Constructing the trajectories of multimorbidity patterns of chronic diseases leading to death at older ages

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Abstract

One key factor to construct sound measures to prevent adverse health outcomes and to allocate healthcare resources for sustainable aging populations is the possibility of identifying precise multimorbidity patterns and seizing their trajectories in time. In both developed and developing countries, understanding the structure of multimorbidity, and most ideally across time, is an urging challenge, so that groups who share the same degree of vulnerability and needs can receive assistance and intervention in a timely manner. Compared to traditional approach like factorial and clustering analysis that have been of standard practice in the literature, combining the probabilistic approach of graphical model and the intuitive visibility of network analysis is emerging quickly as powerful tool in recent years to not only efficiently explore the richness of administrative health data, but also to provide a framework with predictability. By applying these methods on reliable longitudinal data of individuals aged 50 and above residing Emilia-Romagna region (northern Italy) in 2011 and followed up to 2019 (N = 1,010,610), we study the multimorbidity patterns at older ages and their changes across time. Using hidden Markov model based on the estimated multimorbidity patterns, we construct the trajectories of multimorbidity leading to death at older ages.

Introduction

In aging populations, the proportion of individuals affected with two or more diseases, often considered as patients with multimorbidity, is steadily increasing, especially when individuals enter old ages (Chowdhury et al., 2023). The associations between multimorbidity and health outcomes such as disability, frailty, poor quality of life, and even death, are extensively corroborated by many studies (Makovski et al., 2019; Vetrano et al., 2019). Until now, substantial research efforts have been done to understand how diseases co-occur and accumulate across human lifetime, and how this process eventually contributes to the path leading to death. Still, research in this thematic is challenging. One of the challenges is the appropriate method to take into account multimorbidity. Various synthetic measures have been developed to summarize the multimorbidity conditions of the individuals, including the use of number of diseases that individuals are diagnosed with, and the multimorbidity index that was based on medical standpoint such as the Charlson index or the Elixhauser index. However, if the number of total diseases gives limited knowledge about the characteristics of the multimorbidity conditions, the restricted set of diseases that the multimorbidity index was based on might not always be suitable for the population under study (e.g., the Charlson index does not include mental health conditions). Motivating that the chronic conditions would cluster non-randomly under common risk factors into coherent groups that we can identify as multimorbidity patterns, in this study, we apply a novel way to establish multimorbidity patterns using mixed graphical model and network analysis, extracted from the chronic diseases data of residents aged 50 and above at census 2011 in Emilia-Romagna region (northern Italy). We then evaluate the performance of these newly developed multimorbidity patterns in assessing risk of death of individuals, and construct the trajectory of multimorbidity patterns leading to death for each age-group cohort, for females and males.

Data

The data sources for the 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, which help mitigate the risk of selection bias that could undermine the analysis results. From census data, we also obtain other covariates including sex, date of birth (and date of death, if the individual passed away), civil status, education level and place of residence for each individual. Individuals who were present at census date but moved out of the region during follow-up period are right-censored. Individuals who moved into the region after census date are excluded. Only individuals who were diagnosed with at least two chronic diseases during observation period are included in the study. Our final population of patients with multimorbidity include 1,010,610 individuals (557,601 are females and 453,009 are males), of which 306,224 individuals deceased during the follow-up period (162,119 females and 144,105 males). 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 grouped into 30 main chronic conditions following the algorithm that was established by Fortuna et al. (2021) with the consultation of medical experts.

Methods

Our study constitutes of three objectives: establish multimorbidity patterns from population-based chronic conditions data, evaluate the performance of the established multimorbidity patterns in assessing the risk of death at older ages, and construct the multimorbidity patterns trajectory leading to death of the residents.

For the first objective, 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 nodes of chronic diseases into multimorbidity patterns. However, 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, walkstrap) and select the algorithm most suitable to our dataset based on modularity score. The higher the modularity score, the better the algorithm performs. And 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.

For the second objective, we apply Cox models using different variables to take into account the multimorbidity condition of the population. In the first model, we use the total number of chronic diseases that individuals have to account for their multimorbidity conditions. In the second model, we use the newly developed multimorbidity patterns as time-dependent predictor for mortality. We apply both models on the dataset of 8 subgroups, controlling further for level of education and the urban/rural level of their residence. We then use the Akaike Information Criterion (AIC) to compare the performance between two models in each sub-population and evaluate the performance of using the multimorbidity patterns that we established in assessing the risk of death of individuals.

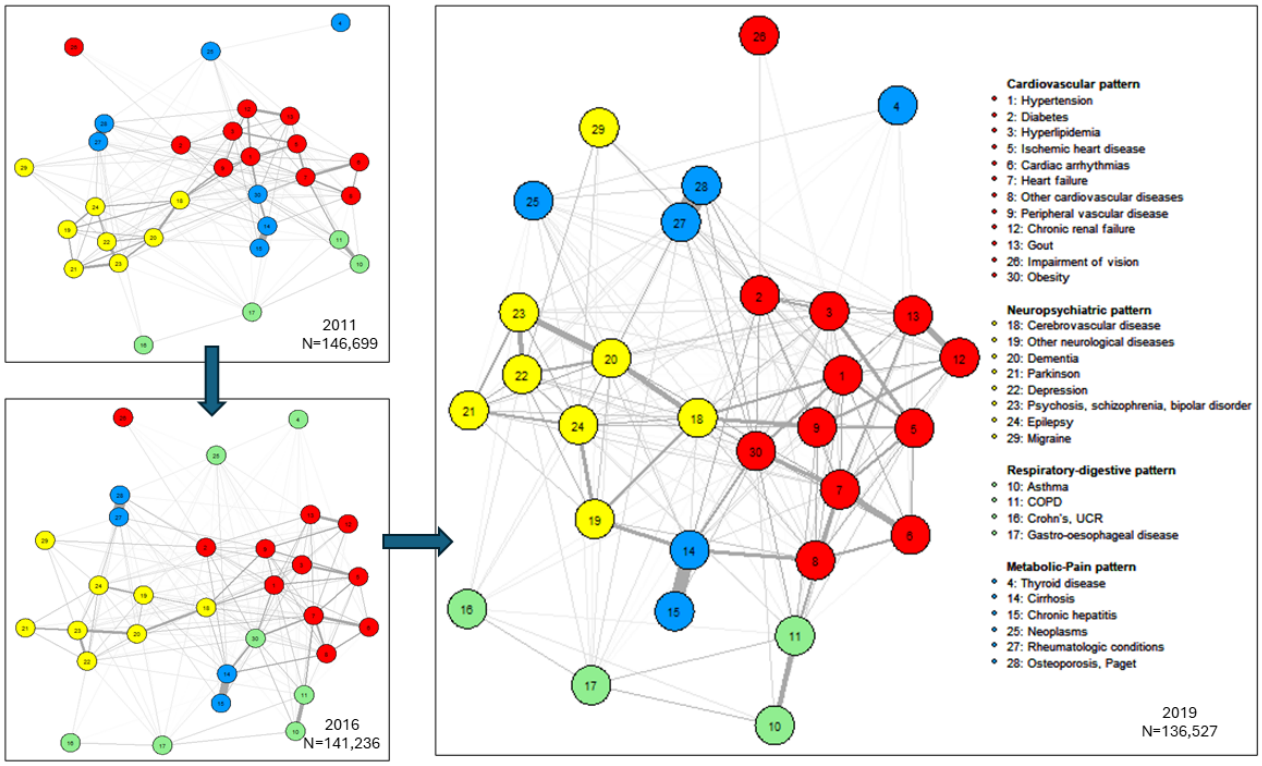
For the third objective, we focus on individuals that deceased during the observation period. On the same stratification system by sex and age-group, we apply hidden Markov model to decode the most probable trajectory of multimorbidity for each sub-population, where the identified multimorbidity patterns serve as the hidden states that drive our observation of chronic diseases in the population across time (Violán et al., 2019).

Results

Identification of multimorbidity patterns at older ages

The figure 1 below displays the estimated network of chronic conditions and the corresponding multimorbidity patterns for females aged 60-69 at census and evaluated in 2011, 2016 and 2019. We identified four coherent groups of chronic conditions, including the cardiovascular group (in red), the neuropsychiatric group (in yellow), the respiratory-digestive group (in green), and the metabolic-pain group (in blue). Within each coherent group, two categories of diseases can be identified. The first category contains the main conditions that characterize the pattern (e.g., heart failure and cardiac arrhythmias in cardiovascular pattern, dementia and epilepsy in neuropsychiatric pattern), and the second category contains the conditions related to the main (e.g., hypertension in cardiovascular pattern). Using 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 (i.e., multimorbidity patterns) are obtained for all sub-populations. Hence, 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.

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

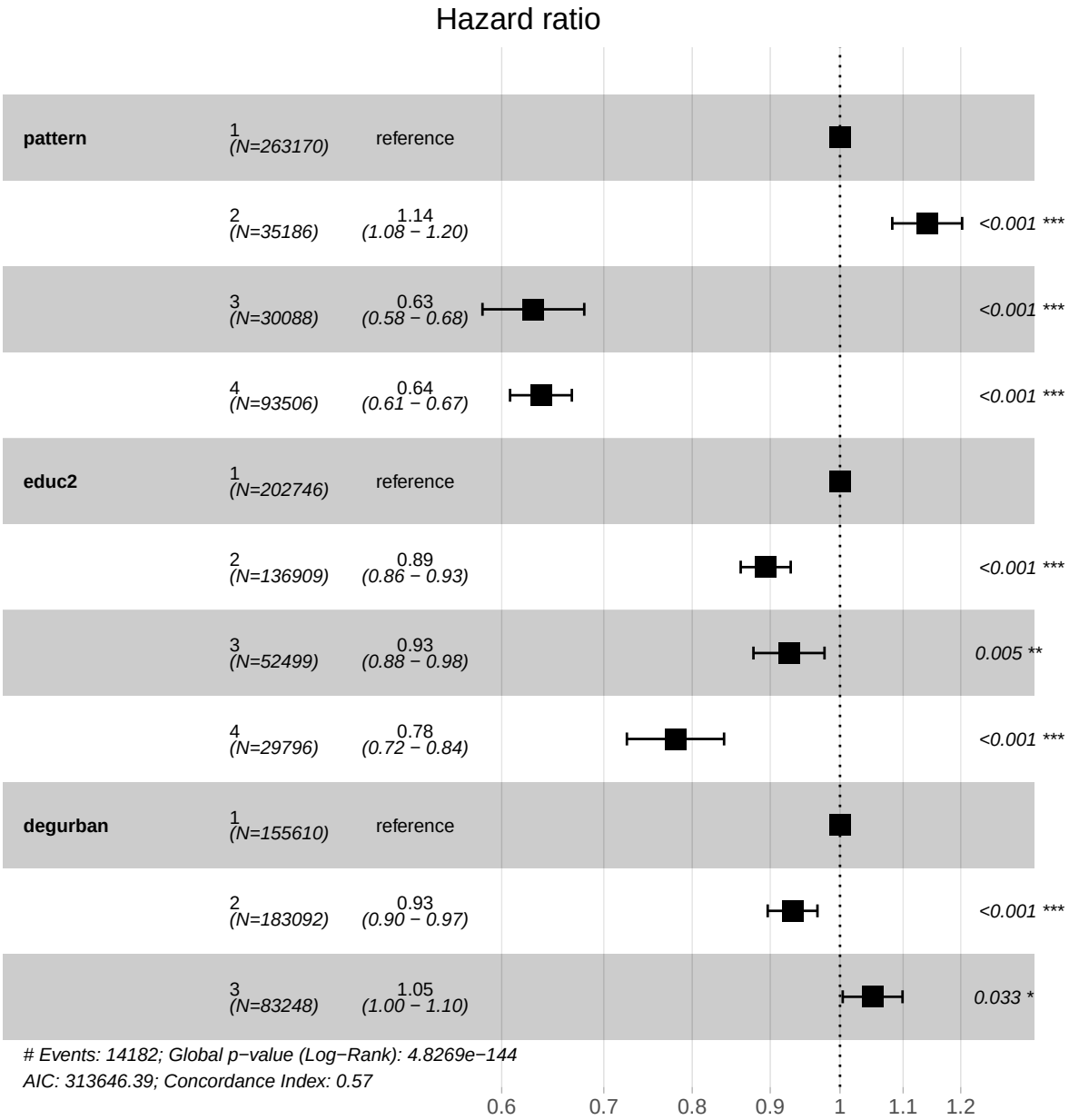


Impact of multimorbidity on mortality at older ages

We run the set of two Cox models previously detailed on the dataset of 8 sub-populations. Both models control for level of education and the rural/urban residence of the individuals. The figures 2 and 3 below present respectively the estimated hazard ratios assessing using the multimorbidity patterns and the number of total diseases for females aged 60-69 at census date and followed up to 2019. The variable of total number of diseases and the variable of multimorbidity patterns are consistently statistically significant in each group, suggesting

the pertinent role that the multimorbidity conditions have in shaping the mortality of individuals for both sexes at older ages. This result is consistent across all sub-populations, for both females and males and for all age-group cohorts.

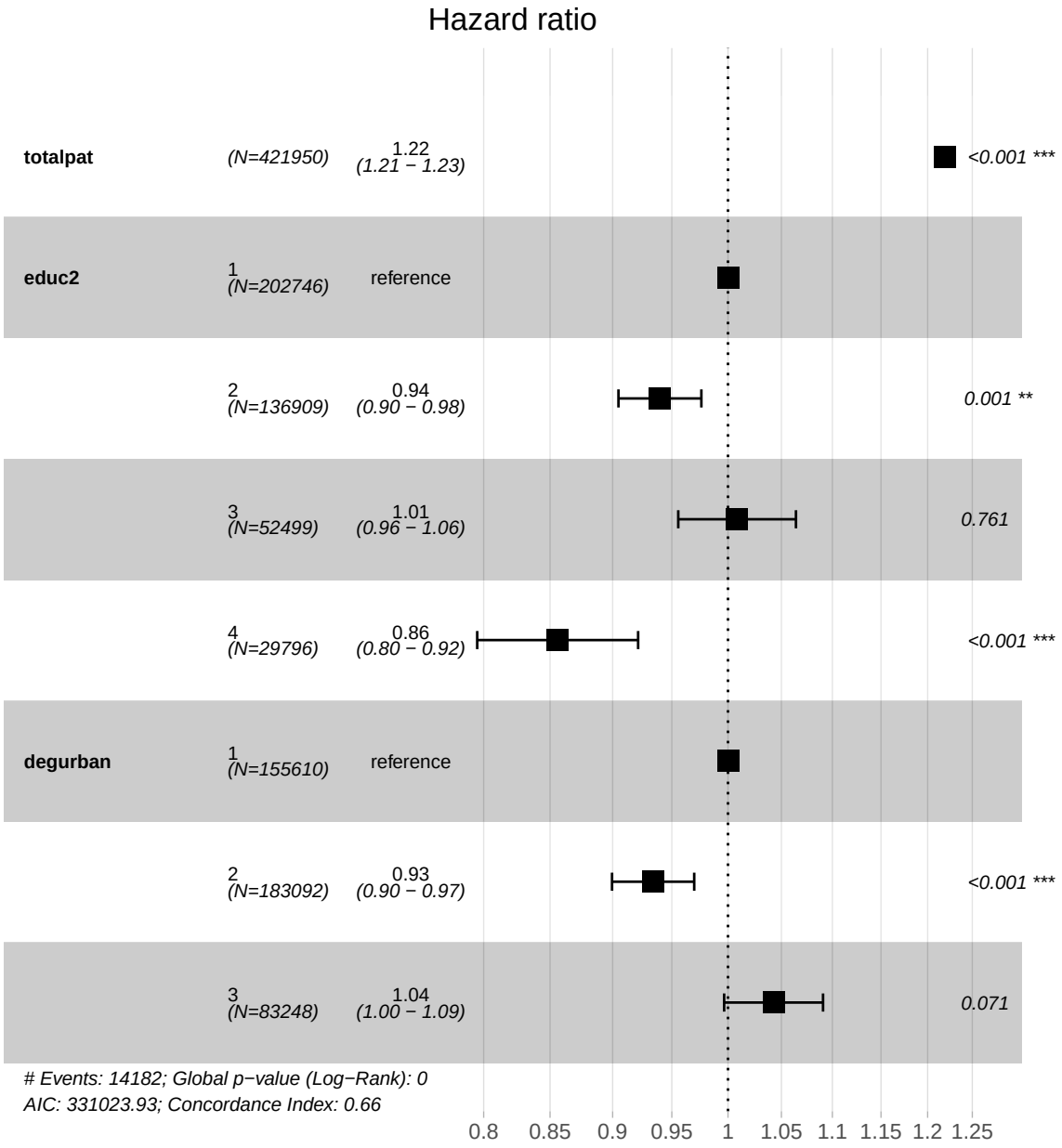
Figure 2: Estimated hazard ratio using multimorbidity patterns as time-dependent predictor for mortality, females aged 60-69 at census 2011, followed up to 2019



Notes: The controlled variables are the multimorbidity patterns (*pattern*) (1 = cardiovascular pattern, 2 = neuropsychiatric pattern, 3 = respiratory-digestive pattern, 4 = metabolic-pain pattern), the level of education (*educ2*) (1 = no education/primary education, 2 = lower secondary education, 3 = upper secondary education, 4 = university), the rural/urban residency (*degurban*) (1 = cities, 2 = small cities or suburbs, 3 = rural areas)

Based on AIC, we also found that the model using our established multimorbidity patterns consistently outperforms the model using the traditional way of taking into account multimorbidity by the number of diseases that individuals are affected with. As illustration, from the results obtained on females population aged 60-69 at census 2011 presented above, the AIC of model using the multimorbidity patterns as predictor (AIC = 313646.39) is lower than that the AIC of model using the total number of chronic diseases for each individual as predictor (AIC = 331023.93). This result brings evidence to the added-values of the novel approach to

Figure 3: Estimated hazard ratio using total number of chronic diseases as predictor for mortality, females aged 60-69 at census, followed up to 2019



Notes: The controlled variables are the total number of chronic conditions (*totalpat*), the level of education (*educ2*) (1 = no education/primary education, 2 = lower secondary education, 3 = upper secondary education, 4 = university), the rural/urban residency (*degurban*) (1 = cities, 2 = small cities or suburbs, 3 = rural areas)

multimorbidity through establishment of patterns using mixed graphical model and network analysis. Other than improving the performance of the model, the time-dependent variable of multimorbidity pattern also sheds light on which patterns are the biggest source of concern for each sex at each age-group and the specific chronic conditions that contribute to it, and thus contributed to the implementation of evidence-informed policies.

Discussion and next steps

In the first part of this work, we applied graphical model and network analysis techniques to establish the multimorbidity patterns, a method that can rigorously extract diseases clustering from data and provide a flexible approach to monitor the multimorbidity situation of any population at any given point without losing its simplicity for practical use. Our statistical approach is designed in a way that leaves no arbitrary choice in every step of the procedures, nor preconceptions about the co-occurrence of the chronic conditions. We followed each age-group cohort (i.e., aged 50-59, 60-69, 70-79 and 80+ at census 2011) of both sexes and estimated their corresponding multimorbidity patterns at different time-points (at 2011, 2016 and 2019), and observed a stability in the structure of multimorbidity patterns across time, across age-group and across sex. With further consultation with medical experts, it is likely that we can think of establishing the multimorbidity patterns that are appropriate for the population.

We also brought evidence that assessing multimorbidity using the patterns that are identified by mixed graphical model and network analysis not only improves the performance of the mortality model but also allows for more interpretations to be drawn from the results, offering a more detailed understanding of the impact of the multimorbidity conditions on the mortality of individuals. However, this higher performance of the newly established multimorbidity patterns does not mean that they should substitute the traditional approach in the literature, as the information that each variable conveys are different in nature. On the contrary, combining both the number of total diseases with the multimorbidity patterns that each individual has in assessing his/her mortality at older ages in mortality modelling might constitute another approach to study multimorbidity at death. As such, the severity of the multimorbidity condition of the individual can be assessed in a more comprehensive way, notably through the number of diseases that the individual was dealing with (and thus informing the potential conflicts between treatments and polypharmacy), and through the nature of the chronic conditions that the individuals most suffer from (via the multimorbidity patterns that the individual belongs to across the years prior to his/her death). This research direction can also be investigated further in the future.

In the second part of our work, we will apply the hidden Markov model on the established multimorbidity patterns previously detailed to characterize the most probable trajectory of multimorbidity patterns for each age group during the years prior to death and the duration that individuals remain in each pattern. By doing so, these results can help us understand in better details the most probable sequence of multimorbidity conditions in different sexes and different age groups that preceded their end. This understanding has potential to contribute to the transition of healthcare system that is organized around single-disease treatment into a system that can adapt better to the increasingly prevalent multimorbidity situations of the population.

References

Alvarez-Galvez, J. and E. Vegas-Lozano (2022). Discovery and classification of complex multimorbidity patterns: unravelling chronicity networks and their social profiles. *Scientific Reports 12*, 20004.

Chowdhury, S. R., D. C. Dasa, T. C. Sunnaa, J. Beyened, and A. Hossainc (2023). Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. *eClinicalMedicine* (57), 101860.

Fortuna, D., E. Berti, and M. L. Nickel, Moro (2021). Multimorbidity epidemiology and health care utilization through combined healthcare administrative databases. *Epidemiologia Prevenzione 45*, 62–71.

Makovski, T. T., S. Schmitz, M. P. Zeegers, S. Stranges, and M. van den Akker (2019). Multimorbidity and quality of life: Systematic literature review and meta-analysis. *Ageing Research Reviews 53*, 100903.

Vetrano, D., K. Palmer, A. Marengoni, E. Marzetti, F. Lattanzio, R. Roller-Wirnsberger, L. S. L., L. Rodríguez-Mañas, R. Bernabei, and G. Onder (2019). Frailty and multimorbidity: A systematic review and meta-analysis. *The Journals of Gerontology Series A 74*(5), 659–666.

Violán, C., S. Fernández-Bertolín, M. Guisado-Clavero, Q. Foguet-Boreu, J. Valderas, J. Manzano, A. Roso-Llorach, and M. Cabrera-Bean (2019). Five-year trajectories of multimorbidity patterns in an elderly mediterranean population using hidden markov models. *Scientific Reports 10*, 16879.