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Characteristics and Factors Associated with Mortality Due to Rare Diseases in Chile, 2002 - 2017

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Abstract: Introduction: Rare diseases are characterized by their low prevalence, chronically debilitating and life-threatening nature. Objective: To determine the characteristics and factors associated with mortality due to rare diseases in Chile from 2002 to 2017. Materials and methods: We conducted an analytical cross-sectional study based on secondary mortality database from the Departamento de Estadística e Información en Salud (DEIS), Ministerio de Salud de Chile (Department of Statistics and Health Information, Chile Ministry of Health) from 2002 to 2017. The specific mortality rates adjusted by age and sex were calculated. A normality analysis was conducted using the Kolmogorov-Smirnov test. In addition, a chi-square test of independence for associations and multivariate logistic regression was applied to determine the probability of death. Results: Between 2008 and 2012, there were 10,718 deaths due to rare diseases, and 53.2% of them occurred among women. The average annual mortality rate was 3.9 per 100,000 inhabitants: 4.1 in women and 3.8 in men. The main causes of mortality among women were Creutzfeldt-Jakob disease, anencephaly and autoinmune hepatitis, and among men were Creutzfeldt-Jakob disease, muscular dystrophy and anencephaly. Women are 1.75 times more likely to die than men (adjusted Odds Ratio (aOR) = 1.75; $IC_{95\%}$ 1.69 - 1.82). The highest probability of dying occurred among children aged 0 - 4 years (aOR = 15.30; $IC_{95\%}$ 14.10 - 19.20). Conclusion: In Chile, women constituted the population group at highest risk of dying from rare diseases during the years 2002 and 2017.

Key words: rare diseases; cost of illness; mortality registries; public health; Chile

1. Introduction

Orphan diseases, also known as rare or infrequent diseases, constitute a large and varied group of health disorders characterized by their low prevalence and high rates of premature mortality [1]. It is estimated that there are 5,000 to 8,000 orphan diseases that could affect between 6% and 8% of the world population. Of these, 80% are of genetic origin, and 20% to 25% are related to diseases of the immune system and, to a lesser extent, to neoplasms and infectious etiologies [1]. They are usually chronically debilitating and very severe, and involve more than one vital organ with multiple motor, sensory and cognitive impairments.

The life expectancy of affected individuals varies widely depending on the severity of the disease, but, in general terms, it is very short. A significant percentage of these patients die at birth and another group of them develop

degenerative diseases over their life cycle [2]. The prevalence is higher in adults due to the excess mortality reported for some orphan diseases in the pediatric population, mainly those due to genetic malformations [3].

The definition of orphan diseases varies between countries, depending on the threshold at which a disease is considered rare. For example, the European Community defines an orphan disease as any health condition with a prevalence of less than 5 cases per 10,000 population. In Japan, this disease is considered rare when there are fewer than 50,000 cases (1 in 2,500), while in Taiwan, China, when the incidence rate is below 1 case per 100,000 people, this disease is considered rare. In the United States, less than 200,000 cases nationwide are classified as orphan disease [3]. In Colombia, it is defined as a disease with a prevalence of less than one case per 5,000 persons [4].

Chile does not have its own definition. As a normative antecedent, there is the draft law on rare diseases, in which the country adopts the classification of the European Union and the United States. Within this framework, it identifies certain human diseases with a very low prevalence and great diversity as orphan diseases, in line with international policy to promote the development of drugs to treat them [5]. In this same horizon, the Chilean Federation of Rare Diseases, made up of patients, family members, health professionals and people sensitized by the issue, has actively participated in the management of Law No. 20850 of 2015, known as "Ricarte Soto Law", through which the care, diagnosis, universal coverage and treatment of 14 specific health conditions associated with orphan diseases is regulated [6].

The real impact of the burden of disease, mortality, diagnostic and therapeutic technologies, and disability-related complications of many of these diseases is unknown. This may be largely due to their low prevalence and, therefore, they constitute new health events for the scientific community in different regions and contexts. Added to the above, there are difficulties with the lack of specificity of codes used in the current disease classification system, since many of them share the same nomenclature with other diseases.

In this sense, mortality analyses represent a valuable tool. On the one hand, they allow updating the knowledge we have about these diseases and, on the other hand, they provide relevant information to indirectly evaluate the advances in relation to timely detection, care, management and follow-up of health conditions associated with orphan diseases. Therefore, the objective of this work is to determine the characteristics and factors associated with mortality due to orphan diseases in Chile, between 2002 and 2017.

2. Materials and Methods

A cross-sectional and analytical study was conducted through which mortality due to orphan diseases in Chile between 2002 and 2017 was characterized, based on secondary data from individual deaths registered in the official database of the Department of Statistics and Health Information, Chile Ministry of Health, as the only secondary source of information.

To determine the cause of death, the official consensus developed in a country of the region based on the International Classification of Diseases in its tenth revision (ICD-10) and the homologation of codes from orphanet [7, 8] were considered, since Chile has not yet defined a specific list of codes. After the code by code review process, 389 diseases were identified as having ICD-10 and 661 were non-specific codes. Finally, 389 that had specific codes or corresponded to ICD-10 were established for the search in the Department of Statistics and Health Information.

We excluded from the analysis 1,185 (0.08%) deaths where age could not be calculated or study variables could not be determined. Univariate analysis was performed by year of death, sex, age groups according to five-year age group, activity, educational level, region and area of residence, and cause of death codes. Qualitative variables were analyzed in terms of absolute and relative frequencies. Quantitative variables were treated using the nonparametric Kolmogorov-Smirnov test to identify normality in the distribution of the data. Correspondingly, Student's t-test or Mann-Withney U test

was used, depending on the observed distribution of the data for the variable age [9].

In addition, specific mortality rates were calculated by gender and age group, and expressed as the number of deaths per 100,000 people per year, using the population predictions for the age group and study years estimated by DEIS as the denominator. According to the World Health Organization (WHO) [10], the annual rate adjusted by age group was estimated using the direct method, taking the world population as the reference population.

In the bivariate analysis, we looked for possible associations between sociodemographic characteristics and orphan disease as a cause of death, considering the latter result as a variable. For this purpose, the chi-squared test of independence was used, and a binary logistic regression analysis was performed to determine the probability of death from this cause by calculating the odds ratio (OR). The significance level was set at less than 5%.

Finally, a multivariate logistic regression model was constructed to estimate the adjusted OR. The independent variables were chosen to enter the model according to the Hosmer-Lemeshow test for bivariate models, i.e. those with a p-value of less than 0.25 [11]. For variables with more than two categories, the standard of creating as many dummy variables as possible (false) was used, which is to subtract one from the total number of categories. The relevance of each variable in the model was evaluated using the parametric Wald test, and variables with a p value less than 0.05 are defined as significant variables [12].

Data processing and data analysis were performed using the statistical package R Studio, version 4.0.3 (2020-10-10), supported by Microsoft Office 2019 tools.

2.1 Ethical considerations

The general ethical aspects established by the WHO for research related to the health of human beings were considered in the design of this work, specifically, from secondary data [13]. The databases did not contain identifying information on the deceased. No persons were involved in the procedures performed, nor was the right to privacy violated, and the results are presented in an overall manner.

3. Results

In Chile, about 1504,726 deaths from all causes were registered between 2002 and 2017, of which 10,718 were directly attributed to orphan diseases, with an average of 669.8 deaths per year. In 2014, the highest number of deaths from this cause was reported, with a total of 753; while 2002 was the year with the lowest number (618) of deaths. The overall trend showed a rising pattern between 2003 and 2016, with a slight decrease in 2017 (Figure 1).

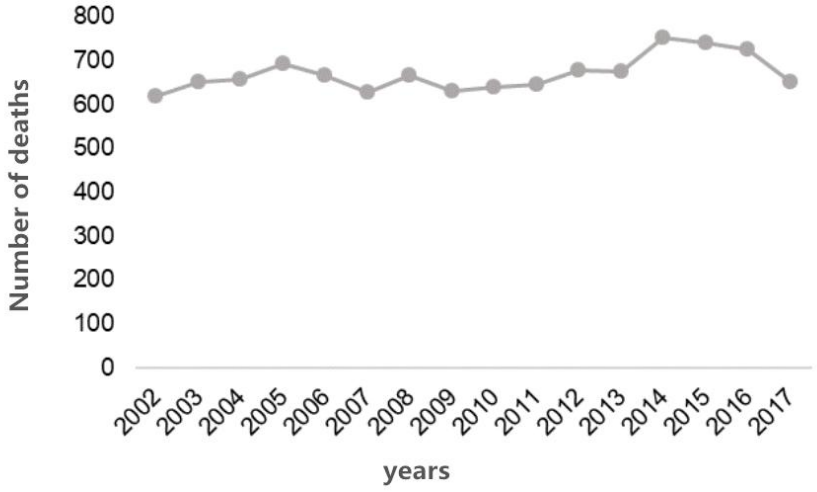


Figure 1. Trends in disease mortality in Chile from 2002 to 2017. Source: Calculation based on official data from the Department of Statistics and Health Information, Chile Ministry of Health.

When analyzing the sociodemographic behavior of the persons who died due to this group of diseases, more than half were women (5,604) and 89.6% (9,600) were classified as inactive (Table 1). In terms of educational level, deaths occurred most frequently in the population with no formal education, with 49.3% (5,287).

Table1. Sociodemographic characteristics associated with deaths due to orphan diseases in Chile, 2002 - 2017.

Variable	Defunciones				χ^2	p
	Enfermedades huérfanas		Otras causas de defunción†			
	n	(%)	n	(%)		
Sexo						
Mujer	5.604	(0,37)	694.312	(46,27)		
Hombre	5.114	(0,34)	795.656	(53,02)	138,05	0,000
Actividad productiva						
Inactivo	9.600	(0,64)	1.262.093	(84,10)		
Activo	1.008	(0,07)	207.228	(13,81)		
Cesante o desocupado	110	(0,01)	20.647	(1,38)	195,17	0,000
Nivel educativo						
Superior	490	(0,03)	74.877	(4,99)		
Medio	1.319	(0,09)	151.462	(10,09)		
Secundaria	881	(0,06)	283.908	(18,92)		
Básico o primaria	2.741	(0,18)	798.230	(53,19)		
Ninguno	5.287	(0,35)	181.491	(12,09)	14.072	0,000
Grupos de edad (años)						
0-4	4.474	(0,30)	30.017	(2,00)		
5-9	197	(0,01)	2.945	(0,20)		
10-14	234	(0,02)	3.812	(0,25)		
15-19	335	(0,02)	10.324	(0,69)		
20-24	278	(0,02)	15.208	(1,01)		
25-29	184	(0,01)	16.448	(1,10)		
30-34	170	(0,01)	18.914	(1,26)		
35-39	205	(0.01)	24.147	(1,61)		
40-44	246	(0,02)	34.188	(2,28)		
45-49	413	(0,03)	47.185	(3,14)		
50-54	517	(0,03)	63.378	(4,22)		
55-59	623	(0,04)	81.920	(5,43)		
60-64	677	(0,05)	81.542	(6,96)		
65 y más	2.165	(0,14)	1'037.355	(69,14)	80.889	0,000
Zona de residencia						
Urbana	9.509	(0,64)	1'286.726	(85,74)		
Rural	1.209	(0,08)	203.242	(13,54)	50.004	0,000

Source: Calculations based on official data from the Department of Statistics and Health Information, Chile Ministry of Health. 4,040 records in which the comparison variables (sex, productive activity, educational level, age and area of residence) were determined were not included.

In relation to the age groups most affected, the highest proportion was found among children aged 0 to 4 years, with 41.7% (4,474), followed by older adults aged 65 years and over, with 20.2% (2,165), and those aged 60 to 64 years, with 6.3% (677). A large proportion of them resided in the urban area, with 88.7% (9,509).

In terms of specific diagnosis, the causes of death did not differ markedly according to sex. Among the leading causes of death in women, the following stand out: Creutzfeldt-Jakob disease, anencephaly, autoimmune hepatitis, primary biliary cirrhosis, unspecified chromosomal anomalies, congenital diaphragmatic hernia, muscular dystrophy, specified congenital heart malformations, bronchopulmonary dysplasia originating in the perinatal period and Guillain-Barré syndrome (Table 2). Meanwhile, in the male population, the following were identified: Creutzfeldt-Jakob disease, muscular dystrophy, anencephaly, congenital diaphragmatic hernia, unspecified chromosomal anomalies, other specified congenital heart malformations, bronchopulmonary dysplasia originating in the perinatal period, Guillain-Barré syndrome, myotonic disorders and thanatophoric dwarfism (Table 2). The median age was 21 years (interquartile range = 61).

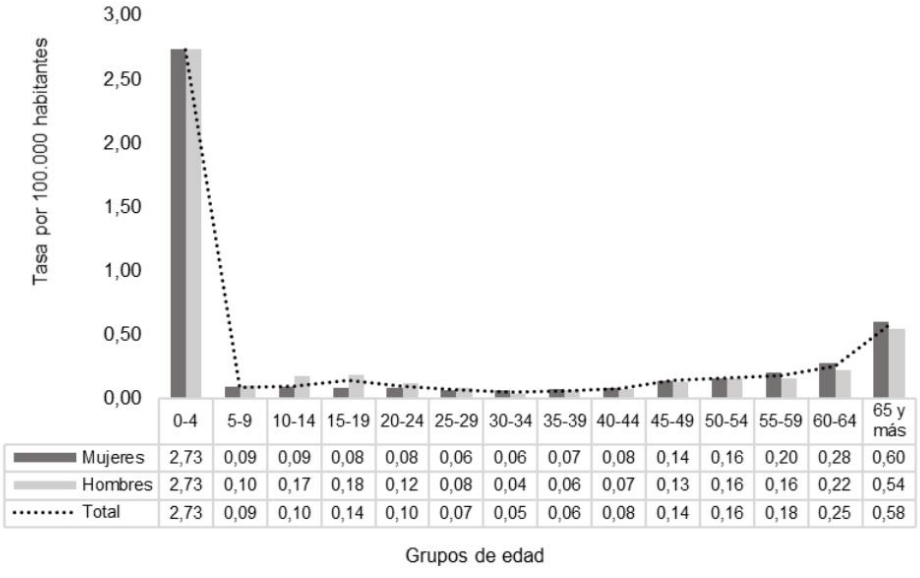
Table 2. Leading causes of mortality due to orphan diseases in men and women, Chile, 2002 - 2017.

Mujeres			Hombres		
	n	%		n	%
Enfermedad de Creutzfeldt-Jakob	593	10,6	Enfermedad de Creutzfeldt-Jakob	510	10,0
Anencefalia	484	8,6	Anencefalia	426	8,3
Hepatitis autoinmunitaria	381	6,8	Distrofia muscular	436	8,5
Cirrosis biliar primaria	267	4,8	Hernia diafragmática congénita	277	5,4
Anomalía cromosómica, no específica	238	4,2	Anomalía cromosómica, no específica	241	4,7
Hernia diafragmática congénita	230	4,1	Otras malformaciones congénitas del corazón, especificadas	179	3,5
Distrofia muscular	135	2,4	Displasia broncopulmonar originada en el periodo neonatal	178	3,5
Otras malformaciones congénitas del corazón, especificadas	130	2,3	Síndrome de Guillain-Barré	171	3,3
Displasia broncopulmonar originada en el periodo neonatal	116	2,1	Hepatitis autoinmunitaria	71	1,4
Síndrome de Guillain-Barré	110	2,0	Miastenia gravis	63	1,2
Miastenia gravis	107	1,9	Cirrosis biliar primaria	20	0,4
Otras enfermedades huérfanas	2.813	50,2	Otras enfermedades huérfanas	2.542	49,7
Total	5.604	100	Total	5.114	100

Source: Calculated based on official data from the Department of Statistics and Health Information, Chile Ministry of Health.

Since the data corresponding to the age variable did not come from a normal distribution in both men and women ($p < 2.2e-16$, Kolmogorov-Smirnov test), it was found that there were statistical differences ($p < 2.2e-16$, Mann-Whitney U test) in the median age in both sexes, that difference being positive in favor of men.

The average mortality rate from rare diseases in Chile during the period was 3.9 per 100,000 inhabitants: 4.1 for women and 3.8 for men. In both cases, the highest rates were observed in children aged 0 to less than 4 years. In general, women had the highest rates, especially after the age of 35. For males, the rates were higher than for females from 5 to 9 years and up to 25 to 29 years (Figure 2). The highest rates for men were in the 45 - 49 age group.



	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65 y más
Mujeres	2,73	0,09	0,09	0,08	0,08	0,06	0,06	0,07	0,08	0,14	0,16	0,20	0,28	0,60
Hombres	2,73	0,10	0,17	0,18	0,12	0,08	0,04	0,06	0,07	0,13	0,16	0,16	0,22	0,54
Total	2,73	0,09	0,10	0,14	0,10	0,07	0,05	0,06	0,08	0,14	0,16	0,18	0,25	0,58

Figure 2. Average annual mortality rate due to orphan diseases by sex and age groups, Chile, 2002 - 2017. Source: Calculation based on official data from the Department of Statistics and Health Information, Chile Ministry of Health.

Table 3. Mortality rate of orphan diseases adjusted by region of residence and age in Chile, 2002 - 2017.

Regiones	Tasa ajustada de mortalidad por 100.000 personas/año																Media
	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Chile	3,9	4,1	4,1	4,3	4,1	3,8	4,0	3,7	3,8	3,7	3,9	3,8	4,2	4,1	4,0	3,5	3,9
Tarapacá	4,8	5,0	4,0	2,0	5,0	8,0	8,0	8,0	4,0	9,0	10,0	10,0	4,0	10,0	7,0	6,0	6,5
Antofagasta	6,0	3,1	1,5	1,5	3,0	2,9	6,7	5,5	2,7	3,4	6,7	4,1	2,4	1,6	3,3	3,3	3,6
Atacama	4,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,7	0,3
Coquimbo	4,0	0,0	0,0	0,0	0,4	0,0	0,0	0,7	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,3
Valparaiso	2,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,7	0,7	0,7	0,7	0,7	0,3
Libertador B. O'Higgins	2,0	0,0	0,0	0,4	0,0	0,7	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,6	0,0	0,0	0,2
Maule	3,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	1,1	1,1	0,5	0,4
Biobío	3,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,2
Araucanía	3,0	0,0	0,0	0,0	0,0	0,0	0,0	0,5	0,0	0,0	0,5	0,0	0,0	0,5	0,0	0,0	0,3
Los Lagos	3,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,6	0,6	1,1	0,5	1,5	0,0	0,5	0,5
Aisén del Gral. C. Ibáñez del Campo	6,0	0,0	0,0	0,0	0,0	0,6	0,0	0,0	0,0	0,0	0,6	0,0	0,0	0,0	0,0	0,0	0,5
Magallanes y de la Antártida Chilena	8,0	0,0	0,0	0,0	0,3	0,0	0,6	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,6
Metropolitana de Santiago	3,0	0,0	0,0	0,0	0,0	0,7	0,0	0,0	0,0	1,1	0,0	0,5	0,0	0,5	0,0	0,5	0,4
Los Ríos	5,0	1,9	0,0	0,0	0,5	0,0	0,0	0,0	0,8	0,0	0,0	0,7	0,0	0,0	0,0	0,0	0,6
Arica y Paniracota	4,0	0,0	0,6	0,0	0,5	0,0	0,0	0,0	0,0	1,8	0,8	0,0	0,0	0,7	0,7	0,0	0,6
Nuble	3,0	0,0	0,9	0,5	0,0	1,0	0,0	0,0	0,0	0,9	0,0	0,8	0,0	0,7	0,0	0,0	0,5

Source: Calculations based on official data from the Department of Statistics and Health Information, Chile Ministry of Health.

In the bivariate analysis between qualitative variables, it was found that sex, activity, educational level, age distributed by groups, and area of residence were associated with deaths due to orphan disease (Table 1). Bivariate logistic regression (crude OR) yielded a statistically significant value for some of the characteristics previously studied, which were corroborated by multivariate logistic regression analysis (adjusted OR).

When considering sex, it was determined that women were 1.75 more likely to die from orphan diseases compared to men (adjusted OR = 1.75; $IC_{95\%}$ 1.69-1.82). Those in inactive conditions showed a 1.32 times greater probability of dying ($_aOR$ = 1.32; $IC_{95\%}$ 1.09-1.59). With respect to educational level, it was found that individuals with no educational level were up to 4.31 times more likely to die from one of these diseases ($_aOR$ = 4.31; $IC_{95\%}$ 3.93-4.73).

Regarding age groups, it was corroborated that the pediatric population (0 to 4 years) continues to present the highest risk of dying ($_aOR$ = 15.30; $IC_{95\%}$ 14.10-19.20), compared to those aged 5 to 9 ($_aOR$ = 6.91; $IC_{95\%}$ 6.00-9.05) and 10 to 14 years ($_aOR$ = 6.37; $IC_{95\%}$ 5.51-8.00). The same was true for those aged 15-19 and 20-24 years, respectively ($_aOR$ = 3.57; $IC_{95\%}$ 3.40-4.35 vs. $_aOR$ = 2.6; $IC_{95\%}$ 1.68-2.48). In addition, it was observed that decedents residing in urban areas were 1.22 times more likely to die from these causes compared to those residing in rural areas ($_aOR$ = 1.22; $IC_{95\%}$ 1.10-1.29) (Table 4).

Table 4. Bivariate and multivariate logistic regression analysis of mortality risk due to orphan diseases in Chile, 2002 - 2017.

Variables	Análisis bivariado			Análisis multivariado		
	OR cruda	IC95%	p	OR ajustado	IC95%	p
Sexo						
Mujer	1,26			1,75		
Hombre*	1	1,21-1,3	<0,001	1	1,69-182	<0,001
Actividad						
Cesante o desocupado	1			1		
Inactivo	1,43	1,18-1,72	<0,001	1,32	1,09-1,59	0,004
Activo	0,91	0,71-1,11	0,366	0,9	0,74-1,09	0,287
Nivel educativo						
Superior*	1			1		
Medio	1,33	1,2-1,48	<0,001	1,33	1,2-1,48	<0,001
Secundaria	0,47	0,42-0,53	<0,001	0,46	0,41-0,52	<0,001
Básico o primaria	0,52	0,48-0,58	<0,001	0,51	0,46-0,56	<0,001
Ninguno	4,45	4,06-4,89	<0,001	4,31	3,93-4,73	<0,001
Grupos de edad (años)						
0-4	16,58	14,21-19,35	<0,001	15,30	14,10-19,20	<0,001
5-9	7,44	6,04-9,17	<0,001	6,91	6,00-9,05	<0,001
10-14	6,83	5,59-8,35	<0,001	6,37	5,51-8,00	<0,001
15-19	3,61	3,4-4,35	<0,001	3,57	3,4-4,35	<0,001
20-24	2,03	1,68-2,46	<0,001	2,06	1,68-2,48	<0,001
25-29	1,24	1,01-1,53	0,041	1,26	1,05-1,55	0,029
30-34*	1					
35-39	0,94	0,77-1,16	0,584	0,93	0,70-1,10	0,488
40-44	0,8	0,66-0,97	0,026	0,8	0,66-0,97	0,011
45-49	0,97	0,81-1,17	0,772	0,93	0,79-1,15	0,452
50-54	0,91	0,76-1,08	0,275	0,86	0,71-1,07	0,101
55-59	0,85	0,72-1,01	0,062	0,81	0,70-1,01	0,013
60-64	0,72	0,61-0,85	<0,001	0,68	0,60-0,81	<0,001
65 y más	0,23	0,2-0,27	<0,001	0,21	0,19-0,27	<0,001
Area de residencia						
Rural*	1					
Urbana	1,24	1,17-1,32	<0,001	1,22	1,10-1,29	<0,001

Source: Calculations based on official data from the Department of Statistics and Health Information, Chile Ministry of Health. OR: crude odds ratio; adjusted OR: adjusted odds ratio; *: reference category.

4. Discussion

From 2002 to 2017, 10,718 people in Chile died from diseases directly related to orphan diseases. However, given their global classification limitations, these numbers may be much higher than the findings presented in this article. This means that many of them may be overlooked or misclassified due to complications [14, 15].

The analysis of sociodemographic characteristics reveals several important elements that help to understand the wide diversity of rare diseases, as behaviour varies not only from disease to disease, but also within the same context to which the affected individuals belong. According to the findings, a representative proportion (52.3%) of these deaths occurred in women. These results coincide with the official data documented by the National Public Health Surveillance System in Colombia, whose trend has shown a more accentuated growth in this population group in the last five years [16].

In part, this could be explained by the fact that a significant percentage of these conditions are of autoimmune origin and it has been shown that immune system alterations predominate in women [17]. However, another study that analyzed deaths from these causes in the same country revealed that 51.4% (3,468) of them occurred in men of all ages [18]. The disabling nature of orphan diseases is related not only to their chronic nature, but also to the high level of disability they cause, which in turn leads to significant economic vulnerability, creating a wide range of needs for patients and their families.

The high proportion (89.4%) of inactive deaths, particularly among children under five and adults over 65, is to some extent reflected in the attribution of 6,639 (61.9%) identified deaths to this group. This trend is consistent with what is reported in the scientific literature on morbidity and premature mortality [19-21]. Regarding educational level, the highest proportion of deaths was concentrated in populations with no schooling.

The behavior of orphan diseases is very heterogeneous. For children, this means a decrease in their physical, psychological, sensory, and behavioral abilities. Lack of education can be understood as a potential risk factor for incidence rate and mortality [22]. Congenital malformations are the main cause of death in Chile. This pattern is consistent with the situation reported by most countries in Latin America, where the number of deaths of children under one year old tends to increase year by year, ranking second to fifth in the number of deaths. This is equivalent to 27% of the mortality rate of children under 5 years old [23].

In another study in Colombia, nearly 22,361 perinatal deaths attributed to congenital malformations were found, with 205.81 to 74.18 deaths per 10,000 live births in a 10-year study [24].

In relation to specific diagnoses, anencephaly constitutes the leading cause of death in children aged 0 to 4 years of both sexes. This data is consistent with the records of newborns between 0 and 28 days in Ireland. From 2006 to 2016 [25], the deaths of newborns between 0 and 28 days accounted for 51.58% of the country's infant mortality burden.

Creutzfeldt-Jakob disease was among the most frequent orphan diseases in the population aged 15 years and in those over 65 years, mainly women. In adults aged 65 and older, the disease may become more prevalent as a leading cause of dementia, with increasing severity with age. In a recent study in Japan, a significant increase in mortality (3.2%; $IC_{95\%}$ 1.4-5.1) and incidence (6.4%; $IC_{95\%}$ 4.7-8.1) was revealed, especially among adults older than 70 years [26].

Muscular dystrophy was one of the diseases that most affected men of all ages in Chile. There is evidence, especially, of the hereditary Duchenne variant, a type of progressive neuromuscular disease that affects one in every 5,000 boys born alive [27]. Another common disease in both sexes was Guillain-Barré. Not common among male populations, this behavior is consistent with a report from another study in Colombia [28].

The age-related findings vary from those reported in Peru, where the median age was 47 years. This shows that orphan diseases are a diverse and complex group that affects patients differently [29]. Differences in overall mortality rates by gender and age group were observed, partially in line with the results reported in the Madrid community in Spain from 1999 to 2003, where these diseases claimed more lives among males of all age groups, and the highest risk of death was determined among individuals under one year of age [30]. The mortality rate of this group of diseases shows that in the same Spanish community, the mortality rate showed an upward trend in 2010 and 2012, reaching 15.4/100,000 annually. The incidence rate of women over 75 years old was the highest, 170.8/100,000, while that of men in the same group was 70.4/100,000 [31]. In Chile, women have the highest mortality rate, especially at the end of their lives. The risk of dying from an orphan disease is higher in the first few years of life for both men and women.

The death behavior varies according to the living area of the deceased, showing obvious regional differences: Santiago, Valparaíso, Biobio, Maule, Araucania and other metropolitan areas have the largest number of deaths. To some extent, this model can be explained by the limited supply of qualified healthcare professionals, the distribution of diagnostic laboratories, and the highly complex distribution of healthcare services for managing these diseases nationwide.

The study found that there was a statistically significant correlation between the death of orphan diseases and gender, activity, education level, age group and residential area. Multivariate logistic regression analysis confirmed this result. The analysis of the generalised linear models showed that the risk of dying from rare diseases was 1.75 times higher for women aged 65 years or older living in urban areas than for men. This finding coincides with that reported in a hospital-based

study in northern Peru ($p < 0.001$; RPa (adjusted prevalence ratio): 1.76; $IC_{95\%}$ 1.67-1.86) [29]. Another analysis conducted in Tuscany, northern Italy, from 2010 to 2018 showed that the death risk of the male population increased significantly, 1.48 times that of the female population (Hazard Ratio, HR = 1.48; $IC_{95\%}$, 1.38-1.58) [34].

An increased risk of death was observed in inactive populations, which may be due to the chronic debilitating nature of these diseases, leading to multiple and severe disabilities. This finding is closely related to the risk of death for individuals without any education. Among them, this proportion is four times higher than those who have received some kind of education. These results are significantly different from the report by Cali of Colombia, whose analysis shows that there is no statistically significant relationship between education level and mortality from these causes.

On the other hand, the risk of death increases up to 15 times in infants aged 0 to 4 years with respect to the rest of the population. This is mainly attributed to very broad and complex structural and physiological alterations associated with genetic anomalies originated during the early stages of embryonic development [35, 36]. In the same work carried out in Cali (Colombia), the highest mortality risk occurred in individuals aged 30 to 44 years ($p < 0.03$; RPa: 14.07; $IC_{95\%}$ 1.23-160.4) [28]. These differences reflect the wide variability in the morbidity and mortality profile of orphan diseases between countries, even within the same region. The risk of death was significantly higher ($_aOR = 1.22$; $IC_{95\%}$ 1.10-1.29) in people who usually resided in urban areas compared to those who lived in more dispersed or rural areas. This confirms what is known about the possibility of timely diagnosis and adequate management in the country's large cities [32].

As limitations of this research, it is worth mentioning that both the calculations of the mortality indicator and the measurement of the risk of dying from this group of diseases were based on secondary information from the official death databases and did not take into account other sources that would help to contrast the information between different databases and thus identify possible deaths that were not reported in the Chilean national vital statistics system. The possible underreporting and lack of specificity or uniformity of diagnoses may affect the final calculation of mortality rates, which could underestimate the real magnitude of deaths due to diseases in Chile.

Another limitation to consider is that, in the multivariate analysis, the methodological strategy of stratification was not used for the activity variable, which could have overestimated the risk of death for this variable given the scope of the data. Similarly, this procedure was not done for deaths in children 0 to 4 years of age. This means that the risk observed in this specific population group could also be yielding higher values, since perinatal and late neonatal mortality vary markedly among them. Even with all these limitations, the results presented in this work show an updated panorama of the mortality situation due to orphan diseases as a whole and the main causes of death in the population attributed to specific diagnoses related to this group of diseases. Therefore, they constitute an input to further deepen the subject and prioritize interventions in those regions and populations most affected, since most of them are premature deaths or deaths before reaching life expectancy. Furthermore, it could be said that this analysis is one of the first in this field that focuses on deaths due to this group of diseases globally and explores the possible factors associated with mortality in our environment.

It is concluded that mortality due to orphan diseases, as a whole, is emerging as a growing public health problem in Chile.

The findings demonstrate the importance of carrying out more studies, but, above all, of advancing in the standardization of a coding and classification system of our own, in accordance with the morbidity and mortality profiles associated with orphan diseases in our context, which will provide timely and quality information for decision-making and guide public health interventions.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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