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Multimorbidity prevalence and patterns at the baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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Abstract

Background: To identify multimorbidity patterns, by sex, according to sociodemographic and lifestyle in ELSA-Brasil.

Methods: Cross-sectional study with 14,516 participants from ELSA-Brasil (2008–2010). Fuzzy c-means was used to identify multimorbidity patterns of 2+ chronic morbidities, where the consequent morbidity had to occur in at least 5% of all cases. Association rule (O/E≥1.5) was used to identify co-occurrence of morbidities, in each cluster, by sociodemographic and lifestyle factors.

Results: The prevalence of multimorbidity was higher in women (73.7%) compared to men (65.3%). Among women, cluster 1 was characterized by hypertension/diabetes (13.2%); cluster 2 had no overrepresented morbidity; and cluster 3 all participants had kidney disease. Among men, cluster 1 was characterized by cirrhosis/hepatitis/obesity; cluster 2, most combinations included kidney disease/migraine (6.6%); cluster 3, no pattern reached association ratio; cluster 4 predominated co-occurrence of hypertension/rheumatic fever, and hypertension/dyslipidemia; cluster 5 predominated diabetes and obesity, and combinations with hypertension (8.8%); and cluster 6 presented combinations of diabetes/hypertension/heart attack/angina/heart failure. Clusters were characterized by higher prevalence of adults, married and participants with university degrees.

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Conclusion: Hypertension/diabetes/obesity were highly co-occurred, in both sexes. Yet, for men, morbidities like cirrhosis/hepatitis were commonly clustered with obesity and diabetes; and kidney disease was commonly clustered with migraine and common mental disorders. The study advances in understanding multimorbidity patterns, benefiting simultaneously or gradually prevention of diseases and multidisciplinary care responses.

Keywords
Multimorbidity, chronic disease, adult, older adult

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Introduction

The accelerated population aging is accompanied by an increase of chronic non-communicable diseases burden and long-term health conditions, which require continuous care management and challenge health systems and economies to mitigate the effects of development and progression of these diseases.[1,2] In this scenario, multimorbidity, defined as the simultaneous occurrence of two or more chronic diseases in the same individual,[3] is a new emerging epidemic.[4]

The epidemiology of multimorbidity and associated factors have been explored mainly in the last decade,[5,6] indicating that it is not an exclusive phenomenon of the older adults. Although there is a relationship between advancing age and accumulating chronic diseases,[7,8] younger adults also live with multiple diseases.[7,9,10] Heterogeneity in terms of definition and sample lead to differences in prevalence estimates and hinder comparisons of multimorbidity results between populations.[5,11] However, this condition is already predominantly in high income countries (HICs) and is increasing in low-and middle-income countries (LMICs).[2,11,12]

Multimorbidity has profound implications for individuals, families, and societies, its management is complicated, and its occurrence is associated with greater use of health services,[2,5,13] worse clinical outcomes, such as hospitalization, disability, and functional decline,[5,13,14] greater risk of death and premature death.[15,16] It is also related to reduced quality of life[17] and catastrophic health expenditures,[13,18] but its impact is even more pronounced in LMICs. These countries suffer with a triple burden of disease in contexts of extreme social inequalities and weakened health systems.[2,11,12] Besides, the emergence of new diseases, such as coronavirus disease 2019, poses more challenges for health systems with increasing complexity in the management of care and worse outcomes for people with multimorbidity.[11]

Identifying multimorbidity patterns and their determinants is a priority for the research agenda.[2] Several studies involve estimates of simple disease counts,[5,8] though there is a limited approach in differentiating individuals with the same count, and different diseases. Most studies focus on diseases as the unit of analysis in assessing multimorbidity patterns, such as factor analysis[19–21] and association rules.[22,23] However, orienting the analysis of multimorbidity patterns at an individual level, and not disease, could have crucial implications for patients. In the current setting of limited evidence on interventions for multimorbidity, such an approach elicits information for the development and implementation of strategies aimed at prevention, diagnosis, treatment and prognosis, and better understanding of the nature and range of the required health services.[24]

Countries have different levels of exposure to potential causal factors and demographic and socioeconomic differences between population and subgroups that can influence disease occurrence and patterns of multimorbidity.[2,13] Also, prevalence of multimorbidity is higher for women, compared to men, indicating that multimorbidity patterns need to be analyzed by sex.[9,25–27] Thus, the present study aims to investigate the prevalence of multimorbidity, to identify clusters based on multimorbidity patterns and to analyze differences among clusters according to sociodemographic and lifestyle factors, by sex, in the baseline of ELSA-Brasil.

Methods

Participants

ELSA-Brasil is a cohort of 15,105 active and retired civil servants aged between 35 and 74 years old from six Brazilian teaching and research institutions in Belo Horizonte (MG), Porto Alegre (RS), Rio de Janeiro (RJ), Salvador (BA), São Paulo (SP) and Vitória (ES). Since 2008, based on robust data, is the first Brazilian multicenter cohort study and the largest cohort about chronic disease in Latin America. ELSA-Brasil offers the possibility to validate multimorbidity patterns in a Brazilian large sample using individuals as the unit of analysis.

Baseline assessments were carried out between 2008 and 2010. These included face to face questionnaires and clinical, laboratory and imaging exams applied by trained and certified interviewers at ELSA-Brasil research centers.

Blood collection was performed in a 12-hour overnight fast by venipuncture shortly after the participant arrived at the research center.[28] Further methodological information was previously published.[29,30]

Participants whose data on any variable was missing, were excluded from the present analysis. The analytical sample of the study consisted of 14,516 participants (response rate=96.1%).

Multimorbidity. Multimorbidity was defined by two or more chronic morbidities, in a group of 15 morbidities with a prevalence ≥1% (excluded Chagas disease): diabetes, dyslipidemia, hypertension, obesity, common mental disorders (CMD), migraine, heart disease (acute myocardial infarction, angina pectoris or heart failure), cancer, rheumatic fever, stroke, asthma, chronic obstructive pulmonary disease/emphysema/chronic bronchitis, cirrhosis, joint problems, and kidney disease. All morbidities had the same weight (1) in the total morbidity count.

Diabetes was defined by self-report or use of medication. When not reported, it was defined by clinical information from fasting plasma glucose (≥126 mg/dL; 7.0 mmol/L), 2-h plasma glucose during the Oral Glucose Tolerance Test 75g (>200 mg/dL; 11.1 mmol/L) or glycated hemoglobin (≥6.5%; 48 mmol/mol).[31] Dyslipidemia was defined by the level of low-density lipoprotein-cholesterol ≥130 mg/dl or when using a lipid-lowering agent.[32]

Hypertension was defined by the systolic arterial pressure ≥140 mmHg or diastolic arterial pressure ≥90 mmHg or antihypertensive medicine use in the two weeks before the interview. Arterial pressure was measured after five minutes' rest in a quiet room with controlled temperature (20–24°C) and using a validated oscillometer device (Omron HEM 705CPINT). Three measurements were taken at one-minute intervals, and we considered the mean of the last two measures.[33,34]

Obesity was defined by the Body Mass Index ≥30 kg/m^2.[35] The participant's body weight and height were measured using specific study clothing, without shoes and props. Standardized protocols and scales of Toledo® brand and Seca® stadiometer were used for measurement.

Participants were classified according to common mental disorders using the Clinical Interview Schedule-Revised (CIS-R) instrument (cut-off point for disorder ≥12 points). CIS-R follows the International Statistical Classification of Diseases and Related Health Problems-Tenth Revision criteria to classify subjects into six categories of disorders (generalized anxiety disorder, mixed anxiety-depressive disorder, depression, phobias, obsessive-compulsive disorder, and panic disorder).[36] Migraine was defined as the presence of definite migraine (International Headache Society- IHS reference codes 1.1-migraine without aura or 1.2-migraine with aura) or probable migraine (IHS reference code 1.6) according to a detailed headache questionnaire based on the IHS criteria.[37,38]

Other morbidities were identified by the report of a previous diagnosis by a physician "Have you been previously told by a physician that you had/have [disease]?". Rheumatic fever included rheumatism with heart trouble, blocked valve and heart murmur requiring medical control. Joint problems included rheumatoid arthritis and lupus erythematosus.

Covariables. The covariables included the following: age (35-59 or 60+), marital status (married, widowed/divorced or single), education (never attended school to incomplete secondary school, complete secondary school, or university degree), per capita household income tercile (low ≤U$1,810.47, medium U$1,810.48-3,686.01 or high U$3,686.02-14,744.01), smoking (never, former, or current), excessive alcohol consumption (no or yes, defined as >210 g alcohol/week for men and 140 g alcohol/week for women),[39] adequate daily fruit or vegetable intake (no or yes, defined by ≥7 times per week)[40] and leisure physical activity by International Physical Activity Questionnaire Short Form (insufficient, moderate, or vigorous).[41–43]

Data analysis

Analyses were stratified by sex. Descriptive statistics were used to summarize overall information and within each cluster. Pearson's Qui-square test was used to assess differences between groups with and without multimorbidity by sex. To perform the clustering, participants with at least two chronic morbidities were included. Multiple Correspondence Analysis was implemented for the set of diseases to reduce dimensionality and explore relationships. The scree plot was used to select the number of dimensions indicated to retain.

The components were used to identify clusters of chronic morbidities based on the fuzzy c means algorithm. The fuzzy clustering, a machine learning technique, forces every individual to belong to every cluster in accordance with its characteristics and by assigning a membership degree factor of belonging (0.1) to each individual with respect to each pattern. This provides the flexibility enabling patients to belong to more than one multimorbidity pattern. The clinical context of multiple possible patterns for everyone makes this technique appropriate for the study of multimorbidity patterns.[44] The stability for the algorithm, the number of clusters, and the parameters were based on the analysis of the fuzzy silhouette, Xie and Beni, partition coefficient, and Partition entropy.[45]

The participant's profile in each cluster was assessed by describing sociodemographic and lifestyle variables comparing clusters by Qui-square test (χ^2). The co-occurrence of chronic morbidities was assessed in each cluster by O/E

ratios (observed/expected calculated by dividing disease prevalence in the cluster by disease prevalence in the overall population). To avoid spurious associations the ratios of which combination were analyzed, and the consequent morbidity had to occur in at least 5% of all cases.[46] A morbidity was considered part of the cluster when everyone in the cluster had the morbidity or when the O/E ratio was ≥1.5. Based on O/E criteria (≥1.5) the 10 most frequent morbidities patterns observed were presented in the study. The R 4.0.1 software was used in all analyses. The level of significance was set at $p < .05$.

Ethics Committee

The ELSA-Brasil study was approved by the Ethics and Research Committees of all institutions participating in the study (National School of Public Health Fiocruz under protocol number 343/06, on September 18th/2006) and registered at the National Research Ethics Committee (letter 976 CONEP/CNS/MS, on August 4th/2006). All participants signed the consent form.

Results

The analytical sample consisted of 54.4% female, mean age of 52.1 (SD 9.1) years, and number of morbidities in the same individual from 0 to 11 (mean=2.5; SD=1.7; median=2.0; Q25=1.0; Q75=4.0). The prevalence of participants with no chronic morbidity was 9.7%, with one chronic morbidity was 20.5%, and with multimorbidity (2+ chronic morbidities) was 69.9% (73.7% for women and 65.3% for men). In both sexes, higher prevalence of multimorbidity was found in adults, with university degree, never smoked and insufficient leisure physical activity. Higher prevalence of multimorbidity was found among excessive alcohol consumption for men (p≤0.05); married and low family per capita income for women (Table 1).

The subsequent results considered only people with multimorbidity. Women were grouped into 3 clusters, while men were grouped into 6 clusters of multimorbidity. The most prevalent conditions for women (see Supplement 1) were dyslipidemia (53.1%), migraine (50.3%), and CMD (43.3%). Most women (65.5%) were grouped in the first cluster, where all had hypertension and diabetes, and none had kidney disease. The strongest association found among the most observed combinations was hypertension, diabetes, obesity, and joint problems (O/E=2.54). Cluster 2 revealed an unspecific group as no morbidities were over-represented (no morbidity co-occurred in at least 5% of all cases), but the most observed combinations were cirrhosis/hepatitis, and kidney diseases (O=12.4%). Cluster 3 was characterized by all women with kidney disease, and the strongest association, among the most observed combination of kidney diseases, was with hypertension, diabetes, and obesity (O/E=3.81) (Table 2).

Amongst men, the most prevalent conditions (see Supplement 2) were dyslipidemia (57.1%), hypertension (55.6%), and obesity (28.8%). The first cluster was characterized by everyone with cirrhosis/hepatitis, and none with chronic obstructive pulmonary disease/emphysema/chronic bronchitis. The most prevalent combination, 7.6%, had cirrhosis/hepatitis, obesity and diabetes. Cluster 2, most combinations included kidney diseases and migraine, and no one had rheumatic fever. Cluster 3 no multimorbidity pattern reached ≥1.5 O/E ratio. Cluster 4 nonspecific chronic morbidities were over-represented (no morbidity co-occurred in at least 5% of all cases), however had the most observed combination (18.0% with asthma and chronic obstructive pulmonary disease/emphysema/chronic bronchitis). Cluster 5 predominately presented a pattern of diabetes, obesity and hypertension, and no chronic obstructive pulmonary disease/emphysema/chronic bronchitis, nor rheumatic fever. The most prevalent combination was 8.8% of diabetes, obesity and joint problems. No men with rheumatic fever nor cirrhosis/hepatitis characterized cluster 6, and the most observed combination was diabetes, hypertension and obesity (6.5%) (Table 2).

Table 3 and 4 presents the sociodemographic characteristics and lifestyle factors, for women and men, according to the multimorbidity clusters. For women all multimorbidity clusters were characterized by 34-59 years old, university degree and insufficient leisure physical activity. Cluster 1 was characterized by low family per capita income, and clusters 2 and 3 by high family per capita income (Table 3).

For men all multimorbidity clusters were characterized by 34-59 years old, university degree, adequate daily fruit or vegetable intake. Clusters 1, 4 and 6 were characterized by medium family per capita income, and clusters 2, 3 and 5 by low family per capita income. Clusters 1, 2, 3 and 6 were characterized by men who never smoked and clusters 4 and 5 by former smokers (Table 4).

Discussion

This study identified clusters of multimorbidity patterns and analyzed their differences according to sociodemographic and lifestyle factors, by sex. Multimorbidity is a global phenomenon with high case prevalence in ELSA-Brasil.

When compared to the prevalence of multimorbidity in HICs (37.9%)[8] and Brazil's 2013 National Health Survey (PNS 2013; 24.2%),[21] ELSA-Brasil findings present higher frequency. These differences may be attributed to the number and type of diseases used to define multimorbidity.[11] For example, prevalence estimates were based on fewer morbidities in studies from Canada (12) and United Kingdom (11), while a larger group of morbidities

Table 1. Sociodemographic characteristics and lifestyle factors, for women and men, according to multimorbidity, ELSA-Brasil, 2008-2010.

Variables	Women	Men	Total
	Multimorbidity *n* (%)	Multimorbidity *n* (%)	*n* (%)
Multimorbidity	5,814 (73.7)	4,329 (65.3)	10.143 (69.9)
Age			
34-59	4,443 (76.4)*	3,161 (73.0)*	11,390 (78.5)
60+	1,371 (23.6)	1,168 (27.0)	3,126 (21.5)
Marital Status			
Married	3,002 (51.6)*	3,543 (81.8)†	9,605 (66.2)
Widowed/Divorced	2,014 (34.7)	568 (13.1)	3,434 (23.6)
Single	798 (13.7)	218 (5.1)	1,477 (10.2)
Education			
Never attended school to incomplete secondary school	640 (11.0)*	774 (17.9)*	1,840 (12.7)
Complete secondary school	2,222 (38.2)	1,365 (31.5)	5,032 (34.7)
University degree	2,952 (50.8)	2,190 (50.6)	7,644 (52.7)
Family per capita income			
Low	2,182 (37.5)*	1,657 (38.3)†	5,345 (36.8)
Medium	1,957 (33.7)	1,455 (33.6)	4,980 (34.3)
High	1,675 (28.8)	1,217 (28.1)	4,191 (28.9)
Smoking			
Never	3,531 (60.7)*	2,022 (46.7)*	8,263 (56.9)
Former	1,540 (26.5)	1,715 (39.6)	4,363 (30.1)
Current	743 (12.8)	592 (13.7)	1,890 (13.0)
Excessive alcohol consumption	198 (3.4)†	570 (13.1) **	1,090 (7.5)
Adequate daily fruit or vegetable intake (≥7/week)	4,244 (73.0)†	2,659 (61.4)†	9,812 (67.6)
Leisure physical activity			
Insufficient	4,727 (81.3)*	3,231 (74.6)*	11,141 (76.7)
Moderate	830 (14.3)	760 (17.6)	2,347 (16.2)
Vigorous	257 (4.4)	338 (7.8)	1,028 (7.1)

*p value ≤0.001.
**p value ≤0.05.
†p value >0.05.

was considered in studies conducted in Singapore (48), Netherlands (28) and Australia (36). The comparability among studies may also be hampered due to methodological differences, such as characteristics of the included participants (age) and data source used to document the presence of morbidities (self-reported, health administrative data, medical examination and/or medication).[47]

The sample profile of ELSA-Brasil contributes to higher multimorbidity prevalence, including older adults, aged 35 and over, as opposed to surveys that include adults aged 18 and over. It shows that multimorbidity also affects young adults and active workers. It warns of a possible impact on absence from work,[48] in addition to the loss of quality of life, worse clinical outcomes,[5,13,14] and risk of premature death.[15,16]

The objective measures, fasting plasma glucose, Oral Glucose Tolerance Test, glycated hemoglobin, low-density lipoprotein-cholesterol, systolic arterial pressure, Body Mass Index, CIS-R and IHS may have favored the high prevalence of multimorbidity, differing from studies that use only self-report medical diagnosis. In ELSA-Brasil baseline 50.4% was previously undiagnosed for diabetes mellitus[49] and 19.8% was unaware of hypertension.[34] Although most cases were diagnosed in the baseline, subsequent waves confirm most cases of diabetes mellitus, hypertension, obesity and dyslipidemia.

As identified in the literature,[9,25–27] the prevalence of multimorbidity was higher among women (73.7%) compared to men (65.3%). This is indicative of an association between sex and multimorbidity supporting the choice of stratifying the analyses.[26] Among women and men with university degree there was a higher percentage with multimorbidity. However, for women, there was higher prevalence in low per capita family income categories.

Table 2. The most frequent multimorbidity patterns (≥ 5%) observed and expected by cluster of women and men, ELSA-Brasil, 2008-2010.

Women Cluster	Combinations of chronic morbidities				Observed (%)	Expected (%)	O/E
1 (*n* = 3,805)	Hypertension	Diabetes			13.2	8.5	1.56
	Hypertension	Diabetes	Obesity		6.8	3.0	2.28
	Hypertension	Diabetes	Joint problems		5.0	3.0	1.63
	Hypertension	Diabetes	Dyslipidemia		7.6	4.7	1.61
	Hypertension	Diabetes	Obesity	Joint problems	2.7	1.1	2.54
	Hypertension	Diabetes	Obesity	Dyslipidemia	3.9	1.7	2.35
	Hypertension	Diabetes	Obesity	Common mental disorder	2.7	1.3	2.01
	Hypertension	Diabetes	Obesity	Migraine	2.6	1.5	1.70
	Hypertension	Diabetes	Dyslipidemia	Joint problems	3.0	1.7	1.79
	Hypertension	Diabetes	Common mental disorder	Joint problems	2.3	1.4	1.70
2 (n = 923)	Obesity	Diabetes			6.8	3.4	1.99
	Hypertension	Stroke			5.3	3.1	1.71
	Hypertension	Diabetes			7.6	4.6	1.63
	Cirrhosis/hepatitis	Kidney diseases			12.4	8.1	1.52
	Cirrhosis/hepatitis	Kidney diseases	Joint problems		5.1	2.7	1.86
	Cirrhosis/hepatitis	Kidney diseases	Migraine		5.5	3.6	1.54
	Hypertension	Obesity	Joint problems		6.7	3.5	1.94
	Hypertension	Obesity	Dyslipidemia		7.7	4.5	1.70
	Cancer	Obesity	Joint problems		5.2	3.2	1.61
	Common mental disorder	Migraine	Joint problems		8.2	5.5	1.51
3 (*n* = 1,086)	Kidney diseases	Hypertension	Diabetes		12.2	6.5	1.87
	Kidney diseases	Hypertension	Heart disease		5.1	2.8	1.83
	Kidney diseases	Obesity	Diabetes		7.6	4.3	1.75
	Kidney diseases	Hypertension	Diabetes	Obesity	6.4	1.7	3.81
	Kidney diseases	Hypertension	Diabetes	Joint problems	6.6	2.3	2.87
	Kidney diseases	Hypertension	Diabetes	Dyslipidemia	8.1	3.3	2.45
	Kidney diseases	Obesity	Diabetes	Dyslipidemia	5.0	2.2	2.27
	Kidney diseases	Dyslipidemia	Diabetes	Joint problems	6.0	3.0	1.97
	Kidney diseases	Hypertension	Obesity	Joint problems	5.8	3.5	1.67
	Kidney diseases	Hypertension	Obesity	Dyslipidemia	8.1	5.0	1.63

Men Cluster	Combinations of chronic morbidities				Observed (%)	Expected (%)	O/E
1 (*n* = 497)	Cirrhosis/ hepatitis	Obesity	Diabetes		7.6	4.1	1.85
	Cirrhosis/ hepatitis	Migraine	Common mental disorder		6.0	3.8	1.58
	Cirrhosis/ hepatitis	Obesity	Diabetes	Joint problems	2.2	0.6	3.46
	Cirrhosis/ hepatitis	Obesity	Diabetes	Hypertension	5.6	1.7	3.38
	Cirrhosis/ hepatitis	Obesity	Diabetes	Common mental disorder	2.4	1.0	2.46

(continued)

Table 2. (continued)

Men Cluster	Combinations of chronic morbidities				Observed (%)	Expected (%)	O/E
	Cirrhosis/ hepatitis	Hypertension	Diabetes	Joint problems	2.4	1.1	2.10
	Cirrhosis/ hepatitis	Obesity	Hypertension	Joint problems	2.8	1.4	1.99
	Cirrhosis/ hepatitis	Obesity	Hypertension	Common mental disorder	3.6	2.2	1.67
	Cirrhosis/ hepatitis	Obesity	Hypertension	Kidney diseases	3.2	2.0	1.63
	Cirrhosis/ hepatitis	Obesity	Diabetes	Dyslipidemia	3.0	1.9	1.57
2 (*n* = 869)	Migraine	Kidney diseases			6.6	4.2	1.55
	Migraine	Kidney diseases	Common mental disorder		6.3	2.9	2.18
	Migraine	Kidney diseases	Dyslipidemia		3.6	2.3	1.54
	Migraine	Kidney diseases	Diabetes		2.6	0.8	3.25
	Diabetes	Kidney diseases	Common mental disorder		2.5	0.9	2.83
	Diabetes	Heart disease	Dyslipidemia		2.1	0.9	2.19
	Diabetes	Heart disease	Common mental disorder		2.3	1.2	1.95
	Migraine	Kidney diseases	Diabetes	Common mental disorder	2.5	0.6	4.54
	Migraine	Kidney diseases	Common mental disorder	Dyslipidemia	3.5	1.6	2.17
	Diabetes	Heart disease	Common mental disorder	Dyslipidemia	1.8	0.6	2.85
3 (*n* = 1,216)*							
4 (*n* = 228)	Common mental disorder	Migraine			9.6	5.1	1.90
	Common mental disorder	Joint problems			11.0	7.3	1.50
	Asthma	Chronic obstructive pulmonary disease/ emphysema/ chronic bronchitis			18.0	11.6	1.55
	Hypertension	Heart disease	Dyslipidemia		11.4	6.2	1.83
	Hypertension	Rheumatic fever	Obesity		13.6	7.5	1.82
	Dyslipidemia	Rheumatic fever	Heart disease		11.4	6.5	1.76
	Hypertension	Dyslipidemia	Kidney diseases		10.5	6.8	1.54
	Hypertension	Dyslipidemia	Obesity		10.5	6.0	1.75

(continued)

Table 2. (continued)

Men Cluster	Combinations of chronic morbidities					Observed (%)	Expected (%)	O/E
	Hypertension	Rheumatic fever	Heart disease			12.7	7.8	1.64
	Hypertension	Rheumatic fever	Diabetes			11.4	7.5	1.53
5 (n = 693)	Diabetes	Obesity				8.8	5.8	1.52
	Cancer	Joint problems	Kidney diseases			3.2	1.9	1.71
	Diabetes	Obesity	Joint problems			8.8	5.8	1.52
	Diabetes	Obesity	Hypertension			6.8	3.0	2.26
	Diabetes	Obesity	Hypertension	Joint problems		6.8	3.0	2.26
	Diabetes	Obesity	Hypertension	Kidney diseases		1.4	0.7	2.02
	Diabetes	Obesity	Hypertension	Dyslipidemia		2.9	1.5	1.91
	Diabetes	Obesity	Hypertension	Common mental disorder		1.3	0.7	1.87
	Diabetes	Obesity	Hypertension	Joint problems	Kidney diseases	1.4	0.7	2.02
	Diabetes	Obesity	Hypertension	Dyslipidemia	Joint problems	2.9	1.5	1.91
6 (n = 826)	Diabetes	Hypertension	Heart disease			3.6	1.4	2.68
	Diabetes	Hypertension	Obesity			6.5	3.3	1.96
	Diabetes	Dyslipidemia	Heart disease			2.7	1.4	1.91
	Dyslipidemia	Hypertension	Heart disease			5.0	2.9	1.69
	Diabetes	Hypertension	Dyslipidemia	Heart disease		2.4	0.8	3.22
	Diabetes	Hypertension	Heart disease	Kidney diseases		3.0	1.2	2.49
	Diabetes	Hypertension	Obesity	Kidney diseases		6.2	3.0	2.07
	Diabetes	Hypertension	Dyslipidemia	Obesity		3.3	1.8	1.77
	Dyslipidemia	Hypertension	Heart disease	Kidney diseases		4.2	2.6	1.62
	Diabetes	Hypertension	Obesity	Dyslipidemia	Kidney diseases	3.3	1.7	1.98

O: observed.
E: expected.
*Cluster 3: no multimorbidity pattern reached the O/E ratio of ≥1.5.

Lower education and deprivation were previously associated with multimorbidity,[50] and these determinants can influence intermediary factors related to lifestyle, access, and use of health services. Furthermore, differences in the prevalence of multimorbidity by sex may reflect gender differences in the search for medical care and consequent diagnosis.

Five of the six conditions that were assessed by ELSA-Brasil were the most prevalent among men and women with multimorbidity: dyslipidemia, hypertension, migraine, CMD, and obesity. The most prevalent conditions co-occurred with each other as dyads and tryads, highlighting patterns of hypertension, diabetes and obesity.[11] For women, these morbidities also co-occurred with kidney disease. The insulin resistance associated with obesity contributes to the development of other cardiovascular risk factors, including hypertension and diabetes. But also, the coexistence of hypertension and diabetes increases the risk for macrovascular and microvascular complications, thus predisposing people to kidney disease.[51]

For men, morbidities like cirrhosis/hepatitis were commonly clustered with obesity and diabetes. Diabetes mellitus and cirrhosis have related etiology underlying liver disease. Most is due to diabetes mellitus, characterized by progressive loss of beta-cell insulin secretion. In the background there's increased insulin resistance, given the link between shared risk factors for nonalcoholic fatty liver disease as the commonest cause of chronic liver disease.[52]

Table 3. Sociodemographic characteristics and lifestyle factors, for women, according to the multimorbidity clusters, ELSA-Brasil, 2008-2010.

Variables	Women (n = 5,814)			
	Cluster n (%)	Cluster 2 n (%)	Cluster 3 n (%)	p value
Age*				≤0.001
34–59	2,946 (77.4)	652 (70.6)	845 (77.8)	
60+	859 (22.6)	271 (29.4)	241 (22.2)	
Marital Status**				0.028
Married	1,950 (51.2)	449 (48.6)	603 (55.5)	
Widowed/ Divorced	1,319 (34.7)	342 (37.1)	353 (32.5)	
Single	536 (14.1)	132 (14.3)	130 (12.0)	
Education*				≤0.001
Never attended school to incomplete secondary school	445 (11.7)	80 (8.7)	115 (10.6)	
Complete secondary school	1,601 (42.1)	257 (27.8)	364 (33.5)	
University degree	1,759 (46.2)	586 (63.5)	607 (55.9)	
Family per capita income*				≤0.001
Low	1,568 (41.2)	250 (27.1)	364 (33.5)	
Medium	1,264 (33.2)	313 (33.9)	380 (31.5)	
High	973 (25.6)	360 (39.0)	342 (35.5)	
Smoking†				0.367
Never	2,308 (60.7)	559 (60.6)	664 (61.1)	
Former	988 (26.1)	255 (27.6)	297 (27.3)	
Current	509 (13.4)	109 (11.8)	125 (11.5)	
Excessive alcohol consumption†	127 (3.3)	34 (3.7)	37 (3.4)	0.874
Adequate daily fruit or vegetable intake (≥7/week)**	2,742 (72.1)	704 (76.3)	798 (73.5)	0.033
Leisure physical activity*				0.001
Insufficient	3,148 (82.7)	717 (77.7)	862 (79.4)	
Moderate	509 (13.4)	150 (16.2)	171 (15.7)	
Vigorous	148 (3.9)	56 (6.1)	53 (4.9)	

*p value ≤0.001.
**p value ≤0.05.
†p value >0.05.

Still for men, kidney disease was commonly clustered with migraine and CMD. The crosstalk between brain and kidney might be bidirectional since chronic kidney disease-related central nervous system conditions, like migraine, are also independent risk factors for chronic kidney disease. Also, it has been reported that depression and chronic kidney disease might be related with poor clinical outcomes, which include hospitalization, kidney function decline, progression to end-stage renal disease, and mortality.[53]

When comparing the lifestyle by cluster, amongst men, higher prevalence of former smokers was found on clusters 4 and 5, where cluster 4, 18% presented asthma and chronic obstructive pulmonary disease/emphysema/chronic bronchitis. Also, high prevalence (15.9%) of excessive alcohol consumption was found in cluster 1, where all men had cirrhosis/hepatitis.

As different analytical methods adjust for multimorbidity by chance to different extents, it is anticipated that multimorbid groups of conditions from different studies vary, limiting comparability to the literature. Most Brazilian studies still focus on disease counts and rely their results about multimorbidity patterns on techniques, such as factor analysis,[19–21] principal component analysis,[54] association rule[22,23] and hierarchical cluster.[55]

The soft technique employed in the present study has the main advantage, it places individuals and not their diseases at the center of the analyses for assessing multimorbidity patterns. Hard clustering (ie. hierarchical clustering, k-means) forces each individual to belong to a single cluster, whereas the chosen soft clustering analysis (fuzzy c-means cluster algorithm) allows for diseases to be linked simultaneously to multiple clusters, more consistent with clinical experience than other approaches frequently found in the literature.[24] In soft techniques one disease can characterize more than one cluster, which allows to build patterns of multimorbidity that take all possible disease combinations into account.[24,44] Despite the evident advantage of soft

Table 4. Sociodemographic characteristics and lifestyle factors, for men, according to the multimorbidity clusters, ELSA-Brasil, 2008-2010.

	Men (n = 4,329)						
Variables	Cluster 1 n (%)	Cluster 2 n (%)	Cluster 3 n (%)	Cluster 4 n (%)	Cluster 5 n (%)	Cluster 6 n (%)	p value
Age*							≤0.001
34–59	384 (77.3)	771 (88.7)	863 (71.0)	136 (59.6)	440 (63.5)	567 (68.6)	
60+	113 (22.7)	98 (11.3)	353 (29.0)	92 (40.4)	253 (36.5)	259 (31.4)	
Marital Status**							0.030
Married	404 (81.3)	677 (77.9)	1,011 (83.1)	183 (80.3)	590 (85.1)	678 (82.1)	
Widowed/ Divorced	66 (13.3)	136 (15.7)	143 (11.8)	33 (14.5)	83 (12.0)	107 (13.0)	
Single	27 (5.4)	56 (6.4)	62 (5.1)	12 (5.3)	20 (2.9)	41 (4.9)	
Education*							≤0.001
Never attended school to incomplete secondary school	53 (10.7)	165 (19.0)	279 (22.9)	37 (16.2)	122 (17.6)	118 (14.2)	
Complete secondary school	129 (26.0)	324 (37.3)	407 (33.5)	58 (25.4)	242 (34.9)	205 (24.8)	
University degree	315 (63.4)	380 (43.7)	530 (43.6)	133 (58.3)	329 (47.5)	503 (61.0)	
Family per capita income*							≤0.001
Low	136 (27.4)	418 (48.1)	522 (42.9)	67 (29.4)	269 (38.8)	245 (29.7)	
Medium	182 (36.6)	281 (32.3)	393 (32.3)	85 (37.3)	220 (31.8)	294 (35.6)	
High	179 (36.0)	170 (19.6)	301 (24.8)	76 (33.3)	204 (29.4)	287 (34.7)	
Smoking*							≤0.001
Never	244 (49.1)	408 (47.0)	557 (45.8)	96 (42.1)	293 (42.3)	424 (51.3)	
Former	177 (35.6)	300 (34.5)	504 (41.5)	98 (43.0)	323 (46.6)	313 (37.9)	
Current	76 (15.3)	161 (18.5)	155 (12.7)	34 (14.9)	77 (11.1)	89 (10.8)	
Excessive alcohol consumption†	79 (15.9)	108 (12.4)	172 (14.1)	26 (11.4)	96 (13.9)	89 (10.7)	0.084
Adequate daily fruit or vegetable intake** (≥7/ week)	316 (63.6)	486 (55.9)	744 (61.2)	145 (63.6)	458 (66.1)	510 (61.7)	0.002
Leisure physical activity†							0.187
Insufficient	364 (73.2)	670 (77.1)	898 (73.8)	174 (76.3)	505 (72.9)	620 (75.1)	
Moderate	93 (18.7)	129 (14.8)	232 (19.1)	30 (13.2)	133 (19.2)	143 (17.3)	
Vigorous	40 (8.1)	70 (8.1)	86 (7.1)	24 (10.5)	55 (7.9)	63 (7.6)	

*p value ≤0.001.
**p value ≤0.05.
†p value >0.05.

clustering technique, so far it has only been applied to the older population.[24,44,56,57]

Some limitations should be discussed. Firstly, the sample profile is based on active and retired civil servants from teaching and research institutions characterized by young age and average high socioeconomic status, which limits the external validity of the findings. Second, the severity of each pattern of multimorbidity and its impact on daily activities were not evaluated. More studies are needed to address these issues and expand knowledge about how each grouping of conditions affects individuals' lives and well-being.

Multimorbidity is a growing challenge worldwide. In the present study, more than half of ELSA-Brasil sample was classified with multimorbidity. The high prevalence of multimorbidity patterns of hypertension, diabetes, obesity, common to men and women, stands out, as the significantly different sociodemographic characteristics and lifestyle factors among the clusters.

The need for a consistent operationalization of multimorbidity is evident. It will enable more accurate estimations of disease burden and, consequently, more effective disease management and resources distribution. This and similar approaches to the epidemiological study of multimorbidity are needed, not only to better understand the complex interactions among co-occurring diseases but also, even more importantly, to improve preventive interventions and optimally address individuals' care needs and the risk of adverse outcomes.

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Author contributions

LPM, OBA, DPP, FEGO, and RHG were responsible for the study conception, design, analysis, and interpretation of the data. LPM was responsible for the drafting of the article. RHG provided access to the database and participated in developing the final text. DC, IB, ALPR, ARB, LACM and MJMF participated in developing the final text. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets presented in this article are not readily available because the ELSA study has government funding, and the database is available only to researchers and students of the research institutions linked to the study. Requests to access the datasets should be directed to elsa@fiocruz.br.

Ethics statement

The studies involving human participants were reviewed and approved by the research ethics committees of all six centers (Federal University of Minas Gerais—UFMG: 186/06; São Paulo University—USP: 669/06; Federal University of Rio Grande do Sul—UFRGS: 194/061; Federal University of Espírito Santo—UFES: 041/06; Federal University of Bahia—UFBA: 027/06; Oswaldo Cruz Foundation—FIOCRUZ: 343/06). The patients/participants provided their written informed consent to participate in this study.

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Supplemental Material

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