Adv Syst Sci Appl 2023; **01**; 22-34
Published online at http://ijassa.ipu.ru.

The Disease Centered Multimorbidity Model at the Example of Type 2 Diabetes Mellitus

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Abstract: Multimorbidity is a condition when few diseases (multimorbidity pattern) are diagnosed in same patient. According to the disease centered model the pattern is formed around one “marker” disease at the expense of other diseases which have non-random relationships with the “marker” disease and between each other. The totality and probabilistic connections between pairs of diseases determine the specifics of the pattern and indicate the possibilities for managing individual and population health as a result of interactions of all components of the the pattern. Algorithms have been developed assessing the degree of non-random connections between pairs of diseases in the pattern and establishing a hierarchical relationship between both “marker” and other diseases as well as between pairs of non-marker diseases. The calculation of non-random statistical relationships between pairs of diseases included in the T2DM (Type 2 Diabetes Mellitus) multimorbidity pattern proved the consistency of the data obtained with the current clinical description of T2DM pathogenesis and complications.

Keywords: multimorbidity, multimorbidity pattern, Type 2 Diabetes Mellitus, expert support, decision making, patient-centered healthcare, cumulative life course impairment, proactive risk management, healthcare.

1. INTRODUCTION

Multimorbidity is defined as the presence of two or more diseases in one person [**Ошибка! Источник ссылки не найден.**]. Attention to multimorbidity has been caused by an increase in life expectancy and the proportion of elderly people suffering from a number of conditions worldwide. The multimorbidity prevalence in older adults varies from 40 to 99% depending on population studied. Major consequences of multimorbidity are disability and functional decline, poor quality of life, high health care costs and complex pharmacological regimes. Currently, there is a transition in multimorbidity perception from a set of separate random diseases to systematic approach assessing multimorbidity pattern as a special condition requiring appropriate clinical and healthcare management decisions. The viability of this approach is the consequence of the appropriate diseases inclusion and exclusion criteria into multimorbidity patterns as well as the assessment of relationships between these diseases [12 - 7]. Some of the approaches aimed at association or, conversely, the division of a set of diseases into patterns are associated with the diseases grouping according to various formal characteristics. This approach is based mainly on the reassessment of statistical data and is

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applicable for disease burden calculation. At the same time, it is extremely difficult to use it for justifying clinical and managerial decisions. The opposite approaches are based on accumulated clinical experience proving the causal relationship of pathogenetic mechanisms of a group of diseases and are the basis for evidence-based solutions in healthcare, but they do not allow us to fully identify and evaluate all the links between diseases forming multimorbid pattern. The complexity and heterogeneity of patients with multimorbidity when using traditional clinical guidelines focused on a single disease quite often complicate and sometimes lead to inadequate clinical solutions like polypragmasia [12, 22, 5]. Cumulative Life Course Impairment (CLCI) and Proactive Risk Management in Healthcare approaches are based on both statistical big data and clinical evidence, with the purpose of economical effectiveness of high-cost innovative interventions and treatment of high-cost patients [2, 13]. Successful solution of the multimorbidity challenge need the concept (description of the basic principles, elements and interrelations between them) realized in form of a mathematical model and practical tools for expert support of healthcare decision making capable combining both the big data processing and the ability to take into account clinical evidence of non-random and causal clinical relationships of diseases. [19]. The group of diabetes mellitus diseases can be considered as the most suitable object for testing of the concept itself and the practical tools as well. This group of conditions includes T1DM (insulin dependent) and T2DM (insulin-non-dependent) with different pathogenesis but similar clinical manifestations. A number of T2DM associations have common hereditary and pathogenetic interrelations (obesity, atherosclerosis, hypothyroidism, coronary heart disease, vascular catastrophes, a number of oncological and neurodegenerative conditions as well as diabetic complications themselves). The T2DM associated diseases influence medical, social and economic disease burden impacting healthcare budgets in many countries what makes T2DM and associated diseases remaining the optimal model for assessing multimorbidity and improving therapeutic approaches as well as health economics decisions [**Ошибка! Источник ссылки не найден.**, 20 - 24].

2. THE OBJECTIVE FOR THE STUDY

Development of multimorbidity model aimed at effective population health management and applicable for practical use in expert support of healthcare decision making.
The following tasks have been solved to achieve the objective:

1. Creation of the multimorbidity concept considering it is a set of provisions and recommendations describing the elements and interrelations between them and aimed at improving of population health and reducing the disease burden.
2. Selection or creation algorithms for evaluating non-random association in pairs of diseases allowing creation a model of a multimorbid pattern that includes a hierarchical list of diseases with the highest values of association with a marker disease and relationships, including also links between non-marker diseases.
3. Practical assessment of concept and the model applicability for expert support of healthcare decision making on the example of T2DM in females considering the condition is a socially significant one with a sufficiently known pathogenesis.

2. METHODS

2.1. Disease centered multimorbidity pattern concept

The first task was accomplished using a combination of Environmental Scanning (200+ publications found in international databases PubMed and EMBASE as well as personal messages from experts) [15, 9] with Analytic Hierarchy Process (AHP) [4, 18] modified for development

and assessment of promising models of healthcare management [14]. The AHP was divided into 2 stages. The objective for the first stage was to formulate the necessary criteria without taking into account whether they were realistic or not. At the second stage the experts had to find the solutions for realization of these criteria and to formulate the tasks for mathematical analyses and modelling of multimorbidity patterns. The expert council consisted of 8 members including 3 experts in healthcare management (and healthcare practitioners as well), 2 endocrinologists specialized in diabetes and 3 mathematicians.

2.2. Algorithms for non-random interrelations assessment between pairs of diseases

The requirements for the mathematical analysis and modelling were formulated during the second stage of AHP. Associative rules machine learning was selected to create algorithms determining the probability of random and non-random connections between pairs of diseases [1].

2.3. Concept and the model assessment at the example of T2DM

Type 2 diabetes mellitus (T2DM) and associated diseases patients were the optimal model for assessing the multimorbidity patterns and improving personalized therapeutic approaches as well as health management decisions. Female patients were selected due to gender differences in pathogenesis and complications of the disease [**Ошибка! Источник ссылки не найден.**, 7 - 24] According to the AHP requirements the standard statistical reporting database provided by local healthcare administration was used. The database contained the data collected during 1 year period about 392 215 visits and diagnosis of 28153 female patients at the age from 30 to 61 years including 1977 patients with T2DM condition.

3. RESULTS AND DICUSSION

3.1. Disease centered multimorbidity pattern concept

The final results of the AHP are shown at the Table 1. The disease-centered multimorbidity pattern is formed around one disease chosen as the basis of the pattern. This disease is grouped together with other diseases that have a non-random connection with it. Any disease represented in the international classification of diseases (ICD-10/ICD-11) can act as a pattern-forming one and it is convenient to use this condition for the pattern identification, so next we use the term "marker" disease or condition to identify the pattern. The totality of such patterns forms the structure of morbidity and prevalence of diseases in selected population, but from practical point of view, the most important patterns are formed around marker diseases that have a greater medical, social and economic disease burden. The value of a non-random connection with other diseases is regarded as a higher probability of their joint manifestation in the same patients. The direction of the connection indicates the probability of appearance of a new disease under the existing one indicating the presence of causal relationships between pairs of diseases. Links from non-marker disease to the marker one may reflect the pathogenesis of the marker disease and also the links from the marker to non-marker ones reflect the pathogenesis of complications. Links between non-marker conditions can also provide additional information about interrelations within the pattern. In addition to connections between pairs of diseases there can be also assessment of risk factors and social health determinants influence on the pattern providing new opportunities for disease management. Non-random connections may indicate the presence of causal relationships between pattern elements, although experimental clinical confirmation is necessary to substantiate them. The direction of non-random connections provides additional information about possible cause-and-effect relationships in pairs of diseases. The hierarchical list of diseases included in the pattern is determined mainly by the value of their non-random association with the "marker" disease.

Based on the above information it is necessary to go through the following stages to form the multimorbidity pattern: identification of the "marker" disease jointly by clinical specialists and health care organizers, calculation of non-random statistical relationships of the "marker" disease

and other conditions (or risk factors and social health determinants depending of the objective of the assessment) based on available standard medical statistics data and in-depth clinical analysis of the identified patterns by medical specialists.

Table 1. The requirements for multimorbidity concept (AHP fist stage results)

Key needs	Breaking points	Requirements for the concept
The ability to reduce the disease burden	Medical (safety, efficacy and efficiency)	Appropriate target setting based on achievable clinical needs. Selection of clinically significant (marker) disease treatment as the primary objective. Improving the effectiveness of treatment of other diseases included in the pattern is a secondary task.
		Identification of non-random links between conditions in the pattern which can be the signs of similar or interrelated pathogenic mechanisms for better interventions allocation.
	Economical (effectiveness)	Economic disease burden is a criteria for marker condition selection.
	Social impact and bioecthical compliance	Social impact of the disease is a criteria for "marker" condition selection.
Compliance with existing Global and local healthcare standards	Clinical guidelines matching	Treatment of single diseases included into pattern is based on existing guidelines but it does not exclude preparing of the new guidelines taking into consideration relationship between diseases in the pattern.
	Regional and local country regulations compliance	Marker disease centered patterns using and accomplishing the existing regulations based on separate disease treatment.
	Applicable or can be adjusted to any healthcare infrastructure	Marker disease centered pattern using the existing diagnostics and treatment facilities as well as patients' journey.
	Financing and reimbursement	Assessing healthcare financing and reimbursement programs criteria for the identification of a marker disease
	Healthcare professionals core competencies	Focusing the concept on existing healthcare professionals' specialization by highlighting the most applicable condition in the multimorbidity pattern.
	Required information for multimorbidity pattern assessment	Existing medical and statistical data using for creation and assessment of multimorbidity pattern.

3.2. Algorithms for non-random interrelations assessment between pairs of diseases

The algorithm for finding strong connections between pairs of diseases was created using association rules.

Let the set $O = \{o_1, o_2, .. o_n\}$ is a set of diseases. Each element of the set represents a separate unique disease found in the available data and takes the value 1 or 0. The following family of sets $P = \{p_1, p_2, .. p_m\}$, is a set of patients and consists of m ordered non-empty sets of non-zero elements from O. Each element of P corresponds to a unique patient from the dataset. It means that, for each patient $p_i \in P$, we have a list of his diagnoses o, without taking into account the number of times he was diagnosed.

Next, we introduce the concept of "rules". In this case, the rule will be introduced as an implication of the following form: $X \Rightarrow Y$, where X, Y – are sets consisting of elements from O. In the future, in accordance with established tradition, this implication will be written as: $X \rightarrow Y$. In our case, the sets X and Y consist of disjoint sets of unique diseases, and we say, "If X, then Y". For example, the set X consists of diseases *{I, J, K}*, and Y of *{L}*, where I, J, K, L are unique

elements of the set *O*. And we will say: "*rule: if {I, J, K}, then {L}*". Actually, "rule" may not contain practical sense. It' just a form to fix directed pair of two sets. The rules with no sense and meaningful ones the characteristics were separated on the base of calculated values. The rules were considered to be valid in case characteristics satisfied high values. Below there is a description of the associative rules stable concepts and the definition of characteristics.

Antecedents – is the conditional designation of the first set of *X* objects. Abbreviated *A*.

Consequences – the conditional designation of the second set of *Y* objects. Abbreviated *C*.

Let Z be a set of variables of interest, t is a set containing Z, then:

Support – coefficient denoting the ratio of the number of sets containing the set *X* to the total number of available sets. In fact, this is the frequency of the presence of set *X* in the studied set of sets *P*.

$$supp(X) = \frac{\{t \in P, Z \subseteq t\}}{|P|}$$

Based on this definition, we introduce $supp(A \to C)$as the frequency of parallel encounters of objects from A and C.

$$supp(A \to C) = supp(A \cup C)$$

$supp(A)$ (by definition) is the frequency of encounters of objects from antecedent among the entire sample of sets; and $supp(C)$ is the frequency of encounters of objects from consequence. Based on the definition of $supp(X)$, it takes values from 0 to 1, $E(supp) \in \mathbb{Q}$. The greater this value, the more often the selected group of objects occurs among all sets at the same time.

$\boldsymbol{conf(A \to C)}$ – directional characteristic – the ratio between $supp(A{-}{>}\ C)$ and the frequency of *A*.

$$conf(A \to C) = \frac{supp(A \to C)}{supp(A)}$$

In fact, $conf(A \to C)$ replaces the concept of conditional probability, i.e., the value will denote the conditional probability of being in the set of objects from *C*, provided there are objects from *A*. $conf(A \to C)$ takes values from 0 to 1, $E(conf) \in \mathbb{Q}$.

Lift – is a coefficient describing the ratio of the dependence of Antecedents and Consequences to their independence. Otherwise, it is the ratio of the validity of the rule when both sets of objects meet together to the validity of the rule when a set of Consequences is met. Based on the definition, this characteristic is symmetrical.

$$lift = \frac{supp(A \to C)}{supp(A) \times supp(C)} = \frac{conf(A \to C)}{supp(C)} = \frac{conf(C \to A)}{supp(A)}$$

It takes values from 0 to infinity, $E(lift) \in \mathbb{Q}$. If it is equal to 1, then A and C are independent. The high values (higher that 1) indicate the more dependence. The smaller values (below 1), indicate counter–dependence.

$\boldsymbol{conv(A \to C)}$ – a high value here means that Consequences strongly depends on Antecedents. Definition of this characteristic is:

$$conv(A \to C) = \frac{1 - supp(C)}{1 - conf(A \to C)}$$

The *Conviction* values from 0 to infinity, $E(conv) \in \mathbb{Q}$. It is equal to 1 in case the elements are independent. Value below 1 indicates counter-dependence. The values higher than 1 indicates non-random dependence. The higher the value of the indicator, the greater the probability of a non-random association of the appearance of another disease in the presence of a marker condition. The highest value (infinity) was obtained when the probability of T2DM diagnosis was estimated in patients with a previously diagnosed marker T2DM condition.

Clinical interpretation of these symbols is presented in the table 2.

Table 2. Clinical interpretation of the most significant final symbols.

Symbol	Range	Clinical interpretation
Support	[0, 1]	Frequency of the disease occurrence in the data set
Support A (antecedent)	[0, 1]	The frequency of the marker disease in the data set (T2DM in the example below)
Support C (consequent)	[0, 1]	Frequency of another disease in A-C pair (another disease in T2DM patients in the example below)
Confidence (A –> C)	[0, 1]	The conditional probability that disease C will randomly or non-randomly occur in the presence of disease A (directional value). This indicator is of interest for assessing the burden of disease in multi-morbidity, since it allows us to estimate the probability of the manifestation of condition C in the presence of condition A and, accordingly, to estimate the total burden of disease A and C in the presence of disease A
Conviction (A –> C)	[0 - ∞]	Indicates the probability of non-random appearance of the disease C under the condition of the disease A (directional value). High values of this indicator can be a sign that there are common pathogenetic mechanisms or external factors (risk factors or social health determinants) contributing to the development of both conditions. If the value is 1, the connection is regarded as random. From 0 to 1 – there is a counter-dependence, i.e., a decrease in the probability of developing disease C in the presence of disease A.

3.3. Concept and the model assessment at the example of T2DM

The *Conviction* (probability of non-random appearance) of diseases under the condition of T2DM is presented in graph format on Fig. 1 making visible the relationship between T2DM and other diseases designated by the ICD-10 codes. Arrows indicate the direction of the connection and their thickness shows its value. There are arrows indicating also the directional relationship between other than T2DM conditions and the probability of their feedback influence on T2DM. The values themselves are presented on Fig. 2. Fig. 3 represents, on the contrary, the conditional probability of the appearance of T2DM in the presence of other (non-marker) diseases. The *convenience* magnitude of these connections is presented Fig. 4 representing a hierarchical list and interactions of the 10 most significant (highest *conviction* values) diseases that can contribute to the development of T2DM. These pictures show a limited number of diseases (10) with the highest *conviction* values with the marker disease (T2DM). The highest *conviction* value on Fig. 4 is infinite (non-random relationship between T2DM and T2DM) but, on the histogram, it is artificially limited. The clinical meaning is quite obvious - if there have been a T2DM patient visit earlier the patient will continue to visit the doctor with T2DM forming a non-random statistical relationship within the same diagnosis. There are few comments below showing the possibility of using of indicated links between diseases in the pattern as a basis for further pathogenesis pathways evaluation by clinicians.

T2DM can influence on the developing of I11.9 (Hypertensive disease with predominant heart damage without (congestive) heart failure) (Fig. 1). This condition is also affected by other

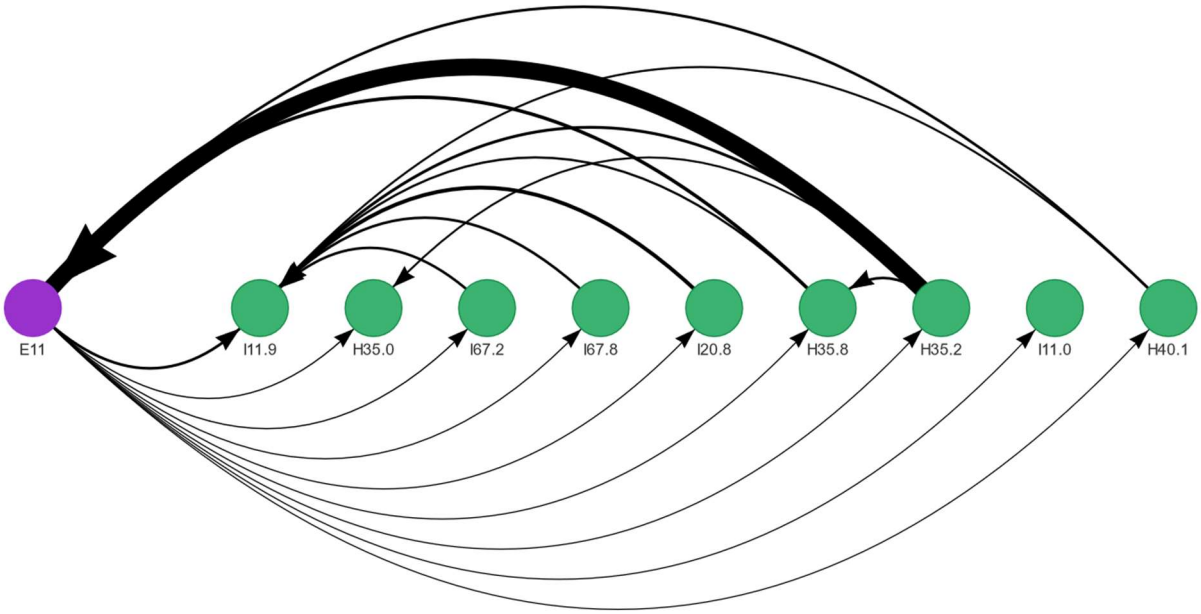

Fig. 1. Conditional probability of non-random association (*conviction*) between existing T2DM (E11) and other diseases (9 diseases with the highest values of the code) in women (graph format). The *conviction* value is demonstrated by the hierarchical order of diseases (the highest is on the left) and the thickness of the arrows (the highest is the thickest).

diseases caused by DM2 and the development of hypertensive disease with predominant heart damage can be considered as the possible result of direct and indirect effects of a complex of diseases included in the T2DM multimorbid pattern [8].

The example of Proliferative retinopathy (H35.2) show that a number of non-marker diseases can be on the one hand a condition for the development of T2DM and on the other hand the T2DM can be a condition for the development of these diseases. Proliferative retinopathy (H35.2) is included in the hierarchical list of diseases that are likely to develop under the existing T2DM (Fig. 1 and 2) and also in the list of conditions pre-existing T2DM (Fig. 3 and 4). In turn, the non-random combination of T2DM and proliferative retinopathy diseases can have quite a strong feedback effect on T2DM, demonstrated by the thickest arrow on Fig. 1.

Thus, there is a complex of two diseases: proliferative retinopathy and T2DM and the development of each of the disease non-randomly depend on the other. The presence of isolated closed non - random connections between separate diseases included in the pattern may be an example of its stratification probably related with some pathogenetic features [**Ошибка! Источник ссылки не найден.**, 20 -24].

Predicting of T2DM by numerous T1DM conditions (10.0; 10.5; 10.6) on Fig. 3 and 4 can be explained as the result of diagnosis clarification and change in the same patients during period of data collection. It can be assumed that the expected stratification of T2DM into 5 or more subtypes will lead to the formation of similar statistical relationships that will need to be taken into account in the clinical interpretation of calculations [**Ошибка! Источник ссылки не найден.**].

Thus, the evaluation on the example of T2DM of the proposed disease-centered multimorbidity concept and the algorithms for assessing of non-random connections between pairs of diseases in T2DM multimorbidity pattern allowed us to obtain data that do not contradict the modern

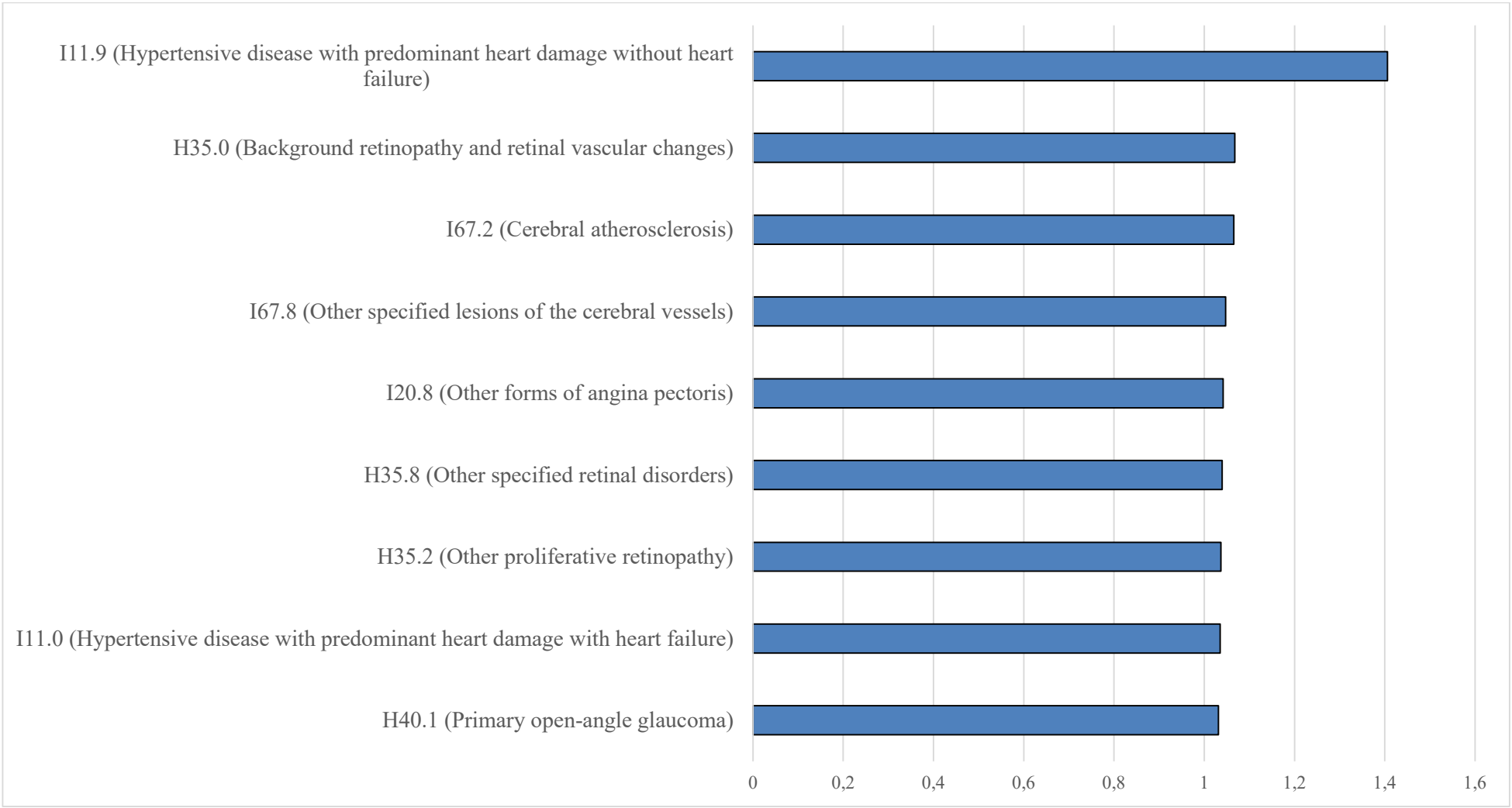

Fig. 2. Value of the conditional probability of non-random association (*conviction*) between existing T2DM (E11) and other diseases (9 diseases with the highest values) in women.

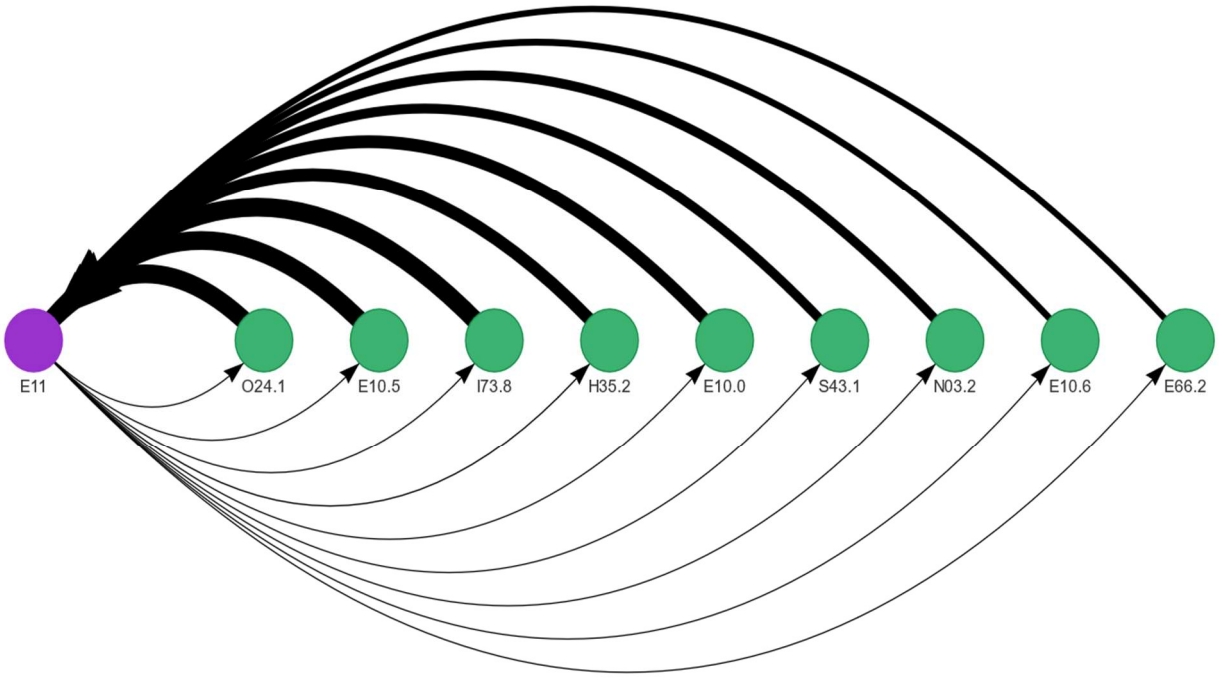

Fig. 3. Conditional probability of non-random association (*conviction*) between existing diseases (9 diseases with the highest values of the code) and T2DM (E11) and other in women (graph format). The *conviction* value is demonstrated by the hierarchical order of diseases (the highest is on the left) and the thickness of the arrows (the highest is the thickest).

understanding of the T2DM pathogenesis and, moreover, are in accordance with the latest research and forecasts in this area. Moreover, the proposed evaluation indicated a number of observations which can be taken as a basis for further evaluation of pathogenesis pathways. It is necessary to remember that the examples demonstrate just statistical assessment and hypothesis requiring clinical evidence.

4. CONCLUSIONS

The research made it possible to formulate the disease-centered multimorbidity concept aimed at improving the efficiency of public health management in modern conditions. Multimorbidity traditionally defined as 2 or more diseases presented in the same patients, and is represented by multimorbidity patterns forming all together the morbidity, disease prevalence and mortality in population. In accordance the disease-centered multimorbidity concept, the pattern of multimorbidity is formed around one marker disease at the expense of other diseases that have a non-random connection with the marker disease and between each other. The totality and probabilistic connections between the pairs of diseases determine the specifics of the pattern and indicate the possibilities for managing individual and population health as a result of the interaction of all components of the system forming the pattern. Calculation algorithms have been developed to assess the degree of non-randomness of connections between pairs of diseases in the pattern of multimorbidity, allowing to build a hierarchical relationship between both marker and other diseases, and between pairs of non-marker diseases. The calculation of non-random statistical relationships between pairs of diseases included in the T2DM multimorbidity pattern proved the consistency of the data obtained with the modern understanding of T2DM pathogenesis and

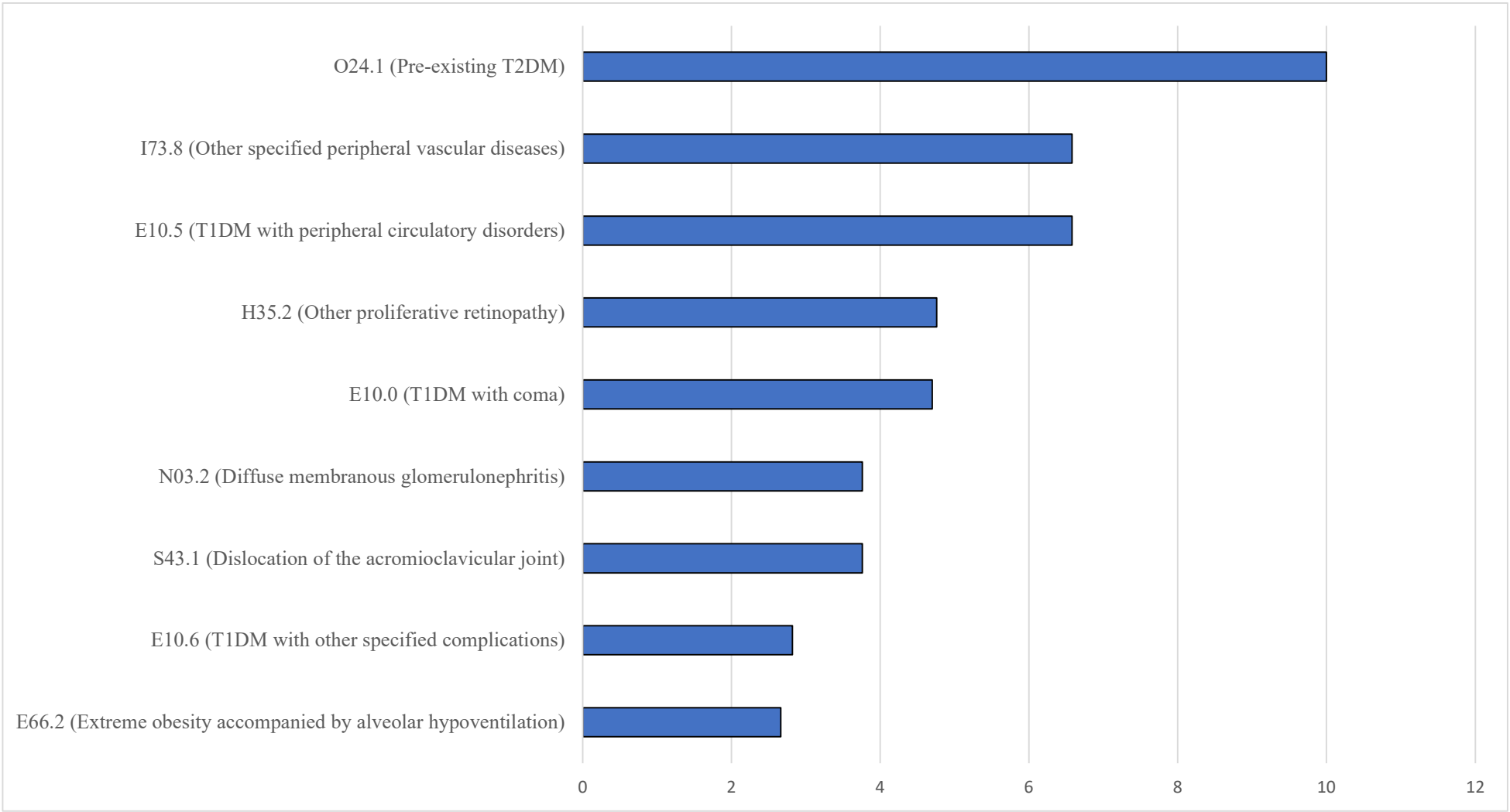

Fig. 4. Value of the conditional probability of non-random association (*conviction*) between existing diseases (9 diseases with the highest values) and T2DM (E11) in women.

complications. At the same time, it should be taken into account that the presented algorithms forming a pattern model around the selected marker disease represent just statistical relationships between pairs of diseases included in the pattern and cannot serve as a basis for clinical decisions by themselves. The same remark applies to defining the boundaries of the pattern that should include the most significant diseases in terms of pathogenesis and disease burden.

Implementation of the proposed model into practice does not require changes in any healthcare infrastructure and financing as well as of the core competences of healthcare practitioners. At the same time, it provides additional opportunities for better and faster understanding of diseases pathogenesis and expert support of healthcare decision making.

A hierarchical list of diseases that have a non-random relationship with a marker disease allows clarifying the structure and the necessary data for creating or improving patient registers. Clarification and identification of common pathogenetic mechanisms of the development of diseases included in the multimedia pattern allows the use of high-cost target therapy for the treatment of a complex of diseases instead of administering numerous interventions to each of the diseases. Such approach makes possible decreasing poligragmasia and increasing the effectiveness healthcare expenditures for high-cost patients.

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