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Multimorbidity patterns: identification and association with clinically relevant outcomes and indicators

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PHD THESIS

Multimorbidity patterns: identification and association with clinically relevant outcomes and indicators

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Resum

Antecedents

La multimorbiditat, definida com la coexistència de dues o més condicions cròniques, és un repte creixent per als sistemes de salut, principalment a causa de l'augment de la seva prevalença, la manca d'estratègies de maneig clínic basades en l'evidència i el seu elevat cost. Hi ha evidència que en pacients amb multimorbiditat, certes condicions cròniques s'agrupen, formant patrons de multimorbiditat. Entendre aquests patrons podria millorar la pràctica clínica influint en decisions sobre atenció personalitzada, estratègies de prevenció i assignació de recursos, optimitzant l'atenció als pacients amb multimorbiditat i abordant les limitacions actuals dels sistemes de salut.

Objectius

L'objectiu d'aquesta tesi és identificar patrons de multimorbiditat i determinar la seva relació amb diferents resultats i indicadors clínicament rellevants. Els objectius específics son: 1) avaluar la relació entre patrons de multimorbiditat i indicadors de qualitat de la medicació en pacients d'edat avançada, 2) identificar patrons de multimorbiditat en pacients adults amb COVID-19 i avaluar-ne la relació amb la gravetat de la infecció i la mortalitat, 3) analitzar les trajectòries longitudinals dels patrons de multimorbiditat en pacients d'edat avançada.

Mètodes

S'han realitzat tres estudis per complir aquests objectius. En el primer estudi, es va examinar la relació entre patrons de multimorbiditat i indicadors de qualitat de la medicació: prescripció potencialment inadequada (PPI) i reaccions adverses a la medicació (RAM). Amb aquest propòsit, es va dur a terme un estudi de cohort prospectiu i multicèntric en 740 pacients $\geq$65 anys hospitalitzats per exacerbació de malalties cròniques. En el segon estudi, es van identificar patrons de multimorbiditat estratificats per edat i sexe en una cohort de dades del mon real de 14286 pacients amb COVID-19 $>$20 anys, avaluant la seva associació amb la gravetat de la infecció i la mortalitat. En el tercer estudi, es va realitzar una anàlisi retrospectiva de 3988 pacients $\geq$65 anys de l'estudi anterior per identificar-ne les trajectòries longitudinals dels patrons de multimorbiditat al llarg de 10 anys (3 punts temporals: temps basal, 5 anys abans, 10 anys abans). En cada estudi es van identificar patrons de multimorbiditat utilitzant l'algoritme d'anàlisi de clústers *fuzzy c-means* i es van realitzar diferents anàlisis estadístiques.

Resultats

En el primer estudi, alguns patrons específics de multimorbiditat, anomenats 'osteoarticular' i 'malalties cròniques menors', van mostrar una major freqüència de PPI i RAMs, particularment relacionats amb benzodiazepines, inhibidors de l'enzim conversiu de l'angiotensina (IECA) i neurolèptics. En el segon estudi, certs patrons de multimorbiditat es van associar amb una major gravetat i mortalitat per COVID-19 en grups específics d'edat i sexe, especialment en edats més joves. En el tercer estudi es van identificar diferents distribucions i trajectòries de patrons de multimorbiditat, amb tres patrons ('malalties metabòliques i vasculars', 'musculoesquelètic i síndrome del dolor crònic', i 'inespecífic') presents en tots els punts temporals. Es van observar trajectòries diverses en la transició de 10 anys abans a 5 anys abans, mentre que es van identificar trajectòries i patrons estables en la transició de 5 anys abans al temps basal.

Conclusions

Els patrons de multimorbiditat identificats mitjançant l'algoritme *fuzzy c-means* s'han associat a diversos indicadors i resultats clínicament rellevants. En pacients d'edat avançada hospitalitzats a causa de l'exacerbació de condicions cròniques, els patrons de multimorbiditat s'han relacionat amb indicadors de qualitat de la medicació, com PPI i RAMs, suggerint la realització de revisions de la medicació específiques. També s'han associat alguns patrons de multimorbiditat a una major gravetat i mortalitat per COVID-19. Finalment, l'estudi de les trajectòries longitudinals de la multimorbiditat ha destacat la naturalesa dinàmica de les condicions cròniques en adults d'edat avançada.

Resumen

Antecedentes

La multimorbilidad, definida como la coexistencia de dos o más condiciones crónicas, es un desafío creciente para los sistemas de salud, principalmente debido al aumento de su prevalencia, la falta de estrategias de manejo clínico basadas en la evidencia y su elevado coste. Hay evidencia que en pacientes con multimorbilidad, ciertas condiciones crónicas se agrupan, formando patrones de multimorbilidad. Entender estos patrones podría mejorar la práctica clínica al influir en decisiones sobre atención personalizada, estrategias de prevención y asignación de recursos, optimizando la atención de los pacientes multimórbidos y abordando las limitaciones actuales de los sistemas de salud.

Objetivos

El objetivo de esta tesis es identificar patrones de multimorbilidad y determinar su relación con distintos resultados e indicadores clínicamente relevantes. Los objetivos específicos son: 1) evaluar la relación entre patrones de multimorbilidad e indicadores de calidad de la medicación en pacientes de edad avanzada, 2) identificar patrones de multimorbilidad en pacientes adultos con COVID-19 y evaluar su relación con la gravedad de la infección y la mortalidad, 3) analizar las trayectorias longitudinales de los patrones de multimorbilidad en pacientes de edad avanzada.

Métodos

Se realizaron tres estudios para cumplir con estos objetivos. En el primer estudio se examinó la relación entre patrones de multimorbilidad e indicadores de calidad de la medicación: prescripción potencialmente inapropiada (PPI) y reacciones adversas a medicamentos (RAM). Para ello, se llevó a cabo un estudio de cohorte prospectivo y multicéntrico en 740 pacientes $\geq$65 años hospitalizados por exacerbación de enfermedades crónicas. En el segundo estudio se identificaron patrones de multimorbilidad en una cohorte de datos del mundo real de 14286 pacientes con COVID-19 $>$20 años, evaluando su asociación con la gravedad de la infección y la mortalidad. En el tercer estudio se realizó un análisis retrospectivo de 3988 pacientes $\geq$65 años del estudio anterior, centrado en identificar las trayectorias longitudinales de los patrones de multimorbilidad lo largo de 10 años (3 puntos temporales: tiempo basal, 5 años antes, 10 años

antes). En cada estudio se identificaron patrones de multimorbilidad utilizando el algoritmo de análisis de clústeres *fuzzy c-means* y se realizaron distintos análisis estadísticos.

Resultados

En el primer estudio, algunos patrones de multimorbilidad específicos, denominados 'osteoarticular' y 'enfermedades crónicas menores', mostraron mayores frecuencias de PPI y RAMs, particularmente relacionados con benzodiazepinas, inhibidores de la enzima convertidora de angiotensina (IECA) y neurolépticos. En el segundo estudio, ciertos patrones de multimorbilidad se asociaron con mayor gravedad y mortalidad por COVID-19 en grupos específicos de edad y sexo, especialmente en edades más jóvenes. En el tercer estudio se identificaron distintas distribuciones y trayectorias de patrones de multimorbilidad, con tres patrones ('enfermedades metabólicas y vasculares', 'musculoesquelético y síndrome del dolor crónico', e 'inespecífico') presentes en todos los puntos temporales. Se observaron trayectorias diversas desde 10 años antes hasta 5 años antes, mientras que se identificaron trayectorias y clústeres estables desde 5 años antes hasta el tiempo basal.

Conclusiones

Los patrones de multimorbilidad identificados mediante el algoritmo *fuzzy c-means* se han asociado a distintos resultados e indicadores clínicamente relevantes. En pacientes de edad avanzada hospitalizados debido a la exacerbación de condiciones crónicas, los patrones de multimorbilidad se han relacionado con indicadores de calidad de la medicación, como PPI y RAMs, lo que sugiere realizar revisiones de la medicación específicas. Asimismo, ciertos patrones de multimorbilidad en pacientes con COVID-19 se han asociado con una mayor gravedad y mortalidad. Finalmente, el estudio de las trayectorias longitudinales de la multimorbilidad ha destacado la naturaleza dinámica de las condiciones crónicas en adultos de edad avanzada.

Abstract

Background

Multimorbidity, defined as the coexistence of two or more chronic conditions, is a growing challenge for healthcare systems mainly due to its rising prevalence, the lack of evidence-based clinical management strategies and its high cost. There is evidence that chronic conditions cluster together forming multimorbidity patterns. Understanding these patterns could improve clinical practice by informing personalised care, prevention strategies and resource allocation, ultimately optimising care for multimorbid patients and addressing the current limitations of healthcare systems.

Objectives

This thesis aimed to identify multimorbidity patterns and determine their relationship with various clinically relevant outcomes and indicators. Three specific objectives were set: 1) to assess the relationship between multimorbidity patterns and quality indicators of medication in older patients, 2) to identify multimorbidity patterns in adult COVID-19 patients and evaluate their relationship with infection severity and mortality, 3) to analyse the longitudinal trajectories of multimorbidity patterns in older patients.

Methods

Three studies were carried out to meet these objectives. The first study was a multicentre, prospective cohort study examining the relationship between multimorbidity patterns and quality indicators of medication (i.e., potentially inappropriate prescribing (PIP) and adverse drug reactions (ADRs)) in 740 patients aged $\geq$65 years hospitalised for chronic disease exacerbation. The second study analysed multimorbidity patterns in a real-world data cohort of 14286 COVID-19 patients aged $>$20 years, assessing their association with infection severity and mortality. The third study was a retrospective analysis of 3988 patients from the previous study, focusing on identifying the longitudinal trajectories of multimorbidity patterns in patients aged $\geq$65 years over a 10-year period (3 time points: baseline, 5 years before, 10 years before). Multimorbidity cluster analysis using the fuzzy c-means algorithm and various statistical analyses were performed in each study.

Results

The first study found that specific multimorbidity clusters, named 'osteoarticular' and 'minor chronic disease', showed higher frequencies of PIP and ADRs, particularly involving benzodiazepines, angiotensin-converting enzyme (ACE) inhibitors, and neuroleptic drugs. The second study revealed that certain multimorbidity patterns were associated with higher COVID-19 severity and mortality in specific age and sex groups. The third study identified distinct multimorbidity cluster distributions and trajectories, with three clusters ('metabolic and vascular diseases', 'musculoskeletal and chronic pain syndrome', and 'unspecific') present across all time points. A variety of trajectories occurred from 10 years to 5 years prior, while stable trajectories and clusters were observed from 5 years to baseline.

Conclusions

Multimorbidity patterns identified through fuzzy c-means algorithm were associated to various clinically relevant outcomes and indicators. In older patients hospitalised due to chronic condition exacerbation, multimorbidity patterns were linked to quality indicators of medication, such as PIP and ADRs, suggesting tailored medication reviews. Additionally, certain multimorbidity patterns in COVID-19 patients were associated with increased severity and mortality. Finally, the study of longitudinal multimorbidity trajectories highlighted the dynamic nature of chronic conditions in older adults.

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1. Introduction

1.1. Definition of multimorbidity

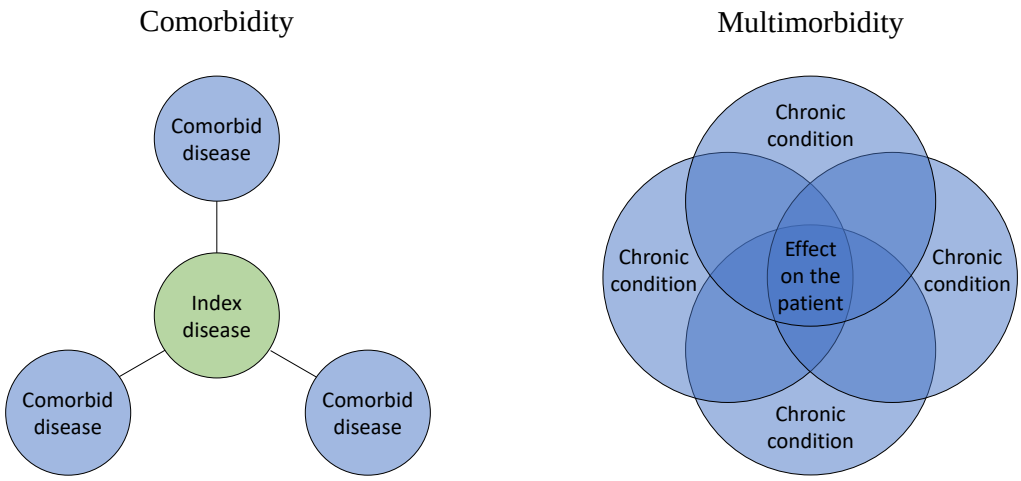
The concept of 'morbidity' refers to any departure from a state of physiological or psychological well-being due to any cause. It is often used interchangeably with the notion of disease; however, morbidity usually encompasses not only the biological dimension of non-health but rather a broader range of health-related states [1]. Regarding the concept of 'multimorbidity', the World Health Organization defines it as the coexistence of two or more chronic conditions in the same individual [2]. Nevertheless, the terminology in medical literature for describing the coexistence of multiple chronic conditions in any given patient has not been uniformly defined [3, 4, 5]. Thus, the research on multimorbidity is fragmented and challenging to interpret due to the lack of a standardised definition and variability in reporting [6, 7].

To address this issue, the Academy of Medical Sciences proposed a more concrete definition of multimorbidity, consistent with that adopted by the World Health Organization, that mostly approximates what has been used among researchers: "The co-existence of two or more chronic conditions, each one of which is either i) a physical non-communicable disease of long duration, such as a cardiovascular disease or cancer, ii) a mental health condition of long duration, such as a mood disorder or dementia or iii) an infectious disease of long duration, such as HIV or hepatitis C" [8].

1.2. Multimorbidity versus comorbidity

Multimorbidity should not be confused with comorbidity. The term 'comorbidity' was coined by Feinstein as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study" [9]. Due to the increasing confusion surrounding the use of these two terms, it was proposed to retain Feinstein's definition for comorbidity (implying an index disease) and define multimorbidity as "the co-existence of two or more chronic conditions, where one is not necessarily more central than the others", excluding acute conditions and emphasising the lack of an index disease [10, 11]. Figure 1 shows a conceptual diagram of comorbidity and multimorbidity.

FIGURE 1: Multimorbidity versus comorbidity



Adapted from Boyd et al. [11]

The conceptual difference between comorbidity and multimorbidity has important implications, as it influences how different parts of the healthcare system view and manage patients with multiple conditions. The concept of comorbidity is more common in biomedical research and clinical practice focused on specific conditions, with most treatments targeting individual diseases. This single-condition focus can be appropriate when a particular disease is the patient's primary concern. However, this disease-centric approach often reinforces the compartmentalised structure of many healthcare systems, resulting in fragmented care for patients with multiple chronic conditions [12, 13].

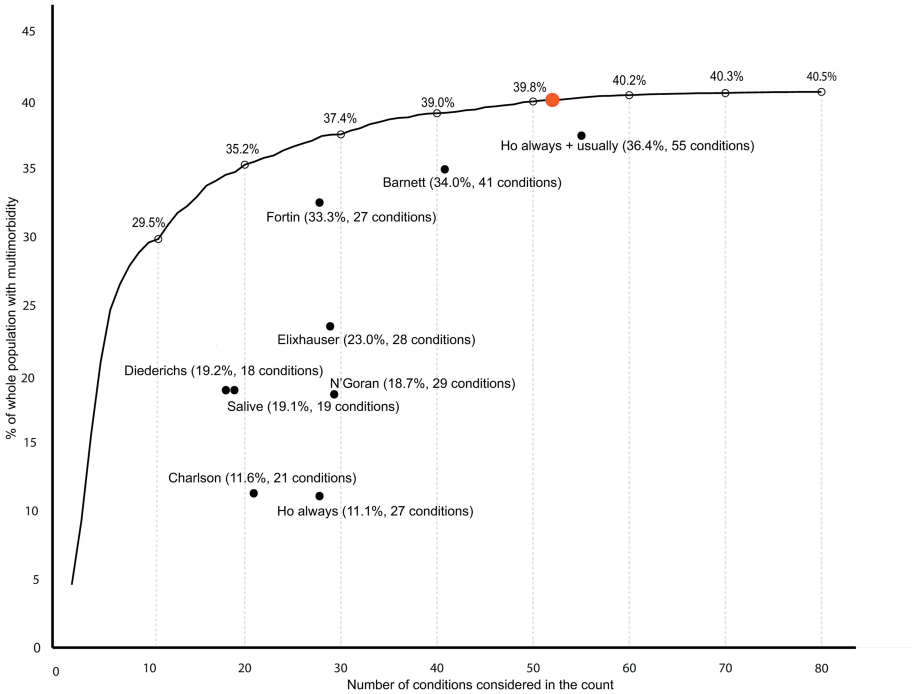
In contrast, multimorbidity emphasises a holistic, patient-centred approach that integrates and prioritises the patient's overall experience and needs. The concept of multimorbidity is highly heterogeneous, encompassing a wide array of patients with various combinations of conditions. Multimorbidity acknowledges that not only health-related factors have an influence on the impact of conditions but also socioeconomic, cultural and environmental factors, along with patient behaviour. This approach supports a more comprehensive and personalised care strategy for patients with multiple chronic conditions, facilitating integrated and cohesive care [12, 13].

1.3. Prevalence of multimorbidity

The estimation of multimorbidity prevalence depends on the definition used, and it becomes even more challenging due to varying levels of healthcare access and chronic condition diagnosis rates across populations. Therefore, the diverse definitions and classifications of multimorbidity result in highly fluctuating prevalence estimates. For instance, a systematic review reported prevalence estimates ranging from approximately 13% (in participants aged 18 or older) to 95% (in participants aged 65 or older) [14], consistent with another one reporting estimates ranging from 13% to 72% in the general population [15].

While some of the reported variations may reflect actual differences in multimorbidity prevalence between populations, it is difficult to separate these from variations caused by differing definitions. As expected, the inclusion of highly prevalent conditions increases the overall multimorbidity prevalence. Similarly, multimorbidity prevalence increases as more conditions are included in its definition, displaying a ceiling effect [16, 17, 18, 19] (Figure 2).

FIGURE 2: Ceiling effect in multimorbidity prevalence when adding additional conditions.



MacRae et al. [19]. Black line: multimorbidity prevalence calculated from 2 to 80 conditions, added from most to least prevalent. Empty black circles: multimorbidity prevalences when 10 to 80 conditions (in tens) were considered. Orange dot: ceiling effect (number of conditions at which RR was >0.99 of multimorbidity prevalence having the same value if 80 conditions were considered). Black dots: multimorbidity prevalence when considering conditions included in existing condition-lists. RR: relative risk.

Despite methodological limitations and gaps in longitudinal data, existing evidence suggests that an increase in multimorbidity prevalence has occurred in many countries over recent decades. While population ageing accounts for some of this increase, other significant factors are also at play. For example, societal-related influences such as changes in lifestyle and cultural behaviours (smoking, sedentarism, poor diet) or shifts in environmental exposures and urbanisation (air pollution, poor living conditions) also contribute to this increased prevalence of chronic conditions and multimorbidity [8, 20]. Furthermore, some advances in healthcare may also contribute to the increased prevalence of chronic conditions, such as higher survival rates following acute events or higher diagnosis rates of asymptomatic conditions [21, 22, 23, 24].

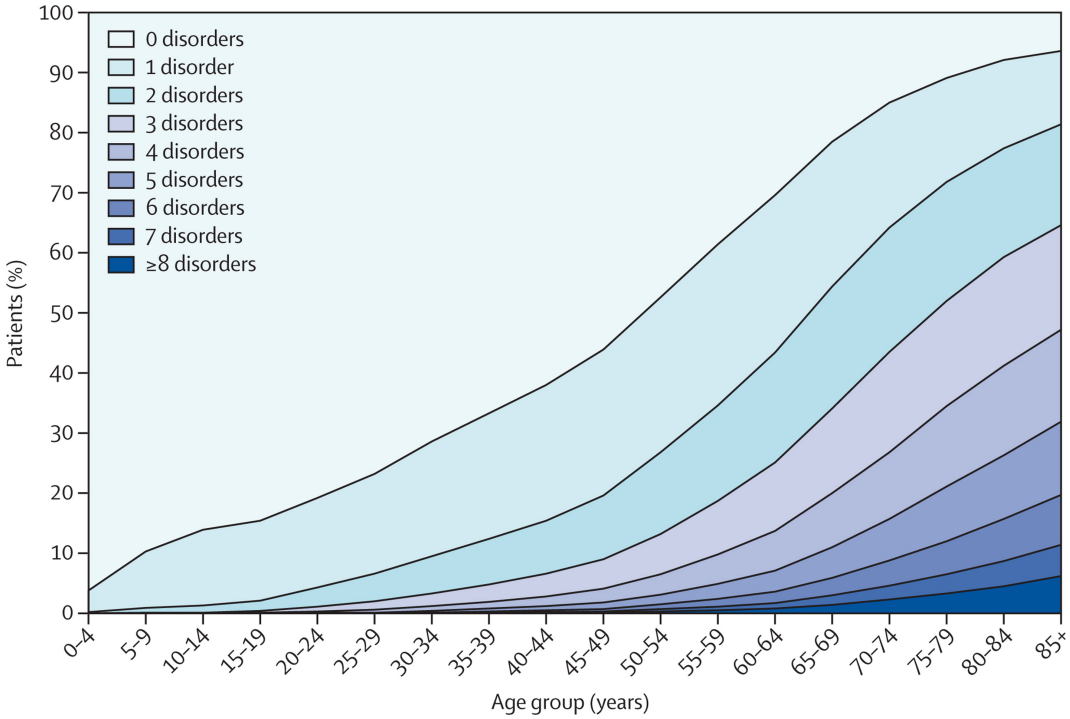
1.4. Determinants of multimorbidity

Increasing age has been associated with higher rates of multimorbidity, irrespective of the definition used, across various populations and countries [14, 25, 26, 27]. Furthermore, the number of morbidities has been found to substantially increase with age [26] (Figure 3). However, some evidence suggests that the rising prevalence of multimorbidity cannot be solely attributed to an ageing population, and multimorbidity is indeed not exclusive to older adults [24, 26]. In this sense, it has been described that onset of multimorbidity may occur 10 to 15 years earlier in socioeconomically deprived patients, highlighting the importance of social determinants of multimorbidity [26].

Lower socioeconomic status and lower education level have been associated with a higher prevalence of multimorbidity [28, 29, 30, 31, 32]. This association is suggested to be driven by environmental factors (such as poor living conditions or air pollution), health-related behaviours (such as higher smoking rates, sedentary behaviour or poor dietary habits), psychosocial issues (like elevated stress levels and inadequate sleep), as well as lower health literacy [8, 20]. However, even after accounting for known risk factors, there are still significant socioeconomic inequalities in the development of multimorbidity [23].

In addition, it is generally reported that multimorbidity is more prevalent in women [14]; however, it remains unclear whether biological sex itself has a direct influence on multimorbidity

FIGURE 3: Increasing number of chronic disorders and multimorbidity with age



Barnett et al. [26].

risk or rather sex acts as a proxy for social, behavioural and gender-specific factors that influence multimorbidity risk or detection [8]. For instance, women may suffer more poverty, and have also been described to be higher healthcare-seekers, leading to more diagnoses and therefore more frequent multimorbidity compared to men [8, 33].

The development of multimorbidity may also be influenced by medications and polypharmacy. For instance, several medications (for example, antipsychotics) are associated with increased cardiovascular risk [34, 35]. Therefore, patients prescribed treatment for a single condition might develop additional chronic conditions as a result of that treatment.

Overall, the development of multimorbidity is a complex process influenced by various factors, often interrelated. In this context, three broad areas have been proposed to classify the different underlying mechanisms of multimorbidity: i) biological mechanisms related to ageing and inflammation; ii) socioeconomic, psychosocial and behavioural social determinants; and iii) medication-related mechanisms [36].

1.5. Impact of multimorbidity

1.5.1. Impact of multimorbidity on patients

The presence of multimorbidity has been associated with functional decline, increased disability and higher mortality risk, even after adjusting for age [25, 37, 38]. Multimorbidity has also been associated with reduced well-being, as measured by self-rated health-related quality of life [39, 40], and an inverse correlation has been reported between quality of life and number of coexisting diseases [40].

Moreover, the coexistence of multiple chronic conditions in a patient, instead of having an additive effect, often leads to complex interactions. For instance, one disease may trigger, worsen or accelerate the progression of other conditions, as seen with diabetes exacerbating conditions like heart disease or renal failure [41]. These interactions complicate clinical management even when conditions are not physiopathologically related. For example, the combination of proprioceptive loss, visual impairment, and osteoporosis may increase the risk of falls and fractures. Similarly, a combination of conditions like hearing and vision loss, memory decline, and mobility issues can lead to social isolation and depression [20].

Furthermore, multimorbidity often brings a significant treatment burden on patients. This includes the need to make substantial behavioural changes, monitor and manage symptoms, organise travel and attendance to multiple appointments, adhere to complex treatment plans coordinating several drugs, face complex administrative processes or cope with uncoordinated social care and healthcare systems [42]. A high treatment burden can lead to emotional distress, physical side effects and strained interpersonal relationships. To cope with this burden, patients may engage in adaptive behaviours or become non-adherent to treatment, which can affect their physical health and relationships with caregivers [43].

Various factors influence the capacity of patients to self-manage and cope with this burden, such as the specific chronic conditions, health literacy, support network or economic situation [44]. Patient capacity can also change over time due to the accumulation of illnesses and/or changes in personal circumstances [44]. Also, the design of healthcare systems may play an essential role. The current design of most healthcare systems, conceived to address individual conditions instead of providing comprehensive, patient-centred care, can further increase the

treatment burden [42, 45, 46]. Treating one condition at a time may result in fragmented (or even contradictory) care, is inefficient and may be unsatisfactory for patients [47, 48]. Therefore, it has been deemed essential to develop patient-centred care approaches that continuously balance high treatment burden against disease management and future risks [36].

Multimorbidity can also lead to polypharmacy, which is usually defined as the routine use of five or more medications [49, 50]. Apart from the implications regarding the previously mentioned treatment burden, polypharmacy increases the probability of drug-drug or drug-disease interactions. This is even more important in older patients, in which physiological changes in drug pharmacokinetics and pharmacodynamics may occur [51, 52]. All in all, this situation poses a challenge for prescribing physicians and may result in a higher probability of adverse outcomes [52, 53, 54].

1.5.2. Impact of multimorbidity on healthcare systems and professionals

As previously stated, the design of most healthcare systems is focused on treating individual conditions instead of offering comprehensive, patient-centred care, often leading to inefficient, fragmented and potentially contradictory care for multimorbid patients [45, 46, 55]. Healthcare professionals may face significant obstacles in the management of multimorbidity due to limited time and resources or challenges in applying multiple clinical guidelines to a single patient, resulting in reduced quality of care [56, 57] and a sense of isolation in decision-making [58].

Multimorbidity is associated with a significant increase in healthcare utilisation, such as higher number of visits, hospitalizations and bed days [59, 60, 61]. Furthermore, patients with multimorbidity including coexisting mental health conditions or issues related to alcohol and substance use, are particularly prone to unplanned hospital admissions for physical conditions [62]. Overall, multimorbid patients contribute to a large portion of the healthcare workload.

Consequently, multimorbidity places a substantial economic burden on healthcare systems. Indeed, an almost exponential relationship has been reported in older adults between multimorbidity and healthcare costs, with a higher cost of care for multimorbid patients than what would be expected from the cost of managing their individual conditions alone [63, 64].

In Catalonia, the number of chronic conditions has been correlated to the mean annual expenditure per patient: 413€ in patients having a single chronic condition, 2413€ in those with five chronic conditions and 9626€ in those with ten chronic conditions. Furthermore, up to 51% of the healthcare budget is allocated to the 5% of the population with the highest morbidity burden [65]. Patients concentrating most healthcare expenditure have been described as the 'high need, high cost' population, and in order to improve outcomes and reduce spending on these patients, an understanding of their particular needs and characteristics is required [66].

Additionally, these significant challenges for healthcare systems are exacerbated by the unprecedented rate of population ageing, which is substantially transforming the demographic landscape. According to the World Health Organization, the proportion of individuals aged 60 years and older is projected to nearly double between 2015 and 2050, increasing from 12% to 22% [67]. This demographic shift will be especially pronounced in Europe, where the old-age dependency ratio (defined as the proportion of the population over 65 relative to the population aged 15–64) is projected to continue increasing [68]. Consequently, the expenditure on health care and long-term care is expected to increase in all EU countries [69]. This situation urges the need to rethink healthcare systems to address the complex needs of an ageing population.

1.6. Methodological approaches to multimorbidity

Addressing multimorbidity requires the development of reliable and consistent methods for its measurement. However, this task is particularly challenging given the variety of situations in which multimorbidity can arise. Adding to this challenge is the aforementioned confusion surrounding the term 'multimorbidity', which has led to significant variability in how this definition is operationalised by researchers. A key aspect is deciding which conditions to include, and different predefined lists are being used which can differ in length, name and type of conditions. According to a systematic review of 566 studies, the number of conditions used for the definition and measurement of multimorbidity ranged from 2 to 285 [6]. Remarkably, only eight conditions were included in more than half of the studies [6]. These findings highlight the methodological heterogeneity and resulting lack of comparability across multimorbidity studies.

Besides, the actual definition and diagnosis of such conditions may also differ between studies [6, 7]. Moreover, uncertainty remains about whether certain condition subgroups should be analysed individually or grouped within broader categories [6, 20]. In addition, the type of conditions to be included may need to be tailored to the subpopulation of interest. For instance, older patients frequently face clinically relevant situations that, while not classified as chronic conditions, complicate clinical management and have an impact on health-related quality of life, such as geriatric syndromes. Geriatric syndromes encompass a range of heterogeneous clinical conditions, such as falls, dizziness and incontinence, which have been identified among the most significant predictors of subsequent health outcomes [70] Although there are recommendations in acknowledging all long-term conditions for optimising care of patients for multimorbidity [55, 71, 72], few publications aimed at these patients take into account these syndromes [73].

On top of the lack of consensus on the operational definition, different data collection methods and data sources have been used in multimorbidity studies. The choice of data source should be guided by the study design and objectives but also by feasibility, especially regarding time and human resources, and data source availability [7]. For example, clinical assessments involving medical record reviews tend to yield the most complete data; nevertheless, this approach is resource intensive and may not be possible in larger studies. Conversely, large administrative databases may be easier to use but may also face data quality issues [7, 74, 75]. Table 1 summarises the main advantages and disadvantages of the five major data sources identified aiming at the measurement of multimorbidity [75].

Various analytical approaches can be used to measure multimorbidity. Firstly, it can be simply conceptualised as the count of concurrent diseases in the same individual. For instance, an increasing number of conditions has been associated with decreasing quality of life [40] or increasing expenditure [65]. However, this approach has several limitations, as it does not account for which conditions are present.

As a result, multimorbidity has also been studied with weighted disease counts, which aim to characterise the impact of different combinations of conditions. Examples include the Charlson Comorbidity Index [76], the Adjusted Clinical Groups (ACG) System [77], the Chronic Disease Score [78], the Cumulative Illness Rating Scale (CIRS) [79]. These approaches assign varying

TABLE 1: Multimorbidity data sources: main advantages and disadvantages

Data source	Advantages	Disadvantages
Clinical assessment: Healthcare professionals conduct clinical visits or review medical records to enter relevant variables in a specific database created for the research objectives.	Complete, reliable, up to date, patient-centred records Comprehensive, rare conditions can be included Detailed clinical information that would be unavailable in diagnoses codes	May be difficult to access and retrieve data Resource intensive
Administrative claims data: Extensive healthcare databases generated from provider billing records of patient interactions (office visits, diagnostic tests, hospital stays, diagnosis codes, prescription dispensing, etc.).	Large sample size, broad representation and generalisation Cost-effective, standardised, efficient De-identified, structured data Comprehensive, rare conditions are included Ability to support longitudinal studies Possible link to other data sources	Conditions not coded or not included on diagnostic lists are not captured Driven by access to and use of healthcare services Possible issues in coding accuracy Collected for non-research purposes Limited type of variables available
Public health survey data: Large-scale surveys that gather information from a sample of individuals to produce quantitative measures of health. These surveys predominantly depend on self-reported information.	Large sample size, broad representation and generalisation Cost-effective, standardised, efficient De-identified, structured data Regularly-fielded survey data allow for longitudinal studies Free access, publicly-available	May not capture undiagnosed conditions Weak clinical specificity (common names are often used instead of clinical terms) Possible bias in responses due to poor understanding of questions Rare conditions are often not considered
Patient-reported data: information gathered directly from patients via questionnaires or interviews regarding diagnosed chronic conditions, usually collected in clinical settings.	Quick access to information (without reviewing patient records or accessing large administrative databases) Reduced underreporting Potential recording errors may be avoided Compatible with promoting self-management, self-care and patient-centredness	Potential recall and social desirability biases Low-literacy and disparity populations may be less able to accurately report their health conditions Brief instruments only provide a general assessment that may lack clinical specificity Resource intensive
Electronic health records data: digital records of patients' health information, covering a broad spectrum of data related to medical history and clinical care.	Real-time, comprehensive, patient-centred records securely available to authorised users Large variety of data (medications, images, test results, etc.) May include data regarding function, symptoms, emotional well-being, or health behaviours	Busy providers may not capture information for all health conditions Missing or outdated data Technological capacity and support staff may be unavailable

Table created based on Johnston et al., Huntley et al., Suls et al. [7, 74, 75]

levels of importance to different conditions based on their severity, prognostic impact, or other relevant factors, acknowledging that not all conditions contribute equally to a patient's overall health burden. These weighted indices are designed to predict potential clinical outcomes and healthcare needs associated with specific disease combinations. These measures, however, may have generalisability problems, and no index has proven universally applicable across all studies [74, 80].

In this context, alternative approaches have emerged to account for the complexity found within multimorbid patients while enabling the identification of defined population subgroups, such as the identification of multimorbidity patterns, based on characterising the non-random association between conditions [8, 81]. Table 2 summarises the main advantages and disadvantages of the most commonly used multimorbidity measures.

1.7. Multimorbidity patterns

There is evidence showing that certain conditions cluster together, forming what are known as multimorbidity patterns. These patterns are identified based on the observation that certain pairs of conditions may co-occur more frequently than expected [14, 81]. Such non-random disease clustering can result from shared environmental exposures, one condition causing another, treatment side-effects, or common genetic mechanisms [20].

Understanding which conditions more often cluster together, which differential effects may have each cluster on health outcomes, and which population subgroups are mostly allocated to each cluster could provide valuable insights. This knowledge could help identify patients at higher risk of developing additional conditions, inform the design of targeted preventive and therapeutic strategies, and optimise resource allocation [8].

1.7.1. Methods to identify multimorbidity patterns

Several different methodologies have been used to identify and analyse multimorbidity patterns, and there is still a debate on the most appropriate one. A systematic review aiming to identify replicable and clinically meaningful multimorbidity patterns identified the most common analytical methods used, hereby summarised: exploratory factor analysis, latent class analysis, cluster analysis of diseases and cluster analysis of individuals [82].

TABLE 2: Multimorbidity measures: main advantages and disadvantages

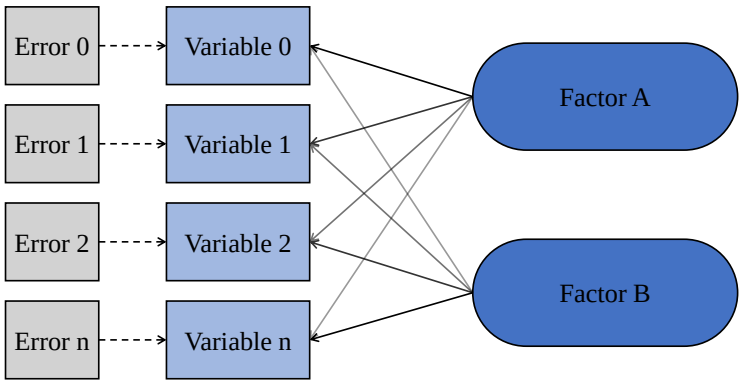
Multimorbidity measure	Advantages	Disadvantages
Count of conditions	Includes all present chronic conditions	Does not reflect which conditions are present
	Simple, easily and broadly ascertained with minimal resources required and reduced subjectivity	Variability between studies: depends on a predefined list
	Comprehensive, can cover a wide spectrum of chronic conditions (geriatric syndromes, risk factors)	May not properly address the complexity of multimorbidity (does not consider the interactions or severity of conditions)
	May be more appropriate in situations where multiple outcomes are examined	Limited clinical relevance
	May be an intuitive summary of multimorbidity burden	May have lower predictive power for adverse outcomes
Weighted measures	Specific, clinically relevant conditions are considered and weighted, accounting for their severity	May not include all present chronic conditions
	Easily interpretable (straightforward numerical value)	May have generalisability problems
	Can be used to evaluate an intervention or to predict an outcome	Effectiveness depends on the specific setting and outcome of interest
	Can provide clinically relevant risk stratification and/or help to allocate resources	No universally optimal index has been found applicable to all studies
	Some measures have been largely used and validated	Information on severity of conditions is required
		May require training and/or subjective judgement of healthcare professionals
Multimorbidity patterns	Comprehensive, can cover a wide spectrum of chronic conditions (geriatric syndromes, risk factors)	Data dependency: relies on large datasets that could be biased or miss information
	Can handle high-dimensional data	Variability between studies: depends on a predefined list
	Can capture complexity and account for the synergistic effects of certain combinations of conditions	Methodological complexity and variability
	May help identify population subgroups with similar needs	May have generalisability problems across populations or healthcare settings
	Conditions can be selected and/or weighted according to the purpose	May have limited predictive value
		May be difficult to standardise and to interpret

Table created based on Huntley et al., Suls et al., [74, 75]

Exploratory factor analysis

Exploratory factor analysis is a statistical method used to identify associations between variables and uncover patterns. The approach behind this analysis is to identify latent factors, operating under the assumption that variables (in this case, chronic conditions) associated with the same factor have a shared underlying mechanism that accounts for their association [83]. It operates by reducing the observed set of variables to a smaller number of latent factors (multimorbidity patterns) that account for the correlated variables [83] (Figure 4). Importantly, variables can be included in more than one factor, i.e. any chronic condition can be related with multiple patterns [82].

FIGURE 4: Exploratory factor analysis



Adapted from Tucker [83]. Variables are those observed or measured (i.e. chronic conditions), with their corresponding measurement errors. Factors are associated to variables through factor loadings (solid arrows) ranging from -1 to 1.

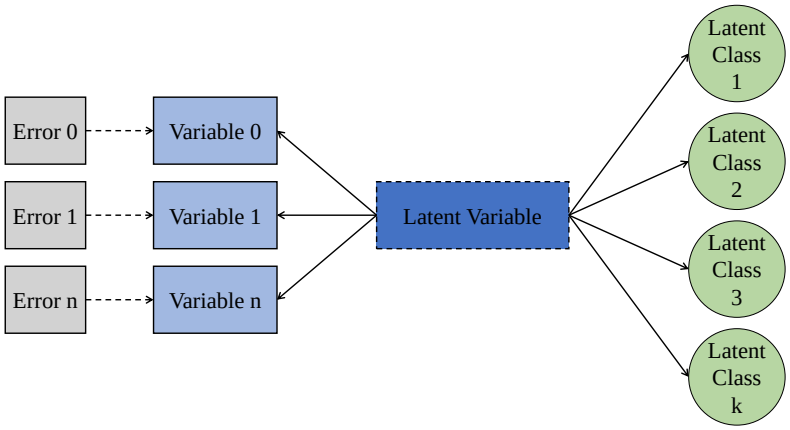
Exploratory factor analysis has been identified as the most frequently used statistical technique in studies identifying multimorbidity patterns in recent systematic reviews [82, 84]. However, a comparative analysis of methods for identifying multimorbidity patterns suggests that while exploratory factor analysis can be useful for describing comorbidity relationships, it may be less effective for in-depth study of multimorbidity patterns, compared to hierarchical cluster analysis [85].

Latent class analysis

Latent class analysis is a statistical technique that identifies clusters of individuals through a probabilistic model that estimates the likely distributions within the data based on the set of

features present in each individual. The assumption of this method is that, although any combination of a given set of features (e.g. chronic conditions) could theoretically occur, only a limited number of these combinations actually do, resulting in a specific set of clusters or latent classes. Within each latent class, individual features have distinct probabilities of occurrence, defining the characteristics of the class. Therefore, latent classes can be formed based on the probability of co-occurrence of various chronic conditions. In this approach, posterior probabilities of cluster membership are calculated for each individual, based on the estimated model parameters. This allows for the allocation of each individual to the most probable latent class [86, 87] (Figure 5). Similar to exploratory factor analysis, latent class analysis assumes that latent variables are the underlying cause of multimorbidity groupings [82].

FIGURE 5: Latent class analysis



Adapted from Aflaki et al. [87] In latent class analysis, the latent variable (dotted square) is postulated to exist but cannot be directly observed, so it is measured indirectly through several indicator variables (1 to n) that are subject to error. The latent variable is the basis for class membership in one of several latent classes (2 to k).

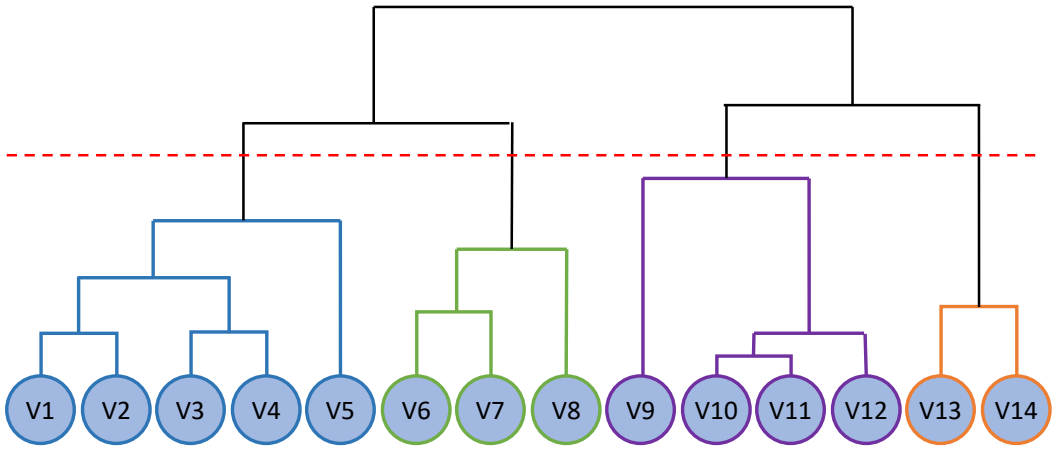
Cluster analysis of diseases

Cluster analysis aims to use a metric of distance between variables to define groups by maximising between-group distance and minimising within-group distance. In contrast to exploratory factor analysis or latent class analysis, it allows to identify homogeneous groups of observations without making assumptions about any casual relationships. Cluster analysis has therefore been deemed well-suited when multimorbidity patterns are expected to be defined as discrete categories that may not necessarily share a common underlying cause [82].

There are two main approaches in cluster analysis: hierarchical and nonhierarchical methods.

Most studies aiming to identify multimorbidity clusters of diseases have used hierarchical cluster analysis [14, 81, 82]. This algorithm constructs a progressively divided structure of clusters by iteratively joining or dividing clusters based on their distance. This result can be visually represented through a tree-like structure called dendrogram (Figure 6). Furthermore, this technique allows for the definition of a cut-off to choose the number of clusters. However, this technique may lack robustness in the identification of patterns in data due to some limitations: the algorithm is highly susceptible to data outliers, it does not allow overlap between clusters and it is computationally expensive [88].

FIGURE 6: Hierarchical cluster analysis



A dendrogram is a tree-like representation of hierarchical clustering that reveals how variables are combined into clusters, showing variables on one axis and their distances in the other. The height of each branching point corresponds to the distance at which any pair of clusters are joined. A cut-off (red dotted line) can be established to determine the final number of clusters.

Cluster analysis of individuals

Cluster analysis can also be used to define multimorbidity patterns by clustering individuals, allowing to identify groups of people with similar disease combinations. Orienting the analysis focusing on individuals rather than diseases could allow for an improved understanding of population subgroups and could inform the development and implementation of refined strategies aimed at patients with multimorbidity [88].

Most studies aiming to identify multimorbidity clusters of individuals have used nonhierarchical cluster analysis [82]. Unlike hierarchical clustering, nonhierarchical algorithms do not build a levelled structure but rather focus specifically on clusters. These algorithms assign individuals to clusters after specifying the number of clusters. In addition, they are more robust

in detecting patterns and can efficiently handle large data sets.

One of the most commonly used nonhierarchical cluster analysis methods is the k-means algorithm [89], which aims to group similar data points (e.g. individuals) together while maximizing the differences between the clusters. The algorithm is initialised by randomly placing k points (where k is the predefined number of clusters) into the data space. These k points will serve as the initial centroids (centre points) of the clusters. After that, two alternating steps are performed:

- Assignment step: each data point is assigned to the cluster with the nearest centroid, based on a chosen distance metric.
- Update step: after all data points are assigned to a cluster, the positions of the k centroids are recalculated so that the new centroid of each cluster is the mean of all data points assigned to that cluster, meaning that the centroid moves to the average position of the points within the cluster.

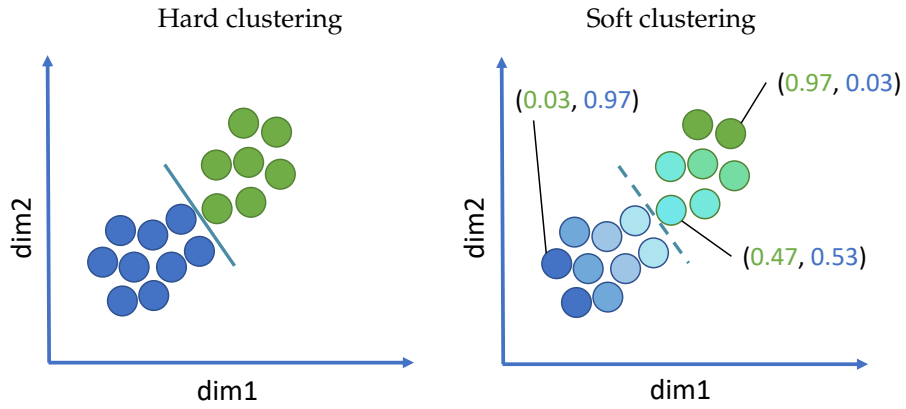
These two steps are undergone until the centroids no longer move (or the coefficients' change between two iterations is lower than the given sensitivity threshold), resulting in an algorithm that allocates individuals into homogenous groups while maximising differences between groups.

The k-means clustering method assigns each individual to a single, specific cluster, which is known as hard clustering. Conversely, soft clustering allows each individual to belong to multiple clusters defined by a membership probability. Therefore, it may allow for a better modelling of the overlap between variables (chronic conditions) and the possibility of individuals being located between clusters [90].

The most widely used soft clustering method is called fuzzy c-means algorithm [91], which is similar to k-means but includes a membership probability for each data point to each cluster. The algorithm starts by initializing a chosen number of c centroids and also assigning random membership values, ensuring the sum equals 1 for each data point. Then, iterative updates are performed: data points are reassigned to clusters based on the distance from the centroids, and the centroids are recalculated as the weighted averages of all the points in the cluster, using the membership probabilities as weights. In this step, the fuzziness parameter m sets the degree of

overlap between clusters, with higher values allowing for more overlap. The process continues until the centroids converge. Figure 7 visually represents the differences between hard and soft clustering.

FIGURE 7: Nonhierarchical clustering: hard versus soft clustering



Adapted from Kumar [92]. Hard clustering assigns each data point to a single cluster. Soft clustering assigns probabilities to data points for belonging to multiple clusters, thus allowing for overlap.

1.8. Commonly identified multimorbidity patterns

Although there is considerable variability, as previously described, both in disease identification and in pattern identification methods, clear patterns of multimorbidity have consistently emerged across multimorbidity studies. The most replicable multimorbidity patterns, in agreement across the literature, are those containing i) cardiovascular and metabolic conditions, ii) mental health conditions and iii) musculoskeletal disorders [81, 82, 93].

The first systematic review on patterns of associative multimorbidity identified these three partially replicable patterns [81]. Afterwards, a quantitative synthesis study of multimorbidity profiling studies consistently identified the cardio-metabolic and mental health groups across four distinct statistical methods [82]. Also, three patterns were partially replicable, as they emerged in some but not all statistical approaches: COPD and asthma, falls and fractures with sensory deficits, Parkinson's disease with cognitive decline [82]. Furthermore, a recent systematic review including studies using primary care electronic health records identified cardiovascular and mental health patterns in all studies, either as standalone or in combination with other conditions [93]. In addition, three more patterns repeatedly emerged in most studies: musculoskeletal, respiratory and gastrointestinal [93].

All in all, it has been deemed unlikely that these results are artefactual. Therefore, further research is needed to develop a better understanding of these existing multimorbidity patterns, their underlying mechanisms and their implications for clinical care and public health.

1.9. Justification

1.9.1. Justification of the research topic

Multimorbidity is turning into an important challenge for healthcare systems due to its increasing prevalence and the lack of evidence on its clinical management. In patients with several chronic conditions, extensive knowledge is often required in therapeutic decisions to achieve an adequate balance between risks and benefits [8, 27]. Despite the growing recognition of multimorbidity as a critical issue, most clinical practice guidelines are based on a single disease paradigm, with few recommendations for patients with multimorbidity, which are typically excluded from clinical trials [56, 94, 95]. This traditional, single-disease framework is then transferred to specialised care settings, most of which are focused on single conditions despite having high rates of patients with multimorbidity [46, 55].

Multimorbidity research is urgently needed and is rapidly evolving from studying a limited number of comorbidities to identifying comprehensive multimorbidity patterns. Multiple studies have identified multimorbidity patterns across different populations and settings, and many replicable multimorbidity patterns have been established [82]. Initially, these studies primarily aimed to describe multimorbidity patterns; however, the need for validation has become increasingly evident. Without validation, the methodological approaches used in multimorbidity profiling could yield artificial clusters resulting from random clustering or overfitting, leading to groupings that are not found in the population of origin. The aim for clustering is to capture underlying patterns that are robust and generalizable. Therefore, validating multimorbidity patterns should be a necessary step before using them to guide clinical practice or further research.

In recent years, there has been a notable rise in multimorbidity studies conducting some form of validation [96]. However, the lack of a "known ground truth" poses a major challenge in validating these clusters. The most common validation approach identified consists in assessing the association of multimorbidity patterns with clinical outcomes [96]. Certain multimorbidity

patterns have been associated with clinical outcomes such as mortality, hospitalisation, disability and quality of life, among others [97, 98, 99, 100, 101, 102]. Therefore, the ability to categorise patients based on a more comprehensive view of their morbidity could be useful in guiding the development of improved care pathways, prevention strategies or resource allocation.

Overall, conducting research on multimorbidity patterns may help address the limitations of current healthcare services and facilitate the transition toward innovative strategies that better serve patients with multiple chronic conditions.

1.9.2. Justification of the research studies comprising the thesis

This PhD thesis is composed of three studies on the identification of multimorbidity patterns and their association with different clinically relevant outcomes.

Study 1: Multimorbidity patterns and quality indicators of medication

Multimorbidity is associated with polypharmacy; however, the relationship between multimorbidity patterns and quality indicators of medication, such as potentially inappropriate prescribing (PIP) and adverse drug reactions (ADRs), remains unexplored in the literature.

PIP encompasses a variety of situations in which prescribing should be revised, particularly in geriatric patients. For example, prescribing medications where the potential benefits do not outweigh the harms, prescribing a duplicate drug, an inappropriate dose or duration; or omitting potentially beneficial medications. PIP includes potentially inappropriate medication (PIM), a well-known risk factor for ADRs [103, 104], as well as potential prescribing omissions (PPO) [105, 106]. Identifying associations between specific multimorbidity patterns and certain PIP and/or ADRs could be very useful for targeting interventions aimed at detecting and preventing such negative outcomes.

Study 2: Multimorbidity patterns and COVID-19 outcomes

The COVID-19 pandemic caused a great burden in healthcare systems, overwhelming care facilities and jeopardising patient care. In this situation, identifying subpopulations at the highest risk became a priority, and the first studies quickly identified a differential vulnerability depending on age and sex [107, 108]. Moreover, studies on the relationship between isolated chronic conditions and COVID-19 infection severity and mortality identified various

chronic conditions as potential risk factors, such as diabetes, obesity, heart failure, hypertension, chronic obstructive pulmonary disease or chronic kidney disease [109, 110].

Noticeably, many of these conditions share some pathophysiological pathways, suggesting that their interactions could increase the risk of poor COVID-19 prognosis, and that their identification would help in the management of the disease. Nevertheless, few research works have examined the interaction between multiple diseases and its impact on COVID-19 outcomes [111] or identified multimorbidity patterns [112]. Furthermore, it is plausible that the multimorbidity patterns in COVID-19 patients may present a relationship with infection severity. Exploring this new approach may offer a more complete picture of the patients' needs and help improve clinical approaches and resource managing. Furthermore, the use of healthcare real-world data may represent an efficient approach in situations where evidence is urgently needed.

Study 3: Longitudinal trajectories of multimorbidity patterns

Multimorbidity patterns in each patient may evolve or change over time forming different trajectories, as chronic conditions may progress and accumulate. However, most studies identifying multimorbidity patterns are cross-sectional, focused on a single time point, and few studies have described the evolution of these patterns over time [113, 114]. It is therefore fundamental to build a better knowledge of the longitudinal evolution or stability in multimorbidity patterns. This could detect patient profiles with similar characteristics and risks, which could benefit from improved and more personalised preventive or therapeutic actions. Furthermore, certain trajectories or the belonging to certain multimorbidity patterns over time could be associated with different outcomes (such as quality of life, disability or mortality) and could allow a better planning of future actions, as well as a more accurate prognosis or future relevant results.

2. Hypotheses

2.1. General hypothesis

Multimorbidity patterns can be identified and may be associated with various clinically relevant outcomes and indicators.

2.2. Specific hypotheses

- Certain multimorbidity patterns may be associated with the presence or with specific types of potentially inappropriate prescribing (PIP).
- Certain multimorbidity patterns may be associated with the presence or with specific types of adverse drug reactions (ADRs).
- Certain multimorbidity patterns may be associated with the development of a severe COVID-19 infection.
- Multimorbidity patterns evolve over time forming different trajectories due to changes in chronic conditions in patients over time.

3. Objectives

The general objective of this PhD thesis was to identify multimorbidity patterns of chronic conditions and determine their relationship with various clinically relevant outcomes and indicators.

To address this general objective, the following specific objectives were set:

- To determine if multimorbidity patterns in older patients are associated with quality indicators of medication such as potentially inappropriate prescribing (PIP) or adverse drug reactions (ADR).
- To identify multimorbidity patterns in adult COVID-19 patients and assess their relationship with severity and/or mortality of infection.
- To identify longitudinal trajectories of multimorbidity patterns in older patients.

4. Methods

To address the objectives of this PhD thesis, three studies were conducted and published in international, peer-reviewed, scientific journals, one for each specific objective: 1) a study on the relationship of multimorbidity patterns with certain quality indicators of medication; 2) a study on the relationship of multimorbidity patterns with COVID-19 infection severity; and 3) a study of longitudinal trajectories of multimorbidity patterns. This chapter will summarise the methodology of each study.

4.1. Study 1: MoPIM study

The first study composing this thesis is part of a larger project, called MoPIM (Morbidity and Potentially Inappropriate Medication). The MoPIM study is an observational, multicentre, prospective cohort study including ≥65-year-old patients admitted to hospital due to an exacerbation of a chronic disease. The general objective of this study is to identify the association between multimorbidity patterns, polypharmacy, potentially inappropriate prescribing (PIP) and the presence of adverse drug reactions (ADRs) in these patients. The MoPIM study was registered at the ClinicalTrials.gov database with the identifier NCT02830425.

Prior to the study included in this thesis, two articles on the MoPIM project were published. Firstly, the study protocol [115], which can be found in Appendix B1. Afterwards, an article identifying the multimorbidity patterns of the cohort [116], which can be found in Appendix B2. Then, a subsequent study was conducted to achieve the first specific objective of this thesis: to determine if multimorbidity patterns in older patients are associated with quality indicators of medication such as PIP and ADRs.

4.1.1. Study design and setting

Multicentre, prospective cohort study including 740 older patients (≥65 years old) hospitalised due to exacerbation of their chronic pathology at the internal medicine or geriatric services of five general teaching hospitals in three different regions of Spain between September 2016 and December 2018. Patients referred to home hospitalisation, admitted because of an acute process

unrelated to any chronic disease or with a fatal outcome expected at the time of admission, were not included.

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the ethics committee of each centre: Comité Ético de investigación Clínica del Parc Taulí (ID: 20166570), Comitè Ètic d'Investigació Clínica Osona per a la Recerca i Educació Sanitàries (FORES) (ID: 2016922-PR153), Comité de Ètica de la Investigación con Medicamentos (CEIm)-Parc de Salut MAR (ID: 2016/6830/I), Comité Ético de Investigación Clínica de Euskadi (ID: PI2016060) and Comité de Ética de Investigación del Hospital Universitario de Canarias (ID: MBM-MOD-2016-01 (2016-56)). No written informed consent was deemed necessary for the study.

4.1.2. Data acquisition and variables

Sociodemographic and clinical variables detailed in Table 3 were retrieved at admission by the clinical team responsible for the patient from the electronic health records. Chronic active conditions, including some risk factors, were recorded from a consensual list of 64 conditions including the 19 categories from the Charlson Comorbidity Index [76] (Table 4) and were weighted according to the required clinical management. Geriatric syndromes and risk factors were recorded from a list of 15 (Table 5).

TABLE 3: Sociodemographic and clinical variables registered at the MoPIM study

Sociodemographic and clinical variables
Patient's code
Date of birth
Sex
Barthel Index (before admission)
Household (alone, relatives or other people, nursing home)
Contact with healthcare services in the 3 previous months due to chronic disease exacerbation
Destination at discharge (home, another hospital, nursing home, death)

The number of chronic medications in the electronic prescription and the STOPP/START criteria (version 2) [117] detected upon admission, along with the active principle involved, were registered by the pharmacist of the team. The STOPP/START (Screening Tool of Older Person's potentially inappropriate Prescriptions / Screening Tool to Alert doctors to Right Treatment)

TABLE 4: Chronic conditions registered at the MoPIM study

Charlson Comorbidity Index	**Other conditions**
AIDS/HIV	Amputation
Any malignancy (excluding skin)	Anaemia
Cerebrovascular disease	Asthma
Chronic pulmonary disease	Cardiac arrhythmia
Congestive heart failure	Cataract
Dementia	Chronic hepatitis (B or C)
Diabetes with complication	Chronic pancreatic disease
Diabetes without complication	Degenerative arthropathy
Hemiplegia	Dermatitis or eczema
Leukaemia	Diverticular disease of the colon
Lymphoma	Drug-related conditions
Metastatic solid tumour	Dyslipidemia
Mild liver disease	Fibromyalgia
Moderate or severe liver disease	Gallstones (previous hepatic colic)
Moderate or severe renal disease	Chronic gastritis or gastro-oesophageal reflux
Myocardial infarction	Glaucoma
Peptic ulcer disease	Gout
Peripheral vascular disease	Haemorrhoids
Rheumatologic disease	Haematologic disorders (myelodysplasia, gammapathy, polycythaemia)
	Hypertension
	Inflammatory osteoarticular disease
	Irritable bowel syndrome
	Ischaemic heart disease without infarction
	Migraine
	Neurologic disorder of the central nervous system
	Non-congestive heart failure
	Non-ischaemic heart disease (myocardiopathy, valvulopathy)
	Non-schizophrenic mental disorders (excluding depression and anxiety)
	Obesity
	Osteoporosis
	Other neurological pathologies (essential tremor)
	Other vascular diseases (ischaemia, aneurysm)
	Parkinson's disease
	Peripheral neuropathy or neuritis
	Post-traumatic stress disorder
	Previous fractures (not hip)
	Previous hip fracture
	Prostatic benign hypertrophy
	Schizophrenia
	Sleep apnoea
	Chronic thyroid disease
	Tuberculosis
	Urinary tract stones (nephritic colic)
	Varicose veins of lower extremities
	Vertigo

TABLE 5: Geriatric syndromes registered at the MoPIM study

Geriatric syndromes	
Acute confusional syndrome/delirium	Incontinence (Urinary/faecal)
Chronic pain	Instability/falls
Cognitive/intellectual impairment	Malnutrition
Constipation	Polypharmacy
Depression/Anxiety	Pressure ulcers
Dysphagia	Sensorial deficit
Frailty	Sleep disorders/Insomnia
Immobility	

criteria are used to identify and evaluate PIP. The 2nd version consists of 114 criteria: 80 STOPP criteria to detect potentially inappropriate medications (PIMs), including 77 explicit criteria and 3 implicit criteria; and 34 START criteria to detect potential prescribing omissions (PPOs). This medication review process was part of the usual patient care routine in all participating centres. Medication was only considered chronic if prescribed at least 3 months before admission, and creams, ointments, healing materials and over-the-counter medicines were not considered.

All STOPP/START criteria were assessed, except for START criteria I (vaccines) due to difficulties of some centres in accessing the information. Regarding the implicit criterion STOPP A1 and given its high frequency, it was divided into the following categories according to the active principle involved, as in a previous study [118]: proton pump inhibitors, hypolipidemics, analgesics, acetylsalicylic acid, antihypertensives and others.

ADRs were identified by the clinical team both at admission and during the course of stay. Active principle involved, occurrence of the ADR at admission or during hospitalisation, and health consequences of ADRs occurring during hospitalisation (death, life-threatening, lengthening of hospitalisation, other) were collected.

Active principles involved in ADRs were categorised in the following drug families: analgesic, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, antiarrhythmic, antibiotic, anticoagulant, antidepressant, antiepileptic, antiplatelet, antipsychotic, antivitamin K, benzodiazepine, beta blocker, bronchodilator, corticoid, loop diuretic, neuroleptic, insulin, opioid, oral anticoagulant, oral antidiabetic, potassium sparing diuretic, proton pump inhibitor, statin, thiazide diuretic and others.

Binary variables were created to describe the presence of any STOPP/START PIP, any STOPP PIM, any START PPO, any ADR, any ADR at admission and any ADR during hospitalisation. This was performed similarly with numerical variables for the number of STOPP/START PIP (excluding implicit criteria STOPP A1, A2, A3), number of STOPP PIM (excluding STOPP A1, A2, A3), number of START PPO, number of ADR, number of ADR at admission and number of ADR during hospitalisation.

4.1.3. Multimorbidity cluster analysis

Multimorbidity patterns were identified in a previous article [116], which can be found in Appendix B2. Chronic conditions were filtered by <2% prevalence and dimensionality reduction for the dataset was conducted with the PCAmix algorithm [119]. Cluster analysis was then performed using the fuzzy c-means algorithm [91], which allowed for the obtaining of patient clusters based on their chronic conditions and geriatric syndromes, with each patient assigned a membership probability to each cluster. A range of statistically significant possibilities was obtained and, after clinical revision and discussion among the research team, an eventual set of four clusters was established. These clusters were labelled 'osteoarticular', 'psychogeriatric', 'minor chronic disease' and 'cardiorespiratory'. Patients were assigned to the cluster where their membership probability was highest.

4.1.4. Statistical analysis

Descriptive analyses were performed for all variables. Bivariate analyses were conducted to assess possible associations between multimorbidity clusters and the presence or type of PIP or ADR by Fisher's exact test. Most frequent PIP criteria were selected with the aim of analysing at least the top 10 criteria for PIMs and PPOs. ADRs were only analysed if present in at least 5 patients of a cluster. Post hoc pairwise Fisher's exact tests were conducted for those previously significant tests ($p<0.05$), and p-values were corrected for multiple hypothesis testing using Benjamini–Hochberg false discovery rate (FDR) method [120] at a 5% cut-off.

Comparisons between the number of PIP or ADR were performed using the Kruskal–Wallis test. Pairwise comparisons between distributions of the number of PIP or ADR among the different clusters were performed using the Kolmogorov–Smirnov test. These comparisons were

performed for the following variables: number of STOPP/START PIP (excluding implicit criteria), number of STOPP PIMs (excluding implicit criteria), number of START PPOs, number of ADRs, number of ADRs at the time of admission and number of ADRs during hospitalisation.

Data processing and statistical analysis were performed with R [121].

4.2. Study 2: MRisk-COVID study

The second study composing this PhD thesis is the MRisk-COVID (Multimorbidity Risk in COVID-19) study. The MRisk-COVID study is an observational, real world data (RWD) study of >20-year-old COVID-19 patients in the first pandemic wave. The aims of this study were to characterise multimorbidity clusters within an adult COVID-19 cohort and to assess the relationship between these clusters and infection severity/mortality. The MRisk-COVID study was registered at the ClinicalTrials.gov database with the identifier NCT04981249.

4.2.1. Study design and cohort

Observational, real world data study based on a cohort of 14286 COVID-19 patients aged >20 years, residing in a healthcare zone in the Northeast region of Spain (Vallès Occidental est), and registered between 27th February and 15th June of 2020 by the Catalan Epidemiological Surveillance Emergency Service (SUVEC) as either confirmed or suspected COVID-19 cases.

The study was approved by the Ethics Committee (CEIm) of the Parc Taulí University Hospital (reference 2021/5067), which waived the requirement of informed consents due to the epidemiological nature of the study and the use of anonymized data provided by PADRIS. This study was conducted according to the principles expressed in the Declaration of Helsinki.

4.2.2. Data acquisition and variables

Data were provided by the Agency for Health Quality and Assessment of Catalonia (AQuAS) in the framework of the Public Data Analysis for Health Research and Innovation Program (PADRIS), under an extraordinary call that took place in April 2020 in order to provide healthcare big data for COVID-19 research studies.

Demographic data were obtained from the Shared Clinical History of Catalonia (HC3) and included age and sex. Clinical records were obtained from any primary healthcare centre and hospital of Catalonia that the individuals attended. The provided records covered from 1923 to 2020 in primary healthcare centres, and from 2016 to 2020 in hospitals. Patients' data were stratified by sex and age, thereby obtaining eight different datasets (groups of 21–45, 46–65, 66–80 and 81–95 years, separated into male and female individuals).

Infection severity was defined as the occurrence of at least one of the following conditions during any of the registered COVID-19 episodes: severe respiratory affection, use of respiratory support, septic shock, multiple organ failure, inflammatory response, admission to intensive care unit, and mortality associated with COVID-19 episodes.

4.2.3. Multimorbidity cluster analysis

The ICD-10-CM codes of the complete diagnoses records were categorised into chronic or acute diseases by the Chronic Condition Indicator v.2021.1 [122], and only chronic conditions were selected. Then, in order to reduce the number of variables for the cluster analysis, diagnoses were grouped and classified by the Clinical Classification Software Refined v.2021.1 (e.g. 'Asthma' and 'Chronic obstructive pulmonary disease and bronchiectasis' were labelled as 'Diseases of the respiratory system') [123].

The clustering procedure was independently applied to each sex-age group. For each stratum, chronic conditions were filtered by prevalence (>2%) and only patients with multimorbidity, as defined by the presence of 2 or more chronic conditions, were included in the analyses. An initial dimension reduction of the dataset was performed by a Multiple Correspondence Analysis, using the elbow criteria in the Scree plot for dimension selection. The resulting data were subjected to soft clustering analysis by the fuzzy c-means algorithm. This algorithm requires two main parameters: the number of desired clusters (C) and the fuzziness (m), which indicates the degree of overlapping membership of the patients to the clusters. This parameter can range from 1 (equivalent to hard, non-overlapping clustering) to infinite. Several values of C (4, 5, 6 and 7) and m (1.1, 1.2, 1.4, 1.5, 2, and 4) were tested. The optimal m was estimated by the mean calculation of five indexes: Calinski–Harabasz, Partition coefficient (both optimal at their highest value), Partition entropy, Fukuyama, and Xie-Beni (the three of them optimal at their lowest value).

The final C for each sex and age stratum was determined through consensus among 11 professionals of the multidisciplinary research group. This agreement was achieved following a Delphi-like selection method that consisted of equal voting through two selection rounds. Consensus was defined when one of the options reached a majority of votes ($\geq$6); cases with lack of consensus or similar voting count were decided through a clinical debate session.

Several indicators were calculated for the chronic conditions in each cluster in order to characterise the specificity and composition of the MM patterns: a) Prevalence within the cluster (%); b) Observed/Expected (O/E) ratio, estimated by dividing the prevalence in the cluster by the prevalence in the corresponding age-sex group cohort; and c) Exclusivity (%), obtained by dividing the number of patients that presented the chronic condition in the cluster by the total number of patients affected by the chronic condition in the corresponding age-sex group cohort. A generic label was assigned to each cluster in an attempt to summarise the most prevalent and overexpressed chronic condition as well as to facilitate the clinical interpretation of the results. Regarding patients, membership percentages were calculated, indicating the degree of belonging of each patient to the selected clusters.

4.2.4. Statistical analysis

Statistical bivariate differences between severe and non-severe cases, as well as dead and survivor cases, were assessed by chi-square tests in the case of categorical/dichotomous variables and Wilcoxon signed-rank tests in the case of continuous variables. The statistical relationship between mortality or severity and multimorbidity clusters was assessed by weighted chi-square tests, where the weight of the variables was the percentage of membership of the patients to each cluster. Patients with less than two chronic conditions were evaluated as an additional "No multimorbidity" group.

Data processing and statistical analysis were performed with R [121].

4.3. Study 3: MTOP study

The third study composing this PhD thesis is the MTOP (Multimorbidity Trajectories in Older Patients) study. The MTOP study is an retrospective, observational study that aims to identify

longitudinal trajectories of multimorbidity patterns in a cohort of older patients. The MTOP study was registered at the ClinicalTrials.gov database with the identifier NCT05717309.

4.3.1. Study design and cohort

The MTOP study is a retrospective observational study using real-world data based on a cohort from a previous study on multimorbidity clusters, called MRisk-COVID study [124]. The MRisk-COVID study included 14286 patients of a region in the Northeast of Spain (Vallès Occidental est, Catalonia), which were either confirmed or suspected COVID-19 cases from 27th February to 15th June 2020. The MRisk-COVID data was deemed suitable to address the aim of the MTOP study, as it provided readily available data on longitudinal chronic morbidity in a cohort of older patients. Patients aged >65 years were selected, resulting in a cohort of 3988 individuals.

The study was approved by the Ethics Committee (CEIm) of the Parc Taulí University Hospital (reference 2022/5051), which waived the requirement of informed consents due to the epidemiological nature of the study and the use of anonymized data. This study was conducted according to the principles expressed in the Declaration of Helsinki.

4.3.2. Data acquisition and variables

Demographic data (sex and age) and clinical data were obtained from the Shared Clinical History of Catalonia (HC3). Clinical data comprised clinical records of all primary healthcare centres in Catalonia. The provided records covered from 1930 to 2020 and encompassed all diagnoses, coded using the ICD-10-CM diagnostic system [125]. Three time points were established: 2020 (baseline, representing the time of data extraction), 2015 (5 years before) and 2010 (10 years before), and active diagnoses at each time were collected.

4.3.3. Multimorbidity cluster analysis

To identify chronic multimorbidity patterns, three steps were performed: identification of chronic conditions, complexity reduction of chronic conditions, and cluster analysis of patients based on these selected features. The following analyses were performed independently for each of the three selected time points.

Firstly, the identification of chronic conditions for inclusion in the analyses was carried out using the Chronic Condition Indicator software v.2021.1 [122]. Then, the selected chronic diagnoses were classified and grouped using the Clinical Classification Software Refined v.2021.1 [123], which allocates specific diagnoses into general chronic condition categories. This step was performed in order to reduce the number of variables for the cluster analysis and increase statistical power, while at the same time collapsing highly similar diagnoses to avoid unnecessary fragmentation. After that, chronic conditions were filtered by >2% prevalence in order to reduce statistical noise. Only patients with two or more chronic conditions were included, regardless of the presence of acute conditions.

Due to the large number of chronic conditions, a dimension reduction was performed by Multiple Correspondence Analysis. The optimal number of dimensions was determined by the elbow criteria in the scree plot. Then, soft clustering analysis was performed using the fuzzy c-means algorithm [91]. Given that it is a stochastic method; a hundred iterations were performed in order to obtain reproducible results. Several values of fuzziness (m) were tested (m=1.1, 1.2, 1.4, 1.5, 2, 4) and the optimal m=1.1 was estimated by the mean calculation of five indexes: Calinski–Harabasz, Partition coefficient, Partition entropy, Fukuyama, and Xie-Beni. Also, several values of the number of clusters (C=4, 5, 6 and 7) were tested. The final C for each time point was reached through statistical criteria and consensus among 6 medical doctors from different specialities. This agreement was achieved following an independent voting process. Consensus was defined when one of the options reached a majority of votes. Cases with lack of consensus or similar voting count were meant to be decided through a clinical debate session, however this turned out not to be necessary.

After establishing multimorbidity clusters, three indicators were calculated for each chronic condition: prevalence within the cluster (%), observed/expected (O/E) ratio (prevalence in the cluster / total prevalence) and exclusivity (patients with the condition in the cluster / total of patients with the condition). Finally, a descriptive label was agreed upon and assigned to each cluster to summarise their over-represented chronic conditions and facilitate clinical interpretation.

4.3.4. Statistical analysis

Each patient was allocated to the most probable cluster at each of the time points. Percentages of patients in each cluster were calculated, including patients with zero or one chronic conditions, which were allocated to a "No multimorbidity" group. Then, trajectories of each patient through the three time points were established. Percentages of patients for all possible trajectories were calculated for the three time points or pairwise (10 years before vs. 5 years before, 5 years before vs. baseline).

A stratified descriptive analysis was conducted by sex and two age groups, thereby obtaining four different patient datasets (groups of 66–80 and >80 years, separated into male and female individuals) and plotting their trajectories separately. Age cut-off was set at 80 years to define very old individuals.

Data processing and statistical analysis were performed with R [121].

4.4. Comparison of methods

The comparison of the methodologies followed in each of the three studies composing this thesis is outlined in Table 6.

TABLE 6: Comparison of objectives and methods of the studies composing the thesis

	Study 1: MoPIM	Study 2: MRisk-COVID	Study 3: MTOP
Objective	To evaluate if any of the previously identified multimorbidity patterns are associated with the presence, number or specific types of potentially inappropriate prescribing (PIP) or adverse drug reactions (ADRs)	To provide an age- and sex-centred characterization of the multimorbidity clusters of an adult COVID-19 cohort and to assess the relationship between these clusters and the severity and mortality of the infection	To identify multimorbidity patterns of chronic conditions in a cohort of older patients, as well as their progression and trajectories in the previous 10 years
Study design	Multicentre, prospective, cross-sectional, observational cohort study	Retrospective, cross-sectional, observational study using real-world data	Retrospective, longitudinal, observational study using real-world data
Cohort	Patients $\geq$65 years old hospitalised due to exacerbation of their chronic pathology at the internal medicine or geriatric services	COVID-19 patients registered by the Catalan Epidemiological Surveillance Emergency Service (SUVEC) aged >20 years	COVID-19 patients registered by the SUVEC aged >65 years
N	740	14286	3988
Study period	Hospitalisations between September 2016 and December 2018	COVID-19 cases registered from 27th February to 15th June 2020	COVID-19 cases registered from 27th February to 15th June 2020
Geographical area	Five general teaching hospitals in Spain: Parc Taulí Hospital Universitari, Consorci Hospitalari de Vic, Hospital del Mar, Hospital de Galdakao and Hospital Universitario de Canarias	Healthcare zone in the Northeast region of Spain (Vallès Occidental est)	Healthcare zone in the Northeast region of Spain (Vallès Occidental est)
Data source	Clinical assessment (medical records review)	Administrative data	Administrative data
Multimorbidity operationalisation	Ad hoc list of 64 chronic conditions + 15 geriatric syndromes, filtered by >2% prevalence	ICD-10-CM codes categorised into chronic conditions (Chronic Condition Indicator v.2021.1), grouped (Clinical Classification Software Refined v.2021.1) and filtered by >2% prevalence	ICD-10-CM codes categorised into chronic conditions (Chronic Condition Indicator v.2021.1), grouped (Clinical Classification Software Refined v.2021.1) and filtered by >2% prevalence
Additional variables	Sociodemographic and clinical, PIP, ADRs	Sex, age, COVID-19 infection severity	Sex, age, date of diagnosis
Multimorbidity cluster analysis	For the whole cohort: weighted chronic conditions + geriatric syndromes $\rightarrow$ PCAmix $\rightarrow$ fuzzy c-means cluster analysis	For each sex-age stratum: unweighted chronic conditions $\rightarrow$ Multiple Correspondence Analysis $\rightarrow$ fuzzy c-means cluster analysis	For each time point: unweighted chronic conditions $\rightarrow$ Multiple Correspondence Analysis $\rightarrow$ fuzzy c-means cluster analysis
Statistical analysis	Descriptive + bivariate statistics: multimorbidity cluster vs PIP / ADRs	Descriptive + bivariate statistics: multimorbidity cluster vs severity / mortality of infection	Descriptive statistics: obtained multimorbidity trajectories and sex-age stratification

5. Results

The results of this PhD thesis correspond to the findings of the studies that comprise it.

5.1. Study 1: MoPIM study

Publication of the first study

Lleal M, Baré M, Ortonobes S, Sevilla-Sánchez D, Jordana R, Herranz S, Gorgas MQ, Espaulella-Ferrer M, Arellano M, de Antonio M, Nazco GJ, Hernández-Luis R, on behalf of the MoPIM Study Group. Comprehensive Multimorbidity Patterns in Older Patients Are Associated with Quality Indicators of Medication-MoPIM Cohort Study. Int J Environ Res Public Health. 2022 Nov 29;19(23):15902.

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Comprehensive Multimorbidity Patterns in Older Patients Are Associated with Quality Indicators of Medication—MoPIM Cohort Study

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Abstract: Multimorbidity is increasing and poses a challenge to the clinical management of patients with multiple conditions and drug prescriptions. The objectives of this work are to evaluate if multimorbidity patterns are associated with quality indicators of medication: potentially inappropriate prescribing (PIP) or adverse drug reactions (ADRs). A multicentre prospective cohort study was conducted including 740 older (≥65 years) patients hospitalised due to chronic pathology exacerbation. Sociodemographic, clinical and medication related variables (polypharmacy, PIP according to STOPP/START criteria, ADRs) were collected. Bivariate analyses were performed comparing previously identified multimorbidity clusters (osteoarticular, psychogeriatric, minor chronic disease, cardiorespiratory) to presence, number or specific types of PIP or ADRs. Significant associations were found in all clusters. The osteoarticular cluster presented the highest prevalence of PIP (94.9%) and ADRs (48.2%), mostly related to anxiolytics and antihypertensives, followed by the minor chronic disease cluster, associated with ADRs caused by antihypertensives and insulin. The psychogeriatric cluster presented PIP and ADRs of neuroleptics and the cardiorespiratory cluster indicators were better overall. In conclusion, the associations that were found reinforce the existence of multimorbidity patterns and support specific medication review actions according to each patient profile. Thus, determining the relationship between multimorbidity profiles and quality indicators of medication could help optimise healthcare processes. Trial registration number: NCT02830425.

Keywords: older patient; multimorbidity; cluster analysis; polypharmacy; potentially inappropriate medication; potential prescribing omission; adverse drug reaction; healthcare quality indicator

1. Introduction

The clinical management of older patients with multiple conditions and pharmaceutical treatments poses a big challenge for healthcare professionals and systems. On top of the ageing population, a high prevalence of multimorbidity (classically defined as the presence of two or more coexisting chronic conditions) has been described worldwide and is expected to continue increasing [1,2]. Therefore, conducting research on how to improve the care of multimorbid patients in healthcare services that have traditionally focused on single diseases should be deemed of the utmost priority [3,4].

Various definitions and research methodologies have been developed in order to shed light on the concept of multimorbidity, and there is accumulating evidence suggesting that chronic conditions give rise to association patterns [5–7]. Although there is no standard yet, many publications have successfully identified multimorbidity patterns [8,9], some of which are repeatedly found among different studies [10]. Furthermore, some patterns have been associated with outcomes such as lower function, higher healthcare utilisation, poor prognosis or higher mortality [11–16]. Therefore, identifying multimorbidity patterns could help design new strategies and guidelines focusing on the most appropriate practices according to each patient profile.

This is remarkably important in older patients who, in addition to multimorbidity, present polypharmacy and age-related factors that can influence and hinder pharmacological prescribing. Some examples include physiological changes in pharmacokinetics and pharmacodynamics, cognitive impairment, functional difficulties or geriatric syndromes [17–20]. All in all, prescribing while balancing the benefits and risks becomes an arduous task.

In this scenario, a lot of attention has been brought to potentially inappropriate prescribing (PIP), which may occur in situations such as prescribing medications with potential benefits that do not outweigh the harms (particularly given the existence of safer alternatives); prescribing an inappropriate dose or duration or a duplicate drug; or omitting potentially beneficial medications. Several tools have been developed to identify PIP, such as the STOPP/START (Screening Tool of Older Person's potentially inappropriate Prescriptions/Screening Tool to Alert doctors to Right Treatment) criteria, the most used and validated in European older adults [21]. These criteria include both potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs). While PPOs can prevent patients from taking essential medication, leading to risks and negative outcomes [22,23], PIMs are a well-known risk factor for adverse drug reactions (ADRs) [24–26]. ADRs are highly frequent in older patients and have been estimated to be responsible for 10–30% of hospital admissions [27,28] as well as to occur in 16% of already hospitalised older patients [29].

Taking into account all these considerations, it is plausible that certain multimorbidity patterns may present an association with specific PIP and/or ADRs. Importantly, there are no publications to date studying this inter-relationship in detail. Identifying associations could pave the way to optimising and focusing medication review actions and improve healthcare in these complex patients, reducing undesired outcomes. The present analyses are part of the MoPIM multicentre cohort study [30], which has various objectives regarding multimorbidity, PIP and ADRs in older patients hospitalised due to chronic condition exacerbation. A set of four multimorbidity patterns were identified in a previous publication [31]; thus, the objectives of this work are to evaluate if any of these previously identified multimorbidity patterns are associated with the presence, number or specific types of PIP or ADRs.

2. Methodology

2.1. Design and Setting

A multicentre prospective cohort study including older patients hospitalised 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 conducted. The detailed

protocol was previously published [30]. 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 hospitalisation, admitted because of an acute process unrelated 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, according to the independent ethics committee.

2.2. Data Acquisition and Variables

The following sociodemographic and clinical data were retrieved from the electronic health records by the clinical team responsible for the patient: patient's code, date of birth, sex, functional status just before admission (Barthel Index) [32], household (alone, with relatives or other people, in a nursing home) and existence of any contact with healthcare services in the 3 months prior to hospitalisation due to exacerbation of any chronic disease and destination at discharge from the present episode of hospitalisation (home, transfer to another hospital, transfer to a nursing home, death). Chronic active conditions were recorded from a consensual list of 64 conditions containing all chronic diseases of the Charlson Comorbidity Index [33] and including some risk factors as well. Geriatric syndromes and risk factors were also recorded from a list of 15 (see protocol [30]).

The number of chronic medications in the electronic prescription at the time of admission and the STOPP/START criteria (version 2) [21] detected upon admission, with the active principle involved, were collected by the pharmacist of the team. The 2nd version of STOPP/START criteria consists of a list of 114 medication indications, developed using a Delphi method by experts from different disciplines, who carried out a literature review. The criteria are directed to prevalent diseases in older patients, are ordered by physiological systems and are easy to relate to active diagnoses. This medication review process was part of the usual patient care routine in all participating centres. Medication was only considered chronic if prescribed at least 3 months before admission, and creams, ointments, healing materials and over-the-counter medicines were not considered. Active principles were considered individually when registering STOPP/START criteria, regardless of the administered drug combinations.

Finally, ADRs were identified by the clinical team both at admission and during the course of stay. ADRs were considered according to the WHO and the European Medicines Agency criteria [34–36]. The active principle involved and whether the ADR occurred at admission or during hospitalisation were collected. Consequences in terms of health (death, life-threatening, lengthening of hospitalisation, other important consequences under medical criteria) were registered if the ADR appeared during hospital stay.

2.3. Sampling and Analysis

Patients included were proportionally distributed to the annual volume of hospitalisations at the internal medicine and/or geriatric services of each centre.

The Updated Charlson Comorbidity Index [37] was calculated, adjusted by age and categorised by tertiles (2–6, 7–8, 9–14).

Multimorbidity patterns were identified using a soft clustering algorithm, as thoroughly described [31]. Firstly, some chronic conditions were grouped according to clinical criteria and then filtered by <2% prevalence, resulting in a list of 40 chronic conditions and 15 geriatric syndromes. Chronic conditions were weighted according to the required clinical management. Then, transformation and dimensionality reduction for the dataset were carried out with the PCAmix algorithm [38], and cluster analysis was performed with the fuzzy c-means algorithm [39]. This technique allowed for obtaining clusters of patients based on their chronic conditions and geriatric syndromes with a membership probability to every cluster. After computing several validation indexes [31], a range of statistically significant possibilities were obtained, and, after clinical revision and discussion among the research team, an eventual set of four clusters was established. These clusters were named

'osteoarticular', 'psychogeriatric', 'minor chronic disease' and 'cardiorespiratory'. Patients were assigned to the cluster where their membership probability was highest.

All STOPP/START criteria were assessed, except for START criteria I (vaccines) due to difficulties of some centres in accessing the information. Regarding the implicit criterion STOPP A1 and given its high frequency, it was divided into the following categories according to the active principle involved: proton pump inhibitors, hypolipidemics, analgesics, acetylsalicylic acid, antihypertensives and others [40].

Active principles involved in ADRs were categorised in the following drug families: analgesic, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, antiarrhythmic, antibiotic, anticoagulant, antidepressant, antiepileptic, antiplatelet, antipsychotic, antivitamin K, benzodiazepine, beta blocker, bronchodilator, corticoid, loop diuretic, neuroleptic, insulin, opioid, oral anticoagulant, oral antidiabetic, potassium sparing diuretic, proton pump inhibitor, statin, thiazide diuretic and others. Equivalence with ATC (Anatomical Therapeutic Chemical) codes can be found in Table S1.

Binary variables were created to describe the presence of any STOPP/START PIP, any STOPP PIM, any START PPO, any ADR, any ADR at admission and any ADR during hospitalisation. This was performed similarly with numerical variables for the number of STOPP/START PIP (excluding implicit criteria STOPP A1, A2, A3), number of STOPP PIM (excluding STOPP A1, A2, A3), number of START PPO, number of ADR, number of ADR at admission and number of ADR during hospitalisation.

Descriptive analyses were performed for all variables. Bivariate analyses were conducted to assess possible associations between multimorbidity clusters and the presence or type of PIP or ADR by the Fisher's exact test. Most frequent PIP criteria were selected with the aim of analysing at least the top 10 criteria for PIMs and PPOs, resulting in a cut-off of 5% of patients of a cluster for STOPP criteria and 3% of patients of a cluster for START criteria. ADRs were only analysed if present in at least 5 patients of a cluster. Post hoc pairwise Fisher's exact tests were conducted for those previously significant tests ($p < 0.05$), and p-values were corrected for multiple hypothesis testing using Benjamini–Hochberg false discovery rate (FDR) method [41] at a 5% cut-off.

Comparisons between number of PIP or ADR were performed using the Kruskal–Wallis test. Pairwise comparisons between distributions of the number of PIP or ADR among the different clusters were performed using the Kolmogorov–Smirnov test. These comparisons were performed for the following variables: number of STOPP/START PIP (excluding implicit criteria, i.e., STOPP A), number of STOPP PIMs (excluding implicit criteria, i.e., STOPP A), number of START PPOs, number of ADRs, number of ADRs at the time of admission and number of ADRs during hospitalisation.

All analyses were performed with R (R Foundation for Statistical Computing, Vienna, Austria) [42].

3. Results

3.1. Sociodemographic and Clinical Characteristics of the Cohort

A total of 740 patients were included; 53.2% were females, and 98.7% were diagnosed with two or more chronic conditions. The mean age was 84.1 (SD 7.0) years, and the mean Barthel Index was 65 (median 75). The cardiorespiratory cluster contained most patients (n = 325, 43.9%), followed by the psychogeriatric (n = 151, 20.4%), osteoarticular (n = 137, 18.5%) and minor chronic disease (n = 127, 17.2%) clusters. Sociodemographic and clinical variables are summarised in Table 1, according to the assigned multimorbidity cluster. The prevalences of chronic conditions and geriatric syndromes are described according to multimorbidity cluster in Table S2. Among all the detected STOPP/START criteria, the most prevalent STOPP criteria were A1: Drugs prescribed without an evidence-based clinical indication (n = 310, 25.7%), D5: Benzodiazepines for $\geq$4 weeks (n = 247, 20.5%) and K1: Benzodiazepines (n = 131, 10.9%), from a total of 1206 criteria detected. The most prevalent START criteria were E5: Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (n = 76, 21.5%), H2: Laxatives in patients receiving

opioids regularly (n = 50, 14.1%) and A8: Appropriate beta-blocker with stable systolic heart failure (n = 39, 11.0%), from a total of 353 criteria detected.

Table 1. Sociodemographic and clinical variables of the cohort according to the assigned multimorbidity clusters.

		Osteo-Articular	Psycho-Geriatric	Minor Chronic Disease	Cardio-Respiratory
n (%)		137 (18.5)	151 (20.4)	127 (17.2)	325 (43.9)
Age at the time of admission (years, mean ± SD)		84.3 ± 6.3	85.1 ± 6.9	83.1 ± 7.2	84.1 ± 7.2
Sex, n (%)	Female	104 (75.9)	85 (56.3)	50 (39.4)	155 (47.7)
	Male	33 (24.1)	66 (43.7)	77 (60.6)	170 (52.3)
Barthel Index (mean ± SD)		61.6 ± 24.7	34.6 ± 31.4	77.4 ± 25.6	75.9 ± 27.2
No. of chronic pathologies (mean ± SD)		11.5 ± 3.6	7.7 ± 3.1	10.2 ± 3.1	7.2 ± 2.3
No. of geriatric syndromes (mean ± SD)		7.7 ± 1.8	9.1 ± 2.0	5.3 ± 2.8	4.2 ± 2.0
No. of chronic prescriptions (mean ± SD)		12.3 ± 4.58	9.5 ± 3.81	11.1 ± 4.0	10.1 ± 4.1
Updated Charlson Comorbidity Index, age-adjusted, n (%)	2–5	27 (19.7)	22 (14.6)	29 (22.8)	70 (21.5)
	6–8	77 (56.2)	87 (57.6)	62 (48.8)	185 (56.9)
	9–14	33 (24.1)	42 (27.8)	36 (28.3)	70 (21.5)
Household, n (%)	Alone	27 (19.7)	15 (9.9)	21 (16.5)	59 (18.2)
	Nursing home	17 (12.4)	35 (23.2)	8 (6.3)	35 (10.8)
	With relatives/other people	93 (67.9)	101 (66.9)	98 (77.2)	231 (71.1)
Chronic pathology exacerbation 3 months prior to admission, n (%)	No	26 (19.0)	37 (24.5)	30 (23.6)	132 (40.6)
	Yes	111 (81.0)	114 (75.5)	97 (76.4)	193 (59.4)
Destination at discharge, n (%)	Home	85 (62.0)	72 (47.7)	93 (73.2)	218 (67.1)
	Nursing home	18 (13.1)	35 (23.2)	13 (10.2)	39 (12.0)
	Another hospital	16 (11.7)	16 (10.6)	16 (12.6)	53 (16.3)
	Death	18 (13.1)	28 (18.5)	5 (3.9)	15 (4.6)

SD: standard deviation.

3.2. Relationship between Multimorbidity Clusters and Potentially Inappropriate Prescribing

A bivariate analysis was performed to test the association of belonging to a cluster and presenting any STOPP/START PIP, STOPP PIMs or START PPOs. Table 2 shows that a significant association was found in all these three variables. Pairwise comparisons (Table S3) showed that the osteoarticular cluster was significantly different from all others regarding the presence of any PIP or any PIMs, and together with the minor chronic disease were significantly different in presence of PPOs from the other two.

Table 2. Presence of any PIP, PIMs or PPOs according to STOPP/START criteria in relation to the assigned multimorbidity clusters.

	Osteo-Articular	Psycho-Geriatric	Minor Chronic Disease	Cardio-Respiratory	p-Value
n (%)	137 (18.5)	151 (20.4)	127 (17.2)	325 (43.9)	
Any STOPP/START PIP	130 (94.9)	118 (78.1)	106 (83.5)	249 (76.6)	<0.001
Any STOPP PIMs	117 (85.4)	109 (72.2)	91 (71.7)	225 (69.2)	0.002
Any START PPOs	93 (67.9)	87 (57.6)	79 (62.2)	148 (45.5)	<0.001

Fisher's exact test p-value is shown. PIP: potentially inappropriate prescribing, PIM: potentially inappropriate medication, PPO: potential prescribing omission.

Next, we compared the number of PIP, PIMs and PPOs between clusters taking into account only explicit criteria. Differences were found between clusters in all three variables (Kruskal–Wallis test: $p < 0.001$ in number of PIP, $p < 0.001$ in number of PIMs, $p = 0.001$ in number of PPOs). Pairwise comparisons between distributions showed that the osteoarticular cluster in both the number of STOPP/START PIP and STOPP PIMs was different from the other clusters (Kolmogorov–Smirnov test: $p < 0.001$ and $p < 0.005$, respectively), meaning that patients of this cluster tend to present a larger number of PIP

and PIMs (Figure S1). No significant differences were found in the distribution of the number of START PPOs.

Then, a bivariate analysis was performed focusing on certain specific criteria, selecting the most frequent ones. Significant associations were found in the STOPP PIM criteria related to benzodiazepines (STOPP D5, G5, K1) or ACE inhibitors/angiotensin receptor blockers (STOPP B11), which were significantly higher in the osteoarticular cluster. PIMs related to proton pump inhibitors (extracted from STOPP A1) were significantly lower in the cardiorespiratory cluster than the rest. PIMs involving neuroleptic drugs (STOPP K2) were most prevalent in patients of the psychogeriatric cluster and least prevalent in those of the cardiorespiratory cluster (Figure 1A, Table S4).

Regarding START PPO analysis, the most frequent criteria were selected and compared between clusters as well. PPOs involving beta blockers (START A8) were positively associated with the cardiorespiratory cluster, while the lack of vitamin D prescribing (START E5) was negatively associated with it. Prescribing the omission of laxatives (START H2) was significantly higher in the osteoarticular and minor chronic disease clusters with respect to the others (Figure 1B, Table S5).

3.3. Relationship between Multimorbidity Clusters and Adverse Drug Reactions

A total of 376 ADRs were reported in 245 patients (33.1%), and 59.6% of those were detected at the time of admission in 153 patients (20.7%). Having an ADR was significantly associated with belonging to particular multimorbidity clusters. Almost half of the patients in the osteoarticular and minor chronic disease clusters suffered at least one ADR, and both clusters were significantly different from the psychogeriatric and cardiorespiratory. When separating ADRs into those detected at the time admission and those occurred during hospital stay, these two clusters also showed a significantly higher percentage of patients (Tables 3 and S6).

Table 3. Presence of any ADR in relation to the assigned multimorbidity clusters.

	Osteo-Articular	Psycho-Geriatric	Minor Chronic Disease	Cardio-Respiratory	*p*-Value
n (%)	137 (18.5)	151 (20.4)	127 (17.2)	325 (43.9)	
Any ADR	66 (48.2)	31 (20.5)	60 (47.2)	88 (27.1)	<0.001
Any ADR at admission	45 (32.8)	22 (14.6)	39 (30.7)	47 (14.5)	<0.001
Any ADR during hospitalisation	32 (23.4)	11 (7.3)	30 (23.6)	47 (14.5)	<0.001

Fisher's exact test *p*-value is shown. ADR: adverse drug reaction.

With respect to the number of ADRs between different clusters, significant differences were found when considering all ADRs, those detected at admission and those occurred during hospitalisation (Kruskal–Wallis test: $p < 0.001$ in all cases). Afterwards, a pairwise comparison of the distributions was performed too, which showed that the osteoarticular and the minor chronic disease clusters presented a different distribution from the psychogeriatric and cardiorespiratory clusters both regarding the total number of ADRs and those detected at the time of admission (Figure S2). No significant differences were found in the distribution of the number of ADRs occurred during hospital stay.

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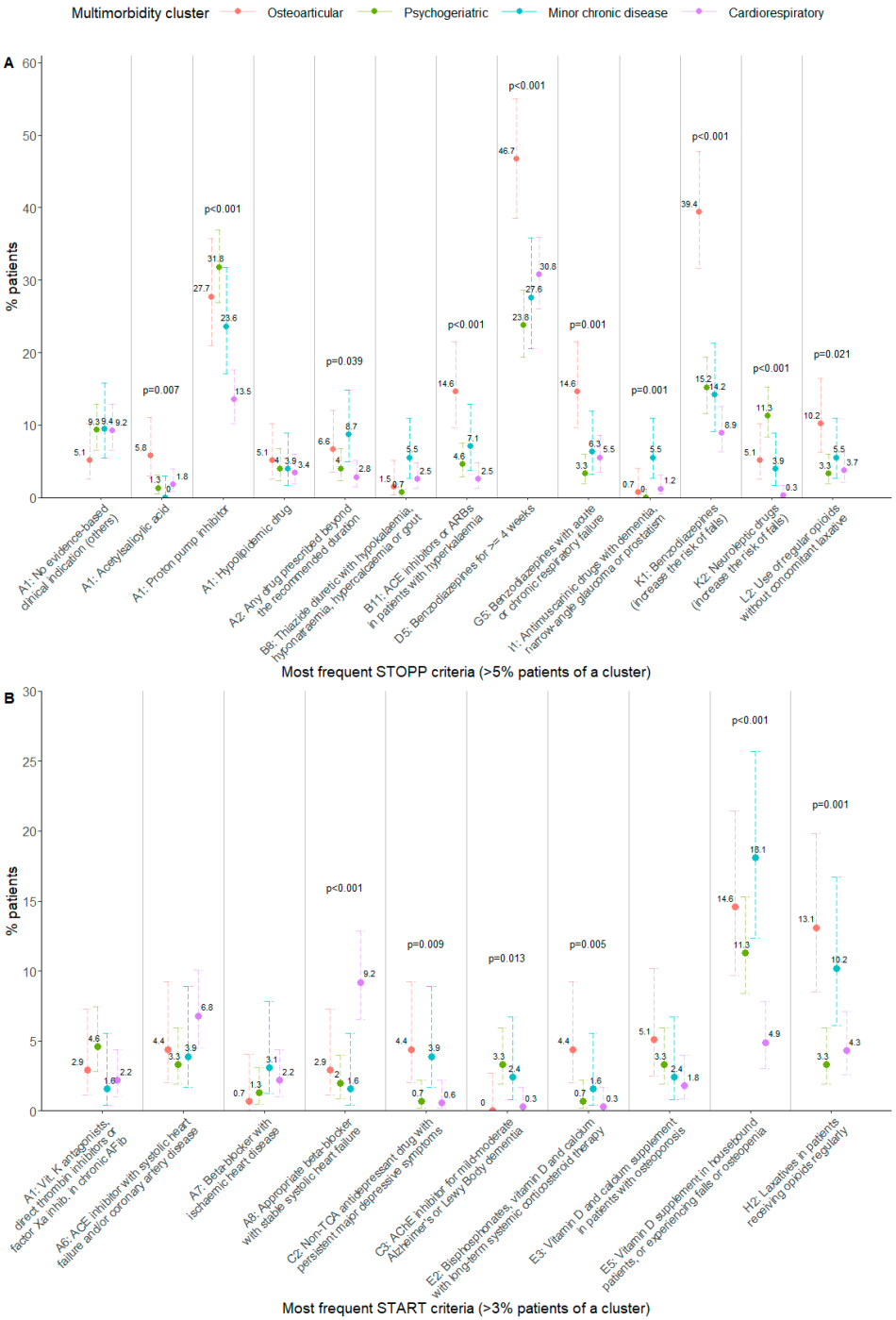

Figure 1. (**A**): Percentage of patients per cluster having the most frequent STOPP PIM criteria. (**B**): Percentage of patients per cluster having the most frequent START PPO criteria. Fisher's exact test *p*-value: *p*-values are shown in the figure when $p < 0.05$. Error bars show 95% confidence interval for the estimated proportion. ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; AFib: atrial fibrillation; TCA: tricyclic antidepressant; AChE: acetylcholinesterase.

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To determine the association of multimorbidity clusters to specific types of ADRs, a bivariate analysis was performed, similarly to the one involving the STOPP/START criteria. Figure 2 shows the percentage of patients that suffered an ADR of a certain drug family according to their assigned multimorbidity cluster, only considering those ADRs detected in at least five patients in a cluster. Patients belonging to the osteoarticular cluster suffered ADRs involving ACE inhibitors more frequently, as well as patients in the minor chronic disease cluster, which more frequently experienced ADRs related to angiotensin receptor blockers or insulin, with respect to the psychogeriatric or cardiorespiratory clusters. Furthermore, ADRs to neuroleptic drugs were more frequently suffered in psychogeriatric patients, and those involving diuretics were also associated with multimorbidity cluster belonging; however, no pairwise differences could be found (Table S7).

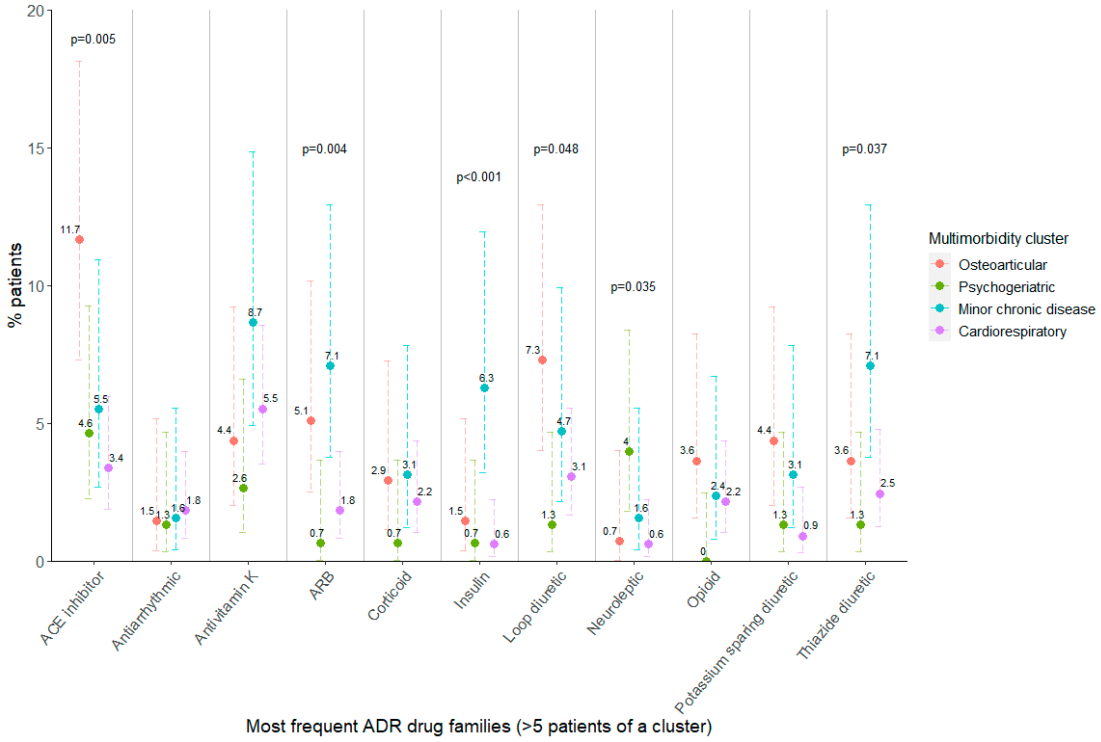

Figure 2. Percentage of patients per cluster having at least one ADR registered in the most frequent drug families. Fisher's exact test *p*-value is shown when $p < 0.05$. ADR: adverse drug reaction; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker. Error bars show 95% confidence interval for the estimated proportion.

Finally, the relationship between multimorbidity cluster and the consequences of ADRs during admission was also tested, and a significant association was found (Figure 3; Fisher's Exact Test: *p*-value = 0.02). For example, 18.8% of patients in the osteoarticular cluster who suffered an ADR during admission faced a life-threatening situation, whereas this did not happen to any patients in the psychogeriatric cluster. Nevertheless, in the psychogeriatric cluster, most ADRs caused a lengthening of hospital stay. None of the ADRs were fatal.

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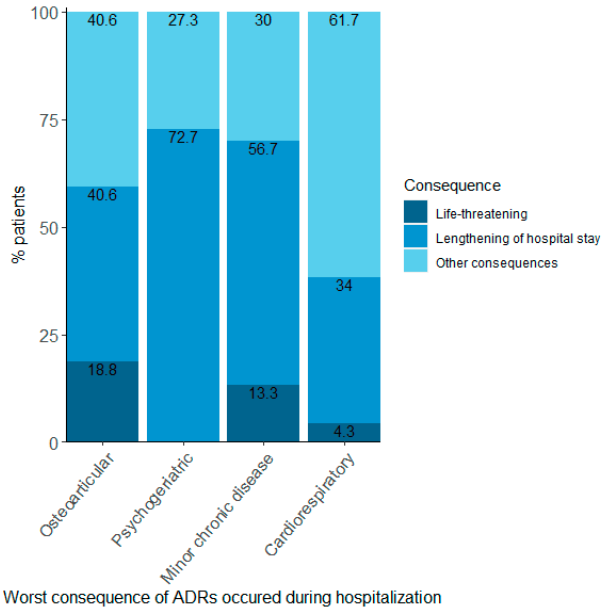

Figure 3. Proportions of patients per cluster according to the worst consequence suffered in those patients with an ADR during hospitalisation. ADR: adverse drug reaction. Fisher's Exact Test: p-value = 0.02.

4. Discussion

4.1. Main Important Results and Novelty

Our study successfully detected significant associations between multimorbidity patterns and specific PIMs, PPOs and ADRs, showing that patients in each multimorbidity cluster tend to present comparable health problems and, therefore, identifying patients with similar needs. The osteoarticular cluster displayed the worst situation regarding PIP and ADRs, particularly related to anxiolytics and antihypertensives. The psychogeriatric cluster, despite having the lowest number of chronic prescriptions, presented PIP of proton pump inhibitors and neuroleptics, with the latter also causing ADRs. The minor chronic disease cluster was associated with ADRs caused by antihypertensives and insulin, and the cardiorespiratory cluster showed fewer PIP and ADRs overall. Altogether, our results support the prioritisation of medication review in patients from the osteoarticular cluster, which accounted for the largest proportion of patients with PIP or ADRs, along with the most severe consequences of ADRs, followed by the minor chronic disease cluster.

This is, to our knowledge, the first study to consider and analyse the relationship of multimorbidity patterns with quality indicators of medication, such as PIP and ADRs. Our approach includes a novel methodology of defining multimorbidity in conjunction with an extensive set of explicit and implicit criteria (STOPP/START) regarding PIMs and PPOs and together with an exhaustive registration of ADRs, providing a unique dataset integrating this information. Significant associations were found between clusters when considering presence, number or specific PIMs, PPOs and ADRs, suggesting that these situations should be differently managed according to each particular patient profile.

4.2. Clinical Implications

The osteoarticular cluster not only presented the highest percentage of patients with at least a PIP or PIM but also a larger number of them than the other clusters. This could be partially explained due to a higher number of chronic prescriptions and is also consistent with the high prevalence found in the three benzodiazepine-related criteria (STOPP D5, G5, K1), frequently coexisting in the same patients. We certainly expected an overall

high prescription of benzodiazepines [43,44], especially in this cluster that has the highest prevalence of depression and anxiety (61.3%). This could even be a result of excessive medicalisation in a female-predominant cluster. It is well-known that benzodiazepine prescribing is excessive [45], and this situation becomes particularly concerning in this patient profile due to its association with negative outcomes such as falls, fractures, dependence and cognitive decline [46]. The almost-ubiquitous prevalence of chronic pain (92.7%), frailty (83.9%) and degenerative arthropathy (81.0%) stress the need for benzodiazepine deprescribing. Nonetheless, we acknowledge the complexity of this process.

Furthermore, we found that side effects in prescribing for pain management might not be properly addressed in the osteoarticular cluster. A significant association with STOPP L2 and START H2 criteria was found, both referring to the requirement of laxative prescription in patients under opioid therapy. This was also found in the minor chronic disease cluster, consistent with its high prevalence of patients with chronic pain (69.3%). Nevertheless, it is plausible that patients in both clusters, which are already taking a large number of medications, could be using some herbal or over-the-counter products. Besides, these results did not correlate well with the prevalence of constipation in the minor chronic disease cluster, which accounted for the lowest proportion (32.3%). This could be explained by differences in the involved opioids, with patients prescribed transdermal fentanyl having less risk of constipation than those on oxycodone or morphine [47,48].

Additionally, the use of antihypertensive and diuretic drugs also posed a challenge in patients from both the osteoarticular and the minor chronic disease clusters (with many registered ADRs) compared to the others. Although it was not always possible to establish significant pairwise comparisons due to a low number of cases, there was a significant association overall. In the specific case of ACE inhibitors, they were found to be significantly different in the osteoarticular cluster as well as detected as PIMs in STOPP criteria B11. Conversely, angiotensin receptor blockers caused ADRs in a higher proportion of patients in the minor chronic disease cluster but were not labelled as inappropriately prescribed. Our results, therefore, suggest that, although side effects of antihypertensive drugs are well-known [49–51], decompensations particularly occur in these patients and may lead to life-threatening situations, which were consistently found to be higher in both clusters. However, these situations may be harder to address, as they might not always be identified as PIMs.

Remarkably, some of the ADRs detected were not caused by a previously identified PIM, revealing one of the limitations of PIP/PPO detection tools. This was especially evident in the minor chronic disease cluster, which unexpectedly presented a high number of ADRs. This cluster appears to be the most heterogeneous of all, and it is possible that this situation may have occurred due to a single disease prescribing approach, where various medications are accumulatively prescribed by different professionals. Moreover, it is also plausible that medication review in these patients, who are the least dependent and are mostly living with other people or alone, was not prioritised.

This situation contrasts with the findings regarding the psychogeriatric cluster, with the lowest number of chronic prescriptions, low number of PIP and ADRs and no in-hospital life-threatening ADRs. This could be explained by an increased effort in medication review and comprehensive clinical management. However, two situations stood out: PIMs of proton pump inhibitors were especially high, and neuroleptics were detected as PIMs and also caused ADRs. These results could be expected, yet problematic, as both are related to a variety of adverse outcomes [52–57], which could cause a high burden in already very frail patients. Therefore, there would still be room for deprescribing.

Lastly, patients in the cardiorespiratory cluster, containing almost half of the cohort, were undoubtedly in the most preferable situation: no remarkable PIMs or ADRs. Only one PPO criterion stood out: lack of a beta blocker prescription, which could be explained by the opposite effect of beta blockers to beta agonists, usually administered in patients with chronic obstructive pulmonary disease (COPD). However, the current literature recommends beta blocker prescribing in patients with heart disease and COPD [58]. All

in all, these patients were minimally dependent, with a low number of chronic conditions and geriatric syndromes. Thus, it is plausible that although they had a chronic pathology exacerbation that led to hospital admission, their health status was overall better and only restricted to cardiorespiratory problems. Therefore, our results suggest these patients might be easier to handle.

Taken together, our results show how multimorbidity profiles built according to chronic conditions and geriatric syndromes have a significant association with PIP and ADRs. On the one hand, these results support the existing evidence on the concept of multimorbidity forming association patterns. The associations found on each profile to some extent validate our methodological approach, which successfully allocates patients with similar situations and needs. On the other hand, these results suggest that appropriate actions according to each patient profile could be taken in hospitals but also in primary care settings, which could be a useful approach to optimise and offer better health care. It is essential to effectively direct efforts in these complex patients, and, in this case, patient categorisation strategies together with multidisciplinary teams could be helpful to address the situation. Thus, further studies are needed to incorporate multimorbidity approaches in all levels of healthcare.

4.3. Comparison to Other Studies

Although there are previous studies on PIP and ADRs in different types of cohorts of multimorbid patients studying the risk factors, outcomes and interventions, the vast majority define multimorbidity with the presence of two or more chronic conditions or consider those from a short list [59–63]. These definitions, although easily determined, become too simplistic in a setting of older hospitalised patients, where almost all are multimorbid (98.7% in our cohort). Therefore, new analytical strategies need to be explored that consider a more comprehensive definition of multimorbidity, as there are currently no publications directly comparable to ours.

The most similar study is the one carried out by Teh et al., in 2018 [14], comparing multimorbidity patterns to the presence of any PIM or any PPO, but without considering explicit criteria nor ADRs. Multimorbidity profiles are built with a similar methodology and agreed upon by consensus among a multidisciplinary team involving clinicians as well. However, the cohort is comprised of community patients over 80 years old, considering a list of 14 conditions and using the first version of STOPP/START criteria, which disallows comparisons. Nonetheless, the cluster with the highest proportion of patients with any PIMs or PPOs is called 'depression and arthritis' and presents the highest prevalence of osteoporosis and osteoarthritis, suggesting that this cluster could be similar to the osteoarticular cluster from our cohort, which also presents depression and anxiety. In this article, the authors conclude that profiles of conditions may carry stronger associations with cross-sectional outcomes than the sum of those conditions.

4.4. Strengths and Limitations

This study presents multiple strengths. As a multicentre study, it presents increased external validity. Its prospective design ensures high data quality by an accurate and thorough registering of variables that may commonly be underreported, such as PIP and ADRs. In this sense, it is important that a multidisciplinary team composed of pharmacists and physicians work together in the medication-review process.

Furthermore, the approach of multimorbidity cluster analysis is novel and methodologically robust, incorporating both chronic conditions and geriatric syndromes and allowing for work with patient profiles instead of single conditions. Moreover, this study has been carried out with a well-defined cohort of hospitalised patients admitted due to chronic condition exacerbation. This constitutes a particularly vulnerable and complex group of patients, who may largely benefit from a reduction in negative outcomes. Finally, the unique approach of the study, considering multimorbidity patterns with specific PIP

and ADRs all together, allows for obtaining a reliable picture of a complex situation that needs to be explored and addressed.

Nonetheless, some limitations of this study need to be taken into account. Firstly, methodological approaches to tackle multimorbidity are highly variable, and there is no consensus on the best practices to determine multimorbidity patterns. The results of this study are conditioned to the predefined multimorbidity patterns, which could be questioned, although they were comprehensive, considering a large list of conditions, and consensually selected by a research team including clinicians. Secondly, there may be differences in the reporting of PIP or ADRs between centres or healthcare professionals, despite the large efforts made to homogenise criteria. Regarding ADRs, active principles alone could not be analysed due to low occurrence so had to be collapsed into higher-level categories. Finally, the direct relationship between PIP and ADRs was not addressed, as this was far from the objectives of these analyses.

5. Conclusions

In older patients admitted to hospital because of chronic conditions' exacerbation, it is possible to define multimorbidity clusters that are associated with quality indicators of medication prescribing such as the presence, number or specific types of PIP and ADRs. These associations validate and support the existence of such clusters and point to specific prescriptions that could be primarily reviewed and made adequate for each patient profile. Thus, determining the relationship between multimorbidity profiles and the quality indicators of medication could be key in remodelling and optimising healthcare processes in order to tackle the increasing prevalence of older patients with multimorbidity.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph192315902/s1, Figure S1: (A): Distribution of the number of STOPP/START PIP according to the assigned multimorbidity cluster. Pairwise comparisons be-tween cluster distributions performed with the Kolmogorov-Smirnov test showed significant differences between the osteoar-ticular cluster and the rest ($p < 0.001$). PIP: Potentially inappropriate prescribing. (B): Distribution of the number of STOPP PIM according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed significant differences between the osteoarticular cluster and the rest ($p < 0.005$). PIM: potentially inappropriate medication. (C): Distribution of the number of START PPO according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed no significant differences ($p > 0.05$). PPO: potential prescribing omission; Figure S2: (A): Distribution of the number of ADRs according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed significant differences between the osteoarticular and the minor chronic disease clusters and the rest ($p < 0.001$). (B): Distribution of the number of ADRs at admission according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed significant differences between the osteoarticular cluster and the minor chronic disease clusters and the rest ($p < 0.05$). (C): Distribution of the number of ADRs during admission according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed no significant differences ($p > 0.05$). ADR: adverse drug reaction; Table S1: Equivalences between names used in ADRs classification and ATC codes; Table S2: Number and percentage of patients with each chronic condition or geriatric syndrome registered according to the assigned multimorbidity cluster; Table S3: *p*-values of post-hoc pairwise; Table S4: *p*-values of post-hoc pairwise; Table S5: *p*-values of post-hoc pairwise; Table S6: *p*-values of post-hoc pairwise; Table S7: *p*-values of post-hoc pairwise.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the institutional review board (or ethics committee) of each centre: Comité Ético de investigación Clínica del Parc Taulí (ID: 20166570), Comitè Ètic d'Investigació Clínica Osona per a la Recerca i Educació Sanitàries (FORES) (ID: 2016922-PR153), Comité de Ètica de la Investigación con Medicamentos (CEIm)-Parc de Salut MAR (ID: 2016/6830/I), Comité Ético de Investigación Clínica de Euskadi (ID: PI2016060) and Comité de Ética de Investigación del Hospital Universitario de Canarias (ID: MBM-MOD-2016-01 (2016-56)). No written informed consent was deemed necessary for this study.

Informed Consent Statement: Written patient consent was waived considering that they were often very old patients, in an acute process with intellectual impairment or delirium, and sometimes living alone or in a nursing home and that it would have been difficult to explain patient consent and make sure it was understood. In this observational study, we considered it important to include patients who were representative of all complex clinical conditions and to elude a possible selection bias (especially frequent in older patients) that would have invalidated the results. On the other hand, data (not included in these analyses) about chronic medications, PIP and intention to modify the treatment, during the first days related to possible PIP, had to be gathered at the beginning of the hospitalisation period and could not be delayed.

Data Availability Statement: The data presented in this study are openly available in Zenodo at DOI 10.5281/zenodo.7371151.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Fortin, M.; Stewart, M.; Poitras, M.-E.; Almirall, J.; Maddocks, H. A Systematic Review of Prevalence Studies on Multimorbidity: Toward a More Uniform Methodology. *Ann. Fam. Med.* **2012**, *10*, 142–151. [CrossRef] [PubMed]
2. Barnett, K.; Mercer, S.W.; Norbury, M.; Watt, G.; Wyke, S.; Guthrie, B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet* **2012**, *380*, 37–43. [CrossRef] [PubMed]
3. The Academy of Medical Sciences. *Multimorbidity: A Priority For Global Health Research*; The Academy of Medical Sciences: London, UK, 2018; Available online: https://acmedsci.ac.uk/file-download/82222577 (accessed on 8 August 2022).
4. Rijken, M.; Struckmann, V.; Van Der Heide, I.; Hujala, A.; Barbabella, F.; Van Ginneken, E.; Schellevis, F. *How to Improve Care For People with Multimorbidity in Europe?* European Observatory on Health Systems and Policies: Brussels, Belgium, 2016; Available online: 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 (accessed on 8 August 2022).
5. Johnston, M.C.; Crilly, M.; Black, C.; Prescott, G.J.; Mercer, S.W. Defining and measuring multimorbidity: A systematic review of systematic reviews. *Eur. J. Public Health* **2019**, *29*, 182–189. [CrossRef] [PubMed]
6. Prados-Torres, A.; Calderón-Larrañaga, A.; Hancco-Saavedra, J.; Poblador-Plou, B.; van den Akker, M. Multimorbidity patterns: A systematic review. *J. Clin. Epidemiol.* **2014**, *67*, 254–266. [CrossRef]
7. Diederichs, C.; Berger, K.; Bartels, D.B. The Measurement of Multiple Chronic Diseases—A Systematic Review on Existing Multimorbidity Indices. *J. Gerontol. Ser. A* **2011**, *66*, 301–311. [CrossRef]
8. Violán, C.; Foguet-Boreu, Q.; Fernández-Bertolín, S.; Guisado-Clavero, M.; Cabrera-Bean, M.; Formiga, F.; Valderas, J.M.; Roso-Llorach, A. Soft clustering using real-world data for the identification of multimorbidity patterns in an elderly population: Cross-sectional study in a Mediterranean population. *BMJ Open* **2019**, *9*, e029594. [CrossRef]
9. Zacarías-Pons, L.; Vilalta-Franch, J.; Turró-Garriga, O.; Saez, M.; Garre-Olmo, J. Multimorbidity patterns and their related characteristics in European older adults: A longitudinal perspective. *Arch. Gerontol. Geriatr.* **2021**, *95*, 104428. [CrossRef]
10. Ng, S.K.; Tawiah, R.; Sawyer, M.; Scuffham, P. Patterns of multimorbid health conditions: A systematic review of analytical methods and comparison analysis. *Int. J. Epidemiol.* **2018**, *47*, 1687–1704. [CrossRef]
11. Juul-Larsen, H.G.; Andersen, O.; Bandholm, T.; Bodilsen, A.C.; Kallemose, T.; Jørgensen, L.M.; Klausen, H.H.; Gilkes, H.; Petersen, J. Differences in function and recovery profiles between patterns of multimorbidity among older medical patients the first year after an acute admission—An exploratory latent class analysis. *Arch. Gerontol. Geriatr.* **2019**, *86*, 103956. [CrossRef]
12. Lleal, M.; Corral-Vázquez, C.; Baré, M.; Comet, R.; Herranz, S.; Baigorri, F.; Gimeno-Miguel, A.; Raurich, M.; Fortià, C.; Navarro, M.; et al. Multimorbidity patterns in COVID-19 patients and their relationship to infection severity: MRisk-COVID study. *PLoS ONE* **2022**. *under review*.
13. Zheng, D.D.; Loewenstein, D.A.; Christ, S.L.; Feaster, D.J.; Lam, B.L.; McCollister, K.E.; Curiel-Cid, R.E.; Lee, D.J. Multimorbidity patterns and their relationship to mortality in the US older adult population. *PLoS ONE* **2021**, *16*, e0245053. [CrossRef] [PubMed]
14. Teh, R.O.; Menzies, O.H.; Connolly, M.J.; Doughty, R.N.; Wilkinson, T.J.; Pillai, A.; Lumley, T.; Ryan, C.; Rolleston, A.; Broad, J.; et al. Patterns of multi-morbidity and prediction of hospitalisation and all-cause mortality in advanced age. *Age Ageing* **2018**, *47*, 261–268. [CrossRef] [PubMed]
15. Juul-Larsen, H.G.; Christensen, L.D.; Bandholm, T.; Andersen, O.; Kallemose, T.; Jørgensen, L.M.; Petersen, J. Patterns of Multimorbidity and Differences in Healthcare Utilization and Complexity Among Acutely Hospitalized Medical Patients (≥65 Years)–A Latent Class Approach. *Clin. Epidemiol.* **2020**, *2020*, 245–259. [CrossRef] [PubMed]
16. Carmona-Pírez, J.; Ioakeim-Skoufa, I.; Gimeno-Miguel, A.; Poblador-Plou, B.; González-Rubio, F.; Muñoyerro-Muñiz, D.; Rodríguez-Herrera, J.; Goicoechea-Salazar, J.A.; Prados-Torres, A.; Villegas-Portero, R. Multimorbidity Profiles and Infection Severity in COVID-19 Population Using Network Analysis in the Andalusian Health Population Database. *Int. J. Environ. Res. Public Health* **2022**, *19*, 3808. [CrossRef] [PubMed]
17. Mangoni, A.A.; Jackson, S.H.D. Age-related changes in pharmacokinetics and pharmacodynamics: Basic principles and practical applications. *Br. J. Clin. Pharmacol.* **2003**, *57*, 6–14. [CrossRef] [PubMed]
18. Motter, F.R.; Fritzen, J.S.; Hilmer, S.N.; Paniz, É.V.; Paniz, V.M.V. Potentially inappropriate medication in the elderly: A systematic review of validated explicit criteria. *Eur. J. Clin. Pharmacol.* **2018**, *74*, 679–700. [CrossRef] [PubMed]
19. Corsonello, A.; Pedone, C.; Incalzi, R.A. Age-Related Pharmacokinetic and Pharmacodynamic Changes and Related Risk of Adverse Drug Reactions. *Curr. Med. Chem.* **2010**, *17*, 571–584. [CrossRef]
20. Boparai, M.K.; Korc-Grodzicki, B. Prescribing for Older Adults. *Mt. Sinai J. Med. A J. Transl. Pers. Med.* **2011**, *78*, 613–626. [CrossRef]
21. O'Mahony, D.; O'Sullivan, D.; Byrne, S.; O'Connor, M.N.; Ryan, C.; Gallagher, P. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. *Age Ageing* **2014**, *44*, 213–218. [CrossRef]
22. Cadogan, C.A.; Ryan, C.; Hughes, C.M. Appropriate Polypharmacy and Medicine Safety: When Many is not Too Many. *Drug Saf.* **2016**, *39*, 109–116. [CrossRef]
23. Cherubini, A.; Corsonello, A.; Lattanzio, F. Underprescription of Beneficial Medicines in Older People: Causes, Consequences and Prevention. *Drugs Aging* **2012**, *29*, 463–475. [CrossRef] [PubMed]
24. Fernández-Regueiro, R.; Fonseca-Aizpuru, E.; López-Colina, G.; Álvarez-Uría, A.; Rodríguez-Ávila, E.; Morís-De-La-Tassa, J. Prescripción inadecuada y efectos adversos a medicamentos en pacientes de edad avanzada. *Rev. Clín. Esp.* **2011**, *211*, 400–406. [CrossRef] [PubMed]

25. Hamilton, H.; Gallagher, P.; Ryan, C.; Byrne, S.; O'Mahony, D. Potentially Inappropriate Medications Defined by STOPP Criteria and the Risk of Adverse Drug Events in Older Hospitalized Patients. *Arch. Intern. Med.* **2011**, *171*, 1013–1019. [CrossRef] [PubMed]
26. Mekonnen, A.B.; Redley, B.; de Courten, B.; Manias, E. Potentially inappropriate prescribing and its associations with health-related and system-related outcomes in hospitalised older adults: A systematic review and meta-analysis. *Br. J. Clin. Pharmacol.* **2021**, *87*, 4150–4172. [CrossRef]
27. Oscanoa, T.J.; Lizaraso, F.; Carvajal, A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. *Eur. J. Clin. Pharmacol.* **2017**, *73*, 759–770. [CrossRef]
28. Cabré, M.; Elias, L.; Garcia, M.; Palomera, E.; Serra-Prat, M. Avoidable hospitalizations due to adverse drug reactions in an acute geriatric unit. Analysis of 3,292 patients. *Med. Clín.* **2018**, *150*, 209–214. [CrossRef]
29. Jennings, E.L.M.; Murphy, K.D.; Gallagher, P.; O'Mahony, D. In-hospital adverse drug reactions in older adults; prevalence, presentation and associated drugs—A systematic review and meta-analysis. *Age Ageing* **2020**, *49*, 948–958. [CrossRef]
30. Baré, M.; Herranz, S.; Jordana, R.; Gorgas, M.Q.; Ortonobes, S.; Sevilla, D.; De Jaime, E.; Ibarra, O.; Martín, C. 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. [CrossRef]
31. Baré, M.; Herranz, S.; Roso-Llorach, A.; Jordana, R.; Violán, C.; Lleal, M.; Roura-Poch, P.; Arellano, M.; Estrada, R.; Nazco, G.J. Multimorbidity patterns of chronic conditions and geriatric syndromes in older patients from the MoPIM multicentre cohort study. *BMJ Open* **2021**, *11*, e049334. [CrossRef]
32. Mahoney, F.I.; Barthel, D.W. Functional evaluation: The Barthel Index. *Md. State Med. J.* **1965**, *14*, 61–65.
33. Charlson, M.E.; Pompei, P.; Ales, K.L.; MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic Dis.* **1987**, *40*, 373–383. [CrossRef] [PubMed]
34. WHO Centre for Health Development. *A Glossary of Terms for Community Health Care and Services for Older Persons*; WHO Kobe Centre for Health Development Ageing and Health Technical Report; World Health Organization: Geneva, Switzerland, 2004; Available online: http://apps.who.int/iris/bitstream/handle/10665/68896/WHO_WKC_Tech.Ser._04.2.pdf (accessed on 27 October 2022).
35. European Medicines Agency; Heads of Medicines Agencies. *Guideline on Good Pharmacovigilance Practices (GVP) Module VI–Management and Reporting of Adverse Reactions to Medicinal Products (Rev 1)*; European Medicines Agency: Amsterdam, The Netherlands, 2014.
36. Mascolo, A.; Scavone, C.; Sessa, M.; di Mauro, G.; Cimmaruta, D.; Orlando, V.; Rossi, F.; Sportiello, L.; Capuano, A. Can causality assessment fulfill the new European definition of adverse drug reaction? A review of methods used in spontaneous reporting. *Pharmacol. Res.* **2017**, *123*, 122–129. [CrossRef] [PubMed]
37. Quan, H.; Li, B.; Couris, C.M.; Fushimi, K.; Graham, P.; Hider, P.; Januel, J.-M.; Sundararajan, V. 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*, 676–682. [CrossRef]
38. Chavent, M.; Kuentz-Simonet, V.; Labenne, A.; Saracco, J. Multivariate analysis of mixed data: The R package PCAmixdata. *arXiv* **2014**, arXiv:1411.4911.
39. Bezdek, J.C.; Ehrlich, R.; Full, W. FCM: The fuzzy c-means clustering algorithm. *Comput. Geosci.* **1984**, *10*, 191–203. [CrossRef]
40. Baré, M.; Lleal, M.; Ortonobes, S.; Gorgas, M.Q.; Sevilla-Sánchez, D.; Carballo, N.; De Jaime, E.; Herranz, S. Factors associated to potentially inappropriate prescribing in older patients according to STOPP/START criteria: MoPIM multicentre cohort study. *BMC Geriatr.* **2022**, *22*, 44. [CrossRef] [PubMed]
41. Benjamini, Y.; Hochberg, Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J. R. Stat. Soc. Ser. B* **1995**, *57*, 289–300. [CrossRef]
42. R Core Team. R: A Language and Environment for Statistical Computing. 2020. Available online: https://www.r-project.org/ (accessed on 20 April 2022).
43. Torres-Bondia, F.; De Batlle, J.; Galván, L.; Buti, M.; Barbé, F.; Piñol-Ripoll, G. Trends in the consumption rates of benzodiazepines and benzodiazepine-related drugs in the health region of Lleida from 2002 to 2015. *BMC Public Health* **2020**, *20*, 818. [CrossRef]
44. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Utilización de medicamentos ansiolíticos e hipnóticos en España [Use of anxiolytic and hypnotic drugs in Spain]. 2021. Available online: https://www.aemps.gob.es/medicamentos-de-uso-humano/observatorio-de-uso-de-medicamentos/informes-ansioliticos-hipnoticos/ (accessed on 6 October 2022).
45. Gerlach, L.B.; Wiechers, I.R.; Maust, D.T. Prescription Benzodiazepine Use Among Older Adults: A Critical Review. *Harv. Rev. Psychiatry* **2018**, *26*, 264–273. [CrossRef]
46. Markota, M.; Rummans, T.A.; Bostwick, J.M.; Lapid, M.I. Benzodiazepine Use in Older Adults: Dangers, Management, and Alternative Therapies. *Mayo Clin. Proc.* **2016**, *91*, 1632–1639. [CrossRef]
47. Hadley, G.; Derry, S.; Moore, R.A.; Wiffen, P.J. Transdermal fentanyl for cancer pain. *Cochrane Database Syst. Rev.* **2013**, *2018*, CD010270. [CrossRef] [PubMed]
48. Ackerman, S.J.; Knight, T.; Schein, J.; Carter, C.; Staats, P. Risk of Constipation in Patients Prescribed Fentanyl Transdermal System or Oxycodone Hydrochloride Controlled-Release in a California Medicaid Population. *Consult. Pharm.* **2004**, *19*, 118–132. [CrossRef] [PubMed]

49. Oliveros, E.; Patel, H.; Kyung, S.; Fugar, S.; Goldberg, A.; Madan, N.; Williams, K.A. Hypertension in older adults: Assessment, management, and challenges. *Clin. Cardiol.* **2019**, *43*, 99–107. [CrossRef]
50. Na Takuathung, M.; Sakuludomkan, W.; Khatsri, R.; Dukaew, N.; Kraivisitkul, N.; Ahmadmusa, B.; Mahakkanukrauh, C.; Wangthaweesap, K.; Onin, J.; Srichai, S.; et al. Adverse Effects of Angiotensin-Converting Enzyme Inhibitors in Humans: A Systematic Review and Meta-Analysis of 378 Randomized Controlled Trials. *Int. J. Environ. Res. Public Health* **2022**, *19*, 8373. [CrossRef] [PubMed]
51. Townsend, R.R. Major Side Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers. UpToDate. Available online: https://www.uptodate.com/contents/major-side-effects-of-angiotensin-converting-enzyme-inhibitors-and-angiotensin-ii-receptor-blockers (accessed on 13 October 2022).
52. Jaynes, M.; Kumar, A.B. The risks of long-term use of proton pump inhibitors: A critical review. *Ther. Adv. Drug Saf.* **2018**, *10*, 2042098618809927. [CrossRef] [PubMed]
53. Al-Aly, Z.; Maddukuri, G.; Xie, Y. Proton Pump Inhibitors and the Kidney: Implications of Current Evidence for Clinical Practice and When and How to Deprescribe. *Am. J. Kidney Dis.* **2020**, *75*, 497–507. [CrossRef]
54. Lee, S.-H.; Hsu, W.-T.; Lai, C.-C.; Esmaily-Fard, A.; Tsai, Y.-W.; Chiu, C.-C.; Wang, J.; Chang, S.-S.; Lee, C. Use of antipsychotics increases the risk of fracture: A systematic review and meta-analysis. *Osteoporos. Int.* **2017**, *28*, 1167–1178. [CrossRef]
55. Nosè, M.; Recla, E.; Trifirò, G.; Barbui, C. Antipsychotic drug exposure and risk of pneumonia: A systematic review and meta-analysis of observational studies. *Pharmacoepidemiol. Drug Saf.* **2015**, *24*, 812–820. [CrossRef]
56. Zhai, Y.; Yin, S.; Zhang, D. Association between Antipsychotic Drugs and Mortality in Older Persons with Alzheimer's Disease: A Systematic Review and Meta-Analysis. *J. Alzheimer's Dis.* **2016**, *52*, 631–639. [CrossRef]
57. Atti, A.; Gozzi, B.F.; Zuliani, G.; Bernabei, V.; Scudellari, P.; Berardi, D.; De Ronchi, D.; Tarricone, I.; Menchetti, M. A systematic review of metabolic side effects related to the use of antipsychotic drugs in dementia. *Int. Psychogeriatr.* **2013**, *26*, 19–37. [CrossRef]
58. Yang, Y.-L.; Xiang, Z.-J.; Yang, J.-H.; Wang, W.-J.; Xu, Z.-C.; Xiang, R.-L. Association of β-blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: A systematic review and meta-analysis. *Eur. Heart J.* **2020**, *41*, 4415–4422. [CrossRef] [PubMed]
59. Jungo, K.T.; Streit, S.; Lauffenburger, J.C. Patient factors associated with new prescribing of potentially inappropriate medications in multimorbid US older adults using multiple medications. *BMC Geriatr.* **2021**, *21*, 163. [CrossRef] [PubMed]
60. Lee, J.Q.; Ying, K.; Lun, P.; Tan, K.T.; Ang, W.; Munro, Y.; Ding, Y.Y. Intervention elements to reduce inappropriate prescribing for older adults with multimorbidity receiving outpatient care: A scoping review. *BMJ Open* **2020**, *10*, e039543. [CrossRef]
61. O'Mahony, D.; Gallagher, P.F.; Lavan, A.H. Methods to reduce prescribing errors in elderly patients with multimorbidity. *Clin. Interv. Aging* **2016**, *11*, 857–866. [CrossRef] [PubMed]
62. O'Mahony, D.; O'Connor, M.N.; Eustace, J.; Byrne, S.; Petrovic, M.; Gallagher, P. The adverse drug reaction risk in older persons (ADRROP) prediction scale: Derivation and prospective validation of an ADR risk assessment tool in older multi-morbid patients. *Eur. Geriatr. Med.* **2018**, *9*, 191–199. [CrossRef]
63. Laatikainen, O.; Sneck, S.; Turpeinen, M. Medication-related adverse events in health care—What have we learned? A narrative overview of the current knowledge. *Eur. J. Clin. Pharmacol.* **2021**, *78*, 159–170. [CrossRef]

5.2. Study 2: MRisk-COVID study

Publication of the second study

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RESEARCH ARTICLE

Multimorbidity patterns in COVID-19 patients and their relationship with infection severity: MRisk-COVID study

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Abstract

Background

Several chronic conditions have been identified as risk factors for severe COVID-19 infection, yet the implications of multimorbidity need to be explored. The objective of this study was to establish multimorbidity clusters from a cohort of COVID-19 patients and assess their relationship with infection severity/mortality.

Methods

The MRisk-COVID Big Data study included 14 286 COVID-19 patients of the first wave in a Spanish region. The cohort was stratified by age and sex. Multimorbid individuals were subjected to a fuzzy c-means cluster analysis in order to identify multimorbidity clusters within each stratum. Bivariate analyses were performed to assess the relationship between severity/mortality and age, sex, and multimorbidity clusters.

Results

Severe infection was reported in 9.5% (95% CI: 9.0–9.9) of the patients, and death occurred in 3.9% (95% CI: 3.6–4.2). We identified multimorbidity clusters related to severity/mortality

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Abbreviations: AQuAS, Agency for Health Quality and Assessment of Catalonia; CC, Chronic condition; COPD, Chronic obstructive pulmonary disease; CV, Cardiovascular; DM, Diabetes mellitus; HC3, Shared Clinical History of Catalonia; ICD-10-CM, International Classification of Diseases, 10th edition, Clinical Modification; ICD-10-PCS, International Classification of Diseases, 10th edition, Procedure Coding System; MM, Multimorbidity; O/E, Observed/Expected; PADRIS, Public Data Analysis for Health Research and Innovation Program; SUVEC, Catalan Epidemiological Surveillance Emergency Service.

in most age groups from 21 to 65 years. In males, the cluster with highest percentage of severity/mortality was *Heart-liver-gastrointestinal* (81–90 years, 34.1% severity, 29.5% mortality). In females, the clusters with the highest percentage of severity/mortality were *Diabetes-cardiovascular* (81–95 years, 22.5% severity) and *Psychogeriatric* (81–95 years, 16.0% mortality).

Conclusion

This study characterized several multimorbidity clusters in COVID-19 patients based on sex and age, some of which were found to be associated with higher rates of infection severity/mortality, particularly in younger individuals. Further research is encouraged to ascertain the role of specific multimorbidity patterns on infection prognosis and identify the most vulnerable morbidity profiles in the community.

Trial registration

NCT04981249. Registered 4 August 2021 (retrospectively registered).

Background

The first wave of the COVID-19 pandemic caused high rates of death and critical infection. The first studies quickly identified a differential vulnerability depending on age and sex, so that higher rates of death and severity were detected in older and male individuals [1, 2].

The study of the relationship between isolated chronic diseases and COVID-19 infection has resulted in the identification of diverse morbidities as potential risk factors, such as diabetes mellitus (DM), obesity, hypertension, heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and cardiovascular (CV) conditions [3–10]. Noticeably, many of these conditions share some pathophysiological pathways, suggesting that their interactions could increase the risk of a poor COVID-19 prognosis, and that their identification would help in the management of the disease. Nevertheless, few research works have examined the interaction between multiple diseases and its impact on COVID-19 outcomes [8, 11–13].

Multimorbidity (MM), which is traditionally defined as the concomitance of two or more chronic conditions (CC) in the same individual, is a highly prevalent issue that increases with age and society ageing [14–17]. Multimorbid patients may present complex profiles associated to pathophysiological interactions that could complicate medical treatment [18, 19]. However, there is no gold standard in the characterization of MM due to the novelty of the research field, and many studies analyse the mere presence or absence of MM, the sole number of CC, pre-established scores such as the Charlson Multimorbidity Index, or the aggregation of CC by factor analysis or hard hierarchical-clustering methods [20–22].

Remarkably, new strategies that more accurately reflect the complex, non-random association of CC in a patient-centred point of view are emerging, such as soft (or fuzzy) clustering analysis [23–25]. This technique has already provided relevant results in previous studies, so that several relationships between MM patterns and clinically relevant outcomes such as disability, adverse drug reactions, hospitalization, or mortality have been identified [26–30].

In order to perform a solid profiling of the MM patterns, detailed medical information is needed. In this sense, the use of Big Data provides a quick and exhaustive covering of large datasets. Indeed, the access to public healthcare Big Data facilitated by several state organisms

enabled rapid analyses, yielding relevant results, and leading to a better handling of the pandemic [13, 31–33].

Given the previous statements, the aim of the present study, encompassed in the MRisk-COVID Big Data project, was to provide an age- and sex-centred characterization of the MM clusters of an adult COVID-19 cohort and to assess the relationship between these clusters and the severity and mortality of the infection.

Methods

Study design and cohort

The MRisk-COVID study is an observational Big Data research project based on a cohort of 14286 COVID-19 patients aged >20 years, residing in a healthcare zone of about 400000 inhabitants in the Northeast region of Spain (Vallès Occidental est). This healthcare zone is situated within the autonomous community of Catalonia, specifically within the province of Barcelona, and encompasses a single reference hospital, Parc Taulí Hospital Universitari. Data were provided by the Agency for Health Quality and Assessment of Catalonia (AQuAS) in the framework of the Public Data Analysis for Health Research and Innovation Program (PADRIS), under an extraordinary call that took place in April 2020 in order to provide healthcare Big Data for COVID-19 research studies.

The cohort of this study is composed by all COVID-19 cases registered between 27th February and 15th June of 2020 by the Catalan Epidemiological Surveillance Emergency Service (SUVEC) as either confirmed cases (identified through positive PCR, ELISA or rapid antibody test), or suspected cases (no positive test result, but exhibited symptoms and were classified as potential cases by physicians). The study did not involve sampling, as it encompasses all individuals who met the inclusion criteria. The International Classification of Diseases, 10th edition, Clinical Modification (ICD-10-CM) codes considered as COVID-19 diagnoses are summarized in S1 Table.

Ethics statement

The study was approved by the Ethics Committee (CEIm) of the Parc Taulí University Hospital (reference 2021/5067), which waived the requirement of informed consents due to the epidemiological nature of the study and the use of anonymized data provided by PADRIS. This study was conducted according to the principles expressed in the Declaration of Helsinki.

Big data processing, data linkage and study outcomes

Demographic information and clinical records were compiled, integrated and analysed. Demographic data were obtained from the Shared Clinical History of Catalonia (HC3) and included age and sex. In order to prevent re-identification of the patients, age was provided by PADRIS in quinquennia, and groups with high risk of re-identification were not included (women aged >95 and men aged >90). Clinical records were obtained from any primary healthcare centre and hospital of Catalonia that the individuals attended. The provided records covered from 1923 to 2020 in primary healthcare centres, and from 2016 to 2020 in hospitals. These data encompassed all diagnoses and hospital procedures, including the index hospitalization episode of COVID-19 infection. Information about admission and discharge circumstances was also provided (S1 Fig). Patients' data were stratified by sex and age, thereby obtaining eight different datasets (groups of 21–45, 46–65, 66–80 and 81–95 years, separated into male and female individuals).

Infection severity was defined as the occurrence of at least one of the following conditions during any of the registered COVID-19 episodes: severe respiratory affection (including insufficiency, failure, or distress); use of respiratory support (including mechanical ventilation or oxygen therapy); septic shock; multiple organ failure (the combination of respiratory failure and any other organ failure); inflammatory response; admission to intensive care unit; and mortality associated with COVID-19 episodes (either registered by epidemiological surveillance, primary care or hospital records). This definition was based on the COVID-19 Treatment Guidelines provided by National Institutes of Health [34], with some modifications under the research group physicians' criteria. The ICD-10-CM and ICD-10 Procedure Coding System (PCS) codes considered as severity conditions are compiled in S1 Table. Besides, mortality was also assessed independently.

Data compilation, processing and statistical analysis were performed using R [35] and RStudio [36].

Multimorbidity cluster analysis

The ICD-10-CM codes of the complete diagnoses records were categorized into chronic or acute diseases by the Chronic Condition Indicator v.2021.1 [37], and only CC were selected. Then, in order to reduce the number of variables for the cluster analysis, diagnoses were grouped and classified by the Clinical Classification Software Refined v.2021.1 [37]. This software provides a hierarchical classification of the diagnoses into general CC categories (e.g. *Asthma*, or *Chronic obstructive pulmonary disease and bronchiectasis*), which, in turn, belong to disease families (e.g. *Diseases of the respiratory system*). The CC of the family *Neoplasms* were manually distributed into two general categories: *Neoplasia (solid tumour)*, and *Hematologic neoplasia*.

The clustering procedure was independently applied to each sex-age group. For each stratum, CC were filtered by prevalence (>2%) and only patients with MM, as defined by the presence of 2 or more CC, were included in the analyses. The clustering methodology was adapted from the one described by Vetrano et al [28]. An initial dimension reduction of the CC datasets was performed by a Multiple Correspondence Analysis, using the elbow criteria in the Scree plot for dimension selection. The resulting data were subjected to soft clustering analysis by the fuzzy c-means algorithm. This algorithm requires two main parameters: the number of desired clusters (C) and the fuzziness (m), which indicates the degree of overlapping membership of the patients to the clusters. This parameter can range from 1 (equivalent to hard, non-overlapping clustering) to infinite. Several values of C (4, 5, 6 and 7) and m (1.1, 1.2, 1.4, 1.5, 2, and 4) were tested. Since fuzzy c-means is a stochastic method, 100 iterations were performed for each combination of C and m in order to obtain mean and reproducible results. The optimal m was estimated by the mean calculation of five indexes: Calinski–Harabasz, Partition coefficient (both optimal at their highest value), Partition entropy, Fukuyama, and Xie-Beni (the three of them optimal at their lowest value).

The final C for each sex and age stratum was determined through consensus among 11 professionals of the multidisciplinary research group. This agreement was achieved following a Delphi-like selection method that consisted on equal voting through two selection rounds. Consensus was defined when one of the options reached a majority of votes (≥6); cases with lack of consensus or similar voting count were decided through a clinical debate session.

Several indicators were calculated for the CC in each cluster in order to characterize the specificity and composition of the MM patterns: a) Prevalence within the cluster (%); b) Observed/Expected (O/E) ratio, estimated by dividing the prevalence in the cluster by the prevalence in the corresponding age-sex group cohort; and c) Exclusivity (%), obtained by dividing

the number of patients that presented the CC in the cluster by the total number of patients affected by the CC in the corresponding age-sex group cohort. A generic label was assigned to each cluster in an attempt to summarize the most prevalent and overexpressed CC as well as to facilitate the clinical interpretation of the results. Regarding patients, membership percentages were calculated, indicating the degree of belonging of each patient to the selected clusters.

Statistical analysis

Statistical bivariate differences between severe and non-severe cases, as well as dead and survivor cases, were measured by chi-square tests in the case of categorical/dichotomous variables (age, sex, and MM) and Wilcoxon signed-rank tests in the case of continuous variables (number of CC).

The statistical relationship between mortality / severity and the MM clusters was assessed by weighted chi-square tests, where the weight of the variables was the percentage of membership of the patients to each cluster. Patients with only one or no CC were evaluated as an additional "No multimorbidity" group. These groups were discarded from the analysis of the 66–80 and 81–95 years strata, due to the scarce number of non-multimorbid cases.

Results

Characteristics of the study population, infection severity and mortality

The study cohort comprised a total of 5411 males (37.9%) and 8875 females (62.1%). The age distribution revealed a mode of 41–45 years (n = 1438). Among the total cohort, 3140 patients had a confirmed COVID-19 infection (22.0%) and 11 146 were suspected cases (78.0%). The 78.9% of the cohort presented MM, and the mean number of CC was 6.0 (standard deviation of 5.4) (Table 1).

According to the selected codes, 1352 of the patients (9.5%; 95% CI: 9.0–9.9) suffered a severe infection. The most frequent severity criteria were oxygen therapy (n = 891, 6.2%), and respiratory failure (n = 880, 6.2%). Regarding isolated mortality, 555 patients (3.9%; 95% CI: 3.6–4.2) died during a COVID-19 associated episode, with 368 cases (66.3%) occurring at a hospital.

The relationship between severity / mortality and the demographic and medical variables (age, sex, MM, and number of CC), identified by bivariate statistical analyses, is presented in Table 1. Descriptive statistics of severe COVID-19 infection stratified by confirmed or suspected cases are shown in S2 Table.

Table 1. Demographic and clinical distribution of the study cohort in relation to severe COVID-19 infection/mortality. SD = standard deviation; OR = Odds Ratio; CI = Confidence Interval.

Variable		Total	Severe infection	p-value	OR [95% CI]	Mortality	p-value	OR [95% CI]
Sex. N (%)	Female	8875	621 (7.0)	<0.001	Reference	267 (3.0)	<0.001	Reference
	Male	5411	731 (13.5)		2.1 [1.8–2.3]	288 (5.3)		1.8 [1.5–2.1]
Age. N (%)	21–45	5599	117 (2.1)	<0.001	Reference	9 (0.2)	<0.001	Reference
	46–65	4699	390 (8.3)		4.2 [3.4–5.2]	67 (1.4)		8.8 [4.6–19.2]
	66–80	2299	480 (20.9)		12.3 [10.0–15.3]	210 (9.1)		61.3 [33.4–129.4]
	81–95	1689	365 (21.6)		12.9 [10.4–16.1]	269 (15.9)		115.6 [63.0–245.5]
Multimorbidity. N (%)	No	3014	50 (1.7)	<0.001	Reference	2 (0.1)	<0.001	Reference
	Yes	11 272	1302 (11.5)		7.7 [5.9–10.4]	553 (4.9)		72.1 [23.4–461.7]
Number of chronic conditions. Mean [SD]		6.05 [5.4]	10.26 [5.7]	<0.001	-	12.01 [5.2]	<0.001	-

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Chronic conditions of the COVID-19 patients

A total of 215 CC were identified, belonging to 20 different families of diseases. The most represented families were *Diseases of the circulatory system* (which contained 33 CC), *Diseases of the genitourinary system* (22 CC), *Mental, behavioural and neurodevelopmental disorders* (22 CC), and *Diseases of the musculoskeletal system and connective tissue* (21 CC). The most prevalent CC were *Essential hypertension* (30.3%), *Anxiety and fear-related disorders* (26.62%), *Obesity* (21.8%), and *Disorders of lipid metabolism* (21.3%).

For each age-sex stratum, different sets of CC with prevalence equal to or greater than 2% were identified and are listed in S3 Table.

Multimorbidity patterns

Fuzzy c-means cluster analysis was performed with a *m* value of 1.1, and *C* values were set to 4 clusters (males of 21–45 years; females of 81–95 years), 5 clusters (males of 81–90 years; females of 21–45, 46–65, and 66–80 years), and 6 clusters (males of 46–65 and 66–80 years).

The resulting MM clusters showed distinct CC distribution in each age-sex stratum. Detailed information on the prevalence, exclusivity, and O/E ratio of each CC per cluster is provided in S4 Table. S2 and S3 Figs illustrate the most representative CC per cluster. The distribution of patients among the different clusters, estimated based on their membership percentages, is summarized in Fig 1 and Table 2.

Clusters involving DM or CV conditions / risk factors were found in all age-sex groups. *Neurodevelopmental disorders* clusters were present in both groups of 21–45 year-olds, and *Neuropsychiatric* patterns were found in the 46–65 year-olds' groups. Clusters grouping *Psychogeriatric* diseases were identified in patients of >65 years, along with the *Cardiorespiratory* and *DM—cardiorespiratory* patterns. Some clusters were sex-specific, like *Cognitive-motor disorders* in males (46–65 and 66–80 years), and osteoinflammatory conditions in females, encompassing the clusters *Osteoinflammatory—psychosomatic* (46–65 years), *Osteoinflammatory—psychosomatic—CV risk factors* (66–80 years), and *Osteoinflammatory—neoplasia* (81–95 years).

Relationship between multimorbidity clusters and severe COVID-19 infection or mortality

The distribution of severe cases and mortality among MM clusters is represented in Fig 1 and detailed in Table 2 along with the *P*-values and odds ratios.

The weighted bivariate analysis showed that clusters of patients in the age ranges of 21–45 and 46–65 displayed $P \leq 0.001$ in relation to severe infection, and clusters of males in the 66–80 cohort presented $P = 0.016$. Among male patients, the clusters with the highest percentage of severe cases were *CV risk factors* (21–45 years, 7.5%), *Cognitive-motor disorders* (46–65 years, 32.9%), *Unspecific with COPD predominance* (66–80 years, 30.4%), and *Heart—liver—gastrointestinal diseases* (81–90 years, 34.1%). In female patients, the clusters associated with the highest percentages of severity were *DM and CV risk factors* (21–45 years, 6.2%), *DM—CV diseases* (46–65 years, 21.2%), *Neoplasia—haematologic* (66–80 years, 19.7%), and *DM—CV diseases* (81–95 years, 22.5%).

Regarding mortality, clusters of females aged 21–65 and males aged 46–65 obtained $P<0.001$, and males aged 66–80 presented $P = 0.02$. The clusters with the highest percentage of mortality among males were *Substance abuse disorders* (21–45 years, 1.7%), *DM—liver diseases* (46–65 years, 7.2%), *Cognitive-motor disorders* (66–80 years, 20.5%), and *Heart—liver—gastrointestinal diseases* (81–90 years, 29.5%). Clusters with the highest percentage of mortality in

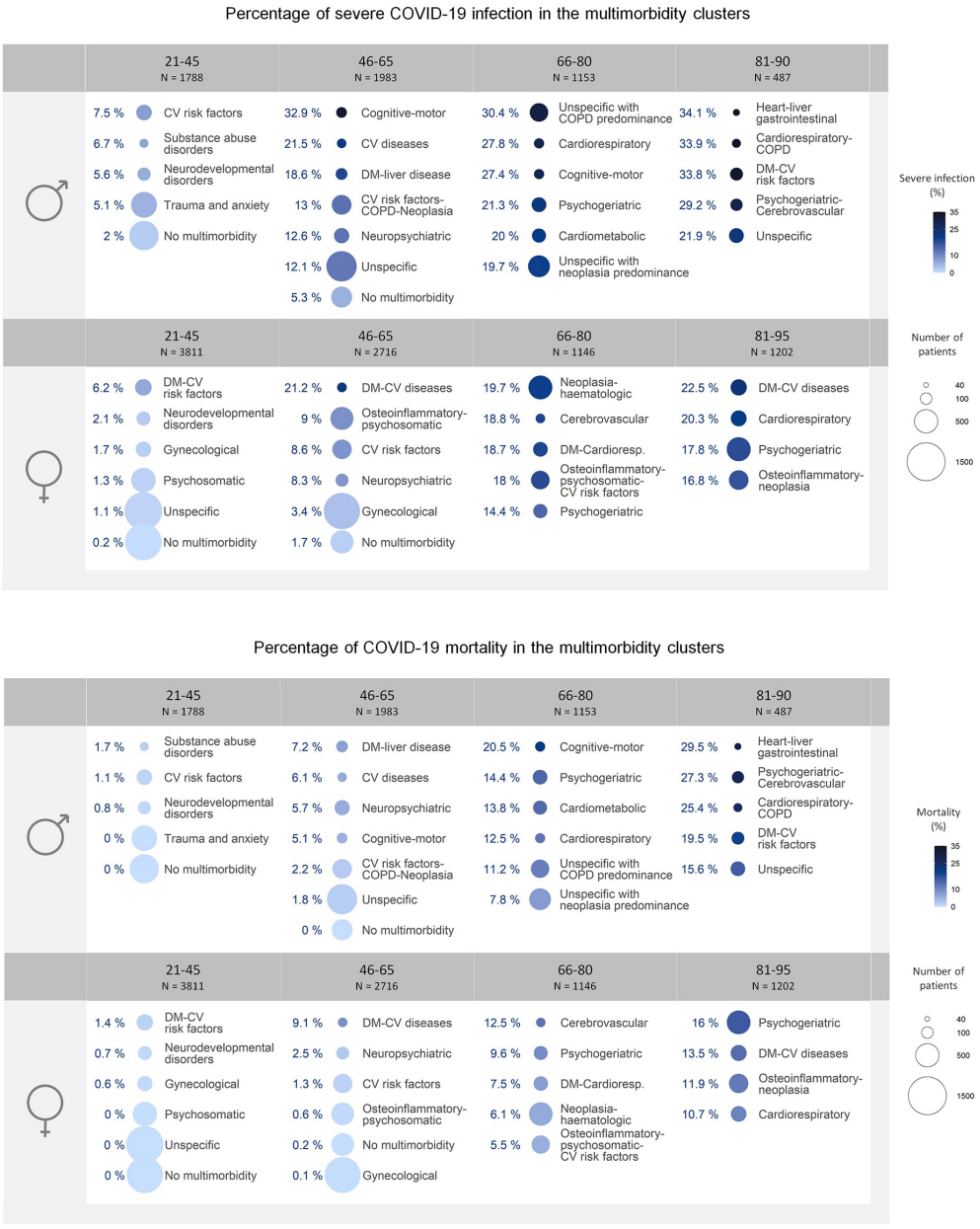

Fig 1. List of multimorbidity clusters per age and sex stratum. The size of the circles represents the population size and the color indicates the percentage of severe COVID-19 cases (upper figure) and mortality (lower figure). COPD = Chronic Obstructive Pulmonary Disease; CV = Cardiovascular.

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Table 2. Distribution of patients per cluster and infection severity or mortality. COPD = Chronic obstructive pulmonary disease; DM = Diabetes mellitus; OR = Odds ratio; CI = Confidence interval; (*) = not included in the bivariate analysis.

	Sex	Cluster	Total	Severe infection	p-value	OR [95% CI]	Mortality	p-value	OR [95% CI]
21–45	Male	Substance abuse disorders	60	4 (6.7%)	0.001	3.5 [0.9–9.9]	1 (1.7%)	0.052	2.2 [0.1–86.7]
		Neurodevelopmental disorders	126	7 (5.6%)		3.1 [1.2–7.2]	1 (0.8%)		Reference
		Cardiovascular risk factors	186	14 (7.5%)		7.2 [3.5–15.0]	2 (1.1%)		2.1 [0.2–65.6]
		Trauma and anxiety	602	31 (5.1%)		2.2 [1.2–4.3]	0 (0.0%)		-
		No multimorbidity	814	16 (2.0%)		Reference	0 (0.0%)		-
		Total	1788	72 (4.0%)			4 (0.2%)		
	Female	Neurodevelopmental disorders	141	3 (2.1%)	<0.001	9.6 [1.6–56.5]	1 (0.7%)	<0.001	1.2 [0.0–47.6]
		Gynecological disorders	174	3 (1.7%)		7.9 [1.3–46.3]	1 (0.6%)		Reference
		DM and cardiovascular risk factors	209	13 (6.2%)		28.6 [9.0–131.5]	3 (1.4%)		2.3 [0.3–66.5]
		Psychosomatic	532	7 (1.3%)		5.9 [1.6–28.9]	0 (0.0%)		-
		Unspecific	1420	16 (1.1%)		4.8 [1.6–21.5]	0 (0.0%)		-
		No multimorbidity	1335	3 (0.2%)		Reference	0 (0.0%)		-
		Total	3811	45 (1.2%)			5 (0.1%)		
46–65	Male	Cardiovascular diseases	65	14 (21.5%)	<0.001	4.8 [2.2–10.0]	4 (6.1%)	<0.001	3.6 [1.0–10.2]
		Cognitive-motor disorders	79	26 (32.9%)		9.3 [4.9–18.1]	4 (5.1%)		3.0 [0.8–8.5]
		DM—liver diseases	97	18 (18.6%)		3.5 [1.7–7.2]	7 (7.2%)		4.3 [1.6–10.4]
		Neuropsychiatric	174	22 (12.6%)		2.6 [1.4–5.0]	10 (5.7%)		3.6 [1.6–7.8]
		Cardiovascular risk factors—COPD—Neoplasia	316	41 (13.0%)		2.5 [1.4-4-4]	7 (2.2%)		1.1 [0.4–2.7]
		Unspecific	876	106 (12.1%)		2.5 [1.5–4.2]	16 (1.8%)		Reference
		No multimorbidity	376	20 (5.3%)		Reference	0 (0.0%)		-
		Total	1983	247 (12.5%)			48 (2.4%)		
	Female	DM—cardiovascular diseases	66	14 (21.2%)	<0.001	16.3 [6.7–42.7]	6 (9.1%)	<0.001	40.5 [6.5–1060.7]
		Neuropsychiatric	120	10 (8.3%)		5.1 [1.9–13.8]	3 (2.5%)		10.7 [1.2–309.5]
		Cardiovascular risk factors	304	26 (8.6%)		5.3 [2.5–12.8]	4 (1.3%)		5.4 [0.7–149.4]
		Osteoinflammatory—psychosomatic	456	41 (9.0%)		5.2 [2.5–12.2]	3 (0.6%)		2.8 [0.3–80.4]
		Gynecological disorders	1311	44 (3.4%)		1.9 [0.9–4.5]	2 (0.1%)		0.6 [0.1–20.7]
		No multimorbidity	459	8 (1.7%)		Reference	1 (0.2%)		Reference
		Total	2716	143 (5.3%)			19 (0.7%)		

(*Continued*)

Table 2. (Continued)

	Sex	Cluster	Total	Severe infection	p-value	OR [95% CI]	Mortality	p-value	OR [95% CI]
66–80	Male	Cardiorespiratory	72	20 (27.8%)	0.016	1.5 [0.8–2.6]	9 (12.5%)	0.020	1.6 [0.7–3.4]
		Cognitive-motor disorders	73	20 (27.4%)		1.2 [0.6–2.2]	15 (20.5%)		3.1 [1.5–6.0]
		Cardiometabolic	145	29 (20.0%)		1.1 [0.6–1.7]	20 (13.8%)		1.8 [1.0–3.3]
		Psychogeriatric	160	34 (21.3%)		1.1 [0.7–1.7]	23 (14.4%)		1.9 [1.1–3.4]
		Unspecific with COPD predominance	276	84 (30.4%)		1.9 [1.4–2.8]	31 (11.2%)		1.4 [0.8–2.4]
		Unspecific with neoplasia predominance	412	81 (19.7%)		Reference	32 (7.8%)		Reference
		No multimorbidity (*)	15	3 (20.0)		-	1 (6.7%)		-
		Total	1153	271 (23.5%)			131 (11.4%)		
	Female	Cerebrovascular	64	12 (18.8%)	0.738	1.2 [0.5–2.7]	8 (12.5%)	0.215	2.2 [0.8–5.5]
		Psychogeriatric	146	21 (14.4%)		Reference	14 (9.6%)		1.9 [0.9–4.2]
		DM—cardiorespiratory	160	30 (18.8%)		1.3 [0.7–2.5]	12 (7.5%)		1.5 [0.7–3.3]
		Osteoinflammatory—psychosomatic—cardiovascular risk factors	272	49 (18.0%)		1.2 [0.7–2.2]	15 (5.5%)		Reference
		Neoplasia—haematologic	493	97 (19.7%)		1.3 [0.8–2.3]	30 (6.1%)		1.0 [0.6–2.1]
		No multimorbidity (*)	11	0 (0.0%)		-	0 (0.0%)		-
		Total	1146	209 (18.2%)			79 (6.9%)		
81–95	Male	Heart—liver—gastrointestinal diseases	44	15 (34.1%)	0.178	2.2 [1.0–4.7]	13 (29.5%)	0.084	2.8 [1.2–6.1]
		Cardiorespiratory—COPD	59	20 (33.9%)		1.6 [0.8–3.2]	15 (25.4%)		1.7 [0.8–3.5]
		Psychogeriatric/cerebrovascular	106	31 (29.2%)		1.5 [0.9–2.7]	29 (27.3%)		2.3 [1.2–4.2]
		DM—cardiovascular risk factors	118	40 (33.9%)		1.7 [1.0–3.0]	23 (19.5%)		1.3 [0.7–2.4]
		Unspecific	160	35 (21.9%)		Reference	25 (15.6%)		Reference
		No multimorbidity (*)	0	0 (-)		-	0 (-)		-
		Total	487	141 (29.0%)			105 (21.6%)		
	Female	Cardiorespiratory	187	38 (20.3%)	0.379	1.4 [0.9–2.2]	20 (10.7%)	0.198	Reference
		DM—cardiovascular diseases	200	45 (22.5%)		1.4 [0.9–2.2]	27 (13.5%)		1.3 [0.7–2.5]
		Osteoinflammatory—neoplasia	310	52 (16.8%)		Reference	37 (11.9%)		1.0 [0.6–1.8]
		Psychogeriatric	501	89 (17.8%)		1.2 [0.8–1.7]	80 (16.0%)		1.7 [1.1–3.0]
		No multimorbidity (*)	4	0 (0.0%)		-	0 (0.0%)		-
		Total	1202	224 (18.6%)			164 (13.6%)		

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females were *DM and CV risk factors* (21–45 years, 1.4%), *DM—CV diseases* (46–65 years, 9.1%), *Cerebrovascular diseases* (66–80 years, 12.5%), and *Psychogeriatric* (81–95 years, 16.0%).

Discussion

The present study assessed the MM patterns associated to the population affected by the first wave of COVID-19 in a Spanish area. The results revealed well-defined MM clusters taking into account age and sex, some of which showed a high severity of COVID-19 infection and mortality, with a stronger relationship in younger age groups.

First of all, defining the study cohort was a vital aspect in order to establish reliable MM profiles. Many studies from the first wave of the pandemic focused only on PCR positive individuals [1, 3, 9, 38]; nevertheless, the critical situation at that time resulted in a small fraction of patients undergoing confirmatory tests in the studied geographic area. The test positivity rate in Catalonia during the selected period peaked at 43.5% and did not drop below the

World Health Organization recommendation of 5% until mid-May, thereby showing the shortage of testing resources [39, 40]. This situation particularly affected older individuals, who suffered the highest mortality rates in nursing homes without testing nor hospital admission [41]. Therefore, excluding these individuals from the cohort could introduce biases in the definition of multimorbidity patterns.

Taking the whole situation into account, the inclusion of suspected cases in the study cohort allowed for a more accurate approximation of the actual affected population. Although this criterion may have resulted in some possible false positives, it helped avoid potential biases associated with factors like age, access to medical testing or socioeconomic situation.

Using fuzzy c-means cluster analysis allowed for the simultaneous classification of patients into different clusters with a certain probability. This method is robust for pattern recognition in situations where clusters tend to overlap [42], such as in individuals with a high prevalence of co-existing conditions. It should be taken into account that the number of clusters *C* depends on the researchers' subjective election, which could affect the reproducibility of the study. Nevertheless, a Delphi-like method was carried out in order to enhance the robustness to the cluster selection, taking advantage of the multidisciplinarity of the research team, which includes members with technical or clinical expertise [43].

In addition, another key methodological aspect of this work was the stratification of the cohort. Given that the accumulation of CC is more frequent at older ages [17, 44], and that males and females have differential tendencies to suffer certain pathologies [45], it was necessary to consider both age and sex perspectives. In fact, previous studies on COVID-19 data from different countries already revealed that men have a higher risk of admission to intensive treatment units (from 14.4% to 44.9%) [1] or adverse outcome (OR: 2.05, 95% CI: 1.39–3.04) [2], which was supported by our bivariate analysis of demographic data. Indeed, several sex-related differences were observed in the MM clusters: patterns related with psychosomatic conditions or osteoinflammatory diseases were more frequent in females, while cognitive-motor, digestive and respiratory disease patterns were more associated to males, consistent with previous findings [23, 46, 47].

Regarding age-related differences, previous works based on the fuzzy c-means algorithm already identified certain MM clusters in cohorts of older patients ($\geq$60 years) that were similar to some patterns observed in the 66–80 and 81–95 age groups in the present study. For example, Vetrano et al identified clusters of cardiometabolic diseases, respiratory diseases, and cognitive / sensory impairment [28], and Akugizibwe et al found clusters of psychiatric conditions and sensory impairments/cancer [27]. Regarding the younger cohorts, a previous stratified study by Prados-Torres et al found some similar clusters by factor analysis, like psychiatric-substance abuse (males of 15–45 years), or cardio-metabolic (all strata) [48].

On the basis of these clusters, the results of the bivariate analyses suggest that certain MM patterns could be associated to higher COVID-19 infection severity or mortality rates in young-middle ages. The fact that this relationship was not strong in older patients may be explained by the inherent risk of old age itself [49, 50], as indicated by the bivariate analysis of demographic parameters. Additionally, other factors could also explain this mild association in older individuals, such as the simple accumulation of morbidities [17, 51, 52], difficulties in accessing healthcare services during the first wave of the pandemic [53], or the adequacy of therapeutic effort policy in age-related cases [54]. Furthermore, geriatric syndromes [55], which are barely coded in medical records, represent an important factor of vulnerability [25]. For example, frailty and disability are commonly detected in older patients and have been described as potential risk factors of critical COVID-19 infection [56, 57]. Nevertheless, in spite of the lack of strong statistical association, several MM clusters of patients in the 66–80

and 81–95 age ranges showed elevated infection severity and mortality rates compared to other clusters.

Therefore, the high percentages of infection severity / mortality displayed by certain MM clusters suggest that these patients may be more vulnerable to poor prognosis caused by COVID-19 infection. Previous pre-pandemic studies already showed some similar MM patterns associated with other adverse outcomes. For example, clusters of psychiatric disorders and CV diseases have been linked to a higher risk of unplanned hospitalization [27], while cognitive / sensory, complex cardiometabolic, respiratory, and age-associated chronic clusters showed increased risk of mortality [28, 58]. Taking into account other COVID-19 studies focusing on individual diseases, several CC that showed high prevalence and O/E ratio in the vulnerable clusters of our study were already identified as risk factors of adverse outcomes, such as COPD [4, 5, 8], liver disease, substance consumption [7], neoplasia [5, 33], and CV pathologies [31, 33]. Nevertheless, the present results indicate that beyond the occurrence of isolated pathologies, the accumulation of CC may represent an additional dimension to consider when facing patient-centered risk evaluations, as suggested by other authors [12].

In any case, the described results should always be interpreted considering the limitations of the study. Although the inclusion criteria took into account the characteristics of the first wave of the pandemic, there are inherent limitations related to this period (concerning data collection, codification and testing). Additionally, it should be considered that Big Data analyses imply some disadvantages, such as difficulties in ensuring data quality and homogeneity [59]. On the other hand, the study data corresponds to a specific region, which ensures a certain uniformity in the characteristics of the population, as well as their clinical management, protocols and codification, mitigating the potential heterogeneity of Big Data. Lastly, it should be noted that the occurrence of COVID-19 severe infection or mortality, or even their relationship with MM clusters, might be influenced by additional factors that were not included in the analyses, such as healthcare-associated features, socioeconomic status, dependency or frailty.

Therefore, these results provide insights into the relationships between MM clusters and severity or mortality, but do not provide a risk prediction. Our methodological approach allowed to explore if a comprehensive set of conditions forming multimorbidity clusters was related to the risk of COVID-19 infection severity or mortality. This approach may offer a complementary picture to the findings of possible further studies with multivariate analyses.

Conclusions

In summary, the present study provided a complete stratified profiling of MM clusters in COVID-19 patients from the first wave of the pandemic, revealing that males, older individuals and patients with certain MM patterns displayed higher probabilities of suffering severe COVID-19 infection or mortality. These findings may contribute to enhance the current knowledge about MM definition as well as to identify the most vulnerable population. This might especially benefit the preventive care of high-risk patients or those with limited access to medical treatment, and might help optimize healthcare policies and future strategies.

Supporting information

S1 Table. List of codes for COVID-19 registration, primary care mortality and severe infection. ICD-10-CM = International Classification of Diseases, 10th edition, Clinical

Modification. ICD-10-PCS = International Classification of Diseases, 10th edition, Procedure Coding System.
(PDF)

S2 Table. Number of patients and prevalence of severe COVID-19 infection according to the type of case (confirmed or suspected).
(PDF)

S3 Table. Chronic conditions with >2% prevalence per age and sex stratum.
(XLSX)

S4 Table. Prevalence (%), Observed/Expected (O/E) ratio, and exclusivity (%) of the chronic conditions per multimorbidity clusters.
(XLSX)

S1 Fig. Source and distribution of the analysed data. The included patients were submitted to an anonymization process. A patient Id code was assigned to each individual, which was maintained through all the different datasets in order to enable data compilation.
(PDF)

S2 Fig. Representation of the Observed/Expected ratio (O/E) and exclusivity (%) of the chronic conditions composing the multimorbidity clusters of male patients. O/E >1 and exclusivity > 1/number of clusters are displayed.
(PDF)

S3 Fig. Representation of the Observed/Expected ratio (O/E) and exclusivity (%) of the chronic conditions composing the multimorbidity clusters of female patients. O/E >1 and exclusivity > 1/number of clusters are displayed.
(PDF)

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References

1. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun 2020; 11:6317. https://doi.org/10.1038/s41467-020-19741-6 PMID: 33298944
2. Booth A, Reed AB, Ponzo S, Yassaee A, Aral M, Plans D, et al. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. PLoS One 2021; 16: e0247461. https://doi.org/10.1371/journal.pone.0247461 PMID: 33661992
3. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk Factors Associated with Mortality among Patients with COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med 2020; 180:1345–55. https://doi.org/10.1001/jamainternmed.2020.3539 PMID: 32667669
4. Atkins JL, Masoli JAH, Delgado J, Pilling LC, Kuo C-L, Kuchel GA, et al. Preexisting Comorbidities Predicting COVID-19 and Mortality in the UK Biobank Community Cohort. J Gerontol A Biol Sci Med Sci 2020; 75:2224–30. https://doi.org/10.1093/gerona/glaa183 PMID: 32687551
5. Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020; 55:2000547. https://doi.org/10.1183/13993003.00547-2020 PMID: 32217650
6. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020; 323:2052–9. https://doi.org/10.1001/jama.2020.6775 PMID: 32320003
7. Reilev M, Kristensen KB, Pottegård A, Lund LC, Hallas J, Ernst MT, et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. Int J Epidemiol 2020; 49:1468–81.
8. Iaccarino G, Grassi G, Borghi C, Ferri C, Salvetti M, Volpe M. Age and Multimorbidity Predict Death Among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension. Hypertension 2020; 76:366–72. https://doi.org/10.1161/HYPERTENSIONAHA.120.15324 PMID: 32564693
9. Poblador-Plou B, Carmona-Pírez J, Ioakeim-Skoufa I, Poncel-Falcó A, Bliek-Bueno K, Cano-Del Pozo M, et al. Baseline chronic comorbidity and mortality in laboratory-confirmed COVID-19 cases: Results from the PRECOVID study in Spain. Int J Environ Res Public Health 2020; 17:5171. https://doi.org/10.3390/ijerph17145171 PMID: 32709002
10. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, et al. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization. Ann Intern Med 2020; 173:773–81. https://doi.org/10.7326/M20-3742 PMID: 32783686
11. Tisminetzky M, Delude C, Hebert T, Carr C, Goldberg RJ, Gurwitz JH. Age, Multiple Chronic Conditions, and COVID-19: A Literature Review. J Gerontol A Biol Sci Med Sci 2021:glaa320.
12. Maddaloni E, D'Onofrio L, Alessandri F, Mignogna C, Leto G, Pascarella G, et al. Cardiometabolic multimorbidity is associated with a worse Covid-19 prognosis than individual cardiometabolic risk factors: A multicentre retrospective study (CoViDiab II). Cardiovasc Diabetol 2020; 19:164. https://doi.org/10.1186/s12933-020-01140-2 PMID: 33004045
13. Clark A, Jit M, Warren-Gash C, Guthrie B, Wang HHX, Mercer SW, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. Lancet Glob Heal 2020; 8:e1003–17. https://doi.org/10.1016/S2214-109X(20)30264-3 PMID: 32553130

14. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. Lancet 2012; 380:37–43. https://doi.org/10.1016/S0140-6736(12)60240-2 PMID: 22579043

15. Yarnall AJ, Sayer AA, Clegg A, Rockwood K, Parker S, Hindle J V. New horizons in multimorbidity in older adults. Age Ageing 2017; 46:882–8. https://doi.org/10.1093/ageing/afx150 PMID: 28985248

16. The Academy of Medical Sciences. Multimorbidity: a priority for global health research. 2018.

17. Mounce LTA, Campbell JL, Henley WE, Tejerina Arreal MC, Porter I, Valderas JM. Predicting incident multimorbidity. Ann Fam Med 2018; 16:322–9. https://doi.org/10.1370/afm.2271 PMID: 29987080

18. National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management. NICE guideline (NG56). 2016.

19. Valderas JM, Starfi B, Sibbald B. Defining Comorbidity: Implications for Understanding Health and Health Services. Ann Fam Med 2009; 7:357–63. https://doi.org/10.1370/afm.983 PMID: 19597174

20. Makovski TT, Schmitz S, Zeegers MP, Stranges S, van den Akker M. Multimorbidity and quality of life: Systematic literature review and meta-analysis. Ageing Res Rev 2019; 53:100903. https://doi.org/10.1016/j.arr.2019.04.005 PMID: 31048032

21. Chudasama Y V., Khunti KK, Zaccardi F, Rowlands A V., Yates T, Gillies CL, et al. Physical activity, multimorbidity, and life expectancy: A UK Biobank longitudinal study. BMC Med 2019; 17:108. https://doi.org/10.1186/s12916-019-1339-0 PMID: 31186007

22. Ng SK, Tawiah R, Sawyer M, Scuffham P. Patterns of multimorbid health conditions: A systematic review of analytical methods and comparison analysis. Int J Epidemiol 2018; 47:1687–704. https://doi.org/10.1093/ije/dyy134 PMID: 30016472

23. Guisado-Clavero M, Roso-Llorach A, López-Jimenez T, Pons-Vigués M, Foguet-Boreu Q, Muñoz MA, et al. Multimorbidity patterns in the elderly: A prospective cohort study with cluster analysis. BMC Geriatr 2018; 18:16. https://doi.org/10.1186/s12877-018-0705-7 PMID: 29338690

24. Tazzeo C, Rizzuto D, Calderón-Larrañaga A, Roso-Llorach A, Marengoni A, Welmer A-K, et al. Multimorbidity patterns and risk of frailty in older community-dwelling adults: a population-based cohort study. Age Ageing 2021:afab138. https://doi.org/10.1093/ageing/afab138 PMID: 34228784

25. Baré M, Herranz S, Roso-Llorach A, Jordana R, Violán C, Lleal M, et al. Multimorbidity patterns of chronic conditions and geriatric syndromes in older patients from the MoPIM multicentre cohort study. BMJ Open 2021; 11:49334. https://doi.org/10.1136/bmjopen-2021-049334 PMID: 34782339

26. Marengoni A, Akugizibwe R, Vetrano DL, Roso-Llorach A, Onder G, Welmer A-K, et al. Patterns of multimorbidity and risk of disability in community-dwelling older persons. Aging Clin Exp Res 2021; 33:457–462. https://doi.org/10.1007/s40520-020-01773-z PMID: 33580869

27. Akugizibwe R, Calderón-Larrañaga A, Roso-Llorach A, Onder G, Marengoni A, Zucchelli A, et al. Multimorbidity Patterns and Unplanned Hospitalisation in a Cohort of Older Adults. J Clin Med 2020; 9:4001. https://doi.org/10.3390/jcm9124001 PMID: 33321977

28. Vetrano DL, Roso-Llorach A, Fernández S, Guisado-Clavero M, Violán C, Onder G, et al. Twelve-year clinical trajectories of multimorbidity in a population of older adults. Nat Commun 2020; 11:3223. https://doi.org/10.1038/s41467-020-16780-x PMID: 32591506

29. Violán C, Foguet-Boreu Q, Fernández-Bertolín S, Guisado-Clavero M, Cabrera-Bean M, Formiga F, 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. BMJ Open 2019; 9:e029594. https://doi.org/10.1136/bmjopen-2019-029594 PMID: 31471439

30. Lleal M, Baré M, Ortonobes S, Sevilla-Sánchez D, Jordana R, Herranz S, et al. Comprehensive Multimorbidity Patterns in Older Patients Are Associated with Quality Indicators of Medication-MoPIM Cohort Study. Int J Environ Res Public Health 2022; 19. https://doi.org/10.3390/ijerph192315902 PMID: 36497976

31. Banerjee A, Pasea L, Harris S, Gonzalez-Izquierdo A, Torralbo A, Shallcross L, et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. Lancet 2020; 395:1715–25. https://doi.org/10.1016/S0140-6736(20)30854-0 PMID: 32405103

32. Jin J, Agarwala N, Kundu P, Harvey B, Zhang Y, Wallace E, et al. Individual and community-level risk for COVID-19 mortality in the United States. Nat Med 2021; 27:264–9. https://doi.org/10.1038/s41591-020-01191-8 PMID: 33311702

33. Semenzato L, Dray-spira R, Weill A, Zureik M. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. Lancet Reg Heal—Eur 2021; 8:100158.

34. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Natl Institutes Heal 2021.

35. R Core Team. R: A language and environment for statistical computing. R Found Stat Comput Vienna, Austria 2014.

36. RStudio Team. RStudio: Integrated Development for R 2015.

37. Agency for Healthcare Research and Quality. Rockville. MD. Healthcare Cost and Utilization Project (HCUP) 2021. www.hcup-us.ahrq.gov/home.jsp.

38. Castro VM, McCoy TH, Perlis RH. Laboratory Findings Associated With Severe Illness and Mortality Among Hospitalized Individuals With Coronavirus Disease 2019 in Eastern Massachusetts. JAMA Netw Open 2020; 3:e2023934. https://doi.org/10.1001/jamanetworkopen.2020.23934 PMID: 33125498

39. Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Coronavirus Pandemic (COVID-19) 2020. https://ourworldindata.org/coronavirus/country/spain.

40. IDESCAT (Statistical Institute of Catalonia). Statistical information to track the impact of Covid-19. https://www.idescat.cat/dades/covid19/?lang=en (accessed June 14, 2023).

41. Comas-Herrera A, Zalakaín J, Litwin C, Hsu AT, Lemmon E, Henderson D, et al. Mortality associated with COVID-19 outbreaks in care homes: early international evidence. 2020.

42. Bezdek JC, Ehrlich R, Full W. FCM: The fuzzy c-means clustering algorithm. Comput Geosci 1984; 10:191–203.

43. Humphrey-Murto SM, Wood TJ, Gonsalves C, Mascioli K, Varpio L. The Delphi Method. Acad Med 2020; 95:168. https://doi.org/10.1097/ACM.0000000000002887 PMID: 31335812

44. Salive ME. Multimorbidity in older adults. Epidemiol Rev 2013; 35:75–83. https://doi.org/10.1093/epirev/mxs009 PMID: 23372025

45. Mauvais-Jarvis F, Merz NB, Barnes PJ, Brinton RD, Carrero J-J, DeMeo DL, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet 2020; 396:565–82. https://doi.org/10.1016/S0140-6736(20)31561-0 PMID: 32828189

46. Violán C, Roso-Llorach A, Foguet-Boreu Q, Guisado-Clavero M, Pons-Vigués M, Pujol-Ribera E, et al. Multimorbidity patterns with K-means nonhierarchical cluster analysis. BMC Fam Pract 2018; 19:108. https://doi.org/10.1186/s12875-018-0790-x PMID: 29969997

47. Foguet-Boreu Q, Violán C, Rodriguez-Blanco T, Roso-Llorach A, Pons-Vigués M, Pujol-Ribera E, et al. Multimorbidity patterns in elderly primary health care patients in a South Mediterranean European region: A cluster analysis. PLoS One 2015; 10:e0141155. https://doi.org/10.1371/journal.pone.0141155 PMID: 26524599

48. Prados-Torres A, Poblador-Plou B, Gimeno-Miguel A, Calderón-Larrañaga A, Poncel-Falcó A, Gimeno-Feliú LA, et al. Cohort Profile: The epidemiology of chronic diseases and multimorbidity. The EpiChron cohort study. Int J Epidemiol 2018; 47:382e–384e. https://doi.org/10.1093/ije/dyx259 PMID: 29346556

49. Girard N, Odille G, Sanchez S, Lelarge S, Mignot A, Putot S, et al. Comment on: "Beyond Chronological Age: Frailty and Multimorbidity Predict In-hospital Mortality in Patients With Coronavirus Disease 2019." J Gerontol A Biol Sci Med Sci 2021; 76:e155–6.

50. Ho FK, Petermann-Rocha F, Gray SR, Jani BD, Vittal Katikireddi S, Niedzwiedz CL, et al. Is older age associated with COVID-19 mortality in the absence of other risk factors? General population cohort study of 470,034 participants. PLoS One 2020; 15:e0241824. https://doi.org/10.1371/journal.pone.0241824 PMID: 33152008

51. Buja A, Claus M, Perin L, Rivera M, Corti MC, Avossa F, et al. Multimorbidity patterns in high-need, high-cost elderly patients. PLoS One 2018; 13:e0208875. https://doi.org/10.1371/journal.pone.0208875 PMID: 30557384

52. Vinjerui KH, Bjerkeset O, Bjorngaard JH, Krokstad S, Douglas KA, Sund ER, et al. Socioeconomic inequalities in the prevalence of complex multimorbidity in a Norwegian population: findings sectional HUNT Study from the cross-sectional HUNT Study. BMJ Open 2020; 10:e036851.

53. Martins Van Jaarsveld G. The Effects of COVID-19 Among the Elderly Population: A Case for Closing the Digital Divide. Front Psychiatry 2020; 11:577427. https://doi.org/10.3389/fpsyt.2020.577427 PMID: 33304283

54. Borsellino P. Limitation of the therapeutic effort: Ethical and legal justification for withholding and/or withdrawing life sustaining treatments. Multidiscip Respir Med 2015; 10:5. https://doi.org/10.1186/s40248-015-0001-8 PMID: 25705381

55. Inouye SK, Studenski S, Tinetti M, Kuchel G. Geriatric Syndromes: Clinical, Research and Policy Implications of a Core Geriatric Concept in older adults related to primary and secondary prevention. J Am Geriatr Soc 2007; 55:780–91.

56. Bellelli G, Rebora P, Valsecchi MG, Bonfanti P, Citerio G, Galimberti S, et al. Frailty index predicts poor outcome in COVID-19 patients. Intensive Care Med 2020; 46:1634–6. https://doi.org/10.1007/s00134-020-06087-2 PMID: 32451583

57. Hussien H, Nastasa A, Apetrii M, Nistor I, Petrovic M, Covic A. Different aspects of frailty and COVID-19: points to consider in the current pandemic and future ones. BMC Geriatr 2021; 21:389. https://doi.org/10.1186/s12877-021-02316-5 PMID: 34176479

58. Zheng DD, Loewenstein DA, Christ SL, Feaster DJ, Lam BL, McCollister KE, et al. Multimorbidity patterns and their relationship to mortality in the US older adult population. PLoS One 2021; 16:e0245053. https://doi.org/10.1371/journal.pone.0245053 PMID: 33471812

59. Andreu-Perez J, Poon CCY, Merrifield RD, Wong STC, Yang G-Z. Big Data for Health. IEEE J Biomed Heal Informatics 2015; 19:1193–208. https://doi.org/10.1109/JBHI.2015.2450362 PMID: 26173222

5.3. Study 3: MTOP study

Publication of the third study

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Trajectories of chronic multimorbidity patterns in older patients: MTOP study

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Abstract

Background Multimorbidity is associated with negative results and poses difficulties in clinical management. New methodological approaches are emerging based on the hypothesis that chronic conditions are non-randomly associated forming multimorbidity patterns. However, there are few longitudinal studies of these patterns, which could allow for better preventive strategies and healthcare planning. The objective of the MTOP (Multimorbidity Trajectories in Older Patients) study is to identify patterns of chronic multimorbidity in a cohort of older patients and their progression and trajectories in the previous 10 years.

Methods A retrospective, observational study with a cohort of 3988 patients aged > 65 was conducted, including suspected and confirmed COVID-19 patients in the reference area of Parc Taulí University Hospital. Real-world data on socio-demographic and diagnostic variables were retrieved. Multimorbidity patterns of chronic conditions were identified with fuzzy c-means cluster analysis. Trajectories of each patient were established along three time points (baseline, 5 years before, 10 years before). Descriptive statistics were performed together with a stratification by sex and age group.

Results 3988 patients aged over 65 were included (58.9% females). Patients with ≥ 2 chronic conditions changed from 73.6 to 98.3% in the 10-year range of the study. Six clusters of chronic multimorbidity were identified 10 years before baseline, whereas five clusters were identified at both 5 years before and at baseline. Three clusters were consistently identified in all time points (*Metabolic and vascular disease, Musculoskeletal and chronic pain syndrome, Unspecific*); three clusters were only present at the earliest time point (*Male-predominant diseases*, *Minor conditions and sensory impairment*, *Lipid metabolism disorders*) and two clusters emerged 5 years before baseline and remained (*Heart diseases* and *Neurocognitive*). Sex and age stratification showed different distribution in cluster prevalence and trajectories.

Conclusions In a cohort of older patients, we were able to identify multimorbidity patterns of chronic conditions and describe their individual trajectories in the previous 10 years. Our results suggest that taking these trajectories into consideration might improve decisions in clinical management and healthcare planning.

Trial registration number NCT05717309.

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Keywords Multimorbidity, Cluster analysis, Trajectories, Longitudinal study, Older patients, Ageing, Chronic conditions

Background

Population ageing is accelerating in Europe, both in number and proportion of older individuals, as the old-age dependency ratio — i.e. population over 65 relative to population aged 15–64— is expected to continue rising. Therefore, European countries face major challenges to guarantee that their healthcare systems are prepared to tackle this demographic shift [1, 2].

One of these growing challenges is the clinical management of patients with multimorbidity. Multimorbidity, usually defined as the presence of two or more chronic conditions, increases with age as chronic conditions accumulate and is associated with complex treatments lacking evidence, a greater use of health resources and a lower quality of life [3–5]. Older patients with multimorbidity are excluded from clinical trials and there are few guidelines with specific recommendations for these patients [6–8]. All in all, multimorbidity poses a challenge for healthcare professionals and systems. Therefore, conducting research on how to improve multimorbid patient care in settings that have traditionally focused on single diseases should be considered a priority [9, 10].

Along these lines, recommendations have been issued to consider all chronic conditions at the same time in order to provide better patient-centred care [10, 11]. Therefore, new alternative, more comprehensive definitions of multimorbidity are being proposed, based on the hypothesis that some chronic conditions non-randomly co-occur giving rise to multimorbidity patterns. In order to obtain a thorough definition of multimorbidity patterns, detailed medical information is required. In this sense, the use of real-world data (RWD) provides valuable, readily available, large datasets [12]. Thus, in recent years, evidence has been accumulating in regards to the existence of such comprehensive multimorbidity patterns [13–18]. In fact, several patterns have already been associated with outcomes such as lower function, higher presence of adverse drug reactions, higher healthcare utilisation, poor prognosis or higher mortality [19–24]. Consequently, identifying multimorbidity patterns might aid in the development of new strategies and guidelines focusing on the most appropriate actions according to each patient profile.

Furthermore, it might be important to consider that multimorbidity profiles of each patient may progress or change over time, forming different multimorbidity trajectories. However, there are few works that have described the progression of these patterns over time [25]. Thus, developing a better knowledge of the transition pathways between multimorbidity patterns could detect profiles of patients with similar characteristics and risks who could benefit from improved, more personalized health care. Likewise, certain trajectories or belonging to certain patterns of multimorbidity over time could be associated with different prognoses or outcomes (quality of life, severity, mortality). This could allow to predict and plan for future actions, and to identify future relevant results or prognoses more accurately.

In addition, a deeper understanding of how multimorbidity develops in older adults would be desirable to plan for and deliver more appropriate care. It may also allow for the identification of targets as well as the development of programs and interventions aimed at minimising the progression and impact of multimorbidity on more distal outcomes. Therefore, these knowledge gains may guide administrators and policy makers in resource allocation. All in all, identifying multimorbidity patterns of chronic conditions and their trajectories over time might help individual patients as well as entire healthcare systems.

In this context, we developed the MTOP (Multimorbidity Trajectories in Older Patients) study, which aims to identify multimorbidity patterns of chronic conditions in a cohort of older patients, as well as their progression and trajectories in the previous 10 years.

Methods

Study design and cohort

The MTOP study is a retrospective observational study using RWD provided by the Agency for Health Quality and Assessment of Catalonia (AQuAS) in the framework of the Public Data Analysis for Health Research and Innovation Program (PADRIS). The study cohort is based on a cohort from a previous study on multimorbidity clusters, called MRisk-COVID study [19]. The MRisk-COVID study included 14,286 patients of a region in the Northeast of Spain (Vallès Occidental est, Catalonia), which were either confirmed or suspected COVID-19 cases from 27th February to 15th June 2020. The MRisk-COVID data was deemed suitable to address the aim of the MTOP study, as it provided readily available data on longitudinal chronic morbidity in a cohort of older patients. Patients aged > 65 years were selected, resulting in a cohort of 3988 individuals.

The study was approved by the Ethics Committee (CEIm) of the Parc Taulí University Hospital (reference 2022/5051), which waived the requirement of informed consents due to the epidemiological nature of the study and the use of anonymized data.

Data processing and linkage

Demographic data (sex and age) and clinical data were obtained from the Shared Clinical History of Catalonia (HC3). In order to reduce patient re-identification risk, as part of the privacy policy of PADRIS, age was provided in categorized quinquennial groups, and age groups with high re-identification risk were excluded (women aged > 95 and men aged > 90).

Clinical data comprised clinical records of all primary healthcare centres in Catalonia. The provided records covered from 1930 to 2020 and encompassed all diagnoses, coded using the ICD-10-CM diagnostic system [26]. Three time points were established: 2020 (baseline, representing the time of data extraction), 2015 (5 years before) and 2010 (10 years before), and active diagnoses at each time were collected.

Data compilation, processing and statistical analysis were performed using R v3.6.0 [27].

Multimorbidity cluster analysis

To identify chronic multimorbidity patterns, three steps were performed: identification of chronic conditions, complexity reduction of chronic conditions, and cluster analysis of patients based on these selected features. The following analyses were performed independently for each of the three selected time points.

Firstly, the identification of chronic conditions for inclusion in the analyses was carried out using the Chronic Condition Indicator software v.2021.1 [28]. This tool allows for the classification of all ICD-10-CM diagnosis codes into four categories: "Chronic condition" (value C), "Acute condition" (value A), "Both a chronic and acute condition" (value B), and "Not applicable, code cannot be used to identify a chronic or acute condition" (value N). All diagnoses with values C or B were selected. Then, these selected diagnoses were classified and grouped using the Clinical Classification Software Refined v.2021.1 [28], which allocates specific diagnoses into general chronic condition categories. This step was performed in order to reduce the number of variables for the cluster analysis and increase statistical power, while at the same time collapsing highly similar diagnoses to avoid unnecessary fragmentation. After that, chronic conditions were filtered by > 2% prevalence in order to reduce statistical noise. Only patients with two or more chronic conditions were included, regardless of the presence of acute conditions.

Due to the large number of chronic conditions, a dimension reduction was performed by Multiple Correspondence Analysis. Optimal number of dimensions was determined by the elbow criteria in the scree plot.

Soft clustering analysis was performed using the fuzzy c-means algorithm [29]. Given that it is a stochastic method; a hundred iterations were performed in order to obtain reproducible results. Several values of fuzziness (m) were tested (m = 1.1, 1.2, 1.4, 1.5, 2, 4) and the optimal m = 1.1 was estimated by the mean calculation of five indexes: Calinski–Harabasz, Partition coefficient, Partition entropy, Fukuyama, and Xie-Beni. Also, several values of the number of clusters (C = 4, 5, 6 and 7) were tested. The final C for each time point was reached through statistical criteria and consensus among 6 medical doctors from different specialties. This agreement was achieved following an independent voting process. Consensus was defined when one of the options reached a majority of votes. Cases with lack of consensus or similar voting count were meant to be decided through a clinical debate session, however this turned out not to be necessary.

After establishing multimorbidity clusters, three indicators were calculated for each chronic condition: prevalence within the cluster (%), observed/expected (O/E) ratio (prevalence in the cluster / total prevalence) and exclusivity (patients with the condition in the cluster / total of patients with the condition). Finally, a descriptive label was agreed upon and assigned to each cluster to summarize their over-represented chronic conditions and facilitate clinical interpretation.

Statistical analysis

Each patient was allocated to the most probable cluster at each of the time points. Percentages of patients in each cluster were calculated, including patients with zero or one chronic conditions, which were allocated to a "No multimorbidity" group. Then, trajectories of each patient through the three time points were established. Percentages of patients for all possible trajectories were calculated for the three time points or pairwise (10 years before vs. 5 years before, 5 years before vs. baseline).

A stratified descriptive analysis was conducted by sex and two age groups, thereby obtaining four different patient datasets (groups of 66–80 and > 80 years, separated into male and female individuals) and plotting their trajectories separately. Age cut-off was set at 80 years to define very old individuals [30].

Results

A total of 3988 patients aged 65 or older were included in the study, with 58.9% females and 42.4% very old individuals (aged > 80). At baseline, 98.3% of patients had multimorbidity as defined by the presence of two or more chronic conditions, whereas 5 years before it was 92.6% and 10 years before, 73.6%. The median number of chronic conditions per patient was 9 at baseline, 6 five years before and 3 ten years before baseline. Cohort characteristics are described in the first column of Table 1.

A total of 73 different chronic condition categories with > 2% prevalence were identified at baseline, 56 categories

Table 1 Descriptive statistics of the cohort. First column contains the figures for the whole cohort, the rest of columns describe patients' characteristics according to their assigned chronic multimorbidity clusters at the three defined time points (10 years before, 5 years before and baseline).

		Total	10 years before							5 years before						Baseline					
			Metabolic and vascular diseases	Male-predominant diseases	Minor conditions and sensory impairment	Musculoskeletal and chronic pain syndrome	Lipid metabolism disorders	Unspecific	No multimorbidity	Heart diseases	Metabolic and vascular diseases	Neurocognitive	Musculoskeletal and chronic pain syndrome	Unspecific	No multimorbidity	Heart diseases	Metabolic and vascular diseases	Musculoskeletal and chronic pain diseases	Neurocognitive	Unspecific	No multimorbidity
n (%)		3988	168 (4.2)	364 (9.1)	370 (9.3)	426 (10.7)	472 (11.8)	854 (21.4)	1334 (33.5)	382 (9.6)	458 (11.5)	559 (14.0)	748 (18.8)	1479 (37.1)	362 (9.1)	447 (11.2)	534 (13.4)	715 (17.9)	903 (22.6)	1306 (32.7)	83 (2.1)
Nº chronic conditions, median (IQR)		9 (6–12)* 6 (4–8)** 3 (1–5)***	5 (4–7)	4 (3–5)	5 (4–7)	4 (3–6)	4 (3–5)	3 (2–5)	1 (0–1)	9 (7–11)	8 (6–10)	6 (5–8)	7 (6–9)	4 (3–6)	1 (0–1)	13 (11–16)	11 (9-13.75)	11 (9–13)	9 (7–12)	6 (4–8)	1 (0–1)
Sex	Female	2348 (58.9)	96 (57.1)	44 (12.1)	291 (78.6)	355 (83.3)	298 (63.1)	528 (61.8)	736 (55.2)	252 (66.0)	197 (43.0)	427 (76.4)	668 (89.3)	611 (41.3)	193 (53.3)	318 (71.1)	137 (25.7)	646 (90.3)	683 (75.6)	522 (40.0)	42 (50.6)
	Male	1640 (41.1)	72 (42.9)	320 (87.9)	79 (21.4)	71 (16.7)	174 (36.9)	326 (38.2)	598 (44.8)	130 (34.0)	261 (57.0)	132 (23.6)	80 (10.7)	868 (58.7)	169 (46.7)	129 (28.9)	397 (74.3)	69 (9.7)	220 (24.4)	784 (60.0)	41 (49.4)
Age group at baseline	66–70	781 (19.6)	32 (19.0)	45 (12.4)	33 (8.9)	83 (19.5)	86 (18.2)	135 (15.8)	367 (27.5)	36 (9.4)	86 (18.8)	65 (11.6)	142 (19.0)	327 (22.1)	125 (34.5)	33 (7.4)	105 (19.7)	145 (20.3)	69 (7.6)	388 (29.7)	41 (49.4)
	71–75	798 (20.0)	32 (19.0)	74 (20.3)	64 (17.3)	89 (20.9)	102 (21.6)	144 (16.9)	293 (22.0)	50 (13.1)	89 (19.4)	62 (11.1)	175 (23.4)	346 (23.4)	76 (21.0)	56 (12.5)	108 (20.2)	188 (26.3)	94 (10.4)	336 (25.7)	16 (19.3)
	76–80	720 (18.1)	36 (21.4)	89 (24.5)	54 (14.6)	86 (20.2)	77 (16.3)	164 (19.2)	214 (16.0)	61 (16.0)	92 (20.1)	88 (15.7)	144 (19.3)	277 (18.7)	58 (16.0)	79 (17.7)	110 (20.6)	151 (21.1)	132 (14.6)	235 (18.0)	13 (15.7)
	81–85	909 (22.8)	39 (23.2)	93 (25.5)	112 (30.3)	93 (21.8)	112 (23.7)	232 (27.2)	228 (17.1)	114 (29.8)	126 (27.5)	144 (25.8)	171 (22.9)	300 (20.3)	54 (14.9)	153 (34.2)	150 (28.1)	128 (17.9)	253 (28.0)	215 (16.5)	10 (12.0)
	86–90	605 (15.2)	24 (14.3)	59 (16.2)	84 (22.7)	57 (13.4)	68 (14.4)	133 (15.6)	180 (13.5)	102 (26.7)	51 (11.1)	134 (24.0)	92 (12.3)	186 (12.6)	40 (11.0)	106 (23.7)	56 (10.5)	81 (11.3)	250 (27.7)	109 (8.3)	3 (3.6)
	91–95	175 (4.4)	5 (3.0)	4 (1.1)	23 (6.2)	18 (4.2)	27 (5.7)	46 (5.4)	52 (3.9)	19 (5.0)	14 (3.1)	66 (11.8)	24 (3.2)	43 (2.9)	9 (2.5)	20 (4.5)	5 (0.9)	22 (3.1)	105 (11.6)	23 (1.8)	0 (0.0)

IQR: interquartile range

* at baseline

** 5 years before

*** 10 years before

were obtained five years before and 32 categories ten years before baseline. Figure S1 shows the prevalence of the selected chronic condition categories along the three time points. The most prevalent diagnoses all along the three time points were essential hypertension and osteoarthritis, followed by other conditions such as urinary incontinence, neurocognitive disorders, obesity or diabetes mellitus.

Five clusters of chronic multimorbidity were identified at baseline in patients with two or more chronic conditions. These clusters were labelled as follows: *Heart diseases*, *Metabolic and vascular diseases*, *Neurocognitive*, *Musculoskeletal and chronic pain syndrome* and *Unspecific*. Similar clusters were found in the time point defined 5 years before; therefore, the same labels were kept. Clusters that were assigned the same label in different time points presented different disease prevalence and presence but overall maintained similar over-represented diagnoses. Six clusters were identified 10 years before and were assigned the following labels: *Metabolic and vascular diseases*, *Male-predominant diseases*, *Minor conditions and sensory impairment*, *Musculoskeletal and chronic pain syndrome*, *Lipid metabolism disorders* and *Unspecific*. All in all, two clusters were found in all of the time points: *Metabolic and vascular diseases* and *Musculoskeletal and chronic pain syndrome*. Prevalence, O/E ratio and exclusivity of all chronic conditions used to define these multimorbidity clusters can be found in Tables S1, S2 and S3.

Membership probabilities of patients to each set of clusters per time point were calculated to describe the possible overlap between clusters (Fig S2). Most patients were found most probably assigned to a certain cluster. Median probability of the most probable cluster in patients at baseline was 99%, while it decreased to 87% and 76% at the time points of 5 years and 10 years before, respectively. Cluster membership became more defined at the later time points, suggesting that a higher disease burden lead to a more defined allocation to a certain cluster.

Descriptive statistics on the individuals' number of chronic conditions, sex and age group according to the assigned multimorbidity cluster are shown in Table 1. Patients in the *heart diseases* clusters had the greatest number of chronic conditions (median was 13 conditions at baseline, 9 conditions five years before), while those in the *unspecific* clusters presented the lowest number (median was 6 conditions at baseline, 4 five years before and 3 ten years before). The *Musculoskeletal and chronic pain syndrome* clusters were those with highest presence of females in all three time points, while the *Male-predominant diseases* cluster had the highest prevalence of males but was only found in the earliest time point (10 years before baseline). Patients in the *No multimorbidity* group presented the largest proportion of youngest individuals (aged 66–70 at baseline) at each of the time points.

Retrospective trajectories of each patient were established along the three time points. Figure 1 shows all trajectories coloured according to the cluster of belonging in the previous time point, proportional to the number of patients transitioning from previous to next cluster. Different patterns of cluster transitioning between time points were found. In the first transition (10 to 5 years before), a variety of trajectories occurred and only 1031 patients (25.9%) transitioned to a similar cluster. Contrarily, in the second transition (5 years before to baseline), most patients (2047, 60.4%) transitioned to the same type of cluster. Frequencies of patients transitioning from clusters between two time points are shown in Figures S3A and B. Regarding entire identified trajectories, frequencies of the most prevalent ones can be found in Table S4. The top 3 complete trajectories involved non-multimorbid patients together with *unspecific* clusters, followed by a trajectory in which patients remained in the *musculoskeletal* cluster for 10 years and a trajectory in which patients transitioned from no multimorbidity to a *neurocognitive* cluster and remained there.

After describing the obtained clusters and trajectories, a stratification by sex and age group was conducted in order to uncover possible differences in those variables. Figure 2 shows the distribution of patients in the identified clusters of each stratum, as well as their trajectories. In males, the *Unspecific* cluster displayed the highest prevalence in both age groups, while in females, it was the *Musculoskeletal and chronic pain syndrome* cluster for the youngest and the *Neurocognitive* cluster for the oldest.

Discussion

Main important results

The findings of this study expand our understanding of the progression in chronic conditions among older patients by evaluating patterns of chronic multimorbidity and their trajectories over a 10-year period. Multimorbidity increased from 73.6 to 98.3% in this time span and the median number of chronic conditions progressed from 3 to 9. Two clusters emerged, named *Heart diseases* and *Neurocognitive*, along with the discontinuation of clusters likely requiring lower levels of disease management, revealing a substantial increase in multimorbidity burden. Furthermore, the differences uncovered by the sex and age stratification suggest that these variables should not be overlooked when planning and designing future actions. All in all, these findings highlight the dynamism and variation of multimorbidity.

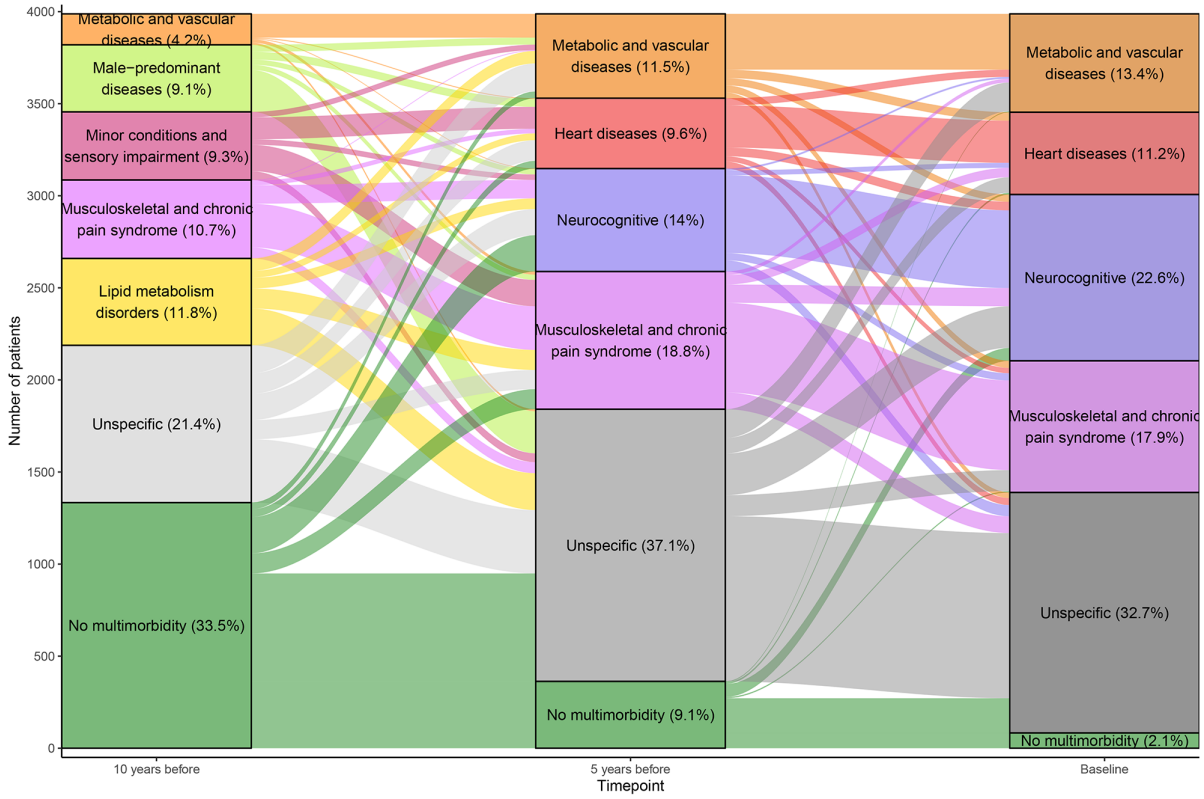

Fig. 1 Prevalence of chronic multimorbidity clusters defined at three different time points over ten years and their trajectories. Bar heights represent the number of patients belonging to the cluster and stripe heights represent patients moving from one cluster to another, in an independent manner for each of the two depicted cluster transitions.

Comparison with other studies

This study explores and contributes to shed light on the trajectories of chronic multimorbidity patterns– i.e. how do patterns of diseases change over time and how do patients transition within these patterns. While several studies have already been exploring trajectories of multimorbidity with various methodologies [25], very few have determined comprehensive multimorbidity patterns with comparable techniques.

Guisado-Clavero and colleagues [31] analysed multimorbidity patterns in patients aged>65 residing in Barcelona (Spain) in a 6-year span. The obtained clusters were found to remain quite similar from the beginning to the end of the study period and retain most patients, similar to our findings comparing our baseline time point to 5 years before. Moreover, from the six identified patterns (named *Musculoskeletal, Endocrine-metabolic, Digestive-respiratory, Cardiovascular, Neuropsychiatric* and *Unspecific*), five of them could be matched to those identified in our analyses. Another study, considering a longer period (12 years) in patients aged≥60 from a Swedish city [32], found highly heterogeneous trajectories from the 6 initially identified multimorbidity patterns (named *Psychiatric and respiratory, Heart, Respiratory and musculoskeletal, Cognitive and sensory impairment, Eye diseases and cancer, Unspecific*) to those identified 12 years later (named *Vascular, Cardiometabolic, Respiratory, Neuropsychiatric, Eye and Musculoskeletal, Unspecific*). Therefore, similar results have been found in terms of identifying multimorbidity patterns, as most of them may be equivalent to ours; however, the results on transitions or trajectories of multimorbidity need to be further studied.

Clinical interpretation of the results

The most common trajectory involving specific clusters was that of patients remaining in the *Musculoskeletal and chronic pain syndrome* cluster all along. This cluster consistently had the highest proportion of females (more than 80%), and not only showed a high prevalence of musculoskeletal and pain-related disorders but also of anxiety and depression. These findings are not surprising, as it is well-known that these conditions are frequent, more common in women, and increase with age [33–35]. Furthermore, this situation represents a significant health burden and may cause a highly negative impact on

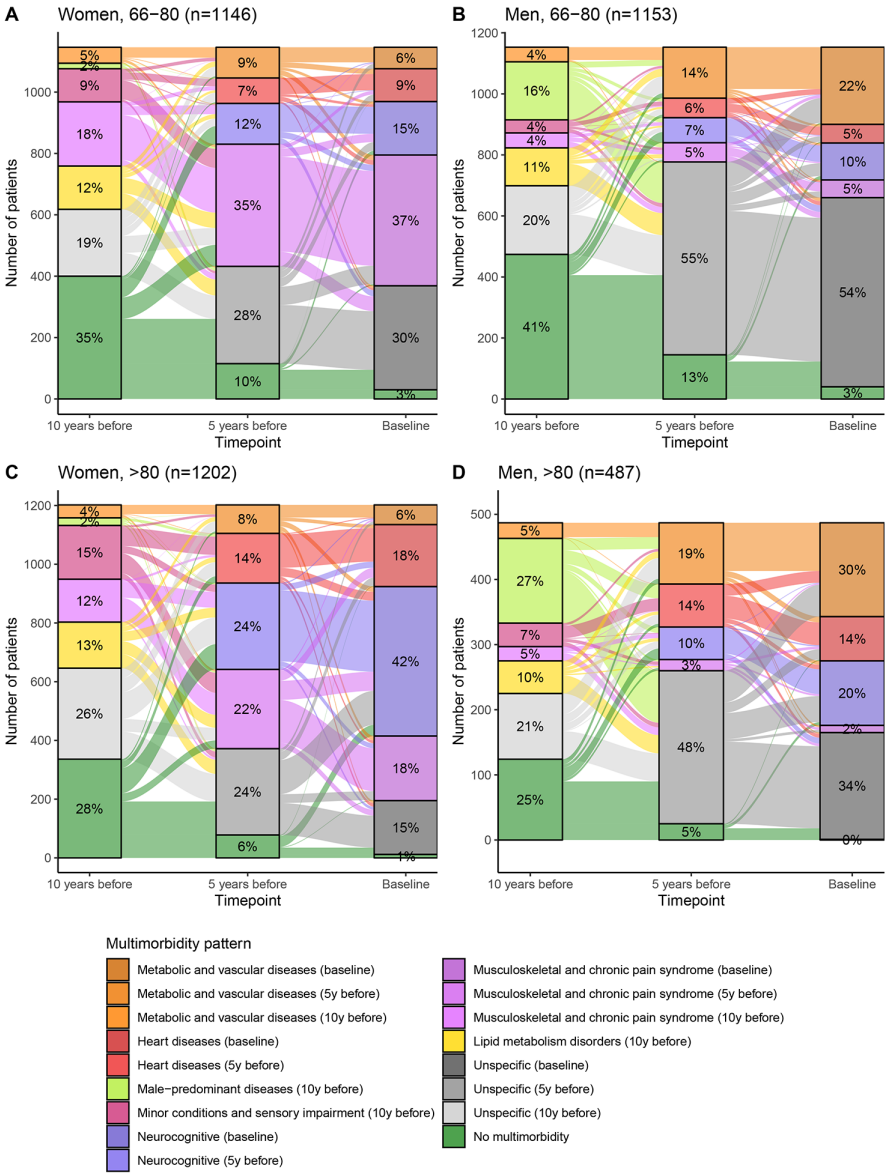

Fig. 2 Prevalence of chronic multimorbidity clusters defined at three different time points over ten years and their trajectories, stratified by sex and age group. Bar heights represent the number of patients belonging to the cluster and stripe heights represent patients moving from one cluster to another, in an independent manner for each of the two depicted cluster transitions.

many aspects of life. Therefore, strong efforts should be directed towards development of better prevention and management strategies to address the complexity of this multimorbidity pattern. In this sense, new approaches are being proposed, such as the creation of highly specialised, interdisciplinary units that consider all aspects involved in the inflammatory vicious cycle of musculoskeletal pain in order to prevent its self-perpetuity and chronicity [36].

The next cluster showing a high consistency across all time points was the so called *Metabolic and vascular diseases*, mainly characterized by diabetes mellitus and peripheral/visceral vascular disease. It was also the specific cluster with the highest proportion of males in the baseline and 5 years before time points. In the earliest time point, this was the *Male-predominant diseases* cluster, with a high prevalence of chronic obstructive pulmonary disease. These findings may be explained as an effect of cardiovascular risk factors, especially tobacco

consumption, which could be the focus of preventive actions [37].

Conversely, the *Heart diseases* and *Neurocognitive* clusters emerged in the second time point of the study. The former was characterized by heart failure, valve disorders or pulmonary heart disease, and the latter composed by neurocognitive disorders or frailty. These conditions have an increasing prevalence with age, so that our findings are coherent. Furthermore, it may be possible that these clusters emerged in our retrospective analysis and were not found in the earliest time point because they might have conferred a higher mortality risk. In fact, a recent study described a higher mortality of individuals in clusters characterized by cardiovascular and neuropsychiatric diseases compared to an unspecific cluster [32]. Moreover, some studies also show how these patterns may be strong contributors to physical decline and disability [38]. All in all, these clusters may encompass those most burdensome, age-dependent disorders in which the potential to reduce disease burden is proposed to come from primary, secondary and tertiary prevention targeting older people and not only middle-aged adults [39]. Thus, it may also be important to explore the inclusion of further clinical variables that might impact patient management such as geriatric syndromes, frailty or drug prescriptions to the analysis and definition of multimorbidity patterns [40–42].

Finally, the *Unspecific* cluster was characterized by a lack of overrepresentation of any chronic conditions so that the association between diseases could have happened by chance. It was composed of cardiovascular risk factors, osteoarthritis or vision impairment, among others. While most patients moved from unspecific to specific clusters, some patients moved from specific to unspecific. In fact, most patients from the *Male-predominant diseases* and the *Lipid metabolism disorders* clusters, moved to the *Unspecific* cluster at the first transition. This situation might be explained by the fact that the reciprocal relationship between diseases changed as a result of participants gradually accumulating new diseases. This resulted in some clusters no longer appearing in the analyses and a possibly higher heterogeneity in the unspecific cluster as age advances. Another important consideration on the *Unspecific* cluster is the large proportion of male individuals, specially aged > 80, present in this cluster, which might be explained by the selection of those healthier oldest individuals.

Strengths and limitations

This study has several strengths. First, the inclusion of an exhaustive set of chronic condition diagnoses in the analyses, which allowed to define a set of comprehensive multimorbidity patterns. For instance, the inclusion of both mental and physical conditions enabled to describe their potential interplay. Second, the robust statistical methodology applied, fuzzy c-means clustering, which allowed to cluster individuals according to their co-occurring conditions and follow their trajectories over time. This is the choice method when there is a tendency of overlap in clusters, which may be frequent in older individuals with highly prevalent conditions. Third, the involvement of a multidisciplinary team in the consensus process of defining the multimorbidity clusters, which provides both statistical and clinical validity. Finally, considering a sex perspective in the stratified analysis, allowed to uncover possible differences between men and women which may help increase gender equity.

Nevertheless, some limitations of this work should also be considered. Despite comprehensively considering chronic conditions, some factors such as frailty, geriatric syndromes, chronic medication or care received could be relevant but are not available. However, this does not invalidate the novel methodological approach. In addition, the unavailability of hospital diagnoses could have introduced possible biases in the data. Nevertheless, the gatekeeping role general practitioners at primary care could be a compensatory mechanism. Another limitation would be the retrospective nature of the study. Therefore, it does not allow to account for trajectories of individuals who did not survive at ten years' times.

Furthermore, the study cohort, composed of COVID-19 cases, might be introducing a bias in the estimated prevalences of chronic conditions in each cluster as well as in the frequencies of patients in each cluster, that may not reflect those of the general population However, taking advantage of this cohort, it is valuable to assess how the trajectories have developed in these patients. Moreover, some limitations are also present regarding the use of RWD from electronic health records, such as unavailability of certain variables or missing information. However, these databases guarantee maximum representation, large patient volumes and detailed information registered with relatively homogeneous criteria.

Possible clinical implications

Multimorbidity is currently challenging the traditional approach of medicine, from clinical practice of professionals treating individual patients to management decisions of policy makers in charge of the organization of entire healthcare services. In this context, suggestions are being made to create integrated programs that connect various clinical specialties and healthcare units, with a primary focus on individual patients, their unique clinical profiles and trajectories. Hence, adopting a longitudinal perspective and considering multimorbidity patterns may contribute to this needed redefinition and reorientation of healthcare delivery towards multimorbid patients.

The findings in this study may help in the development of higher personalised medicine in multimorbidity and could also potentially be used to promote healthier aging. The stratification by sex and age allowed to identify possible clusters and trajectories on which some actions could be focused in order to define specific clinical protocols, prevention strategies, reorganization of healthcare circuits or planning for future needs. Thus, our findings support the design of future randomized clinical studies aimed at improving the clinical management of multimorbidity.

Moreover, this study is a contribution to P4 (predictive, personalised, preventive, and participatory) medicine, which is based on the analysis of large amounts of data, the use of artificial intelligence assistance and the organization of multidisciplinary teams to bring more efficient care to geriatric patients. All in all, both clinicians managing co-occurring chronic conditions and health policy makers allocating resources for care may benefit from understanding how diseases cluster together and, moreover, how multimorbidity might progress over time.

Conclusions

Trajectories of chronic multimorbidity patterns in older patients are identifiable and show a high level of complexity and fluctuation over time. In a cohort of older patients (65+years old), we were able to identify multimorbidity patterns of chronic conditions and describe their individual trajectories in the previous 10 years using RWD and cluster analysis. Taken together, our results suggest that, while further research is needed to develop a deeper understanding, considering multimorbidity patterns and their trajectories, along with incorporating a sex perspective, might improve decisions in clinical management and healthcare planning.

Abbreviations

RWD	Real-world data
O/E	observed/expected

Supplementary Information

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Supplementary Material 1 (Figure S1)

Supplementary Material 2 (Table S1)

Supplementary Material 3 (Table S2)

Supplementary Material 4 (Table S3)

Supplementary Material 5 (Figure S2)

Supplementary Material 6 (Table S4)

Supplementary Material 7 (Figure S3)

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Author contributions
ML conceived the study, obtained funding, performed data integration and statistical and graphical analysis of the results, participated in the interpretation and discussion of the results, wrote the first version of the manuscript and is responsible for the overall content as guarantor. MaB conceived the study, obtained funding, participated in the interpretation and discussion of the results and reviewed several manuscript versions. MoB, RC, SH, RJ and JO provided clinical insight and participated in the interpretation and discussion of the results. All authors read and approved the final manuscript.

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Data availability
Data cannot be publicly shared because of confidentiality. Data used for this analysis are available from the Government of Catalonia Institutional Data Access (PADRIS Program) for researchers who meet the criteria for access to confidential data. Inquiries of access to aggregated data should be addressed to AQuAS director (direccio.aquas@gencat.cat), under the following conditions: http://aquas.gencat.cat/ca/ambits/analitica-dades/padris/.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee (CEIm) of the Parc Taulí University Hospital (reference 2022/5051), which waived the requirement of informed consents of patients due the epidemiological nature of the study and the use of anonymized data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. World Health Organization. Ageing and health. 2022. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health. Accessed 19 May 2023.
2. Publications Office of the European Union. Ageing Europe - Looking at the lives of older people in the EU– 2020 edition. Luxembourg; 2020.
3. Lugtenberg M, Burgers JS, Clancy C, Westert GP, Schneider EC. Current guidelines have limited applicability to patients with comorbid conditions: a systematic analysis of evidence-based guidelines. PLoS ONE. 2011;6(10):e25987. https://doi.org/10.1371/journal.pone.0025987.
4. Palladino R, Pennino F, Finbarr M, Millett C, Triassi M. Multimorbidity and Health outcomes in older adults in ten European Health systems, 2006-15. Health Aff (Millwood). 2019;38:613–23. https://doi.org/10.1377/hlthaff.2018.05273.
5. Calderón-Larrañaga A, Vetrano DL, Ferrucci L, Mercer SW, Marengoni A, Onder G, et al. Multimorbidity and functional impairment-bidirectional interplay, synergistic effects and common pathways. J Intern Med. 2019;285:255–71. https://doi.org/10.1111/joim.12843.
6. Buffel du Vaure C, Dechartres A, Battin C, Ravaud P, Boutron I. 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. https://doi.org/10.1136/bmjopen-2016-012265
7. Muth C, Blom JW, Smith SM, Johnell K, Gonzalez-Gonzalez AI, Nguyen TS, et al. Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus. J Intern Med. 2019;285:272–88. https://doi.org/10.1111/JOIM.12842.
8. Okeowo D, Patterson A, Boyd C, Reeve E, Gnjidic D, Todd A. Clinical practice guidelines for older people with multimorbidity and life-limiting illness: what are the implications for deprescribing? Ther Adv drug Saf. 2018;9:619–30. https://doi.org/10.1177/2042098618795770.
9. The Academy of Medical Sciences. Multimorbidity: a priority for global health research. The Academy of Medical Sciences: London, UK. 2018. https://acmedsci.ac.uk/file-download/82222577.
10. Rijken M, Struckmann V, Van Der Heide I, Hujala A, Barbabella F, Van Ginneken E 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.
11. van der Heide I, Snoeijs SP, Boerma WGW, Schellevis FG, Rijken MP. How to strengthen patient-centredness in caring for people with multimorbidity in Europe? 2017. http://europepmc.org/books/NBK464537.
12. Andreu-Perez J, Poon CCY, Merrifield RD, Wong STC, Yang G-Z. Big Data for Health. IEEE J Biomed Heal Inf. 2015;19:1193–208. https://doi.org/10.1109/JBHI.2015.2450362
13. Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. J Clin Epidemiol. 2014;67:254–66. https://doi.org/10.1016/j.jclinepi.2013.09.021.
14. Ng SK, Tawiah R, Sawyer M, Scuffham P. Patterns of multimorbid health conditions: a systematic review of analytical methods and comparison analysis. Int J Epidemiol. 2018;47:1687–704. https://doi.org/10.1093/ije/dyy134.
15. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PLoS ONE. 2014;9:e102149. https://doi.org/10.1371/journal.pone.0102149
16. Kudesia P, Salimarouny B, Stanley M, Fortin M, Stewart M, Terry A, et al. The incidence of multimorbidity and patterns in accumulation of chronic conditions: a systematic review. J Comorbidity. 2021;11:2633556521103280. https://doi.org/10.1177/26335565211032880.
17. Busija L, Lim K, Szoeke C, Sanders KM, McCabe MP. Do replicable profiles of multimorbidity exist? Systematic review and synthesis. Eur J Epidemiol. 2019;34:1025–53. https://doi.org/10.1007/s10654-019-00568-5
18. Ho IS, Azcoaga-Lorenzo A, Akbari A, Black C, Davies J, Hodgins P, et al. Examining variation in the measurement of multimorbidity in research: a systematic review of 566 studies. Lancet Public Heal. 2021;6:e587–97. https://doi.org/10.1016/S2468-2667(21)00107-9
19. Lleal M, Corral-Vazquez C, Baré M, Comet R, Herranz S, Baigorri F, et al. Multimorbidity patterns in COVID-19 patients and their relationship with infection severity: MRisk-COVID study. PLoS ONE. 2023;18:e0290969. https://doi.org/10.1371/JOURNAL.PONE.0290969.
20. Juul-Larsen HG, Christensen LD, Bandholm T, Andersen O, Kallemose T, Jørgensen LM, 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. https://doi.org/10.2147/CLEP.S226586.
21. Juul-Larsen HG, Andersen O, Bandholm T, Bodilsen AC, Kallemose T, Jørgensen LM, et al. Differences in function and recovery profiles between patterns of multimorbidity among older medical patients the first year after an acute admission—An exploratory latent class analysis. Arch Gerontol Geriatr. 2020;86:103956. https://doi.org/10.1016/j.archger.2019.103956.
22. Zheng DD, Loewenstein DA, Christ SL, Feaster DJ, Lam BL, McCollister KE, et al. Multimorbidity patterns and their relationship to mortality in the US older adult population. PLoS ONE. 2021;16:e0245053. https://doi.org/10.1371/journal.pone.0245053.
23. Teh RO, Menzies OH, Connolly MJ, Doughty RN, Wilkinson TJ, Pillai A, et al. Patterns of multi-morbidity and prediction of hospitalisation and all-cause mortality in advanced age. Age Ageing. 2018;47:261–8. https://doi.org/10.1093/AGEING/AFX184.
24. Lleal M, Baré M, Ortonobes S, Sevilla-Sánchez D, Jordana R, Herranz S, et al. Comprehensive multimorbidity patterns in older patients are Associated with Quality indicators of Medication—MoPIM Cohort Study. Int J Environ Res Public Health. 2022;19:15902. https://doi.org/10.3390/IJERPH192315902/S1.
25. Cezard G, McHale CT, Sullivan F, Bowles JKF, Keenan K. Studying trajectories of multimorbidity: a systematic scoping review of longitudinal approaches and evidence. BMJ Open. 2021;11(11):e048485. https://doi.org/10.1136/BMJOPEN-2020-048485.
26. National Center for Health Statistics (NCHS). International Classification of Diseases, Tenth Revision, clinical modification (ICD-10-CM). Hyattsville, MD: National Center for Health Statistics; 2010.
27. R Core Team. R: A Language and Environment for Statistical Computing. 2020. https://www.r-project.org/.
28. Agency for Healthcare Research and Quality. Rockville. MD. Healthcare Cost and Utilization Project (HCUP). 2021. www.hcup-us.ahrq.gov/home.jsp.
29. Bezdek JC, Ehrlich R, Full W. FCM: the fuzzy c-means clustering algorithm. Comput Geosci. 1984;10:191–203.
30. Eurostat. Population projections in the EU - Statistics Explained. 2023. https://ec.europa.eu/eurostat/statistics-explained/index.php?oldid=497115. Accessed 19 May 2023.
31. Guisado-Clavero M, Roso-Llorach A, López-Jimenez T, Pons-Vigués M, Foguet-Boreu Q, Muñoz MA, et al. Multimorbidity patterns in the elderly: a prospective cohort study with cluster analysis. BMC Geriatr. 2018;18:16. https://doi.org/10.1186/s12877-018-0705-7
32. Vetrano DL, Roso-Llorach A, Fernández S, Guisado-Clavero M, Violán C, Onder G, et al. Twelve-year clinical trajectories of multimorbidity in a population of older adults. Nat Commun. 2020;11:1–9. https://doi.org/10.1038/s41467-020-16780-x.
33. Watt FE. Musculoskeletal pain and menopause. Post Reprod Heal. 2018;24:34–43. https://doi.org/10.1177/2053369118757537.
34. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open. 2016;6:10364. https://doi.org/10.1136/BMJOPEN-2015-010364.
35. Wolf JM, Cannada L, Van Heest AE, O'Connor MI, Ladd AL. Male and female differences in musculoskeletal disease. J Am Acad Orthop Surg. 2015;23:339–47. https://doi.org/10.5435/JAAOS-D-14-00020.
36. Bonanni R, Cariati I, Tancredi V, Iundusi R, Gasbarra E, Tarantino U. Chronic Pain in Musculoskeletal diseases: do you know your enemy? J Clin Med 2022. 2022;11(2609):11:2609. https://doi.org/10.3390/JCM11092609.
37. Grech J, Norman IJ, Sammut R. Effectiveness of intensive stand-alone smoking cessation interventions for individuals with diabetes: a systematic review and intervention component analysis. Tob Induc Dis. 2023;21:57. https://doi.org/10.18332/TID/162329.
38. Vetrano DL, Rizzuto D, Calderón-Larrañaga A, Onder G, Welmer AK, Bernabei R, et al. Trajectories of functional decline in older adults with neuropsychiatric and cardiovascular multimorbidity: a Swedish cohort study. PLOS Med. 2018;15:e1002503. https://doi.org/10.1371/JOURNAL.PMED.1002503.
39. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet (London England). 2015;385:549–62. https://doi.org/10.1016/S0140-6736(14)61347-7.
40. Baré M, Herranz S, Roso-Llorach A, Jordana R, Violán C, Lleal M, et al. Multimorbidity patterns of chronic conditions and geriatric syndromes in older patients from the MoPIM multicentre cohort study. BMJ Open. 2021;11:e049334. https://doi.org/10.1136/bmjopen-2021-049334.

41. Marengoni A, Zucchelli A, Vetrano DL, Armellini A, Botteri E, Nicosia F, et al. Beyond chronological age: Frailty and Multimorbidity Predict In-Hospital mortality in patients with Coronavirus Disease 2019. J Gerontol Biol Sci Med Sci. 2021;76(3):e38–45. https://doi.org/10.1093/gerona/glaa291.
42. Villén N, Roso-Llorach A, Gallego-Moll C, Danes-Castells M, Fernández-Bertolin S, Troncoso-Mariño A, et al. Polypharmacy patterns in Multimorbid Older People with Cardiovascular Disease: longitudinal study. Geriatr. 2022;7(6):141. https://doi.org/10.3390/GERIATRICS7060141/S1.

6. Discussion

6.1. Main findings

The aim of this PhD thesis was to identify multimorbidity patterns of chronic conditions and determine their relationship with various clinically relevant outcomes and indicators. Three studies were conducted focused on multimorbidity patterns to assess their potential relationship with quality indicators of medication, severity or mortality of infection and to assess their longitudinal trajectories. These studies revealed that it is possible to identify multimorbidity patterns that are related to relevant outcomes and indicators defined at specific time points, and that multimorbidity patterns can also be longitudinally analysed and tracked.

In the MoPIM study, significant associations were found between multimorbidity patterns and quality indicators of chronic medication. Notably, certain patterns were associated with the presence or number of PIMs, PPOs and ADRs, and also with specific types. This finding suggests that patients within each cluster tend to present comparable situations, potentially identifying groups of patients with similar healthcare needs. Two clusters, named 'osteoarticular' and 'minor chronic disease', were associated with worse indicators overall. These clusters included different patient profiles but comprised those patients with higher number of chronic conditions and higher number of chronic medications. Taken together, these results suggest that chronic medication could be tailored according to each particular patient profile, focusing on those medications most problematic to each cluster.

In the MRisk-COVID study, multimorbidity clusters were defined and some were found to be associated with adverse outcomes of an acute COVID-19 infection. In this case, clusters were defined by stratification into age groups and sex, revealing associations between certain multimorbidity patterns and both infection severity and mortality, particularly in clusters comprising young and middle-aged patients with cardiovascular or metabolic conditions. Overall, these findings suggest that beyond the occurrence of isolated pathologies, the coexistence of chronic conditions may represent an additional dimension to consider when facing acute situations.

Regarding the MTOP study, it goes beyond the cross-sectional nature of most multimorbidity studies by describing how multimorbidity patterns change over a 10-year period with the accumulation of conditions in patients, and which trajectories are formed. The findings show that some patterns emerged earlier than others, with more burdensome clusters replacing less severe ones over time. Nevertheless, by the end of the studied period, patients developed a certain multimorbidity profile and remained within it. Importantly, the study highlights the role of sex and age in these patterns and trajectories. All in all, the results of the study emphasise the dynamism and variation of multimorbidity, underscoring the need for further longitudinal studies that may inform future decisions.

6.2. Operationalising multimorbidity: list of chronic conditions

Despite the current broad agreement on defining multimorbidity as the presence of two or more chronic conditions, there is a lack of consensus on how to operationalise this definition in research studies. As a result, studies have been using different measures in terms of numbers, labels, types and severity of conditions to be included. Consequently, there is a pressing need for consensus studies that define core and study-dependent conditions to include in multimorbidity measures [6].

Nevertheless, at the time of designing the MoPIM study, no operational definition of multimorbidity had been proposed, although this issue had already been raised [81]. Therefore, an ad hoc list of conditions was defined, based on consensus among the physician researchers of the project. This list was derived from the 114 groups defined by Salisbury and colleagues [17] and included the 19 categories of the Charlson Comorbidity Index [76], ultimately encompassing 64 chronic conditions. This selection was considered an appropriate balance between comprehensiveness and data collection effort and it was also defined taking into account that a 2% prevalence threshold would be set in the multimorbidity cluster analysis. A recent systematic review at that time revealed that of 14 included studies on multimorbidity patterns, only one considered more than 64 conditions, further confirming the comprehensiveness of data collection [81]. Additionally, geriatric syndromes, which may both contribute to and result from multimorbidity, were also recorded and included in the clustering procedure. Often overlooked in traditional disease-focused models, geriatric syndromes may be crucial to understanding the full picture of health in older adults.

Over these recent years, the rapid increase in multimorbidity research has led to the development of new, reproducible methods of operational definitions of multimorbidity, primarily based on the grouping of clinical codes, such as those of the International Classification of Diseases [125]. A first comprehensive proposal of operationalisation was developed by Calderón-Larrañaga and colleagues, composed of 918 chronic ICD-10 codes that were grouped into 60 chronic disease categories [126]. Of these 60 categories, 35 were equivalent to those defined in the MoPIM project, 15 were partially equivalent due to different groupings, 1 was not registered ('chromosomal abnormalities'), and the remaining 9 consisted of various "Other" categories, including a variety of low-prevalence conditions. Therefore, the conditions not registered in the MoPIM study but present in this list were were low-prevalence conditions and thus falling outside the scope of the MoPIM project.

More recently, a Delphi consensus study by Ho and colleagues [127] defined 24 conditions to always include in multimorbidity studies, 22 of which are present in the MoPIM study; and 35 conditions to include unless there was a good reason not to, 24 of which were retrieved in the MoPIM study. The two chronic conditions from the 'always include' section in this consensus list that were not included in the MoPIM list are cystic fibrosis and Addison's disease, both of which are low-prevalence conditions as well.

In addition to selecting diagnostic codes from closed, predefined lists, an alternative approach can be employed by initially grouping all codes without exclusion and performing a selection later on, for example, through prevalence filtering. This process will result in a more specific dataset of chronic conditions tailored to the selected subpopulation of study. This was the methodological approach used in the MRisk-COVID and MTOP studies. Using two different software tools, namely Chronic Condition Indicator [122] and Clinical Classification Software Refined [123], chronic conditions can be selected and grouped into clinically meaningful categories. While this approach does not define a limited set of categories, which may limit reproducibility, it enables a more customised analysis. Therefore, it has been used in many studies defining multimorbidity patterns with clustering algorithms [128, 129, 130].

6.3. Analytical approaches to identify multimorbidity patterns

Multimorbidity researchers have used several statistical methods to define multimorbidity patterns, with the choice of method often depending on the aims of the analysis, as summarised in the Introduction subsection 1.7.1.

In the studies composing this thesis, the aim was to define clusters of patients and evaluate their relationships with various outcomes and indicators. In this situation, actionable clusters were needed containing groups of similar patients. This concept is aligned with nonhierarchical cluster analysis of individuals, which aims to identify groups of most similar individuals (not necessarily sharing a common underlying cause), by maximising similarity within clusters and difference between clusters [82].

Furthermore, by applying soft clustering with the fuzzy c-means algorithm, we could perform a probabilistic membership approach that allows to model a more realistic situation from a biological perspective, as patients may be located between clusters rather than forcedly assigned to a single cluster. This is different from the membership probabilities obtained in latent class analysis as it has an underlying assumption of mutually exclusive classes, whereas soft clustering allows for true overlap by design. Indeed, it has been suggested that the simultaneous linking of individuals to multiple clusters that allows soft clustering may be more closely aligned with clinical experience compared to other methodological approaches [90].

An important aspect when performing cluster analysis is to define the number of clusters, as an inappropriate choice can introduce random error, leading to false positives (identifying artefactual profiles from too many clusters) or false negatives (missing clinically important profiles from too few clusters). However, since the true number of multimorbidity patterns is unknown, it is not currently possible to directly estimate false positives and negatives in multimorbidity profiling studies. Therefore, it has been recommended to use at least two methods to determine the optimal number of profiles and to clearly report them [82]. Accordingly, this recommendation was adopted in the three studies, where various clustering validation indexes (such as the partition coefficient and partition entropy) were calculated. These indexes are important tools for evaluating clustering quality and selecting the appropriate number of clusters, providing quantitative measures of performance based on data distribution and distance between

clusters [131]. After selecting a range of statistically validated solutions, these were discussed among a multidisciplinary clinical team for consistency along with the clinical observations to determine a final solution.

6.4. Multimorbidity patterns identified across studies

The three studies composing this PhD thesis have obtained similar results despite their different settings and aims, allowing for a joint interpretation.

As described in previous studies and reviews, clusters containing cardiovascular conditions are among the most replicable [81, 82, 93]. Indeed, cardiovascular clusters were found in all three studies, although with varying characteristics. In the MRisk-COVID study, cardiovascular clusters were identified across all sex-age groups. In younger individuals, these clusters were primarily composed of risk factors such as hypertension and disorders of lipid metabolism, while in middle-aged and older patients, they included heart conditions like heart failure, ischaemic heart disease and cardiac dysrhythmias. These findings were expected and consistent with the progression of cardiovascular diseases over time. In the MoPIM study, a 'cardiorespiratory' cluster was identified, whereas in the MTOP study, two separate clusters were identified ('heart diseases', 'metabolic and vascular') rather than a single cluster. The identification of replicable patterns, either as standalone clusters or in combination with other conditions, is consistent with the findings of a systematic review by Beridze and colleagues, who identified a cardiovascular pattern that often contained other conditions such as endocrine, metabolic or renal conditions depending on the study [93].

A second type of cluster was also found in all three studies containing musculoskeletal conditions and chronic pain together with anxiety and depression, consistent with clinical findings reporting their connection [132] as well as with the repeatedly identified 'musculoskeletal' cluster [81, 82, 93]. This type of cluster was labelled 'osteoarticular' in MoPIM study, 'osteoinflammatory' in MRisk-COVID study and 'musculoskeletal and chronic pain syndrome' in MTOP study. It was associated with worse quality indicators of medication and a long and stable trajectory, but it was not associated to COVID-19 infection severity or mortality, and it consistently had a higher proportion of women. It is indeed well-known that these are frequent conditions, specially in women, that increase with age and represent a significant health burden that may

cause a highly negative impact on many aspects of life [132, 133, 134, 135].

Finally, many clusters labelled as 'unspecific' were found in MRisk-COVID and MTOP studies, also previously described in the literature [98, 101, 113, 130, 136, 137]. These unspecific clusters can appear when using clustering analysis, probably determining a heterogeneous group of individuals, yet containing the most similar individuals within the cluster and most distant to the other clusters. Unspecific clusters can either include no overrepresented conditions or sets of apparently discordant conditions. The unspecific clusters in the MRisk-COVID study (excluding the 'unspecific with COPD predominance' cluster) included more males than females and were the clusters with lowest percentage of infection severity and mortality. Those in the MTOP study gradually changed from predominantly female to male and had the lowest number of chronic conditions.

Various findings in the literature are consistent with the results obtained in this thesis, also suggesting a lower morbidity and better outcomes in unspecific clusters. Marengoni and colleagues identified an unspecific pattern composed by the group of individuals that were youngest, with lowest number of co-occurring diseases and best functional and cognitive status [101]. Also, Ioakeim-Skoufa and colleagues described that patients in the unspecific pattern were the youngest and had a lower prevalence of nutritional and endocrine-metabolic disorders compared to other clusters [130]. In a longitudinal study by Vetrano et. al., similar to the MTOP study, individuals in the unspecific cluster were the youngest and healthiest but also the most likely to transition between clusters at each time point [113]. Furthermore, many studies have identified particular multimorbidity patterns presenting a higher risk of unplanned hospitalisations, unplanned readmissions and longer in-hospital stays [98], frailty [136] or dementia [137], compared to unspecific clusters.

6.5. Strengths and limitations

6.5.1. Strengths

This PhD thesis is composed of three studies which have undergone a peer review process and have been published in international scientific journals. These studies are the result of three competitively funded projects: MoPIM study was funded by the Instituto de Salud Carlos III-FEDER (PI15/00552) and the REDISSEC research network (RD16/0001/0002); MRisk-COVID

study was selected in an extraordinary call by the Public Data Analysis for Health Research and Innovation Program (PADRIS) and received funding from Institut d'Investigació i Innovació Parc Taulí (CIR2020/023); MTOP study was funded by the Institut d'Investigació i Innovació Parc Taulí (CIR2021/038). Furthermore, all these studies are the result of the collaboration of a multicentre and multidisciplinary group of experienced researchers and clinicians. All these facts highlight the relevance, quality and novelty of this research.

This thesis covers a highly relevant topic, as it is crucial to explore and build knowledge about different aspects related to multimorbidity due to its rapid increase and the challenge it poses to patients, healthcare professionals and entire healthcare systems. Taking into account the complexity inherent to multimorbidity research, another strength of this work is that multimorbidity is addressed in different but complementary situations. This provides an overview of possible settings, designs and data sources that can be used depending on the study purpose. Indeed, this thesis contains cross-sectional approaches, comparing multimorbidity patterns to either chronic (drug prescribing) or acute (COVID-19 infection) situations; and a longitudinal approach. Also, one study is based on data obtained by medical records review while the others use real-world data.

The main methodological strength of this thesis is the robust and comprehensive approach followed in all projects. Multimorbidity clusters have been defined from a comprehensive set of conditions and built with an algorithm of soft clustering that is best suited for this kind of data: the fuzzy c-means algorithm. This algorithm clusters individuals based on their co-occurring conditions and assigns a membership probability to each cluster rather than a binary allocation. Therefore, it is the choice method for pattern recognition when there is an overlap between clusters. This is indeed the typical situation in multimorbidity analyses involving older adults, who present with a high prevalence of co-occurring conditions. Furthermore, the final choice of multimorbidity patterns was conducted in all studies on both statistical and clinical criteria, using a Delphi-like selection method to reach consensus.

The main strengths of each of the studies are summarised in Table 7.

TABLE 7: Main strengths of the studies composing this PhD thesis

Study	Strengths
Study 1: MoPIM	Multicentre study: increased external validity
	Prospective design, it ensures high data quality by an accurate and thorough registering of variables that may commonly be underreported, such as PIP and ADRs
	Cohort of hospitalised patients admitted due to chronic condition exacerbation, a vulnerable and complex group of patients who may benefit from a reduction in adverse outcomes
	Multidisciplinary team composed of pharmacists and physicians jointly performing the medication-review process
	Incorporation of both chronic conditions and geriatric syndromes in the definition of multimorbidity clusters
	Robust methodological identification of multimorbidity patterns (statistically and clinically)
	Novel and comprehensive design combining multimorbidity patterns with specific PIP and ADRs
Study 2: MRisk-COVID	Large sample size, allowing to define stratified multimorbidity patterns
	Stratification by sex and age, allowing to uncover possible differences and helping increase sex and age equity
	Comprehensive, structured, standardised data, linked from various sources (epidemiological surveillance, primary care, hospital)
	Inclusion of an exhaustive set of chronic condition diagnoses (both mental and physical) in the analyses, which allowed to define a set of comprehensive multimorbidity patterns
	Inclusion of detailed diagnoses and procedures, which allowed to precisely define COVID-19 infection severity
	Robust methodological identification of multimorbidity patterns (statistically and clinically)
Study 3: MTOP	Large sample size, allowing to define reliable longitudinal multimorbidity patterns and trajectories
	Comprehensive, structured, standardised data
	Inclusion of an exhaustive set of chronic condition diagnoses (both mental and physical) in the analyses, which allowed to define a set of comprehensive multimorbidity patterns
	Robust methodological identification of multimorbidity patterns (statistically and clinically)
	Sex perspective in the stratified analysis, allowed to uncover possible differences between men and women which may help increase sex equity.
	One of few longitudinal studies of multimorbidity patterns

6.5.2. Limitations

Alongside its strengths, this thesis work presents certain limitations that warrant consideration. The main limitation of the thesis is the large methodological variability inherent in studies identifying multimorbidity patterns. The lack of consensus on how to define these patterns gives rise to high methodological heterogeneity between studies and thus hinders straightforward comparability, potentially impacting the reliability of results. Nonetheless, some relevant results have been obtained, concordant with previous literature.

Another potential limitation when trying to identify multimorbidity patterns and uncover associations with certain outcomes or indicators is the lack of information on the relevance, severity or clinical management required for each chronic condition. Certain conditions may either be asymptomatic, well-controlled or not yet reaching a certain level of progression, leading to variability in their impact. This situation was partially addressed in the MoPIM study, where multimorbidity patterns were defined and weighted according to the clinical management that each condition required. Despite the possible subjectivity in this weighting, it provided valuable insights. Nevertheless, this approach required direct clinical assessment by a physician, which is not feasible when doing research with large databases containing diagnoses codes, as in MRisk-COVID and MTOP studies, where multimorbidity patterns could only be defined by the presence or absence of diagnoses.

Furthermore, data source, availability or collection methods can pose some limitations in multimorbidity research. Reviewing medical records, as in the MoPIM study, is resource intensive and human-dependent, with possible reporting differences between centres or healthcare professionals. On the other hand, real world data analyses, as in MRisk-COVID and MTOP studies, may also present some limitations, such as lower data quality and data heterogeneity.

The main limitations of each of the studies are summarised in Table 8, along with their potential impact and strategies used to minimise it.

TABLE 8: Main limitations of the studies composing this PhD thesis

Study	Limitations	Potential impact and minimisation strategies
Study 1: MoPIM	The results of this study are conditioned to the predefined multimorbidity patterns	These patterns could be questioned, although they were comprehensive, considering a large list of conditions, and consensually selected by a multidisciplinary research team
	There may be differences in the identification of PIP or reporting of ADRs between centres or healthcare professionals	Large efforts were made to homogenise criteria
Study 2: MRisk-COVID	Inherent limitations concerning data collection, codification and testing related to the period (first pandemic wave)	The described results should always be interpreted considering this situation
	Inclusion of suspected COVID-19 cases in the study cohort	Despite potentially introducing false positives, it helped avoid biases related to age, access to testing, and socioeconomic factors, as the critical situation led to limited confirmatory tests
	Groups with high risk of re-identification were not included (women aged >95 and men aged >90)	The described results should always be interpreted considering this situation
	Small, specific geographic region	May not be representative to larger regions; however, it ensures a certain uniformity (population, clinical management, protocols, codification), thus mitigating the potential heterogeneity
	Additional factors that were not included in the analyses, such as healthcare-associated features, socioeconomic status, dependency or frailty may be relevant	The described results should always be interpreted considering this situation.
Study 3: MTOP	Despite comprehensively considering chronic conditions, some factors (such as frailty or chronic medication) could be relevant but are not available	The described results should always be interpreted considering this situation
	Retrospective nature of the study, it does not account for trajectories of individuals that did not survive at ten years' time	The estimated prevalences of chronic conditions per cluster and the proportions of patients in each cluster may be different to those in the general population, although providing these estimations was not the aim of the study.
	The study cohort is composed of COVID-19 cases	The estimated prevalences of chronic conditions per cluster and the proportions of patients in each cluster may be different to those in the general population, although providing these estimations was not the aim of the study.

6.6. Implications

6.6.1. Implications on clinical practice

Research of multimorbidity patterns has the potential to improve clinical management of patients with multiple chronic conditions by guiding towards better clinical decision-making, enhancing personalised care and risk stratification, aiding patient-centred and holistic approaches and informing resource allocation and policy development [8]. The studies comprising this thesis uncover some possible directions in which to focus and change the current practice. Most importantly, these findings may contribute to the design of tailored interventions aimed at patients with multimorbidity, given that the performed analyses are based on individuals rather than diseases.

Firstly, the findings of MoPIM study highlight the importance of tailored medication review strategies in patients with multimorbidity. More specifically, the results on the osteoarticular cluster (with a high prevalence of chronic pain, anxiety, depression, and benzodiazepine use) underscore the need for deprescribing benzodiazepines to avoid negative outcomes like falls, fractures and cognitive decline. Furthermore, the management of pain and side effects, such as constipation from opioids, as well as to the ADRs from antihypertensive drugs, may require closer attention in these patients. Overall, the results suggest that taking appropriate actions, such as performing comprehensive medication reviews through multidisciplinary collaboration and patient categorization according to multimorbidity profiles, may help optimise care, particularly regarding quality indicators of medication. In fact, in a subsequent study from the MoPIM project with the same cohort, a significant reduction in PIM was achieved through a multidisciplinary pharmacotherapy review, mostly by deprescription of benzodiazepines in patients from the osteoarticular cluster [138].

Moreover, multimorbidity patterns can also be related to outcomes involving acute situations. As initially described regarding COVID-19, some coexisting conditions increase the severity and mortality of infections, particularly cardiovascular conditions [109, 139]. These findings correlate with the identified multimorbidity patterns with highest severity and mortality, especially in younger groups, composed of cardiovascular conditions. Additionally, it has been reported that severe COVID-19 infection also raises the risk of cardiovascular events occurring

afterwards [140]. Thus, there seems to be a bidirectional relationship between COVID-19 and cardiovascular conditions, highlighting the importance of contemplating the whole range of chronic conditions in patients. In addition, studying the interplay of multimorbidity profiles and outcomes of an acute infection may help develop new methodologies and approaches able to identify the most vulnerable patients in the event of a new pandemic.

Furthermore, multimorbidity patterns are complex and may change over time. Therefore, describing and understanding the factors driving multimorbidity trajectories may help develop preventive strategies for groups of people at high risk of transitioning to a cluster associated with adverse health outcomes. Two of the described clusters –'Metabolic and vascular diseases' and 'Musculoskeletal and chronic pain syndrome'– were consistently found across all time points, calling for integrated management approaches and suggesting early interventions and comprehensive care approaches provided by specialised, interdisciplinary units focused on each patient profile.

Finally, the findings from all the studies in this thesis highlight the importance of incorporating a sex perspective in the clinical management of multimorbidity and related outcomes. As is well known, the prevalence of certain chronic conditions differs between men and women, and similarly, the distribution of multimorbidity patterns also differs by sex. For instance, we observed a clear predominance of women in musculoskeletal disease patterns, which were linked to worse quality indicators of medication and long multimorbidity trajectories. Conversely, the combination of metabolic and cardiovascular conditions more present in men could be addressed by lifestyle preventive measures. Indeed, sex differences in multimorbidity, inappropriate medication and adverse outcomes of inpatient care were found in a subsequent study of the MoPIM project [141]. All in all, these findings suggest that men and women could benefit from targeted interventions designed for their specific multimorbidity profile, including strategies to prevent or mitigate the onset of additional conditions, optimise treatment choices, and address the psychosocial factors associated with these health challenges.

6.6.2. Implications on future research

This PhD thesis helps improve our understanding of multimorbidity patterns and their characteristics, either related to quality indicators, adverse outcomes of an infection, or longitudinal evolution. Furthermore, it provides insights on how further studies should be conducted in

this emerging field of research in order to gain a deeper insight into multimorbidity patterns, their implications and their applicability.

First of all, some findings from this thesis could benefit from confirmation in larger, high-quality databases including a representative sample of the population of interest. In this regard, having readily available and well-structured data on key indicators or outcomes, such as those related with quality of medication, would be essential. Nevertheless, most clinical information in electronic health records is embedded within clinical notes from various sources and may not be retrievable. These notes may provide a huge amount of data with high potential to improve healthcare; however, manually reviewing such data would entail an unrealistic cost and time. Therefore, exploring natural language processing algorithms could provide enhanced information compared to structured data alone.

Additionally, the rapid advances in statistical and machine learning methodologies may offer valuable opportunities to improve our knowledge and refine the characterization of multimorbidity patterns. For instance, more sophisticated approaches could be pursued, such as advanced machine learning methods, that have not yet been tried in the study of multimorbidity and may have great potential [142]. Beyond advancing in data analytics methodologies, the field continues to face several additional challenges and open questions. These include issues related to data preparation and processing, integrating prior expert knowledge, and translating the final results into clinical practice guidelines [142].

Furthermore, the results of the MTOP study support the design of further longitudinal studies, which could improve our understanding of the temporal dynamics of multimorbidity patterns and may substantially improve clinical management. Larger, representative cohorts and longer follow-up periods should be considered, ideally considering entire medical records. In fact, there has been a recent increase in publications of multimorbidity longitudinal studies [130, 143, 144, 145].

Finally, the findings of this thesis suggest that, once multimorbidity patterns are clearly identified, they may help design tailored interventions such as the implementation of clinical pathways or organizational changes. Then, selected clinical outcomes could be assessed after these interventions, compared to routine clinical practice.

7. Conclusions

- Multimorbidity patterns identified by soft clustering using the fuzzy c-means algorithm can be associated with various outcomes and indicators of interest.
- Multimorbidity clusters identified in older patients hospitalised due to chronic condition exacerbation are associated with quality indicators of medication, including the presence, number and specific types of potentially inappropriate prescribing (PIP) and adverse drug reactions (ADRs).
- The associations found between certain multimorbidity profiles and certain quality indicators of medication validate and support the existence of such clusters, suggesting areas for targeted interventions and tailored medication reviews according to patient profiles.
- The study of multimorbidity clusters stratified by age and sex in COVID-19 patients revealed distinct profiles of patients associated with severe infection and mortality.
- Trajectories of multimorbidity patterns in older patients exhibit considerable complexity and fluctuation over time, emphasizing the dynamic nature of chronic conditions in this population.

Bibliography

1. Porta M. A Dictionary of Epidemiology. 6th Ed. Oxford University Press, 2016
2. World Health Organization. Multimorbidity. 2016. Available from: https://iris.who.int/handle/10665/252275 [Accessed on: 2024 Jul 19]
3. Almirall J, Fortin M. The coexistence of terms to describe the presence of multiple concurrent diseases. J Comorb 2013; 3:4–9. DOI: 10.15256/joc.2013.3.22
4. Le Reste JY, Nabbe P, Manceau B, Lygidakis C, Doerr C, Lingner H, et al. The European General Practice Research Network presents a comprehensive definition of multimorbidity in family medicine and long term care, following a systematic review of relevant literature. J Am Med Dir Assoc 2013 May; 14(5):319–25. DOI: 10.1016/j.jamda.2013.01.001
5. Willadsen TG, Bebe A, Køster-Rasmussen R, Jarbøl DE, Guassora AD, Waldorff FB, et al. The role of diseases, risk factors and symptoms in the definition of multimorbidity - a systematic review. Scand J Prim Health Care 2016 Jun; 34(2):112–21. DOI: 10.3109/02813432.2016.1153242
6. Ho ISS, Azcoaga-Lorenzo A, Akbari A, Black C, Davies J, Hodgins P, et al. Examining variation in the measurement of multimorbidity in research: a systematic review of 566 studies. Lancet Public Health 2021 Aug; 6(8):e587–e597. DOI: 10.1016/S2468-2667(21)00107-9
7. Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. Eur J Public Health 2019 Feb; 29(1):182–9. DOI: 10.1093/eurpub/cky098
8. The Academy of Medical Sciences. Multimorbidity: a priority for global health research. 2018. Available from: https://acmedsci.ac.uk/file-download/82222577 [Accessed on: 2024 Jul 19]
9. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. J Chro-nic Dis 1970 Dec; 23(7):455–68. DOI: 10.1016/0021-9681(70)90054-8
10. Van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity: what's in a name? A review of literature. European Journal of General Practice 1996 Jan; 2(2):65–70. DOI: 10.3109/13814789609162146

11. Boyd CM, Fortin M. Future of Multimorbidity Research: How Should Understanding of Multimorbidity Inform Health System Design? Public Health Rev 2010 Dec; 32(2):451–74. DOI: 10.1007/BF03391611

12. Valderas JM, Starfi B, Sibbald B. Defining Comorbidity: Implications for Understanding Health and Health Services. Annals Of Family Medicine 2009; 7(4):357–63. DOI: 10.1370/afm.983

13. Harrison C, Fortin M, van den Akker M, Mair F, Calderón-Larrañaga A, Boland F, et al. Comorbidity versus multimorbidity: Why it matters. J Comorb 2021 Mar; 11:2633556521993993. DOI: 10.1177/2633556521993993

14. Violán C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, et al. Prevalence, Determinants and Patterns of Multimorbidity in Primary Care: A Systematic Review of Observational Studies. PLOS One 2014 Jul; 9(7):e102149. DOI: 10.1371/journal.pone.0102149

15. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A Systematic Review of Prevalence Studies on Multimorbidity: Toward a More Uniform Methodology. Ann Fam Med 2012 Mar; 10(2):142–51. DOI: 10.1370/afm.1337

16. Van den Akker M, Buntinx F, Roos S, Knottnerus JA. Problems in determining occurrence rates of multimorbidity. J Clin Epidemiol 2001 Jul; 54(7):675–9. DOI: 10.1016/s0895-4356(00)00358-9

17. Salisbury C, Johnson L, Purdy S, Valderas JM, Montgomery AA. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. Br J Gen Pract 2011 Jan; 61(582):e12–e21. DOI: 10.3399/bjgp11X548929

18. Ho ISS, Azcoaga-Lorenzo A, Akbari A, Davies J, Hodgins P, Khunti K, et al. Variation in the estimated prevalence of multimorbidity: systematic review and meta-analysis of 193 international studies. BMJ Open 2022 Apr; 12(4):e057017. DOI: 10.1136/bmjopen-2021-057017

19. MacRae C, McMinn M, Mercer SW, Henderson D, McAllister DA, Ho I, et al. The impact of varying the number and selection of conditions on estimated multimorbidity prevalence: A cross-sectional study using a large, primary care population dataset. PLoS Med 2023 Apr; 20(4):e1004208. DOI: 10.1371/journal.pmed.1004208

20. Langenberg C, Hingorani AD, Whitty CJM. Biological and functional multimorbidity—from mechanisms to management. Nat Med 2023 Jul; 29(7):1649–57. DOI: 10.1038/s41591-023-02420-6

21. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. Eur J Gen Pract 2008; 14 Suppl 1:28–32. DOI: 10.1080/13814780802436093

22. King DE, Xiang J, Pilkerton CS. Multimorbidity Trends in United States Adults, 1988-2014. J Am Board Fam Med 2018; 31(4):503–13. DOI: 10.3122/jabfm.2018.04.180008

23. Katikireddi SV, Skivington K, Leyland AH, Hunt K, Mercer SW. The contribution of risk factors to socioeconomic inequalities in multimorbidity across the lifecourse: a longitudinal analysis of the Twenty-07 cohort. BMC Med 2017 Aug; 15(1):152. DOI: 10.1186/s12916-017-0913-6

24. Van Oostrom SH, Gijsen R, Stirbu I, Korevaar JC, Schellevis FG, Picavet HSJ, et al. Time Trends in Prevalence of Chronic Diseases and Multimorbidity Not Only due to Aging: Data from General Practices and Health Surveys. PLOS One 2016 Aug; 11(8):e0160264. DOI: 10.1371/journal.pone.0160264

25. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev 2011 Sep; 10(4):430–9. DOI: 10.1016/j.arr.2011.03.003

26. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012 Jul; 380(9836):37–43. DOI: 10.1016/S0140-6736(12)60240-2

27. Palladino R, Pennino F, Finbarr M, Millett C, Triassi M. Multimorbidity And Health Outcomes In Older Adults In Ten European Health Systems, 2006-15. Health Aff 2019 Apr; 38(4):613–23. DOI: 10.1377/hlthaff.2018.05273

28. Pathirana TI, Jackson CA. Socioeconomic status and multimorbidity: a systematic review and meta-analysis. Aust N Z J Public Health 2018 Apr; 42(2):186–94. DOI: 10.1111/1753-6405.12762

29. Knies G, Kumari M. Multimorbidity is associated with the income, education, employment and health domains of area-level deprivation in adult residents in the UK. Sci Rep 2022 May; 12(1):7280. DOI: 10.1038/s41598-022-11310-9

30. McLean G, Gunn J, Wyke S, Guthrie B, Watt GCM, Blane DN, et al. The influence of socioeconomic deprivation on multimorbidity at different ages: a cross-sectional study. Br J Gen Pract 2014 Jul; 64(624):e440–447. DOI: 10.3399/bjgp14X680545

31. Garin N, Koyanagi A, Chatterji S, Tyrovolas S, Olaya B, Leonardi M, et al. Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study. J Gerontol A Biol Sci Med Sci 2016; 71(2):205–14. DOI: 10.1093/gerona/glv128

32. Ingram E, Ledden S, Beardon S, Gomes M, Hogarth S, McDonald H, et al. Household and area-level social determinants of multimorbidity: a systematic review. J Epidemiol Community Health 2021 Mar; 75(3):232–41. DOI: 10.1136/jech-2020-214691

33. Thompson AE, Anisimowicz Y, Miedema B, Hogg W, Wodchis WP, Aubrey-Bassler K. The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPC study. BMC Fam Pract 2016 Mar; 17(1):38. DOI: 10.1186/s12875-016-0440-0

34. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol 2011 Oct; 8:114–26. DOI: 10.1038/nrendo.2011.156

35. Ozenberger K, Alexander GC, Shin JI, Whitsel EA, Qato DM. Use of prescription medications with cardiovascular adverse effects among older adults in the United States. Pharmacoepidemiol Drug Saf 2022 Oct; 31(10):1027–38. DOI: 10.1002/pds.5477

36. Skou ST, Mair FS, Fortin M, Guthrie B, Nunes BP, Miranda JJ, et al. Multimorbidity. Nat Rev Dis Primers 2022 Jul; 8(1):1–22. DOI: 10.1038/s41572-022-00376-4

37. Ryan A, Wallace E, O'Hara P, Smith SM. Multimorbidity and functional decline in community-dwelling adults: a systematic review. Health Qual Life Outcomes 2015 Oct; 13:168. DOI: 10.1186/s12955-015-0355-9

38. Nunes BP, Flores TR, Mielke GI, Thumé E, Facchini LA. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. Arch Gerontol Geriatr 2016; 67:130–8. DOI: 10.1016/j.archger.2016.07.008

39. Kanesarajah J, Waller M, Whitty JA, Mishra GD. Multimorbidity and quality of life at mid-life: A systematic review of general population studies. Maturitas 2018 Mar; 109:53–62. DOI: 10.1016/j.maturitas.2017.12.004

40. Makovski TT, Schmitz S, Zeegers MP, Stranges S, van den Akker M. Multimorbidity and quality of life: Systematic literature review and meta-analysis. Ageing Research Reviews 2019 Aug; 53:100903. DOI: 10.1016/j.arr.2019.04.005

41. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. Nat Rev Endocrinol 2022 Sep; 18(9):525–39. DOI: 10.1038/s41574-022-00690-7

42. Mair FS, May CR. Thinking about the burden of treatment. BMJ 2014 Nov; 349:g6680. DOI: 10.1136/bmj.g6680

43. Demain S, Gonçalves AC, Areia C, Oliveira R, Marcos AJ, Marques A, et al. Living with, managing and minimising treatment burden in long term conditions: a systematic review of qualitative research. PLOS One 2015; 10(5):e0125457. DOI: 10.1371/journal.pone.0125457

44. May CR, Eton DT, Boehmer K, Gallacher K, Hunt K, MacDonald S, et al. Rethinking the patient: using Burden of Treatment Theory to understand the changing dynamics of illness. BMC Health Serv Res 2014 Dec; 14(1):1–11. DOI: 10.1186/1472-6963-14-281

45. Hughes LD, McMurdo MET, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. Age Ageing 2013 Jan; 42(1):62–9. DOI: 10.1093/ageing/afs100

46. Salisbury C. Multimorbidity: Redesigning health care for people who use it. The Lancet 2012; 380(9836):7–9. DOI: 10.1016/S0140-6736(12)60482-6

47. Noël PH, Frueh BC, Larme AC, Pugh JA. Collaborative care needs and preferences of primary care patients with multimorbidity. Health Expect 2005 Mar; 8(1):54–63. DOI: 10.1111/j.1369-7625.2004.00312.x

48. Paddison CAM, Saunders CL, Abel GA, Payne RA, Campbell JL, Roland M. Why do patients with multimorbidity in England report worse experiences in primary care? Evidence from the General Practice Patient Survey. BMJ Open 2015 Mar; 5(3):e006172. DOI: 10.1136/bmjopen-2014-006172

49. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr 2017 Oct; 17(1):230. DOI: 10.1186/s12877-017-0621-2

50. World Health Organization. Medication safety in polypharmacy: technical report. 2019. Available from: https://www.who.int/publications/i/item/WHO-UHC-SDS-2019.11 [Accessed on: 2024 Oct 25]
51. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 2004 Jan; 57(1):6–14. DOI: 10.1046/J.1365-2125.2003.02007.X
52. Corsonello A, Pedone C, Incalzi R. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem 2010 Jan; 17(6):571–84. DOI: 10.2174/092986710790416326
53. Mangoni AA, Jarmuzewska EA. Incorporating pharmacokinetic data into personalised prescribing for older people: challenges and opportunities. Eur Geriatr Med 2021 Jan; 12:435–42. DOI: 10.1007/s41999-020-00437-5
54. Hilmer SN, Gnjidic D. Prescribing for frail older people. Aust Prescr 2017 Oct; 40(5):174–8. DOI: 10.18773/austprescr.2017.055
55. Rijken M, Struckmann V, van der Heide I, Hujala A, Barbabella F, van Ginneken E, et al. How to improve care for people with multimorbidity in Europe? Policy Brief 23. Copenhagen: European Observatory on Health Systems and Policies, 2016. Available from: https://eurohealthobservatory.who.int/publications/i/how-to-improve-care-for-people-with-multimorbidity-in-europe [Accessed on: 2024 Sep 22]
56. Muth C, Kirchner H, van den Akker M, Scherer M, Glasziou P. Current guidelines poorly address multimorbidity: pilot of the interaction matrix method. J Clin Epidemiol 2014 Nov; 67(11):1242–50. DOI: 10.1016/J.JCLINEPI.2014.07.004
57. Zulman DM, Asch SM, Martins SB, Kerr EA, Hoffman BB, Goldstein MK. Quality of care for patients with multiple chronic conditions: the role of comorbidity interrelatedness. J Gen Intern Med 2014 Mar; 29(3):529–37. DOI: 10.1007/s11606-013-2616-9
58. Sinnott C, Mc Hugh S, Browne J, Bradley C. GPs' perspectives on the management of patients with multimorbidity: systematic review and synthesis of qualitative research. BMJ Open 2013 Sep; 3(9):e003610. DOI: 10.1136/bmjopen-2013-003610
59. Foguet-Boreu Q, Violán C, Roso-Llorach A, Rodriguez-Blanco T, Pons-Vigués M, Muñoz-Pérez MA, et al. Impact of multimorbidity: acute morbidity, area of residency and use of health services across the life span in a region of south Europe. BMC Family Practice 2014 Mar; 15(1):55. DOI: 10.1186/1471-2296-15-55

60. Frølich A, Ghith N, Schiøtz M, Jacobsen R, Stockmarr A. Multimorbidity, healthcare utilization and socioeconomic status: A register-based study in Denmark. PLOS One 2019; 14(8):e0214183. DOI: 10.1371/journal.pone.0214183

61. Palladino R, Tayu Lee J, Ashworth M, Triassi M, Millett C. Associations between multimorbidity, healthcare utilisation and health status: evidence from 16 European countries. Age Ageing 2016 May; 45(3):431–5. DOI: 10.1093/ageing/afw044

62. Cicek M, Hayhoe B, Otis M, Nicholls D, Majeed A, Greenfield G. Depression and unplanned secondary healthcare use in patients with multimorbidity: A systematic review. PLOS One 2022; 17(4):e0266605. DOI: 10.1371/journal.pone.0266605

63. Lehnert T, Heider D, Leicht H, Heinrich S, Corrieri S, Luppa M, et al. Review: health care utilization and costs of elderly persons with multiple chronic conditions. Med Care Res Rev 2011 Aug; 68(4):387–420. DOI: 10.1177/1077558711399580

64. Tran PB, Kazibwe J, Nikolaidis GF, Linnosmaa I, Rijken M, van Olmen J. Costs of multimorbidity: a systematic review and meta-analyses. BMC Med 2022 Jul; 20(1):234. DOI: 10.1186/s12916-022-02427-9

65. Vela E, Clèries M, Vella VA, Adroher C, García-Altés A, Vela E, et al. Análisis poblacional del gasto en servicios sanitarios en Cataluña (España): ¿qué y quién consume más recursos? Gaceta Sanitaria 2019 Feb; 33(1):24–31. DOI: 10.1016/j.gaceta.2017.05.017

66. Hayes SL, Salzberg CA, McCarthy D, Radley DC, Abrams MK, Shah T, et al. High-Need, High-Cost Patients: Who Are They and How Do They Use Health Care? A Population-Based Comparison of Demographics, Health Care Use, and Expenditures. Vol. 26. The Commonwealth Fund, 2016. DOI: 10.26099/7h07-zq20

67. World Health Organization. Ageing and health. 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health [Accessed on: 2024 May 19]

68. Eurostat. Population projections in the EU - Statistics Explained. 2023. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?oldid=497115 [Accessed on: 2024 May 19]

69. European Commission. Directorate General for Economic and Financial Affairs. 2024 ageing report: economic & budgetary projections for the EU Member States (2022-2070). Institutional Paper 279. Luxembourg: Publications Office of the European Union, 2024. DOI: 10.2765/022983

70. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 2007 May; 55(5):780–91. DOI: 10.1111/j.1532-5415.2007.01156.x

71. National Institute for Health and Care Excellence (NICE). Multimorbidity: clinical assessment and management. NICE guideline 56. 2016. Available from: https://www.nice.org.uk/guidance/ng56 [Accessed on: 2024 Aug 24]

72. Van der Heide I, Snoeijs SP, Boerma WGW, Schellevis FG, Rijken MP. How to strengthen patient-centredness in caring for people with multimorbidity in Europe? Policy Brief 22. Copenhagen: European Observatory on Health Systems and Policies, 2017. Available from: https://eurohealthobservatory.who.int/publications/i/how-to-strengthen-patient-centredness-in-caring-for-people-with-multimorbidity-in-europe [Accessed on: 2024 Sep 22]

73. Clerencia-Sierra M, Calderón-Larrañaga A, Martínez-Velilla N, Vergara-Mitxeltorena I, Aldaz-Herce P, Poblador-Plou B, et al. Multimorbidity patterns in hospitalized older patients: Associations among chronic diseases and geriatric syndromes. PLOS One 2015 Jul; 10(7):e0132909. DOI: 10.1371/journal.pone.0132909

74. Huntley AL, Johnson R, Purdy S, Valderas JM, Salisbury C. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. Ann Fam Med 2012; 10(2):134–41. DOI: 10.1370/afm.1363

75. Suls J, Bayliss EA, Berry J, Bierman AS, Chrischilles EA, Farhat T, et al. Measuring Multimorbidity: Selecting the Right Instrument for the Purpose and the Data Source. Med Care 2021 Aug; 59(8):743. DOI: 10.1097/MLR.0000000000001566

76. Charlson ME, Peter P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5):373–83. DOI: 10.1016/0021-9681(87)90171-8

77. Starfield B, Weiner J, Mumford L, Steinwachs D. Ambulatory care groups: a categorization of diagnoses for research and management. Health Serv Res 1991 Apr; 26(1):53–74

78. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol 1992 Feb; 45(2):197–203. DOI: 10.1016/0895-4356(92)90016-g

79. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968 May; 16(5):622–6. DOI: 10.1111/j.1532-5415.1968.tb02103.x

80. Byles JE, D'Este C, Parkinson L, O'Connell R, Treloar C. Single index of multimorbidity did not predict multiple outcomes. J Clin Epidemiol 2005 Oct; 58(10):997–1005. DOI: 10.1016/j.jclinepi.2005.02.025

81. Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. J Clin Epidemiol 2014 Mar; 67(3):254–66. DOI: 10.1016/j.jclinepi.2013.09.021

82. Busija L, Lim K, Szoeke C, Sanders KM, McCabe MP. Do replicable profiles of multimorbidity exist? Systematic review and synthesis. Eur J Epidemiol 2019 Nov; 34(11):1025–53. DOI: 10.1007/s10654-019-00568-5

83. Tucker LR MR. Exploratory factor analysis. University of Illinois, 1997. Available from: https://labs.dgsom.ucla.edu/hays/files/view/docs/factor.pdf [Accessed on: 2024 Oct 17]

84. Ng SK, Tawiah R, Sawyer M, Scuffham P. Patterns of multimorbid health conditions: a systematic review of analytical methods and comparison analysis. Int J Epidemiol 2018 Oct; 47(5):1687–704. DOI: 10.1093/ije/dyy134

85. Roso-Llorach A, Violán C, Foguet-Boreu Q, Rodriguez-Blanco T, Pons-Vigués M, Pujol-Ribera E, et al. Comparative analysis of methods for identifying multimorbidity patterns: a study of 'real-world' data. BMJ Open 2018 Mar; 8(3):e018986. DOI: 10.1136/bmjopen-2017-018986

86. Banfield JD, Raftery AE. Model-Based Gaussian and Non-Gaussian Clustering. Biometrics 1993; 49(3):803–21. DOI: 10.2307/2532201

87. Aflaki K, Vigod S, Ray JG. Part I: A friendly introduction to latent class analysis. J Clin Epidemiol 2022 Jul; 147:168–70. DOI: 10.1016/j.jclinepi.2022.05.008

88. Violán C, Roso-Llorach A, Foguet-Boreu Q, Guisado-Clavero M, Pons-Vigués M, Pujol-Ribera E, et al. Multimorbidity patterns with K-means nonhierarchical cluster analysis. BMC Fam Pract 2018; 19(1):108. DOI: 10.1186/s12875-018-0790-x

89. Hartigan JA, Wong MA. Algorithm AS 136: A K-Means Clustering Algorithm. J R Stat Soc Ser C Appl Stat 1979; 28(1):100–8. DOI: 10.2307/2346830

90. Violán C, Foguet-Boreu Q, Fernández-Bertolín S, Guisado-Clavero M, Cabrera-Bean M, Formiga F, 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. BMJ Open 2019 Aug; 9(8):e029594. DOI: 10.1136/bmjopen-2019-029594

91. Bezdek JC, Ehrlich R, Full W. FCM: The fuzzy c-means clustering algorithm. Computers & Geosciences 1984 Jan; 10:191–203. DOI: 10.1016/0098-3004(84)90020-7

92. Kumar S. C-Means Clustering Explained. Available from: https://builtin.com/data-science/c-means [Accessed on: 2025 Feb 19]

93. Beridze G, Abbadi A, Ars J, Remelli F, Vetrano DL, Trevisan C, et al. Patterns of multimorbidity in primary care electronic health records: A systematic review. J Multimorb Comorb 2024; 14. DOI: 10.1177/26335565231223350

94. Buffel du Vaure C, Dechartres A, Battin C, Ravaud P, Boutron I. 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(9):e012265. DOI: 10.1136/bmjopen-2016-012265

95. Okeowo D, Patterson A, Boyd C, Reeve E, Gnjidic D, Todd A. Clinical practice guidelines for older people with multimorbidity and life-limiting illness: what are the implications for deprescribing? Ther Adv Drug Saf 2018 Nov; 9(11):619–30. DOI: 10.1177/2042098618795770

96. Dhafari TB, Pate A, Azadbakht N, Bailey R, Rafferty J, Jalali-najafabadi F, et al. A scoping review finds a growing trend in studies validating multimorbidity patterns and identifies five broad types of validation methods. J Clin Epidemiol 2024 Jan; 165:111214. DOI: 10.1016/j.jclinepi.2023.11.004

97. Zheng DD, Loewenstein DA, Christ SL, Feaster DJ, Lam BL, McCollister KE, et al. Multimorbidity patterns and their relationship to mortality in the US older adult population. PLOS One 2021 Jan; 16(1). Ed. by Latham-Mintus K:e0245053. DOI: 10.1371/journal.pone.0245053

98. Calderón-Larrañaga A, Roso-Llorach A, Onder G, Marengoni A, Zucchelli A, Rizzuto D, et al. Multimorbidity Patterns and Unplanned Hospitalisation in a Cohort of Older Adults. J Clin Med 2020 Dec; 9(12). Ed. by Akugizibwe R:4001

99. Teh RO, Menzies OH, Connolly MJ, Doughty RN, Wilkinson TJ, Pillai A, et al. Patterns of multi-morbidity and prediction of hospitalisation and all-cause mortality in advanced age. Age Ageing 2018 Mar; 47(2):261–8. DOI: 10.1093/AGEING/AFX184

100. Marengoni A, Tazzeo C, Calderón-Larrañaga A, Roso-Llorach A, Onder G, Zucchelli A, et al. Multimorbidity Patterns and 6-Year Risk of Institutionalization in Older Persons: The Role of Social Formal and Informal Care. J Am Med Dir Assoc 2021 Oct; 22(10):2184–2189.e1. DOI: 10.1016/J.JAMDA.2020.12.040

101. Marengoni A, Akugizibwe R, Vetrano DL, Roso-Llorach A, Onder G, Welmer AK, et al. Patterns of multimorbidity and risk of disability in community-dwelling older persons. Aging Clin Exp Res 2021 Feb; 33:457–62. DOI: 10.1007/s40520-020-01773-z

102. Zheng DD, McCollister KE, Christ SL, Lam BL, Feaster DJ, Lee DJ. Chronic condition patterns in the US population and their association with health related quality of life. Preventive Medicine 2020 Jul; 136:106102. DOI: 10.1016/j.ypmed.2020.106102

103. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med 2011 Jun; 171(11):1013–9. DOI: 10.1001/archinternmed.2011.215

104. Mekonnen AB, Redley B, de Courten B, Manias E. Potentially inappropriate prescribing and its associations with health-related and system-related outcomes in hospitalised older adults: A systematic review and meta-analysis. Br J Clin Pharmacol 2021 Nov; 87(11):4150–72. DOI: 10.1111/BCP.14870

105. Barry PJ, Gallagher P, Ryan C, O'mahony D. START (screening tool to alert doctors to the right treatment) an evidence-based screening tool to detect prescribing omissions in elderly patients. Age Ageing 2007 Nov; 36(6):632–8. DOI: 10.1093/ageing/afm118

106. Cadogan CA, Ryan C, Hughes CM. Appropriate Polypharmacy and Medicine Safety: When Many is not Too Many. Drug Saf 2016 Feb; 39(2):109–16. DOI: 10.1007/s40264-015-0378-5

107. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun 2020; 11(1):6317

108. Booth A, Reed AB, Ponzo S, Yassaee A, Aral M, Plans D, et al. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. PLOS One 2021; 16(3):e0247461

109. Atkins JL, Masoli JAH, Delgado J, Pilling LC, Kuo CL, Kuchel GA, et al. Preexisting Comorbidities Predicting COVID-19 and Mortality in the UK Biobank Community Cohort. J Gerontol A Biol Sci Med Sci 2020 Oct; 75(11). Ed. by Newman AB:2224–30. DOI: 10.1093/gerona/glaa183

110. Reilev M, Kristensen KB, Pottegård A, Lund LC, Hallas J, Ernst MT, et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. Int J Epidemiol 2020; 49(5):1468–81. DOI: 10.1093/ije/dyaa140

111. Tisminetzky M, Delude C, Hebert T, Carr C, Goldberg RJ, Gurwitz JH. Age, Multiple Chronic Conditions, and COVID-19: A Literature Review. J Gerontol A Biol Sci Med Sci 2020 Dec; 77(4):872–8. DOI: 10.1093/gerona/glaa320

112. Carmona-Pírez J, Gimeno-Miguel A, Bliek-Bueno K, Poblador-Plou B, Díez-Manglano J, Ioakeim-Skoufa I, et al. Identifying multimorbidity profiles associated with COVID-19 severity in chronic patients using network analysis in the PRECOVID Study. Sci Rep 2022 Dec; 12(1). DOI: 10.1038/S41598-022-06838-9

113. Vetrano DL, Roso-Llorach A, Fernández S, Guisado-Clavero M, Violán C, Onder G, et al. Twelve-year clinical trajectories of multimorbidity in a population of older adults. Nat Commun 2020 Dec; 11(1):1–9. DOI: 10.1038/s41467-020-16780-x

114. Guisado-Clavero M, Roso-Llorach A, López-Jimenez T, Pons-Vigués M, Foguet-Boreu Q, Muñoz MA, et al. Multimorbidity patterns in the elderly: A prospective cohort study with cluster analysis. BMC Geriatr 2018; 18(1):16. DOI: 10.1186/s12877-018-0705-7

115. Baré M, Herranz S, Jordana R, Gorgas MQ, Ortonobes S, Sevilla D, 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 Jan; 10(1):e033322. DOI: 10.1136/bmjopen-2019-033322

116. Baré M, Herranz S, Roso-Llorach A, Jordana R, Violán C, Lleal M, et al. Multimorbidity patterns of chronic conditions and geriatric syndromes in older patients from the MoPIM multicentre cohort study. BMJ Open 2021 Nov; 11(11):e049334. DOI: 10.1136/bmjopen-2021-049334

117. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 2015 Mar; 44(2):213–8. DOI: 10.1093/ageing/afu145

118. Baré M, Lleal M, Ortonobes S, Gorgas MQ, Sevilla-Sánchez D, Carballo N, et al. Factors associated to potentially inappropriate prescribing in older patients according to STOPP/START criteria: MoPIM multicentre cohort study. BMC geriatrics 2022 Dec; 22(1). DOI: 10.1186/S12877-021-02715-8

119. Chavent M, Kuentz V, Labenne A, Liquet B, Saracco J. PCAmixdata: Multivariate Analysis of Mixed Data. R package version 3.1. 2017. Available from: https://CRAN.R-project.org/package=PCAmixdata

120. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J Royal Stat Soc Ser B Stat Methodol 1995 Jan; 57(1):289–300. DOI: 10.1111/J.2517-6161.1995.TB02031.X

121. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria, 2024. Available from: https://www.R-project.org/

122. Healthcare Cost and Utilization Project (HCUP). Chronic Condition Indicator (CCI) for ICD-10-CM. Rockville, MD: Agency for Healthcare Research and Quality, 2021. Available from: https://hcup-us.ahrq.gov/toolssoftware/chronic_icd10/chronic_icd10.jsp [Accessed on: 2024 Nov 4]

123. Healthcare Cost and Utilization Project (HCUP). Clinical Classifications Software Refined (CCSR). Rockville, MD: Agency for Healthcare Research and Quality, 2021. Available from: https://hcup-us.ahrq.gov/toolssoftware/ccsr/ccs_refined.jsp [Accessed on: 2024 Nov 4]

124. Lleal M, Corral-Vázquez C, Baré M, Comet R, Herranz S, Baigorri F, et al. Multimorbidity patterns in COVID-19 patients and their relationship with infection severity: MRisk-COVID study. PLOS One 2023 Aug; 18(8):e0290969. DOI: 10.1371/JOURNAL.PONE.0290969

125. National Center for Health Statistics (NCHS). International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Hyattsville, MD: National Center for Health Statistics, 2010

126. Calderón-Larrañaga A, Vetrano DL, Onder G, Gimeno-Feliu LA, Coscollar-Santaliestra C, Carfí A, et al. Assessing and Measuring Chronic Multimorbidity in the Older Population: A Proposal for Its Operationalization. J Gerontol A Biol Sci Med Sci 2017 Oct; 72(10):1417–23. DOI: 10.1093/gerona/glw233

127. Ho ISS, Azcoaga-Lorenzo A, Akbari A, Davies J, Khunti K, Kadam UT, et al. Measuring multimorbidity in research: Delphi consensus study. BMJ Med 2022; 1(1):e000247. DOI: 10.1136/bmjmed-2022-000247

128. Ioakeim-Skoufa I, Clerencia-Sierra M, Moreno-Juste A, Elías de Molins Peña C, Poblador-Plou B, Aza-Pascual-Salcedo M, et al. Multimorbidity Clusters in the Oldest Old: Results from the EpiChron Cohort. Int J Environ Res Public Health 2022 Aug; 19(16):10180. DOI: 10.3390/ijerph191610180

129. Jansana A, Poblador-Plou B, Gimeno-Miguel A, Lanzuela M, Prados-Torres A, Domingo L, et al. Multimorbidity clusters among long-term breast cancer survivors in Spain: Results of the SURBCAN study. Int J Cancer 2021; 149(10):1755–67. DOI: 10.1002/ijc.33736

130. Ioakeim-Skoufa I, González-Rubio F, Aza-Pascual-Salcedo M, Laguna-Berna C, Poblador-Plou B, Vicente-Romero J, et al. Multimorbidity patterns and trajectories in young and middle-aged adults: a large-scale population-based cohort study. Front Public Health 2024 May; 12:1349723. DOI: 10.3389/fpubh.2024.1349723

131. Verma RK, Tiwari R, Thakur PS. Partition Coefficient and Partition Entropy in Fuzzy C Means Clustering. J Sci Res Rep 2023 Dec; 29(12):1–6. DOI: 10.9734/jsrr/2023/v29i121812

132. Bonanni R, Cariati I, Tancredi V, Iundusi R, Gasbarra E, Tarantino U. Chronic Pain in Musculoskeletal Diseases: Do You Know Your Enemy? J Clin Med 2022 May; 11(9):2609. DOI: 10.3390/JCM11092609

133. Watt FE. Musculoskeletal pain and menopause. Post reproductive health 2018 Mar; 24(1):34–43. DOI: 10.1177/2053369118757537

134. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open 2016 May; 6(6):10364. DOI: 10.1136/BMJOPEN-2015-010364

135. Wolf JM, Cannada L, Van Heest AE, O'Connor MI, Ladd AL. Male and female differences in musculoskeletal disease. The Journal of the American Academy of Orthopaedic Surgeons 2015 Jun; 23(6):339–47. DOI: 10.5435/JAAOS-D-14-00020

136. Tazzeo C, Rizzuto D, Calderón-Larrañaga A, Roso-Llorach A, Marengoni A, Welmer AK, et al. Multimorbidity patterns and risk of frailty in older community-dwelling adults: a population-based cohort study. Age Ageing 2021 Nov; 50(6):2183. DOI: 10.1093/AGEING/AFAB138

137. Valletta M, Vetrano DL, Xia X, Rizzuto D, Roso-Llorach A, Calderón-Larrañaga A, et al. Multimorbidity patterns and 18-year transitions from normal cognition to dementia and death: A population-based study. J Intern Med 2023 Sep; 294(3):326–35. DOI: 10.1111/joim.13683

138. Ortonobes S, Herranz S, Lleal M, Sevilla-Sánchez D, Jordana R, Mascaró O, et al. Multidisciplinary medication review during older patient hospitalization according to STOPP/START criteria reduces potentially inappropriate prescriptions: MoPIM cohort study. BMC Geriatr 2024 Jul; 24(1):584. DOI: 10.1186/s12877-024-05185-w

139. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020 May; 323(20):2052–9. DOI: 10.1001/jama.2020.6775

140. Raisi-Estabragh Z, Cooper J, Salih A, Raman B, Lee AM, Neubauer S, et al. Cardiovascular disease and mortality sequelae of COVID-19 in the UK Biobank. Heart 2022 Dec; 109(2):119–26. DOI: 10.1136/heartjnl-2022-321492

141. Baré M, Lleal M, Sevilla-Sánchez D, Ortonobes S, Herranz S, Ferrandez O, et al. Sex Differences in Multimorbidity, Inappropriate Medication and Adverse Outcomes of Inpatient Care: MoPIM Cohort Study. International Journal of Environmental Research and Public Health 2023; 20(4). DOI: 10.3390/ijerph20043639

142. Hassaine A, Salimi-Khorshidi G, Canoy D, Rahimi K. Untangling the complexity of multimorbidity with machine learning. Mech Ageing Dev 2020 Sep; 190:111325. DOI: 10.1016/j.mad.2020.111325

143. Carrasco-Ribelles LA, Cabrera-Bean M, Danés-Castells M, Zabaleta-del-Olmo E, Roso-Llorach A, Violán C. Contribution of Frailty to Multimorbidity Patterns and Trajectories:

Longitudinal Dynamic Cohort Study of Aging People. JMIR Public Health Surveill 2023 Jun; 9:e45848. DOI: 10.2196/45848

144. Villén N, Roso-Llorach A, Gallego-Moll C, Danes-Castells M, Fernández-Bertolin S, Troncoso Mariño A, et al. Polypharmacy Patterns in Multimorbid Older People with Cardiovascular Disease: Longitudinal Study. Geriatrics 2022; 7(6). DOI: 10.3390/geriatrics7060141

145. Roso-Llorach A, Vetrano DL, Trevisan C, Fernández S, Guisado-Clavero M, Carrasco-Ribelles LA, et al. 12-year evolution of multimorbidity patterns among older adults based on Hidden Markov Models. Aging 2022 Nov; 14(24):9805–17. DOI: 10.18632/aging.204395

Appendix A. Supplementary files

The following sections of this Appendix contain all supplementary files of the publications that compose this PhD thesis.

A1. Study 1: MoPIM study

The supplementary files of this study include 7 tables and 2 figures.

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MDPI

Table S1. Equivalences between names used in ADRs classification and ATC codes.

Name	ATC Code
Analgesic	M01A
Angiotensin-converting enzyme (ACE) inhibitor	C09A
Angiotensin II receptor blocker	C09C
Antiarrhythmic	C01
Antibiotic	J01
Anticoagulant	B01AB
Antidepressant	N06A
Antiepileptic	N03A
Antiplatelet	B01AC
Antivitamin K	B01AA
Benzodiazepine	N05BA
Beta blocker	C07
Bronchodilator	R03
Corticoid	H02A
Loop diuretic	C03C
Hypnotic	N05C
Insulin	A10A
Neuroleptic	N05A
Opioid	N02A
Oral anticoagulant	B01AE, B01AF
Oral antidiabetic	A10B
Potassium sparing diuretic	C03D
Proton pump inhibitor	A02BC
Statin	C10AA
Thiazide diuretic	C03A

ATC: Anatomical Therapeutic Chemical.

Table S2. Number and percentage of patients with each chronic condition or geriatric syndrome registered according to the assigned multimorbidity cluster.

Chronic Condition or Geriatric Syndrome	Osteo-Articular	Psycho-Geriatric	Minor Chronic Disease	Cardio-Respiratory
Acute confusional syndrome/delirium	51 (37.2)	102 (67.5)	29 (22.8)	53 (16.3)
Amputation	7 (5.1)	2 (1.3)	4 (3.1)	3 (0.9)
Anaemia	77 (56.2)	64 (42.4)	76 (59.8)	117 (36.0)
Asthma	32 (23.4)	11 (7.3)	10 (7.9)	29 (8.9)
Cardiac arrhythmia	86 (62.8)	77 (51.0)	77 (60.6)	183 (56.3)
Cerebrovascular disease	40 (29.2)	53 (35.1)	36 (28.3)	59 (18.2)
Chronic gastritis or gastro-oesophageal reflux	25 (18.2)	11 (7.3)	19 (15.0)	39 (12.0)
Chronic pain	127 (92.7)	82 (54.3)	88 (69.3)	105 (32.3)
Chronic renal insufficiency	81 (59.1)	50 (33.1)	73 (57.5)	116 (35.7)
Chronic thyroid disease	44 (32.1)	19 (12.6)	23 (18.1)	49 (15.1)
Cognitive/Intellectual impairment	32 (23.4)	130 (86.1)	35 (27.6)	32 (9.8)
Constipation	78 (56.9)	88 (58.3)	41 (32.3)	133 (40.9)
COPD	41 (29.9)	38 (25.2)	49 (38.6)	145 (44.6)
Degenerative arthropathy	111 (81.0)	79 (52.3)	81 (63.8)	114 (35.1)
Dementia	17 (12.4)	98 (64.9)	24 (18.9)	40 (12.3)

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Depression or anxiety	84 (61.3)	52 (34.4)	37 (29.1)	95 (29.2)
Diabetes mellitus with organ damage	28 (20.4)	21 (13.9)	34 (26.8)	50 (15.4)
Diabetes mellitus without organ damage	27 (19.7)	57 (37.7)	36 (28.3)	81 (24.9)
Drug-related conditions	22 (16.1)	19 (12.6)	7 (5.5)	19 (5.8)
Dyslipidaemia	89 (65.0)	50 (33.1)	88 (69.3)	133 (40.9)
Dysphagia	36 (26.3)	78 (51.7)	28 (22.0)	17 (5.2)
Frailty	115 (83.9)	138 (91.4)	59 (46.5)	145 (44.6)
Gallstones (previous hepatic colic)	18 (13.1)	12 (7.9)	16 (12.6)	33 (10.2)
Gout	30 (21.9)	14 (9.3)	54 (42.5)	39 (12.0)
Heart failure	89 (65.0)	79 (52.3)	71 (55.9)	204 (62.8)
Hematologic disorders	8 (5.8)	3 (2.0)	14 (11.0)	11 (3.4)
Hypertension	121 (88.3)	119 (78.8)	111 (87.4)	252 (77.5)
Immobility	101 (73.7)	143 (94.7)	55 (43.3)	131 (40.3)
Incontinence (urinary/fecal)	33 (24.1)	112 (74.2)	16 (12.6)	31 (9.5)
Inflammatory osteoarticular disease	19 (13.9)	4 (2.6)	12 (9.4)	14 (4.3)
Instability/falls	93 (67.9)	59 (39.1)	51 (40.2)	83 (25.5)
Ischemic heart disease without infarction	38 (27.7)	17 (11.3)	27 (21.3)	38 (11.7)
Malnutrition	12 (8.8)	65 (43.0)	5 (3.9)	65 (20.0)
Mild liver disease	5 (3.6)	7 (4.6)	7 (5.5)	13 (4.0)
Moderate or severe liver disease	3 (2.2)	3 (2.0)	1 (0.8)	12 (3.7)
Myocardial infarction	28 (20.4)	11 (7.3)	26 (20.5)	46 (14.2)
Neoplasia	16 (11.7)	18 (11.9)	25 (19.7)	52 (16.0)
Neurologic disorder of the central nervous system	11 (8.0)	9 (6.0)	4 (3.1)	8 (2.5)
Non-ischemic heart disease	58 (42.3)	31 (20.5)	58 (45.7)	91 (28.0)
Obesity	58 (42.3)	24 (15.9)	43 (33.9)	68 (20.9)
Osteoporosis	49 (35.8)	13 (8.6)	12 (9.4)	29 (8.9)
Parkinson's disease	10 (7.3)	9 (6.0)	5 (3.9)	10 (3.1)
Peptic ulcer disease	10 (7.3)	8 (5.3)	12 (9.4)	16 (4.9)
Peripheral neuropathy or neuritis	21 (15.3)	9 (6.0)	18 (14.2)	13 (4.0)
Peripheral vascular disease	21 (15.3)	13 (8.6)	22 (17.3)	49 (15.1)
Polypharmacy	133 (97.1)	115 (76.2)	123 (96.9)	220 (67.7)
Pressure ulcers	10 (7.3)	60 (39.7)	10 (7.9)	15 (4.6)
Previous fractures (not hip)	57 (41.6)	28 (18.5)	19 (15.0)	35 (10.8)
Previous hip fracture	22 (16.1)	14 (9.3)	4 (3.1)	27 (8.3)
Rheumatologic disease	8 (5.8)	3 (2.0)	5 (3.9)	16 (4.9)
Sensory deficit	58 (42.3)	70 (46.4)	49 (38.6)	137 (42.2)
Sleep apnoea	29 (21.2)	7 (4.6)	18 (14.2)	12 (3.7)
Sleep disorders/Insomnia	90 (65.7)	86 (57.0)	51 (40.2)	106 (32.6)
Varicose veins	59 (43.1)	25 (16.6)	43 (33.9)	37 (11.4)
Vertigo	42 (30.7)	13 (8.6)	7 (5.5)	15 (4.6)

COPD: chronic obstructive pulmonary disease.

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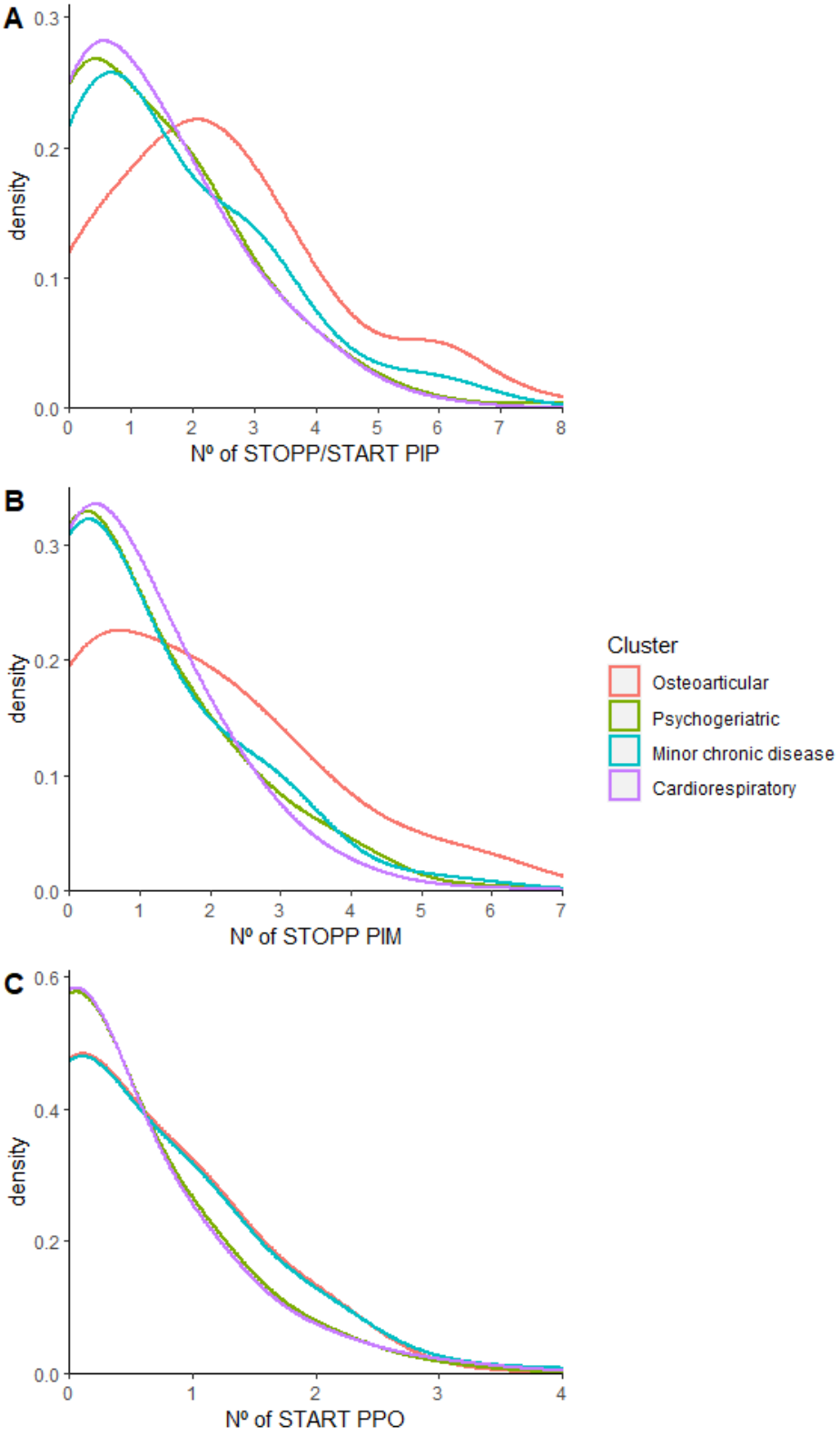

Figure S1. A: Distribution of the number of STOPP/START PIP according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed significant differences between the osteoarticular cluster and the rest ($p < 0.001$). PIP: Potentially inappropriate prescribing. **B**: Distribution of the number of STOPP PIM according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed significant differences between the osteoarticular cluster and the rest ($p < 0.005$). PIM: potentially inappropriate medication. **C**: Distribution of the number of START PPO according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed no significant differences ($p > 0.05$). PPO: potential prescribing omission.

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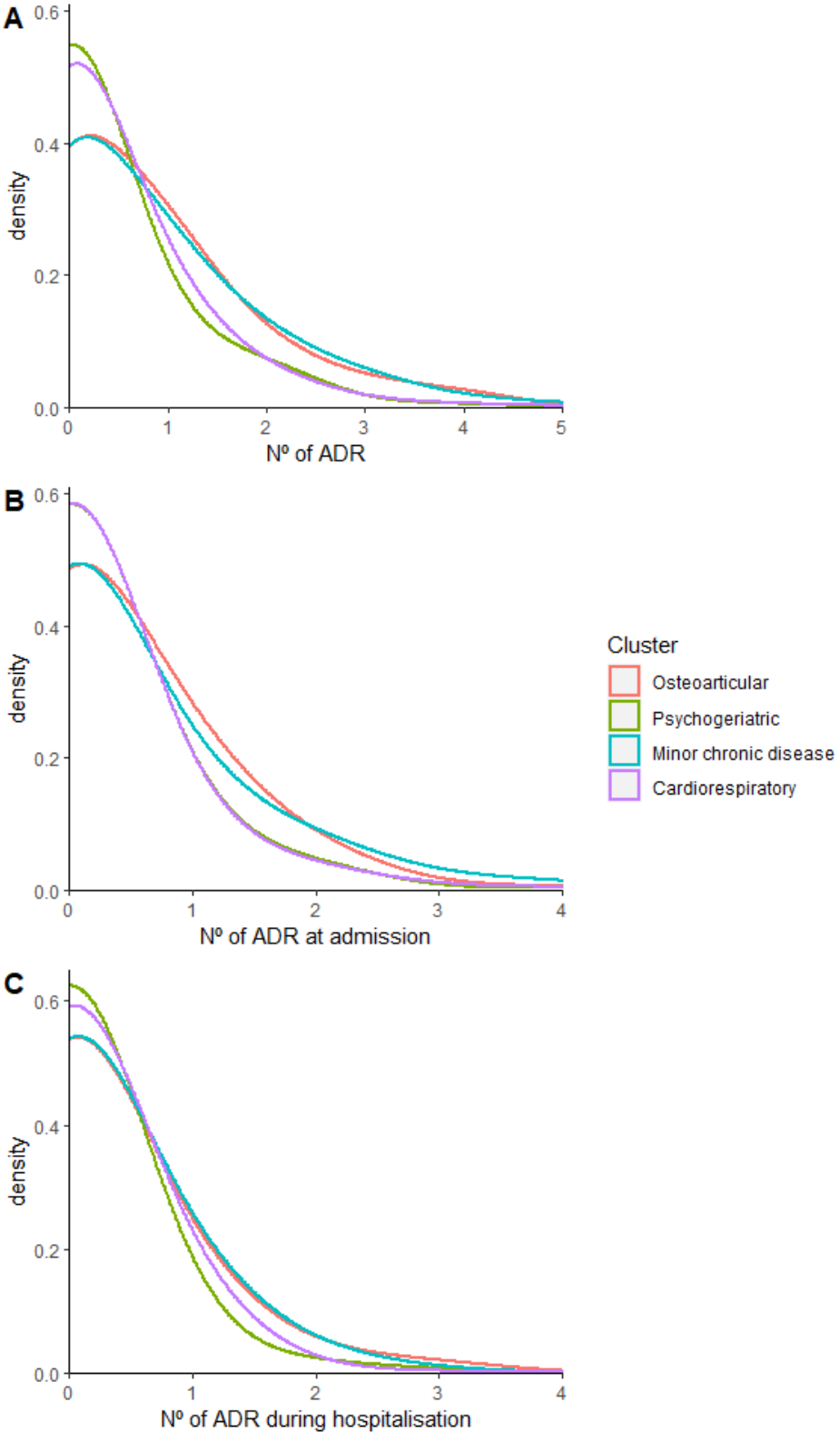

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Figure S2. A: Distribution of the number of ADRs according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed significant differences between the osteoarticular and the minor chronic disease clusters and the rest ($p < 0.001$). **B**: Distribution of the number of ADRs at admission according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed significant differences between the osteoarticular cluster and the minor chronic disease clusters and the rest ($p < 0.05$). **C**: Distribution of the number of ADRs during admission according to the assigned multimorbidity cluster. Pairwise comparisons between cluster distributions performed with the Kolmogorov-Smirnov test showed no significant differences ($p > 0.05$). ADR: adverse drug reaction.

Table S3. *p*-values of post-hoc pairwise.

	Osteoarticular vs. Psychogeriatric	Osteoarticular vs. Minor Chronic Disease	Osteoarticular vs. Cardiorespiratory	Psychogeriatric vs. Minor Chronic Disease	Psychogeriatric vs. Cardiorespiratory	Cardiorespiratory vs. Minor Chronic Disease
Any PIP	**<0.001**	**0.009**	**<0.001**	0.347	0.815	0.19
Any PIM	**0.014**	**0.014**	**0.002**	1	0.779	0.779
Any PPO	**0.037**	1	**0.012**	**0.037**	0.998	**0.012**

Fisher's exact test assessing for association between the presence of any potentially inappropriate prescribing (PIP), potentially inappropriate medication (PIM) or potential prescribing omission (PPO), according to STOPP/START criteria, and multimorbidity cluster belonging (osteoarticular, psychogeriatric, minor chronic disease or cardiorespiratory). Benjamini-Hochberg correction was applied at a false discovery rate of 5%. $p < 0.05$ are shown in bold.

Table S4. *p*-values of post-hoc pairwise.

	Osteoarticular vs. Psychogeriatric	Osteoarticular vs. Minor Chronic Disease	Osteoarticular vs. Cardiorespiratory	Psychogeriatric vs. Minor Chronic Disease	Psychogeriatric vs. Cardiorespiratory	Cardiorespiratory vs. Minor Chronic Disease
Any STOPP A1: Acetylsalicylic acid	0.103	**0.044**	0.102	0.602	1	0.287
Any STOPP A1: Proton pump inhibitor	0.519	0.519	**0.001**	0.213	**<0.001**	**0.022**
Any STOPP A2	0.641	0.643	0.198	0.266	0.643	0.06
Any STOPP B11	**0.013**	0.112	**<0.001**	0.444	0.311	0.055
Any STOPP D5	**<0.001**	**0.003**	**0.003**	0.568	0.192	0.568
Any STOPP G5	**0.004**	0.088	**0.007**	0.4	0.436	0.823
Any STOPP I1	0.571	0.061	1	**0.023**	0.469	**0.042**
Any STOPP K1	**<0.001**	**<0.001**	**<0.001**	0.866	0.086	0.146
Any STOPP K2	0.103	0.771	**0.003**	**0.04**	**<0.001**	**0.015**
Any STOPP L2	**0.047**	0.356	**0.047**	0.522	1	0.522

Fisher's exact test assessing for association between the presence of any STOPP criteria previously significantly associated, and multimorbidity cluster belonging (osteoarticular, psychogeriatric, minor chronic disease or cardiorespiratory). Benjamini-Hochberg correction was applied at a false discovery rate of 5%. $p < 0.05$ are shown in bold.

Table S5. *p*-values of post-hoc pairwise.

	Osteoarticular vs. Psychogeriatric	Osteoarticular vs. Minor	Osteoarticular vs. Cardiorespiratory	Psychogeriatric vs. Minor	Psychogeriatric vs. Cardiorespiratory	Cardiorespiratory vs. Minor Chronic Disease

		Chronic Disease		Chronic Disease		
Any START A8	0.854	0.854	**0.037**	1	**0.01**	**0.01**
Any START C2	0.112	1	0.06	0.144	1	0.062
Any START C3	0.138	0.165	1	0.877	0.082	0.138
Any START E2	0.169	0.427	**0.02**	0.594	0.594	0.384
Any START E5	0.506	0.506	**0.003**	0.185	**0.037**	**<0.001**
Any START H2	**0.007**	0.68	**0.007**	**0.039**	0.802	**0.039**

Fisher's exact test assessing for association between the presence of any START criteria previously significantly associated, and multimorbidity cluster belonging (osteoarticular, psychogeriatric, minor chronic disease or cardiorespiratory). Benjamini-Hochberg correction was applied at a false discovery rate of 5%. $p < 0.05$ are shown in bold.

Table S6. *p*-values of post-hoc pairwise.

	Osteoarticular vs. Psychogeriatric	Osteoarticular vs. Minor Chronic Disease	Osteoarticular vs. Cardiorespiratory	Psychogeriatric vs. Minor Chronic Disease	Psychogeriatric vs. Cardiorespiratory	Cardiorespiratory vs. Minor Chronic Disease
Any ADR	**<0.001**	0.902	**<0.001**	**<0.001**	0.168	**<0.001**
Any ADR at admission	**0.001**	0.95	**<0.001**	**0.002**	1	**<0.001**
Any ADR during admission	**0.001**	1	**0.041**	**0.001**	**0.041**	**0.041**

Fisher's exact test assessing for association between the presence of any adverse drug reaction (ADR), detected at the time of admission or during admission, and multimorbidity cluster belonging (osteoarticular, psychogeriatric, minor chronic disease or cardiorespiratory). Benjamini-Hochberg correction was applied at a false discovery rate of 5%. $p < 0.05$ are shown in bold.

Table S7. *p*-values of post-hoc pairwise.

	Osteoarticular vs. Psychogeriatric	Osteoarticular vs. Minor Chronic Disease	Osteoarticular vs. Cardiorespiratory	Psychogeriatric vs. Minor Chronic Disease	Psychogeriatric vs. Cardiorespiratory	Cardiorespiratory vs. Minor Chronic Disease
Any ADR ACE inhibitor	**0.093**	0.169	**0.01**	0.788	0.727	0.442
Any ADR Neuroleptic	0.371	0.732	1	0.472	0.087	0.472
Any ADR ARB	0.059	0.609	0.099	**0.038**	0.528	**0.045**
Any ADR Insulin	0.727	0.106	0.727	**0.039**	1	**0.005**
Any ADR Loop diuretic	0.094	0.446	0.145	0.296	0.446	0.446
Any ADR Thiazide diuretic	0.412	0.412	0.54	0.083	0.54	0.083

Fisher's exact test assessing for association between the presence of any adverse drug reaction (ADR) previously significantly associated, and multimorbidity cluster belonging (osteoarticular, psychogeriatric, minor chronic disease or cardiorespiratory). Benjamini-Hochberg correction was applied at a false discovery rate of 5%. $p < 0.05$ are shown in bold. ACE: angiotensin-converting enzyme. ARB: angiotensin II receptor blocker.

A2. Study 2: MRisk-COVID study

The supplementary files of this study include 4 tables and 2 figures.

Table S1. List of codes for COVID-19 registration, primary care mortality and severe infection.

ICD-10-CM = International Classification of Diseases, 10th edition, Clinical Modification

ICD-10-PCS = International Classification of Diseases, 10th edition, Procedure Coding System

CODES FOR COVID-19 REGISTRATION		
ICD-10-CM	**Description**	
B342	Coronavirus infection, unspecified	
B9721	SARS-associated coronavirus as the cause of diseases classified elsewhere	
B9729	Other coronavirus as the cause of diseases classified elsewhere	
J1281	Pneumonia due to SARS-associated coronavirus	
J1289	Other viral pneumonia	
U071	COVID-19	
Z20828	Contact with and (suspected) exposure to other viral communicable diseases	
CODES FOR MORTALITY (PRIMARY CARE)		
ICD-10-CM	**Description**	**Category**
R99	Ill-defined and unknown cause of mortality	Mortality
CODES FOR SEVERE INFECTION: DIAGNOSES		
ICD-10-CM	**Description**	**Category**
J80	Acute respiratory distress syndrome	ARDS
R6511	Systemic inflammatory response syndrome (SIRS) of non-infectious origin with acute organ dysfunction	Inflammatory response
R6520	Severe sepsis without septic shock	Inflammatory response
D65	Disseminated intravascular coagulation [defibrination syndrome]	Organ failure
E271	Primary adrenocortical insufficiency	Organ failure
I2609	Other pulmonary embolism with acute cor pulmonale	Organ failure
I2699	Other pulmonary embolism without acute cor pulmonale	Organ failure
I501	Left ventricular failure, unspecified	Organ failure
I5020	Unspecified systolic (congestive) heart failure	Organ failure
I5021	Acute systolic (congestive) heart failure	Organ failure
I5030	Unspecified diastolic (congestive) heart failure	Organ failure
I5031	Acute diastolic (congestive) heart failure	Organ failure
I5043	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure	Organ failure
I50810	Right heart failure, unspecified	Organ failure
I50811	Acute right heart failure	Organ failure
I50813	Acute on chronic right heart failure	Organ failure
I5082	Biventricular heart failure	Organ failure
I5083	High output heart failure	Organ failure
I5089	Other heart failure	Organ failure
I509	Heart failure, unspecified	Organ failure
K7200	Acute and subacute hepatic failure without coma	Organ failure
K7201	Acute and subacute hepatic failure with coma	Organ failure
K7290	Hepatic failure, unspecified without coma	Organ failure
K7291	Hepatic failure, unspecified with coma	Organ failure
N170	Acute kidney failure with tubular necrosis	Organ failure
N171	Acute kidney failure with acute cortical necrosis	Organ failure
N172	Acute kidney failure with medullary necrosis	Organ failure
N178	Other acute kidney failure	Organ failure
N179	Acute kidney failure, unspecified	Organ failure
N19	Unspecified kidney failure	Organ failure
N990	Postprocedural (acute) (chronic) kidney failure	Organ failure
J9600	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	Respiratory failure
J9601	Acute respiratory failure with hypoxia	Respiratory failure
J9602	Acute respiratory failure with hypercapnia	Respiratory failure
J9620	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	Respiratory failure

J9621	Acute and chronic respiratory failure with hypoxia	Respiratory failure
J9622	Acute and chronic respiratory failure with hypercapnia	Respiratory failure
J9690	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia	Respiratory failure
J9691	Respiratory failure, unspecified with hypoxia	Respiratory failure
J9692	Respiratory failure, unspecified with hypercapnia	Respiratory failure
R6521	Severe sepsis with septic shock	Septic shock
CODES FOR SERIOUS INFECTION: PROCEDURES		
ICD-10-PCS	**Description**	**Category**
5A1935Z	Respiratory Ventilation, Less than 24 Consecutive Hours	Invasive mechanical ventilation
5A1945Z	Respiratory Ventilation, 24-96 Consecutive Hours	Invasive mechanical ventilation
5A1955Z	Respiratory Ventilation, Greater than 96 Consecutive Hours	Invasive mechanical ventilation
5A09357	Assistance with Respiratory Ventilation, Less than 24 Consecutive Hours, Continuous Positive Airway Pressure	Noninvasive mechanical ventilation
5A09358	Assistance with Respiratory Ventilation, Less than 24 Consecutive Hours, Intermittent Positive Airway Pressure	Noninvasive mechanical ventilation
5A09359	Assistance with Respiratory Ventilation, Less than 24 Consecutive Hours, Continuous Negative Airway Pressure	Noninvasive mechanical ventilation
5A0935B	Assistance with Respiratory Ventilation, Less than 24 Consecutive Hours, Intermittent Negative Airway Pressure	Noninvasive mechanical ventilation
5A0935Z	Assistance with Respiratory Ventilation, Less than 24 Consecutive Hours	Noninvasive mechanical ventilation
5A09457	Assistance with Respiratory Ventilation, 24-96 Consecutive Hours, Continuous Positive Airway Pressure	Noninvasive mechanical ventilation
5A09458	Assistance with Respiratory Ventilation, 24-96 Consecutive Hours, Intermittent Positive Airway Pressure	Noninvasive mechanical ventilation
5A09459	Assistance with Respiratory Ventilation, 24-96 Consecutive Hours, Continuous Negative Airway Pressure	Noninvasive mechanical ventilation
5A0945B	Assistance with Respiratory Ventilation, 24-96 Consecutive Hours, Intermittent Negative Airway Pressure	Noninvasive mechanical ventilation
5A0945Z	Assistance with Respiratory Ventilation, 24-96 Consecutive Hours	Noninvasive mechanical ventilation
5A09557	Assistance with Respiratory Ventilation, Greater than 96 Consecutive Hours, Continuous Positive Airway Pressure	Noninvasive mechanical ventilation
5A09558	Assistance with Respiratory Ventilation, Greater than 96 Consecutive Hours, Intermittent Positive Airway Pressure	Noninvasive mechanical ventilation
5A09559	Assistance with Respiratory Ventilation, Greater than 96 Consecutive Hours, Continuous Negative Airway Pressure	Noninvasive mechanical ventilation
5A0955B	Assistance with Respiratory Ventilation, Greater than 96 Consecutive Hours, Intermittent Negative Airway Pressure	Noninvasive mechanical ventilation
5A0955Z	Assistance with Respiratory Ventilation, Greater than 96 Consecutive Hours	Noninvasive mechanical ventilation
3E0F7GC	Introduction of Other Therapeutic Substance into Respiratory Tract, Via Natural or Artificial Opening	Oxygen therapy
3E0F7SF	Introduction of Other Gas into Respiratory Tract, Via Natural or Artificial Opening	Oxygen therapy
5A05121	Extracorporeal Hyperbaric Oxygenation, Intermittent	Oxygen therapy
5A0512C	Extracorporeal Supersaturated Oxygenation, Intermittent	Oxygen therapy
5A05221	Extracorporeal Hyperbaric Oxygenation, Continuous	Oxygen therapy
5A0522C	Extracorporeal Supersaturated Oxygenation, Continuous	Oxygen therapy
5A09357	Assistance with Respiratory Ventilation, Less than 24 Consecutive Hours, Continuous Positive Airway Pressure	Oxygen therapy
5A09457	Assistance with Respiratory Ventilation, 24-96 Consecutive Hours, Continuous Positive Airway Pressure	Oxygen therapy
5A09557	Assistance with Respiratory Ventilation, Greater than 96 Consecutive Hours, Continuous Positive Airway Pressure	Oxygen therapy

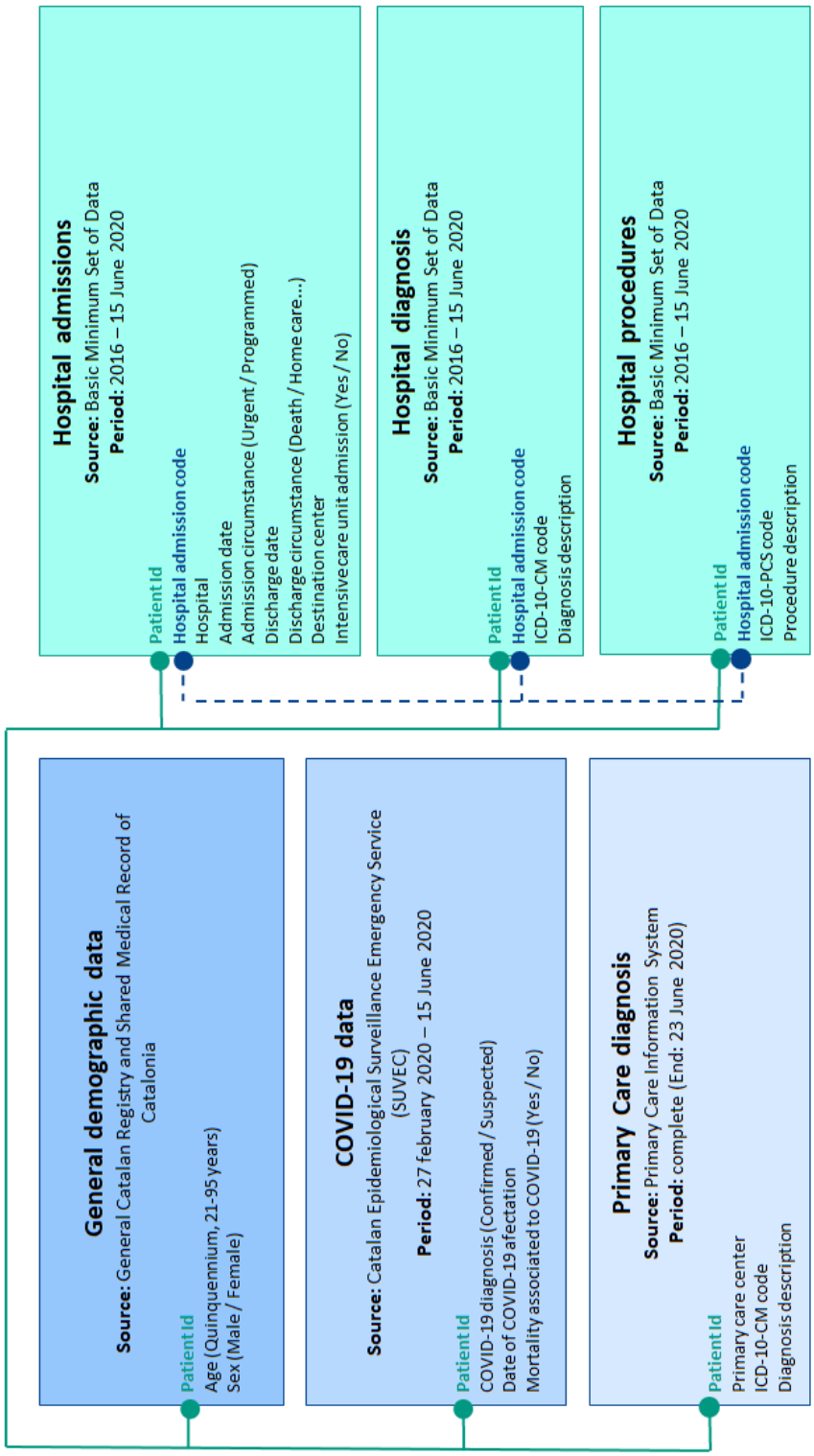


Figure S1: Source and distribution of the analysed data. The included patients were submitted to an anonymization process. A patient ID code was assigned to each individual, which was maintained through all the different datasets in order to enable data compilation.

Table S2. Number of patients and prevalence of severe COVID-19 infection according to the type of case (confirmed or suspected).

	Severe COVID-19 infection, N (%)				
	Total	21-45	46-65	66-80	81+
Confirmed	930 (29.6)	97 (11.0)	315 (29.9)	357 (53.8)	161 (29.5)
Suspected	184 (1.7)	16 (0.3)	57 (1.6)	61 (3.7)	50 (4.4)
Total	1114 (7.8)	113 (2.0)	372 (7.9)	418 (18.2)	211 (12.5)

Table S3. Chronic conditions with >2% prevalence per age and sex stratum.

[This table is originally an Excel file, which is shown in the next 4 pages.]

Male

21-45	
Category	Prevalence (%)
Anxiety and fear-related disorders	33,3
Other specified and unspecified upper respiratory disease	22,9
Obesity	20,6
Neurodevelopmental disorders	17,9
Disorders of lipid metabolism	13,1
Schizophrenia spectrum and other psychotic disorders	12,6
Sleep wake disorders	12,3
Epilepsy; convulsions	12,2
Disorders of teeth and gingiva	11,5
Essential hypertension	11,1
Asthma	10,6
Other specified joint disorders	10,2
Esophageal disorders	8,5
Urinary incontinence	8,0
Other specified and unspecified nutritional and metabolic disorders	7,9
Headache; including migraine	7,9
Depressive disorders	7,6
Spondylopathies/spondyloarthropathy (including infective)	7,6
Other specified inflammatory condition of skin	7,6
Disruptive, impulse-control and conduct disorders	7,4
Thyroid disorders	7,3
Scoliosis and other postural dorsopathic deformities	6,0
Alcohol-related disorders	5,5
Symptoms of mental and substance use conditions	5,4
Hearing loss	5,3
Trauma- and stressor-related disorders	4,6
Cannabis-related disorders	4,6
Diseases of white blood cells	4,4
Diabetes mellitus without complication	4,4
Other specified and unspecified liver disease	4,1
Stimulant-related disorders	4,0
Neoplasia (solid tumour)	3,6
Conduction disorders	3,5
Nerve and nerve root disorders	3,5
Miscellaneous mental and behavioral disorders/conditions	3,2
Other specified and unspecified disorders of the ear	3,0
Acute and chronic tonsillitis	3,0
Cerebral palsy	2,9
Cardiac dysrhythmias	2,7
Paralysis (other than cerebral palsy)	2,7
Other specified and unspecified gastrointestinal disorders	2,6
Chromosomal abnormalities	2,6
Obsessive-compulsive and related disorders	2,6
Personality disorders	2,5
Parkinson`s disease	2,3
Osteoarthritis	2,2
Other specified nervous system disorders	2,2
Nutritional deficiencies	2,1
Hepatitis	2,1

46-65	
Category	Prevalence (%)
Essential hypertension	42,4
Disorders of lipid metabolism	34,1
Obesity	29,4
Anxiety and fear-related disorders	26,5
Sleep wake disorders	23,3
Other specified and unspecified nutritional and metabolic disorders	19,0
Diabetes mellitus without complication	18,8
Neoplasia (solid tumour)	16,9
Spondylopathies/spondyloarthropathy (including infective)	15,8
Other specified and unspecified upper respiratory disease	15,6
Hyperplasia of prostate	14,0
Other specified and unspecified liver disease	13,3
Osteoarthritis	13,1
Chronic obstructive pulmonary disease and bronchiectasis	12,9
Other specified joint disorders	12,4
Neurodevelopmental disorders	12,1
Depressive disorders	11,6
Disorders of teeth and gingiva	11,4
Urinary incontinence	11,3
Esophageal disorders	11,0
Coronary atherosclerosis and other heart disease	9,6
Hearing loss	9,6
Alcohol-related disorders	9,4
Epilepsy; convulsions	8,9
Cardiac dysrhythmias	8,5
Thyroid disorders	8,3
Other specified inflammatory condition of skin	7,5
Schizophrenia spectrum and other psychotic disorders	7,2
Gout	6,7
Peripheral and visceral vascular disease	6,6
Cataract and other lens disorders	6,6
Chronic kidney disease	6,4
Conduction disorders	6,0
Nerve and nerve root disorders	5,9
Diabetes mellitus with complication	5,7
Heart failure	5,3
Diverticulosis and diverticulitis	5,3
Diseases of white blood cells	5,1
Trauma- and stressor-related disorders	5,1
Hepatitis	5,0
Headache; including migraine	4,7
Asthma	4,7
Miscellaneous mental and behavioral disorders/conditions	4,5
Gastritis and duodenitis	4,4
Acute myocardial infarction	4,4
Neurocognitive disorders	4,4
Glaucoma	4,3
Paralysis (other than cerebral palsy)	3,8
Disruptive, impulse-control and conduct disorders	3,7
Symptoms of mental and substance use conditions	3,6
Coagulation and hemorrhagic disorders	3,6
Gastroduodenal ulcer	3,6
Other and ill-defined heart disease	3,5
Nonrheumatic and unspecified valve disorders	3,2
Nutritional deficiencies	3,2
Cerebral infarction	3,1
Scoliosis and other postural dorsopathic deformities	3,0
Non-pressure ulcer of skin	3,0
Digestive congenital anomalies	2,9
Hypertension with complications and secondary hypertension	2,7
Hematologic neoplasia	2,7
Malnutrition	2,6
Myocarditis and cardiomyopathy	2,3
Other specified and unspecified endocrine disorders	2,3
Myopathies	2,2
Pressure ulcer of skin	2,2
Other specified nervous system disorders	2,2
Chromosomal abnormalities	2,1
Obsessive-compulsive and related disorders	2,1
Other specified hereditary and degenerative nervous system conditions	2,1

Male

66-80	
Category	Prevalence (%)
Essential hypertension	72,1
Disorders of lipid metabolism	49,0
Hyperplasia of prostate	43,5
Diabetes mellitus without complication	39,4
Neoplasia (solid tumour)	33,7
Chronic obstructive pulmonary disease and bronchiectasis	32,0
Obesity	31,6
Osteoarthritis	30,1
Cataract and other lens disorders	29,1
Other specified and unspecified nutritional and metabolic disorders	29,0
Sleep wake disorders	26,9
Urinary incontinence	26,6
Cardiac dysrhythmias	24,6
Chronic kidney disease	23,9
Coronary atherosclerosis and other heart disease	23,3
Neurocognitive disorders	23,3
Conduction disorders	22,7
Heart failure	18,6
Hearing loss	18,5
Spondylopathies/spondyloarthropathy (including infective)	17,3
Peripheral and visceral vascular disease	17,2
Anxiety and fear-related disorders	15,8
Diabetes mellitus with complication	15,1
Depressive disorders	14,2
Esophageal disorders	13,7
Other specified and unspecified liver disease	12,8
Glaucoma	11,1
Disorders of teeth and gingiva	11,0
Gout	10,7
Other specified and unspecified upper respiratory disease	10,7
Diverticulosis and diverticulitis	10,6
Thyroid disorders	10,0
Alcohol-related disorders	9,8
Nonrheumatic and unspecified valve disorders	9,4
Other specified joint disorders	9,3
Acute myocardial infarction	8,4
Cerebral infarction	8,2
Other specified inflammatory condition of skin	8,0
Other and ill-defined heart disease	7,2
Diseases of white blood cells	7,0
Nutritional deficiencies	7,0
Hypertension with complications and secondary hypertension	6,7
Other general signs and symptoms	6,7
Symptoms of mental and substance use conditions	6,0
Coagulation and hemorrhagic disorders	5,9
Gastroduodenal ulcer	5,9
Osteoporosis	5,9
Pressure ulcer of skin	5,5
Nerve and nerve root disorders	5,5
Nervous system signs and symptoms	5,1
Asthma	4,9
Retinal and vitreous conditions	4,8
Miscellaneous mental and behavioral disorders/conditions	4,8
Other specified hereditary and degenerative nervous system conditions	4,8
Pulmonary heart disease	4,8
Myocarditis and cardiomyopathy	4,6
Malnutrition	4,4
Epilepsy; convulsions	4,4
Gastritis and duodenitis	4,3
Respiratory failure; insufficiency; arrest	4,0
Non-pressure ulcer of skin	4,0
Biliary tract disease	3,9
Schizophrenia spectrum and other psychotic disorders	3,9
Parkinson`s disease	3,9
Paralysis (other than cerebral palsy)	3,9
Digestive congenital anomalies	3,7
Chronic rheumatic heart disease	3,6
Aortic; peripheral; and visceral artery aneurysms	3,6
Other specified and unspecified lower respiratory disease	3,4
Trauma- and stressor-related disorders	3,3
Acquired foot deformities	3,2
Sequela of cerebral infarction and other cerebrovascular disease	3,1
Other specified and unspecified endocrine disorders	3,1
Hematologic neoplasia	3,0
Neurodevelopmental disorders	3,0
Systemic lupus erythematosus and connective tissue disorders	3,0
Headache; including migraine	3,0
Transient cerebral ischemia	3,0
Disruptive, impulse-control and conduct disorders	2,9
Myopathies	2,9
Other specified nervous system disorders	2,9
Occlusion or stenosis of precerebral or cerebral arteries without infarction	2,8
Nephritis; nephrosis; renal sclerosis	2,4
Other and ill-defined cerebrovascular disease	2,3
Hepatitis	2,3
Other specified and unspecified circulatory disease	2,1
Scoliosis and other postural dorsopathic deformities	2,1

81-95	
Category	Prevalence (%)
Essential hypertension	78,4
Urinary incontinence	56,9
Hyperplasia of prostate	55,2
Disorders of lipid metabolism	50,5
Neurocognitive disorders	47,0
Osteoarthritis	42,3
Diabetes mellitus without complication	41,3
Cardiac dysrhythmias	39,8
Chronic kidney disease	39,2
Cataract and other lens disorders	38,6
Chronic obstructive pulmonary disease and bronchiectasis	36,8
Conduction disorders	32,9
Neoplasia (solid tumour)	32,7
Heart failure	32,4
Coronary atherosclerosis and other heart disease	31,2
Sleep wake disorders	29,4
Obesity	26,1
Other specified and unspecified nutritional and metabolic disorders	25,9
Hearing loss	24,4
Depressive disorders	20,5
Peripheral and visceral vascular disease	20,3
Spondylopathies/spondyloarthropathy (including infective)	18,9
Nonrheumatic and unspecified valve disorders	16,8
Gout	16,6
Diabetes mellitus with complication	15,2
Anxiety and fear-related disorders	14,8
Diverticulosis and diverticulitis	14,2
Symptoms of mental and substance use conditions	12,9
Pressure ulcer of skin	12,5
Cerebral infarction	12,3
Esophageal disorders	12,3
Nervous system signs and symptoms	11,9
Other general signs and symptoms	11,9
Nutritional deficiencies	11,7
Thyroid disorders	11,5
Glaucoma	11,1
Disorders of teeth and gingiva	10,1
Other specified and unspecified upper respiratory disease	9,9
Other and ill-defined heart disease	9,7
Hypertension with complications and secondary hypertension	8,8
Acute myocardial infarction	8,2
Other specified inflammatory condition of skin	8,2
Parkinson`s disease	8,0
Other specified and unspecified liver disease	7,8
Coagulation and hemorrhagic disorders	7,6
Pulmonary heart disease	7,0
Other specified hereditary and degenerative nervous system conditions	7,0
Disruptive, impulse-control and conduct disorders	6,2
Other specified joint disorders	6,0
Non-pressure ulcer of skin	6,0
Gastroduodenal ulcer	5,8
Osteoporosis	5,8
Retinal and vitreous conditions	5,5
Diseases of white blood cells	5,3
Gastritis and duodenitis	5,3
Malnutrition	5,3
Digestive congenital anomalies	4,7
Miscellaneous mental and behavioral disorders/conditions	4,7
Asthma	4,7
Occlusion or stenosis of precerebral or cerebral arteries without infarction	4,3
Systemic lupus erythematosus and connective tissue disorders	4,3
Respiratory failure; insufficiency; arrest	4,3
Chronic rheumatic heart disease	4,1
Aortic; peripheral; and visceral artery aneurysms	4,1
Transient cerebral ischemia	4,1
Myocarditis and cardiomyopathy	3,5
Biliary tract disease	3,5
Trauma- and stressor-related disorders	3,5
Acquired foot deformities	3,5
Nervous system pain and pain syndromes	3,5
Other specified and unspecified endocrine disorders	3,3
Paralysis (other than cerebral palsy)	3,3
Epilepsy; convulsions	3,3
Nerve and nerve root disorders	3,3
Hepatitis	3,1
Alcohol-related disorders	3,1
Other and ill-defined cerebrovascular disease	2,9
Sequela of cerebral infarction and other cerebrovascular disease	2,7
Blindness and vision defects	2,7
Hematologic neoplasia	2,7
Scoliosis and other postural dorsopathic deformities	2,7
Headache; including migraine	2,5
Other specified and unspecified hematologic conditions	2,3
Lung disease due to external agents	2,3
Other specified and unspecified gastrointestinal disorders	2,1
Nephritis; nephrosis; renal sclerosis	2,1
Other specified and unspecified diseases of bladder and urethra	2,1
Sequela of specified infectious disease conditions	2,1
Polyneuropathies	2,1
Other specified nervous system disorders	2,1

Female

21-45	
Category	Prevalence (%)
Anxiety and fear-related disorders	44,7
Obesity	22,3
Headache; including migraine	21,9
Other specified and unspecified upper respiratory disease	21,6
Thyroid disorders	20,0
Menstrual disorders	16,6
Depressive disorders	11,8
Asthma	11,7
Complications specified during the puerperium	10,0
Other specified inflammatory condition of skin	9,3
Disorders of teeth and gingiva	8,8
Female infertility	8,1
Trauma- and stressor-related disorders	8,0
Scoliosis and other postural dorsopathic deformities	7,7
Sleep wake disorders	7,6
Other specified joint disorders	6,8
Urinary incontinence	6,6
Nerve and nerve root disorders	6,4
Other specified and unspecified endocrine disorders	6,2
Spondylopathies/spondyloarthropathy (including infective)	6,0
Essential hypertension	5,7
Esophageal disorders	5,3
Disorders of lipid metabolism	5,3
Neurodevelopmental disorders	4,7
Hearing loss	4,5
Other specified and unspecified nutritional and metabolic disorders	4,4
Neoplasia (solid tumour)	4,1
Other specified and unspecified gastrointestinal disorders	4,0
Other specified female genital disorders	3,7
Complications specified during childbirth	3,6
Diseases of white blood cells	3,5
Epilepsy; convulsions	3,1
Pituitary disorders	3,0
Other specified complications in pregnancy	2,7
Diabetes mellitus without complication	2,7
Acquired foot deformities	2,6
Acute and chronic tonsillitis	2,6
Endometriosis	2,4
Nutritional deficiencies	2,3
Coagulation and hemorrhagic disorders	2,2
Other specified and unspecified liver disease	2,1
Gastritis and duodenitis	2,1
Feeding and eating disorders	2,1

46-65	
Category	Prevalence (%)
Anxiety and fear-related disorders	43,5
Essential hypertension	29,0
Obesity	28,6
Thyroid disorders	26,1
Disorders of lipid metabolism	24,2
Depressive disorders	20,2
Osteoarthritis	18,7
Sleep wake disorders	17,2
Other specified and unspecified upper respiratory disease	16,5
Menopausal disorders	16,0
Spondylopathies/spondyloarthropathy (including infective)	15,5
Other specified and unspecified nutritional and metabolic disorders	15,5
Urinary incontinence	15,0
Headache; including migraine	13,5
Nerve and nerve root disorders	13,1
Neoplasia (solid tumour)	12,2
Other specified joint disorders	10,5
Diabetes mellitus without complication	10,2
Esophageal disorders	9,5
Disorders of teeth and gingiva	9,4
Asthma	8,8
Trauma- and stressor-related disorders	8,6
Menstrual disorders	8,1
Other specified inflammatory condition of skin	7,8
Other specified and unspecified liver disease	7,7
Hearing loss	7,1
Acquired foot deformities	6,9
Nutritional deficiencies	6,5
Neurodevelopmental disorders	5,9
Osteoporosis	5,8
Cataract and other lens disorders	5,7
Chronic obstructive pulmonary disease and bronchiectasis	5,4
Scoliosis and other postural dorsopathic deformities	4,9
Epilepsy; convulsions	4,6
Cardiac dysrhythmias	4,4
Gastritis and duodenitis	4,1
Nonmalignant breast conditions	4,0
Diseases of white blood cells	3,8
Glaucoma	3,8
Prolapse of female genital organs	3,7
Other specified and unspecified endocrine disorders	3,6
Diverticulosis and diverticulitis	3,3
Schizophrenia spectrum and other psychotic disorders	2,9
Digestive congenital anomalies	2,8
Conduction disorders	2,8
Other specified and unspecified gastrointestinal disorders	2,7
Diabetes mellitus with complication	2,5
Systemic lupus erythematosus and connective tissue disorders	2,5
Nonrheumatic and unspecified valve disorders	2,3
Heart failure	2,2
Chronic kidney disease	2,2
Peripheral and visceral vascular disease	2,2
Coronary atherosclerosis and other heart disease	2,1

Female

66-80		81-95	
Category	Prevalence (%)	Category	Prevalence (%)
Essential hypertension	70,1	Urinary incontinence	82,6
Osteoarthritis	53,0	Essential hypertension	82,1
Disorders of lipid metabolism	48,0	Neurocognitive disorders	63,7
Obesity	44,4	Osteoarthritis	60,8
Urinary incontinence	43,1	Disorders of lipid metabolism	42,0
Depressive disorders	35,2	Chronic kidney disease	39,2
Anxiety and fear-related disorders	34,7	Depressive disorders	34,2
Diabetes mellitus without complication	32,8	Sleep wake disorders	32,7
Thyroid disorders	31,4	Obesity	31,6
Cataract and other lens disorders	31,2	Cardiac dysrhythmias	31,5
Other specified and unspecified nutritional and metabolic disorders	30,9	Cataract and other lens disorders	31,5
Sleep wake disorders	28,9	Diabetes mellitus without complication	31,0
Neurocognitive disorders	27,7	Heart failure	30,6
Osteoporosis	25,8	Other specified and unspecified nutritional and metabolic disorders	29,9
Spondylopathies/spondyloarthropathy (including infective)	24,3	Anxiety and fear-related disorders	26,6
Cardiac dysrhythmias	22,0	Osteoporosis	26,0
Neoplasia (solid tumour)	20,9	Hearing loss	25,2
Heart failure	19,7	Thyroid disorders	24,3
Chronic kidney disease	19,6	Other general signs and symptoms	20,0
Esophageal disorders	15,6	Spondylopathies/spondyloarthropathy (including infective)	19,9
Hearing loss	15,5	Conduction disorders	17,5
Conduction disorders	14,4	Pressure ulcer of skin	15,9
Diabetes mellitus with complication	13,4	Nutritional deficiencies	15,4
Chronic obstructive pulmonary disease and bronchiectasis	13,2	Symptoms of mental and substance use conditions	14,6
Nutritional deficiencies	12,4	Glaucoma	14,5
Other specified joint disorders	12,3	Neoplasia (solid tumour)	14,0
Other specified and unspecified upper respiratory disease	12,3	Coronary atherosclerosis and other heart disease	13,4
Asthma	12,0	Nonrheumatic and unspecified valve disorders	13,4
Nonrheumatic and unspecified valve disorders	11,8	Esophageal disorders	13,4
Other specified and unspecified liver disease	11,5	Nervous system signs and symptoms	11,8
Coronary atherosclerosis and other heart disease	11,0	Chronic obstructive pulmonary disease and bronchiectasis	11,6
Acquired foot deformities	11,0	Diverticulosis and diverticulitis	10,9
Nerve and nerve root disorders	10,3	Asthma	10,1
Glaucoma	9,8	Diabetes mellitus with complication	9,9
Disorders of teeth and gingiva	9,5	Other and ill-defined heart disease	9,4
Diverticulosis and diverticulitis	9,2	Other specified hereditary and degenerative nervous system conditions	9,1
Prolapse of female genital organs	8,7	Nervous system pain and pain syndromes	8,4
Menopausal disorders	8,4	Other specified and unspecified upper respiratory disease	8,4
Other specified hereditary and degenerative nervous system conditions	7,7	Cerebral infarction	8,3
Other general signs and symptoms	7,7	Retinal and vitreous conditions	8,0
Systemic lupus erythematosus and connective tissue disorders	7,2	Hypertension with complications and secondary hypertension	7,9
Symptoms of mental and substance use conditions	7,2	Systemic lupus erythematosus and connective tissue disorders	7,4
Other and ill-defined heart disease	7,1	Other specified joint disorders	7,3
Pressure ulcer of skin	7,0	Pulmonary heart disease	7,1
Other specified inflammatory condition of skin	6,7	Peripheral and visceral vascular disease	6,9
Headache; including migraine	6,5	Acquired foot deformities	6,8
Trauma- and stressor-related disorders	6,3	Scoliosis and other postural dorsopathic deformities	6,8
Hypertension with complications and secondary hypertension	6,3	Disorders of teeth and gingiva	5,9
Scoliosis and other postural dorsopathic deformities	6,0	Prolapse of female genital organs	5,9
Gastritis and duodenitis	5,8	Nerve and nerve root disorders	5,9
Digestive congenital anomalies	5,8	Other specified and unspecified liver disease	5,8
Retinal and vitreous conditions	5,7	Non-pressure ulcer of skin	5,7
Cerebral infarction	5,6	Parkinson`s disease	5,1
Peripheral and visceral vascular disease	5,6	Digestive congenital anomalies	4,8
Nervous system signs and symptoms	5,6	Epilepsy; convulsions	4,7
Nervous system pain and pain syndromes	5,4	Chronic rheumatic heart disease	3,8
Pulmonary heart disease	5,2	Menopausal disorders	3,8
Other specified and unspecified endocrine disorders	5,2	Trauma- and stressor-related disorders	3,8
Diseases of white blood cells	4,9	Disruptive, impulse-control and conduct disorders	3,8
Other specified and unspecified gastrointestinal disorders	4,7	Other specified inflammatory condition of skin	3,8
Parkinson`s disease	4,5	Other specified and unspecified endocrine disorders	3,8
Schizophrenia spectrum and other psychotic disorders	4,1	Miscellaneous mental and behavioral disorders/conditions	3,8
Biliary tract disease	3,9	Coagulation and hemorrhagic disorders	3,3
Myocarditis and cardiomyopathy	3,8	Gastritis and duodenitis	3,1
Chronic rheumatic heart disease	3,6	Headache; including migraine	3,0
Epilepsy; convulsions	3,4	Other specified and unspecified gastrointestinal disorders	2,9
Coagulation and hemorrhagic disorders	3,3	Other and ill-defined cerebrovascular disease	2,8
Hepatitis	3,2	Gastroduodenal ulcer	2,8
Gastroduodenal ulcer	3,0	Biliary tract disease	2,7
Malnutrition	3,0	Drug induced or toxic related condition	2,7
Rheumatoid arthritis and related disease	2,9	Acute myocardial infarction	2,6
Gout	2,9	Transient cerebral ischemia	2,6
Hematologic neoplasia	2,8	Paralysis (other than cerebral palsy)	2,5
Miscellaneous mental and behavioral disorders/conditions	2,8	Schizophrenia spectrum and other psychotic disorders	2,3
Paralysis (other than cerebral palsy)	2,7	Malnutrition	2,3
Acute myocardial infarction	2,6	Crystal arthropathies (excluding gout)	2,3
Respiratory failure; insufficiency; arrest	2,6	Respiratory failure; insufficiency; arrest	2,3
Non-pressure ulcer of skin	2,5	Gout	2,2
Drug induced or toxic related condition	2,3	Hepatitis	2,1
Disruptive, impulse-control and conduct disorders	2,3	Diseases of white blood cells	2,0
Bipolar and related disorders	2,2	Hematologic neoplasia	2,0
Other specified nervous system disorders	2,2		
Nephritis; nephrosis; renal sclerosis	2,1		
Neurodevelopmental disorders	2,1		

Table S4. Prevalence (%), Observed/Expected (O/E) ratio, and exclusivity (%) of the chronic conditions per multimorbidity cluster

[This table is originally an Excel file, which is shown in the following 22 pages.]

Males, 21-45 (1 out of 2)

Substance abuse disorders			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Stimulant-related disorders	48,02	11,99	73,21
Cannabis-related disorders	41,06	8,89	54,25
Hepatitis	16,95	8,26	50,40
Alcohol-related disorders	43,38	7,82	47,77
Personality disorders	16,53	6,71	40,96
Other specified nervous system disorders	9,57	4,44	27,11
Depressive disorders	25,62	3,37	20,58
Paralysis (other than cerebral palsy)	8,81	3,30	20,16
Cerebral palsy	8,82	3,07	18,74
Neoplasia (general)	9,43	2,63	16,02
Disorders of teeth and gingiva	26,22	2,28	13,92
Symptoms of mental and substance use condition	11,81	2,17	13,25
Miscellaneous mental and behavioral disorders/c	6,32	1,99	12,13
Nutritional deficiencies	3,61	1,76	10,73
Anxiety and fear-related disorders	55,50	1,67	10,18
Obsessive-compulsive and related disorders	4,27	1,66	10,15
Other specified and unspecified liver disease	6,49	1,58	9,65
Urinary incontinence	12,58	1,57	9,59
Sleep wake disorders	19,19	1,56	9,51
Cardiac dysrhythmias	3,93	1,47	8,98
Epilepsy; convulsions	17,84	1,46	8,91
Schizophrenia spectrum and other psychotic disor	18,18	1,44	8,79
Osteoarthritis	3,09	1,43	8,75
Diabetes mellitus without complication	6,30	1,43	8,72
Other specified and unspecified nutritional and m	11,06	1,40	8,54
Disorders of lipid metabolism	18,09	1,38	8,40
Diseases of white blood cells	5,94	1,35	8,22
Esophageal disorders	10,18	1,19	7,29
Neurodevelopmental disorders	19,42	1,09	6,64
Essential hypertension	11,29	1,02	6,22
Thyroid disorders	6,23	0,85	5,22
Other specified inflammatory condition of skin	6,33	0,83	5,08
Disruptive, impulse-control and conduct disorders	5,93	0,80	4,90
Obesity	16,30	0,79	4,82
Conduction disorders	2,72	0,78	4,76
Asthma	8,25	0,78	4,76
Other specified and unspecified gastrointestinal d	1,72	0,67	4,10
Scoliosis and other postural dorsopathic deformiti	4,00	0,67	4,10
Other specified and unspecified upper respiratory	14,20	0,62	3,79
Chromosomal abnormalities	1,58	0,61	3,75
Trauma- and stressor-related disorders	2,72	0,59	3,60
Other specified joint disorders	5,66	0,56	3,40
Acute and chronic tonsillitis	1,24	0,42	2,54
Hearing loss	1,95	0,37	2,23
Headache; including migraine	2,74	0,35	2,11
Other specified and unspecified disorders of the e	0,88	0,30	1,80
Spondylopathies/spondyloarthropathy (including	0,88	0,12	0,71
Nerve and nerve root disorders	0,40	0,11	0,70
Parkinson`s disease	0,00	0,00	0,00

Neurodevelopmental disorders			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Parkinson`s disease	13,45	5,95	76,96
Cerebral palsy	16,05	5,58	72,16
Disruptive, impulse-control and conduct disorders	37,90	5,13	66,28
Symptoms of mental and substance use condition	27,61	5,07	65,61
Urinary incontinence	40,23	5,02	64,95
Epilepsy; convulsions	56,92	4,66	60,24
Neurodevelopmental disorders	81,18	4,54	58,75
Schizophrenia spectrum and other psychotic disor	53,83	4,26	55,11
Other specified nervous system disorders	8,54	3,96	51,21
Paralysis (other than cerebral palsy)	9,90	3,71	47,95
Obsessive-compulsive and related disorders	9,50	3,70	47,83
Chromosomal abnormalities	9,36	3,65	47,14
Other specified and unspecified disorders of the e	7,92	2,66	34,39
Nutritional deficiencies	5,42	2,64	34,15
Personality disorders	6,21	2,52	32,60
Thyroid disorders	14,46	1,98	25,66
Stimulant-related disorders	7,49	1,87	24,18
Disorders of teeth and gingiva	20,52	1,78	23,07
Neoplasia (general)	6,21	1,73	22,36
Hepatitis	3,29	1,60	20,71
Scoliosis and other postural dorsopathic deformiti	9,32	1,57	20,24
Miscellaneous mental and behavioral disorders/c	4,51	1,42	18,33
Conduction disorders	4,77	1,37	17,65
Alcohol-related disorders	7,52	1,36	17,54
Cannabis-related disorders	6,05	1,31	16,93
Sleep wake disorders	15,69	1,27	16,46
Other specified and unspecified nutritional and m	9,64	1,22	15,77
Diabetes mellitus without complication	4,92	1,11	14,41
Depressive disorders	8,27	1,09	14,08
Esophageal disorders	9,19	1,08	13,94
Hearing loss	5,48	1,03	13,28
Essential hypertension	10,93	0,99	12,74
Other specified and unspecified upper respiratory	19,01	0,83	10,74
Other specified and unspecified liver disease	3,06	0,75	9,64
Diseases of white blood cells	3,21	0,73	9,40
Osteoarthritis	1,56	0,72	9,37
Anxiety and fear-related disorders	22,58	0,68	8,78
Obesity	13,08	0,63	8,19
Other specified inflammatory condition of skin	4,59	0,60	7,81
Disorders of lipid metabolism	7,91	0,60	7,78
Cardiac dysrhythmias	1,06	0,40	5,14
Asthma	3,20	0,30	3,92
Acute and chronic tonsillitis	0,80	0,27	3,46
Trauma- and stressor-related disorders	1,14	0,25	3,19
Other specified joint disorders	2,09	0,21	2,65
Nerve and nerve root disorders	0,65	0,18	2,39
Other specified and unspecified gastrointestinal d	0,36	0,14	1,82
Spondylopathies/spondyloarthropathy (including	0,50	0,07	0,85
Headache; including migraine	0,26	0,03	0,42

Males, 21-45 (2 out of 2)

Cardiovascular risk factors			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Other specified and unspecified liver disease	10,00	2,43	46,58
Diabetes mellitus without complication	9,99	2,26	43,32
Thyroid disorders	13,81	1,89	36,24
Cardiac dysrhythmias	4,94	1,85	35,40
Disorders of lipid metabolism	23,56	1,79	34,30
Essential hypertension	19,81	1,79	34,18
Obesity	34,34	1,66	31,84
Osteoarthritis	3,40	1,58	30,15
Other specified and unspecified disorders of the e	4,68	1,57	30,05
Esophageal disorders	13,00	1,53	29,20
Other specified and unspecified gastrointestinal d	3,89	1,52	29,03
Nerve and nerve root disorders	5,20	1,49	28,50
Asthma	15,40	1,46	27,87
Other specified and unspecified nutritional and m	11,47	1,45	27,76
Other specified and unspecified upper respiratory	33,20	1,45	27,75
Chromosomal abnormalities	3,66	1,43	27,27
Miscellaneous mental and behavioral disorders/cc	4,48	1,41	26,91
Conduction disorders	4,43	1,27	24,29
Nutritional deficiencies	2,55	1,24	23,80
Parkinson`s disease	2,72	1,20	23,02
Diseases of white blood cells	5,28	1,20	22,87
Spondylopathies/spondyloarthropathy (including	8,72	1,15	21,97
Disorders of teeth and gingiva	13,20	1,15	21,96
Sleep wake disorders	14,09	1,14	21,89
Neoplasia (general)	4,00	1,11	21,29
Other specified inflammatory condition of skin	8,28	1,09	20,86
Hearing loss	5,46	1,02	19,56
Personality disorders	2,45	0,99	18,99
Disruptive, impulse-control and conduct disorders	7,30	0,99	18,89
Schizophrenia spectrum and other psychotic disor	12,32	0,98	18,67
Symptoms of mental and substance use condition	5,00	0,92	17,58
Obsessive-compulsive and related disorders	2,34	0,91	17,44
Hepatitis	1,86	0,91	17,34
Alcohol-related disorders	4,71	0,85	16,27
Epilepsy; convulsions	10,36	0,85	16,22
Trauma- and stressor-related disorders	3,89	0,84	16,12
Neurodevelopmental disorders	15,01	0,84	16,08
Depressive disorders	6,09	0,80	15,34
Scoliosis and other postural dorsopathic deformiti	4,66	0,78	14,97
Urinary incontinence	6,12	0,76	14,61
Anxiety and fear-related disorders	25,25	0,76	14,52
Other specified joint disorders	7,04	0,69	13,25
Headache; including migraine	5,07	0,64	12,28
Acute and chronic tonsillitis	1,66	0,56	10,67
Paralysis (other than cerebral palsy)	1,36	0,51	9,77
Cerebral palsy	0,85	0,30	5,68
Cannabis-related disorders	1,06	0,23	4,41
Other specified nervous system disorders	0,28	0,13	2,50
Stimulant-related disorders	0,23	0,06	1,11

Trauma and anxiety			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Headache; including migraine	10,89	1,38	85,19
Acute and chronic tonsillitis	4,01	1,35	83,32
Other specified joint disorders	13,27	1,31	80,70
Trauma- and stressor-related disorders	5,76	1,25	77,09
Spondylopathies/spondyloarthropathy (including	9,40	1,24	76,48
Nerve and nerve root disorders	3,86	1,11	68,40
Anxiety and fear-related disorders	35,78	1,08	66,52
Other specified inflammatory condition of skin	8,14	1,07	66,25
Other specified and unspecified gastrointestinal d	2,70	1,05	65,05
Hearing loss	5,61	1,05	64,93
Asthma	10,85	1,03	63,45
Scoliosis and other postural dorsopathic deformiti	5,85	0,98	60,69
Diseases of white blood cells	4,25	0,96	59,51
Other specified and unspecified upper respiratory	21,38	0,93	57,73
Obesity	18,40	0,89	55,14
Conduction disorders	3,01	0,86	53,30
Sleep wake disorders	10,39	0,84	52,13
Osteoarthritis	1,80	0,84	51,73
Cardiac dysrhythmias	2,18	0,82	50,48
Depressive disorders	6,14	0,81	50,00
Esophageal disorders	6,83	0,80	49,57
Disorders of lipid metabolism	10,52	0,80	49,51
Other specified and unspecified nutritional and m	6,13	0,78	47,93
Essential hypertension	8,40	0,76	46,86
Miscellaneous mental and behavioral disorders/cc	2,19	0,69	42,63
Disorders of teeth and gingiva	7,63	0,66	41,05
Neoplasia (general)	2,34	0,65	40,33
Other specified and unspecified liver disease	2,27	0,55	34,13
Other specified and unspecified disorders of the e	1,63	0,55	33,76
Diabetes mellitus without complication	2,40	0,54	33,56
Thyroid disorders	3,88	0,53	32,89
Nutritional deficiencies	1,04	0,51	31,32
Obsessive-compulsive and related disorders	1,02	0,40	24,58
Cannabis-related disorders	1,82	0,39	24,41
Paralysis (other than cerebral palsy)	0,96	0,36	22,13
Chromosomal abnormalities	0,91	0,35	21,84
Other specified nervous system disorders	0,67	0,31	19,18
Neurodevelopmental disorders	5,35	0,30	18,53
Alcohol-related disorders	1,65	0,30	18,43
Schizophrenia spectrum and other psychotic disor	3,56	0,28	17,43
Epilepsy; convulsions	2,89	0,24	14,63
Hepatitis	0,38	0,19	11,55
Urinary incontinence	1,40	0,18	10,85
Disruptive, impulse-control and conduct disorders	1,19	0,16	9,93
Personality disorders	0,30	0,12	7,45
Symptoms of mental and substance use condition	0,31	0,06	3,57
Cerebral palsy	0,16	0,06	3,42
Stimulant-related disorders	0,10	0,02	1,51
Parkinson`s disease	0,00	0,00	0,02

Females, 21-45 (1 out of 3)

Neurodevelopmental disorders			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Neurodevelopmental disorders	73,79	15,62	89,02
Epilepsy; convulsions	47,66	15,53	88,52
Urinary incontinence	42,32	6,43	36,65
Pituitary disorders	7,34	2,42	13,81
Disorders of teeth and gingiva	18,75	2,13	12,14
Scoliosis and other postural dorsopathic deformiti	16,06	2,09	11,93
Diseases of white blood cells	7,11	2,05	11,68
Hearing loss	7,84	1,75	9,97
Esophageal disorders	9,09	1,72	9,79
Sleep wake disorders	11,16	1,48	8,43
Diabetes mellitus without complication	3,53	1,33	7,56
Other specified and unspecified nutritional and m	5,08	1,14	6,51
Disorders of lipid metabolism	5,53	1,05	5,96
Other specified inflammatory condition of skin	9,24	0,99	5,65
Other specified and unspecified upper respiratory	19,49	0,90	5,15
Obesity	19,65	0,88	5,01
Menstrual disorders	13,78	0,83	4,74
Feeding and eating disorders	1,67	0,81	4,62
Essential hypertension	4,46	0,79	4,49
Asthma	8,24	0,71	4,02
Thyroid disorders	13,59	0,68	3,87
Coagulation and hemorrhagic disorders	1,39	0,64	3,63
Acute and chronic tonsillitis	1,67	0,64	3,62
Anxiety and fear-related disorders	28,41	0,64	3,62
Complications specified during childbirth	1,87	0,51	2,94
Other specified and unspecified endocrine disorde	3,18	0,51	2,91
Depressive disorders	6,00	0,51	2,89
Headache; including migraine	8,95	0,41	2,33
Other specified female genital disorders	1,44	0,39	2,24
Other specified and unspecified liver disease	0,77	0,37	2,10
Nerve and nerve root disorders	2,13	0,33	1,90
Nutritional deficiencies	0,75	0,33	1,89
Trauma- and stressor-related disorders	2,46	0,31	1,76
Other specified joint disorders	1,50	0,22	1,25
Female infertility	1,72	0,21	1,21
Other specified and unspecified gastrointestinal d	0,81	0,20	1,15
Gastritis and duodenitis	0,24	0,12	0,66
Complications specified during the puerperium	0,80	0,08	0,46
Spondylopathies/spondyloarthropathy (including	0,19	0,03	0,18
Neoplasia (general)	0,07	0,02	0,10
Acquired foot deformities	0,03	0,01	0,07
Endometriosis	0,02	0,01	0,04
Other specified complications in pregnancy	0,00	0,00	0,01

Gynecological disorders			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Complications specified during childbirth	46,66	12,84	90,17
Other specified complications in pregnancy	32,96	12,18	85,57
Coagulation and hemorrhagic disorders	16,10	7,38	51,87
Complications specified during the puerperium	40,47	4,06	28,50
Obesity	69,79	3,12	21,95
Other specified and unspecified liver disease	4,56	2,17	15,27
Female infertility	15,32	1,90	13,32
Gastritis and duodenitis	3,23	1,57	11,01
Other specified and unspecified endocrine disorde	7,72	1,24	8,72
Nutritional deficiencies	2,72	1,20	8,46
Diabetes mellitus without complication	2,92	1,10	7,70
Disorders of teeth and gingiva	9,45	1,07	7,54
Thyroid disorders	18,90	0,94	6,63
Other specified female genital disorders	3,20	0,87	6,11
Diseases of white blood cells	2,98	0,86	6,02
Asthma	9,88	0,85	5,95
Menstrual disorders	13,87	0,84	5,88
Urinary incontinence	5,45	0,83	5,82
Nerve and nerve root disorders	5,25	0,82	5,78
Scoliosis and other postural dorsopathic deformiti	6,22	0,81	5,69
Esophageal disorders	4,27	0,81	5,67
Endometriosis	1,95	0,80	5,64
Headache; including migraine	17,50	0,80	5,62
Trauma- and stressor-related disorders	5,91	0,74	5,22
Other specified inflammatory condition of skin	6,60	0,71	4,97
Other specified and unspecified nutritional and m	3,12	0,70	4,93
Anxiety and fear-related disorders	30,60	0,68	4,81
Disorders of lipid metabolism	3,34	0,63	4,44
Sleep wake disorders	4,46	0,59	4,15
Pituitary disorders	1,76	0,58	4,08
Other specified and unspecified upper respiratory	12,25	0,57	3,99
Acquired foot deformities	1,29	0,49	3,46
Spondylopathies/spondyloarthropathy (including	2,82	0,47	3,31
Hearing loss	2,10	0,47	3,30
Depressive disorders	5,38	0,45	3,19
Other specified and unspecified gastrointestinal d	1,47	0,36	2,55
Other specified joint disorders	2,19	0,32	2,26
Essential hypertension	1,75	0,31	2,18
Neoplasia (general)	1,21	0,29	2,07
Feeding and eating disorders	0,58	0,28	1,99
Neurodevelopmental disorders	1,30	0,28	1,93
Epilepsy; convulsions	0,72	0,24	1,65
Acute and chronic tonsillitis	0,07	0,03	0,18

Females, 21-45 (2 out of 3)

DM and cardiovascular risk factors			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Diabetes mellitus without complication	26,39	9,90	83,57
Essential hypertension	52,60	9,30	78,53
Disorders of lipid metabolism	32,65	6,17	52,10
Other specified and unspecified liver disease	11,37	5,41	45,69
Nutritional deficiencies	10,81	4,78	40,35
Other specified and unspecified nutritional and m	17,98	4,05	34,15
Obesity	54,95	2,46	20,77
Other specified and unspecified endocrine disorde	14,23	2,29	19,32
Nerve and nerve root disorders	11,15	1,75	14,75
Depressive disorders	19,87	1,68	14,18
Thyroid disorders	32,42	1,62	13,66
Pituitary disorders	4,85	1,60	13,53
Other specified joint disorders	10,89	1,59	13,46
Other specified female genital disorders	5,83	1,59	13,39
Neoplasia (general)	6,43	1,56	13,17
Diseases of white blood cells	4,91	1,41	11,94
Sleep wake disorders	10,65	1,41	11,90
Menstrual disorders	22,92	1,38	11,69
Esophageal disorders	7,05	1,33	11,24
Acute and chronic tonsillitis	3,39	1,29	10,89
Headache; including migraine	27,96	1,28	10,78
Hearing loss	5,60	1,25	10,54
Asthma	14,05	1,20	10,16
Spondylopathies/spondyloarthropathy (including	7,12	1,19	10,05
Other specified complications in pregnancy	3,19	1,18	9,95
Other specified and unspecified gastrointestinal d	4,43	1,10	9,27
Anxiety and fear-related disorders	46,80	1,05	8,84
Acquired foot deformities	2,71	1,03	8,72
Urinary incontinence	6,19	0,94	7,94
Disorders of teeth and gingiva	8,25	0,94	7,91
Other specified and unspecified upper respiratory	18,66	0,87	7,30
Other specified inflammatory condition of skin	7,77	0,83	7,03
Endometriosis	1,79	0,74	6,23
Female infertility	5,65	0,70	5,91
Epilepsy; convulsions	1,76	0,57	4,84
Coagulation and hemorrhagic disorders	1,18	0,54	4,58
Trauma- and stressor-related disorders	4,23	0,53	4,49
Scoliosis and other postural dorsopathic deformiti	3,85	0,50	4,23
Gastritis and duodenitis	0,97	0,47	3,98
Feeding and eating disorders	0,72	0,35	2,96
Neurodevelopmental disorders	1,50	0,32	2,68
Complications specified during the puerperium	2,99	0,30	2,53
Complications specified during childbirth	0,10	0,03	0,24

Psychosomatic			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Gastritis and duodenitis	7,58	3,68	79,04
Trauma- and stressor-related disorders	26,04	3,27	70,29
Acquired foot deformities	8,32	3,17	68,07
Sleep wake disorders	23,33	3,09	66,34
Depressive disorders	36,14	3,05	65,59
Other specified joint disorders	14,86	2,18	46,76
Neoplasia (general)	8,60	2,09	44,84
Esophageal disorders	10,46	1,98	42,46
Spondylopathies/spondyloarthropathy (including	10,84	1,81	38,95
Nerve and nerve root disorders	11,29	1,77	38,01
Anxiety and fear-related disorders	73,71	1,65	35,41
Other specified and unspecified liver disease	3,33	1,58	34,03
Feeding and eating disorders	3,15	1,53	32,81
Endometriosis	3,44	1,42	30,50
Headache; including migraine	29,35	1,34	28,80
Urinary incontinence	8,19	1,24	26,71
Disorders of teeth and gingiva	10,84	1,23	26,45
Hearing loss	5,13	1,14	24,56
Nutritional deficiencies	2,54	1,12	24,08
Other specified female genital disorders	3,90	1,06	22,82
Coagulation and hemorrhagic disorders	2,15	0,99	21,19
Other specified and unspecified gastrointestinal d	3,91	0,97	20,80
Other specified and unspecified upper respiratory	19,71	0,91	19,62
Other specified inflammatory condition of skin	7,63	0,82	17,57
Acute and chronic tonsillitis	2,11	0,81	17,29
Asthma	9,17	0,79	16,87
Thyroid disorders	15,66	0,78	16,79
Menstrual disorders	12,71	0,77	16,48
Diseases of white blood cells	2,37	0,68	14,66
Female infertility	5,43	0,67	14,43
Scoliosis and other postural dorsopathic deformiti	5,01	0,65	14,03
Obesity	14,15	0,63	13,61
Other specified and unspecified endocrine disorde	3,89	0,63	13,44
Other specified and unspecified nutritional and m	2,60	0,58	12,56
Complications specified during the puerperium	5,48	0,55	11,80
Disorders of lipid metabolism	2,23	0,42	9,05
Pituitary disorders	1,19	0,39	8,42
Essential hypertension	1,28	0,23	4,87
Epilepsy; convulsions	0,67	0,22	4,66
Complications specified during childbirth	0,74	0,20	4,37
Other specified complications in pregnancy	0,38	0,14	3,00
Neurodevelopmental disorders	0,56	0,12	2,53
Diabetes mellitus without complication	0,04	0,02	0,35

Females, 21-45 (3 out of 3)

Unspecific			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Acute and chronic tonsillitis	3,11	1,19	68,02
Other specified and unspecified gastrointestinal d	4,66	1,15	66,23
Female infertility	9,17	1,14	65,13
Other specified inflammatory condition of skin	10,54	1,13	64,79
Scoliosis and other postural dorsopathic deformiti	8,58	1,12	64,11
Other specified and unspecified upper respiratory	24,04	1,11	63,93
Asthma	12,82	1,10	63,00
Menstrual disorders	17,67	1,07	61,21
Pituitary disorders	3,18	1,05	60,16
Thyroid disorders	20,63	1,03	59,06
Feeding and eating disorders	2,07	1,00	57,61
Endometriosis	2,43	1,00	57,59
Complications specified during the puerperium	9,87	0,99	56,72
Diseases of white blood cells	3,37	0,97	55,70
Other specified and unspecified endocrine disorde	6,03	0,97	55,61
Other specified female genital disorders	3,55	0,97	55,44
Headache; including migraine	20,03	0,91	52,47
Hearing loss	4,04	0,90	51,63
Spondylopathies/spondyloarthropathy (including	4,95	0,83	47,51
Anxiety and fear-related disorders	36,89	0,83	47,32
Disorders of teeth and gingiva	7,06	0,80	45,96
Other specified and unspecified nutritional and m	3,24	0,73	41,84
Neoplasia (general)	2,86	0,69	39,83
Nerve and nerve root disorders	4,40	0,69	39,56
Obesity	15,05	0,67	38,66
Other specified joint disorders	4,32	0,63	36,26
Esophageal disorders	2,84	0,54	30,83
Disorders of lipid metabolism	2,62	0,50	28,45
Nutritional deficiencies	0,99	0,44	25,23
Urinary incontinence	2,63	0,40	22,88
Acquired foot deformities	0,90	0,34	19,68
Coagulation and hemorrhagic disorders	0,71	0,33	18,74
Trauma- and stressor-related disorders	2,53	0,32	18,24
Depressive disorders	2,92	0,25	14,15
Essential hypertension	0,98	0,17	9,93
Sleep wake disorders	1,21	0,16	9,18
Gastritis and duodenitis	0,19	0,09	5,31
Neurodevelopmental disorders	0,32	0,07	3,85
Other specified and unspecified liver disease	0,11	0,05	2,91
Complications specified during childbirth	0,14	0,04	2,28
Other specified complications in pregnancy	0,07	0,03	1,47
Diabetes mellitus without complication	0,04	0,01	0,82
Epilepsy; convulsions	0,02	0,01	0,33

Males, 46-65 (1 out of 3)

Cardiovascular diseases			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Myocarditis and cardiomyopathy	37,97	16,49	66,80
Heart failure	64,43	12,18	49,33
Other and ill-defined heart disease	37,66	10,81	43,77
Nonrheumatic and unspecified valve disord	33,57	10,37	42,01
Acute myocardial infarction	35,87	8,24	33,35
Coronary atherosclerosis and other heart di	67,61	7,05	28,57
Cardiac dysrhythmias	47,90	5,66	22,92
Conduction disorders	33,90	5,62	22,75
Peripheral and visceral vascular disease	30,16	4,57	18,52
Chronic kidney disease	26,88	4,19	16,98
Diabetes mellitus with complication	22,04	3,89	15,76
Chronic obstructive pulmonary disease and	40,83	3,15	12,78
Other specified and unspecified endocrine d	6,77	2,94	11,91
Obsessive-compulsive and related disorders	6,02	2,84	11,52
Hypertension with complications and secon	7,72	2,82	11,42
Other specified hereditary and degenerativ	5,75	2,80	11,33
Asthma	12,94	2,77	11,23
Diabetes mellitus without complication	47,20	2,51	10,17
Symptoms of mental and substance use cor	8,70	2,41	9,77
Non-pressure ulcer of skin	7,13	2,39	9,66
Disruptive, impulse-control and conduct dis	8,89	2,38	9,64
Chromosomal abnormalities	5,02	2,37	9,61
Thyroid disorders	19,57	2,37	9,58
Pressure ulcer of skin	4,98	2,22	9,01
Malnutrition	5,79	2,22	8,97
Neurocognitive disorders	9,42	2,16	8,76
Sleep wake disorders	48,45	2,08	8,41
Nerve and nerve root disorders	12,08	2,06	8,36
Gastritis and duodenitis	8,56	1,94	7,84
Gastroduodenal ulcer	6,79	1,92	7,76
Disorders of lipid metabolism	64,42	1,89	7,65
Alcohol-related disorders	17,73	1,89	7,64
Obesity	53,92	1,84	7,43
Scoliosis and other postural dorsopathic del	5,42	1,81	7,34
Spondylopathies/spondyloarthropathy (incl	27,92	1,77	7,16
Depressive disorders	18,97	1,64	6,64
Essential hypertension	68,24	1,61	6,51
Urinary incontinence	17,59	1,56	6,32
Miscellaneous mental and behavioral disorc	6,88	1,54	6,22
Cataract and other lens disorders	9,99	1,52	6,14
Cerebral infarction	4,33	1,42	5,75
Coagulation and hemorrhagic disorders	4,65	1,31	5,31
Disorders of teeth and gingiva	14,86	1,30	5,28
Schizophrenia spectrum and other psychoti	9,34	1,29	5,24
Other specified inflammatory condition of s	9,72	1,29	5,23
Hearing loss	12,35	1,29	5,22
Hyperplasia of prostate	17,77	1,27	5,14
Neurodevelopmental disorders	15,04	1,25	5,05
Other specified and unspecified upper respi	19,37	1,25	5,04
Gout	7,71	1,16	4,69
Osteoarthritis	15,10	1,16	4,68
Paralysis (other than cerebral palsy)	4,19	1,10	4,47
Other specified nervous system disorders	2,38	1,09	4,42
Other specified and unspecified nutritional	20,54	1,08	4,38
Esophageal disorders	11,59	1,06	4,29
Other specified and unspecified liver diseas	13,65	1,02	4,15
Nutritional deficiencies	3,31	1,02	4,14
Myopathies	2,29	1,02	4,13
Neoplasia (general)	16,82	0,99	4,02
Anxiety and fear-related disorders	24,99	0,94	3,82
Epilepsy; convulsions	7,39	0,83	3,36
Diverticulosis and diverticulitis	4,23	0,80	3,24
Hepatitis	3,57	0,72	2,90
Trauma- and stressor-related disorders	3,60	0,71	2,86
Glaucoma	2,96	0,69	2,79
Digestive congenital anomalies	1,75	0,61	2,48
Hematologic neoplasia	1,53	0,56	2,27
Other specified joint disorders	6,83	0,55	2,23
Diseases of white blood cells	2,14	0,42	1,70
Headache; including migraine	1,34	0,28	1,15

Cognitive-motor disorders			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Myopathies	30,18	13,47	66,66
Pressure ulcer of skin	24,98	11,15	55,17
Paralysis (other than cerebral palsy)	39,31	10,36	51,24
Malnutrition	26,20	10,03	49,61
Cerebral infarction	30,51	10,01	49,52
Other specified nervous system disorders	20,00	9,18	45,43
Neurocognitive disorders	24,77	5,69	28,14
Coagulation and hemorrhagic disorders	13,27	3,74	18,51
Diseases of white blood cells	16,16	3,17	15,67
Glaucoma	12,19	2,84	14,05
Gastroduodenal ulcer	9,43	2,66	13,16
Diabetes mellitus with complication	14,90	2,63	13,02
Urinary incontinence	28,15	2,50	12,37
Neoplasia (general)	41,63	2,46	12,17
Other specified hereditary and degenerativ	5,03	2,45	12,12
Non-pressure ulcer of skin	7,18	2,40	11,89
Hematologic neoplasia	6,57	2,40	11,88
Miscellaneous mental and behavioral disorc	9,89	2,21	10,92
Cardiac dysrhythmias	18,29	2,16	10,69
Nutritional deficiencies	6,83	2,11	10,44
Hepatitis	10,23	2,06	10,17
Chronic obstructive pulmonary disease and	26,40	2,04	10,09
Trauma- and stressor-related disorders	10,16	1,99	9,86
Esophageal disorders	19,52	1,78	8,82
Epilepsy; convulsions	15,31	1,72	8,51
Alcohol-related disorders	16,09	1,71	8,47
Diabetes mellitus without complication	29,38	1,56	7,74
Other specified and unspecified nutritional	28,22	1,49	7,36
Hypertension with complications and secon	4,06	1,48	7,33
Depressive disorders	16,10	1,39	6,88
Peripheral and visceral vascular disease	8,91	1,35	6,68
Other specified and unspecified liver diseas	17,83	1,34	6,63
Gastritis and duodenitis	5,74	1,30	6,43
Chronic kidney disease	8,26	1,29	6,38
Disruptive, impulse-control and conduct dis	4,71	1,26	6,25
Scoliosis and other postural dorsopathic del	3,70	1,24	6,13
Hyperplasia of prostate	17,28	1,23	6,11
Thyroid disorders	10,00	1,21	5,98
Nerve and nerve root disorders	6,78	1,16	5,74
Nonrheumatic and unspecified valve disord	3,73	1,15	5,71
Cataract and other lens disorders	7,29	1,11	5,47
Essential hypertension	46,90	1,11	5,47
Disorders of lipid metabolism	37,68	1,10	5,47
Gout	7,25	1,09	5,38
Anxiety and fear-related disorders	27,69	1,04	5,17
Other specified and unspecified endocrine d	2,24	0,97	4,81
Conduction disorders	5,67	0,94	4,65
Coronary atherosclerosis and other heart di	8,42	0,88	4,35
Obesity	23,52	0,80	3,96
Symptoms of mental and substance use cor	2,84	0,79	3,90
Hearing loss	7,48	0,78	3,86
Acute myocardial infarction	3,28	0,75	3,73
Other specified inflammatory condition of s	5,66	0,75	3,72
Spondylopathies/spondyloarthropathy (incl	11,81	0,75	3,70
Disorders of teeth and gingiva	8,28	0,73	3,60
Diverticulosis and diverticulitis	3,71	0,70	3,47
Sleep wake disorders	14,67	0,63	3,11
Obsessive-compulsive and related disorders	1,09	0,52	2,56
Other specified and unspecified upper respi	7,68	0,49	2,44
Neurodevelopmental disorders	5,83	0,48	2,39
Heart failure	2,55	0,48	2,39
Headache; including migraine	2,20	0,47	2,30
Osteoarthritis	5,83	0,45	2,21
Other specified joint disorders	3,94	0,32	1,57
Asthma	1,39	0,30	1,47
Schizophrenia spectrum and other psychoti	0,89	0,12	0,61
Other and ill-defined heart disease	0,17	0,05	0,24
Digestive congenital anomalies	0,04	0,02	0,07
Myocarditis and cardiomyopathy	0,01	0,00	0,01
Chromosomal abnormalities	0,00	0,00	0,00

Males, 46-65 (2 out of 3)

Diabetes and liver disease			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Diabetes mellitus with complication	57,16	10,09	60,67
Chronic kidney disease	42,65	6,65	40,00
Non-pressure ulcer of skin	19,35	6,48	38,93
Other specified and unspecified endocrine d	14,61	6,35	38,14
Peripheral and visceral vascular disease	37,01	5,61	33,72
Hypertension with complications and secon	15,21	5,55	33,38
Nutritional deficiencies	15,14	4,68	28,13
Heart failure	24,21	4,58	27,51
Diabetes mellitus without complication	82,30	4,38	26,32
Hepatitis	18,35	3,69	22,16
Alcohol-related disorders	34,61	3,68	22,14
Coronary atherosclerosis and other heart di	34,55	3,61	21,67
Gout	20,50	3,08	18,51
Cerebral infarction	9,22	3,02	18,17
Other specified and unspecified liver diseas	38,08	2,86	17,19
Chronic obstructive pulmonary disease and	34,69	2,68	16,11
Acute myocardial infarction	11,52	2,65	15,90
Myocarditis and cardiomyopathy	5,75	2,50	15,01
Other and ill-defined heart disease	8,34	2,39	14,38
Neurocognitive disorders	10,03	2,30	13,84
Hematologic neoplasia	5,74	2,10	12,60
Obesity	59,64	2,03	12,20
Cataract and other lens disorders	12,92	1,96	11,77
Essential hypertension	82,17	1,94	11,64
Cardiac dysrhythmias	15,62	1,85	11,09
Disorders of lipid metabolism	61,60	1,81	10,86
Depressive disorders	20,49	1,77	10,64
Esophageal disorders	19,06	1,74	10,46
Neoplasia (general)	28,82	1,70	10,23
Coagulation and hemorrhagic disorders	5,97	1,68	10,12
Thyroid disorders	13,94	1,68	10,12
Other specified and unspecified nutritional	31,54	1,66	9,99
Conduction disorders	9,66	1,60	9,62
Malnutrition	4,09	1,57	9,41
Pressure ulcer of skin	3,48	1,55	9,35
Sleep wake disorders	34,79	1,49	8,96
Diverticulosis and diverticulitis	7,84	1,48	8,91
Other specified nervous system disorders	3,09	1,42	8,53
Miscellaneous mental and behavioral disorc	5,96	1,33	8,00
Nerve and nerve root disorders	7,72	1,32	7,93
Diseases of white blood cells	6,71	1,31	7,90
Other specified joint disorders	16,17	1,31	7,85
Nonrheumatic and unspecified valve disord	3,81	1,18	7,07
Osteoarthritis	14,76	1,13	6,79
Other specified inflammatory condition of s	8,29	1,10	6,62
Disorders of teeth and gingiva	12,54	1,10	6,62
Gastritis and duodenitis	4,69	1,06	6,38
Glaucoma	4,36	1,02	6,10
Paralysis (other than cerebral palsy)	3,75	0,99	5,94
Digestive congenital anomalies	2,78	0,97	5,85
Spondylopathies/spondyloarthropathy (incl	14,78	0,93	5,62
Asthma	4,26	0,91	5,48
Hearing loss	7,63	0,80	4,78
Urinary incontinence	8,75	0,78	4,67
Other specified hereditary and degenerative	1,56	0,76	4,58
Hyperplasia of prostate	10,66	0,76	4,58
Gastroduodenal ulcer	2,56	0,72	4,34
Anxiety and fear-related disorders	19,09	0,72	4,33
Myopathies	1,28	0,57	3,44
Trauma- and stressor-related disorders	2,90	0,57	3,41
Scoliosis and other postural dorsopathic del	1,35	0,45	2,71
Symptoms of mental and substance use cor	1,53	0,42	2,55
Other specified and unspecified upper respi	4,70	0,30	1,82
Headache; including migraine	1,30	0,28	1,65
Epilepsy; convulsions	1,77	0,20	1,19
Disruptive, impulse-control and conduct dis	0,71	0,19	1,14
Obsessive-compulsive and related disorders	0,39	0,18	1,11
Schizophrenia spectrum and other psychoti	1,17	0,16	0,98
Chromosomal abnormalities	0,16	0,08	0,46
Neurodevelopmental disorders	0,37	0,03	0,19

Neuropsychiatric			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Chromosomal abnormalities	16,50	7,80	84,58
Neurodevelopmental disorders	90,47	7,49	81,29
Disruptive, impulse-control and conduct dis	26,98	7,23	78,37
Symptoms of mental and substance use cor	24,51	6,79	73,68
Epilepsy; convulsions	54,24	6,10	66,12
Schizophrenia spectrum and other psychoti	43,66	6,05	65,61
Obsessive-compulsive and related disorders	12,62	5,96	64,70
Urinary incontinence	53,13	4,72	51,17
Scoliosis and other postural dorsopathic del	12,80	4,29	46,50
Paralysis (other than cerebral palsy)	11,72	3,09	33,48
Non-pressure ulcer of skin	7,28	2,44	26,44
Neurocognitive disorders	10,48	2,40	26,09
Pressure ulcer of skin	4,85	2,16	23,46
Other specified nervous system disorders	4,10	1,88	20,41
Disorders of teeth and gingiva	20,55	1,80	19,58
Nutritional deficiencies	5,43	1,68	18,20
Cataract and other lens disorders	9,65	1,46	15,88
Thyroid disorders	9,90	1,20	12,98
Digestive congenital anomalies	3,37	1,18	12,76
Other specified and unspecified upper respi	17,93	1,15	12,50
Other specified hereditary and degenerative	2,14	1,04	11,31
Hepatitis	4,92	0,99	10,72
Anxiety and fear-related disorders	25,83	0,97	10,57
Hyperplasia of prostate	12,69	0,91	9,83
Sleep wake disorders	20,63	0,88	9,59
Nonrheumatic and unspecified valve disord	2,59	0,80	8,67
Coagulation and hemorrhagic disorders	2,72	0,77	8,31
Esophageal disorders	8,28	0,76	8,20
Other specified inflammatory condition of s	5,63	0,75	8,11
Hearing loss	7,06	0,74	7,99
Other specified and unspecified endocrine d	1,61	0,70	7,57
Other specified and unspecified nutritional	11,42	0,60	6,52
Diseases of white blood cells	2,88	0,56	6,12
Depressive disorders	6,50	0,56	6,09
Glaucoma	2,18	0,51	5,50
Miscellaneous mental and behavioral disorc	2,14	0,48	5,19
Conduction disorders	2,87	0,47	5,15
Peripheral and visceral vascular disease	2,76	0,42	4,54
Essential hypertension	17,37	0,41	4,44
Cerebral infarction	1,12	0,37	3,98
Other specified joint disorders	4,17	0,34	3,65
Osteoarthritis	4,39	0,34	3,65
Chronic kidney disease	2,14	0,33	3,63
Other and ill-defined heart disease	1,08	0,31	3,35
Disorders of lipid metabolism	9,89	0,29	3,15
Chronic obstructive pulmonary disease and	3,49	0,27	2,93
Malnutrition	0,68	0,26	2,83
Obesity	7,57	0,26	2,80
Gastritis and duodenitis	1,02	0,23	2,51
Cardiac dysrhythmias	1,71	0,20	2,19
Other specified and unspecified liver diseas	2,67	0,20	2,18
Alcohol-related disorders	1,83	0,19	2,11
Gastroduodenal ulcer	0,56	0,16	1,72
Heart failure	0,80	0,15	1,64
Spondylopathies/spondyloarthropathy (incl	1,90	0,12	1,31
Headache; including migraine	0,57	0,12	1,30
Diabetes mellitus without complication	2,25	0,12	1,30
Diverticulosis and diverticulitis	0,63	0,12	1,29
Asthma	0,53	0,11	1,22
Diabetes mellitus with complication	0,60	0,11	1,15
Neoplasia (general)	1,66	0,10	1,07
Nerve and nerve root disorders	0,51	0,09	0,95
Gout	0,51	0,08	0,84
Coronary atherosclerosis and other heart di	0,22	0,02	0,25
Trauma- and stressor-related disorders	0,09	0,02	0,20
Hypertension with complications and secon	0,02	0,01	0,09
Myocarditis and cardiomyopathy	0,02	0,01	0,07
Acute myocardial infarction	0,01	0,00	0,02
Myopathies	0,00	0,00	0,01
Hematologic neoplasia	0,00	0,00	0,00

Males, 46-65 (3 out of 3)

CV risk factors - COPD - Neoplasia			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Gastritis and duodenitis	13,40	3,03	59,57
Depressive disorders	31,24	2,70	53,02
Osteoarthritis	34,67	2,65	52,12
Nerve and nerve root disorders	14,40	2,46	48,36
Trauma- and stressor-related disorders	11,99	2,35	46,14
Digestive congenital anomalies	6,67	2,33	45,81
Asthma	10,17	2,18	42,81
Gout	14,21	2,13	41,93
Esophageal disorders	22,40	2,05	40,18
Sleep wake disorders	46,66	2,00	39,28
Other specified and unspecified liver diseas	26,39	1,98	38,93
Spondylopathies/spondyloarthropathy (incl	30,42	1,92	37,81
Gastroduodenal ulcer	6,75	1,90	37,41
Chronic obstructive pulmonary disease and	23,71	1,83	35,99
Alcohol-related disorders	17,21	1,83	35,99
Miscellaneous mental and behavioral disorc	8,19	1,83	35,91
Diverticulosis and diverticulitis	9,39	1,77	34,86
Obesity	50,22	1,71	33,59
Other specified joint disorders	20,87	1,69	33,12
Headache; including migraine	7,97	1,68	33,09
Anxiety and fear-related disorders	43,68	1,65	32,37
Cataract and other lens disorders	10,80	1,64	32,18
Other specified inflammatory condition of s	12,16	1,61	31,72
Other specified hereditary and degenerative	3,21	1,56	30,74
Hyperplasia of prostate	21,62	1,54	30,33
Conduction disorders	9,22	1,53	30,01
Disorders of lipid metabolism	51,15	1,50	29,47
Other specified and unspecified nutritional	27,03	1,42	27,98
Diseases of white blood cells	6,93	1,36	26,69
Other specified and unspecified upper respi	20,68	1,33	26,11
Essential hypertension	55,42	1,31	25,65
Hearing loss	12,21	1,27	25,02
Glaucoma	5,38	1,25	24,62
Hypertension with complications and secon	3,42	1,25	24,52
Neoplasia (general)	20,63	1,22	23,94
Hematologic neoplasia	3,32	1,21	23,83
Cardiac dysrhythmias	10,20	1,21	23,68
Diabetes mellitus without complication	22,42	1,19	23,44
Disorders of teeth and gingiva	12,99	1,14	22,40
Other and ill-defined heart disease	3,86	1,11	21,74
Coagulation and hemorrhagic disorders	3,91	1,10	21,66
Acute myocardial infarction	4,75	1,09	21,44
Other specified and unspecified endocrine c	2,49	1,08	21,27
Coronary atherosclerosis and other heart di	10,23	1,07	20,98
Thyroid disorders	8,37	1,01	19,87
Peripheral and visceral vascular disease	6,43	0,97	19,14
Hepatitis	4,61	0,93	18,21
Chronic kidney disease	5,82	0,91	17,84
Obsessive-compulsive and related disorders	1,82	0,86	16,94
Nutritional deficiencies	2,73	0,84	16,60
Neurocognitive disorders	3,25	0,75	14,64
Urinary incontinence	7,50	0,67	13,08
Heart failure	3,49	0,66	12,97
Malnutrition	1,65	0,63	12,43
Myopathies	1,31	0,59	11,53
Scoliosis and other postural dorsopathic def	1,62	0,54	10,66
Other specified nervous system disorders	0,83	0,38	7,44
Nonrheumatic and unspecified valve disord	1,19	0,37	7,22
Epilepsy; convulsions	3,21	0,36	7,08
Schizophrenia spectrum and other psychoti	2,53	0,35	6,88
Cerebral infarction	0,86	0,28	5,52
Diabetes mellitus with complication	1,41	0,25	4,89
Non-pressure ulcer of skin	0,58	0,19	3,79
Neurodevelopmental disorders	2,31	0,19	3,76
Symptoms of mental and substance use con	0,58	0,16	3,18
Pressure ulcer of skin	0,30	0,14	2,67
Myocarditis and cardiomyopathy	0,22	0,10	1,89
Disruptive, impulse-control and conduct dis	0,33	0,09	1,72
Paralysis (other than cerebral palsy)	0,31	0,08	1,60
Chromosomal abnormalities	0,04	0,02	0,34

Unspecific			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Headache; including migraine	5,25	1,11	60,50
Hearing loss	9,34	0,97	53,12
Other specified and unspecified upper respi	14,87	0,96	52,09
Other specified joint disorders	11,72	0,95	51,58
Hematologic neoplasia	2,48	0,91	49,42
Neoplasia (general)	15,08	0,89	48,57
Diverticulosis and diverticulitis	4,68	0,89	48,24
Glaucoma	3,70	0,86	46,93
Essential hypertension	36,05	0,85	46,29
Other specified inflammatory condition of s	6,16	0,82	44,61
Spondylopathies/spondyloarthropathy (incl	12,88	0,81	44,41
Hyperplasia of prostate	11,31	0,81	44,02
Other specified and unspecified nutritional	15,24	0,80	43,77
Anxiety and fear-related disorders	21,28	0,80	43,75
Disorders of lipid metabolism	27,16	0,80	43,41
Disorders of teeth and gingiva	8,88	0,78	42,52
Diseases of white blood cells	3,93	0,77	41,93
Thyroid disorders	6,30	0,76	41,47
Obesity	21,57	0,73	40,02
Asthma	3,24	0,69	37,79
Trauma- and stressor-related disorders	3,51	0,69	37,53
Coagulation and hemorrhagic disorders	2,35	0,66	36,08
Hepatitis	3,27	0,66	35,83
Gastroduodenal ulcer	2,32	0,65	35,61
Miscellaneous mental and behavioral disorc	2,78	0,62	33,77
Digestive congenital anomalies	1,73	0,61	33,03
Diabetes mellitus without complication	10,70	0,57	31,03
Other specified and unspecified liver diseas	7,56	0,57	30,93
Sleep wake disorders	13,12	0,56	30,65
Osteoarthritis	7,33	0,56	30,56
Other specified hereditary and degenerative	1,13	0,55	29,91
Cardiac dysrhythmias	4,57	0,54	29,42
Nonrheumatic and unspecified valve disord	1,74	0,54	29,32
Nerve and nerve root disorders	3,08	0,53	28,67
Gout	3,50	0,53	28,65
Cataract and other lens disorders	3,46	0,52	28,57
Esophageal disorders	5,64	0,51	28,05
Conduction disorders	3,08	0,51	27,82
Scoliosis and other postural dorsopathic def	1,46	0,49	26,65
Acute myocardial infarction	2,04	0,47	25,57
Coronary atherosclerosis and other heart di	4,25	0,44	24,18
Alcohol-related disorders	4,08	0,43	23,65
Hypertension with complications and secon	1,17	0,43	23,26
Nutritional deficiencies	1,34	0,41	22,49
Chronic obstructive pulmonary disease and	5,25	0,41	22,11
Schizophrenia spectrum and other psychoti	2,74	0,38	20,68
Peripheral and visceral vascular disease	2,11	0,32	17,40
Gastritis and duodenitis	1,40	0,32	17,26
Cerebral infarction	0,95	0,31	17,07
Malnutrition	0,80	0,31	16,74
Depressive disorders	3,55	0,31	16,73
Other and ill-defined heart disease	1,06	0,30	16,51
Other specified and unspecified endocrine c	0,69	0,30	16,30
Myocarditis and cardiomyopathy	0,69	0,30	16,22
Chronic kidney disease	1,78	0,28	15,17
Myopathies	0,58	0,26	14,23
Other specified nervous system disorders	0,55	0,25	13,76
Epilepsy; convulsions	2,24	0,25	13,73
Urinary incontinence	2,56	0,23	12,39
Non-pressure ulcer of skin	0,51	0,17	9,29
Neurocognitive disorders	0,68	0,16	8,53
Neurodevelopmental disorders	1,62	0,13	7,32
Symptoms of mental and substance use cor	0,46	0,13	6,92
Heart failure	0,60	0,11	6,16
Chromosomal abnormalities	0,19	0,09	5,01
Diabetes mellitus with complication	0,47	0,08	4,50
Paralysis (other than cerebral palsy)	0,23	0,06	3,26
Obsessive-compulsive and related disorders	0,12	0,06	3,18
Disruptive, impulse-control and conduct dis	0,20	0,05	2,88
Pressure ulcer of skin	0,01	0,01	0,33

Females, 46-65 (1 out of 3)

DM - Cardiovascular diseases			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Heart failure	62,14	28,05	82,04
Diabetes mellitus with complication	37,86	15,26	44,63
Coronary atherosclerosis and other heart dis	30,15	14,48	42,35
Chronic kidney disease	31,96	14,43	42,19
Nonrheumatic and unspecified valve disorde	30,41	13,46	39,36
Cardiac dysrhythmias	59,06	13,33	38,99
Conduction disorders	31,08	11,31	33,09
Peripheral and visceral vascular disease	21,77	10,03	29,33
Diabetes mellitus without complication	59,48	5,86	17,15
Other specified and unspecified endocrine di	18,63	5,19	15,18
Chronic obstructive pulmonary disease and b	24,62	4,59	13,43
Osteoporosis	17,22	2,99	8,74
Cataract and other lens disorders	17,01	2,98	8,70
Asthma	25,36	2,89	8,46
Glaucoma	10,64	2,79	8,16
Other specified and unspecified liver disease	21,33	2,78	8,14
Essential hypertension	78,25	2,70	7,89
Disorders of lipid metabolism	63,10	2,61	7,63
Sleep wake disorders	42,40	2,47	7,21
Other specified and unspecified nutritional a	37,78	2,44	7,15
Nutritional deficiencies	15,25	2,34	6,85
Obesity	66,04	2,31	6,76
Diverticulosis and diverticulitis	7,55	2,27	6,65
Urinary incontinence	33,78	2,25	6,58
Osteoarthritis	40,47	2,17	6,35
Neoplasia (general)	23,75	1,94	5,68
Schizophrenia spectrum and other psychotic	5,55	1,90	5,55
Depressive disorders	38,27	1,90	5,55
Other specified inflammatory condition of sk	13,72	1,77	5,18
Hearing loss	11,53	1,63	4,76
Systemic lupus erythematosus and connectiv	3,99	1,61	4,70
Thyroid disorders	41,53	1,59	4,65
Esophageal disorders	14,33	1,50	4,40
Gastritis and duodenitis	5,63	1,38	4,04
Spondylopathies/spondyloarthropathy (inclu	20,79	1,34	3,92
Trauma- and stressor-related disorders	11,38	1,33	3,89
Other specified joint disorders	13,66	1,30	3,80
Disorders of teeth and gingiva	11,68	1,25	3,66
Prolapse of female genital organs	4,64	1,25	3,65
Diseases of white blood cells	4,52	1,19	3,47
Digestive congenital anomalies	3,03	1,07	3,12
Anxiety and fear-related disorders	43,55	1,00	2,93
Neurodevelopmental disorders	5,93	1,00	2,92
Nerve and nerve root disorders	8,86	0,68	1,98
Acquired foot deformities	4,18	0,61	1,77
Menopausal disorders	9,53	0,60	1,74
Headache; including migraine	7,67	0,57	1,67
Other specified and unspecified upper respira	9,06	0,55	1,60
Menstrual disorders	3,03	0,38	1,10
Epilepsy; convulsions	1,64	0,36	1,05
Scoliosis and other postural dorsopathic defc	1,61	0,33	0,97
Other specified and unspecified gastrointesti	0,10	0,04	0,10
Nonmalignant breast conditions	0,05	0,01	0,04

Neuropsychatric			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Neurodevelopmental disorders	88,48	14,90	79,49
Epilepsy; convulsions	60,53	13,26	70,75
Schizophrenia spectrum and other psychotic	35,67	12,20	65,06
Urinary incontinence	81,87	5,45	29,07
Scoliosis and other postural dorsopathic defc	19,01	3,90	20,80
Disorders of teeth and gingiva	23,28	2,49	13,28
Nutritional deficiencies	9,87	1,52	8,09
Esophageal disorders	14,10	1,48	7,90
Nonrheumatic and unspecified valve disorde	3,29	1,46	7,76
Chronic kidney disease	2,93	1,32	7,05
Other specified and unspecified endocrine di	4,25	1,19	6,32
Digestive congenital anomalies	3,33	1,18	6,27
Other specified and unspecified nutritional a	17,62	1,14	6,08
Cataract and other lens disorders	6,10	1,07	5,69
Sleep wake disorders	18,08	1,05	5,61
Chronic obstructive pulmonary disease and b	5,38	1,00	5,35
Osteoporosis	5,16	0,90	4,78
Obesity	25,06	0,88	4,68
Other specified inflammatory condition of sk	6,59	0,85	4,53
Depressive disorders	16,34	0,81	4,32
Hearing loss	5,67	0,80	4,27
Coronary atherosclerosis and other heart dis	1,60	0,77	4,11
Other specified and unspecified upper respira	12,54	0,76	4,05
Heart failure	1,67	0,75	4,01
Thyroid disorders	19,61	0,75	4,00
Diabetes mellitus without complication	7,61	0,75	4,00
Diabetes mellitus with complication	1,71	0,69	3,67
Glaucoma	2,45	0,64	3,42
Systemic lupus erythematosus and connectiv	1,45	0,59	3,13
Other specified and unspecified liver disease	4,31	0,56	3,00
Essential hypertension	16,04	0,55	2,95
Menstrual disorders	4,23	0,52	2,80
Disorders of lipid metabolism	12,64	0,52	2,79
Conduction disorders	1,41	0,51	2,73
Anxiety and fear-related disorders	21,27	0,49	2,61
Cardiac dysrhythmias	2,14	0,48	2,58
Other specified and unspecified gastrointesti	1,18	0,44	2,33
Osteoarthritis	7,69	0,41	2,20
Menopausal disorders	5,98	0,37	1,99
Trauma- and stressor-related disorders	3,15	0,37	1,97
Other specified joint disorders	3,62	0,34	1,84
Asthma	2,57	0,29	1,57
Diverticulosis and diverticulitis	0,83	0,25	1,33
Nonmalignant breast conditions	0,96	0,24	1,28
Neoplasia (general)	2,93	0,24	1,28
Diseases of white blood cells	0,91	0,24	1,27
Peripheral and visceral vascular disease	0,50	0,23	1,23
Prolapse of female genital organs	0,84	0,23	1,20
Spondylopathies/spondyloarthropathy (inclu	3,36	0,22	1,16
Acquired foot deformities	0,86	0,12	0,66
Nerve and nerve root disorders	1,27	0,10	0,51
Headache; including migraine	1,01	0,08	0,40
Gastritis and duodenitis	0,02	0,00	0,02

Females, 46-65 (2 out of 3)

Cardiovascular risk factors			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Diabetes mellitus without complication	49,26	4,86	65,49
Diabetes mellitus with complication	9,32	3,76	50,68
Chronic kidney disease	8,12	3,67	49,47
Diseases of white blood cells	9,78	2,57	34,62
Essential hypertension	74,12	2,55	34,45
Disorders of lipid metabolism	53,00	2,19	29,55
Cataract and other lens disorders	12,32	2,15	29,07
Obesity	59,76	2,09	28,21
Coronary atherosclerosis and other heart dis	4,25	2,04	27,51
Other specified and unspecified liver disease	15,40	2,01	27,10
Glaucoma	7,57	1,99	26,79
Other specified and unspecified nutritional a	29,96	1,94	26,14
Chronic obstructive pulmonary disease and b	10,13	1,89	25,49
Peripheral and visceral vascular disease	3,68	1,70	22,88
Neoplasia (general)	19,20	1,57	21,18
Sleep wake disorders	26,43	1,54	20,74
Schizophrenia spectrum and other psychotic	4,42	1,51	20,38
Hearing loss	10,28	1,45	19,56
Depressive disorders	27,94	1,39	18,69
Thyroid disorders	34,37	1,31	17,74
Systemic lupus erythematosus and connectiv	3,15	1,27	17,14
Urinary incontinence	18,88	1,26	16,96
Disorders of teeth and gingiva	11,41	1,22	16,47
Osteoarthritis	22,75	1,22	16,45
Nerve and nerve root disorders	14,50	1,11	14,91
Cardiac dysrhythmias	4,77	1,08	14,51
Diverticulosis and diverticulitis	3,42	1,03	13,87
Anxiety and fear-related disorders	43,62	1,00	13,54
Digestive congenital anomalies	2,82	0,99	13,42
Other specified inflammatory condition of sk	7,53	0,97	13,10
Esophageal disorders	8,40	0,88	11,89
Conduction disorders	2,42	0,88	11,87
Trauma- and stressor-related disorders	6,99	0,82	11,03
Menstrual disorders	6,35	0,79	10,62
Asthma	6,75	0,77	10,37
Other specified and unspecified gastrointesti	2,07	0,77	10,32
Nutritional deficiencies	4,96	0,76	10,27
Prolapse of female genital organs	2,70	0,73	9,78
Menopausal disorders	11,14	0,70	9,40
Heart failure	1,49	0,67	9,06
Other specified and unspecified upper respir	10,41	0,63	8,50
Spondylopathies/spondyloarthropathy (inclu	9,69	0,63	8,43
Nonrheumatic and unspecified valve disorde	1,39	0,62	8,32
Headache; including migraine	7,77	0,58	7,78
Epilepsy; convulsions	2,60	0,57	7,68
Gastritis and duodenitis	1,95	0,48	6,44
Other specified joint disorders	4,92	0,47	6,32
Acquired foot deformities	3,00	0,43	5,86
Other specified and unspecified endocrine di	1,22	0,34	4,60
Nonmalignant breast conditions	0,88	0,22	2,97
Scoliosis and other postural dorsopathic defc	1,00	0,20	2,76
Neurodevelopmental disorders	1,14	0,19	2,58
Osteoporosis	0,81	0,14	1,90

Osteoinflammatory - psychosomatic			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Gastritis and duodenitis	13,77	3,38	68,17
Other specified and unspecified gastrointesti	7,72	2,86	57,65
Digestive congenital anomalies	7,71	2,72	54,90
Systemic lupus erythematosus and connectiv	6,22	2,51	50,62
Esophageal disorders	23,73	2,49	50,29
Acquired foot deformities	17,14	2,48	50,07
Spondylopathies/spondyloarthropathy (inclu	38,41	2,48	49,99
Other specified joint disorders	25,16	2,40	48,35
Osteoarthritis	44,04	2,36	47,65
Prolapse of female genital organs	8,32	2,24	45,14
Osteoporosis	12,36	2,15	43,30
Scoliosis and other postural dorsopathic defc	10,30	2,11	42,64
Asthma	17,70	2,02	40,71
Sleep wake disorders	34,46	2,00	40,46
Nerve and nerve root disorders	26,01	1,98	40,03
Other specified and unspecified upper respir	32,75	1,98	40,00
Nutritional deficiencies	12,87	1,98	39,88
Diverticulosis and diverticulitis	6,54	1,97	39,73
Depressive disorders	38,06	1,89	38,11
Other specified and unspecified endocrine di	6,68	1,86	37,58
Trauma- and stressor-related disorders	13,90	1,63	32,81
Headache; including migraine	21,42	1,59	32,10
Hearing loss	11,11	1,57	31,64
Other specified and unspecified liver disease	11,59	1,51	30,51
Glaucoma	5,51	1,45	29,18
Anxiety and fear-related disorders	61,93	1,42	28,76
Chronic obstructive pulmonary disease and b	7,58	1,41	28,55
Menopausal disorders	22,40	1,40	28,26
Other specified and unspecified nutritional a	21,18	1,37	27,64
Other specified inflammatory condition of sk	10,44	1,35	27,18
Urinary incontinence	19,41	1,29	26,09
Disorders of lipid metabolism	30,83	1,27	25,72
Obesity	36,12	1,26	25,51
Thyroid disorders	33,00	1,26	25,48
Cataract and other lens disorders	6,45	1,13	22,76
Essential hypertension	31,29	1,08	21,76
Diseases of white blood cells	3,80	1,00	20,14
Disorders of teeth and gingiva	9,30	0,99	20,07
Nonmalignant breast conditions	3,90	0,98	19,74
Nonrheumatic and unspecified valve disorde	2,17	0,96	19,36
Peripheral and visceral vascular disease	1,97	0,91	18,28
Cardiac dysrhythmias	3,97	0,90	18,11
Neoplasia (general)	10,97	0,90	18,10
Conduction disorders	2,13	0,78	15,68
Menstrual disorders	5,93	0,74	14,85
Epilepsy; convulsions	2,41	0,53	10,66
Diabetes mellitus without complication	4,55	0,45	9,06
Coronary atherosclerosis and other heart dis	0,90	0,43	8,69
Heart failure	0,25	0,11	2,28
Schizophrenia spectrum and other psychotic	0,22	0,08	1,52
Neurodevelopmental disorders	0,39	0,07	1,32
Diabetes mellitus with complication	0,10	0,04	0,81
Chronic kidney disease	0,08	0,04	0,77

Females, 46-65 (3 out of 3)

Osteoinflammatory - psychosomatic			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Gastritis and duodenitis	13,77	3,38	68,17
Other specified and unspecified gastrointesti	7,72	2,86	57,65
Digestive congenital anomalies	7,71	2,72	54,90
Systemic lupus erythematosus and connectiv	6,22	2,51	50,62
Esophageal disorders	23,73	2,49	50,29
Acquired foot deformities	17,14	2,48	50,07
Spondylopathies/spondyloarthropathy (inclu	38,41	2,48	49,99
Other specified joint disorders	25,16	2,40	48,35
Osteoarthritis	44,04	2,36	47,65
Prolapse of female genital organs	8,32	2,24	45,14
Osteoporosis	12,36	2,15	43,30
Scoliosis and other postural dorsopathic defo	10,30	2,11	42,64
Asthma	17,70	2,02	40,71
Sleep wake disorders	34,46	2,00	40,46
Nerve and nerve root disorders	26,01	1,98	40,03
Other specified and unspecified upper respir	32,75	1,98	40,00
Nutritional deficiencies	12,87	1,98	39,88
Diverticulosis and diverticulitis	6,54	1,97	39,73
Depressive disorders	38,06	1,89	38,11
Other specified and unspecified endocrine di	6,68	1,86	37,58
Trauma- and stressor-related disorders	13,90	1,63	32,81
Headache; including migraine	21,42	1,59	32,10
Hearing loss	11,11	1,57	31,64
Other specified and unspecified liver disease	11,59	1,51	30,51
Glaucoma	5,51	1,45	29,18
Anxiety and fear-related disorders	61,93	1,42	28,76
Chronic obstructive pulmonary disease and b	7,58	1,41	28,55
Menopausal disorders	22,40	1,40	28,26
Other specified and unspecified nutritional a	21,18	1,37	27,64
Other specified inflammatory condition of sk	10,44	1,35	27,18
Urinary incontinence	19,41	1,29	26,09
Disorders of lipid metabolism	30,83	1,27	25,72
Obesity	36,12	1,26	25,51
Thyroid disorders	33,00	1,26	25,48
Cataract and other lens disorders	6,45	1,13	22,76
Essential hypertension	31,29	1,08	21,76
Diseases of white blood cells	3,80	1,00	20,14
Disorders of teeth and gingiva	9,30	0,99	20,07
Nonmalignant breast conditions	3,90	0,98	19,74
Nonrheumatic and unspecified valve disorde	2,17	0,96	19,36
Peripheral and visceral vascular disease	1,97	0,91	18,28
Cardiac dysrhythmias	3,97	0,90	18,11
Neoplasia (general)	10,97	0,90	18,10
Conduction disorders	2,13	0,78	15,68
Menstrual disorders	5,93	0,74	14,85
Epilepsy; convulsions	2,41	0,53	10,66
Diabetes mellitus without complication	4,55	0,45	9,06
Coronary atherosclerosis and other heart dis	0,90	0,43	8,69
Heart failure	0,25	0,11	2,28
Schizophrenia spectrum and other psychotic	0,22	0,08	1,52
Neurodevelopmental disorders	0,39	0,07	1,32
Diabetes mellitus with complication	0,10	0,04	0,81
Chronic kidney disease	0,08	0,04	0,77

Gynecological disorders			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Nonmalignant breast conditions	5,22	1,31	75,97
Menstrual disorders	9,81	1,22	70,64
Menopausal disorders	16,14	1,01	58,60
Headache; including migraine	13,47	1,00	58,05
Neoplasia (general)	11,32	0,93	53,76
Anxiety and fear-related disorders	39,05	0,90	52,17
Trauma- and stressor-related disorders	7,41	0,87	50,30
Other specified inflammatory condition of sk	6,68	0,86	50,02
Thyroid disorders	21,67	0,83	48,14
Disorders of teeth and gingiva	7,49	0,80	46,52
Other specified and unspecified upper respir	13,05	0,79	45,85
Nerve and nerve root disorders	9,61	0,73	42,57
Acquired foot deformities	4,96	0,72	41,64
Osteoporosis	4,09	0,71	41,28
Diseases of white blood cells	2,66	0,70	40,51
Prolapse of female genital organs	2,58	0,69	40,22
Hearing loss	4,86	0,68	39,77
Other specified joint disorders	7,18	0,68	39,68
Asthma	5,88	0,67	38,89
Diverticulosis and diverticulitis	2,20	0,66	38,42
Conduction disorders	1,73	0,63	36,63
Spondylopathies/spondyloarthropathy (inclu	9,75	0,63	36,50
Other specified and unspecified endocrine di	2,24	0,63	36,31
Nutritional deficiencies	3,92	0,60	34,92
Obesity	17,15	0,60	34,85
Disorders of lipid metabolism	14,29	0,59	34,31
Cataract and other lens disorders	3,32	0,58	33,77
Depressive disorders	11,57	0,57	33,32
Other specified and unspecified nutritional a	8,79	0,57	33,00
Essential hypertension	16,47	0,57	32,95
Scoliosis and other postural dorsopathic defo	2,76	0,57	32,83
Glaucoma	2,13	0,56	32,44
Other specified and unspecified liver disease	4,13	0,54	31,25
Other specified and unspecified gastrointesti	1,38	0,51	29,59
Peripheral and visceral vascular disease	1,06	0,49	28,28
Osteoarthritis	8,79	0,47	27,35
Chronic obstructive pulmonary disease and b	2,51	0,47	27,18
Sleep wake disorders	7,69	0,45	25,97
Cardiac dysrhythmias	1,97	0,44	25,82
Esophageal disorders	4,19	0,44	25,53
Nonrheumatic and unspecified valve disorde	0,98	0,43	25,19
Systemic lupus erythematosus and connectiv	1,04	0,42	24,41
Digestive congenital anomalies	1,09	0,38	22,29
Gastritis and duodenitis	1,50	0,37	21,33
Urinary incontinence	5,51	0,37	21,30
Coronary atherosclerosis and other heart dis	0,62	0,30	17,34
Neurodevelopmental disorders	1,40	0,24	13,68
Epilepsy; convulsions	0,77	0,17	9,86
Schizophrenia spectrum and other psychotic	0,38	0,13	7,49
Diabetes mellitus without complication	0,75	0,07	4,30
Heart failure	0,10	0,04	2,61
Chronic kidney disease	0,02	0,01	0,52
Diabetes mellitus with complication	0,01	0,00	0,21

Males, 66-80 (1 out of 3)

Cardiorespiratory			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Pulmonary heart disease	65,01	13,70	86,10
Chronic rheumatic heart disease	37,58	10,43	65,54
Respiratory failure; insufficiency; arrest	38,56	9,75	61,28
Nonrheumatic and unspecified valve disord	49,07	5,22	32,79
Heart failure	87,52	4,70	29,52
Other and ill-defined heart disease	33,33	4,63	29,07
Myocarditis and cardiomyopathy	19,93	4,36	27,40
Osteoporosis	23,83	4,05	25,44
Other specified and unspecified lower respi	12,16	3,55	22,29
Myopathies	9,85	3,40	21,35
Cardiac dysrhythmias	70,10	2,85	17,90
Alcohol-related disorders	27,15	2,78	17,49
Non-pressure ulcer of skin	10,46	2,64	16,62
Biliary tract disease	9,73	2,52	15,82
Chronic obstructive pulmonary disease and	78,76	2,46	15,47
Other specified nervous system disorders	7,02	2,42	15,21
Nutritional deficiencies	16,53	2,35	14,77
Retinal and vitreous conditions	11,02	2,28	14,33
Hematologic neoplasia	6,68	2,24	14,06
Acute myocardial infarction	17,81	2,11	13,27
Conduction disorders	47,06	2,08	13,04
Diabetes mellitus with complication	31,11	2,06	12,94
Sleep wake disorders	55,25	2,05	12,91
Chronic kidney disease	47,62	1,99	12,52
Coronary atherosclerosis and other heart di	43,92	1,89	11,85
Other specified and unspecified liver disease	24,11	1,88	11,81
Obesity	58,64	1,86	11,68
Other specified joint disorders	16,96	1,82	11,44
Peripheral and visceral vascular disease	30,42	1,77	11,10
Diseases of white blood cells	12,18	1,73	10,89
Coagulation and hemorrhagic disorders	10,18	1,73	10,86
Other general signs and symptoms	11,36	1,70	10,69
Scoliosis and other postural dorsopathic def	3,52	1,67	10,50
Hypertension with complications and secon	10,88	1,63	10,23
Other specified and unspecified circulatory	3,39	1,61	10,09
Gout	16,67	1,56	9,77
Systemic lupus erythematosus and connecti	4,48	1,50	9,43
Thyroid disorders	14,61	1,46	9,17
Diabetes mellitus without complication	55,77	1,42	8,90
Diverticulosis and diverticulitis	15,03	1,41	8,88
Aortic; peripheral; and visceral artery aneur	5,05	1,40	8,81
Malnutrition	6,15	1,40	8,80
Esophageal disorders	18,51	1,35	8,48
Nerve and nerve root disorders	7,22	1,32	8,32
Headache; including migraine	3,76	1,26	7,91
Disorders of teeth and gingiva	13,81	1,26	7,90
Depressive disorders	17,88	1,26	7,89
Cataract and other lens disorders	35,08	1,21	7,58
Urinary incontinence	31,36	1,18	7,40
Glaucoma	12,71	1,15	7,21
Disorders of lipid metabolism	56,22	1,15	7,20
Hyperplasia of prostate	49,49	1,14	7,15
Spondylopathies/spondyloarthropathy (incl	19,61	1,13	7,12
Pressure ulcer of skin	6,23	1,13	7,08
Osteoarthritis	33,52	1,12	7,01
Other specified inflammatory condition of s	8,88	1,11	6,97
Neoplasia (general)	37,36	1,11	6,96
Nervous system signs and symptoms	5,52	1,08	6,80
Gastroduodenal ulcer	6,34	1,08	6,77
Anxiety and fear-related disorders	16,83	1,06	6,69
Other specified and unspecified nutritional a	30,83	1,06	6,68
Neurocognitive disorders	24,72	1,06	6,67
Essential hypertension	76,42	1,06	6,66
Symptoms of mental and substance use con	5,97	1,00	6,27
Other specified and unspecified endocrine d	3,06	1,00	6,26
Trauma- and stressor-related disorders	3,11	0,96	6,01
Miscellaneous mental and behavioral disord	4,47	0,93	5,82
Transient cerebral ischemia	2,74	0,92	5,77
Sequela of cerebral infarction and other cer	2,81	0,91	5,74
Other specified and unspecified upper respi	9,70	0,91	5,69
Other specified hereditary and degenerative	4,09	0,85	5,31
Gastritis and duodenitis	3,40	0,79	4,96
Asthma	3,81	0,77	4,86
Digestive congenital anomalies	2,75	0,75	4,69
Hearing loss	12,13	0,65	4,11
Nephritis; nephrosis; renal sclerosis	1,50	0,63	3,97
Cerebral infarction	5,03	0,62	3,87
Other and ill-defined cerebrovascular diseas	1,40	0,61	3,84
Epilepsy; convulsions	2,64	0,60	3,78
Hepatitis	1,32	0,58	3,64
Occlusion or stenosis of precerebral or cerel	1,51	0,54	3,37
Neurodevelopmental disorders	1,40	0,47	2,94
Schizophrenia spectrum and other psychoti	1,16	0,30	1,88
Paralysis (other than cerebral palsy)	1,15	0,30	1,87
Acquired foot deformities	0,84	0,26	1,66
Parkinson`s disease	0,26	0,07	0,41
Disruptive, impulse-control and conduct dis	0,08	0,03	0,18

Cognitive-motor disorders			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Paralysis (other than cerebral palsy)	27,35	7,07	45,43
Sequela of cerebral infarction and other cer	18,95	6,16	39,58
Other and ill-defined cerebrovascular diseas	13,87	6,07	39,00
Cerebral infarction	42,22	5,17	33,18
Occlusion or stenosis of precerebral or cerel	13,97	4,97	31,91
Transient cerebral ischemia	13,76	4,61	29,58
Non-pressure ulcer of skin	17,09	4,32	27,76
Nervous system signs and symptoms	21,72	4,26	27,37
Other specified and unspecified endocrine d	11,30	3,68	23,61
Nutritional deficiencies	25,39	3,61	23,20
Malnutrition	15,46	3,52	22,60
Other specified and unspecified circulatory	7,23	3,43	22,03
Other general signs and symptoms	22,25	3,33	21,40
Pressure ulcer of skin	18,03	3,26	20,92
Disruptive, impulse-control and conduct dis	9,34	3,22	20,70
Coagulation and hemorrhagic disorders	18,90	3,21	20,62
Aortic; peripheral; and visceral artery aneur	10,77	2,99	19,21
Hepatitis	6,56	2,87	18,44
Myopathies	8,05	2,77	17,82
Nephritis; nephrosis; renal sclerosis	6,38	2,69	17,28
Peripheral and visceral vascular disease	45,52	2,64	16,98
Diabetes mellitus with complication	39,03	2,58	16,59
Trauma- and stressor-related disorders	8,36	2,57	16,53
Systemic lupus erythematosus and connecti	7,21	2,41	15,51
Osteoporosis	14,10	2,39	15,38
Diseases of white blood cells	16,27	2,31	14,87
Acute myocardial infarction	19,35	2,29	14,73
Miscellaneous mental and behavioral disorc	10,89	2,25	14,47
Urinary incontinence	58,64	2,20	14,15
Neurocognitive disorders	49,77	2,14	13,73
Chronic kidney disease	50,53	2,11	13,58
Hematologic neoplasia	6,27	2,10	13,48
Coronary atherosclerosis and other heart di	47,80	2,05	13,18
Symptoms of mental and substance use con	12,24	2,05	13,16
Other specified hereditary and degenerative	8,66	1,79	11,51
Diverticulosis and diverticulitis	17,28	1,62	10,44
Cardiac dysrhythmias	39,87	1,62	10,41
Other specified and unspecified liver disease	19,76	1,54	9,89
Depressive disorders	21,80	1,53	9,83
Disorders of lipid metabolism	74,89	1,53	9,81
Other specified and unspecified lower respi	5,16	1,51	9,67
Scoliosis and other postural dorsopathic def	3,14	1,49	9,58
Parkinson`s disease	5,75	1,49	9,55
Other specified and unspecified nutritional a	42,76	1,47	9,47
Heart failure	27,33	1,47	9,42
Thyroid disorders	14,56	1,45	9,33
Diabetes mellitus without complication	56,03	1,42	9,14
Cataract and other lens disorders	41,27	1,42	9,11
Glaucoma	15,51	1,40	9,00
Other and ill-defined heart disease	9,98	1,38	8,89
Gastritis and duodenitis	5,84	1,36	8,72
Hearing loss	24,98	1,35	8,65
Hypertension with complications and secon	8,83	1,32	8,49
Nonrheumatic and unspecified valve disord	12,43	1,32	8,49
Neoplasia (general)	44,13	1,31	8,40
Other specified joint disorders	12,09	1,30	8,34
Disorders of teeth and gingiva	13,83	1,26	8,08
Gastroduodenal ulcer	7,40	1,26	8,07
Anxiety and fear-related disorders	19,04	1,20	7,73
Essential hypertension	85,78	1,19	7,64
Osteoarthritis	35,24	1,17	7,53
Other specified nervous system disorders	3,38	1,17	7,49
Hyperplasia of prostate	50,38	1,16	7,44
Spondylopathies/spondyloarthropathy (incl	19,63	1,13	7,28
Conduction disorders	25,63	1,13	7,26
Chronic obstructive pulmonary disease and	35,50	1,11	7,13
Alcohol-related disorders	10,73	1,10	7,07
Esophageal disorders	14,69	1,07	6,88
Digestive congenital anomalies	3,69	1,00	6,42
Epilepsy; convulsions	4,37	1,00	6,39
Other specified inflammatory condition of s	7,60	0,95	6,10
Nerve and nerve root disorders	5,13	0,94	6,05
Sleep wake disorders	25,25	0,94	6,03
Myocarditis and cardiomyopathy	4,12	0,90	5,79
Other specified and unspecified upper respi	9,65	0,90	5,78
Schizophrenia spectrum and other psychoti	3,28	0,85	5,45
Obesity	26,08	0,83	5,31
Gout	8,69	0,81	5,20
Retinal and vitreous conditions	3,29	0,68	4,37
Biliary tract disease	2,62	0,68	4,35
Headache; including migraine	1,96	0,66	4,22
Chronic rheumatic heart disease	2,16	0,60	3,85
Respiratory failure; insufficiency; arrest	1,95	0,49	3,16
Asthma	2,22	0,45	2,89
Neurodevelopmental disorders	1,09	0,36	2,34
Pulmonary heart disease	1,50	0,32	2,03
Acquired foot deformities	0,77	0,24	1,56

Males, 66-80 (2 out of 3)

Cardiometabolic			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Diabetes mellitus with complication	53,66	3,55	45,25
Nephritis; nephrosis; renal sclerosis	8,29	3,50	44,55
Non-pressure ulcer of skin	13,52	3,42	43,59
Myocarditis and cardiomyopathy	15,06	3,30	42,01
Acute myocardial infarction	26,77	3,17	40,45
Heart failure	52,98	2,84	36,25
Coronary atherosclerosis and other heart di	66,09	2,84	36,17
Peripheral and visceral vascular disease	48,26	2,80	35,71
Other specified and unspecified endocrine c	8,27	2,69	34,28
Other specified and unspecified circulatory	5,14	2,44	31,07
Nonrheumatic and unspecified valve disord	22,51	2,39	30,51
Other and ill-defined cerebrovascular diseas	5,38	2,36	30,04
Chronic kidney disease	54,47	2,28	29,05
Diabetes mellitus without complication	84,70	2,15	27,42
Hypertension with complications and secon	14,25	2,13	27,20
Conduction disorders	46,98	2,07	26,41
Aortic; peripheral; and visceral artery aneur	7,25	2,01	25,64
Other and ill-defined heart disease	14,20	1,97	25,11
Cardiac dysrhythmias	43,64	1,77	22,61
Other specified nervous system disorders	5,00	1,72	21,96
Malnutrition	7,27	1,66	21,10
Biliary tract disease	6,40	1,65	21,08
Cerebral infarction	12,68	1,55	19,78
Disorders of lipid metabolism	75,59	1,54	19,65
Nutritional deficiencies	10,54	1,50	19,12
Retinal and vitreous conditions	7,24	1,50	19,09
Occlusion or stenosis of precerebral or cerel	4,18	1,49	18,94
Gout	15,30	1,43	18,19
Other specified and unspecified nutritional a	41,35	1,43	18,18
Transient cerebral ischemia	4,24	1,42	18,10
Obesity	44,64	1,42	18,04
Asthma	6,83	1,39	17,70
Other specified and unspecified liver disease	17,05	1,33	16,94
Gastritis and duodenitis	5,69	1,32	16,83
Paralysis (other than cerebral palsy)	5,03	1,30	16,59
Spondylopathies/spondyloarthropathy (incl	22,43	1,30	16,52
Sleep wake disorders	34,12	1,27	16,17
Essential hypertension	90,33	1,25	15,96
Chronic obstructive pulmonary disease and	38,43	1,20	15,31
Thyroid disorders	11,14	1,11	14,18
Cataract and other lens disorders	31,85	1,10	13,96
Neoplasia (general)	36,52	1,08	13,80
Glaucoma	11,57	1,04	13,32
Gastroduodenal ulcer	6,04	1,03	13,07
Systemic lupus erythematosus and connecti	2,98	1,00	12,70
Nervous system signs and symptoms	5,05	0,99	12,64
Disorders of teeth and gingiva	10,55	0,96	12,25
Other specified inflammatory condition of s	7,67	0,96	12,23
Other general signs and symptoms	6,31	0,94	12,04
Diverticulosis and diverticulitis	9,92	0,93	11,90
Osteoarthritis	27,53	0,92	11,68
Other specified joint disorders	8,53	0,92	11,67
Diseases of white blood cells	6,30	0,90	11,43
Other specified and unspecified upper respi	9,42	0,88	11,20
Chronic rheumatic heart disease	3,06	0,85	10,81
Sequela of cerebral infarction and other cer	2,61	0,85	10,81
Miscellaneous mental and behavioral disorc	4,03	0,83	10,62
Alcohol-related disorders	8,08	0,83	10,56
Neurocognitive disorders	18,84	0,81	10,31
Digestive congenital anomalies	2,97	0,80	10,26
Hyperplasia of prostate	34,04	0,78	9,97
Urinary incontinence	20,70	0,78	9,91
Hearing loss	14,23	0,77	9,78
Pressure ulcer of skin	4,22	0,76	9,73
Depressive disorders	10,28	0,72	9,20
Symptoms of mental and substance use con	4,08	0,68	8,70
Hepatitis	1,53	0,67	8,53
Coagulation and hemorrhagic disorders	3,88	0,66	8,40
Esophageal disorders	7,92	0,58	7,36
Nerve and nerve root disorders	3,09	0,57	7,23
Anxiety and fear-related disorders	8,41	0,53	6,78
Disruptive, impulse-control and conduct dis	1,52	0,53	6,70
Trauma- and stressor-related disorders	1,66	0,51	6,52
Headache; including migraine	1,31	0,44	5,61
Acquired foot deformities	1,39	0,44	5,60
Scoliosis and other postural dorsopathic def	0,89	0,42	5,38
Schizophrenia spectrum and other psychoti	1,62	0,42	5,35
Other specified hereditary and degenerative	2,02	0,42	5,31
Respiratory failure; insufficiency; arrest	1,50	0,38	4,85
Pulmonary heart disease	1,79	0,38	4,80
Osteoporosis	2,15	0,37	4,66
Other specified and unspecified lower respi	1,19	0,35	4,42
Myopathies	0,79	0,27	3,48
Hematologic neoplasia	0,81	0,27	3,48
Epilepsy; convulsions	1,09	0,25	3,15
Parkinson`s disease	0,33	0,09	1,10
Neurodevelopmental disorders	0,08	0,03	0,32

Psychogeriatric			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Parkinson`s disease	21,29	5,51	77,31
Schizophrenia spectrum and other psychotic	19,98	5,17	72,56
Neurodevelopmental disorders	14,23	4,76	66,88
Disruptive, impulse-control and conduct dis	13,63	4,70	66,00
Symptoms of mental and substance use con	26,91	4,50	63,23
Epilepsy; convulsions	18,51	4,21	59,15
Pressure ulcer of skin	18,09	3,27	45,89
Other general signs and symptoms	20,73	3,10	43,58
Urinary incontinence	80,13	3,01	42,26
Neurocognitive disorders	68,76	2,95	41,46
Nervous system signs and symptoms	13,29	2,61	36,62
Depressive disorders	35,50	2,49	35,01
Other specified hereditary and degenerative	11,72	2,42	34,04
Sequela of cerebral infarction and other cer	6,59	2,14	30,08
Other specified nervous system disorders	6,18	2,13	29,91
Miscellaneous mental and behavioral disord	9,28	1,92	26,96
Osteoporosis	9,17	1,56	21,88
Nutritional deficiencies	10,44	1,49	20,86
Alcohol-related disorders	14,10	1,45	20,30
Scoliosis and other postural dorsopathic def	2,88	1,36	19,16
Anxiety and fear-related disorders	21,09	1,33	18,72
Paralysis (other than cerebral palsy)	5,11	1,32	18,54
Gastritis and duodenitis	5,28	1,23	17,21
Hyperplasia of prostate	52,78	1,21	17,04
Sleep wake disorders	32,54	1,21	16,99
Glaucoma	13,12	1,19	16,64
Other specified inflammatory condition of sl	9,39	1,17	16,48
Disorders of teeth and gingiva	12,70	1,16	16,23
Respiratory failure; insufficiency; arrest	4,46	1,13	15,85
Trauma- and stressor-related disorders	3,66	1,13	15,83
Hearing loss	19,60	1,06	14,84
Cerebral infarction	7,84	0,96	13,47
Asthma	4,70	0,96	13,41
Chronic obstructive pulmonary disease and	29,97	0,94	13,15
Essential hypertension	66,97	0,93	13,03
Digestive congenital anomalies	3,18	0,86	12,09
Conduction disorders	18,17	0,80	11,25
Hematologic neoplasia	2,36	0,79	11,09
Osteoarthritis	23,66	0,79	11,05
Cataract and other lens disorders	21,41	0,74	10,34
Other specified and unspecified nutritional a	21,17	0,73	10,25
Gout	7,73	0,72	10,12
Spondylopathies/spondyloarthropathy (incl	12,06	0,70	9,78
Diabetes mellitus without complication	27,22	0,69	9,71
Other and ill-defined heart disease	4,94	0,69	9,62
Gastroduodenal ulcer	3,87	0,66	9,23
Diverticulosis and diverticulitis	6,99	0,66	9,23
Cardiac dysrhythmias	16,14	0,66	9,21
Thyroid disorders	6,48	0,65	9,08
Disorders of lipid metabolism	31,55	0,64	9,03
Chronic kidney disease	15,31	0,64	8,99
Hepatitis	1,46	0,64	8,99
Systemic lupus erythematosus and connecti	1,89	0,63	8,89
Other specified and unspecified lower respi	2,12	0,62	8,68
Obesity	19,25	0,61	8,57
Esophageal disorders	8,19	0,60	8,39
Headache; including migraine	1,75	0,59	8,24
Other specified and unspecified liver disease	7,48	0,58	8,19
Biliary tract disease	2,15	0,56	7,80
Occlusion or stenosis of precerebral or cerel	1,53	0,54	7,62
Other specified and unspecified upper respi	5,74	0,54	7,51
Non-pressure ulcer of skin	2,10	0,53	7,45
Malnutrition	2,26	0,51	7,22
Heart failure	9,38	0,50	7,07
Coronary atherosclerosis and other heart di	11,18	0,48	6,74
Coagulation and hemorrhagic disorders	2,69	0,46	6,42
Neoplasia (general)	14,31	0,42	5,95
Peripheral and visceral vascular disease	7,18	0,42	5,85
Hypertension with complications and secon	2,78	0,42	5,85
Myopathies	1,11	0,38	5,36
Transient cerebral ischemia	1,10	0,37	5,17
Diabetes mellitus with complication	5,46	0,36	5,07
Myocarditis and cardiomyopathy	1,57	0,34	4,82
Other specified joint disorders	3,13	0,34	4,71
Nephritis; nephrosis; renal sclerosis	0,70	0,29	4,12
Nonrheumatic and unspecified valve disorde	2,54	0,27	3,80
Retinal and vitreous conditions	1,25	0,26	3,64
Diseases of white blood cells	1,46	0,21	2,91
Aortic; peripheral; and visceral artery aneur	0,68	0,19	2,66
Chronic rheumatic heart disease	0,64	0,18	2,49
Other and ill-defined cerebrovascular diseas	0,37	0,16	2,28
Pulmonary heart disease	0,73	0,15	2,16
Acute myocardial infarction	1,11	0,13	1,85
Nerve and nerve root disorders	0,42	0,08	1,08
Other specified and unspecified circulatory	0,14	0,07	0,94
Other specified and unspecified endocrine d	0,09	0,03	0,43
Acquired foot deformities	0,01	0,00	0,03

Males, 66-80 (3 out of 3)

Unspecific with COPD predominance			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Headache; including migraine	6,83	2,29	55,51
Diverticulosis and diverticulitis	21,68	2,04	49,54
Acquired foot deformities	5,78	1,83	44,41
Digestive congenital anomalies	6,62	1,80	43,60
Gastritis and duodenitis	7,55	1,75	42,60
Other specified joint disorders	15,92	1,71	41,50
Esophageal disorders	22,54	1,64	39,93
Other specified and unspecified liver disease	20,91	1,63	39,59
Osteoarthritis	48,67	1,62	39,33
Hearing loss	29,34	1,58	38,44
Coagulation and hemorrhagic disorders	9,23	1,57	38,08
Other specified and unspecified upper respi	16,77	1,56	38,00
Hepatitis	3,56	1,56	37,85
Hypertension with complications and secon	10,30	1,54	37,45
Asthma	7,45	1,51	36,77
Other specified hereditary and degenerative	7,16	1,48	35,96
Disorders of teeth and gingiva	16,24	1,48	35,92
Thyroid disorders	14,58	1,46	35,35
Spondylopathies/spondyloarthropathy (incl	25,09	1,45	35,20
Biliary tract disease	5,54	1,43	34,82
Obesity	44,66	1,42	34,39
Gout	15,12	1,41	34,25
Nerve and nerve root disorders	7,66	1,41	34,14
Systemic lupus erythematosus and connecti	4,17	1,39	33,88
Diseases of white blood cells	9,78	1,39	33,81
Gastroduodenal ulcer	8,06	1,37	33,27
Sleep wake disorders	36,17	1,35	32,67
Anxiety and fear-related disorders	20,85	1,32	32,02
Retinal and vitreous conditions	6,30	1,30	31,65
Other specified inflammatory condition of s	10,23	1,28	31,07
Miscellaneous mental and behavioral disord	6,11	1,26	30,70
Disorders of lipid metabolism	61,35	1,25	30,39
Other specified and unspecified nutritional a	35,98	1,24	30,14
Cataract and other lens disorders	34,28	1,18	28,63
Trauma- and stressor-related disorders	3,82	1,18	28,57
Hyperplasia of prostate	48,84	1,12	27,27
Essential hypertension	80,62	1,12	27,14
Neoplasia (general)	37,65	1,12	27,10
Conduction disorders	24,80	1,09	26,57
Myopathies	3,15	1,09	26,40
Alcohol-related disorders	10,55	1,08	26,27
Chronic obstructive pulmonary disease and	33,86	1,06	25,72
Aortic; peripheral; and visceral artery aneur	3,66	1,02	24,67
Other specified and unspecified endocrine d	3,02	0,98	23,81
Diabetes mellitus without complication	38,11	0,97	23,52
Acute myocardial infarction	7,97	0,95	22,96
Depressive disorders	12,68	0,89	21,64
Osteoporosis	5,17	0,88	21,33
Malnutrition	3,85	0,88	21,31
Other specified and unspecified circulatory d	1,84	0,87	21,20
Cardiac dysrhythmias	21,29	0,87	21,02
Other specified and unspecified lower respi	2,96	0,86	21,00
Occlusion or stenosis of precerebral or cerel	2,28	0,81	19,73
Coronary atherosclerosis and other heart di	18,78	0,81	19,59
Transient cerebral ischemia	2,40	0,80	19,49
Other and ill-defined heart disease	5,44	0,76	18,35
Chronic kidney disease	18,01	0,75	18,31
Glaucoma	7,51	0,68	16,49
Scoliosis and other postural dorsopathic def	1,37	0,65	15,75
Other specified nervous system disorders	1,87	0,64	15,66
Peripheral and visceral vascular disease	11,10	0,64	15,65
Nephritis; nephrosis; renal sclerosis	1,51	0,64	15,46
Myocarditis and cardiomyopathy	2,83	0,62	15,07
Hematologic neoplasia	1,72	0,57	13,96
Nutritional deficiencies	3,88	0,55	13,42
Neurocognitive disorders	12,04	0,52	12,55
Heart failure	9,22	0,49	12,02
Urinary incontinence	12,98	0,49	11,84
Nonrheumatic and unspecified valve disorde	4,48	0,48	11,57
Diabetes mellitus with complication	7,13	0,47	11,47
Cerebral infarction	3,61	0,44	10,74
Parkinson`s disease	1,56	0,40	9,81
Other and ill-defined cerebrovascular diseas	0,81	0,35	8,62
Chronic rheumatic heart disease	1,16	0,32	7,80
Epilepsy; convulsions	1,27	0,29	7,04
Pressure ulcer of skin	1,40	0,25	6,15
Respiratory failure; insufficiency; arrest	0,87	0,22	5,35
Symptoms of mental and substance use con	0,95	0,16	3,85
Disruptive, impulse-control and conduct dis	0,43	0,15	3,57
Schizophrenia spectrum and other psychotic	0,41	0,11	2,59
Paralysis (other than cerebral palsy)	0,41	0,11	2,57
Non-pressure ulcer of skin	0,39	0,10	2,41
Other general signs and symptoms	0,47	0,07	1,71
Nervous system signs and symptoms	0,30	0,06	1,44
Pulmonary heart disease	0,15	0,03	0,77
Neurodevelopmental disorders	0,06	0,02	0,46
Sequela of cerebral infarction and other cer	0,02	0,01	0,16

Uspecific with neoplasia predominance			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Acquired foot deformities	4,08	1,29	46,74
Hematologic neoplasia	3,62	1,21	43,94
Nerve and nerve root disorders	6,50	1,19	43,18
Scoliosis and other postural dorsopathic def	2,31	1,09	39,64
Neoplasia (general)	35,21	1,04	37,79
Glaucoma	11,42	1,03	37,34
Other specified and unspecified lower respi	3,21	0,94	33,94
Other specified and unspecified upper respi	9,42	0,88	31,82
Hyperplasia of prostate	37,39	0,86	31,13
Cataract and other lens disorders	24,40	0,84	30,38
Gastroduodenal ulcer	4,81	0,82	29,59
Essential hypertension	58,90	0,82	29,57
Esophageal disorders	10,96	0,80	28,95
Anxiety and fear-related disorders	12,25	0,77	28,06
Other specified inflammatory condition of s	5,99	0,75	27,14
Neurodevelopmental disorders	2,23	0,75	27,06
Retinal and vitreous conditions	3,59	0,74	26,92
Trauma- and stressor-related disorders	2,38	0,73	26,55
Diseases of white blood cells	5,07	0,72	26,10
Myopathies	2,05	0,71	25,59
Other specified and unspecified nutritional a	20,24	0,70	25,28
Asthma	3,31	0,67	24,37
Hearing loss	12,38	0,67	24,17
Spondylopathies/spondyloarthropathy (incl	11,52	0,67	24,09
Disorders of lipid metabolism	32,37	0,66	23,91
Osteoarthritis	19,41	0,65	23,39
Chronic obstructive pulmonary disease and	20,50	0,64	23,21
Digestive congenital anomalies	2,34	0,63	22,95
Thyroid disorders	6,33	0,63	22,88
Hepatitis	1,42	0,62	22,55
Gout	6,65	0,62	22,46
Other specified joint disorders	5,74	0,62	22,34
Obesity	19,18	0,61	22,02
Transient cerebral ischemia	1,81	0,60	21,90
Diabetes mellitus without complication	23,17	0,59	21,31
Epilepsy; convulsions	2,49	0,57	20,50
Disorders of teeth and gingiva	5,95	0,54	19,62
Systemic lupus erythematosus and connecti	1,62	0,54	19,59
Aortic; peripheral; and visceral artery aneur	1,89	0,52	19,01
Malnutrition	2,30	0,52	18,98
Cerebral infarction	4,28	0,52	18,96
Cardiac dysrhythmias	12,81	0,52	18,85
Headache; including migraine	1,53	0,51	18,51
Occlusion or stenosis of precerebral or cerel	1,43	0,51	18,43
Alcohol-related disorders	4,93	0,51	18,32
Chronic kidney disease	11,59	0,48	17,56
Depressive disorders	6,46	0,45	16,43
Other and ill-defined cerebrovascular diseas	1,02	0,45	16,22
Biliary tract disease	1,72	0,45	16,14
Coagulation and hemorrhagic disorders	2,54	0,43	15,62
Conduction disorders	9,68	0,43	15,46
Neurocognitive disorders	9,82	0,42	15,28
Sleep wake disorders	11,30	0,42	15,22
Nervous system signs and symptoms	2,13	0,42	15,12
Paralysis (other than cerebral palsy)	1,60	0,41	15,01
Peripheral and visceral vascular disease	6,99	0,41	14,71
Other specified and unspecified circulatory d	0,85	0,40	14,67
Nephritis; nephrosis; renal sclerosis	0,96	0,40	14,62
Urinary incontinence	10,62	0,40	14,45
Sequela of cerebral infarction and other cer	1,16	0,38	13,63
Other specified and unspecified liver disease	4,81	0,38	13,58
Nonrheumatic and unspecified valve disorde	3,33	0,35	12,83
Coronary atherosclerosis and other heart di	8,01	0,34	12,46
Schizophrenia spectrum and other psychotic	1,30	0,34	12,17
Other specified and unspecified endocrine d	0,99	0,32	11,60
Miscellaneous mental and behavioral disord	1,52	0,32	11,42
Osteoporosis	1,84	0,31	11,31
Hypertension with complications and secon	1,99	0,30	10,77
Other general signs and symptoms	1,95	0,29	10,59
Pressure ulcer of skin	1,56	0,28	10,23
Diverticulosis and diverticulitis	2,94	0,28	10,02
Other specified nervous system disorders	0,78	0,27	9,77
Gastritis and duodenitis	1,15	0,27	9,68
Respiratory failure; insufficiency; arrest	1,04	0,26	9,52
Chronic rheumatic heart disease	0,94	0,26	9,50
Other and ill-defined heart disease	1,78	0,25	8,95
Diabetes mellitus with complication	3,63	0,24	8,69
Nutritional deficiencies	1,68	0,24	8,64
Other specified hereditary and degenerative	1,05	0,22	7,86
Acute myocardial infarction	1,57	0,19	6,74
Heart failure	2,94	0,16	5,72
Myocarditis and cardiomyopathy	0,62	0,14	4,91
Symptoms of mental and substance use con	0,79	0,13	4,79
Pulmonary heart disease	0,54	0,11	4,15
Disruptive, impulse-control and conduct dis	0,23	0,08	2,85
Non-pressure ulcer of skin	0,24	0,06	2,17
Parkinson`s disease	0,19	0,05	1,81

Females, 66-80 (1 out of 3)

Cerebrovascular			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Paralysis (other than cerebral palsy)	45,22	16,56	93,44
Cerebral infarction	68,28	12,30	69,42
Nervous system signs and symptoms	41,68	7,51	42,38
Miscellaneous mental and behavioral disorde	13,79	4,89	27,60
Hepatitis	9,87	3,11	17,56
Drug induced or toxic related condition	6,30	2,75	15,53
Disruptive, impulse-control and conduct diso	6,15	2,68	15,14
Coagulation and hemorrhagic disorders	8,47	2,60	14,66
Malnutrition	7,40	2,47	13,93
Diabetes mellitus with complication	33,01	2,46	13,91
Cardiac dysrhythmias	52,11	2,37	13,35
Epilepsy; convulsions	7,12	2,13	12,00
Neurocognitive disorders	57,86	2,09	11,80
Symptoms of mental and substance use conc	13,67	1,89	10,68
Pressure ulcer of skin	13,15	1,89	10,66
Urinary incontinence	80,51	1,87	10,55
Other general signs and symptoms	14,24	1,86	10,49
Diabetes mellitus without complication	57,02	1,74	9,82
Coronary atherosclerosis and other heart dis	18,99	1,72	9,73
Nonrheumatic and unspecified valve disorde	19,92	1,69	9,52
Other specified and unspecified liver disease	19,22	1,68	9,47
Acute myocardial infarction	4,27	1,67	9,43
Other specified nervous system disorders	3,56	1,61	9,11
Other specified inflammatory condition of sk	10,44	1,56	8,80
Heart failure	28,89	1,47	8,30
Chronic kidney disease	27,95	1,43	8,06
Depressive disorders	48,49	1,38	7,77
Hypertension with complications and second	8,58	1,37	7,74
Disorders of lipid metabolism	65,21	1,36	7,66
Essential hypertension	88,51	1,26	7,12
Rheumatoid arthritis and related disease	3,66	1,26	7,10
Hearing loss	18,42	1,19	6,70
Trauma- and stressor-related disorders	7,48	1,18	6,65
Nervous system pain and pain syndromes	6,09	1,13	6,39
Gastritis and duodenitis	6,51	1,12	6,32
Gastroduodenal ulcer	3,32	1,11	6,26
Anxiety and fear-related disorders	37,44	1,08	6,09
Obesity	46,58	1,05	5,92
Osteoporosis	26,94	1,04	5,89
Osteoarthritis	54,28	1,03	5,79
Thyroid disorders	31,65	1,01	5,69
Conduction disorders	14,21	0,99	5,58
Spondylopathies/spondyloarthropathy (inclu	23,84	0,98	5,53
Sleep wake disorders	27,67	0,96	5,40
Menopausal disorders	7,84	0,94	5,28
Biliary tract disease	3,62	0,93	5,27
Other specified and unspecified nutritional a	28,28	0,91	5,16
Other and ill-defined heart disease	6,39	0,90	5,05
Nephritis; nephrosis; renal sclerosis	1,88	0,89	5,02
Neoplasia (general)	17,92	0,86	4,84
Systemic lupus erythematosus and connectiv	6,10	0,84	4,76
Bipolar and related disorders	1,85	0,84	4,74
Other specified joint disorders	10,19	0,83	4,66
Asthma	9,85	0,82	4,64
Glaucoma	7,84	0,80	4,52
Diverticulosis and diverticulitis	7,28	0,79	4,48
Disorders of teeth and gingiva	7,48	0,79	4,44
Hematologic neoplasia	2,14	0,76	4,28
Other specified and unspecified endocrine di	3,91	0,75	4,24
Diseases of white blood cells	3,60	0,74	4,19
Neurodevelopmental disorders	1,57	0,74	4,18
Prolapse of female genital organs	6,44	0,74	4,17
Other specified hereditary and degenerative	5,64	0,74	4,15
Cataract and other lens disorders	22,20	0,71	4,02
Non-pressure ulcer of skin	1,73	0,70	3,95
Esophageal disorders	10,85	0,70	3,93
Nutritional deficiencies	8,24	0,66	3,74
Acquired foot deformities	6,57	0,60	3,36
Chronic obstructive pulmonary disease and b	7,69	0,58	3,29
Myocarditis and cardiomyopathy	2,11	0,56	3,14
Gout	1,59	0,55	3,09
Nerve and nerve root disorders	5,54	0,54	3,03
Other specified and unspecified upper respir	6,02	0,49	2,75
Other specified and unspecified gastrointesti	2,22	0,47	2,68
Peripheral and visceral vascular disease	2,60	0,47	2,64
Retinal and vitreous conditions	2,14	0,37	2,11
Parkinson`s disease	1,61	0,36	2,02
Digestive congenital anomalies	1,67	0,29	1,62
Scoliosis and other postural dorsopathic defc	1,53	0,25	1,44
Schizophrenia spectrum and other psychotic	0,36	0,09	0,49
Headache; including migraine	0,26	0,04	0,23
Pulmonary heart disease	0,14	0,03	0,16
Chronic rheumatic heart disease	0,09	0,02	0,14
Respiratory failure; insufficiency; arrest	0,02	0,01	0,04

Psychogeriatric			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Neurodevelopmental disorders	15,72	7,43	95,56
Schizophrenia spectrum and other psychotic	26,05	6,29	80,88
Bipolar and related disorders	10,95	4,97	63,92
Other general signs and symptoms	33,52	4,37	56,22
Disruptive, impulse-control and conduct diso	9,74	4,25	54,65
Miscellaneous mental and behavioral disorde	11,59	4,11	52,87
Parkinson`s disease	18,37	4,09	52,57
Epilepsy; convulsions	11,86	3,54	45,55
Pressure ulcer of skin	23,00	3,30	42,48
Symptoms of mental and substance use conc	23,55	3,26	41,91
Neurocognitive disorders	70,19	2,54	32,62
Urinary incontinence	87,68	2,04	26,16
Nervous system signs and symptoms	8,86	1,60	20,52
Drug induced or toxic related condition	3,43	1,50	19,26
Disorders of teeth and gingiva	14,24	1,50	19,23
Other specified nervous system disorders	2,79	1,27	16,30
Non-pressure ulcer of skin	2,93	1,19	15,29
Other specified hereditary and degenerative	9,03	1,18	15,15
Hepatitis	3,52	1,11	14,28
Nervous system pain and pain syndromes	5,90	1,10	14,11
Other specified inflammatory condition of sk	7,04	1,05	13,52
Scoliosis and other postural dorsopathic defc	6,19	1,03	13,28
Depressive disorders	36,01	1,02	13,14
Other specified and unspecified nutritional a	31,55	1,02	13,11
Coagulation and hemorrhagic disorders	3,28	1,01	12,94
Diabetes mellitus without complication	32,49	0,99	12,74
Other specified and unspecified endocrine di	4,33	0,83	10,71
Sleep wake disorders	23,92	0,83	10,64
Diabetes mellitus with complication	10,90	0,81	10,46
Essential hypertension	55,92	0,80	10,25
Digestive congenital anomalies	4,44	0,76	9,82
Osteoporosis	19,55	0,76	9,73
Disorders of lipid metabolism	36,02	0,75	9,64
Thyroid disorders	21,53	0,69	8,82
Anxiety and fear-related disorders	22,96	0,66	8,50
Malnutrition	1,90	0,64	8,17
Peripheral and visceral vascular disease	3,46	0,62	8,01
Obesity	26,30	0,59	7,61
Glaucoma	5,75	0,59	7,56
Osteoarthritis	30,04	0,57	7,29
Retinal and vitreous conditions	3,24	0,57	7,28
Esophageal disorders	8,39	0,54	6,92
Cataract and other lens disorders	16,51	0,53	6,81
Chronic kidney disease	10,29	0,53	6,76
Other and ill-defined heart disease	3,72	0,52	6,71
Nutritional deficiencies	6,46	0,52	6,68
Diseases of white blood cells	2,36	0,49	6,27
Hearing loss	7,20	0,46	5,97
Spondylopathies/spondyloarthropathy (inclu	11,14	0,46	5,89
Diverticulosis and diverticulitis	4,13	0,45	5,80
Neoplasia (general)	9,30	0,45	5,72
Paralysis (other than cerebral palsy)	1,18	0,43	5,57
Gastroduodenal ulcer	1,27	0,43	5,47
Chronic obstructive pulmonary disease and b	5,60	0,42	5,44
Biliary tract disease	1,56	0,40	5,16
Rheumatoid arthritis and related disease	1,11	0,38	4,91
Respiratory failure; insufficiency; arrest	0,95	0,37	4,78
Other specified and unspecified liver disease	4,25	0,37	4,77
Other specified joint disorders	4,41	0,36	4,60
Systemic lupus erythematosus and connectiv	2,58	0,36	4,58
Other specified and unspecified upper respir	4,36	0,35	4,54
Cardiac dysrhythmias	7,47	0,34	4,36
Prolapse of female genital organs	2,75	0,32	4,05
Heart failure	6,07	0,31	3,97
Gastritis and duodenitis	1,79	0,31	3,97
Hematologic neoplasia	0,85	0,30	3,86
Asthma	3,50	0,29	3,75
Acute myocardial infarction	0,70	0,27	3,50
Headache; including migraine	1,74	0,27	3,44
Menopausal disorders	2,16	0,26	3,32
Hypertension with complications and second	1,41	0,22	2,89
Conduction disorders	3,09	0,22	2,77
Nonrheumatic and unspecified valve disorde	2,39	0,20	2,60
Chronic rheumatic heart disease	0,69	0,19	2,44
Coronary atherosclerosis and other heart dis	2,00	0,18	2,34
Other specified and unspecified gastrointesti	0,82	0,17	2,25
Nerve and nerve root disorders	1,79	0,17	2,24
Gout	0,49	0,17	2,18
Cerebral infarction	0,86	0,16	2,00
Trauma- and stressor-related disorders	0,97	0,15	1,97
Acquired foot deformities	1,44	0,13	1,69
Nephritis; nephrosis; renal sclerosis	0,03	0,01	0,19
Myocarditis and cardiomyopathy	0,00	0,00	0,01
Pulmonary heart disease	0,01	0,00	0,01

Females, 66-80 (2 out of 3)

DM - cardiorespiratory			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Myocarditis and cardiomyopathy	23,25	6,14	86,22
Pulmonary heart disease	31,77	6,11	85,87
Chronic rheumatic heart disease	21,14	5,85	82,25
Respiratory failure; insufficiency; arrest	13,83	5,41	76,08
Heart failure	86,12	4,38	61,59
Hypertension with complications and second	26,91	4,30	60,45
Other and ill-defined heart disease	30,59	4,29	60,24
Gout	12,25	4,21	59,18
Acute myocardial infarction	9,60	3,76	52,79
Nonrheumatic and unspecified valve disorde	43,72	3,70	52,04
Coronary atherosclerosis and other heart dis	40,41	3,67	51,55
Non-pressure ulcer of skin	8,88	3,60	50,59
Diabetes mellitus with complication	46,32	3,46	48,60
Peripheral and visceral vascular disease	18,95	3,41	47,96
Chronic kidney disease	63,23	3,23	45,43
Other specified and unspecified endocrine di	15,37	2,96	41,55
Cardiac dysrhythmias	64,12	2,91	40,91
Conduction disorders	34,96	2,43	34,21
Other specified nervous system disorders	4,91	2,23	31,35
Diabetes mellitus without complication	70,69	2,16	30,31
Coagulation and hemorrhagic disorders	6,82	2,09	29,41
Nutritional deficiencies	22,53	1,81	25,49
Gastroduodenal ulcer	5,30	1,77	24,87
Hematologic neoplasia	4,90	1,74	24,40
Nervous system pain and pain syndromes	9,26	1,72	24,22
Chronic obstructive pulmonary disease and b	22,77	1,72	24,21
Other specified and unspecified liver disease	19,73	1,72	24,20
Rheumatoid arthritis and related disease	5,00	1,72	24,15
Obesity	72,98	1,64	23,09
Other specified hereditary and degenerative	12,40	1,62	22,72
Sleep wake disorders	46,54	1,61	22,63
Systemic lupus erythematosus and connectiv	11,53	1,60	22,42
Retinal and vitreous conditions	9,07	1,58	22,24
Pressure ulcer of skin	10,66	1,53	21,51
Nephritis; nephrosis; renal sclerosis	3,22	1,52	21,41
Glaucoma	14,79	1,51	21,24
Other specified and unspecified gastrointesti	6,86	1,47	20,65
Disorders of lipid metabolism	67,89	1,41	19,87
Essential hypertension	92,44	1,32	18,52
Biliary tract disease	5,08	1,31	18,43
Asthma	15,16	1,27	17,78
Depressive disorders	44,53	1,26	17,75
Diverticulosis and diverticulitis	11,54	1,26	17,69
Thyroid disorders	37,12	1,18	16,63
Urinary incontinence	50,33	1,17	16,41
Osteoporosis	28,98	1,12	15,77
Other general signs and symptoms	8,60	1,12	15,76
Neoplasia (general)	23,16	1,11	15,58
Other specified and unspecified nutritional a	34,03	1,10	15,46
Spondylopathies/spondyloarthropathy (inclu	26,55	1,09	15,34
Malnutrition	3,27	1,09	15,33
Osteoarthritis	57,43	1,08	15,24
Cataract and other lens disorders	33,18	1,06	14,95
Nervous system signs and symptoms	5,83	1,05	14,76
Nerve and nerve root disorders	10,67	1,04	14,54
Other specified inflammatory condition of sk	6,76	1,01	14,18
Hepatitis	3,20	1,01	14,16
Other specified joint disorders	12,41	1,01	14,14
Acquired foot deformities	10,68	0,97	13,63
Anxiety and fear-related disorders	32,79	0,94	13,27
Menopausal disorders	7,90	0,94	13,27
Symptoms of mental and substance use conc	6,80	0,94	13,22
Hearing loss	14,11	0,91	12,79
Disorders of teeth and gingiva	8,63	0,91	12,74
Neurocognitive disorders	24,58	0,89	12,49
Esophageal disorders	13,75	0,88	12,39
Epilepsy; convulsions	2,90	0,87	12,17
Trauma- and stressor-related disorders	5,44	0,86	12,05
Prolapse of female genital organs	7,42	0,85	11,95
Diseases of white blood cells	4,05	0,83	11,73
Drug induced or toxic related condition	1,91	0,83	11,71
Scoliosis and other postural dorsopathic defc	4,83	0,81	11,33
Other specified and unspecified upper respir	9,56	0,77	10,89
Cerebral infarction	4,19	0,76	10,61
Gastritis and duodenitis	3,79	0,65	9,16
Digestive congenital anomalies	3,63	0,62	8,78
Disruptive, impulse-control and conduct diso	1,26	0,55	7,72
Parkinson`s disease	2,41	0,54	7,55
Miscellaneous mental and behavioral disorde	1,29	0,46	6,45
Schizophrenia spectrum and other psychotic	1,75	0,42	5,94
Headache; including migraine	2,31	0,35	4,98
Bipolar and related disorders	0,63	0,29	4,05
Neurodevelopmental disorders	0,00	0,00	0,01
Paralysis (other than cerebral palsy)	0,00	0,00	0,01

Osteoinflammatory - psychosomatic - cardiovascular risk factors			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Other specified and unspecified gastrointesti	9,73	2,08	49,98
Nervous system pain and pain syndromes	11,11	2,07	49,59
Retinal and vitreous conditions	11,62	2,03	48,67
Spondylopathies/spondyloarthropathy (inclu	48,92	2,01	48,27
Headache; including migraine	12,73	1,95	46,86
Esophageal disorders	30,33	1,95	46,67
Nephritis; nephrosis; renal sclerosis	3,99	1,89	45,27
Hearing loss	29,08	1,88	45,00
Scoliosis and other postural dorsopathic defc	11,12	1,86	44,54
Asthma	22,10	1,84	44,25
Diverticulosis and diverticulitis	16,45	1,80	43,08
Nerve and nerve root disorders	18,34	1,78	42,68
Nutritional deficiencies	21,97	1,77	42,43
Chronic obstructive pulmonary disease and b	23,22	1,76	42,16
Digestive congenital anomalies	10,06	1,73	41,53
Gastroduodenal ulcer	5,13	1,71	41,10
Other specified and unspecified upper respir	21,05	1,71	40,95
Other specified hereditary and degenerative	12,90	1,68	40,40
Anxiety and fear-related disorders	57,78	1,66	39,94
Other specified joint disorders	20,52	1,66	39,92
Systemic lupus erythematosus and connectiv	11,98	1,66	39,78
Gastritis and duodenitis	9,62	1,65	39,71
Osteoporosis	40,01	1,55	37,19
Depressive disorders	54,10	1,54	36,83
Prolapse of female genital organs	13,22	1,52	36,38
Trauma- and stressor-related disorders	9,16	1,44	34,66
Osteoarthritis	75,43	1,42	34,18
Acquired foot deformities	15,65	1,42	34,11
Cataract and other lens disorders	43,93	1,41	33,80
Parkinson`s disease	6,18	1,38	33,01
Other specified and unspecified nutritional a	41,67	1,35	32,34
Sleep wake disorders	38,34	1,33	31,84
Menopausal disorders	10,82	1,29	31,01
Disorders of teeth and gingiva	12,13	1,28	30,60
Neurocognitive disorders	34,68	1,25	30,08
Conduction disorders	17,84	1,24	29,80
Urinary incontinence	52,78	1,23	29,40
Symptoms of mental and substance use conc	8,85	1,22	29,38
Thyroid disorders	36,57	1,17	27,98
Glaucoma	11,37	1,16	27,89
Drug induced or toxic related condition	2,65	1,16	27,79
Rheumatoid arthritis and related disease	3,23	1,11	26,63
Non-pressure ulcer of skin	2,71	1,10	26,38
Disorders of lipid metabolism	52,66	1,10	26,31
Hepatitis	3,45	1,09	26,14
Essential hypertension	76,03	1,08	26,01
Obesity	47,51	1,07	25,67
Other specified and unspecified liver disease	12,25	1,07	25,66
Other specified and unspecified endocrine di	5,15	0,99	23,77
Biliary tract disease	3,73	0,96	23,11
Other specified nervous system disorders	2,09	0,95	22,78
Hematologic neoplasia	2,67	0,95	22,75
Chronic kidney disease	18,47	0,94	22,66
Other and ill-defined heart disease	6,73	0,94	22,64
Other specified inflammatory condition of sk	6,26	0,94	22,44
Epilepsy; convulsions	3,12	0,93	22,34
Diseases of white blood cells	4,10	0,85	20,30
Peripheral and visceral vascular disease	4,69	0,84	20,27
Coagulation and hemorrhagic disorders	2,63	0,81	19,33
Cardiac dysrhythmias	17,59	0,80	19,17
Heart failure	15,32	0,78	18,71
Disruptive, impulse-control and conduct diso	1,74	0,76	18,27
Neoplasia (general)	15,82	0,76	18,18
Nonrheumatic and unspecified valve disorde	8,79	0,74	17,86
Nervous system signs and symptoms	4,10	0,74	17,71
Diabetes mellitus without complication	23,64	0,72	17,31
Pressure ulcer of skin	4,92	0,71	16,95
Coronary atherosclerosis and other heart dis	7,73	0,70	16,84
Bipolar and related disorders	1,48	0,67	16,15
Respiratory failure; insufficiency; arrest	1,55	0,61	14,60
Malnutrition	1,80	0,60	14,43
Hypertension with complications and second	3,73	0,60	14,33
Acute myocardial infarction	1,48	0,58	13,90
Other general signs and symptoms	4,11	0,54	12,87
Gout	1,15	0,40	9,48
Miscellaneous mental and behavioral disorde	1,11	0,39	9,46
Cerebral infarction	2,16	0,39	9,34
Diabetes mellitus with complication	5,07	0,38	9,08
Myocarditis and cardiomyopathy	1,11	0,29	7,04
Schizophrenia spectrum and other psychotic	0,77	0,19	4,47
Pulmonary heart disease	0,85	0,16	3,91
Chronic rheumatic heart disease	0,42	0,12	2,79
Paralysis (other than cerebral palsy)	0,03	0,01	0,30
Neurodevelopmental disorders	0,00	0,00	0,00

Females, 66-80 (3 out of 3)

Neoplasia - haematologic			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Diseases of white blood cells	6,41	1,32	57,50
Neoplasia (general)	26,75	1,28	55,67
Malnutrition	3,32	1,11	48,14
Biliary tract disease	4,29	1,11	48,03
Acquired foot deformities	11,97	1,09	47,21
Menopausal disorders	9,08	1,08	47,13
Hematologic neoplasia	2,90	1,03	44,70
Trauma- and stressor-related disorders	6,52	1,03	44,67
Headache; including migraine	6,68	1,02	44,49
Prolapse of female genital organs	8,72	1,00	43,45
Other specified inflammatory condition of sk	6,33	0,94	41,06
Thyroid disorders	29,50	0,94	40,87
Other specified and unspecified upper respir	11,60	0,94	40,86
Gastritis and duodenitis	5,47	0,94	40,86
Cataract and other lens disorders	29,02	0,93	40,43
Glaucoma	8,73	0,89	38,78
Digestive congenital anomalies	5,12	0,88	38,25
Essential hypertension	61,48	0,88	38,09
Obesity	38,52	0,87	37,70
Nerve and nerve root disorders	8,90	0,86	37,51
Osteoarthritis	45,70	0,86	37,50
Rheumatoid arthritis and related disease	2,49	0,86	37,21
Other specified joint disorders	10,41	0,84	36,68
Disorders of lipid metabolism	40,35	0,84	36,51
Other specified and unspecified liver disease	9,46	0,83	35,90
Other specified and unspecified nutritional a	24,15	0,78	33,93
Disorders of teeth and gingiva	7,22	0,76	32,99
Anxiety and fear-related disorders	25,72	0,74	32,20
Osteoporosis	18,66	0,72	31,41
Esophageal disorders	10,80	0,69	30,09
Diabetes mellitus without complication	22,50	0,69	29,83
Asthma	8,16	0,68	29,58
Hearing loss	10,54	0,68	29,55
Sleep wake disorders	19,61	0,68	29,49
Scoliosis and other postural dorsopathic defo	4,06	0,68	29,41
Diverticulosis and diverticulitis	6,10	0,67	28,94
Systemic lupus erythematosus and connectiv	4,73	0,65	28,46
Nephritis; nephrosis; renal sclerosis	1,37	0,65	28,12
Hepatitis	2,03	0,64	27,87
Conduction disorders	9,13	0,64	27,64
Gout	1,74	0,60	26,06
Drug induced or toxic related condition	1,36	0,59	25,71
Spondylopathies/spondyloarthropathy (inclu	13,97	0,57	24,96
Chronic obstructive pulmonary disease and b	7,57	0,57	24,90
Depressive disorders	19,88	0,56	24,51
Other specified and unspecified gastrointesti	2,63	0,56	24,45
Coagulation and hemorrhagic disorders	1,78	0,54	23,67
Gastroduodenal ulcer	1,54	0,51	22,31
Cardiac dysrhythmias	11,26	0,51	22,22
Nutritional deficiencies	6,19	0,50	21,66
Peripheral and visceral vascular disease	2,70	0,49	21,12
Other specified nervous system disorders	1,04	0,47	20,46
Acute myocardial infarction	1,20	0,47	20,38
Other specified and unspecified endocrine di	2,36	0,45	19,73
Retinal and vitreous conditions	2,60	0,45	19,70
Coronary atherosclerosis and other heart dis	4,95	0,45	19,54
Nonrheumatic and unspecified valve disorde	4,89	0,41	17,98
Diabetes mellitus with complication	5,53	0,41	17,94
Other specified hereditary and degenerative	3,10	0,40	17,58
Urinary incontinence	17,33	0,40	17,48
Chronic kidney disease	7,69	0,39	17,09
Hypertension with complications and second	2,10	0,34	14,59
Neurocognitive disorders	8,28	0,30	13,01
Chronic rheumatic heart disease	1,03	0,29	12,39
Bipolar and related disorders	0,56	0,26	11,14
Pulmonary heart disease	1,20	0,23	10,04
Cerebral infarction	1,10	0,20	8,62
Pressure ulcer of skin	1,34	0,19	8,39
Schizophrenia spectrum and other psychotic	0,78	0,19	8,22
Epilepsy; convulsions	0,61	0,18	7,94
Heart failure	3,36	0,17	7,43
Nervous system pain and pain syndromes	0,70	0,13	5,69
Other and ill-defined heart disease	0,88	0,12	5,37
Parkinson`s disease	0,50	0,11	4,84
Symptoms of mental and substance use cond	0,80	0,11	4,81
Other general signs and symptoms	0,82	0,11	4,66
Nervous system signs and symptoms	0,59	0,11	4,63
Respiratory failure; insufficiency; arrest	0,26	0,10	4,49
Disruptive, impulse-control and conduct diso	0,22	0,10	4,21
Non-pressure ulcer of skin	0,22	0,09	3,79
Miscellaneous mental and behavioral disorde	0,23	0,08	3,62
Myocarditis and cardiomyopathy	0,31	0,08	3,59
Paralysis (other than cerebral palsy)	0,04	0,02	0,69
Neurodevelopmental disorders	0,01	0,01	0,24

Males, 81-90 (1 out of 3)

Heart - liver - gastrointestinal diseases			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Other specified and unspecified gastrointestina	8,65	4,21	38,14
Biliary tract disease	14,69	4,21	38,11
Chronic rheumatic heart disease	16,16	3,94	35,63
Acquired foot deformities	13,60	3,90	35,29
Myocarditis and cardiomyopathy	11,98	3,43	31,07
Pulmonary heart disease	22,94	3,29	29,76
Other and ill-defined heart disease	30,44	3,15	28,56
Polyneuropathies	6,40	3,12	28,21
Sequela of specified infectious disease conditic	6,30	3,07	27,78
Alcohol-related disorders	8,80	2,86	25,88
Gastritis and duodenitis	15,01	2,81	25,45
Lung disease due to external agents	5,89	2,61	23,59
Miscellaneous mental and behavioral disorder:	11,79	2,50	22,61
Non-pressure ulcer of skin	14,70	2,47	22,35
Paralysis (other than cerebral palsy)	8,07	2,46	22,25
Heart failure	79,32	2,44	22,14
Osteoporosis	13,45	2,34	21,19
Systemic lupus erythematosus and connective	9,86	2,29	20,70
Diseases of white blood cells	12,06	2,26	20,45
Blindness and vision defects	5,84	2,19	19,80
Other specified and unspecified liver disease	15,76	2,02	18,29
Cerebral infarction	24,77	2,01	18,21
Gout	32,80	1,97	17,86
Coagulation and hemorrhagic disorders	14,93	1,96	17,79
Respiratory failure; insufficiency; arrest	8,44	1,96	17,71
Other specified inflammatory condition of skin	16,01	1,95	17,65
Trauma- and stressor-related disorders	6,49	1,86	16,84
Nonrheumatic and unspecified valve disorders	31,32	1,86	16,84
Cardiac dysrhythmias	73,38	1,84	16,68
Other specified joint disorders	10,82	1,82	16,45
Nervous system signs and symptoms	21,23	1,78	16,14
Other specified and unspecified endocrine disc	5,74	1,75	15,82
Epilepsy; convulsions	5,64	1,72	15,54
Nerve and nerve root disorders	5,63	1,71	15,52
Nervous system pain and pain syndromes	5,95	1,71	15,44
Diverticulosis and diverticulitis	24,02	1,69	15,35
Acute myocardial infarction	13,72	1,67	15,12
Other and ill-defined cerebrovascular disease	4,79	1,66	15,08
Coronary atherosclerosis and other heart disea	51,34	1,64	14,89
Retinal and vitreous conditions	8,47	1,53	13,83
Sequela of cerebral infarction and other cerebı	4,08	1,53	13,83
Esophageal disorders	18,67	1,52	13,72
Occlusion or stenosis of precerebral or cerebra	6,45	1,50	13,55
Conduction disorders	48,54	1,48	13,38
Nutritional deficiencies	17,26	1,47	13,35
Chronic obstructive pulmonary disease and brc	53,29	1,45	13,13
Obesity	36,18	1,39	12,56
Hearing loss	33,81	1,38	12,53
Aortic; peripheral; and visceral artery aneurysr	5,64	1,37	12,43
Osteoarthritis	55,48	1,31	11,88
Other specified hereditary and degenerative n	9,10	1,30	11,81
Hyperplasia of prostate	70,26	1,27	11,52
Glaucoma	13,86	1,25	11,32
Disruptive, impulse-control and conduct disorc	7,67	1,24	11,27
Hypertension with complications and secondar	10,98	1,24	11,26
Depressive disorders	25,46	1,24	11,23
Digestive congenital anomalies	5,73	1,21	10,98
Chronic kidney disease	47,16	1,20	10,89
Hepatitis	3,69	1,20	10,84
Neoplasia (general)	38,63	1,18	10,71
Sleep wake disorders	33,84	1,15	10,44
Diabetes mellitus without complication	47,53	1,15	10,43
Neurocognitive disorders	54,04	1,15	10,41
Essential hypertension	89,34	1,14	10,31
Disorders of lipid metabolism	57,03	1,13	10,22
Other specified and unspecified upper respirat	11,08	1,12	10,18
Urinary incontinence	63,01	1,11	10,03
Nephritis; nephrosis; renal sclerosis	2,25	1,10	9,93
Anxiety and fear-related disorders	14,06	0,95	8,61
Spondylopathies/spondyloarthropathy (includi	17,86	0,95	8,56
Peripheral and visceral vascular disease	18,91	0,93	8,42
Transient cerebral ischemia	3,76	0,92	8,29
Hematologic neoplasia	2,37	0,89	8,04
Other general signs and symptoms	10,10	0,85	7,68
Other specified and unspecified diseases of bla	1,72	0,84	7,57
Other specified and unspecified nutritional and	20,63	0,80	7,22
Cataract and other lens disorders	29,59	0,77	6,94
Pressure ulcer of skin	9,09	0,73	6,57
Gastroduodenal ulcer	3,81	0,66	6,01
Malnutrition	3,48	0,65	5,90
Thyroid disorders	7,13	0,62	5,62
Diabetes mellitus with complication	9,14	0,60	5,44
Asthma	2,50	0,53	4,79
Symptoms of mental and substance use condit	6,78	0,52	4,75
Disorders of teeth and gingiva	5,13	0,51	4,62
Parkinson`s disease	3,20	0,40	3,62
Scoliosis and other postural dorsopathic defor	0,95	0,36	3,23
Other specified nervous system disorders	0,64	0,31	2,84
Other specified and unspecified hematologic c	0,58	0,26	2,34
Headache; including migraine	0,02	0,01	0,06

Cardiorespiratory - COPD			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Lung disease due to external agents	12,09	5,35	65,08
Respiratory failure; insufficiency; arrest	19,55	4,53	55,09
Pulmonary heart disease	29,81	4,27	51,89
Chronic rheumatic heart disease	15,66	3,81	46,35
Other and ill-defined heart disease	32,32	3,35	40,70
Nonrheumatic and unspecified valve disorders	51,27	3,05	37,01
Occlusion or stenosis of precerebral or cerebra	12,74	2,95	35,90
Alcohol-related disorders	8,19	2,66	32,32
Other specified and unspecified gastrointestina	5,37	2,61	31,77
Sequela of specified infectious disease conditic	5,30	2,58	31,37
Other specified and unspecified endocrine disc	8,41	2,56	31,10
Nervous system pain and pain syndromes	8,87	2,54	30,88
Heart failure	77,86	2,40	29,17
Myocarditis and cardiomyopathy	8,15	2,33	28,36
Hypertension with complications and secondar	20,23	2,29	27,85
Asthma	9,76	2,07	25,13
Chronic obstructive pulmonary disease and brc	73,42	2,00	24,28
Nerve and nerve root disorders	6,47	1,97	23,92
Aortic; peripheral; and visceral artery aneurysr	7,81	1,90	23,11
Osteoporosis	10,66	1,85	22,54
Sleep wake disorders	51,29	1,75	21,23
Coronary atherosclerosis and other heart disea	53,31	1,71	20,76
Esophageal disorders	20,84	1,69	20,56
Biliary tract disease	5,78	1,66	20,12
Obesity	41,51	1,59	19,35
Cardiac dysrhythmias	63,23	1,59	19,29
Other specified inflammatory condition of skin	13,01	1,58	19,25
Sequela of cerebral infarction and other cerebı	3,88	1,45	17,68
Other specified and unspecified upper respirat	14,26	1,45	17,58
Disruptive, impulse-control and conduct disorc	8,91	1,45	17,57
Glaucoma	15,87	1,43	17,39
Chronic kidney disease	53,16	1,36	16,48
Diverticulosis and diverticulitis	19,18	1,35	16,45
Hyperplasia of prostate	74,48	1,35	16,39
Nervous system signs and symptoms	15,95	1,34	16,28
Peripheral and visceral vascular disease	27,16	1,34	16,24
Gout	22,10	1,33	16,15
Conduction disorders	43,50	1,32	16,09
Hepatitis	4,02	1,31	15,87
Hearing loss	31,40	1,29	15,62
Other specified and unspecified liver disease	9,90	1,27	15,41
Coagulation and hemorrhagic disorders	9,45	1,24	15,12
Nutritional deficiencies	14,40	1,23	14,95
Other general signs and symptoms	14,55	1,22	14,85
Osteoarthritis	51,63	1,22	14,83
Disorders of lipid metabolism	61,18	1,21	14,72
Spondylopathies/spondyloarthropathy (includi	22,86	1,21	14,71
Other specified hereditary and degenerative n	8,33	1,19	14,51
Neoplasia (general)	37,59	1,15	14,00
Polyneuropathies	2,34	1,14	13,88
Malnutrition	6,06	1,14	13,81
Anxiety and fear-related disorders	16,71	1,13	13,74
Other specified and unspecified nutritional and	28,99	1,12	13,62
Transient cerebral ischemia	4,56	1,11	13,49
Trauma- and stressor-related disorders	3,81	1,09	13,28
Acute myocardial infarction	8,95	1,09	13,24
Disorders of teeth and gingiva	10,58	1,05	12,78
Gastritis and duodenitis	5,61	1,05	12,77
Essential hypertension	81,82	1,04	12,68
Other specified joint disorders	6,18	1,04	12,61
Depressive disorders	21,29	1,04	12,60
Non-pressure ulcer of skin	6,16	1,03	12,57
Cataract and other lens disorders	39,78	1,03	12,53
Acquired foot deformities	3,58	1,03	12,46
Thyroid disorders	11,42	0,99	12,07
Urinary incontinence	56,32	0,99	12,03
Blindness and vision defects	2,52	0,94	11,46
Neurocognitive disorders	43,99	0,94	11,37
Epilepsy; convulsions	2,99	0,91	11,06
Cerebral infarction	11,21	0,91	11,05
Diseases of white blood cells	4,85	0,91	11,03
Paralysis (other than cerebral palsy)	2,96	0,90	10,94
Retinal and vitreous conditions	4,58	0,83	10,04
Nephritis; nephrosis; renal sclerosis	1,69	0,82	10,02
Miscellaneous mental and behavioral disorder:	3,87	0,82	9,96
Scoliosis and other postural dorsopathic defor	2,08	0,78	9,46
Hematologic neoplasia	2,04	0,76	9,28
Other and ill-defined cerebrovascular disease	2,18	0,76	9,20
Parkinson`s disease	5,85	0,73	8,88
Pressure ulcer of skin	9,12	0,73	8,85
Systemic lupus erythematosus and connective	3,13	0,73	8,82
Digestive congenital anomalies	3,20	0,68	8,23
Diabetes mellitus without complication	27,63	0,67	8,14
Symptoms of mental and substance use condit	8,51	0,66	7,99
Other specified nervous system disorders	1,14	0,55	6,73
Other specified and unspecified hematologic c	1,00	0,44	5,36
Diabetes mellitus with complication	4,12	0,27	3,29
Other specified and unspecified diseases of bla	0,49	0,24	2,91
Gastroduodenal ulcer	1,03	0,18	2,18
Headache; including migraine	0,29	0,12	1,45

Males, 81-90 (2 out of 3)

Psychogeriatric/cerebrovascular			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Sequela of cerebral infarction and other cerebr	8,00	3,00	65,43
Other specified and unspecified hematologic c	6,75	2,99	65,20
Symptoms of mental and substance use condit	35,52	2,75	59,95
Pressure ulcer of skin	30,91	2,47	53,88
Other general signs and symptoms	29,34	2,46	53,79
Disruptive, impulse-control and conduct disorc	15,01	2,44	53,20
Paralysis (other than cerebral palsy)	7,96	2,42	52,90
Parkinson`s disease	18,90	2,36	51,52
Epilepsy; convulsions	6,69	2,04	44,46
Nervous system signs and symptoms	24,20	2,03	44,36
Neurocognitive disorders	90,04	1,91	41,81
Miscellaneous mental and behavioral disorders	8,93	1,89	41,30
Osteoporosis	10,33	1,80	39,22
Cerebral infarction	20,62	1,67	36,55
Urinary incontinence	93,24	1,64	35,79
Hepatitis	5,01	1,63	35,50
Depressive disorders	31,68	1,54	33,69
Malnutrition	8,10	1,52	33,14
Blindness and vision defects	3,97	1,49	32,46
Other and ill-defined cerebrovascular disease	4,11	1,43	31,18
Nutritional deficiencies	16,54	1,41	30,85
Nervous system pain and pain syndromes	4,92	1,41	30,79
Other specified and unspecified diseases of bla	2,80	1,36	29,78
Other specified hereditary and degenerative ne	9,16	1,31	28,65
Gastroduodenal ulcer	6,76	1,18	25,67
Sleep wake disorders	33,04	1,13	24,56
Hearing loss	27,24	1,11	24,34
Aortic; peripheral; and visceral artery aneurysr	4,20	1,02	22,31
Hyperplasia of prostate	54,97	1,00	21,73
Polyneuropathies	2,01	0,98	21,37
Sequela of specified infectious disease conditic	1,96	0,95	20,80
Gastritis and duodenitis	4,74	0,89	19,37
Retinal and vitreous conditions	4,87	0,88	19,19
Other specified and unspecified nutritional and	21,92	0,85	18,49
Osteoarthritis	35,80	0,85	18,48
Trauma- and stressor-related disorders	2,88	0,83	18,02
Coagulation and hemorrhagic disorders	6,23	0,82	17,91
Thyroid disorders	9,41	0,82	17,87
Diseases of white blood cells	4,36	0,82	17,81
Essential hypertension	63,66	0,81	17,72
Diabetes mellitus without complication	33,46	0,81	17,70
Headache; including migraine	1,97	0,80	17,46
Chronic obstructive pulmonary disease and bro	28,98	0,79	17,22
Diverticulosis and diverticulitis	10,62	0,75	16,36
Disorders of lipid metabolism	37,85	0,75	16,36
Transient cerebral ischemia	3,00	0,73	15,97
Obesity	18,92	0,73	15,84
Chronic kidney disease	28,44	0,73	15,83
Cardiac dysrhythmias	28,59	0,72	15,67
Other specified and unspecified endocrine disc	2,28	0,69	15,17
Occlusion or stenosis of precerebral or cerebra	2,88	0,67	14,56
Spondylopathies/spondyloarthropathy (includi	12,59	0,67	14,54
Disorders of teeth and gingiva	6,57	0,65	14,26
Cataract and other lens disorders	25,04	0,65	14,16
Alcohol-related disorders	1,92	0,62	13,62
Diabetes mellitus with complication	9,32	0,61	13,39
Hematologic neoplasia	1,64	0,61	13,37
Anxiety and fear-related disorders	8,90	0,60	13,14
Conduction disorders	19,66	0,60	13,07
Nephritis; nephrosis; renal sclerosis	1,22	0,59	12,94
Other specified inflammatory condition of skin	4,84	0,59	12,86
Gout	9,73	0,59	12,78
Other specified and unspecified liver disease	4,53	0,58	12,68
Other specified joint disorders	3,45	0,58	12,63
Neoplasia (general)	18,57	0,57	12,42
Digestive congenital anomalies	2,60	0,55	12,03
Glaucoma	6,08	0,55	11,96
Other specified and unspecified upper respirat	5,16	0,52	11,44
Peripheral and visceral vascular disease	9,50	0,47	10,20
Respiratory failure; insufficiency; arrest	1,88	0,44	9,51
Esophageal disorders	5,36	0,44	9,50
Scoliosis and other postural dorsopathic defor	1,00	0,37	8,14
Heart failure	11,68	0,36	7,86
Non-pressure ulcer of skin	2,11	0,35	7,72
Nerve and nerve root disorders	1,11	0,34	7,36
Acquired foot deformities	1,13	0,32	7,06
Pulmonary heart disease	2,22	0,32	6,95
Nonrheumatic and unspecified valve disorders	5,00	0,30	6,49
Myocarditis and cardiomyopathy	1,02	0,29	6,37
Hypertension with complications and secondar	2,52	0,29	6,22
Systemic lupus erythematosus and connective	1,07	0,25	5,40
Chronic rheumatic heart disease	1,01	0,25	5,39
Asthma	1,09	0,23	5,04
Other and ill-defined heart disease	2,20	0,23	4,98
Other specified nervous system disorders	0,29	0,14	3,09
Coronary atherosclerosis and other heart disea	4,29	0,14	3,00
Lung disease due to external agents	0,19	0,08	1,85
Other specified and unspecified gastrointestina	0,15	0,07	1,61
Acute myocardial infarction	0,07	0,01	0,19
Biliary tract disease	0,02	0,00	0,10

DM - cardiovascular risk factors			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Diabetes mellitus with complication	44,86	2,95	71,23
Acute myocardial infarction	22,07	2,69	64,82
Other specified nervous system disorders	5,08	2,47	59,63
Non-pressure ulcer of skin	13,47	2,26	54,59
Peripheral and visceral vascular disease	44,24	2,18	52,50
Diabetes mellitus without complication	81,56	1,98	47,67
Other specified and unspecified diseases of bla	3,80	1,85	44,64
Coronary atherosclerosis and other heart disea	53,37	1,71	41,26
Gastroduodenal ulcer	9,66	1,68	40,54
Nerve and nerve root disorders	5,46	1,66	40,09
Gout	27,60	1,66	40,03
Transient cerebral ischemia	6,73	1,64	39,55
Thyroid disorders	18,73	1,63	39,30
Other specified joint disorders	9,60	1,61	38,88
Nephritis; nephrosis; renal sclerosis	3,20	1,56	37,63
Systemic lupus erythematosus and connective	6,66	1,54	37,23
Disorders of lipid metabolism	75,06	1,49	35,85
Chronic kidney disease	56,77	1,45	34,92
Conduction disorders	46,44	1,41	34,10
Glaucoma	15,61	1,41	33,97
Other specified and unspecified nutritional and	33,94	1,31	31,65
Other specified and unspecified endocrine disc	4,29	1,31	31,52
Heart failure	40,25	1,24	29,93
Biliary tract disease	4,29	1,23	29,64
Coagulation and hemorrhagic disorders	9,33	1,23	29,63
Other specified and unspecified upper respirat	12,07	1,22	29,54
Malnutrition	6,54	1,22	29,53
Nutritional deficiencies	14,27	1,22	29,42
Aortic; peripheral; and visceral artery aneurysr	4,95	1,21	29,08
Obesity	31,12	1,19	28,79
Digestive congenital anomalies	5,63	1,19	28,74
Anxiety and fear-related disorders	17,27	1,17	28,18
Other specified inflammatory condition of skin	9,48	1,15	27,86
Essential hypertension	89,07	1,14	27,40
Depressive disorders	23,03	1,12	27,05
Parkinson`s disease	8,90	1,11	26,81
Scoliosis and other postural dorsopathic defor	2,95	1,10	26,64
Other and ill-defined cerebrovascular disease	3,14	1,09	26,35
Occlusion or stenosis of precerebral or cerebra	4,53	1,05	25,32
Spondylopathies/spondyloarthropathy (includi	19,62	1,04	25,05
Retinal and vitreous conditions	5,73	1,03	24,95
Trauma- and stressor-related disorders	3,60	1,03	24,88
Cardiac dysrhythmias	40,91	1,03	24,78
Cataract and other lens disorders	39,19	1,02	24,49
Neoplasia (general)	32,96	1,01	24,36
Neurocognitive disorders	47,07	1,00	24,15
Disorders of teeth and gingiva	10,04	1,00	24,07
Chronic obstructive pulmonary disease and bro	36,31	0,99	23,84
Hematologic neoplasia	2,55	0,96	23,05
Blindness and vision defects	2,52	0,94	22,73
Acquired foot deformities	3,16	0,90	21,83
Urinary incontinence	50,45	0,89	21,40
Hyperplasia of prostate	48,95	0,89	21,38
Osteoarthritis	37,17	0,88	21,20
Other specified and unspecified liver disease	6,79	0,87	20,99
Nonrheumatic and unspecified valve disorders	14,21	0,84	20,35
Hearing loss	19,92	0,82	19,67
Diseases of white blood cells	4,15	0,78	18,75
Pressure ulcer of skin	9,43	0,75	18,16
Diverticulosis and diverticulitis	10,54	0,74	17,95
Asthma	3,50	0,74	17,90
Sleep wake disorders	21,14	0,72	17,37
Nervous system signs and symptoms	8,31	0,70	16,83
Gastritis and duodenitis	3,63	0,68	16,39
Disruptive, impulse-control and conduct disorc	4,18	0,68	16,35
Esophageal disorders	8,33	0,68	16,32
Hypertension with complications and secondar	5,37	0,61	14,68
Cerebral infarction	7,43	0,60	14,54
Other general signs and symptoms	6,44	0,54	13,05
Myocarditis and cardiomyopathy	1,88	0,54	12,98
Other specified hereditary and degenerative ne	3,60	0,52	12,43
Other and ill-defined heart disease	4,89	0,51	12,22
Symptoms of mental and substance use condit	6,24	0,48	11,64
Nervous system pain and pain syndromes	1,66	0,47	11,45
Miscellaneous mental and behavioral disorders	2,20	0,47	11,22
Epilepsy; convulsions	1,36	0,42	10,02
Other specified and unspecified gastrointestina	0,76	0,37	8,90
Osteoporosis	2,09	0,36	8,79
Paralysis (other than cerebral palsy)	1,12	0,34	8,19
Headache; including migraine	0,83	0,34	8,17
Alcohol-related disorders	0,94	0,31	7,37
Hepatitis	0,89	0,29	6,96
Pulmonary heart disease	1,16	0,17	3,99
Sequela of cerebral infarction and other cerebr	0,33	0,12	3,01
Other specified and unspecified hematologic c	0,05	0,02	0,50
Sequela of specified infectious disease conditic	0,03	0,02	0,39
Lung disease due to external agents	0,03	0,02	0,37
Respiratory failure; insufficiency; arrest	0,04	0,01	0,21
Chronic rheumatic heart disease	0,02	0,01	0,13
Polyneuropathies	0,01	0,01	0,12

Males, 81-90 (3 out of 3)

Unspecific			
Chronic condition	Prevalence (%)	O/E ratio	Exclusivity (%)
Headache; including migraine	5,47	2,22	72,87
Scoliosis and other postural dorsopathic defor	4,27	1,60	52,53
Asthma	6,78	1,44	47,14
Hematologic neoplasia	3,76	1,41	46,25
Disorders of teeth and gingiva	13,57	1,35	44,27
Cataract and other lens disorders	49,24	1,28	41,88
Digestive congenital anomalies	5,76	1,22	40,02
Hypertension with complications and seconda	10,75	1,22	39,98
Esophageal disorders	14,97	1,22	39,90
Neoplasia (general)	38,30	1,17	38,52
Spondylopathies/spondyloarthropathy (includi	21,37	1,13	37,14
Polyneuropathies	2,28	1,11	36,42
Anxiety and fear-related disorders	16,36	1,11	36,33
Diverticulosis and diverticulitis	14,63	1,03	33,89
Osteoarthritis	43,30	1,02	33,61
Other specified and unspecified liver disease	7,75	0,99	32,62
Other specified hereditary and degenerative n	6,93	0,99	32,59
Retinal and vitreous conditions	5,40	0,97	31,99
Diseases of white blood cells	5,20	0,97	31,96
Essential hypertension	76,20	0,97	31,89
Other specified and unspecified upper respirat	9,38	0,95	31,26
Hepatitis	2,89	0,94	30,83
Nephritis; nephrosis; renal sclerosis	1,84	0,90	29,48
Other specified and unspecified nutritional and	22,87	0,88	29,02
Hyperplasia of prostate	48,77	0,88	28,99
Systemic lupus erythematosus and connective	3,66	0,85	27,86
Hearing loss	20,72	0,85	27,84
Other specified nervous system disorders	1,73	0,84	27,71
Trauma- and stressor-related disorders	2,87	0,82	26,98
Other specified and unspecified hematologic c	1,83	0,81	26,61
Sleep wake disorders	23,61	0,80	26,40
Gastritis and duodenitis	4,23	0,79	26,02
Gastroduodenal ulcer	4,48	0,78	25,61
Glaucoma	8,56	0,77	25,35
Thyroid disorders	8,80	0,77	25,13
Cardiac dysrhythmias	28,61	0,72	23,58
Obesity	18,64	0,71	23,46
Acquired foot deformities	2,48	0,71	23,36
Conduction disorders	23,38	0,71	23,36
Disorders of lipid metabolism	35,16	0,70	22,85
Transient cerebral ischemia	2,84	0,69	22,70
Other specified inflammatory condition of skin	5,60	0,68	22,38
Chronic kidney disease	26,14	0,67	21,88
Chronic obstructive pulmonary disease and bro	24,11	0,66	21,54
Myocarditis and cardiomyopathy	2,26	0,65	21,21
Alcohol-related disorders	1,95	0,63	20,82
Urinary incontinence	35,94	0,63	20,75
Coronary atherosclerosis and other heart disea	19,10	0,61	20,09
Sequela of specified infectious disease conditio	1,23	0,60	19,65
Cerebral infarction	7,37	0,60	19,64
Other specified and unspecified gastrointestina	1,22	0,60	19,57
Coagulation and hemorrhagic disorders	4,52	0,60	19,54
Other specified joint disorders	3,52	0,59	19,42
Nonrheumatic and unspecified valve disorders	9,90	0,59	19,31
Epilepsy; convulsions	1,89	0,58	18,92
Other and ill-defined cerebrovascular disease	1,59	0,55	18,19
Malnutrition	2,87	0,54	17,62
Respiratory failure; insufficiency; arrest	2,30	0,53	17,48
Diabetes mellitus without complication	20,19	0,49	16,06
Symptoms of mental and substance use conditi	6,18	0,48	15,67
Depressive disorders	9,65	0,47	15,43
Other specified and unspecified diseases of bla	0,94	0,46	15,10
Miscellaneous mental and behavioral disorder	2,15	0,45	14,92
Blindness and vision defects	1,10	0,41	13,55
Other and ill-defined heart disease	3,98	0,41	13,53
Gout	6,68	0,40	13,18
Nerve and nerve root disorders	1,31	0,40	13,10
Aortic; peripheral; and visceral artery aneurysr	1,63	0,40	13,06
Peripheral and visceral vascular disease	7,83	0,39	12,64
Pressure ulcer of skin	4,78	0,38	12,53
Chronic rheumatic heart disease	1,56	0,38	12,50
Neurocognitive disorders	17,57	0,37	12,27
Biliary tract disease	1,28	0,37	12,03
Nervous system pain and pain syndromes	1,22	0,35	11,43
Nutritional deficiencies	4,07	0,35	11,43
Heart failure	10,78	0,33	10,91
Occlusion or stenosis of precerebral or cerebra	1,40	0,33	10,67
Other general signs and symptoms	3,85	0,32	10,62
Parkinson`s disease	2,24	0,28	9,17
Lung disease due to external agents	0,63	0,28	9,10
Osteoporosis	1,45	0,25	8,26
Pulmonary heart disease	1,57	0,23	7,40
Diabetes mellitus with complication	3,07	0,20	6,64
Acute myocardial infarction	1,66	0,20	6,63
Nervous system signs and symptoms	2,32	0,19	6,40
Other specified and unspecified endocrine disc	0,64	0,19	6,39
Paralysis (other than cerebral palsy)	0,57	0,17	5,72
Non-pressure ulcer of skin	0,50	0,08	2,77
Disruptive, impulse-control and conduct disorc	0,30	0,05	1,60
Sequela of cerebral infarction and other cereb	0,00	0,00	0,04

Females, 81-95 (1 out of 2)

Cardiorespiratory			
Chronic condition	Prevalence (%	O/E ra	Exclusivity (%)
Chronic rheumatic heart disease	15,07	3,92	61,16
Respiratory failure; insufficiency; arrest	8,16	3,62	56,47
Pulmonary heart disease	24,13	3,40	53,01
Gout	6,15	2,83	44,19
Drug induced or toxic related condition	7,01	2,63	40,92
Other and ill-defined heart disease	23,39	2,50	39,00
Nonrheumatic and unspecified valve disorders	31,99	2,40	37,34
Hypertension with complications and secondary hy	17,52	2,23	34,80
Chronic obstructive pulmonary disease and bronchi	25,08	2,16	33,70
Asthma	21,66	2,14	33,43
Menopausal disorders	8,22	2,14	33,39
Coagulation and hemorrhagic disorders	6,67	2,00	31,15
Nerve and nerve root disorders	11,84	2,00	31,13
Heart failure	60,99	1,99	31,04
Crystal arthropathies (excluding gout)	4,29	1,91	29,70
Other specified and unspecified liver disease	10,83	1,85	28,91
Diseases of white blood cells	3,66	1,83	28,49
Hepatitis	3,76	1,80	28,10
Hematologic neoplasia	3,59	1,79	27,92
Esophageal disorders	22,88	1,71	26,71
Retinal and vitreous conditions	13,63	1,70	26,51
Nervous system pain and pain syndromes	14,20	1,68	26,26
Other specified and unspecified gastrointestinal dis	4,89	1,67	26,07
Other specified and unspecified upper respiratory c	13,93	1,67	26,02
Trauma- and stressor-related disorders	6,36	1,66	25,83
Diverticulosis and diverticulitis	17,96	1,64	25,61
Conduction disorders	28,63	1,63	25,46
Other specified inflammatory condition of skin	6,22	1,62	25,25
Non-pressure ulcer of skin	9,17	1,62	25,19
Cardiac dysrhythmias	50,66	1,61	25,10
Obesity	50,17	1,59	24,72
Spondylopathies/spondyloarthropathy (including in	31,48	1,58	24,71
Gastroduodenal ulcer	4,47	1,57	24,55
Thyroid disorders	37,83	1,56	24,28
Biliary tract disease	4,10	1,54	23,94
Prolapse of female genital organs	9,07	1,53	23,85
Nutritional deficiencies	22,91	1,49	23,26
Digestive congenital anomalies	7,08	1,49	23,19
Scoliosis and other postural dorsopathic deformitie	10,15	1,48	23,12
Systemic lupus erythematosus and connective tissu	10,90	1,47	22,87
Other specified joint disorders	10,61	1,46	22,77
Gastritis and duodenitis	4,47	1,45	22,56
Anxiety and fear-related disorders	37,78	1,42	22,12
Other specified and unspecified endocrine disorder	5,29	1,41	21,96
Acquired foot deformities	9,45	1,38	21,53
Depressive disorders	47,12	1,38	21,46
Chronic kidney disease	53,46	1,37	21,29
Cataract and other lens disorders	42,81	1,36	21,21
Other and ill-defined cerebrovascular disease	3,82	1,35	20,97
Hearing loss	33,86	1,34	20,94
Peripheral and visceral vascular disease	9,27	1,34	20,87
Disruptive, impulse-control and conduct disorders	5,06	1,32	20,55
Osteoarthritis	79,42	1,31	20,37
Transient cerebral ischemia	3,38	1,31	20,35
Coronary atherosclerosis and other heart disease	17,47	1,30	20,27
Headache; including migraine	3,89	1,30	20,19
Sleep wake disorders	42,23	1,29	20,12
Osteoporosis	33,42	1,28	20,00
Other specified and unspecified nutritional and met	37,55	1,26	19,59
Disorders of lipid metabolism	52,69	1,25	19,56
Glaucoma	17,59	1,21	18,88
Diabetes mellitus with complication	11,37	1,15	17,99
Disorders of teeth and gingiva	6,73	1,14	17,69
Essential hypertension	92,34	1,13	17,54
Nervous system signs and symptoms	13,20	1,12	17,48
Neoplasia (general)	15,41	1,10	17,14
Malnutrition	2,43	1,08	16,84
Miscellaneous mental and behavioral disorders/cor	3,96	1,05	16,43
Urinary incontinence	84,78	1,03	16,01
Diabetes mellitus without complication	31,44	1,02	15,83
Acute myocardial infarction	2,42	0,94	14,59
Symptoms of mental and substance use conditions	13,61	0,93	14,52
Cerebral infarction	7,58	0,92	14,31
Neurocognitive disorders	57,52	0,90	14,08
Other specified hereditary and degenerative nervou	7,95	0,87	13,63
Other general signs and symptoms	16,61	0,83	12,92
Pressure ulcer of skin	12,24	0,77	12,04
Epilepsy; convulsions	3,35	0,72	11,18
Schizophrenia spectrum and other psychotic disord	1,67	0,72	11,15
Paralysis (other than cerebral palsy)	1,72	0,69	10,70
Parkinson`s disease	2,93	0,58	8,97

DM - cardiovascular diseases			
Chronic condition	Prevalence (%)	O/E ra	Exclusivity (%)
Acute myocardial infarction	10,22	3,95	65,94
Diabetes mellitus with complication	38,50	3,91	65,24
Non-pressure ulcer of skin	15,15	2,67	44,54
Respiratory failure; insufficiency; arrest	5,65	2,51	41,87
Gout	5,19	2,39	39,93
Peripheral and visceral vascular disease	16,36	2,36	39,40
Coronary atherosclerosis and other heart disease	31,38	2,34	38,97
Other and ill-defined heart disease	21,03	2,25	37,55
Heart failure	66,17	2,16	36,05
Diabetes mellitus without complication	65,22	2,11	35,15
Biliary tract disease	5,51	2,06	34,40
Pulmonary heart disease	14,23	2,01	33,46
Other specified and unspecified endocrine disorder	7,49	1,99	33,26
Paralysis (other than cerebral palsy)	4,98	1,99	33,16
Nonrheumatic and unspecified valve disorders	25,90	1,94	32,37
Conduction disorders	33,65	1,92	32,04
Nervous system pain and pain syndromes	15,48	1,84	30,64
Miscellaneous mental and behavioral disorders/cor	6,89	1,83	30,60
Chronic rheumatic heart disease	6,96	1,81	30,26
Malnutrition	3,95	1,75	29,23
Cardiac dysrhythmias	53,83	1,71	28,55
Nutritional deficiencies	26,26	1,71	28,54
Cerebral infarction	13,95	1,69	28,18
Hypertension with complications and secondary hy	13,19	1,68	28,05
Epilepsy; convulsions	7,85	1,68	28,03
Chronic kidney disease	64,86	1,66	27,65
Transient cerebral ischemia	4,23	1,64	27,31
Other specified joint disorders	11,83	1,63	27,18
Other specified hereditary and degenerative nervou	13,69	1,50	25,11
Diverticulosis and diverticulitis	16,17	1,48	24,67
Drug induced or toxic related condition	3,94	1,47	24,59
Gastritis and duodenitis	4,55	1,47	24,57
Nervous system signs and symptoms	17,18	1,46	24,37
Spondylopathies/spondyloarthropathy (including in	28,85	1,45	24,24
Other specified and unspecified liver disease	8,43	1,44	24,07
Hematologic neoplasia	2,88	1,44	24,03
Obesity	45,29	1,43	23,89
Diseases of white blood cells	2,81	1,40	23,37
Crystal arthropathies (excluding gout)	3,13	1,39	23,20
Disorders of lipid metabolism	58,03	1,38	23,07
Chronic obstructive pulmonary disease and bronchi	15,80	1,36	22,73
Nerve and nerve root disorders	7,98	1,35	22,47
Neoplasia (general)	18,63	1,33	22,18
Thyroid disorders	31,73	1,31	21,80
Menopausal disorders	4,88	1,27	21,23
Prolapse of female genital organs	7,50	1,27	21,13
Coagulation and hemorrhagic disorders	4,11	1,23	20,55
Retinal and vitreous conditions	9,86	1,23	20,54
Other and ill-defined cerebrovascular disease	3,49	1,23	20,49
Other specified and unspecified nutritional and met	36,60	1,22	20,44
Depressive disorders	41,38	1,21	20,18
Other specified inflammatory condition of skin	4,63	1,20	20,11
Hearing loss	30,32	1,20	20,07
Systemic lupus erythematosus and connective tissu	8,74	1,18	19,63
Essential hypertension	96,16	1,17	19,56
Glaucoma	16,91	1,16	19,43
Sleep wake disorders	37,70	1,15	19,23
Hepatitis	2,27	1,09	18,17
Osteoarthritis	65,94	1,09	18,11
Urinary incontinence	87,35	1,06	17,66
Cataract and other lens disorders	33,16	1,05	17,59
Digestive congenital anomalies	4,99	1,05	17,50
Asthma	10,41	1,03	17,21
Acquired foot deformities	6,99	1,02	17,03
Trauma- and stressor-related disorders	3,89	1,01	16,92
Other specified and unspecified gastrointestinal dis	2,94	1,01	16,81
Esophageal disorders	12,80	0,96	15,99
Scoliosis and other postural dorsopathic deformitie	6,51	0,95	15,88
Disorders of teeth and gingiva	5,63	0,95	15,85
Osteoporosis	24,54	0,94	15,72
Neurocognitive disorders	56,95	0,89	14,92
Anxiety and fear-related disorders	23,76	0,89	14,89
Disruptive, impulse-control and conduct disorders	3,34	0,87	14,50
Other general signs and symptoms	17,30	0,86	14,41
Gastroduodenal ulcer	2,40	0,85	14,11
Pressure ulcer of skin	13,35	0,84	14,05
Other specified and unspecified upper respiratory c	6,85	0,82	13,70
Parkinson`s disease	3,92	0,77	12,85
Symptoms of mental and substance use conditions	11,21	0,77	12,81
Headache; including migraine	2,22	0,74	12,31
Schizophrenia spectrum and other psychotic disord	1,46	0,63	10,44

Females, 81-95 (2 out of 2)

Osteoinflammatory - neoplasia			
Chronic condition	Prevalence (%)	O/E ra	Exclusivity (%)
Hepatitis	3,43	1,64	42,52
Other specified and unspecified gastrointestinal dis	4,47	1,53	39,61
Other specified and unspecified upper respiratory c	12,59	1,51	39,02
Scoliosis and other postural dorsopathic deformitie	9,82	1,43	37,13
Other specified inflammatory condition of skin	5,42	1,41	36,54
Glaucoma	19,76	1,36	35,21
Acquired foot deformities	9,28	1,36	35,09
Cataract and other lens disorders	42,58	1,35	35,01
Digestive congenital anomalies	6,43	1,35	34,96
Diverticulosis and diverticulitis	14,75	1,35	34,90
Esophageal disorders	17,62	1,32	34,13
Nerve and nerve root disorders	7,80	1,32	34,07
Hematologic neoplasia	2,62	1,31	33,78
Trauma- and stressor-related disorders	4,88	1,27	32,88
Menopausal disorders	4,77	1,24	32,13
Other specified and unspecified liver disease	7,11	1,22	31,50
Retinal and vitreous conditions	9,73	1,21	31,42
Prolapse of female genital organs	6,89	1,16	30,07
Spondylopathies/spondyloarthropathy (including in	22,71	1,14	29,57
Neoplasia (general)	15,72	1,12	29,01
Headache; including migraine	3,35	1,12	28,87
Osteoporosis	28,65	1,10	28,47
Gastroduodenal ulcer	3,10	1,09	28,22
Asthma	10,78	1,07	27,62
Anxiety and fear-related disorders	27,91	1,05	27,12
Osteoarthritis	63,46	1,04	27,02
Coagulation and hemorrhagic disorders	3,47	1,04	26,85
Diseases of white blood cells	2,03	1,01	26,23
Systemic lupus erythematosus and connective tissu	7,52	1,01	26,21
Essential hypertension	82,90	1,01	26,14
Crystal arthropathies (excluding gout)	2,26	1,00	25,94
Sleep wake disorders	32,64	1,00	25,81
Hearing loss	25,12	1,00	25,79
Disorders of teeth and gingiva	5,88	0,99	25,66
Disorders of lipid metabolism	41,24	0,98	25,42
Thyroid disorders	23,30	0,96	24,82
Gastritis and duodenitis	2,92	0,94	24,42
Obesity	29,38	0,93	24,03
Other specified and unspecified nutritional and me	27,04	0,90	23,41
Other and ill-defined cerebrovascular disease	2,57	0,90	23,39
Other specified hereditary and degenerative nervo	8,02	0,88	22,80
Nervous system pain and pain syndromes	7,35	0,87	22,55
Transient cerebral ischemia	2,16	0,84	21,61
Other specified joint disorders	5,92	0,82	21,11
Chronic obstructive pulmonary disease and bronchi	9,42	0,81	21,01
Depressive disorders	27,61	0,81	20,87
Hypertension with complications and secondary hy	6,33	0,81	20,87
Chronic kidney disease	31,41	0,80	20,76
Nutritional deficiencies	12,29	0,80	20,70
Conduction disorders	13,95	0,80	20,59
Urinary incontinence	63,91	0,77	20,03
Nonrheumatic and unspecified valve disorders	10,32	0,77	20,00
Biliary tract disease	2,05	0,77	19,85
Cardiac dysrhythmias	23,82	0,76	19,58
Coronary atherosclerosis and other heart disease	9,83	0,73	18,93
Cerebral infarction	5,95	0,72	18,63
Neurocognitive disorders	44,25	0,69	17,98
Diabetes mellitus without complication	21,08	0,68	17,61
Peripheral and visceral vascular disease	4,20	0,61	15,70
Acute myocardial infarction	1,57	0,61	15,68
Drug induced or toxic related condition	1,56	0,59	15,14
Pressure ulcer of skin	9,20	0,58	15,00
Other specified and unspecified endocrine disorder	2,15	0,57	14,81
Disruptive, impulse-control and conduct disorders	2,06	0,54	13,91
Other general signs and symptoms	10,53	0,53	13,60
Heart failure	15,99	0,52	13,50
Other and ill-defined heart disease	4,57	0,49	12,64
Nervous system signs and symptoms	5,59	0,48	12,30
Symptoms of mental and substance use conditions	6,83	0,47	12,11
Non-pressure ulcer of skin	2,25	0,40	10,26
Epilepsy; convulsions	1,79	0,38	9,89
Miscellaneous mental and behavioral disorders/cor	1,39	0,37	9,56
Parkinson`s disease	1,81	0,35	9,18
Paralysis (other than cerebral palsy)	0,86	0,34	8,90
Schizophrenia spectrum and other psychotic disord	0,77	0,33	8,53
Chronic rheumatic heart disease	1,23	0,32	8,32
Gout	0,64	0,29	7,62
Pulmonary heart disease	2,00	0,28	7,30
Diabetes mellitus with complication	2,41	0,24	6,32
Malnutrition	0,47	0,21	5,44
Respiratory failure; insufficiency; arrest	0,04	0,02	0,47

Psychogeriatric			
Chronic condition	Prevalence (%)	O/E ra	Exclusivity (%)
Schizophrenia spectrum and other psychotic disord	3,90	1,67	69,87
Parkinson`s disease	8,40	1,65	69,01
Symptoms of mental and substance use conditions	21,14	1,45	60,56
Other general signs and symptoms	28,28	1,41	59,07
Pressure ulcer of skin	22,33	1,41	58,91
Neurocognitive disorders	80,70	1,27	53,02
Disruptive, impulse-control and conduct disorders	4,68	1,22	51,04
Epilepsy; convulsions	5,69	1,22	50,90
Malnutrition	2,61	1,16	48,49
Paralysis (other than cerebral palsy)	2,83	1,13	47,24
Urinary incontinence	91,34	1,11	46,30
Nervous system signs and symptoms	12,90	1,10	45,86
Miscellaneous mental and behavioral disorders/cor	3,90	1,04	43,41
Disorders of teeth and gingiva	5,78	0,97	40,79
Cerebral infarction	7,68	0,93	38,89
Headache; including migraine	2,77	0,92	38,63
Other specified hereditary and degenerative nervo	8,36	0,92	38,47
Depressive disorders	30,65	0,90	37,48
Essential hypertension	72,07	0,88	36,76
Other specified and unspecified nutritional and me	26,11	0,87	36,56
Anxiety and fear-related disorders	22,83	0,86	35,87
Osteoporosis	22,28	0,86	35,81
Other and ill-defined cerebrovascular disease	2,38	0,84	35,15
Sleep wake disorders	27,24	0,83	34,84
Osteoarthritis	50,09	0,82	34,49
Hearing loss	20,00	0,79	33,20
Gastroduodenal ulcer	2,25	0,79	33,12
Disorders of lipid metabolism	32,06	0,76	31,95
Neoplasia (general)	10,62	0,76	31,68
Diabetes mellitus without complication	23,25	0,75	31,42
Systemic lupus erythematosus and connective tissu	5,55	0,75	31,29
Transient cerebral ischemia	1,90	0,73	30,73
Chronic kidney disease	28,35	0,72	30,30
Other specified and unspecified endocrine disorder	2,69	0,72	29,97
Thyroid disorders	16,89	0,70	29,11
Other specified joint disorders	5,02	0,69	28,94
Gastritis and duodenitis	2,10	0,68	28,45
Nutritional deficiencies	10,10	0,66	27,51
Obesity	20,68	0,65	27,35
Cardiac dysrhythmias	20,13	0,64	26,77
Glaucoma	9,19	0,63	26,48
Acquired foot deformities	4,31	0,63	26,34
Cataract and other lens disorders	19,70	0,63	26,20
Prolapse of female genital organs	3,53	0,60	24,95
Trauma- and stressor-related disorders	2,24	0,58	24,38
Digestive congenital anomalies	2,77	0,58	24,35
Peripheral and visceral vascular disease	3,98	0,57	24,03
Scoliosis and other postural dorsopathic deformitie	3,90	0,57	23,87
Esophageal disorders	7,39	0,55	23,17
Chronic obstructive pulmonary disease and bronchi	6,26	0,54	22,56
Conduction disorders	9,18	0,52	21,91
Diseases of white blood cells	1,05	0,52	21,91
Coronary atherosclerosis and other heart disease	7,01	0,52	21,83
Biliary tract disease	1,39	0,52	21,81
Asthma	5,25	0,52	21,74
Retinal and vitreous conditions	4,12	0,51	21,52
Spondylopathies/spondyloarthropathy (including in	10,20	0,51	21,48
Coagulation and hemorrhagic disorders	1,71	0,51	21,45
Other specified and unspecified upper respiratory c	4,24	0,51	21,27
Crystal arthropathies (excluding gout)	1,14	0,51	21,16
Nervous system pain and pain syndromes	4,14	0,49	20,56
Non-pressure ulcer of skin	2,71	0,48	20,01
Heart failure	14,21	0,46	19,41
Drug induced or toxic related condition	1,23	0,46	19,34
Other specified inflammatory condition of skin	1,66	0,43	18,10
Other specified and unspecified gastrointestinal dis	1,22	0,42	17,51
Hypertension with complications and secondary hy	3,05	0,39	16,28
Other specified and unspecified liver disease	2,17	0,37	15,53
Diverticulosis and diverticulitis	3,87	0,35	14,82
Hematologic neoplasia	0,68	0,34	14,27
Menopausal disorders	1,22	0,32	13,25
Nerve and nerve root disorders	1,75	0,29	12,33
Hepatitis	0,56	0,27	11,20
Other and ill-defined heart disease	2,42	0,26	10,81
Diabetes mellitus with complication	2,46	0,25	10,45
Nonrheumatic and unspecified valve disorders	3,28	0,25	10,29
Gout	0,43	0,20	8,26
Pulmonary heart disease	1,06	0,15	6,23
Acute myocardial infarction	0,23	0,09	3,79
Respiratory failure; insufficiency; arrest	0,06	0,03	1,19
Chronic rheumatic heart disease	0,02	0,01	0,26

Figure S2: Representation of the Observed/Expected ratio (O/E) and exclusivity (%) of the chronic conditions composing the multimorbidity clusters of male patients. O/E >1 and exclusivity > 1/number of clusters are displayed.

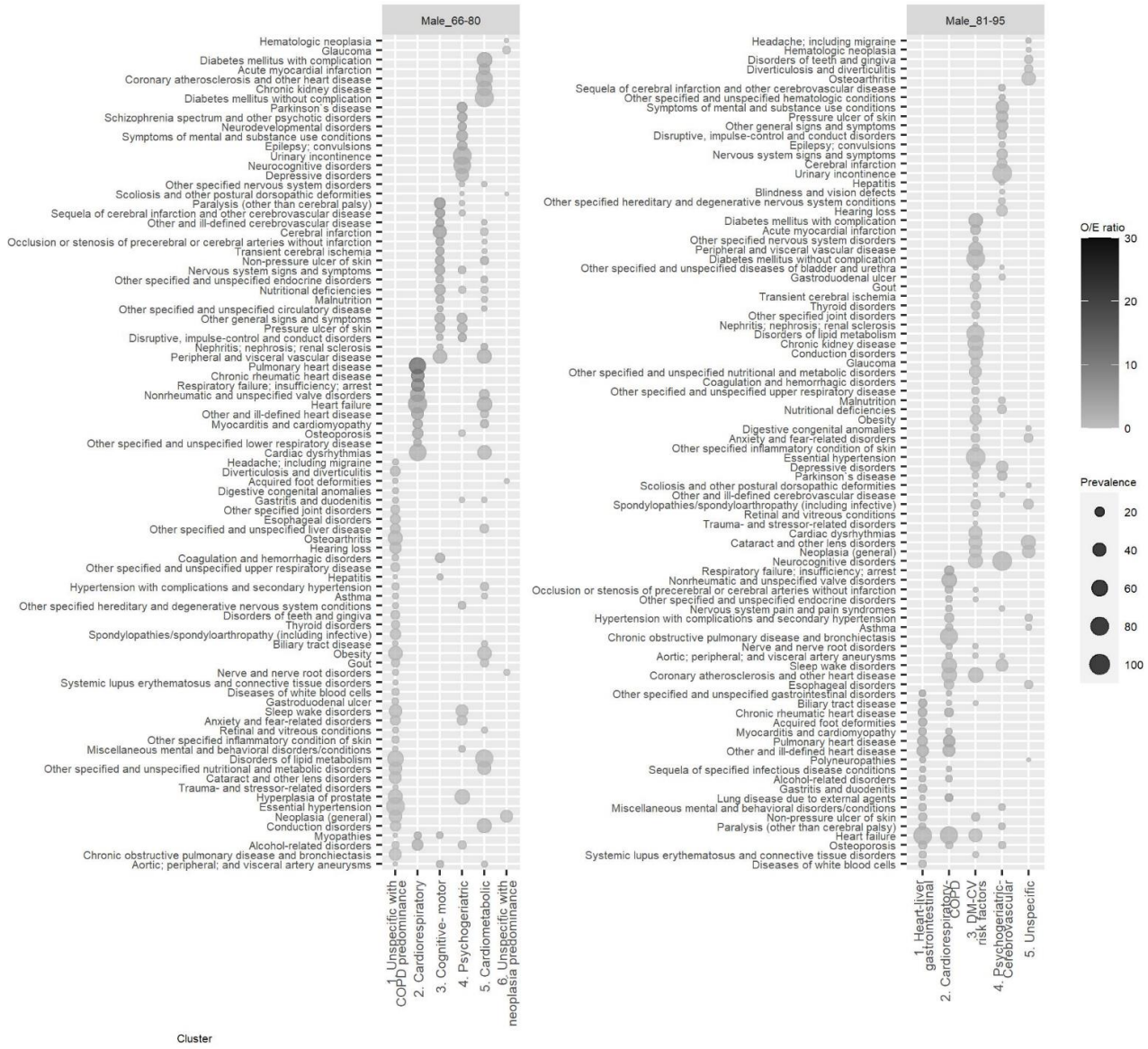
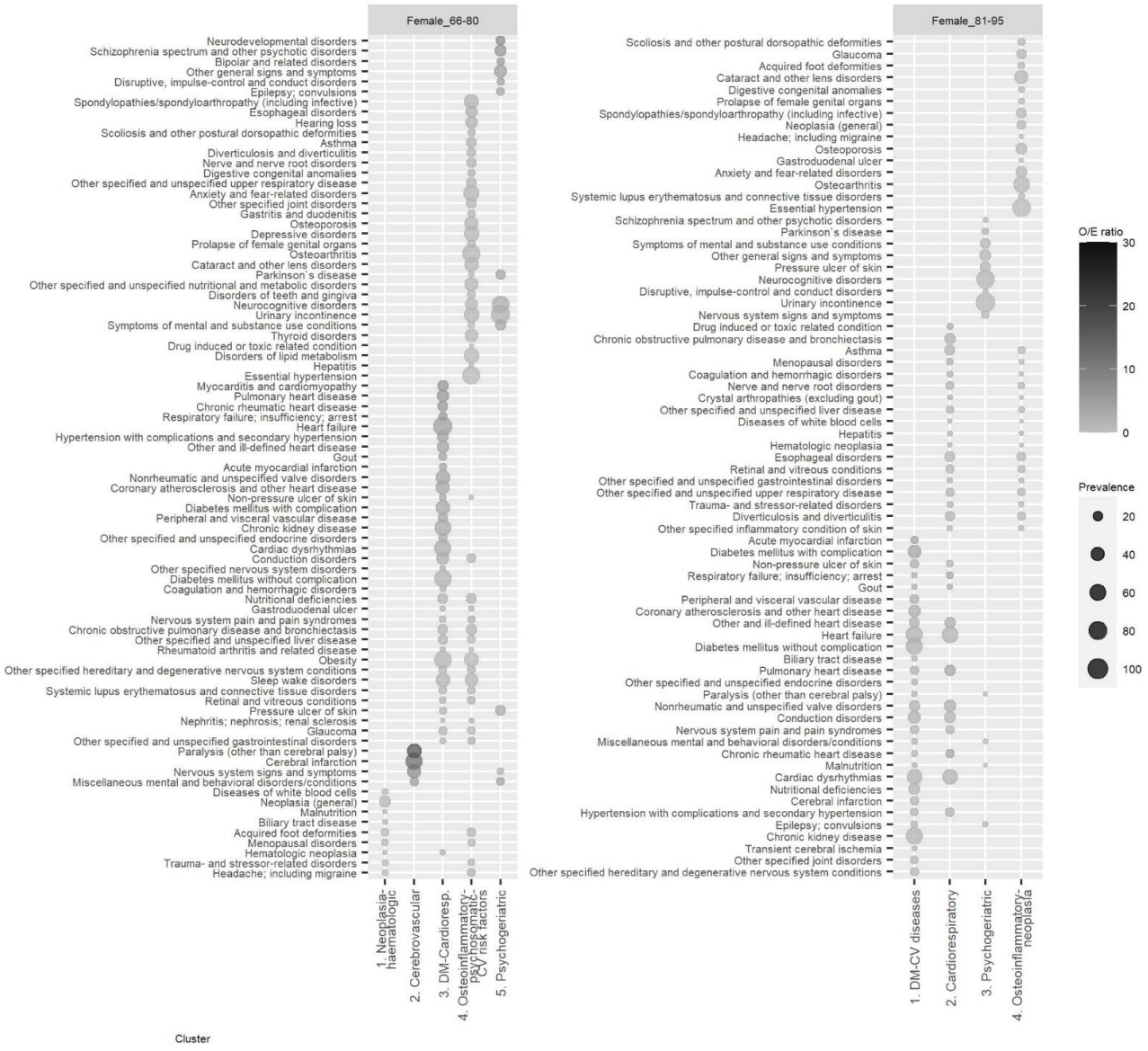

Male_66-80
Hematologic neoplasia
Glaucoma
Diabetes mellitus with complication
Acute myocardial infarction
Coronary atherosclerosis and other heart disease
Chronic kidney disease
Diabetes mellitus without complication
Parkinson s disease
Schizophrenia spectrum and other psychotic disorders
Neurodevelopmental disorders
Symptoms of mental and substance use conditions
Epilepsy; convulsions
Urinary incontinence
Neurocognitive disorders
Depressive disorders
Other specified nervous system disorders
Scoliosis and other postural dorsopathic deformities
Paralysis (other than cerebral palsy)
Sequela of cerebral infarction and other cerebrovascular disease
Other and ill-defined cerebrovascular disease
Cerebral infarction
Occlusion or stenosis of precerebral or cerebral arteries without infarction
Transient cerebral ischemia
Non-pressure ulcer of skin
Nervous system signs and symptoms
Other specified and unspecified endocrine disorders
Nutritional deficiencies
Malnutrition
Other specified and unspecified circulatory disease
Other general signs and symptoms
Pressure ulcer of skin
Disruptive, impulse-control and conduct disorders
Nephritis; nephrosis; renal sclerosis
Peripheral and visceral vascular disease
Pulmonary heart disease
Chronic rheumatic heart disease
Respiratory failure; insufficiency; arrest
Nonrheumatic and unspecified valve disorders
Heart failure
Other and ill-defined heart disease
Myocarditis and cardiomyopathy
Osteoporosis
Other specified and unspecified lower respiratory disease
Cardiac dysrhythmias
Headache; including migraine
Diverticulosis and diverticulitis
Acquired foot deformities
Digestive congenital anomalies
Gastritis and duodenitis
Other specified joint disorders
Esophageal disorders
Other specified and unspecified liver disease
Osteoarthritis
Hearing loss
Coagulation and hemorrhagic disorders
Other specified and unspecified upper respiratory disease
Hepatitis
Hypertension with complications and secondary hypertension
Asthma
Other specified hereditary and degenerative nervous system conditions
Disorders of teeth and gingiva
Thyroid disorders
Spondylopathies/spondyloarthropathy (including infective)
Biliary tract disease
Obesity
Gout
Nerve and nerve root disorders
Systemic lupus erythematosus and connective tissue disorders
Diseases of white blood cells
Gastroduodenal ulcer
Sleep wake disorders
Anxiety and fear-related disorders
Retinal and vitreous conditions
Other specified inflammatory condition of skin
Miscellaneous mental and behavioral disorders/conditions
Disorders of lipid metabolism
Other specified and unspecified nutritional and metabolic disorders
Cataract and other lens disorders
Trauma- and stressor-related disorders
Hyperplasia of prostate
Essential hypertension
Neoplasia (general)
Conduction disorders
Myopathies
Alcohol-related disorders
Chronic obstructive pulmonary disease and bronchiectasis
Aortic; peripheral; and visceral artery aneurysms
1. Unspecific with COPD predominance
2. Cardiorespiratory
3. Cognitive- motor
4. Psychogeriatric
5. Cardiometabolic
6. Unspecific with neoplasia predominance
Cluster
Male_81-95
Headache; including migraine
Hematologic neoplasia
Disorders of teeth and gingiva
Diverticulosis and diverticulitis
Osteoarthritis
Sequela of cerebral infarction and other cerebrovascular disease
Other specified and unspecified hematologic conditions
Symptoms of mental and substance use conditions
Pressure ulcer of skin
Other general signs and symptoms
Disruptive, impulse-control and conduct disorders
Epilepsy; convulsions
Nervous system signs and symptoms
Cerebral infarction
Urinary incontinence
Hepatitis
Blindness and vision defects
Other specified hereditary and degenerative nervous system conditions
Hearing loss
Diabetes mellitus with complication
Acute myocardial infarction
Other specified nervous system disorders
Peripheral and visceral vascular disease
Diabetes mellitus without complication
Other specified and unspecified diseases of bladder and urethra
Gastroduodenal ulcer
Gout
Transient cerebral ischemia
Thyroid disorders
Other specified joint disorders
Nephritis; nephrosis; renal sclerosis
Disorders of lipid metabolism
Chronic kidney disease
Conduction disorders
Glaucoma
Other specified and unspecified nutritional and metabolic disorders
Coagulation and hemorrhagic disorders
Other specified and unspecified upper respiratory disease
Malnutrition
Nutritional deficiencies
Obesity
Digestive congenital anomalies
Anxiety and fear-related disorders
Other specified inflammatory condition of skin
Essential hypertension
Depressive disorders
Parkinson s disease
Scoliosis and other postural dorsopathic deformities
Other and ill-defined cerebrovascular disease
Spondylopathies/spondyloarthropathy (including infective)
Retinal and vitreous conditions
Trauma- and stressor-related disorders
Cardiac dysrhythmias
Cataract and other lens disorders
Neoplasia (general)
Neurocognitive disorders
Respiratory failure; insufficiency; arrest
Nonrheumatic and unspecified valve disorders
Occlusion or stenosis of precerebral or cerebral arteries without infarction
Other specified and unspecified endocrine disorders
Nervous system pain and pain syndromes
Hypertension with complications and secondary hypertension
Asthma
Chronic obstructive pulmonary disease and bronchiectasis
Nerve and nerve root disorders
Aortic; peripheral; and visceral artery aneurysms
Sleep wake disorders
Coronary atherosclerosis and other heart disease
Esophageal disorders
Other specified and unspecified gastrointestinal disorders
Biliary tract disease
Chronic rheumatic heart disease
Acquired foot deformities
Myocarditis and cardiomyopathy
Pulmonary heart disease
Other and ill-defined heart disease
Polyneuropathies
Sequela of specified infectious disease conditions
Alcohol-related disorders
Gastritis and duodenitis
Lung disease due to external agents
Miscellaneous mental and behavioral disorders/conditions
Non-pressure ulcer of skin
Paralysis (other than cerebral palsy)
Heart failure
Osteoporosis
Systemic lupus erythematosus and connective tissue disorders
Diseases of white blood cells
1. Heart-liver gastrointestinal
2. Cardiorespiratory-COPD
3. DM-CV risk factors
4. Psychogeriatric-Cerebrovascular
5. Unspecific
O/E ratio
30
20
10
0
Prevalence
20
40
60
80
100

Figure S3: Representation of the Observed/Expected ratio (O/E) and exclusivity (%) of the chronic conditions composing the multimorbidity clusters of female patients. O/E >1 and exclusivity > 1/number of clusters are displayed.


Female_66-80
Neurodevelopmental disorders
Schizophrenia spectrum and other psychotic disorders
Bipolar and related disorders
Other general signs and symptoms
Disruptive, impulse-control and conduct disorders
Epilepsy; convulsions
Spondylopathies/spondyloarthropathy (including infective)
Esophageal disorders
Hearing loss
Scoliosis and other postural dorsopathic deformities
Asthma
Diverticulosis and diverticulitis
Nerve and nerve root disorders
Digestive congenital anomalies
Other specified and unspecified upper respiratory disease
Anxiety and fear-related disorders
Other specified joint disorders
Gastritis and duodenitis
Osteoporosis
Depressive disorders
Prolapse of female genital organs
Osteoarthritis
Cataract and other lens disorders
Parkinson's disease
Other specified and unspecified nutritional and metabolic disorders
Disorders of teeth and gingiva
Neurocognitive disorders
Urinary incontinence
Symptoms of mental and substance use conditions
Thyroid disorders
Drug induced or toxic related condition
Disorders of lipid metabolism
Hepatitis
Essential hypertension
Myocarditis and cardiomyopathy
Pulmonary heart disease
Chronic rheumatic heart disease
Respiratory failure; insufficiency; arrest
Heart failure
Hypertension with complications and secondary hypertension
Other and ill-defined heart disease
Gout
Acute myocardial infarction
Nonrheumatic and unspecified valve disorders
Coronary atherosclerosis and other heart disease
Non-pressure ulcer of skin
Diabetes mellitus with complication
Peripheral and visceral vascular disease
Chronic kidney disease
Other specified and unspecified endocrine disorders
Cardiac dysrhythmias
Conduction disorders
Other specified nervous system disorders
Diabetes mellitus without complication
Coagulation and hemorrhagic disorders
Nutritional deficiencies
Gastroduodenal ulcer
Nervous system pain and pain syndromes
Chronic obstructive pulmonary disease and bronchiectasis
Other specified and unspecified liver disease
Rheumatoid arthritis and related disease
Obesity
Other specified hereditary and degenerative nervous system conditions
Sleep wake disorders
Systemic lupus erythematosus and connective tissue disorders
Retinal and vitreous conditions
Pressure ulcer of skin
Nephritis; nephrosis; renal sclerosis
Glaucoma
Other specified and unspecified gastrointestinal disorders
Paralysis (other than cerebral palsy)
Cerebral infarction
Nervous system signs and symptoms
Miscellaneous mental and behavioral disorders/conditions
Diseases of white blood cells
Neoplasia (general)
Malnutrition
Biliary tract disease
Acquired foot deformities
Menopausal disorders
Hematologic neoplasia
Trauma- and stressor-related disorders
Headache; including migraine
1. Neoplasia-haematologic
2. Cerebrovascular
3. DM-Cardioresp.
4. Osteoinflammatory-psychosomatic-CV risk factors
5. Psychogeriatric
Cluster
Female_81-95
Scoliosis and other postural dorsopathic deformities
Glaucoma
Acquired foot deformities
Cataract and other lens disorders
Digestive congenital anomalies
Prolapse of female genital organs
Spondylopathies/spondyloarthropathy (including infective)
Neoplasia (general)
Headache; including migraine
Osteoporosis
Gastroduodenal ulcer
Anxiety and fear-related disorders
Osteoarthritis
Systemic lupus erythematosus and connective tissue disorders
Essential hypertension
Schizophrenia spectrum and other psychotic disorders
Parkinson's disease
Symptoms of mental and substance use conditions
Other general signs and symptoms
Pressure ulcer of skin
Neurocognitive disorders
Disruptive, impulse-control and conduct disorders
Urinary incontinence
Nervous system signs and symptoms
Drug induced or toxic related condition
Chronic obstructive pulmonary disease and bronchiectasis
Asthma
Menopausal disorders
Coagulation and hemorrhagic disorders
Nerve and nerve root disorders
Crystal arthropathies (excluding gout)
Other specified and unspecified liver disease
Diseases of white blood cells
Hepatitis
Hematologic neoplasia
Esophageal disorders
Retinal and vitreous conditions
Other specified and unspecified gastrointestinal disorders
Other specified and unspecified upper respiratory disease
Trauma- and stressor-related disorders
Diverticulosis and diverticulitis
Other specified inflammatory condition of skin
Acute myocardial infarction
Diabetes mellitus with complication
Non-pressure ulcer of skin
Respiratory failure; insufficiency; arrest
Gout
Peripheral and visceral vascular disease
Coronary atherosclerosis and other heart disease
Other and ill-defined heart disease
Heart failure
Diabetes mellitus without complication
Biliary tract disease
Pulmonary heart disease
Other specified and unspecified endocrine disorders
Paralysis (other than cerebral palsy)
Nonrheumatic and unspecified valve disorders
Conduction disorders
Nervous system pain and pain syndromes
Miscellaneous mental and behavioral disorders/conditions
Chronic rheumatic heart disease
Malnutrition
Cardiac dysrhythmias
Nutritional deficiencies
Cerebral infarction
Hypertension with complications and secondary hypertension
Epilepsy; convulsions
Chronic kidney disease
Transient cerebral ischemia
Other specified joint disorders
Other specified hereditary and degenerative nervous system conditions
1. DM-CV diseases
2. Cardiorespiratory
3. Psychogeriatric
4. Osteoinflammatory-neoplasia
O/E ratio
30
20
10
0
Prevalence
20
40
60
80
100

A3. Study 3: MTOP study

The supplementary files of this study include 4 tables and 3 figures.

Figure S1. Prevalence of each chronic condition in the three time points analysed (baseline, 5 years before, 10 years before). Chronic conditions were identified and grouped according to Chronic Condition Indicator and Chronic Condition Classification, filtered for >2% prevalence and ordered by prevalence at baseline.

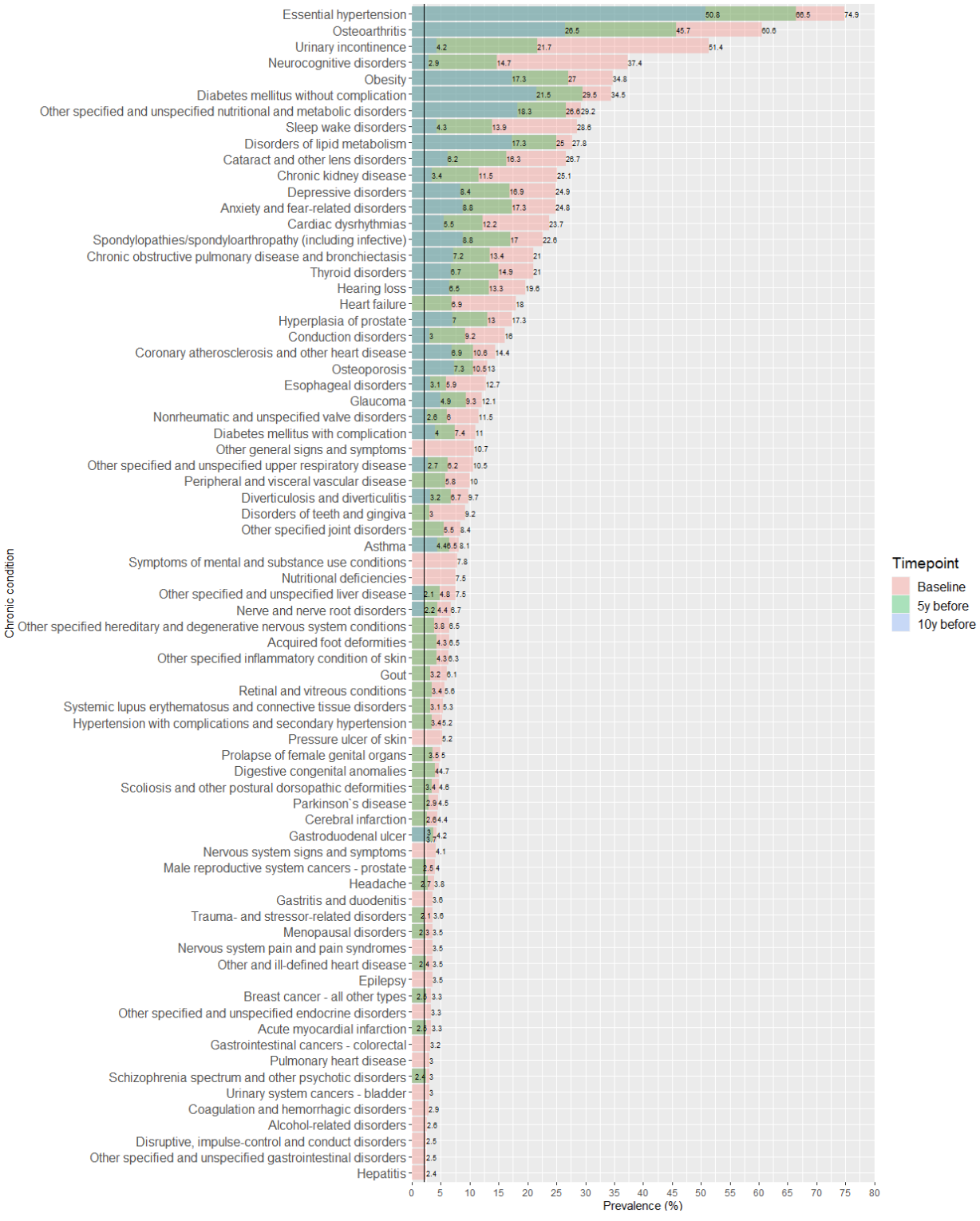


Figure S2. Distribution of multimorbidity cluster membership probabilities per patient (each column represents a patient) at the three defined time points. A: baseline. B: 5 years before baseline. C: 10 years before baseline.

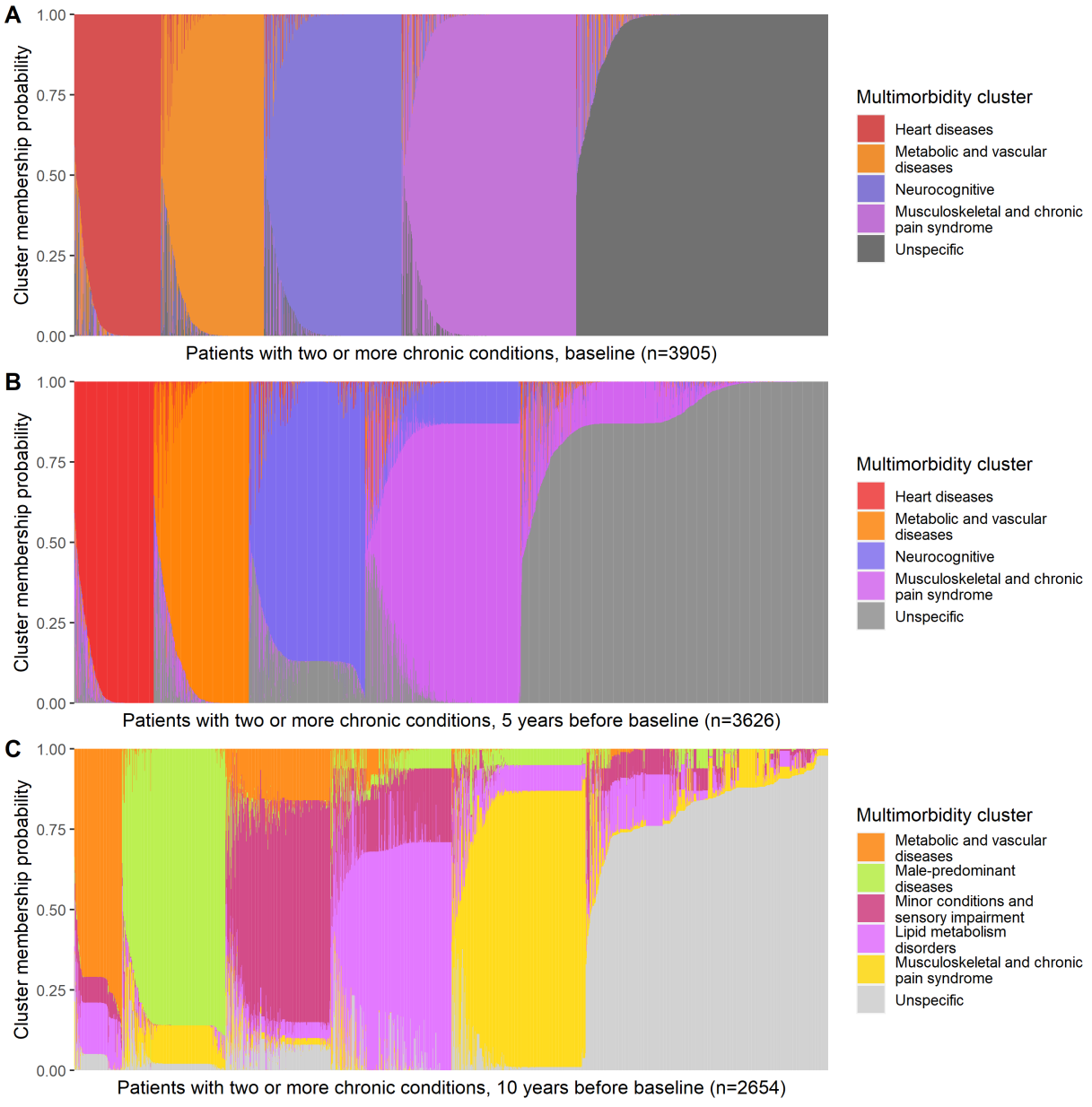


Figure S3. Proportion of patients transitioning from one cluster to another between time points. A: 10 years before baseline versus 5 years before baseline time points (column %). B: 5 years before baseline versus baseline time points (column %).

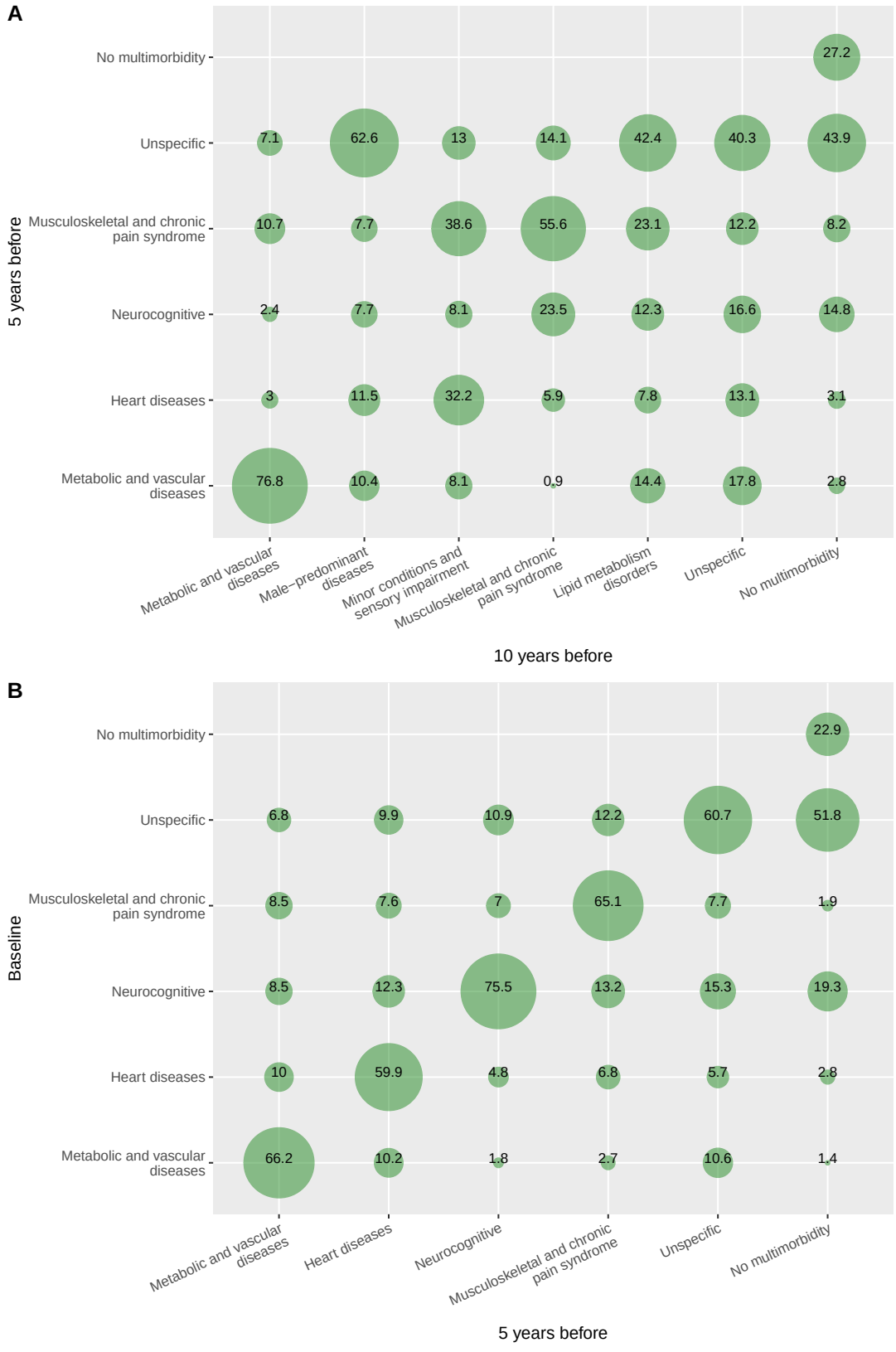


Table S1. Prevalence, Observed/Expected (O/E) ratio and exclusivity of chronic conditions used to define multimorbidity clusters (>2% prevalence) at the 10 years before time point.

Chronic condition	Prevalence MVD	O/E ratio MVD	Exclusivity MVD	Prevalence MPD	O/E ratio MPD	Exclusivity MPD	Prevalence SI	O/E ratio SI	Exclusivity SI	Prevalence MSK	O/E ratio MSK	Exclusivity MSK	Prevalence LMD	O/E ratio LMD	Exclusivity LMD	Prevalence UN	O/E ratio UN	Exclusivity UN	Total prevalence
Essential hypertension	66,9	1,0	7,8	52,1	0,8	11,0	62,7	1,0	14,1	40,4	0,6	10,2	69,4	1,1	19,0	85,3	1,3	37,9	65,6
Osteoarthritis	39,0	1,3	9,7	17,3	0,6	7,8	58,3	1,9	28,0	36,3	1,2	19,6	27,1	0,9	15,9	19,9	0,6	18,9	30,7
Diabetes mellitus without complication	57,8	2,0	15,5	16,0	0,6	7,8	21,7	0,8	11,2	21,4	0,7	12,4	23,8	0,8	15,0	37,3	1,3	38,1	28,6
Other specified and unspecified nutritional and metabolic disorders	25,6	1,0	8,0	22,9	0,9	12,9	20,1	0,8	12,0	29,2	1,2	19,7	6,8	0,3	5,0	35,6	1,4	42,3	24,6
Obesity	38,6	1,6	12,3	7,6	0,3	4,4	39,1	1,6	24,0	16,3	0,7	11,3	15,5	0,6	11,6	29,7	1,2	36,2	23,9
Disorders of lipid metabolism	17,8	0,8	6,0	16,6	0,7	10,1	13,7	0,6	8,8	22,6	1,0	16,4	69,0	3,0	54,2	3,5	0,2	4,5	22,9
Anxiety and fear-related disorders	11,6	1,0	7,9	6,6	0,6	8,1	19,5	1,7	25,4	20,6	1,8	30,3	7,9	0,7	12,6	6,0	0,5	15,6	11,3
Spondylopathies/spondyloarthropathy (including infective)	18,7	1,8	13,4	10,8	1,0	14,1	15,8	1,5	21,7	18,4	1,7	28,6	9,0	0,8	15,1	2,6	0,2	7,2	10,7
Depressive disorders	12,0	1,1	8,6	5,3	0,5	6,9	13,4	1,3	18,4	27,2	2,5	42,2	4,8	0,4	8,1	5,8	0,5	15,9	10,7
Osteoporosis	5,0	0,5	4,0	4,5	0,5	6,6	14,0	1,5	21,6	25,5	2,7	44,6	5,6	0,6	10,6	4,1	0,4	12,6	9,5
Hyperplasia of prostate	3,8	0,4	3,1	47,1	5,1	71,0	2,0	0,2	3,3	1,6	0,2	2,9	7,4	0,8	14,4	1,7	0,2	5,3	9,2
Chronic obstructive pulmonary disease and bronchiectasis	7,4	0,8	6,4	35,4	4,0	55,4	5,3	0,6	8,8	5,5	0,6	10,2	4,7	0,5	9,5	3,0	0,3	9,7	8,9
Hearing loss	8,9	1,0	7,7	11,6	1,3	18,3	14,6	1,7	24,3	8,8	1,0	16,5	7,1	0,8	14,5	5,6	0,6	18,6	8,8
Cataract and other lens disorders	13,5	1,6	12,1	9,7	1,1	15,9	18,4	2,2	31,8	5,1	0,6	10,0	5,5	0,6	11,6	5,4	0,6	18,6	8,5
Coronary atherosclerosis and other heart disease	9,9	1,2	9,0	10,1	1,2	16,5	6,5	0,8	11,3	5,3	0,6	10,4	6,2	0,7	13,2	11,5	1,4	39,6	8,5
Thyroid disorders	10,7	1,3	9,8	3,7	0,4	6,1	10,7	1,3	18,7	15,0	1,8	29,6	7,2	0,9	15,4	5,9	0,7	20,5	8,4
Cardiac dysrhythmias	5,5	0,7	5,6	7,4	1,0	13,6	9,4	1,3	18,5	3,8	0,5	8,4	3,3	0,4	7,9	11,8	1,6	46,0	7,5
Glaucoma	12,7	1,9	14,4	8,9	1,3	18,2	6,1	0,9	13,2	6,1	0,9	14,8	7,3	1,1	19,4	4,6	0,7	20,0	6,8
Asthma	10,3	1,8	13,4	4,2	0,7	9,9	11,6	2,0	29,1	9,8	1,7	27,6	1,8	0,3	5,5	2,9	0,5	14,5	5,9
Sleep wake disorders	9,9	1,7	12,9	3,3	0,6	7,8	13,1	2,2	33,0	5,3	0,9	15,0	3,3	0,6	10,0	4,3	0,7	21,3	5,8
Urinary incontinence	2,9	0,5	3,8	2,1	0,4	5,1	6,4	1,1	16,2	7,5	1,3	21,2	6,4	1,1	19,8	6,8	1,2	33,9	5,8
Chronic kidney disease	4,7	1,0	7,7	4,3	0,9	13,0	3,3	0,7	10,4	3,1	0,7	11,1	6,9	1,5	26,7	4,9	1,1	31,1	4,6
Diabetes mellitus with complication	41,5	9,1	69,7	0,3	0,1	1,0	2,4	0,5	7,7	4,2	0,9	15,5	0,1	0,0	0,5	0,9	0,2	5,7	4,6
Diverticulosis and diverticulitis	8,1	1,8	14,0	5,5	1,3	17,5	11,3	2,6	37,7	2,0	0,5	7,6	3,1	0,7	12,8	1,6	0,4	10,5	4,4
Esophageal disorders	6,1	1,5	11,5	5,7	1,4	19,3	7,9	1,9	28,7	4,3	1,1	17,7	4,5	1,1	19,8	0,4	0,1	3,0	4,1
Conduction disorders	9,4	2,4	18,1	4,2	1,1	14,8	4,5	1,1	16,7	2,6	0,7	11,0	6,8	1,7	30,8	1,2	0,3	8,6	4,0
Gastroduodenal ulcer	2,3	0,6	4,6	10,6	2,8	38,6	1,4	0,4	5,4	4,3	1,1	18,8	6,3	1,7	29,7	0,4	0,1	2,8	3,8
Neurocognitive disorders	0,3	0,1	0,7	1,9	0,5	7,1	2,5	0,7	10,1	7,0	1,9	31,4	2,3	0,6	11,1	5,0	1,4	39,6	3,7
Other specified and unspecified upper respiratory disease	6,5	1,9	14,4	3,2	0,9	12,9	7,4	2,1	31,6	6,8	2,0	32,7	0,8	0,2	4,4	0,5	0,1	4,1	3,5
Nonrheumatic and unspecified valve disorders	6,4	2,0	15,0	2,8	0,9	11,9	10,8	3,3	48,7	1,1	0,3	5,6	1,0	0,3	5,4	1,5	0,5	13,5	3,3
Nerve and nerve root disorders	18,6	6,2	47,2	1,1	0,4	4,9	3,0	1,0	14,5	5,3	1,8	29,1	0,7	0,2	4,1	0,0	0,0	0,3	3,0
Other specified and unspecified liver disease	2,4	0,8	6,3	1,4	0,5	6,6	3,1	1,0	15,4	2,0	0,7	11,2	8,6	2,9	52,4	0,8	0,3	8,0	2,9

MVD: metabolic and vascular diseases. MPD: male-predominant diseases. SI: minor conditions and sensory impairment. MSK: musculoskeletal and chronic pain syndrome. LMD: lipid metabolism disorders. UN: unspecific

Table S2. Prevalence, Observed/Expected (O/E) ratio and exclusivity of chronic conditions used to define multimorbidity clusters (>2% prevalence) at the 5 years before time point.

Chronic condition	Prevalence HD	O/E ratio HD	Exclusivity HD	Prevalence MVD	O/E ratio MVD	Exclusivity MVD	Prevalence NC	O/E ratio NC	Exclusivity NC	Prevalence MSK	O/E ratio MSK	Exclusivity MSK	Prevalence UN	O/E ratio UN	Exclusivity UN	Total prevalence
Essential hypertension	81,8	1,2	12,6	85,8	1,3	16,1	57,2	0,9	13,8	63,2	0,9	19,6	63,1	0,9	37,9	66,9
Osteoarthritis	54,3	1,4	14,5	36,8	1,0	11,9	41,0	1,1	17,1	60,3	1,6	32,4	23,2	0,6	24,1	38,7
Diabetes mellitus without complication	32,0	1,1	10,9	87,4	2,9	36,3	23,6	0,8	12,7	16,7	0,6	11,5	21,4	0,7	28,6	30,1
Obesity	47,4	1,7	17,4	52,6	1,9	23,4	19,7	0,7	11,3	31,5	1,1	23,3	17,1	0,6	24,5	28,1
Other specified and unspecified nutritional and metabolic disorders	26,9	1,0	10,2	34,6	1,3	15,9	25,0	0,9	14,8	28,8	1,1	21,9	25,2	0,9	37,2	27,3
Disorders of lipid metabolism	26,8	1,1	10,9	26,9	1,1	13,3	21,3	0,8	13,6	31,7	1,2	26,0	22,9	0,9	36,3	25,4
Urinary incontinence	32,4	1,5	15,3	18,9	0,9	10,8	59,7	2,7	44,2	16,2	0,7	15,4	7,8	0,4	14,3	21,8
Cataract and other lens disorders	29,4	1,7	17,7	9,8	0,6	7,2	15,8	0,9	14,9	21,9	1,3	26,5	14,5	0,8	33,8	17,2
Depressive disorders	18,3	1,1	11,3	14,7	0,9	11,0	31,6	1,9	30,5	22,6	1,3	28,1	8,0	0,5	19,2	16,7
Anxiety and fear-related disorders	15,4	0,9	9,5	11,1	0,7	8,3	22,6	1,3	21,8	31,8	1,9	39,5	8,7	0,5	20,9	16,7
Spondylopathies/spondyloarthropathy (including infective)	15,7	1,0	10,3	18,3	1,2	14,5	11,9	0,8	12,2	29,3	1,9	38,8	9,4	0,6	24,1	15,7
Thyroid disorders	16,5	1,2	12,0	12,5	0,9	11,0	16,9	1,2	19,2	22,9	1,6	33,5	8,6	0,6	24,3	14,2
Sleep wake disorders	20,5	1,4	14,9	23,4	1,7	20,7	13,7	1,0	15,7	17,1	1,2	25,2	8,3	0,6	23,5	14,1
Hyperplasia of prostate	15,7	1,1	11,8	13,0	0,9	11,8	7,0	0,5	8,2	8,6	0,6	13,0	18,8	1,4	55,1	13,7
Neurocognitive disorders	10,2	0,7	7,7	5,5	0,4	5,0	52,3	3,8	62,1	6,2	0,5	9,5	5,3	0,4	15,6	13,6
Hearing loss	15,5	1,2	12,0	14,7	1,1	13,8	12,8	1,0	15,4	18,9	1,4	29,3	9,8	0,7	29,5	13,4
Chronic obstructive pulmonary disease and bronchiectasis	17,7	1,4	14,4	16,8	1,3	16,6	7,3	0,6	9,3	10,5	0,8	17,3	13,4	1,1	42,4	12,7
Cardiac dysrhythmias	49,5	4,2	43,4	8,2	0,7	8,7	6,3	0,5	8,7	6,1	0,5	10,8	8,3	0,7	28,4	11,8
Chronic kidney disease	28,0	2,4	24,6	24,8	2,1	26,4	10,1	0,9	13,9	6,9	0,6	12,2	6,7	0,6	22,9	11,8
Osteoporosis	10,1	1,0	10,0	1,6	0,2	1,9	14,3	1,4	22,1	23,9	2,3	47,8	4,7	0,5	18,2	10,4
Coronary atherosclerosis and other heart disease	26,1	2,7	27,4	24,8	2,5	31,6	5,7	0,6	9,5	4,3	0,4	9,0	5,5	0,6	22,5	9,8
Glaucoma	6,3	0,7	6,7	17,3	1,8	22,7	6,6	0,7	11,1	11,1	1,2	24,0	8,4	0,9	35,5	9,6
Conduction disorders	16,0	1,8	18,6	18,8	2,1	26,6	3,4	0,4	6,2	7,7	0,9	18,1	6,7	0,8	30,5	8,9
Diverticulosis and diverticulitis	11,9	1,7	17,5	6,8	1,0	12,2	5,3	0,8	12,2	10,9	1,6	32,4	4,5	0,6	25,7	7,0
Asthma	9,1	1,4	14,0	5,4	0,8	10,0	6,2	0,9	14,9	13,4	2,0	41,7	3,2	0,5	19,4	6,7
Heart failure	43,8	6,8	70,3	7,5	1,2	14,6	2,9	0,5	7,3	0,9	0,1	3,1	0,7	0,1	4,7	6,4
Other specified and unspecified upper respiratory disease	4,8	0,8	7,8	4,5	0,7	9,0	4,5	0,7	11,4	14,2	2,2	46,7	3,9	0,6	25,1	6,3
Esophageal disorders	5,8	0,9	9,6	6,4	1,0	13,0	4,0	0,6	10,4	11,2	1,8	37,8	4,5	0,7	29,2	6,2
Diabetes mellitus with complication	2,3	0,4	3,9	44,4	7,3	90,9	1,1	0,2	3,0	0,3	0,0	0,9	0,2	0,0	1,3	6,1
Peripheral and visceral vascular disease	7,0	1,2	12,6	20,5	3,6	44,5	1,7	0,3	4,9	3,2	0,5	11,4	3,8	0,7	26,6	5,8
Other specified joint disorders	4,1	0,8	7,9	5,6	1,0	13,0	3,5	0,6	10,5	11,6	2,1	44,7	3,2	0,6	24,0	5,4
Nonrheumatic and unspecified valve disorders	39,3	7,8	80,3	1,5	0,3	3,8	0,8	0,2	2,7	1,2	0,2	5,1	1,0	0,2	8,1	5,0

Other specified and unspecified liver disease	4,4	0,9	9,0	6,2	1,2	15,5	3,2	0,6	10,4	8,4	1,7	34,9	3,7	0,7	30,1	5,0
Acquired foot deformities	4,3	0,9	9,7	1,4	0,3	3,8	3,3	0,7	11,8	12,4	2,7	56,2	2,1	0,5	18,4	4,6
Nerve and nerve root disorders	3,1	0,7	7,1	8,7	1,9	23,9	2,7	0,6	9,7	9,0	2,0	41,4	2,0	0,4	18,0	4,6
Other specified inflammatory condition of skin	5,5	1,2	12,7	7,5	1,7	21,0	2,7	0,6	9,7	4,6	1,0	21,4	3,9	0,9	35,2	4,5
Digestive congenital anomalies	3,5	0,8	8,5	4,9	1,1	14,3	3,4	0,8	12,7	7,3	1,7	35,8	3,0	0,7	28,6	4,2
Other specified hereditary and degenerative nervous system conditions	3,0	0,8	7,8	7,5	1,9	23,8	6,3	1,6	25,6	5,7	1,4	30,0	1,3	0,3	12,8	3,9
Gastroduodenal ulcer	3,8	1,0	10,7	3,3	0,9	11,1	1,9	0,5	8,4	5,3	1,4	29,8	3,6	1,0	40,0	3,7
Hypertension with complications and secondary hypertension	17,4	4,8	49,7	3,9	1,1	13,6	2,4	0,7	10,8	2,3	0,6	13,2	1,1	0,3	12,6	3,6
Retinal and vitreous conditions	2,8	0,8	8,3	4,2	1,2	14,8	3,2	0,9	14,7	5,4	1,5	31,7	2,7	0,8	30,6	3,5
Gout	4,9	1,4	14,8	8,1	2,4	29,9	1,1	0,3	5,3	2,2	0,6	13,2	3,1	0,9	36,8	3,4
Scoliosis and other postural dorsopathic deformities	4,7	1,4	14,6	1,5	0,5	5,7	2,6	0,8	12,5	7,5	2,3	47,3	1,6	0,5	19,8	3,3
Prolapse of female genital organs	3,7	1,1	11,7	0,8	0,2	3,1	4,1	1,3	20,5	8,6	2,7	55,2	0,8	0,2	9,4	3,3
Systemic lupus erythematosus and connective tissue disorders	3,9	1,3	13,0	1,9	0,6	7,8	3,7	1,2	19,1	6,6	2,1	43,8	1,3	0,4	16,3	3,1
Disorders of teeth and gingiva	1,3	0,4	4,4	6,2	2,1	25,7	2,1	0,7	11,3	4,1	1,4	28,3	2,3	0,8	30,3	3,0
Parkinson`s disease	1,0	0,3	3,4	2,1	0,7	8,8	13,4	4,5	73,5	0,9	0,3	6,2	0,6	0,2	8,2	3,0
Headache	0,8	0,3	3,0	1,0	0,4	4,7	2,1	0,8	12,7	7,4	2,7	56,4	1,6	0,6	23,2	2,7
Other and ill-defined heart disease	15,5	6,0	61,8	1,4	0,5	6,9	1,3	0,5	8,4	1,7	0,7	13,9	0,6	0,2	9,0	2,6
Male reproductive system cancers - prostate	0,8	0,3	3,4	2,3	0,9	11,3	0,8	0,3	5,0	1,4	0,6	11,6	4,4	1,7	68,8	2,6
Breast cancer - all other types	5,3	2,2	22,3	1,9	0,8	9,8	2,9	1,2	19,2	3,4	1,4	28,6	1,2	0,5	20,0	2,5
Menopausal disorders	0,9	0,4	3,9	1,9	0,8	10,1	2,1	0,9	14,1	7,7	3,2	66,7	0,3	0,1	5,1	2,4
Acute myocardial infarction	3,7	1,6	16,0	8,9	3,8	47,2	0,6	0,3	4,1	1,0	0,4	8,9	1,4	0,6	23,8	2,4
Cerebral infarction	5,1	2,2	23,0	2,5	1,1	13,5	3,9	1,7	27,6	0,7	0,3	6,8	1,7	0,7	29,2	2,3
Schizophrenia spectrum and other psychotic disorders	0,2	0,1	0,9	0,3	0,2	1,9	11,1	4,9	79,0	0,2	0,1	2,1	0,9	0,4	16,2	2,3
Trauma- and stressor-related disorders	1,1	0,5	5,4	1,9	0,9	10,7	1,8	0,8	13,6	4,9	2,3	47,2	1,3	0,6	23,2	2,2

HD: heart diseases. MVD: metabolic and vascular diseases. MSK: musculoskeletal and chronic pain syndrome. NC: neurocognitive. UN: unspecific

Table S3. Prevalence, Observed/Expected (O/E) ratio and exclusivity of chronic conditions used to define multimorbidity clusters (>2% prevalence) at the baseline time point.

Chronic condition	Prevalence HD	O/E ratio HD	Exclusivity HD	Prevalence MVD	O/E ratio MVD	Exclusivity MVD	Prevalence MSK	O/E ratio MSK	Exclusivity MSK	Prevalence NC	O/E ratio NC	Exclusivity NC	Prevalence UN	O/E ratio UN	Exclusivity UN	Total prevalence
Essential hypertension	83,3	1,2	13,4	85,7	1,2	16,6	75,4	1,1	19,9	67,3	1,0	22,1	58,4	0,8	28,0	70,1
Urinary incontinence	64,2	1,3	15,0	39,9	0,8	11,3	43,7	0,9	16,8	93,6	1,9	44,7	17,5	0,4	12,2	48,2
Osteoarthritis	63,1	1,4	15,6	35,4	0,8	10,6	73,4	1,6	29,8	44,2	1,0	22,3	29,5	0,6	21,8	45,6
Obesity	51,4	1,5	17,2	44,6	1,3	18,0	47,2	1,4	25,9	20,4	0,6	13,9	24,9	0,7	24,9	33,7
Diabetes mellitus without complication	37,3	1,1	12,9	83,0	2,5	34,7	24,0	0,7	13,6	28,2	0,9	19,9	18,4	0,6	19,0	32,6
Neurocognitive disorders	28,7	0,9	10,5	18,3	0,6	8,1	22,6	0,7	13,5	75,9	2,5	56,5	10,5	0,3	11,4	30,9
Other specified and unspecified nutritional and metabolic disorders	30,8	1,1	12,6	33,3	1,2	16,4	31,9	1,2	21,3	27,2	1,0	22,6	22,2	0,8	27,0	27,6
Sleep wake disorders	42,1	1,6	17,8	27,0	1,0	13,8	34,1	1,3	23,6	29,4	1,1	25,3	15,5	0,6	19,5	26,7
Cataract and other lens disorders	31,1	1,2	13,3	24,5	0,9	12,6	37,0	1,4	25,9	20,6	0,8	17,9	23,9	0,9	30,4	26,4
Disorders of lipid metabolism	25,6	1,0	11,0	28,8	1,1	14,9	34,5	1,3	24,3	21,3	0,8	18,6	24,4	0,9	31,2	26,3
Chronic kidney disease	51,2	2,1	23,7	42,8	1,8	23,9	19,5	0,8	14,8	24,6	1,0	23,1	10,6	0,4	14,6	24,4
Depressive disorders	30,7	1,4	15,3	14,2	0,6	8,5	33,0	1,5	26,9	35,1	1,5	35,6	9,2	0,4	13,7	22,7
Anxiety and fear-related disorders	24,7	1,1	12,7	13,0	0,6	8,0	44,3	2,0	37,1	23,3	1,1	24,3	11,7	0,5	17,9	22,0
Cardiac dysrhythmias	61,2	2,9	32,8	25,6	1,2	16,5	13,1	0,6	11,4	16,0	0,8	17,4	13,7	0,7	21,9	21,1
Spondylopathies/spondyloarthropathy (including infective)	20,1	1,1	12,1	20,9	1,1	15,2	39,1	2,1	38,5	12,2	0,7	15,0	10,7	0,6	19,2	18,7
Thyroid disorders	27,8	1,5	17,1	12,2	0,7	9,1	31,5	1,7	31,9	15,8	0,9	19,8	12,0	0,7	22,1	18,3
Hearing loss	19,6	1,1	12,1	19,7	1,1	14,7	24,6	1,3	24,8	18,2	1,0	22,9	13,9	0,8	25,5	18,3
Chronic obstructive pulmonary disease and bronchiectasis	24,6	1,4	16,3	29,6	1,7	23,6	12,8	0,7	13,8	9,9	0,6	13,3	16,8	1,0	33,1	17,1
Hyperplasia of prostate	14,1	0,8	9,4	29,3	1,7	23,6	4,4	0,3	4,8	10,4	0,6	14,2	24,0	1,4	47,9	16,9
Heart failure	68,3	4,5	51,3	20,9	1,4	19,0	5,8	0,4	7,1	9,9	0,7	15,1	3,4	0,2	7,6	15,0
Conduction disorders	25,9	1,8	20,5	29,1	2,0	27,9	13,4	0,9	17,4	5,8	0,4	9,3	10,5	0,7	24,8	14,2
Esophageal disorders	15,7	1,3	14,1	12,0	1,0	13,0	21,8	1,7	32,2	8,7	0,7	16,0	9,2	0,7	24,6	12,5
Coronary atherosclerosis and other heart disease	29,7	2,4	27,3	30,5	2,5	33,9	4,4	0,4	6,6	6,8	0,6	12,7	7,1	0,6	19,5	12,3
Osteoporosis	12,0	1,0	11,3	3,3	0,3	3,7	27,8	2,3	42,7	14,2	1,2	27,1	5,4	0,5	15,2	12,0
Glaucoma	10,9	0,9	10,7	16,3	1,4	19,3	15,7	1,4	25,2	8,7	0,8	17,5	9,3	0,8	27,3	11,5
Age-related physical debility	10,0	0,9	10,4	7,7	0,7	9,6	2,9	0,3	5,0	33,6	3,1	71,1	1,2	0,1	3,8	10,9
Other specified and unspecified upper respiratory disease	8,2	0,8	9,3	8,2	0,8	11,1	20,9	2,1	38,5	3,8	0,4	8,8	9,6	1,0	32,2	10,0
Diverticulosis and diverticulitis	14,9	1,6	18,1	13,4	1,4	19,7	13,4	1,4	26,7	5,9	0,6	14,6	5,8	0,6	20,9	9,3
Peripheral and visceral vascular disease	10,9	1,2	13,4	38,5	4,2	57,0	3,7	0,4	7,4	4,2	0,5	10,4	3,2	0,4	11,8	9,2
Nonrheumatic and unspecified valve disorders	46,2	5,2	59,2	5,9	0,7	9,1	5,0	0,6	10,4	1,9	0,2	4,8	4,3	0,5	16,5	8,8
Disorders of teeth and gingiva	5,6	0,6	7,3	12,1	1,4	19,2	8,6	1,0	18,4	7,2	0,8	19,3	9,2	1,1	35,8	8,6
Diabetes mellitus with complication	8,5	1,0	11,6	43,4	5,2	71,2	2,3	0,3	5,2	3,1	0,4	8,7	0,8	0,1	3,4	8,3

Other specified joint disorders	6,9	0,9	10,0	8,5	1,1	14,8	16,3	2,1	38,7	2,7	0,3	8,0	6,6	0,8	28,5	7,8
Symptoms of mental and substance use conditions	6,5	0,8	9,4	2,9	0,4	5,2	2,1	0,3	4,9	26,3	3,4	78,0	0,6	0,1	2,4	7,7
Asthma	13,8	1,8	20,2	4,1	0,5	7,2	16,2	2,1	38,9	4,0	0,5	11,8	5,0	0,7	21,9	7,7
Nutritional deficiencies	13,9	1,8	20,7	7,5	1,0	13,5	15,0	2,0	36,6	6,4	0,8	19,5	2,2	0,3	9,8	7,6
Other specified and unspecified liver disease	7,4	1,0	11,6	11,0	1,5	20,9	12,1	1,7	31,4	3,3	0,5	10,5	5,4	0,8	25,6	7,1
Acquired foot deformities	6,4	1,0	11,3	2,9	0,5	6,1	16,9	2,6	48,6	3,1	0,5	11,0	4,4	0,7	22,9	6,4
Nerve and nerve root disorders	4,1	0,6	7,3	8,5	1,3	18,3	18,2	2,8	52,6	1,8	0,3	6,3	2,9	0,5	15,5	6,4
Other specified hereditary and degenerative nervous system conditions	5,9	1,0	10,8	7,5	1,2	16,4	9,4	1,5	27,9	9,6	1,5	35,5	1,7	0,3	9,4	6,2
Other specified inflammatory condition of skin	6,9	1,1	12,8	7,7	1,3	17,1	7,6	1,2	22,9	3,3	0,5	12,3	6,3	1,0	34,9	6,1
Gout	8,4	1,4	15,7	19,0	3,1	42,6	2,3	0,4	6,9	2,2	0,4	8,2	4,8	0,8	26,6	6,1
Retinal and vitreous conditions	9,4	1,7	19,6	4,5	0,8	11,3	9,4	1,7	32,0	3,7	0,7	15,6	3,5	0,6	21,5	5,4
Pressure ulcer of skin	3,1	0,6	6,5	2,3	0,4	5,8	1,9	0,4	6,6	18,1	3,4	78,3	0,4	0,1	2,8	5,3
Hypertension with complications and secondary hypertension	21,1	4,0	45,5	6,3	1,2	16,3	4,2	0,8	14,9	1,7	0,3	7,6	2,4	0,5	15,6	5,2
Systemic lupus erythematosus and connective tissue disorders	6,8	1,4	15,4	5,2	1,1	14,3	10,2	2,0	37,8	4,0	0,8	18,3	2,1	0,4	14,2	5,0
Digestive congenital anomalies	6,0	1,3	14,4	3,8	0,8	11,0	9,6	2,0	37,7	3,2	0,7	15,9	2,9	0,6	21,0	4,7
Cerebral infarction	6,3	1,4	16,4	6,1	1,4	19,2	2,5	0,6	10,6	6,5	1,5	34,5	2,5	0,6	19,3	4,3
Parkinson`s disease	2,6	0,6	6,8	2,1	0,5	6,6	2,1	0,5	9,0	12,9	3,0	69,1	1,1	0,3	8,5	4,3
Prolapse of female genital organs	4,9	1,2	13,1	0,6	0,1	1,9	14,2	3,3	61,6	2,5	0,6	13,5	1,2	0,3	9,9	4,3
Scoliosis and other postural dorsopathic deformities	6,8	1,6	18,5	1,0	0,2	3,2	9,3	2,2	41,2	3,4	0,8	18,8	2,3	0,5	18,3	4,1
Nervous system signs and symptoms	6,4	1,6	17,9	3,1	0,8	10,2	3,0	0,7	13,5	8,9	2,2	50,4	1,0	0,2	8,0	4,1
Gastroduodenal ulcer	3,1	0,8	8,7	6,8	1,7	23,0	4,1	1,0	18,9	2,9	0,7	16,8	3,9	1,0	32,6	4,0
Male reproductive system cancers - prostate	1,6	0,4	4,9	7,5	2,0	27,0	0,7	0,2	3,5	1,2	0,3	7,1	6,4	1,7	57,6	3,8
Headache	0,7	0,2	2,1	1,5	0,4	5,5	12,1	3,3	61,4	1,7	0,5	10,6	2,2	0,6	20,3	3,6
Trauma- and stressor-related disorders	3,4	0,9	10,7	3,2	0,9	12,0	7,9	2,2	40,6	2,2	0,6	13,7	2,5	0,7	22,9	3,6
Nervous system pain and pain syndromes	5,4	1,5	17,1	1,6	0,5	6,3	6,7	1,9	34,9	6,2	1,7	40,0	0,2	0,1	1,7	3,6
Gastritis and duodenitis	1,6	0,4	5,0	5,0	1,4	19,2	8,1	2,3	42,1	2,6	0,7	16,6	1,8	0,5	17,1	3,6
Other and ill-defined heart disease	18,8	5,4	61,0	1,6	0,5	6,4	2,1	0,6	11,0	1,1	0,3	7,5	1,5	0,4	14,1	3,5
Menopausal disorders	2,4	0,7	8,1	0,8	0,2	3,1	12,3	3,6	67,4	1,3	0,4	8,8	1,3	0,4	12,5	3,4
Epilepsy	3,2	1,0	11,3	1,4	0,4	6,0	1,2	0,4	6,6	7,0	2,2	49,6	2,5	0,8	26,5	3,2
Other specified and unspecified endocrine disorders	5,8	1,8	20,7	5,2	1,7	22,5	5,5	1,8	32,5	1,9	0,6	13,8	1,0	0,3	10,5	3,1
Gastrointestinal cancers - colorectal	4,5	1,4	16,2	2,4	0,8	10,5	2,1	0,7	12,3	1,4	0,4	10,2	4,8	1,5	50,9	3,1
Breast cancer - all other types	6,9	2,3	25,7	0,5	0,2	2,4	5,6	1,8	34,0	2,7	0,9	20,3	1,6	0,5	17,6	3,0
Acute myocardial infarction	4,0	1,3	15,1	13,5	4,5	61,0	0,6	0,2	3,9	0,5	0,2	3,6	1,5	0,5	16,4	3,0
Urinary system cancers - bladder	1,0	0,3	3,9	7,7	2,6	36,0	0,8	0,3	5,1	1,1	0,4	9,0	4,0	1,4	46,0	2,9

Coagulation and hemorrhagic disorders	6,0	2,1	23,7	3,5	1,2	16,6	1,6	0,5	10,1	2,7	0,9	21,4	2,4	0,8	28,2	2,9
Schizophrenia spectrum and other psychotic disorders	1,5	0,6	6,3	0,4	0,1	1,9	0,3	0,1	2,1	8,5	3,1	72,3	1,4	0,5	17,4	2,7
Pulmonary heart disease	20,5	8,1	91,1	0,6	0,2	3,3	0,2	0,1	1,4	0,0	0,0	0,3	0,3	0,1	4,0	2,5
Alcohol-related disorders	1,8	0,7	8,1	6,9	2,7	37,4	0,4	0,1	2,6	1,3	0,5	12,3	3,0	1,2	39,6	2,5
Disruptive, impulse-control and conduct disorders	3,7	1,5	16,7	1,7	0,7	9,2	0,6	0,2	4,5	7,1	2,8	65,4	0,3	0,1	4,1	2,5
Other specified and unspecified gastrointestinal disorders	1,4	0,6	6,7	2,0	0,8	11,4	6,6	2,8	52,1	1,6	0,7	15,3	1,0	0,4	14,5	2,3
Hepatitis	3,7	1,7	19,4	1,6	0,8	10,3	2,6	1,2	22,7	1,6	0,7	17,1	1,9	0,9	30,5	2,1

HD: heart diseases. MVD: metabolic and vascular diseases. MSK: musculoskeletal and chronic pain syndrome. NC: neurocognitive. UN: unspecific

Table S4. Topmost frequent chronic multimorbidity cluster trajectories across the three defined time points (10 years before, 5 years before, baseline), filtered up to 90% cumulative frequency.

10 years before	5 years before	Baseline	n	%
No multimorbidity	Unspecific	Unspecific	398	9.98
No multimorbidity	No multimorbidity	Unspecific	188	4.71
Unspecific	Unspecific	Unspecific	184	4.61
Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	169	4.24
No multimorbidity	Neurocognitive	Neurocognitive	151	3.79
Male-predominant diseases	Unspecific	Unspecific	135	3.39
Lipid metabolism disorders	Unspecific	Unspecific	118	2.96
Metabolic & vascular diseases	Metabolic & vascular diseases	Metabolic & vascular diseases	100	2.51
Unspecific	Neurocognitive	Neurocognitive	100	2.51
Minor conditions & sensory impairm.	Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	98	2.46
Unspecific	Metabolic & vascular diseases	Metabolic & vascular diseases	93	2.33
Minor conditions & sensory impairm.	Heart diseases	Heart diseases	89	2.23
No multimorbidity	No multimorbidity	No multimorbidity	82	2.06
Musculoskeletal & chronic pain synd.	Neurocognitive	Neurocognitive	78	1.96
No multimorbidity	Unspecific	Neurocognitive	78	1.96
No multimorbidity	No multimorbidity	Neurocognitive	70	1.76
No multimorbidity	Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	70	1.76
Unspecific	Unspecific	Neurocognitive	67	1.68
Lipid metabolism disorders	Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	65	1.63
Unspecific	Heart diseases	Heart diseases	62	1.55
Unspecific	Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	60	1.50
Male-predominant diseases	Unspecific	Metabolic & vascular diseases	44	1.10
No multimorbidity	Unspecific	Metabolic & vascular diseases	44	1.10
Lipid metabolism disorders	Neurocognitive	Neurocognitive	43	1.08
Lipid metabolism disorders	Metabolic & vascular diseases	Metabolic & vascular diseases	40	1.00
No multimorbidity	Unspecific	Musculoskeletal & chronic pain synd.	40	1.00
Musculoskeletal & chronic pain synd.	Unspecific	Unspecific	40	1.00
Unspecific	Unspecific	Metabolic & vascular diseases	39	0.98
No multimorbidity	Neurocognitive	Unspecific	31	0.78
Male-predominant diseases	Metabolic & vascular diseases	Metabolic & vascular diseases	30	0.75
Unspecific	Unspecific	Musculoskeletal & chronic pain synd.	30	0.75
Lipid metabolism disorders	Unspecific	Neurocognitive	29	0.73
Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	Neurocognitive	28	0.70
No multimorbidity	Unspecific	Heart diseases	26	0.65
Male-predominant diseases	Unspecific	Neurocognitive	26	0.65
Minor conditions & sensory impairm.	Neurocognitive	Neurocognitive	25	0.63
Unspecific	Unspecific	Heart diseases	24	0.60
No multimorbidity	Musculoskeletal & chronic pain synd.	Unspecific	24	0.60
Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	Unspecific	24	0.60
No multimorbidity	Metabolic & vascular diseases	Metabolic & vascular diseases	23	0.58
Minor conditions & sensory impairm.	Musculoskeletal & chronic pain synd.	Neurocognitive	22	0.55
Lipid metabolism disorders	Heart diseases	Heart diseases	21	0.53
No multimorbidity	Heart diseases	Heart diseases	21	0.53
Male-predominant diseases	Neurocognitive	Neurocognitive	21	0.53
Lipid metabolism disorders	Unspecific	Metabolic & vascular diseases	20	0.50
Unspecific	Metabolic & vascular diseases	Heart diseases	19	0.48
Male-predominant diseases	Heart diseases	Heart diseases	19	0.48
Unspecific	Heart diseases	Neurocognitive	19	0.48
Minor conditions & sensory impairm.	Unspecific	Unspecific	19	0.48
Lipid metabolism disorders	Unspecific	Musculoskeletal & chronic pain synd.	18	0.45
Lipid metabolism disorders	Musculoskeletal & chronic pain synd.	Unspecific	18	0.45
Unspecific	Musculoskeletal & chronic pain synd.	Neurocognitive	17	0.43
Unspecific	Metabolic & vascular diseases	Neurocognitive	16	0.40
Lipid metabolism disorders	Musculoskeletal & chronic pain synd.	Neurocognitive	16	0.40
Minor conditions & sensory impairm.	Metabolic & vascular diseases	Metabolic & vascular diseases	15	0.38
Lipid metabolism disorders	Unspecific	Heart diseases	15	0.38
Unspecific	Neurocognitive	Heart diseases	14	0.35
Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	Heart diseases	14	0.35
Unspecific	Musculoskeletal & chronic pain synd.	Heart diseases	14	0.35
Minor conditions & sensory impairm.	Unspecific	Neurocognitive	14	0.35

Male-predominant diseases	Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	14	0.35
Unspecific	Neurocognitive	Unspecific	14	0.35
Musculoskeletal & chronic pain synd.	Heart diseases	Heart diseases	13	0.33
Unspecific	Heart diseases	Metabolic & vascular diseases	12	0.30
Metabolic & vascular diseases	Metabolic & vascular diseases	Heart diseases	12	0.30
Minor conditions & sensory impairm.	Musculoskeletal & chronic pain synd.	Heart diseases	12	0.30
Male-predominant diseases	Unspecific	Heart diseases	12	0.30
Unspecific	Metabolic & vascular diseases	Musculoskeletal & chronic pain synd.	12	0.30
Unspecific	Metabolic & vascular diseases	Unspecific	12	0.30
Musculoskeletal & chronic pain synd.	Unspecific	Neurocognitive	11	0.28
Musculoskeletal & chronic pain synd.	Neurocognitive	Musculoskeletal & chronic pain synd.	11	0.28
Unspecific	Neurocognitive	Musculoskeletal & chronic pain synd.	11	0.28
Metabolic & vascular diseases	Musculoskeletal & chronic pain synd.	Musculoskeletal & chronic pain synd.	11	0.28
Male-predominant diseases	Unspecific	Musculoskeletal & chronic pain synd.	11	0.28
Unspecific	Heart diseases	Unspecific	11	0.28

Appendix B. Additional articles

The following sections of this Appendix contain additional articles related to the publications that compose this PhD thesis.

B1. MoPIM study protocol

Article reference:

Baré M, Herranz S, Jordana R, Gorgas MQ, Ortonobes S, Sevilla D, De Jaime E, Ibarra O, Martín C. Multimorbidity patterns in chronic older patients, potentially inappropriate prescribing and adverse drug reactions: protocol of the multicentre prospective cohort study MoPIM. BMJ Open. 2020 Jan 26;10(1):e033322.

Open access Protocol

BMJ Open

Multimorbidity patterns in chronic older patients, potentially inappropriate prescribing and adverse drug reactions: protocol of the multicentre prospective cohort study MoPIM

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ABSTRACT

Introduction Multimorbidity is a major challenge for current healthcare systems and professionals. From the different approaches that have been proposed to analyse this issue, the hypothesis of the existence of association patterns of different chronic conditions is gaining visibility. In addition, multimorbidity can be associated to polypharmacy, which can lead to a higher risk of potentially inappropriate prescribing (PIP) and consequently to adverse drug reactions (ADRs). The general objective of this novel study is to identify the association between PIP, multimorbidity patterns, polypharmacy and the presence of ADRs in older patients admitted for exacerbation of chronic diseases.

Methods and analysis The MoPIM (morbidity, potentially inappropriate medication) study is a multicentre prospective cohort study of an estimated sample of 800 older (≥65 years) patients admitted to five general hospitals in Spain due to an exacerbation of a chronic disease. Patients referred to home hospitalisation, admitted due to an acute process or with a fatal outcome expected at the time of admission are excluded. Sociodemographic data, chronic morbidities and geriatric syndromes, number of chronic prescribed medications, PIP at admission to hospital and on discharge, according to the newest screening tool of older screening tool of older person's potentially inappropriate prescriptions/screening tool to alert doctors to right treatment criteria, and ADRs during hospitalisation are being collected. Multimorbidity patterns will be identified using cluster analyses techniques, and the frequency of polypharmacy, PIP and ADRs will be calculated. Finally, the possible relationship between those indicators will be identified through bivariate and multivariate analyses.

Ethics and dissemination The project has been 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. The results will be actively and mainly disseminated through publication in peer-reviewed journals and communications in scientific conferences.

Trial registration number NCT02830425.

Strengths and limitations of this study

- ► To our knowledge, this is the first published study that includes objectives related to chronic multimorbidity, appropriateness of medication and adverse drug reactions during hospitalisation at the same time, in older patients.
- ► Data of multimorbidity include also identification of chronic exacerbated diseases that cause hospitalisation, geriatric syndromes and functional status.
- ► The multicentre cohort design as well as the innovative analytical approach of multimorbidity patterns can lead to novel results in this field.
- ► Adverse drug reactions rate could be subject to an infra-estimation if active efforts to identify them are not complete.

INTRODUCTION

Multimorbidity and possible patterns

In recent years, the healthcare landscape has changed dramatically, with the considerable and gradual increase of older patients with multiple chronic health conditions.[1] Multimorbidity has become an important challenge for the health system due to, on the one hand, the population ageing (which increases the percentage of people with multimorbidity) and, on the other hand, the difficulty of clinical management of patients with multimorbidity.[1 2] Far from treating diseases or isolated processes, in patients with several chronic pathologies, and especially at times of decompensation, the complexity inherent to this type of patients becomes more evident.

In addition, in older patients, a process of exacerbation or decompensation of chronic problems may coincide with the existence of geriatric syndromes such as acute confusional syndrome or frailty. In these cases, therapeutic decisions may require great knowledge and skills for sharing decision making to achieve an adequate balance between risks and benefits for the patient.[3] However, clinical practice guidelines do not usually consider or resolve the uncertainties related to these situations. In fact, randomised controlled trials often exclude patients with concomitant pathologies.[4]

Currently, basic knowledge about the interrelationship of diseases is very limited, partly because of the existing confidence in a scientific method that maximises internal validity but excludes patients with comorbidity in both observational studies and clinical trials. Attempts to study multimorbidity clash with the absence of an internationally agreed definition and quantification.[5] A systematic review of Violan *et al*[6] identified important variations in both the definition of multimorbidity and its prevalence in different contexts and ages. Despite these variations, multimorbidity is much more frequent in older patients.[7 8] Among the different definitions, the one that advocates for the existence of association patterns of some of these chronic diseases, either because they coincide, or because they share some physiopathological mechanisms, is recently gaining strength.[9 10]

Polypharmacy, PIP and ADRs

Polypharmacy is a remarkable feature of patients with multiple chronic pathologies. For this same reason, the prevalence of polypharmacy is usually high in the older population.[11] Although there is no consensus on the minimum number of prescribed drugs to consider a patient as polymedicated, the chronic daily consumption of five or more drugs is a commonly accepted figure.[12] Polypharmacy, in turn, is associated with a higher probability of adverse drug reactions (ADRs). In older people, this probability is even higher as a result of physiological changes associated with ageing, changes in the pharmacokinetic and pharmacodynamic behaviour of drugs, functional problems and social aspects. It has been estimated that ADRs are responsible for up to 30% of hospital admissions in older patients.[13] Potentially inappropriate prescribing (PIP) of drugs and poor monitoring of prescribed treatments are predisposing factors for the appearance of ADRs.[13] Fernandez *et al*[14] observed that 69% of the ADRs detected in hospitalised polymedicated older patients were due to treatments that were identified as inappropriate. In 2011, Hamilton and colleagues also identified an association between overtreatment and ADRs in patients.[15]

The STOPP-START criteria

There are several tools to evaluate potentially inadequate prescribing.[16–18] Among all of them, the explicit criteria STOPP-START (screening tool of older person's potentially inappropriate prescriptions/screening tool to alert doctors to right treatment) are the most used and validated in European older people. In fact, they were developed under the aegis of the European Union Geriatric Medicine Society.[19] STOPP-START criteria include drug interactions and therapeutic duplicity.[19] The 2008 version consisted of a list of 84 medication indications, developed using a Delphi method applied to experts from different disciplines, who carried out a literature review. The criteria are directed to prevalent diseases in older patients and are ordered by physiological systems. These criteria are easy to relate to active diagnoses and to the patients' medication lists that appear in their electronic health records. The systematic review published by Hill-Taylor et al in 2013[16] concluded that these criteria were more sensitive than those of Beers to detect PIP. In 2015, O'Mahony *et al*[20] published an updated version that includes 114 criteria, which was subsequently translated into Spanish.[21]

It should be noted that although the criteria for evaluating PIP can be helpful in making decisions, the clinical and social context of the patient has to be always taken into account. Hence there is need to share and assess the findings or PIP detected with the prescribing professional. Fortunately, it is increasingly common to use these or other criteria to identify a possible treatment inadequacy and assess a possible deprescription or prescription. However, its systematic use could be far from being real.

In recent years, many studies have been published using the STOPP-START criteria to assess the adequacy of medications in the community, socio-health centres and/or nursing homes, and the hospital setting.[14 18 22–28] At the time of initiating this study, no published analyses were available with the objective to describe the relationships between multimorbidity, PIP and ADRs.

Multimorbidity, polypharmacy, PIP and ADRs

Given the importance of this phenomenon, it is necessary to deepen our knowledge to offer the best clinical care and optimise health outcomes.

Taking into account all the previous considerations, the hypotheses of the study were, first, that the morbidity of older patients admitted to hospital due to exacerbation of their chronic pathology may show certain patterns or profiles of association. Second, that geriatric syndromes may be relevant in these patterns, and that these patterns may be associated with greater polypharmacy and PIP. And third, that potentially inappropriate medications, or some of them, may, in turn, be associated with a greater presence of ADRs, already detected at the time of hospital admission or developed during the same hospitalisation, compared with those patients with no medication inappropriateness.

Objectives

The general objective of the study is to identify the association between multimorbidity, polypharmacy, PIP and the presence of ADRs in older patients admitted for

Baré M, *et al*. *BMJ Open* 2020;**10**:e033322. doi:10.1136/bmjopen-2019-033322

exacerbation of chronic diseases. The specific objectives are to:

1. Identify and describe the PIP of chronic medication according to STOPP-START criteria at the time of admission and on discharge.
2. Estimate the prevalence of multimorbidity and, together with geriatric syndromes and risk factors, identify possible morbidity association patterns in older patients admitted as a result of an exacerbation of their chronic disease.
3. Describe the possible polypharmacy (≥5 chronic medications) of those patients.
4. Assess the difference in PIP on admission and at discharge.
5. Evaluate if any of the possible multimorbidity patterns are associated with greater PIP or with specific types of PIP.
6. Analyse the possible association between the amount or the types of PIP and the number or types of ADRs.

METHODS AND ANALYSIS

Design and setting

A multicentre prospective cohort study has been designed, including patients admitted to the internal medicine or geriatric services of five general hospitals in three different regions of Spain: Parc Taulí Hospital Universitari, Consorci Hospitalari de Vic, Hospital del Mar, Hospital de Galdakao and Complejo Hospitalario Universitario de Canarias. All of them have an internal medicine and/or geriatric service and are part of, or collaborate with, the Spanish Health Services Research on Chronic Patients Network (REDISSEC). In addition, a process of medication review is established in all of them, using criteria for older patients.

Inclusion criteria

Patients older than 64 years admitted to the internal medicine or geriatrics service as a result of the exacerbation or decompensation of their chronic pathology are included. A stay of >48 hours in hospital is considered an admission.

No written informed consent was deemed necessary for this study.

Exclusion criteria

Patients referred to home hospitalisation (patient at home but the clinical team provides punctual attention by telephone or home visits), those admitted due to an acute process not related to the chronic diseases (for example, an infection) according to clinical judgement of the corresponding physician or those with a fatal outcome expected at the time of admission are not included.

In the case that various patients met the inclusion criteria during the same day, and so that the clinical team could take the tasks of registering all variables of the study together with their care tasks, they were sorted alphabetically and selected the first of all of them to be included in this study.

Only patients attended by the physician participating in the study are included.

During recruitment, which lasted from September 2016 until the end of 2018, each patient was included only once.

Data acquisition

Each patient is monitored until hospital discharge (or death during hospitalisation), with data collection during the first days of admission to hospital ward and at the time of discharge.

As part of the usual patient care routine for older patients, the pharmacist of the clinical committee reviews the prescribed chronic medication at the time of admission. STOPP/START (SS) criteria are checked for each patient. These consist of 80 STOPP criteria (which detect medication that would not meet criteria for indication to a patient or a specific clinical situation or medications prescribed included drug-drug and drug-disease interactions) and 34 START criteria (detect medication that would be recommended to incorporate, including some vaccines).[20] For each patient, possible PIP are recorded at the time of admission and, following the usual practice, the clinical committee evaluates the PIP together with the possible modification of the medication according to the SS criteria. For the purposes of the study, the criteria are re-applied and recorded by the pharmacist to the prescribed medication on discharge, in this case without evaluation by the clinical committee.

In addition, ADRs notified to the pharmacy department by the clinical team or registered in the clinical course are identified by the pharmacist, and the consequences derived from them are classified as well as if they have been resolved at the time of discharge. According to the WHO and the European Medicine Agencies, an ADR is any undesirable event that has happened to the patient while using a medication and there is a suspicion that it is caused by the medication, including: (a) any noxious, unintended and undesired effect of a drug after doses used in humans for prophylaxis, diagnosis or therapy and (b) noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product.[29 30] As a routine standard practice, a physician, a nurse, a clinical assistant or the pharmacist can notify any ADRs to the pharmacy department or to the electronic notification system for adverse reactions to medication, held by the Spanish Ministry of Health.

Variables

The different types of information obtained according to the moment of monitoring are shown in figure 1. All of them are described below:

a. Sociodemographic: patient's code, centre, date of birth, sex, type of cohabitation (alone, with relatives or other people, in a nursing home).

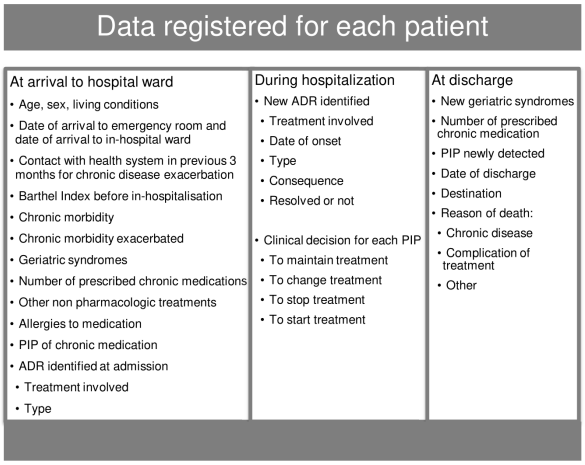

Figure 1 Data registered for each patient included in the morbidity, potentially inappropriate medication study. ADR, adverse drug reactions; PIP, potentially inappropriate prescribing.

b. Clinical: date of arrival at the emergency room, date of admission, date of discharge, destination at discharge (home, transfer to another hospital, transfer to another service of the hospital itself, transfer to a nursing home), cause of the death (chronic illness, complication or others), functional status just before entering the hospital (Barthel index), existence of hospitalisation and/or visits to healthcare services in the three previous months due to exacerbation of any chronic pathology, existence of pharmacological allergies and active principles involved.

Chronic active diseases of the patient are recorded. For this purpose, the physicians of the project have defined, on a consensual basis, a limited list of 64 chronic problems or conditions, coming from the 114 groups defined by Salisbury and colleagues,[8] and including the 19 categories of the Charlson Index.[31] In order to define the list of conditions to be recorded, the physicians that participated in the project considered the subjective estimated frequency of the condition in older hospitalised patients in their departments. Following the same criteria as Salisbury, a condition is considered to be chronic when it lasts 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.[8]

For each of the chronic condition (see table 1), it is also recorded if they have required attention or clinical management throughout the hospitalisation, and the attending physician of the clinical team assigns a (subjective) correlative score (1, 2, 3…) to each one, according to the importance or weight during the attention process. Thus, chronic problems that have not had any significance during hospitalisation do not represent any score. Drug-related conditions of this list refer to poor management of medication for a chronic disease that have clinical

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 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	
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)	

Continued

Table 1 Continued

Chronic conditions	Geriatric syndromes and risk factors
39.Hypertension	
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 (miocardiopatie, valvulopatie)	
47.Non-schizophrenic mental disorders (excluding depression and anxiety)	
48.Obesity	
49.Osteoporosis	
50.Other neurological pathologies (essential tremor)	
51.Other vascular diseases (ischaemia, aneurism)	
52.Parkinson's 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	

implications in that hospitalisation (as, for example, any drug intolerance or an excess drug poisoning).

Specific geriatric syndromes 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) are also recorded, as usual. Two of the departments systematically apply a recently developed scale for frailty,[32] while the others consider clinical judgement (although based on the same variables).

c. Pharmacological: Number of chronic medications of the electronic prescribing at the time of admission and discharge, SS criteria detected on admission, active principle involved, clinical decisions to modify the prescription associated with the PIP detected, SS criteria detected on discharge and the active principle involved in the PIP detected. Medication is only considered chronic if it has been prescribed, at least, 3 months ago. Active principles were only considered separately, regardless of the combinations. Creams, ointments and healing material were not considered.
d. ADRs identified both at the time of admission and during the course of admission: drug involved, type of ADR according to the Wills and Brown classification[33] (predictable, unpredictable, continuous or prolonged, with carcinogenic effect, rebound effect), start date if it appeared along stay in the hospital, consequences in terms of health (causes death, threatens life, lengthens the time of hospitalisation, other important consequences under medical criteria) and if they are resolved during admission or at discharge.

Pilot study

At the beginning of the recruitment, the first 10 admissions per centre were selected to validate the data collection instruments and identify the problems that could arise during this stage. Then, relevant changes were made in the protocol and in the questionnaires.

Sampling and analysis

An estimated consecutive sample of 800 patients meeting the inclusion criteria are being selected, proportionally distributed to the volume of income of the medicine and/or geriatric services of each centre.

The sample size calculation was based on the indicator 'Prevalence of patients with PIP'. Taking into consideration the variability of the prevalence for older patients in a published review,[16] that ranged between 21% and 79% of cases fulfilling any STOPP/START criteria, estimation was based on a prevalence of PIP of 50% (which would provide the highest number of patients to include), an alpha risk of 5% and a power of 80%. Then, a minimum of 400 patients would be required for estimation of the prevalence of PIP in the whole sample. In order to increase the statistical power of the bivariate and multivariate analyses, and specifically the proposed cluster analysis, for which there is no sample calculation formula, and taking also into account the feasibility and possible difficulties of each centre and the funding of the project, the initial sample size was increased by 100%.

According to the objectives of the study, the following steps of data analysis will be performed:

The **main descriptive indicators** will be:

- Number and percentage of patients with PIP, both on admission and at discharge.
- Number and percentage of the STOPP-START criteria identified on admission and at discharge.
- Number and percentage of polymedicated patients (≥5 chronic active principles).
- Number and percentage distribution of chronic pathologies.
- Number and percentage of geriatric syndromes and risk factors.
- Number and percentage of the chronic pathologies that have motivated admission due to exacerbation.

- Number and percentage of patients with any ADR detected on or during admission.

b) The possible multimorbidity patterns will be identified using a cluster analysis algorithm, similar to that used by Marengoni *et al*.[34] With that intention, diseases or syndromes with a very low prevalence will be excluded to avoid statistical noise and therefore spurious findings in the cluster solutions. To characterise the multimorbidity patterns corresponding to each cluster of individuals, the frequency of chronic diseases or syndromes in each cluster will be calculated. Observed/expected ratios will be calculated by dividing the prevalence of a given disease within a cluster by its prevalence in the overall population. The exclusivity of different diseases, defined as the fraction of participants with the disease included in the cluster over the total number of participants with the disease, will be also calculated.

c) To evaluate the relationship between multimorbidity and PIP, and to analyse the possible association between PIP and ADRs, a bivariate analysis will be carried out, where the variables will be treated quantitatively and/or categorically (number of morbidities, number of PIP or ADRs, patterns of morbidity, existence of PIP or ADRs, types of PIP or ADRs). Parametric or non-parametric tests will be applied according to the normal distribution of the PIP or ADRs number. In addition, ORs and their CI will be estimated at 95% among multimorbidity patterns, existence of PIP as well as between PIP and ADRs detected at the time of admission.

d) Finally, multiple regression and multilevel analysis techniques (where the levels would be the patient and the hospital) will be applied to adjust for other possible factors (such as age, sex, Barthel index or previous visits) statistically significant in the bivariate analysis or those clinically relevant, where the dependent variable, PIP or ADRs, according to objective, may be dichotomous or quantitative. The adjusted β coefficients and their 95% CI, and the exponentials of β (OR) will be estimated according to whether it is a multiple linear regression or a generalised estimating equation model.

All analyses will be performed with R (R Foundation for Statistical Computing, Vienna, V.3.6.0) and SPSS (IBM Corp, V.25.0). First results are expected to be available by the end of 2019.

Patient and public involvement

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

ETHICS AND DISSEMINATION

All the personal data will be anonymised, assigning a code to each patient, exclusive of the study, so that they no longer relate to identifiable people.

The dissemination plan includes publication in peer-reviewed journals of several disciplines such as internal medicine, geriatrics or public health, as well as research communications in some scientific conferences and mass media. Other kind of dissemination activities to clinicians, managers and policy makers will be done in the proper format.

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Contributors MB, the principal investigator, conceived the study and wrote the protocol, in collaboration with SH, RJ, and MQG. SO, DS, EDJ, OI and CM reviewed and made amendments to its preliminary version. They also contributed to the design of the final questionnaires and were responsible of the organisation of the fieldwork in each centre. All of the members of the study group participated in the inclusion of patients, as well as in the collection and quality assessment of clinical data for each patient.

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REFERENCES

1 Palladino R, Pennino F, Finbarr M, *et al*. Multimorbidity and health outcomes in older adults in ten European health systems, 2006–15. *Health Aff* 2019;38:613–23.
2 The Academy of Medical Sciences. Multimorbidity: a priority for global health research, 2015. Available: https://acmedsci.ac.uk/file-download/82222577
3 Zulman DM, Asch SM, Martins SB, *et al*. Quality of care for patients with multiple chronic conditions: the role of comorbidity interrelatedness. *J Gen Intern Med* 2014;29:529–37.
4 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.
5 Calderón-Larrañaga A, Vetrano DL, Ferrucci L, *et al*. Multimorbidity and functional impairment-bidirectional interplay, synergistic effects and common pathways. *J Intern Med* 2019;285:255–71.
6 Violan C, Foguet-Boreu Q, Flores-Mateo G, *et al*. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS One* 2014;9:e102149.
7 Fortin M, Stewart M, Poitras M-E, *et al*. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012;10:142–51.
8 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.
9 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.
10 Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, *et al*. Multimorbidity patterns: a systematic review. *J Clin Epidemiol* 2014;67:254–66.
11 Gutiérrez-Valencia M, Aldaz Herce P, Lacalle-Fabo E, *et al*. Prevalence of polypharmacy and associated factors in older adults in Spain: data from the National health survey 2017. *Medicina Clínica* 2019;153:141–50.
12 Masnoon N, Shakib S, Kalisch-Ellett L, *et al*. What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017;17.
13 Cabré M, Elias L, Garcia M, *et al*. Avoidable hospitalizations due to adverse drug reactions in an acute geriatric unit. Analysis of 3,292 patients. *Medicina Clínica* 2018;150:209–14.
14 Fernández-Regueiro R, Fonseca-Aizpuru E, López-Colina G, *et al*. Prescripción inadecuada Y efectos adversos a medicamentos en pacientes de edad avanzada. *Rev Clin Esp* 2011;221:400–6.
15 Hamilton H, Gallagher P, Ryan C, *et al*. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. *Arch Intern Med* 2011;171:1013–9.
16 Hill-Taylor B, Sketris I, Hayden J, *et al*. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. *J Clin Pharm Ther* 2013;38:360–72.
17 Patterson SM, Cadogan CA, Kerse N, *et al*. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev* 2014:CD008165.
18 Motter FR, Fritzen JS, Hilmer SN, *et al*. Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria. *Eur J Clin Pharmacol* 2018;74:679–700.
19 Gallagher P, Ryan C, Byrne S, *et al*. STOPP (screening tool of older Person's prescriptions) and start (screening tool to alert doctors to right treatment). consensus validation. *Int J Clin Pharmacol Ther* 2008;46:72–83.
20 O'Mahony D, O'Sullivan D, Byrne S, *et al*. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2014;44:213–8.
21 Delgado Silveira E, Montero Errasquín B, Muñoz García M, *et al*. Mejorando La prescripción de medicamentos en Las personas mayores: Una nueva edición de Los criterios STOPP-START. *Revista Española de Geriatría y Gerontología* 2015;50:89–96.
22 García-Gollarte F, Baleriola-Júlvez J, Ferrero-López I, *et al*. Inappropriate drug prescription at nursing home admission. *J Am Med Dir Assoc* 2012;13:83.e9–83.e15.
23 Sevilla-Sánchez D, Molist-Brunet N, Amblàs-Novellas J, *et al*. Potentially inappropriate medication at hospital admission in patients with palliative care needs. *Int J Clin Pharm* 2017;39:1018–30.
24 San-José A, Agustí A, Vidal X, *et al*. Inappropriate prescribing to older patients admitted to hospital: a comparison of different tools of misprescribing and underprescribing. *Eur J Intern Med* 2014;25:710–6.
25 Salgueiro E, Elizarde BC, Elola AI, *et al*. [The most common STOPP/START criteria in Spain. A review of the literature]. *Rev Esp Geriatr Gerontol* 2018;53:274–8.
26 Moriarty F, Bennett K, Cahir C, *et al*. Potentially inappropriate prescribing according to STOPP and START and adverse outcomes in community-dwelling older people: a prospective cohort study. *Br J Clin Pharmacol* 2016;82:849–57.
27 Gibert P, Cabaret M, Moulis M, *et al*. Optimizing medication use in elderly people in primary care: impact of STOPP criteria on inappropriate prescriptions. *Arch Gerontol Geriatr* 2018;75:16–19.
28 Thomas RE, Thomas BC. A systematic review of studies of the STOPP/START 2015 and American geriatric Society beers 2015 criteria. *Curr Aging Sci* 2019;26:187–92.
29 European Medicines Agency and Heads of Medicines Agencies. *Guideline on good pharmacovigilance practices (GVP) module VI – management and reporting of adverse reactions to medicinal products (Rev 1*, 2014.
30 Mascolo A, Scavone C, Sessa M, *et al*. Can causality assessment fulfill the new European definition of adverse drug reaction? A review of methods used in spontaneous reporting. *Pharmacol Res* 2017;123:122–9.
31 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
32 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.
33 Wills S, Brown D. A proposed new means of classifying adverse reactions to medicines. *Pharm J* 1999;262:163–5.
34 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;72.

B2. MoPIM study: multimorbidity patterns

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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, hospitalised 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% to 99.07%), the most frequent were hypertension (81.49%, 95% CI 78.53% to 84.12%) and heart failure (59.86%, 95% CI 56.29% to 63.34%). The most prevalent geriatric syndrome was polypharmacy (79.86%, 95% CI 76.82% to 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 reorganise healthcare circuits or processes to tackle the increasing number of older, multimorbid patients.

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 standardised, thus hindering comparability with other studies.

Trial registration number NCT02830425.

BACKGROUND

According to the most recent Eurostat baseline population projections, old-age dependency ratio (population 65 years and over divided by population 15–64 years) 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 (CM).[3 4] Most clinical

practice guidelines are focused on single diseases, with limited recommendations for multimorbid patients,[5] and, in addition, randomised 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 CM of old patients.[12] In fact, the purpose of multimorbidity characterisation (ie, predicting outcomes or use of health services, improving quality of care, organising 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 hospitalisation. 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 hospitalised 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 hospitalisation, 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 hospitalisation due to exacerbation of any chronic disease, and destination at discharge from the present episode of hospitalisation (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 online 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 *et al*[20] and including the 19 categories of the Charlson Index.[21] Following the same criteria as Salisbury *et al*, 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 hospitalisation (such as any drug intolerance or an excess drug poisoning).

Additionally, for each of the CC, it was also recorded if they had required CM (both at admission and during hospitalisation) 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 hospitalisation, 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 hospitalisation.

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 hospitalisations 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 organisational 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 categorised 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 first 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 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, four 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 V.3.6.0 and SPSS V.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

A total of 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

Table 1 Sociodemographic and clinical variables of the studied cohort

Sociodemographic and clinical variables		N	%	95% CI
Age	<70	33	4.46	3.19 to 6.20
	70–74	48	6.49	4.93 to 8.50
	75–79	82	11.08	9.02 to 13.55
	80–84	181	24.46	21.50 to 27.68
	85–89	232	31.35	28.11 to 34.78
	90–94	134	18.11	15.50 to 21.05
	≥95	30	4.05	2.85 to 5.73
Sex	Female	394	53.24	49.64 to 56.81
	Male	346	46.76	43.19 to 50.36
Barthel Index	<20	90	12.16	10.00 to 14.71
	20–35	76	10.27	8.28 to 12.67
	40–55	124	16.76	14.24 to 19.62
	60–95	294	39.73	36.27 to 43.30
	100	156	21.08	18.30 to 24.17
Age adjusted, updated Charlson Comorbidity Index	2–5	148	20.00	17.28 to 23.03
	6–8	411	55.54	51.94 to 59.08
	9–14	181	24.46	21.50 to 27.68
Household	With relatives/other people	523	70.68	67.30 to 73.84
	Nursing home	95	12.84	10.62 to 15.44
	Alone	122	16.49	13.99 to 19.33
Chronic disease exacerbation 3 months prior to admission	No	225	30.41	27.20 to 33.81
	Yes (total)	515	69.59	66.19 to 72.80
	Primary care	342	46.22	42.65 to 49.82
	Emergencies	263	35.54	32.17 to 39.06
	Hospital admission	193	26.08	23.05 to 29.36
	Outpatient care	8	1.08	0.55 to 2.12
	Home care	14	1.89	1.13 to 3.15
Conditions requiring clinical management	1	302	40.81	37.36 to 44.39
	2	216	29.19	26.03 to 32.57
	3	106	14.32	11.98 to 17.03
	4	72	9.73	7.80 to 12.08
	5	28	3.78	2.63 to 5.41
	6	13	1.76	1.03 to 2.98
	7	2	0.27	0.07 to 0.98
	8	1	0.14	0.007 to 0.76
Destination at discharge	Home	468	63.24	59.71 to 66.64
	Nursing home	105	14.19	11.86 to 16.89
	Another hospital	101	13.65	11.36 to 16.31
	Exitus	66	8.92	7.07 to 11.19
Multimorbidity	No	10	1.35	1.35 to 1.36
	Yes	730	98.65	98.23 to 99.07

or more CC (98.65%; 95% CI 98.23% to 99.07%), with a median of 8 CC and 6 GS per patient. Nearly 70% had consulted a healthcare service in the 3 months prior to hospitalisation due to chronic disease exacerbation.

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% to 84.12%) and heart failure (59.86%, 95% CI 56.29% to 63.34%) (see online

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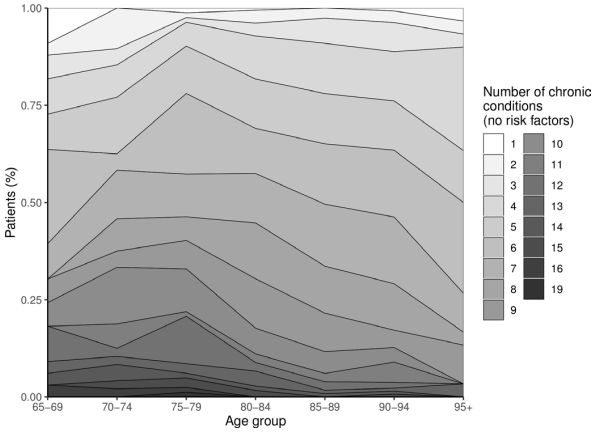

Figure 1 Distribution of the number of chronic conditions (excluding the following risk factors: hypertension, dyslipidaemia, obesity, osteoporosis and drug-related conditions) in relation to age groups.

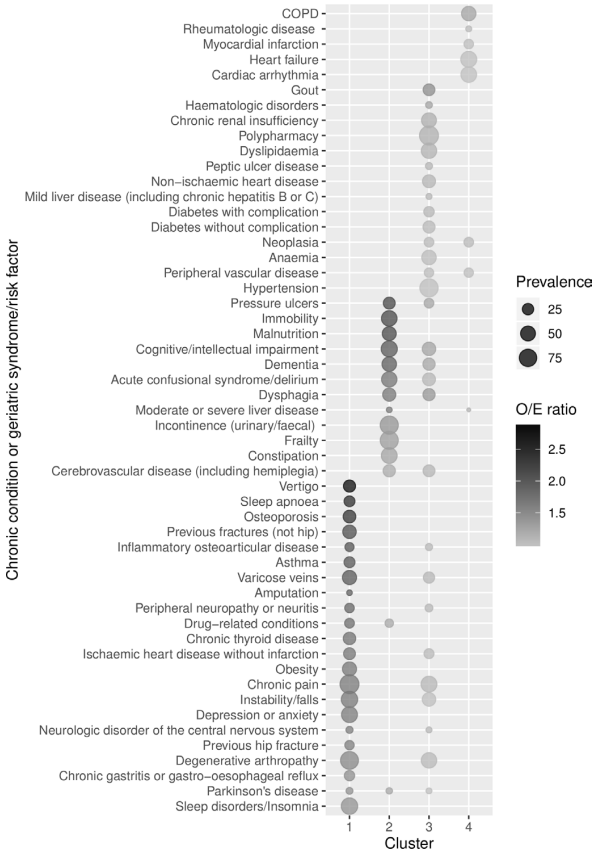

Figure 2 Observed/expected (O/E) ratio and prevalence of chronic conditions and geriatric syndromes/risk factors per multimorbidity cluster. Conditions with exclusivity >25% and O/E ratios >1 in each cluster are represented. Conditions are ordered by O/E ratio and from cluster 1 to 4. COPD, chronic obstructive pulmonary disease.

supplemental table 2). Heart failure was also the main cause of hospitalisation (30.7% of patients had CM score=1), followed by chronic obstructive pulmonary disease (COPD) (20.7%) (online 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% to 82.60%), followed by frailty (61.76%, 95% CI 58.20% to 65.19%). Females had a significantly higher number of GS compared with 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 online supplemental table 4) for all CC and GS). Sociodemographic and clinical characteristics of patients in each cluster are described in table 2.

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%).

Table 2 Sociodemographic and clinical variables of the multimorbidity clusters

		Osteoarticular	Psychogeriatric	Minor chronic disease	Cardiorespiratory
Number of patients included, n (%)		132 (17.8)	153 (20.7)	179 (24.2)	276 (37.3)
Age at admission (year, 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)

DISCUSSION

This 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 four different multimorbidity patterns, named osteoarticular, psychogeriatric, cardiorespiratory 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 CM) 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 hospitalisation and even a similar short-term prognosis at that time. For this reason, the importance of their pathologies in the course of hospitalisation was also taken into account. Hence, the ones that tend to have a minimal impact on CM, 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 CM, 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 *et al*[17] analysed multimorbidity patterns in hospitalised older patients. Their methodological and analytical approach was slightly different, and they did not take into account the weight of the diseases during the hospitalisation process; however, they found a similar percentage of multimorbidity (99.7%) and four 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 CM of the patient during hospitalisation, thus providing a better picture of the possible complexity and needs during hospitalisation.

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. First, 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. Second, 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 standardised 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 hospitalisation 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 CM. 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 hospitalisation. 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 reorganise circuits, processes or healthcare models to tackle the increasing number of older, multimorbid patients.

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Contributors MB conceived and supervised the study, discussed the results, wrote the first version of the manuscript and is responsible for the overall content as guarantor. SH, RJ, MA, RE and GJN participated in patient inclusion, data collection and discussion of the results and revised the manuscript. AR-L 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-P 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. Available: 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.
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* 2019;38:613–23.
4 The Academy of Medical Sciences. Multimorbidity: a priority for global health research, 2018. Available: 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:e25987.
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.
7 Fortin M, Stewart M, Poitras M-E, *et al*. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012;10:142–51.
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.
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.
10 Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, *et al*. Multimorbidity patterns: a systematic review. *J Clin Epidemiol* 2014;67:254–66.
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.
12 Lu F-P, Chang W-C, Wu S-C. 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.
13 Heide vander I, Snoeijs SP, Boerma WGW. How to strengthen patient-centredness in caring for people with multimorbidity in Europe? 2017. Available: http://europepmc.org/books/NBK464537
14 Rijken M, Struckmann V, Heide VD I. How to improve care for people with multimorbidity in Europe? 2016. Available: 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. Available: 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.
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.
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.
19 Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel index for stroke rehabilitation. *J Clin Epidemiol* 1989;42:703–9.
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.
21 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
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.
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.
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. *BMJ Open* 2019;9:e029594.
25 Chavent M, Kuentz-Simonet V, Labenne A. Multivariate analysis of mixed data: the R package PCAmixdata.. *arXiv* 2017 https://arxiv.org/abs/1411.4911v4
26 Karlis D, Saporta G, Spinakis A. A simple rule for the selection of principal components. *Commun Stat Theory Methods* 2003;32:643–66.
27 Zhao Q. Cluster validity in clustering methods, 2012. Available: 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.
29 Marengoni A, Roso-Llorach A, Vetrano DL. 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.
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.
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.
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.
33 Nguyen QD, Wu C, Odden MC, *et al*. Multimorbidity patterns, frailty, and survival in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2019;74:1265–70.
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.
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.
36 Ward K, Reuben D. Comprehensive geriatric assessment. In: *UpToDate*, 2020. https://www.uptodate.com/contents/comprehensive-geriatric-assessment