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Multimorbidity Patterns in Older Adults: An Approach to the Complex Interrelationships Among Chronic Diseases

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Background and Aims. There is a growing need for evidence based answers to multimorbidity, especially in primary care settings. The aim was estimate the prevalence and patterns of multimorbidity in a Mexican population of public health institution users ≥60 years old.

Methods. Observational and multicenter study was carried out in four family medicine units in Mexico City; included older men and women who attended at least one consultation with their family doctor during 2013. The most common diseases were grouped into 11 domains. The observed and expected rates, as well as the prevalence ratios, were calculated for the pairs of the more common domains. Logistic regression models were developed to estimate the magnitude of the association. Cluster and principal components analyses were performed to identify multimorbidity patterns.

Results. Half of all of the patients who were ≥60 years old and treated by a family doctor had multimorbidity. The most common disease domains were hypertensive and endocrine diseases. The highest prevalence of multimorbidity concerned the renal domain. The domain pairs with the strongest associations were endocrine + renal and hypertension + cardiac. The cluster and principal components analyses revealed five consistent patterns of multimorbidity.

Conclusions. The domains grouped into five patterns could establish the framework for developing treatment guides, deepen the knowledge of multimorbidity, develop strategies to prevent it, decrease its burden, and align health services to the care needs that doctors face in daily practice.

Key Words: Multimorbidity, Older adults, Chronic diseases, Complexity, Primary care.

Introduction

Multimorbidity is the concurrence of two or more chronic diseases in one person (1,2). Reports of its prevalence vary between 20 and 30% of the general population and between 55 and 98% among older adults (1). This age-related difference is due to various reasons, including the source of information used (e.g., questionnaires, clinical records, administrative data), the methodology applied, the analyzed age groups, the diagnoses considered, and the population studied (3–6). Furthermore, this condition has had a global effect because of the rapid modification of the demographic structure in recent decades in most countries (7,8). The World Health Organization reported that life expectancy exceeded 70 years old in 2013, and this longevity trend is on the raise (9,10). Worldwide, the proportion of people ≥60 years of age has gradually increased. In 1960, this age group represented 8.1% of the world's population; in 2000 and 2013, these figures were 10% and 11.7%,

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respectively (11). Also, chronic health problems replaced infectious diseases as the main reason for seeking healthcare over the last century (1). In 1990, 26.6 million deaths resulting from non-communicable diseases (NCDs) were reported throughout the world, a figure that increased to 34.5 million in 2010 (12). Besides, the incidence and mortality of NCDs increase with age; in 2012, 58% of all deaths related to NCDs happened among people over 70 years old (9).

Often, patients with NCDs have more than one chronic disease, which makes their treatment more complex and requires permanent monitoring for their control (13). These situations place pressure on healthcare systems to provide efficient and quality care that prioritizes primary care (3,14–16) to reduce the risks of hospitalization, premature death, loss of functionality, depression, polymedication, and poor quality of life (1).

According to the 2010 census data, ten million adults ≥60 years old live in Mexico, representing 9% of the total population, with an annual growth rate of 3.8% (17). Of these adults, 36.2% are affiliated with the Mexican Social Security Institute (IMSS in Spanish) (18) which is the largest public healthcare institution in Mexico that provides services to formal workers and their families. The frequency of NCDs in the Mexican population over 60 years old reaches up to 67% (19), and multimorbidity rates are also high in this age group. For example, a study of older adult users of the family medicine services of the IMSS with non-cancer pain syndrome found that the average number of NCDs per older adult was 3.6 (SD ± 1.4) (20). However, studies on the patterns of multimorbidity in this age group are scarce. The objective of this study was to estimate the prevalence and patterns of multimorbidity in a sample of older adults attending to IMSS family medicine units (FMUs).

Material and Methods

Design and Procedures

This observational, retrospective and multicenter study was based on information extracted from the electronic clinical records (ECRs) of four IMSS FMUs (two located north and two south of Mexico City). These FMUs were selected for having similar characteristics on their structure, organization, services provided, and number of affiliates.

The sample consisted of 77,573 men and women aged ≥60 years who attended at least one consultation with their family doctor during 2013. The age, sex, and diagnosis of each patient were extracted from the ECRs and coded based on the Internal Classification of Diseases and Related Health Problems (ICD-10).

The Medical Research Committee of the IMSS approved this study, considering it exempt from informed consent because participants were not at risk (i.e., anonymous information collected from ECRs).

ECR Characteristics and Disease Selection

The IMSS ECRs are composed of several databases that are interconnected with information concerning medical histories, physical exams, medical visit notes, the progression of patients with specific diseases (e.g., diabetes, prenatal care, and hypertension), and care provided by other levels of care and services. The notes from each visit include the registry of the codified diagnoses based on the ICD-10. To select the diagnoses to be analyzed, two investigators (DML and HRM) reviewed the frequencies of the diagnoses recorded during the patients' last visits and grouped them into domains based on the criteria proposed by other authors (4) that are supported by the domains of the Cumulative Illness Rating Scale (CIRS). In total, 11 domains were included, and each one consisted of its respective ICD-10 codes (Table 1). Multimorbidity was defined as the presence of morbidity in two or more domains.

Statistical Analysis

Prevalence was calculated per 100 people for each domain selected and considering the presence or absence of multimorbidity. In addition, the rates were estimated for the most common pairs of domains. The estimated prevalence (i.e., the product of the individual rates) and the prevalence ratio (observed/expected) were calculated for each pair of domains. We used the χ^2 test to determine the independence of each pair of domains, and built logistic regression models (both crude and adjusted for age, sex, and the other domains) between each pair of domains to estimate the magnitude of their association.

To establish multimorbidity patterns, we used cluster and principal components analyses as grouping methods.

Table 1. The domains included in the analysis and the ICD-10 codes included in the domains

Number	Domain	ICD-10 codes
1.	Endocrine	E10–E14
2.	Psychological	F32, F32.0, F32.1, F33, F33.0–F33.4, F40–F48
3.	Neurological	G20, G25.9, G30, G43, G44, G51, G45, G57.0, G62.8, G62.9, G63
4.	Hypertension	I10–I15
5.	Cardiac	I20, I20.0–I20.9, I25, I49.8, I49.9, I50.0
6.	Vascular	E78.0–E78.5, I70, I83, I87.2
7.	Respiratory	J40, J42, J43, J44, J45
8.	Upper gastrointestinal	K21, K25, K26, K27, K28, K29, K29.7
9.	Musculoskeletal	M05, M06, M06.8, M06.9, M13, M15, M16, M17, M18, M19, M20, M54, M79, M80, M81
10.	Renal	N18.0–N18.9, N19
11.	Neoplasia	C00–D48

The cluster analysis grouped domains based on their relative proximity. Within the hierarchical clustering approach each domain starts as an individual cluster that gradually merges with the closest clusters. Subsequently, we evaluated the number of clusters through using a dendrogram and the agglomeration coefficient. To measure and evaluate the distance between two clusters, the average linkage method and Yule's *Q* similarity measure were used.

The principal components analysis was performed with varimax rotation to facilitate the interpretation of the component loads. To determine the optimal number of components, the comparative fit index and the Tucker-Lewis index were used, and the criterion for the loading factors was fixed at ≥0.30. STATA version 11 was used to perform the statistical analyses.

Results

The analyzed sample included 77,573 adults ≥60 years old, of whom 58.2% were women. The average age of the sample was 70.5 ± 8 years; 17.9% (n = 13,583) had no record of chronic disease, 32.1% (n = 24,914) were diagnosed with a chronic disease, and the remaining 50% reported multimorbidity.

The most prevalent disease domains in the sample were hypertension (49.5%), endocrine (32.7%), musculoskeletal (26.2%), and vascular (21.9%). The highest prevalence that we detected as a unique domain was hypertension (11.7%), and the lowest was renal (0.2%); however, the highest prevalence of multimorbidity (92.3%), with 3.3 ± 1.1 domains (Table 2), was found for those who were in the renal domain. Into each domain, diseases with highest prevalence were hypertension, diabetes mellitus, disorders of lipoprotein metabolism, and venous insufficiency chronic peripheral; the rest showed prevalence lower than 10% (Table 3).

Table 4 shows the observed and expected rates of the 19 pairs of domains that coincided as well as their crude and adjusted odds ratios (ORs). Of the pairs of analyzed domains, 11 had a greater chance of associating (i.e., an observed prevalence higher than expected), a finding that was maintained in the crude logistic regression. After adjusting for age, sex, and the other domains, the endocrine + vascular combination was no longer significant. However, the pairs of domains that coincided and had stronger association were endocrine + renal (OR = 3.60; 95% CIs = 3.27−3.91), hypertension + cardiac (OR = 2.57; 95% CIs = 2.39−2.75), and hypertension + renal (OR = 2.50; 95% CIs = 2.26−2.73).

A cluster analysis based on the domains in which we used the average linkage method and Yule's Q similarity value showed an integration of five clusters. The cluster that had the shortest distance integrated the endocrine and renal domains; the second cluster included the cardiac, respiratory, and hypertension domains; the third grouped the psychological and neurological domains; the fourth cluster included the vascular, upper gastrointestinal, and musculoskeletal domains; and the fifth cluster included the neoplasia domain (Figure 1).

The principal components analysis produced five eigenvalues greater than one, which were obtained from the interactions; thus, five components were integrated. Loads of the domains ≥0.30 that integrated component 1 were the vascular, upper gastrointestinal, and musculoskeletal domains; the component 2 loads were the hypertension, cardiac, and respiratory domains; the component 3 load was neoplasia; the component 4 loads were the psychological, neurological, and renal domains; and the component 5 load was the endocrine domain (Table 5).

Discussion

This study revealed consistent associations among the studied domains and identified multimorbidity patterns using different analysis methods. The prevalence results showed that for every 100 patients ≥60 years old who were treated

Table 2. Prevalence of selected domains

	Total		One disease		Multimorbidity		
Domain	***n***	**Prevalence**	***n***	**Prevalence**	***n***	**Prevalence**	**Mean ± SD**
Hypertension	38,405	49.5	9,111	11.7	29,294	76.3	2.7 ± 0.8
Endocrine	25,371	32.7	6,682	8.6	18,689	73.7	2.8 ± 0.9
Musculoskeletal	20,306	26.2	3,919	5.1	16,387	80.7	2.8 ± 0.9
Vascular	16,974	21.9	2,031	2.6	14,943	88.0	2.9 ± 0.9
Respiratory	6,099	7.9	820	1.1	5,279	86.6	3.1 ± 1.0
Upper gastrointestinal	5,268	6.8	555	0.7	4,713	89.5	3.2 ± 1.0
Cardiac	4,000	5.2	403	0.5	3,597	89.9	3.2 ± 1.1
Psychological	3,659	4.7	379	0.5	3,280	89.6	3.2 ± 1.0
Neurological	2,633	3.4	354	0.5	2,279	86.6	3.1 ± 1.0
Neoplasia	2,561	3.3	497	0.6	2,064	80.6	3.0 ± 1.0
Renal	2,130	2.7	164	0.2	1,966	92.3	3.3 ± 1.1

Table 3. Prevalence of diseases in each domain

Domains and diseases	Prevalence
1. Endocrine	
Diabetes mellitus	32.7
2. Pshychological	
Depression	0.1
Neurotic disorders	4.7
3. Neurological	
Parkinson's disease	0.9
Alzheimer's disease	0.3
Migraine and other headache syndromes	1.3
Transient cerebral ischaemic attacks	0.2
Other polyneuropathies	0.7
4. Hypertension	49.5
5. Cardiac	
Ischemic heart diseases	4.2
Arrhytmias	0.9
Heart failure	0.3
6. Vascular	
Disorders of lipoprotein metabolism	14.1
Atherosclerosis	0.1
Venous insufficiency chronic peripheral	10.1
7. Respiratory	
Bronchitis	1.2
Emphysema and other obstructive pulmonary disease	6.8
Asthma	0.7
8. Upper gastrointestinal	
Gastro-oesophageal reflux disease	0.7
Gastric, duodenal, peptic, and gastrojejunal ulcer	0.1
Gastritis	6.1
9. Musculoskeletal	
Rheumatoid arthritis	1.9
Other arthritis	0.8
Arthrosis	18.1
Acquired deformities of fingers and toes	0.4
Dorsalgia	6.8
Soft tissue disorders	0.6
Osteoporosis with and without fracture	2.5
10. Renal	
Chronic renal failure	2.7
11. Neoplasia	3.3

by a family doctor, 50 showed multimorbidity. Although it is challenging to make comparisons because of the variations in the source of data used, the age groups, and the diseases studied, this result is consistent with a recent report in Australia, despite that represents a different context than Mexico (21). Besides, the higher prevalence of the hypertension and endocrine domains in the individual analysis of domains coincides with the results of a population-based survey for this same age group conducted in 2012 (18), and in the case of hypertension, the individual analysis of domains coincides with results in other populations (21–23).

The finding regarding the combination of conditions is noticeable because the prevalence of multimorbidity was higher in the presence of the diseases included in the renal domain but lower in the endocrine and hypertension domains. Other authors have reported up to a 25 times higher likelihood of multimorbidity in patients with kidney failure, whereas this probability has been reported as three times greater in patients with hypertension (24).

A notable result is that of the 11 pairs of diseases that coincided, two of the three pairs that included the highest association included the hypertension domain (with cardiac and renal), and the highest prevalence included the renal domain (with endocrine). From a pathophysiological viewpoint, this result is plausible because kidney failure is a complication linked to diabetes mellitus (via the endocrine domain) (25,26) and hypertension (27). In ischemic heart disease, the presence of arrhythmias and heart failure (i.e., cardiac diseases included in the cardiac domain) are complications related to hypertension (27,28). The identification of the endocrine domain association with the renal domain is particularly important in Mexico because between 15% and 30% of patients with diabetes already have microalbuminuria at the time of diagnosis (24). Moreover, diabetes was the cause of end-stage kidney disease in approximately 40% of patients who underwent peritoneal dialysis (29).

A cluster analysis made it possible to obtain a complete profile of the association between diseases in this population and confirm some of the associations that have been reported. For example, the association between the cardiac and respiratory domains has been described in the literature and has epidemiological (30,31) and physiological support (32,33). The integration of the psychological and neurological domains has emerged as the potential mechanism for the presence of the alterations in the regulatory mood circuits caused by vascular problems. The presence of cognitive impairment, among others, has been reported as a risk factor for depression and anxiety (23,34–36). The associations among the vascular, upper gastrointestinal, and musculoskeletal domains can be explained from two perspectives: the first is related to the connective tissue changes that occur in aging, which has been linked to a low-grade inflammation process (37–39); the second is related to the adverse events related to the pharmacological treatment of diseases included in the musculoskeletal domain. Importantly, this combination of diseases has already been reported (39,40). Finally, the separation of the neoplasia domain into its own cluster seems reasonable because this group of diseases is heterogeneous. Although the most common risk factors (age, smoking, poor diet, obesity, and physical inactivity) are shared by other conditions (41), the risk factors of a specific tumor can be unique, as has been documented (21,42), which supports this finding.

Although the cluster analysis was based on distance and the principal components analysis was based on correlations, the results obtained are generally consistent. The differences between both can be explained because the cluster analysis places each domain in a single cluster, whereas the principal components analysis places them in more than

Table 4. The pairs of domains that coincide as well as their observed and expected rates per 100 inhabitants

Domains	*n*	Prevalence		Observed/Expected	p[b]	Logistic regression OR (95% CIs)	
		Observed	Expected[a]			Simple	Adjusted
Hypertension + Endocrine	14,787	19.1	16.2	1.18	0.0	1.6 (1.6−1.7)	1.7 (1.6−1.7)
Hypertension + Musculoskeletal	10,759	13.9	13.0	1.07	0.0	1.2 (1.1−1.2)	1.1 (1.1−1.2)
Hypertension + Vascular	9,914	12.8	10.8	1.18	0.0	1.5 (1.5−1.6)	1.6 (1.5−1.6)
Hypertension + Respiratory	3,707	4.8	3.9	1.23	0.0	1.6 (1.5−1.7)	1.5 (1.4−1.6)
Hypertension + Upper gastrointestinal	2,860	3.7	3.4	1.10	0.0	1.2 (1.3−1.6)	1.2 (1.2−1.4)
Hypertension + Cardiac	2,817	3.6	2.6	1.42	0.0	2. 5 (2.3−2.7)	2.5 (2.3−2.7)
Hypertension + Psychological	2,044	2.6	2.3	1.13	0.0	1.3 (1.2−1.4)	1.2 (1.1−1.3)
Hypertension + Neurological	1,412	1.8	1.7	1.08	0.0	1.1 (1.1−1.2)	1.2 (0.9−1.0)
Hypertension + Neoplasia	1,269	1.6	1.6	1.00	0.9	1.0 (0.9−1.0)	1.0 (0.9−1.1)
Hypertension + Renal	1,492	1.9	1.4	1.41	0.0	2.4 (2.2−2.6)	2.5 (2.2−2.7)
Endocrine + Musculoskeletal	5,195	6.7	8.6	0.78	0.0	0.6 (0.6−0.6)	0.6 (0.6−0.6)
Endocrine + Vascular	5,672	7.3	7.2	1.02	0.0	1.0 (1.0−1.0)	1.0 (0.9−1.0)
Endocrine + Respiratory	1,718	2.2	2.6	0.86	0.0	0.7 (0.7−0.8)	0.8 (0.7−0.8)
Endocrine + Upper gastrointestinal	1,454	1.9	2.2	0.84	0.0	0.7 (0.7−0.8)	0.7 (0.7−0.8)
Endocrine + Cardiac	1,344	1.7	1.7	1.03	0.2	1.0 (0.9−1.1)	1.0 (1.0−1.1)
Endocrine + Psychological	1,015	1.3	1.5	0.85	0.0	0.7 (0.7−0.8)	0.7 (0.7−0.8)
Endocrine + Neurological	857	1.1	1.1	1.00	0.8	0.9 (0.8−0.9)	1.0 (0.9−1.0)
Endocrine + Neoplasia	702	0.9	1.1	0.84	0.0	0.7 (0.7−0.8)	0.7 (0.7−0.8)
Endocrine + Renal	1,321	1.7	0.9	1.90	0.0	3.5 (3.1−3.8)	3.60 (3.2−3.9)

[a]Product of the individual rates; [b]χ^2 test of independence between the observed and expected rates.

one. Identifying of multimorbidity patterns could be potentially applicable from clinical perspective for designing treatment and prognosis guidelines. In the public health area, classification of population at risk might be relevant for improving distributive equity at the health systems level.

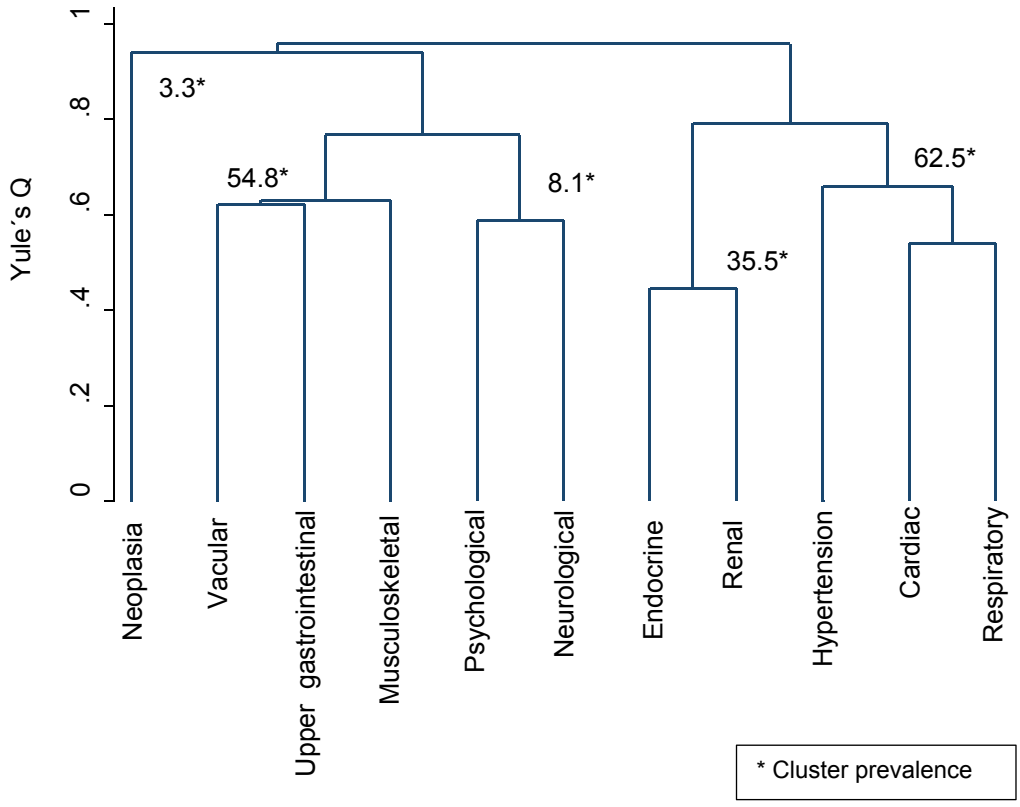

Figure 1. Dendrogram using the Yule's Q similarity measure. (A color figure can be found in the online version of this article.)

Table 5. Loads of the domains with values ≥0.30

	Components				
Domains	**1**	**2**	**3**	**4**	**5**
Prevalence	54.8	62.5	3.3	10.9	32.7
Hypertension		0.4007			
Endocrine					0.6438
Musculoskeletal	0.5472				
Vascular	0.3464				
Respiratory		0.5575			
Upper gastrointestinal	0.3289				
Cardiac		0.5884			
Psychological				0.4409	
Neurological				0.5558	
Neoplasia			0.6154		
Renal				0.3578	

Some limitations should be recognized. The use of ECRs as a source of information is not free from underreporting errors in diagnosis, severity and duration of diseases. Likewise, although this study included an analysis of a large population of older adults, they are users of healthcare services at an urban institution; therefore, the reported results only represent the rates in this population. Additional population surveys will be potential sources of information to confirm these findings, and longitudinal studies will allow evaluating possible modifications of diseases patterns as consequence of their complexity.

Conclusions

This study identified relevant evidence of the health status of older adults attending primary care services that can inform health policies for this age group. In a context of growing complexity of the interrelationships among the domains resulting from this study, is reasonable to determine that healthcare services require new models of care and innovative approaches to integrate better prevention and treatment of common chronic diseases and their combinations. In this sense, is clear that priority should be directed toward primary care, since it is the frontline that must be reoriented and strengthened (13) because is this level of care where older adults with multimorbidity are often treated. The complexity of multimorbidity patterns should fuel the development of clinical practice guidelines congruent with this new scenario that also must be into the academic curriculum and continuing education programs of health care providers (14). Resilient healthcare systems should be able to tackle this challenge to be able to achieve the health objectives of the population under their care.

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References

1. Marengoni A, Anglemana S, Melisa R, et al. Aging with multimorbidity: A systematic review of the literature. Ageing Res Rev 2011;10:430–439.
2. Valderas JM, Starfield B, Sibbald B, et al. Defining comorbidity: implications for understanding health and health services. Ann Fam Med 2009;7:357–363.
3. Fortin M, Bravo G, Hudon C, et al. Prevalence of multimorbidity among adults seen in family practice. Ann Fam Med 2005;3:223–228.
4. Britt HC, Harrison CM, Miller GC, et al. Prevalence and patterns of multimorbidity in Australia. Med J Aust 2008;189:72–77.
5. Sinnige J, Braspenning J, Schellevis F, et al. The prevalence of disease clusters in older adults with multiple chronic diseases- a systematic literature review. PLoS One 2013;8:e79641.
6. Violan C, Foguet-Boreu Q, Flores-Mateo G, et al. Prevalence, determinants and patterns of multimorbidity in primary care: A systematic review of observational studies. PLoS One 2014;9:e102149.
7. Bloom DE. 7 billion and counting. Science 2011;333:562–569.
8. Cohen JE. Human population: the next half century. Science 2003;302:1172–1175.
9. WHO. Health in 2015: from MDGs, Millennium Development Goals to SDGs, Sustainable Development Goals. World Health Organization. http://apps.who.int/iris/bitstream/10665/200009/1/9789241565110_eng.pdf?ua=1. Accessed March 11, 2016.
10. WHO. Global Health Observatory data repository. Life expectancy Data by WHO region. World Health Organization (online). http://apps.who.int/gho/data/view.main.690?lang=en. Accessed March 11, 2016.
11. WHO. Global Health Observatory data repository. Population Data by WHO region. World Health Organization (online). http://apps.who.int/gho/data/view.main.POP2020?lang=en. Accessed March 11, 2016.
12. Atun R, Jaffar S, Nishtar S, et al. Improving responsiveness of health systems to non-communicable diseases. Lancet 2013;381:690–697.
13. Beaglehole R, Epping-Jordan J, Patel V, et al. Improving the prevention and management of chronic disease in low-income and middle-income countries: a priority for primary health care. Lancet 2008;372:940–949.
14. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380:37–43.
15. Salisbury C, Johnson L, Purdy S, et al. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. Br J Gen Pract 2011;61:e12–e21.
16. Salisbury C. Multimorbidity: redesigning health care for people who use it. Lancet 2012;380:7–9.
17. INEGI. Mujeres y hombres en México 2011. México: Instituto Nacional de Estadística y Geografía-Instituto Nacional de las Mujeres; 2012.
18. Gutiérrez JP, Rivera-Dommarco J, Shamah-Levy T, et al. Encuesta Nacional de Salud y Nutrición 2012. Resultados Nacionales. Cuernavaca, México: Instituto Nacional de Salud Pública; 2012.
19. Samper-Ternent R, Michaels-Obregon A, Wong R, et al. Older adults under a mixed regime of infectious and chronic diseases. Salud Publica Mex 2012;54:487–495.
20. Doubova SV, Torres-Arreola LP, Rosas-Carrasco O, et al. Calidad de la prescripción en los adultos mayores con síndrome doloroso de origen no oncológico usuarios de los servicios de Medicina Familiar. Rev Invest Clin 2007;59:428–436.
21. Islam MM, Valderas JM, Yen L, et al. Multimorbidity and comorbidity of chronic diseases among the senior Australians: Prevalence and Patterns. PLoS One 2014;9:e83783.
22. Formiga F, Ferrer A, Sanz H, et al. Patterns of comorbidity and multimorbidity in the oldest old: The Octabaix study. Eur J Intern Med 2013;24:40–44.
23. Marengoni A, Rizzuto D, Wang HX, et al. Patterns of chronic multimorbidity in the elderly population. J Am Geriatr Soc 2009;57:225–230.

24. Van den Bussche H, Koller D, Kolonko T, et al. Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. BMC Public Health 2011;11:101.
25. Chawla T, Sharma D, Singh A. Role of the renin angiotensin system in diabetic nephropathy. World J Diabetes 2010;1:141−145.
26. Rahimi Z, Zaveleh OM, Rahimi Z, et al. AT2R-1332 G: A polymorphism and diabetic nephropathy in type 2 diabetes mellitus patients. J Renal Inj Prev 2013;2:97−101.
27. Rosas-Peralta M, Lara-Esqueda A, Pastelín-Hernández G, et al. Re-encuesta Nacional de Hipertensión Arterial (RENAHTA): Consolidación Mexicana de los Factores de Riesgo Cardiovascular. Cohorte Nacional de Seguimiento. Arch Cardiol Mex 2005;75:96−111.
28. Drazner MH. The progression of hypertensive heart disease. Circulation 2011;123:327−334.
29. Rull JA, Aguilar-Salinas CA, Rojas R, et al. Epidemiology of type 2 diabetes in Mexico. Arch Med Res 2005;36:188−196.
30. Schünemann HJ, Dorn J, Grant BJ, et al. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest 2000;118:656−664.
31. Hole DJ, Watt GC, Davey-Smith G, et al. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. BMJ 1996;313:711−715.
32. Sin DD, Paul-Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? Circulation 2003;107:1514−1519.
33. Van Eeden S, Leipsic J, Paul Man SF, et al. The relationship between lung inflammation and cardiovascular disease. Am J Respir Crit Care Med 2012;186:11−16.
34. Lenze EJ, Mulsant BH, Shear MK, et al. Anxiety symptoms in elderly patients with depression what is the best approach to treatment? Drugs Aging 2002;19:753−760.
35. Eric J, Lenze EJ, Mulsant BH, et al. Comorbidity of depression and anxiety disorders in later life. Depress Anxiety 2001;14:86−93.
36. Schäfer I, Von-Leitner EC, Schön G, et al. Multimorbidity patterns in the elderly: A new approach of diseases clustering identifies complex interrelations between chronic conditions. PLoS One 2010;5:e15941.
37. Chung HY, Cesari M, Anton S, et al. Molecular inflammation: Underpinnings of aging and age related diseases. Ageing Res Rev 2009;8:18−30.
38. Pupek M, Pawłowicz R, Lindner K, et al. Occurrence of fibronectin−fibrin complexes in plasma of patients with multimorbidity due to the inflamm-aging phenomenon. Exp Gerontol 2016;77:19−28.
39. Foguet-Boreu Q, Violán C, Rodriguez-Blanco T, et al. Multimorbidity patterns in elderly primary health care patients in a south mediterranean european region: A cluster analysis. PLoS One 2015;10:e0141155.
40. Cornell JE, Pugh JA, Williams JW, et al. Multimorbidity clusters: Clustering binary data from multimorbidity clusters: Clustering binary data from a large administrative medical database. Appl Multivar Res 2007;12:163−182.
41. Eyre H, Kahn R, Robertson RM, et al. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. Diabetes Care 2004;27:1812−1824.
42. Vu T, Finch CF, Day L. Patterns of comorbidity in community-dwelling older people hospitalized for fall-related injury: A cluster analysis. BMC Geriatr 2011;11:45.