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Estimating disease prevalence from drug utilization data using the Random Forest algorithm

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Background: Aggregated claims data on medication are often used as a proxy for the prevalence of diseases, especially chronic diseases. However, linkage between medication and diagnosis tend to be theory based and not very precise. Modelling disease probability at an individual level using individual level data may yield more accurate results. Methods: Individual probabilities of having a certain chronic disease were estimated using the Random Forest (RF) algorithm. A training set was created from a general practitioners database of 276 723 cases that included diagnosis and claims data on medication. Model performance for 29 chronic diseases was evaluated using Receiver Operating Curves, by measuring the Area Under the Curve (AUC). Results: The diseases for which model performance was best were Parkinson’s disease (AUC = .89, 95% CI = .77–1.00), diabetes (AUC = .87, 95% CI = .85–.90), osteoporosis (AUC = .87, 95% CI = .81–.92) and heart failure (AUC = .81, 95% CI = .74–.88). Five other diseases had an AUC >.75: asthma, chronic enteritis, COPD, epilepsy and HIV/AIDS. For 16 of 17 diseases tested, the medication categories used in theory-based algorithms were also identified by our method, however the RF models included a broader range of medications as important predictors. Conclusion: Data on medication use can be a useful predictor when estimating the prevalence of several chronic diseases. To improve the estimates, for a broader range of chronic diseases, research should use better training data, include more details concerning dosages and duration of prescriptions, and add related predictors like hospitalizations.

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Introduction

Information on disease prevalence is important for assessing the health needs of populations. Several sources can deliver population disease prevalence estimates, such as surveys, dedicated epidemiologic studies using diagnostics or administrative data sources. Drug use data, especially on prescription drugs, has also frequently been used to estimate disease prevalence. In many countries insurers or providers maintain extensive prescription databases, allowing easy access to national drug use data.

Drug use has several advantages over other sources. Surveys are costly to execute on a large scale. Hospital discharge registers are large, but involve hospital-related events only. In addition, in the Netherlands, the GP-serves as a gatekeeper, implying that patients—except in emergencies—can only visit a medical specialist with a referral of the GP. This means that the GP sees both patients that see only the GP and those he refers to specialist care. Hospital data is therefore more likely that GP data to underestimate the prevalence. GP-registers containing diagnosis codes are not readily available in all countries. Furthermore, GPs may have different coding habits, hindering comparisons between GPs.

While drug use data is often recorded without a diagnosis, some studies base disease prevalence on direct links of specific drug use to the presence of certain diseases. The links are based on literature or medical guidelines. For two reasons, this procedure is problematic. First, many drugs are used for the treatment of multiple diseases; assuming that all patients who take a specific drug do have a specific disease will then lead to overestimation. Second, some patients with a disease are not prescribed the specific drug, and this will lead to underestimation of prevalence.

To overcome these two problems, it is better to estimate the probability of having a specific disease given all different medications a person uses. Avoiding any a priori assumption on the relationship between the drugs and diagnoses, machine learning algorithms can be used to estimate this relation from data. In this paper more specifically the Random Forest (RF) algorithm will be applied, as this method yielded the best results in comparison with others.

This algorithm requires a test set with both diagnosis data and drug use. This diagnosis data could also be used directly to estimate disease prevalence. This is the case particularly when it is possible to assume that the set containing diagnosis data is representative for the population of interest. However, using the diagnosis data in combination with drug use as proposed alters the assumption. Rather than that the diagnosis data should be representative for the population of interest, the relationship between diagnosis and drug use should be similar as in the population of interest. This might be a more reasonable assumption in many cases, as medical professionals are influenced by standardized prescription guidelines. Countries which do have a prescription registration, but lack population surveys on disease prevalence, as is often the case, can use the relation derived in comparable countries to obtain prevalence estimates.

Existing applications of RF analysis to the problem of disease prevalence estimates have some limitations. Chaudhry used RF to predict the population prevalence of diabetes and dementia from administrative data in GP and hospital records. However, his choice of predictors was informed by a priori knowledge. Khalilia et al. predicted the presence of eight diseases with RF from hospital in-patient data, but did not make any population prevalence estimates.

In contrast, we apply the RF approach to a broad range of 29 diseases. The RF algorithm allows us to select important predictors from the full range of possible drug use predictors. Afterwards, we have a list of predictors for comparison with existing theory based lists of predictors, e.g. the Dutch Pharmacotherapeutic compass. The objective of this paper hence is to examine for which diseases the prevalence can be estimated using the RF algorithm, and if so, to see which drug groups should be used.

Methods

Random Forest

Estimating the probability that an individual has a certain disease could be considered a mathematical classification problem. RF is a non-parametric method to address classification problems. For implementation the R-package 'Random Forest' was used.

Data

Drug use data of the entire Dutch population is available from the National Health Care Institute (ZiN). The ZiN claims database covers all outpatient prescriptions reimbursed under the Dutch mandatory Health Insurance scheme. Drugs were classified in 204 pharmaceutical groups according to the four position ATC-code. To these groups, age and gender were added as predictors. The dataset contained 47 million individual prescription records in 2010, covering a population of 16.7 million, of which 70% had at least one prescription.

A training set with disease information was obtained from the primary care database of the Netherlands Institute for Health Services Research (NIVEL). As every citizen is required to have a GP—with the exception of those living institutionalized—this means the dataset is likely to cover the whole Dutch population, with the exception of the 80+ population of which in 2010 a significant part lived institutionalized. All patient contacts were labelled with a diagnostic code, ICPC. A person was defined to have a disease when he/she had at least one contact with a GP for this disease over a period of 3 years. All GP-patients with full data available over 2008–2010 were selected. This resulted in a training set of 276,723 individuals. The selection of 29 diseases was based on a list provided by O’Halloran et al. See Supplementary file S1 for details. We combined the available data (drug utilization, age and gender, and ICPC codes) at Statistics Netherlands within the System of Social Statistical Datasets (SSD). The SSD allows data from different administrative registers to be combined using an anonymous patient identifier for research purposes.

Implementation of RF

Usually, all observations in a training set and all predictors are combined in one RF-analysis. However, within the SSD system, computing power is limited, and analysis with our dataset (276,723 records with 206 variables) proved to be difficult. We therefore used a two-step approach. First, for each chronic disease, persons with the disease were randomly selected, up to a maximum of 5000 patients. To this set, an equal number of persons without the disease was randomly selected and added. For each of these smaller sets, the RF algorithm was applied. The variable importance measure, defined as the average decrease in accuracy when a predictor is left out of the analysis, was evaluated. For each disease, the 10 drug groups with the highest variable importance were selected. By selecting 10 drug groups, the most important predictors were included for all diseases, while limiting the computing times. Second, a new dataset was created for each disease based on the full training set, but only age, gender and the drug groups selected in the first step were added as predictors (276,723 records with 12 variables for each disease), and we applied RF a second time. For each disease this second RF-model was then applied to obtain the probability of having this disease for each individual in the prescriptions database, hence for the 11.6 million Dutch inhabitants that were reimbursed a prescription drug in 2010. The model was also applied to the remaining 5. million Dutch individuals without any prescription. They received for each of the 29 diseases a probability equivalent to the age and gender specific probability in the training set for those diagnosed with the disease, but not receiving any prescription.
To measure the performance of the final RF-models, the area under the Receiver-Operator Curve (AUC) was measured for the training set for each disease separately. An AUC-value above .7 is generally considered useful. To prevent overfitting, 10-fold cross validation was applied.

The AUC and a 95% confidence interval around the AUC-value were obtained using the R-package ‘cvAUC’. If the lower boundary of this interval was above .5, we considered the model to perform better than a random prediction.

The predicted population prevalence by age and gender for the Netherlands was graphically compared with a prevalence estimate based on direct extrapolation of the training set prevalence. Correlations were computed as well for the six diseases with lower confidence bound (95%) of the AUC >.70. The age range considered was 30–80 years, since the prevalence below 30 is very low for most chronic diseases and the 80+ population was not well covered in our training set.

For a binary classification of each individual, a cut-off needs to be chosen. This was done by setting an age and disease-specific cut-off value. All persons with a probability higher than the cut-off were classified as ‘ill’. The cut-off was chosen to minimize the deviation between the observed and the predicted prevalence in the training set for each age, gender and disorder.

### Results

Table 1 gives descriptives for the training set. The average annual number of different pharmaceutical drugs taken by patients in the training set was 2.9, which is very comparable with the utilization in the total Dutch population in the same year (2.8). Table 1 also shows that the number of ATC groups utilized by an individual patient rises proportionally with the number of chronic diseases present.

Table 2 lists the AUC values produced by our analysis, sorted by average AUC. For 17 diseases the lower boundary of the 95% AUC confidence interval was >.5. For 10 diseases the average AUC was .7 or higher, but for only six the lower boundary of the AUC 95% confidence interval was >=.7: Parkinson’s disease, diabetes mellitus, osteoporosis, heart failure, asthma and chronic obstructive pulmonary disease (COPD).

There is some association between the frequency of the disease and the prediction of the AUC. For almost all 12 diseases with a prevalence in the training set higher than 100 per 10 000 persons, the prediction is better than a random assignment. The only exception is anxiety disorder (154 cases per 10 000 persons), with a very poor performance and AUC of .56 (95% cf. = .50–.61). For 11 out of 17 diseases with a frequency below 100 per 10 000 persons, performance is poor, i.e. the lower boundary of the AUC 95% confidence interval was below .5. A notable exception was Parkinson’s disease which
**Table 3 Predictors of chronic diseases in Random Forest analysis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>ATC4 groups with strongest relation with disease in RF-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson's disease*</td>
<td>N04B A04A Birthyear L04A A07E C10A C08B N05A C03C N06D</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>A10A A10B C10A B01A H04A C09A C08B C08C C03C C07A</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>M05B A12A A11C L04A C10A B01A C09D D01A C09C D06A</td>
</tr>
<tr>
<td>Heart failure</td>
<td>C03C C03D C02D A01C C08D C08C C01D C03A C01A C07B</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease*</td>
<td>R03A R03B R06A A01A R01A N06B J01F R05D A06A J01C</td>
</tr>
<tr>
<td>Chronic enteritis/colitis ulcerosa</td>
<td>A07E L04A L01B B03B A06A J01M A11C A07D N02A M01A</td>
</tr>
<tr>
<td>HIV/AIDS*</td>
<td>J05A J01E J04A J01F N01B J07B D06B A02B J01C J01A</td>
</tr>
<tr>
<td>Asthma*</td>
<td>R03A R03B R03C Birthyear H02A A07A S01G R01A R06A R05D</td>
</tr>
<tr>
<td>Epilepsy*</td>
<td>N03A N05B Birthyear A03F N05A B01A N06A D04A D11A N05C</td>
</tr>
<tr>
<td>Coronary heart disease*</td>
<td>C01D C08D C03C C01B C03A C09A D06A C01E C09C B03A</td>
</tr>
<tr>
<td>Visual disorder</td>
<td>S01E S01B Birthyear S01C A10B S01F D02A S01A A10A S01X</td>
</tr>
<tr>
<td>Schizophrenia*</td>
<td>N05A N05B N05C N04A N06A N06B Birthyear N03A N06C</td>
</tr>
<tr>
<td>Rheumatoid arthritis*</td>
<td>L04A A01B A07E B03B N02A L01B H02A D02B M05B D06A</td>
</tr>
<tr>
<td>Dementia*</td>
<td>N06D Birthyear N05A A12A C03C N03A M05B Y D03D C09D</td>
</tr>
<tr>
<td>Congenital neurological anomaly</td>
<td>M03B G04B N03A J01X D07X N05A J01E A12A D01A N05B</td>
</tr>
<tr>
<td>Multiple sclerosis*</td>
<td>L03A M03B G04B N03A N06A N04B B03B S01A J01X C03C</td>
</tr>
<tr>
<td>Cancer*</td>
<td>Birthyear L02B H03A Y D06A A04A Gender L02A G03C A12A</td>
</tr>
<tr>
<td>Chronic alcohol abuse*</td>
<td>N07B N05A Birthyear N05B G04C A02B N06A M04A A10B N05C</td>
</tr>
<tr>
<td>Depressive disorder*</td>
<td>N06A N05A N05B N06B N05C N07B N03A A03F A11C G04B</td>
</tr>
<tr>
<td>Stroke (including TIA)</td>
<td>B01A V03A C01D C01B C07A Birthyear C08C C01A S01C S01E</td>
</tr>
<tr>
<td>Congenital cardiovascular anomaly</td>
<td>B01A C07A J01C N03A C09A D06A R03B Y D02A S02C</td>
</tr>
<tr>
<td>Chronic back or neck disorder*</td>
<td>N02A M01A A02B A06A N02B C05A S02C N03A H02A R05D</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Birthyear B01A Gender M04A C10A N02B C10B C03A S01E N02A</td>
</tr>
<tr>
<td>Anxiety disorder, neurosis, PTSS</td>
<td>N06A N05B N05A C07A N01B N05C A03F N06A N03A D05A</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>N05A N03A D02A D06A A06A N05B Y D10A S01F N01B</td>
</tr>
<tr>
<td>Hearing disorder</td>
<td>Birthyear L02A B02A S01X D05A G04C H02A A10B C08D C07B</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Gender G03A A06A A01A Y J01X G03H R05D G01A A12B</td>
</tr>
<tr>
<td>Gastric or duodenal ulcer*</td>
<td>A02B D05A G04B A07A A03A A03F M01A A11C D06B A06A</td>
</tr>
<tr>
<td>Tuberculosis*</td>
<td>J04A D02A D07X C01B J01A C08C C03C S01C S02C C03E</td>
</tr>
</tbody>
</table>

Legend: First column gives name of chronic disease. The next 10 columns list the predictors used in the final RF-model, in order of decreasing importance. To facilitate comparison, diseases are presented in the same order as in table 2.

a: For these diseases, comparison is possible with pharmaceutical groups listed in risk adjustment compulsory insurance. The shaded groups are also used for the detection of these diseases by Dutch insurers.32

b: These diseases have been compared with ATC-groups mentioned in the relevant Dutch treatment guidelines. The shaded groups are included in these guidelines.33–37

despite a low frequency (15 per 10 000 persons) seems to be very predictable from drugs utilization.

In table 3 predictors of all model output from the RF-analysis are ranked by importance. The shaded areas denote drugs that are also mentioned as indicator drugs for these diseases in the theoretical drug classifications we compared with. Only for cancer we found no similarities. For all other diseases, the ATC codes mentioned by insurers and guidelines are also strong predictors for the corresponding diseases in our RF-models. However, our models show a number of additional predictors for most disorders. Supplementary file S2 gives more information.

The actual prevalence in the training set and the calculated prevalence based on applying the final RF-models have been compared for the six diseases with a lower bound of the AUC 95% confidence interval >.7. Except Asthma, correlations are above .9. Asthma shows correlations of .43 for males and .66 for females, indicating poor performance. Looking at the graphs for osteoporosis, a large discrepancy exists between predicted and observed prevalence around the age of 70. Figure 1 gives an example (COPD, male). A full set of figures is found in Supplementary file S3.

**Discussion**

For a broad range of 29 diseases, RF was used to predict disease prevalence based on medication use. Predictive performance was acceptable for 6 out of 29 diseases and would result in reliable estimates of population prevalence. Furthermore, we find that theory-based indicator drugs were included in the range of diseases identified by the RF model. This seems to be independent from the performance of the models, which indicates that the RF algorithm can also be used to identify suitable predictors, even in those cases where the predictive performance is low. Especially for diabetes, heart failure and COPD we observe a high correlation between estimated and observed population.

Our outcomes can be compared with a few other studies. Chaudhry20 predicted the presence of diabetes with an AUC of .95 and dementia with an AUC of .875, higher than the .87 and .67 we found. However, for dementia he used dementia-coded doctor visits as predictors, while we use this as our definition of disease. Khalilia et al.23 used data on hospital stays as predictors, on a very large set (8 million records). A training set was generated by bootstrapping. The average AUC he reports (.88) is much higher than those we found. For the two diseases which could be directly compared (diabetes and osteoporosis) he finds almost the same AUC (.879 and .870 respectively) as we found, .87 for both. Compared with these two previous studies, we included a relatively broad range of diseases and added the comparison with theory-based models.

While the method seems useful for some diseases, the predictive performance is still low for most diseases. This could have multiple causes. First, for some diseases, there is no standard pattern of drugs included in all treatment options. In addition, drugs might be
prescribed for multiple diseases. For instance, the two strongest predictors for asthma and COPD are the same (R03A and R03B, table 3). As a result, misclassification of asthma and COPD patients is likely to occur, which has not been further investigated in this study. Furthermore, patients and GPs may deal with diseases in different ways. Based on patient characteristics a GP will sometimes advise lifestyle changes instead of drugs, but will treat similar cases in other instances immediately with drugs. In addition, the patient may have treatment preferences. The relationship between diagnosis and drugs can also change over time. Innovation or policy changes can strongly influence prescription behaviour, making regular calibration of the algorithms necessary.

Second, the predictive power is likely limited due to weaknesses of the current data. In the current training set, only 3 years of diagnoses are used. While many patients with a chronic disease are visiting a GP more than once every 3 years, some patients who visit less frequently will not occur as diseased in the training set. Furthermore, some diseases might not be treated primarily by a GP, but directly in the hospital, also resulting in missing diagnoses in the training set. As the training set serves as a ‘golden standard’, any diagnosis errors in the training set will translate into the final predictions. Investing in a smaller set of persons for which disease diagnosis is even more reliable, e.g. through the use of cohort studies may provide a training set with better performance. The disadvantage of such a cohort, and the advantage of our current approach is that for rare diseases, relationships between disease and drugs would have to be derived from only a very limited number of disease cases.

Next to errors in disease diagnosis, drug use measures could also be improved. Drug use often varies between years. Grouping multiple years of drug use could improve results. Also, more complete drug utilization data could be obtained by including inpatient drugs. For some diseases, utilizing more detailed pharmaceutical predictors, such as ATC4 or ATC5 groups, would improve results.

Even though improvements might be needed to obtain reliable prevalence estimates for most diseases, for 16 out of 17 diseases for which theory-based predictors were found within existing guidelines, important similarities were found. This means that even though the predictive power of the algorithm on the current data is insufficient, it is still possible to identify relevant drug groups. Compared with purely theory-based models, the RF algorithms have the important advantage of coming with confidence intervals and information about model performance. From this similarity we also infer that Dutch general practitioners broadly follow existing pharmaceutical guidelines. Cancer was the only disease for which the drugs found using the RF algorithm differ from theory. This could be the result of grouping all cancers together, and many drugs used in cancer treatment were not covered by the dataset as they were prescribed in a hospital setting.

We do not want to suggest that prediction models can entirely replace current GP registers or population surveys. On the contrary, since without these registries the models cannot be built or validated. However, even in countries like the Netherlands which are covered by both population surveys and GP networks the method is of practical value, as it allows for analysis on subgroups, such as regions or stratifications by socio-economic status. The primary care database used as training set has been enlarged in recent years, but still covers at this moment only 10% of the population and the Dutch GPs. Using drug use will allow for better prevalence estimates for the 90% not covered.

Because the full population is covered in the prescription data we use, and the model provides estimates of the probability of having a disease at the individual level, other useful applications would be pre-selecting subjects for medical trials, or making case-mix corrections, e.g. for comparing hospital performance.

To conclude, combining diagnosis data and drug use by the RF algorithm provides can be a useful tool to predict population prevalence. Applications include situations where the diagnosis data is not necessarily representative for the population of interest,
but the relation found between diagnosis and drug use is representative. Furthermore, it can be used to select relevant drug use groups in almost all cases.

**Supplementary data**

Supplementary data are available at EURPUB online.

**Acknowledgements**

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*Conflicts of interest:* None declared.

**Key points**

- Disease prevalences can be estimated from drug use data by Random Forest (RF), a machine learning tool.
- No prior knowledge about the relationship between drug use data predictors and disease is needed.
- Survey-based prevalence estimates can easily be elaborated with indepth subgroup analyses
- Routine application in public health planning and monitoring is possible.

**References**

Increase in emergency department visits related to cannabis reported using syndromic surveillance system

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Background: Cannabis is illegal in France but, as in many countries, legalization is under debate. In the United States, an increase of emergency department (ED) visits related to cannabis exposure (CE) in infants and adults was reported. In France, a retrospective observational study also suggested an increase of CE in children under 6 years old. This study only included toddlers and the data sources used did not allow repeated analysis for monitoring.

Methods: Our study aimed to evaluate the trend in visits for CE in ED in patients younger than 27 years old in Southern France. A cross-sectional study using the Electronic Emergency Department Abstracts (EEDA) included in the national Syndromic Surveillance System. CE visits were defined using International Classification of Disease (ICD-10). Results: From 2009 to 2014, 16 EDs consistently reported EEDA with <5% missing diagnosis code. Seven hundred and ninety seven patients were admitted for CE including 49 (4.1%) children under 8 years old. From 2009–11 to 2012–14, the rate of CE visits increased significantly across all age groups. The highest increase was in the 8–14 years old (+144%; 1.85–4.51, P < 0.001) and was also significant in children under 8 (0.53–1.06; P = 0.02). Among children under 8, hospitalization rate (75.5% vs. 16.8%; P < 0.001) and intensive care unit admissions (4.1% vs. 0.1%; P < 0.001) were higher compared with patients older than 8 years. Conclusion: These trends occurred despite cannabis remaining illegal. EEDA could be useful for monitoring CE in EDs.

Introduction

Cannabis is illegal in France but, as in many countries, legalization is under debate. Survey data could be used to evaluate the prevalence of cannabis use in the general population whereas emergency department (ED) visits for cannabis exposure (CE) are symptomatic of pathologic situations associated with cannabis. Zhu used ED visits in the United States to report an increase in CE visits in adults.1 In the USA, various studies2–6 using Poison Control Center (PCC) data2–6 or hospital data2–6,7 have reported that legalization of cannabis was associated with an increase in un-intentional cannabis ingestions by young children. In France, without any change in cannabis law, an increase in phone calls to PCC was first reported in 2009.9 In 2017, Claudet also reported an increase in hospital admissions for CE in a retrospective observational study (2004–14) using hospital data and retrospective reading of patients’ medical file.10 However, this study could have over-estimated the increase, since during the first years of the study, only inpatients’ medical file was computerized. Children who had not been admitted to hospital following the ED visit were thus not caught in the study in many EDs. Moreover, the methodology used did not allow for an easy analysis repetition to survey the trend. In France, each ED admission has to be reported daily through Electronic Emergency Department Abstracts (EEDA). These EEDA are transmitted to OSCOUR network included in the French Syndromic Surveillance (SSS) System SurSaUD coordinated by Public Health France.11 EEDA have previously been used for various epidemiological studies in EDs.12–15 Our study aimed to measure, in southern France, the trend of CE visits in EDs, in children and young adults, using daily available data included in the French national SSS.

Methods

Data source

Our cross-sectional study analysed EEDA related to patients younger than 27 years old. EEDA have been included in the French SSS since 2004. They are directly collected from patients’ computerized medical file filled in during medical consultations. Details of this network have been published elsewhere.3,4 The Provence-Alpes-Côte d’Azur