug use in the background unscreened population of the same age and city (Figure-1). Drug use of both the PREVEND participants and the background population was monitored from the InterAction DataBase (IADB), which contains pharmacy-dispensing data of a population of approximately 500,000 subjects in the Northern part of the Netherlands. This database contains, among other things, the name of the drug, the date the drugs were prescribed and their ATC (Anatomical Therapeutical Chemical) code. The use of over-the-counter drugs and in-patient prescriptions is not included [19].

As the PREVEND study is designed to investigate the impact of urinary albumin excretion on renal and cardiovascular disease progression in the general population, the overall PREVEND cohort of 8592 subjects is enriched for the presence of an elevated albuminuria (the screened enriched cohort). Design and methods of the PREVEND study have been described in detail elsewhere [20,21]. In the present analysis subjects with available drug information from the pharmacy prescription database at least 6 months prior to the screening were included. Of the 3432 subjects of the screened aselect cohort 2650 were eligible for analysis, and of the 8592 subjects of the enriched cohort 6751 were eligible. The screened subjects were seen for a second screening after a median follow up of 4.2 years. After both screenings the subjects and their general physicians were informed in case of hypertension (>160/100 in 1997/98 and, dependent on age and cardiovascular risk, >140/90 in 2001/2), and hyperlipidemia (>8.0 or >5.0 in case of a previous myocardial infarction) to contact their general practitioner, as it was advisable to start blood pressure lowering or lipid lowering treatment [22]. After the first screening 3.0%, and 3.9% of the subjects in the screened aselect cohort received a letter to consider the start of blood pressure-or lipid-lowering drugs, respectively. After the second screening these percentages were 6.0% and 4.3%, respectively. We did not advice on the use of antithrombotic drugs. In the screened enriched cohort 5.5 and 4.6 of the subjects received a letter to start blood pressure- or lipid-lowering treatment respectively, after the first screening, and 6.7 and 5.3 after the second screening.
As reference group we used data of 181,993 subjects aged between 28 and 75 years old at July 1st 1998, living in the city of Groningen, and not participating in the PREVEND screening program, and of which pharmacy data were available from at least 6 months before July 1st 1998 (hypothetical screening date). We randomly selected 10,600 subjects of this cohort matched on age and sex of the PREVEND random sample of 2650 available subjects. Of these subjects, we excluded those who were on insulin prior to screening (as was done for inclusion in the PREVEND study) [20-21]. Thus, 10,434 subjects in the unscreened reference-group are available for analysis. We studied the drug use for at least 180 days before the screening date until 31st of December 2004, thus allowing an approximately 6.5 years of follow-up.

**The drugs studied**

The drugs studied are categorised according to World Health Organisation following of the Anatomical Therapeutic Chemical (ATC) classification system [23]. The study evaluated two major drug groups. First, the screening-related drugs (drugs prescribed to improve cardiovascular and renal outcome). This group consists of blood pressure lowering drugs, including diuretics (ATC code C03) beta blockers (C07), calcium channel blockers (C08) and drugs interfering in the renin angiotensin system (C09), lipid lowering drugs (C10), blood glucose lowering drug (A10B for prevalence and A10 for incidence) and antithrombotic drugs (B01). The second group studied are screening-unrelated drugs, e.g. drugs of which the screening is not intended to influence its use. To that purpose we evaluated use of benzodiazepine and antidepressants (N05BA, N05CD, N05CF, N06A, and N06CA), H-2 receptor antagonists and proton pump inhibitors (A02BA and A02BC), and

![Flow chart of the study design](image-url)
pain killers (M01, M03B and N02). We choose for these drug classes as stress (due to the awareness of being at risk) might result in more frequent use of these agents.

**Statistical analysis**
Analyses were performed using SPSS version 13.0 software (SPSS, Chicago, IL, USA). The proportion of the subjects who had received at least one prescription in the 6 months before screening is presented as prevalent drug use at screening. The proportion of the subjects who started to use a drug following the screening is presented as the cumulative incidence. The incidence figures include the subjects who did not use a selected drug 180 days before the screening. The cumulative incidence is presented by Kaplan-Meier survival estimation from the screening date until 6.5 years of follow-up. Subjects who moved out of the city of Groningen were censored. The proportional hazard ratio with 95% confidence intervals is used to calculate the difference between index and reference group.

**RESULTS**

**Prevalence of drug use prior to the screening**
Of the 2650 subjects in the screened aselect cohort and the 10,434 subjects in the unscreened cohort (reference group), 42% were male and mean age on the first screening date was 49.4 years. Of the 6751 subjects in the enriched cohort 47.3% were male and mean age was 50.0 years.

Table-1 shows the prevalent use of studied drug groups in the 6 months prior to the baseline screening. The prevalent use of screening related drugs was not significantly different between the screened aselect cohort (19.1%, 95% CI 17.6-20.6) and the unscreened cohort (20.6%; 19.8-21.4, \( p = 0.09 \)). In the subgroups, the prevalent use of blood pressure lowering and lipid lowering drugs before the screening was not significantly different between the screened aselect cohort and the unscreened cohort PREVEND (15.3% vs 16.5% and 4.9% vs 4.9%, respectively). In contrast, the use of blood glucose lowering and antithrombotic drugs was significantly lower in the screened aselect cohort (1.2% and 5.1% resp.) than in the unscreened group (2.2% and 7.3%, resp.). In the screened enriched cohort the use of screening related drugs was higher (22.2%; 21.2-23.2) than in the unscreened cohort (\( p = 0.01 \)). This was due to a greater use of especially blood pressure- and blood glucose- lowering drugs.
<table>
<thead>
<tr>
<th>Selected drugs</th>
<th>Unscreened Cohort n = 10,434</th>
<th>Screened aselect cohort n = 2650</th>
<th>p-value †</th>
<th>Screened enriched cohort n = 6751</th>
<th>p-value ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening-related drugs (%)</td>
<td>2149 (20.6)</td>
<td>506 (19.1)</td>
<td>0.09</td>
<td>1500 (22.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>1. Blood pressure lowering drugs (BPLD)</td>
<td>1721 (16.5)</td>
<td>406 (15.3)</td>
<td>0.14</td>
<td>1211 (17.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>2. Lipid lowering drugs (LLD)</td>
<td>509 (4.9)</td>
<td>131 (4.9)</td>
<td>0.89</td>
<td>359 (5.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>3. Oral blood glucose lowering drugs (BGLD)</td>
<td>232 (2.2)</td>
<td>32 (1.2)</td>
<td>0.001</td>
<td>113 (1.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>4. Anti thrombotic drugs (ATD)</td>
<td>765 (7.3)</td>
<td>136 (5.1)</td>
<td>&lt;0.001</td>
<td>479 (7.1)</td>
<td>0.56</td>
</tr>
<tr>
<td>Screening-unrelated drugs (%)</td>
<td>3676 (35.2)</td>
<td>849 (32.0)</td>
<td>0.02</td>
<td>2203 (32.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1. Benzodiazepines and antidepressants</td>
<td>1909 (18.3)</td>
<td>395 (14.9)</td>
<td>&lt;0.001</td>
<td>1027 (15.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2. H-2 receptor antagonist and proton-pump inhibitors</td>
<td>755 (7.2)</td>
<td>191 (7.2)</td>
<td>0.96</td>
<td>498 (7.4)</td>
<td>0.73</td>
</tr>
<tr>
<td>3. Painkillers</td>
<td>2236 (21.4)</td>
<td>544 (20.5)</td>
<td>0.31</td>
<td>1381 (20.5)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*p-value † indicates whether drug use differs between screened aselect cohort and unscreened cohort as reference, using chi-square test; p-value ‡ indicates whether drug use differs between screened enriched cohort and unscreened cohort as reference, using chi-square test;
THE EFFECT OF SCREENING ON DRUG USE

The use of screening-unrelated drugs before the screening was significantly lower in the screened aselect (32.0%; 30.3-33.8) and the screened enriched cohort (32.6%; 31.5-33.8) as compared to the unscreened reference group (35.2%; 34.1-36.4; \(p<0.05\)). When studying the various drug subgroups, prevalent use was significantly lower in both screened cohorts for benzodiazepines and antidepressants (14.9% and 15.2% \(\text{vs}\) 18.3%, both \(p<0.001\)), while the use of H-2 receptor antagonist and proton pump inhibitors, and also painkillers was not significantly different between the two screened cohorts and the unscreened reference group.

![Graphs](Figure-2)

*Figure-2.* Cumulative incidence of use of screening-related drugs, e.g. blood pressure lowering drugs (2A), lipid lowering drugs (2B), oral blood glucose lowering drugs (2C) and anti-thrombotic drugs (2D) in the screened aselect cohort (continuous dark-line), the screened enriched cohort (continuous gray-line) and the unscreened reference cohort (broken line).
### Table-2. Cumulative incident use of selected drugs at 6.5 years after the baseline screening

<table>
<thead>
<tr>
<th>Selected drugs</th>
<th>Unscreened cohort</th>
<th>Screened aselect cohort</th>
<th>HR (95% CI) †</th>
<th>Screened enriched cohort</th>
<th>HR (95% CI) ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening-related drugs (%)</td>
<td>26.0</td>
<td>27.9</td>
<td>1.02 (0.94-1.12)</td>
<td>32.2</td>
<td>1.20 (1.13-1.29)</td>
</tr>
<tr>
<td>1. Blood pressure lowering drugs (BPLD)</td>
<td>20.8</td>
<td>21.5</td>
<td>0.98 (0.88-1.08)</td>
<td>25.8</td>
<td>1.18 (1.10-1.27)</td>
</tr>
<tr>
<td>2. Lipid lowering drugs (LLD)</td>
<td>10.2</td>
<td>12.8</td>
<td>1.20 (1.05-1.36)</td>
<td>15.5</td>
<td>1.39 (1.27-1.52)</td>
</tr>
<tr>
<td>3. Oral blood glucose lowering drugs (BGLD)</td>
<td>3.9</td>
<td>4.0</td>
<td>0.99 (0.79-1.23)</td>
<td>5.5</td>
<td>1.28 (1.11-1.48)</td>
</tr>
<tr>
<td>4. Anti thrombotic drugs (ATD)</td>
<td>12.0</td>
<td>11.4</td>
<td>0.89 (0.78-1.02)</td>
<td>13.5</td>
<td>0.99 (0.90-1.08)</td>
</tr>
<tr>
<td>Screening-unrelated drugs (%)</td>
<td>70.4</td>
<td>72.0</td>
<td>1.04 (0.97-1.10)</td>
<td>71.9</td>
<td>1.04 (0.99-1.09)</td>
</tr>
<tr>
<td>1. Benzodiazepines and antidepressants</td>
<td>35.9</td>
<td>36.2</td>
<td>0.98 (0.90-1.06)</td>
<td>35.9</td>
<td>0.98 (0.93-1.04)</td>
</tr>
<tr>
<td>2. H-2 receptor antagonist and proton-pump inhibitors</td>
<td>31.7</td>
<td>27.3</td>
<td>0.83 (0.72-0.95)</td>
<td>27.6</td>
<td>0.86 (0.78-0.95)</td>
</tr>
<tr>
<td>3. Painkillers</td>
<td>60.7</td>
<td>64.7</td>
<td>1.07 (1.01-1.14)</td>
<td>64.2</td>
<td>1.07 (1.03-1.12)</td>
</tr>
</tbody>
</table>

† Hazard Ratio (HR) of drug use at 6.5 years after the baseline screening, between screened aselect cohort and unscreened cohort as reference group, matched for sex and age, using Cox-regression analysis.; ‡ Hazard Ratio (HR) of drug use at 6.5 years after the baseline screening, between screened enriched cohort and unscreened cohort as reference group, adjusted by sex and baseline age, using Cox-regression analysis.
The incidence of drug use in the screened aselect cohort
At the end of the follow up there was no difference in the cumulative overall incidence of drug use between the screened aselect cohort and the unscreened reference cohort, neither for the screening-related drugs (27.9 vs 26.0%; HR 1.02, 95% CI 0.94-1.12) nor for the screening-unrelated drugs (72.0 vs 70.4%; HR 1.04, 0.97-1.10). If anything, the use of non screening-related drugs was lower in the screened aselect cohort (Table-2).

The cumulative incidences of blood pressure lowering, blood glucose lowering and antithrombotic drugs were not different between the screened aselect and the unscreened cohort. The cumulative incidence of new drug use at the end of the 6.5 year follow up amounted to 21.5 and 20.8% for blood pressure lowering drugs (Figure-2a), 4.0 and 3.9% for blood glucose lowering drugs (Figure-2c) and 11.4 and 12.0% for the antithrombotic drugs (Figure-2d), in the screened aselect cohort and the reference group, respectively. The incidence of the use of lipid lowering drugs however, was higher in the screened aselect cohort compared to the reference group (HR 1.20; 95% CI 1.05-1.36) (Figure-2b). This seems to be manifest especially in the first year and after about 4 years of follow up, e.g. at the time of both screenings. When looking at the various subgroups of screening-unrelated drugs, the subjects in the screened aselect cohort started the use of benzodiazepines and anti-depressants, H2 receptor antagonists and proton pump inhibitors, and painkillers at a comparable frequency as in the background population (Figure-3 a-c).

The incidence of drug use in the screened enriched cohort
At the end of the follow up the cumulative incidence of use of screening related drugs was greater in the screened enriched cohort compared to the unscreened cohort (32.2 vs 26.0%; HR 1.20, 1.13-1.29), while the use of screening unrelated drugs was not different between both groups (71.9 vs 70.4%; HR 1.04, 0.99-1.09) (Table-2). The higher incidence of use of screening related drugs was manifest for the three drug groups on which we gave therapeutic advice (blood pressure-, lipid- and blood glucose-lowering drugs), but not for the other cardioprotective agents for which we did not give specific advice, e.g. antithrombotic drugs (Table-2 and Figure-3). When looking at the various subgroups of screening unrelated drug groups, the use of benzodiazepine and antidepressant was not different between the screened enriched cohort and the unscreened cohort, while drugs for acid related disorders were used less frequently in the screened cohort and painkillers were used more frequently.
DISCUSSION.

Our data show that screening for hypertension, diabetes and hyperlipidemia does not result in a higher drug use in a screened aselect sample of the population as compared to the background non-screened population. Screening neither influenced the incidence of the use of drugs which are related to the rationale of the screening program, nor for screening unrelated drugs. Only the use of lipid lowering drugs was higher, especially shortly after the first and second screening.

At first sight, we were impressed by the finding that in a screening amongst the general population in the age range of 28-75 years 21.5% of the subjects that were not yet on antihypertensives at the time of the screening started to use those drugs in a period of 6.5 years and 12.8% and 11.4% started lipid
lowering and antithrombotic treatment, respectively. These figures suggest a clear medicalisation of the screened population. We however found nearly identical figures on incident drug use in the unscreened reference group. This emphasizes that screening per se does not lead to medicalisation, but that cardio- and renoprotective drug use in the general population is growing rapidly. That data are in agreement with other studies that showed a growing use of both antihypertensives [24-25] and lipid lowering drugs [25-27]. This growth has been argued to be related to both pharmaceutical marketing and publication [28-30] and better implementation of, and adherence to, guidelines [31].

The data on incident use of lipid lowering drugs show the impact of the screening procedure itself. Both after the baseline screening (year 0.0), as well as after the second screening (year 4.2) the two curves dissociate, the screened aselect cohort using lipid lowering drugs more frequently. This, at least partly may be related to the fact that 4.0% and 4.3% of the screened subjects were sent a letter after the first and second screening, respectively, to start such treatment. After a given time period however, this difference disappears. Notice that the discrepancy is more pronounced after the second screening. In those years (2001/02) prescribing lipid lowering drugs was widely advocated in guidelines in our country. As a consequence the use of these agents increases not only in the screened aselect cohort, but also in the unscreened population.

We could also interpret our data as a failure of screening programs to optimise drug treatment by starting treatment in an earlier, still asymptomatic phase. Our data on drug use in the screened enriched cohort, e.g the group of subjects enriched for the presence of albuminuria, nicely show that screening for risk factors should be carried out in a targeted population. Only then subjects with risk factors are selected from the population and screening may thus become cost-effective [22]. A pre-screening on albuminuria may be an adequate approach to reach that goal [18,34]. The impact of the information to the participant that specific treatment should be started is clear from the difference in incident drug use between the aselect and enriched cohort. That the treatment is limited only to the categories advised is also clear from the finding that the use of antithrombotic drugs (on which we did not advice) was not higher in the enriched cohort.

At baseline, for some drug groups the use was lower in the screened aselect sample than in the non-participants. This was the case for oral blood glucose lowering drugs and antithrombotic drugs, for the group of screening unrelated drugs in general, and benzodiazepines and antidepressants in particular. It illustrates that participants in a screening are in general healthier than non-participants. The lower prevalence of oral blood glucose lowering drugs in the
screened population may be due to the fact that insulin using diabetics were not included in our screening program (as PREVEND wants to evaluate the impact of albuminuria in the general population instead of in the diabetic population). This may well explain the fact that subjects participating in the screening were also less frequently using antithrombotic drugs. Our finding of a higher use of psychotropic medication in non-participants to the screening is in line with data from the Tromso Health Study. In that study patients with psychiatric disorders had an approximately 20% lower attendance rate to the health survey, and non-participants to the survey had a 2.5 times higher prevalence of psychiatric disorders than did participants [33].

Our study has some shortcomings. First, we measured drug use from a pharmacy database. That means that the drugs reported have been delivered to the patient. We however, are not informed on the actual drug use by the patient. Second, we are not aware whether the patients used blood pressure lowering drugs indeed as antihypertensive or for another indication, such as beta blocking drugs for angina or ACE inhibitors for heart failure. This uncertainty regarding the diagnosis is less likely a problem for the other drug categories. Third, drug use is just one of the components of medicalisation. We for example are not aware on medical consumption in general, such as frequency of physician-contacts, medical diagnostic procedures or life style changes.

It is a strength of our study that we were able to compare drug use in a screened cohort with that in a large cohort in the same city, matched for sex and age. Second, we could provide data on a long period of follow-up (6.5 years). Third, drug prescription data have been validated to be a reliable form of information on drug use and have the advantage over patient histories, that the latter are hampered by recall bias [34]. Moreover, in the Netherlands most of the drugs are delivered on prescription via the pharmacies, and a patient receives nearly always all drugs from the same pharmacy.

In conclusion, our data show that a screening program to improve cardiovascular and renal outcome does not lead to a higher drug use than in an unscreened population. The data also show that a targeted screening, that is a screening in a cohort that likely is at higher risk, contributes to a greater drug use, but only in the drug classes expected and not in an overall undue drug use.
REFERENCES


THE EFFECT OF SCREENING ON DRUG USE


