

From multimorbid to general population, documenting the trajectories of chronic diseases multimorbidity patterns at older ages

Linh H.K. Dang¹, Nicola Caranci², Giulia Roli¹, Rosella Rettaroli¹, and Rossella Miglio¹

¹*Department of Statistical Sciences, University of Bologna*

²*Department of Innovation in Health and Social Care, Direction of Health and Welfare, Emilia-Romagna Region*

Introduction

Over the last decades, chronic health conditions have replaced infectious diseases in accounting for the majority of health burden, most of them are furthermore related to aging (Chowdhury et al., 2023). And the burden of multimorbidity is likely to be even more substantial when considering multimorbidity of chronic diseases. Following one of the four action areas in United Nations guidelines for Decade of Healthy Aging, the healthcare system is shifting from single-disease to a more integrated healthcare system where patient-centered approach is prioritized (WHO, 2023). In such context, understanding the evolution of multimorbidity patterns at older ages across time has become an urging challenge to provide timely evidence for efficient policy planning.

From a technical perspective, the core idea behind identifying patterns of multimorbidity is to reduce the complex, high-dimensional data of chronic diseases into a more interpretable form, such as a two-dimensional representation, based on which grouping can be done, while trying to preserve as much of information as possible. In recent years, a combination of graphical model and network analysis appears to us as a reliable method (Alvarez-Galvez and Vegas-Lozano, 2022). However, three challenges still remain when the focus is to study the transition of multimorbidity patterns across time. First, it is unclear to which extent the identified groups of chronic diseases of a given population are consistent across time, i.e., whether we are modeling the trajectories of comparable multimorbidity groups across time? Second, how can we quantify and explicitly record these individual transitions on empirical data? Third, how can we model these transitions to have a better understanding of the trajectories of multimorbidity patterns at older ages? On the other hand, previous studies investigating multimorbidity patterns across time focus on multimorbid population, would it be possible to extend the longitudinal study of multimorbidity patterns to general population? In this study, we present a structured solution to address these challenges and questions.

Data

The data sources for this study include census data in 2011, population register, and hospital administrative data from 2011 to 2019 in Emilia-Romagna region (Italy), which are linked together using a linkage record process based on unique personal identification. The census data combined with population register provide a representative data of the population residing in the region at the census date, and also an opportunity to extend our research to general population. For the first part of this study, we focus on the individuals who were diagnosed with at least two chronic diseases during observation period are included in the study (N=1,010,571). We stratify our population by sex and by age group following age at census (50-59, 60-69, 70-79, 80+), resulting in 8 subgroups, and we conduct analyses systematically for each subgroup. The individual medical conditions are retrieved from hospital administrative data, where the recorded chronic diseases are classified in ICD9-CM and their coding process also benefited from the consultation of medical experts.

Methods

To study the evolution of individual multimorbidity patterns across time, three key elements need to be identified, which corresponds to three steps of our study.

First step, we use mixed graphical model to estimate the network structure of the chronic conditions for each sub-population (Alvarez-Galvez and Vegas-Lozano, 2022). This approach allows us to obtain, as output, a network of chronic diseases where the edge linking the nodes of chronic diseases represents the pairwise partial correlation between them. On the base of this network, we apply communities detection algorithm from network analysis to cluster the chronic diseases into multimorbidity patterns. Rather than choosing arbitrarily a graph-based clustering algorithm, we apply systematically 7 most-widely used communities detection algorithms (e.g., edge-between, fast greedy, Louvain) and select the algorithm most suitable to our dataset based on modularity score. The higher the modularity score, the better the algorithm performs. We apply systematically this optimal algorithm on the estimated network for 2 sexes, 4 age-groups and at 3 time-points (in 2011, 2016 and 2019), extracting results from these 24 estimated networks.

Second step, even though each disease belongs only to one pattern, each individual can belong to multiple patterns simultaneously, and there might be a need to assign one unique multimorbidity pattern to each patient for modeling purpose. This objective can be conceptualized as assigning the pattern that is most substantial for each patient at each time-point. However, the rationale of how a pattern can be considered as "substantial" varies depending on the purpose of the study. Our objective is to suggest a method under network perspective that could be flexible enough so that researchers can incorporate their own ideas of what multimorbidity pattern can be substantial for an individual at a given time. In this paper, we focus on the pattern whose management or prevention can contribute to reduce the burden of outcomes for individuals and society. From network perspective, we define the diseases belonging to this pattern as the ones that hold strong associations with other diseases and are likely to be caused by other diseases. We rely on two metrics, the strength centrality and the in-degree measurements respectively, to quantify these characteristics. We compute the strength centrality from the undirected network of chronic diseases estimated by mixed graphical model and the in-degree from the Bayesian network of chronic diseases estimated using the hill-climbing algorithm. We obtain the score for each disease by summing their strength and in-degree within each network. If the individual belongs to only one pattern, we assign that pattern for the individual. If the individual belongs to more than one pattern, we assign the pattern that has a higher number of diseases. If the number of diseases between different patterns of an individual is equal, we assign the individual to the pattern that has the highest score that is computed as detailed above.

Third step, we model multimorbidity patterns transition across time using Markov model with misclassification (Jackson et al., 2003). For each individual i at time t , there is a true underlying process of multimorbidity pattern transition governed by a process $S_i(t)$, which is described by a matrix of transition intensities Q estimated from data. This true underlying process cannot be observed directly from data, but through realizations $O_i(t)$ (i.e., the observed multimorbidity patterns identified by graphical models and network analysis). These observed states $O_i(t)$ are generated conditionally on true states $S_i(t)$, herein with misclassification to into account any factors that could be the cause behind the difference between what the true underlying process dictate and what we observe from data but might not be detected.

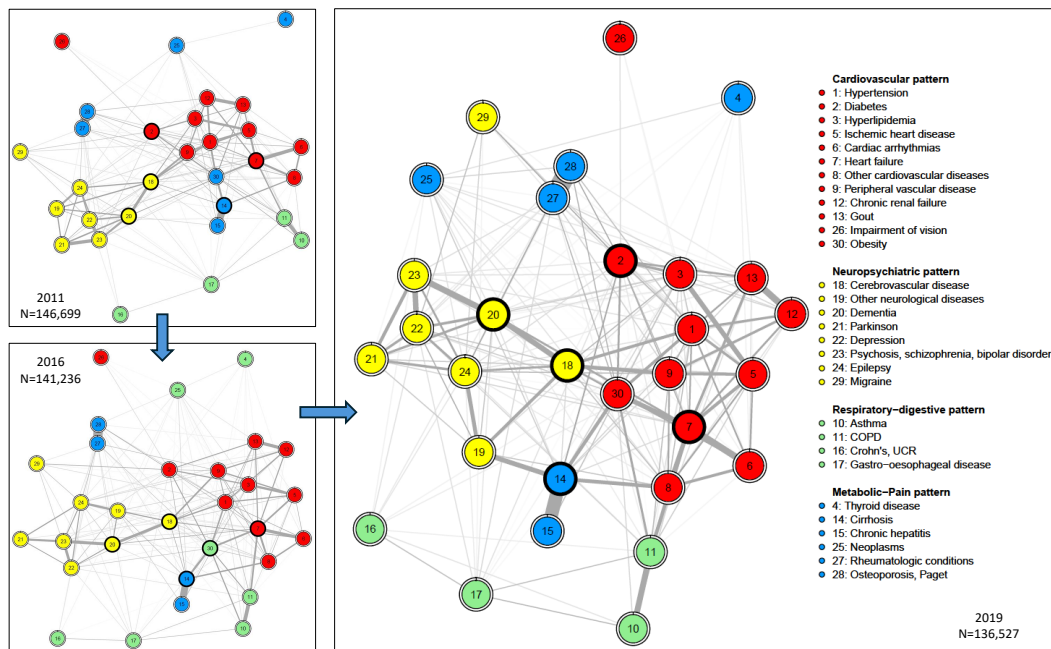
Based on the observed consistency across time of the identified multimorbidity patterns, we obtained the empirical records of individual trajectories of multimorbidity patterns across three time-points (2011, 2016 and 2019). We consider each multimorbidity pattern as a multimorbidity "state" of the individual. Our study thus includes five states for transition modeling: cardiovascular, neuropsychiatric, respiratory-digestive, metabolic-pain pattern, and death. Each individual can move back and forth from one pattern to any other pattern, as well as directly from any given pattern to death (but not vice versa).

Preliminary results

Identification of multimorbidity patterns at older ages across time

Applying systematically the optimal algorithm on 24 networks that were estimated for each of 2 sexes, 4 age groups and at 3 different time-points, the same four coherent groups are obtained for all sub-populations: the cardiovascular group, the neuropsychiatric group), the respiratory-digestive group, and the metabolic-pain group. Even if the structure of the estimated chronic diseases network would necessarily change across time – as the information given from the survivors to estimate these networks change at each time-point in both number of survivors and the accumulation of chronic conditions among survivors–, the multimorbidity patterns structure, as defined by the clusters given by the optimal algorithm, remains relatively stable. This empirical consistency across time is a necessary condition for further trajectories analysis that considers each multimorbidity pattern as a state. To our best knowledge, we are the first to verify this empirical consistency, in particular for hard-clustered groups of chronic diseases, where each disease can belong to only one pattern. The validation found in our study population allows us to proceed with the two next steps without any additional assumptions.

Figure 1: Estimated network of chronic conditions and corresponding multimorbidity patterns, females aged 60-69 at census, in 2011, 2016, 2019



Notes: "Neoplasms" herein include both benign and malignant diagnosed cases

Multimorbidity patterns transition before death

We used scoring method to assign an unique pattern to each individual, before applying systematically Markov model with misclassification on empirical multimorbidity pattern transition data of 8 subgroups, and estimated the corresponding transition intensities Q for each subgroup. The forecasted transition probabilities matrix $P(t)$ was estimated using the relationship $P(t) = \exp(tQ)$ (Jackson et al., 2003). As an illustration, we assumed that the transition intensities would remain the same over the next 10 years for each subpopulation and estimated the transition probabilities for a typical individual in each subgroup moving from one multimorbidity pattern to another. This forecast period is herein arbitrary for illustrative purpose, it should be changed according to different applications. The resulted transition probabilities matrices are presented in table 1 for female populations.

From the preliminary results, we obtained three remarks. First, within each subgroup, we found that male multimorbid patients consistently had higher risk of death than their female counterparts given the same multimorbidity pattern. Second, across age-group cohorts and sexes, individuals who were identified as having neuropsychiatric pattern had the

highest probabilities of dying in the next 10 years compared to all other patterns. Third, except for the neuropsychiatric pattern, older adults who were identified in any other patterns would have the highest probability of transitioning to cardiovascular pattern within the next 10 years, and those who were already identified as belonging to cardiovascular pattern also had the highest probability of remaining in the same pattern.

Table 1: Estimated transition probabilities between multimorbidity patterns in 10 years, female populations

Females 50-59	Cardiovascular	Neuropsychiatric	Respiratory/Digestive	Metabolic/Pain	Death
Cardiovascular	0.63	0.08	0.06	0.18	0.06
Neuropsychiatric	0.34	0.35	0.06	0.17	0.08
Respiratory/Digestive	0.39	0.09	0.16	0.31	0.06
Metabolic/Pain	0.38	0.09	0.09	0.38	0.06
Death	0	0	0	0	1
Females 60-69	Cardiovascular	Neuropsychiatric	Respiratory/Digestive	Metabolic/Pain	Death
Cardiovascular	0.63	0.09	0.03	0.13	0.12
Neuropsychiatric	0.29	0.36	0.03	0.13	0.18
Respiratory/Digestive	0.39	0.10	0.14	0.26	0.11
Metabolic/Pain	0.38	0.10	0.06	0.35	0.11
Death	0	0	0	0	1
Females 70-79	Cardiovascular	Neuropsychiatric	Respiratory/Digestive	Metabolic/Pain	Death
Cardiovascular	0.51	0.08	0.03	0.08	0.30
Neuropsychiatric	0.22	0.28	0.02	0.06	0.41
Respiratory/Digestive	0.32	0.10	0.20	0.12	0.26
Metabolic/Pain	0.32	0.10	0.05	0.28	0.25
Death	0	0	0	0	1
Females 80+	Cardiovascular	Neuropsychiatric	Respiratory/Digestive	Metabolic/Pain	Death
Cardiovascular	0.18	0.03	0.02	0.03	0.74
Neuropsychiatric	0.06	0.08	0.01	0.02	0.83
Respiratory/Digestive	0.12	0.03	0.08	0.04	0.74
Metabolic/Pain	0.13	0.04	0.03	0.15	0.66
Death	0	0	0	0	1

Next steps

The first part of the study demonstrated the added-values of studying multimorbidity patterns trajectories under network perspective and how the trajectories of multimorbidity patterns can be investigated for any given population in this framework. In the second part of our study, we will extend our approach to the general population, taking into account also individuals without chronic diseases or diagnosed with only one chronic disease from 2011 to 2019. This extension requires several non-negligible complications, notably to include an additional state for individuals who are considered healthy (i.e., having less than two chronic diseases) in the potential transition paths. Documenting the trajectories of multimorbidity leading to death at older ages is an urging challenge, and having more insights – however rough – at the level of general population can be valuable.

References

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