SCANDINAVIAN JOURNAL OF PRIMARY HEALTH CARE, 2016
VOL. 34, NO. 3, 215–223
http://dx.doi.org/10.1080/02813432.2016.1207138

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS

Can routine information from electronic patient records predict a future diagnosis of alcohol use disorder?

Torgeir Gilje Lid[a,b,c], Geir Egil Eide[a,d], Ingvild Dalen[e] and Eivind Meland[a]

[a]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; [b]Research Unit for General Practice, Uni Health, Uni Research, Bergen, Norway; [c]Centre for Alcohol and Drug Research, Stavanger University Hospital, Stavanger, Norway; [d]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway; [e]Department of Research, Stavanger University Hospital, Stavanger, Norway

ABSTRACT

Objective: To explore whether information regarding potentially alcohol-related health incidents recorded in electronic patient records might aid in earlier identification of alcohol use disorders.
Design: We extracted potentially alcohol-related information in electronic patient records and tested if alcohol-related diagnoses, prescriptions of codeine, tramadol, ethylmorphine, and benzodiazepines; elevated levels of gamma-glutamyl-transferase (GGT), and mean cell volume (MCV); and new sick leave certificates predicted specific alcohol use disorder.
Setting: Nine general practitioner surgeries with varying size and stability.
Subjects: Totally 20,764 patients with active electronic patient record until data gathering and with a history of at least four years without a specific alcohol use disorder after turning 18 years of age.
Methods: The Cox proportional hazard analysis with time-dependent covariates of potential accumulated risks over the previous four years.
Main outcome measures: Time from inclusion until the first specific alcohol use disorder, defined by either an alcohol specific diagnostic code or a text fragment documenting an alcohol problem.
Results: In the unadjusted and adjusted Cox-regression with time-dependent covariates all variables were highly significant with adjusted hazard ratios ranging from 1.25 to 3.50. Addictive drugs, sick leaves, GGT, MCV and International Classification for Primary Care version 2 (ICPC-2), and International Classification of Diseases version 10 (ICD-10) diagnoses were analyzed. Elevated GGT and MCV, ICD-10-diagnoses, and gender demonstrated the highest hazard ratios.
Conclusions: Many frequent health problems are potential predictors of an increased risk or vulnerability for alcohol use disorders. However, due to the modest hazard ratios, we were unable to establish a clinically useful tool.

KEY POINTS

- Alcohol is potentially relevant for many health problems, but current strategies for identification and intervention in primary health care have not been successful.
- Many frequent clinical problems recorded in electronic patient records may indicate an increased risk for alcohol related health problems.
- The hazard ratios were modest and the resulting predictive model was unsatisfactory for diagnostic purposes. If we accepted a sensitivity as low as 0.50, the specificity slightly exceeded 0.75. With a low prevalent condition, it is obvious that the false positive problem will be vast.
- In addition to responding to elevated blood levels of liver enzymes, general practitioners should be aware of alcohol as a potentially relevant factor for patients with repeated events of many mental and psychosocial diagnoses and new sick leaves and repeated prescriptions of addictive drugs.

ARTICLE HISTORY
Received 9 September 2015
Accepted 27 March 2016

KEYWORDS
Alcohol-related disorders; computerized patient records; early diagnosis; general practice; Norway

Introduction

General practitioners (GPs) as health care providers for the general public are important actors in dealing with alcohol-related health problems.[1] The link between alcohol consumption and numerous health problems is strong, and earlier identification of risky or harmful drinking is regarded essential, both in public health terms and for the individual patient.[2–4] The preferred

CONTACT Torgeir Gilje Lid giljelid@gmail.com Rasmus Risas Gate 54, N-4015 Stavanger, Norway

method for identification and treatment of risky or harmful drinking has, for the past decades, been screening and brief intervention (SBI), but important questions concerning the effectiveness of SBI in routine health care settings remain unanswered.[5,6] Furthermore, recent large scale implementation studies have failed to show effect.[7–9]

However, it is known that GPs regard dealing with alcohol-related health problems a legitimate part of their responsibility.[10–13] The recent recognition of the lack of robust evidence for SBI in routine health care settings necessitates further research. Recently, approaches based on clinical relevance instead of screening measures have been studied.[14–16] Health incidents or changes in the patient's life are used as indicators of potential relevance for addressing alcohol. These have been coined as pragmatic case finding [14] or semi-systematic method,[15] they not only focus primarily on clinical signs, but also focus on targeted screening in some routine situations. These strategies focus on the present clinical situation and the awareness that alcohol may be relevant for a patient's health, both as a possible cause and as a complicating factor for their health problems. GPs struggle with asking about alcohol out of context, as in general screening, but asking based on potential relevance in a specific clinical situation is probably a better foundation for interventions.[17,18]

In general practice, the patient records will often contain information gathered through many years. Almost all GPs in Norway use electronic patient records (EPR), but the systems are not highly functional in systematizing relevant information.[19] Not only the patient's present health problem, but also previous incidents may indicate relevance for talking about alcohol.

The aim of this study was to explore whether information regarding potentially alcohol-related health incidents recorded in EPRs might aid in earlier recognition of alcohol related health problems.

Design, methods, and material

Nine GP surgeries in the Stavanger region in south west of Norway were recruited. They were chosen on the basis of maximal variety in size (1–7 doctors) and stability (high turnover to high stability), and all had applied EPR for at least 10 years. The total number of doctors was 36. All 20,764 patients with an active EPR (alive and registered with a doctor the month prior to data gathering) were included. Gender, year of birth, name of registered doctor and surgery were registered, and the patients were given a unique, non-reversible eight-digit code with letters and numbers. After completion of data gathering, the eight-digit code was replaced and the patients were consecutively numbered. Doctors and surgeries were also numbered.

A vast majority of GP surgeries in the region at that time used the same EPR system, and a computer program designed to extract data from records in this system was made. We tested a pilot version of the computer program in the largest surgery during March 2011, and then an automatized version was tested and applied a few months later.

We extracted data that might be alcohol-related to test these data against comprehensive alcohol use disorder (c-AUD) as endpoint. C-AUD was defined as either an alcohol use disorder (AUD) according to ICPC-2 or ICD-10 [3,4] or a text fragment (AUD text fragment) documenting that an alcohol problem was dealt with. In Norway, ICPC-2 is applied in general practice, whereas the specialized health care system applies ICD-10. ICD-10-diagnoses for AUD were translated to ICPC-2 in 2010 applying standardized tables,[20] in order to identify ICPC-2-diagnoses for AUD. The diagnostic codes in ICD-10 are more specific (three to four figures) compared to ICPC-2 (two figures), thus to retain the specificity of AUD in ICD-10 we used the corresponding ICPC-2-code solely if "alcohol" was included in the text-field of the ICPC-2-diagnosis. See Appendix A for all diagnoses included in AUD.

Clinical experience indicates that the threshold for identifying an AUD with a formal diagnosis may be high in general practice. We wanted to include as outcome situations where an AUD was documented in the running text of the EPR, but where no formal diagnosis was made. We identified the word "alcohol" in the running text, either alone or as a compound word (in Norwegian compound words are frequently used when the English expression would contain two or three words, e.g., *"alkoholmisbruk"*, English: alcohol abuse). Compound words highly indicative of an AUD were defined as an AUD text fragment. All versions of compound words containing "alcohol" were assessed manually and either defined as an AUD text fragment or not. The validity of this AUD text fragment was tested by performing a second data collection in one surgery to explore the context of the AUD text fragment by manually assessing a 12 word text fragment with the compound word with "alcohol" in the middle. This was done for a three-year period (January 2001 to December 2003) in one of the surgeries of medium size. We found 102 fragments which had been defined as AUD text fragments, and for 20 of these (20%) it

was evident that the alcohol problem in question was someone else's, most frequently a parent. We also identified 171 text fragments with "alcohol" originally not identified as an AUD text fragment. Of these, as many as 105 (60%) dealt with a real alcohol problem for the patient. Many of the patients had several such text fragments. This suggests that our method of defining an AUD text fragment is more prone to underestimate than overestimate the prevalence of an AUD.

The term c-AUD was defined as either an AUD or an AUD text fragment or both and used as outcome for the analyses. Censoring date was defined as the first of the month prior to data gathering, or the last predictor event if more recent. Start of follow-up ($t = 0$) for all patients were defined after an observation period of four years free from c-AUD in the record.

Predictors were firstly potentially alcohol-related ICD-10-diagnoses with attributable fractions larger than 0.3.[3,4] These diagnoses were translated to ICPC-2, with a consequently lower precision level due to the wider categories of ICPC-2. We included other ICPC-2-diagnoses where there is evidence of a potential causal relation with alcohol consumption.[15,21,22] See Appendix A for all diagnoses used as predictor events. Other predictors were number of new sick leaves, non-narcotic controlled substances (class B-drugs in Norway) and elevated blood levels for GGT and MCV.[23–26] A new sick leave was defined as a full time (not partial) sick leave with at least 16 days since a previous sick leave. Class B-drugs were the non-narcotic controlled substances codeine, tramadol, ethylmorphine, and benzodiazepines, including z-drugs. Gender was included as predictor.

All patients had a total history of 4–21 years, and all had an active patient record until data collection. For patients with a record prior to the age of 18, their observation period started from 1 January, the year they turned 18. Observations stopped at the age of 80 years. All readable data in the EPRs were scanned by the program, including incoming reports.

Statistical methods

For descriptive statistics, we used mean, median, and range. Correlations were estimated by Spearman's rho.[27] Time from inclusion to c-AUD was analyzed applying the Cox proportional hazards model [28] including time-dependent covariates.[29,30] The covariate values were updated at each time point for the following types of predictor events: B-drugs, new sick leaves, elevated blood levels for GGT and MCV, alcohol-related ICPC-2 and ICD-10 diagnoses. Thus, the following variables were included in the Cox-regression models: gender, number of new sick leaves, number of prescriptions of class B drugs, number of elevated GGT and MCV levels, number of alcohol-related ICD-10 diagnoses and number of alcohol-related ICPC-2 diagnoses.

To do the analyses, the data file was organized in long format with one line per event date and varying number of lines per patient. Both simple and multiple Cox-regression were run. Results are reported as unadjusted and adjusted hazard ratios (HR), respectively, with 95% confidence intervals (CI) and p values from Wald tests. The analyses were done using Stata 13 (College Station, TX) and all predictors were reported per 10 predictor events. We excluded from the model predictor events more than four years prior to the present predictor event.[31] Predictor events prior to $t = 0$ were summed up and added to the events, however they were also gradually excluded during the first four years after $t = 0$.

From the final multiple Cox-regression model, a prognostic index was defined equal to the fitter linear predictor equation in the model. Receiver operator characteristics (ROC) of this index was evaluated against the patients' c-AUD status four years after each update of the index (i.e., new predictor event) by calculating sensitivity and specificity and plotting the corresponding ROC curve.[27]

Results

The 20,764 patients, 43% of which were males, had follow-up times of up to 17.0 years after $t = 0$, with a median of 12.5 years (Table 1). The maximum number of events for each predictor is very high, though the medians are low, demonstrating that most patients have a small number of events for each predictor. 2.9% of the patients had a positive end point (c-AUD), of which 53.3% male. When splitting up, we found that 43% of these had an AUD (1.3% of all patients, 67.9%

Table 1. Descriptive statistics for $n = 20{,}764$ patients from nine general practice surgeries in the Stavanger area in Norway accrued from March to August of 2011.

Variables	Mean	Median	Range
Follow-up time, years	6.5	12.5	0.0–17.0
Age at start of follow-up, years	43.4	42.0	22–79
Born	1956	1957	1916–1988
No. of predictor events			
Class B drugs	28.6	5	0–774
New sick leave	5.9	3	0–143
Elevated laboratory test	0.7	0	0–66
ICD-10-diagnoses	0.3	0	0–50
ICPC-2-diagnoses	2.4	1	0–130
Cumulative predictor events	37.8	16	0–870

Abbreviations: ICD-10: International Classification of Diseases, version 10; ICPC-2: International Classification of Primary Care, version 2.

male), whereas 57% had only AUD text fragment (1.6% of all patients, 41.1% male).

In the simple Cox-regression, all variables were significant, and only class B prescriptions and gender had an HR lower than 2 per 10 events (Table 2). In the adjusted Cox-regression the HR was highest for elevated blood tests for GGT and MCV with 3.5 per 10 events, and just below 2 for ICD-10 diagnoses, gender, and new sick leaves. All variables were highly significant. The lowest estimates were class B drugs and ICPC-2 diagnoses.

We made a prognostic index from all significant regression coefficients in the adjusted model. ROC of this index compared to status four years later gave a fairly modest area under the curve (AUC) of 0.72 (Figure 1).[32,33] The curve reveals that with a sensitivity of 0.5, the corresponding specificity is slightly above 0.75.

Table 2. Results from Cox regression of alcohol use disorder with time-dependent covariates for 20,764 patients from nine general practice surgeries in the Stavanger area in Norway accrued from March to August of 2011.

	Unadjusted estimates			Adjusted estimates		
Variables	HR	95% CI	*p*	HR	95% CI	*p*
Gender (male)	1.71	(1.46, 2.01)	<0.001	1.94	(1.65, 2.29)	<0.001
No. of predictor events						
Class B drugs[a]	1.27	(1.24, 1.31)	<0.001	1.25	(1.21, 1.28)	<0.001
New sick leave[a]	2.16	(1.81, 2.58)	<0.001	1.81	(1.50, 2.19)	<0.001
Elevated lab test[a]	3.62	(2.93, 4.46)	<0.001	3.50	(2.79, 4.39)	<0.001
ICD-10-diagnoses[a]	2.51	(1.51, 4.18)	<0.029	2.00	(1.07, 3.72)	0.009
ICPC-2-diagnoses[a]	2.29	(2.01, 2.61)	0.001	1.43	(1.16, 1.78)	0.002

Abbreviations: HR: hazard ratio; CI: confidence interval; ICD-10: International Classification of Diseases, version 10; ICPC-2: International Classification of Primary Care, version 2.
[a]Per 10 predictor events.

Discussion

Our findings show that repeated incidents of many common clinical problems in general practice represent an increased risk of identifying an AUD later on, but the results are not strong enough to enable the development of a clinically relevant identification strategy. Elevated blood tests of GGT and MCV, new sick leaves, prescriptions of class B drugs, and a wide variety of diagnoses were significantly associated with increased risk of a future AUD, though the HRs were fairly modest. All predictors represent frequent incidents in general practice, where the patient trajectories often are long.

Sample and methods

In this study, we have included all patients who had an active EPR until data collection and for at least four years after they turned 18 years of age instead of collecting data on a sample of eligible patients. This ensures realistic data. The variables were chosen with adults in mind, and data prior to the year they turned 18 was therefore not included in the material. In old age, the number of health problems rapidly increase,

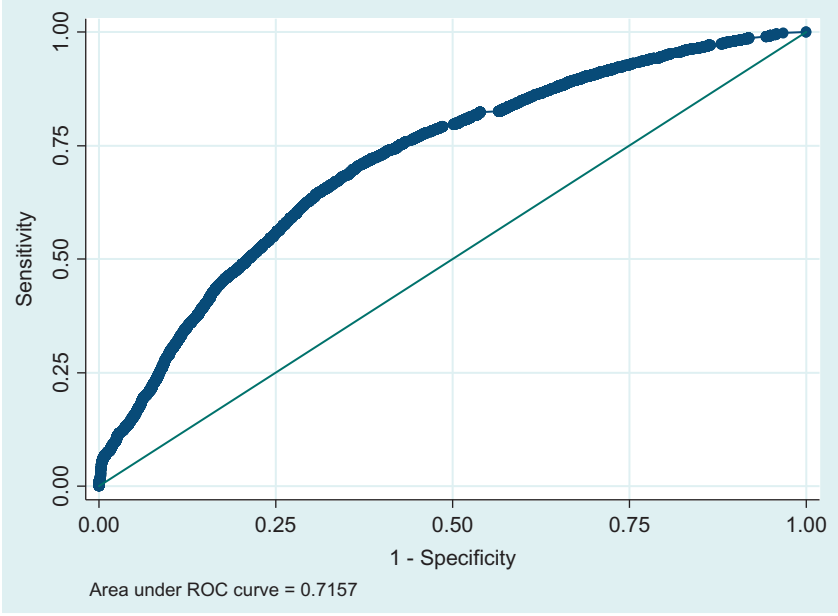

Figure 1. Receiver operator characteristics (ROC) curve for prognostic index (gender, elevated lab tests, class B-drugs, new sick leaves, and alcohol-related ICPC-2 and ICD-10 diagnoses), for $n = 16{,}814$ patients from the Stavanger area in Norway, for comprehensive alcohol use disorder. Abbreviations: ICD-10: International Classification of Diseases, version 10; ICPC-2: International Classification of Primary Care, version 2.

and collecting data for the prediction of future health problems is less relevant.

Other data from the EPRs than the chosen variables were not collected, apart from gender, year of birth, doctor and surgery, and first and last entry in the EPR. We chose to exclude predictor events more than four years prior to a predictor event, because recent events in a patient's life, documented in the EPR, probably have a higher impact on present health. This view was supported by the fact that the HRs were lower when performing Cox-regressions without exclusion of predictor events more than four years prior (analyses not shown).

Significance of the results

We wanted to explore whether clinical information, as recorded in the EPR, might aid the doctors in establishing relevance for addressing alcohol. Several HRs were around 2, though the analyses were done per 10 predictor events. But the number of such events for a patient may be very high, and all predictors represent frequent clinical problems in general practice. Many different kinds of events sum up the risk as the model indicates. Our validation of the AUD text fragment indicated that our definition of c-AUD is underestimating the diagnosis.

Gender was more strongly associated with AUD than with c-AUD, indicating a lower threshold for applying a specific diagnosis to a recognized alcohol problem if the patient is male. A gender difference in SBI is also described in a Cochrane review, but whether the gender difference is primarily caused by identification or treatment differences is not known.[5,34] Elevated blood levels of GGT and MCV is a recognized starting point for alcohol talks in general practice, and their relevance has been tested in previous studies.[14,24,35] Such changes are late effects of too high alcohol consumption, and many psychosocial problems may occur much earlier.[15,36] We found low estimate for ICPC-2 diagnoses, perhaps because this is a composite variable, composed by converted diagnoses from ICD-10,[3,4] pragmatic case finding,[14] and early clinical signs [15] (Appendix A).

The AUC of the ROC-curve was fairly modest, and the direct clinical relevance is modest. We have chosen to exclude predictor events more than four years prior to the present event. Previous events sum up and constitute an ever increasing risk, but previous difficulties and problems are also overcome and sometimes balanced by positive experiences. While events early in life may have strong effects on present and future health, information in the EPR will probably not be a strong indicator of relevant events in early lifetime.[37]

If our choice of predictors has been adequate, the results indicate that using patient record data to establish a threshold value for identifying an AUD is futile because of lack of sensitivity and specificity. But our findings point to the fact that many frequent clinical problems normally not conceived as caused by alcohol consumption, over time may be related to alcohol consumption. The predictor events constituting a potential risk, as well as the opportunities to intervene, increase over time in general practice. Even interventions with minor effect may potentially add up in the long run, when applied many times and for many patients.[38,39]

SBI has shown a lack of diagnostic accuracy, intervention efficacy, and feasibility.[8,11,17,40] Methods focusing on the present situation and the patient's problem will probably increase relevance and recognition for the patient.[14,15,18] We should bear in mind that alcohol use may represent attempts to master a challenging life as viewed from the patients' perspective.[41] An open and respectful dialogue is needed to explore how alcohol may be relevant for health, coping and well-being.

Strengths and limitations of the study

The large variety in size and stability for the surgeries supports external validity.[42] The extensive number of 36 participating GPs and 20,764 patients together with the long observation period of 4–21 years further strengthens the external validity.

Being an exploratory study in EPRs, the data is highly affected by everyday habits, flaws and inaccuracies in diagnostic work, interventions and documentation. Because of a maximum observation period of 21 years, many doctors have been replaced over the years, thus several doctors may have been responsible for each patient's EPR. The resulting diagnostic variability probably reduces the internal validity of the study, but strengthens the external validity.[42] When facing uncertainty, the result of the diagnostic process will vary greatly between doctors.[43]

Many address alcohol and document the interventions without proper diagnosis, but it is also likely that many interventions are not documented in the EPR. In addition, we have also demonstrated that c-AUD underestimated real alcohol problems in patients at least in the EPRs that were examined. Since we have no direct assessments of the patients, we know nothing about the real prevalence of alcohol related health problems in the material. As the data are completely

anonymous, we are not able to test our data against registers as the Cause of Death Registry or the Norwegian Registry Database, nor may we trace a patient moving from one surgery to another.

Sick leaves were difficult to trace uniformly by the data extraction software because of the extensive time frame, and many sick leaves, especially before 2000, had to be excluded. The results for sick leaves are therefore less robust. The composite variable of ICPC-2 diagnoses obscures the potential relation between diagnoses or clusters of diagnoses and AUD. In future studies, ICPC-2-diagnoses should probably be grouped in clinically meaningful clusters in order to be able to detect stronger correlations than we have found. The screening of text fragments may also be more extensively utilized in further studies, to explore relations between alcohol-related health problems and different clinical situations described but not diagnoses in the EPR.

Implications

We have shown that many everyday health problems may, over time, indicate an increased risk of a future AUD. The variables explored in this study may be just as important as vulnerability factors as they are potentially early signs of an alcohol-related health problem. Our findings emphasize the importance of asking about alcohol consumption in many common clinical situations, exemplified by the variables in this study. The unsatisfactory diagnostic accuracy precludes the development of a clinically useful tool, but this is not a valid objection to asking about alcohol consumption based on potential relevance.

Many patients may be aware of the possible relation between their health problem and alcohol consumption.[38] Other patients may be unaware of such a relation. A GP addressing this possible relation in an open, non-judgmental manner may represent one of many important elements in a long and winding road to permanent change.

Acknowledgements

We wish to express our gratitude to all doctors at the participating surgeries, and especially Asgeir Haugedal for invaluable support and assistance in the initial process. We also wish to thank Alexander Løvik Stevenson, who helped putting all the gathered data together, enabling further adaptation and analysis. But most of all, we wish to thank Magne Rekdal, who designed the software that made this project possible.

Ethical approval: The study was approved by the Regional Committee for Medical Research Ethics.

Disclosure statement

We are aware of no real, potential or perceived conflicts of interest for any of the authors.

Funding information

The study was funded by Research in General Practice, Norwegian Medical Association, and Centre for Alcohol and Drug Research, Stavanger University Hospital, Norway.

References

[1] Rehm J, Anderson P, Manthey J, et al. Alcohol use disorders in primary health care: what do we know and where do we go? Alcohol Alcohol. 2016;51:422–427.

[2] Norstrom T, Ramstedt M. Mortality and population drinking: a review of the literature. Drug Alcohol Rev. 2005;24:537–547.

[3] Rehm J, Baliunas D, Borges GL, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. Addiction. 2010;105:817–843.

[4] Jones L, Belllis MA, Dedmann D, et al. Alcohol-attributable fractions for England, alcohol-attributable mortality and hospital admissions. Liverpool: Liverpool John Moores University, Centre for Public Health FoHaASS; 2008.

[5] O'Donnell A, Anderson P, Newbury-Birch D, et al. The impact of brief alcohol interventions in primary healthcare: a systematic review of reviews. Alcohol Alcohol. 2014;49:66–78.

[6] Saitz R. The best evidence for alcohol screening and brief intervention in primary care supports efficacy, at best, not effectiveness: you say tomāto, I say tomăto? That's not all it's about. Addict Sci Clin Pract. 2014;9:14.

[7] Kaner E, Bland M, Cassidy P, et al. Effectiveness of screening and brief alcohol intervention in primary care (SIPS trial): pragmatic cluster randomised controlled trial. BMJ. 2013;346:e8501.

[8] van Beurden I, Anderson P, Akkermans RP, et al. Involvement of general practitioners in managing alcohol problems: a randomized controlled trial of a tailored improvement programme. Addiction. 2012;107:1601–1611.

[9] Butler CC, Simpson SA, Hood K, et al. Training practitioners to deliver opportunistic multiple behaviour change counselling in primary care: a cluster randomised trial. BMJ. 2013;346:f1191.

[10] Andreasson S, Hjalmarsson K, Rehnman C. Implementation and dissemination of methods for prevention of alcohol problems in primary health care: a feasibility study. Alcohol Alcohol. 2000;35:525–530.

[11] Nygaard P, Aasland OG. Barriers to implementing screening and brief interventions in general practice: findings from a qualitative study in Norway. Alcohol Alcohol. 2011;46:52–60.

[12] Rush BR, Powell LY, Crowe TG, et al. Early intervention for alcohol use: family physicians' motivations and perceived barriers. CMAJ. 1995;152:863–869.
[13] Aasland OG, Johannesen A. Screening and brief intervention for alcohol problems in Norway. Not a big hit among general. Nordisk Alkohol Narkotikatidskrift. 2008;25:515–521.
[14] Lid TG, Malterud K. General practitioners' strategies to identify alcohol problems: a focus group study. Scand J Prim Health Care. 2012;30:64–69.
[15] Reinholdz HK, Bendtsen P, Spak F. Different methods of early identification of risky drinking: a review of clinical signs. Alcohol Alcohol. 2011;46:283–291.
[16] Reinholdz H, Fornazar R, Bendtsen P, et al. Comparison of systematic versus targeted screening for detection of risky drinking in primary care. Alcohol Alcohol. 2013;48:172–179.
[17] Beich A, Gannik D, Malterud K. Screening and brief intervention for excessive alcohol use: qualitative interview study of the experiences of general practitioners. BMJ. 2002;325:870.
[18] Guassora AD, Baarts C. Smoking cessation advice in consultations with health problems not related to smoking? Relevance criteria in Danish general practice consultations. Scand J Prim Health Care. 2010;28:221–228.
[19] Christensen T, Faxvaag A, Loerum H, et al. Norwegians GPs' use of electronic patient record systems. Int J Med Inform. 2009;78:808–814.
[20] 2010: KITH from 2012: The Norwegian Directorate of Health; [cited 2010 Oct 21]. Historic link, still accessible, new link provided. Available from: 2010: http://kith.no/upload/1899/ICD10-2006_to_ICPC2_mapping%28RTV_240306%29.txt 2015: https://helsedirektoratet.no/Documents/Medisinske%20koder%20og%20kodeverk/ICPC-2/ICPC-2n-v42-ICD10tolCPC2-CSV%202015.txt.
[21] Rehm J, Mathers C, Popova S, et al. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet. 2009;373:2223–2233.
[22] Day E, Copello A, Hull M. Assessment and management of alcohol use disorders. BMJ. 2015;350:h715.
[23] Johansson E, Bockerman P, Uutela A. Alcohol consumption and sickness absence: evidence from microdata. Eur J Public Health. 2009;19:19–22.
[24] Aertgeerts B, Buntinx F, Ansoms S, et al. Screening properties of questionnaires and laboratory tests for the detection of alcohol abuse or dependence in a general practice population. Br J Gen Pract. 2001;51:206–217.
[25] Daeppen JB, Anex F, Leutwyler J, et al. Role of high normal gamma-glutamyltransferase level in identifying heavy alcohol use in young men. Alcohol. 2004;32:157–161.
[26] Robinson J, Sareen J, Cox BJ, et al. Self-medication of anxiety disorders with alcohol and drugs: results from a nationally representative sample. J Anxiety Disord. 2009;23:38–45.
[27] Altman DG. Practical statistics for medical research. London: Chapman and Hall; 1991. XII, 611 s. p.
[28] Cox DR. Regression models and life-tables. J Roy Stat Soc. 1972;34:187–220.
[29] Crowley J, Hu M. Covariance analysis of heart transplant survival data. J Am Stat Assoc. 1977;72:27–36.
[30] Therneau T, Crowson C. The comprehensive R archive network; 2015; [cited 2015 Sep 1]. Available from: https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf.
[31] Abrahamowicz M, Bartlett G, Tamblyn R, et al. Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. J Clin Epidemiol. 2006;59:393–403.
[32] Søreide K, Kørner H, Søreide JA. Diagnostic accuracy and receiver-operating characteristics curve analysis in surgical research and decision making. Ann Surg. 2011;253:27–34.
[33] Nygård Y, Haukaas SA, Eide GE, et al. Prostate cancer antigen-3 (PCA3) and PCA3-based nomograms in the diagnosis of prostate cancer: an external validation of Hansen's nomogram on a Norwegian cohort. Scand J Urol. 2015;49:8–15.
[34] Kaner EF, Dickinson HO, Beyer F, et al. The effectiveness of brief alcohol interventions in primary care settings: a systematic review. Drug Alcohol Rev. 2009;28:301–323.
[35] Coulton S, Drummond C, James D, et al. Opportunistic screening for alcohol use disorders in primary care: comparative study. BMJ. 2006;332:511–517.
[36] Cornel M, Knibbe RA, Knottnerus JA, et al. Predictors for hidden problem drinkers in general practice. Alcohol Alcohol. 1996;31:287–296.
[37] Anda RF, Butchart A, Felitti VJ, et al. Building a framework for global surveillance of the public health implications of adverse childhood experiences. Am J Prev Med. 2010;39:93–98.
[38] Aasland OG, Bruusgaard D, Rutle O. Alcohol problems in general practice. Br J Addict. 1987;82:197–201.
[39] Nilsen P, Bendtsen P, McCambridge J, et al. When is it appropriate to address patients' alcohol consumption in health care – national survey of views of the general population in Sweden. Addict Behav. 2012;37:1211–1216.
[40] Lid TG, Nesvåg S, Meland E. When general practitioners talk about alcohol: exploring facilitating and hampering factors for pragmatic case finding. Scand J Public Health. 2015;43:153–158.
[41] Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14:245–258.
[42] Shadish WR, Cook TD, Campbell DT. Experimental and quasi-experimental designs for generalized causal inference. Boston: Houghton Mifflin; 2002. XXI, 623 s. p.
[43] Maeland S, Werner EL, Rosendal M, et al. Sick-leave decisions for patients with severe subjective health complaints presenting in primary care: a cross-sectional study in Norway, Sweden, and Denmark. Scand J Prim Health Care. 2013;31:227–234.

Appendix A: Alcohol use disorders and alcohol-related disorders in ICD-10 and ICPC-2

Outcome – alcohol use disorders ICD-10 [3]

E24.4	Alcohol-induced pseudo-Cushing's syndrome
F10	Mental and behavioural disorders due to use of alcohol
F10.0	Acute intoxication F10.00-F10.07
F10.1	Harmful use
F10.2	Dependence syndrome F10.20-F10.26
F10.3	Withdrawal state F10.30-F10.31
F10.4	Withdrawal state with delirium F10.40-F10.41
F10.5	Psychotic disorder F10.50-F10.56
F10.6	Amnesic syndrome
F10.7	Residual and late onset psychotic disorder F10.70-F10.75
F10.8	Other mental and behavioural disorders
F10.9	Unspecified mental and behavioural disorder
G31.2	Degeneration of nervous system due to alcohol
G62.1	Alcoholic polyneuropathy
G72.1	Alcoholic myopathy
I42.6	Alcoholic cardiomyopathy
K29.2	Alcoholic gastritis
K70	Alcoholic liver disease
K70.1	Alcoholic hepatitis
K70.2	Alcoholic fibrosis and sclerosis of liver
K70.3	Alcoholic cirrhosis of liver
K70.4	Alcoholic hepatic failure
K70.9	Alcoholic liver disease, unspecified
K85.2	Alcohol-induced acute pancreatitis
K86.0	Alcohol-induced chronic pancreatitis
O35.4	Maternal care for (suspected) damage to fetus from alcohol
P04.3	Fetus and newborn affected by maternal use of alcohol
Q86.0	Fetal alcohol syndrome (dysmorphic)
R78.0	Finding of alcohol in blood
T51	Toxic effect of alcohol
T51.0	Ethanol
T51.1	Methanol
T51.9	Alcohol unspecified
X45	Accidental poisoning by and exposure to alcohol
X65	Intentional self-poisoning by and exposure to alcohol
Y15	Poisoning by and exposure to alcohol, undetermined intent

Outcome – Alcohol use disorders ICPC-2. Converted from ICD-10 [3]

P15	Chronic alcohol abuse
P16	Acute alcohol abuse
A23*	Risk factor NOS
A86*	Toxic effect non-medicinal substance
A90*	Congenital anomaly nos/multiple
A99*	Disease/condition of unspecified nature/site
D87*	Stomach function disorders
D97*	Liver disease NOS
D99*	Disease digestive system other
K84*	Heart disease other
N94*	Peripheral neuritis/neuropathy

*Only when the word 'alcohol' in different versions is included in the diagnostic text

Predictor events – Alcohol-related diagnoses, ICD-10 [3]

C00-C14	Malignant neoplasms of lip, oral cavity and pharynx
C15	Malignant neoplasm of esophagus
C32	Malignant neoplasm of larynx
G40-G41	Epilepsy and status epilepticus
I10-I15	Hypertensive diseases
I47-I48	Cardiac arrhythmias
I60-I62,	Hemorrhagic stroke
I85	Esophageal varices
K22.6	Gastro-oesophageal laceration-haemorrhage syndrome
K73, K74	Liver cirrhosis
K85, K86.1	Acute and chronic pancreatitis
L40 exl L40.5	Psoriasis
O03	Spontaneous abortion

Predictor events – Alcohol-related diagnoses, ICPC-2. Converted from ICD-10 [3]

D77	Malignant digestive neoplasm other/NOS
D87	Stomach function disorder
D97	Liver disease NOS
D99	Disease digestive system other
K78	Atrial fibrillation/flutter
K79	Paroxysmal tachycardia
K80	Cardiac arrhythmia NOS
K86	Hypertension uncomplicated
K87	Hypertension complicated
K99	Cardiovascular disease other
N88	Epilepsy
R85	Malignant neoplasm respiratory other
S91	Psoriasis
W82	Abortion spontaneous

Predictor events – Other potentially alcohol-related diagnoses from ICPC-2, based on Rehm et al. and Reinholdz et al. [15,21]

D07	Dyspepsia/indigestion
N01	Headache
P01	Feeling anxious/nervous/tense
P06	Sleep disturbance
P18	Medication abuse
P74	Anxiety disorder/anxiety state
P76	Depressive disorder
Z12	Relationship problem with partner
Z13	Partner's behaviour problem
Z16	Relationship problem with child
Z20	Relationship problem parent/family member
Z21	Behaviour problem parent/family member
Z24-29	Relationship problem friend, assault/harmful event problem, fear of a social problem, limited function/disability, social problem
A80	Trauma/injury NOS
F75	Contusion/hemorrhage eye

F77 Injury eye other
H78 Superficial injury of ear
H79 Ear injury other
L72-81, L96 Fractures, sprains, dislocations, etc.
N80 Head injury other
S16 Bruise/contusion
S18 Laceration/cut
S19 Skin injury other