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# Measuring Adverse Drug Effects on Multimorbidity using Tractable Bayesian Networks

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## Abstract

Managing patients with multimorbidity often results in polypharmacy: the prescription of multiple drugs. However, the long-term effects of specific combinations of drugs and diseases are typically unknown. In particular, drugs prescribed for one condition may result in adverse effects for the other. To investigate which types of drugs may affect the further progression of multimorbidity, we query models of diseases and prescriptions that are learned from primary care data. State-of-the-art *tractable* Bayesian network representations, on which such complex queries can be computed efficiently, are employed for these large medical networks. Our results confirm that prescriptions may lead to unintended negative consequences in further development of multimorbidity in cardiovascular diseases. Moreover, a drug treatment for one disease group may affect diseases of another group.

## 1 Introduction

There is currently an increased interest in multimorbidity, i.e., the co-occurrence of at least two, but often more, chronic or acute diseases and medical conditions within a person [14]. Due to the ageing population and other socio-economic factors, its prevalence is increasing: over two-thirds of the elderly population in the Western world have at least three chronic conditions [1].

Clinicians who aim to manage patients with multiple diseases are confronted with different guidelines, each meant to manage an isolated disorder. By combining these recommendations, a patient may receive many different drugs. Unfortunately, it is not unlikely that a drug prescribed for one condition may result in an adverse effect for the other [3, 4]. In September 2016, the National Institute for Health and Care Excellence (NICE) in the United Kingdom published the first clinical guideline on multimorbidity which emphasized patient-centred care [7]. Given the more generalist and multidisciplinary nature of multimorbidity, clinical validation tools were recommended.

One significant issue with multimorbidity is polypharmacy [12]. Drugs are often introduced to prevent future morbidity and mortality, but in context of multimorbidity they may instead increase the burden. Primary care e-health records can help identify markers of increased treatment burden, but until now, there have been relatively few tools that indicate which drugs may be harmful to a patient with multiple diseases.

We employ tractable Bayesian network learning to answer the main question in this paper: what is the effect of various treatments on the further development of multimorbidity? To that end, we present the first method for learning Bayesian networks that can answer these complex type of questions. Our learned network models interactions between multiple diseases and drug treatments in the primary care. By identifying which treatment could potentially harm the patient and increase the burden of multimorbidity even further, this work aims to provide the first step towards better recommendations to reduce the effects of treatment on the problem of multimorbidity.

## 2 Methods

In this paper, we investigate the effect of various treatments on further multimorbidity development. More concretely, we answer the question: Which drug treatment groups increase the probability of suffering from more diseases within a group, a group being either cardiovascular or musculo-skeletal diseases. Furthermore, we are interested in the number of additional diseases a patient typically gets.

### 2.1 Data

The data used for analysis were obtained from the Netherlands institute for health services research Primary Care Database (NPCD, formerly known as the LINH database). All Dutch inhabitants are obligated to register with a general practice, and the NPCD registry contains information of routinely recorded data from about all patients of approximately 90 general practices. Longitudinal data of approximately one and a half million patient years, covering 2003-2011, were used in our analysis. Patient data is available for the whole time frame, unless the patient moved out of the practice or the practice itself opted out. Our analysis includes 222,506 patients, aged over 35 years. 166,881 of the patients were randomly picked as training data, 22,250 as validation data and 33,375 as test data.

Table 1: Drug groups under consideration

Code	Name	Prevalence at baseline
C01	Cardiac therapy	0.072
C02	Antihypertensives	0.060
C03	Diuretics	0.006
C04	Peripheral vasodilators	0.142
C05	Vasoprotectives	0.001
C07	Beta blocking agents	0.037
C08	Calcium channel blockers	0.162
C09	Agents acting on the renin-angiotensin system	0.066
C10	Lipid modifying agents	0.145
M01	Anti-inflammatory and antirheumatic products	0.123
M02	Topical products for joint and muscular pain	0.333
M03	Muscle relaxants	0.005
M04	Antigout preparations	0.002
M05	Drugs for treatment of bone diseases	0.011
M09	Other drugs for disorders of the musculo-skeletal system	0.021
N02	Analgesics	0.008

The data was split in two time-periods:  $T_1 = [2003 - 2006]$  and  $T_2 = [2007 - 2011]$ . We used  $T_1$  as the situation at baseline, and  $T_2$  as the situation we aim to predict. We selected 16 cardiovascular and 26 musculo-skeletal diseases (respectively group K and L of the International Classification of Primary Care, ICPC). Two groups were used so that the effects of treatments could be measured, both within the same group of diseases and between groups. Furthermore, we considered 16 groups of drug treatment, listed in table 1, which are related to the two groups of diseases under consideration: all ATC codes classified in the sections *cardiovascular system* (C) and *musculo-skeletal system* (M). Additionally, we included *analgesics* (N02), because we hypothesize that this drug may be overprescribed for various conditions.

### 2.2 Procedure

We model the medical domain by a Bayesian network which we subsequently use for answering our research questions. Bayesian networks have been used before to investigate multimorbidity [9, 10].

They are popular because of their compact and intuitive nature. However, using them for answering queries about the domain does not scale well, as this problem is in general NP-hard, even for simple marginal queries. Tractable learning is a new promising field that focuses on learning Bayesian networks and other types of probabilistic graphical models that guarantee to answer certain classes of queries within limited time. Which classes of queries can be answered efficiently depends on the tractable representation. The most general representation that is being used today are Sentential Decision Diagrams (SDDs) [6, 2]. Its query space includes symmetric queries which aggregate over a subset of the variables. This allows us to reason on a higher level, for example, by asking queries about the class of cardiovascular diseases instead of a specific type of heart attack.

This paper presents the first method for learning Bayesian networks that efficiently answer symmetric queries efficiently, by using SDDs as their tractable representation. SDDs are highly flexible representations which facilitate adaptation of established non-tractable learners to tractable SDD learners. The Bayesian network is encoded as an SDD using ENC2 of Chavira and Darwiche (2008) [5]. Ordering-based search, rather than structure search, was used, as it performs equally well and usually faster [13]. Essentially, a fixed variable ordering facilitates learning the optimal network structure efficiently. Hence, searching for the best structure can be reduced to searching for the best ordering. The ordering, which is initially random, gets improved by greedily swapping variables that result in the best score. Local optima are avoided using restarts and Tabu lists. Tractable ordering-based search guarantees tractability by using a score that favors tractable models. Unfortunately, this extra score criterion makes it hard to learn the optimal network structure, even when the ordering is known. Nevertheless, searching over the order is advantageous because of its speed.

We adapted the algorithm to use decision trees for the conditional probability distributions (CPT-trees) instead of tables as they are shown to be able to capture complex domains with less variables and are therefore more tractable [8]. To find a good structure for an ordering, the CPT-trees are greedily grown, optimizing the improvement in likelihood penalized with the decrease in tractability [11]. This continues until the likelihood converges or as long as learning time and tractability constraints allow it. Next, two variables are swapped in the ordering. The swap that provides the highest upperbound on likelihood increase, is selected. It is executed by removing all the edges to the swapped variables in the Bayesian network. This process of growing CPT-trees and swapping variables is repeated as long as time allows. Note that the last model is not necessarily the best one found by the process. A model is picked from all the seen models based on its validation set likelihood

We learned Bayesian networks for three days with 60 restarts. The parameters have a symmetric Dirichlet distribution with parameter  $\alpha \in \{1.0, 0.1, 0.001, 0.00001\}$  as a prior. The minimum contribution in log likelihood of a split needs to be 0.0001. The maximum SDD size is 2,000,000. The maximum time for adding splits is 900s. The tabu list size is 10.

The selected model is used to calculate the probability of suffering from additional diseases within a group, both in general and after receiving a specific drug treatment. These probabilities are compared to see which drug treatments increase the probability. To investigate the size of the increment, we calculate the probability of an increment of size  $k \in \{1, 2, 3, 4\}$ . To calculate the probabilities, the SDD of the chosen model is queried, using the publically available software.<sup>1</sup>

### 2.3 Analysis

Table 2 gives the odds of suffering from additional diseases within a group, after receiving a certain drug treatment. It is calculated as follows:

$$\frac{\Pr(\#diseases \text{ in group in } T_2 > \#diseases \text{ in group in } T_1 \mid \text{drug treatment in } T_1)}{\Pr(\#diseases \text{ in group in } T_2 > \#diseases \text{ in group in } T_1)}$$

This number is 1 if the drug has no influence on the number of diseases and is greater or smaller than 1 when it respectively increases or decreases the number of diseases. The denominator of the fraction is 0.35 for cardiovascular and 0.44 for musculo-skeletal diseases. Big increases are marked in bold. Table 3 lists the probabilities of getting exactly  $k$  more diseases when there is an increase.

<sup>1</sup><https://dtai.cs.kuleuven.be/software/learnsdd/>

Table 2: The odds of suffering from additional diseases within a group, after receiving a certain drug treatment.

Drug group	Disease group		Drug group	Disease group	
	Cardiovascular	Musculo-skeletal		Cardiovascular	Musculo-skeletal
C01	<b>1.17</b>	0.89	M01	1.02	0.92
C02	0.98	0.95	M02	<b>1.20</b>	0.76
C03	<b>1.18</b>	1.01	M03	1.00	1.00
C04	0.89	0.88	M04	1.00	1.00
C05	1.00	1.00	M05	0.95	0.95
C07	1.00	0.93	M09	<b>1.30</b>	0.85
C08	0.98	0.94			
C09	0.89	0.91	N02	<b>1.46</b>	0.88
C10	0.89	0.90			

Table 3: The probabilities of getting exactly  $k$  more diseases when there is an increase.

k	1	2	3	4
Pr( $k$ more cardiovascular diseases)	0.68	0.23	0.07	0.02
Pr( $k$ more musculo-skeletal diseases)	0.47	0.28	0.14	0.07

### 3 Results

Prescriptions may lead to unintended negative consequences in further development of multimorbidity. Our results indeed show that there is a relationship between drugs and increase of cardiovascular diseases, but not of musculo-skeletal diseases. Notably, prescriptions may affect diseases in different subgroup from the disease that is being treated. For example, drugs for disorders of the musculo-skeletal system (M02 and M09) and analgesics (N02) seem to have a negative effect on cardiovascular health. These results are not sufficient to conclude causal relationships but they do emphasize the importance of a multidisciplinary approach in the context of multimorbidity. Note that these negative effects may be different between subgroups of diseases. Our results in table 3 suggest that if cardiovascular health decreases, the number of additional diagnoses is limited compared to the musculo-skeletal subgroup.

### 4 Conclusion

In this paper we investigated the effect of various treatments on further multimorbidity development, employing Bayesian network learning to model the domain. Although Bayesian networks have been used before to investigate multimorbidity, scaling such an analysis to larger networks which include prescriptions, requires tractable representations [9, 10]. In this work we examined two groups of diseases and discovered that prescription for one group can negatively effect the multimorbidity of the other group. Furthermore, these effects may differ between groups. This underlines the importance of a multidisciplinary approach in the context of multimorbidity. Future work will include analysis of more types of diseases and drug treatments.

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