



Pneumonia is the Leading Cause of Death from Respiratory Diseases at High Altitude In La Paz, Bolivia

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Abstract

Chronic obstructive pulmonary disease (COPD) and asthma are major contributors to mortality resulting from respiratory diseases among sea-level populations. In high altitude environments, located between 2500 and 3600 meters, where oxygen availability decreases (hypoxia), pulmonary edema has been identified as the main cause of mortality among transient visitors to such high regions. However, despite the existence of physiological adaptations among permanent residents of high altitudes (characterized by increased ventilation, increased red blood cell counts, vasodilation, and an increased muscle contraction pump), extensive research on fatal respiratory diseases that prevalence in this demographic remains low. In this research effort, we analyzed 1,214 mortality records from 2017 in La Paz, Bolivia (located at 3,600 meters). Our results indicate that pneumonia is the leading cause of death in these high-altitude Bolivian cities. This is in stark contrast to pneumonia's position as the fourth leading cause of death at sea level, accentuating the distinctive health challenges faced by populations residing at high altitudes.

Keywords: Mortality, Respiratory System Diseases, ICD-10, FIRS.

Introduction

Chronic obstructive pulmonary disease (COPD) and asthma emerge as prominent contributors to mortality within the respiratory disease spectrum among populations residing at sea level ^[1]. In contrast, acute manifestations of high-altitude exposure, such as high-altitude pulmonary edema (HAPE) ^[2] and high-altitude cerebral edema (HACE) ^[3], have attracted attention as the most serious conditions found at elevations above 2,500 meters. These sicknesses are usually attributed to precipitous ascents to high altitudes, often exemplified by people traveling from sea level to high-altitude destinations for recreational or sporting activities, including activities such as skiing and mountaineering. However, the literature rarely clarifies that these statistics predominantly

encompass people acutely exposed to high altitude (HA) hypoxia, and not to those permanently inhabiting elevated regions. Moreover, while extensive research has been conducted on the physiological responses of individuals ascending to high altitudes for short to moderate periods, a paucity of knowledge surrounds the prevalence of respiratory diseases culminating in death among permanent residents from high altitude regions. In fact, it has long been presumed that the incidence of such pathologies may differs fundamentally from that at sea level, due to the fact that permanent high-altitude residents have developed intricate physiological, cellular, subcellular, and molecular adaptations that allow them to thrive in hypoxic environments ^[4].

In the Andean region of Bolivia, the first comprehensive study on mortality was carried out by the Pan American Health

Organization (PAHO) in 2000 [5]. This exhaustive analysis involved the scrutiny of 10,744 Medical Certificates of Death (CEMEUD) from official cemeteries scattered throughout Bolivian cities. The findings revealed circulatory diseases, external incidents with accidents, intentional injuries and assaults, along with neoplastic pathologies, as the main causes of mortality [5]. Subsequently, the Institute for Research in Health and Development (INSAD) began an additional investigation, examining 2,082 documented deaths within the General and Jardín in La Paz cemeteries, located at an altitude of 3,600 meters above sea level (masl). This study revealed that external incidents had priority, closely followed by cardiovascular diseases as the main cause of death [6]. Finally, an INSAD study, which covered the mortality profiles of La Paz between 1999 and 2009, revealed a prevalence of malignant neoplasms of the cervix as the main cause of mortality among women, while cardiovascular diseases dominated as the main cause of death among men [6]. However, it is essential to underline that none of these studies delved into the specific etiological factors governing mortality related to respiratory diseases, emphasizing the notable gap in scientific exploration in this domain. The urban center of La Paz in Bolivia is home to an extensive population estimated at approximately 2,706,000 inhabitants [7], was the focal point of this research. Our analysis covered 1,214 mortality records obtained from the Single Medical Certificate of Death (CEMEUD), obtained from the General, Jardín and Prados de Ventilla Cemeteries. These cemeteries together constitute the main necropolises within the urban landscape of the city. Our results reveal that pneumonia is the preeminent etiological agent, mainly responsible for deaths related to respiratory diseases within this metropolitan area. These results constitute a crucial reference source for comparative epidemiological studies between residents of sea-level and high-altitude regions.

Methods

Study design

This descriptive and retrospective study is based on deaths between January and June 2017 in La Paz, Bolivia. A total of 1,214 mortality records (unique death medical certificates - CEMEUD) were reviewed from the General and Jardín cemeteries and the Prados de Ventilla Cemetery. These cemeteries represent the official burial grounds within the city of La Paz, distinct from smaller unauthorized cemeteries scattered across various regions on the periphery. The main cause of death registered in the CEMEUD was coded according to the 10th version of the International Classification of Diseases (ICD-10). For each case, sex, age were also registered.

Natural environment

High altitude is defined as the altitudinal range that covers between 2,500 and 5,000 meters above sea level (masl). La Paz, Bolivia, is located between 3,600 and 4,150 masl, within the tropical geographic zone (delimited by the Tropic of Cancer and the Tropic of Capricorn), characterized by diurnal temperature fluctuations of about 15 degrees, and annual temperature spectrum ranges from -5 to +27 oC. High altitude land at this geographic zone exhibits fertility and devoid of perpetual snow throughout the year. As such, La Paz stands as one of the most prominent high-altitude urban centers in the world, with a population of 2,706,000 inhabitants. As a fully developed metropolis, La Paz is counts with an international airport, more than 70 hospitals, along with educational institutions encompassing schools, universities and research centers. The Bolivian Institute of Altitude Biology (IBBA), affiliated with the Faculty of Medicine of the Universidad Mayor de San Andrés,

stands as the center par excellence dedicated to the systematic exploration of acclimatization and adaptation to high altitude environments.

Mortality records

Mortality records in La Paz, Bolivia, are required by law to include essential information, such as sex, date of birth, date of death, place of death, and cause of death. Additionally, mortality records in Bolivia expand their scope to cover the educational level and profession of the deceased. Indeed, there is a minority of these records that present incomplete data or cases of ambiguity. However, in the context of this study, meticulous scrutiny led to the exclusion of all records that presented uncertainties, with special emphasis on those related to the residential data of the individuals considered.

Population sample

In this study, a comprehensive review was carried out to compare deaths related to respiratory problems with all causes of mortality recorded in the database. Following this comprehensive review, a refined approach was adopted, employing a meticulous selection process to isolate and consider exclusively deaths that could be unequivocally attributed directly to respiratory causes. This selection was intended to improve the precision and specificity of subsequent analytical efforts, ensuring an investigation focused on the complexities of airway-related deaths, free of extraneous factors.

Inclusion / exclusion criteria

Comprehensive inclusion criteria for mortality records within this study encompassed individuals whose death was due to respiratory diseases, excluding, however, those whose deaths were attributed to respiratory system conditions directly associated with tuberculosis and neoplasia. This selective exclusion sought to ensure a nuanced approach to respiratory conditions other than the specificities of neoplastic respiratory diseases. Furthermore, all mortality records considered in this research belonged exclusively to individuals born, resident, and ultimately succumbed to the high-altitude environment in the city of La Paz. This meticulous delineation of inclusion and exclusion criteria underscored the study's commitment to precision and relevance in exploring the complexities of airway-related deaths within the specific high-altitude context.

Ethics declaration

Medical certification, clinical records, and other relevant mortality data were handled with the utmost discretion and treated confidentially. Thus, the commitment to preserve anonymity and respect the confidentiality of individuals occupied a prominent place in the research methodology used in this study, underlining ethical considerations and compliance with privacy regulations within scientific research.

Data analysis

The absolute and relative frequencies were calculated separately for deaths from all causes and those linked to respiratory diseases. Frequencies were also calculated considering sex, 5-year age groups, and month of death. The years of potential life lost (YPLL) were calculated according to the following formula: $YPPL = \sum((L - i) * d_i)$. Where: L : life expectancy at birth, i : age of death, d_i : number of deaths at age i . Data analysis and histograms were done using Rstudio (R Core Team 2022). Life expectancy data was obtained from [8]. According to Bolivian law, no IRB agreement is necessary for this kind of research.

Results

A total of 1,214 mortality records from La Paz and El Alto cities in Bolivia were analyzed corresponding to the first six months of 2017 and obtained from the three main (largest) cemeteries of these cities: the General Cemetery of La Paz, the Garden Cemetery of La Paz, and the Prados de Ventilla Cemetery of El Alto (4150 masl). All records reviewed corresponded to habitual inhabitants of La Paz and El Alto (located at 3,600 and 4,150 masl, respectively), who were born, lived, and died at these elevations. Furthermore, based on surnames, all the cases reviewed corresponded to people who can be identified as natives and mestizos from highland regions. Data on the cause of death, and sex, are presented in **Table 1**.

Respiratory diseases are the third cause of death in the high-altitude inhabitants of La Paz and El Alto.

The analysis revealed that circulatory and neoplastic diseases are the first (17.2 %) and second (15.4 %) most important causes of mortality in residents from the cities of La Paz and El Alto. Respiratory diseases represented the third most important cause of mortality (11.4 %), closely followed by metabolic (11.3 %), digestive (11.1 %), and genitourinary (9.6 %) diseases. Other less frequent causes of death were also identified (**Fig. 1 A**). When the records were analyzed by sex, respiratory diseases in men (10.5 %) and women (12.4 %) represented the fourth most important cause of death. Circulatory, digestive, and neoplastic diseases were the three most relevant causes in men (**Fig. 1B - left**); and circulatory, neoplastic and metabolic diseases in women (**Fig. 1B -right**). Regarding the age of death, 5% (in men) and 4% (in women) of deaths occurred in children under 5. Deaths occurred mostly between 60 and 79 in adult men (**Fig. 1C - left**), and between 70 and 94 in women (**Fig. 1C - right**).

Pneumonia is the main respiratory disease that causes death in the high-altitude inhabitants of La Paz and El Alto.

Among the respiratory diseases that cause death in high-altitude in La Paz and El Alto residents, pneumonia ranked first with 40.5%. This was followed by other systemic respiratory diseases (24%) and respiratory diseases affecting the interstitium (20.7%).

Table 1: Main causes of death reported in La Paz, Bolivia. International Classification of Diseases, 10th version.

General causes of death	Number of cases (Men)	%	Number of cases (Women)	%	Total number of cases
Circulatory system diseases	97	16.1%	112	18.3%	209
Neoplastic diseases	76	12.6%	111	18.1%	187
Respiratory system diseases	63	10.5%	76	12.4%	139
Endocrine, nutritional, and metabolic diseases	58	9.7%	79	12.9%	137
Digestive apparatus diseases	83	13.8%	52	8.5%	135
Genitourinary diseases	53	8.8%	64	10.4%	117
Infectious and parasitary diseases	32	5.3%	20	3.3%	52
Nervous system diseases	28	4.7%	23	3.8%	51
Extreme causes of morbidity and mortality	31	5.2%	13	2.1%	44
Unclassified clinical and laboratory findings	19	3.2%	21	3.4%	40
Mental health and behavioral conditions	21	3.5%	5	0.8%	26
Affections during the perinatal period	14	2.3%	8	1.3%	22
Traumatism, poisoning, and external causes	10	1.7%	6	1%	16
Bone, muscular and connective tissues diseases	4	0.7%	7	1.1%	11
Pregnancy, birth, and post-birth complications	3	0.5%	7	1.1%	10
Inherited malformations and chromosomic anomalies	4	0.7%	3	0.5%	7
Skin or subcutaneous tissue-related diseases	3	0.5%	3	0.5%	6
Blood diseases and immune system affections	2	0.3%	3	0.5%	5

Respiratory diseases, such as chronic diseases of the respiratory tract, the pleura, and lungs due to external pathogens, each represented about 5% of deaths (**Table 2**). Suppurative and necrotic respiratory diseases and acute respiratory tract infections were below 3% (**Fig. 2A**). Using the classification suggested by the Forum of International Respiratory Disease Societies (FIRS), our analysis confirmed that pneumonia (41.3%) is the most prevalent death-causing disease in high-altitude residents, followed by other diseases of the respiratory system (33.1%), diseases affecting the interstitium (20.7%), obstructive pulmonary diseases (4.1%), and asthma (0.8%) (**Fig. 2B**). When these records were analyzed by sex, pneumonia (38.6%) was the main cause of death in men, followed by other diseases of the respiratory system (28.1 %) and diseases affecting the respiratory interstitium. (**Fig. 3C - left**). In women, pneumonia (42.2%) was followed by diseases affecting the respiratory interstitium (25%) and other diseases of the respiratory system (20.3%). (**Fig. 3C - right**). Regarding the age of death, 19.3% (in men) and 18.8% (in women) corresponded to children under 5, while 43.8% (in men) and 53% (in women) corresponded to residents between 75 and 99 (**Fig. 2D**).

Deaths from respiratory causes in high-altitude residents are strongly associated with education, artisanal work, and home as the main place of death.

When classified according to the level of schooling, 38.6% of deaths occurred in men and 20.3% in women who completed secondary school, and 19% in those who completed elementary school (**Fig 3A**). For several individuals, the educational level could not be determined (represented as No Data in our plots).

When analyzed by type of work, results showed that 24.6% of the men who died from respiratory causes were artisans, with office employees, retirees, and students accounting for 15.8%, 10.5%, and 12.3% of deaths, respectively (**Fig 3B - left**). Among women, 50% of respiratory deaths occurred among domestic workers (**Fig 3B - right**). Finally, 51.8% of men and 53.1% of women died at home and not in a hospital setting (**Fig 3C**).

Table 2: Death cases registered for respiratory diseases in the first six months of 2017 in La Paz, Bolivia. Number of cases by sex, percent and the total number of cases.

Respiratory diseases	Number of cases (Men)	%	Number of cases (Women)	%	Total number of cases
Pneumonia	22	38.6%	27	42.2%	49
Other respiratory system diseases	16	28.1%	13	20.3%	29
Respiratory diseases affecting mainly the interstitium	9	15.8%	16	25%	25
Lung diseases caused by external pathogens	4	7%	1	1.6%	5
Other diseases of the pleura	3	5.3%	2	3.1%	5
Acute respiratory tract infections	-	-	1	1.6%	1
Chronic lower respiratory tract diseases	2	3.5%	4	6.3%	6
Suppurative and necrotic conditions of the lower respiratory tract	1	1.8%	-	-	1

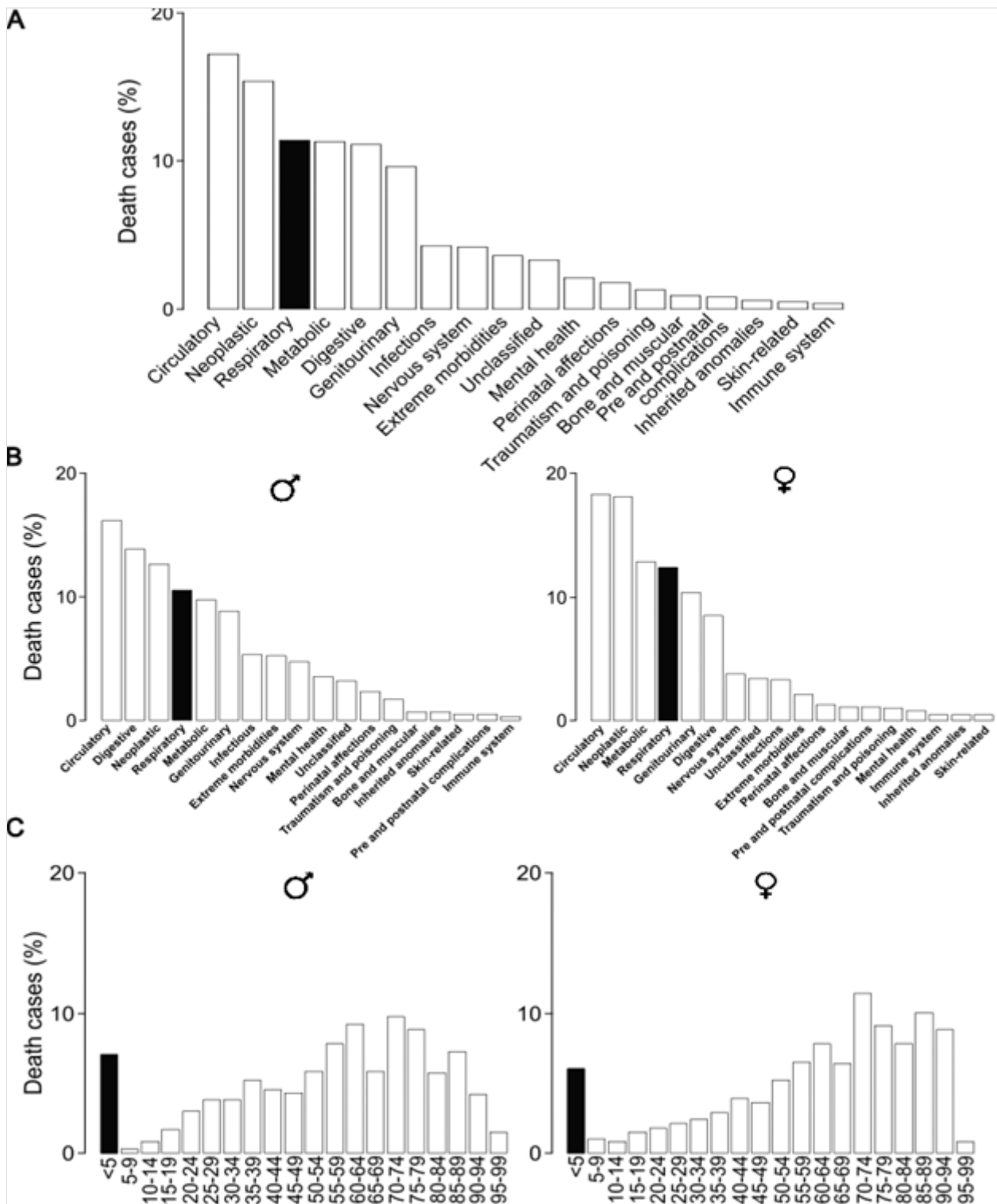


Figure 1: Death causes registered for diseases following the CID (version 10) (A) and FIRS (B) classifications, in La Paz, in the first six months of 2017. Disease classification among men and women (C). Death cases registered according to age ranges in men and women (D).

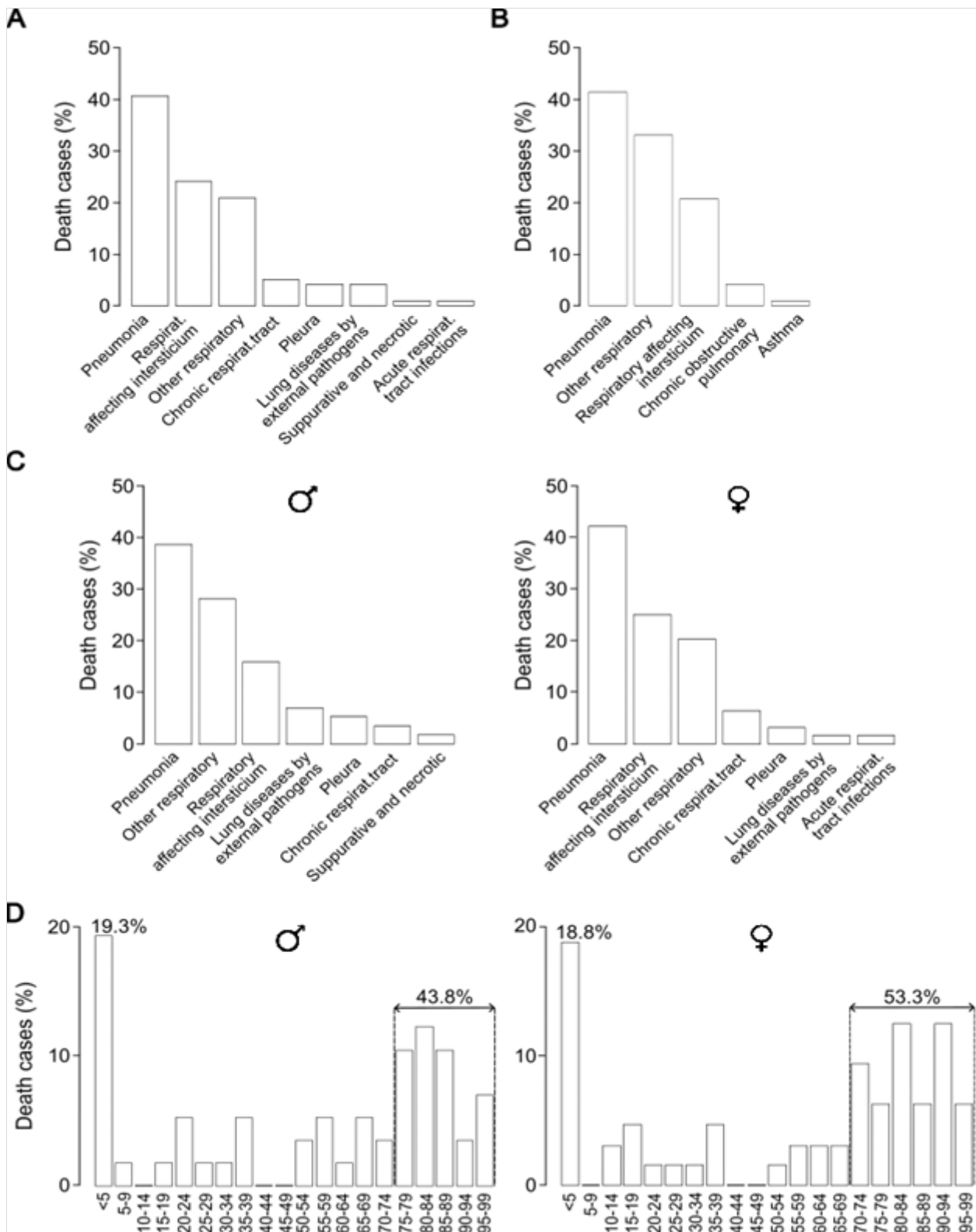


Figure 2: Death cases (%) for respiratory diseases in La Paz in the first six months of 2017 following the CID (version 10) (A) and FIRS (B) classification. Cases reported by sex for the CID classification (C). Death cases by sex per age range (D), percentages for infants under 5 and people over 70-74 were the highest among all age groups.

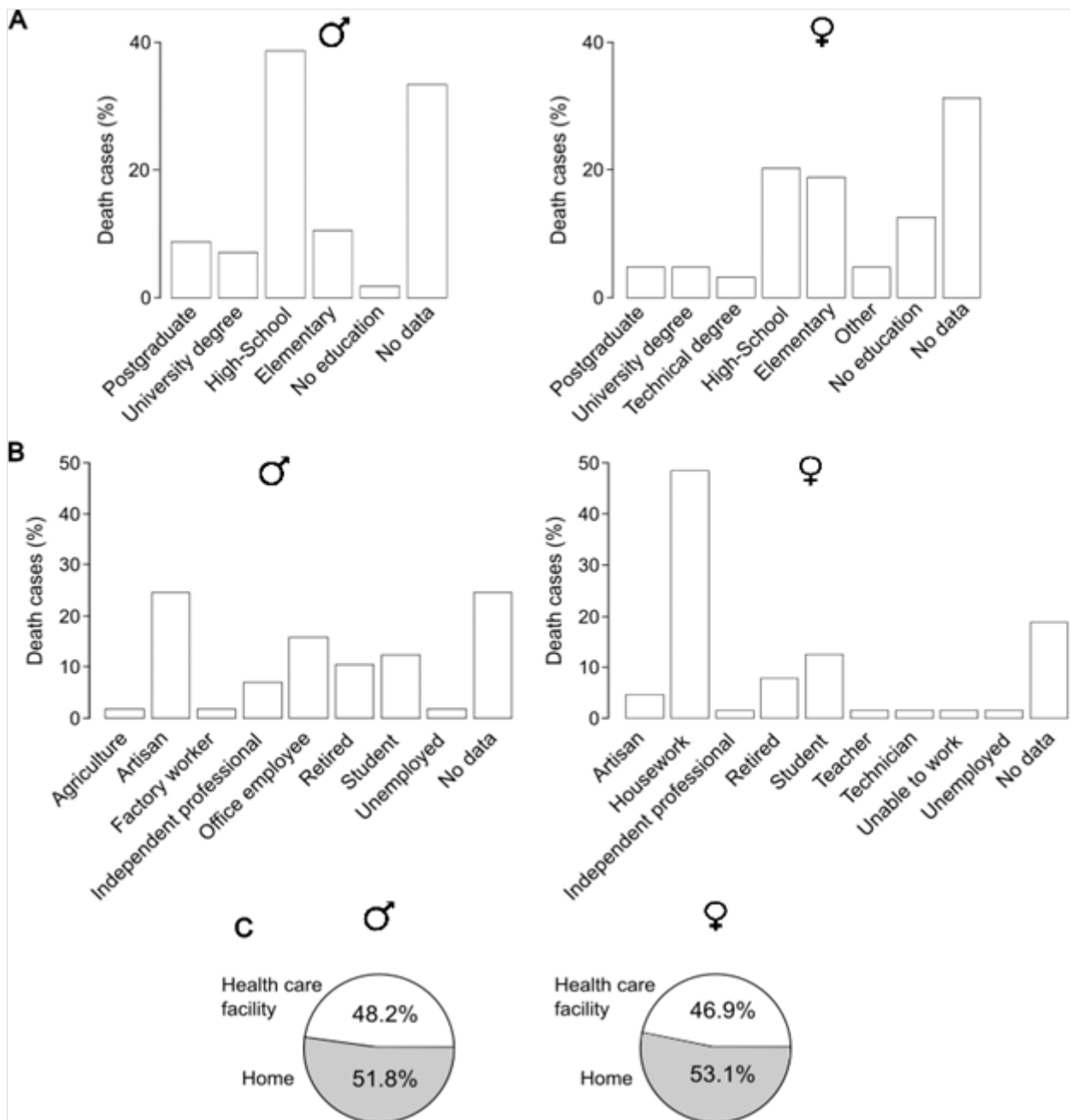


Figure 3: Death cases registered for respiratory diseases according to educational (A) and professional levels (B). Percentages of reported deaths according to the place of death per sex (C).

Years of Potential Life Lost

The estimation of the years of potential life lost (YPLL) summarizes the years that all the people who died, in this study, from respiratory-disease-related causes would have lived had they reached the life expectancy at birth. Considering values of life expectancy at birth of 75.6 years for women and 69.1 years for men [8], we calculated the years of potential life lost to be 22.6 and 15.9 for men and women respectively.

Discussion

In the present study, we used 1,214 death certificates from the General and Jardin cemeteries of the city of La Paz, and the Ventilla Cemetery of the city of El Alto, in Bolivia, to investigate the causes of deaths from respiratory diseases in residents of large populations in altitude. The main findings of this study were: 1) respiratory diseases occupy the third leading cause of death, after circulatory and neoplastic diseases; 2) Pneumonia is the main disease causing death; 3) Our results suggest a strong association between deaths from respiratory diseases with education levels,

types of work and place of death; and 4) The potential years of life lost in high altitude inhabitants are 22.6 in men and 15.9 in women.

Diseases of the respiratory system constitute a public health problem worldwide due to the high mortality and morbidity rates, accounting for a large number of health resources. Although not a new problem, it has begun to gain importance as other infectious diseases have been controlled and prevented [9]. In Bolivia, few studies have determined the causes of mortality according to the etiology of respiratory diseases (acute or chronic, in children and/or adults) [9]. However, chronic obstructive pulmonary disease (COPD) is known to be one of the most prevalent diseases [9]. In fact, by reviewing medical records in third-level health centers in La Paz, the prevalence of COPD was estimated at 12.9% [10].

Our study reveals that respiratory diseases in La Paz represent the third cause of death, after heart disease and neoplastic diseases. In Latin America, causes of mortality vary greatly [11]. For instance, communicable, maternal, neonatal, and nutritional diseases had the highest proportional mortality in the cities of the Peruvian jungle. In contrast, cancer mortality was highest in Chile,

southern Brazil, and the Argentine pampas. Mortality from cardiovascular diseases and other noncommunicable diseases was highest in the central and northeastern parts of Mexico. Injury deaths from violent injuries ranged from 0% to 20% in proportional mortality in Mexico, Colombia, and Brazil, and 4% to 19% from unintentional injuries in Peru and Brazil. These studies also revealed that a higher socioenvironmental index was associated with a relatively lower proportion of communicable, maternal, neonatal, nutritional diseases and injuries, and a higher proportion of deaths from cancer, cardiovascular disease, and other noncommunicable diseases [12]. Likewise, higher levels of education, access to water and sanitation, and less overcrowding were associated with greater life expectancy, a relatively lower proportion of deaths from communicable, maternal, neonatal, and nutritional diseases, but a higher proportion of deaths from cancer, cardiovascular diseases, and others [13].

Considering respiratory diseases specifically, in 2019, before the COVID-19 pandemic, about 1.4 billion new respiratory infections and 177,000 deaths of all ages were reported in South America, with significant differences between countries, age groups and sexes [14]. Chronic respiratory diseases like COPD, asthma, occupational lung diseases, and pulmonary hypertension accounted for 534,242 deaths in both sexes (50% deaths per men and women). [15]. The countries with the highest mortality rate (age-standardized deaths per 100,000) were Honduras (58.7), Argentina (55.5), Haiti (50.0), Bolivia (46.9), Nicaragua (43.8), Uruguay (42.4), and Guyana (39.5) [16].

Importantly, none of these reports analyzed the distribution of these diseases by geographic altitude, a major gap in epidemiological studies since many of the largest and most populated cities in Latin American countries are located at high altitude, including La Paz in Bolivia (3,600 masl - 2,706,000 inhabitants); Quito in Ecuador (2,850 masl - 2,001,388 inhabitants); Bogotá in Colombia (2,651 masl - 7,181,000 inhabitants); and Mexico City in Mexico (2,651 masl - 8,851,080 inhabitants) (Arias-Reyes C, 2021). Our study reveals that pneumonia is the disease that most frequently leads to death in high-altitude residents of La Paz and El Alto, Bolivia pointing to geographic altitude as an important factor in the etiology of respiratory diseases. These results align with studies showing that pneumonia is the third leading cause of death worldwide, with a higher incidence among children ≤ 5 years and adults ≥ 50 years [17]. Pneumonia has also been identified as a frequent cause of doctor visits, hospitalization, and death among older adults in Latin America [17]. Our results clearly indicate that mortality caused by pneumonia increases significantly in high-altitude environments.

Finally, our study also suggest a strong association between these causes of death with education, artisan work, and home as the main place of death. These results are in accordance with statistics from the National Institute of Statistics (INE) of Bolivia [18], which show that more than 70% of the population have elementary and high school education; that artisan work is the most predominant occupation; and that more than 50% of the population lacks the resources (or awareness of the severity of the disease) to attend a hospital.

In conclusion, this epidemiological study of the main causes of death due to diseases in residents of high altitudes of La Paz and El Alto in Bolivia reveals that respiratory diseases are the third cause of death, with pneumonia accounting for the highest number of deaths. The populations at greatest risk are children under 5 years of age and adults over 70 years of age, with no significant differences between men and women. These studies are

highly relevant since they will allow the Ministry of Health to identify more effective and effective protection policies.

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