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Impact of the COVID-19 pandemic in mortality due to respiratory diseases: A comparative analysis of 2021 and 2020 vs 2019 in Spain

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Abstract

Introduction: We previously reported an increase in respiratory mortality in 2020 in Spain after COVID-19. It is unclear if this rise is sustained in the longer-term. We aimed to determine whether respiratory mortality in 2021 in Spain returned to pre-pandemic levels.

Material and Methods: In an observational, large study using official INE data, we explored deaths due to respiratory diseases, that is, all causes of death by the standard WHO list of diseases of the respiratory system plus COVID-19, tuberculosis and lung cancer. Using the latest available official data of Spain, we analysed changes in the mortality pattern in Spain from January 2019 to December 2021. We endorsed STROBE guidance for observational research.

Results: There were 98,714 deaths due to respiratory diseases in 2021 in Spain, corresponding to 21.9% of all deaths, becoming second in the ranking of causes of death. Respiratory diseases mortality in Spain has not returned to pre-pandemic levels in 2021, still with an increase of 30.3% (95% C.I. 30.2-30.4) compared to rates in 2019. All respiratory-specific causes of death decreased in 2021, except for lung cancer, that increased in women and decreased in men compared to 2019 (both $p < 0.05$). In a multivariate analysis some established risk factors for respiratory diseases mortality were confirmed, such as male gender and older age; further, an association with reduced mortality in rural Spain was observed, still with a large geographical variability.

Conclusions: The COVID-19 pandemic has had a lasting impact on deaths due to respiratory diseases and certain specific causes of death in 2021, and it has disproportionately affected certain regions.

Abstract word count: 262 words

**Impacto de la pandemia de COVID-19 en la mortalidad por enfermedades respiratorias:
Análisis comparativo de 2021 y 2020 vs 2019 en España**

Resumen

Introducción: Previamente informamos de un aumento de la mortalidad respiratoria en 2020 en España tras la COVID-19. No está claro si este aumento se mantiene a largo plazo. Nuestro objetivo fue determinar si la mortalidad respiratoria en 2021 en España volvió a los niveles previos a la pandemia.

Métodos: En un gran estudio observacional con datos oficiales del INE, exploramos las muertes por enfermedades respiratorias, es decir, todas las causas de muerte según la lista estándar de enfermedades del sistema respiratorio de la OMS más COVID-19, tuberculosis y cáncer de pulmón. Utilizando los últimos datos oficiales disponibles de España, analizamos los cambios en el patrón de mortalidad en España desde enero de 2019 hasta diciembre de 2021. Seguimos la guía STROBE para investigación observacional.

Resultados: Se produjeron 98.714 muertes por enfermedades respiratorias en 2021 en España, lo que corresponde al 21,9% del total de muertes, situándose en el segundo lugar del ranking de causas de muerte. La mortalidad por enfermedades respiratorias en España no ha vuelto a los niveles previos a la pandemia en 2021, aún con un aumento del 30,3% (I.C. 95% 30,2-30,4) respecto a las tasas de 2019. Todas las causas de muerte específicas de las vías respiratorias disminuyeron en 2021, excepto el cáncer de pulmón, que aumentó en mujeres y disminuyó en hombres en comparación con 2019 (ambos $p < 0,05$). En un análisis multivariado se confirmaron algunos factores de riesgo establecidos para la mortalidad por enfermedades respiratorias, como el género masculino y la edad avanzada; además, se observó una asociación con reducción de la mortalidad en la España rural, aún con una gran variabilidad geográfica.

Conclusiones: La pandemia de COVID-19 ha tenido un impacto duradero en las muertes por enfermedades respiratorias y ciertas causas específicas de muerte en 2021, y ha afectado de manera desproporcionada a ciertas regiones.

Palabras clave: Certificado de defunción; COVID-19; Enfermedades del sistema respiratorio; INE; Mortalidad

Introduction

The COVID-19 pandemic has had a significant impact on mortality around the world, with many countries experiencing a surge in deaths during the initial months of the pandemic. We previously reported an increase in respiratory mortality in 2020 in Spain, with a corresponding decrease in other due to substitution of causes of death.¹

Others have reported increases in cancer and chronic conditions mortality, such as diabetes, cardiovascular diseases, and some oncological diseases, related with the interruption of population-based early detection programmes and diagnostic and therapeutic delays associated with the collapse in primary care and associated hospital services, adding significant stress to already overstretched health systems.² Many of these general, global aspects need to be implemented and carefully assessed in Spain.³ Three years and counting from the onset of the COVID-19 pandemic,⁴ with the perspective of seven pandemic waves, and with a population vaccination coverage above 80% in most age strata in Spain, it is unclear if this mortality rise will sustain in the longer-term.

The diseases of the respiratory "system" in the current classification of the WHO (and any competent national bodies) do not fully reflect the reality of all diseases certainly affecting the respiratory system, and do not include conditions that are part of the day-to-day care of patients from pulmonologists, such as tuberculosis, lung cancer or COVID-19 itself, among others. A dialogue to try to correct and interpret well future statistics remains necessary.

In this research, we aimed to determine whether proportionate mortality by respiratory diseases, including tuberculosis, lung cancer and COVID-19 in Spain returned to pre-pandemic levels before COVID-19 in 2021.

Methods

We endorsed STROBE guidance for observational research.⁵ We had a particular interest in deaths due to respiratory diseases, that is all causes of death by the standard WHO list of diseases of the respiratory system plus COVID-19, tuberculosis and lung cancer. Using the latest available data from the Instituto Nacional de Estadística (INE) of Spain,^{6,7} we analysed proportionate mortality trends in Spain from January 2019 to December 2021. In particular, we used 2019 as the reference year, free from COVID-19, and report proportionate mortality in 2020 and in 2021.

Mortality microdata data were obtained from the INE website⁸. As previously indicated,¹ the so-called Short List of 101 causes of death ICD-10, and its correspondence with ICD-9, was reviewed and regrouped for Group VIII - Diseases of the respiratory system: Flu; Pneumonia; Chronic diseases of the lower respiratory tract (except asthma); Asthma; Respiratory insufficiency; and Other diseases of the respiratory system; and also other diseases of the respiratory system such as tuberculosis, or of daily practice in the field of Pulmonology such as malignant tumours of the trachea, bronchi and lung, were added as respiratory causes of death (what we have labelled as Group VIII-bis) . The causes "COVID-19 Virus identified" and "COVID-19 Virus not identified (suspected)" were also included (**Table 1**). A descriptive analysis of the absolute frequencies of deaths and proportionate mortality by gender, age, and Autonomous Communities (regions) was performed. The percentages of change in proportionate mortality between pre-pandemic (2019) and post-pandemic (2020 and 2021)

years were calculated. A crude and multivariable logistic regression analysis was performed with the microdata to obtain the odds ratios (ORs) and their 95% confidence interval (CI), as estimators of the association of the independent variables with mortality. We had a new, particular interest in an analysis by size of the location and location of birth of those deceased. In any comparison, a value of $p < 0.05$ was considered statistically significant.^{9,10,11}

Results

There were 98,714 deaths due to respiratory diseases in 2021 in Spain (VIII-bis in our classification), corresponding to 21.9% of all deaths, becoming second in the ranking of causes of death, right after diseases of the circulatory system with 119,196 (26.4%), and ahead of cancer with 75,549 (16.8%) (**Table 1**). Our results show that respiratory mortality in Spain has not returned to pre-pandemic levels in 2021, still with an increase of 30.3% (95% C.I. 30.2-30.4) compared to background rates in 2019 (it was a 68.5% (95% C.I. 68.4-68.6) increase in 2020).

When we analyzed mortality by respiratory-specific causes of death versus 2019, we found that all significantly or nominally decreased in 2021 (**Table 2**), except for lung cancer, that increased in women and decreased in men compared to 2019 (both $p < 0.05$) (**Table 3 & Figure 1**). Additionally, we observed large regional differences by Autonomous Communities in mortality, with some regions experiencing a greater impact on overall, respiratory-related and specific respiratory diseases mortality compared to others.

In the multivariate logistic regression analysis some established risk factors for respiratory diseases mortality were confirmed, such as male gender and older age; further, a protection in rural Spain was observed, still with a large geographical variability, and those born from elsewhere in Europe and Latin America had significantly lower respiratory mortality compared to others born in any other continents (**Table 4 & Figure 2**).

Finally, with an intention to be comprehensive in our descriptive analyses, the number of deaths and percentage of mortality by diseases of the respiratory system in 2021 in Spain are presented by Autonomous Community (**eTable 1**), and also by age (**eTable 2**).

Discussion

We report that the COVID-19 pandemic has had a lasting impact on both general and specific causes of death due to respiratory diseases in 2021 in Spain, and it has disproportionately affected certain regions, mainly Madrid and Catalunya. By accounting COVID-19, tuberculosis and lung cancer deaths within the WHO list of diseases of the respiratory system, it can be stated that 21.9% of all deaths in 2021 in Spain were due to respiratory diseases, becoming second in the ranking of causes of death. Respiratory mortality in Spain has not returned to pre-pandemic levels in 2021, still with an increase of 30.3% compared to background rates in 2019.

Respiratory conditions are responsible for a large population burden of disease, morbidity and mortality, both in Spain and in the world. According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), of the 50.5 million deaths that occurred in 1990 in the world, 4.3 million were attributed to pneumonia, 2.2 million to tuberculosis, 2.0 million to chronic obstructive pulmonary disease (COPD) and 0.95 million to lung cancer. In addition, it was estimated that for 2020, of the 68.3 million predictable deaths, 11.9 million would be from

respiratory causes as per the standard WHO list, estimating that they became the third cause of death in 2020.¹² In Spain, with a relatively aged population and yet with alarming rates of smoking,¹³ and of smoking-related deaths,^{14,15} respiratory diseases also have a huge impact on individual and population health.^{16,17} Its magnitude and diversity mean that the clinical management of respiratory health, beyond Pulmonology, also requires a large part of the daily dedication of health professionals in Primary Care, Internal Medicine and other specialties.^{18,19}

It is well known that respiratory mortality statistics from death certificates are underreported compared to cancer, cardiovascular and metabolic diseases. This bias occurs for various reasons.^{20,21} Among other, it is a clinical challenge to attribute a death to a respiratory cause, since the symptoms and determinants are non-specific and overlap with those of cardiovascular or other diseases, and many patients with chronic respiratory diseases die with them and not from them.^{22,23} Current standardized coding manuals for death certificates from the World Health Organization (WHO), as well as from the European Union and its EUROSTAT, or from the National Institute of Statistics (INE) are homogeneous. The INE is governed by the rules established by the WHO as established by Regulation (EU) No. 328/2011 of the Commission of April 5, 2011, which applies Regulation (EC) No. 1338/2008 of the European Parliament and of the Council on Community statistics on public health and on health and safety at work. Regarding statistics on the causes of respiratory death, only those from Group VIII (with ICD10 062-067) are considered as causes of death of the Respiratory System, namely: Influenza; Pneumonia; Chronic diseases of the lower respiratory tract (except asthma); Asthma; Respiratory insufficiency; and Other diseases of the respiratory system.²⁴ However, as above mentioned, other diseases that also directly affect the respiratory system such as tuberculosis, or daily practice in the field of Pulmonology and Thoracic Surgery such as lung cancer ("malignant tumours of the trachea, bronchi and lung"), are considered for statistical purposes as deaths of infectious and oncological causes, respectively, might be reconsidered as respiratory as well in future reclassifications.

This analysis has a number of strengths such as its immediacy, urgency, obvious relevance, and internal consistency. In addition, it contributes to the current debate on classifying by underlying cause vs. all basic death contributions. In particular, all INE Causes of Death Statistics offer data on the basic cause of death and also on all those other diseases that have contributed to death and that the certifying doctor has reported on the medical death certificate (multiple causes). All of them can be considered as advantages. However, we must highlight a series of limitations related with an observational study design, and some of which are inherent to the death certificate. In general, it is considered established that many patients with COPD, asthma or other respiratory diseases die with them as mentioned above.^{25,26}

Explanatory factors are the general population's lack of knowledge about respiratory diseases and the lack of specificity of most respiratory symptoms and signs, compared to other major causes of disease and death, such as cardiovascular or oncological causes. This will require the design of complex long-term strategies, and therefore difficult to implement. However, overestimation should be avoided. Strictly speaking, the COVID-19 clinical care task of the pulmonologist could only be considered directly in deaths occurring in the hospital. For example, during the first wave in Spain, people who died in residences, or at their homes, did not represent a true care burden to pulmonologist. Of course, Pulmonology shares the treatment and management of respiratory patients with Internal Medicine, Primary Care and other specialties. Multisectoral coordination and dialogue should contribute to a better management of these patients.

Our findings suggest that, while proportionate mortality has largely returned to pre-pandemic levels overall, the pandemic has had a lasting impact on deaths due to respiratory diseases and certain specific causes of death, and has disproportionately affected certain regions. We conclude that respiratory mortality in Spain has not returned to pre-pandemic levels in 2021, still with an increase of 30.3% compared to background rates in 2019. Further research is needed to understand the factors contributing to these differences and to inform policies aimed at reducing respiratory diseases mortality in the post-pandemic era.

Table 1. Number of deaths, proportionate mortality (%) and percent change by causes of death in Spain in 2019, 2020 and 2021.

Cause	Total (N = 1,363,223)	2019 (n = 418,703) ^a	2020 (n = 493,776) ^b	2021 (n = 450,744) ^c	Change in % Between 2020 vs. 2019	Change in % Between 2021 vs. 2019
I- Infectious and parasitic diseases	17,405 (1.3%)	5,902 (1.4%)	5,759 (1.2%)^d	5,744 (1.3%)	-17.3	-9.6
II- Tumours	226,822 (16.6%)	75,774 (18.1%)	75,499 (15.3%)	75,549 (16.8%)	-15.5	-7.4
III- Diseases of the blood and haematopoietic organs, and certain disorders affecting the mechanism of immunity	6,279 (0.5%)	2,012 (0.5%)	2,062 (0.4%)	2,205 (0.5%)	-13.1	1.8
IV- Endocrine, nutritional and metabolic diseases	43,765 (3.2%)	13,351 (3.2%)	15,290 (3.1%)	15,124 (3.4%)	-2.9	5.2
V- Mental and behavioural disorders	65,105 (4.8%)	22,896 (5.5%)	21,697 (4.4%)	20,512 (4.6%)	-17.0	-16.8
VI- Diseases of the nervous system and sensory organs	78,642 (5.8%)	26,120 (6.2%)	27,508 (5.6%)	25,014 (5.5%)	-19.6	-11.0
VII- Diseases of the circulatory system	355,664 (26.1%)	116,615 (27.9%)	119,853 (24.3%)	119,196 (26.4%)	-10.7	-5.1
VIII- bis Diseases of the respiratory system (+COVID-19)	308,983 (22.7%)	70,389 (16.8%)	139,880 (28.3%)	98,714 (21.9%)	68.5	30.3
COVID -19 (alone)	114,922 (8.4%)	--	74,839 (15.2%)	40,083 (8.9%)	--	--
IX- Diseases of the digestive system	66,166 (4.9%)	22,038 (5.3%)	21,565 (4.4%)	22,563 (5.0%)	-17.0	-4.9
X- Diseases of the skin and subcutaneous tissue	5,698 (0.4%)	1,775 (0.4%)	1,902 (0.4%)	2,021 (0.4%)	-9.1	5.8
XI- Diseases of the musculoskeletal system and connective tissues	15,500 (1.1%)	5,162 (1.2%)	5,225 (1.1%)	5,113 (1.1%)	-14.2	-8.0
XII- Diseases of the genitourinary system	91,206 (6.7%)	28,917 (6.9%)	30,632 (6.2%)	31,657 (7.0%)	-10.2	1.7
XIII- Pregnancy, childbirth and puerperium	27 (0.0%)	6 (0.0%)	10 (0.0%)	11 (0.0%)	41.3	70.3
XIV- Conditions originating in the perinatal period	1,630 (0.1%)	584 (0.1%)	518 (0.1%)	528 (0.1%)	-24.8	-16.0
XV- Congenital malformations, deformities and	2,471 (0.2%)	815 (0.2%)	823 (0.2%)	833 (0.2%)	-14.4	-5.1

chromosomal abnormalities						
XVI- Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	28,810 (2.1%)	10,206 (2.4%)	9,475 (1.9%)	9,129 (2.0%)	-21.3	-16.9
XVII- External causes of mortality	49,050 (3.6%)	16,141 (3.9%)	16,078 (3.3%)	16,831 (3.7%)	-15.5	-3.1

^aPercentage of each cause of death compared to the total causes of death in 2019.

^bPercentage of each cause of death compared to the total causes of death in 2020.

^cPercentage of each cause of death compared to the total causes of death in 2021.

^dSignificant differences ($p < 0.01$) against causes of death in 2019 are indicated by bold text.

Table 2. Number of deaths, proportionate mortality (%) and percent change by diseases of the respiratory system in Spain in 2019 to 2021.

Cause	Total (N = 1,363,223)	2019 (n = 418,703) ^a	2020 (n = 493,776) ^b	2021 (n = 450,744) ^c	Change in % Between 2020 vs. 2019	Change in % Between 2021 vs. 2019
00A Covid-19 Virus identified	99,802 (7.3%)	--	60,358 (12.2%)^d	39,444 (8.8%)	--	--
00B Covid-19 Unidentified virus (suspected)	15,076 (1.1%)	--	14,481 (2.9%)	595 (0.1%)	--	--
00C Covid-19 associated multisystemic inflammatory syndrome COVID-19	44 (0.0%)	--	0 (0.0%)	44 (0.0%)	--	--
002 Tuberculosis and its late effects	589 (0.0%)	217 (0.1%)	198 (0.0%)	174 (0.0%)	-22.6%	-25.5%
018 Malignant tumour of the trachea, bronchi and lung	66,363 (4.9%)	22,007 (5.3%)	21,918 (4.4%)	22,438 (5.0%)	-15.6%	-5.3%
019 Other respiratory and intrathoracic malignancies	1,462 (0.1%)	484 (0.1%)	502 (0.1%)	476 (0.1%)	-12.1%	-8.6%
062 Influenza (includes influenza due to identified pandemic or zoonotic influenza viruses)	2,377 (0.2%)	1,459 (0.3%)	894 (0.2%)	24 (0.0%)	-48.0%	-98.5%
063 Pneumonia	24,951 (1.8%)	9,384 (2.2%)	8,768 (1.8%)	6,799 (1.5%)	-20.8%	-32.7%
064 Chronic lower respiratory tract diseases (except asthma)	35,095 (2.6%)	12,815 (3.1%)	11,786 (2.4%)	10,494 (2.3%)	-22.0%	-23.9%
065 Asthma	2,742 (0.2%)	993 (0.2%)	948 (0.2%)	801 (0.2%)	-19.0%	-25.1%
066 Respiratory failure	6,159 (0.5%)	2,171 (0.5%)	2,039 (0.4%)	1,949 (0.4%)	-20.4%	-16.6%

067 Other diseases of the respiratory system	54,323 (4.0%)	20,859 (5.0%)	17,988 (3.6%)	15,476 (3.4%)	-26.9%	-31.1%
TOTAL "Causes of death of the respiratory system"	308,983 (22.7%)	70,389 (16.8%)	139,880 (28.3%)	98,714 (21.9%)	68.5%	30.3%
001-102 I-XXII.All Causes	1,363,223 (100.0%)	418,703 (30.7%)	493,776 (36.2%)	450,744 (33.06%)	17.9%	7.7%

^aPercentage of each cause of death compared to the total causes of death in 2019.

^bPercentage of each cause of death compared to the total causes of death in 2020.

^cPercentage of each cause of death compared to the total causes of death in 2021.

^dSignificant differences ($p < 0.01$) against 2019 causes are indicated by bold text.

Table 3. Number of deaths and percentage of mortality by diseases of the respiratory system in 2019, 2020 and 2021 in Spain, by gender.

Cause	Men			Women		
	2019	2020 ^a	2021 ^b	2019	2020	2021
00A Covid-19 Virus identified	-	32,498 (13.0%)^c	22,449 (9.7%)	-	27,860 (11.4%)	16,995 (7.7%)
00B Covid-19 Unidentified virus (suspected)	-	6,419 (2.6%)	309 (0.1%)	-	8,062 (3.3%)	286 (0.1%)
00C Covid-19 associated multisystemic inflammatory syndrome COVID-19	-	0 (0.0%)	29 (0.0%)	-	0 (0.0%)	15 (0.0%)
002 Tuberculosis and its late effects	134 (0.1%)	124 (0.0%)	111 (0.0%)	83 (0.0%)	74 (0.0%)	63 (0.0%)
018 Malignant tumour of the trachea, bronchi and lung	16,935 (8.0%)	16,615 (6.7%)	16,772 (7.2%)	5,072 (2.5%)	5,303 (2.2%)	5,666 (2.6%)
019 Other malignant tumours of the trachea, bronchi and lung	332 (0.2%)	359 (0.1%)	316 (0.1%)	152 (0.1%)	143 (0.1%)	160 (0.1%)
062 Influenza (includes influenza due to identified pandemic or zoonotic influenza viruses)	680 (0.3%)	446 (0.2%)	14 (0.0%)	779 (0.4%)	448 (0.2%)	10 (0.0%)
063 Pneumonia	4,837 (2.3%)	4,704 (1.9%)	3,831 (1.7%)	4,547 (2.2%)	4,064 (1.7%)	2,968 (1.4%)
064 Chronic lower respiratory tract diseases (except asthma)	9,749 (4.6%)	8,832 (3.5%)	7,925 (3.4%)	3,066 (1.5%)	2,954 (1.2%)	2,569 (1.2%)
065 Asthma	158 (0.1%)	212 (0.1%)	175 (0.1%)	835 (0.4%)	736 (0.3%)	626 (0.3%)
066 Respiratory failure	903 (0.4%)	927 (0.4%)	824 (0.4%)	1,268 (0.6%)	1,112 (0.5%)	1,125 (0.5%)
067 Other diseases of the respiratory system	9,983 (4.7%)	8,714 (3.5%)	7,968 (3.4%)	10,876 (5.3%)	9,274 (3.8%)	7,508 (3.4%)

TOTAL "Causes of death of the respiratory system"	43,711 (20.6%)	79,850 (32.0%)	60,723 (26.2%)	26,678 (12.9%)	60,030 (24.6%)	37,991 (17.3%)
001-102 I-XXII.All Causes	212,683 (30.7%)	249,664 (36.0%)	231,410 (33.4%)	206,020 (30.8%)	244,112 (36.5%)	219,334 (32.8%)

^aPercentage of each cause of death compared to the total causes of death for Men in its respective year.

^bPercentage of each cause of death compared to the total causes of death for Women in its respective year.

^dSignificant differences ($p < 0.01$) against 2019 causes are indicated by bold text.

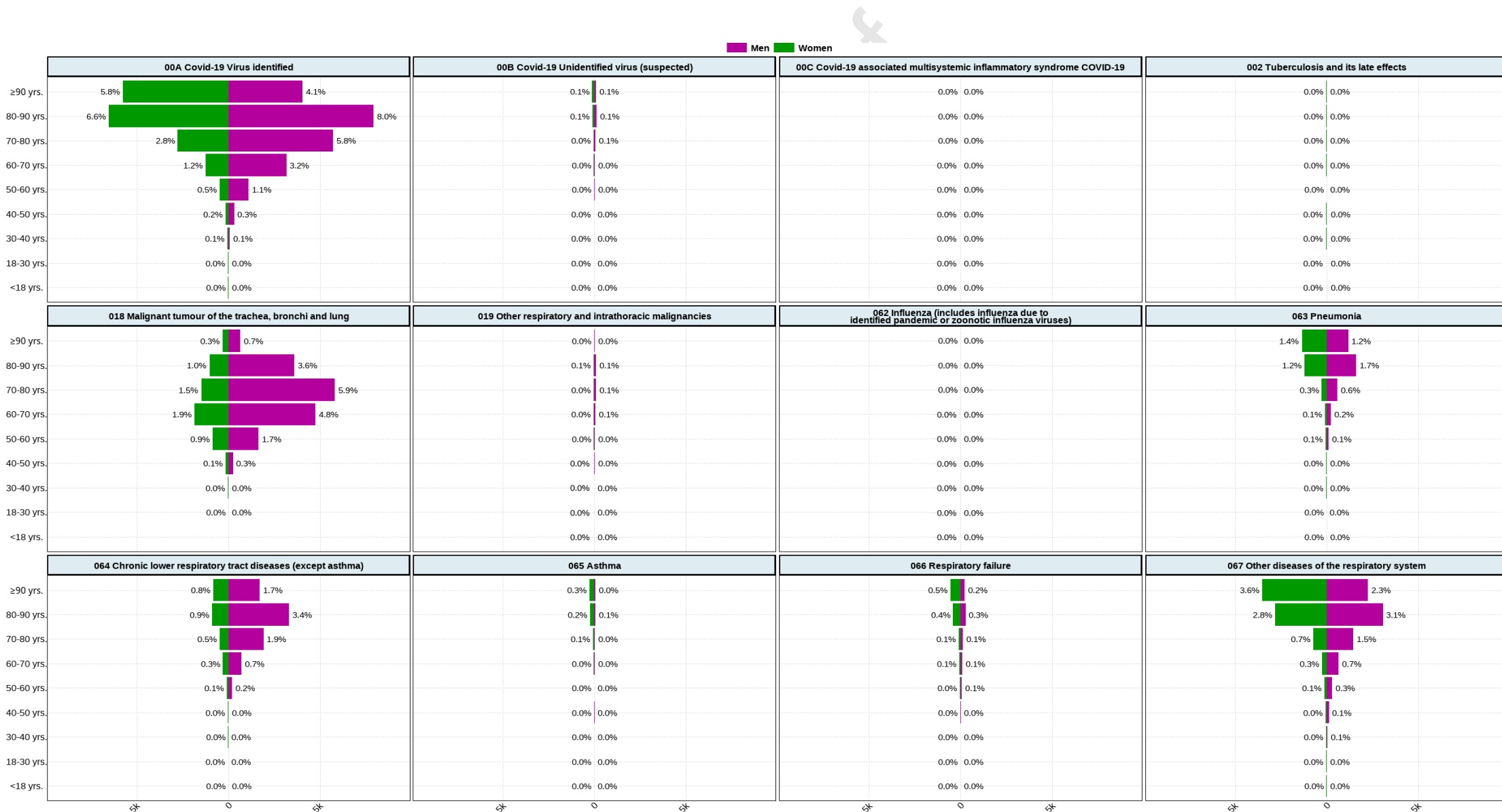


Figure 1: Population pyramid of respiratory system compared to the total causes of death of the respiratory system in 2021.

Table 4: Odds ratio for respiratory mortality (excluding COVID-19) in Spain in 2021, crude and multivariate.

Variable	Category	Crude		Multivariate	
		OR [95%CI]	p-value ^a	OR [95%CI]	p-value
Gender	Men	1.884 [1.850 - 1.918]	<0.001	1.771 [1.738 - 1.804]	<0.001
	Women	Ref	--	Ref	--
Autonomous communities	Andalucía	Ref	--	Ref	--
	Aragón	1.055 [1.000 - 1.113]	0.050	1.072 [1.015 - 1.132]	0.012
	Canarias	1.469 [1.404 - 1.537]	< 0.001	1.462 [1.396 - 1.530]	< 0.001
	Cantabria	1.175 [1.089 - 1.267]	< 0.001	1.199 [1.111 - 1.294]	< 0.001
	Castilla La Mancha	1.181 [1.129 - 1.235]	< 0.001	1.224 [1.169 - 1.281]	< 0.001
	Castilla y León	0.975 [0.935 - 1.016]	0.222	0.995 [0.954 - 1.038]	0.823
	Cataluña	1.034 [1.003 - 1.067]	0.033	1.060 [1.027 - 1.094]	< 0.001
	Ceuta	1.284 [1.033 - 1.597]	0.024	1.304 [1.044 - 1.628]	0.019
	Valencia	0.984 [0.951 - 1.018]	0.353	0.992 [0.958 - 1.027]	0.650
	Extremadura	1.200 [1.136 - 1.268]	< 0.001	1.231 [1.163 - 1.302]	< 0.001
	Galicia	1.162 [1.119 - 1.207]	< 0.001	1.208 [1.162 - 1.255]	< 0.001
	Islas Baleares	1.074 [1.006 - 1.148]	0.033	1.087 [1.017 - 1.162]	0.015
	La Rioja	1.075 [0.970 - 1.191]	0.171	1.102 [0.993 - 1.223]	0.067
	Madrid	1.384 [1.340 - 1.429]	< 0.001	1.400 [1.354 - 1.448]	< 0.001
	Melilla	1.309 [1.025 - 1.673]	0.031	1.392 [1.084 - 1.788]	0.009
	Navarra	1.074 [0.991 - 1.163]	0.080	1.105 [1.020 - 1.198]	0.015
	País Vasco	0.936 [0.894 - 0.980]	0.005	0.955 [0.912 - 1.001]	0.055
	Asturias	1.026 [0.970 - 1.084]	0.375	1.066 [1.007 - 1.128]	0.028
	Murcia	1.083 [1.024 - 1.146]	0.005	1.103 [1.042 - 1.168]	< 0.001
Age Range	<18 years	Ref	--	--	--
	[18 - 29 years]	1.304 [0.839 - 2.029]	0.238	1.257 [0.808 - 1.956]	0.311
	[30 - 39 years]	2.737 [1.901 - 3.940]	< 0.001	2.687 [1.865 - 3.870]	< 0.001
	[40 - 49 years]	4.078 [2.906 - 5.722]	< 0.001	3.977 [2.832 - 5.582]	< 0.001
	[50 - 59 years]	7.417 [5.320 - 10.340]	< 0.001	7.105 [5.093 - 9.912]	< 0.001
	[60 - 69 years]	10.163 [7.298 - 14.153]	< 0.001	9.675 [6.943 - 13.482]	< 0.001

	[70 - 79 years]	8.203 [5.892 - 11.421]	< 0.001	7.970 [5.721 - 11.103]	< 0.001
	[80 - 89 years]	6.014 [4.321 - 8.372]	< 0.001	6.267 [4.500 - 8.730]	< 0.001
	[≥ 90 years]	4.993 [3.586 - 6.951]	< 0.001	5.649 [4.055 - 7.870]	< 0.001
Municipal residence size	Capital of province	<i>Ref</i>	--	--	--
	No information	0.549 [0.457 - 0.661]	< 0.001	0.579 [0.477 - 0.702]	< 0.001
	10.000 inhabitants or less	0.906 [0.885 - 0.928]	< 0.001	0.925 [0.902 - 0.947]	< 0.001
	10.001 to 20.000	0.914 [0.886 - 0.944]	< 0.001	0.932 [0.902 - 0.963]	< 0.001
	20.001 to 50.000	0.941 [0.915 - 0.967]	< 0.001	0.951 [0.924 - 0.978]	< 0.001
	50.001 to 100.000	0.968 [0.937 - 1.000]	0.047	0.956 [0.924 - 0.988]	0.008
	Greater than 100.000	0.995 [0.9627 - 1.028]	0.745	0.936 [0.905 - 0.968]	< 0.001
Country aggregations	Spain	<i>Ref</i>	--	--	--
	Africa	0.787 [0.678 - 0.913]	0.002	0.923 [0.792 - 1.077]	0.310
	North America	0.711 [0.475 - 1.066]	0.099	0.683 [0.454 - 1.027]	0.067
	Latin America	0.735 [0.643 - 0.839]	<0.001	0.760 [0.665 - 0.870]	<0.001
	Asia	0.774 [0.579 - 1.035]	0.084	0.748 [0.557 - 1.004]	0.053
	Europe (not Spain)	0.902 [0.854 - 0.954]	< 0.001	0.859 [0.810 - 0.911]	<0.001

CI: confidence interval; ^aSignificant differences ($p < 0.05$) are indicated by bold text.

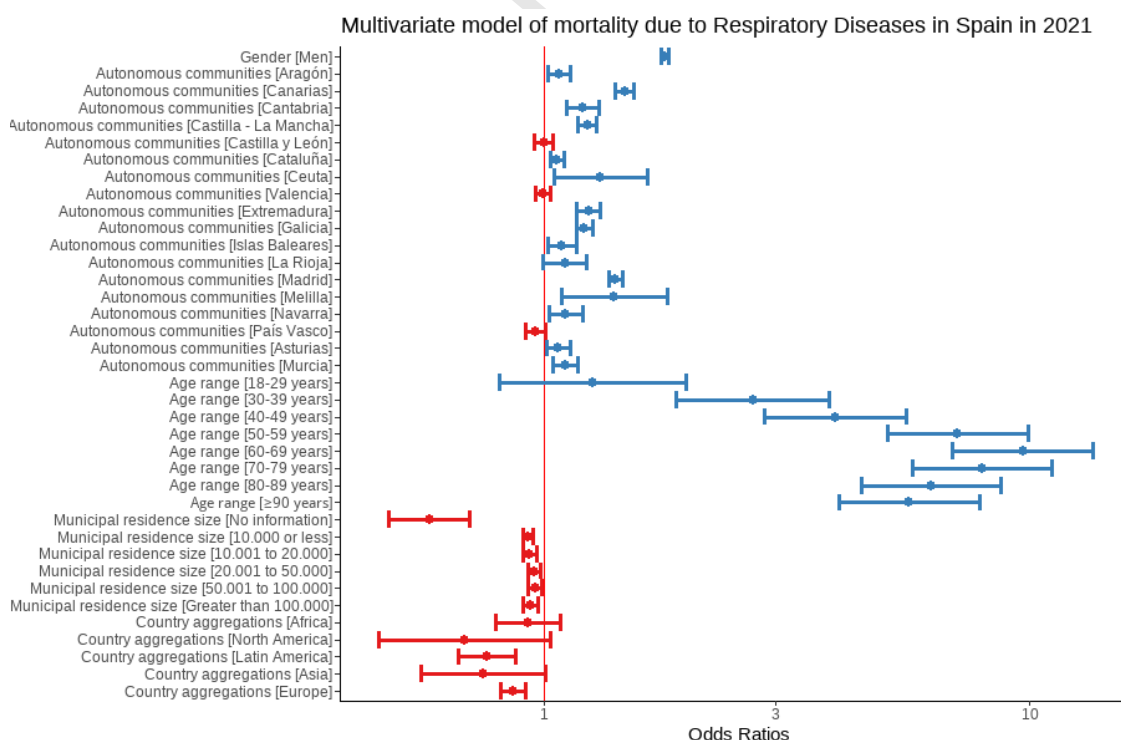


Figure 2. Forest plot of mortality predictors for Respiratory Diseases excluding COVID-19 [in Spain in 2021]

ONLINE APPENDIX:

eTable 1. Number of deaths and percentage of mortality by diseases of the respiratory system in 2021 in Spain by autonomous community.

Cause	Andalucía	Aragón	Canarias	Cantabria	Castilla La Mancha	Castilla y León	Cataluña	Ceuta	Madrid	Navarra	Valencia	Extremadura	Galicia	Islas Baleares	La Rioja	Melilla	País Vasco	Asturias	Murcia	España
00A Covid-19 Virus identified	6,647 (40.6%) ^a	1,396 (42.8%) ^b	614 (17.4%)	239 (21.9%)	2,171 (42.8%)	2,645 (42.6%)	7,017 (44.8%)	61 (37.2%)	5,855 (42.5%)	353 (32.0%)	5,331 (46.7%)	1,067 (38.1%)	1,541 (25.3%)	577 (33.7%)	252 (36.5%)	68 (47.2%)	1,640 (38.4%)	935 (35.5%)	1,035 (38.5%)	39,444 (40.0%)
00B Covid-19 Unidentified virus (suspected)	74 (0.5%)	25 (0.8%)	13 (0.4%)	2 (0.2%)	22 (0.4%)	67 (1.1%)	56 (0.4%)	7 (4.3%)	74 (0.5%)	2 (0.2%)	118 (1.0%)	3 (0.1%)	28 (0.5%)	2 (0.1%)	3 (0.4%)	0 (0.0%)	32 (0.7%)	49 (1.9%)	18 (0.7%)	595 (0.6%)
00C Covid-19 associated multisystemic inflammatory syndrome COVID-19	32 (0.2%)	1 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	2 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	44 (0.0%)
002 Tuberculosis and its late effects	28 (0.2%)	12 (0.4%)	3 (0.1%)	4 (0.4%)	6 (0.1%)	19 (0.3%)	21 (0.1%)	2 (1.2%)	15 (0.1%)	3 (0.3%)	18 (0.2%)	5 (0.2%)	12 (0.2%)	4 (0.2%)	1 (0.1%)	3 (2.1%)	7 (0.2%)	9 (0.3%)	2 (0.1%)	174 (0.2%)
018 Malignant tumour of the trachea, bronchi and lung	3,742 (22.8%)	745 (22.9%)	974 (27.6%)	347 (31.7%)	903 (17.8%)	1,321 (21.3%)	3,369 (21.5%)	33 (20.1%)	2,640 (19.2%)	342 (31.0%)	2,540 (22.2%)	621 (22.2%)	1,588 (26.1%)	518 (30.2%)	142 (20.6%)	22 (15.3%)	1,225 (28.7%)	735 (27.9%)	631 (23.5%)	22,438 (22.7%)
019 Other respiratory and intrathoracic malignancies	68 (0.4%)	17 (0.5%)	17 (0.5%)	10 (0.9%)	16 (0.3%)	27 (0.4%)	81 (0.5%)	1 (0.6%)	58 (0.4%)	12 (1.1%)	49 (0.4%)	12 (0.4%)	29 (0.5%)	3 (0.2%)	7 (1.0%)	0 (0.0%)	40 (0.9%)	14 (0.5%)	15 (0.6%)	476 (0.5%)
062 Influenza (includes influenza due to identified pandemic or zoonotic influenza viruses)	4 (0.0%)	1 (0.0%)	4 (0.1%)	1 (0.1%)	1 (0.0%)	1 (0.0%)	5 (0.0%)	0 (0.0%)	5 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	24 (0.0%)
063 Pneumonia	1,007 (6.1%)	244 (7.5%)	564 (16.0%)	64 (5.9%)	410 (8.1%)	434 (7.0%)	845 (5.4%)	11 (6.7%)	1,030 (7.5%)	71 (6.4%)	769 (6.7%)	266 (9.5%)	446 (7.3%)	110 (6.4%)	38 (5.5%)	7 (4.9%)	130 (3.0%)	134 (5.1%)	219 (8.1%)	6,799 (6.9%)
064 Chronic lower respiratory tract diseases (except asthma)	1,788 (10.9%)	358 (11.0%)	445 (12.6%)	154 (14.1%)	599 (11.8%)	546 (8.8%)	1,644 (10.5%)	23 (14.0%)	1097 (8.0%)	128 (11.6%)	1,143 (10.0%)	284 (10.1%)	746 (12.3%)	258 (15.1%)	60 (8.7%)	17 (11.8%)	559 (13.1%)	286 (10.9%)	359 (13.4%)	10,494 (10.6%)
065 Asthma	124 (0.8%)	18 (0.6%)	18 (0.5%)	7 (0.6%)	39 (0.8%)	57 (0.9%)	136 (0.9%)	1 (0.6%)	54 (0.4%)	12 (1.1%)	72 (0.6%)	18 (0.6%)	74 (1.2%)	10 (0.6%)	5 (0.7%)	0 (0.0%)	72 (1.7%)	57 (2.2%)	27 (1.0%)	801 (0.8%)
066 Respiratory failure	410 (2.5%)	24 (0.7%)	66 (1.9%)	27 (2.5%)	67 (1.3%)	85 (1.4%)	343 (2.2%)	1 (0.6%)	478 (3.5%)	13 (1.2%)	145 (1.3%)	40 (1.4%)	111 (1.8%)	26 (1.5%)	22 (3.2%)	1 (0.7%)	48 (1.1%)	21 (0.8%)	21 (0.8%)	1,949 (2.0%)
067 Other diseases of the respiratory system	2,460 (15.0%)	417 (12.8%)	816 (23.1%)	237 (21.7%)	835 (16.5%)	998 (16.1%)	2,150 (13.7%)	24 (14.6%)	2472 (17.9%)	167 (15.1%)	1,239 (10.8%)	485 (17.3%)	1,513 (24.8%)	204 (11.9%)	160 (23.2%)	26 (18.1%)	519 (12.1%)	393 (14.9%)	361 (13.4%)	15,476 (15.7%)
TOTAL "Causes of death of the respiratory system"	16,384 (20.5%)	3,258 (22.4%)	3,534 (20.3%)	1,093 (17.8%)	5,070 (24.5%)	6,202 (20.9%)	15,667 (22.6%)	164 (25.3%)	13,784 (28.0%)	1,103 (18.9%)	11,424 (22.7%)	2,801 (22.8%)	6,089 (18.5%)	1,713 (19.4%)	690 (20.3%)	144 (28.4%)	4,272 (18.7%)	2,633 (19.7%)	2,689 (21.2%)	98,714 (21.9%)
001-102 I-XXII.All Causes	80,050 (17.8%) ^c	14,557 (3.2%)	17,410 (3.9%)	6,144 (1.4%)	20,664 (4.6%)	29,636 (6.6%)	69,264 (15.4%)	649 (0.1%)	49,299 (10.9%)	5,842 (1.3%)	50,333 (11.2%)	12,268 (2.7%)	32,924 (7.3%)	8,843 (2.0%)	33,94 (0.8%)	507 (0.1%)	22,893 (5.1%)	13,397 (3.0%)	12,670 (2.8%)	450,744 (100%)

a. Percentage of each cause of death compared to the total causes of death in each autonomous community.

b. Significant differences ($p < 0.01$) are indicated by bold text.

c. Percentage of the total causes of death compared to the total causes of death in Spain in 2021.

eTable 2. Number of deaths and percentage of mortality by diseases of the respiratory system in 2021 in Spain by age range.

Cause	≤ 18 yrs.	18-29 yrs.	30-39 yrs.	40-49 yrs.	50-59 yrs.	60-69 yrs.	70-79 yrs.	80-89 yrs.	≥ 90 yrs.
00A Covid-19 Virus identified	8 (0.0%) ^a	47 (0.0%)	142 (0.1%)	474 (0.5%)	1,588 (1.6%)	4,393 (4.5%)	8,488 (8.6%)	14,475 (14.7%)	9,829 (10.0%)
00B Covid-19 Unidentified virus (suspected)	0 (0.0%)	2 (0.0%)	1 (0.0%)	4 (0.0%)	20 (0.0%)	43 (0.0%)	90 (0.1%)	224 (0.2%)	211 (0.2%)
00C Covid-19 associated multisystemic inflammatory syndrome COVID-19	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	2 (0.0%)	1 (0.0%)	8 (0.0%)	22 (0.0%)	10 (0.0%)
002 Tuberculosis and its late effects	0 (0.0%)	1 (0.0%)	4 (0.0%)	12 (0.0%)	16 (0.0%)	25 (0.0%)	36 (0.0%)	51 (0.1%)	29 (0.0%)
018 Malignant tumour of the trachea, bronchi and lung	0 (0.0%)	6 (0.0%)	44 (0.0%)	405 (0.4%)	2,498 (2.5%)	6,599 (6.7%)	7,295 (7.4%)	4,611 (4.7%)	980 (1.0%)
019 Other respiratory and intrathoracic malignancies	2 (0.0%)	3 (0.0%)	6 (0.0%)	17 (0.0%)	49 (0.0%)	91 (0.1%)	117 (0.1%)	157 (0.2%)	34 (0.0%)
062 Influenza (includes influenza due to identified pandemic or zoonotic influenza viruses)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	1 (0.0%)	4 (0.0%)	7 (0.0%)	11 (0.0%)
063 Pneumonia	6 (0.0%)	4 (0.0%)	22 (0.0%)	46 (0.0%)	164 (0.2%)	338 (0.3%)	865 (0.9%)	2,822 (2.9%)	2,532 (2.6%)
064 Chronic lower respiratory tract diseases (except asthma)	4 (0.0%)	1 (0.0%)	7 (0.0%)	43 (0.0%)	309 (0.3%)	1,008 (1.0%)	2,391 (2.4%)	4,199 (4.3%)	2,532 (2.6%)
065 Asthma	3 (0.0%)	3 (0.0%)	4 (0.0%)	18 (0.0%)	21 (0.0%)	46 (0.0%)	91 (0.1%)	307 (0.3%)	308 (0.3%)
066 Respiratory failure	4 (0.0%)	10 (0.0%)	9 (0.0%)	35 (0.0%)	84 (0.1%)	149 (0.2%)	221 (0.2%)	679 (0.7%)	758 (0.8%)
067 Other diseases of the respiratory system	17 (0.0%)	18 (0.0%)	79 (0.1%)	177 (0.2%)	409 (0.4%)	912 (0.9%)	2,191 (2.2%)	5,887 (6.0%)	5,786 (5.9%)
TOTAL "Causes of death of the respiratory system"	44 (0.0%)	95 (0.0%)	319 (0.1%)	1,232 (0.3%)	5,160 (1.1%)	13,606 (3.0%)	21,797 (4.8%)	33,441 (7.4%)	23,020 (5.1%)
001-102 I-XXII.All Causes	1,625 (0.4%)	1,657 (0.4%)	2,967 (0.7%)	8,805 (2.0%)	24,340 (5.4%)	48,411 (10.7%)	83,197 (18.5%)	153,921 (34.1%)	125,821 (27.9%)

^a.Percentage of each cause of death of respiratory system compared to the total causes of death of the respiratory system in 2021 ($n=98,714$).

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