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MULTIMORBIDITY PATTERNS OF CHRONIC CONDITIONS AND GERIATRIC SYNDROMES IN OLDER PATIENTS FROM THE MoPIM MULTICENTRE COHORT STUDY.

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ABSTRACT

Objectives: To estimate the frequency of chronic conditions and geriatric syndromes in older patients admitted to hospital because of an exacerbation of their chronic conditions, and to identify multimorbidity clusters in these patients.

Design: Multicentre, prospective cohort study.

Setting: Internal medicine or geriatric services of five general teaching hospitals in Spain.

Participants: 740 patients aged 65 and older, hospitalized because of an exacerbation of their chronic conditions between September 2016 and December 2018.

Primary and secondary outcome measures: Active chronic conditions and geriatric syndromes (including risk factors) of the patient, a score about clinical management of chronic conditions during admission, and destination at discharge were collected, among other variables. Multimorbidity patterns were identified using fuzzy c-means cluster analysis, taking into account the clinical management score. Prevalence, observed/expected ratio and exclusivity of each chronic condition and geriatric syndrome were calculated for each cluster, and the final solution was approved after clinical revision and discussion among the research team.

Results: 740 patients were included (mean age 84.12 years, SD 7.01; 53.24% female). Almost all patients had two or more chronic conditions (98.65%; 95%CI 98.23-99.07), the most frequent were hypertension (81.49%, 95%CI 78.53-84.12) and heart failure (59.86%, 95%CI 56.29-63.34). The most prevalent geriatric

syndrome was polypharmacy (79.86%, 95%CI 76.82-82.60). Four statistically and clinically significant multimorbidity clusters were identified: osteoarticular, psychogeriatric, cardiorespiratory and minor chronic disease. Patient level variables such as sex, Barthel Index, number of chronic conditions or geriatric syndromes, chronic disease exacerbation 3 months prior to admission or destination at discharge differed between clusters.

Conclusions: In older patients admitted to hospital because of the exacerbation of chronic health problems, it is possible to define multimorbidity clusters using soft clustering techniques. These clusters are clinically relevant and could be the basis to reorganize healthcare circuits or processes to tackle the increasing number of older, multimorbid patients.

Trial registration number NCT02830425, 12th July 2016

Keywords: Multimorbidity, patterns, soft clustering, older, chronic conditions, geriatric syndromes.

Strengths and limitations of this study

- The multimorbidity analysis in this study has been developed from a patient-centred point of view, considering a wide range of long-term conditions that may require healthcare in older people.
- To the best of our knowledge, this is the first published study of multimorbidity clusters in older patients to include chronic diseases weighted by a clinical management score and geriatric syndromes.
- Soft clustering is an innovative, methodologically robust technique that can lead to reliable results in the field of multimorbidity analysis.

- The list of chronic conditions and geriatric syndromes used in this study is comprehensive but not standardized, thus hindering comparability with other studies.

BACKGROUND

According to the most recent Eurostat baseline population projections, old-age dependency ratio (population 65y and over divided by population 15-64y) is about 32% in the European Union (EU) and it is expected to reach 52% in 2050, meaning that the EU's population will continue to grow older[1]. Together with the fact that chronic conditions (CC) are the main cause of disability and mortality in Europe, this implies that the coexistence of two or more chronic health conditions, which constitutes the classic definition of multimorbidity, is becoming increasingly common[2].

Multimorbidity is therefore turning into an important challenge for the health system because of the expanding proportion of older people with multiple CC and treatments as well as the difficulties associated with their clinical management[3,4]. Most clinical practice guidelines are focused on single diseases, with limited recommendations for multimorbid patients[5], and, in addition, randomized clinical trials often exclude older patients with multimorbidity[6]. Despite the importance of multimorbidity in clinical practice, different methodological approaches are still under debate and there is no gold standard, which makes it difficult to compare different estimations around the world[7–9].

One of the novel, increasingly widespread definitions of multimorbidity considers the non-spurious association of certain CC by sharing pathophysiological

mechanisms, giving rise to disease association patterns or clusters[10]. Other clinically relevant situations such as geriatric syndromes (GS) may also be considered in the definition of these patterns, since they might have a great impact on the health-related quality of life and clinical management of old patients[11]. In fact, the purpose of multimorbidity characterization (i.e., predicting outcomes or use of health services, improving quality of care, organizing healthcare services, etc.), will have an influence on its definition. From a patient-centred point of view, a global consideration of all conditions that may require healthcare attention is necessary, even if they are not the reason for hospitalization. Along these lines, some countries have explicitly recommended to acknowledge all long-term conditions for optimising care of adult patients by reducing, for example, possible inappropriate treatments, multiple healthcare appointments or poor health-related quality of life[12–14].

During the past decade, there has been an increasing amount of publications that consider multimorbidity[15], but few have focused on multimorbidity patterns in older patients and even fewer take into account GS[16]. For this reason, we launched a multicentre study in 2016 with multiple aims related to multimorbidity, appropriateness of chronic treatments and adverse drug reactions in older patients[17]. The objectives of the present analyses were to estimate the frequency of CC and GS in older patients admitted to hospital because of an exacerbation of their CC, and to identify possible multimorbidity patterns in these patients.

METHODS

Design and setting

A multicentre, prospective cohort study including older patients hospitalized at the internal medicine or geriatric services at five general teaching hospitals in three different regions of Spain between September 2016 and December 2018 was designed. The detailed protocol was previously published[17].

For the purposes of the study, older patients (≥65 years old) admitted as a result of the exacerbation of their chronic pathology were included. Patients referred to home hospitalization, admitted because of an acute process not related to any chronic disease, or with a fatal outcome expected at the time of admission were not included.

No written informed consent was deemed necessary for this study.

Data acquisition and variables

The following sociodemographic and clinical data was retrieved by the clinical team responsible for the patient: patient's code, date of birth, sex, functional status just before entering the hospital (Barthel index)[18], household (alone, with relatives or other people, in a nursing home), existence of any contact with healthcare services (primary care, emergencies, hospital admission, outpatient care, home care) in the 3 months prior to hospitalization due to exacerbation of any chronic disease, and destination at discharge from the present episode of hospitalization (home, transfer to another hospital, transfer to a nursing home, *exitus*).

Active CC of the patient at arrival to hospital, including some risk factors, were collected (see Supplemental Table 1). For this purpose, the physicians of the project defined, on a consensual basis, a limited list of 64 CC, coming from the

114 groups defined by Salisbury and colleagues[19] and including the 19 categories of the Charlson Index[20]. Following the same criteria as Salisbury, a condition was considered to be chronic when it lasted for at least 6 months, including past conditions that require ongoing disease or risk management, important conditions with a significant risk of recurrence, or past conditions that have continuing implications for patient management[19]. Drug-related conditions of this list refer to poor management of medication related to a chronic disease that has clinical implications in that hospitalization (such as any drug intolerance or an excess drug poisoning).

Additionally, for each of the CC, it was also recorded if they had required clinical management (both at admission and during hospitalization) by assigning a (subjective) correlative score (CM=1, 2, 3...) to each one, according to their clinical importance during the attention process. Thus, CC that did not have any significance during hospitalization, although recorded, had a score equal to zero.

Specific GS and risk factors (acute confusional syndrome/delirium, chronic pain, cognitive/intellectual impairment, constipation, depression or anxiety, dysphagia, frailty, immobility, incontinence (urinary/faecal), instability/falls, malnutrition, polypharmacy, pressure ulcers, sensorial deficit, sleep disorders/insomnia) were also recorded. Two of the departments systematically apply a recently developed scale for frailty [21], while the others consider clinical judgement (although based on the same variables).

In order to address potential sources of bias, a pilot study was conducted with the first 10 admissions per centre to validate the data collection process and identify problems that could arise. After that, proper changes were made in the

protocol and questionnaire. All available information sources were consulted in order to register CC and GS, and the defined list was not closed. Nonetheless, the registration of CC and GS was based on clinical criteria.

Sampling and analysis

A consecutive sample of 740 patients meeting the inclusion criteria were included, proportionally distributed to the annual volume of hospitalizations of the medicine and/or geriatric services of each centre. The estimated sample of 800 patients (see protocol[17]) could not be reached due to organizational reasons in one of the participating centres.

For the purposes of the analyses, some CC were grouped according to clinical criteria: Hemiplegia was included in cerebrovascular disease; metastatic solid tumour, leukaemia, lymphoma and any malignancy were grouped into 'neoplasia'; hepatitis B and C were included in mild liver disease, and both congestive and non-congestive heart failure were grouped into 'heart failure'. Other diseases were finally excluded of the analyses considering that they have no impact on acute healthcare (cataract, dermatitis, diverticular disease of the colon, glaucoma, haemorrhoids, other vascular diseases and prostatic benign hypertrophy). In the end, 51 CC and 15 GS were analysed.

The updated Charlson Comorbidity Index[22], age adjusted, was computed and categorized according to tertiles distribution.

Descriptive statistics were performed to assess patient clinical and sociodemographic characteristics and to obtain overall prevalence estimates of CC and GS, stratified by sex. Multimorbidity was firstly defined as the presence

of two or more CC. Cumulative number of CC and GS per patient were computed, respectively.

Multimorbidity patterns

CC or GS with a prevalence <2% were excluded to avoid statistical noise and therefore spurious findings in the cluster solutions, leaving a list of 40 CC and 15 GS. In order to take into account if a CC had required clinical management (CM), a ratio variable (R) was computed as follows:

If CC=0 & CM=0 → R=0

If CC=1 & CM=m → R=1/m; max (m) = max value (CM) = 8;

If CC=1 & CM=0 → R= 0.1

All patients were included, without regard to having multimorbidity, so as to obtain clusters that were more representative. Data for the analysis comprised the ratio (R) and syndrome (GS) variables.

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 centres (similar to *k*-means) but with fuzziness so that individuals may belong to more than one pattern. Through this technique, we obtained clusters of individuals and a membership matrix, which indicates the degree of participation of each subject in each cluster.

As a first step, and similarly to Violán *et. al.*[23], the PCAmix algorithm for categorical (GS) and continuous data (R) was implemented to reduce and transform the dataset to all continuous data[24]. To decide the number of retained

dimensions, the Karlis-Saporta-Spinaki rule was used[25]. Then, a soft clustering algorithm was applied to fuzzily distribute the population into a set of clusters, corresponding to the different multimorbidity patterns. We computed three validation indices to obtain the optimal number of clusters (K) and the optimal value of the fuzziness parameter (m): the partition coefficient whose optimal choice for coefficient is at the maximum, and the Xie-Beni and the partition entropy validation indices, whose optimal indices are at the minimum[26]. Considering the stochastic nature of the clusters, and the requirement of stable multimorbidity clusters, 100 independent clustering repetitions were applied to obtain the stable final solution.

To characterize the multimorbidity patterns corresponding to each cluster of individuals, the prevalence of CC and GS in each cluster was calculated. Observed/expected (O/E) ratios were calculated by dividing the prevalence of a given disease within a cluster by its prevalence in the overall population. The exclusivity of CC and GS, defined as the fraction of patients with the disease in the cluster over the total number of patients with the disease, was also calculated. A disease or a syndrome was considered to be relevant in a given cluster of individuals when its O/E ratio was >1 and its exclusivity was >25%[27–29]. The statistical significant final solution ranged from 4 to 8 clusters. After clinical revision and discussion among the research team, 4 different clusters were considered to make clinical sense according to the objective of the clustering. There is currently no consensus in the literature on the criteria used to select the number of clusters or the O/E ratio cut-off point due to, in part, the novelty of the analysis.

Finally, sociodemographic and clinical variables were described for all patients assigned to each cluster. Analyses were performed using R 3.6.0 and SPSS 22.

Patient and Public Involvement

Since this was an observational study with variables and outcomes related to the healthcare process, this research was developed without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results.

RESULTS

740 patients aged 65 years or older were included, with a mean age of 84.12 years (SD 7.01), a 53.24% of females and a mean Barthel Index of 65.07 (median 75). Sociodemographic and clinical variables are summarised in Table 1. Almost all patients had two or more CC (98.65%; 95%CI 98.23-99.07), with a median of 8 CC and 6 GS per patient. Nearly 70% had consulted a health care service in the 3 months prior to hospitalization due to chronic disease exacerbation.

Table 1. Sociodemographic and clinical variables of the studied cohort.

Sociodemographic and clinical variables		N	%	95% CI
Age	< 70	33	4.46	3.19 - 6.20
	70-74	48	6.49	4.93 - 8.50
	75-79	82	11.08	9.02 - 13.55
	80-84	181	24.46	21.50 - 27.68
	85-89	232	31.35	28.11 - 34.78
	90-94	134	18.11	15.50 - 21.05
	>= 95	30	4.05	2.85 - 5.73
Sex	Female	394	53.24	49.64 - 56.81
	Male	346	46.76	43.19 - 50.36
Barthel index	< 20	90	12.16	10.00 - 14.71
	20-35	76	10.27	8.28 - 12.67
	40-55	124	16.76	14.24 - 19.62
	60-95	294	39.73	36.27 - 43.30
	100	156	21.08	18.30 - 24.17
Age adjusted, updated Charlson	2-5	148	20.00	17.28 - 23.03

Sociodemographic and clinical variables		N	%	95% CI
Comorbidity Index	6-8	411	55.54	51.94 - 59.08
	9-14	181	24.46	21.50 - 27.68
Household	With relatives/other people	523	70.68	67.30 - 73.84
	Nursing home	95	12.84	10.62 - 15.44
	Alone	122	16.49	13.99 - 19.33
Chronic disease exacerbation 3 months prior to admission	No	225	30.41	27.20 - 33.81
	Yes (total)	515	69.59	66.19 - 72.80
	Primary care	342	46.22	42.65 - 49.82
	Emergencies	263	35.54	32.17 - 39.06
	Hospital admission	193	26.08	23.05 - 29.36
	Outpatient care	8	1.08	0.55 - 2.12
	Home care	14	1.89	1.13 - 3.15
Destination at discharge	Home	468	63.24	59.71 - 66.64
	Nursing home	105	14.19	11.86 - 16.89
	Another hospital	101	13.65	11.36 - 16.31
	Exitus	66	8.92	7.07 - 11.19
Multimorbidity	No	10	1.35	1.35 - 1.36
	Yes	730	98.65	98.23 - 99.07

CI = Confidence interval

Figure 1 shows the distribution of the number of CC by age groups. The most frequent CC were hypertension (81.49%, 95%CI 78.53-84.12) and heart failure (59.86%, 95%CI 56.29-63.34) (see Supplemental Table 2). Heart failure was also the main cause of hospitalization (30.7% of patients had CM score=1), followed by COPD (20.7%) (Supplemental Table 3).

There were some differences in CC between sexes, with females having more frequently heart failure, degenerative arthropathy, obesity, hip fracture, thyroid disease, asthma, osteoporosis, vertigo and non-schizophrenic mental disorders. Males, in turn, had more frequently COPD, gout, neoplasia, peripheral arteriopathy and ulcerative disease.

The most prevalent GS was polypharmacy (79.86%, 95%CI 76.82-82.60), followed by frailty (61.76%, 95%CI 58.20-65.19). Females had a significantly higher number of GS compared to males (Wilcoxon rank sum test, $p < 0.001$), as

well as a higher prevalence of depression/anxiety, chronic pain, constipation, frailty, urinary/faecal incontinence and immobility.

Four statistically and clinically significant multimorbidity clusters or patterns were identified in our study population. For all clusters, CC and GS with an observed/expected ratio >1 and exclusivity >25% are represented in Figure 2 (see also Supplemental Table 4). Sociodemographic and clinical characteristics of patients in each cluster are described in Table 2.

Table 2. Sociodemographic and clinical variables of the multimorbidity clusters.

		Osteoarticular	Psycho-geriatric	Minor chronic conditions	Cardio-respiratory
Number of patients included, n (%)		132 (17.8)	153 (20.7)	179 (24.2)	276 (37.3)
Age at admission (y, mean ± SD)		84.03 ± 6.48	84.51 ± 7.25	83.94 ± 7.19	84.06 ± 7.03
Sex, n (%)	Male	34 (25.7)	66 (42.8)	99 (55.5)	147 (53.4)
	Female	98 (74.3)	87 (57.2)	80 (44.5)	129 (46.6)
Barthel Index (mean ± SD)		63.06 ± 24.78	47.62 ± 34.94	64.96 ± 33.56	75.76 ± 27.52
Total nº chronic conditions (mean ± SD)		11.5 ± 3.64	7.68 ± 3.19	8.86 ± 3.08	7.59 ± 2.61
Total nº geriatric syndromes / risk factors (mean ± SD)		7.76 ± 2.07	8.16 ± 2.82	6.4 ± 3.32	4.42 ± 2
Charlson Comorbidity Index, n (%)	2-5	26 (19.9)	24 (15.6)	37 (20.4)	61 (22.2)
	6-8	73 (55.1)	89 (58.5)	96 (53.8)	153 (55.3)
	9-14	33 (25.0)	40 (25.9)	46 (25.7)	62 (22.6)
Household, n (%)	With relatives / other people	91 (68.7)	103 (67.2)	133 (74.5)	196 (71.1)
	Nursing home	16 (11.8)	28 (18.4)	23 (12.8)	28 (10.3)
	Alone	26 (19.5)	22 (14.3)	23 (12.7)	52 (18.7)
Chronic disease exacerbation 3 months prior to the index admission, n (%)	No	24 (18.3)	46 (30.1)	48 (27.0)	106 (38.5)
	Yes (total)	108 (81.7)	107 (69.9)	130 (73.0)	170 (61.5)
	Primary care	83 (62.7)	66 (43.3)	92 (51.6)	101 (36.5)
	Emergencies	71 (53.6)	40 (26.2)	69 (38.5)	83 (30.2)
	Hospital admission	49 (37.1)	46 (30.1)	47 (26.1)	51 (18.6)
	Outpatient care	1 (0.7)	0 (0.3)	3 (1.4)	4 (1.4)
	Home care	2 (1.5)	2 (1.1)	3 (1.8)	7 (2.6)
Destination at discharge, n (%)	Home	86 (65.3)	83 (54.0)	111 (62.0)	188 (68.1)
	Nursing home	15 (11.1)	33 (21.3)	26 (14.5)	32 (11.5)
	Another hospital	15 (11.3)	17 (11.3)	26 (14.7)	42 (15.3)
	Exitus	16 (12.3)	20 (13.3)	16 (8.8)	14 (4.9)

SD = standard deviation.

The first cluster, named *osteoarticular*, included 132 patients (17.8%) having osteoporosis, fractures, inflammatory osteoarticular disease, chronic pain and degenerative arthropathy. Moreover, vertigo, sleep apnoea, asthma, depression/anxiety and sleep disorders were also over-represented. This cluster included patients with the highest number of both CC and GS. About three quarters were female, and most of them (82%) accessed healthcare services 3 months prior to this admission.

Cluster 2, called *psychogeriatric*, had 152 patients (20.7%) and included mostly GS: pressure ulcers, immobility, malnutrition, cognitive impairment, dementia, incontinence and frailty. Patients in this group had a mean Barthel index lower than 50 and a high number of GS. Furthermore, nearly 20% of them were living in a nursing home and in-hospital mortality was about 13%.

Cluster 3, named *minor chronic disease*, had 179 (24.2%) patients, and represents a group of patients with a variety of conditions, such as hypertension, dyslipidaemia, anaemia, gout, chronic renal insufficiency, polypharmacy, non-ischaemic heart disease, and diverse GS. O/E ratios were close to 1 in most cases.

Finally, cluster 4, called *cardiorespiratory*, included 276 (37.3%) patients. The over-represented diagnoses were COPD, heart failure and cardiac arrhythmia, although the O/E ratios were very low. In this cluster, with the lowest number of CC and GS, and a Barthel index greater than 75, nearly 40% had no healthcare consultation for a chronic disease exacerbation in the previous 3 months. This group had the lowest in-hospital mortality (5%).

DISCUSSION

The present study aimed to identify multimorbidity patterns in patients aged 65 and above admitted to hospital because of an exacerbation of CC. The soft clustering technique used, together with clinical criteria, was able to identify 4 different multimorbidity patterns, named osteoarticular, psychogeriatric, cardio-respiratory and minor chronic disease, in a patient-centred approach taking into account the importance of each disease in hospital management. Remarkably, high chronic multimorbidity was found in all patients, regardless of the cluster. To the best of our knowledge, this is the only study published to date that has analysed multimorbidity patterns taking into account both CC (with their weight during clinical management) and GS in this type of patients. Hence, these identified patterns allow us to take a further step towards understanding the patients' current or future healthcare needs.

All clusters contain groups of conditions that make sense and are mostly pathophysiologically related. From the clinical point of view, these clusters resemble patient profiles that are intuitively perceived. Moreover, some descriptive variables such as sex, Barthel index, mean number of CC or GS, chronic pathology exacerbations in previous months, or hospital mortality, are distributed in such a way that they may reinforce the distinction of these groups.

Coexistence of CC and GS was observed in all clusters except for the cardiorespiratory, reinforcing the need to consider other clinically relevant situations rather than only CC. In particular, the exclusivity and prevalence of GS such as immobility, malnutrition, cognitive impairment or dementia were considerable in the psychogeriatric cluster.

Interestingly, highly prevalent CC, such as heart failure and COPD, which also frequently involve clinical management, only showed remarkable exclusivity and O/E ratio in the cardiorespiratory pattern and were not over-represented elsewhere. This highlights the fact that even though some CC may not be over-represented in a cluster, they can have a high prevalence and therefore need to be properly addressed too.

With respect to the osteoarticular cluster, it displayed a pattern of female predominance, with many CC and GS, high healthcare needs in recent months due to their chronic pathology, and high in-hospital mortality. Thus, this profile would identify a group of patients with a high probability of decompensation and death.

Finally, the so-called minor chronic diseases cluster was not very well defined. It included some risk factors (hypertension, dyslipidaemia, polypharmacy) as well as some CC and GS. Thus, it would be possible that it does not represent a real cluster but either the set of cases that did not belong anywhere else.

It should be noted that the type of analysis, the purpose for designing these patterns and also their interpretation could all lead to different results or conclusions. For instance, our aim in defining multimorbidity patterns in this cohort was to identify profiles of patients with similar needs and even a similar short-term prognosis at that time. For this reason, the importance of their pathologies in the course of hospitalization was taken into account. Hence, the ones that tend to have a minimal impact on clinical management, such as risk factors like hypertension or dyslipidaemia did not have a leading role in the patterns.

Comparison with other studies

Given the type of patients under study and the methodological approach to identify multimorbidity patterns, there are few publications to directly compare our results to. Clerencia-Sierra and colleagues[16] analysed multimorbidity patterns in hospitalized older patients. Their methodological and analytical approach was slightly different, and they did not take into account the weight of the diseases during the hospitalization process; however, they found a similar percentage of multimorbidity (99.7%) and 4 patterns that partially coincide with those of our study: cardiovascular, induced-dependency, falls, and osteoarticular.

Furthermore, several authors have published data on patterns identified from primary care electronic records in different age groups, with lists of non-comparable chronic problems and using different techniques (cluster analysis, exploratory factor analysis or latent class analysis)[16,28–33]. These results would not be directly comparable with our study, but all of them highlight the ability to identify association patterns of chronic diseases.

Strengths and limitations

The strengths of this study are the prospective design, ensuring data quality by thorough record keeping, the ascertainment of all CC and GS of the patient, as well as the use of a novel clustering technique. Soft clustering is a methodologically robust technique less susceptible to outliers in the data, choice of distance measure and the inclusion of inappropriate or irrelevant variables[23]. Besides, our approach focuses on the patient instead of the pathologies, using a comprehensive list of conditions that includes both CC and GS, and determining a probability of belonging to each cluster. Additionally, we have taken into account

the relative importance of the different CC in the clinical management of the patient during hospitalization, thus providing a better picture of the possible complexity and needs during hospitalization.

Furthermore, our work is not only limited to the identification of possible patterns. We have validated them, in some way, by analysing some of the patients' variables such as sex, number of CC, previous contacts with the health system, hospital mortality or need for a nursing home.

Nonetheless, our study presents some limitations that need to be considered. Firstly, the identification of chronic pathologies does not exclusively follow a validated list of codes but either an adaptation of different ones, a fact that could hinder comparability with other studies on multimorbidity. Secondly, as this study is not longitudinal, the chronology in which CC or GS appear cannot be analysed. It is possible for a patient to evolve from one pattern to another throughout life, as some authors have already pointed out[34], and therefore, the results only show the present situation. However, given the purpose of the defined patterns, this would not in itself be a limitation.

The clinical conditions severity or other possible aggravating factors have neither been taken into account. Nevertheless, the registration of a variable that takes into account the relevance of each CC during the care process acts, in some way, as an indirect indicator of complexity when dealing with patients admitted because of decompensation.

Clinical implications

These patterns are not a picture of the community but of older patients in geriatric or internal medicine departments, which are generally in more need of health

services and more complex clinical management. However, not all of these patients have the same requirements. In fact, one in five patients (the psychogeriatric cluster) caused a great burden to both the patient and their relatives while the patients in the most frequent cluster (cardiorespiratory), with lower dependency and less GS, seemed to have better immediate outcome. Therefore, it is possible that the therapeutic objectives should be different in these patients. More importantly, the ability to distinguish patients more objectively than with the mere clinical impression may allow the design of better processes, services or alternatives to conventional hospitalization. In addition, some patterns may include patients with an increased risk of potentially inappropriate prescription or adverse drug reactions. These aspects will be the object of future analyses.

Finally, the development of clinical practice guidelines according to these patterns needs to be considered, although it may be difficult given the magnitude of the diseases comprised in each pattern [4,13]

Conclusions

In conclusion, in older patients admitted to hospital because of the exacerbation of chronic health problems, it is possible to define multimorbidity clusters or patterns using appropriate statistical techniques. These patterns make clinical sense and could be the basis to reorganize circuits, processes or healthcare models to tackle the increasing number of older, multimorbid patients.

List of abbreviations

CC: chronic condition

GS: geriatric syndrome

CM: clinical management

O/E: observed/expected

COPD: chronic obstructive pulmonary disease

Figure captions

Figure 1. Distribution of the number of chronic conditions (excluding the following risk factors: hypertension, dyslipidaemia, obesity, osteoporosis and drug-related conditions) in relation to age groups.

Figure 2. Observed/Expected (O/E) ratio and prevalence of chronic conditions and geriatric syndromes/risk factors per multimorbidity cluster. Conditions with exclusivity >25% and O/E ratios >1 in each cluster are represented. Conditions are ordered by O/E ratio and from cluster 1 to 4. *COPD: Chronic Obstructive Pulmonary Disease*

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

MB conceived and supervised the study, discussed the results, wrote the first version of the manuscript. SH, RJ, EdJ, RE and CM participated in patient inclusion, data collection and discussion of the results and revised the manuscript. AR executed the analysis and interpretation of multimorbidity clusters. CV collaborated in the execution of the analyses and in the interpretation of the multimorbidity patterns. ML participated in the statistical and graphical analysis of the results, in the discussion of the results and the revision of several manuscript versions. PR collaborated in the questionnaires' design, patient inclusion, data collection and discussion of results and revised the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1 Eurostat - Data Explorer. https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=tps00200&lang=en (accessed 21 Oct 2020).

2 OECD/EU. Health at a Glance: Europe 2018 State of Health in the EU

Cycle. 2018. doi:10.1787/health_glance_eur-2018-en

3 Palladino R, Pennino F, Finbarr M, *et al.* Multimorbidity And Health Outcomes In Older Adults In Ten European Health Systems, 2006-15. *Health Aff (Millwood)* 2019;**38**:613–23. doi:10.1377/hlthaff.2018.05273

4 The Academy of Medical Sciences. Multimorbidity: a priority for global health research. 2015. https://acmedsci.ac.uk/file-download/82222577

5 Lugtenberg M, Burgers JS, Clancy C, *et al.* Current guidelines have limited applicability to patients with comorbid conditions: A systematic analysis of evidence-based guidelines. *PLoS One* 2011;**6**. doi:10.1371/journal.pone.0025987

6 Buffel du Vaure C, Dechartres A, Battin C, *et al.* Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials.gov: A systematic review of registration details. *BMJ Open* 2016;**6**:e012265. doi:10.1136/bmjopen-2016-012265

7 Fortin M, Stewart M, Poitras ME, *et al.* A systematic review of prevalence studies on multimorbidity: Toward a more uniform methodology. *Ann Fam Med* 2012;**10**:142–51. doi:10.1370/afm.1337

8 Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases - A systematic review on existing multimorbidity indices. *J Gerontol A Biol Sci Med Sci* 2011;**66**:301–11. doi:10.1093/gerona/glq208

9 Roso-Llorach A, Violán C, Foguet-Boreu Q, *et al.* Comparative analysis of methods for identifying multimorbidity patterns: A study of 'real-world'

data. *BMJ Open* 2018;**8**:e018986. doi:10.1136/bmjopen-2017-018986

10 Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, *et al.* Multimorbidity patterns: A systematic review. *J Clin Epidemiol* 2014;**67**:254–66. doi:10.1016/j.jclinepi.2013.09.021

11 Lu FP, Chang WC, Wu SC. Geriatric conditions, rather than multimorbidity, as predictors of disability and mortality among octogenarians: A population-based cohort study. *Geriatr Gerontol Int* 2016;**16**:345–51. doi:10.1111/ggi.12480

12 van der Heide I, Snoeijs SP, Boerma WGW, *et al.* How to strengthen patient-centredness in caring for people with multimorbidity in Europe? 2017.http://europepmc.org/books/NBK464537

13 Rijken M, Struckmann V, Van Der Heide I, *et al.* How to improve care for people with multimorbidity in Europe? 2016.https://www.euro.who.int/en/about-us/partners/observatory/publications/policy-briefs-and-summaries/how-to-improve-care-for-people-with-multimorbidity-in-europe

14 NICE. Multimorbidity: clinical assessment and management NICE guideline. 2016. www.nice.org.uk/guidance/ng56

15 Catalá-López F, Alonso-Arroyo A, Page MJ, *et al.* Mapping of global scientific research in comorbidity and multimorbidity: A cross-sectional analysis. *PLoS One* 2018;**13**:e0189091. doi:10.1371/journal.pone.0189091

16 Clerencia-Sierra M, Calderón-Larrañaga A, Martínez-Velilla N, *et al.*

Multimorbidity patterns in hospitalized older patients: Associations among chronic diseases and geriatric syndromes. *PLoS One* 2015;**10**:e0132909. doi:10.1371/journal.pone.0132909

17 Baré M, Herranz S, Jordana R, *et al.* Multimorbidity patterns in chronic older patients, potentially inappropriate prescribing and adverse drug reactions: protocol of the multicentre prospective cohort study MoPIM. *BMJ Open* 2020;**10**:e033322. doi:10.1136/bmjopen-2019-033322

18 Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. *J Clin Epidemiol* 1989;**42**:703–9. doi:10.1016/0895-4356(89)90065-6

19 Salisbury C, Johnson L, Purdy S, *et al.* Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2011;**61**:e12-21. doi:10.3399/bjgp11X548929

20 Charlson ME, Peter P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987;**40**:373–83. doi:10.1016/0021-9681(87)90171-8

21 Amblàs-Novellas J, Martori JC, Espaulella J, *et al.* Frail-VIG index: A concise frailty evaluation tool for rapid geriatric assessment. *BMC Geriatr* 2018;**18**:29. doi:10.1186/s12877-018-0718-2

22 Quan H, Li B, Couris CM, *et al.* Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;**173**:676–82.

doi:10.1093/aje/kwq433

23 Violán C, Foguet-Boreu Q, Fernández-Bertolín S, *et al.* Soft clustering using real-world data for the identification of multimorbidity patterns in an elderly population: cross-sectional study in a Mediterranean population. 2019;**9**:e029594. doi:10.1136/bmjopen-2019-029594

24 Chavent M, Kuentz-Simonet V, Labenne A, *et al.* Multivariate analysis of mixed data: the R package PCAmixdata. arXiv preprint, https://arxiv.org/abs/1411.4911v4. 2017.

25 Karlis D, Saporta G, Spinakis A. A simple rule for the selection of principal components. *Commun Stat - Theory Methods* 2003;**32**:643–66. doi:10.1081/STA-120018556

26 Zhao Q. *Cluster Validity in Clustering Methods*. 2012.http://cs.joensuu.fi/sipu/pub/qinpei-thesis.pdf

27 Guisado-Clavero M, Roso-Llorach A, López-Jimenez T, *et al.* Multimorbidity patterns in the elderly: A prospective cohort study with cluster analysis. *BMC Geriatr* 2018;**18**:16. doi:10.1186/s12877-018-0705-7

28 Marengoni A, Roso-Llorach A, Vetrano DL, *et al.* Patterns of Multimorbidity in a Population-Based Cohort of Older People: Sociodemographic, Lifestyle, Clinical, and Functional Differences. *J Gerontol A Biol Sci Med Sci* 2019;**75**:798–805. doi:10.1093/gerona/glz137

29 Violán C, Roso-Llorach A, Foguet-Boreu Q, *et al.* Multimorbidity patterns with K-means nonhierarchical cluster analysis. *BMC Fam Pract*

2018;**19**:108. doi:10.1186/s12875-018-0790-x

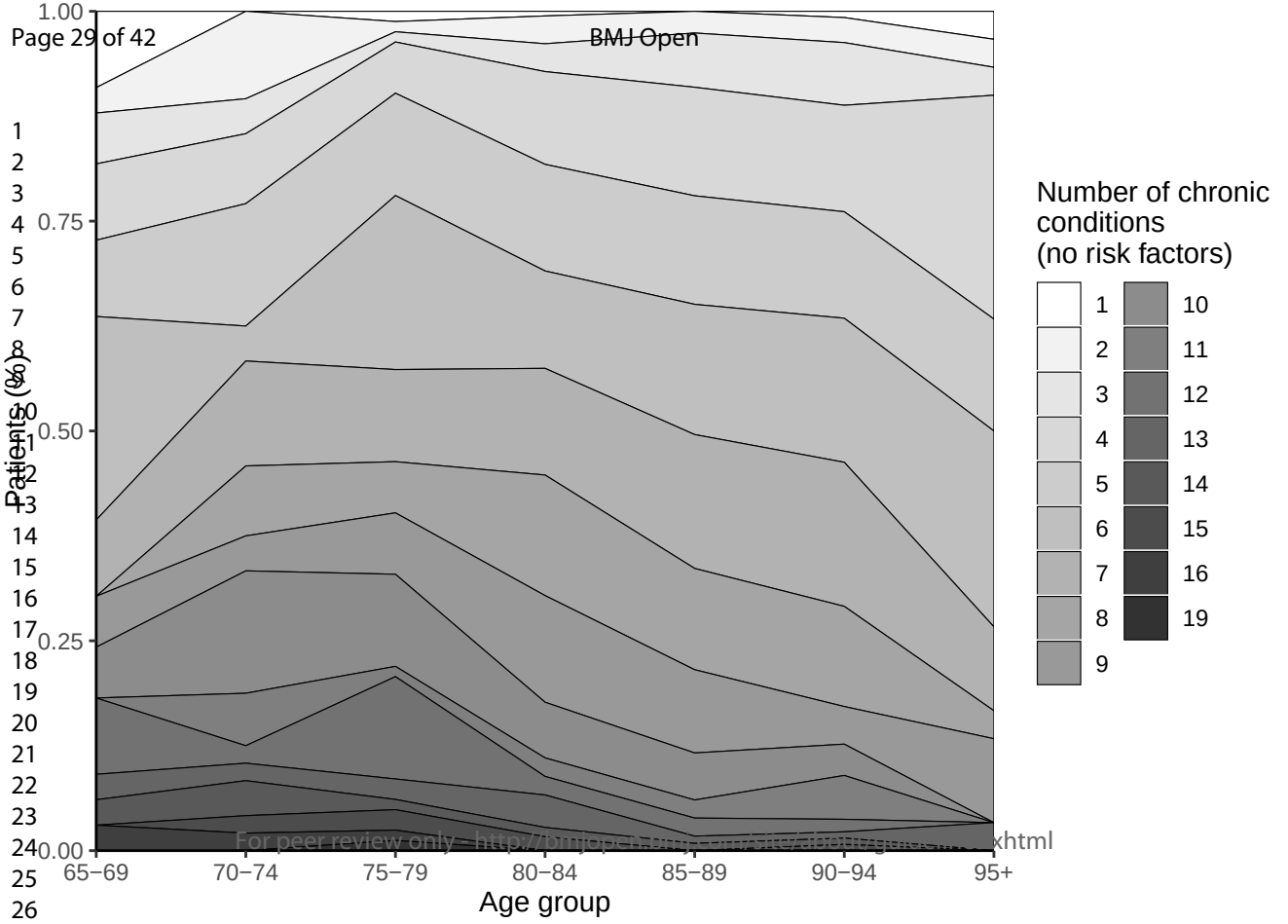
30 Juul-Larsen HG, Christensen LD, Bandholm T, *et al.* Patterns of multimorbidity and differences in healthcare utilization and complexity among acutely hospitalized medical patients (≥65 years) – a latent class approach. *Clin Epidemiol* 2020;**12**:245–59. doi:10.2147/CLEP.S226586

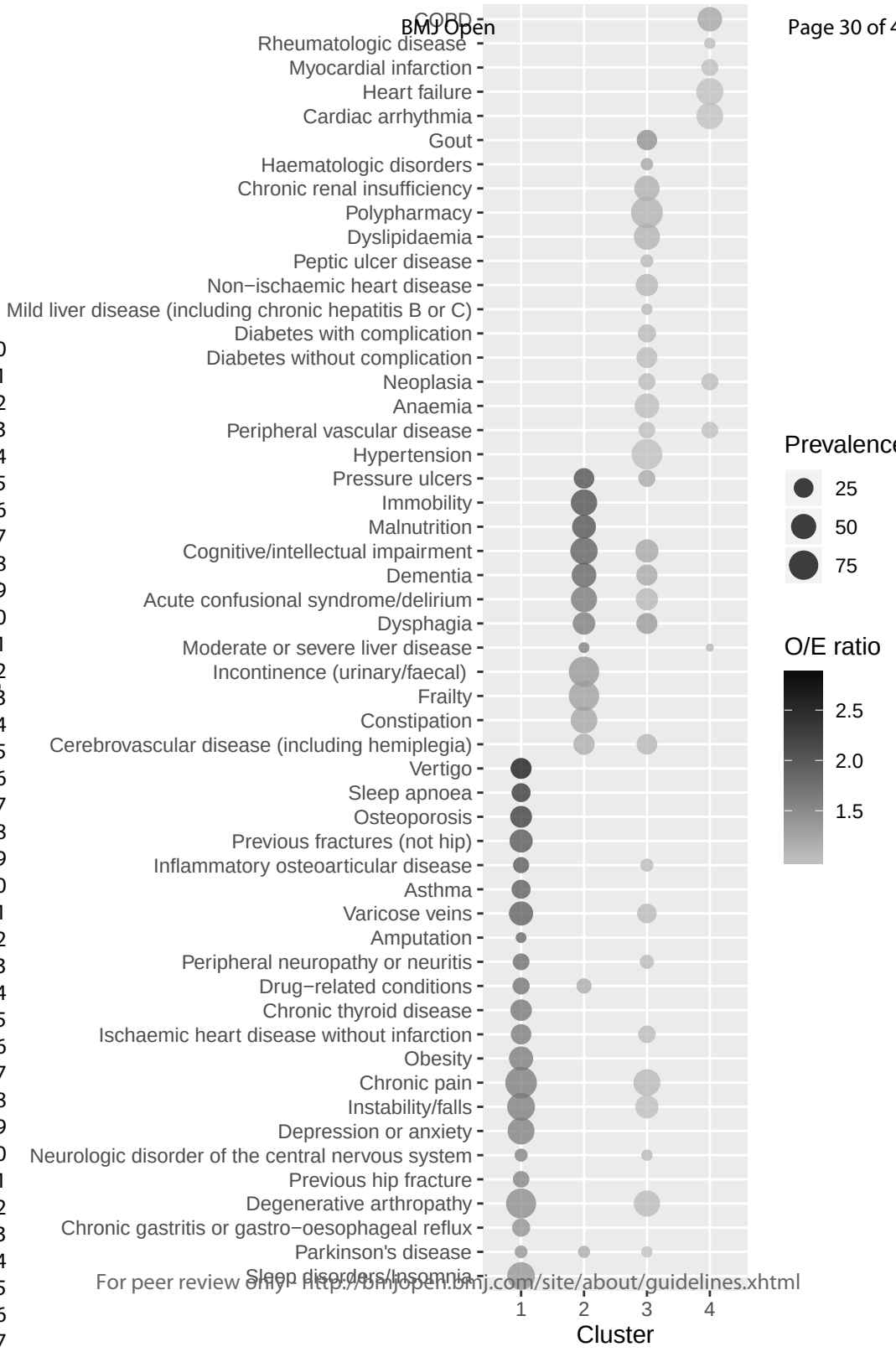
31 Zhu Y, Edwards D, Mant J, *et al.* Characteristics, service use and mortality of clusters of multimorbid patients in England: a population-based study. *BMC Med* 2020;**18**:78. doi:10.1186/s12916-020-01543-8

32 Nguyen QD, Wu C, Odden MC, *et al.* Multimorbidity patterns, frailty, and survival in community-dwelling older adults. *Journals Gerontol - Ser A Biol Sci Med Sci* 2019;**74**:1265–70. doi:10.1093/gerona/gly205

33 Poblador-Plou B, van den Akker M, Vos R, *et al.* Similar multimorbidity patterns in primary care patients from two European regions: results of a factor analysis. *PLoS One* 2014;**9**:e100375. doi:10.1371/journal.pone.0100375

34 Vetrano DL, Roso-Llorach A, Fernández S, *et al.* Twelve-year clinical trajectories of multimorbidity in a population of older adults. *Nat Commun* 2020;**11**:1–9. doi:10.1038/s41467-020-16780-x





Supplemental Table 1. Chronic conditions and geriatric syndromes recorded.

Chronic conditions	**Geriatric syndromes and risk factors**
Charlson Index	
1. AIDS/HIV	Acute confusional syndrome/delirium
2. Any malignancy (excluding skin)	Chronic pain
3. Cerebrovascular disease	Cognitive/Intellectual impairment
4. Chronic obstructive pulmonary disease	Constipation
5. Congestive heart failure	Depression or Anxiety
6. Dementia	Dysphagia
7. Diabetes with complication	Frailty
8. Diabetes without complication	Immobility
9. Hemiplegia	Incontinence (Urinary/faecal)
10. Leukaemia	Instability/falls
11. Lymphoma	Malnutrition
12. Metastatic solid tumour	Polypharmacy
13. Mild liver disease	Pressure ulcers
14. Moderate or severe liver disease	Sensorial deficit
15. Moderate or severe renal disease	Sleep disorders/Insomnia
16. Myocardial infarction	
17. Peptic ulcer disease	
18. Peripheral vascular disease	
19. Rheumatologic disease	
Other conditions	
20. Amputation	
21. Anaemia	
22. Asthma	
23. Cardiac arrhythmia	
24. Cataract	
25. Chronic hepatitis (B or C)	
26. Chronic pancreatic disease	
27. Degenerative arthropathy	
28. Dermatitis or eczema	

29. Diverticular disease of the colon
30. Drug-related conditions
31. Dyslipidaemia (risk factor)
32. Fibromyalgia
33. Gallstones (previous hepatic colic)
34. Chronic gastritis or gastro-oesophageal reflux
35. Glaucoma
36. Gout
37. Haemorrhoids
38. Haematologic disorders (myelodysplastic syndrome, gammapathy, polycythaemia)
39. Hypertension (risk factor)
40. Inflammatory osteoarticular disease
41. Irritable bowel syndrome
42. Ischaemic heart disease without infarction
43. Migraine
44. Neurologic disorder of the central nervous system
45. Non-congestive heart failure
46. Non-ischaemic heart disease (miocardiopathy, valvulopathy)
47. Non-schizophrenic mental disorders (excluding depression and anxiety)
48. Obesity (risk factor)
49. Osteoporosis (risk factor)
50. Other neurological pathologies (essential tremor)
51. Other vascular diseases (ischaemia, aneurism)
52. Parkinsonôs disease
53. Peripheral neuropathy or neuritis
54. Post-traumatic stress disorder
55. Previous fractures (not hip)
56. Previous hip fracture

57. Prostatic benign hypertrophy
58. Schizophrenia
59. Sleep apnoea
60. Chronic thyroid disease
61. Tuberculosis
62. Urinary tract stones (nephritic colic)
63. Varicose veins of lower extremities
64. Vertigo

Supplemental Table 2. Prevalence rates of chronic conditions and geriatric syndromes / risk factors in the study population by sex, separately listed in decreasing order of total prevalence rate.

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
CHRONIC CONDITIONS									
Risk factors									
Hypertension	330	83.76	79.79 - 87.07	273	78.90	74.30 - 82.87	603	81.49	78.53 - 84.12
Dyslipidaemia	189	47.97	43.08 - 52.90	171	49.42	44.19 - 54.67	360	48.65	45.06 - 52.25
Obesity	127	32.23	27.81 - 37.00	66	19.08	15.28 - 23.55	193	26.08	23.05 - 29.36
Osteoporosis	82	20.81	17.09 - 25.09	21	6.07	4.00 - 9.10	103	13.92	11.61 - 16.60
Drug-related conditions	44	11.17	8.42 - 14.66	23	6.65	4.47 - 9.78	67	9.05	7.19 - 11.34
Chronic Diseases									
Heart failure	255	64.72	59.88 - 69.28	188	54.34	49.07 - 59.51	443	59.86	56.29 - 63.34
Cardiac arrhythmia	216	54.82	49.89 - 59.67	207	59.83	54.58 - 64.86	423	57.16	53.57 - 60.68
Degenerative arthropathy	228	57.87	52.94 - 62.64	157	45.38	40.21 - 50.64	385	52.03	48.43 - 55.61
Anaemia	182	46.19	41.33 - 51.13	152	43.93	38.80 - 49.20	334	45.14	41.58 - 48.74
Moderate or severe renal disease	164	41.62	36.86 - 46.55	156	45.09	39.93 - 50.35	320	43.24	39.72 - 46.84
Chronic obstructive pulmonary disease (COPD)	90	22.84	18.97 - 27.24	183	52.89	47.63 - 58.09	273	36.89	33.49 - 40.43
Non-ischaemic heart disease	125	31.73	27.33 - 36.48	113	32.66	27.93 - 37.77	238	32.16	28.90 - 35.61
Diabetes without complication	101	25.63	21.57 - 30.17	100	28.90	24.38 - 33.89	201	27.16	24.08 - 30.48
Cerebrovascular disease (including hemiplegia)	95	24.11	20.15 - 28.57	93	26.88	22.48 - 31.78	188	25.41	22.40 - 28.66
Dementia	103	26.14	22.05 - 30.70	76	21.97	17.92 - 26.62	179	24.19	21.24 - 27.40
Varicose veins of lower extremities	98	24.87	20.86 - 29.37	66	19.08	15.28 - 23.55	164	22.16	19.32 - 25.29
Previous fracture (not hip)	87	22.08	18.27 - 26.44	52	15.03	11.65 - 19.18	139	18.78	16.13 - 21.76
Gout	57	14.47	11.34 - 18.28	80	23.12	18.99 - 27.84	137	18.51	15.88 - 21.47
Chronic thyroid disease	93	23.60	19.68 - 28.04	42	12.14	9.11 - 16.00	135	18.24	15.63 - 21.19
Diabetes with complication	70	17.77	14.31 - 21.85	63	18.21	14.50 - 22.62	133	17.97	15.37 - 20.90
Ischaemic heart disease without infarction	58	14.72	11.56 - 18.56	62	17.92	14.24 - 22.31	120	16.22	13.74 - 19.05
Myocardial infarction	47	11.93	9.09 - 15.50	64	18.50	14.76 - 22.93	111	15.00	12.61 - 17.75
Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	29	7.36	5.17 - 10.37	82	23.70	19.52 - 28.45	111	15.00	12.61 - 17.75
Peripheral vascular disease	31	7.87	5.60 - 10.95	74	21.39	17.39 - 26.01	105	14.19	11.86 - 16.89
Chronic gastritis or gastro-oesophageal reflux	55	13.96	10.88 - 17.73	42	12.14	9.11 - 16.00	97	13.11	10.87 - 15.73

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
Asthma	74	18.78	15.23 - 22.93	8	2.31	1.18 - 4.50	82	11.08	9.02 - 13.55
Gallstones	39	9.90	7.33 - 13.25	40	11.56	8.61 - 15.36	79	10.68	8.65 - 13.11
Vertigo	54	13.71	10.66 - 17.45	23	6.65	4.47 - 9.78	77	10.41	8.41 - 12.81
Previous hip fracture	52	13.20	10.21 - 16.90	15	4.34	2.64 - 7.03	67	9.05	7.19 - 11.34
Sleep apnoea	34	8.63	6.24 - 11.82	32	9.25	6.63 - 12.76	66	8.92	7.07 - 11.19
Peripheral neuropathy or neuritis	27	6.85	4.75 - 9.79	34	9.83	7.12 - 13.42	61	8.24	6.47 - 10.45
Inflammatory osteoarticular disease	26	6.60	4.54 - 9.49	23	6.65	4.47 - 9.78	49	6.62	5.04 - 8.65
Peptic ulcer disease	11	2.79	1.57 - 4.93	35	10.12	7.36 - 13.74	46	6.22	4.69 - 8.19
Haematologic disorders	14	3.55	2.13 - 5.88	22	6.36	4.24 - 9.44	36	4.86	3.53 - 6.66
Parkinsonôs disease	15	3.81	2.32 - 6.19	19	5.49	3.54 - 8.42	34	4.59	3.31 - 6.35
Rheumatologic disease	22	5.58	3.72 - 8.31	10	2.89	1.58 - 5.24	32	4.32	3.08 - 6.04
Mild liver disease (including chronic hepatitis B or C)	12	3.05	1.75 - 5.25	20	5.78	3.77 - 8.76	32	4.32	3.08 - 6.04
Neurologic disorder of the CNS	11	2.79	1.57 - 4.93	21	6.07	4.00 - 9.10	32	4.32	3.08 - 6.04
Moderate or severe liver disease	9	2.28	1.21 - 4.28	10	2.89	1.58 - 5.24	19	2.57	1.65 - 3.98
Amputation	4	1.02	0.40 - 2.58	12	3.47	1.99 - 5.96	16	2.16	1.34 - 3.48
Urinary tract stones	9	2.28	1.21 - 4.28	5	1.45	0.62 - 3.34	14	1.89	1.13 - 3.15
Non-schizophrenic mental disorders	11	2.79	1.57 - 4.93	1	0.29	0.01 - 1.62	12	1.62	0.93 - 2.81
Irritable bowel syndrome	7	1.78	0.86 - 3.62	4	1.16	0.45 - 2.93	11	1.49	0.83 - 2.64
Chronic pancreatic disease	4	1.02	0.40 - 2.58	6	1.73	0.80 - 3.73	10	1.35	0.74 - 2.47
Tuberculosis	5	1.27	0.54 - 2.94	4	1.16	0.45 - 2.93	9	1.22	0.64 - 2.30
Other neurological pathologies	3	0.76	0.26 - 2.21	6	1.73	0.80 - 3.73	9	1.22	0.64 - 2.30
Fibromyalgia	6	1.52	0.70 - 3.28	2	0.58	0.16 - 2.08	8	1.08	0.55 - 2.12
Migraine	4	1.02	0.40 - 2.58	0	0.00	0.00 - 1.10	4	0.54	0.21 - 1.38
Schizophrenia	1	0.25	0.01 - 1.42	2	0.58	0.16 - 2.08	3	0.41	0.14 - 1.19
Post-traumatic stress disorder	1	0.25	0.01 - 1.42	2	0.58	0.16 - 2.08	3	0.41	0.14 - 1.19
AIDS/HIV	0	0.00	0.00 ï 0.00	0	0.00	0.00 ï 0.00	0	0.00	0.00 ï 0.00
GERIATRIC SYNDROMES AND RISK FACTORS									
Polypharmacy	310	78.68	74.37 - 82.44	281	81.21	76.76 - 84.98	591	79.86	76.82 - 82.60
Frailty	269	68.27	63.52 - 72.67	188	54.34	49.07 - 59.51	457	61.76	58.20 - 65.19
Incontinence (Urinary/faecal)	273	69.29	64.57 - 73.64	157	45.38	40.21 - 50.64	430	58.11	54.52 - 61.61
Chronic pain	231	58.63	53.71 - 63.39	171	49.42	44.19 - 54.67	402	54.32	50.72 - 57.88
Constipation	201	51.02	46.09 - 55.92	139	40.17	35.14 - 45.42	340	45.95	42.39 - 49.55

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
Sleep disorders/Insomnia	189	47.97	43.08 - 52.90	144	41.62	36.54 - 46.88	333	45.00	41.45 - 48.60
Sensorial deficit	169	42.89	38.10 - 47.83	145	41.91	36.83 - 47.17	314	42.43	38.92 - 46.02
Instability/falls	158	40.10	35.38 - 45.01	128	36.99	32.08 - 42.20	286	38.65	35.21 - 42.21
Depression or anxiety	193	48.98	44.08 - 53.91	75	21.68	17.66 - 26.32	268	36.22	32.83 - 39.74
Acute confusional syndrome / delirium	118	29.95	25.64 - 34.65	117	33.82	29.03 - 38.95	235	31.76	28.50 - 35.20
Cognitive/Intellectual impairment	133	33.76	29.26 - 38.56	96	27.75	23.29 - 32.69	229	30.95	27.72 - 34.37
Immobility	114	28.93	24.68 - 33.60	78	22.54	18.46 - 27.23	192	25.95	22.92 - 29.22
Dysphagia	78	19.80	16.16 - 24.01	81	23.41	19.26 - 28.15	159	21.49	18.68 - 24.59
Malnutrition	76	19.29	15.70 - 23.47	71	20.52	16.60 - 25.09	147	19.86	17.15 - 22.89
Pressure ulcers	57	14.47	11.34 - 18.28	38	10.98	8.11 - 14.72	95	12.84	10.62 - 15.44

Supplemental Table 3. Weight as an indicator of importance on clinical management assigned to each chronic condition. Weight values range from 0 to 8, where 0 means no clinical management was required and 1 to 8 indicate clinical management from main cause of hospitalization (1) to chronic condition requiring the least medical attention (8). Chronic conditions are displayed in alphabetical order.

Chronic conditions	Weight 0		Weight 1		Weight 2		Weight 3		Weight 4		Weight 5		Weight 6		Weight 7		Weight 8	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
AIDS/HIV	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Amputation	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Anaemia	596	80.54	28	3.78	46	6.22	40	5.41	19	2.57	8	1.08	3	0.41	0	0	0	0
Asthma	704	95.14	30	4.05	3	0.41	2	0.27	1	0.14	0	0	0	0	0	0	0	0
Rheumatologic disease	729	98.51	5	0.68	3	0.41	3	0.41	0	0	0	0	0	0	0	0	0	0
Cardiac arrhythmia	595	80.41	35	4.73	69	9.32	28	3.78	10	1.35	3	0.41	0	0	0	0	0	0
Cerebrovascular disease (including hemiplegia)	703	95	28	3.78	3	0.41	3	0.41	2	0.27	1	0.14	0	0	0	0	0	0
Chronic gastritis or gastro-oesophageal reflux	733	99.05	4	0.54	1	0.14	1	0.14	1	0.14	0	0	0	0	0	0	0	0
Chronic pancreatic disease	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Chronic obstructive pulmonary disease (COPD)	554	74.86	153	20.68	19	2.57	8	1.08	5	0.68	0	0	1	0.14	0	0	0	0
Chronic thyroid disease	722	97.57	2	0.27	1	0.14	4	0.54	7	0.95	3	0.41	1	0.14	0	0	0	0
Degenerative arthropathy	718	97.03	3	0.41	7	0.95	4	0.54	4	0.54	3	0.41	1	0.14	0	0	0	0
Dementia	687	92.84	32	4.32	14	1.89	4	0.54	3	0.41	0	0	0	0	0	0	0	0
Diabetes with complication	710	95.95	9	1.22	7	0.95	5	0.68	4	0.54	2	0.27	3	0.41	0	0	0	0
Diabetes without complication	698	94.32	11	1.49	5	0.68	13	1.76	8	1.08	2	0.27	1	0.14	2	0.27	0	0
Drug-related conditions	722	97.57	5	0.68	3	0.41	3	0.41	4	0.54	1	0.14	1	0.14	1	0.14	0	0
Dyslipidaemia	735	99.32	0	0	0	0	0	0	4	0.54	1	0.14	0	0	0	0	0	0
Fibromyalgia	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Gallstones	730	98.65	6	0.81	3	0.41	1	0.14	0	0	0	0	0	0	0	0	0	0
Gout	737	99.59	0	0	0	0	2	0.27	0	0	1	0.14	0	0	0	0	0	0
Haematologic disorders	730	98.65	2	0.27	5	0.68	2	0.27	1	0.14	0	0	0	0	0	0	0	0
Heart failure	410	55.41	227	30.68	85	11.49	13	1.76	4	0.54	0	0	1	0.14	0	0	0	0
Hypertension	698	94.32	10	1.35	14	1.89	12	1.62	4	0.54	2	0.27	0	0	0	0	0	0
Inflammatory osteoarticular disease	727	98.24	8	1.08	1	0.14	1	0.14	1	0.14	1	0.14	1	0.14	0	0	0	0
Irritable bowel syndrome	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ischaemic heart disease without infarction	714	96.49	10	1.35	14	1.89	1	0.14	0	0	1	0.14	0	0	0	0	0	0

Migraine	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mild liver disease (including chronic hepatitis B or C)	733	99.05	5	0.68	0	0	1	0.14	0	0	0	0	0	0	0	0	1	0.14
Moderate or severe liver disease	724	97.84	12	1.62	2	0.27	1	0.14	0	0	1	0.14	0	0	0	0	0	0
Moderate or severe renal disease	552	74.59	39	5.27	77	10.41	44	5.95	23	3.11	4	0.54	1	0.14	0	0	0	0
Myocardial infarction	716	96.76	20	2.7	3	0.41	1	0.14	0	0	0	0	0	0	0	0	0	0
Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	724	97.84	5	0.68	7	0.95	1	0.14	1	0.14	2	0.27	0	0	0	0	0	0
Neurologic disorder of the CNS	736	99.46	2	0.27	2	0.27	0	0	0	0	0	0	0	0	0	0	0	0
Non-ischaemic heart disease	695	93.92	15	2.03	16	2.16	12	1.62	0	0	2	0.27	0	0	0	0	0	0
Non-schizophrenic mental disorders	732	98.92	2	0.27	2	0.27	1	0.14	2	0.27	1	0.14	0	0	0	0	0	0
Obesity	737	99.59	0	0	1	0.14	2	0.27	0	0	0	0	0	0	0	0	0	0
Osteoporosis	730	98.65	2	0.27	3	0.41	2	0.27	2	0.27	0	0	1	0.14	0	0	0	0
Other neurological pathologies	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Parkinson's disease	737	99.59	3	0.41	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Peptic ulcer disease	737	99.59	2	0.27	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Peripheral neuropathy or neuritis	737	99.59	1	0.14	1	0.14	1	0.14	0	0	0	0	0	0	0	0	0	0
Peripheral vascular disease	728	98.38	9	1.22	1	0.14	1	0.14	0	0	0	0	1	0.14	0	0	0	0
Post-traumatic stress disorder	739	99.86	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Previous fracture (not hip)	730	98.65	5	0.68	2	0.27	2	0.27	1	0.14	0	0	0	0	0	0	0	0
Previous hip fracture	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Schizophrenia	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sleep apnoea	716	96.76	5	0.68	9	1.22	5	0.68	1	0.14	4	0.54	0	0	0	0	0	0
Tuberculosis	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urinary tract stones	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Varicose veins of lower extremities	725	97.97	1	0.14	6	0.81	2	0.27	4	0.54	2	0.27	0	0	0	0	0	0
Vertigo	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Supplemental table 4. Prevalence, Observed/Expected (O/E) ratios and exclusivity of chronic conditions and geriatric syndromes / risk factors per multimorbidity cluster. Conditions with prevalence >2% were included. O/E ratios were calculated by dividing the prevalence of a disease within the cluster by its prevalence in the overall population. Exclusivity was calculated by dividing the number of patients with the disease in the cluster by the total number of participants with the disease. Conditions are ordered by decreasing O/E ratio of cluster 1.

	Cluster 1			Cluster 2			Cluster 3			Cluster 4		
	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)
Vertigo	29.58	2.84	50.67	9.52	0.91	18.92	6.85	0.66	15.90	4.05	0.39	14.52
Sleep apnoea	22.11	2.48	44.19	5.82	0.65	13.50	8.12	0.91	21.99	4.85	0.54	20.33
Osteoporosis	33.39	2.40	42.76	9.95	0.71	14.79	9.44	0.68	16.38	9.72	0.70	26.07
Previous fracture (not hip)	39.67	2.11	37.65	17.87	0.95	19.68	15.16	0.81	19.49	11.66	0.62	23.19
Inflammatory osteoarticular disease	13.61	2.06	36.65	2.78	0.42	8.69	7.21	1.09	26.31	5.03	0.76	28.36
Asthma	22.50	2.03	36.19	9.37	0.85	17.49	7.77	0.70	16.94	8.72	0.79	29.37
Varicose veins of lower extremities	44.58	2.01	35.86	15.2	0.69	14.19	24.37	1.10	26.56	13.89	0.63	23.40
Amputation	4.190	1.94	34.56	1.72	0.8	16.45	2.00	0.92	22.30	1.55	0.71	26.69
Peripheral neuropathy or neuritis	15.37	1.86	33.23	6.00	0.73	15.06	9.03	1.10	26.46	5.58	0.68	25.26
Drug-related conditions	16.31	1.80	32.12	11.23	1.24	25.66	7.41	0.82	19.76	5.45	0.60	22.46
Chronic thyroid disease	32.14	1.76	31.40	13.73	0.75	15.57	16.06	0.88	21.26	15.52	0.85	31.77
Ischaemic heart disease without infarction	27.75	1.71	30.5	10.85	0.67	13.84	17.59	1.08	26.20	12.79	0.79	29.46
Obesity	44.29	1.70	30.27	19.14	0.73	15.18	25.15	0.96	23.28	21.84	0.84	31.27
Chronic pain	91.68	1.69	30.09	50.3	0.93	19.15	59.72	1.10	26.55	35.23	0.65	24.22
Instability/falls	65.05	1.68	30.00	36.74	0.95	19.66	40.06	1.04	25.03	26.19	0.68	25.30
Depression or Anxiety	60.05	1.66	29.56	35.49	0.98	20.27	30.57	0.84	20.38	28.89	0.80	29.79
Neurologic disorder of the CNS	7.10	1.64	29.28	4.92	1.14	23.54	4.78	1.11	26.72	2.37	0.55	20.47
Previous hip fracture	14.76	1.63	29.06	9.23	1.02	21.08	6.20	0.69	16.55	8.08	0.89	33.31
Degenerative arthropathy	80.19	1.54	27.48	48.11	0.92	19.13	56.15	1.08	26.06	38.08	0.73	27.34
Chronic gastritis or gastro-oesophageal reflux	19.39	1.48	26.37	9.09	0.69	14.35	12.6	0.96	23.22	12.66	0.97	36.07
Parkinson's disease	6.72	1.46	26.07	5.73	1.25	25.78	4.77	1.04	25.08	2.84	0.62	23.06
Sleep disorders/Insomnia	64.93	1.44	25.72	51.57	1.15	23.70	42.58	0.95	22.85	33.41	0.74	27.73
Moderate or severe renal disease	59.30	1.37	24.44	29.11	0.67	13.92	51.19	1.18	28.59	38.27	0.88	33.05
Non-ischaemic heart disease	43.07	1.34	23.87	23.15	0.72	14.89	36.01	1.12	27.04	29.46	0.92	34.20

Myocardial infarction	19.88	1.33	23.63	10.00	0.67	13.79	14.68	0.98	23.64	15.64	1.04	38.94
Dyslipidaemia	64.28	1.32	23.55	35.21	0.72	14.97	55.63	1.14	27.62	44.11	0.91	33.86
Frailty	81.11	1.31	23.41	82.71	1.34	27.70	55.05	0.89	21.53	45.26	0.73	27.36
Anaemia	59.26	1.31	23.40	42.23	0.94	19.35	47.71	1.06	25.53	38.34	0.85	31.72
Gallstones	13.87	1.30	23.16	10.6	0.99	20.54	9.66	0.90	21.85	9.85	0.92	34.46
Haematologic disorders	6.24	1.28	22.88	2.80	0.58	11.91	6.24	1.28	30.99	4.46	0.92	34.22
Constipation	57.53	1.25	22.32	58.53	1.27	26.35	36.80	0.80	19.34	39.36	0.86	31.99
Incontinence (Urinary/faecal)	72.26	1.24	22.17	82.95	1.43	29.52	54.73	0.94	22.75	39.78	0.68	25.56
Gout	22.86	1.23	22.01	9.85	0.53	11.01	27.66	1.49	36.08	15.32	0.83	30.90
Diabetes with complication	21.71	1.21	21.53	14.68	0.82	16.89	19.79	1.10	26.59	16.84	0.94	34.99
Polypharmacy	96.12	1.20	21.45	64.75	0.81	16.77	92.87	1.16	28.08	72.07	0.90	33.70
Rheumatologic disease	5.08	1.17	20.93	4.16	0.96	19.91	3.34	0.77	18.66	4.69	1.08	40.50
Dysphagia	24.83	1.16	20.60	36.49	1.70	35.13	29.98	1.40	33.70	6.09	0.28	10.58
Cerebrovascular disease (including hemiplegia)	29.02	1.14	20.36	30.75	1.21	25.04	28.38	1.12	26.98	18.79	0.74	27.62
Acute confusional syndrome/delirium	36.00	1.13	20.21	54.77	1.72	35.67	35.27	1.11	26.82	14.71	0.46	17.30
Heart failure	66.53	1.11	19.81	57.88	0.97	20.00	54.09	0.90	21.82	61.52	1.03	38.37
Peripheral vascular disease	15.71	1.11	19.74	10.69	0.75	15.58	14.98	1.06	25.50	14.89	1.05	39.17
Hypertension	89.07	1.09	19.48	78.13	0.96	19.83	84.73	1.04	25.11	77.62	0.95	35.57
Cardiac arrhythmia	61.85	1.08	19.29	52.03	0.91	18.82	56.49	0.99	23.87	58.20	1.02	38.02
Peptic ulcer disease	6.70	1.08	19.22	5.00	0.80	16.64	6.97	1.12	27.09	6.17	0.99	37.05
Sensorial deficit	39.51	0.93	16.60	44.27	1.04	21.58	43.84	1.03	24.95	41.89	0.99	36.87
Immobility	23.10	0.89	15.87	56.49	2.18	45.03	26.23	1.01	24.41	10.21	0.39	14.69
Moderate or severe liver disease	2.23	0.87	15.46	4.33	1.69	34.91	0.69	0.27	6.51	2.96	1.15	43.11
Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	12.74	0.85	15.15	13.39	0.89	18.46	16.19	1.08	26.07	16.20	1.08	40.32
Chronic obstructive pulmonary disease (COPD)	29.97	0.81	14.48	27.29	0.74	15.30	34.75	0.94	22.75	46.90	1.27	47.47
Mild liver disease (including chronic hepatitis B or C)	3.41	0.79	14.04	4.69	1.08	22.41	4.81	1.11	26.84	4.25	0.98	36.70
Cognitive/Intellectual impairment	23.44	0.76	13.50	62.07	2.01	41.48	39.53	1.28	30.85	11.74	0.38	14.17
Diabetes without complication	20.64	0.76	13.54	30.98	1.14	23.59	29.45	1.08	26.18	26.69	0.98	36.69
Pressure ulcers	7.44	0.58	10.33	28.11	2.19	45.28	16.20	1.26	30.48	4.78	0.37	13.90
Dementia	12.34	0.51	9.10	47.13	1.95	40.30	30.43	1.26	30.38	13.10	0.54	20.23
Malnutrition	8.69	0.44	7.80	42.75	2.15	44.50	13.57	0.68	16.50	16.60	0.84	31.20

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Multimorbidity patterns of chronic conditions and geriatric syndromes in older patients from the MoPIM multicentre cohort study.

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MULTIMORBIDITY PATTERNS OF CHRONIC CONDITIONS AND GERIATRIC SYNDROMES IN OLDER PATIENTS FROM THE MoPIM MULTICENTRE COHORT STUDY.

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ABSTRACT

Objectives: To estimate the frequency of chronic conditions and geriatric syndromes in older patients admitted to hospital because of an exacerbation of their chronic conditions, and to identify multimorbidity clusters in these patients.

Design: Multicentre, prospective cohort study.

Setting: Internal medicine or geriatric services of five general teaching hospitals in Spain.

Participants: 740 patients aged 65 and older, hospitalized because of an exacerbation of their chronic conditions between September 2016 and December 2018.

Primary and secondary outcome measures: Active chronic conditions and geriatric syndromes (including risk factors) of the patient, a score about clinical management of chronic conditions during admission, and destination at discharge were collected, among other variables. Multimorbidity patterns were identified using fuzzy c-means cluster analysis, taking into account the clinical management score. Prevalence, observed/expected ratio and exclusivity of each chronic condition and geriatric syndrome were calculated for each cluster, and the final solution was approved after clinical revision and discussion among the research team.

Results: 740 patients were included (mean age 84.12 years, SD 7.01; 53.24% female). Almost all patients had two or more chronic conditions (98.65%; 95%CI 98.23-99.07), the most frequent were hypertension (81.49%, 95%CI 78.53-84.12) and heart failure (59.86%, 95%CI 56.29-63.34). The most prevalent geriatric

syndrome was polypharmacy (79.86%, 95%CI 76.82-82.60). Four statistically and clinically significant multimorbidity clusters were identified: osteoarticular, psychogeriatric, cardiorespiratory and minor chronic disease. Patient level variables such as sex, Barthel Index, number of chronic conditions or geriatric syndromes, chronic disease exacerbation 3 months prior to admission or destination at discharge differed between clusters.

Conclusions: In older patients admitted to hospital because of the exacerbation of chronic health problems, it is possible to define multimorbidity clusters using soft clustering techniques. These clusters are clinically relevant and could be the basis to reorganize healthcare circuits or processes to tackle the increasing number of older, multimorbid patients.

Trial registration number NCT02830425, 12th July 2016

Keywords: Multimorbidity, patterns, soft clustering, older, chronic conditions, geriatric syndromes.

Strengths and limitations of this study

- The multimorbidity analysis in this study has been developed considering a wide range of long-term conditions that may require healthcare in older people.
- To the best of our knowledge, this is the first published study of multimorbidity clusters in older patients to include chronic diseases weighted by a clinical management score and geriatric syndromes.
- Soft clustering is an innovative, methodologically robust technique that can lead to reliable results in the field of multimorbidity analysis.

- The list of chronic conditions and geriatric syndromes used in this study is comprehensive but not standardized, thus hindering comparability with other studies.

BACKGROUND

According to the most recent Eurostat baseline population projections, old-age dependency ratio (population 65y and over divided by population 15-64y) is about 32% in the European Union (EU) and it is expected to reach 52% in 2050, meaning that the EU's population will continue to grow older[1]. Together with the fact that chronic conditions (CC) are the main cause of disability and mortality in Europe, this implies that the coexistence of two or more chronic health conditions, which constitutes the classic definition of multimorbidity, is becoming increasingly common[2].

Multimorbidity is therefore turning into an important challenge for the health system because of the expanding proportion of older people with multiple CC and treatments as well as the difficulties associated with their clinical management[3,4]. Most clinical practice guidelines are focused on single diseases, with limited recommendations for multimorbid patients[5], and, in addition, randomized clinical trials often exclude older patients with multimorbidity[6]. Despite the importance of multimorbidity in clinical practice, different criteria about which conditions should be considered and how to aggregate them are still under debate, which makes it difficult to compare different estimations around the world[7–9].

One of the novel, increasingly widespread definitions of multimorbidity considers the non-spurious association of certain CC by sharing pathophysiological

mechanisms, giving rise to disease association patterns[10]. In order to identify those patterns, different statistical methodologies have been explored. Among these techniques, soft clustering allows to focus on patients rather than diagnoses and is a useful method when there is a high overlap of diagnoses between patients, as it enables patients to belong to more than one multimorbidity pattern with a certain probability[11]

Besides CC, other clinically relevant situations such as geriatric syndromes (GS) may also be considered in the definition of these patterns, since they might have a great impact on the health-related quality of life and clinical management of old patients[12]. In fact, the purpose of multimorbidity characterization (i.e., predicting outcomes or use of health services, improving quality of care, organizing healthcare services, etc.), will have an influence on its definition. In order to have an accurate picture of the morbidity of each patient, a global consideration of all conditions that may require healthcare attention is necessary, even if they are not the reason for hospitalization. Along these lines, some countries have explicitly recommended to acknowledge all long-term conditions for optimising care of adult patients by reducing, for example, possible inappropriate treatments, multiple healthcare appointments or poor health-related quality of life[13–15].

During the past decade, there has been an increasing amount of publications that consider multimorbidity[16], but few have focused on multimorbidity patterns in older patients and even fewer take into account GS[17]. For this reason, we launched a multicentre study in 2016 with multiple aims related to multimorbidity, appropriateness of chronic treatments and adverse drug reactions in older patients[18]. The objectives of the present analyses were to estimate the frequency of CC and GS in older patients admitted to hospital because of an

exacerbation of their CC, and to identify possible multimorbidity patterns in these patients.

METHODS

Design and setting

A multicentre, prospective cohort study including older patients hospitalized at the internal medicine or geriatric services at five general teaching hospitals in three different regions of Spain between September 2016 and December 2018 was designed. The detailed protocol was previously published[18].

For the purposes of the study, older patients (≥65 years old) admitted as a result of the exacerbation of their chronic pathology were included. Patients referred to home hospitalization, admitted because of an acute process not related to any chronic disease, or with a fatal outcome expected at the time of admission were not included.

No written informed consent was deemed necessary for this study.

Data acquisition and variables

The following sociodemographic and clinical data was retrieved by the clinical team responsible for the patient: patient's code, date of birth, sex, functional status just before entering the hospital (Barthel index)[19], household (alone, with relatives or other people, in a nursing home), existence of any contact with healthcare services (primary care, emergencies, hospital admission, outpatient care, home care) in the 3 months prior to hospitalization due to exacerbation of any chronic disease, and destination at discharge from the present episode of

hospitalization (home, transfer to another hospital, transfer to a nursing home, *exitus*).

Active CC of the patient at arrival to hospital, including some risk factors, were collected (see Supplemental Table 1). For this purpose, the physicians of the project defined, on a consensual basis, a limited list of 64 CC, coming from the 114 groups defined by Salisbury and colleagues[20] and including the 19 categories of the Charlson Index[21]. Following the same criteria as Salisbury, a condition was considered to be chronic when it lasted for at least 6 months, including past conditions that require ongoing disease or risk management, important conditions with a significant risk of recurrence, or past conditions that have continuing implications for patient management[20]. Drug-related conditions of this list refer to poor management of medication related to a chronic disease that has clinical implications in that hospitalization (such as any drug intolerance or an excess drug poisoning).

Additionally, for each of the CC, it was also recorded if they had required clinical management (both at admission and during hospitalization) by assigning a (subjective) correlative score (CM=1, 2, 3...) to each one, according to their clinical importance during the attention process. Thus, CC that did not have any significance during hospitalization, although recorded, had a score equal to zero. This correlative score was later used to compute a ratio to reflect the weight of each CC in each patient in the index hospitalization.

Specific GS and risk factors (acute confusional syndrome/delirium, chronic pain, cognitive/intellectual impairment, constipation, depression or anxiety, dysphagia, frailty, immobility, incontinence (urinary/faecal), instability/falls, malnutrition,

polypharmacy, pressure ulcers, sensorial deficit, sleep disorders/insomnia) were also recorded. Two of the departments systematically apply a recently developed scale for frailty [22], while the others consider clinical judgement (although based on the same variables).

In order to address potential sources of bias, a pilot study was conducted with the first 10 admissions per centre to validate the data collection process and identify problems that could arise. After that, proper changes were made in the protocol and questionnaire. All available information sources were consulted in order to register CC and GS, and the defined list was not closed. Nonetheless, the registration of CC and GS was based on clinical criteria.

Sampling and analysis

A consecutive sample of 740 patients meeting the inclusion criteria were included, proportionally distributed to the annual volume of hospitalizations of the medicine and/or geriatric services of each centre. The estimated sample of 800 patients (see protocol[18]) could not be reached due to organizational reasons in one of the participating centres.

For the purposes of the analyses, some CC were grouped according to clinical criteria: Hemiplegia was included in cerebrovascular disease; metastatic solid tumour, leukaemia, lymphoma and any malignancy were grouped into 'neoplasia'; hepatitis B and C were included in mild liver disease, and both congestive and non-congestive heart failure were grouped into 'heart failure'. Other diseases were finally excluded of the analyses considering that they have no impact on acute healthcare (cataract, dermatitis, diverticular disease of the

colon, glaucoma, haemorrhoids, other vascular diseases and prostatic benign hypertrophy). In the end, 51 CC and 15 GS were analysed.

The updated Charlson Comorbidity Index[23], age adjusted, was computed and categorized according to tertiles distribution.

Descriptive statistics were performed to assess patient clinical and sociodemographic characteristics and to obtain overall prevalence estimates of CC and GS, stratified by sex. Multimorbidity was firstly defined as the presence of two or more CC. Cumulative number of CC and GS per patient were computed, respectively.

Multimorbidity patterns

CC or GS with a prevalence <2% were excluded to avoid statistical noise and therefore spurious findings in the cluster solutions, leaving a list of 40 CC and 15 GS. In order to take into account if a CC had required clinical management (CM), a ratio variable (R) was computed as follows:

If CC=0 & CM=0 → R=0

If CC=1 & CM=m → R=1/m; max (m) = max value (CM) = 8;

If CC=1 & CM=0 → R= 0.1

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 centres (similar to *k*-means) but with fuzziness so that individuals may belong to more than one pattern. Through this technique, we

obtained clusters of individuals and a membership matrix, which indicates the degree of participation of each subject in each cluster.

As a first step, and similarly to Violán *et. al.*[24], the PCAmix algorithm for categorical and continuous data (GS and R variables respectively) was implemented to reduce and transform the dataset to all continuous data[25]. To decide the number of retained dimensions, the Karlis-Saporta-Spinaki rule was used[26]. Then, a soft clustering algorithm was applied to fuzzily distribute the population into a set of clusters, corresponding to the different multimorbidity patterns. We computed three validation indices to obtain the optimal number of clusters (K) and the optimal value of the fuzziness parameter (m): the partition coefficient whose optimal choice for coefficient is at the maximum, and the Xie-Beni and the partition entropy validation indices, whose optimal indices are at the minimum[27]. Considering the stochastic nature of the clusters, and the requirement of stable multimorbidity clusters, 100 independent clustering repetitions were applied to obtain the stable final solution.

To describe each identified cluster of individuals, the prevalence of CC and GS in each one was calculated. Observed/expected (O/E) ratios were calculated by dividing the prevalence of a given disease within a cluster by its prevalence in the overall population. The exclusivity of CC and GS, defined as the fraction of patients with the disease in the cluster over the total number of patients with the disease, was also calculated. A CC or a GS was considered to be relevant in a given cluster of individuals when its O/E ratio was >1 and its exclusivity was >25%[28–30]. The statistical significant final solution ranged from 4 to 8 clusters. After clinical revision and discussion among the research team, 4 different clusters were considered to be consistent with the clinical observations as well

as the objective of the clustering. There is currently no consensus in the literature on the criteria used to select the number of clusters or the O/E ratio cut-off point due to, in part, the novelty of the analysis.

Finally, sociodemographic and clinical variables were described for all patients assigned to each cluster. Analyses were performed using R 3.6.0 and SPSS 22.

Patient and Public Involvement

Since this was an observational study with variables and outcomes related to the healthcare process, this research was developed without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results.

RESULTS

740 patients aged 65 years or older were included, with a mean age of 84.12 years (SD 7.01), a 53.24% of females and a mean Barthel Index of 65.07 (median 75). Sociodemographic and clinical variables are summarised in Table 1. Almost all patients had two or more CC (98.65%; 95%CI 98.23-99.07), with a median of 8 CC and 6 GS per patient. Nearly 70% had consulted a health care service in the 3 months prior to hospitalization due to chronic disease exacerbation.

Table 1. Sociodemographic and clinical variables of the studied cohort.

Sociodemographic and clinical variables		N	%	95% CI
Age	< 70	33	4.46	3.19 - 6.20
	70-74	48	6.49	4.93 - 8.50
	75-79	82	11.08	9.02 - 13.55
	80-84	181	24.46	21.50 - 27.68
	85-89	232	31.35	28.11 - 34.78
	90-94	134	18.11	15.50 - 21.05
	>= 95	30	4.05	2.85 - 5.73
Sex	Female	394	53.24	49.64 - 56.81

Sociodemographic and clinical variables		N	%	95% CI
	Male	346	46.76	43.19 - 50.36
Barthel index	< 20	90	12.16	10.00 - 14.71
	20-35	76	10.27	8.28 - 12.67
	40-55	124	16.76	14.24 - 19.62
	60-95	294	39.73	36.27 - 43.30
	100	156	21.08	18.30 - 24.17
Age adjusted, updated Charlson Comorbidity Index	2-5	148	20.00	17.28 - 23.03
	6-8	411	55.54	51.94 - 59.08
	9-14	181	24.46	21.50 - 27.68
Household	With relatives/other people	523	70.68	67.30 - 73.84
	Nursing home	95	12.84	10.62 - 15.44
	Alone	122	16.49	13.99 - 19.33
Chronic disease exacerbation	No	225	30.41	27.20 - 33.81
3 months prior to admission	Yes (total)	515	69.59	66.19 - 72.80
	Primary care	342	46.22	42.65 - 49.82
	Emergencies	263	35.54	32.17 - 39.06
	Hospital admission	193	26.08	23.05 - 29.36
	Outpatient care	8	1.08	0.55 - 2.12
	Home care	14	1.89	1.13 - 3.15
Conditions requiring clinical management (CM)	1	302	40.81	37.36 - 44.39
	2	216	29.19	26.03 - 32.57
	3	106	14.32	11.98 - 17.03
	4	72	9.73	7.80 - 12.08
	5	28	3.78	2.63 - 5.41
	6	13	1.76	1.03 - 2.98
	7	2	0.27	0.07 - 0.98
	8	1	0.14	0.007 - 0.76
Destination at discharge	Home	468	63.24	59.71 - 66.64
	Nursing home	105	14.19	11.86 - 16.89
	Another hospital	101	13.65	11.36 - 16.31
	Exitus	66	8.92	7.07 - 11.19
Multimorbidity	No	10	1.35	1.35 - 1.36
	Yes	730	98.65	98.23 - 99.07

CI = Confidence interval

Figure 1 shows the distribution of the number of CC by age groups. The most frequent CC were hypertension (81.49%, 95%CI 78.53-84.12) and heart failure (59.86%, 95%CI 56.29-63.34) (see Supplemental Table 2). Heart failure was also the main cause of hospitalization (30.7% of patients had CM score=1), followed by COPD (20.7%) (Supplemental Table 3).

There were some differences in CC between sexes, with females having more frequently heart failure, degenerative arthropathy, obesity, hip fracture, thyroid disease, asthma, osteoporosis, vertigo and non-schizophrenic mental disorders. Males, in turn, had more frequently COPD, gout, neoplasia, peripheral arteriopathy and ulcerative disease.

The most prevalent GS was polypharmacy (79.86%, 95%CI 76.82-82.60), followed by frailty (61.76%, 95%CI 58.20-65.19). Females had a significantly higher number of GS compared to males (Wilcoxon rank sum test, $p < 0.001$), as well as a higher prevalence of depression/anxiety, chronic pain, constipation, frailty, urinary/faecal incontinence and immobility.

Four statistically and clinically significant multimorbidity clusters or patterns were identified in our study population. For all clusters, CC and GS with an observed/expected ratio >1 and exclusivity >25% are represented in Figure 2 (see also Supplemental Table 4 for all CC and GS). Sociodemographic and clinical characteristics of patients in each cluster are described in Table 2.

Table 2. Sociodemographic and clinical variables of the multimorbidity clusters.

		Osteoarticular	Psycho-geriatric	Minor chronic conditions	Cardio-respiratory
Number of patients included, n (%)		132 (17.8)	153 (20.7)	179 (24.2)	276 (37.3)
Age at admission (y, mean ± SD)		84.03 ± 6.48	84.51 ± 7.25	83.94 ± 7.19	84.06 ± 7.03
Sex, n (%)	Male	34 (25.7)	66 (42.8)	99 (55.5)	147 (53.4)
	Female	98 (74.3)	87 (57.2)	80 (44.5)	129 (46.6)
Barthel Index (mean ± SD)		63.06 ± 24.78	47.62 ± 34.94	64.96 ± 33.56	75.76 ± 27.52
Total nº chronic conditions (mean ± SD)		11.5 ± 3.64	7.68 ± 3.19	8.86 ± 3.08	7.59 ± 2.61
Total nº geriatric syndromes / risk factors (mean ± SD)		7.76 ± 2.07	8.16 ± 2.82	6.4 ± 3.32	4.42 ± 2
Charlson Comorbidity Index, n (%)	2-5	26 (19.9)	24 (15.6)	37 (20.4)	61 (22.2)
	6-8	73 (55.1)	89 (58.5)	96 (53.8)	153 (55.3)
	9-14	33 (25.0)	40 (25.9)	46 (25.7)	62 (22.6)
Household, n (%)	With relatives / other people	91 (68.7)	103 (67.2)	133 (74.5)	196 (71.1)

		Osteoarticular	Psycho-geriatric	Minor chronic conditions	Cardio-respiratory
	Nursing home	16 (11.8)	28 (18.4)	23 (12.8)	28 (10.3)
	Alone	26 (19.5)	22 (14.3)	23 (12.7)	52 (18.7)
Chronic disease exacerbation 3 months prior to the index admission, n (%)	No	24 (18.3)	46 (30.1)	48 (27.0)	106 (38.5)
	Yes (total)	108 (81.7)	107 (69.9)	130 (73.0)	170 (61.5)
	Primary care	83 (62.7)	66 (43.3)	92 (51.6)	101 (36.5)
	Emergencies	71 (53.6)	40 (26.2)	69 (38.5)	83 (30.2)
	Hospital admission	49 (37.1)	46 (30.1)	47 (26.1)	51 (18.6)
	Outpatient care	1 (0.7)	0 (0.3)	3 (1.4)	4 (1.4)
	Home care	2 (1.5)	2 (1.1)	3 (1.8)	7 (2.6)
Destination at discharge, n (%)	Home	86 (65.3)	83 (54.0)	111 (62.0)	188 (68.1)
	Nursing home	15 (11.1)	33 (21.3)	26 (14.5)	32 (11.5)
	Another hospital	15 (11.3)	17 (11.3)	26 (14.7)	42 (15.3)
	Exitus	16 (12.3)	20 (13.3)	16 (8.8)	14 (4.9)

SD = standard deviation.

The first cluster, named *osteoarticular*, included 132 patients (17.8%) having osteoporosis, fractures, inflammatory osteoarticular disease, chronic pain and degenerative arthropathy. Moreover, vertigo, sleep apnoea, asthma, depression/anxiety and sleep disorders were also over-represented. This cluster included patients with the highest number of both CC and GS. About three quarters were female, and most of them (82%) accessed healthcare services 3 months prior to this admission.

Cluster 2, called *psychogeriatric*, had 152 patients (20.7%) and included mostly GS: pressure ulcers, immobility, malnutrition, cognitive impairment, dementia, incontinence and frailty. Patients in this group had a mean Barthel index lower than 50 and a high number of GS. Furthermore, nearly 20% of them were living in a nursing home and in-hospital mortality was about 13%.

Cluster 3, named *minor chronic disease*, had 179 (24.2%) patients, and represents a group of patients with a variety of conditions, such as hypertension, dyslipidaemia, anaemia, gout, chronic renal insufficiency, polypharmacy, non-

ischaemic heart disease, and diverse GS. O/E ratios were close to 1 in most cases.

Finally, cluster 4, called *cardiorespiratory*, included 276 (37.3%) patients. The over-represented diagnoses were COPD, heart failure and cardiac arrhythmia, although the O/E ratios were very low. In this cluster, with the lowest number of CC and GS, and a Barthel index greater than 75, nearly 40% had no healthcare consultation for a chronic disease exacerbation in the previous 3 months. This group had the lowest in-hospital mortality (5%).

DISCUSSION

The present study aimed to identify multimorbidity patterns in patients aged 65 and above admitted to hospital because of an exacerbation of CC. The soft clustering technique used, together with clinical criteria, was able to identify 4 different multimorbidity patterns, named osteoarticular, psychogeriatric, cardio-respiratory and minor chronic disease, in a patient-centred approach taking into account the importance of each disease in hospital management. Remarkably, high chronic multimorbidity was found in all patients, regardless of the cluster. To the best of our knowledge, this is the only study published to date that has analysed multimorbidity patterns taking into account both CC (with their weight during clinical management) and GS in this type of patients. Hence, these identified patterns allow us to take a further step towards understanding the patients' current or future healthcare needs.

Two very important aspects of multimorbidity patterns analysis are the purpose for designing such patterns and the target population, which clearly condition the obtained results or conclusions. For instance, our aim in defining multimorbidity

patterns in this cohort was to identify profiles of patients with similar clinical needs during the index hospitalization and even a similar short-term prognosis at that time. For this reason, the importance of their pathologies in the course of hospitalization was also taken into account. Hence, the ones that tend to have a minimal impact on clinical management, such as risk factors like hypertension or dyslipidaemia did not have a leading role in the patterns.

All clusters contain coherent groups of conditions that are mostly pathophysiologically related. From the clinical point of view, these clusters resemble patient profiles that are intuitively perceived. Moreover, some descriptive variables such as sex, Barthel index, mean number of CC or GS, chronic pathology exacerbations in previous months, or hospital mortality, are distributed in such a way that they may reinforce the distinction of these groups.

Coexistence of CC and GS was observed in all clusters except for the cardiorespiratory, reinforcing the need to consider other clinically relevant situations rather than only CC. In particular, the exclusivity and prevalence of GS such as immobility, malnutrition, cognitive impairment or dementia were considerable in the psychogeriatric cluster.

Interestingly, highly prevalent CC, such as heart failure and COPD, which also frequently involve clinical management, only showed remarkable exclusivity and O/E ratio in the cardiorespiratory pattern and were not over-represented elsewhere. This highlights the fact that even though some CC may not be over-represented in a cluster, they can have a high prevalence and therefore need to be properly addressed too.

With respect to the osteoarticular cluster, it displayed a pattern of female predominance, with many CC and GS, high healthcare needs in recent months due to their chronic pathology, and high in-hospital mortality. Thus, this profile would identify a group of patients with a high probability of decompensation and death.

Finally, the so-called minor chronic diseases cluster was not very well defined. It included some risk factors (hypertension, dyslipidaemia, polypharmacy) as well as some CC and GS. Thus, it would be possible that it does not represent a real cluster but either the set of cases that did not belong anywhere else.

Comparison with other studies

Given the type of patients under study and the methodological approach to identify multimorbidity patterns, there are few publications to directly compare our results to. Clerencia-Sierra and colleagues[17] analysed multimorbidity patterns in hospitalized older patients. Their methodological and analytical approach was slightly different, and they did not take into account the weight of the diseases during the hospitalization process; however, they found a similar percentage of multimorbidity (99.7%) and 4 patterns that partially coincide with those of our study: cardiovascular, induced-dependency, falls, and osteoarticular.

Furthermore, several authors have published data on patterns identified from primary care electronic records in different age groups, with lists of non-comparable chronic problems and using different techniques (cluster analysis, exploratory factor analysis or latent class analysis)[17,29–34]. These results would not be directly comparable with our study, but all of them highlight the ability to identify association patterns of chronic diseases.

Strengths and limitations

The strengths of this study are the prospective design, ensuring data quality by thorough record keeping, the ascertainment of all CC and GS of the patient, as well as the use of a novel clustering technique. Soft clustering is a methodologically robust technique less susceptible to outliers in the data, choice of distance measure and the inclusion of inappropriate or irrelevant variables[24]. Besides, our approach focuses beyond organ diseases by incorporating GS, and using a comprehensive list retrieved by the clinical team. Additionally, we have taken into account the relative importance of the different CC in the clinical management of the patient during hospitalization, thus providing a better picture of the possible complexity and needs during hospitalization.

Furthermore, our work is not only limited to the identification of possible patterns. We have validated them, in some way, by analysing some of the patients' variables such as sex, number of CC, previous contacts with the health system, hospital mortality or need for a nursing home.

Nonetheless, our study presents some limitations that need to be considered. Firstly, the identification of chronic pathologies does not exclusively follow a validated list of codes but either an adaptation of different ones, a fact that could hinder comparability with other studies on multimorbidity. Secondly, as this study is not longitudinal, the chronology in which CC or GS appear cannot be analysed. It is possible for a patient to evolve from one pattern to another throughout life, as some authors have already pointed out[35], and therefore, the results only show the present situation. However, given the purpose of the defined patterns, this would not in itself be a limitation.

From a clinical point of view, the lack of usage of standard scales or diagnostic criteria for determining all CC or GS could question the validity of this information. However, the study gathered the data as it was routinely registered in the different departments. Frailty should derive from a comprehensive assessment of the patient in a standardized way that still lacks of systematic implementation in the healthcare routine[36]. Nevertheless, our multimorbidity study wanted to go a little further, also considering GS (frailty included), an unusual fact in the bibliography on clusters of multimorbidity in older patients in spite of its importance for decision making in the clinical practice.

The clinical conditions severity or other possible aggravating factors have neither been gathered. Nevertheless, the registration of a variable that takes into account the relevance of each CC during the care process acts, in some way, as a proxy of the importance of each disease in the index hospitalization when dealing with patients admitted because of decompensation. Considering the purpose of defining the patterns in the whole study, and not knowing useful precedents in the consulted bibliography, the assignment made by the medical professional who attended the patient was an easy, simple measure, and shared by all professionals at the time of writing the clinical course.

Clinical implications

These patterns are not a picture of the community but of older patients in geriatric or internal medicine departments, which are generally in more need of health services and more complex clinical management. However, not all of these patients have the same requirements. In fact, one in five patients (the psychogeriatric cluster) caused a great burden to both the patient and their

relatives while the patients in the most frequent cluster (cardiorespiratory), with lower dependency and less GS, seemed to have better immediate outcome. Therefore, it is possible that the therapeutic objectives should be different in these patients. More importantly, the ability to distinguish patients more objectively than with the mere clinical impression may allow the design of better processes, services or alternatives to conventional hospitalization. Indeed, the identification of multimorbidity patterns in subsets of the population in order to detect underlying factors, understand their burden on patients and develop preventive strategies is considered a research priority. Finally, the development of clinical practice guidelines according to these patterns needs to be considered, although it may be difficult given the magnitude of the diseases comprised in each pattern [4,14]. In addition, some patterns may include patients with an increased risk of potentially inappropriate prescription or adverse drug reactions. These aspects will be the object of future analyses.

Conclusions

In conclusion, in older patients admitted to hospital because of the exacerbation of chronic health problems, it is possible to define multimorbidity clusters or patterns using appropriate statistical techniques. These patterns seem clinically coherent and could be the basis to reorganize circuits, processes or healthcare models to tackle the increasing number of older, multimorbid patients.

List of abbreviations

CC: chronic condition

GS: geriatric syndrome

CM: clinical management

O/E: observed/expected

COPD: chronic obstructive pulmonary disease

Figure captions

Figure 1. Distribution of the number of chronic conditions (excluding the following risk factors: hypertension, dyslipidaemia, obesity, osteoporosis and drug-related conditions) in relation to age groups.

Figure 2. Observed/Expected (O/E) ratio and prevalence of chronic conditions and geriatric syndromes/risk factors per multimorbidity cluster. Conditions with exclusivity >25% and O/E ratios >1 in each cluster are represented. Conditions are ordered by O/E ratio and from cluster 1 to 4. *COPD: Chronic Obstructive Pulmonary Disease*

Ethics approval statement

This study was approved by the clinical research ethics committees of each centre: Comité Ético de investigación Clínica del Parc Taulí, Comitè Ètic d'Investigació Clínica Osona per a la Recerca i Educació Sanitàries (FORES), Comité de Ètica de la Investigación con Medicamentos (CEIm)-Parc de Salut MAR, Comité Ético de Investigación Clínica de Euskadi, Comité de Ética de Investigación del Hospital Universitario de Canarias. No written informed consent was deemed necessary for this study.

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

MB conceived and supervised the study, discussed the results, wrote the first version of the manuscript. SH, RJ, MA, RE and GJN participated in patient inclusion, data collection and discussion of the results and revised the manuscript. AR executed the analysis and interpretation of multimorbidity clusters. CV collaborated in the execution of the analyses and in the interpretation of the multimorbidity patterns. ML participated in the statistical and graphical analysis of the results, in the discussion of the results and the revision of several manuscript versions. PR collaborated in the questionnaires' design, patient inclusion, data collection and discussion of results and revised the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1 Eurostat - Data Explorer. https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=tps00200&lang=en (accessed 21 Oct 2020).

2 OECD/EU. Health at a Glance: Europe 2018 State of Health in the EU Cycle. 2018. doi:10.1787/health_glance_eur-2018-en

3 Palladino R, Pennino F, Finbarr M, *et al.* Multimorbidity And Health Outcomes In Older Adults In Ten European Health Systems, 2006-15. *Health Aff (Millwood)* 2019;**38**:613–23. doi:10.1377/hlthaff.2018.05273

4 The Academy of Medical Sciences. Multimorbidity: a priority for global health research. 2018. https://acmedsci.ac.uk/file-download/82222577

5 Lugtenberg M, Burgers JS, Clancy C, *et al.* Current guidelines have limited applicability to patients with comorbid conditions: A systematic analysis of evidence-based guidelines. *PLoS One* 2011;**6**. doi:10.1371/journal.pone.0025987

6 Buffel du Vaure C, Dechartres A, Battin C, *et al.* Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials.gov: A systematic review of registration details. *BMJ Open* 2016;**6**:e012265. doi:10.1136/bmjopen-2016-012265

7 Fortin M, Stewart M, Poitras ME, *et al.* A systematic review of prevalence studies on multimorbidity: Toward a more uniform methodology. *Ann Fam Med* 2012;**10**:142–51. doi:10.1370/afm.1337

8 Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases - A systematic review on existing multimorbidity indices. *J Gerontol A Biol Sci Med Sci* 2011;**66**:301–11. doi:10.1093/gerona/glq208

9 Roso-Llorach A, Violán C, Foguet-Boreu Q, *et al.* Comparative analysis of methods for identifying multimorbidity patterns: A study of 'real-world' data. *BMJ Open* 2018;**8**:e018986. doi:10.1136/bmjopen-2017-018986

10 Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, *et al.* Multimorbidity patterns: A systematic review. *J Clin Epidemiol* 2014;**67**:254–66. doi:10.1016/j.jclinepi.2013.09.021

11 Jyoti Bora D, Kumar Gupta A. A Comparative study Between Fuzzy Clustering Algorithm and Hard Clustering Algorithm. *Int J Comput Trends Technol* 2014;**10**.http://www.ijcttjournal.org (accessed 26 Aug 2021).

12 Lu FP, Chang WC, Wu SC. Geriatric conditions, rather than multimorbidity, as predictors of disability and mortality among octogenarians: A population-based cohort study. *Geriatr Gerontol Int* 2016;**16**:345–51. doi:10.1111/ggi.12480

13 van der Heide I, Snoeijs SP, Boerma WGW, *et al.* How to strengthen patient-centredness in caring for people with multimorbidity in Europe? 2017.http://europepmc.org/books/NBK464537

14 Rijken M, Struckmann V, Van Der Heide I, *et al.* How to improve care for people with multimorbidity in Europe? 2016. https://www.euro.who.int/en/about-us/partners/observatory/publications/policy-briefs-and-summaries/how-to-

improve-care-for-people-with-multimorbidity-in-europe

15 NICE. Multimorbidity: clinical assessment and management NICE guideline. 2016. www.nice.org.uk/guidance/ng56

16 Catalá-López F, Alonso-Arroyo A, Page MJ, *et al.* Mapping of global scientific research in comorbidity and multimorbidity: A cross-sectional analysis. *PLoS One* 2018;**13**:e0189091. doi:10.1371/journal.pone.0189091

17 Clerencia-Sierra M, Calderón-Larrañaga A, Martínez-Velilla N, *et al.* Multimorbidity patterns in hospitalized older patients: Associations among chronic diseases and geriatric syndromes. *PLoS One* 2015;**10**:e0132909. doi:10.1371/journal.pone.0132909

18 Baré M, Herranz S, Jordana R, *et al.* Multimorbidity patterns in chronic older patients, potentially inappropriate prescribing and adverse drug reactions: protocol of the multicentre prospective cohort study MoPIM. *BMJ Open* 2020;**10**:e033322. doi:10.1136/bmjopen-2019-033322

19 Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. *J Clin Epidemiol* 1989;**42**:703–9. doi:10.1016/0895-4356(89)90065-6

20 Salisbury C, Johnson L, Purdy S, *et al.* Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2011;**61**:e12-21. doi:10.3399/bjgp11X548929

21 Charlson ME, Peter P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.

J Chron Dis 1987;**40**:373–83. doi:10.1016/0021-9681(87)90171-8

22 Amblàs-Novellas J, Martori JC, Espaulella J, *et al.* Frail-VIG index: A concise frailty evaluation tool for rapid geriatric assessment. *BMC Geriatr* 2018;**18**:29. doi:10.1186/s12877-018-0718-2

23 Quan H, Li B, Couris CM, *et al.* Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;**173**:676–82. doi:10.1093/aje/kwq433

24 Violán C, Foguet-Boreu Q, Fernández-Bertolín S, *et al.* Soft clustering using real-world data for the identification of multimorbidity patterns in an elderly population: cross-sectional study in a Mediterranean population. 2019;**9**:e029594. doi:10.1136/bmjopen-2019-029594

25 Chavent M, Kuentz-Simonet V, Labenne A, *et al.* Multivariate analysis of mixed data: the R package PCAmixdata. arXiv preprint, https://arxiv.org/abs/1411.4911v4. 2017.

26 Karlis D, Saporta G, Spinakis A. A simple rule for the selection of principal components. *Commun Stat - Theory Methods* 2003;**32**:643–66. doi:10.1081/STA-120018556

27 Zhao Q. *Cluster Validity in Clustering Methods*. 2012.http://cs.joensuu.fi/sipu/pub/qinpei-thesis.pdf

28 Guisado-Clavero M, Roso-Llorach A, López-Jimenez T, *et al.* Multimorbidity patterns in the elderly: A prospective cohort study with cluster analysis. *BMC Geriatr* 2018;**18**:16. doi:10.1186/s12877-018-0705-

7

29 Marengoni A, Roso-Llorach A, Vetrano DL, *et al.* Patterns of Multimorbidity in a Population-Based Cohort of Older People: Sociodemographic, Lifestyle, Clinical, and Functional Differences. *J Gerontol A Biol Sci Med Sci* 2019;**75**:798–805. doi:10.1093/gerona/glz137

30 Violán C, Roso-Llorach A, Foguet-Boreu Q, *et al.* Multimorbidity patterns with K-means nonhierarchical cluster analysis. *BMC Fam Pract* 2018;**19**:108. doi:10.1186/s12875-018-0790-x

31 Juul-Larsen HG, Christensen LD, Bandholm T, *et al.* Patterns of multimorbidity and differences in healthcare utilization and complexity among acutely hospitalized medical patients (≥65 years) – a latent class approach. *Clin Epidemiol* 2020;**12**:245–59. doi:10.2147/CLEP.S226586

32 Zhu Y, Edwards D, Mant J, *et al.* Characteristics, service use and mortality of clusters of multimorbid patients in England: a population-based study. *BMC Med* 2020;**18**:78. doi:10.1186/s12916-020-01543-8

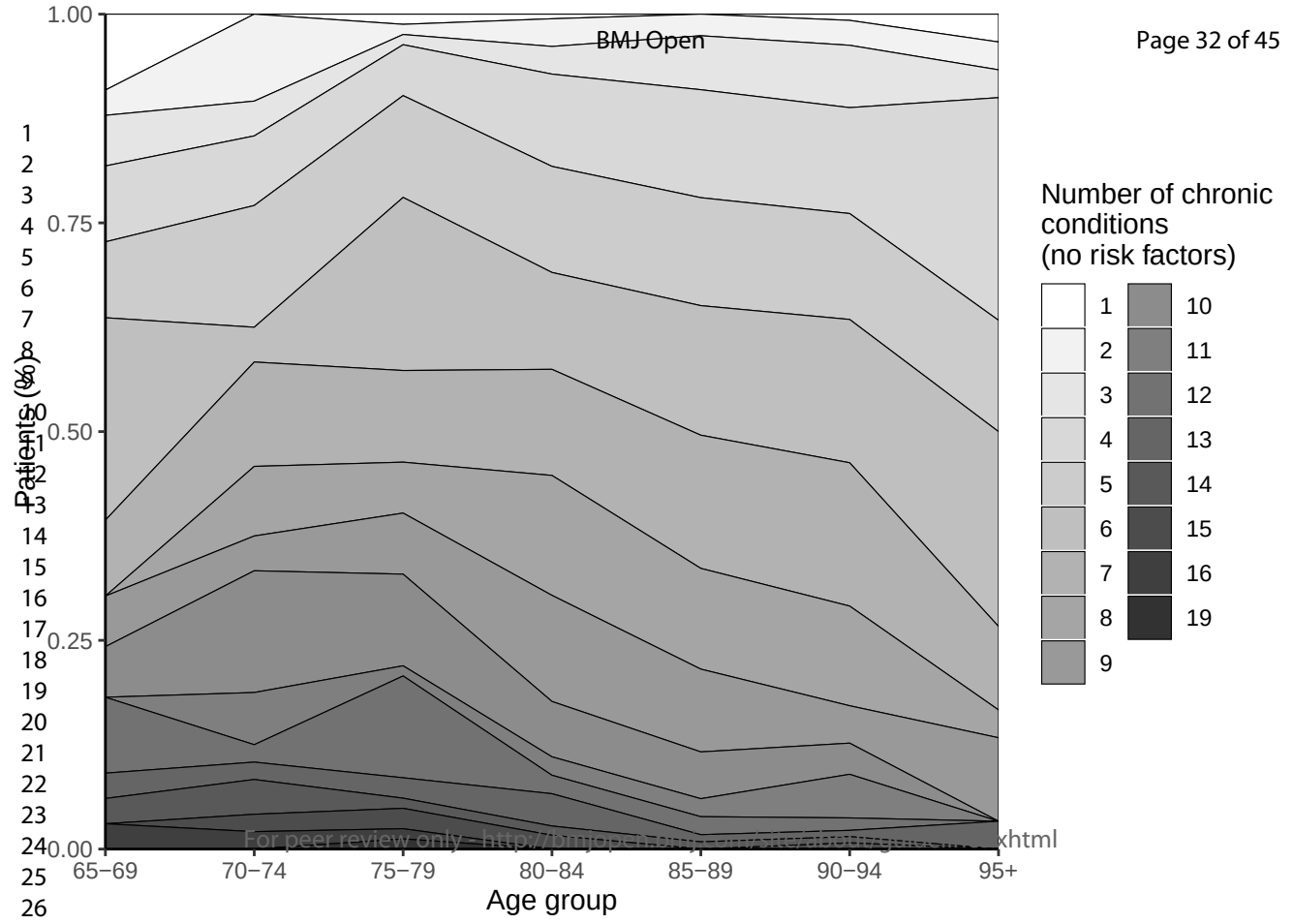
33 Nguyen QD, Wu C, Odden MC, *et al.* Multimorbidity patterns, frailty, and survival in community-dwelling older adults. *Journals Gerontol - Ser A Biol Sci Med Sci* 2019;**74**:1265–70. doi:10.1093/gerona/gly205

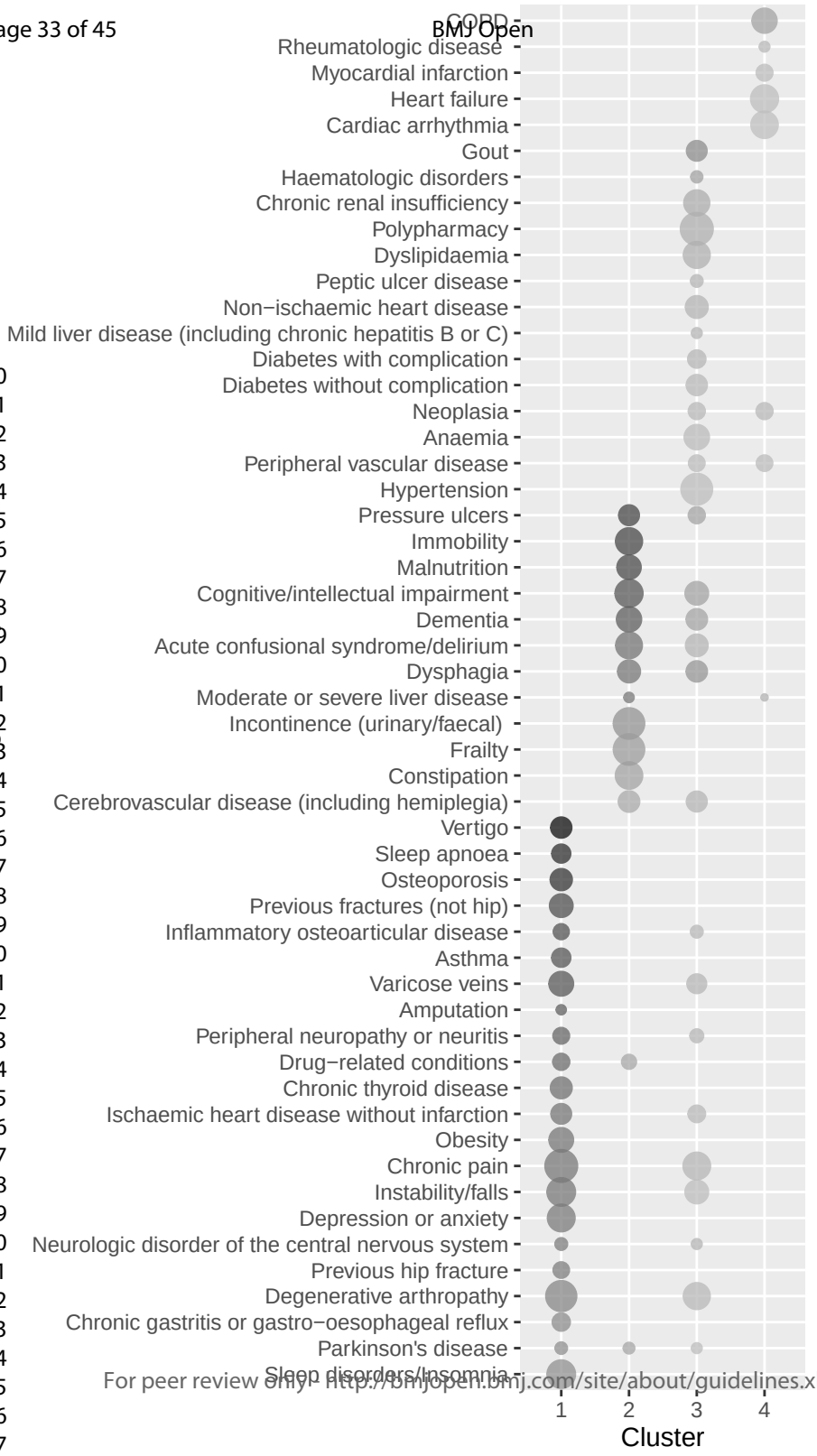
34 Poblador-Plou B, van den Akker M, Vos R, *et al.* Similar multimorbidity patterns in primary care patients from two European regions: results of a factor analysis. *PLoS One* 2014;**9**:e100375. doi:10.1371/journal.pone.0100375

35 Vetrano DL, Roso-Llorach A, Fernández S, *et al.* Twelve-year clinical

trajectories of multimorbidity in a population of older adults. *Nat Commun* 2020;**11**:1–9. doi:10.1038/s41467-020-16780-x

36 Ward K, Reuben D. Comprehensive geriatric assessment. In: *UpToDate*. 2020. https://www.uptodate.com/contents/comprehensive-geriatric-assessment (accessed 2 Sep 2021).





Supplemental Table 1. Chronic conditions and geriatric syndromes recorded.

Chronic conditions	Geriatric syndromes and risk factors
Charlson Index	
1. AIDS/HIV	Acute confusional syndrome/delirium
2. Any malignancy (excluding skin)	Chronic pain
3. Cerebrovascular disease	Cognitive/Intellectual impairment
4. Chronic obstructive pulmonary disease	Constipation
5. Congestive heart failure	Depression or Anxiety
6. Dementia	Dysphagia
7. Diabetes with complication	Frailty
8. Diabetes without complication	Immobility
9. Hemiplegia	Incontinence (Urinary/faecal)
10. Leukaemia	Instability/falls
11. Lymphoma	Malnutrition
12. Metastatic solid tumour	Polypharmacy
13. Mild liver disease	Pressure ulcers
14. Moderate or severe liver disease	Sensorial deficit
15. Moderate or severe renal disease	Sleep disorders/Insomnia
16. Myocardial infarction	
17. Peptic ulcer disease	
18. Peripheral vascular disease	
19. Rheumatologic disease	
Other conditions	
20. Amputation	
21. Anaemia	
22. Asthma	
23. Cardiac arrhythmia	
24. Cataract	
25. Chronic hepatitis (B or C)	
26. Chronic pancreatic disease	
27. Degenerative arthropathy	
28. Dermatitis or eczema	

29. Diverticular disease of the colon
30. Drug-related conditions
31. Dyslipidaemia (risk factor)
32. Fibromyalgia
33. Gallstones (previous hepatic colic)
34. Chronic gastritis or gastro-oesophageal reflux
35. Glaucoma
36. Gout
37. Haemorrhoids
38. Haematologic disorders (myelodysplastic syndrome, gammapathy, polycythaemia)
39. Hypertension (risk factor)
40. Inflammatory osteoarticular disease
41. Irritable bowel syndrome
42. Ischaemic heart disease without infarction
43. Migraine
44. Neurologic disorder of the central nervous system
45. Non-congestive heart failure
46. Non-ischaemic heart disease (miocardiopathy, valvulopathy)
47. Non-schizophrenic mental disorders (excluding depression and anxiety)
48. Obesity (risk factor)
49. Osteoporosis (risk factor)
50. Other neurological pathologies (essential tremor)
51. Other vascular diseases (ischaemia, aneurism)
52. Parkinsonôs disease
53. Peripheral neuropathy or neuritis
54. Post-traumatic stress disorder
55. Previous fractures (not hip)
56. Previous hip fracture

57. Prostatic benign hypertrophy
58. Schizophrenia
59. Sleep apnoea
60. Chronic thyroid disease
61. Tuberculosis
62. Urinary tract stones (nephritic colic)
63. Varicose veins of lower extremities
64. Vertigo

Supplemental Table 2. Prevalence rates of chronic conditions and geriatric syndromes / risk factors in the study population by sex, separately listed in decreasing order of total prevalence rate.

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
CHRONIC CONDITIONS									
Risk factors									
Hypertension	330	83.76	79.79 - 87.07	273	78.90	74.30 - 82.87	603	81.49	78.53 - 84.12
Dyslipidaemia	189	47.97	43.08 - 52.90	171	49.42	44.19 - 54.67	360	48.65	45.06 - 52.25
Obesity	127	32.23	27.81 - 37.00	66	19.08	15.28 - 23.55	193	26.08	23.05 - 29.36
Osteoporosis	82	20.81	17.09 - 25.09	21	6.07	4.00 - 9.10	103	13.92	11.61 - 16.60
Drug-related conditions	44	11.17	8.42 - 14.66	23	6.65	4.47 - 9.78	67	9.05	7.19 - 11.34
Chronic Diseases									
Heart failure	255	64.72	59.88 - 69.28	188	54.34	49.07 - 59.51	443	59.86	56.29 - 63.34
Cardiac arrhythmia	216	54.82	49.89 - 59.67	207	59.83	54.58 - 64.86	423	57.16	53.57 - 60.68
Degenerative arthropathy	228	57.87	52.94 - 62.64	157	45.38	40.21 - 50.64	385	52.03	48.43 - 55.61
Anaemia	182	46.19	41.33 - 51.13	152	43.93	38.80 - 49.20	334	45.14	41.58 - 48.74
Moderate or severe renal disease	164	41.62	36.86 - 46.55	156	45.09	39.93 - 50.35	320	43.24	39.72 - 46.84
Chronic obstructive pulmonary disease (COPD)	90	22.84	18.97 - 27.24	183	52.89	47.63 - 58.09	273	36.89	33.49 - 40.43
Non-ischaemic heart disease	125	31.73	27.33 - 36.48	113	32.66	27.93 - 37.77	238	32.16	28.90 - 35.61
Diabetes without complication	101	25.63	21.57 - 30.17	100	28.90	24.38 - 33.89	201	27.16	24.08 - 30.48
Cerebrovascular disease (including hemiplegia)	95	24.11	20.15 - 28.57	93	26.88	22.48 - 31.78	188	25.41	22.40 - 28.66
Dementia	103	26.14	22.05 - 30.70	76	21.97	17.92 - 26.62	179	24.19	21.24 - 27.40
Varicose veins of lower extremities	98	24.87	20.86 - 29.37	66	19.08	15.28 - 23.55	164	22.16	19.32 - 25.29
Previous fracture (not hip)	87	22.08	18.27 - 26.44	52	15.03	11.65 - 19.18	139	18.78	16.13 - 21.76
Gout	57	14.47	11.34 - 18.28	80	23.12	18.99 - 27.84	137	18.51	15.88 - 21.47
Chronic thyroid disease	93	23.60	19.68 - 28.04	42	12.14	9.11 - 16.00	135	18.24	15.63 - 21.19
Diabetes with complication	70	17.77	14.31 - 21.85	63	18.21	14.50 - 22.62	133	17.97	15.37 - 20.90
Ischaemic heart disease without infarction	58	14.72	11.56 - 18.56	62	17.92	14.24 - 22.31	120	16.22	13.74 - 19.05
Myocardial infarction	47	11.93	9.09 - 15.50	64	18.50	14.76 - 22.93	111	15.00	12.61 - 17.75
Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	29	7.36	5.17 - 10.37	82	23.70	19.52 - 28.45	111	15.00	12.61 - 17.75
Peripheral vascular disease	31	7.87	5.60 - 10.95	74	21.39	17.39 - 26.01	105	14.19	11.86 - 16.89
Chronic gastritis or gastro-oesophageal reflux	55	13.96	10.88 - 17.73	42	12.14	9.11 - 16.00	97	13.11	10.87 - 15.73

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
Asthma	74	18.78	15.23 - 22.93	8	2.31	1.18 - 4.50	82	11.08	9.02 - 13.55
Gallstones	39	9.90	7.33 - 13.25	40	11.56	8.61 - 15.36	79	10.68	8.65 - 13.11
Vertigo	54	13.71	10.66 - 17.45	23	6.65	4.47 - 9.78	77	10.41	8.41 - 12.81
Previous hip fracture	52	13.20	10.21 - 16.90	15	4.34	2.64 - 7.03	67	9.05	7.19 - 11.34
Sleep apnoea	34	8.63	6.24 - 11.82	32	9.25	6.63 - 12.76	66	8.92	7.07 - 11.19
Peripheral neuropathy or neuritis	27	6.85	4.75 - 9.79	34	9.83	7.12 - 13.42	61	8.24	6.47 - 10.45
Inflammatory osteoarticular disease	26	6.60	4.54 - 9.49	23	6.65	4.47 - 9.78	49	6.62	5.04 - 8.65
Peptic ulcer disease	11	2.79	1.57 - 4.93	35	10.12	7.36 - 13.74	46	6.22	4.69 - 8.19
Haematologic disorders	14	3.55	2.13 - 5.88	22	6.36	4.24 - 9.44	36	4.86	3.53 - 6.66
Parkinsonôs disease	15	3.81	2.32 - 6.19	19	5.49	3.54 - 8.42	34	4.59	3.31 - 6.35
Rheumatologic disease	22	5.58	3.72 - 8.31	10	2.89	1.58 - 5.24	32	4.32	3.08 - 6.04
Mild liver disease (including chronic hepatitis B or C)	12	3.05	1.75 - 5.25	20	5.78	3.77 - 8.76	32	4.32	3.08 - 6.04
Neurologic disorder of the CNS	11	2.79	1.57 - 4.93	21	6.07	4.00 - 9.10	32	4.32	3.08 - 6.04
Moderate or severe liver disease	9	2.28	1.21 - 4.28	10	2.89	1.58 - 5.24	19	2.57	1.65 - 3.98
Amputation	4	1.02	0.40 - 2.58	12	3.47	1.99 - 5.96	16	2.16	1.34 - 3.48
Urinary tract stones	9	2.28	1.21 - 4.28	5	1.45	0.62 - 3.34	14	1.89	1.13 - 3.15
Non-schizophrenic mental disorders	11	2.79	1.57 - 4.93	1	0.29	0.01 - 1.62	12	1.62	0.93 - 2.81
Irritable bowel syndrome	7	1.78	0.86 - 3.62	4	1.16	0.45 - 2.93	11	1.49	0.83 - 2.64
Chronic pancreatic disease	4	1.02	0.40 - 2.58	6	1.73	0.80 - 3.73	10	1.35	0.74 - 2.47
Tuberculosis	5	1.27	0.54 - 2.94	4	1.16	0.45 - 2.93	9	1.22	0.64 - 2.30
Other neurological pathologies	3	0.76	0.26 - 2.21	6	1.73	0.80 - 3.73	9	1.22	0.64 - 2.30
Fibromyalgia	6	1.52	0.70 - 3.28	2	0.58	0.16 - 2.08	8	1.08	0.55 - 2.12
Migraine	4	1.02	0.40 - 2.58	0	0.00	0.00 - 1.10	4	0.54	0.21 - 1.38
Schizophrenia	1	0.25	0.01 - 1.42	2	0.58	0.16 - 2.08	3	0.41	0.14 - 1.19
Post-traumatic stress disorder	1	0.25	0.01 - 1.42	2	0.58	0.16 - 2.08	3	0.41	0.14 - 1.19
AIDS/HIV	0	0.00	0.00 ï 0.00	0	0.00	0.00 ï 0.00	0	0.00	0.00 ï 0.00
GERIATRIC SYNDROMES AND RISK FACTORS									
Polypharmacy	310	78.68	74.37 - 82.44	281	81.21	76.76 - 84.98	591	79.86	76.82 - 82.60
Frailty	269	68.27	63.52 - 72.67	188	54.34	49.07 - 59.51	457	61.76	58.20 - 65.19
Incontinence (Urinary/faecal)	273	69.29	64.57 - 73.64	157	45.38	40.21 - 50.64	430	58.11	54.52 - 61.61
Chronic pain	231	58.63	53.71 - 63.39	171	49.42	44.19 - 54.67	402	54.32	50.72 - 57.88
Constipation	201	51.02	46.09 - 55.92	139	40.17	35.14 - 45.42	340	45.95	42.39 - 49.55

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
Sleep disorders/Insomnia	189	47.97	43.08 - 52.90	144	41.62	36.54 - 46.88	333	45.00	41.45 - 48.60
Sensorial deficit	169	42.89	38.10 - 47.83	145	41.91	36.83 - 47.17	314	42.43	38.92 - 46.02
Instability/falls	158	40.10	35.38 - 45.01	128	36.99	32.08 - 42.20	286	38.65	35.21 - 42.21
Depression or anxiety	193	48.98	44.08 - 53.91	75	21.68	17.66 - 26.32	268	36.22	32.83 - 39.74
Acute confusional syndrome / delirium	118	29.95	25.64 - 34.65	117	33.82	29.03 - 38.95	235	31.76	28.50 - 35.20
Cognitive/Intellectual impairment	133	33.76	29.26 - 38.56	96	27.75	23.29 - 32.69	229	30.95	27.72 - 34.37
Immobility	114	28.93	24.68 - 33.60	78	22.54	18.46 - 27.23	192	25.95	22.92 - 29.22
Dysphagia	78	19.80	16.16 - 24.01	81	23.41	19.26 - 28.15	159	21.49	18.68 - 24.59
Malnutrition	76	19.29	15.70 - 23.47	71	20.52	16.60 - 25.09	147	19.86	17.15 - 22.89
Pressure ulcers	57	14.47	11.34 - 18.28	38	10.98	8.11 - 14.72	95	12.84	10.62 - 15.44

Supplemental Table 3. Weight as an indicator of importance on clinical management assigned to each chronic condition. Weight values range from 0 to 8, where 0 means no clinical management was required and 1 to 8 indicate clinical management from main cause of hospitalization (1) to chronic condition requiring the least medical attention (8). Chronic conditions are displayed in alphabetical order.

Chronic conditions	Weight 0		Weight 1		Weight 2		Weight 3		Weight 4		Weight 5		Weight 6		Weight 7		Weight 8	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
AIDS/HIV	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Amputation	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Anaemia	596	80.54	28	3.78	46	6.22	40	5.41	19	2.57	8	1.08	3	0.41	0	0	0	0
Asthma	704	95.14	30	4.05	3	0.41	2	0.27	1	0.14	0	0	0	0	0	0	0	0
Rheumatologic disease	729	98.51	5	0.68	3	0.41	3	0.41	0	0	0	0	0	0	0	0	0	0
Cardiac arrhythmia	595	80.41	35	4.73	69	9.32	28	3.78	10	1.35	3	0.41	0	0	0	0	0	0
Cerebrovascular disease (including hemiplegia)	703	95	28	3.78	3	0.41	3	0.41	2	0.27	1	0.14	0	0	0	0	0	0
Chronic gastritis or gastro-oesophageal reflux	733	99.05	4	0.54	1	0.14	1	0.14	1	0.14	0	0	0	0	0	0	0	0
Chronic pancreatic disease	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Chronic obstructive pulmonary disease (COPD)	554	74.86	153	20.68	19	2.57	8	1.08	5	0.68	0	0	1	0.14	0	0	0	0
Chronic thyroid disease	722	97.57	2	0.27	1	0.14	4	0.54	7	0.95	3	0.41	1	0.14	0	0	0	0
Degenerative arthropathy	718	97.03	3	0.41	7	0.95	4	0.54	4	0.54	3	0.41	1	0.14	0	0	0	0
Dementia	687	92.84	32	4.32	14	1.89	4	0.54	3	0.41	0	0	0	0	0	0	0	0
Diabetes with complication	710	95.95	9	1.22	7	0.95	5	0.68	4	0.54	2	0.27	3	0.41	0	0	0	0
Diabetes without complication	698	94.32	11	1.49	5	0.68	13	1.76	8	1.08	2	0.27	1	0.14	2	0.27	0	0
Drug-related conditions	722	97.57	5	0.68	3	0.41	3	0.41	4	0.54	1	0.14	1	0.14	1	0.14	0	0
Dyslipidaemia	735	99.32	0	0	0	0	0	0	4	0.54	1	0.14	0	0	0	0	0	0
Fibromyalgia	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Gallstones	730	98.65	6	0.81	3	0.41	1	0.14	0	0	0	0	0	0	0	0	0	0
Gout	737	99.59	0	0	0	0	2	0.27	0	0	1	0.14	0	0	0	0	0	0
Haematologic disorders	730	98.65	2	0.27	5	0.68	2	0.27	1	0.14	0	0	0	0	0	0	0	0
Heart failure	410	55.41	227	30.68	85	11.49	13	1.76	4	0.54	0	0	1	0.14	0	0	0	0
Hypertension	698	94.32	10	1.35	14	1.89	12	1.62	4	0.54	2	0.27	0	0	0	0	0	0
Inflammatory osteoarticular disease	727	98.24	8	1.08	1	0.14	1	0.14	1	0.14	1	0.14	1	0.14	0	0	0	0
Irritable bowel syndrome	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ischaemic heart disease without infarction	714	96.49	10	1.35	14	1.89	1	0.14	0	0	1	0.14	0	0	0	0	0	0

Migraine	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mild liver disease (including chronic hepatitis B or C)	733	99.05	5	0.68	0	0	1	0.14	0	0	0	0	0	0	0	0	1	0.14
Moderate or severe liver disease	724	97.84	12	1.62	2	0.27	1	0.14	0	0	1	0.14	0	0	0	0	0	0
Moderate or severe renal disease	552	74.59	39	5.27	77	10.41	44	5.95	23	3.11	4	0.54	1	0.14	0	0	0	0
Myocardial infarction	716	96.76	20	2.7	3	0.41	1	0.14	0	0	0	0	0	0	0	0	0	0
Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	724	97.84	5	0.68	7	0.95	1	0.14	1	0.14	2	0.27	0	0	0	0	0	0
Neurologic disorder of the CNS	736	99.46	2	0.27	2	0.27	0	0	0	0	0	0	0	0	0	0	0	0
Non-ischaemic heart disease	695	93.92	15	2.03	16	2.16	12	1.62	0	0	2	0.27	0	0	0	0	0	0
Non-schizophrenic mental disorders	732	98.92	2	0.27	2	0.27	1	0.14	2	0.27	1	0.14	0	0	0	0	0	0
Obesity	737	99.59	0	0	1	0.14	2	0.27	0	0	0	0	0	0	0	0	0	0
Osteoporosis	730	98.65	2	0.27	3	0.41	2	0.27	2	0.27	0	0	1	0.14	0	0	0	0
Other neurological pathologies	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Parkinson's disease	737	99.59	3	0.41	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Peptic ulcer disease	737	99.59	2	0.27	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Peripheral neuropathy or neuritis	737	99.59	1	0.14	1	0.14	1	0.14	0	0	0	0	0	0	0	0	0	0
Peripheral vascular disease	728	98.38	9	1.22	1	0.14	1	0.14	0	0	0	0	1	0.14	0	0	0	0
Post-traumatic stress disorder	739	99.86	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Previous fracture (not hip)	730	98.65	5	0.68	2	0.27	2	0.27	1	0.14	0	0	0	0	0	0	0	0
Previous hip fracture	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Schizophrenia	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sleep apnoea	716	96.76	5	0.68	9	1.22	5	0.68	1	0.14	4	0.54	0	0	0	0	0	0
Tuberculosis	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urinary tract stones	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Varicose veins of lower extremities	725	97.97	1	0.14	6	0.81	2	0.27	4	0.54	2	0.27	0	0	0	0	0	0
Vertigo	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Supplemental table 4. Prevalence, Observed/Expected (O/E) ratios and exclusivity of chronic conditions and geriatric syndromes / risk factors per multimorbidity cluster. Conditions with prevalence >2% were included. O/E ratios were calculated by dividing the prevalence of a disease within the cluster by its prevalence in the overall population. Exclusivity was calculated by dividing the number of patients with the disease in the cluster by the total number of participants with the disease. Conditions are ordered by decreasing O/E ratio of cluster 1.

	Cluster 1			Cluster 2			Cluster 3			Cluster 4		
	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)
Vertigo	29.58	2.84	50.67	9.52	0.91	18.92	6.85	0.66	15.90	4.05	0.39	14.52
Sleep apnoea	22.11	2.48	44.19	5.82	0.65	13.50	8.12	0.91	21.99	4.85	0.54	20.33
Osteoporosis	33.39	2.40	42.76	9.95	0.71	14.79	9.44	0.68	16.38	9.72	0.70	26.07
Previous fracture (not hip)	39.67	2.11	37.65	17.87	0.95	19.68	15.16	0.81	19.49	11.66	0.62	23.19
Inflammatory osteoarticular disease	13.61	2.06	36.65	2.78	0.42	8.69	7.21	1.09	26.31	5.03	0.76	28.36
Asthma	22.50	2.03	36.19	9.37	0.85	17.49	7.77	0.70	16.94	8.72	0.79	29.37
Varicose veins of lower extremities	44.58	2.01	35.86	15.2	0.69	14.19	24.37	1.10	26.56	13.89	0.63	23.40
Amputation	4.190	1.94	34.56	1.72	0.8	16.45	2.00	0.92	22.30	1.55	0.71	26.69
Peripheral neuropathy or neuritis	15.37	1.86	33.23	6.00	0.73	15.06	9.03	1.10	26.46	5.58	0.68	25.26
Drug-related conditions	16.31	1.80	32.12	11.23	1.24	25.66	7.41	0.82	19.76	5.45	0.60	22.46
Chronic thyroid disease	32.14	1.76	31.40	13.73	0.75	15.57	16.06	0.88	21.26	15.52	0.85	31.77
Ischaemic heart disease without infarction	27.75	1.71	30.5	10.85	0.67	13.84	17.59	1.08	26.20	12.79	0.79	29.46
Obesity	44.29	1.70	30.27	19.14	0.73	15.18	25.15	0.96	23.28	21.84	0.84	31.27
Chronic pain	91.68	1.69	30.09	50.3	0.93	19.15	59.72	1.10	26.55	35.23	0.65	24.22
Instability/falls	65.05	1.68	30.00	36.74	0.95	19.66	40.06	1.04	25.03	26.19	0.68	25.30
Depression or Anxiety	60.05	1.66	29.56	35.49	0.98	20.27	30.57	0.84	20.38	28.89	0.80	29.79
Neurologic disorder of the CNS	7.10	1.64	29.28	4.92	1.14	23.54	4.78	1.11	26.72	2.37	0.55	20.47
Previous hip fracture	14.76	1.63	29.06	9.23	1.02	21.08	6.20	0.69	16.55	8.08	0.89	33.31
Degenerative arthropathy	80.19	1.54	27.48	48.11	0.92	19.13	56.15	1.08	26.06	38.08	0.73	27.34
Chronic gastritis or gastro-oesophageal reflux	19.39	1.48	26.37	9.09	0.69	14.35	12.6	0.96	23.22	12.66	0.97	36.07
Parkinson's disease	6.72	1.46	26.07	5.73	1.25	25.78	4.77	1.04	25.08	2.84	0.62	23.06
Sleep disorders/Insomnia	64.93	1.44	25.72	51.57	1.15	23.70	42.58	0.95	22.85	33.41	0.74	27.73
Moderate or severe renal disease	59.30	1.37	24.44	29.11	0.67	13.92	51.19	1.18	28.59	38.27	0.88	33.05
Non-ischaemic heart disease	43.07	1.34	23.87	23.15	0.72	14.89	36.01	1.12	27.04	29.46	0.92	34.20

Myocardial infarction	19.88	1.33	23.63	10.00	0.67	13.79	14.68	0.98	23.64	15.64	1.04	38.94
Dyslipidaemia	64.28	1.32	23.55	35.21	0.72	14.97	55.63	1.14	27.62	44.11	0.91	33.86
Frailty	81.11	1.31	23.41	82.71	1.34	27.70	55.05	0.89	21.53	45.26	0.73	27.36
Anaemia	59.26	1.31	23.40	42.23	0.94	19.35	47.71	1.06	25.53	38.34	0.85	31.72
Gallstones	13.87	1.30	23.16	10.6	0.99	20.54	9.66	0.90	21.85	9.85	0.92	34.46
Haematologic disorders	6.24	1.28	22.88	2.80	0.58	11.91	6.24	1.28	30.99	4.46	0.92	34.22
Constipation	57.53	1.25	22.32	58.53	1.27	26.35	36.80	0.80	19.34	39.36	0.86	31.99
Incontinence (Urinary/faecal)	72.26	1.24	22.17	82.95	1.43	29.52	54.73	0.94	22.75	39.78	0.68	25.56
Gout	22.86	1.23	22.01	9.85	0.53	11.01	27.66	1.49	36.08	15.32	0.83	30.90
Diabetes with complication	21.71	1.21	21.53	14.68	0.82	16.89	19.79	1.10	26.59	16.84	0.94	34.99
Polypharmacy	96.12	1.20	21.45	64.75	0.81	16.77	92.87	1.16	28.08	72.07	0.90	33.70
Rheumatologic disease	5.08	1.17	20.93	4.16	0.96	19.91	3.34	0.77	18.66	4.69	1.08	40.50
Dysphagia	24.83	1.16	20.60	36.49	1.70	35.13	29.98	1.40	33.70	6.09	0.28	10.58
Cerebrovascular disease (including hemiplegia)	29.02	1.14	20.36	30.75	1.21	25.04	28.38	1.12	26.98	18.79	0.74	27.62
Acute confusional syndrome/delirium	36.00	1.13	20.21	54.77	1.72	35.67	35.27	1.11	26.82	14.71	0.46	17.30
Heart failure	66.53	1.11	19.81	57.88	0.97	20.00	54.09	0.90	21.82	61.52	1.03	38.37
Peripheral vascular disease	15.71	1.11	19.74	10.69	0.75	15.58	14.98	1.06	25.50	14.89	1.05	39.17
Hypertension	89.07	1.09	19.48	78.13	0.96	19.83	84.73	1.04	25.11	77.62	0.95	35.57
Cardiac arrhythmia	61.85	1.08	19.29	52.03	0.91	18.82	56.49	0.99	23.87	58.20	1.02	38.02
Peptic ulcer disease	6.70	1.08	19.22	5.00	0.80	16.64	6.97	1.12	27.09	6.17	0.99	37.05
Sensorial deficit	39.51	0.93	16.60	44.27	1.04	21.58	43.84	1.03	24.95	41.89	0.99	36.87
Immobility	23.10	0.89	15.87	56.49	2.18	45.03	26.23	1.01	24.41	10.21	0.39	14.69
Moderate or severe liver disease	2.23	0.87	15.46	4.33	1.69	34.91	0.69	0.27	6.51	2.96	1.15	43.11
Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	12.74	0.85	15.15	13.39	0.89	18.46	16.19	1.08	26.07	16.20	1.08	40.32
Chronic obstructive pulmonary disease (COPD)	29.97	0.81	14.48	27.29	0.74	15.30	34.75	0.94	22.75	46.90	1.27	47.47
Mild liver disease (including chronic hepatitis B or C)	3.41	0.79	14.04	4.69	1.08	22.41	4.81	1.11	26.84	4.25	0.98	36.70
Cognitive/Intellectual impairment	23.44	0.76	13.50	62.07	2.01	41.48	39.53	1.28	30.85	11.74	0.38	14.17
Diabetes without complication	20.64	0.76	13.54	30.98	1.14	23.59	29.45	1.08	26.18	26.69	0.98	36.69
Pressure ulcers	7.44	0.58	10.33	28.11	2.19	45.28	16.20	1.26	30.48	4.78	0.37	13.90
Dementia	12.34	0.51	9.10	47.13	1.95	40.30	30.43	1.26	30.38	13.10	0.54	20.23
Malnutrition	8.69	0.44	7.80	42.75	2.15	44.50	13.57	0.68	16.50	16.60	0.84	31.20

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.