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

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What is already known about this subject

- Screening of the population may result in medicalization.
- There is no report about the effect of a health screening programme on drug prescribing.

What this study adds

- Screening of the general population for cardiovascular risk factors does not lead to more drug prescribing, for either screening-related or screening-unrelated drugs.
- The incidence of drug use increases in screened subjects with high risk, but only for drugs related to the purpose of screening.
- For screening to be successful, i.e. increased drug use in the detected diseased subjects, it has to be performed in a population expected to be at increased risk.

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Aim

To evaluate the effect of a cardio-renal screening programme on desired and undue drug use.

Methods

Data from the PREVEND cohort (Prevention of REnal and Vascular ENd-stage Disease) were used. The drug use of screened (randomly) selected subjects ($n = 2650$) was compared with unscreened subjects, matched for age and sex ($n = 10\,434$). Drug use in the overall PREVEND cohort, enriched for albuminuria ($n = 6751$), was also studied. Screening-related drugs (antihypertensive, antilipidaemic, antidiabetic and antithrombotic) were selected, as well as screening-unrelated drugs (benzodiazepines, drugs for acid-related disorders and painkillers). Time to first prescription after screening is presented as Kaplan–Meier curves.

Results

After 6.5 years of follow-up, the incidence of drug use was not significantly different between the screened, randomly selected and unscreened cohorts. Antihypertensives were used by 21.5 and 20.8%, respectively; antilipidaemic 12.8 and 10.2%, antidiabetics 4.0 and 3.9%, and antithrombotic 11.4 and 12.0%. Screening-unrelated drugs were used at comparable frequencies. Compared with the unscreened cohort, screening-related drugs were prescribed more frequently for subjects in the enriched cohort (25.8, 15.5, 5.5 and 13.5% for antihypertensive, antilipidaemic, antidiabetic and antithrombotic, respectively), whereas screening-unrelated drugs were used at comparable frequencies.

Conclusions

The incidence of drug use did not differ between the screened, randomly selected and unscreened cohorts. Screening does not lead to more drug prescription, thus arguing against the fear of undue medicalization after screening. The data also show that, for screening to be successful, it should be performed in a targeted population, such as one enriched for albuminuria.

Introduction

A population screening is meant to select people at risk of an unfavourable health outcome for further investigation and subsequent advice and treatment. The most important benefit from detecting disease at an early 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, hyperlipidaemia and proteinuria can reduce the incidence and progression of cardiovascular and renal disease [1–5].

Whereas only a small proportion of those screened will benefit from the screening programme, some may also experience harm [6, 7]. It is known, for example, 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 they were screened [7–10]. It has also been argued that screening may result in medicalization [6, 11, 12] and thus may lead to increased drug use [13–15]. Indeed, hypertension and vascular disease screening programmes have been found to result in 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, have not compared the use of cardio- and reno-protective drugs in the screened population with use in the unscreened population. They have also not tested 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 for which they were tested.

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

Methods

Design

Data were used from the PREVEND screening programme (Prevention of REnal and Vascular ENd-stage Disease), running in the city of Groningen, the Netherlands. Drug use was studied in a random sample of 3432 subjects of the Groningen population aged 28–75 years (see [18] for a description of the cohort). Drug use in this screened, randomly selected cohort was compared with the that in the background unscreened population of the

Figure 1

Flow chart of the study design

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 Anatomical Therapeutic Chemical (ATC) code. The use of over-the-counter drugs and in-patient prescriptions was 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 was enriched for the presence of elevated albuminuria (the screened enriched cohort). The 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, randomly selected 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 hyperlipidaemia (>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 subjects in the screened, randomly selected 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. No advice was given on the use of anti-thrombotic drugs. In the screened enriched cohort 5.5% and 4.6% of 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, data were used of 181 993 subjects aged between 28 and 75 years on 1 July 1998, living in the city of Groningen, and not participating in the PREVEND screening programme, and for whom pharmacy data were available from at least 6 months before 1 July 1998 (hypothetical screening date). We randomly selected 10 600 subjects of this cohort matched for age and sex with the PREVEND random sample of 2650 available subjects. Of these subjects, those were excluded 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 were available for analysis. Drug use was studied for at least 180 days before the screening date until 31 December 2004, thus allowing approximately 6.5 years of follow-up.

Drugs studied

The drugs studied are categorized according to World Health Organization following the ATC classification system [23]. Two major drug groups were evaluated. First, the screening-related drugs (prescribed to improve cardiovascular and renal outcome), consisting of blood pressure-lowering drugs, including diuretics (ATC code C03) β -blockers (C07), calcium channel blockers (C08) and drugs interfering in the renin–angiotensin system (C09), lipid-lowering drugs (C10), blood glucose-lowering drugs (A10B for prevalence and A10 for incidence) and antithrombotic drugs (B01). The second group were screening-unrelated drugs, i.e. drugs whose screening is not intended to influence their use. Use of benzodiazepine and antidepressants (N05BA, N05CD, N05CF, N06A and N06CA), H-2 receptor antagonists and proton pump inhibitors (A02BA and A02 BC), and pain killers (M01, M03B and N02) was evaluated. These drug classes were chosen because stress (due to the awareness of being at risk) might result in their more frequent use.

Statistical analysis

Analyses were performed using SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA). The proportion of 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 subjects who started to use a drug following screening is presented as the

cumulative incidence. The incidence figures include subjects who did not use a selected drug 180 days before 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 (HR) with 95% confidence intervals (CI) is used to calculate the difference between the index and reference groups.

Results

Prevalence of drug use prior to the screening

Of the 2650 subjects in the screened, randomly selected cohort and the 10 434 subjects in the unscreened cohort (reference group), 42% were male and their mean age on first screening was 49.4 years. Of the 6751 subjects in the enriched cohort, 47.3% were male and their mean age was 50.0 years.

Table 1 shows the prevalent use of the 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 randomly selected 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 screening was not significantly different between the screened randomly selected cohort and the unscreened PREVEND cohort (15.3% vs. 16.5% and 4.9% vs. 4.9%, respectively). In contrast, the use of blood glucose-lowering and anti-thrombotic drugs was significantly lower in the screened, randomly selected cohort (1.2% and 5.1%, respectively) than in the unscreened group (2.2% and 7.3%, respectively). 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.

The use of screening-unrelated drugs before the screening was significantly lower in the screened, randomly selected (32.0%; 30.3, 33.8) and screened enriched cohorts (32.6%; 31.5, 33.8) compared with 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% vs. 18.3%, both $P < 0.001$), whereas the use of H-2 receptor antagonists and proton pump inhibitors, and also painkillers was not significantly different between the two screened cohorts and the unscreened reference group.

Table 1

Use of selected drugs in the 6 months prior to the screening

Selected drugs	Unscreened cohort <i>n</i> = 10 434	Screened randomly-selected cohort <i>n</i> = 2650	<i>P</i> -value*	Screened enriched cohort <i>n</i> = 6751	<i>P</i> -value†
Screening-related drugs (%)	2149 (20.6)	506 (19.1)	0.09	1500 (22.2)	0.01
1 Blood pressure-lowering drugs	1721 (16.5)	406 (15.3)	0.14	1211 (17.9)	0.01
2 Lipid lowering drugs	509 (4.9)	131 (4.9)	0.89	359 (5.3)	0.06
3 Oral blood glucose-lowering drugs	232 (2.2)	32 (1.2)	0.001	113 (1.7)	0.01
4 Antithrombotic drugs	765 (7.3)	136 (5.1)	<0.001	479 (7.1)	0.56
Screening-unrelated drugs (%)	3676 (35.2)	849 (32.0)	0.02	2203 (32.6)	<0.001
1 Benzodiazepines and antidepressants	1909 (18.3)	395 (14.9)	<0.001	1027 (15.2)	<0.001
2 H ₂ receptor antagonist and proton pump inhibitors	755 (7.2)	191 (7.2)	0.96	498 (7.4)	0.73
3 Painkillers	2236 (21.4)	544 (20.5)	0.31	1381 (20.5)	0.13

**P*-value indicates whether drug use differs between screened, randomly selected cohort and unscreened cohort as reference, using χ^2 test. †*P*-value indicates whether drug use differs between screened, enriched cohort and unscreened cohort as reference, using χ^2 test.

The incidence of drug use in the screened, randomly selected cohort

At the end of the follow-up there was no difference in the cumulative overall incidence of drug use between the screened, randomly selected cohort and the unscreened reference cohort, either for screening-related drugs (27.9 vs. 26.0%; HR 1.02, 95% CI 0.94, 1.12) or for screening-unrelated drugs (72.0 vs. 70.4%; HR 1.04, 95% CI 0.97, 1.10). If anything, the use of nonscreening-related drugs was lower in the screened randomly selected cohort (Table 2).

The cumulative incidences of blood pressure-lowering, blood glucose-lowering and antithrombotic drugs were not different between the screened, randomly selected cohort and the unscreened cohort. The cumulative incidence of new drug use at the end of the 6.5 years' 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, randomly selected cohort and the reference group, respectively. The incidence of the use of lipid-lowering drugs, however, was higher in the screened, randomly selected cohort compared with the reference group (HR 1.20; 95% CI 1.05, 1.36) (Figure 2B). This seemed to be manifest especially in the first year and after about 4 years of follow-up, e.g. at the time of both screenings. As regards the various

subgroups of screening-unrelated drugs, subjects in the screened, randomly selected cohort started the use of benzodiazepines and antidepressants, H₂ receptor antagonists and proton pump inhibitors, and painkillers at a frequency comparable to that of the background population (Figure 3A–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 with the unscreened cohort (32.2 vs. 26.0%; HR 1.20; 95% CI 1.13, 1.29), whereas the use of screening-unrelated drugs was not different between the two groups (71.9 vs. 70.4%; 1.04; 0.99, 1.09) (Table 2). The higher incidence of use of screening-related drugs was apparent for the three drug groups for which therapeutic advice was given (blood pressure-, lipid- and blood glucose-lowering drugs), but not for the other cardioprotective agents for which specific advice was not given, e.g. antithrombotic drugs (Table 2 and Figure 3). As regards the various subgroups of screening-unrelated drug groups, the use of benzodiazepine and antidepressants was not different between the screened, enriched cohort and the unscreened cohort, whereas drugs for acid-related disorders were used less frequently in the screened cohort and painkillers were used more frequently.

Table 2

Cumulative incident use of selected drugs at 6.5 years after the baseline screening

Selected drugs	Unscreened cohort (SE)	Screened randomly-selected cohort (SE)	HR (95% CI)*	Screened enriched cohort (SE)	HR (95% CI)†
Screening-related drugs (%)	26.0 (0.005)	27.9 (0.01)	1.02 (0.94, 1.12)	32.2 (0.007)	1.20 (1.13, 1.29)
1 Blood pressure-lowering drugs	20.8 (0.004)	21.5 (0.009)	0.98 (0.88, 1.08)	25.8 (0.006)	1.18 (1.10, 1.27)
2 Lipid-lowering drugs	10.2 (0.003)	12.8 (0.007)	1.20 (1.05, 1.36)	15.5 (0.005)	1.39 (1.27, 1.52)
3 Oral blood glucose-lowering drugs	3.9 (0.002)	4.0 (0.004)	0.99 (0.79, 1.23)	5.5 (0.003)	1.28 (1.11, 1.48)
4 Antithrombosis drugs	12.0 (0.003)	11.4 (0.006)	0.89 (0.78, 1.02)	13.5 (0.004)	0.99 (0.90, 1.08)
Screening-unrelated drugs (%)	70.4 (0.006)	72.0 (0.01)	1.04 (0.97, 1.10)	71.9 (0.007)	1.04 (0.99, 1.09)
1 Benzodiazepines and antidepressants	35.9 (0.005)	36.2 (0.01)	0.98 (0.90, 1.06)	35.9 (0.006)	0.98 (0.93, 1.04)
2 H-2 receptor antagonist and proton pump inhibitors	31.7 (0.008)	27.3 (0.01)	0.83 (0.72, 0.95)	27.6 (0.01)	0.86 (0.78, 0.95)
3 Painkillers	60.7 (0.005)	64.7 (0.01)	1.07 (1.01, 1.14)	64.2 (0.007)	1.07 (1.03, 1.12)

SE, Standard error. *Hazard ratio (HR) of drug use at 6.5 years after the baseline screening, between screened, randomly selected cohort and unscreened cohort as reference group matched for sex and age, using Cox regression analysis. †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.

Discussion

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

The finding that, in a screening of the general population aged 28–75 years, 21.5% of subjects not yet on antihypertensives at the time of screening started to use those drugs in a period of 6.5 years and 12.8% and 11.4% started lipid-lowering and antithrombotic treatments, respectively, was, at first sight, impressive. These figures suggest a clear medicalization of the screened population. However, nearly identical figures were found on incident drug use in the unscreened reference group. This emphasizes that screening *per se* does not lead to medicalization, but that cardio- and renoprotective drug use in the general population is growing rapidly. These data are in agreement with other studies that have shown growing use of both antihypertensive [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, randomly selected cohort using lipid-lowering drugs more frequently. This may be related, at least in part, to the fact that 4.0% and 4.3% of the screened subjects were sent a letter after the first and second screenings, respectively, to start such treatment. After a given time period, however, this difference disappears. It is noteworthy that the discrepancy is more pronounced after the second screening. In those years (2001/2002) the prescribing of lipid-lowering drugs was widely advocated in guidelines in our country. As a consequence, the use of these agents increased not only in the screened, randomly selected cohort, but also in the unscreened population.

These data can also be interpreted as a failure of screening programmes to optimize 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, demonstrate well that screening for risk factors should be carried out in a targeted population. Only then will subjects with risk factors be selected from the population and screening become cost effective [22]. Prescreening for albuminuria may be an adequate approach to attain that goal [18, 34]. The impact on the

Figure 2

Cumulative incidence of use of screening-related drugs, e.g. blood pressure-lowering drugs (A), lipid-lowering drugs (B), oral blood glucose-lowering drugs (C) and antithrombosis drugs (D) in the screened, randomly selected cohort (continuous dark line), the screened enriched cohort (continuous grey line) and the unscreened reference cohort (broken line). Unscreened cohort (I), (---); Screened selected cohort (II), (- -); Screened enriched cohort (III), (—)

participant of the information that specific treatment should be started is clear from the difference in incident drug use between the selected and enriched cohorts. That the treatment is limited only to the categories advised is also clear from the finding that the use of antithrombotic drugs (on which advice was not given) was not higher in the enriched cohort.

At baseline, for some drug groups the use was lower in the screened, randomly selected sample than in 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 for benzodiazepines and antidepressants in particular. It illustrates that participants in a screening are in general healthier than nonparticipants. 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 programme (as PREVENT wants to evaluate the impact of albuminuria in the general population instead of in the diabetic population) [32]. 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 nonparticipants in the screening is in line with data from the Tromsø Health Study, in which patients with psychiatric disorders had an approximately 20% lower attendance rate to the health survey, and nonparticipants in the survey had a 2.5 times higher prevalence of psychiatric disorders than did participants [33].

Our study has some shortcomings. First, drug use was measured from a pharmacy database. That means that the drugs reported had been delivered to the patient. However, there was no information on the actual drug

Figure 3

Cumulative incidence of use of screening-unrelated drugs, e.g. benzodiazepines and antidepressants (A), H2 receptor antagonists and proton pump inhibitors (B) and painkillers (C) in the screened, randomly selected cohort (continuous dark line), the screened enriched cohort (continuous grey line) and the unscreened reference cohort (broken line). Unscreened cohort (I), (---); Screened selected cohort (II), (- - -); Screened enriched cohort (III), (---)

use by the patient. Second, it was not known whether the patients used blood pressure-lowering drugs as antihypertensives or for some other indication, such as β -blocking drugs for angina or ACE inhibitors for heart failure. This uncertainty regarding the diagnosis is less likely to be a problem for the other drug categories. Third, drug use is just one of the components of medicalization. For example, we are not aware of medical consumption in general, such as frequency of physician contacts, medical diagnostic procedures or life style changes.

A strength of our study is that it was possible 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 were able to provide data on a long period of follow-up (6.5 years). Third, the study was based on electronic drug-dispensing data from community phar-

macies. The computerized pharmacy database (from IADB) was used, which provides valid and reliable information on drug use. Previous studies have shown that dispensing data from Dutch pharmacies offer an accurate picture of the use of prescription drugs outside the hospital. The drug prescription data have been validated as a reliable form of information on drug use and have the advantage over patient histories, that the latter are hampered by recall bias [34, 35]. Moreover, in the Netherlands most drugs are delivered on prescription via the pharmacies, and a patient nearly always receives all drugs from the same pharmacy.

In conclusion, our data show that a screening programme to improve cardiovascular and renal outcome does not lead to a higher drug use than in an unscreened population. The data also show that targeted screening, i.e. screening in a cohort likely to be at higher risk,

contributes to greater drug use, but only in the drug classes expected and not in overall undue drug use.

Competing interests: None declared.

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