Purchases of prescription drugs before an alcohol-related death: a ten-year follow-up study using linked routine data

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Abstract

Background: Physician's intention to prescribe drugs could potentially be used to improve targeting of alcohol interventions and enhanced disease management to patients with a high risk of severe alcohol-related harm within outpatient settings. **Methods:** Comparison of ten-year incidence trajectories of 13.8 million reimbursed purchases of prescription drugs among 303,057 Finnish men and women of whom 7490 ultimately died due to alcohol-related causes (Alc+), 14,954 died without alcohol involvement (Alc-), and 280,613 survived until the end of 2007. **Results:** 5–10 years before death, 88% of the persons with an Alc+ death had received prescription medication, and over two-thirds (69%) had at least one reimbursed purchase of drugs for the alimentary tract and metabolism, the cardiovascular system, or the nervous system. Among persons with an Alc+ death, the incidence rate (IR) for purchases of hypnotics and sedatives was 1.38 times higher (95% confidence interval (CI):1.32,1.44) compared to those with an Alc- death, and 4.07 times higher (95%CI:3.92,4.22) compared to survivors; and the IR for purchases of anxiolytics was 1.40 times higher (95%CI:1.34,1.47) compared to those with an Alc- death, and 3.61 times higher (95%CI:3.48,3.78) compared to survivors. **Conclusions:** Using physician's intention to prescribe drugs affecting the alimentary tract and metabolism, cardiovascular system and nervous system could potentially be used to flag patients who might benefit from screening, targeted interventions or enhanced disease management. In particular, patients who are to be prescribed anxiolytics, hypnotics and sedatives, and antidepressants may benefit from enhanced interventions targeted to problem drinking.

Keywords: Alcohol, cohort study, mortality, outpatient, prescription drugs, problem drinking

1. Introduction

It has been shown that problem drinkers seek treatment more likely for somatic symptoms (Jackson et al. 1995, Nordström et al. 2008, Rehm et al. 2015), and for symptoms of mental health problems such as anxiety or depression than for problem drinking per se (Proude et al. 2006, Proodfoot and Teesson 2009, Edlund et al. 2012. As a result, even severe forms of problem drinking may go undetected in primary care (Paul et al. 2014).

The recommended procedure for identifying and treating problem drinking in primary health care settings is based on screening, brief interventions, and referral to treatment (SBIRT). However, SBIRT or its components are rarely implemented in primary care (Rehm et al. 2016). In particular, referral to treatment among those identified as problem drinkers is markedly low, generally being below 20% (Rehm et al. 2016). There is thus a need to develop methods that can improve early identification of problem drinking and referral to treatment among primary care patients.

Use of electronic health records and other routinely collected healthcare data provides an opportunity to develop automated data-mining based algorithms that can prompt and remind physicians and other healthcare personnel e.g. to implement SBIRT to high-risk patients. The fact that many of the common comorbidities among problem drinkers are managed by medication (Gossop et al. 2007, Smith and Book 2010) potentially provides an opportunity to improve detection of problem drinking if this information can be used as a flag for targeting alcohol interventions and enhanced disease management within outpatient settings more effectively. Therefore, the purpose of this study was to explore the feasibility and potential of using physicians' intention to prescribe drugs as a flag for screening problem drinking and targeting interventions and enhanced disease management for preventing severe alcohol-related health outcomes within outpatient healthcare settings i.e. within primary and secondary care settings. Using longitudinal linked routine data on reimbursements of prescription drugs, we aimed to establish incidence trajectories of prescription drugs over a ten-year period before death for problem drinkers who ultimately died due to alcohol-related causes. We used alcohol-related death as a retrospective marker of severe problem drinking.

We used those who died without established alcohol involvement as a reference group. Comparison against survivors will provide a general population baseline for reimbursement of prescription drugs over the study period.

2. Data and methods

2.1 Ethics statement

The sampling and data linkage were approved by the ethics committee of Statistics Finland (TK-53-1783-96).

2.2 Study population

The original register-based study population consists of an 11% random sample of the population living in Finland in 1987–2007. Because our focus was on the healthcare contacts of people who died, we collected an additional random sample of deaths occurring during the study period, altogether representing 80% of all deaths (the maximum permitted). Routine data from the nation-wide administrative registers of Statistics Finland (causes of death and sociodemographic factors) and the Social Insurance Institution of Finland (drug reimbursement) were linked to the study data. Statistics Finland carried out the sampling and data linkage using a unique personal identity code issued to all Finnish residents and available in the registers used in this study. All data were anonymized and de-identified by Statistics Finland prior to analyses.

We included Finnish men and women born in 1943–1977 who were aged 28–64 years at the time of death, or for survivors at the end of follow-up in 2005–07. Persons who immigrated or emigrated during the study period were excluded (n=9899, including 516 deaths). The final study data consisted of 303,057 individuals who either died from alcohol-related causes (“Alc+ deaths”, n=7490) or from other causes (“Alc- deaths”, n=14,954), or who survived (n=280,613).

2.3 Causes of death

We used the International Classification of Diseases tenth revision (ICD–10) Finnish modification codes to identify causes of death. Web Table S1 shows the ICD–10 codes we used in identifying alcohol-related deaths, and the distribution of alcohol-related causes of deaths in our data. In addition to underlying causes of death we used also contributory causes to identify e.g. deaths with alcohol intoxication or dependence as a contributing factor. Among those who died due to alcohol-related causes, the three most common causes of death were mental and behavioral disorders related to alcohol (n=3006, 40%), alcoholic diseases of the stomach, liver and pancreas (n=3031, 40%), and accidental poisoning by and exposure to alcohol (n=1101, 15%). Among the other deceased the three most common causes of death were cancer (n=6032, 40%), diseases of the circulatory system (n=4246, 28%), and external causes (n=2206, 15%).

2.4 Reimbursements for prescription drugs

All permanent residents of Finland are covered under the National Health Insurance (NHI) scheme, which provides partial reimbursement for the cost of outpatient drugs prescribed by a physician. By using the information recorded in the NHI register all purchases of reimbursed prescription drugs (drug purchases) among the study population were traced back for a period of ten years before death/end of follow-up. We used the Anatomical Therapeutic Chemical (ATC) classification to categorize the drugs (Anatomical Therapeutic Chemical classification system). Diagnoses of the conditions for which the drugs were prescribed for were not available. There were 13.8 million medication reimbursements during the ten-year follow-up in our data.

2.5 Statistical analyses

We compare cumulative incidence rates for drug purchases over the 10-year period before death/end of follow-up. Incidence rate ratios (IRR) are presented with their 95% confidence intervals. We used generalized estimating equations (GEE) to estimate the average annual number of purchases of prescription drugs, while adjusting for the effects of sex and age at death/end of follow-up. This method also adjusts the standard errors for the within-subject clustering of data over repeated measurements. The results from these

models are presented as estimated marginal means with their 95% confidence intervals. SAS/STAT software's GENMOD procedure was used to perform the GEE analyses.

3. Results

Men were overrepresented among those who ultimately died due to alcohol-related causes (82% men among Alc+ deaths) and among those who died without alcohol involvement (64% men among Alc- deaths), compared to survivors (50% men). The mean age of death among those with an Alc+ death was 51.9 years (SD=7.7) and 53.8 years (SD=7.8) among those with an Alc- death. The mean age at the end of follow-up among survivors was 46.6 years (SD=10.2).

3.1 Purchases of prescription drugs

The majority (88%) of the persons with an Alc+ death had purchased prescription drugs at least once during 5 to 10 years before death (Figure S1), and had thus been in contact with the healthcare system already several years before death. There was no difference between Alc+ deaths, Alc- deaths and survivors in the cumulative proportion of persons who had purchases any prescription drugs. However, the level of use of prescription drugs differed across these three groups. The mean annual number of purchases showed that those with an Alc+ death (mean=10.1; 95%CI: 9.8-10.5), and Alc- death (mean=12.6; 95%CI:12.3-12.9) purchased on average over two-times more prescription drugs compared to survivors (mean=3.8; 95%CI:3.7-4.0), when sex and age at death/end of follow-up were adjusted for.

3.2 What type of drugs were purchased?

Prescription drugs from the ATC categories A (alimentary tract and metabolism), C (cardiovascular system), and N (nervous system) were relatively more common among those with an Alc+ death and Alc- death compared to survivors (Table S2). Drugs from the category N were most common among Alc+ deaths: 74% of them had at least one purchase of drugs from the category N during the follow-up, compared to 69% among Alc- deaths and 38% among the survivors. The proportion that category N drugs made of all reimbursed drug purchases in these three groups was 40% (307,535/773,682) among Alc+ deaths, 29% (585

849/2,032,613) among Alc- deaths, and 19% (2,045,945/11,034,694) among survivors. Overall, purchases from the categories A, C and N in the three groups represented 70%, 62% and 44% of all purchases. Based on these findings, we focused our further analyses on categories A, C and N.

3.3 Opportunities to identify at-risk problem drinkers

To assess the feasibility of using drug prescription information in outpatient settings, it is important to know whether a sufficiently large proportion of persons in the target population can be theoretically identified and reached before their illness has progressed beyond its optimum intervention stage. For this purpose, Figure 1 shows cumulative incidence trajectories for the most common prescription drugs within the selected three ATC first level categories (A, C, N). We used the period 5 to 10 years before death to represent early intervention opportunities and the period 1 to 4 years before death to represent late intervention opportunities.

[Figure 1]

The most common drugs prescribed within the category A were anti-acid preparations and drugs for treating diabetes (Figure 1, panels A–C). About one-third of those with an Alc+ death had been prescribed drugs for the alimentary tract and metabolism by the fifth year before death (panel C).

The most common drugs prescribed in the category C were blood pressure lowering agents and beta-blockers (panels D–F). About one-third of those with an Alc+ death had been prescribed drugs for the cardiovascular system by the fifth year before death (panel F).

The previously noted high proportion of drugs from the category N among those with an Alc+ death compared to others, was mainly attributable to anxiolytics, hypnotics and sedatives, and antidepressants (panels J–L). By the fifth year before death 47% (95%CI:46,49; panel M) of the persons with an Alc+ death had been prescribed one of these drugs at least once, which was more than among those with an Alc- death (34%, 95%CI:34,36) or among survivors (18%, 95%CI:17-18).

All in all, of the persons with an Alc+ death about 69% (95%CI:68,70) had at least one prescription for drugs from categories A, C or N by the fifth year before death (panel O), which did not differ from those with an Alc- death (67%, 95%CI:66,68), but was higher than among survivors (44%, 95%CI:44,45).

3.4 Category N drugs

To quantify the difference in incident purchases of anxiolytics, hypnotics and sedatives, and antidepressants, Table 1 shows the incidence rate ratios (IRR) for these three ATC category N drugs among those with an Alc+ death, Alc- death, and survivors. Compared to survivors, the crude incidence rate among those with an Alc+ death was over three times higher for anxiolytics (IRR=3.61, 95%CI: 3.48, 3.75) and four times higher for hypnotics and sedatives (IRR=4.07, 95%CI: 3.92, 4.22). Furthermore, compared to those with an Alc- death, those with an Alc+ death had 40% higher (IRR=1.40, 95%CI: 1.34, 1.47) incidence rate for anxiolytics, and 38% higher (IRR=1.38, 95%CI: 1.32, 1.44) for hypnotics and sedatives.

[Table 1]

To provide further insight of the high incident prescriptions of anxiolytics, hypnotics and sedatives, and antidepressants we listed the generic drug names of the most frequently purchased drugs within these categories among those with an Alc+ death (Figure 2). These listed drugs represented 80% (95%CI:79,80) of all reimbursed purchases within the ATC category N among those with an Alc+ death, which was higher than among those with an Alc- death (72%, 95%CI:71,72) and among survivors (67%, 95%CI:67,68). The most commonly prescribed benzodiazepines (diazepam, chlordiazepoxide, oxazepam, alprazolam, and temazepam) and benzodiazepine related drugs (zopiclone) alone represented 63% (95%CI:63,64) of these purchases among those with an Alc+ death, which also was higher than in the other groups (56%, 95%CI:56,57 and 43%, 95%CI:43,44; respectively). Selective serotonin reuptake inhibitors (fluoxetine and citalopram) represented 12% (95%CI:12,13) of all category N drug purchases among those with an Alc+ death as well as among those with an Alc- death, which was less than among survivors (20%, 95%CI:19,20).

[Figure 2]

The number of purchases of drugs specifically developed for preventing relapse after detoxification, such as disulfiram (2425 purchases over the 10 year period) and naltrexone (26 purchases over the 10 year period) among those with an Alc+ death were very low (see Table S3 for a detailed listing of purchases of individual drugs in ATC N category).

4. Discussion

4.1 Summary of main findings

We established the cumulative incident trajectories of reimbursed purchases of prescription drugs over a ten-year period before death among those who ultimately died due to alcohol-related causes in order to assess the feasibility of using information on drug prescriptions in outpatient settings as a potential signal to the physician or other healthcare personnel to target enhanced disease management for preventing severe alcohol-related health outcomes. Based on prescription data, 88% of those who ultimately died due to alcohol-related causes were in contact with a physician in outpatient settings in the period 5 to 10 years before death and 69% were prescribed drugs from three ATC categories, namely drugs prescribed for alimentary tract and metabolism, cardiovascular system, and nervous system. Furthermore, even compared to those who died without alcohol involvement, purchases of anxiolytics, hypnotics and sedatives, and antidepressants were more common among those who ultimately died due to alcohol-related causes. Compared to the general population (survivors) the ten-year combined cumulative incidence rate for these drugs was over two times higher among those who ultimately died due to alcohol-related causes. The largest, a four-fold, difference was seen for hypnotics and sedatives. Benzodiazepines were the single most common group of prescription drugs and zopiclone the single most common drug purchased among those who ultimately died due to alcohol-related causes.

4.2 Methodological considerations

The advantage of this nation-wide register-based retrospective study was that it enabled us to capture 80% of all deaths that occurred in the Finnish general population during the study period, i.e. the data included nearly the full population of men and women who died at ages 28–64. Because all information came from administrative registers, self-report or non-response bias did not affect our results.

The retrospective longitudinal design with information retrieved for each study year enabled us to establish group-level trajectories of incident purchases of prescription drugs for 10 years before death/end of follow-up. Our prescription data captured all outpatient settings, including primary and secondary care, but not drugs delivered during hospital inpatient visits. Our analyses focused on information on purchases of prescription drugs that were reimbursed by the Finnish NHI scheme and were thus recorded in the reimbursed prescription drugs register. This register covers the majority of prescription drugs used to treat various illnesses, but excludes some drugs that have not been approved by the Pharmaceuticals Pricing Board of the Finnish Ministry of Social Affairs and Health. Purchases of over-the-counter drugs are not reimbursed and therefore not included in the register. The reimbursement data available for this study was limited to years 1987-2007, which means that potential changes in prescription practices after 2007 were not captured by our data. Future research should aim to replicate these finding with a more recent data.

Our target population was problem drinkers who are at risk of experiencing severe alcohol-related health outcomes. However, because we used information on alcohol-related deaths in order to retrospectively define problem drinking status, we were not able to identify persons with less severe forms of problem drinking who may have different profiles and trajectories of drug prescriptions during their life course.

An important limitation of our data is that we did not have information on the diagnoses of the conditions which the drugs were prescribed for. Therefore we were not able to distinguish the patients treated for problem drinking. Taking into account that e.g. many of the ATC category N drugs prescribed to those who ultimately died due to alcohol-related causes are commonly used to treat alcohol dependence and symptoms of alcohol withdrawal (Wackernah et al. 2014, Zindel and Kranzler 2014, Mirijello et al. 2015), it is likely that some of these persons were identified as problem drinkers at the time of prescribing these drugs.

The potential confounding effect of this can be evaluated against the current evidence on treatment rates among problem drinkers in primary care settings. Despite of evidence-based guidelines and recommendations for implementing SBIRT in primary care, physicians implement alcohol interventions or refer problem drinkers to specialist care relatively rarely. Referral rates for problem drinkers identified in primary care settings are generally below 20% (Rehm et al. 2016). The paucity of current levels of

implementing SBIRT, whether screening, providing brief interventions, or referring high-risk patients to specialist care, therefore indicates that problem drinking needs to be managed much more effectively in primary care settings. In other words, even if some of those defined as problem drinkers in our study were identified as problem drinkers, it is likely that at group level the treatment of these problem drinkers could have been improved e.g. by providing an automated prompt to physicians to implement SBIRT based on their intention to prescribe drugs affecting the nervous system.

4.3 Interpretation of main results

We identified three ATC 1st level groups of purchased prescription drugs more characteristic to problem drinkers than to the general population, namely alimentary tract and metabolism, cardiovascular system, and nervous system. Problem drinking is known to have direct adverse effects on these organ groups (Room et al. 2005), and additionally, well-known co-morbidities of problem drinking are represented in them, e.g. depression (Boden and Fergusson 2011) and hypertension (Rehm et al. 2016). Also drugs from categories such as anti-infectives for systemic use, musculo-skeletal system, and respiratory system were commonly purchased by problem drinkers. While this indicates additional co-morbidities among problem drinkers, and thus additional opportunities for identifying problem drinkers, these drug categories were not similarly characteristic to problem drinkers as were drugs prescribed for alimentary tract and metabolism, cardiovascular system, and nervous system.

Our finding that the incidence rates for purchases of anxiolytics, hypnotics and sedatives, and antidepressants were higher among those who ultimately died due to alcohol-related causes compared to general population or those who died without alcohol involvement, may reflect the fact that these drugs are commonly used to treat e.g. symptoms of alcohol withdrawal.

Our results add to the existing evidence (Gossop et al. 2007) by showing that the contact with healthcare among persons at risk of severe alcohol-related harm occurs several years before death. We used the time period five to ten years before death to indicate opportunities for early detection of problem drinking and opportunities for enhanced disease management aimed to prevent disease progression. Based on that cutoff, over two-thirds of those who ultimately died due to alcohol-related causes could have been reached for

screening, intervention, and enhanced patient management based on physicians' intention to prescribe drugs from the above mentioned three ATC categories. This finding together with an earlier Finnish study on hospital admissions among those who later died from alcohol-related causes (Paljärvi et al. 2016) show that persons at risk of severe problem drinking were within the reach of health system for preventive interventions early on during their life-course.

Perhaps the most important finding of our study is that the patients at risk of severe alcohol-related health outcomes used prescription drugs for which asking about patient's history of alcohol consumption is clinically relevant and medically justified (Ilomäki et al. 2013). In other words, the implication of these results to the physician prescribing drugs for alimentary tract and metabolism, cardiovascular system, and nervous system is that asking about patient's alcohol consumption when intending to prescribe these drugs, is not only relevant in relation to treating and managing the patient's current disease but also in terms of preventing future severe alcohol-related harm.

4.3.1 Implications of types of drugs prescribed

Our results can be put into context by contrasting the drug purchase data against the recommendations for treating alcohol use disorders (AUDs). Drugs used to treat AUDs come mainly from the groups of antiepileptics, antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants. It should be noted that because we did not have access to the diagnoses used to prescribe these drugs, we do not know whether these drugs were e.g. prescribed to treat primary depression or anxiety, or to treat primary AUD.

Depending on the severity of symptoms, co-morbidities and the stage of treatment, different drugs are indicated for treating symptoms of AUDs. In our data, the most commonly purchased drug among problem drinkers was zopiclone, which is a non-benzodiazepine hypnotic with an indication of managing alcohol withdrawal-related insomnia (Arnedt et al. 2007). Problem drinkers also frequently purchased long-acting benzodiazepines (e.g. chlordiazepoxide and diazepam), which are the recommended first-line treatment for symptoms of alcohol withdrawal during detoxification (Amato et al. 2010). However, problem drinkers also frequently bought short-acting benzodiazepines (e.g. oxazepam and alprazolam). This may be explained by the fact that short-acting benzodiazepines are recommended over long-acting ones among patients with liver

problems (Addolorato et al. 2016); and deaths due to alcohol-related liver diseases were relatively common in our data.

Anticonvulsants/antiepileptics can be used in treating symptoms of alcohol withdrawal (e.g. carbamazepine, clonazepam and valproic acid), but the total number of problem drinkers who purchased these drugs over the ten-year period before death was low compared to anxiolytics, and hypnotics and sedatives. Similarly, problem drinkers purchased neuroleptics/antipsychotics that can be used e.g. to treat alcohol withdrawal-related hallucinations or to reduce alcohol craving, but the number of persons using these drugs was also low. Therefore, based on the purchases of the drugs and the patterning of purchases of these drugs, it can be speculated that these problem drinkers were potentially treated mainly for mild to moderate symptoms of alcohol withdrawal and/or AUD between five to ten years before death.

Among AUD patients, antidepressants are commonly prescribed with the aim of reducing alcohol drinking (Zindel and Kranzler 2014). The two most frequently purchased antidepressants among those who ultimately died due to alcohol-related death were selective serotonin reuptake inhibitors (SSRIs), and both of these (fluoxetine and citalopram) have showed modest efficacy in treating patients with AUD and co-morbid depression (Zindel and Kranzler 2014). However, it has been suggested that antidepressants should not be used as a stand-alone treatment but should be combined with drugs specifically developed to reduce drinking, such as naltrexone (Nunes and Levin 2004, Pettinati et al. 2010). Our data showed that purchases of naltrexone (and disulfiram) were practically non-existent over the ten-year period before death among problem drinkers. This may reflect physicians' tendency to prefer other types of drugs over alcohol-specific drugs as was shown in the US among substance abuse specialist who preferred prescribing antidepressants over naltrexone and disulfiram (Mark et al. 2003). Another potential explanation to this finding is again the relatively high prevalence of alcohol-related deaths due to liver diseases among problem drinkers in our data. Disulfiram and naltrexone can induce liver injury or increase the risk of liver failure among patients with alcoholic liver disease (Addolorato et al. 2016). However, the finding of very low use of alcohol-specific drugs warrants further investigation in order to establish why AUD treatment-specific drugs were not used (prescribed or purchased) among those problem drinkers who ultimately died due to alcohol-related causes

(Mark et al. 2003). This requires access to detailed medical histories of these patients, which we did not have.

5. Conclusions

Our results suggest that using information of physician's intention to prescribe drugs in particular for alimentary tract and metabolism, cardiovascular system, and nervous system can potentially be used to prompt physicians, or other qualified healthcare personnel, to take a more detailed medical history in relation to problem drinking and in relation to risk factors for progression of problem drinking. In particular, patients presenting with conditions indicating use of anxiolytics, hypnotics and sedatives, and antidepressants are likely to benefit from enhanced screening and targeted interventions on problem drinking in outpatient healthcare settings (Gossop et al. 2007). Together with earlier evidence from hospital settings (Paljärvi et al. 2016), these results from outpatient settings show that the prevention of severe alcohol-related harm among treatment seeking population calls for improved alcohol screening and disease management across health care settings, for example by developing automated electronic health records based applications aimed to improve the uptake of alcohol SBIRT.

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Figure legends

Figure 1. Cumulative incidence of reimbursed purchases of drugs affecting the alimentary tract and metabolism, the cardiovascular system, and the nervous system (panels A to O) separately for those who ultimately died due to alcohol-related causes, those who died without alcohol involvement, and for the survivors during the ten-year period before death/end of follow-up. Individual drug groups shown in the panels are the most common drugs prescribed within their respective ATC 1st level category.

Figure 2. Drugs with most reimbursed purchases listed by name (ATC code in the parenthesis). Proportion (%) that these drugs make of all purchases within the category of anxiolytics, hypnotics and sedatives, and antidepressants among those who had at least one such purchase during the follow-up period, separately for those who died due to alcohol-related causes, those who died with alcohol involvement, and for the survivors. Error bars represent the 95% confidence interval.

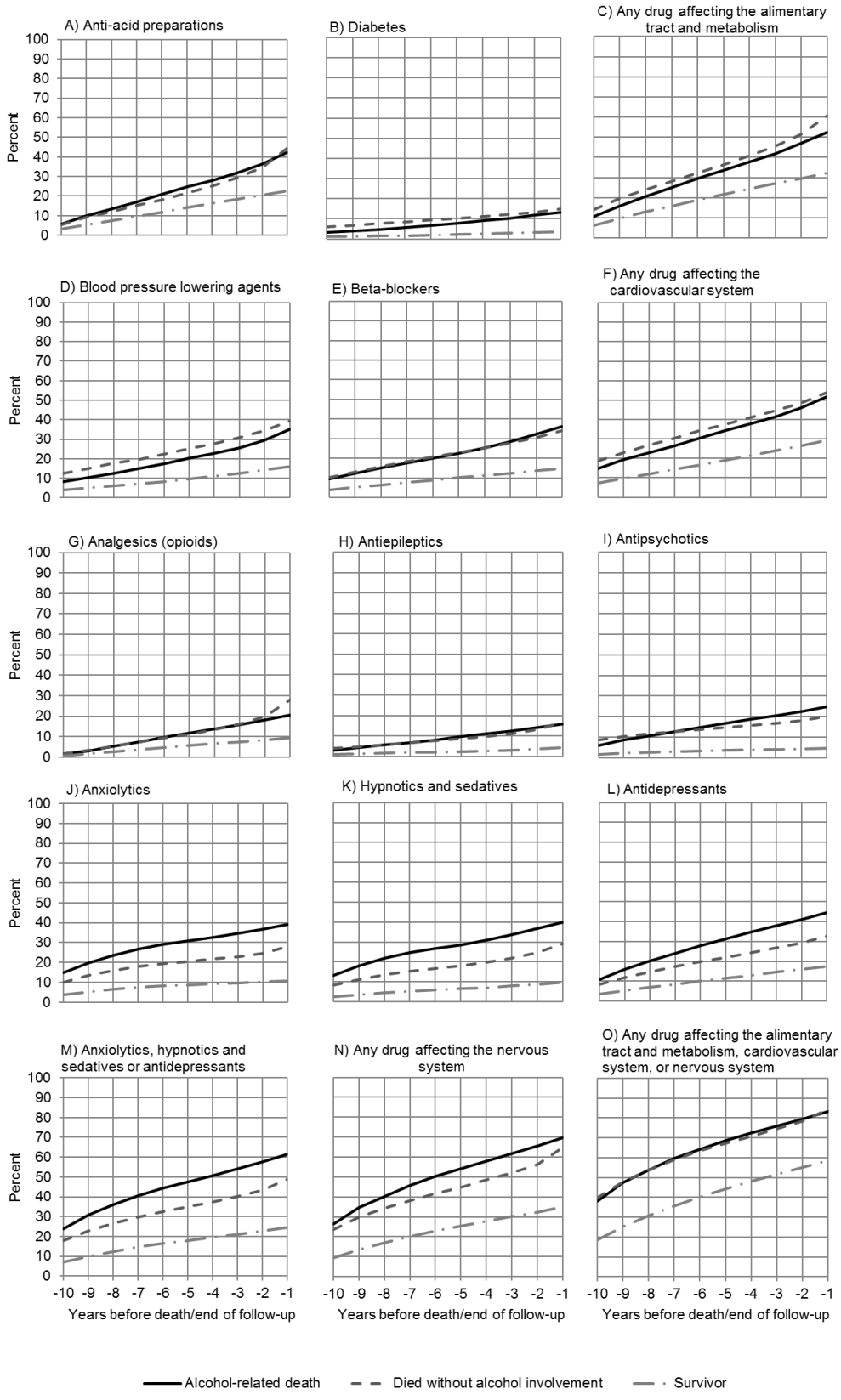
A) Anti-acid preparations
B) Diabetes
C) Any drug affecting the alimentary tract and metabolism
D) Blood pressure lowering agents
E) Beta-blockers
F) Any drug affecting the cardiovascular system
G) Analgesics (opioids)
H) Antiepileptics
I) Antipsychotics
J) Anxiolytics
K) Hypnotics and sedatives
L) Antidepressants
M) Anxiolytics, hypnotics and sedatives or antidepressants
N) Any drug affecting the nervous system
O) Any drug affecting the alimentary tract and metabolism, cardiovascular system, or nervous system
Percent
0 10 20 30 40 50 60 70 80 90 100
-10 -9 -8 -7 -6 -5 -4 -3 -2 -1
Years before death/end of follow-up
Alcohol-related death
Died without alcohol involvement
Survivor

Figure 1.

Table 1. Incidence rates and their 95% confidence intervals (CI) for anxiolytics, hypnotics and sedatives, and antidepressants over the ten-year follow-up period separately for those who died due to alcohol-related causes, those who died without alcohol involvement, and survivors, and the incidence rate ratios (IRR) compared to survivors.

	Cases	Total population	Incidence per 100 persons (95%CI)	IRR[a] (95%CI)	IRR[b] (95%CI)
Anxiolytics					
Alcohol-related deaths	2940	7490	39.3 (37.9, 40.7)	3.61 (3.48, 3.75)	1.40 (1.34, 1.47)
Deaths without alcohol involvement	4190	14954	28.0 (27.2, 28.9)	2.58 (2.50, 2.66)	1.00
Survivors	30490	280613	10.9 (10.7, 11.0)	1.00	0.39 (0.38, 0.40)
Hypnotics and sedatives					
Alcohol-related deaths	2999	7490	40.0 (38.6, 41.5)	4.07 (3.92, 4.22)	1.38 (1.32, 1.44)
Deaths without alcohol involvement	4345	14954	29.1 (28.2, 29.9)	2.95 (2.86, 3.05)	1.00
Survivors	27623	280613	9.8 (9.7, 9.9)	1.00	0.34 (0.33, 0.35)
Antidepressants					
Alcohol-related deaths	3339	7490	44.6 (43.1, 46.1)	2.56 (2.47, 2.65)	1.36 (1.30, 1,42)
Deaths without alcohol involvement	4920	14954	32.9 (31.9, 33.8)	1.89 (1.84, 1.95)	1.00
Survivors	48813	280613	17.4 (17.2, 17.6)	1.00	0.53 (0.51, 0.54)
Anxiolytics, hypnotics and sedatives, or antidepressants					
Alcohol-related deaths	4592	7490	61.3 (59.6, 63.1)	2.49 (2.41, 2.56)	1.25 (1.21, 1.30)
Deaths without alcohol involvement	7331	14954	49.0 (47.9, 50.2)	1.99 (1.94, 2.04)	1.00
Survivors	69194	280613	24.7 (24.5, 24.8)	1.00	0.50 (0.49, 0.51)

a) Survivors as a reference category; b) Those who died without alcohol involvement as a reference category

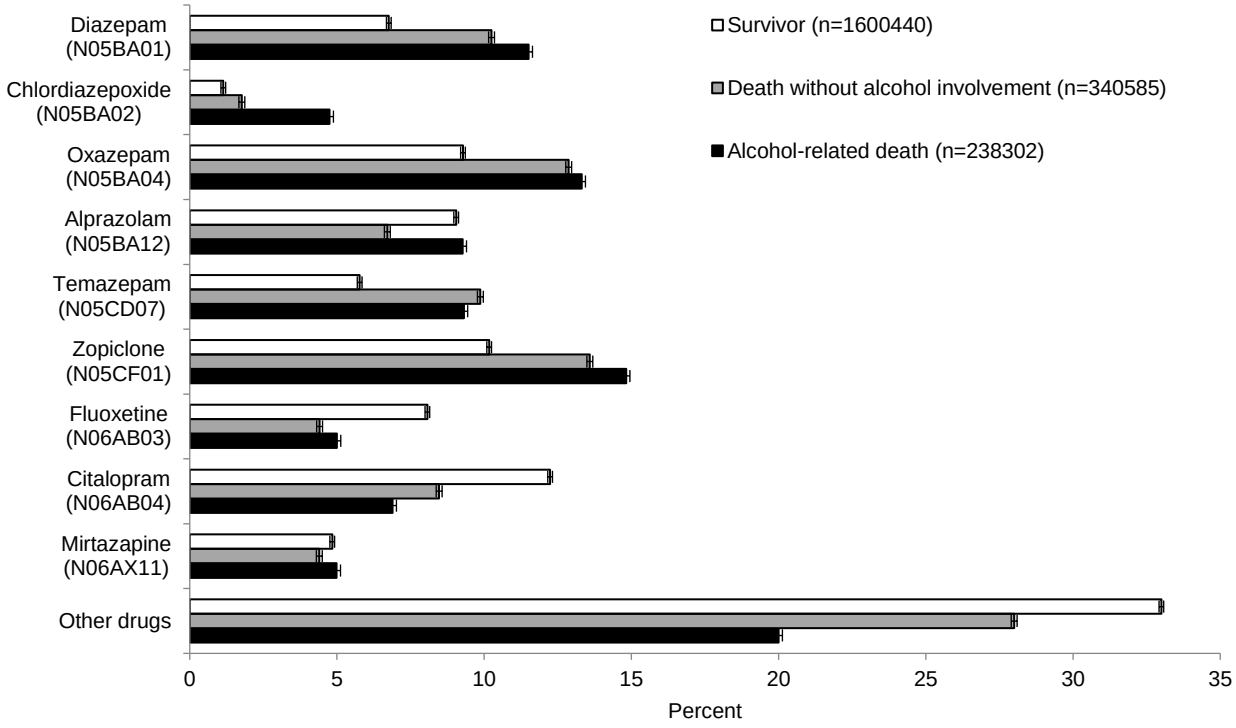
Diazepam (N05BA01)
Chlordiazepoxide (N05BA02)
Oxazepam (N05BA04)
Alprazolam (N05BA12)
Temazepam (N05CD07)
Zopiclone (N05CF01)
Fluoxetine (N06AB03)
Citalopram (N06AB04)
Mirtazapine (N06AX11)
Other drugs
Survivor (n=1600440)
Death without alcohol involvement (n=340585)
Alcohol-related death (n=238302)
0
5
10
15
20
25
30
35
Percent

Figure 2.