

Multilevel temporal Bayesian networks can model longitudinal change in multimorbidity

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Abstract

Objectives: Although the course of single diseases can be studied using traditional epidemiologic techniques, these methods cannot capture the complex joint evolutionary course of multiple disorders. In this study, multilevel temporal Bayesian networks were adopted to study the course of multimorbidity in the expectation that this would yield new clinical insight.

Study Design and Setting: Clinical data of patients were extracted from 90 general practice registries in the Netherlands. One and half million patient-years were used for analysis. The simultaneous progression of six chronic cardiovascular conditions was investigated, correcting for both patient and practice-related variables.

Results: Cumulative incidence rates of one or more new morbidities rapidly increase with the number of morbidities present at baseline, ranging up to 47% and 76% for 3- and 5-year follow-ups, respectively. Hypertension and lipid disorders, as health risk factors, increase the cumulative incidence rates of both individual and multiple disorders. Moreover, in their presence, the *observed* cumulative incidence rates of combinations of cardiovascular disorders, that is, multimorbidity differs significantly from the *expected* rates.

Conclusion: There are clear synergies between health risks and chronic diseases when multimorbidity within a patient progresses over time. The method used here supports a more comprehensive analysis of such synergies compared with what can be obtained by traditional statistics. © 2013 Elsevier Inc. All rights reserved.

Keywords: Multimorbidity; Interpractice variation; Synergy; Multilevel analysis; Bayesian networks; Cardiovascular disease

1. Introduction

Recent epidemiologic research indicates that up to two-third of all patients older than 65 years in the Western world have more than one chronic disorder at the same time. This is referred to as *comorbidity* or *multimorbidity*. Although comorbidity is usually defined in relationship to a specific index condition, as in the seminal definition by Feinstein [1], the term “multimorbidity” has been introduced to refer to any co-occurrence of two or more medical, especially chronic, conditions within a person at the same time

[2,3]. Multimorbidity can be simply measured by computing various basic statistics: the number of chronic disorders per patient; corrected for age, gender, and socioeconomic demographics [4–7]; odds that describe the ratio between observed and expected prevalence rates for specific disease combinations [8–11]; and disease clusters using principal component analysis [12–15].

Although systematic reviews [16–18] have given insight into the rates of cross-sectional co-occurrence, the progression over time of interactions between chronic cardiovascular diseases and related disorders is sparsely documented [19]. More insight into such interactions would help in personalizing the therapeutic management of patients with multimorbidity. As clinical knowledge is mostly organized around single diseases, that knowledge may not be fully applicable to patients with multimorbidity [20,21]. The care of patients with multimorbidity can be improved by any method that tailors the advice to the patient’s specific characteristics [22].

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What is new?

Key findings

- The urbanization level of a general practice is associated with the cumulative incidence of chronic cardiovascular conditions, in particular those with a high prevalence, that is, obesity, hypertension, dyslipidemia, diabetes mellitus, and ischemic heart disease.
- The overall multimorbidity rate of chronic cardiovascular (related) disorders rapidly increases when multimorbidity is already present at baseline.
- When multimorbidity progresses over time, certain disease combinations develop more quickly than what can be expected from individual disease progression. This synergistic effect happens particularly in the presence of hypertension and dyslipidemia.

What this adds to what was known?

- Multimorbidity is about not only pairs of diseases but also how multiple diseases in patients interact and how this interaction changes over time. For the first time, this proper perspective on multimorbidity is described and analyzed using the new technique of multilevel temporal Bayesian networks. This new method supports not only finding multiple associations and how these change over time but also which of these represent a direct association or a confounder, and how factors indirectly influence each other.

What is the implication and what should change now?

- Although standard multilevel regression methods are very useful to explain a single disease with respect to a set of patient and practice-related observable variables, multilevel Bayesian networks allow exploring the joint distribution of multiple diseases and their interactions, which are highly relevant in multimorbidity research.
- Clinical guidelines for patients with multimorbidity can be improved when the advice incorporates all the patient's specific characteristics. Because the network in the methodology used here can be personalized for a specific patient, it provides a valuable tool for the development of such tailored clinical guidelines.

Recent explorations of patient data from primary care registries to quantify associations between chronic disorders have shown these to be valuable for obtaining a broad

picture of multimorbidity [21,23,24]. In this article, we will use such registries to assess three aspects of the joint progression of chronic cardiovascular multimorbidity: (1) dependency on the practice's urbanity, (2) the synergistic effects between disorders when they evolve over time, and (3) the progression of the overall multimorbidity rate.

Patient data in primary care registries are often clustered by practices, introducing particular biases in the patient's diagnosis due to practice-related effects. For example, the urbanity of the practice's area or the physician's experience. Multilevel regression analysis is the standard method of choice in these situations [25]. However, it does not allow analyzing multiple disease outcomes simultaneously. Therefore, we adopted the method of *multilevel Bayesian networks* (MBNs) that do offer such support [26]. When used for the analysis of temporal data, the advantage of an MBN is that the disorders and their interaction are treated as uncertain. The representation goes beyond showing how pairs of disorders are associated to each other. Furthermore, we can extend an MBN to analyze multiple outcomes at multiple time points. The latter gives rise to *multilevel temporal Bayesian networks* (MTBNs).

In summary, we developed a multimorbidity model that yields a much better insight into interactions, progression over time, and the accumulation of chronic disorders than that existing statistical models are able to provide. Moreover, we show that posterior probabilities computed from the model at follow-ups can be tailored to any set of conditions present at baseline, which can provide valuable input for *personalized* clinical decision-making.

2. Methods

2.1. Data collection

The data used for analysis were obtained from the Netherlands Information Network of General Practice (LINH). All Dutch inhabitants are obligatory registered with a general practice, and the LINH registry contains information of routinely recorded data from almost all patients of approximately 90 general practices. Longitudinal data of approximately one and half million patient-years, covering the decade 2002–2011, from patients aged more than 35 years, were used in our analysis. Patient data are available for the whole time frame, unless patient moved out of the practice or the practice itself opted out.

We used the definition of a “chronic disorder” given by O'Halloran et al. [27], which in turn was based on the International Classification of Primary Care (ICPC) codes. Principally, our focus was on chronic cardiovascular diseases and related disorders, and in our model, we included the following chronic disorders: obesity, hypertension, lipid disorder, diabetes mellitus, heart failure, stroke, ischemic heart disease, retinopathy, and nephropathy. The first three disorders are seen as health risks. Previous research has

indicated that also some noncardiovascular comorbidities are associated with cardiovascular disorders [21,28]. Therefore, the diagnoses of other chronic noncardiovascular disorders were modeled as well but only as a single variable.

Laboratory results and medication were not always consistent with the diagnoses present in the LINH database. For example, insulin was sometimes prescribed to patients who were not diagnosed with diabetes mellitus according to the data. To compensate for such missing or incorrect information, we used laboratory results and medication to infer the diagnosis of obesity, hypertension, dyslipidemia, and diabetes mellitus, in conjunction to the ICPC codes. This correction method has some limitations. For example, although statins are typically prescribed for lipid disorders, one cannot conclude that any patient who uses this drug has a lipid disorder [29]. Similarly, blood pressure–lowering medication is sometimes prescribed for other cardiovascular disorders than hypertension.

Corrections were made using the following rules adopted from the Dutch guidelines on cardiovascular risk management [30], which are in line with the European guidelines on cardiovascular risk management in clinical practice [29]. For obesity, a body mass index of more than 30 kg/m²; for hypertension, a high blood pressure (systolic > 140 mm Hg or diastolic > 90 mm Hg) within at least two recurring measurements; for dyslipidemia, an abnormal blood lipid profile (low-density lipoprotein > 3 mmol/l, high-density lipoprotein < 1 mmol/l, or triglycerides > 2 mmol/l); and for diabetes mellitus, a fasting glucose ≥ 6 mmol/l, or a prescription of either insulin or oral blood glucose–lowering medication. See Appendix at www.jclinepi.com for more details on data collection and the ICPC codes used for identification of the disorders used in the model.

2.2. Statistical analyses

As the patient data in the LINH data set were obtained from several general practices, differences among those general practices may have a confounding effect on the probability distributions. Taking into account the hierarchical structure into statistical models demands for a multilevel approach. We used MBNs in our analysis [26]. Bayesian networks provide a powerful framework for the representation of knowledge and reasoning under uncertainty [31], and they have had a significant impact on the modeling and the analysis of medical data [32]. The statistical relationships in such models can be learned from patient data. Recently, it was shown that when applying MBNs to a set of hierarchically structured disease variables, the outcome of multiple diseases can be very well predicted using an MBN [26]. With a receiver operating characteristic curve, it was demonstrated that a single MBN outperformed the use of multilevel regression models for each disease separately.

The use of a network-based approach to human disease, so-called *network medicine*, was recently acknowledged to be useful when researching complex disease pathways [33]. In an MBN, the disease variables are also represented as nodes in a network, but the associations have a direction, and probabilistic associations are represented by arrows. When there is an arrow from node *i* to node *j*, then *i* is called a *parent* of *j*, and *j* is called a *child* of *i*. Although we cannot assume that these arrows represent true causality, often they do. Temporal arrows always point from the past to the future, and here, a causal interpretation is even more natural. Each node is associated with a multinomial probability distribution for each configuration of the parent nodes. The interactions or moderating effects between parent nodes on their common child are therefore captured in these local probability distributions.

In the MBN used for this paper, we modeled the patient's status in terms of the predefined disorders at baseline using the first 5 years of the data in retrospect, with a registration minimum of 3 years. The population used here is a fixed cohort of patients that were alive at baseline. The disease status 3 and 5 years after the baseline was also included in the model, although patients might have been deceased or moved to another practice at that time. Building the complete MBN required two major steps:

1. Specifying the qualitative nature of the relationships in the network,
2. Specifying the local probability distributions of the disease variables.

For step 1, all the disorders were represented as binary nodes, that is, the disorder is present yes or no. Age was discretized into four age groups. The subnetworks constituting the resulted three time slices were then connected in such a way that each disorder variable had at least one directed arrow to the same variable in the next time slice. By doing this, the MBN is transformed into an MTBN. The urbanity of the practice was operationalized to control for several potential confounding factors, that is, it was included as a higher level variable in the MTBN.

Although the relationships between the disease variables, that is, the arrows in the network, can be specified by the user itself, we learned these relationships from the data. One reason for this is to see whether unknown relationships could be revealed. Both the relationships between disease variables within a time slice and between different time slices were learned using a score-based searching method in the statistical R package *bnlearn* (<http://www.r-project.org/>) [34]. We assumed that the qualitative nature of associations between disease variables do not vary over time, that is, the network structure remains the same for each time slice. To ensure a multilevel structure and specific medical knowledge, dependencies between disease variables can be secured or avoided through black- and white listing. For example, if an association between a demographic node *C* and a disease node *D* was found by the

structure learning algorithm, the corresponding arrow in the network clearly should be $C \rightarrow D$. Therefore, all possible arrows $D_i \rightarrow C_j$ were blacklisted.

For step 2, we assumed that although the network structure remains the same for each time slice, the parameters of the local probability distributions were allowed to change over time. The latter condition is known as the condition of nonstationarity. Once the complete structure was determined, the local probability distributions were estimated using 1,000 bootstrapped samples from the data set, that is, we computed $P(D_t^i | \text{parents}(D_t^i))$ with $D_t^i=1$ if disease i is present at time t and $D_t^i=0$ otherwise. Note that $\text{parents}(D_t^i)$ is determined by the network structure; it can contain disease variables of several types, for example, age, a health risk factor, or another disease, from both current and previous time slices. The variance induced by the urbanization level (a practice level variable), age, and gender, in the multilevel model was explained by using Markov Chain Monte Carlo simulation in WinBUGS (MRC Biostatistics Unit, Cambridge, UK) [35]. For ease of use, the learned structure and parameters were put into the software package SamIam (Automated Reasoning Group, University Of California, Los Angeles).

The total number of disorders present simultaneously in patients, that is, the multimorbidity rate, was calculated using nodes M_t that kept track of the number of disorders present in time slice t . The probability distribution of these nodes is deterministic, that is:

$$P(M_t = q | D_t^1, D_t^2, \dots, D_t^n) = \begin{cases} 1 & \text{if } \sum_{i=1}^n D_t^i = q \\ 0 & \text{otherwise} \end{cases} \quad (1)$$

The value q then represents the number of simultaneously present disorders. See Appendix at www.jclinepi.com for more details on the implementation of MTBNs.

Once the local probability distributions were determined, we were able to answer the questions mentioned in the Introduction. The urbanity effects were derived by conditioning on a specific value of the corresponding node in the network. Second, for each time slice, we determined whether cumulative incidence rates of disease combinations significantly deviated by increased occurrence from what might be expected from individual cumulative incidence rates, assuming statistical independence. Mathematically, this can be expressed for two disorders i_1 and i_2 as:

$$P(D_{t_1}^{i_1}, D_{t_1}^{i_2} | R_t) \gg P(D_{t_1}^{i_1} | R_t)P(D_{t_1}^{i_2} | R_t) \quad (2)$$

with R_t the set of health risks R_t^k present at time t . Because the size of the studied patient population favors reaching significance easily, we also examined the clinical importance of such deviations.

By conditioning on the multimorbidity rate M_t in a specific time slice, the model allowed us to predict the multimorbidity rate in the next time slice, which is mathematically expressed by

$$P(M_t = q | M_{t-1} = r). \quad (3)$$

We are particularly interested in the probabilities for $q > r$ because if these are large, the number of simultaneous disorders increases with time. These probabilities can be biased because of possible disease shifts, that is, the patient acquires a new disorder but also loses one, keeping the multimorbidity rate equal. To evaluate this effect, we calculated how much acquired disorders sustained in the next time slice, mathematically:

$$P(D_t^i = 1 | D_{t-1}^i = 1). \quad (4)$$

If these probabilities are close to one, the effects of disease shifts are considered to be minimal.

3. Results

The final MTBN consists of three time slices modeling chronic cardiovascular disease progression. The associations in the MTBN are summarized in Table 1. The complete network structure representing all the parent–child relations, and thus the qualitative nature of the underlying multivariate distributions, is available online in the Appendix at www.jclinepi.com together with the corresponding code for parameter estimation. Evidently, age had a significant association with all other variables. However, gender did not have a significant association with CVD, except for ischemic heart disease.

Data of a total of 182,396 patients were used for analysis. The median and mean age of the patients at baseline were 53 and 55 years, respectively. At the end of the 5-year follow-up, 8.5% of these patients had dropped out of the registry. This happened because of death, patients moved to a nursery home, or practice not present in the registry. Their disease status until this event was included in our analysis.

For all health risks and chronic disorders that were incorporated into the model, cumulative incidence rates, with their standard errors, were estimated for each time slice. These were differentiated for age and urbanity, and to examine the model’s validity further, we also made model predictions for diabetics and nondiabetics. Besides the individual rates, we also calculated rates of comorbidity patterns. Details on demographics and probability estimations are available online in the Appendix at www.jclinepi.com. The effect of urbanity on disease probabilities, corrected for age and gender, is shown in Fig. 1.

Table 2 shows the evaluation of synergies, as defined in Eq. (2), in which cumulative incidence rates of the comorbidity patterns are compared with the rates of single disorders. As dyslipidemia and hypertension are the major predictors of cardiovascular morbidities, we computed the conditional probabilities in the absence and presence of these conditions from the MTBN. Some of the comorbidity patterns deviate significantly from the expected values. For

Table 1. Associations between cardiovascular diseases, known from the literature, and learned from the data

Chronic disease	Associations known from the literature	Associations learned from the data	
		Direct ^a	Indirect ^b
Diabetes mellitus	Age, dyslipidemia, hypertension, ischemic heart disease, heart failure, nephropathy, retinopathy obesity, stroke ^c [37], and practice [43]	Age, dyslipidemia, hypertension, ischemic heart disease, heart failure, nephropathy, and retinopathy	Practice, obesity, and stroke
Ischemic heart disease	Age, gender, obesity, dyslipidemia, hypertension, diabetes mellitus, heart failure, stroke ^c [29], retinopathy [44], and practice [23]	Age, gender, dyslipidemia, hypertension, diabetes mellitus, and heart failure	Practice, obesity, stroke, <i>nephropathy</i> , and retinopathy
Heart failure	Age, obesity, dyslipidemia, hypertension, diabetes mellitus, ischemic heart disease, nephropathy, and stroke ^c [45]	Age, hypertension, diabetes mellitus, ischemic heart disease, stroke, and nephropathy	<i>Practice</i> , obesity, dyslipidemia, and <i>retinopathy</i>
Stroke	Age, obesity, dyslipidemia, hypertension, diabetes mellitus, ischemic heart disease, heart failure ^c [29], and practice [23]	Age, dyslipidemia, hypertension, and heart failure	Practice, obesity, diabetes mellitus, ischemic heart disease, <i>nephropathy</i> , and <i>retinopathy</i>
Nephropathy	Age, gender, hypertension, diabetes mellitus, ischemic heart disease, heart failure, stroke [46], and retinopathy [47]	Age, hypertension, diabetes mellitus, and heart failure	<i>Practice</i> , <i>obesity</i> , dyslipidemia, ischemic heart disease, and retinopathy
Retinopathy	Age, dyslipidemia, hypertension, diabetes mellitus ^c [37], ischemic heart disease [44], and nephropathy [47]	Age, hypertension, and diabetes mellitus	<i>Practice</i> , <i>obesity</i> , dyslipidemia, ischemic heart disease, <i>heart failure</i> , and nephropathy

Italicized associations were not directly clear from the used literature.

^a Direct associations correspond to a direct arrow between diseases in the MTBN.

^b Indirect associations correspond to diseases that have another disease between them or share a common child or parent in the MTBN.

^c Clinical guidelines.

example, at 5-year follow-up, the probability of ischemic heart disease and heart failure together is 5.4% when both dyslipidemia and hypertension are present. However, using Eq. (2), the product of their individual rates is only 2.9%. The true incidence is thus almost twice as high, which indicates an interaction between the two disorders in relation to hypertension and dyslipidemia. This phenomenon can be found for several comorbidity patterns through each time slice. Because probabilities of disease combinations are relatively low, we consider absolute increments, rather than relative increments, in which an increment of 0.5% is considered to be of clinical relevance.

Fig. 2 shows the multimorbidity rates, as defined in Eq. (3). For patients having one or more health risks, the probability of obtaining a new health risk is relatively low, compared with the presence of other cardiovascular disorders. In that case, the cumulative incidence rate rapidly increases with the number of conditions present in the previous time slice. For example, when having two disorders at baseline, the probability of obtaining one or more cardiovascular disorders after 3-year follow-up is approximately $19\% + 3\% = 22\%$, following the arrows from node 2 (at baseline) to nodes 3 and 4 plus (at 3-year follow-up) at the right-hand side of Fig. 2. From the remaining 78%, those who attracted no new cardiovascular disorder within 3 years, another 32% gets one or more disorders at 5-year follow-up, making the total probability 47%.

Table 3 shows the persistence probabilities of individual disorders at follow-ups, as defined in Eq. (4). For most disorders, more than 90% sustained in the next time slice. Obesity is the major exception on this.

4. Discussion

In this study, the new method of MTBNs was used to precisely capture the *qualitative* and *quantitative* time course of chronic cardiovascular multimorbidity in general practices. Bayesian network methods have not been used before in multimorbidity analysis. Although the discovered network dependences are sometimes similar to the associations described in medical literature, discovered by standard statistical means, the global picture of how chronic disorders and risk factors influence each other, as represented by a MBN, is new. It gives an overview of *direct* and *indirect* associations and it quantifies transition rates, all in one representation. The results obtained are discussed in more detail in the following.

4.1. Evaluation of the network structure

The associations summarized in Table 1 are compared with current knowledge reflected in recent clinical guidelines and the medical literature. A distinction is made between direct and indirect dependences, something not

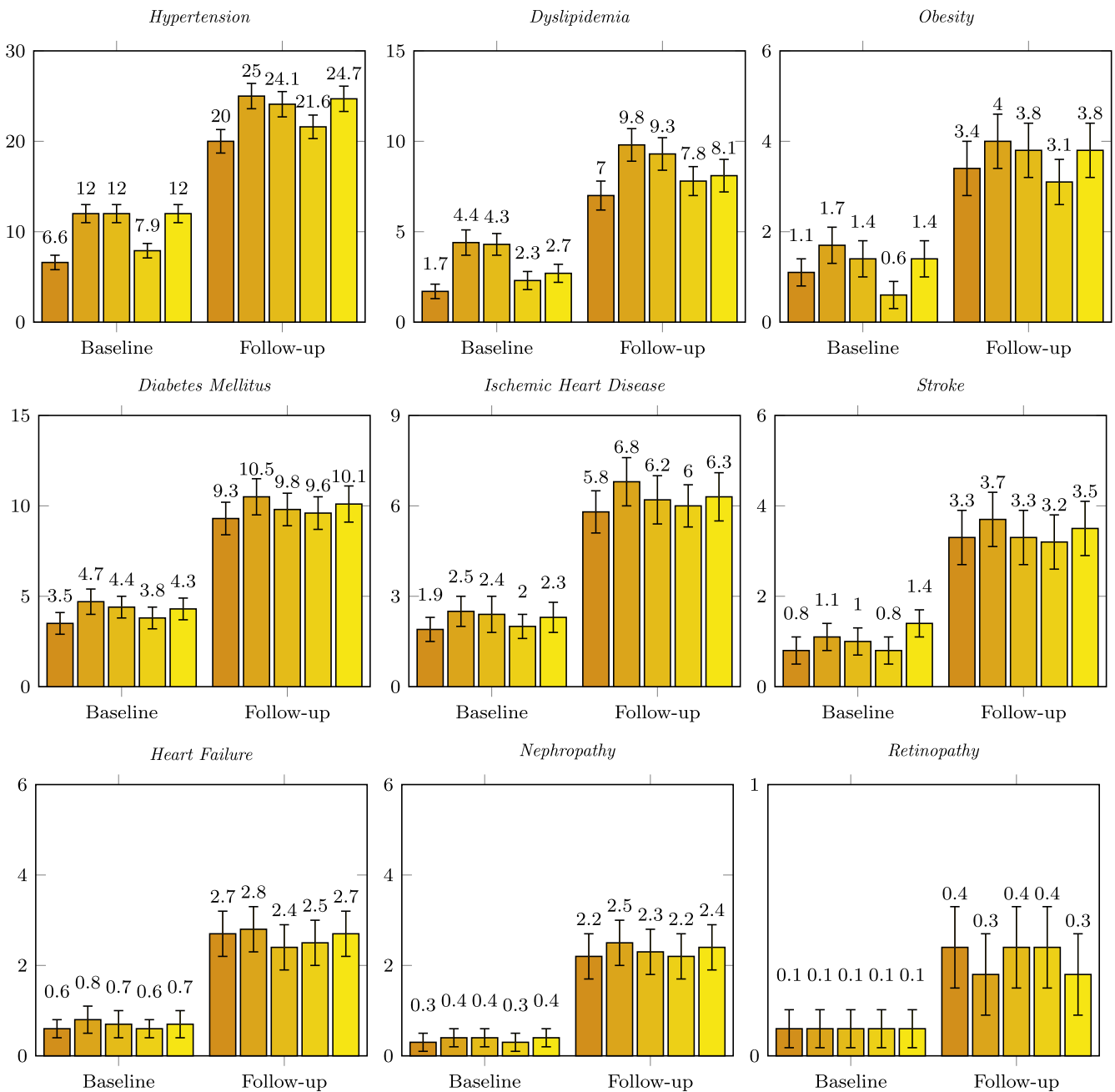


Fig. 1. The effect of the urbanization level, varying from very high urban areas (> 2,500 addresses per km², orange) to rural areas (< 500 addresses per km², yellow), on cumulative disease incidence at baseline and 5-year follow-up. Numbers are corrected for age and gender and provided with a 95% confidence interval (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

possible when using standard statistical methods. For example, represented in the MTBN, there is an indirect association between dyslipidemia and heart failure via, that is, conditional on, ischemic heart disease and hypertension. This is in line with clinical guidelines on heart failure, which state that there is no reason to prescribe a statin in the absence of an ischemic cause of heart failure [29].

Other disorders share a common parent in the network structure, for example, both retinopathy and nephropathy share diabetes mellitus and hypertension as a common

parent. The investigation of either of them in the presence of the other is thus only of beneficial value if either diabetes mellitus or hypertension is also present.

The analysis shows that gender-induced associations are insignificant or small, and in case it is small, it is of little clinical significance. The exception on this is ischemic heart disease, in which it is well established that gender is significant [36].

The comorbid associations between cardiovascular-related disorders and other chronic disorders [28] are also

Table 2. Probability of having comorbid combinations of chronic cardiovascular diseases at baseline, and after 3- and 5-year follow-ups, under the condition of the presence or absence of health risks

Risk Factors	BaseLine				3 years follow-up				5 years follow-up			
	None	DL	HT	DL+HT	None	DL	HT	DL+HT	None	DL	HT	DL+HT
Comorbidity												
DM+IHD	0.2	2.6	1.8	6.2	0.7	5.8	4.4	11.2	1.0	6.8	5.4	14.0
DM+HF	<.1	0.5	0.7	1.3	0.4	1.6	2.1	3.9	0.5	2.5	3.0	5.0
DM+NP	<.1	0.3	0.4	0.9	0.3	1.1	2.0	3.8	0.5	1.7	3.1	5.0
DM+ST	<.1	0.7	0.7	2.6	0.2	1.9	2.1	5.3	0.4	2.4	2.9	6.4
DM+RP	<.1	0.1	0.1	0.2	0.1	0.2	0.2	0.3	0.1	0.3	0.3	0.4
IHD+ST	<.1	0.6	0.4	1.7	0.2	1.6	1.3	3.8	0.3	2.3	2.0	4.9
IHD+NP	<.1	<.1	0.2	0.5	0.1	0.6	1.0	2.0	0.2	1.1	1.7	3.4
IHD+HF	<.1	0.8	0.9	1.8	0.4	2.1	2.2	3.9	0.6	2.8	3.2	5.4
ST+HF	<.1	0.1	0.3	0.4	0.2	0.5	0.9	1.4	0.3	0.9	1.4	2.2
NP+HF	<.1	<.1	0.1	0.2	0.1	0.4	0.9	1.1	0.3	0.6	1.5	2.0

Abbreviations: DL, dyslipidemia; HT, hypertension; DM, diabetes mellitus; IHD, ischemic heart disease; HF, heart failure; NP, nephropathy; ST, stroke; RP, retinopathy.

Results are shown in percentages. The yellow part of the circle represents the expected value based on individual rates, the surplus is colored in orange or red (see also Eq. (2) of the article). Red circles represent cumulative incidence rates, which deviate significantly ($P < 0.001$) from the expected values and have a clinical importance as well (absolute increase $> 0.5\%$). They indicate the clinically significant interactions.

recognized in our model; obesity, hypertension, dyslipidemia, and diabetes mellitus are associated with noncardiovascular disorders. Moreover, the temporal associations show that diabetes mellitus is a direct predictor of such disorders in follow-ups.

Although the network structure indicates that obesity is a good predictor of hypertension and dyslipidemia, we observe that direct associations between obesity and conditions other than hypertension and dyslipidemia are missing. For example, one would have expected an arrow from obesity to diabetes mellitus because it is well known that an elevated body mass index or waist circumferences are associated with diabetes mellitus [37]. Hence, the effect of obesity on other conditions is probably underestimated in the data explored, in particular because of low persistence at follow-ups in the database. The latter does not mean that most patients actually lose weight but that registries do not properly keep track on this matter. However, if we leave obesity out of the model, it has little effect on the structure and the associated probabilities are minimally affected (data not shown).

4.2. Quantitative analysis

The prevalences of morbidity and comorbidity patterns at 3-year follow-up are comparable with prevalences obtained from previous studies using LINH data [11] and earlier results within the Netherlands [4]. The associations among age, diabetes, and cardiovascular multimorbidity are quantitatively well recognized by the model. The multilevel approach allowed us to differentiate probabilities for practice-related variables. Where other researchers showed an association between multimorbidity and socioeconomic status [8,21], we modeled the urbanity of the practice along with the disease variables. In case of obesity, hypertension, dyslipidemia, diabetes mellitus, and ischemic heart disease, the urbanization level had a significant effect on the prevalence. In these cases, the cumulative incidences of moderate and high-urban areas were mostly above average, whereas these incidences of low and very high urban areas were mostly below average. Rural areas show on average incidences comparable with the overall average.

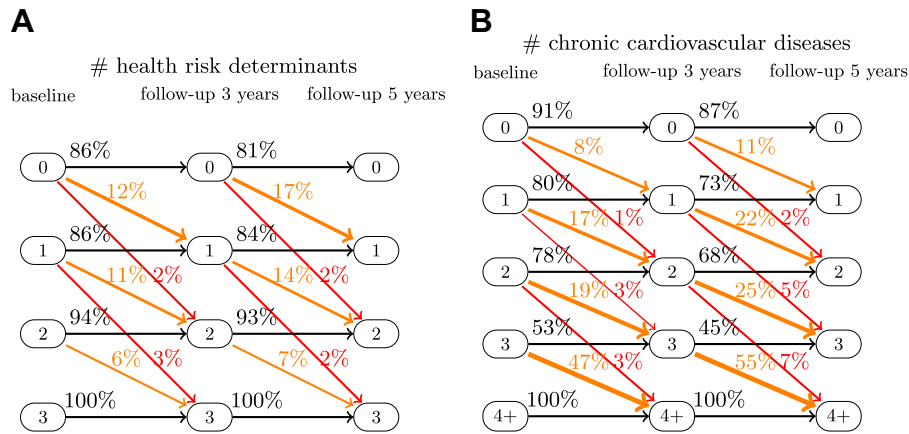


Fig. 2. Transition probabilities of (A) health risks and (B) chronic cardiovascular diseases (see also Eq. (3) of the article). Health risks are obesity, dyslipidemia, and hypertension. Chronic cardiovascular diseases are diabetes mellitus, ischemic heart disease, heart failure, stroke, retinopathy, and nephropathy. The left (black) percentages and lines represent patients who do not acquire a new determinant or chronic disease within the next time slice, whereas the middle (orange) and right (red) percentages and lines represent patients acquiring respectively one or two new health risks or chronic diseases within the next time slice (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

The effect of multiple cardiovascular risk factors was already outlined in Ref. [38], indicating that the 5-year cardiovascular risk can go up to 44% when certain risk factors, for example, hypertension, total cholesterol, smoking, high-density lipoprotein, gender, diabetes, and high age, are present. Their results indicate, for example, that a smoking male patient of age more than 60 years with diabetes, high total cholesterol and low high-density lipoprotein has a 5-year cardiovascular risk of 22% and 44% for low and high systolic blood pressures, respectively. We can do more or less the same exercise as aforementioned: the 5-year cardiovascular risk for a male diabetic living in a rural area, aged between 65 and 80 years, and having a lipid disorder is 28% for nonhypertensive patients and 55% for hypertensive patients.

However, the multiple-risk attributions in their approach could only be derived by adding the risk factors consecutively in a specific order. In our model, there is no restriction on the number of disease variables used as a predictor

and the number of disease variables being predicted. For example, the 5-year cardiovascular risk of *two or more* new diseases is 10% and 23% for the patient aforementioned. It also implies that we can condition on a specific cardiovascular disease already present. When conditioning on heart failure, the effect on cardiovascular risk is the highest, for example, a male hypertensive diabetic with dyslipidemia, living in a rural area, aged between 65 and 80 years, and with heart failure already present at baseline has a 5-year risk of 71% to obtain another cardiovascular disease and 27% for two or more diseases.

Although any other cardiovascular risk score also represents a personalization, the major difference with an MTBN is that in an MTBN not all disease variables need to be known. In fact, an MTBN captures all predictions for *any* disease variable within the model for *any subset* of the remaining variables. This means that one can also reason the other way around: given the presence of certain diseases, one can make predictions about the presence of specific risk factors, for example, hypertension or lipid disorders are more likely to be present in the presence of cardiovascular diseases. In Fig. 3, an example is shown of personalization, indicating that multimorbidity at baseline predicts future multimorbidity better than the demographics do. This is in line with the idea that the patient’s *biological* age is of more importance in relationship to morbidity than *chronological* age [39] and the relation between frailty and the accumulation of deficits [40].

In summary, an MTBN can be used to make predictions for multiple diseases in many ways. To our knowledge, this is new in multimorbidity research, and Table 2 only reflects a particular personalization of cardiovascular risk. It reveals multiple interactions between chronic cardiovascular diseases and related disorders, which occur more frequently at follow-ups compared with baseline. We shall not discuss

Table 3. Persistence of individual chronic diseases, that is, the probability (in percentages) of a disorder being present at follow-ups under the condition that this disorder was present in the previous time slice (see also Eq. (4) of the article)

Chronic disorder	$t_0 \rightarrow t_1$	$t_1 \rightarrow t_2$
Obesity	40	33
Dyslipidemia	78	90
Hypertension	95	97
Diabetes mellitus	95	91
Ischemic heart disease	94	98
Heart failure	95	99
Stroke	90	91
Nephropathy	98	99
Retinopathy	99	99
Other	66	90

t_0 = baseline; t_1 = 3-year follow-up, and t_2 = 5-year follow-up.

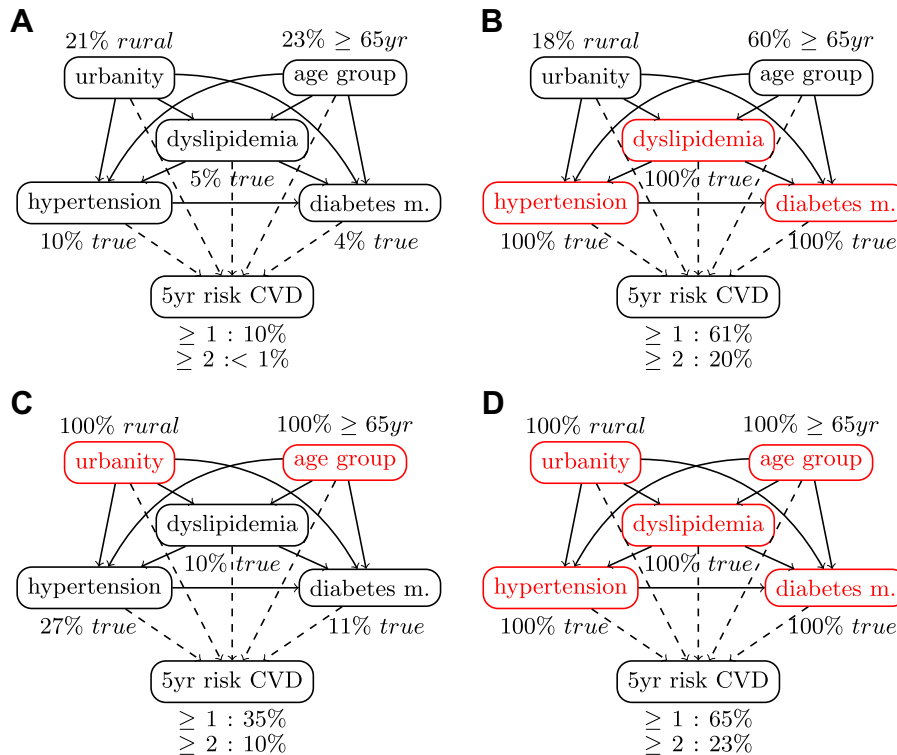


Fig. 3. Personalization of a subset of the disease model. Straight lines represent the atemporal associations at baseline, and dashed lines represent the temporal associations between baseline conditions and the 5-year cardiovascular risk. Part figure (A) shows the 5-year risk on a cardiovascular (related) disease (ischemic heart disease, heart failure, stroke, retinopathy, or nephropathy) of the general Dutch population aged more than 35 years. This probability is 10%, and within this population, we have the following prior probabilities of risk factors: 21% lives in a rural area, 23% is older than 65 years, 10% has hypertension, 5% has dyslipidemia, and 4% has diabetes mellitus. The part figures (B), (C), and (D) show how probabilities change when specific information of the patient is incorporated. (B) represents patients with hypertension, dyslipidemia, and diabetes at baseline but without knowledge about the patient’s demographics. The 5-year risk has increased to 61%, and it is estimated that 18% lives in a rural area and 60% is more than 65 years old. (C) represents patients older than 65 years, living in a rural area but without knowledge about the patient’s disease status. The 5-year risk on CVD has increased to 45% and it is estimated that cumulative incidences of risk factors are doubled or more. (D) is the combination of (B) and (C), showing that the 5-year risk has gained only a little with respect to (B). CVD, cardiovascular disease.

every interaction in detail, but it appears that the presence of hypertension or dyslipidemia is a necessary precondition for finding clinically significant interactions. For example, the combination of ischemic heart disease and heart failure is much higher as expected after 3- and 5-year follow-ups. Alternatively, although cumulative incidences increase over time, they behave as expected, for example, in the case of ischemic heart disease in combination with stroke. This fits with the fact that only an indirect association exists in the model.

Another new aspect of our model is the temporal associations. They cause the incidence of chronic disorders to rise quickly over time. In particular, the probability of acquiring at least one new chronic cardiovascular disorder increases with the number of chronic cardiovascular disorders already present, regardless of age (Fig. 2). At 3-year follow-up, this is respectively 9%, 20%, 22%, and 47%, for zero to three disorders present at baseline. At 5-year follow-up, this has increased to respectively 21%, 42%, 47%, and 76%. In reality, these numbers can be even higher because of disease shifts. Because the probability of

sustaining a chronic disorder is at least 90%, for the ones we used in our model, we believe this effect is minimal.

Cross-sectional research of other registries shows that the prevalence of multimorbidity can be up to 90% [4–6,21]. Moreover, 80% of the elderly patients with heart failure face at least *four* chronic comorbidities [28]. These numbers are comparable with the prevalences of cardiovascular comorbidity at follow-ups retrieved in our model. However, the prevalence of cardiovascular multimorbidity, in particular for diabetes mellitus, ischemic heart disease, and stroke, is much lower at baseline in our model. This indicates the importance of the temporal dimension; estimates cannot be directly extrapolated to follow-ups, for example, using the prevalences of a higher age group.

4.3. Strength, limitations, and implications

The major strength of the results is that the obtained MTBN allows analyzing several aspects of multimorbidity in a single model. Our research encompassed an analysis of

data obtained from public health registries, and because of the size of the data set used, significant results could be established. Although the data used here contained more patients and more disease variables as mostly present in controlled studies, it also contains more noise and typically involved more preprocessing. Controlled studies are relatively small in size and often exclude patients with multimorbidity. There are some exceptions on this, for example, recently, a cohort study of nearly 15,000 elderly people had a focus on the epidemiology of chronic diseases using a variety of biomarkers and noninvasive measurements [41]. But most of its research had a single-disease focus. We recommend to apply Bayesian networks here as well to discover the coherence between the multiple biomarkers and disorders present in such studies.

Several aspects of the results could have been analyzed by alternative methods. For instance, multistate models could have been used to analyze the transition rates in the multimorbidity number, a separate multilevel regression model for each disease to investigate the urbanity effects, and a chi-square test to see if the joint prevalence of two conditions is higher than would be expected. However, investigating more complex interactions, like in Table 2, would require logistic regression with added *interaction terms* [42]. Logistic regression demands building a separate model for each disorder; in this way, the insight into the qualitative nature of the interactions between the disorders would be lost.

With an MTBN, we also avoid the redundancy that is obtained when using multiple separate regression models for each disease. For example, if we regress disease D on disease D' in one model and in another model D' on D, we obtain two parameters for the same association. This could produce certain ambiguity because the two models do not necessarily have to provide the same odds ratio for that pair. In summary, the MTBN used here allows analyzing all the results presented in this article without losing any of the epidemiologic coherence between all the disease variables. To our knowledge, this is new in multimorbidity research, and there is no *single* alternative that analyzes multimorbidity the way we did.

There are some aspects of registries that introduce a certain bias. Patients who did not visit their physician within the used time frame are not included in the data. Although we explored a decade of patient data within a time frame of 10 years and patients of age 35 years and older, making the proportion of missing patients likely to be very low, prevalences are probably slightly overestimated. On the other hand, in public health registries, data are missing and there are also incorrectly coded diagnoses, implying that prevalences might also be underestimated. Clinical guidelines often recommend specific additional investigations, making it that certain disorders are discovered more likely than others. For example, retinopathy in a diabetic may only be discovered because of the recommendation mentioned in the guideline of visiting an ophthalmologist.

In our results, there is a considerable prevalence change between the baseline and follow-ups. Partly, this is because the population has aged 5 years. On the other hand, the absence of a diagnosis is interpreted as the absence of the corresponding disease, however, certain pathophysiology could already be present at baseline without knowing it. This delay in diagnosis also makes longitudinal associations between disorders less detectable.

5. Conclusions

Several attempts have been made in the literature to capture prevalences of multimorbidity. Lately, electronic databases of general practices are used more and more to quantify these numbers on a larger scale, but there is no clear method that fully describes how multiple disease evolve over time. Traditional statistical techniques are very useful to evaluate a single-disease framework by which most medical care, research, and education is configured. However, a multiple-disease orientation requires a more complementary strategy.

In that respect, the MTBN used here is a valuable step forward in multimorbidity research. It combines the advantages of a temporal Bayesian network together with a multilevel analysis, and it was able to discover complex multimorbidity patterns of chronic diseases within health care data. First, the model was shown to be valid by comparing known disease interactions for diabetes mellitus with those present in the network structure. Second, several new disease interactions, qualitative and quantitative, for 3- and 5-year follow-ups were discovered, showing that cumulative incidence rates are accelerated in the presence of multimorbidity. Especially, the presence of conditions such as hypertension, dyslipidemia, and diabetes mellitus accelerates cardiovascular risk significantly.

The article only discusses the most significant results that can be obtained from an analysis of the MTBN model. The model itself can be used to extract many other relevant conclusions. We conclude that Bayesian network models make the analysis and visualization of the interactions between chronic disorders and their evolutionary course more comprehensive than traditional statistical techniques. They can be used to answer a variety of clinical and epidemiologic questions without losing the context of these dependences out of sight. This is of great importance in the management of multimorbidity and the aim to adopt personalized clinical guidelines. The next step in multimorbidity research might be to address mortality rates, differentiated for cardiovascular and noncardiovascular chronic diseases, in the same way as was done here for multimorbidity rates.

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Appendix A

Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jclinepi.2013.06.018>

References

- [1] Feinstein A. The pretherapeutic classification of comorbidity in chronic disease. *J Chronic Dis* 1970;23:455–68.
- [2] van den Akker M, Buntinx F, Knottnerus J. Comorbidity or multimorbidity; what's in a name? A review of the literature. *Eur J Gen Pract* 1996;2:65–70.
- [3] van den Akker M, Buntinx F, Roos S, Knottnerus J. Problems in determining occurrence rates of multimorbidity. *J Clin Epidemiol* 2001;54:675–9.
- [4] van den Akker M, Buntinx F, Metsemakers J, Roos S, Knottnerus J. Multimorbidity in general practice: prevalence, incidence and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol* 1998;51:367–75.
- [5] Wolff J, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med* 2002;162:2269–76.
- [6] Fortin M, Hudon C, Haggerty J, van den Akker M, Almirall J. Prevalence estimates of multimorbidity: a comparative study of two sources. *BMC Health Serv Res* 2010;10:111–7.
- [7] Uijen A, van Lisdonk E. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gen Pract* 2008;14(1):28–32.
- [8] Salisbury C, Johnson L, Purdy S, Valderas J, Montgomery A. Epidemiology and impact of multimorbidity in primary care. *Br J Gen Pract* 2011;61(582):e12–21.
- [9] Gunn J, Ayton D, Densley K, Pallant J, Chondros P, Herrman H, et al. The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort. *Soc Psychiatry Psychiatr Epidemiol* 2012;47:175–84.
- [10] Britt H, Harrison C, Miller G, Knox S. Prevalence and patterns of multimorbidity in Australia. *Med J Aust* 2008;189:72–7.
- [11] van Oostrom S, Picavet H, van Gelder B, Lemmens L, Hoeymans N, Verheij R, et al. Multimorbidity and comorbidity in the Dutch population—data from general practices. *Nederlands Tijdschrift voor Geneeskunde* 2011;155:A3193.
- [12] Holden L, Scuffham P, Hilton M, Muspratt A, Ng S, Whiteford H. Patterns of multimorbidity in working Australians. *Popul Health Metrics* 2011;9(1):115–20.
- [13] Schäfer I, von Leitner E, Schön G, Koller D, Hansen H, Kolonko T, et al. Multimorbidity patterns in the elderly: a new approach of disease clustering identifies complex interrelations between chronic conditions. *Plos One* 2010;5(12):e15941.
- [14] Marengoni A, Rizzuto D, Wang H, Winblad B, Fratiglioni L. Patterns of chronic multimorbidity in the elderly population. *J Am Geriatr Soc* 2009;57:225–30.
- [15] Kirchberger I, Meisinger C, Heier M, Zimmerman A, Thorand B, Autenrieth C, et al. Patterns of multimorbidity in the aged population—results from the KORA-Age study. *PLoS One* 2012;7(1):e30556.
- [16] Caughey C, Vitry A, Gilbert A, Roughead E. Prevalence of comorbidity of chronic diseases in Australia. *BMC Public Health* 2008;8:221–33.
- [17] Diederichs C, Berger K, Bartels D. The measurement of multiple chronic diseases—a systematic review on existing multimorbidity indices. *J Gerontol A Biol Sci Med Sci* 2011;66(3):301–11.
- [18] Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev* 2011;10:430–9.
- [19] Glynn L, Buckley B, Reddan D, Newell J, Hinde J, Dinneen S, et al. Multimorbidity and risk among patients with established cardiovascular disease. *Br J Gen Pract* 2008;58:488–94.
- [20] Boyd C, Darer J, Boulton C, Fried L, Boulton L, Wu A. Clinical practice guidelines and quality of care for older patients, with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005;294:716–24.
- [21] Barnett K, Mercer S, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380:37–43.
- [22] Guthrie B, Payne K, Alderson P, McMurdo M, Mercer S. Adapting clinical guidelines to take account of multimorbidity. *BMJ* 2012;345:e6341.
- [23] Hippisley-Cox J, Hammersley V, Pringle M, Coupland C, Crown N, Wright L. Methodology for assessing the usefulness of general practice data for research in one research network. *Health Informatics J* 2004;10:91–109.
- [24] Wong A, Boshuizen H, Schellevis F, Kommer G, Polder J. Longitudinal administrative data can be used to examine multimorbidity, provided false discoveries are controlled for. *J Clin Epidemiol* 2011;64:1109–17.
- [25] Hox J. *Multilevel analysis: techniques and applications*. New York, USA: Routledge; 2010.
- [26] Lappenschaar M, Hommersom A, Lucas P, Lagro J, Visscher S. Multilevel Bayesian networks for the analysis of hierarchical health data. *Artif Intelligence Med* 2013;57:171–83.
- [27] O'Halloran J, Miller G, Britt H. Defining chronic conditions for primary care with ICPC-2. *Fam Pract* 2004;21:381–6.
- [28] van der Wel M, Jansen R, Bakx J, Bor H, OldeRikkert M, van Weel C. Non-cardiovascular co-morbidity in elderly patients with heart failure outnumbers cardiovascular co-morbidity. *Eur J Heart Fail* 2007;9:709–15.
- [29] Perk J, de Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2012;33:1635–701.
- [30] Wiersma T, Smulders Y, Stehouwer C, et al. *Multidisciplinary guideline on cardiovascular risk management*. Houten, The Netherlands: Bohn Stafleu van Loghum; 2011.
- [31] Pearl J. *Probabilistic reasoning in intelligent systems*. San Francisco, CA, USA: Morgan Kaufmann; 1988.
- [32] Lucas P, van der Gaag L, Abu-Hanna A. Bayesian networks in biomedicine and health-care. *Artif Intelligence Med* 2004;30(3):201–14.
- [33] Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet* 2011;12(1):56–68.
- [34] Scutari M. Learning Bayesian networks with the bnlearn R package. *J Stat Softw* 2010;35(3):1–22.
- [35] Spiegelhalter D, Thomas A, Best N, Lunn D. *WinBUGS user manual; version 1.4*. Cambridge, UK: MRC Biostatistics Unit; 2001.
- [36] Vaccarino V, Badimon L, Corti R, de Wit C, Dorobantu M, Hall A, et al. Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors? Position paper from the working group on coronary pathophysiology and microcirculation of the European Society of Cardiology. *Cardiovasc Res* 2011;90:9–17.
- [37] Ryden L, Standl E, Bartnik M, van den Berghe G, Betteridge J, de Boer M, et al. European Society of Cardiology guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. *Eur Heart J* 2007;28:88–136.
- [38] Jackson R, Lawes C, Bennett D, Milne R, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. *Lancet* 2005;365:434–41.

- [39] Mitnitski A, Graham J, Mogilner A, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. *BMC Geriatr* 2002;2:1–8.
- [40] Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol Med Sci* 2007;62A(7):722–7.
- [41] Hofman A, van Duijn C, Franco O, Ikram M, Janssen H, Klaver C, et al. The Rotterdam Study: 2012 objectives and design update. *Eur J Epidemiol* 2012;26:657–86.
- [42] Jaccard J, Turrisi R. Interaction effects in multiple regression. Sage University papers series on quantitative applications in the social sciences. Thousand Oaks, CA: Sage; 2003:07–072.
- [43] Nielen M, Schellevis F, Verheij R. Inter-practice variation in diagnosing hypertension and diabetes mellitus: a cross-sectional study in general practice. *BMC Fam Pract* 2009;10:1–6.
- [44] Rong J, Yu C, Yang P, Chen J. Diabetic retinopathy: a predictor of coronary artery disease. *Diabetes Vasc Dis Res* 2012. online first: 1–8.
- [45] McMurray J, Adamopoulos S, Anker S, Auricchio A, Böhm M, Dickstein K, et al. European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2012;33:1787–847.
- [46] Weiner D, Tighiouart H, Amin M, Stark P, MacLeod B, Griffith J, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol* 2004;15:1307–15.
- [47] Magri C, Calleja N, Buhagiar C, Fava S, Vassallo J. Factors associated with diabetic nephropathy in subjects with proliferative retinopathy. *Int Urul Nephrol* 2012;44:197–206.