BioMed Research International

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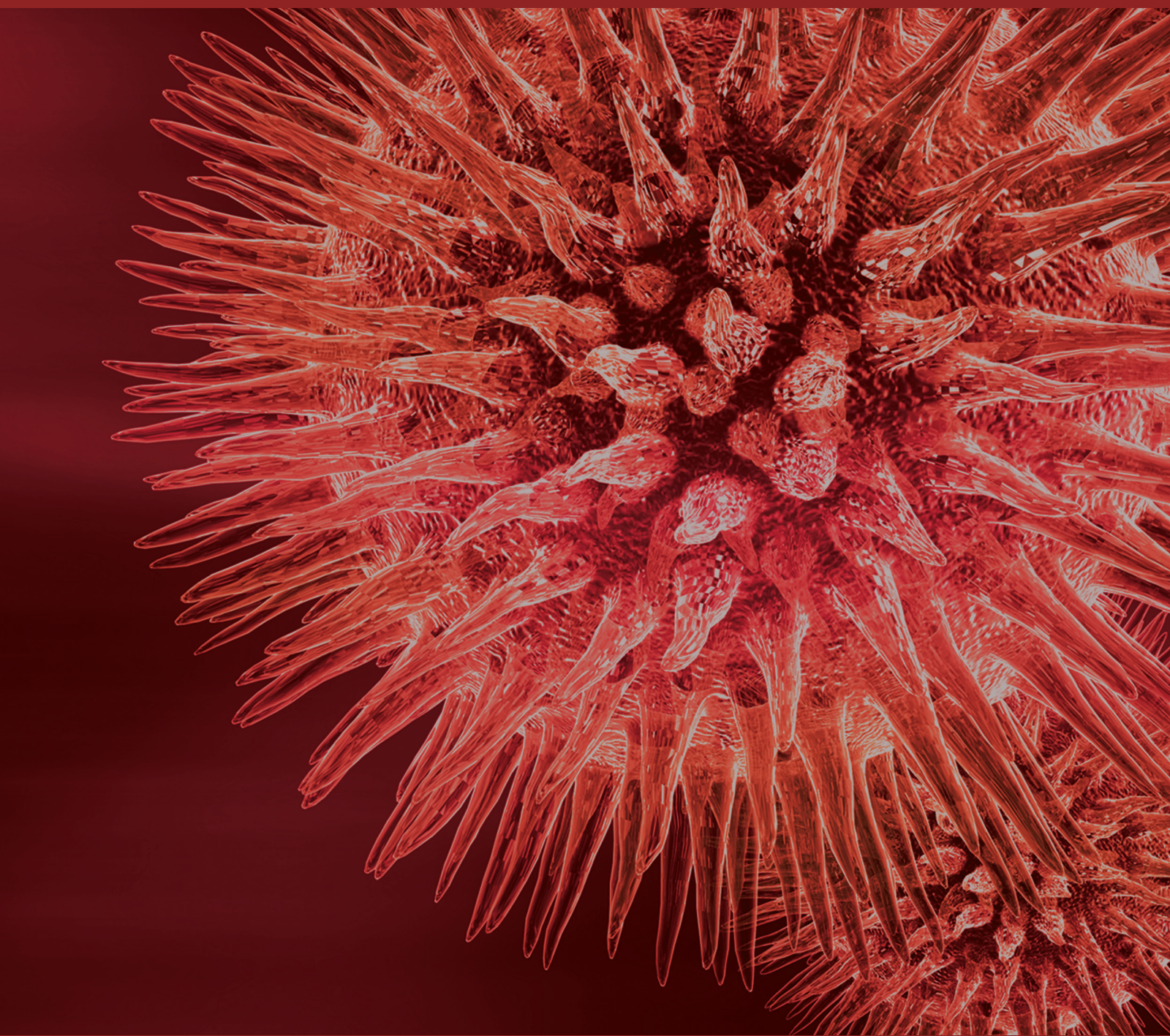
Guest Editors: A. Marengoni, R. J. F. Melis, A. Prados Torres, and G. Onder



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Editorial

Multimorbidity: Epidemiology and Models of Care

A. Marengoni,[1] R. J. F. Melis,[2] A. Prados Torres,[3] and G. Onder[4]

[1]*Department of Clinical and Experimental Sciences, University of Brescia, 25123 Brescia, Italy*
[2]*Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, Netherlands*
[3]*IIS Aragon, Aragon Health Sciences Institute (IACS), 50009 Zaragoza, Spain*
[4]*Department of Geriatrics, Catholic University of Sacred Heart, 00168 Rome, Italy*

Correspondence should be addressed to A. Marengoni; alessandra.marengoni@unibs.it

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Due to the aging of the population, the prevalence of chronic diseases is progressively increasing and most older adults experience the cooccurrence of multiple diseases, a condition known as multimorbidity. It has been estimated that 60% of persons aged 65 years or older are affected by multimorbidity, the reason why the condition is sometimes referred to as the "most common chronic disease" [1]. The appearance of clusters and patterns of patients and diseases in different context and populations group has been also demonstrated [2, 3]. Advanced age, female gender, low socioeconomic status, and education are among the main risk factors for the development of multimorbidity. This suggests, for example, that early life learned risk behaviours may affect the development of this condition [2]. Compared to those with single conditions, persons with multimorbidity are more likely to experience negative health outcomes, including mortality, hospitalization, and functional and cognitive decline, leading ultimately to poorer quality of life and increased care costs. Persons with multimorbidity have the most complex health needs but, due to the current disease-oriented approach in healthcare, they face highly fragmented care that leads to incomplete, inefficient, ineffective, and even potentially harmful interventions [4].

In this special issue, investigators reported studies into the subject from all over the world (i.e., Canada, India, Panama, Portugal, Netherlands, and UK). They contributed to increasing the knowledge on multimorbidity by focusing on clustering of chronic diseases and methods to evaluate multimorbidity and its impact on clinical outcomes, including functional status, quality of life, compliance to physical activity, depression, and cognitive impairment. Sanghamitra Pati and colleagues described and validated a new tool for multimorbidity assessment in India. Although it is known that low and middle income countries with socioeconomic development and westernization of lifestyle are no longer "immune" to multimorbidity, multimorbidity is still underexplored in these countries. This study definitively contributed to estimating the magnitude and impact of multimorbidity in primary care practice populations in developing countries. Joanna Collerton and colleagues examined the extent and complexity of the morbidity burden in the Newcastle 85+ Study, a population-based cohort study. The authors used cluster analysis to identify patterns of diseases within multimorbidity and to compare clusters on medication and healthcare use. A cluster approach was used also by Sarah Dörenkamp and colleagues. Their objective was to identify clusters of multimorbidity associated with physical activity, using data from the Dutch cohort study SMILE. They evidenced that the lowest rate of physical activity and guideline compliance was reported in patients with heart disease, respiratory disease, and diabetes mellitus. Several potential uses of a cluster medicine approach deserve to be highlighted: (1) New research hypotheses on possible shared pathological pathway for clusters of specific diseases can be developed. (2) Prevention can be implemented. (3) Groups of people at high risk of adverse outcomes can be identified. (4) Prevalence of use of potentially inappropriate medication or adverse drug reactions could be higher in different clusters.

(5) Clinical trials could be carried out in groups of the elderly affected by specific clusters of diseases. (6) Treatment can be better tailored to the individual person because it enables actively evaluating the presence of and dealing with comorbidities known to cooccur. (7) Finally, the severity of a disease can be approximated by its connections with other diseases for patients with the same number of diagnoses [3, 5].

Filipe Prazeres and colleagues described the translation of the European General Practice Research Network Multimorbidity definition according to Portuguese cultural and linguistic features. The definition of multimorbidity is now available in a new language, Portuguese. The operationalization of the definition and its availability in the local language will raise Portuguese GPs' awareness about multimorbidity and allow future national and international research. Villarreal and colleagues reported first data on the association of multimorbidity with the cooccurrence of cognitive impairment and depression alone in older persons living in Panama. In the older population, depression is frequent and it also commonly coexists with other chronic medical conditions. On one hand, chronic diseases increase the risk of depression due to the presence of disability, pain, and polypharmacy in multimorbid persons. On the other hand, depression can negatively affect adherence to medications and to a healthy lifestyle that are needed to prevent other clinical conditions. This points at the complexities underlying disease cooccurrence and the mechanism of reciprocity, which is a phenomenon that is perhaps understudied in medicine to understand the relationships between determinants and outcomes. Finally, Aline Ramond-Roquin and colleagues evaluated the association between different multimorbidity measures and physical quality of life. Studies aiming to quantify the impact of multimorbidity on quality of life showed wide heterogeneity in terms of the intensity of this association. It has been suggested that the lack of a uniform way to measure multimorbidity may explain a significant part of this variability. The length of the list of candidate conditions considered has a great impact on the estimations of physical health-related quality of life. The selection of different methods to measure multimorbidity is critical in determining both prevalence of multimorbidity and its association with the outcome of interest. The simple count of diseases has both advantages and disadvantages. A relevant advantage of this approach is that it expresses multimorbidity in an additive form, and it conveniently differentiates people at each level of morbidity. Second, each individual disease contributes to the disease count, avoiding problems of insufficient statistical power, especially if rare diseases are evaluated. On the contrary, one of the most reported disadvantages is that all diseases are scored equally, independently of their severity.

Despite the increasing interest of the researchers in this field, there is still a remarkable gap between the harmful impact of multimorbidity at the individual and societal level and the amount of scientific and clinical research devoted to this topic. Contributions to this special issue filled some gaps in the field providing useful tools to measure multimorbidity and data exploring the prevalence, type, and impact of the presence of multiple cooccurring diseases.

A. Marengoni
R. J. F. Melis
A. Prados Torres
G. Onder

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Research Article

Different Multimorbidity Measures Result in Varying Estimated Levels of Physical Quality of Life in Individuals with Multimorbidity: A Cross-Sectional Study in the General Population

Aline Ramond-Roquin,[1,2,3,4] Jeannie Haggerty,[5] Mireille Lambert,[2] Jose Almirall,[2] and Martin Fortin[1,2]

[1] *Département de Médecine de Famille et de Médecine d'Urgence, Université de Sherbrooke, 3001 12e Avenue Nord, Sherbrooke, Québec, Canada J1H 5H3*
[2] *Centre Intégré Universitaire de Santé et de Services Sociaux du Saguenay-Lac-Saint-Jean, 305 Saint-Vallier, Chicoutimi, Canada*
[3] *Département de Médecine Générale, Université d'Angers, L'Université Nantes Angers Le Mans, 1 rue Haute de Reculée, 49045 Angers Cedex 01, France*
[4] *Laboratoire d'Ergonomie et d'Épidémiologie en Santé au Travail, Université d'Angers, L'Université Nantes Angers Le Mans, 1 rue Haute de Reculée, 49045 Angers Cedex 01, France*
[5] *Faculty of Medicine, McGill University, Montreal, Canada*

Correspondence should be addressed to Martin Fortin; martin.fortin@usherbrooke.ca

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Introduction. Multimorbidity adversely affects health-related quality of life. Methodological factors may impact the magnitude of this relationship. *Objective*. To evaluate how physical health-related quality of life varies in individuals with multimorbidity depending on the length of the list of candidate conditions considered. *Methods*. Secondary analysis from PRECISE, a cohort study of the general adult population of Quebec, Canada. Multimorbidity was measured using the 21-chronic condition list from the Disease Burden Morbidity Assessment, and physical health-related quality of life was measured using the physical component summary (PCS) of SF-12v2. The PCS was calculated, (a) using 2 or more conditions from the 21-condition list (MM2+, 21) and then from a reduced 6-condition list (MM2+, 6) and (b) using three or more conditions from each list (MM3+, 21, and MM3+, 6). *Results*. The analysis included 1,710 individuals (mean age 51.3, 40.5% men). Multimorbidity prevalence ranged from 63.8% (MM2+, 21 conditions) to 3.8% (MM3+, 6 conditions). The mean [95% CI] PCS dropped from 45.7 [CI: 45.0–46.3] (MM2+, 21) to 40.2 [CI: 38.7–41.8] (MM2+, 6) and from 44.2 [CI: 43.4–44.9] (MM3+, 21) to 34.8 [CI: 31.9–37.6] (MM3+, 6). *Conclusion*. The length of the list of candidate conditions considered has a great impact on the estimations of physical health-related quality of life.

1. Introduction

Prevalence of multimorbidity, which refers to the cooccurrence of multiple chronic conditions in the same individual, has increased over the last decades in the general population [1–3]. Because of its association with multiple negative consequences at the individual, healthcare systems, and societal levels, multimorbidity is now acknowledged by some as a research priority [4–6]. Outcomes associated with multimorbidity still need to be explored.

Health-related quality of life, which is a multidimensional concept that refers to physical, psychological, and social domains of health, is adversely affected by the presence of multimorbidity [7–9]. The increasing number of concurrent chronic conditions has been found to be strongly associated with lower scores of health-related quality of life [10–15]. This

association seems to be exacerbated in younger people and in the most deprived populations and perhaps to a lesser extent in women [10, 11, 16, 17]. The physical component of health-related quality of life seems to be more affected by multimorbidity than the mental component [18, 19].

Studies aiming to quantify the impact of multimorbidity on the quality of life show wide heterogeneity in terms of the intensity of this association [18]. It has been suggested that the lack of a uniform way to measure multimorbidity may explain a significant part of this variability. However, these studies also presented other important methodological differences (population studied, measure of quality of life, etc.) which prevented the evaluation of the own impact of multimorbidity measure on the heterogeneity observed.

Multimorbidity can be measured using either simple count of conditions or weighted measures which take into account the severity of each existing condition [20]. The use of weighted measures of multimorbidity seems to reveal a stronger association with health-related quality of life, probably because higher scores do not necessarily mean higher number of chronic conditions [21]. However, most operational definitions of multimorbidity in the literature have been based on a simple count of conditions. In such cases, a minimal number of conditions are required to be considered as "multimorbid," often two or more conditions (MM2+) or three or more conditions (MM3+) in a single individual [22].

Independent of whether a weighted measure or a simple count is used, an important aspect of its measurement is the list of conditions screened as present or not in a given individual. This methodological aspect applies to every study on multimorbidity. Many different lists of potential conditions have been proposed, with a median number of 14 conditions [20], with some being as short as six conditions [9, 19] and others as long as 40 [17, 23]. It is known that differences in the list of conditions considered to measure multimorbidity have a considerable influence on estimates of the prevalence of multimorbidity [24]. However, the influence of the list of conditions on the estimated level of the physical component of health-related quality of life in individuals with multimorbidity has yet to be investigated.

2. Objectives

This study aimed to evaluate how estimates of physical health-related quality of life vary in individuals with multimorbidity depending on the length of the list of candidate conditions, using different operational definitions of multimorbidity.

3. Methods

3.1. Study Design and Setting. This cross-sectional study builds on a secondary analysis of data collected for a larger project, the Program of Research on the Evolution of a Cohort Investigating Health System Effects (PRECISE) [25]. This project aimed to examine the effects of the transformation of primary healthcare services on a population's health. The PRECISE study was conducted in four local healthcare networks in Quebec, Canada, located in metropolitan, urban, rural, and remote settings. Details of the method and sampling strategies used are described in the study protocol reported elsewhere [25].

3.2. Population Recruitment. The present study included a randomly selected sample recruited from March to April 2010 in the general population by random digital dialing. Once contact was made, staff selected the eligible adult in the household with the most recent birthday to ensure random selection. Participants had to be community-dwelling adults, aged between 25 and 75 years, without major cognitive impairment, able to respond to written and oral questions in English or French, and to reside in one of the four networks identified.

3.3. Data Collection. At recruitment, participants reported on sociodemographic information: age, gender, household income, education level, perceived financial situation, house ownership, presence or absence of medical insurance, and possession of a retirement plan. We produced a data-driven classification of socioeconomic status based on the last five variables and classified individuals into four clusters: elite group, middle-high, middle-low, and low. This aimed to capture the multidimensional nature of socioeconomic status into a single variable. Definitional criteria for the four socioeconomic clusters are described elsewhere [26].

Two weeks after recruitment, participants completed a self-administered questionnaire (paper or online) or a questionnaire administered by telephone that included sections to measure (1) multimorbidity and (2) physical health-related quality of life.

Measurement of Multimorbidity. The instrument comprised a list of 21 chronic conditions adapted from the Disease Burden Morbidity Assessment (DBMA). It has been validated to measure multimorbidity, including validation in a population from Quebec, with a good predictive value for health-related quality of life [8, 27, 28]. To determine the presence of a condition, for 20 out of 21 conditions, the instruction to the participants was as follows: "*Please, indicate if you have been told by a health professional that you have any of the following illnesses*." For the 21st condition, "overweight," the participant was invited to self-report his or her height and weight, from which we calculated the Body Mass Index (BMI). We considered the presence of overweight when the BMI was higher than 24.9 Kg/m^2 [29]. The number of conditions for each individual was first summed up based on the full list of 21 conditions (shown in the results section). We then summed up the number of conditions based on a reduced list of six conditions (out of 21) to correspond to a list previously used in the literature to study health-related quality of life and multimorbidity [9, 19]. Any missing value was considered as an absent condition. We also applied successively two operational definitions of multimorbidity, MM2+ then MM3+. Therefore, multimorbidity was successively measured in four different ways in this study: MM2+ (21); MM2+ (6); MM3+ (21); and MM3+ (6). Given that the list of six conditions was a sublist of the 21 conditions, it follows that, for each of

the operational definitions of multimorbidity, the individuals considered as multimorbid according to the 6-condition list constituted a subsample of those considered as multimorbid according to the 21-condition list.

Measurement of Physical Health-Related Quality of Life. The physical component of health-related quality of life was measured using the SF-12, version 2 [30, 31], a short form version of SF-36 [32], a generic instrument validated in a Canadian population [33]. The physical component summary is calculated from weighted scores of both the mental and the physical dimensions of the SF-12v2. The physical component summary ranges from 0 to 100, with a population-normed mean of 50 and a standard deviation of 10, where a 5-point difference is considered clinically significant [34]. Lower scores refer to lower physical quality of life.

3.4. Data Analysis. We first studied the sociodemographic characteristics and the number of chronic conditions in the whole population, then in individuals with multimorbidity, using successively each of the four multimorbidity measures. We then looked at an assumption underlying the main analyses; namely, whether there was a statistically significant association between multimorbidity and physical health-related quality of life, adjusted for sociodemographic covariates, for each of the four multimorbidity measures.

To evaluate how estimates of physical health-related quality of life vary with the length of the list of candidate conditions considered, we estimated the average level (mean values and 95% confidence intervals) of the physical component of health-related quality of life in individuals with multimorbidity and highlighted the resulting variation using the 21-condition list or the 6-condition list. We conducted these analyses successively using each of the two operational definitions of multimorbidity. Finally, we repeated all these analyses stratifying by age, gender, and socioeconomic status, in order to determine if the variations observed were consistent within each of these subgroups of individuals. For the stratified analysis, age was considered in three groups (25–44 years old, 45–64 years old, and 65–75 years old), based on previous literature on multimorbidity [35].

Categorical variables were described with absolute numbers and percentages. Quantitative variables were described using means and standard deviations (SD). Confidence intervals (95% CI) around estimated means of physical health-related quality of life were calculated using standard errors of the means, with appropriate statistics in the case of small samples. Analysis of covariance (ANCOVA) was used to characterize the association between multimorbidity and physical health-related quality of life, with modelling physical health-related quality of life according to multimorbidity status and sociodemographic covariates. All analyses were done using the SPSS version 20 software.

The study was approved by the ethics committee of the Centre de Santé et de Services Sociaux de Chicoutimi, as well as the research ethics committee of Hôpital Charles Lemoyne, QC, Canada.

Table 1: Sociodemographic characteristics of the study population (N = 1,710).

	Study population
Age, mean (SD) *22 missing*	51.3 (12.5)
Males, *n* (%):	693 (40.5)
Annual household income (CAN$), *n* (%) *46 missing*	
Less than 20,000	196 (11.5)
20,000 to 49,999	699 (40.9)
50,000 or more	769 (45.0)
Education level, *n* (%) *8 missing*	
Less than high school	376 (22.0)
Completed high school	521 (30.5)
College/university	805 (47.1)
Socioeconomic status[a], *n* (%) *66 missing*	
Low	230 (13.5)
Middle-low	345 (20.2)
Middle-high	733 (42.9)
Elite group	336 (19.6)

SD: standard deviation; [a]Socioeconomic classes were derived from a data-driven combination of the following variables: education level, perceived financial situation, house ownership, presence or absence of medical insurance, and possession of a retirement plan.

4. Results

A total of 1,710 individuals participated in the PRECISE study and their data were included in these analyses. Among the study population, mean (SD) age was 51.3 (SD 12.5) years and there were 693 (40.5%) men. The main sociodemographic characteristics of the participants are presented in Table 1.

Regarding chronic conditions, absence of overweight was imputed to 57 individuals due to missing values. For every other condition, there was either 0 or 1 missing value. Prevalence of each individual chronic condition in the study population is shown in Table 2. Considering the 21-condition list, 272 individuals (15.9%) reported no chronic condition, and the mean number of chronic conditions was 2.9 (SD 2.4). Alternatively, when the 6-condition list was considered, 1,016 individuals (59.4%) reported no chronic condition and the mean number of chronic conditions was 0.6 (SD 0.8).

As expected, a clinically and statistically significant association between multimorbidity status and physical health-related quality of life was observed for each of the four multimorbidity measures, adjusting for age, gender, and socioeconomic status. Depending on the multimorbidity measures, adjusted regression parameters associated with multimorbidity ranged from 8.57 to 10.92 ($p < 0.001$ for each parameter).

Prevalence of multimorbidity as well as level of physical health-related quality of life in those considered as multimorbid largely varied depending on the multimorbidity measure used (Figures 1 and 2). Using the MM2+ definition, individuals with multimorbidity defined by the 21-condition list (n = 1091, 63.8% of the total population) had a mean

Table 2: Prevalence of each individual chronic condition in the study population (N = 1,710).

	n (%)
Angina/coronary artery disease	124 (7.3)
Asthma	176 (10.3)
Chronic obstructive pulmonary disease	66 (3.9)
Diabetes	145 (8.5)
Hypertension	477 (27.9)
Stroke	21 (1.2)
Back pain	353 (20.6)
Osteoarthritis	361 (21.1)
Rheumatoid arthritis	44 (2.6)
Osteoporosis	94 (5.5)
Other illnesses of joints or limbs, lasting for 6 months or more	205 (12.0)
Cancer (within the past 5 years)	65 (3.8)
Cholesterol, elevated	439 (25.7)
Colon problem	123 (7.2)
Congestive heart failure	37 (2.2)
Depression	221 (12.9)
Hard of hearing	213 (12.5)
Overweight	1000 (58.5)
Stomach problem	356 (20.8)
Thyroid disorder	198 (11.6)
Vision problem	137 (8.0)

Conditions in bold are common to the two lists: full list (21 conditions) and reduced list (6 conditions).

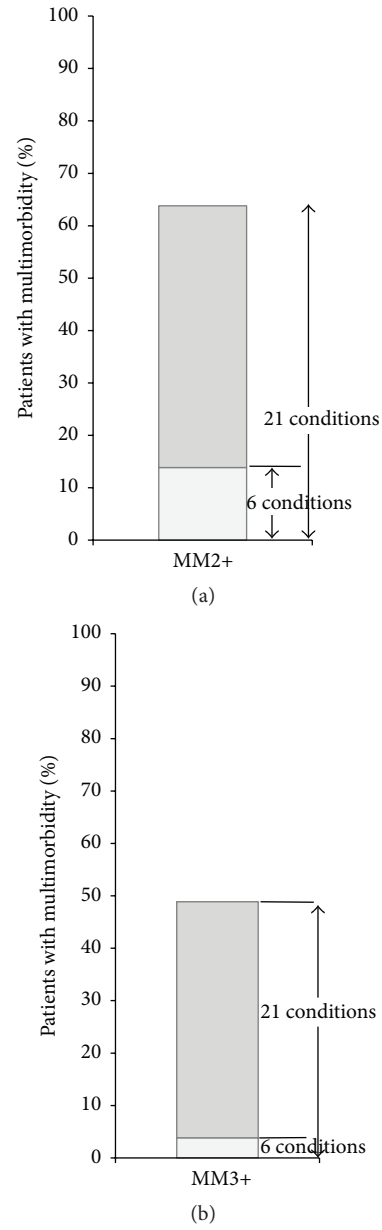

Figure 1: Prevalence of multimorbidity, depending on the multimorbidity measure. Operational definitions of multimorbidity: MM2+: having two or more chronic conditions; MM3+: having three or more chronic conditions.

physical component summary (95% CI) of 45.7 (CI: 45.0–46.3), while the group defined by the 6-condition list (n = 237, 13.8% of the total population) scored 40.2 (CI: 38.7–41.7) on average. Using the MM3+ definition, individuals with multimorbidity defined by the 21-condition list (n = 836, 48.9% of the total population) had a mean physical component summary (95% CI) of 44.2 (CI: 43.4–44.9), while the group defined by the 6-condition list (n = 66, 3.8% of the total population) scored 34.8 (CI: 31.9–37.6) on average.

Regarding sociodemographic variables, using a reduced list of conditions led to the selection of a subgroup of older and more deprived individuals, with a higher proportion of men (Table 3). This was true for both operational definitions of multimorbidity (MM2+ and MM3+).

Analyses stratified by age, gender, and socioeconomic level revealed similar patterns in the variations of estimates of quality of life within each of the subgroups of individuals successively considered (Figures 3(a), 3(b), and 3(c)). Using the 6-condition list consistently resulted in lower estimates of average physical health-related quality of life compared to using the 21-condition list. As in the main analysis, the variations observed in the stratified analyses were larger with the MM3+ operational definition than with the MM2+ operational definition.

Interestingly, using a reduced list of conditions to measure multimorbidity resulted in selecting people with substantially higher numbers of chronic conditions (Table 3). For example, the mean number of conditions as documented in the list of 21 conditions was 4.2 (SD 2.1) in individuals considered as multimorbid based on the MM2+ (21) definition while it was 6.1 (SD 2.3) in those considered as multimorbid based on the MM2+ (6) definition.

5. Discussion

This study suggests that different measures of multimorbidity result in significant variations in estimates of physical health-related quality of life within the same population. Our

Table 3: Main characteristics of the individuals with multimorbidity, depending on the multimorbidity measure.

Measure of multimorbidity	MM2+		MM3+	
	21 conditions (n = 1091)	6 conditions (n = 237)	21 conditions (n = 836)	6 conditions (n = 66)
Age: mean (SD)	55.0 (11.4)	59.0 (9.7)	56.3 (10.6)	59.5 (8.7)
Males: n (%)	455 (41.7)	111 (46.8)	352 (42.1)	33 (50.0)
Socioeconomic status[a]: n (%)				
Low	165 (15.1)	50 (22.4)	137 (16.4)	17 (28.3)
Middle-low	227 (20.8)	47 (21.1)	176 (21.1)	13 (21.7)
Middle-high	456 (41.8)	96 (43.0)	346 (41.4)	28 (46.7)
Elite group	200 (18.3)	30 (13.5)	143 (17.1)	2 (3.3)
Chronic conditions: mean number (SD)				
As documented by the 21-c. list[b]	4.2 (2.1)	6.1 (2.3)	4.8 (1.2)	7.8 (2.4)
As documented by the 6-c. list[c]	0.9 (0.9)	2.3 (0.6)	1.1 (0.9)	3.2 (0.5)

SD: standard deviation; [a]Socioeconomic classes were derived from a data-driven combination of the following variables: education level, perceived financial situation, house ownership, presence or absence of medical insurance, and possession of a retirement plan; [b]21-condition list; [c]6-condition list.
Missing data for each variable are not reported in this table because their number differed depending on the group considered. They ranged from 2 missing values (age, MM3+, 6 conditions) to 43 missing values (socioeconomic status, MM2+, 21 conditions).

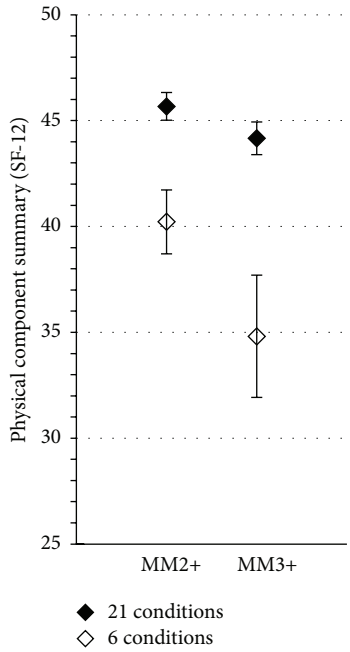

Figure 2: Estimates of the average level (mean values and 95% confidence intervals) of the physical component of health-related quality of life in individuals with multimorbidity, depending on the multimorbidity measure. Operational definitions of multimorbidity: MM2+: having two or more chronic conditions; MM3+: having three or more chronic conditions.

results show that using a reduced list of conditions leads to lower levels of estimated physical health-related quality of life in individuals with multimorbidity, independent of age, gender, and socioeconomic status, and whichever operational definition of multimorbidity was used (MM2+ or MM3+).

In fact, using a reduced list of conditions leads to the selection of a subgroup of individuals with an especially high number of existing chronic conditions, in comparison to the whole population considered as multimorbid based on a longer list. Each condition an individual has, whether documented or not, impacts his or her quality of life. It is therefore not surprising that people considered as multimorbid based on a reduced list of conditions have a higher number of existing chronic conditions while reporting lower physical quality of life.

The two lists used in this study were chosen for their contrast in terms of number of candidate conditions and because the six conditions of the reduced list were also included in the full list of 21 conditions. However, not one of these lists captures the whole range of the potential chronic conditions [36]. The use of any limited list, regardless of its length, necessarily implies a certain amount of unmeasured variability, due to unlisted conditions, and introduces a systematic bias towards the selection of individuals with higher degrees of multimorbidity. In that sense, using an open list of conditions to measure multimorbidity would result in a more accurate representation of reality, while being associated with other important challenges, such as reproducibility of the measure or optimal granularity in recording.

Beyond number, the nature of conditions considered in any list influences the estimated level of health-related quality of life. Among the 21 conditions from our full list, our 6-condition list included some which are among those with the highest impact on health-related quality of life (chronic obstructive pulmonary disease and stroke) and some which are among those with the lowest impact (hypertension or diabetes) [15, 16, 37]. We therefore believe that the variation observed in our study does not primarily result from the nature of conditions considered in the lists, but rather from the number of candidate conditions itself.

In our study, estimated prevalence of multimorbidity varied as much as 3.8% to 63.8% depending on the measure used. Moreover, the variations observed in the estimates of quality of life were 5.5 point units (means 45.7 to 40.2) with MM2+ and 9.4 points (means 44.2 to 34.8), with MM3+. These variations are larger than what is considered as the minimal clinically important difference for this score, namely, 5 points

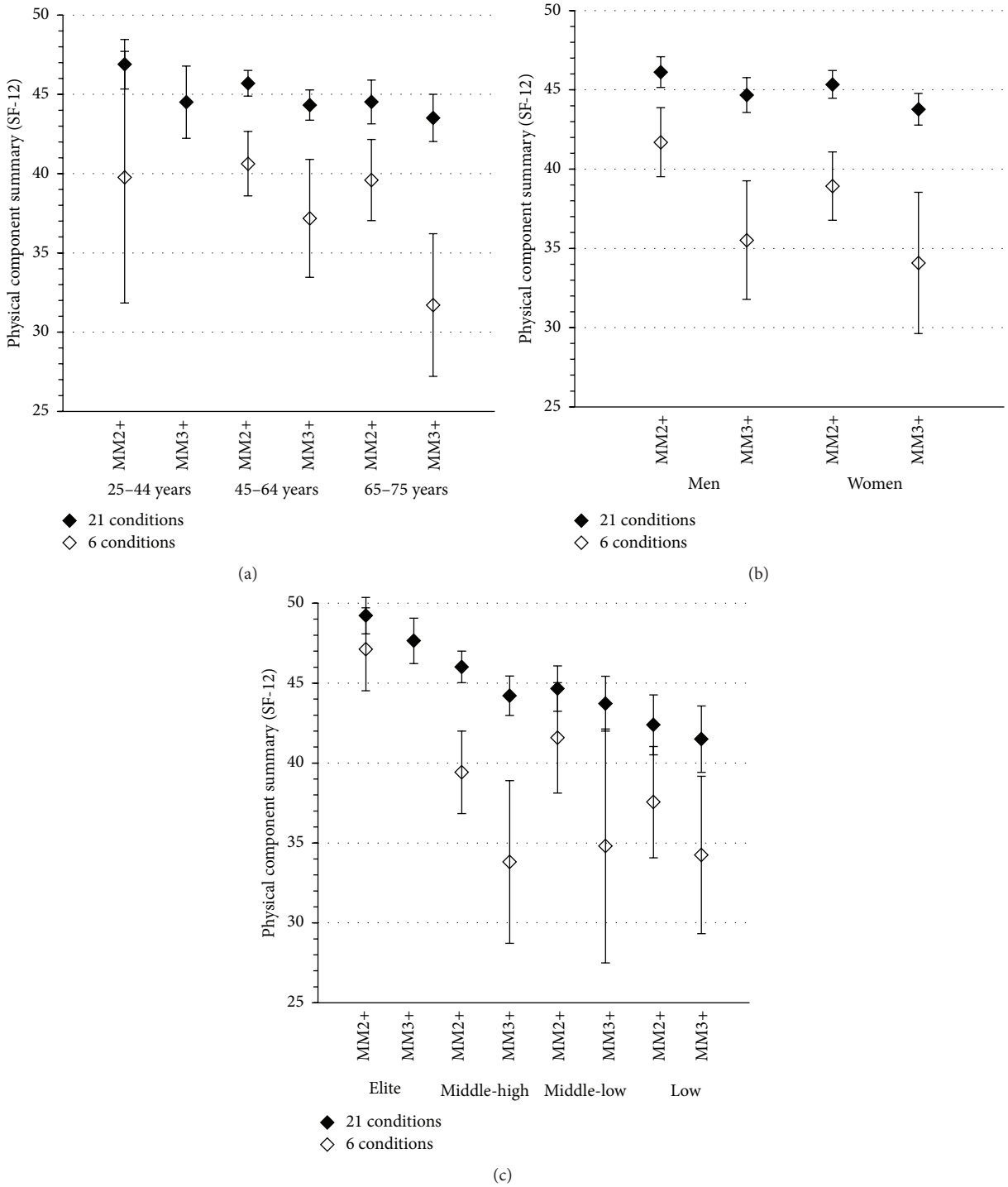

Figure 3: Estimates of the average level (mean values and 95% confidence intervals) of the physical component of health-related quality of life in individuals with multimorbidity, depending on the multimorbidity measure, stratified by age (a), gender (b), and socioeconomic status (c). Operational definitions of multimorbidity: MM2+: having two or more chronic conditions; MM3+: having three or more chronic conditions. Estimates were not computed in the case of multimorbidity measured as MM3+ based on the 6-condition list for young people "25–44 years" and for the "elite" group, due to insufficient subsample size (4 and 2 individuals, resp.).

[38]. This illustrates how such methodological issues have the potential to considerably impact results and indicates that careful methodological considerations are required when measuring multimorbidity. The variations resulting from the alternative use of any other multimorbidity measures might be of different intensity from those observed in our study, but more stringent measures of multimorbidity will necessarily tend to identify smaller and sicker subgroups.

In addition to the quality of life, many other outcomes have been associated with the number of chronic conditions, such as disability [10, 13], psychological distress [12, 39], mortality [40], healthcare utilization [12, 41], or costs [41]. We believe that the choice of multimorbidity measure, and especially the length of the list of conditions, may also induce substantial variations when estimating the outcomes in multimorbid patients. Although stringent measures may be relevant for clinical purposes, short lists of conditions should be avoided in epidemiological studies: the shorter the list, the more biased the estimates of multimorbidity prevalence and related outcomes.

This study was based on data from the PRECISE cohort that constituted a representative sample of the Quebec general population at baseline [25]. The sample included in this study underrepresented young and deprived individuals, who were not as many to return their questionnaire (data not shown). However, the aim of this study was not to provide estimates of the physical component of health-related quality of life to be extrapolated to the general population, but rather to document variation in estimates resulting from using different multimorbidity measures. It is unlikely that this response bias has contributed to the results in any way. Prevalence of certain chronic conditions and of multimorbidity, as well as health-related quality of life, has been shown to present substantial international variations [10, 42, 43]. However, the impact of chronic conditions on health-related quality of life seems to be quite similar across countries [44]. Therefore, although our estimates may be not generalized to other populations, some variation in health-related quality of life could also be observed, within other cultural environments, when using different multimorbidity measures. We had to rely on the self-reported presence of chronic conditions to measure multimorbidity and, hence, either overreporting or underreporting may have occurred. This might affect the prevalence of some conditions in the sample. However, we do not think that this possibility would have an important impact on the differences observed with the use of different lists of conditions, which is the main message of this study.

6. Conclusion

Previous research had hypothesized that heterogeneity in multimorbidity measures may generate variability when studying quality of life in multimorbid individuals. This study demonstrated how different multimorbidity measures actually result in significant variation in the estimates of physical health-related quality of life within the same population. It argues for careful methodological consideration when measuring multimorbidity and its association with different outcomes. Standardization of the measure of multimorbidity is needed to allow the comparison of the results across different studies on multimorbidity.

In this regard, we recommend the use of a list of candidate conditions that is sufficiently long. Determining the ideal length is beyond the scope of this study, but it should be a compromise between lists that are too short, which will produce seriously biased estimates (6-condition lists being in this category) and lists that are too long, which can be difficult to manage. In order to reach a satisfying compromise, we suggest that both prevalence and impact for individuals and communities should be taken into account when choosing which conditions to include in the list.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

Authors' Contributions

Jeannie Haggerty and Martin Fortin designed the original study (PRECISE) and coordinated the data collection. Aline Ramond-Roquin, Mireille Lambert, and Jose Almirall suggested the research questions and designed the analysis with approval from the other authors. Aline Ramond-Roquin and Jose Almirall conducted the analysis of data. Aline Ramond-Roquin drafted the paper with Mireille Lambert and Jose Almirall under the guidance of Martin Fortin and Jeannie Haggerty. All the authors contributed to the writing by critically reviewing the paper and gave the final approval of the version submitted.

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Research Article

Development and Validation of a Questionnaire to Assess Multimorbidity in Primary Care: An Indian Experience

Sanghamitra Pati,[1] Mohammad Akhtar Hussain,[2] Subhashisa Swain,[1] Chris Salisbury,[3] Job F. M. Metsemakers,[4] J. André Knottnerus,[4] and Marjan van den Akker[4,5]

[1]*Indian Institute of Public Health, Bhubaneswar, Public Health Foundation of India, Bhubaneswar, Odisha 751024, India*
[2]*Division of Epidemiology and Biostatistics, School of Public Health, The University of Queensland, Brisbane, QLD 4006, Australia*
[3]*Centre for Academic Primary Care, School of Social and Community Medicine, University of Bristol, Bristol BS8 2PS, UK*
[4]*Department of Family Medicine, School Caphri, Maastricht University, 6200 MD Maastricht, Netherlands*
[5]*Department of General Practice, KU Leuven, 3000 Leuven, Belgium*

Correspondence should be addressed to Sanghamitra Pati; drsanghamitra12@gmail.com

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Multimorbidity remains an underexplored domain in Indian primary care. We undertook a study to assess the prevalence, correlates, and outcomes of multimorbidity in primary care settings in India. This paper describes the process of development and validation of our data collection tool "Multimorbidity Assessment Questionnaire for Primary Care (MAQ-PC)." An iterative process comprising desk review, chart review, and expert consultations was undertaken to generate the questionnaire. The MAQ-PC contained items on chronic conditions, health care utilization, health related quality of life, disease severity, and sociodemographics. It was first tested with twelve adults for comprehensibility followed by test-retest reliability with 103 patients from four primary care practices. For interrater reliability, two interviewers separately administered the questionnaire to sixteen patients. MAQ-PC displayed strong internal consistency (Cronbach's alpha: 0.69), interrater reliability (Cohen's Kappa: 0.78–1), and test-retest reliability (ICC: 0.970–0.741). Substantial concordance between self-report and physician diagnosis (Scott Kappa: 0.59–1.0) was observed for listed chronic conditions indicating strong concurrent validity. Nearly 54% had one chronic condition and 23.3% had multimorbidity. Our findings demonstrate MAQ-PC to be a valid and reliable measure of multimorbidity in primary care practice and suggest its potential utility in multimorbidity research in India.

1. Introduction

Multimorbidity, the concurrent presence of two or more chronic conditions in individuals, is emerging as a daunting health challenge globally with substantial impact on health care utilization, quality of life, and health outcomes [1, 2]. Furthermore, low and middle income countries (LMICs) with socioeconomic development and westernization of lifestyle are no longer immune to this challenge as demonstrated by the reported high prevalence of multimorbidity in Brazil, Ghana, Indonesia, and Vietnam [3–5]. Similar to other LMICs, India, home to one-fourth of the world's population, is exhibiting a rising trend of chronic diseases and thus multimorbidity could be an attendant phenomenon [6–8]. The sheer volume of India's population with concomitant magnitude of multimorbidity can place critical demands on existing health care delivery systems [8]. Contrastingly, multimorbidity is still underexplored in India with the available evidence being mostly from secondary data sources, confined to selected population groups and encompassing few chronic conditions [9]. This may not be representative of the real magnitude since measurement methods strongly influence the observed prevalence of multimorbidity thus underscoring the need for an explicit, validated measurement tool [10].

Our systematic review of multimorbidity studies in the south of Asia has confirmed the lack of uniformity in assessment of multimorbidity with the conspicuous absence of reports from primary care in India [9]. This is a vitally

important knowledge gap, as primary care constitutes the scaffold of health care delivery in the country and the complex care needs of multimorbid patients require appropriate redesigning of primary care services [11]. Moreover, only prevalence of multimorbidity may not be sufficient to inform health services as the typology of conditions and severity level also influence the health care to be delivered and the subsequent outcomes [11]. Although clinical data retrieved from patients' records can yield accurate estimation of multimorbidity, our chart review of four urban primary care practices found that multiple chronic conditions are often not recorded in practice. Furthermore, unlike western countries, primary care databases are not routinely maintained in India; hence extraction of medical records from specialist facilities will present a skewed picture [12].

Aiming at addressing the aforementioned knowledge gap, we undertook a study to explore the magnitude of multimorbidity and its correlates and outcomes in a primary care setting.

It is expected that this information would help public health researchers in India and similar settings to estimate the magnitude and impact of multimorbidity in primary care practice populations.

2. Design and Methods

The study was undertaken in Odisha, an Indian state (approximate population share of 4% of the total population of India) with average health indicators and comparable health system characteristics [13]. Considering the absence of standardized assessment instruments, with proper medical records being unavailable, we first developed and contextualized a tool so as to identify and quantify multimorbidity. We decided to use patient self-reports to elicit information, as they have demonstrated predictive ability of real morbidity [14, 15].

We aimed to develop and validate our Multimorbidity Assessment Questionnaire for Primary Care (MAQ-PC). To examine multimorbidity in primary care in Indian context, with no gold standard available, we followed an iterative process to design a comprehensive tool. This comprised two phases. The first phase is the development of the questionnaire, selecting the domains and their measurements, translating the questionnaire to local language for cultural adaptability, and testing its comprehensibility. The second phase involved reliability and validity testing. The steps are outlined in Figure 1 (supplementary file in Supplementary Material available online at http://dx.doi.org/10.1155/2016/6582487).

2.1. Selection and Development of Domains. Following domains were selected by the research team through literature review and consultation with an expert group and six primary care physicians. The expert group comprised two senior faculty members of the Department of Family and Community Medicine at the state medical colleges, two clinicians from the Odisha branch of the Indian Medical Association (IMA), two diseases control program managers from the state public health directorate, and four internationally acclaimed researchers in multimorbidity. It was decided to select six primary care physicians working in public and private settings. The three private primary care facilities were selected in consultation with the Odisha branch of IMA, while for public primary care facility selection the state public health department's advice was sought. To ensure representativeness, one public facility and one private facility each from the rural, urban, and tribal regions were selected.

Table 1: List of chronic diseases.

Diseases included		
Sl. number	Name	Questions asked for self-reported doctor diagnosis
(1)	Diabetes	Yes
(2)	Hypertension	Yes
(3)	Arthritis	Yes
(4)	Acid peptic disease	Yes
(5)	Asthma	Yes
(6)	Heart disease	Yes
(7)	Stroke	Yes
(8)	Chronic kidney disease	Yes
(9)	Chronic liver disease (alcohol)	Yes
(10)	Chronic back ache	Yes
(11)	Tuberculosis	Yes
(12)	Filariasis	Yes
(13)	Visual difficulty	Yes
(14)	Deafness	Yes
(15)	Cancer	Yes
(16)	Dementia	Yes
(17)	Epilepsy	Yes
(18)	Thyroid	Yes

Depression was screened by using PHQ-9.

(1) Multimorbidity Estimation. To measure multimorbidity, we decided to have an exhaustive list of chronic diseases commonly prevalent in primary care. We first undertook a systematic search of the available studies in India and other south Asian countries to determine if any of them used a list for the most frequently reported chronic conditions [9]. Next, chart review of four primary care practices (two each from urban and rural area) was done to add relevant chronic conditions to the list generated from systematic search. The draft list was shared with the six primary care physicians who were requested to indicate how important (marginal or very severe) they considered each particular chronic disease and to mention additional diseases to the list, if any. Finally, a consolidated list of 18 conditions (Table 1) was incorporated in the questionnaire. To ascertain the presence of chronic conditions, we used patient self-report [15]. The questions were phrased to elicit whether the patient had ever been told by a doctor or any other health care provider that they had any of the listed chronic health problems. We used simple vernacular language (Odiya) that could be understood by individuals without any prior medical knowledge (Have you

even been diagnosed by a physician with…?). In addition to the self-report, we used the Patient Health Questionnaire-9 to capture undiagnosed depression [16].

(2) Outcomes. To explore the impact of multimorbidity, we included self-reported severity, health related quality of life, and health care utilization. We did not include health care expenditure for the sake of brevity:

(a) Severity Assessment. Functional limitation was used as proxy for disease severity. For each identified morbidity, we included a subquestion asking how much the particular health problem gets in the way of daily activities (e.g., not at all, a little, or a great deal) [17].

(b) Health Related Quality of Life (HRQL). To explore health related quality of life, we included two questions on self-rated physical and mental health (e.g., poor, good, or excellent) and SF-12 (already validated for Indian population) [18].

(c) Health Care Utilization. To examine the health care utilization, we included questions that asked about number of outpatient consultations and inpatient admissions at different health care facilities in the past twelve months and medication use for each reported chronic illness [19].

(3) Covariates. We included age (in completed years), sex (male/female), place of residence (urban/semiurban/rural), ethnicity (social caste/tribe), religion (Hinduism/Islam/Christianity/others), educational level (illiterate/primary education/high school or secondary education/graduate and above), marital status (never married/currently married/separated or divorced/widow or widower), and annual family income [13].

We hypothesized that the MAQ-PC would identify patients to have multimorbidity when they have self-reported multiple chronic conditions; we expected that the overall judgment of self-reported measures of multimorbidity would correlate strongly with physician diagnoses and would also have high internal consistency with other domains (outcomes).

2.2. Translation and Cultural Adaptation. We followed a standard process to ensure the quality of translation (Figure 2, supplementary file). Primary forward translation from international English into vernacular language (Odiya) was performed by two translators independently according to the standard WHO protocol [20]. The primary translation was then evaluated for authenticity by two primary care physicians well versed in both languages. The primary translators discussed apparent differences between the translated versions with the research team and then agreement was reached.

2.3. Expert Consultation, Cognitive Debriefing, and Pretesting. The primary care physicians and international experts were consulted to respond to the questionnaire to obtain an initial impression of how easy the questions were to read out, understand, and answer and their feedback was incorporated. Next, the instrument was cognitively tested with 12 adults of diverse ages and socioeconomic strata (six men and six women) for comprehensibility. Structured interviews were performed with them to evaluate whether all the items in the MAQ-PC were understood as intended and to examine the appropriateness of the questionnaire in the local context. The responses were evaluated by the research team and the translation team to check if required information is being captured or not. Based upon it, the questionnaire was revised. Next step involved a small scale operational testing of the questionnaire in one primary health centre to check the logistic feasibility. The time taken to complete the questionnaire was around 20–25 minutes.

Based on the cumulative observations of above three processes, we incorporated few changes in the MAQ-PC. We added open options for three additional chronic conditions not enlisted in our questionnaire. Insurance availability and utilization were added. Since we found difficulty in capturing near exact information for income, we included an additional measure of socioeconomic status, above poverty line (APL)/below poverty line (BPL), adopted by the state government for categorizing people based on income [21]. As the patients expressed difficulty in recalling the year of diagnosis and chronology of appearance for each chronic condition, these questions were omitted. An interviewer's manual was prepared detailing out the instructions for each question. The final version of MAQ-PC is described in Table 2.

2.4. Piloting. We examined the reliability and validity of MAQ-PC final version through a large scale pilot testing in four (two public and two private) purposively selected primary care practices in different cities and regions (rural, urban, semiurban, and tribal) in the state. Adult patients over 18 years of age attending outpatient clinic of these primary health care centres were included as study participants. Exit interview was conducted with eligible patients soon after their physician consultation. Informed consent to take part in the interview was obtained from each patient after briefing them about the study and its objectives. A total of 120 patients were recruited through a systematic random sampling from the selected four facilities. Four specially trained nurses administered the questionnaire to patients and examined the physician's prescription. The data collection took place under the direct supervision of the principal investigator (SP) and the research team.

All 120 patients were then invited to take part in the two-day retest. As there was increased likelihood of getting different responses to the question "disease severity and activity limitation" because of the treatment or medication, we confined our retest analyses to day 2. A total of 103 participants turned up for the retest and were then administered the MAQ-PC by the same nurses. For each reported chronic condition, we examined physicians' prescriptions and noted the diagnoses. Additionally, to test interrater or interobserver reliability, another 16 patients were purposively selected and

Table 2: Domains, items, and measurement tools in MAQ-PC.

Domain	Measure	Validation process
	Chronic conditions	
Diseases (18 with 3 additional open options)	Close ended question of self-reported doctor diagnosed diseases, symptoms, and prescription check	Scott Kappa value
Depression	Patient Health Questionnaire-9	Test-retest reliability and interrater reliability Internal consistency
Medication	Close ended question according to expert group	Test-retest reliability and interrater reliability Internal consistency
	Health care utilization	
Frequency of hospital visits in last one year for any chronic disease	Open ended question for outpatient visit in last one year [WHO-SAGE]	Test-retest reliability and interrater reliability Internal consistency
Frequency of inpatient admission in last one year for any chronic disease	Open ended question for hospitalization [WHO-SAGE]	Test-retest reliability and interrater reliability Internal consistency
Number of medicines being taken daily	Open ended question for number of medicines taken	Test-retest reliability and interrater reliability Internal consistency
	Health related quality of life	
Self-rated overall health	Scales	Cognitive briefing Test-retest reliability and interrater reliability Internal consistency
SF-12	Mental components Physical components	Cognitive briefing Test-retest reliability and interrater reliability Internal consistency
	Severity of the disease	
Limitation in activities due to health problems	Impact of individual chronic disease on activity limitation	Test-retest reliability and interrater reliability
Frequency of hospital visits for current disease	Adopted from WHO-SAGE 2010	Test-retest reliability and interrater reliability
	Sociodemographic	
Age of the patient	Annual Health Survey, India	Internal consistency
Gender	Annual Health Survey, India	Internal consistency
Marital status	Annual Health Survey, India	Internal consistency
Education	Annual Health Survey, India	Internal consistency
Net household income per month	Annual Health Survey, India	Internal consistency
Socioeconomic status	According to the government of Odisha	Internal consistency
Religion and social caste	Annual Health Survey, India	Internal consistency
Health insurance	Close ended questionnaire developed	Internal consistency

MAQ-PC was administered to them by two members of the research team (MAH and SS) within 24 hours. Each observer was blinded to the results of the other assessment. The agreement was checked by the principal investigator (SP).

All data were entered and analysed using Statistical Package for the Social Sciences version 20 (SPSS Inc., Chicago, IL). Descriptive statistics were calculated and presented as proportion, mean, and standard deviation (SD). The prevalence of multimorbidity was measured in terms of the presence of two or more self-reported chronic conditions. The mean score, interclass correlation coefficient, and Cronbach's alpha coefficient for each domain were calculated to examine the internal consistency using the Kuder-Richardson formula [22]. For interobserver reliability, we determined the observed agreement between two interviewers using Cohen's Kappa statistics [23]. The mean score for each domain was computed to estimate the Kappa value. The concurrent validity of MAQ-PC was assessed by testing the hypotheses that MAQ-PC self-reported morbidity correlates strongly with diagnosed multimorbidity. The level of concordance (self-reports and physician's prescription) for each condition was calculated using Scott Kappa statistics (prevalence-adjusted bias-adjusted Kappa).

3. Results

3.1. Sample Characteristics. To assess if our study sample was representative of the primary care population, we studied key characteristics of included patients (Table 3, supplementary file). Out of 103 respondents who participated in test and retest (86% of first sample), 45% ($n = 46$) were female. The mean age of the study participants was 44.96 ± 5. 32 years with no significant sex difference (female, 45.9, versus male, 44.2).

3.2. Multimorbidity. Nearly 54% of respondents had at least one self-reported chronic condition enlisted. The prevalence of multimorbidity was 23% (male, 22%, versus female, 25%) and around 10% of respondents had three or more chronic conditions. Frequently reported chronic conditions were acid peptic disease (25%), arthritis (17%), hypertension (18%), and chronic back pain (8%), while stroke, cancer, renal disease, and depression were reported very less (Figure 1).

3.3. Internal Consistency. The overall consistency of the MAQ-PC was found to be 0.69 for all 52 items with Cronbach's alpha value for individual domain ranging from 0.66 for health related quality of life to 0.89 for depression (Table 3).

3.4. Interobserver Reliability. Both observers reported similar prevalence of multimorbidity. We observed a substantial to almost perfect agreement between the two interviewers. Lowest agreement was seen for depression (Table 4).

3.5. Test-Retest Reliability. The test-retest reliability score for each domain is denoted in Table 5. We found strong test-retest correlation in multimorbidity assessment domain [ICC: 0.970], followed by quality of life physical component score [ICC: 0.912] and disease severity [ICC: 0.903]. Lowest correlation was seen for the item self-rated overall health [ICC: 0.741].

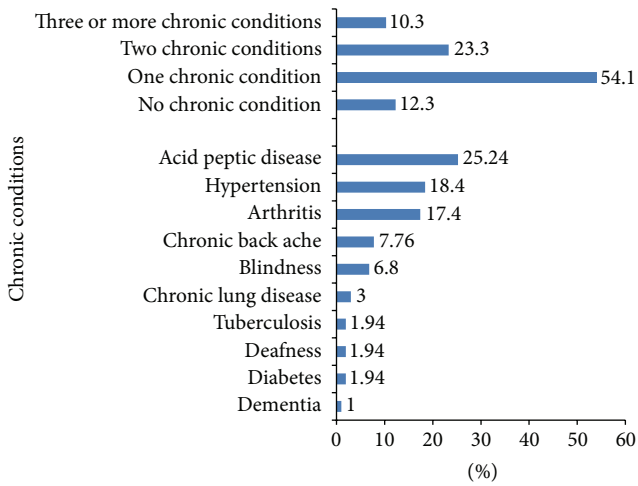

Figure 1: Prevalence of chronic conditions.

Table 3: Measure of internal consistency of MAQ-PC.

Domains	Number of items	Cronbach's alpha coefficient
Sociodemographic	8	0.741
Health care utilization	3	0.651
Chronic diseases	18	0.712
Depression	9	0.891
Disease severity	2	0.671
Health related quality of life	12	0.664
Overall	52	0.693

3.6. Concurrent Validity. The correlations between the self-report and physician's prescription are presented in Table 6. The summative multimorbidity score between the first and follow-up interviews was strongly correlated thus demonstrating self-report to be adequately predictive of diagnosed morbidity. The level of agreement was highest for visual problem, tuberculosis, and dementia while being moderate for diabetes and hearing problems.

3.7. Ethical Consideration. The study was conducted in accordance with the Declaration of Helsinki. It was approved by the Institutional Ethics Committee of Public Health Foundation of India, New Delhi, and necessary permission was granted by the Government of Odisha. Written informed consent was obtained from all respondents following an explanation of the study's aims and procedures. Participation was purely voluntary and all steps have been taken to ensure confidentiality.

Table 4: Interobserver reliability (Cohen's Kappa statistics).

Theoretical construct and facets	Observer 1 Mean [SD]	Observer 2 Mean [SD]	Kappa	Strength of agreement
Chronic conditions				
Diseases and other health problems	1.61 [0.86]	1.61 [0.86]	1	Nearly perfect agreement
Depression	1.92 [0.88]	1.83 [0.83]	0.784	Moderate agreement
Health care utilization				
Frequency of hospital visits in last one year	0.98 [1.46]	0.97 [1.39]	0.921	Substantial agreement
Frequency of inpatient admission in last one year	0.30 [0.61]	0.35 [0.76]	0.874	Substantial agreement
Number of medicines taken	0.46 [0.79]	0.39 [0.68]	0.851	Substantial agreement
Health related quality of life				
Self-rated overall health	3.53 [0.68]	3.87 [0.75]	0.812	Substantial agreement
SF-12 mental component score	44.25 [9.64]	45.27 [8.67]	0.791	Moderate agreement
SF-12 physical component score	43.57 [4.72]	43.91 [5.13]	0.786	Moderate agreement
Severity				
Limitation in activities due to health problems	7.00 [5.93]	7.12 [6.15]	0.831	Substantial agreement
Multimorbidity				
Multimorbidity (≥2 chronic conditions)%	13.16	13.16	1	<0.001

Table 5: Measures of reliability (test-retest reliability) for different domains of MAQ-PC.

Domains	N	Test Mean [SD]	Retest Mean [SD]	P value of the difference	ICC*
Chronic conditions	103	1.61 [0.86]	1.60 [0.82]	0.932	0.970
Depression	103	1.92 [0.88]	1.86 [0.84]	0.617	0.817
Health care utilization					
Frequency of hospital visits in last one year	103	0.98 [1.46]	0.96 [1.42]	0.920	0.822
Frequency of inpatient admission in last one year	103	0.30 [0.61]	0.33 [0.62]	0.726	0.881
Number of medicines taken	103	0.46 [0.79]	0.49 [0.78]	0.784	0.841
Health related quality of life					
Self-rated overall health	103	3.53 [0.68]	3.41 [0.72]	0.220	0.741
SF-12 MCS	103	44.25 [9.64]	43.95 [9.67]	0.823	0.893
SF-12 PCS	103	43.57 [4.72]	43.61 [5.12]	0.953	0.912
Severity of the disease					
Limitation in activities due to health problems	103	7.00 [5.93]	6.89 [5.60]	0.891	0.903
Multimorbidity (%)	103	23.03	23.01	0.897	0.963

*Interclass correlation.

4. Discussion

Information on presence and composition of multimorbidity could inform routine clinical practice and impetus for research. Since the magnitude of multimorbidity is largely reliant upon the way it is measured, we designed a comprehensive tool, MAQ-PC, to elicit data on self-reported prevalence, correlates, and outcomes of multimorbidity in patients attending primary care practices [24]. The questionnaire intended to measure individuals' count of chronic conditions, outcomes (severity, self-rated health, quality of life, physician consultation, and medications), and sociodemographic correlates. We found multimorbidity prevalence to be higher than previously reported findings [24]. This is expected, as we included a larger number of chronic conditions and collected data from patients attending primary care facility.

In this pilot, the MAQ-PC identified hypertension, arthritis, and acid peptic disease as the most common morbidities, while stroke, cancer, renal disease, and depression were the least frequently mentioned morbidities. As health system characteristics influence the type of conditions patients would present with, the conditions which were more frequent could be predominantly diagnosed and treated in primary care [25]. The extreme low number of morbidities, stroke, cancer, depression, and renal disease, could be due to the low prevalence of these conditions in the community and a small sample size of our pilot [26]. Moreover, some of these patients might be consulting specialists for their

Table 6: Concordance between self-reported and physician's prescription based chronic conditions.

Items	Number of cases (n = 103)	Number of cases according to prescription (n = 103)	Scott Kappa	Strength of agreement
Chronic conditions				
Arthritis	26	24	0.71	Substantial agreement
Hypertension	21	20	0.73	Substantial agreement
Diabetes	6	7	0.59	Moderate agreement
Chronic lung disease	7	7	0.69	Substantial agreement
Acid peptic disease	33	32	0.66	Substantial agreement
Thyroid problem	0	0		
Heart disease	0	0		
Stroke	0	0		
Visual problem	11	10	0.95	Nearly perfect agreement
Hearing problem	5	5	0.58	Moderate agreement
Chronic back ache	10	10	0.67	Substantial agreement
Tuberculosis	4	4	1.00	Nearly perfect agreement
Epilepsy	0	0		
Chronic kidney disease	0	0		
Dementia	4	3	0.85	Nearly perfect agreement
Filariasis	0	0		

illnesses, which could be another contributing reason [25]. Interestingly, even though depression was underreported, a good proportion of undiagnosed patients had higher PHQ-9 score. This suggests that these patients either have not attributed much significance to related symptoms or may not have consulted the physician at all.

We observed the MAQ-PC to exhibit significant test-retest reliability with a substantial degree of agreement between self-reported chronic condition and physician diagnosis (derived from prescription and medicine verifications). Such high level of agreement between the self-reported and physician diagnoses suggests the utility of the patient's self-report as a valid proxy measure for these conditions. For few conditions, where the agreement was relatively lower, the patients might be having the disease in milder form or initial stages and can perceive the symptoms though not being detected by the treating physicians. Another plausible explanation could be the fact that patients are not fully aware of their prevailing illness despite having confirmed diagnosis. The latter might be related to the lower health literacy as majority of our patients had lower literacy [27]. Further analysis into the predictors of concordance might yield useful insights.

4.1. Strengths and Limitations. Instruments contingent on availability and accuracy of medical records may have limited utility for clinical and research purposes owing to the deficient routine data management system in resource-limited countries like India [28]. Given the understanding that primary care practice characteristics in LMICs may not be comparable with those of western countries, this work for the first time has developed a multimorbidity assessment tool and contextualized it for Indian primary care.

When compared to multimorbidity measurement methods available till date in LMICs, our approach and instrument are scientifically superior in many aspects. The questionnaire was generated through an iterative process of desk review and chart review, translation, and cultural adaptation, pretested with cognitive interviews including negotiation between the primary care physicians and the research team. These steps helped assure content and face validity. This is reflected by the questionnaire displaying good psychometric properties with Cronbach's alpha and ICC indicating it to be internally consistent and reliable in this setting. Furthermore, many of the domains draw on already validated questionnaire which reinforces the robustness.

Our MAQ-PC has positive features of being brief and easily understandable by patients and at the same time being comprehensive enough to include commonly prevalent chronic conditions in primary care patients. Each questionnaire on an average took 20–25 minutes to complete and thus can easily be administered at outpatient setting either by a physician or by other health care professionals. Employing self-report allows identifying multimorbidity by simple count and the results from the item scales can be easily scored and readily interpretable. Moreover, the questionnaire enquires about the treatment and limitations imposed by specific diseases which can be used as a surrogate marker of the severity of the disease.

However, some limitations need to be acknowledged while using this MAQ-PC. It has been shown previously that list of diseases reported on the basis of prescriptions may not be fully accurate, as many conditions remain undiagnosed, so using this method as the gold standard may not be ideal. Additionally, with any questionnaire-based technique, there is a potential for recall bias. Though patients had the option of

mentioning any additional diseases that were not listed, it is possible that patients may not recall milder forms of existing comorbid diseases and this may inadvertently leave out some important conditions. We did not elicit information on the duration and order of appearance of individual diseases, thus weakening our severity score. Our outcome assessment is not comprehensive as it did not include health care expenditure as we were apprehensive of time constraint and also our primary objective was to examine multimorbidity prevalence, pattern, and health outcomes. Lastly, we have only examined the appropriateness of questionnaire in primary care patients, thus restricting the possibility of extrapolating to other groups of patients like those attending more specialized care and having complex patterns of multimorbidity. Despite these limitations, we believe that MAQ-PC, being a reliable and valid descriptor of individual chronic morbidities, has utility as a tool for identifying and quantifying multimorbidity in primary care.

4.2. Future Research Directions. Future studies need to examine the suitability of MAQ-PC to measure multimorbidity in other outpatient care settings, where medical records are unavailable. Further development of this questionnaire might include specific enquiry about the duration and chronological order of multiple chronic conditions and health care expenditure. Since the number of chronic diseases increases with age and multimorbidity is a frequently observed geriatric phenomenon, it is necessary to test the applicability of this tool in geriatric population particularly.

5. Conclusion

To summarize, MAQ-PC is a comprehensive tool for obtaining data on patient self-reported multimorbidity in primary care. Our results demonstrate this questionnaire to be a valid and reliable measure of multimorbidity in a variety of chronic conditions and primary care patients. The instrument also provides information on severity of the individual conditions and impact on quality of life which suits the need in primary care to identify patient groups that might benefit from more coordinated and holistic care. We believe MAQ-PC may find applicability in assessing multimorbidity and its impact, following multimorbidity trajectory, designing therapeutic targets across wide range of health care settings in India.

Disclosure

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Disclaimer

The principal investigator who is also the corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Deconstructing Complex Multimorbidity in the Very Old: Findings from the Newcastle 85+ Study

Joanna Collerton,[1,2] Carol Jagger,[1,2] Mohammad E. Yadegarfar,[1,2] Karen Davies,[1,2] Stuart G. Parker,[1,2] Louise Robinson,[1,2] and Thomas B. L. Kirkwood[1,3]

[1]*Newcastle University Institute for Ageing, Campus for Ageing and Vitality, Newcastle upon Tyne NE4 5PL, UK*
[2]*Institute of Health and Society, Newcastle University, Baddiley Clark Building, Richardson Road, Newcastle upon Tyne NE2 4AX, UK*
[3]*Institute for Cell and Molecular Bioscience, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK*

Correspondence should be addressed to Joanna Collerton; joanna.collerton@ncl.ac.uk

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Objectives. To examine the extent and complexity of the morbidity burden in 85-year-olds; identify patterns within multimorbidity; and explore associations with medication and healthcare use. *Participants*. 710 men and women; mean (SD) age 85.5 (0.4) years. *Methods*. Data on 20 chronic conditions (diseases and geriatric conditions) ascertained from general practice records and participant assessment. Cluster analysis within the multimorbid sample identified subgroups sharing morbidity profiles. Clusters were compared on medication and healthcare use. *Results*. 92.7% (658/710) of participants had multimorbidity; median number of conditions: 4 (IQR 3–6). Cluster analysis (multimorbid sample) identified five subgroups sharing similar morbidity profiles; 60.0% (395/658) of participants belonged to one of two high morbidity clusters, with only 4.9% (32/658) in the healthiest cluster. Healthcare use was high, with polypharmacy (≥5 medications) in 69.8% (459/658). Between-cluster differences were found in medication count ($p = 0.0001$); hospital admissions ($p = 0.022$); and general practitioner ($p = 0.034$) and practice nurse consultations ($p = 0.011$). Morbidity load was related to medication burden and use of some, but not all, healthcare services. *Conclusions*. The majority of 85-year-olds had extensive and complex morbidity. Elaborating participant clusters sharing similar morbidity profiles will help inform future healthcare provision and the identification of common underlying biological mechanisms.

1. Introduction

The concept of multimorbidity, the cooccurrence of two or more chronic diseases in an individual [1], is attracting increasing research and clinical interest (the related term "comorbidity" is reserved for morbidity cooccurring in relation to a specific index disease [2]). Prevalence estimates for multimorbidity range from 20 to 30% in "all age" populations and are as high as 55–98% in older populations [3]. The cooccurrence of multiple diseases is associated with numerous adverse outcomes including disability, poor quality of life, high healthcare use, and mortality [3, 4]. The provision of effective and cost-effective care for people with multimorbidity presents a major challenge for healthcare systems worldwide and is the subject of on-going debate [5–8]. In the setting of multiple diseases, current approaches to chronic disease management—based largely on the single disease paradigm—can result in complex, fragmented, costly, and potentially ineffective (or even injurious) care [9, 10].

Most multimorbidity research to date has focused on measures based on a simple disease count [11], and there is limited data on how and why particular conditions cooccur and the specific combinations or patterns found. Improved understanding of such patterns would inform the development of better healthcare for patients with multimorbidity and facilitate the identification of common underlying biological mechanisms thereby potentially leading to novel preventive and therapeutic measures [12].

People aged 85 years and over comprise the most rapidly expanding age group in most parts of the world [13]. Whilst multimorbidity is the norm in the very old [14, 15], there is little detailed information on the morbidity profiles found

in this age group. In this paper we examine the extent and complexity of the morbidity burden in a population-based sample of 85-year-olds (using the concepts of comorbidity and multimorbidity), identify patterns of morbidity, and explore associations between morbidity profiles and medication and healthcare use. To study morbidity within a population requires comprehensive data on a representative group, which in the case of very old people is rarely available given the inherent difficulty in working with this potentially frail and vulnerable group. We used data from the Newcastle 85+ Study, a population-based cohort study capturing detailed information on the health of a large, representative sample who were all aged 85 at baseline [16, 17]. Considerable effort was invested to secure inclusion of the notably hard-to-reach groups, particularly those living in care homes or with dementia [18]. A novelty of our approach is the use of cluster analysis to identify distinct subgroups of participants with similar combinations of conditions. Furthermore, we included not only chronic diseases but also geriatric syndromes and impairments. Such conditions are as prevalent as chronic diseases in older people and have a marked effect on quality of life, disability, institutionalisation, healthcare use [19], and quality of care [20]. However, they fall outside the disease-focused medical model and have seldom been included in multimorbidity measures.

2. Materials and Methods

2.1. Study Population. Full details of the Newcastle 85+ Study have been reported [16–18]. In brief, members of the 1921 birth cohort living in Newcastle upon Tyne or North Tyneside (North East England) were recruited at around age 85 using general practice patient lists as the sampling frame. People living in institutions and those with cognitive impairment were included. Recruitment and baseline assessment took place over a 17-month period in 2006-2007.

2.2. Study Protocol. Comprehensive measures of health were collected at baseline across multiple clinical, biological, and psychosocial domains. A health assessment—comprising questionnaires, measurements, function tests, and a fasting blood sample—was carried out in the participant's usual residence by a research nurse. General practice medical records were reviewed for diagnosed diseases, prescribed medication, and use of general practice services. In the UK, patients are registered with a single general practice which acts as a gatekeeper to secondary care and receives details of all hospital admissions and outpatient attendances. The review of general practice records included hospital correspondence to ensure that all recorded disease diagnoses were extracted, irrespective of where and when the diagnosis was made.

2.3. Diseases and Geriatric Syndromes/Impairments Examined. Fifteen chronic diseases and five geriatric syndromes or impairments (hereafter termed "geriatric conditions") were selected for investigation. The selection criteria included known impact on morbidity, mortality, and/or healthcare use; availability in the baseline Newcastle 85+ Study dataset; prevalence greater than 3% at study baseline; and less than 10% missing values. Table 1 lists the 20 conditions examined, together with data sources and ascertainment criteria [21–25]. A systematic review by Diederichs et al. [26] recommended the inclusion of 11 core conditions in any multimorbidity measure, of which we included 10. We were unable to include depression due to the high proportion (15%) of participants with missing data for the depression measure used (15 item Geriatric Depression Scale, GDS-15 [27]); this was mainly because the GDS cannot be used in people with severe cognitive impairment. We included the majority of the chronic conditions prioritised by the UK NHS Quality and Outcomes Framework for General Practice [28].

2.4. Medication. Data on prescribed medication was extracted from the general practice records; all participant medication prescribed for use in the month prior to the health assessment was recorded. A count of medications was created after first excluding items such as seasonal vaccinations, diagnostic/monitoring agents, wound-management products, and catheter/stoma products.

2.5. Use of Healthcare Services. Data on all consultations with general practitioners and general practice employed nurses (other community nurses were not included) was obtained from the general practice records; a timeframe of 12 months prior to the health assessment was used. Only contacts with the participant's registered general practice were recorded; contacts with externally provided "out of hours" general practice services were excluded. Data on overnight hospital admissions and contacts with outpatient and "Accident and Emergency" services and "Day Hospital" and other intermediate care services was obtained by questionnaire (administered by the research nurse as part of the health assessment). A timeframe of three months was used for outpatient and "Accident and Emergency" services and 12 months for overnight hospital admissions and intermediate care services.

2.6. Other Measures. Data on disability level was obtained by nurse-administered questionnaire. A disability score (maximum 17) was calculated from the total number of activities of daily living performed with difficulty or requiring an aid/appliance or personal help [17].

2.7. Ethical Approval. The research complied with the requirements of the Declaration of Helsinki. Ethical approval was obtained from the Newcastle and North Tyneside 1 Research Ethics Committee (reference number 06/Q0905/2). Written informed consent was obtained from participants; where people lacked capacity to consent, for example, because of cognitive impairment, a formal written opinion was sought from a relative or carer as previously reported [18].

2.8. Statistical Analysis. We first compared the sample with complete data on all 20 conditions (analytic sample) to the sample without complete data. Mann-Whitney U tests were used for nonnormally distributed continuous variables and

Table 1: 20 diseases and geriatric conditions examined; data sources and ascertainment criteria.

Diseases (15)		
Disease	Data source	Criteria
Hypertension	General practice (GP) records	Documented diagnosis of hypertension regardless of date.
Ischaemic heart disease	GP records and health assessment (HA) electrocardiogram (ECG)	Documented diagnosis of angina or myocardial infarction or coronary artery bypass grafts or coronary angioplasty or coronary stent regardless of date. Participants without a preexisting diagnosis could be additionally assigned on the basis of Minnesota codes [21] commencing 1-1 or 5-1 on 12 lead ECG conducted as part of the health assessment.
Heart failure	GP records	Documented diagnosis of heart failure regardless of date.
Atrial fibrillation or flutter	HA ECG	Minnesota codes 8-3-1 or 8-3-2 on 12 lead ECG conducted as part of the health assessment.
Cerebrovascular disease	GP records	Documented diagnosis of stroke or transient ischaemic attack or carotid endarterectomy regardless of date.
Peripheral vascular disease	GP records	Documented diagnosis of peripheral vascular disease regardless of date.
Osteoarthritis	GP records	Documented diagnosis of osteoarthritis or cervical spondylosis or lumbar spondylosis regardless of date.
Inflammatory arthritis	GP records	Documented diagnosis of rheumatoid arthritis or psoriatic arthropathy or ankylosing spondylitis regardless of date.
Osteoporosis	GP records	Documented diagnosis of osteoporosis regardless of date.
Chronic obstructive pulmonary disease	GP records	Documented diagnosis of chronic obstructive pulmonary disease (COPD) regardless of date.
Asthma	GP records	Documented diagnosis of asthma excluding childhood asthma and excluding asthma in conjunction with COPD.
Thyroid disease	GP records	Documented diagnosis of hypothyroidism or hyperthyroidism regardless of date.
Diabetes mellitus	GP records	Documented diagnosis of diabetes mellitus regardless of date.
Cancer within previous 5 years	GP records	Documented diagnosis of cancer diagnosed within previous 5 years excluding nonmelanoma skin cancer.
Renal impairment	HA serum creatinine	Estimated glomerular filtration rate of less than 45 mL/min/1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [22] using serum creatinine measured as part of the health assessment. This cut point identifies Stages 3B, 4, and 5 Chronic Kidney Disease [23].
Geriatric conditions (5)		
Geriatric condition	Data source	Criteria
Urinary incontinence	HA questionnaire	Moderate, severe, or profound incontinence (classified on basis of frequency of episodes and volume of urine leakage [24]) or catheterised for previous 12 months.
Falls	HA questionnaire	Two or more falls in previous 12 months.
Visual impairment	HA questionnaire	Self-reported difficulty recognizing a friend across the road or reading ordinary newsprint, with aids if worn.
Hearing impairment	HA questionnaire	Self-reported difficulty hearing someone taking in a quiet room or following a conversation with background noise, with aids if worn.
Cognitive impairment	HA cognitive test	Standardised minimental state examination score [25] of 21 or lower.

ordinal variables (disability score, education), and χ^2 tests for categorical variables (sex, place of residence, and prevalence of individual conditions). Sex differences in the prevalence of individual conditions and in multimorbidity were examined by χ^2 tests and sex differences in the total number of conditions by Mann-Whitney U tests. Cluster analysis was used in the sample with multimorbidity ($N = 658$) to identify distinct subgroups of participants with similar combinations of conditions. We first computed a dissimilarity matrix, based on Jaccard's similarity coefficient, on participants' morbidity profiles, and then performed an agglomerative hierarchical cluster analysis [29] using the Calinski/Harabasz index to identify the optimal number of clusters. To characterise between-cluster differences in morbidity profiles, we compared the prevalence of each condition within a specific cluster to that in the total sample with multimorbidity. We defined "higher than average prevalence" as a ratio of prevalence in the cluster to prevalence in the total sample of 1.2 : 1 or higher and "lower than average prevalence" as a ratio of 0.8 : 1 or lower. Clusters were compared by χ^2 tests for sex distribution, place of residence, and healthcare variables (any use) and by Kruskal-Wallis tests for number of medications

and healthcare variables (number of contacts/length of hospital stay). Analyses were performed using STATA version 12.0.

3. Results

3.1. Sample Selection. Details of sample selection for the Newcastle 85+ Study have been reported [17] (and see the Appendix; see Supplementary Material available online at http://dx.doi.org/10.1155/2016/8745670). The recruited cohort was sociodemographically representative of the local population and of England and Wales, including the proportion in care homes [17]. The present analysis required data from both the health assessment and review of general practice records which was available for 845 participants, 58.2% (845/1453) of those eligible to participate. Complete data on all 20 conditions was available for 710 of these participants (84.0%) who formed the sample for the principal analyses (Appendix, Supplementary Figure 1). Missing data arose from noncompletion of questionnaires, electrocardiograms or blood tests. Comparison of the groups with and without complete data showed that those with missing data were more likely to be female, to be resident in an institution, to have a higher prevalence of osteoporosis, urinary incontinence, and cognitive impairment, and to be more disabled than those with complete data (Appendix, Supplementary Table 1).

3.2. Sample Characteristics. Of the 710 participants with complete data on all 20 conditions, the mean (standard deviation) age was 85.5 (0.4) years, 59.9% (425/710) were women and 99.6% (707/710) were of white ethnicity, reflecting the norm for a UK population of this age (Table 2). The majority (80.7%, 573/710) were living in standard (nonsupported) housing, with 13.4% (95/710) in sheltered accommodation and 5.9% (42/710) in an institution (all care homes). Of those not living in an institution, 60.6% (404/667) were living alone.

3.3. Prevalence of 20 Diseases and Geriatric Conditions. Hypertension (57.8%, 410/710), osteoarthritis (57.0%, 405/710), and ischaemic heart disease (36.1%, 256/710) were the most prevalent diseases. Hearing impairment (60.4%, 429/710), visual impairment (36.2%, 257/710), and urinary incontinence (31.3%, 222/710) were the most prevalent geriatric conditions (Table 2). Women had a significantly higher prevalence of osteoarthritis, osteoporosis, thyroid disease, and urinary incontinence than men, whilst men had a higher prevalence of atrial fibrillation/flutter and hearing impairment (Appendix, Supplementary Table 2).

3.4. Comorbidity for Each of the 20 Diseases and Geriatric Conditions. Figure 1 shows the prevalence of each of the 20 conditions with and without comorbidity, that is, the cooccurrence of at least one other condition. Supplementary Table 3 (Appendix) shows, for each index condition, the proportion of cases with comorbidity together with the median number of cooccurring conditions (for cases with at least one cooccurring condition). We present the data both including and excluding geriatric conditions in the definition of cooccurring condition. Individual diseases and geriatric conditions very rarely occurred in isolation. When geriatric conditions were included as cooccurring conditions, over 96% of cases of any index condition had at least one other cooccurring condition. The median (interquartile range, IQR) number of cooccurring conditions ranged from 4 (3–5) for hypertension, osteoarthritis, visual impairment, and hearing impairment up to 6 (4–7) for heart failure. Excluding geriatric conditions from the definition of cooccurring condition generally had little effect on the proportion of disease cases with comorbidity; the median (IQR) number of cooccurring diseases ranged from 2 (2–4) for hypertension to 4 (3–5) for heart failure and cancer (within five years).

Table 2: Sample characteristics: 710 participants with complete data on all 20 conditions.

Age, mean (SD) years	85.5 (0.4)
Female, % (*n*)	59.9 (425)
White ethnicity, % (*n*)	99.6 (707)
Living arrangements, % (*n*)	
Standard (nonsupported) housing	80.7 (573)
Sheltered housing	13.4 (95)
Institution	5.9 (42)
Years in full-time education, % (*n*)	
0–9	64.7 (458)
10-11	22.7 (161)
12+	12.6 (89)
Diseases, % (*n*)	
Hypertension	57.8 (410)
Ischaemic heart disease	36.1 (256)
Heart failure	11.1 (79)
Atrial fibrillation or flutter	13.5 (96)
Cerebrovascular disease	21.1 (150)
Peripheral vascular disease	7.3 (52)
Osteoarthritis	57.0 (405)
Inflammatory arthritis	3.8 (27)
Osteoporosis	12.1 (86)
Chronic obstructive pulmonary disease	16.5 (117)
Asthma	4.1 (29)
Diabetes mellitus	13.5 (96)
Thyroid disease	14.8 (105)
Cancer within 5 years	6.2 (44)
Renal impairment	23.8 (169)
Geriatric conditions, % (*n*)	
Urinary incontinence	31.3 (222)
Falls	17.2 (122)
Visual impairment	36.2 (257)
Hearing impairment	60.4 (429)
Cognitive impairment	6.9 (49)
Disability score*, median (IQR)	3 (1–6)

*Total number of activities of daily living performed with difficulty or requiring an aid/appliance or personal help [17].

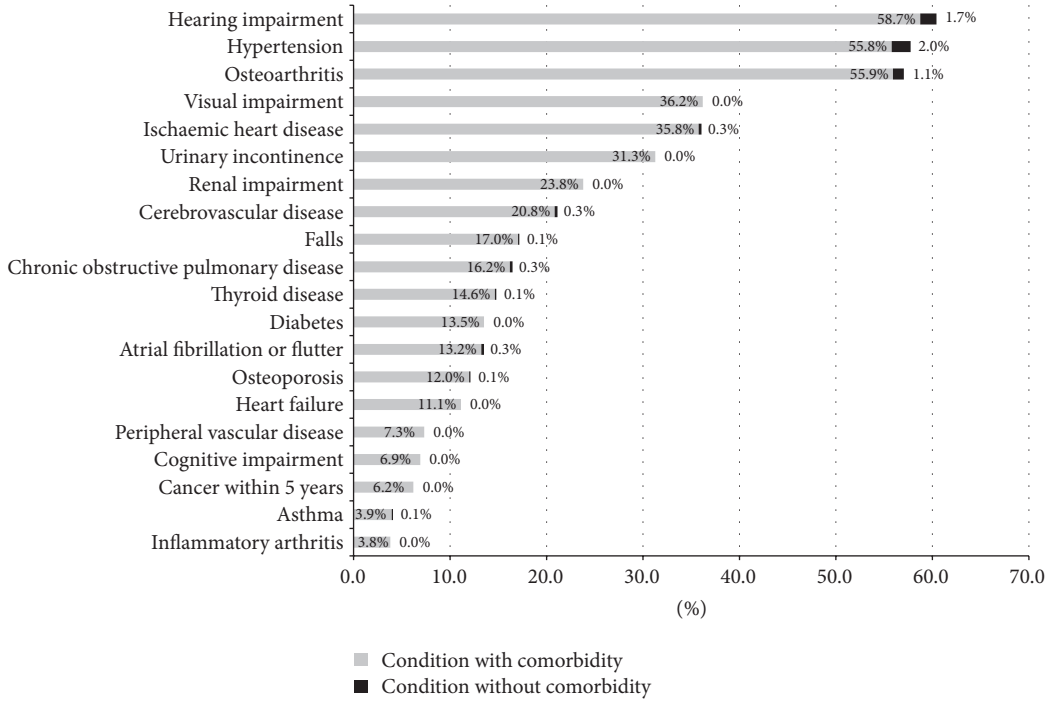

Figure 1: Prevalence of 20 diseases and geriatric conditions, with comorbidity (grey) and without comorbidity (black), in complete case sample (N = 710).

3.5. Total Count of Diseases and Geriatric Conditions. The median total number of conditions (diseases and geriatric conditions) per participant was 4 (IQR, 3–6) and this was higher in women (median 5, IQR 3–6) than men (median 4, IQR 3–6); p value = 0.01. The median number of diseases was 3 (IQR 2–4) and for geriatric conditions it was 1 (IQR 1-2). Less than 1% (6/710) of participants had none of the 20 conditions and 6.5% (46/710) had only one condition, whilst 8.9% (63/710) had 8 or more conditions. The prevalence of multimorbidity (two or more conditions) was 92.7% (658/710) and was slightly, but not significantly, higher in women (93.6%, 398/425) than men (91.2%, 260/285); p value = 0.225.

3.6. Clusters of Participants with Similar Morbidity Profiles. The F-statistic implied that the optimal number of clusters lays between four and six, and subjective review suggested that a five-cluster solution would yield groups of most clinical relevance. The five clusters varied in prevalence within the multimorbid sample; sex distribution; morbidity profile and the mix found between diseases and geriatric conditions; and use of healthcare services and prescribed medication. Table 3 provides summary details of the cluster groups, ordered and labelled alphabetically by cluster prevalence. Table 4 lists condition prevalence by cluster, highlighting those conditions occurring at higher and lower than average prevalence (bold text = higher, ratio of prevalence in cluster to prevalence in total sample with multimorbidity ≥1.2 : 1; italic text = lower, ratio ≤0.8 : 1). Figure 2 shows the prevalence of the 20 conditions within each of the five clusters and in the total sample with multimorbidity.

The most common clusters—A (32.1% of multimorbid sample, 211/658) and B (28.0%, 184/658)—were both characterised by very high morbidity (10 conditions occurring at higher than average prevalence). The pattern in Cluster A was disease-based, whilst Cluster B had a mix of diseases and geriatric conditions. In Cluster A, 10 diseases (hypertension, heart failure, atrial fibrillation/flutter, cerebrovascular disease, peripheral vascular disease, renal impairment, diabetes, asthma, thyroid disease, and cancer) occurred at higher than average prevalence, whilst most of the geriatric conditions occurred at lower than average prevalence. In contrast, in Cluster B five diseases occurred at higher than average prevalence (atrial fibrillation/flutter, cerebrovascular disease, diabetes, inflammatory arthritis, and thyroid disease), together with all five geriatric conditions. Clusters C (22.6% of sample, 149/658) and D (12.5%, 82/658) were characterised by intermediate morbidity; four and six conditions, respectively, occurred at higher than average prevalence, comprising a mix of diseases and geriatric conditions. Cluster E (4.9% of sample, 32/658), the least common group, appeared to be the healthiest cluster; whilst five conditions occurred at higher than average prevalence (mix of diseases and geriatric conditions), 14 of the 20 conditions occurred at zero or low prevalence. Higher than average prevalence was found for three diseases (ischaemic heart disease, inflammatory arthritis, and osteoporosis) and one geriatric condition (hearing impairment) in Cluster C; three diseases (osteoarthritis, chronic obstructive pulmonary disease, and asthma) and three geriatric conditions (urinary incontinence, falls, and cognitive impairment) in Cluster D; and two diseases (atrial fibrillation/flutter and chronic obstructive airways disease)

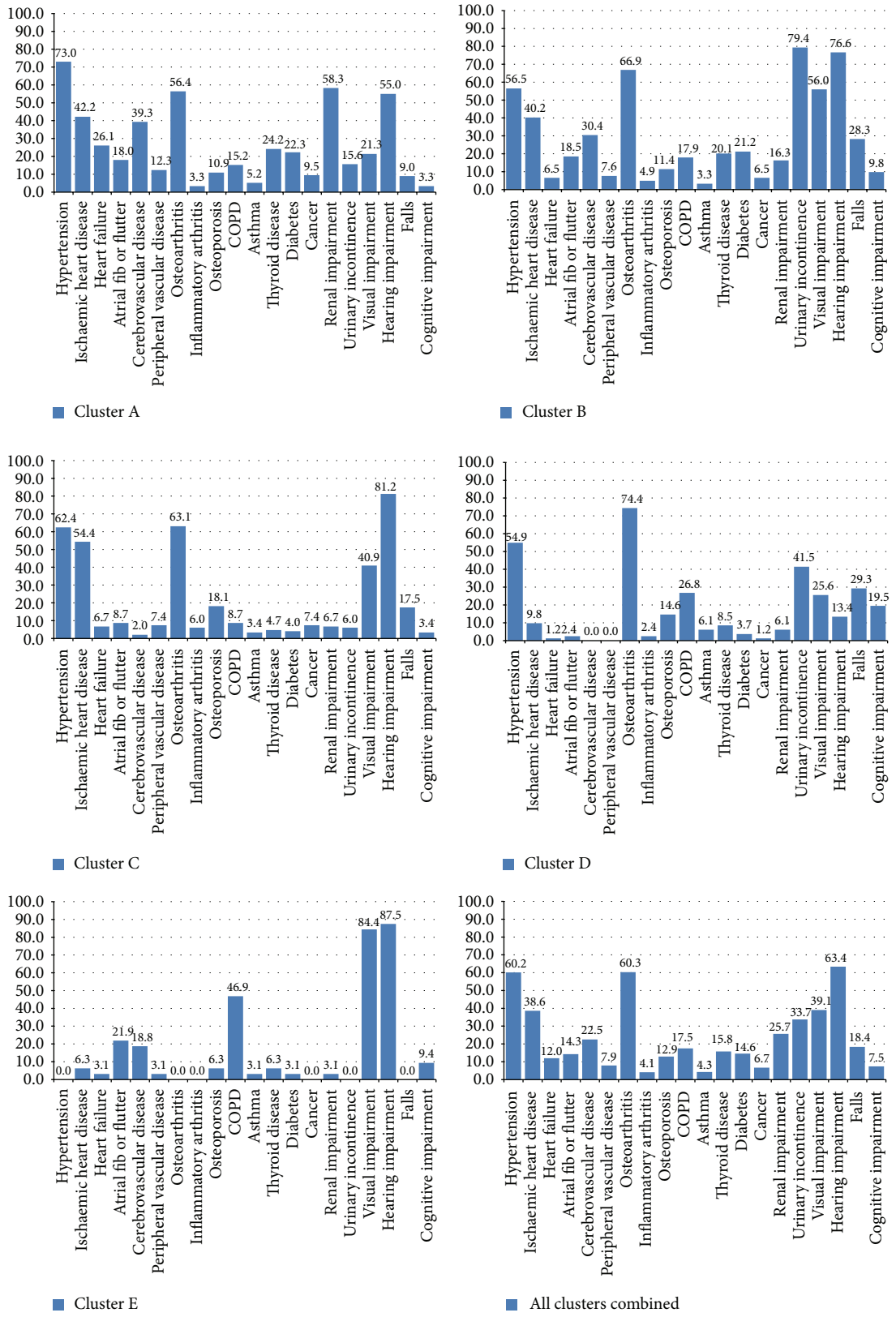

Figure 2: Prevalence of 20 diseases and geriatric conditions in each cluster group, and in total sample with multimorbidity.

Table 3: Description of five clusters of participants with similar morbidity profiles identified in sample with multimorbidity ($N = 658$).

Cluster	Prevalence within multimorbid sample % (n)	Female % (n)	Median (IQR) number of conditions	Number of diseases/geriatric conditions occurring at higher than average prevalence*	Conditions† occurring at higher than average prevalence: prevalence, % (ratio of prevalence in cluster to prevalence in total multimorbid sample)	Number of diseases/geriatric conditions occurring at lower than average prevalence*	Conditions† occurring at lower than average prevalence: prevalence, % (ratio of prevalence in cluster to prevalence in total multimorbid sample)
A	32.1 (211)	56.4 (119)	5 (3–7)	10/0	Hypertension 73.0 (1.2) Renal impairment 58.3 (2.3) Cerebrovascular disease 39.3 (1.8) Heart failure 26.1 (2.2) Thyroid disease 24.2 (1.5) Diabetes mellitus 22.3 (1.5) Atrial fibrillation/flutter 18.0 (1.3) Peripheral vascular disease 12.3 (1.6) Cancer 9.5 (1.4) Asthma 5.2 (1.2)	2/4	*Cognitive impairment 3.3 (0.5)* Inflammatory arthritis 3.3 (0.8) *Falls 9.0 (0.5)* Osteoporosis 10.9 (0.8) *Urinary incontinence 15.6 (0.5)* *Visual impairment 21.3 (0.6)*
B	28.0 (184)	66.3 (122)	6 (5–7)	5/5	*Urinary incontinence 79.4 (2.4)* *Hearing impairment 76.6 (1.2)* *Visual impairment 56.0 (1.4)* Cerebrovascular disease 30.4 (1.4) *Falls 28.3 (1.5)* Diabetes mellitus 21.2 (1.5) Thyroid disease 20.1 (1.3) Atrial fibrillation/flutter 18.5 (1.3) *Cognitive impairment 9.8 (1.3)* Inflammatory arthritis 4.9 (1.2)	3/0	Asthma 3.3 (0.8) Heart failure 6.5 (0.5) Renal impairment 16.3 (0.6)
C	22.6 (149)	53.0 (79)	4 (3–5)	3/1	*Hearing impairment 81.2 (1.3)* Ischaemic heart disease 54.4 (1.4) Osteoporosis 18.1 (1.4) Inflammatory arthritis 6.0 (1.5)	8/2	Cerebrovascular disease 2.0 (0.1) *Cognitive impairment 3.4 (0.5)* Asthma 3.4 (0.8) Diabetes mellitus 4.0 (0.3) Thyroid disease 4.7 (0.3) *Urinary incontinence 6.0 (0.2)* Renal impairment 6.7 (0.3) Heart failure 6.7 (0.6) Chronic obstructive pulmonary disease 8.7 (0.5) Atrial fibrillation/flutter 8.7 (0.6)

Table 3: Continued.

Cluster	Prevalence within multimorbid sample % (*n*)	Female % (*n*)	Median (IQR) number of conditions	Number of diseases/geriatric conditions occurring at higher than average prevalence*	Conditions† occurring at higher than average prevalence: prevalence, % (ratio of prevalence in cluster to prevalence in total multimorbid sample)	Number of diseases/geriatric conditions occurring at lower than average prevalence*	Conditions† occurring at lower than average prevalence: prevalence, % (ratio of prevalence in cluster to prevalence in total multimorbid sample)
D	12.5 (82)	75.6 (62)	3 (2–4)	3/3	Osteoarthritis 74.4 (1.2) *Urinary incontinence 41.5 (1.2)* *Falls 29.3 (1.6)* Chronic obstructive pulmonary disease 26.8 (1.5) *Cognitive impairment 19.5 (2.6)* Asthma 6.1 (1.4)	10/2	Cerebrovascular disease 0.0 (0.0) Peripheral vascular disease 0.0 (0.0) Heart failure 1.2 (0.1) Cancer 1.2 (0.2) Atrial fibrillation/flutter 2.4 (0.2) Inflammatory arthritis 2.4 (0.6) Diabetes mellitus 3.7 (0.3) Renal impairment 6.1 (0.2) Thyroid disease 8.5 (0.5) Ischaemic heart disease 9.8 (0.3) *Hearing impairment 13.4 (0.2)* *Visual impairment 25.6 (0.7)*
E	4.9 (32)	50.0 (16)	3 (2–4)	2/3	*Hearing impairment 87.5 (1.4)* *Visual impairment 84.4 (2.2)* Chronic obstructive pulmonary disease 46.9 (2.7) Atrial fibrillation/flutter 21.9 (1.5) *Cognitive impairment 9.4 (1.3)*	13/2	Hypertension 0.0 (0.0) Osteoarthritis 0.0 (0.0) Inflammatory arthritis 0.0 (0.0) Cancer 0.0 (0.0) *Urinary incontinence 0.0 (0.0)* *Falls 0.0 (0.0)* Renal impairment 3.1 (0.1) Diabetes mellitus 3.1 (0.2) Heart failure 3.1 (0.3) Peripheral vascular disease 3.1 (0.4) Asthma 3.1 (0.7) Ischaemic heart disease 6.3 (0.2) Thyroid disease 6.3 (0.4) Osteoporosis 6.3 (0.5) Cerebrovascular disease 18.8 (0.8)

*Higher than average prevalence of a condition defined as a ratio of prevalence in cluster to prevalence in total sample with multimorbidity ≥1.2 : 1. Lower than average prevalence of a condition defined as a ratio of prevalence in cluster to prevalence in total sample with multimorbidity ≤0.8 : 1.
†Geriatric conditions (syndromes/impairments) are shown in italic font.

Table 4: Prevalence (%) of 20 conditions in each cluster and in total sample with multimorbidity. Conditions occurring at higher than average prevalence* are shown in bold text; those occurring at lower than average prevalence* are shown in italic text.

	Cluster A $n = 211$	Cluster B $n = 184$	Cluster C $n = 149$	Cluster D $n = 82$	Cluster E $n = 32$	Total multimorbid sample $n = 658$
Diseases						
Hypertension	**73.0**	56.5	62.4	54.9	*0.0*	60.2
Ischaemic heart disease	42.2	40.2	**54.4**	*9.8*	*6.3*	38.6
Heart failure	**26.1**	*6.5*	*6.7*	*1.2*	*3.1*	12.0
Atrial fibrillation or flutter	**18.0**	**18.5**	*8.7*	*2.4*	**21.9**	14.3
Cerebrovascular disease	**39.3**	**30.4**	*2.0*	*0.0*	*18.8*	22.5
Peripheral vascular disease	**12.3**	7.6	7.4	*0.0*	*3.1*	7.9
Osteoarthritis	56.4	66.9	63.1	**74.4**	*0.0*	60.3
Inflammatory arthritis	*3.3*	**4.9**	**6.0**	*2.4*	*0.0*	4.1
Osteoporosis	*10.9*	11.4	**18.1**	14.6	*6.3*	12.9
Chronic obstructive pulmonary disease	15.2	17.9	*8.7*	**26.8**	**46.9**	17.5
Asthma	**5.2**	*3.3*	*3.4*	**6.1**	*3.1*	4.3
Thyroid disease	**24.2**	**20.1**	*4.7*	*8.5*	*6.3*	15.8
Diabetes mellitus	**22.3**	**21.2**	*4.0*	*3.7*	*3.1*	14.6
Cancer within 5 years	**9.5**	6.5	7.4	*1.2*	*0.0*	6.7
Renal impairment	**58.3**	*16.3*	*6.7*	*6.1*	*3.1*	25.7
Geriatric conditions						
Urinary incontinence	*15.6*	**79.4**	*6.0*	**41.5**	*0.0*	33.7
Visual impairment	*21.3*	**56.0**	40.9	*25.6*	**84.4**	39.1
Hearing impairment	55.0	**76.6**	**81.2**	*13.4*	**87.5**	63.4
Falls	*9.0*	**28.3**	17.5	**29.3**	*0.0*	18.4
Cognitive impairment	*3.3*	**9.8**	*3.4*	**19.5**	**9.4**	7.5

*Higher than average prevalence of a condition defined as a ratio of prevalence in cluster to prevalence in total sample with multimorbidity ≥1.2 : 1. Lower than average prevalence of a condition defined as a ratio of prevalence in cluster to prevalence in total sample with multimorbidity ≤0.8 : 1.

and three geriatric conditions (visual impairment, hearing impairment, and cognitive impairment) in Cluster E. Four conditions—hypertension, osteoarthritis, hearing impairment, and visual impairment—occurred at high prevalence in at least four of the five clusters.

The total number of conditions amongst cluster group members reflected the cluster morbidity profile; Clusters A and B had the highest total number of conditions (medians of five and six, resp.) with Clusters C, D, and E having lower numbers (medians of four, three, and three, resp.). There was a significant difference in sex distribution between the clusters (p value = 0.002). Overall, women comprised 60.5% (398/658) of the total sample with multimorbidity, whereas Cluster E had equal numbers of men and women and in Cluster D the proportion of women was 75.6% (62/82). Only 6.4% (42/658) of participants with multimorbidity were living in an institution (all in care homes); the prevalence was somewhat higher in Clusters B (9.8%, 18/184) and D (9.8% 8/82), p value = 0.056, which may reflect the high proportion with cognitive impairment in those clusters.

3.7. Medication and Healthcare Use. Participants with multimorbidity were high consumers of healthcare, particularly primary care (Table 5). Prescribed medication burden was also high, with polypharmacy (five or more medications) in 69.8% (459/658) of participants and 17.3% (114/658) prescribed 10 or more medications. Between-cluster differences were found in the number of medications (p value = 0.0001); overnight hospital admissions (proportion admitted at least once in previous 12 months, p value = 0.022); general practitioner consultations (proportion consulting at least once in previous 12 months, p-value = 0.034); and general practice nurse consultations (proportion consulting at least once in previous 12 months, p value = 0.011 plus number of consultations for those consulting, p value = 0.009). For medication, hospital admissions, and general practice nurse consultations, the level of use generally reflected cluster morbidity load with higher use found in Clusters A and B. In those with at least one hospital admission, there was some suggestion of a higher total length of stay in Cluster B, although the difference did not reach statistical significance (p value = 0.058). Whilst there were cluster differences in the proportion consulting their general practitioner at least once during the previous 12 months, the high percentage found in all clusters (87.8–97.3%) makes it difficult to determine whether this variation is of clinical significance. The number of general practitioner contacts, amongst those who consulted, was similar across clusters. Given the difference in sex distribution between clusters and that we have previously found sex differences in general practice nurse consultations in this cohort (women having lower levels of use than

Table 5: Medication and healthcare use in total sample with multimorbidity and cluster groups.

	Total multimorbid sample (n = 658)	Cluster A (n = 211)	Cluster B (n = 184)	Cluster C (n = 149)	Cluster D (n = 82)	Cluster E (n = 32)	p value*
Previous 1 month							
Prescribed medication†							
Median (interquartile range) number of items	6 (4–9)	7 (5–9)	7 (4–9)	6 (4–8)	5 (3–7)	3 (1–6.5)	**0.0001**
Previous 3 months							
Any outpatient attendance, % (n)‡	34.1 (223)	37.1 (78)	35.9 (65)	33.6 (50)	24.4 (20)	31.3 (10)	0.319
Median (interquartile range) number of outpatient attendances‡,§	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	0.859
Any "Accident and Emergency" attendance, % (n)‡	7.6 (50)	7.1 (15)	7.1 (13)	8.7 (13)	4.9 (4)	15.6 (5)	0.380
Median (interquartile range) number of "Accident and Emergency" attendances‡,§	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	0.609
Previous 12 months							
Any overnight hospital admission, % (n)‡	22.5 (148)	27.6 (58)	25.0 (46)	20.1 (30)	11.0 (9)	15.6 (5)	**0.022**
Median (interquartile range) total length of stay (days)‡,§	7 (3–17)	6 (2–15)	13 (5–23)	5 (2–14)	7 (3–14)	4 (3–7)	0.058
Any "Day Hospital" attendance, % (n)‡	7.6 (50)	9.1 (19)	7.7 (14)	4.0 (6)	7.3 (6)	16.1 (5)	0.163
Any other intermediate care service contacts, % (n)‡	7.1 (46)	4.7 (10)	8.9 (16)	10.3 (15)	3.7 (3)	6.5 (2)	0.171
Any consultations with own general practitioner, % (n)†	93.3 (614)	91.5 (193)	97.3 (179)	93.3 (139)	87.8 (72)	96.9 (31)	**0.034**
Median (interquartile range) number of general practitioner consultations†,§	5 (3–9)	6 (3–9)	5 (3–8)	5 (3–9)	5 (3.5–9)	4 (2–9)	0.638
Any consultations with general practice nurse, % (n)†	81.0 (533)	84.8 (179)	81.5 (150)	83.9 (125)	69.5 (57)	68.8 (22)	**0.011**
Median (interquartile range) number of general practice nurse consultations†,§	3 (2–5)	3 (2–6)	2.5 (1–5)	3 (1–5)	2 (1–4)	2 (1–4)	**0.009**

* p value for no difference between cluster groups.

†Data source: review of general practice records.

‡Data source: nurse-administered questionnaire.

§Median (interquartile range) reported for those participants with at least one contact with service.

men) [17], we repeated the analysis of general practice nurse consultations adjusting for sex. Between-cluster differences remained in both the proportion consulting (p value = 0.026) and the number of consultations (p value < 0.001).

4. Discussion

We have reported novel data detailing the extensive and complex morbidity burden found in a UK population-based cohort of 85-year-olds and the relationship between morbidity profiles and medication and healthcare use. Novel aspects of our approach include the use of cluster analysis to identify distinct subgroups of participants with similar combinations of conditions and the inclusion of geriatric syndromes and impairments in addition to diseases. We found that chronic diseases and geriatric conditions were both common in the very old and that individual conditions very rarely occurred in isolation. Multimorbidity was almost universal and the average number of conditions was high. Cluster analysis identified five distinct subgroups of participants with similar patterns of morbidity. The two most prevalent clusters, accounting for 60% of the sample, showed very high levels of morbidity; one was predominantly disease-based, whilst the other comprised a mix of diseases and geriatric conditions. The healthiest profile accounted for only 5% of the sample and, even in this "healthy" cluster, participants still had an average of three conditions. Participants with multimorbidity were high consumers of healthcare, particularly primary care, and prescribed medication burden was high with polypharmacy (five or more prescribed medications) found in almost 70%.

It should be noted that cluster analysis is an exploratory technique and different clustering algorithms can produce varying results [30]. However, our findings of disease combinations which mirror known groupings and the between-cluster differences in healthcare use provide evidence of the validity of our approach. Cluster A included five interlinked "circulatory" diseases (hypertension, heart failure, atrial fibrillation/flutter, cerebrovascular disease, and peripheral vascular disease) and three diseases associated with circulatory disease (diabetes, thyroid disease, and renal impairment). Cluster A also included cancer which could be linked to circulatory diseases through the common risk factor of smoking. Cluster B included the established groupings of atrial fibrillation/flutter with cerebrovascular disease and with thyroid disease and diabetes with cerebrovascular disease. Another recognised pairing was that of atrial fibrillation and cognitive impairment found in Clusters B and E. Geriatric syndromes tended to cluster together in line with previous reports [31, 32]. All five geriatric conditions occurred at higher than average prevalence in Cluster B and three conditions in Clusters D and E; in contrast, most geriatric conditions were less prevalent in Cluster A. Geriatric syndromes are thought to result from impairments across multiple systems; they may share common risk factors and pathophysiological mechanisms and could be amenable to unified intervention strategies [19]. Of note, Clusters C, D, and E included less familiar disease groupings, for example, ischaemic heart disease, inflammatory arthritis, and osteoporosis (Cluster C), and some diseases in Cluster A (asthma) and Cluster B (inflammatory arthritis) do not readily "fit" with the rest of the cluster. Disentangling the basis of such "unfamiliar" associations may point the way to promising new avenues of research [33].

Recent systematic reviews of studies of multimorbidity patterns confirm the paucity of research in this area, particularly in the very old [33, 34]. Cluster analysis has been used in a small number of studies [30, 35–41], many of which focused on specific groups such as the hospitalised elderly [37], Native Americans [38], US Veterans [39], and homeless veterans [40]. Most studies used the approach of clustering by condition rather than by participant [35–39, 41]; this produces somewhat crude groupings and has the drawback that each condition can only appear in one cluster (an artefact of the clustering algorithm [39]), as well as it being less straightforward to assign study participants to cluster groups and therefore to examine associations with outcomes. Only two studies have, as we did, clustered by participant to identify distinct subgroups of people sharing similar morbidity profiles, neither of which used population-based samples [30, 40].

Few studies have focused on the very old, all of which used cluster analysis with clustering by condition. Marengoni et al. examined morbidity patterns in the Kungsholmen study (n = 1077, aged 77 and over) [36]; Formiga et al. in the Octobaix study (n = 328 aged 85) [41]; and Dong et al. in the ELSA 85 study (n = 496, aged 85) [35]. Five clusters were identified in the Kungsholmen cohort: circulatory; cardiopulmonary; dementia, depression and hip fracture; diabetes and visual impairment; and cancer with anaemia [36]. The Octobaix cohort had four main clusters: circulatory plus visual impairment; dementia, Parkinson's disease, peripheral vascular disease, dyslipidaemia, and anaemia; chronic obstructive pulmonary disease and malignancy; and hearing impairment [41]. Five main clusters were found in women from the Elsa 85 cohort: vascular; cardiopulmonary; dementia and affective disorders; osteoarthritis and urinary incontinence; and malignancy and thyroid disease [35]. Our study builds on these findings by including a larger sample size of the very old and a larger number of conditions (with osteoarthritis, incontinence and falls included) and by using an alternative approach of clustering by participant rather than by condition. Marked methodological heterogeneity between studies makes direct comparison of the patterns problematic; however the finding of circulatory cluster(s) is a common theme across all studies of the very old, including our own.

Studies of multimorbidity patterns, in all age groups, were the focus of a recent systematic review by Prados-Torres et al. [33]. Fourteen studies were included, 8 of which focused on participants over 60 years whilst 3 included individuals as young as 15; the Kungsholmen study was the only study focusing on the very old [36]. Ninety-seven disease patterns were identified across the 14 studies. The considerable methodological variation between studies—in age group, setting, number and types of conditions included, ascertainment criteria, and statistical techniques—makes direct comparison difficult. Nevertheless, three broad groups of

patterns were highlighted: a cardiovascular/cardiometabolic group, found in 10/14 studies; a mental health group, in 10/14 studies (at least one mental health problem, most commonly depression and/or anxiety); and a musculoskeletal group, in 10/14 studies (at least one musculoskeletal condition, most commonly arthropathy, back/neck pain, and/or osteoporosis). In each of these broad groups, a wide range of additional comorbidities was found, only some of which had logical associations. Comparing these findings to studies of the very old, all three broad groups can be seen in the Elsa 85 cohort [35], two in the Kungsholmen cohort [36], and one in the Octobaix cohort [41]. In the Newcastle 85+ cohort, our finding of a cardiometabolic cluster (Cluster A), together with musculoskeletal conditions in Clusters C and D, would fit with these broad trends, although we found osteoarthritis to be of high prevalence in four of our five clusters. We were unable to include measures of mental health in our analysis. Whilst it would be interesting to further analyse pattern differences between the very old and younger age groups, the marked methodological differences between studies precludes meaningful interpretation.

Strengths of this study include its population-based sample, which included the institutionalised and those with cognitive impairment, and the domiciliary assessment which avoids the selection bias inherent in clinic-based assessment of this age group. The use of dual data sources is a further strength; disease ascertainment from medical records is more reliable than self-report in older age groups, particularly in those challenged by multimorbidity or cognitive impairment [42–44], whilst participant assessment is superior for geriatric conditions which may be undiagnosed and/or their presence poorly documented [45]. Our work has a number of limitations. The sample analysed ($n = 710$) represents 49% of those eligible to participate. Within the limits of the analysis possible, it does not appear that study nonparticipants were less healthy than participants although those with cognitive impairment may have been underrepresented [46]. However, those participants excluded from the analysis due to missing data were less healthy than those with complete data, and consequently our data may underestimate the scale of multimorbidity. Some important conditions were excluded due to absence in the study dataset or a high rate of missing values, for example, mental health problems; hence our estimate of multimorbidity is somewhat conservative. Our sample derives from a single urban area in North East England, with predominantly white ethnicity. Whilst 85-year-olds in this area are sociodemographically and ethnically similar to those in England and Wales as a whole [17], they may differ from those in other parts of the world.

The extensive and complex morbidity burden found in the majority of very old people presents a considerable challenge for healthcare services. Current approaches to chronic disease management are focused largely on a single disease paradigm. In patients with many conditions, application of multiple disease-specific guidelines can lead to clinical chaos, polypharmacy, and interactions between strategies for individual conditions [47, 48]. Healthcare can become fragmented, costly, and potentially ineffective (or even injurious) [9, 10]. Despite growing recognition of the importance of multimorbidity, there remains insufficient data to inform evidence-based care for multimorbid patients of any age [49] and the knowledge gap is particularly acute in older people [3]. Clinical trials routinely exclude patients with cooccurring conditions [50], and older people are consistently underrepresented [50, 51]. Clinical practice guidelines focused on the index disease fail to address the needs of people with complex multimorbidity [47, 48, 52]; furthermore they rarely include information on the quality of research evidence in older people or give specific recommendations for older people [48, 53]. Strategies proposed to improve the care of patients with multimorbidity [5–7, 54–58] will need to be appropriate to the very old who, as we have shown, have a considerable and complex morbidity burden. In the UK, the demarcations between (and within) primary care, community health services, and secondary care and between health and social care are increasingly seen as a barrier to providing the personalised and coordinated approach needed by older people with multimorbidity. The National Health Service is therefore supporting the creation of major new models of care integrated around the patient and their needs, which will cross traditional organisational and departmental boundaries [59].

5. Conclusions

The majority of 85-year-olds in this population-based cohort in North East England had extensive and complex morbidity. The elaboration of clusters of older people sharing similar morbidity profiles is likely, in time, to help throw light on shared pathophysiological processes, creating the potential for novel preventive measures and targeted therapies. Furthermore, it will inform the development of healthcare services which are better able to meet the complex needs of the very old.

Disclosure

The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of Interests

The authors declare that their institution had financial support from the UK Medical Research Council and the Biotechnology and Biological Sciences Research Council (G0500997), Dunhill Medical Trust (R124/0509), and the Newcastle Healthcare Charity in terms of funding the submitted work; Joanna Collerton provides consultancy services to the Academic Health Science Network for the North East and North Cumbria, Carol Jagger is supported by the AXA Research Fund (funding of Research Chair), the other authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; there are no other relationships or activities that could appear to have influenced the submitted work.

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Research Article

Disease Combinations Associated with Physical Activity Identified: The SMILE Cohort Study

Sarah Dörenkamp,[1] Ilse Mesters,[1] Jan Schepers,[2] Rein Vos,[2,3] Marjan van den Akker,[4,5] Joep Teijink,[1,6] and Rob de Bie[1]

[1]*Department of Epidemiology and CAPHRI School for Public Health and Primary Care, Functioning and Rehabilitation Programme, Maastricht University, 6229 ER Maastricht, Netherlands*
[2]*Department of Methodology and Statistics, CAPHRI School for Public Health and Primary Care, Maastricht University, 6229 ER Maastricht, Netherlands*
[3]*Department of Medical Informatics, Erasmus University Rotterdam, 3015 CE Rotterdam, Netherlands*
[4]*Department of Family Medicine, CAPHRI School for Public Health and Primary Care, Maastricht University, 6229 ER Maastricht, Netherlands*
[5]*Department of General Practice, Catholic University of Leuven, 3000 Leuven, Belgium*
[6]*Department of Vascular Surgery, Catharina Hospital, 5623 EJ Eindhoven, Netherlands*

Correspondence should be addressed to Sarah Dörenkamp; sarah.dorenkamp@maastrichtuniversity.nl

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In the search of predictors of inadequate physical activity, an investigation was conducted into the association between multimorbidity and physical activity (PA). So far the sum of diseases used as a measure of multimorbidity reveals an inverse association. How specific combinations of chronic diseases are associated with PA remains unclear. The objective of this study is to identify clusters of multimorbidity that are associated with PA. Cross-sectional data of 3,386 patients from the 2003 wave of the Dutch cohort study SMILE were used. Ward's agglomerative hierarchical clustering was executed to establish multimorbidity clusters. Chi-square statistics were used to assess the association between clusters of chronic diseases and PA, measured in compliance with the Dutch PA guideline. The highest rate of PA guideline compliance was found in patients the majority of whom suffer from liver disease, back problems, rheumatoid arthritis, osteoarthritis, and inflammatory joint disease (62.4%). The lowest rate of PA guideline compliance was reported in patients with heart disease, respiratory disease, and diabetes mellitus (55.8%). Within the group of people with multimorbidity, those suffering from heart disease, respiratory disease, and/or diabetes mellitus may constitute a priority population as PA has proven to be effective in the prevention and cure of all three disorders.

1. Introduction

Multimorbidity, defined as the coexistence of two or more chronic diseases, is progressively more prevalent with age [1–3]. Patients with multimorbidity tend to have a poorer functional status, diminished quality of life and make more use of ambulatory and inpatient healthcare [4]. However, the growing prevalence of patients with multiple chronic diseases not only is the result of ageing and advances in medical care, but is also related to modifiable factors like unhealthy lifestyle behaviours; various studies have shown a strong association between an unfavourable lifestyle and many chronic diseases [5–7]. It is therefore important to consider lifestyle as a relevant strategy for the secondary prevention and cure of multimorbidity in patients.

Regular physical activity (PA) has proven to be effective in the prevention and cure of chronic conditions [8]. An inverse relationship has been shown between regular PA and cardiovascular disease, thromboembolic stroke, hypertension, osteoporosis, diabetes mellitus type II, obesity, colon cancer, breast cancer, anxiety, and depression [9]. In a study of Kaplan et al. [10] the absence of thirteen chronic diseases was

related to frequent PA. In addition to the association between PA and isolated chronic diseases, the association between PA and multimorbidity has recently been explored in older patients in a cross-sectional study by Autenrieth et al. [11]. This study showed an inverse relationship between PA and multimorbidity among men aged 65–94 years. We wish to stress here that the analysis of the study of Kaplan et al. [10] was based on the sum of 13 chronic diseases, while Autenrieth et al. [11] defined multimorbidity as the presence of ≥2 chronic diseases from a list of 13 diseases. Both studies used the sum of diseases as a measure for multimorbidity. Using the summation of diseases as a measure of multimorbidity has been criticised as comparing apples and oranges [12]. The resulting composite expresses multimorbidity in an additive form. A more comprehensive approach is suggested that takes into account how chronic diseases are distributed and aggregate in the population, whereby any clustering of chronic diseases keeps the unique contribution of each disease salient [13]. In addition, it allows an examination of how specific combinations of chronic diseases may interact to affect physical activity behaviour. We hypothesise that certain combinations of chronic diseases may present a stronger association with physical activity as previous studies have already shown that the cumulative effect of chronic diseases is not simply additive [12]. Awareness of the association between specific combinations of chronic diseases and limited physical activity levels could facilitate the development of more targeted counselling strategies and treatment plans.

Prior work has shown an inverse relationship between the number of chronic diseases and physical activity. Yet, to our knowledge no study has assessed the association between specific disease clusters and physical activity. This study therefore goes beyond prior work in the field of multimorbidity and investigates which clusters of multiple chronic diseases are associated with PA in a large representative sample of older Dutch people above 55 years of age, measured in compliance with the Dutch PA guideline.

2. Method

2.1. Study Design and Setting. This cross-sectional study is part of a dynamic prospective cohort study, the Study of Medical Information and Lifestyles in Eindhoven (SMILE), the Netherlands. The SMILE cohort study was performed between 2002 and 2010 and was a joint project between Maastricht University and the Eindhoven Corporation of Primary Health Care Centres (SGE), including nine centres representing 32 general practitioners. Data for the SMILE cohort study was collected in two ways: (1) information on morbidity, mortality, medication use, and healthcare facility utilisation was continuously registered using electronic medical records (EMRs) in the nine primary healthcare centres and (2) information on lifestyles and chronic diseases was collected by using annual self-administered paper questionnaires. Information on physical activity was collected annually in November. The self-reported chronic disease questionnaire was collected annually in May among all adults aged 55 years and older. The SMILE study protocol has been published [14] and approved by the Medical Ethics Committee of the Maastricht Academic Hospital (MEC 07-4-030). To enhance transparency and reproducibility, this paper has been written according to the STROBE checklist for cohort studies.

2.2. Participants. Registrees (12 years and older) of the participating healthcare centres were invited to participate in the overall study. All patients signed informed consent forms. Adult data (from patients aged 55 years and older) from 2003 was used in the present study since that year included the largest number of patients who completed both questionnaires (n = 3,386).

2.3. Variables. Compliance with the Dutch PA guideline, which states that every adult should accumulate 30 minutes or more of moderate intense physical activity (4 METs) on at least five, or preferably all, days of the week [15], was the primary outcome measurement (1 = compliance with the guideline; 0 = no compliance with the guideline). Cluster variables included the presence or absence of 15 self-reported chronic diseases. The derived clusters operated as independent variables.

2.4. Data Sources/Measurement. Data about the level of physical activity came from the adult questionnaire and self-reported chronic diseases data was extracted from the 55+ questionnaire.

2.4.1. Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH). Physical activity was measured by the "Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH)" [15]. Patients were asked to refer to an average week in the past few months. The SQUASH questionnaire was structured in a way that made it possible to assess compliance with the Dutch PA guideline. The SQUASH consists of three main queries: number of active days per week, average time per day, and intensity. All physical activities were prestructured in (a) commuting activities, (b) leisure-time activities, (c) household activities, and (d) activities at work and at school. Examples for each category of physical activity (a–d) were given as activities at work, household activities, and sports. Example activities were chosen based on an intensity of 4 METs but did not include light activities at work and light household activities. These light activities entail a considerable amount of time per day and therefore contribute to the habitual activity level. Moreover, in conformity with the SQUASH questionnaire, manual hobbies were excluded in the SQUASH due to their low MET values (~2 METs); however, hobbies that do have meaningful MET values were noted under sports.

An intensity score and a total activity score were allocated to all activities. Each activity was assigned a MET value using the Ainsworth compendium for physical activities, in which one MET is defined as the energy expenditure for sitting quietly [16]. For each intensity category, cut-off points were defined based on the Dutch PA guideline [15]. Activities between 1.6 and 2.9 METs were classified as lightly intense, between 3 and 5.9 METs as moderately intense, and ≥6 METs as vigorously intense [15, 16]. The total minutes

of each activity were calculated by multiplying frequency (days/week) by duration (minutes/day).

2.4.2. Self-Reported Chronic Disease Questionnaire. The presence or absence of 15 chronic diseases was measured using the self-reported chronic disease questionnaire. This questionnaire is based on a medical screening questionnaire of the Dutch Association of General Practitioners (LHV) [17]. Patients had to record their actual health status for the following fifteen chronic diseases: chronic bronchitis, emphysema, and asthma; heart disease or myocardial infarction; severe bowel disease; liver disease or cirrhosis; severe kidney disease; diabetes mellitus; malignancy or cancer; epilepsy; migraine; stroke or stroke-related complaints; inflammatory joint disease; rheumatoid arthritis; osteoarthritis of knees, hips, and hands; severe back problems, hernia, sciatica, or osteoarthritis; and persistent injury from an accident at home, in sports, school/work, or traffic. Data on chronic diseases were binary (1 = a given disease is present; 0 = a given disease is absent). An open question in the questionnaire allowed patients to add other present chronic diseases that were not listed in the questionnaire. To maximise the use of available data, all chronic diseases noted in the open question ($N = 1{,}077$) were incorporated in the data gathered from the completed self-reported chronic disease questionnaires. Two researchers, assisted by a medical specialist, separately assigned the diseases noted in the open question to the existing categories in the chronic disease questionnaire (JT).

2.5. Bias. Cluster analysis algorithms assume that there are no missing values. Solutions are developed if values are missing; however, these are only technically valid if the values are missing completely at random (MCAR). In the self-reported chronic disease questionnaires, missing values are observed ranging from 592 (17.5%) for epilepsy to 818 (24.2%) for inflammatory joint disease. We assume that these missing values are not completely random (MNAR) [18] but are the result of inadequate instructions being provided with the chronic disease questionnaire. Patients were asked to indicate in a dichotomous prestructured form (yes/no) which of the 15 chronic diseases they suffer from. The hypothesis is that a proportion of patients followed this instruction by only indicating the presence of a certain disorder without explicitly registering the absence (by ticking "no") of all other diseases listed. Following this hypothesis, all missing values for the 15 chronic diseases were interpreted and recoded as "disease being absent."

2.6. Statistical Analysis. The aim of the analysis was to identify clusters of chronic diseases based on their relative similarity or dissimilarity (distance). Cluster analysis is used because it best fits the aim of our study, namely, to identify meaningful groups of patients with chronic diseases. Because there is not a one-and-only valid approach to establish groups of patients in relation to chronic diseases, the two most frequently applied forms of clustering, namely, Ward's agglomerative hierarchical clustering and K-means clustering, were used.

First, the most widely used form of clustering [18–20], Ward's agglomerative hierarchical clustering, applying squared Euclidean distance as a similarity measure, was performed. Each individual disease starts as an individual cluster which is then gradually agglomerated with the next most similar cluster on the basis of a proximity measurement using a predefined fusion algorithm [19]. Distances are recalculated and diseases reassigned until all are in a single cluster. Robust groups of chronic diseases are obtained at the point where the individual clusters are as homogeneous as possible within clusters and as heterogeneous as possible in relation to the other clusters [20]. As the number of clusters was not known a priori, a series of cluster analyses with predefined cluster numbers ranging from 2 to 5 was performed. The agglomerative coefficient, the dendrogram, and the pseudo-F statistic were used to determine the appropriate number of clusters. The pseudo-F statistic (ratio of the mean sum of squares between groups to the mean sum of squares within groups [20]) was calculated to capture the "tightness" of clusters. The following formula was used to calculate the pseudo-F statistic:

$$\text{Pseudo-}F = \frac{(\text{SS}(\text{T}) - \text{SS}(\text{W}))\,/\,(N-1)}{\text{WGSS}/\,(n-N)}. \quad (1)$$

In the above formula, SS(T) is the total sum of squares, SS(W) is the within-group sum of squares, and N is the number of clusters. A larger pseudo-F statistic indicates a better cluster solution. Second, based on the findings obtained from using Ward's agglomerative hierarchical clustering, a K-means cluster analysis was executed to check our findings. Unlike the hierarchical clustering method, K-means starts by assigning patients randomly to one cluster and proceeds with iteration. Patients were gradually reassigned to minimise the within-cluster variation. This iteration was continued until the smallest within-cluster variation was reached. One thousand combinations of random starts were investigated. Cross-tabulation using chi-square statistics was performed to assess the association between established clusters of chronic diseases and compliance with the Dutch PA guideline. To get full insight into the association between multimorbidity and physical activity and to study the consequences of branching of clusters Ward's two-to-five-cluster solution will be studied. Disease frequency distributions within each cluster were evaluated using crosstabs. The sociodemographic characteristics of all patients belonging to each cluster in each cluster solution were determined using descriptive and frequency statistics.

3. Results

3.1. Participants. Both the general adult questionnaire and the additional 55+ questionnaire were returned by 3,386 patients.

Fifty-three per cent were female and the average age of patients was 68 years (range: 55–95 years). The average length and bodyweight of patients were 1.70 m (range: 1.41–1.99 m) and 75 kg (range: 40 kg–185 kg), respectively. Osteoarthritis of knees, hips, and hands was the most prevalent disease (23%).

Table 1: Characteristics of the study population.

Characteristics[a]	Total population $N = 3,386$	Males (47.1%) $n = 1,595$	Females (52.9%) $n = 1,791$
Age (years)	67.5 ± 8.3	67.5 ± 8.2	67.5 ± 8.4
Length (cm)	170.0 ± 8.8	176.2 ± 6.6	164.3 ± 6.5
Body weight (kg)	75.1 ± 13.8	80.4 ± 13.3	70.3 ± 12.3
Chronic bronchitis, emphysema, and asthma	321 (9.5)	148 (9.3)	173 (9.2)
Heart disease or myocardial infarction	299 (8.8)	180 (11.3)	119 (6.6)
Severe bowel disease	112 (3.3)	51 (3.2)	61 (3.4)
Liver disease or cirrhosis	16 (0.5)	9 (0.6)	7 (0.4)
Severe kidney disease	48 (1.4)	25 (1.6)	23 (1.3)
Diabetes mellitus	230 (6.8)	122 (7.6)	108 (6.0)
Malignancy	77 (2.3)	44 (2.8)	33 (1.8)
Epilepsy	20 (0.6)	7 (0.4)	13 (0.7)
Migraine	158 (4.7)	52 (3.3)	106 (5.9)
Stroke or stroke-related complaints	70 (2.1)	35 (2.2)	35 (2.0)
Inflammatory joint disease	302 (8.9)	115 (7.2)	187 (10.4)
Rheumatoid arthritis	150 (4.4)	43 (2.7)	107 (6.0)
Osteoarthritis of knees, hips, or hands	780 (23.0)	290 (18.2)	490 (27.4)
Severe back problems, hernia, sciatica, or osteoarthritis	517 (15.3)	239 (15.0)	278 (15.5)
Persistent injury from an accident at home, in sports, school/work	132 (3.9)	61 (3.8)	71 (4.0)

[a]Dichotomous variables are presented as N (%) and continuous variables as the mean ± standard deviation.

Table 2: Agglomerative coefficient and pseudo-F statistic for hierarchical clustering.

Number of clusters	Agglomeration last step	Coefficient current step	Score change	Pseudo-F	p value
2	2847.045	2516.781	330.264	1533.167[b]	0.000
3	2516.781	2307.600	209.181[a]	767.332	0.000

[a]Demarcation point → 2 clusters.
[b]Ratio of between-cluster variance to within-cluster variance largest → 2 clusters.

The prevalence of heart disease or myocardial infarction was approximately twice as high in males as in females (11.3% versus 6.6%, resp.). In comparison, musculoskeletal disorders like inflammatory joint disease (7.2% versus 10.4%), rheumatoid arthritis (2.7% versus 6.0%), and osteoarthritis of knees, hips, and hands (18.2% versus 27.4%) were less prevalent among females compared with males (Table 1). Prevalence rates of all fifteen chronic diseases from the SMILE cohort (measured in the Eindhoven region) were comparable with national prevalence rates in Dutch older adults [21, 22].

3.2. Multimorbidity Clusters

Two-Cluster Solution. For Ward's agglomerative hierarchical clustering, the stepwise agglomerative coefficients and the pseudo-F statistic suggested a two-cluster solution being most feasible (Table 2). K-means clustering displayed consistent results, with the sum of squares (SS) being 2177.8 and pseudo-F being 1318.4.

Figure 1 shows for each disease how the patients (i.e., the patients that have the disease in question) are distributed across the two clusters. For instance, the first bar in the figure shows that of the patients who have chronic bronchitis, emphysema, and asthma, 10% are assigned to cluster one and 90% are part of cluster two. Detailed information about the importance and distribution of each chronic disease in the clustering can be found in Appendix A.

Of the patients who have severe bowel disease 96.4% are included in cluster one. Of the patients with severe kidney disease or cancer also the majority is involved in cluster one (85.4% and 81.1%, resp.). Similarly of the patients with epilepsy (65.0%), migraine (71.5%), stroke, or stroke-related complaints (87.1%) and persistent injury from an accident at home, in sports, school/work, or traffic (80.3%) the majority is a member of the first cluster. In other words, cluster one is the dominant cluster for severe bowel disease, severe kidney disease, cancer, epilepsy, migraine, stroke, and persistent injury from an accident.

Cluster two is dominated by respiratory disease, heart disease, liver diseases, diabetes mellitus, inflammatory joint disease, rheumatoid arthritis, osteoarthritis, and severe back problems. Of the patients with chronic bronchitis, emphysema and asthma 90.0% are in cluster two. Of the patients

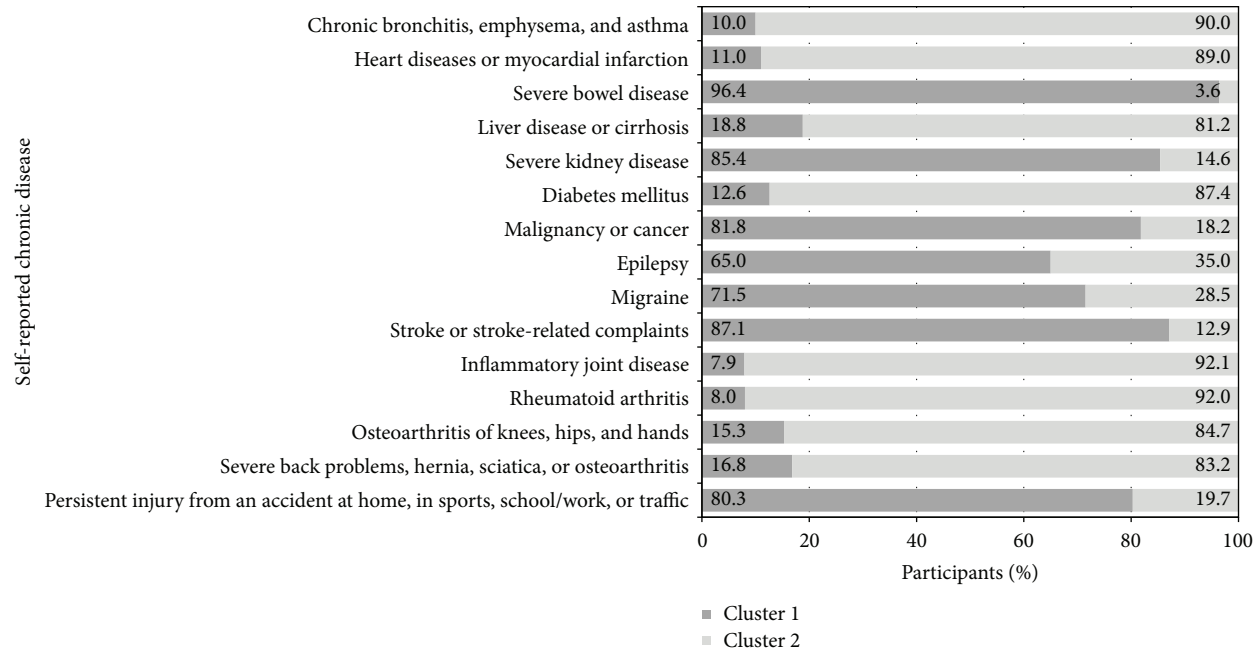


Figure 1: The distribution of patients that suffer from one of the 15 chronic diseases across the two clusters.

with myocardial infarction 89.0% are in cluster two and 81.3% of the patients suffering from liver disease or cirrhosis are included in the second cluster. The majority of the patients with diabetes mellitus (87.4%), inflammatory joint disease (92.1%), rheumatoid arthritis (92.0%), osteoarthritis of knees, hips, and hands (84.7%), and severe back problems, hernia, sciatica, or osteoarthritis (82.3%) are also member of cluster two.

A resumed description of the two clusters is also presented in Figure 2.

3.2.1. Association between Clusters and Physical Activity

Two-Cluster Solution. Of the total of 3,386 patients, 60.8% (N = 2,060) complied with the Dutch physical activity (PA) guideline. Of the people belonging to cluster one, 61.8% complied with the Dutch PA guideline, and, of the people belonging to cluster two, 59.4% complied with this guideline. The proportion of respondents that complied with the Dutch PA guideline was not significantly different between the two clusters (chi-square: 1.847; $p = 0.174$).

Although statistically a two-cluster solution was identified as being most optimal, the aim of this study was to discover the combination of diseases that not only cluster but also interact with physical activity. To explore whether further branching of clusters might provide information regarding the relationship between clusters and physical activity, analysis proceeded with a Ward's three-cluster solution.

3.3. Multimorbidity Clusters

Three-Cluster Solution. The results of Ward's three-cluster solution are presented in Figure 2, with Ward's two- and three-cluster solutions shown on the horizontal axis. The boxes below each cluster solution represent the clusters and contain the diseases in each cluster. Ward's three-cluster solution showed that the first cluster remained the same while cluster two separated further (Figure 2). The third cluster contained patients the majority of whom had heart disease or myocardial infarction (77.6%), diabetes mellitus (83.9%), and/or chronic bronchitis, emphysema, and asthma (82.9%).

3.3.1. Association between Clusters and Physical Activity

Three-Cluster Solution. The proportion of adults that comply with the Dutch PA guideline is highest in cluster two (62.4%), followed by cluster one (61.8%) and finally cluster three (55.8%). The relationship between the three-disease clusters and PA guideline compliance was statistically significant (chi-square: 7.968; $p = 0.019$).

Ward's four-cluster solution led to a cluster containing a single disease (heart disease). First, because a single disease does not represent a multimorbidity cluster and hence does not fit the aim of the present study, clustering was stopped after Ward's three-cluster solution. Second, all other clusters presented in the four-cluster solution were comparable which supports our decision to stick to the three-cluster solution (Appendix B).

4. Discussion

The aim of the present study was to assess the relationship between multimorbidity clusters and compliance with the Dutch physical activity (PA) guideline. The two-cluster solution showed no significant association with PA guideline compliance. Further exploration revealed a significant relationship between three multimorbidity clusters and physical activity. The highest rate of PA guideline compliance

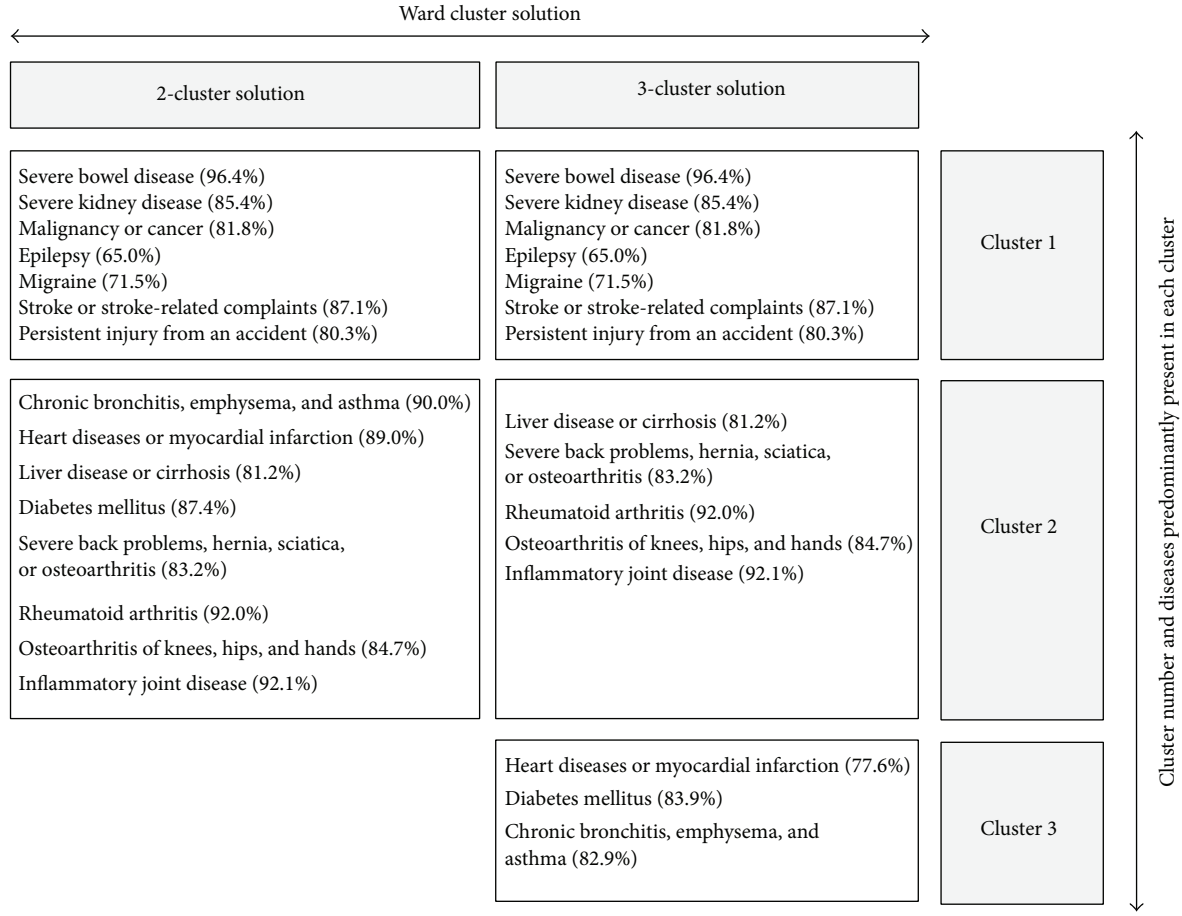


Figure 2: Description of identified clusters according to Ward's agglomerative hierarchical two- and three-cluster solution.

(62.4%) was found in cluster two, of which the majority of patients had liver disease, back problems, rheumatoid arthritis, osteoarthritis, and inflammatory joint disease. The lowest rate of PA guideline compliance (55.8%) was reported in patients with heart disease, respiratory disease, and diabetes mellitus. Compared with the average Dutch proportion of older adults (e.g., 68.6% [21, 22]), fewer people adhered to the Dutch physical activity guideline in all three clusters.

The main limitation of the present study is its cross-sectional design, which prevents the establishment of any causal inference. The quantity of missing values ranging from 17.5% (epilepsy) to 24.2% (inflammatory joint disease) in the self-reported chronic disease questionnaire formed a limitation. To obtain as much information as possible, we interpreted missing values as absence of the disease, and this may have caused the disease burden in this population to have been underestimated. As a control, patient characteristics were checked, revealing comparable results for patients with and without missing data on chronic diseases. Furthermore, the presence of chronic diseases was measured via a self-reported questionnaire, and one may well wonder whether a patient is able to report this information adequately. Informed consent issues prevented us from being able to check the self-reported data against data registered in electronic medical records (EMRs). Nevertheless, previous research on the SMILE cohort identified a high level of agreement between self-reports of chronic diseases and information from EMRs [23]. The high level of agreement between medical records and patients' reports in this large community-based cohort supports the accuracy of self-reported data used in answering the research question. The self-reported chronic disease questionnaire could be considered limited and without any assessment of disease severity, and this may have led to an under- or overestimation of the true burden of chronic diseases. Moreover, people tend to overestimate their physical activity level [24], which might have introduced another systematic bias. Also not considered were seasonal influences that could influence the amount of PA performed. Yet, the SQUASH questionnaire represents a reliable and valid measurement instrument for population samples [15]. Finally, while a measure of social desirability may also have influenced the patients' answers, the respondents remained anonymous to researchers and were assured that their information would not be reported to their general practitioner. Despite these limitations, this study is the first to examine the relationship between clusters of chronic diseases and physical activity.

The first analysis revealed two clusters for which no association with PA was detected. The clusters found were broad (representing at least seven diseases) and diverse in terms of types of the diseases embodied in each cluster. As

previous research had shown an inverse relationship between multimorbidity and PA, the question of which specific disease combinations are associated with PA remained unanswered. Therefore, the exploration was continued with the three-cluster solution and we found that only the initial second cluster had branched out into two new ones. The results of the three-cluster solution showed that cluster one remained unchanged and that heart disease, respiratory disease, and diabetes had separated from the original cluster two to form a third cluster. The relationship between the three-cluster solution and PA was significant. The third cluster had the lowest proportion of people who were compliant with the Dutch PA guideline. The highest proportion of people who were compliant was found in cluster two, which had a compliance proportion similar to cluster one.

As people in cluster three showed lower activity levels on average, it might be worthwhile to examine the diseases found in this cluster, namely, heart disease, respiratory disease, and diabetes mellitus. It may not be surprising that this combination of diseases formed a separate cluster given that they are highly prevalent diseases that have been shown to be interrelated. For example, Howard et al. [25] estimated that the relative risk of developing cardiovascular disease is two to eight times higher in people with diabetes mellitus compared with nondiabetics. The relationship between respiratory disease and cardiovascular disease seems to be related to systemic inflammation and chronic infections [26]. Systemic inflammation also seems to contribute to the triangle association as there seem to be increased inflammatory markers in diabetes mellitus and respiratory disorders. Reactive Oxygen Species (ROS) injure the airways and promote inflammation and are considered an underlying cause of insulin resistance. Moreover, all three diseases may be intimately intertwined because they share the same risk factors (e.g., smoking, obesity, hyperlipidaemia, and hypertension) [27].

The fact that the diseases in cluster three showed the lowest proportion of PA guideline compliance could be expected. The inverse relationship between cardiovascular disease, respiratory disease and diabetes mellitus, as individual disorders, and physical activity has been studied extensively [25–27].

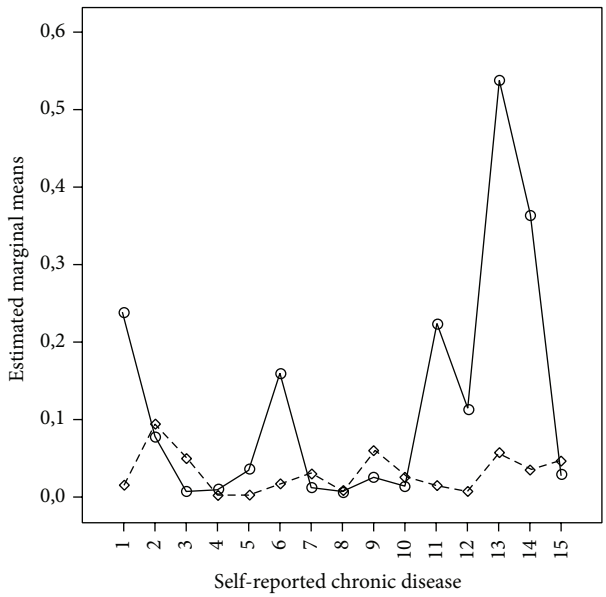
To our knowledge, only four studies have until now investigated the relationship between multimorbidity and PA [10, 11, 28, 29]. Three of these four studies found an inverse relationship between multimorbidity and physical activity levels [10, 11, 29]. The results of these studies concur with those presented by Hudon et al. [28] who reported that multimorbidity was not associated with physical activity levels. Measurement differences in the assessment of multimorbidity and PA challenge the comparability of results. First, regarding the estimation of chronic diseases, correspondence existed as all four studies used self-reported data and counted the number of chronic diseases. Nevertheless, the chronic diseases listed in the survey or questionnaire and the cut-off point of the disease count defining multimorbidity were dissimilar. Second, differences in PA measurement might have contributed to the variation observed in the results as physical activity is a complex and multidimensional dependent variable which makes population-based measurement difficult. Kaplan et al. [10] asked patients to report the number of times in the past month that they had taken part in recreational PA lasting ≥ 15 minutes. Similarly, Hudon et al. [28] measured PA by the number of recreational PA sessions of 20–30 minutes during the preceding three months. The PASE, an instrument that measures the level of physical activity for individuals aged 65 years and older, was used in the study of Autenrieth et al. [11]. The PASE is comprised of self-reported occupational, household, and leisure items over a one-week period. However, to reach sufficient content validity van Poppel et al. [30] recommended in 2010 (after the study of Kaplan et al. [10] and Hudon et al. [28] had been published, but before Autenrieth and colleagues started their investigation) that each questionnaire assessing total physical activity should at least measure duration and frequency in all settings (household, work, transport, recreation, and sport). Both the International Physical Activity Questionnaire (IPAQ) used by Cimarras-Otal et al. [29] and the Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH), which was used in this study, follow this recommendation. The IPAQ and the SQUASH questionnaires allow for a more detailed assessment as they include questions on activity frequency, duration, and intensity and make it possible to determine if a person meets the current recommendation for physical activity. It is important to emphasise that multimorbidity was classified into categories (0, 1, 2, and ≥3 diseases) in all four previously conducted studies. This study is the first which explores the relationship with PA using chronic disease clusters. Investigating the relationship between the number of chronic diseases and compliance with the Dutch PA guideline in the present SMILE cohort study revealed a statistically significant inverse relationship ($p = 0.004$). Although in the present study a cluster analysis was performed because contentwise it fitted our primary aim best, other data reduction methods and procedures are expected to reveal comparable groups of patients [31, 32].

In conclusion, this study adds to our knowledge of the relationship between multimorbidity and physical activity. In addition to the inverse relationship of the number of chronic diseases and PA, the present study showed that the cluster of patients with cardiovascular disease, respiratory disease, and/or diabetes type II reported the lowest physical activity levels. Belonging to a specific cluster of diseases does make a difference and it is important for general practitioners and physiotherapists to help especially patients with cardiovascular disease, respiratory disease, and/or diabetes to initiate and maintain appropriate physical activity levels. It seems worthwhile to further explore the relationship between multimorbidity clusters and outcomes like physical activity, because it helps to deliver more targeted and effective care for patients.

Appendices

A. Importance and Distribution of Each Chronic Disease in the Clustering

Figure 3 shows a plot of the cluster centroids with each disease being a cluster variable. These cluster centroids



Self-reported chronic disease[a]
(1) Chronic bronchitis, emphysema, and asthma
(2) Heart disease or myocardial infarction
(3) Severe bowel disease
(4) Liver disease or cirrhosis
(5) Severe kidney disease
(6) Diabetes mellitus
(7) Malignancy or cancer
(8) Epilepsy
(9) Migraine
(10) Stroke or stroke-related complaints
(11) Inflammatory joint disease
(12) Rheumatoid arthritis
(13) Osteoarthritis of knees, hips, and hands
(14) Severe back problems, hernia, sciatica, or osteoarthritis
(15) Persistent injury from an accident at home, in sports, school/work

[a]For the ease of presentation self-reported chronic diseases were listed as number 1 to number 15. The box describes which of the fifteen self-reported chronic diseases belongs to each disease code (1–15)

Figure 3: The proportion of patients as a function of chronic disease and cluster division.

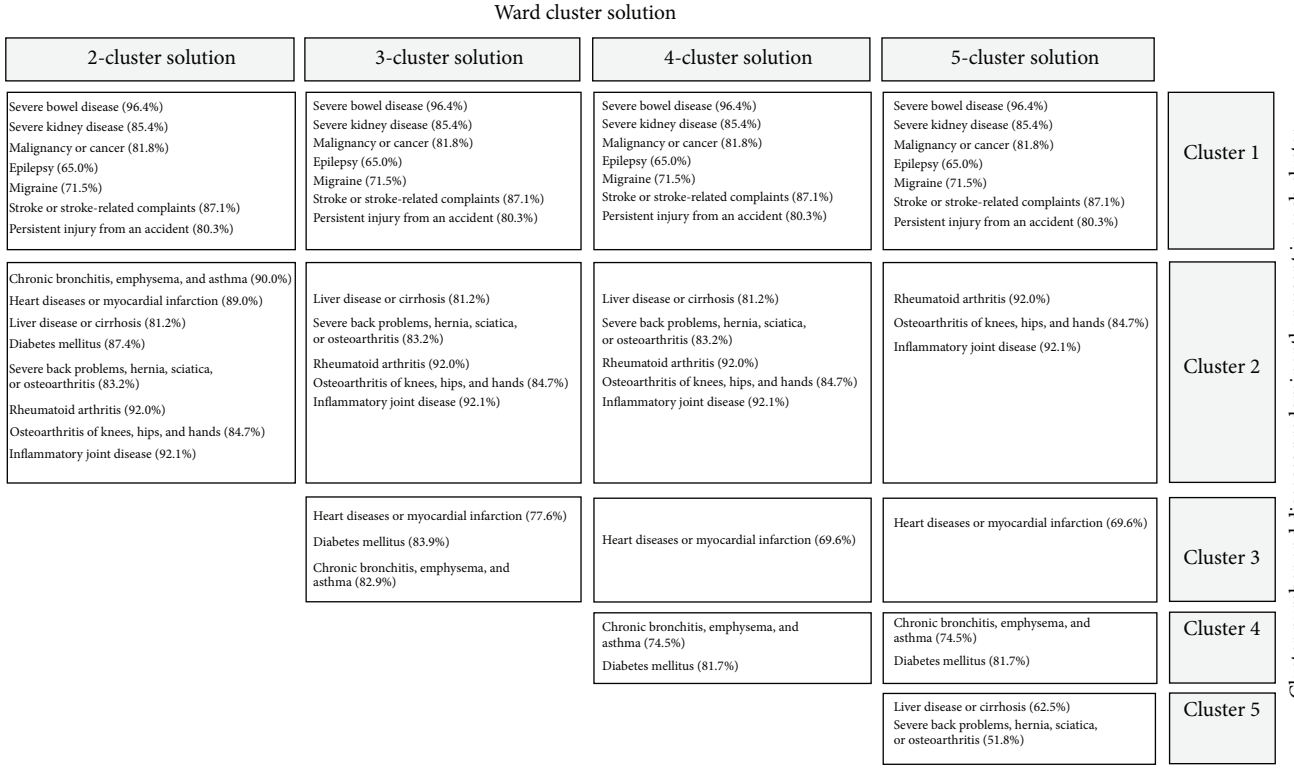


Figure 4: Description of identified clusters according to Ward's agglomerative hierarchical two-to-five-cluster solutions.

show for each chronic disease (1–15) and for each cluster (dotted and straight line) the proportion of patients (i.e., subjects who have the disease in question). To illustrate, the proportion of subjects with chronic bronchitis, emphysema, and asthma is higher in cluster two compared to cluster one. Moreover, based on these proportions one may identify which chronic diseases are most important in distinguishing between the two clusters of subjects. Clusters one and two differ predominantly with regard to the proportion of occurrence of chronic bronchitis, emphysema, and asthma (21.5% versus 1.6%, resp.); heart diseases or myocardial infarction (1.6% versus 19.8%, resp.); diabetes mellitus (1.4% versus 14.9%, resp.); inflammatory joint disease (1.2% versus 20.7%, resp.); osteoarthritis of knees, hips, and hands (5.8% versus 49.1%, resp.); and severe back problems, hernia, sciatica, or osteoarthritis (4.3% versus 31.9%, resp.).

B. Identified Clusters according to the Two-to-Five-Cluster Solution

See Figure 4.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Research Article

Cognitive Impairment, Depression, and Cooccurrence of Both among the Elderly in Panama: Differential Associations with Multimorbidity and Functional Limitations

Alcibiades E. Villarreal,[1,2] Shantal Grajales,[1] Lineth Lopez,[3] Gabrielle B. Britton,[1] and Panama Aging Research Initiative[1]

[1]*Centro de Neurociencias y Unidad de Investigación Clínica, Instituto de Investigaciones Científicas y Servicios de Alta Tecnología (INDICASAT AIP), Ciudad del Saber, Panama*
[2]*Department of Biotechnology, Acharya Nagarjuna University, Guntur 522 510, India*
[3]*Department of Hematology, Complejo Hospitalario Dr. Arnulfo Arias Madrid de la Caja de Seguro Social, Panama City, Panama*

Correspondence should be addressed to Gabrielle B. Britton; gbritton@indicasat.org.pa

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Cognitive impairment and depression are common mental health problems among the elderly, although few studies have examined their cooccurrence in older adults in Latin America. The purpose of this study was to examine cognitive impairment, depression, and cooccurrence of the two conditions and associated factors in a sample of older adults in Panama. This study included 304 community-dwelling elderly (≥65 years) individuals. Participants underwent a clinical interview and assessments of cognitive function by the Minimental State Examination and depressive symptoms by the Geriatric Depression Scale. Limitations in basic (BADL) and instrumental (IADL) activities in daily living and the presence of chronic illnesses were recorded. Multinomial regression analysis revealed that cooccurrence of cognitive impairment and depressive symptoms was explained by increasing age (OR: 3.2, 95% CI: 1.20, 8.30), low education (OR: 3.3, 95% CI: 1.33, 8.38), having four or more chronic conditions (OR: 11.5, 95% CI: 2.84, 46.63), and BADL limitations (OR: 5.0, 95% CI: 1.26, 19.68). Less education and limitations in BADL and IADL increased the odds of cognitive impairment alone, while less education and three or more chronic conditions increased the odds of depression alone. These findings underscore the relevance of assessing cognitive impairment in the elderly as part of a long-term approach to managing depression and vice versa.

1. Introduction

Latin America and Caribbean (LAC) region is experiencing one of the fastest rates of population aging [1]. Population-based studies confirm that rates of common age-related chronic illnesses such as dementia and mild cognitive impairment (MCI) are similar to those of developed countries [2, 3], and cross-sectional surveys from a multicenter cohort [4] revealed high prevalence of depression (21.5–33.2%) across six cities in the region [5]. These studies reveal concomitant rates of modifiable risk factors for depression and cognitive impairment such as diabetes, cardiovascular disease, and illiteracy. Consequently, the burden of age-related disorders is expected to be especially high in LAC countries in the coming decades.

Older adults are disproportionately affected by several chronic conditions. Among the elderly, chronic conditions such as cognitive impairment and depression are interrelated and often coexist [6–9], and at least one report confirms that each condition alone contributes to the increase of an older person's risk for mortality [10]. Recent studies have shown that subjects with MCI present more depressive symptoms compared with those without cognitive impairment [7, 11, 12]. Additionally, in a study of community-dwelling adults in Spain aged 65 years and older, the coexistence of cognitive impairment and depression was found to be associated with

chronic illnesses and impairment in activities of daily living [13]. In that study, the primary medical conditions associated with coexisting cognitive impairment and depression included dementia, congestive heart failure, cerebrovascular disease, and diabetes, most of which were distinct from those associated with cognitive impairment alone or depression alone [13]. In elderly subjects, the convergence of depressive symptoms with other chronic conditions may represent a barrier to diagnosis and subsequent treatment of depression [14]. Taken together, these results suggest that, in the geriatric population with cognitive decline, depression, or both conditions coexisting, individuals should be screened for other conditions such as chronic diseases [13, 15].

Studies have shown that depression is associated also with functional limitations during aging, and this relationship is influenced by physical limitations that arise as a product of chronic illness comorbidity, namely, stroke, respiratory problems, cancer, and diabetes [14, 16]. Besides depression and comorbidities, functional disability can be significantly influenced by cognitive impairment. An early study demonstrated that cognitive status can be a predictor of functional status independently of whether individuals present psychiatric disorders [17]. Since then, longitudinal studies have shown that difficulties in the performance of activities of daily living are greater in subjects with cognitive impairment, and, further, cognitive decline is correlated with declines in activities of daily living performance over time [18]. More studies are needed to establish the combined effects of cognitive decline and depression on chronic conditions and limitations in activities of daily living.

In the present study, we conducted the first examination of depressive symptoms, cognitive impairment, or both conditions coexisting and their association with functional disability and multimorbidity in a sample of elderly individuals in Panama, an upper middle-income country in the LAC region. Although Panama is advancing toward an aged society [19], there is lack of research focused on age-related chronic conditions [20]. Age-related health problems are complicated by high rates of poverty, low education, and lack of access to health care, which affect vulnerable populations such as the elderly disproportionately. Also, systematic screening of cognitive function and depression is lacking in primary and community-based health care for adults despite evidence of its utility in predicting mortality [10]. Therefore, research regarding potentially modifiable risk factors for cognitive impairment and depressive symptoms in older adults could be important for developing effective geriatric health care public initiatives. Based on previous reports [7, 13], we hypothesized that cognitive function and depressive symptoms would be associated independently and in combination with functional disability and chronic illness comorbidity.

2. Methods

2.1. Participants. Data from this study came from the Panama Aging Research Initiative (PARI) study, the first-ever study of Panamanian aging. PARI participants were recruited from the outpatient geriatric services of the largest public hospital of the Social Security (CSS) located in Panama, the capital city of Panama. Inclusion criteria included being 65 years or older, willingness to participate in the baseline interview and three follow-up visits over the course of 12–18 months, and provision of informed consent. Exclusion criteria included any medical condition that required hospitalization and participation in an ongoing clinical study at the time of enrollment.

The present report constitutes an analysis of the data collected during the baseline interview and 3-to-6-month (M = 4.5 months, SD = 1.9) follow-up assessment of cognitive function and depressive symptoms. At baseline, each participant underwent a physical exam and clinical interview and responded to items regarding demographic factors, medical conditions, and functional status. Interviewers included physicians, medical students, and graduate students. In total, 423 participants were enrolled and 326 community-dwelling (noninstitutionalized) persons completed the baseline interview and follow-up assessments of cognitive function and depressive symptoms. Of these, 15 participants were excluded because they were illiterate and seven were excluded due to serious mental or physical disabilities. The present report includes data from 304 participants.

An analysis comparing the 97 participants who did not return to complete the follow-up assessment with those who did revealed that a greater proportion of those who did not return were older (80+ years of age, 58.9% versus 43.9%) and more likely to have at least one BADL (71.6% versus 52.1%) and at least one IADL (81.1% versus 68.0%) limitation than those who returned.

2.2. Ethics Statement. The study protocol was approved by the National Bioethics Committee of the Instituto Conmemorativo Gorgas de Estudios de la Salud and the Institutional Bioethics Committee of the CSS. Each participant (or informant/caregiver) signed informed consent forms and patient confidentiality was not breached in accordance with the Declaration of Helsinki (1964).

2.3. Variables and Instruments. Participants underwent an interview, physical exam, clinical interview, and nonfasting blood draw. The 30-item Spanish version of the Minimental State Examination (MMSE) was used as a measure of global cognition [21]. The reverse spelling of the word "world" in the attention item was used instead of the backward serial sevens. MMSE scores were adjusted for age and level of education [22]. Two categories were defined using the MMSE test scores: cognitively impaired (<24) and unimpaired (≥24). Depressive symptoms were assessed with the Spanish version of the 30-item Geriatric Depression Scale (GDS-30) [23, 24]. The instrument was applied by the investigator reading the items out loud and asking the participants to respond to each of the items. A cut-off score of ≥11 on the GDS was used to classify depressed individuals. Thus, in this report, the term *depression* is used to describe those participants who scored ≥11 on the GDS.

Chronic conditions were recorded through self-report and were assessed by answers to questions regarding physician diagnosis and current medications. Subjects were asked, "Has a doctor or nurse ever told you that you had…?" The following conditions were assessed: hypertension, coronary

Table 1: Frequency of cognitive impairment, depressive symptoms, and the cooccurrence of both.

	No depressive symptoms (GDS < 11) Number (%) 95% CI	Depressive symptoms (GDS ≥ 11) Number (%) 95% CI	Total Number (%) 95% CI
No cognitive impairment (MMSE ≥ 24)	150 (49.3) 43.8, 54.9	55 (18.1) 14.2, 22.8	205 (67.4) 62.0, 72.5
Cognitive impairment (MMSE < 24)	65 (21.4) 17.1, 26.3	34 (11.2) 8.1, 15.2	99 (32.6) 27.6, 38.0
Total	215 (70.7) 65.4, 75.6	89 (29.3) 24.5, 34.6	304 (100%)

GDS: Geriatric Depression Scale (30-item); MMSE: Minimental State Examination.

heart disease, diabetes, stroke, cancer, chronic lung disease, and arthritis. The number of chronic diseases was reported as a categorical disease indicator of whether a participant had at least one, two, three, or four or more conditions (the smallest two categories were grouped due to small numbers). Participants were asked also to report whether they smoked currently or had ever smoked, and responses were dichotomized as "current/past smoker" versus "never smoked."

Performance in activities of daily living was evaluated through self-report. Subjects were asked to indicate whether they had any difficulty performing the following seven BADL: transferring, bathing, dressing, grooming, toileting, feeding, and continence. Likewise, disability in seven IADL was evaluated: leaving the home independently in public or private transportation, preparing a meal, using a telephone, grocery shopping, performing basic house chores (housekeeping, laundry), handling money, and taking medications. IADL scores were corrected in cases where the individual had never performed a task. A score of zero (0) was assigned when the subject was able to perform the task without difficulty; a score of one (1) was assigned when the subject was able to perform the task with difficulty or was unable to perform the task. Limitations in BADL and IADL were dichotomized into "none" versus "at least one."

2.4. Statistical Analysis. Analyses were performed using SPSS 21.0 statistical software. Descriptive statistics (frequency and percentage) were computed for all variables across groups and categorical differences were examined using chi square analysis. We applied multinomial logistic regression to identify factors associated with three outcomes, cognitive impairment alone, depression alone, and coexisting cognitive impairment and depression, using the absence of cognitive impairment and depression as the reference category. Odds ratios (OR) and 95% confidence intervals (95% CI) are presented in each case. Statistical significance was set at $p < .05$.

3. Results

3.1. Demographics of the Sample. Table 1 summarizes the distribution of cognitive impairment, depression, and cooccurrence of the two in the study sample. According to the MMSE performance, 21.4% (95% CI: 17.1, 26.3) of participants were found to have cognitive impairment without depression and 11.2% (95% CI: 8.1, 15.2) were classified as having both cognitive impairment and depression. According to the GDS, 18.1% (95% CI: 14.2, 22.8) of participants were found to have depression without cognitive impairment. Notably, almost half (49.3%; 95% CI: 43.8, 54.9) of participants were classified as having neither cognitive impairment nor depression. Average MMSE score was 23.9 (SD = 5.6) and average GDS score was 8.0 (SD = 5.7). MMSE and GDS scores were significantly correlated ($r = -0.13$, $p = .024$), indicating that better cognitive function was associated with less depression symptomatology.

In this study, we evaluated the demographic factors, number of chronic conditions, and presence of functional limitations as a function of cognitive status, depression, and the cooccurrence of both conditions (Table 2). Participant ages ranged from 65 to 102 years with a mean age of 78.2 (SD = 7.5). Approximately 66% of participants were female ($n = 200$) and approximately half the sample (52.6%) completed primary education or less. Participants reported an average of 1.9 (SD = 1.0) chronic illnesses. The oldest participants (≥80 years) presented more cognitive impairment and cooccurring cognitive impairment and depression than younger participants. Less educated participants also presented more cognitive impairment, depression, and cooccurring cognitive impairment and depression than participants whose schooling extended beyond primary school. Participants with four chronic conditions or more presented more cooccurring depression and cognitive impairment and depression alone than those with fewer chronic conditions. With regard to functional limitations, participants with at least one BADL limitation or one IADL limitation were more likely to present cognitive impairment alone or cooccurring cognitive impairment and depression than those with no limitations.

3.2. Factors Associated with Cognitive Impairment, Depressive Symptoms, and Both Conditions Coexisting. Multinomial logistic regression analyses confirmed significant associations of age, education, number of chronic conditions, and BADL limitations with cooccurring cognitive impairment and depression (Table 3). The oldest participants (≥80 years) were 3.2 times more likely (95% CI: 1.20, 8.30) to be classified

Table 2: Comparisons of sociodemographic factors, multimorbidity, and limitations in BADL and IADL among participants with neither cognitive impairment nor depression (n = 150), cognitive impairment only (n = 65), depression only (n = 55), and cooccurring cognitive impairment and depression (n = 34).

	Neither cognitive impairment nor depression	Cognitive impairment	Depression	Cooccurring cognitive impairment and depression	χ^2	p
	Number (%)	Number (%)	Number (%)	Number (%)		
Gender						
Male	60 (57.7)	20 (19.2)	14 (13.5)	10 (9.6)	4.80	.187
Female	90 (45.0)	45 (22.5)	41 (20.5)	24 (12.0)		
Age						
65–79 years	98 (55.7)	31 (17.6)	38 (21.6)	9 (5.1)	22.78	<.001
80+ years	52 (40.6)	34 (26.6)	17 (13.3)	25 (19.5)		
Marital status						
Widowed/single/divorced	72 (47.1)	35 (22.9)	26 (17.0)	20 (13.1)	1.83	.608
Married/partnered	78 (51.7)	30 (19.9)	29 (19.2)	14 (9.3)		
Education						
≤6 years	60 (37.5)	45 (28.1)	32 (20.0)	23 (14.4)	20.54	<.001
>6 years	90 (62.5)	20 (13.9)	23 (16.0)	11 (7.6)		
Smoking						
Never smoked	102 (49.3)	47 (22.7)	36 (17.4)	22 (10.6)	0.88	.828
Current/past smoker	48 (49.5)	18 (18.6)	19 (19.6)	12 (12.4)		
Chronic conditions						
0-1	47 (61.0)	24 (31.2)	2 (2.6)	4 (5.2)		
2	60 (60.0)	21 (21.0)	12 (12.0)	7 (7.0)	69.86	<.001
3	31 (43.7)	15 (21.1)	16 (22.5)	9 (12.7)		
4+	12 (21.4)	5 (8.9)	25 (44.6)	14 (25.0)		
BADL limitations						
None	76 (75.2)	4 (4.0)	18 (17.8)	3 (3.0)	51.17	<.001
At least one	74 (36.5)	61 (30.0)	37 (18.2)	31 (15.3)		
IADL limitations						
None	70 (66.0)	6 (5.7)	26 (24.5)	4 (3.8)	39.72	<.001
At least one	80 (40.4)	59 (29.8)	29 (14.6)	30 (15.2)		

BADL: basic activities of daily living; IADL: instrumental activities of daily living.

as cognitively impaired and depressed as younger participants. Likewise, those with less schooling (≤6 years) were 3.3 times more likely (95% CI: 1.33, 8.38) to be cognitively impaired and depressed compared to those whose schooling extended beyond primary school. In addition, having four or more chronic illnesses (OR: 11.5, 95% CI: 2.84, 46.63) and at least one BADL limitation (OR: 5.0, 95% CI: 1.26, 19.68) was associated with greater likelihood of cooccurring cognitive impairment and depression. After fitting the multinomial logistic regression, lower education levels remained significantly associated with cognitive impairment alone (OR: 2.8, 95% CI: 1.39, 5.72) and depression alone (OR: 2.4, 95% CI: 1.13, 4.98), but age was not associated with either condition alone. Lastly, functional limitations in at least one BADL or IADL remained significantly associated with cognitive impairment (ps < .02) but only marginally significant for depression alone. Suffering three or more chronic conditions was significantly associated with depression (ps < .003), but multimorbidity was not associated with cognitive impairment alone. Gender, marital status, and smoking status were not significantly associated with any condition.

4. Discussion

In the present study, we assessed cognitive impairment, depression, and cooccurrence of the two conditions and related factors in subjects aged 65 and older. Significant associations were observed between education and BADL and IADL limitations and cognitive impairment alone, while educational level and multimorbidity were associated with depression alone. The factors specifically related to coexisting cognitive impairment and depression were low education, having four or more chronic illnesses, and having at least one limitation in BADL. These results are consistent with previous studies that show that poor cognitive function and depressive symptoms cooccur among the community-dwelling elderly

Table 3: Multinomial logistic regression model predicting the effect of functional limitations and multimorbidity on cognitive impairment, depression, and both of them coexisting, adjusting for sociodemographic factors and smoking history.

Characteristic	Cognitive impairment ($n = 65$)		Depression ($n = 55$)		Cognitive impairment and depression ($n = 34$)	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Gender						
Female	1.0 (.43, 2.48)	.941	1.9 (.74, 4.82)	.184	1.4 (.46, 4.56)	.533
Male	—		—		—	
Age						
80+ years	1.1 (.52, 2.13)	.879	.9 (.40, 2.04)	.804	3.2 (1.20, 8.30)	.020
65–79 years	—		—		—	
Marital status						
Widowed/single/divorced	1.4 (.66, 2.97)	.381	1.1 (.50, 2.49)	.782	1.9 (.69, 5.15)	.214
Married/partnered	—		—		—	
Education						
≤6 years	2.8 (1.39, 5.72)	.004	2.4 (1.13, 4.98)	.022	3.3 (1.33, 8.38)	.010
>6 years	—		—		—	
Smoking						
Current/past smoker	.7 (.30, 1.55)	.354	1.1 (.47, 2.43)	.877	1.0 (.38, 2.80)	.962
Never smoked	—		—		—	
Chronic conditions						
0-1	—		—		—	
2	.6 (.26, 1.42)	.252	4.5 (.93, 21.43)	.062	1.0 (.26, 4.17)	.950
3	.6 (.25, 1.55)	.307	11.8 (2.43, 56.81)	.002	2.3 (.59, 8.77)	.235
4+	.6 (.17, 2.04)	.396	53.2 (10.54, 268.19)	<.001	11.5 (2.84, 46.63)	.001
BADL limitations						
At least one	9.6 (3.07, 29.74)	<.001	2.3 (.95, 5.42)	.064	5.0 (1.26, 19.68)	.022
None	—		—		—	
IADL limitations						
At least one	3.4 (1.25, 9.53)	.017	.4 (.17, 1.05)	.063	1.4 (.39, 5.26)	.593
None	—		—		—	

and are associated with chronic illnesses and impairment in activities of daily living [6, 7, 13]. Although we did not examine the association between cognitive impairment and depression and individual chronic illnesses, we showed that suffering three or more chronic illnesses was associated with the greatest likelihood of depression alone whereas suffering four or more chronic illnesses was associated with coexisting cognitive impairment and depression. In contrast, no significant association was found between chronic illnesses and cognitive impairment alone. Depression in the elderly has been shown to be associated with nonpsychiatric hospitalization, longer length of hospital stay, and higher mortality [25–27]. Importantly, the combined impact of cognitive impairment and depression has been shown to increase the risk for mortality relative to either condition alone [10].

Our results also confirm that depressive symptomatology is correlated with cognitive impairment. In a study in Japanese individuals aged 65 years and older, cognitive impairment was more prevalent in individuals with depression, and, conversely, individuals with mild cognitive impairment were more likely to develop depression [7]. Likewise, in a population-based study of elderly individuals aged 60 years and older in Mexico examining cognitive impairment and depression, assessed with the MMSE and GDS, respectively, cognitive impairment was associated with depression as well as with being older than 75 years, being unmarried, and having less education [6]. In the same study, depression was associated with the same factors as cognitive impairment in addition to being female, but the study did not examine the factors associated with the combination of cognitive impairment and depression. Although most studies in Latin America have found that women are marginally more at risk for cognitive impairment and depression, we did not find associations between cognitive impairment or depression and gender. However, low educational achievement, which is often linked to poverty or lower socioeconomic status, showed a strong association with cognitive impairment, depression, and the cooccurrence of both conditions. These results are consistent with reports of associations between low levels of education with poorer mental health and increased risk of disease comorbidity [28] and suggest that individuals in Panama whose studies extend beyond primary school are more likely to age in better health. This finding is particularly relevant in Panama where the average educational level is 9.2 years [29].

Numerous studies have confirmed an association between increasing depression and disability [7, 13, 30, 31]. Disability in the elderly, characterized by the loss of ability to perform activities of daily living, is associated with significant burdens, including increased risk of hospitalization, institutionalization, and mortality [32, 33]. Moreover, different chronic conditions such as diabetes, mild cognitive impairment, dementia, and cerebrovascular events, such as stroke, affect the elderly disproportionately relative to the other conditions [13, 34]. Population-based studies in seven Latin American cities indicate that the proportion of community-dwelling adults aged 60 years and older reporting any BADL or IADL disability is approximately 19%, and 44% had more than one chronic condition [30], a finding which underscores the burden of disease and disability in the region.

An important limitation of the present study is the nature of the sample (outpatient-based) and the selection bias that resulted from the loss of older and more impaired subjects, and thus our results most likely underestimate the extent of cognitive impairment and depression in the elderly population of Panama. Another limitation is that self-reported disability and chronic illnesses may be affected by sociocultural factors, and so comparisons of our results with those of other LAC countries should be made with caution. Although evidence suggests that self-report provides accurate estimates of disability and disease comorbidity [35] and predicts mortality and other clinical health measures [36], recent evidence suggests that individuals of lower socioeconomic status show less reliable self-assessments of health [37]. Lastly, our data were obtained over a short time span and do not address the relationship between multimorbidity and progression of cognitive decline and depressive symptoms. Each of these limitations is being addressed in ongoing studies. Study strengths include providing the first report of cognitive impairment and depression in the elderly in Panama, as well as the use of detailed clinical interviews to record the presence of chronic illnesses and other patient information and the use of multiple items for assessing BADL and IADL.

5. Conclusions

Previous studies have shown that in late life coexisting depression and cognitive impairment may contribute to an elderly person's vulnerability. To our knowledge, ours is the first report from Panama of coexisting cognitive impairment and depressive symptomatology in community-dwelling adults of any age. Our results add to the existing knowledge regarding the presence of cognitive impairment and geriatric depression and their associated clinical factors, namely, multimorbidity and limitations in activities of daily living. Importantly, cooccurrence of cognitive impairment and depression complicates treatment in the elderly, and thus assessments of cognitive impairment in this population should be part of a long-term approach to managing depression and vice versa. The current study supports the hypothesis that multimorbidity particularly affects elderly individuals with depression alone and with coexisting depression and cognitive impairment and sets the stage for additional studies examining the long-term outcomes in follow-up studies.

Conflict of Interests

The authors declare they have no conflict of interests.

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Research Article

Defining Multimorbidity: From English to Portuguese Using a Delphi Technique

Filipe Prazeres,[1,2] Luiz Miguel Santiago,[1,3] and José Augusto Simões[1,4]

[1] *Faculdade de Ciências da Saúde, Universidade da Beira Interior, 6200-506 Covilhã, Portugal*
[2] *Centro de Saúde de Aveiro, 3810-042 Aveiro, Portugal*
[3] *USF Topázio, 3020-171 Coimbra, Portugal*
[4] *USF Marquês de Marialva, 3060-123 Cantanhede, Portugal*

Correspondence should be addressed to Filipe Prazeres; filipeprazeresmd@gmail.com

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Objective. To translate the European General Practice Research Network multimorbidity definition according to Portuguese cultural and linguistic features. *Methods*. Similar to the process completed in several other European countries, a forward and backward translation of the English multimorbidity definition using the Delphi technique was performed in Portugal. *Results*. Twenty-three general practitioners (GPs)—14 males and 9 females—agreed to form the Portuguese expert panel for the Delphi process (59% acceptance rate). The Portuguese definition of multimorbidity was achieved after two Delphi rounds with a mean (SD) consensus score for final round of 8.43/9 (0.73). *Conclusion*. With this paper the definition of multimorbidity is now available in a new language—Portuguese. Its availability in the local language will raise Portuguese GPs' awareness about multimorbidity and allow future national and international research. The operationalization of the definition will allow an easier identification of patients with multimorbidity.

1. Introduction

Clinicians working in the primary health care context, namely, family physicians and general practitioners (GPs), deal with the broad spectrum of conditions affecting each individual seeking a medical consultation. In this setting, most of the time it is not possible to pinpoint an index disease, nor is it useful for the patient's care [1]. Therein lies the main difference between comorbidity and multimorbidity; the former always involves the presence of an index disease [2]. Thus, the majority of GP visits comprise individuals with multimorbidity [3]. The most frequent measure of multimorbidity is the presence of 2 or more chronic diseases in the same person [4]. Although this is a useful operational definition, the construct of multimorbidity is still difficult to define in clinical terms [5]. Recently, after a systematic literature review, the European General Practice Research Network published a comprehensive definition which states that "multimorbidity is defined as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor. Any biopsychosocial factor, any somatic risk factor, the social network, the burden of diseases, the health care consumption, and the patient's coping strategies may function as modifiers (of the effects of multimorbidity). Multimorbidity may modify the health outcomes and lead to an increased disability or a decreased quality of life or frailty" [6]. This definition aims to be especially useful in long term care and in family medicine settings [6] and at the same time to be valid for future collaborative research [7]. For this last purpose, it has been translated into ten European languages [7]. The Portuguese language was not one of them.

In Portugal, the 40-year history of family medicine led to the recognition of its importance in the country's health care delivery [8]. Multimorbidity is present in around 70% of the adult patients attending primary care in Portugal [9], and this high prevalence will produce significant difficulties in the provision of medical care. Using a definition of multimorbidity in the country's own language will standardize the

Table 1: Characteristics of the expert panel.

	Portuguese translation ($n = 23$)	Global average of previous translations [7] ($n = 229$)	P value
Males, %	60.87	50.69	0.51*
Mean (SD) age, years	45.78 (12.82)	48.26	0.36†
Mean (SD) years of practice	18.09 (13.28)	18.82	0.79†
Mean (SD) number of English publications	6.13 (7.12)	5.91	0.88†
Mean (SD) number of other publications	15.09 (15.24)	20.45	0.11†

*Fisher's exact test.
†Student's t-test.

identification of multimorbid patients while simultaneously enabling future collaborative projects as well as addressing more effectively this overwhelming medical problem.

It is expected that this definition will have a broad suitability to other Portuguese language settings and countries. The British Council's report "Languages for the Future" [10] identifies Portuguese as one of the ten languages most vital to UK over the next 20 years. With approximately 203 million speakers, Portuguese is the sixth most spoken language in the world [10], the third most spoken language in the Western Hemisphere, and the first most spoken language in the Southern Hemisphere [11].

In this study, the authors aimed to translate the English multimorbidity definition according to Portuguese cultural and linguistic features using a forward-backward translation by a Delphi technique.

2. Materials and Methods

Similar to the process completed in Bosnia, Bulgaria, Croatia, France, Germany, Greece, Italy, Poland, and Spain [7], a forward and backward translation of the English multimorbidity definition [6] using the Delphi technique was performed in Portugal. This technique is easily adapted to reach a consensus in a variety of issues [12], including medical research [13].

The first phase involved translating the definition from English to Portuguese (forward translation). This was done by a team of one official translator and one physician; both were native Portuguese speakers.

In the next phase the Delphi process was implemented. Aiming at a sample size between 10 to 30 national expert GPs as recommended by the European General Practice Research Network [7], 39 possible participants were individually contacted by email to receive the original English multimorbidity definition and its translation into Portuguese. GPs were selected on the basis of having a Portuguese nationality, being fluent in English (understanding/speaking/writing), being involved in clinical practice, in research, and/or in teaching activities, and having the willingness to dedicate the time to this method of discussion. The expert panel was requested to rate their level of agreement with the Portuguese translation on a Likert-type scale ranging from 1 = "absolutely no agreement" to 9 = "full agreement." If a rating less than 7 was given it was mandatory to justify the reasons for that evaluation. Consensus was defined as at least 70% of the GPs rating 7 or above the Portuguese definition. If a consensus was not reached in the first round, the expert panel's remarks were compiled into a unified translation, and a subsequent round of assessment was followed in the same way as for the first one. This process was repeated until a consensual translation was found. The participating GPs' characteristics (gender, age, years of practice, number of English publications, and number of other publications) were collected by a self-administered questionnaire conducted through email.

When a consensual Portuguese translation was reached it was submitted to a Portuguese linguist from the University of Coimbra (Portugal) for validation.

The final phase involved translating the consensual definition in Portuguese to English (backward blind translation). This was done by a team of one official translator (native English speaker) and one physician. They had no previous knowledge of the original definition. Subsequently, the authors of the study compared the back-translated version with its original version for linguistic congruence and cultural relevancy.

As no patient was involved in the study, no formal ethics approval was necessary. Consent was inferred by participants' completion of the survey.

A descriptive analysis was performed and both Fisher's exact test and Student's t-test were used to compare the current study's expert panel with the panel of the previous translations. P values <0.05 were considered statistically significant.

3. Results

Twenty-three GPs (14 males and 9 females) agreed to form the Portuguese expert panel for the Delphi process (59% acceptance rate). All members of the expert panel satisfied the inclusion criteria. The profile of the Portuguese GPs did not differ significantly from that of the previous translations [7] (Table 1).

The Portuguese definition of multimorbidity was achieved after two Delphi rounds with a mean (SD) consensus score for final round of 8.43 (0.73). Only one expert rated the forward translation below 7 (95.7% approval rate). The expert panel produced 43 comments in total. The terms which originated remarks were "burden of disease" and "health outcomes." Minor grammatical annotations were

Table 2: Portuguese final translation and the backward translation.

Portuguese final version	Portuguese final version translated into English
A multimorbilidade é definida como qualquer combinação de uma doença crónica com pelo menos uma outra doença (aguda ou crónica), ou com um fator biopsicossocial (associado ou não), ou com um fator de risco somático.	Multimorbidity is defined as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor.
Qualquer fator biopsicossocial, qualquer fator de risco somático, a rede social, a carga das doenças, o consumo de cuidados de saúde e as estratégias de adaptação do doente podem funcionar como modificadores (dos efeitos da multimorbilidade).	Any biopsychosocial factor, any somatic risk factor, the social network, the burden of diseases, the health care consumption, and the patient's coping strategies may function as modifiers (of the effects of multimorbidity).
A multimorbilidade pode modificar os resultados em saúde e levar a um aumento da incapacidade, à diminuição da qualidade de vida ou à fragilidade.	Multimorbidity may modify the health outcomes and lead to an increased disability or a decreased quality of life or frailty.

frequently suggested, recorded, and incorporated into the definition.

Table 2 shows the final consensual Portuguese definition of multimorbidity and the backward translation as accepted by the authors of this study. No changes were found in comparison with the original English definition.

4. Discussion

With the current study the translation of the English multimorbidity definition into Portuguese was achieved.

No universal guidelines exist on how to apply the Delphi technique [14]. Some authors have even stated that the advantages and disadvantages of this method are equally weighted [12]. Nonetheless, with methodological precision and research rigour the Delphi technique can be properly and efficiently used [14]. In the current study, the successful methodology employed in previous translations was adopted.

The Portuguese translation was the end result of the reviews of an expert panel of practicing GPs that verified that the terms expressed in the definition complied with the ones in use in Portugal. The Portuguese panel had similar characteristics to the average of the panels of the previous translations [7]. This ratifies the thorough selection process used to choose the GP experts in this study. The challenged terms were the same as in the other countries' translations; this may be explained by the fact that those expressions are less commonly used on a daily basis. In the second round this was overcome and the backward translation did not reveal any changes in comparison with the original English definition.

5. Conclusion

With this paper the definition of multimorbidity is now available in a new language—Portuguese. Its availability in the local language will raise Portuguese GPs' awareness about multimorbidity and allow future national and international research. The operationalization of the definition will allow an easier identification of patients with multimorbidity.

Ethical Approval

As no patient was involved in the study, no formal ethics approval was deemed necessary.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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