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Multimorbidity at sea level and high-altitude urban and rural settings: The CRONICAS Cohort Study

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Abstract

Objective: To characterize the prevalence and clustering of multimorbidity in four diverse geographical settings in Peru.

Methods: Multimorbidity, defined as having ≥2 chronic conditions, was studied in adults aged ≥35 years in four diverse settings in Peru: Lima, Tumbes, and urban and rural Puno. Six of these conditions (alcohol disorder, asthma, chronic obstructive pulmonary disease, depression, diabetes, and hypertension) were cataloged as objectively ascertained chronic conditions and paired in dyads to explore clusters of multimorbidity.

Results: We analyzed data from 2890 adults, mean age 55.2 years, 49% males. Overall, 19.1% of participants had multimorbidity, ranging from 14.7% in semi-urban Tumbes to 22.8% in Lima. The dyads with the highest coexistence (approximately 20%) were observed in hypertension and diabetes in Tumbes, whereas the dyads with lowest coexistence (approximately 1%) were those involving asthma in all study sites. In terms of clusters, Tumbes showed a predominance of hypertension and diabetes, urban and rural Puno a predominance of depression and alcohol disorders, and Lima a higher degree of coexistence of all of the six conditions than in the other clusters.

Conclusion: Multimorbidity is common and the pattern of clusters is highly heterogeneous. The conditions to prioritize will vary in each setting.

Keywords

Multimorbidity, epidemiology, urbanization, Peru

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What is already known?

The coexistence of chronic conditions, also known as multimorbidity, is common.

There is very limited understanding of which clusters of multimorbidity are more common in resource-poor settings.

What are the new findings?

In this population-based study covering a combination of sea level and high-altitude urban and rural settings from a low- and middle-income country, we studied both physical and mental disorders and multimorbidity and its clustering patterns.

We confirm that multimorbidity is common, and more so in urban areas, and provide unique insights into the heterogeneous pattern of clustering of chronic conditions across sea level and high altitude settings.

What do the new findings imply?

Understanding the burden of multimorbidity and the patterns of clustering of chronic conditions across settings is key to inform a range of disciplines from health policy, including resource allocation, to guide prevention efforts and clinical practice.

Introduction

Noncommunicable diseases (NCDs), including cardiovascular disease, diabetes, chronic lung diseases, and cancer, are of concern to sustainable development agendas because of their considerable burden to nations, particularly in low- and middle-income countries (LMICs).[1] Many LMICs have experienced important and rapid changes as expressed by the demographic, economic, epidemiological, nutritional, and urban transitions observed in recent decades, translating into populations with longer life expectancies and with a growing burden of NCDs, particularly in urban areas. Populations in LMICs confront major challenges for patient care, health system's organization, and health-care delivery. In addition, the dual burden of chronic and infectious diseases introduce further challenges, and opportunities, for multimorbidity.[2]

Multimorbidity, commonly defined as the coexistence of $\geq$2 chronic conditions,[3] provides a different perspective to evaluate current challenges and gaps in population's health[4–6] and includes both physical and mental disorders. Yet, it poses major challenges, particularly in LMICs,[7] where the monitoring of NCDs and multimorbidity in resource-limited settings has been largely hampered by inadequate surveillance systems with poor quality of data.[8] In high-income settings, the study of multimorbidity usually takes advantage of the availability of electronic health-care records and claims data,[4,9–12] a resource that is not necessarily available in many LMICs. Some examples of studies of multimorbidity in LMICs setting exist,[13–18] and the understanding of clusters of multimorbidity has been established but with a high heterogeneity in their methodological approach[19–21] and largely based on studies from high-income settings, yet it remains limited with regard to the evidence arising from LMICs.[7] Researching not only the existence of multimorbidity in LMICs but its different clusters have been established as a priority in the field.[6,7]

We sought to characterize the prevalence and clustering of multimorbidity in four diverse geographical settings, taking advantage of a population-based cohort study in Peru. Given the high burden of NCDs in urban areas, we hypothesized that multimorbidity would be greater in urban than in rural settings.

Methods

Study design and setting

Cross-sectional assessment of chronic conditions of an ongoing longitudinal cohort study conducted in four Peruvian settings that differed by degree of urbanization, level of ambient versus household air pollution, and high altitude,[22] Pampas de San Juan de Miraflores, a periurban community in Lima with 60,000 people in about 4 km^2; Puno, a city in southeastern Peru at 3825 m above sea level with 150,000 inhabitants where biomass fuels are used almost exclusively in rural villages; and a group of communities in Tumbes, in northern Peru, with about 20,000 people in 80 km^2, where rural villages have become intermixed with rapidly growing urban sections.

Participants

Individuals aged $\geq$35 years, full-time residents in the area, were invited to participate in the study. We identified a sex-and-age stratified random sample (35–44, 45–54, 55–64 and $\geq$65 years) of potentially eligible subjects and only one participant per household was enrolled. In Puno, we also stratified recruitment by urban versus rural locations. Recruitment began in September 2010 and was conducted until about 1000 participants with complete information per site were enrolled.

Study procedures

Fieldwork personnel and site coordinators were trained on participant selection, protection and ethics of human subjects, informed consent procedures, interviewing, clinical assessment, and coding. The modules included formal lectures and demonstrations. All team members received a copy of an Interviewer's Manual. Field personnel and coordinators were capable of conducting interviews and performing clinical assessments. A detailed description of training was provided elsewhere.[22]

For the study of multimorbidity, no electronic medical records were available, hence information on a certain number of conditions were generated through a variety of approaches. Upon enrollment, participants were asked to respond to a sociodemographics, risk factors, and history of cardiopulmonary symptoms questionnaire. Fieldworkers in rural areas were fluent in Aymara or Quechua, and the survey was administered face-to-face by the study team to those with poor literacy. Fieldworkers measured weight, height, blood pressure, and spirometry before and after bronchodilators. Fasting blood samples were obtained and analyzed in a single facility, and the quality of assays was checked with regular external standards and internal duplicate assays monitored by BioRad (www.biorad.com). Plasma glucose was measured using an enzymatic colorimetric method (GOD-PAP; Modular P-E/Roche-Cobas, Germany). Spirometry was conducted using the Easy-On-PC spirometer (NDD, Zurich, Switzerland) before and after 200 mcg of inhaled salbutamol via a spacer. Trained technicians measured pre- and post-bronchodilator spirometry in participants following joint American Thoracic Society and European Respiratory Society guidelines,[23] and we adapted a standardized grading system for quality control, review, and interpretation. Detailed information of measurement techniques and evaluation were reported elsewhere.[22]

Study variables

Since this analysis was performed using baseline information of participants enrolled in a cardiopulmonary cohort, the most common chronic noncommunicable conditions related to cardiovascular, metabolic, and pulmonary diseases were evaluated. Multimorbidity, the primary outcome of interest and studied within a cardiopulmonary cohort, was defined as $\geq$2 chronic conditions of the following 12: alcohol disorder, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), depression, gastroesophageal reflux, heart disease, hypertension, lung cancer, peripheral artery disease, stroke, and type 2 diabetes mellitus. We provide a detailed summary of definitions of chronic conditions used for this study in Table 1. Six of these conditions, that is, alcohol disorder, asthma, COPD, depression, diabetes, and hypertension, were cataloged as objectively ascertained chronic conditions and paired in dyads to explore clusters of multimorbidity. We based this decision on the capability to objectively ascertain these by clinical assessments, medication use, laboratory tests, and use of validated scales.

Other variables included sex, age categories (35–44, 45–54, 55–64, and $\geq$65 years), education (<6 years, 7–11 years, and 12 or more years), socioeconomic status (wealth index based on household income, assets, and household facilities).[34]

Table 1. Variable definitions.

Chronic condition	Definition used
Alcohol disorder	AUDIT score $\geq$8 points.[24] The AUDIT has been previously validated in Spanish[25] and used in Peru.[26]
Asthma	Two out of the following three conditions: clinical diagnosis of asthma, current use of asthma medications, or wheezing in the last 12 months.[27]
Chronic bronchitis	Presence of phlegm production on most days for at least 3 months a year for 2 consecutive years.[28]
COPD	Presence of airflow limitation characterized by a post-bronchodilator ratio of FEV_1/FVC < 70%.[23]
Depression	A score of $\geq$23 in the Spanish-validated version of the Center for Epidemiologic Studies Depression Scale.[29,30] This higher cutoff value for "probable depression" correlates more closely with current depression status.[29]
Gastroesophageal reflux	Self-report of physician diagnosis.
Heart disease	Self-report physician diagnosis of heart failure, arrhythmia, and coronary artery disease (i.e. angina and myocardial infarction) assessed using standardized questionnaires (see http://www2.phri.ca/pure/home.htm).
Hypertension	Any of the following conditions: SBP $\geq$ 140 mmHg; DBP $\geq$ 90 mmHg; and self-report of physician diagnosis and current use of antihypertensive drugs.[31]
Lung cancer	Self-report of physician diagnosis.
Peripheral artery disease	Defined as an ankle–brachial index (systolic blood pressure in the ankle divided by the systolic blood pressure in the arm) under 0.91.[32]
Stroke	Self-report of physician diagnosis.
Type 2 diabetes	Any of the following conditions: fasting glucose $\geq$126 mg/dL; self-report of physician diagnosis and currently receiving antihyperglycemic medications.[33]

COPD: chronic obstructive pulmonary disease; AUDIT: Alcohol Use Disorders Identification Test; FEV_1/FVC: forced expiratory volume in 1 s to forced vital capacity; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Biostatistical methods

Overall prevalence estimates of multimorbidity and single chronic conditions, and corresponding 95% CIs, were calculated, stratified by site. We then examined the frequency of co-occurrence between pairs of objectively assessed chronic conditions by study site. We used a multivariable multinomial logistic regression to determine the association between multimorbidity and sociodemographic factors. Statistical analyses were conducted in Stata (StataCorp, College Station, Texas, USA) and R (www.r-project.org).

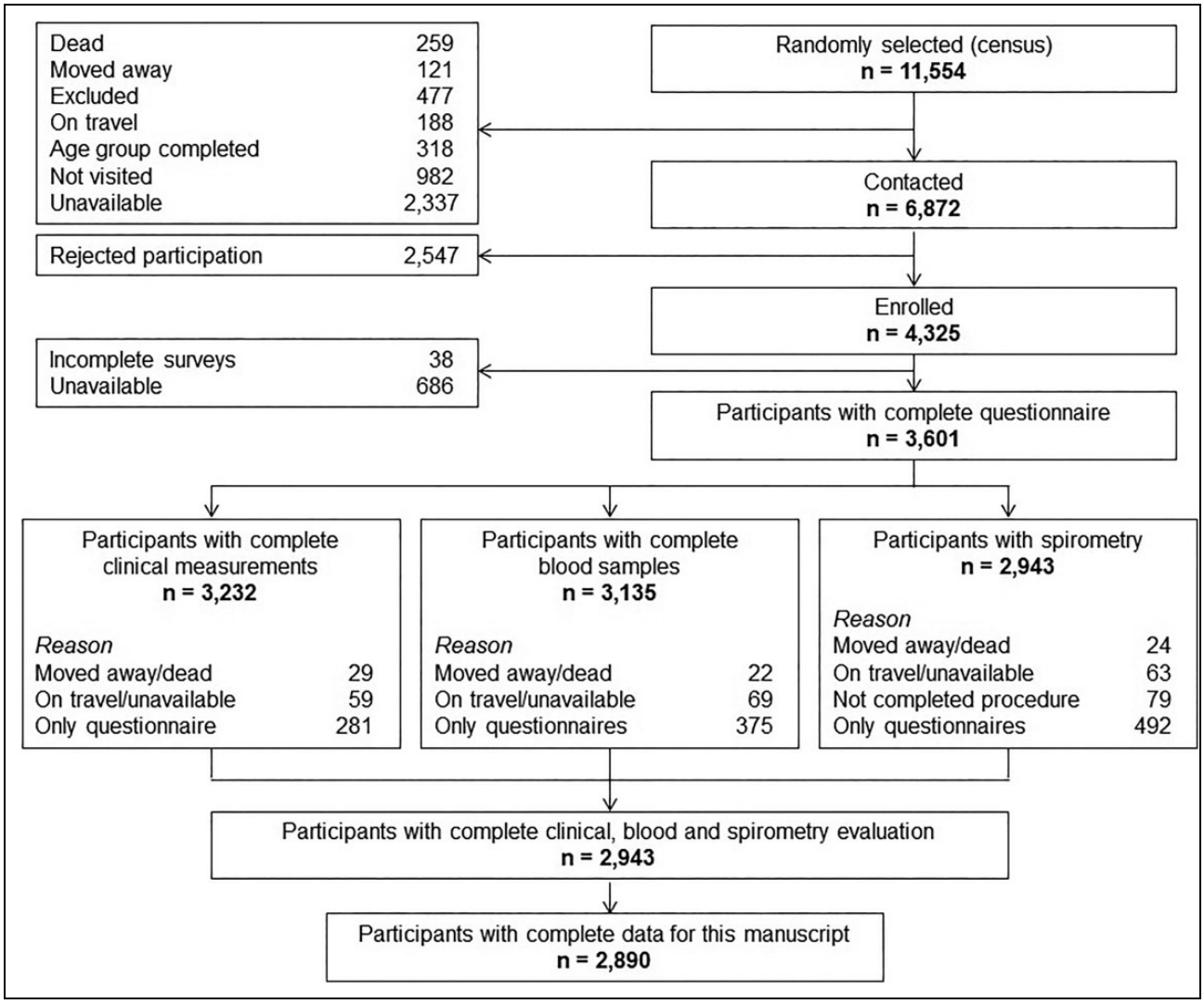

Figure 1. Study participants flowchart, all sites.

Research ethics

All participants provided verbal informed consent after our research team read the entire informed consent document to them and any questions were answered. Informed consents were verbal because of high illiteracy rates. The study was approved by the Institutional Review Boards at Universidad Peruana Cayetano Heredia and A.B. PRISMA, in Lima, Peru, and at the Bloomberg School of Public Health, Johns Hopkins University, in Baltimore, USA.

Results

Participant characteristics

Of the 6872 contacted individuals, 3601 (52.4%) agreed to participate and had a complete questionnaire assessment. Of these, 2890 participants (80.3%) completed all clinical, blood, and spirometry evaluations (Figure 1, detailed flowcharts, for each geographical site, are provided in Supplemental Materials 1 to 3). Participant characteristics by multimorbidity status (Table 2) indicate that 21.6% had $\geq$12 years of education, and 89.9% had a family income <USD 550 dollars per month. Multimorbidity was more common in urban areas, among males, older adults, and those with lower education and lower socioeconomic status.

Prevalence of single chronic conditions

The number of chronic conditions in our study sample ranged from zero to six. A total of 44.9% (95%CI 43.1–46.7%) of participants did not have any chronic condition, and 36.0% (95%CI 34.2–37.8%) had only one chronic condition. Hypertension, depression, and alcohol disorder were the most prevalent chronic conditions across all settings, but with different patterns between settings (Table 3). The less prevalent conditions across sites were lung cancer and stroke.

Table 2. Population characteristics according to the number of chronic conditions.

	Number of chronic conditions[a]			
	0	1	≥2	*p* Value
Sex				
Female	695 (47.4%)	501 (34.2%)	270 (18.4%)	0.02
Male	602 (42.3%)	540 (37.9%)	282 (19.8%)	
Age				
35–44 years	404 (56.1%)	236 (32.8%)	80 (11.1%)	<0.001
45–54 years	362 (48.4%)	278 (37.2%)	108 (14.4%)	
55–64 years	316 (42.4%)	270 (36.2%)	159 (21.3%)	
65+ years	215 (31.9%)	255 (37.8%)	205 (30.4%)	
Education level				
<6 years	510 (39.6%)	494 (38.3%)	285 (22.1%)	<0.001
7–11 years	476 (48.8%)	330 (33.8%)	170 (17.4%)	
12 or more years	311 (49.9%)	216 (34.7%)	96 (15.4%)	
Socioeconomic status (tertiles)				
Low	350 (40.1%)	345 (39.6%)	177 (20.3%)	0.02
Middle	461 (46.1%)	353 (35.3%)	186 (18.6%)	
High	486 (47.7%)	343 (33.7%)	189 (18.6%)	
Study site				
Lima (Capital, urban)	432 (43.8%)	330 (33.4%)	225 (22.8%)	<0.001
Puno (urban)	191 (39.4%)	196 (40.4%)	98 (20.2%)	
Puno (rural)	178 (37.5%)	206 (43.5%)	90 (19.0%)	
Tumbes (semi-urban)	496 (52.5%)	309 (32.7%)	139 (14.7%)	

[a]Percentages are shown in rows. Results may not add up due to missing values.

Table 3. Prevalence of multimorbidity and single chronic conditions by study site, according to degree of urbanization.

	Lima, highly urbanized ($n = 987$)	Puno, urban ($n = 485$)	Puno, rural ($n = 474$)	Tumbes, semi urban ($n = 944$)	Overall ($n = 2890$)
Multimorbidity, % (95% CI)	22.8 (20.2–25.5)	20.2 (16.7–24.1)	19.0 (15.5–22.8)	14.7 (12.5–17.1)	19.1 (17.7–20.6)
Single chronic conditions, % (95% CI)					
Alcohol disorder	12.1 (10.1–14.3)	18.6 (15.2–22.3)	17.5 (14.2–21.2)	11.3 (9.4–13.5)	13.8 (12.6–15.1)
Asthma	4.8 (3.5–6.3)	1.2 (0.5–2.7)	0.0 (0.0–0.8)	1.0 (0.4–1.8)	2.1 (1.6–2.7)
Chronic bronchitis	8.9 (7.2–10.9)	7.0 (4.9–9.7)	8.2 (5.9–11.1)	1.3 (0.7–2.2)	6.0 (5.1–6.9)
COPD	6.1 (4.7–7.8)	6.2 (4.2–8.7)	9.9 (7.4–13.0)	3.5 (2.4–4.9)	5.9 (5.1–6.8)
Depression	17.6 (15.3–20.2)	20.6 (17.1–24.5)	31.0 (26.9–35.4)	5.7 (4.3–7.4)	16.4 (15.1–17.8)
Gastroesophageal reflux	6.1 (4.7–7.8)	9.9 (7.4–12.9)	3.6 (2.1–5.7)	0.1 (0.0–0.6)	4.4 (3.6–5.2)
Heart disease	5.6 (4.2–7.2)	5.8 (3.9–8.2)	0.2 (0.0–1.2)	3.3 (2.2–4.6)	4.0 (3.3–4.8)
Hypertension	19.8 (17.3–22.4)	10.5 (7.9–13.6)	11.2 (8.5–14.4)	26.1 (23.3–29.0)	18.9 (17.4–20.3)
Lung cancer	0.1 (0.0–0.6)	0.0 (0.0–0.8)	0.0 (0.0–0.8)	0.0 (0.0–0.4)	0.03 (0.0–0.2)
Peripheral artery disease	1.4 (0.8–2.4)	1.0 (0.3–2.4)	0.4 (0.1–1.5)	4.4 (3.2–6.0)	2.2 (1.7–2.8)
Stroke	1.0 (0.5–1.9)	0.2 (0.0–1.1)	0.0 (0.0–0.8)	0.2 (0.0–0.8)	0.4 (0.2–0.8)
Type 2 diabetes	5.5 (4.1–7.1)	6.6 (4.6–9.2)	3.2 (1.8–5.2)	9.7 (7.9–11.8)	6.7 (5.8–7.7)

COPD: chronic obstructive pulmonary disease; CI: confidence interval.

Hypertension was more common at sea level (Tumbes and Lima) than at high altitude (urban and rural Puno), whereas depression and alcohol disorders were more prevalent at high altitude than at sea level. Some other conditions were mainly prevalent in only one of the four sites of study, such as asthma in Lima or peripheral artery disease in Tumbes. The prevalence of chronic bronchitis and COPD in Tumbes was lower than all the other sites. History of heart disease and gastroesophageal reflux were more commonly reported in urban than rural sites.

Certain single chronic conditions had a higher prevalence in males than in females: alcohol disorder (25% vs. 3%; $p < 0.001$) and COPD (8% vs. 4%; $p < 0.001$); whereas others were higher in females than in males: depression (25% vs. 8%; $p < 0.001$), asthma (3% vs.1%; $p = 0.007$), heart disease (5% vs. 3% $p = 0.03$), and gastroesophageal reflux (5% vs. 4%; $p = 0.04$).

Table 4. Distribution of pairs of objectively assessed chronic conditions.[a]

	Alcohol disorder ($n = 401$)	Asthma ($n = 62$)	COPD ($n = 173$)	Diabetes ($n = 194$)	Depression ($n = 477$)	Hypertension ($n = 548$)
Alcohol disorder		6.5% (4)	16.2% (28)	8.3% (16)	10.7% (51)	11.9% (65)
Asthma	1.0% (4)		6.9% (12)	2.1% (4)	4.2% (20)	2.4% (13)
COPD	7.0% (28)	19.4% (12)		2.6% (5)	8.0% (38)	7.9% (43)
Diabetes	4.0% (16)	6.5% (4)	2.9% (5)		6.3% (30)	13.7% (75)
Depression	12.7% (51)	32.3% (20)	22.0% (38)	15.5% (30)		13.9% (76)
Hypertension	16.2% (65)	21.0% (13)	24.9% (43)	38.7% (75)	15.9% (76)	

COPD: chronic obstructive pulmonary disease.

[a]Values shown in this table are to be read in a vertical manner. For each index condition, found in the columns, we calculated the proportion of participants that had an additional comorbid chronic condition. For example, 19% of participants who reported having asthma also had COPD, whereas 6% had diabetes and 32% had depression, and so on. Similarly, among all those with COPD, 7% reported having asthma, 3% had diabetes, 22% had depression, and so on. Columns do not add up to 100% because not all individuals do have an additional comorbid condition.

Prevalence and clusters of multimorbidity

Multimorbidity was present in 19% of participants and was more prevalent in urban than in rural settings. In terms of geographical altitude, the two high altitude sites (Puno urban and Puno rural) had a similar prevalence of multimorbidity, 20% and 19%, respectively, whereas the prevalence at the sea level sites (Lima and Tumbes) ranged from 23% to 15% (Table 3).

The distribution of pairs of objectively ascertained chronic conditions, only six of the total conditions evaluated, shows that hypertension was the most common condition coexisting with all the other conditions except asthma, hypertension was present in 39% of people with diabetes, and depression was present in 32% of those with asthma (Table 4).

As shown in Figure 2 and accounting for disease prevalence and the size of coexistence of single chronic conditions, different clusters of multimorbidity were observed in different areas. Depression followed by hypertension and alcohol disorder were, in general, the conditions with the highest prevalences by study sites. The highest coexistence of conditions (approximately 20%) was observed in hypertension and diabetes in Tumbes, whereas the dyads with lowest coexistence (approximately 1%) were those involving asthma in all study sites. Combining the disease prevalence and the coexistence of single conditions affords the visualization of different clusters of multimorbidity by study site, with Tumbes showing a predominance of hypertension and diabetes, urban and rural Puno showing a predominance of depression and alcohol disorders, and Lima showing a higher degree of coexistence of all of the six conditions than in the other clusters.

Determinants of multimorbidity

We summarized the single variable and multivariable relationship between multimorbidity and sociodemographic factors in Table 5. Males were 27% more likely than females to have multimorbidity. Older subjects were also more likely to have multimorbidity, up to four times higher in adults aged ≥65 years than in those aged 35–44 years. There was no association between multimorbidity and either education or socioeconomic status. Participants who lived in urban settings (Lima and Puno urban) had a 50% higher odds (odds ratio = 1.50, 95% confidence interval 1.32–1.70) of having multimorbidity than did their counterparts who lived in nonurban settings (Puno rural and Tumbes).

Discussion

The clustering of multimorbidity is highly heterogenous, and one in five participants were classified as having multimorbidity. Given the diversity of geographical scenarios and study sites, our findings signal to major challenges for chronic disease prevention and health-care delivery in resource-poor LMIC settings. Of the chronic conditions studied, depression, hypertension, and alcohol disorder were the most prevalent. Despite differences in multimorbidity by degree of urbanization, a heterogeneous pattern of clusters of multimorbidity was observed. Knowledge of such heterogeneity can shape local policies and resource allocation.

Multimorbidity has been reported to be a leading driver of global disability, and its contribution will continue to increase with an aging population.[35] Current structures of health systems, including in LMICs where specialized human resources are scarce, are not designed to deal with multimorbidity, requiring "a radical rethink of health systems [to] enable preparation for the rapid transition that has brought such a burden of multimorbidity and disability."[36]

While many examples of studies of multimorbidity in LMIC setting exist,[13–18] most comparisons of multimorbidity prevalence estimates will likely differ because of differences in study design and setting; differences in the age and sex distributions of the population under study; whether chronic conditions were measured or self-reported; and because of limited data availability around noncommunicable chronic diseases, including mental health, in most of LMICs. In addition, the controversy

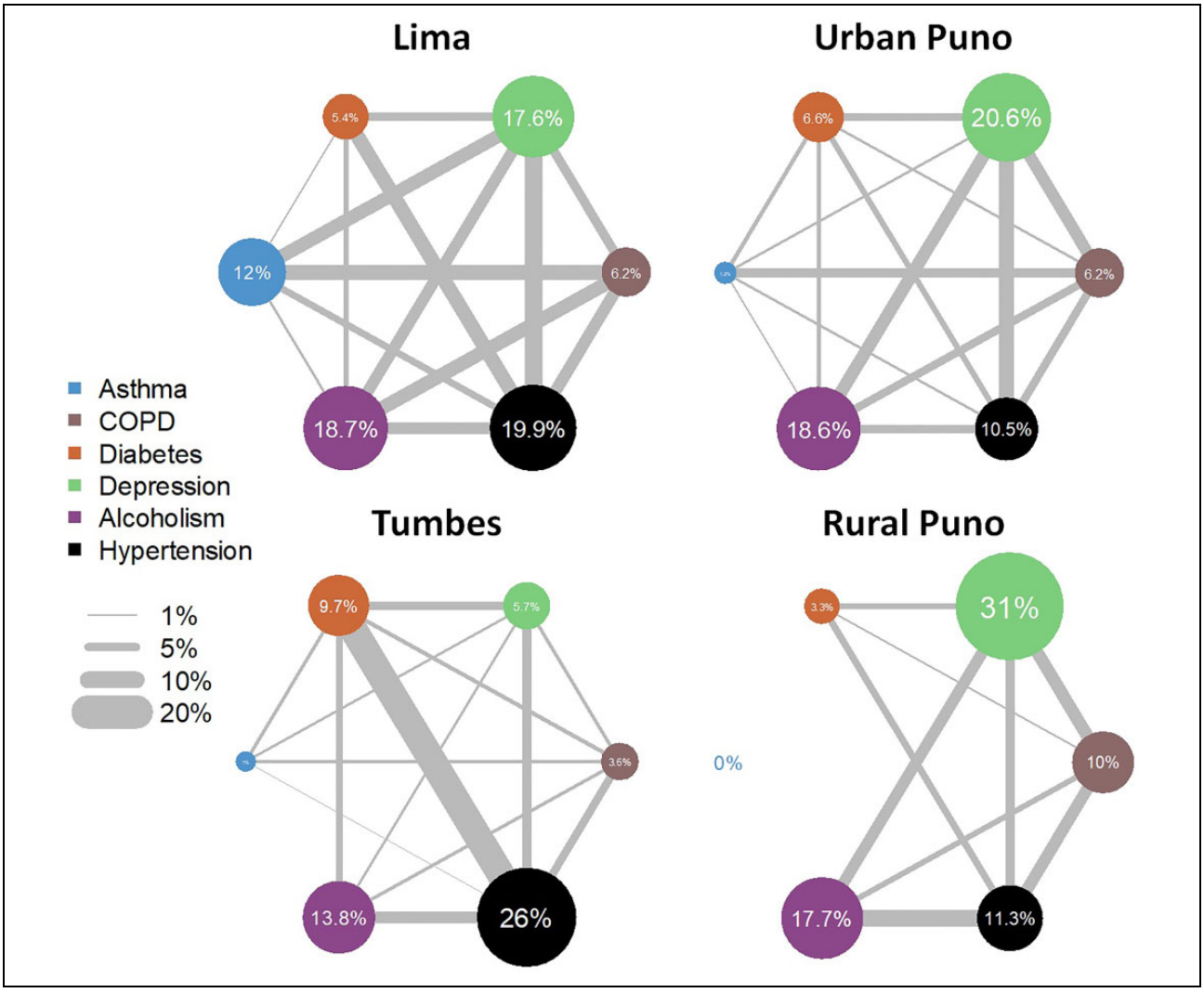

Figure 2. Clusters of multimorbidity by dyads of objectively assessed chronic conditions according to study site.

surrounding the different manners of aggregation of multimorbidity and limited data generation for NCDs will certainly restrict a direct comparison of prevalence estimates with other studies.

In our study, we examined prevalence of multimorbidity ($\geq$2 conditions) using both measured and self-reported chronic conditions across a variety of geographical settings, and the prevalence of multimorbidity, considering only 12 conditions, was almost 20%. The prevalence of multimorbidity has been reported at 33% in Argentina,[37] 64% in Mexico,[16] and ranging from 17.5% in Colombia to 37.3% in Jamaica.[13] Even in high-income countries, previous investigations have found a highly heterogeneous prevalence of multimorbidity due to differences in sources of data and type of participants. For example, the prevalence of multimorbidity in Scotland (primary care setting, 40 conditions studied), United States (medicare data, 21 chronic conditions), Australia (children and adults attending general practice, physician-reported chronic disease data), and Canada (primary care setting, physician-reported multimorbidity) was 23%,[4] 20%,[38] 47%,[39] and 89%,[40] respectively. Another study in the United States examined six self-reported chronic conditions and found that the prevalence of multimorbidity was 31% in 13,232 adults aged $\geq$50 years.[41]

To inform action, both in the clinical and policy fronts, our findings contribute with important messages, for example, hypertension, depression, and alcohol disorder, were the most prevalent entities and guide toward a better understanding of the interactions between physical and mental chronic conditions, including opportunities for integration.[42] Our study found that diabetes prevalence was heterogeneous by study site, and among those with diabetes, its co-occurrence with hypertension was particularly high, almost 40%. We also show a higher burden of COPD in rural Puno and a high burden of asthma in Lima. Our study also describes the importance of interaction effects between chronic pulmonary diseases and other cardiometabolic comorbidities, as previously described.[43,44] Chronic pulmonary conditions like COPD may be associated with

Table 5. Factors associated with multimorbidity using multinomial logistic regression.[a]

	Multinomial logistic regression	
	1 versus 0	≥2 versus 0
Sex, OR (95%CI)		
Female	1 (Reference)	1 (Reference)
Male	**1.34 (1.13–1.60)**	**1.27 (1.03–1.57)**
Age, OR (95%CI)		
35–44 years	1 (Reference)	1 (Reference)
45–54 years	**1.27 (1.01–1.60)**	**1.45 (1.05–2.01)**
55–64 years	**1.35 (1.07–1.72)**	**2.40 (1.75–3.30)**
65+ years	**1.72 (1.31–2.24)**	**4.22 (3.02–5.90)**
Education level, OR (95%CI)		
<6 years	1 (Reference)	1 (Reference)
7–11 years	**0.77 (0.62–0.95)**	0.86 (0.66–1.11)
12 or more years	**0.71 (0.54–0.93)**	0.72 (0.51–1.02)
Socioeconomic status (tertiles), OR (95%CI)		
Low	1 (Reference)	1 (Reference)
Middle	0.90 (0.72–1.12)	0.88 (0.67–1.16)
High	0.82 (0.64–1.05)	0.79 (0.58–1.08)
Study site, OR (95%CI)		
Lima (Capital, urban)	1 (Reference)	1 (Reference)
Puno (urban)	**1.48 (1.13–1.94)**	1.08 (0.78–1.50)
Puno (rural)	1.28 (0.96–1.69)	0.82 (0.58–1.17)
Tumbes (semi-urban)	**0.74 (0.60–0.91)**	**0.48 (0.37–0.63)**

OR: odds ratio; CI: confidence interval.
[a]Estimates presented in bold are those with p values <0.05.

low-grade systemic inflammation which may consequently increase the risk of cardiovascular and metabolic diseases.[45] In our study, participants with COPD also had comorbid hypertension (25%) and comorbid depression (22%), both higher than the average in the whole study sample.

The interplay of geography and urbanization, more or less urban together with high or lower altitude, has a major role in the expression of the phenotypes of chronic conditions. While we observed a gradient in the prevalence of multimorbidity according to study sites and a tendency toward higher prevalences in the urban areas, there was no a clear pattern by geographical altitude. Our study advances the understanding of the coexistence of chronic conditions across a diversity of settings, including the identification of specific clusters of multimorbidity, and this information can guide prioritization and resource allocation. A better understanding of multimorbidity, and its predominant clusters, on health outcomes will become increasingly important in resource-limited settings as the coexistence of chronic conditions may increase symptom burden, worsen functional performance,[46] and increase hospitalization and mortality risk.[47,48] Many studies have reported an association between multimorbidity and low socioeconomic status, but in the case of multimorbidity in LMICs, as in our study, this is not always the case.[7] One potential explanation is that our participants and the study settings are from low-income areas relative to the national average. Another possibility may be related to the fact that Peru, as a population, has experienced a recent demographic transition with increases in life expectancy, and the burden of multimorbidity is in its early stages.

Major strengths of our work include the population-based and random selection of participants in sea level and high-altitude sites, the measurement of objective clinical and laboratory markers including spirometry, and the presence of both physical and mental health conditions. Some limitations are also worth considering. Only 12 chronic conditions, most of them related to cardiometabolic and pulmonary diseases, were considered, and some of them were self-reported. In general, substantial agreement between self-report questionnaire and medical record data has been reported, except for the case of heart failure.[49] In addition, although some selection bias might arise due to low response rate, the main priority in this cohort study was to guarantee low attrition during follow-up. Finally, while the aggregation of multimorbidity as two or more chronic conditions is helpful, but it does not provide an indication of the severity of the conditions studied, its complications, the quality of life of individuals, and its role with regard to future major events or hard outcomes. At this stage, however, we consider relevant the purpose of the multimorbidity approach as this enabled us to move beyond the single-disease framework.

In summary, our study found that one in five subjects have multimorbidity, and it was more common in urban than rural areas, and the patterns of clusters of multimorbidity are not necessarily shared across sites. Understanding and addressing the complexity of the clustering of multimorbidity in LMICs calls for the need to develop an integrated approach in the management and care of chronic conditions. Tackling multimorbidities is the way forward, particularly in settings where human and financial resources are scarce, and health services are fragmented. The heterogeneous patterns of clusters of multimorbidity observed across sea level and high-altitude areas call to revisit the typical countrywide "one-size-fits-all" type of policies to address single chronic conditions, as the conditions to prioritize will vary in each setting.

CRONICAS Cohort Study Group

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Author contributions

JJM, LS, RHG, and WC conceived, designed, and supervised the overall study. JJM, ABO, and WC coordinated and supervised fieldwork activities in Lima, Tumbes, and Puno. JJM, ABO, and WC developed the idea for this manuscript and wrote the first draft. ABO and WC led the statistical analysis. All authors participated in writing of manuscript, provided important intellectual content, and gave their final approval of the version submitted for publication.

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Data availability

The data set and code used for this analysis are available at https://figshare.com/articles/CRONICAS_Cohort_Study_Baseline_Multimorbidity/748212.

Supplemental material

Supplemental material for this article is available online.

References

1. Nugent R, Bertram MY, Jan S, et al. Investing in non-communicable disease prevention and management to advance the Sustainable Development Goals. *Lancet* 2018; 391(10134): 2029–2035.
2. Oni T and Unwin N. Why the communicable/non-communicable disease dichotomy is problematic for public health control strategies: implications of multimorbidity for health systems in an era of health transition. *Int Health* 2015; 7(6): 390–399.
3. Diederichs C, Berger K and Bartels DB. The measurement of multiple chronic diseases—a systematic review on existing multimorbidity indices. *J Gerontol A Biol Sci Med Sci* 2011; 66(3): 301–311.
4. 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(9836): 37–43.
5. NICE: Multimorbidity: clinical assessment and management, https://www.nice.org.uk/guidance/ng56. (2017, accessed 15 September 2017).
6. The Academy of Medical Sciences. *Addressing the global challenge of multimorbidity: lessons from BRICS countries*. London: Academy of Medical Sciences, 2017.
7. The Academy of Medical Sciences. *Multimorbidity: a priority for global health research*. London: Academy of Medical Sciences, 2018.
8. Alwan A, Maclean DR, Riley LM, et al. Monitoring and surveillance of chronic non-communicable diseases: progress and capacity in high-burden countries. *Lancet* 2011; 376(9755): 1861–1868.
9. Wyatt KD, Stuart LM, Brito JP, et al. Out of context: clinical practice guidelines and patients with multiple chronic conditions: a systematic review. *Med Care* 2014; 52(Suppl 3): S92–S100.
10. Nicholson K, Terry AL, Fortin M, et al. Examining the prevalence and patterns of multimorbidity in Canadian primary healthcare: a methodologic protocol using a national electronic medical record database. *J Comorb* 2015; 5: 150–161.
11. Schafer I, Kaduszkiewicz H, Nguyen TS, et al. Multimorbidity patterns and 5-year overall mortality: results from a claims data-based observational study. *J Comorb* 2018; 8(1): 2235042X18816588.
12. Willadsen TG, Siersma V, Nicolaisdottir DR, et al. Multimorbidity and mortality: a 15-year longitudinal registry-based nationwide Danish population study. *J Comorb* 2018; 8(1): 2235042X18804063.
13. Macinko J, Andrade FCD, Nunez BP, et al. Primary care and multimorbidity in six Latin American and Caribbean countries. *Rev Panam Salud Publica* 2019; 43: e8.
14. Afshar S, Roderick PJ, Kowal P, et al. Multimorbidity and the inequalities of global ageing: a cross-sectional study of 28 countries using the world health surveys. *BMC Public Health* 2015; 15: 776.
15. Arokiasamy P, Uttamacharya U, Jain K, et al. The impact of multimorbidity on adult physical and mental health in low- and middle-income countries: What does the study on global ageing and adult health (SAGE) reveal? *BMC Med* 2015; 13: 178.
16. Garin N, Koyanagi A, Chatterji S, et al. Global multimorbidity patterns: a cross-sectional, population-based, multi-country study. *J Gerontol A Biol Sci Med Sci* 2016; 71(2): 205–214.
17. Stubbs B, Koyanagi A, Veronese N, et al. Physical multimorbidity and psychosis: comprehensive cross sectional analysis including 242,952 people across 48 low- and middle-income countries. *BMC Med* 2016; 14(1): 189.

18. Vancampfort D, Koyanagi A, Ward PB, et al. Chronic physical conditions, multimorbidity and physical activity across 46 low- and middle-income countries. *Int J Behav Nutr Phys Act* 2017; 14(1): 6.
19. Prados-Torres A, Calderon-Larranaga A, Hancco-Saavedra J, et al. Multimorbidity patterns: a systematic review. *J Clin Epidemiol* 2014; 67(3): 254–266.
20. 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(7): e102149.
21. Fortin M, Stewart M, Poitras ME, et al. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012; 10(2): 142–151.
22. Miranda JJ, Bernabe-Ortiz A, Smeeth L, et al. Addressing geographical variation in the progression of non-communicable diseases in Peru: the CRONICAS cohort study protocol. *BMJ Open* 2012; 2(1): e000610.
23. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; 26(2): 319–338.
24. Daeppen JB, Yersin B, Landry U, et al. Reliability and validity of the alcohol use disorders identification test (AUDIT) imbedded within a general health risk screening questionnaire: results of a survey in 332 primary care patients. *Alcohol Clin Exp Res* 2000; 24(5): 659–665.
25. Alvarado ME, Garmendia ML, Acuna G, et al. Assessment of the alcohol use disorders identification test (AUDIT) to detect problem drinkers. *Rev Med Chil* 2009; 137(11): 1463–1468.
26. Ludford KT, Vagenas P, Lama JR, et al. Screening for drug and alcohol use disorders and their association with HIV-related sexual risk behaviors among men who have sex with men in Peru. *PLoS One* 2013; 8(8): e69966.
27. Lodrup Carlsen KC, Haland G, Devulapalli CS, et al. Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study. *Allergy* 2006; 61(4): 454–460.
28. de Oca MM, Halbert RJ, Lopez MV, et al. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. *Eur Respir J* 2012; 40(1): 28–36.
29. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977; 1(3): 385–401.
30. Ruiz-Grosso P, Loret de Mola C, Vega-Dienstmaier JM, et al. Validation of the Spanish Center for Epidemiological Studies Depression and Zung Self-rating Depression Scales: a comparative validation study. *PLoS One* 2012; 7(10): e45413.
31. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; 42(6): 1206–1252.
32. Grenon SM, Gagnon J and Hsiang Y. Video in clinical medicine. Ankle–brachial index for assessment of peripheral arterial disease. *N Engl J Med* 2009; 361(19): e40.
33. World health organization: *Definition, diagnosis and classification of diabetes mellitus and its complications*. Geneva: World health organization, 1999.
34. Howe LD, Galobardes B, Matijasevich A, et al. Measuring socio-economic position for epidemiological studies in low- and middle-income countries: a methods of measurement in epidemiology paper. *Int J Epidemiol* 2012; 41(3): 871–886.
35. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386(9995): 743–800.
36. Atun R. Transitioning health systems for multimorbidity. *Lancet* 2015; 386(9995): 721–722.
37. Olivares DE, Chambi FR, Chani EM, et al. Risk factors for chronic diseases and multimorbidity in a primary care context of central Argentina: a web-based interactive and cross-sectional study. *Int J Environ Res Public Health* 2017; 14(3): pii: E251.
38. Schneider KM, O'Donnell BE and Dean D. Prevalence of multiple chronic conditions in the United States' Medicare population. *Health Qual Life Out* 2009; 7: 82.
39. Harrison C, Britt H, Miller G, et al. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. *BMJ Open* 2014; 4(7): e004694.
40. Fortin M, Bravo G, Hudon C, et al. Prevalence of multimorbidity among adults seen in family practice. *Ann Fam Med* 2005; 3(3): 223–228.
41. Koroukian SM, Warner DF, Owusu C, et al. Multimorbidity redefined: prospective health outcomes and the cumulative effect of co-occurring conditions. *Prev Chronic Dis* 2015; 12: E55.
42. Diez-Canseco F, Toyama M, Ipince A, et al. Integration of a technology-based mental health screening program into routine practices of primary health care services in Peru (the Allillanchu project): development and implementation. *J Med Internet Res* 2018; 20(3): e100.
43. Siebeling L, Puhan MA, Muggensturm P, et al. Characteristics of Dutch and Swiss primary care COPD patients—baseline data of the ICE COLD ERIC study. *Clin Epidemiol* 2011; 3: 273–283.
44. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187(7): 728–735.
45. Barnes PJ and Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009; 33(5): 1165–1185.
46. von Leupoldt A, Taube K, Lehmann K, et al. The impact of anxiety and depression on outcomes of pulmonary rehabilitation in patients with COPD. *Chest* 2011; 140(3): 730–736.
47. Mannino DM, Thorn D, Swensen A, et al. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; 32(4): 962–969.
48. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186(2): 155–161.
49. Okura Y, Urban LH, Mahoney DW, et al. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol* 2004; 57(10): 1096–1103.