Research Article

Patterns of Multimorbidity in a Population-Based Cohort of Older People: Sociodemographic, Lifestyle, Clinical, and Functional Differences

Alessandra Marengoni, PhD,^{1,2,*}† Albert Roso-Llorach, MSc,^{3,4,†} Davide L. Vetrano, MD, PhD,^{1,5,6} Sergio Fernández-Bertolín, MSc,^{3,4} Marina Guisado-Clavero, MD,^{3,4} Concepción Violán, PhD,^{3,4} and Amaia Calderón-Larrañaga, PhD¹

¹Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Sweden. ²Department of Clinical and Experimental Sciences, University of Brescia, Italy. ³Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Spain. ⁴Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain. ⁵Department of Geriatrics, Catholic University of Rome, Italy. ⁶Centro di Medicina dell'Invecchiamento, Fondazione Policlinico "A. Gemelli," Scientific Institute for Research and Healthcare (IRCCS), Rome, Italy.

*Address correspondence to: Alessandra Marengoni, PhD, Department of Clinical and Experimental Sciences, University of Brescia, Viale Europa 11, 25123 Brescia, Italy. E-mail: alessandra.marengoni@unibs.it

†First shared authorship.

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Abstract

Background: The aim of this study is to identify clusters of older persons based on their multimorbidity patterns and to analyze differences among clusters according to sociodemographic, lifestyle, clinical, and functional characteristics.

Methods: We analyzed data from the Swedish National Study on Aging and Care in Kungsholmen on 2,931 participants aged 60 years and older who had at least two chronic diseases. Participants were clustered by the fuzzy *c*-means cluster algorithm. A disease was considered to be associated with a given cluster when the observed/expected ratio was ≥ 2 or the exclusivity was $\geq 25\%$.

Results: Around half of the participants could be classified into five clinically meaningful clusters: respiratory and musculoskeletal diseases (RESP-MSK) 15.7%, eye diseases and cancer (EYE-CANCER) 10.7%, cognitive and sensory impairment (CNS-IMP) 10.6%, heart diseases (HEART) 9.3%, and psychiatric and respiratory diseases (PSY-RESP) 5.4%. Individuals in the CNS-IMP cluster were the oldest, with the worst function and more likely to live in a nursing home; those in the HEART cluster had the highest number of co-occurring diseases and drugs, and they exhibited the highest mean values of serum creatinine and C-reactive protein. The PSY-RESP cluster was associated with higher levels of alcoholism and neuroticism. The other half of the cohort was grouped in an unspecific cluster, which was characterized by gathering the youngest individuals, with the lowest number of co-occurring diseases, and the best functional and cognitive status.

Conclusions: The identified multimorbidity patterns provide insight for setting targets for secondary and tertiary preventative interventions and for designing care pathways for multimorbid older people.

Keywords: Multimorbidity pattern, Older adults, Swedish National Study on Aging and Care in Kungsholmen (SNAC-K)

Since the beginning of the last century, chronic diseases have progressively replaced infectious diseases in terms of their prevalence and impact on human health. Caring for people with chronic conditions has emerged as one of the major challenges facing health care systems, which remain rooted in episodic and acute care. The world-

wide aging phenomenon, along with individuals' longer survival following formerly fatal events, are the main drivers of the increasing burden of chronic diseases. As a consequence, the prevalence of *multimorbidity*, defined as the coexistence of two or more chronic diseases in the same person, is as high as 90% in older adults (1).

Despite the increasing number of studies on the occurrence of multimorbidity across age, gender, and socioeconomic strata, its epidemiology remains poorly understood. In fact, given the wide heterogeneity of people suffering from multimorbidity, no single definition or operationalization seems to serve both research and clinical purposes effectively. For example, the exclusive use of a quantitative approach (ie, the number of co-occurring chronic diseases) fails to capture the clustering of chronic diseases in patterns of multimorbidity (2). Studies attempting to describe multimorbidity patterns have used different methodological approaches to address this issue, such as estimation of observed to expected ratios or odds ratios among the most commonly coexisting dyads or triads of chronic conditions, or cluster and factor analyses to identify systematic groupings among diseases. However, these statistical techniques limit interpretation of results and clinical applicability in, for example, their need for large samples, multiple comparisons, overestimation of effect sizes, and the forcing of diseases into single clusters according to similarity or dissimilarity measures. Moreover, previous studies have focused on identifying patterns of diseases rather than clusters of individuals (3), which has prevented researchers from characterizing such patterns in terms of their clinical and social significance. Although some studies have described multimorbidity patterns in terms of their associated burden of polypharmacy (4) or hospital care (5), other individual-level characteristics such as sociodemographic, lifestyle, clinical, and physical and cognitive functional measures have not yet been explored.

In the present study, we aim to build on previous work by applying a *soft* clustering technique (ie, the fuzzy *c*-means cluster algorithm) to analyze patterns of multimorbidity in a population-based Swedish cohort study of older people. *Soft* techniques (*c*-means) present the following advantages over the *hard* clustering algorithms (in other words, hierarchical clustering, *k*-means) predominantly used in past studies. First, individuals, and not diseases, are grouped in clusters according to their commonly co-occurring diseases. Second, instead of forcing individuals to belong to one specific cluster, participants are assigned a probability of membership in all identified clusters, which makes more sense from a biological perspective. Finally, one disease can characterize more than one cluster, which allows us to build patterns of multimorbidity that take all possible disease combinations into account (6,7). In summary, by using soft clustering techniques, we place individuals and not their diseases at the center of our analyses (8).

The specific objectives of our study are (i) to identify clusters of older people based on their multimorbidity patterns and (ii) to analyze differences among clusters according to sociodemographic, lifestyle, clinical, and functional characteristics.

Methods

Study Population

We used baseline data from the population-based Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) (9). This study consists of community-dwelling and institutionalized older adults aged 60 years and older. Of people born between 1898 and 1943, living in the Kungsholmen district of Stockholm (Sweden), a random sample from 11 age cohorts was invited to participate in the study. Those who accepted were evaluated between 2001 and 2004 for the first time and subsequently followed up every 6 years (those aged <78 years) or every 3 years (those aged ≥78 years). At baseline, 3,363 people were examined (participation rate, 73%). In our study, 432

participants were excluded because they did not fulfill the inclusion criteria of having multimorbidity (ie, two or more chronic diseases) at baseline. As expected, those excluded were younger, more educated, and less likely to be female than those included in the study ($p < .001$).

Study Variables

At each study wave, SNAC-K participants undergo a comprehensive clinical and functional assessment by trained physicians, nurses, and neuropsychologists. Physicians collect information on diagnoses via physical examination, medical history, examination of medical charts, self-reported information, and/or proxy interviews. Clinical parameters, lab tests, medication, and inpatient and outpatient care data are also used to identify specific conditions. All diagnoses are coded according to the International Classification of Diseases 10th revision (ICD-10) and classified into 60 chronic disease categories in accordance with a clinically driven methodology (1). Diseases with a prevalence of <2% were excluded to avoid statistical noise and therefore spurious findings in the models. Drugs are coded in accordance with the Anatomical Therapeutic Chemical (ATC) classification.

Participants' demographics (ie, age, sex, education, occupation, living arrangement, and civil status) and lifestyle factors are collected during nurse interviews. Educational attainment was categorized as elementary, high school, and university or higher; main occupation was categorized as manual or non-manual based on the longest job held during the person's lifetime. Civil status was categorized as unmarried, married, divorced, and widowed; smoking was categorized as never, former, and current; and alcohol consumption was categorized as never/occasional, light/moderate, and heavy. Following the recommendations of the World Health Organization (WHO) and the American College of Sports Medicine (ACSM), participants were categorized in three different groups according to the intensity of their physical activity: inadequate (less than or equal to two to three times per month of light and/or moderate/intense exercise), health-enhancing (light exercise several times per week or every day), and fitness-enhancing (moderate/intense exercise several times per week or every day) (10,11).

Life satisfaction was measured using the self-reported index developed by Neugarten and colleagues (12) (LSI-A), which captures five components: zest versus apathy, resolution and fortitude, congruence between desired and achieved goals, positive self-concept, and mood. The LSI-A consists of 12 positive and 8 negative items; in this study, the negative items were reversed and the final scores transformed to a 0–100 scale with higher values indicating greater life satisfaction (13). The social network index combined indicators of self-reported social connections and social support according to the procedure adopted in the National Social Life, Health, and Aging Project (NSHAP Study) (14) and was subsequently categorized into tertiles labeled as poor, moderate, or rich (15). Self-rated health was assessed by asking participants; "In general, how would you describe your health?" and categorized as very good/excellent and good/poor.

Level of disability was measured as the number of basic activities of daily living (bathing, dressing, toileting, continence, transferring, and eating) and instrumental activities of daily living (grocery shopping, meal preparation, housekeeping, laundry, managing money, using the telephone, taking medications, and using public transportation) a person was unable to perform independently. People living in institutions were assumed to depend on others for grocery shopping, meal preparation, housekeeping, and laundry. Balance was measured as the time (in seconds) a participant could stand on one

leg (up to 60 seconds). Grip strength was measured with a dynamometer and converted to kilograms. Participants were seated with their arm resting on a table and their elbow flexed at 90 degrees. Walking speed was assessed by asking participants to walk 6 m, or 2.44 m if the participant reported walking slowly. If the participant was unable to walk or attempted unsuccessfully to walk, a value of 0 was recorded. Cognitive status was assessed by physicians with the Mini-Mental State Examination, which ranges from 30 to 0 (from best to worst possible score). Participants' serum albumin (g/L), creatinine ($\mu\text{mol/L}$), and C-reactive protein (mmol/L) levels were measured at Karolinska Institutet's laboratory following standard procedures.

Statistical Analysis

Multimorbidity patterns were identified using the fuzzy *c*-means cluster analysis algorithm, which belongs to the family of soft clustering algorithms. The algorithm estimates *c* cluster centers (similar to *k*-means) but with fuzziness, so that individuals may belong to more than one pattern. We used the technique to obtain clusters of individuals as well as a membership matrix that indicated the degree of participation of each subject in each cluster. Through dimensionality reduction (that is, multiple correspondence analysis) we then obtained the input data for the clustering of participants. To determine the number of retained dimensions, the Karlis-Saporta-Spinaki rule was used (16). Different degrees of fuzzification and several validation indices were considered to estimate the optimal number of clusters (7). Given the stochastic nature of the clusters, we ran 100 independent clustering repetitions to obtain the average final solution. The consistency and significance of the final solution was evaluated based on clinical criteria. For cross-validation of the model, we randomly sorted individuals into two independent data sets and compared their validation indices. Indices were computed and averaged over 100 repetitions.

To examine the disease patterns characterizing each cluster, observed/expected ratios were calculated by dividing the prevalence of a given disease within a cluster by its prevalence in the overall population. *Disease exclusivity*, defined as the fraction of participants with the disease included in the cluster over the total number of participants with the disease, was also calculated. A disease was considered to be associated with a given cluster when the observed/expected ratio was ≥ 2 or the exclusivity was $\geq 25\%$ (17,18). The clusters were further compared for the distribution of sociodemographic, lifestyle, clinical, and functional variables using analysis of variance and chi-square tests. Statistical analyses were performed using R 3.5.1 and Stata 15.

Results

The study population consisted of 2,931 individuals. The participants' mean age was 76.1 years, and 66.6% were female. Six point five percent were living in a nursing home. The mean number of chronic condition was 4.5, and the mean number of drugs was 4.4. A total of 39 chronic disease categories had a prevalence of $\geq 2\%$ and were included in the cluster analyses (Table 1).

The following multimorbidity patterns were detected in our population: psychiatric and respiratory diseases (PSY-RESP) 5.4%, heart diseases (HEART) 9.3%, eye diseases and cancer (EYE-CANCER) 10.7%, cognitive and sensory impairments (CNS-IMP) 10.6%, and respiratory and musculoskeletal diseases (RESP-MSK) 15.7%. Around half of the study population (48.4%) could not be

classified into any of the abovementioned patterns but constituted a cluster where nonspecific chronic conditions were over-represented, and which was named UNSPECIFIC. A clinical description of the patterns in terms of diseases with the highest observed/expected ratio and exclusivity values is reported in Supplementary Table S1. In addition, Figure 1 depicts all diseases with observed/expected ratios ≥ 2 and/or exclusivity values $\geq 25\%$ in each cluster. The PSY-RESP cluster included individuals with neurotic, stress-related and somatoform disorders, depression, sleep disorders (both insomnia and obstructive sleep apnea), and other unspecified neurological and psychiatric conditions; it also included asthma. The HEART cluster included several cardiac diseases along with cerebrovascular disease, diabetes, migraine, and inflammatory arthropathies. The EYE-CANCER cluster included several eye impairments and solid cancers. The CNS-IMP cluster included dementia, psychiatric and cerebrovascular diseases, and visual and hearing problems. The RESP-MSK cluster included the two most frequent respiratory diseases (ie, asthma and chronic obstructive pulmonary disease) and obstructive sleep apnea.

In Table 2, the five clusters are compared with the UNSPECIFIC one in terms of sociodemographic, lifestyle, clinical, and functional characteristics. The PSY-RESP cluster was associated with higher values of alcoholism and neuroticism. The HEART cluster grouped people with the highest number of co-occurring chronic diseases and drug use and the highest levels of serum creatinine and C-reactive protein. Individuals in the EYE-CANCER cluster exhibited the lowest muscle strength. The CNS-IMP cluster grouped people of very old ages who lived in nursing homes and had the lowest physical functional status. Finally, the part of the population not classified in any specific cluster included the youngest people with the lowest mean number of chronic diseases, the best functional and cognitive and status, and the highest life satisfaction.

Discussion

In the present study, around half of a Swedish cohort of older adults could be classified into five clinically meaningful clusters, named psychiatric and respiratory diseases (PSY-RESP), heart diseases (HEART), respiratory and musculoskeletal diseases (RESP-MSK), cognitive and sensory impairments (CNS-IMP), and eye diseases and cancer (EYE-CANCER). These clusters showed significantly different sociodemographic, lifestyle, clinical, and functional profiles. The other half of the study population was grouped in an unspecific cluster characterized by being younger, having lower numbers of co-occurring diseases and drug use, and good functional and cognitive abilities.

The PSY-RESP cluster included people with asthma along with psychiatric conditions. The co-occurrence of these diseases could be a result of chronic drug treatment with steroids, which can increase neuroticism, depression, and sleep disorders (19). Besides, asthma symptoms have been associated with depression, even in older participants (20). This cluster grouped relatively young people with alcohol abuse problems and low life satisfaction. The association between alcohol use and psychiatric disorders is well known (21), and this study confirms such an association in older persons. Poor quality of life in people affected by psychiatric and respiratory disorders has also been reported previously (22,23).

The HEART cluster illustrates the well-known link between cardio- and cerebrovascular diseases; atrial fibrillation and heart failure are both risk factors for stroke (24), and diabetes is a risk

Table 1. Disease Prevalence at Baseline in the Swedish National Study on Aging and Care in Kungsholmen (*N* = 2,931)

Rank	Chronic Conditions	Prevalence (%)
1	Hypertension	73.29
2	Dyslipidemia	50.12
3	Chronic kidney diseases	37.84
4	Ischemic heart disease	17.50
5	Colitis and related diseases	14.43
6	Osteoarthritis and other degenerative joint diseases	14.23
7	Anemia	13.68
8	Deafness, hearing impairment	13.07
9	Obesity	13.07
10	Heart failure	12.04
11	Thyroid diseases	11.84
12	Atrial fibrillation	11.02
13	Dementia	10.85
14	Depression and mood diseases	10.44
15	Solid neoplasm	10.10
16	Diabetes	9.96
17	Cerebrovascular disease	8.94
18	Osteoporosis	7.68
19	Other musculoskeletal and joint diseases	7.44
20	Dorsopathies	7.30
21	Asthma	6.86
22	Glaucoma	6.38
23	Cataract and other lens diseases	6.24
24	Other eye diseases	5.70
25	Chronic obstructive pulmonary disease, emphysema, chronic bronchitis	5.66
26	Autoimmune diseases	5.12
27	Esophagus, stomach, and duodenum diseases	4.95
28	Blindness, visual impairment	4.91
29	Inflammatory arthropathies	4.57
30	Prostate diseases	4.50
31	Other cardiovascular diseases	3.92
32	Neurotic, stress-related, and somatoform diseases	3.55
33	Other genitourinary diseases	2.87
34	Cardiac valve diseases	2.83
35	Migraine and facial pain syndromes	2.59
36	Other psychiatric and behavioral diseases	2.52
37	Sleep disorders	2.39
38	Other neurological diseases	2.18
39	Bradycardias and conduction diseases	2.12

factor for stroke and coronary heart disease (25). The high prevalence of migraine in this cluster may be explained by either brain vascular pathology or by the drugs prescribed for cardiac diseases, such as nitrates (26,27). The high number of co-occurring chronic conditions and drugs were distinctive of individuals belonging to this cluster. This cluster had the second highest percentage of persons, after the CNS-IMP cluster, with limitations in activities of daily living and instrumental activities of daily living. Individuals in this cluster also showed the highest serum creatinine and C-reactive protein levels. Expression of proinflammatory cytokines increases throughout the human life span, and this increase is correlated with cardiovascular health (28). Chronic low-grade inflammation, in turn, promotes autonomic imbalance, stimulates remodeling, depresses cardiac function, prompts endothelial dysfunction, and leads to a progression of atherosclerosis and impaired renal function (29).

The RESP-MSK cluster included osteoporosis possibly related to the chronic treatment of asthma and chronic obstructive pulmonary disease with steroids (30). Vitamin D deficiency could also underlie both respiratory and skeletal disorders; vitamin D supplements are beneficial both in preventing exacerbations of chronic obstructive

pulmonary disease and improving bone density measures (31,32). The presence of upper gastrointestinal system disorders can also be related to the treatment of respiratory diseases and the use of diphosphonates in osteoporosis (33), whereas thyroid and other autoimmune diseases are often correlated (34).

The EYE-CANCER cluster included several eye impairments and solid cancers. A high percentage of participants in this cluster were widowed, which is explained by their higher age. Old age may also explain why they have the lowest grip strength.

The CNS-IMP cluster brings to light the association recently found between sensorial impairment and dementia. Hearing deficits have attracted much interest, motivated by strong evidence that impaired hearing is a risk factor for cognitive decline and dementia (35,36). The relationship between vision loss and dementia has been evaluated in cross-sectional and longitudinal studies; the 3C cohort study suggested that poor vision, in particular near vision loss, may be an indicator of dementia risk at short and middle term (37). Retinal microvasculature pathology has been associated with vascular dementia, especially in persons with diabetes (38). Multiple sensorial impairments have also been found to increase dementia

Figure 1. Chronic diseases characterizing clusters of older people identified at baseline in the Swedish National Study on Aging and Care in Kungsholmen ($N = 2,931$). PSY-RESP: psychiatric and respiratory diseases; HEART: heart diseases; EYE-CANCER: eye diseases and cancer; CNS-IMP: cognitive and sensory impairments; RESP-MSK: respiratory and musculoskeletal diseases; O/E ratio: observed/expected ratio.

risk (39). Persons in this cluster were very old and had the worst levels of physical and cognitive function; this justifies why 43% of them were living in a nursing home. Any disease in the cluster could explain the functional impairment, particularly dementia and cerebrovascular diseases (40). This cluster grouped the highest percentage of people who were manual workers with low education. Low educational attainment and a manual occupation during early life have been consistently associated with an increased risk of dementia (41) and poor income in later life. Finally, this cluster was also characterized by having the highest percentage of persons with a poor social network and inadequate physical activity levels.

Clinical and Public Health Implications

Despite the high prevalence of multimorbidity in the older population, knowledge about how chronic diseases co-occur in single individuals is limited. Furthermore, findings from different studies are hardly comparable with the literature in the field because of differing methodological approaches.

In a previous study from an older Swedish population, the coexistence of diseases was evaluated with a cluster analysis approach (2).

Cluster analysis groups diseases according to their similarity forcing each disease to be part of one single cluster; this approach can be particularly useful to generate new research hypotheses on the pathophysiological correlations as well as the strength of causal associations between diseases. Conversely, the soft technique employed in the present study has the main advantage to group individuals who, according to their commonly co-occurring diseases, belong to different multimorbidity patterns, enabling one same disease to belong to more than one cluster. In addition, individuals are provided with a probability to belong to each of the identified clusters, and the most probable membership was investigated in our analyses. This methodology can be advantageous to describe the overall health status of a specific population, providing particularly useful information from a clinical point of view.

First, groups of people at high risk of adverse health outcomes can be identified and may benefit from targeted secondary and tertiary preventative interventions. For example, individuals in the HEART cluster may develop disabilities for a number of reasons, such as dyspnea in heart failure, stroke sequelae, and/or peripheral atherosclerosis and neuropathy from diabetes. Yet a correct identification of the exact cause of the functional limitations could be particularly important to this group of individuals to plan correct measures and

Table 2. Sociodemographic, Lifestyle, Clinical, and Functional Differences Among Clusters of Older People at Baseline in Swedish National Study on Aging and Care in Kungsholmen (*N* = 2,931)

	PSY-RESP	HEART	EYE-CANCER	CNS-IMP	RESP-MSK	UNSPECIFIC	ALL
<i>n</i> (%)	159 (5.4)	272 (9.3)	313 (10.7)	309 (10.6)	460 (15.7)	1,418 (48.4)	2,931
Sociodemographic factors							
Female sex (%)	74.2	59.2	72.5	76.9	74.4	61.0	66.6
Age, mean	73.3	82.3	83.2	88.2	73.9	71.8	76.1
Living in a nursing home (%)	5.8	6.0	4.1	43.2	1.8	0.7	6.5
Civil status (%)							
Unmarried	17.0	16.2	16.1	21.1	17.8	16.4	17.1
Married	35.2	35.5	25.1	25.8	38.4	49.5	40.6
Divorced	20.9	8.2	11.2	7.5	16.8	13.0	12.8
Widow	26.9	40.1	47.6	45.6	27.0	21.1	29.5
Education (%)							
Elementary	16.9	25.1	21.8	34.8	19.3	14.4	19.1
High school	47.6	56.1	56.5	47.4	49.5	50.1	50.9
University	35.5	18.8	21.8	17.7	31.1	35.5	30.0
Occupation (%)							
Manual worker	19.1	31.7	33.0	39.8	24.0	21.5	25.6
Non-manual worker	80.9	68.3	67.0	60.2	76.0	78.5	74.4
Life satisfaction score, mean	46.5	49.6	53.3	48.2	57.3	60.1	57.1
Social network (%)							
Poor	39.7	50.1	43.2	67.7	31.8	27.0	34.9
Moderate	35.8	24.4	36.5	21.3	35.4	35.8	33.8
Rich	24.5	25.5	20.3	11.0	32.9	37.2	31.2
Lifestyle factors							
Smoking (%)							
Never	43.6	45.4	59.2	60.1	45.5	46.7	48.7
Former	35.1	44.1	31.2	30.9	39.7	38.3	37.5
Current	21.3	10.6	9.6	9.0	14.8	15.0	13.8
Alcohol consumption (%)							
Never/occasional	39.7	52.7	51.2	77.6	40.4	30.1	40.8
Light/moderate	36.9	37.2	35.0	17.3	42.1	53.1	43.8
Heavy	23.4	10.1	13.8	5.1	17.5	16.9	15.3
Physical activity (%)							
Inadequate	42.4	56.0	44.7	82.9	31.1	22.7	36.9
Health-enhancing	40.2	36.3	45.8	14.4	50.1	52.5	45.2
Fitness-enhancing	17.4	7.7	9.6	2.6	18.8	24.7	17.9
Clinical and functional factors							
Self-rated health (%)							
Very good/excellent	15.4	5.1	23.0	14.8	23.6	43.3	32.5
Good/poor	84.6	94.9	77.0	85.2	76.4	56.7	67.5
Chronic conditions, mean	5.7	7.7	6.0	5.5	4.7	3.2	4.5
Drugs, mean	6.2	7.7	5.0	6.1	5.3	2.8	4.4
Serum albumin (g/L), mean	41.5	40.5	40.0	38.7	40.9	42.0	41.2
Serum creatinine (umol/L), mean	86.1	107.5	95.8	98.6	87.7	87.3	90.9
Serum CRP (mmol/L), mean	6.5	8.7	6.9	8.6	7.3	6.1	6.8
ADL + IADL limitations, mean	1.3	2.1	1.4	7.2	0.7	0.3	1.4
Balance test (s), mean	22.9	9.2	9.6	4.3	22.7	30.1	22.6
Grip strength test (N), mean	22.2	22.7	20.3	23.7	22.2	26.7	24.7
Walking speed (m/s), mean	0.9	0.6	0.7	0.3	0.9	1.1	0.9
MMSE test, mean	27.7	27.6	27.7	16.6	28.6	28.8	27.4

Notes: PSY-RESP = psychiatric and respiratory diseases; HEART = heart diseases; EYE-CANCER = eye diseases and cancer; CNS-IMP = cognitive and sensory impairments; RESP-MSK = respiratory and musculoskeletal diseases; CRP = C-reactive protein; ADL = activities of daily living; IADL = instrumental activities of daily living; MMSE = Mini-Mental State Examination. Missing values (%): age (0.3), civil status (0.5), education (1.1), occupation (2.7), life satisfaction score (39.2), social network (11.6), smoking (3.3), alcohol consumption (3.2), self-rated health (31.4), drugs (0.2), serum albumin (8.6), serum creatinine (8.6), serum CRP (10.0), ADL + IADL limitations (3.8), balance test (10.4), grip strength (25.1), walking speed (4.0), MMSE test (6.8). The distribution of all variables was significantly different across clusters ($p < .001$).

prevent disability. People in the CNS-IMP cluster could be systematically screened for functional impairment; if present, physical rehabilitation could be prescribed that might delay the progression to disability. Although no improvement has been shown in cognitive

functions, there is promising evidence that exercise programs may improve the ability to perform activities of daily living for people with dementia (42). People in the PSY-RESP cluster may benefit from specific interventions designed to reduce alcohol abuse and

subsequently improve their quality of life. Individuals in the EYE-CANCER cluster, characterized by a low muscle strength, may be screened for sarcopenia, given the known association between low muscle mass and chemotoxicity (43).

Second, care management could be improved for people with specific patterns characterized, for example, by polypharmacy and therefore a high frequency of potentially inappropriate medication and adverse drug reactions (44). Recent guidelines specifically developed for people with multimorbidity underline the potential treatment burden for patients prescribed a high number of drugs (45), such as those in the HEART cluster. In fact, certain therapeutic regimens that are appropriate for diseases affecting people in middle adulthood could be associated with the development of specific patterns of co-occurring diseases in late life. Some examples are chronic steroid treatment for respiratory diseases and the development of skeletal and psychiatric disorders (30), or chronic treatment with anticholinergic drugs for psychiatric diseases and the development of dementia in older age (46).

Finally, the group of people included in the UNSPECIFIC cluster is particularly interesting from both a research and prevention point of view. In fact, people in this pattern, despite suffering from two or more chronic diseases, were relatively younger, suggesting that aging itself is the main driver of disease clustering. This finding strengthens the idea that aging and multimorbidity share pathophysiological mechanisms (28) and that their connection is more evident when we analyze not only the number but also the patterns of diseases. Furthermore, the identification of this group of people is fundamental to plan interventions for the primary prevention of disease accumulation and to distribute health care resources accordingly.

Strengths and Limitations

The main strength of this study is the statistical technique, applied to allow clustering individuals according to their co-occurring diseases. The fuzzy *c*-means cluster algorithm is used for pattern recognition when clusters tend to overlap, which is most often the case in older adults. Other strengths are the high number of very old people in the cohort and the comprehensive list of both mental and physical chronic conditions included in the analyses. Limitations include the cross-sectional design of the study and the average high socioeconomic status of participants in SNAC-K, which limits the external validity of the findings.

Conclusion

In the present study, half of a cohort of older adults could be classified into five clinically meaningful clusters. These clusters showed significantly different sociodemographic, lifestyle, clinical, and functional profiles. This and similar approaches to the epidemiological study of multimorbidity are needed, not only to better understand the complex interactions among co-occurring diseases but also, even more importantly, to improve preventive interventions and optimally address individuals' care needs and the risk of adverse outcomes.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Author Contributions

A.R.L., D.L.V., and A.C.L. developed the study concept and design. A.R.L. performed the data analysis, and A.M., D.L.V., and A.C.L. contributed to the interpretation of the results. A.M. and A.R.L. drafted the manuscript. All authors provided critical revisions and approved the final version of the manuscript for submission.

Conflict of Interest

None reported.

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