



Universidad Autónoma  
de Madrid

**Biblos-e Archivo**  
Repositorio Institucional UAM

Repositorio Institucional de la Universidad Autónoma de Madrid

<https://repositorio.uam.es>

Esta es la **versión de autor** del artículo publicado en:

This is an **author produced version** of a paper published in:

Gerontology 69.6 (2023):716-727

**DOI:** <https://doi.org/10.1159/000529406>

**Copyright:** © 2023 Karger

El acceso a la versión del editor puede requerir la suscripción del recurso

Access to the published version may require subscription

## **Research article**

### **Multimorbidity patterns in older adults:**

#### **the role of social variables and lifestyle behaviors**

**Author Names:** Francisco Félix Caballero<sup>1</sup>, Alberto Lana<sup>2</sup>, Ellen A. Struijk<sup>1</sup>, Lucía Arias-Fernández<sup>3</sup>, Juan Cárdenas-Valladolid<sup>4-6</sup>, Miguel Ángel Salinero-Fort<sup>5,7-9</sup>, José R. Banegas<sup>1</sup>, Fernando Rodríguez-Artalejo<sup>1,10</sup>, Esther Lopez-Garcia<sup>1,10</sup>

#### **Author Affiliations:**

<sup>1</sup>Department of Preventive Medicine and Public Health. Universidad Autónoma de Madrid and CIBER of Epidemiology and Public Health, Madrid

<sup>2</sup>Department of Medicine. Universidad de Oviedo/ISPA, Oviedo

<sup>3</sup>Primary Health Care Network. Asturias Health Service, Asturias

<sup>4</sup>Dirección Técnica de Sistemas de Información. Gerencia Asistencial de Atención Primaria, Servicio Madrileño de Salud, Madrid

<sup>5</sup>Fundación de Investigación e Innovación Biosanitaria de Atención Primaria, Madrid

<sup>6</sup>Enfermería. Universidad Alfonso X El Sabio, Villanueva de la Cañada

<sup>7</sup>Subdirección General de Investigación Sanitaria. Consejería de Sanidad, Madrid

<sup>8</sup>Red de Investigación en Servicios de Salud en Enfermedades Crónicas

<sup>9</sup>Grupo de Envejecimiento y Fragilidad de las personas mayores. IdIPAZ, Madrid

<sup>10</sup>IMDEA-Food Institute. CEI UAM+CSIC, Madrid

**Short Title:** Multimorbidity patterns in older adults

#### **Corresponding Author:**

Francisco Félix Caballero or Esther Lopez-Garcia

Department of Preventive Medicine and Public Health

School of Medicine

Universidad Autónoma de Madrid

C/ Arzobispo Morcillo, s/n

28029 Madrid, Spain.

E-mail: felix.caballero@uam.es, esther.lopez@uam.es

**Number of Tables: 5.**

**Number of Figures: 0.**

**Word count: 3530.**

**Keywords:** Multimorbidity patterns; Chronic disease categories; Social variables; Lifestyle behaviors; Exploratory factor analysis.

## ABSTRACT

**Introduction:** While some conditions clusters represent the chance co-occurrence of common individual conditions, others may represent shared causal factors. The aims of this study were to identify multimorbidity patterns in older adults, and to explore the relationship between social variables, lifestyle behaviors, and the multimorbidity patterns identified.

**Methods:** This was a cross-sectional design. Data came from 3273 individuals aged  $\geq 65$  from the Seniors-ENRICA-2 cohort; information on 60 chronic diseases categories, categorized according to the 2<sup>nd</sup> edition of the International Classification of Primary Care and the 10th edition of the International Classification of Diseases, was obtained from clinical records linkage. To identify multimorbidity patterns, an exploratory factor analysis was conducted over chronic disease categories with prevalence  $>5\%$ , using Oblimin rotation and Kaiser's eigenvalues-greater-than-one rule. The association between multimorbidity patterns and their potential determinants was assessed with multivariable linear regression.

**Results:** The three-factor solution (*Musculoskeletal diseases and mental disorders*, *Cardiometabolic diseases*, and *Cardiopulmonary diseases*) explained 64.5% of the total variance. Being older, lower occupational category, higher levels of loneliness, lower levels of physical activity, and higher body mass index were associated with higher scores in the multimorbidity patterns identified. Female sex was linked to the *Musculoskeletal diseases and mental disorders* pattern, while being male was revealed to the two remaining multimorbidity patterns. A high diet quality was inversely related to *Cardiometabolic diseases*, while optimal sleep duration was inversely related to *Cardiopulmonary diseases*.

**Discussion/Conclusion:** Three multimorbidity patterns were identified in older adults. Multimorbidity patterns were differently associated with social variables and lifestyles behavioral factors.

1    **Introduction**

2    As life expectancy increases, the likelihood for an individual to develop several  
3    concomitant morbidities also increases. Therefore, the prevalence of multimorbidity is  
4    rising over recent decades [1] and is considered a global health care and public health  
5    priority [2]. However, not all older adults develop multimorbidity, and their  
6    determinants remain unknown.

7    Multimorbidity is defined as the co-existence of two or more chronic conditions [2].  
8    Although the number of coexisting diseases is a major proxy of biological aging [3], it  
9    is also possible to define concordant multimorbidities, since predictably certain  
10   morbidities develop together because they share a common etiology. The identification  
11   of which diseases, how many, and in what manner they should be assessed to measure  
12   multimorbidity is still a matter of debate [4].

13   Determinants of multimorbidity are mostly unknown. As in unique chronic conditions,  
14   social factors and lifestyle behaviors may underlie multimorbidity. Multimorbidity is  
15   known to be more prevalent in females and in people of low socio-economic status [5].  
16   In addition, multimorbidity has been linked to loneliness [6, 7], but there is a need to  
17   clarify whether it is also associated with social isolation, as it would allow a better  
18   targeting of public health measures. In addition, while a healthy lifestyle has been  
19   associated with a longer life expectancy in different populations [8-10], the effect of  
20   lifestyle behaviors, how and which of them contribute to multimorbidity, or interact  
21   with each other to exacerbate the development of clusters of chronic conditions, also  
22   needs to be investigated [2].

23   Since most of the previous studies on multimorbidity relied on information from  
24   clinical-administrative data sets, they lacked information on social and lifestyle factors

that are not usually measured in clinical practice. In the present study, social variables and lifestyles behavioral factors were well characterized and linked to accurate data on physician-diagnosed diseases by means of primary care electronic clinical records. A wide set of chronic diseases was used to characterize multimorbidity and the main aim of this study was to identify the most common multimorbidity patterns and their potential determinants in a Spanish population of community-dwelling older adults.

Several efforts have been done to disentangle the multimorbidity patterns on primary care older patients [11-13]. However, the determinants of these patterns should be explored, considering potential factors beyond sociodemographic and socioeconomic variables. Our hypothesis was that different multimorbidity patterns would have different determinants associated, and social variables and lifestyle behaviors could have a differential association with multimorbidity.

## **Materials and Methods**

### *Study design*

This was a cross-sectional study using baseline data from the Seniors-ENRICA II cohort (Study on Nutrition and Cardiovascular Risk in Spain), a population-based cohort study involving 3273 non-institutionalized subjects older than 65 years.

Participants were selected between December 2015 and June 2017 by sex- and district-stratified random sampling of all community-dwelling individuals holding a national healthcare card and living in the city of Madrid and four nearby towns. A computer-assisted telephone interview (CATI) was performed to gather information on sociodemographic data, lifestyle behaviors and health conditions, and two home visits were subsequently conducted to collect biological samples and perform a physical examination. The study design was similar to the procedure used in the Seniors-

ENRICA-1 cohort [14]. Additional information on study methods is reported elsewhere [15, 16].

All participants provided written informed consent and the Clinical Research Committee of La Paz University Hospital in Madrid approved the study protocol for the Seniors-ENRICA-2 cohort (PI-1793, PI-3554). In addition, the Research Central Commission of Madrid Regional Health Service (SERMAS), Primary Health Care, provided permission to access to the medical histories data set. The quality of the primary care electronic clinical record has previously been validated for research purposes [17], and the data set has been widely used to study the epidemiology of cardiovascular risk factors in the study population [18].

#### *Chronic disease categories*

Participants' information was linked with electronic health records, so physician-based diagnoses and their date were available to define multimorbidity. Chronic diseases were coded based on the International Classification of Primary Care, 2<sup>nd</sup> edition (ICPC-2) in primary care settings and the 10<sup>th</sup> edition of the International Classification of Diseases (ICD-10) in hospital settings. An international operational measure of multimorbidity was used, and chronic diseases were grouped into a list of 60 mutually exclusive conditions, as proposed by Calderón-Larrañaga et al. [4]. To identify multimorbidity patterns, those diagnoses coded up until December 2017 were used.

#### *Social variables*

Participants' socioeconomic status was estimated by the highest educational level attained (primary education or less, secondary school, and university), and householder's occupational category. The latest occupation was considered for those retired participants, and the categorization proposed by Lostao et al. [19] for the Spanish



population was employed: *professionals and managers* (professionals and employers-managers), *lower non-manual workers* (clerks and administrative personnel, service and sales workers, self-employed workers, and supervisors), *skilled manual workers* and *unskilled manual workers* (semi-skilled manual workers and unskilled manual workers).

An index of social isolation was computed, based on the following four components: 1) not living with a partner; 2) not attending to any organization, senior club or religious services; 3) having less than weekly contact with family members (other than those living with the participant); and 4) having less than weekly contact with friends or neighbors. Each component was score as 1, resulting a total value ranged from 0 to 4, with higher scores indicating a greater degree of isolation [20].

Loneliness was assessed by means of the 3-item UCLA Loneliness Scale, which has shown adequate reliability and validity for measuring loneliness in large surveys [21]. This scale comprises the following three items: 1) “How often do you feel that you lack companionship?”; 2) “How often do you feel left out?”; and 3) “How often do you feel isolated from others?”. These items were assessed on a three-point scale (1 = hardly ever; 2 = some of the time; 3 = often) and were added up to produce a loneliness score ranging from 3 to 9, with higher scores indicating higher levels of loneliness. In the present study, the UCLA Loneliness Scale showed an adequate internal reliability (Cronbach’s alpha = 0.82; mean inter-item correlation = 0.61).

#### *Lifestyle behaviors*

Habitual food consumption was collected with a validated diet history [22]. Diet quality was assessed by the Alternate Healthy Eating Index-2010 (AHEI-2010) [23], which is based on a set of 11 foods and nutrients predictive of chronic disease risk. A value of 10 is assigned to low/no intakes of unhealthy foods and nutrients, while a value of 0 is

assigned to higher consumption of unhealthy dietary components, with intakes between the minimum and maximum levels being proportionally scored. A high diet quality was defined as an AHEI-2010 score in the top 40% of the distribution of values [10].

Physical activity was assessed with the validated questionnaire developed in the EPIC cohort study in Spain [24]. Participants were asked how many hours they spent in a typical week during the last year on each of the following activities: walking, cycling, gardening, do-it-yourself activities at home, playing sports (running, fitness, aerobics, swimming, soccer, tennis, etc.), and climbing stairs. Tertiles of physical activity (in metabolic equivalent tasks, h/week) were derived from the time spent for each participant.

Sleep duration was obtained with the question: “How many hours do you usually sleep per day?”. The question included sleep at night and during the day. Participants were asked to specify the number of hours and minutes they slept, and the interviewer rounded the figure to the nearest whole number. In the present study, optimal sleep duration was defined as sleeping 7-8 h per day [25].

Weight and height were measured in standardized conditions, and the body mass index (BMI) was calculated as weight (kg) divided by squared height (m). Three categories for BMI were considered: <25, 25–29.9 (overweight), and  $\geq 30$  kg/m<sup>2</sup> (obesity).

Tobacco consumption was self-reported, and participants categorized as “never smokers” and “current or former smokers”. Alcohol consumption was measured in g/day with the validated diet history abovementioned and tertiles of the distribution were derived.

*Statistical analysis*

The analysis was conducted over 3264 participants, because nine of the original sample did not provide their sufficient identification data to be linked with medical records.

Frequency analyses were used to assess the prevalence of chronic disease categories. A stratified analysis by sex was provided and the chi-squared test was used to assess potential sex differences in the prevalence of chronic diseases.

An exploratory factor analysis (EFA) was conducted to detect the latent structure among the chronic diseases considered, using a tetrachoric correlation matrix. To increase the robustness of the associations between diagnoses and disease patterns found, the EFA was conducted over only those chronic disease categories with a prevalence  $\geq 5\%$  in the overall sample.

The principal factor method was used and the number of factors to be extracted was selected according to the eigenvalues-greater-than-one rule proposed by Kaiser [26]. An oblique rotation, Oblimin, was performed to better interpret the nature of the factors, since the factors were assumed to be associated with each other. The factors resulting from the EFA were interpreted as multimorbidity patterns and each factor loading represented the association of each chronic disease category with the corresponding factor. For determining the chronic disease categories which formed each multimorbidity pattern those factor loadings equal to or higher than 0.25 were considered as relevant. To obtain factor scores for each participant, the approach described by Jackson et al. [27] was applied: the factor loading for each condition was multiplied by 1 or 0 (i.e., present or absent condition), before summing these to obtain total scores for each participant. The total scores for each factor were transformed into a 0-100 scale, with higher scores indicating a higher adherence to the corresponding pattern.

After identifying a general structure in the overall population, the factorial equivalence between males and females was assessed by means of the Tucker's congruence coefficient [28]. This coefficient ranges between 0 and 1 and is used to assess the similarity of factor interpretations, with values between 0.85 and 0.94 suggesting a fair similarity, and values  $\geq 0.95$  indicating that the factor structure can be considered equal between the populations compared [29].

Multivariable linear regression models were finally considered to explore the association between social variables, including sex, socioeconomic status, social isolation and loneliness, and the factor scores derived for each of the multimorbidity patterns identified. An additional multivariable-adjusted linear regression model for each multimorbidity pattern was built to include lifestyle behaviors as independent variables, together with those abovementioned. While the initial sample considered for the main analysis comprised the 3264 participants, the adjusted analyses including lifestyle behaviors (diet quality, physical activity, sleep duration, BMI, tobacco consumption, and alcohol consumption) were conducted over a subset of participants, since diet history (used for assessing diet quality and alcohol consumption) was measured only in 2784 of these participants.

Statistical analyses were conducted using Stata 16.1 [30].

## Results

The mean (SD) age of the 3264 participants was 71.9 (4.5) years, with a 53.1% of females. In the overall sample, 17.0% of the participants had *university studies* and 22.6% reported being *professionals and managers*, as their highest householder's occupation (**Table 1**).

The 60 chronic disease categories initially considered were listed in **Table 2**. The highest prevalence rates were observed for *dyslipidemia* (61.6%), *hypertension* (58.8%), *other musculoskeletal and joint diseases* (48.3%), and *osteoarthritis and other degenerative joint diseases* (36.2%). When comparing by sex, the highest effect sizes were found for *osteoporosis* (Cramer's  $V=0.46$ ), *thyroid diseases* ( $V=0.31$ ), and *osteoarthritis and other degenerative joint diseases* ( $V=0.30$ ). In these cases, the highest prevalence rates were found for females.

The factor analysis was conducted over a list of 36 chronic disease categories with prevalence rates higher than 5% in the overall sample. The Kaiser-Meyer-Olkin index was equal to 0.67 and the percentage of variance accounted for by the three-factor solution was 64.5%. The highest factor loadings observed in the first factor corresponded to *depression and mood diseases*, *osteoarthritis and other degenerative joint diseases*, and *osteoporosis*, also observing a high loading for *other psychiatric and behavioral diseases*. Therefore, this factor was named as *Musculoskeletal diseases and mental disorders* (**Table 3**). *Diabetes*, *hypertension*, *obesity*, and *ischemic heart disease* loaded on the second one, which was named *Cardiometabolic diseases*. Finally, the third factor was characterized by *Cardiopulmonary diseases*.

For the 36 chronic disease categories included in the factor analysis, the mean (SD) number of chronic diseases in the sample was 6.2 (3.1). Significant differences were observed by sex, with females having a higher number of chronic diseases than males [7.0 (3.1) in females vs. 5.3 (2.7) in males,  $p<0.001$ ]. When comparing the structure of multimorbidity patterns in males and females, the Tucker's congruence coefficient was 0.90, suggesting a moderately high similarity in the underlying multimorbidity patterns structure among sexes. **Supplementary Table S1** shows that the number of chronic diseases was highly correlated with the factor score in *Musculoskeletal diseases and*

192 *mental disorders* [ $r=0.87$ ; 95% CI = (0.86, 0.88)], and moderately correlated with the  
193 factor scores in *Cardiometabolic diseases* [ $r=0.53$ ; 95% CI = (0.51, 0.56)] and  
194 *Cardiopulmonary diseases* [ $r=0.50$ ; 95% CI = (0.47, 0.52)].

195 In multivariable analysis (**Table 4**), females presented higher scores in *Musculoskeletal*  
196 *diseases and mental disorders* ( $p<0.001$ ), while males had higher scores in  
197 *Cardiometabolic diseases* and *Cardiopulmonary diseases* ( $p<0.001$  in both cases).

198 Regarding social variables, higher scores in loneliness and being older were related to  
199 higher scores in the three multimorbidity patterns identified; on the other hand, no  
200 significant associations were found for social isolation. A moderate correlation between  
201 loneliness and social isolation was observed [ $r=0.22$ ; 95% CI = (0.19, 0.26)]. In terms  
202 of householder's occupation, a higher score in the three patterns was found for *unskilled*  
203 *manual workers* when compared to *professional and managers* ( $p<0.001$ ). Those with  
204 primary education or less showed a higher score in *Musculoskeletal diseases and mental*  
205 *disorders* ( $p<0.001$ ) and *Cardiometabolic diseases* ( $p=0.04$ ) than those with university  
206 studies ( $p<0.001$ ).

207 When including lifestyle behaviors in the models over the subset of participants with  
208 this information, higher levels of physical activity and a BMI below 25 kg/m<sup>2</sup> were  
209 associated with lower scores in the three multimorbidity patterns identified (**Table 5**).

210 High diet quality was inversely related to *Cardiometabolic diseases* ( $p=0.02$ ), while  
211 optimal sleep duration was inversely related to *Cardiopulmonary diseases* ( $p=0.02$ ).

212 Those with optimal sleep duration showed also a lower score in the *Musculoskeletal*  
213 *diseases and mental disorders* ( $p=0.04$ ). Finally, those who never smoked showed lower  
214 scores in the *Cardiometabolic diseases* and *Cardiopulmonary diseases* patterns ( $p=0.01$   
215 and  $p<0.001$ , respectively), while those in the bottom tertile of the distribution of

alcohol consumption showed higher scores in the three multimorbidity patterns than those in the upper tertile.

## **Discussion/Conclusion**

This study identified a few multimorbidity patterns among a wide list of chronic disease categories, which allows international comparison and exploration of the factorial structure associated. Although initially a list of 60 mutually exclusive chronic conditions was considered, only those chronic conditions with a prevalence higher than 5% in the study sample were included in the statistical analyses, in order to improve the robustness of the findings. Finally, a total of 36 chronic conditions were considered to identify different multimorbidity patterns and potential determinants associated.

The three multimorbidity patterns identified were moderately correlated across them and shared common factors associated: older people and those with lower occupational category, higher levels of loneliness, low physical activity, and high BMI presented higher multimorbidity levels in the three patterns. Sex was significantly associated with all these patterns but in a different way: females had higher scores in the *Musculoskeletal and mental health disorders* pattern, while males had higher scores in the *Cardiometabolic diseases* and *Cardiopulmonary diseases* patterns. Beyond these associations, the remaining covariates showed a differential relationship with multimorbidity patterns: 1) non-optimal sleep duration and low educational attainment were associated with higher levels of *Musculoskeletal and mental health disorders*; 2) high diet quality and never smoking were related to lower levels of *Cardiometabolic diseases*; and 3) optimal sleep duration and never smoking were associated with lower levels of *Cardiopulmonary diseases*.

The existence of non-random associations between chronic diseases is a reality for the entire population [11, 13]. The present study focused on the older population and has identified three multimorbidity patterns grouping the initial list of chronic diseases. Other previous studies also found a three-factor structure: Jackson et al. [27] identified three factors that were labelled as *Musculoskeletal/somatic*, *Neurological/mental health*, and *Cardiovascular*, in a sample of Australian females aged 76-81; while Garin et al. [31] identified three multimorbidity patterns named as *Cardio-respiratory*, *Metabolic*, and *Mental-auricular* disorders from a list of 12 chronic conditions, using a sample of non-institutionalized older adults from nine countries. Although these studies, also based on older populations, have found slightly different patterns, the observed differences may be partly explained by the different systems for classifying chronic diseases [4, 32, 33].

Our results showed that the most frequent chronic diseases were most prevalent in females. Moreover, females reported a higher number of chronic diseases than males, in the same line that previous results in adults over 65 years [12]. On the other hand, males presented higher scores in the *Cardiometabolic diseases* and *Cardiopulmonary diseases* patterns. It should be considered, however, that cardiovascular diseases could be underestimated in females because they can be under-recognized and underdiagnosed [34].

In a cross-sectional study, Bezerra de Souza et al. [7] found that multimorbidity was more prevalent in females, older adults, and people with low educational attainment, and was positively associated with higher BMI (overweight and obese) and higher levels of loneliness. By contrast, higher education level and occupational position have been also associated with multimorbidity by Dugravot et al. [5]. We obtained similar results, although a significant association for educational attainment was only observed



for the *Musculoskeletal diseases and mental disorders* pattern. Our results also showed a relationship between higher levels of loneliness and higher scores in the three multimorbidity patterns identified, in line with previous studies on multimorbidity [6, 35] and suggesting that social variables can be determinants of different multimorbidity patterns.

We have defined social isolation in terms of living in partnership, contact with family and friends, and participation in civic organizations (Ref.). Feeling of loneliness (Ref.) and different dimensions of social networks (Ref.), as social isolation, might not have the same effect on morbidity since they represent different concepts. In our study, social isolation and loneliness were moderately correlated, but while higher levels of loneliness were associated with higher levels of multimorbidity according to the three patterns identified, no significant associations were found for social isolation. In a same line with the results obtained in our study, a previous work conducted in older population found that loneliness had a stronger association with health status than several components of the social network as size and quality of the network, and frequency of contact (Ref.). Our findings showed that higher physical activity, BMI below 25 kg/m<sup>2</sup>, and optimal sleep duration were associated with a lower score in the *Musculoskeletal diseases and mental disorders* pattern; higher physical activity, BMI below 25 kg/m<sup>2</sup>, high diet quality, and never smoking were correlated with lower scores in the *Cardiometabolic diseases* pattern; finally, higher physical activity, BMI below 25 kg/m<sup>2</sup>, optimal sleep duration, and never smoking were related to lower scores in the *Cardiopulmonary diseases* pattern. Also, in a sample of Spanish older people, multimorbidity increased as physical activity decreased [36]. Dhalwani et al. [37] found an inverse dose-response association between physical activity and multimorbidity. In a cross-sectional survey conducted over middle-aged and older adults, Nicholson et al.

[38] found that the odds of multimorbidity were higher for those reporting either short or long (in both cases, non-optimal) sleep duration. A linear dose-response relationship between the number of chronic conditions and sleep problems has also been observed in older adults from nine different countries [39]. Regarding diet, our results suggested that those with high diet quality, measured by AHEI-2010 index, presented lower scores in the *Cardiometabolic diseases* pattern, but no association was found for the two remaining patterns. Previously, a healthy dietary pattern has been associated with longer life expectancy<sup>10</sup> and lower incidence of chronic diseases [40].

Positive associations between overweight or obesity and multimorbidity have been found in the literature [41], although its specific role in older adults should be disentangled because loss of weight could be a marker of impending expansion of multimorbidity [42]. Our results on current and past cigarette smoking and *Cardiometabolic* and *Cardiopulmonary diseases* are in line with other previous studies in older adults [43, 44]. Regarding alcohol consumption, a controversial result is that those with a low consumption presented higher scores in the multimorbidity patterns identified than those in the upper tertile of the distribution. A similar result was found in a cross-sectional study [45], where daily or weekly alcohol intake was linked to lower odds of multimorbidity in middle-aged people. However, since our results came from a cross-sectional design and causality cannot be inferred. On the other hand, alcohol consumption is an important contributor to global disease burden [46].

A systematic review found that factor analysis was the most widely used analytical method for identifying multimorbid condition groups in previous studies, with most of them using tetrachoric correlation matrices for binary data and oblique methods of rotation to account for the potential correlations across factors [47]. Moreover, the Tucker's congruence coefficient was used in our study to test the similarity in the

underlying structure of multimorbidity patterns by sex. A comparative analysis of methods for identifying multimorbidity patterns indicates that exploratory factor analysis is useful for describing comorbid relationships [48]. One of the main strengths of the present study is that the covariates considered in the regression models include a wide range of variables. While previous studies have been generally focused on general multimorbidity, our study has identified multimorbidity patterns and their determinants associated, linking the medical histories to socio-demographics, social variables, and lifestyle behaviors. Moreover, a wide set of chronic diseases has been used and adequately coded in our study, using the ICPC-2 in primary care settings and the ICD-10 in hospital settings.

Among the potential limitations is the cross-sectional design of this study. Longitudinal research is needed to explore the temporal relationship between the study variables. Although subjective perception of loneliness has been found to be associated with the multimorbidity patterns identified, the role of social isolation in this association remains to be disentangled. Future longitudinal studies could explore the prospective association between social variables and multimorbidity patterns, even considering alternative approaches for defining social isolations in older adults. Other social variables as social participation, size of the social network or quality of the social network should be assessed in these studies. Although the sample size of this study could be considered as moderately large, the frequencies of some chronic diseases were low and were not included in the factor analysis.

In conclusion, different multimorbidity patterns were identified and had different determinants. The differential effect of social variables and lifestyle behaviors on multimorbidity patterns should be confirmed in longitudinal studies; if this is the case,

338 they may inform public health policy on prevention and better management of the  
339 growing, burdensome, and challenging problem of multimorbidity.

**Conflict of interest statement:**

The authors declare that there is no conflict of interest regarding the publication of this article.

**Funding sources:**

This study has been funded by Instituto de Salud Carlos III through the FIS projects 19/319, 19/665 and 20/01040 (Instituto de Salud Carlos III, State Secretary of R+D+I), and co-funded by a European Regional Development Fund, “A way of shaping Europe”. The funding agencies had no role in study design, data analysis, interpretation of results, manuscript preparation or in the decision to submit this manuscript for publication.

**Statement of authorship:**

The authors’ responsibilities were as follows: The authors’ responsibilities were as follows: EL-G created the study concept and design; FFC provided statistical expertise and drafted the manuscript; EL-G supervised the work; JRB, FRA and EL-G obtained funding; AL, EAS, LA-F, JC-V, MAS-F, JRB and FR-A provided input and critical feedback after reviewing the first draft. All authors have read and approved the manuscript as submitted and are prepared to take public responsibility for the work.

## References

- 1 Prince MJ, Wu F, Guo Y, Gutierrez-Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. *Lancet* 2015;385(9967):549-62.
- 2 The Academy of Medical Sciences. Multimorbidity: a priority for global health research (online). Available at: <https://acmedsci.ac.uk/file-download/82222577> Accessed August 25, 2022.
- 3 Ferrucci L, González-Freire M, Fabbri E, Simonsick E, Tanaka T, Moore Z, et al. Measuring biological aging in humans: a quest. *Aging Cell* 2020;19(2):e13080. doi: 10.1111/accel.13080.
- 4 Calderón-Larrañaga A, Vetrano DL, Onder G, Gimeno-Feliu LA, Coscollar-Santaliestra C, Carfi A, et al. Assessing and measuring chronic multimorbidity in the older population: a proposal for its operationalization. *J Gerontol A Biol Sci Med Sci* 2017;72(10):1417-23.
- 5 Dugravot A, Fayosse A, Dumurgier J, Bouillon K, Ben Rayana T, Schnitzler A, et al. Social inequalities in multimorbidity, frailty, disability, and transitions to mortality: a 24-year follow-up of the Whitehall II cohort study. *Lancet Public Health* 2020;5(1):e42-50.
- 6 Kristensen K, König HH, Hajek A. The association of multimorbidity, loneliness, social exclusion and network size: findings from the population-based German Ageing Survey. *BMC Public Health* 2019;19:1383. doi: 10.1186/s12889-019-7741-x.
- 7 Bezerra de Souza DL, Oliveras-Fabregas A, Espelt A, Bosque-Prous M, de Camargo-Cancela M, Teixidó-Compañó E, et al. Multimorbidity and its associated factors among

adults aged 50 and over: A cross-sectional study in 17 European countries. PLoS One 2021;16(2):e0246623. doi: 10.1371/journal.pone.0246623.

8 Tamakoshi A, Kawado M, Ozasa K, Tamakoshi K, Lin Y, Yagyu K, et al. Impact of smoking and other lifestyle factor son life expectancy among Japanese: findings from the Japan Collaborative Cohort (JACC) study. J Epidemiol 2010;20(5):370-6.

9. Li K, Hüsing A, Kaaks R. Lifestyle risk factors and residual life expectancy at age 40: a German cohort study. BMC Med 2014;12:59. doi: 10.1186/1741-7015-12-59.

10 Li Y, Pan A, Wang DD, Liu X, Dhana K, Franco OH, et al. Impact of healthy lifestyle factor on life expectancies in the US population. Circulation 2018;138(4):345-55.

11 Prados-Torres A, Poblador-Plou B, Calderón-Larrañaga A, Gimeno-Feliu LA, González-Rubio F, Poncel-Falcó A, et al. Multimorbidity patterns in primary care: interactions among chronic diseases using factor analysis. PLoS One 2012;7(2):e32190. doi: 10.1371/journal.pone.0032190.

12 Abad-Díez JM, Calderón-Larrañaga A, Poncel-Falcó A, Poblador-Plou B, Calderón-Meza JM, Sicras-Mainar A, et al. Age and gender differences in the prevalence and patterns of multimorbidity in the older population. BMC Geriatr 2014;14:75. doi: 10.1186/1471-2318-14-75.

13 Ioakeim-Skoufa I, Poblador-Plou B, Carmona-Pérez J, Díez-Manglano J, Navickas R, Gimeno-Feliu LA, et al. Multimorbidity patterns in the general population: Results from the EpiChron Cohort Study. Int J Environ Res Public Health 2020;17(12):4242. doi: 10.3390/ijerph17124242.

- 14 Rodríguez-Artalejo F, Graciani A, Guallar-Castillón P, León-Muñoz LM, Zuluaga MC, López-García E, et al. Rationale and methods of the study on nutrition and cardiovascular risk in Spain (ENRICA). *Rev Esp Cardiol* 2011;64(10):876–82.
- 15 Estrada de León DB, Struijk EA, Caballero FF, Sotos-Prieto M, Rodríguez-Artalejo F, López-García E. Prolonged nightly fasting and lower-extremity functioning in community-dwelling older adults. *Br J Nutr* 2021;126(9):1347-54.
- 16 Ortolá R, García-Esquinas E, Sotos-Prieto M, Struijk Ea, Caballero FF, López-García E, et al. Mediterranean diet and changes in frequency, severity and localization of pain in older adults: the Seniors-ENRICA cohorts. *J Gerontol A Biol Sci Med Sci* 2022;77(1):122-30.
- 17 de Burgos-Lunar C, Salinero-Fort MA, Cárdenas-Valladolid J, Soto-Díaz S, Fuentes-Rodríguez CY, Abánades-Herranz JC, et al. Validation of diabetes mellitus and hypertension diagnosis in computerized medical records in primary health care. *BMC Med Res Methodol* 2011;11:146. doi: 10.1186/1471-2288-11-146.
- 18 Gil Montalbán E, Ortiz Marrón H, López-Gay Lucio-Villegas D, Zorrilla Torrás B, Arrieta Blanco F, Nogales Aguado P. Validity and concordance of electronic health records in primary care (AP-Madrid) for surveillance of diabetes mellitus. PREDIMERC study. *Gac Sanit* 2014;28(5):393-6.
- 19 Lostao L, Regidor E, Gimeno D, Netuveli G, Blane D. Socioeconomic patterns in health services use in Great Britain and Spain before and after the health system reforms of the 1990s. *Health & Place* 2011;17(3):830-5.
- 20 Shankar A, McMunn A, Banks J, Steptoe A. Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychol* 2011;30(4):377-85.



- 21 Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A short scale for measuring loneliness in large surveys: results from two population-based studies. *Res Aging* 2004;26(6):655-72.
- 22 Guallar-Castillón P, Sagardui-Villamor J, Balboa-Castillo T, Sala-Vila A, Ariza-Astolfi MJ, Sarrión-Pelous MD, et al. Validity and reproducibility of a Spanish dietary history. *PLoS One* 2014;9(1):e86074. doi: 10.1371/journal.pone.0086074.
- 23 Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, et al. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr* 2012;142(6):1009-18.
- 24 Pols MA, Peeters PH, Ocké MC, Slimani N, Bueno-de-Mesquita HB, Collette HJ. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. *Int J Epidemiol* 1997;26(Suppl 1):S181-9.
- 25 Campanini MZ, Guallar-Castillón P, Rodríguez-Artalejo F, López-García E. Mediterranean diet and changes in sleep duration and indicators of sleep quality in older adults. *Sleep* 2017;40(3). doi: 10.1093/sleep/zsw083.
- 26 Kaiser HF. The application of electronic computers to factor analysis. *Educ Psychol Meas* 1960;20(1):141-51.
- 27 Jackson CA, Jones M, Tooth L, Mishra GD, Byles J, Dobson A. Multimorbidity patterns are differentially associated with functional ability and decline in a longitudinal cohort of older women. *Age Ageing* 2015;44(5):810-16.
- 28 Tucker LR. Personnel Research Sections Report 984. In *A method for synthesis of factor analysis studies*. Washington DC: Department of the Army, 1951.

- 29 Lorenzo-Seva U, Ten Berge JMF. Tucker's congruence coefficient as a meaningful index of factor similarity. *Methodology* 2006;2(2):57-64.
- 30 StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC, 2019.
- 31 Garin N, Koyanagi A, Chatterji S, Tyrovolas S, Olaya B, Leonardi M, et al. Global multimorbidity patterns: a cross-sectional, population-based, multi-country study. *J Gerontol A Biol Sci Med Sci* 2016;71(2):205-14.
- 32 Johns Hopkins University. The Johns Hopkins ACG System (online). Available at: <https://www.hopkinsacg.org> Accessed August 25, 2022.
- 33 Salisbury C, Johnson L, Purdy S, Valderas JM, Montgomery AA. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2011;61(582):e12-21.
- 34 Vogel B, Acevedo M, Appelman Y, Bairey-Merz CN, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet* 2021;397(10292):2385-438.
- 35 Stickley A, Koyanagi A. Physical multimorbidity and loneliness: a population-based study. *PLoS One* 2018;13(1):e0191651. doi: 10.1371/journal.pone.0191651.
- 36 Latorre-Román PA, Carmona-Torres JM, Cobo-Cuenca AI, Laredo-Aguilera JA. Physical activity, ability to walk, weight status, and multimorbidity levels in older Spanish people: the National Health Survey (2009-2017). *Int J Environ Res Public Health* 2020;17(12):4333. doi: 10.3390/ijerph17124333.

- 37 Dhalwani NN, O'Donovan G, Zaccardi F, Hamer M, Yates T, Davies M, et al. Long terms trends of multimorbidity and association with physical activity in older English population. *Int J Behav Nutr Phys* 2016;13:8. doi: 10.1186/s12966-016-0330-9.
- 38 Nicholson K, Rodrigues R, Anderson KK, Wilk P, Guaiana G, Stranges S. Sleep behaviours and multimorbidity occurrence in middle-aged and older adults: findings from the Canadian Longitudinal Study on Aging (CLSA). *Sleep Med* 2020;75:156–162.
- 39 Koyanagi A, Garin N, Olaya B, Ayuso-Mateos JL, Chatterji S, Leonardi M, et al. Chronic conditions and sleep problems among adults aged 50 years or over in nine countries: a multi-country study. *PLoS One* 2014;9(12):e114742. doi: 10.1371/journal.pone.0114742.
- 40 Li Y, Schoufour J, Wang DD, Dhana K, Pan A, Liu X, et al. Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type 2 diabetes: prospective cohort study. *BMJ* 2020;368:I6669. doi: <https://doi.org/10.1136/bmj.l6669>.
- 41 Jovic D, Marinkovic J, Vukovic D. Association between body mass index and prevalence of multimorbidity: a cross-sectional study. *Public Health* 2016;139:103-111.
- 42 Fabbri E, Tanaka T, An Y, Zoli M, Bandinelli S, Guralnik JM, et al. Loss of weight in obese older adults: a biomarker of impending expansion of multimorbidity? *J Am Geriatr Soc* 2015;63(9):1791-97.
- 43 Gopal DM, Kalogeropoulos AP, Georgiopoulou VV, Smith AL, Bauer DC, Newman AB, et al. Cigarette smoking exposure and heart failure risk in older adults: the Health, Aging, and Body Composition Study. *Am Heart J* 2012;164(2):236-42.

- 44 Tolstrup JS, Hvidtfeldt UA, Flachs EM, Spiegelman D, Heitmann BL, Bälter K, et al. Smoking and risk of coronary heart disease in younger, middle-aged, and older adults. *Am J Public Health* 2014;104(1):96-102.
- 45 Sakib MN, Shooshtari S, St. John P, Menec V. The prevalence of multimorbidity and associations with lifestyle factors among middle-aged Canadians: an analysis of Canadian Longitudinal Study on Aging data. *BMC Public Health* 2019;19(1):243. doi: 10.1186/s12889-019-6567-x.
- 46 GBD 2016 Alcohol and Drug Use Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry* 2018;5(12):987-1012.
- 47 Ng SK, Tawiah R, Sawyer M, Scuffham P. Patterns of multimorbid health conditions: a systematic review of analytical methods and comparison analysis. *Int J Epidemiol* 2018;47(5):1687-704.
- 48 Roso-Llorach A, Violán C, Foguet-Boreu Q, Rodríguez-Blanco T, Pons-Vigués M, Pujol-Ribera E, et al. Comparative analysis of methods for identifying multimorbidity patterns: a study of ‘real-world’ data. *BMJ Open* 2018;8(3):e018986. doi: 10.1136/bmjopen-2017-018986.