



## Original article

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

Joan B. Soriano<sup>a,b,\*</sup>, Adrián Peláez<sup>b,c</sup>, Esteve Fernández<sup>b,d,e,f</sup>, Julio Ancochea<sup>b,c,g</sup><sup>a</sup> Facultat de Medicina, Universitat de les Illes Balears, Palma, Spain<sup>b</sup> Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain<sup>c</sup> Servicio de Neumología, Hospital Universitario de la Princesa, Madrid, Spain<sup>d</sup> Unidad de Control del Tabaco, Centro Colaborador de la OMS para el Control del Tabaco, Institut Català d'Oncologia, Barcelona, Spain<sup>e</sup> Grupo de Investigación en Control del Tabaco, Programa de Epidemiología y Salud Pública (EPIBELL), Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain<sup>f</sup> Facultat de Medicina y Ciencias de la Salud, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain<sup>g</sup> Facultat de Medicina, Universidad Autónoma de Madrid, Madrid, Spain

## ARTICLE INFO

## Article history:

Received 1 March 2023

Accepted 9 April 2023

## Keywords:

Death certificate

COVID-19

Diseases of the respiratory system

INE

Mortality

## 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 National Institute of Statistics 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 analyzed 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% CI 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.

© 2023 The Author(s). Published by Elsevier España, S.L.U. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

## Impacto de la pandemia de COVID-19 en la mortalidad por enfermedades respiratorias: análisis comparativo de 2021 y 2020 frente a 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 Instituto Nacional de Estadística exploramos las muertes por enfermedades respiratorias, es decir, todas las causas de muerte según la lista estándar de enfermedades del sistema respiratorio de la Organización Mundial de la Salud 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.

## Palabras clave:

Certificado de defunción

COVID-19

Enfermedades del sistema respiratorio

Instituto Nacional de Estadística

Mortalidad

\* Corresponding author.

E-mail address: [jb.soriano@uib.eu](mailto:jb.soriano@uib.eu) (J.B. Soriano).

**Resultados:** Se produjeron 98.714 muertes por enfermedades respiratorias en 2021 en España, lo que corresponde a 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, aun con un aumento de 30,3% (IC 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 la reducción de la mortalidad en la España rural, aun 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.

© 2023 El Autor(s). Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY (<http://creativecommons.org/licenses/by/4.0/>).

## 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.<sup>1</sup>

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.<sup>2</sup> Many of these general, global aspects need to be implemented and carefully assessed in Spain.<sup>3</sup> Three years and counting from the onset of the COVID-19 pandemic,<sup>4</sup> 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 by 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.<sup>5</sup> 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,<sup>6,7</sup> we analyzed 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 were obtained from the INE website.<sup>8</sup> As previously indicated,<sup>1</sup> 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.<sup>9–11</sup>

## 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% CI 30.2–30.4) compared to background rates in 2019 (it was a 68.5% (95% CI 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 and Fig. 1). Additionally, we observed large regional differences by Autonomous Communities, with some regions experiencing a greater impact on overall, respiratory-related and specific respiratory diseases mortality compared to others.

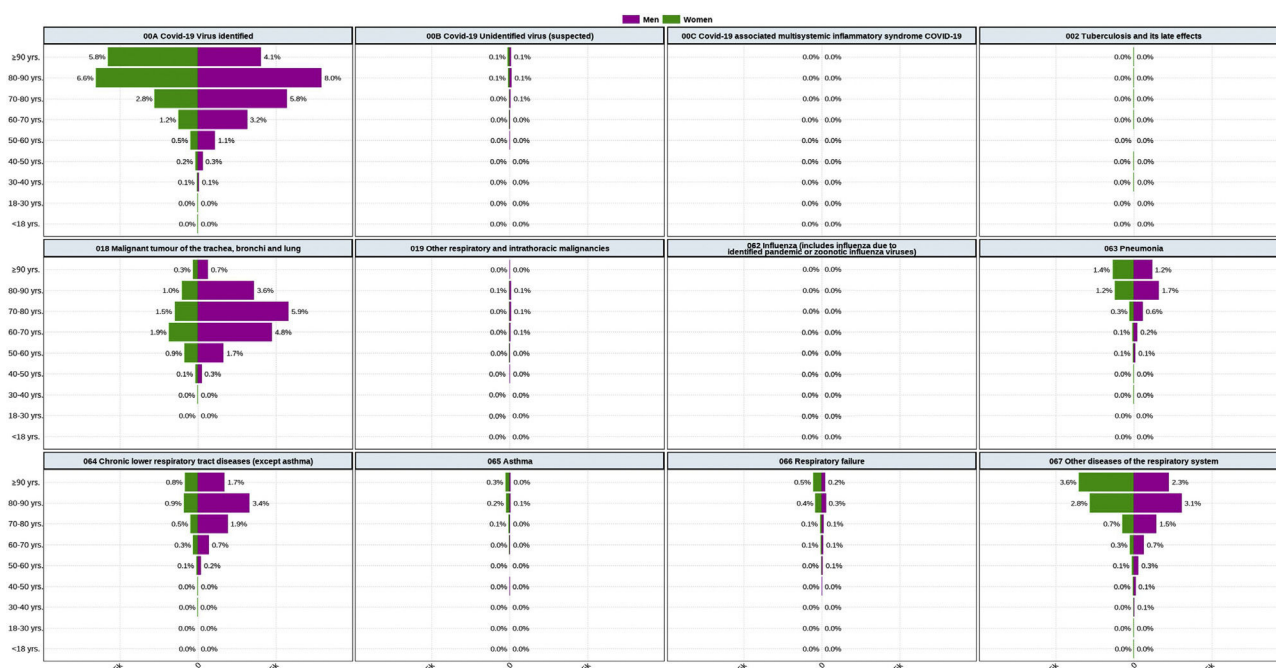
In the multivariate logistic regression analysis some established risk factors for respiratory diseases mortality were confirmed, such as male gender and older age; further, a protection in rural Spain was observed, still with a large geographical variability, and those born from elsewhere in Europe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

**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) <sup>a</sup>	2020 (n = 493,776) <sup>b</sup>	2021 (n = 450,744) <sup>c</sup>	Change in % between 2020 vs. 2019	Change in % between 2021 vs. 2019
I Infectious and parasitic diseases	17,405 (1.3%)	5902 (1.4%)	<b>5759 (1.2%)<sup>d</sup></b>	<b>5744 (1.3%)</b>	−17.3	−9.6
II Tumours	226,822 (16.6%)	75,774 (18.1%)	<b>75,499 (15.3%)</b>	<b>75,549 (16.8%)</b>	−15.5	−7.4
III Diseases of the blood and haematopoietic organs, and certain disorders affecting the mechanism of immunity	6279 (0.5%)	2012 (0.5%)	<b>2062 (0.4%)</b>	2205 (0.5%)	−13.1	1.8
IV Endocrine, nutritional and metabolic diseases	43,765 (3.2%)	13,351 (3.2%)	15,290 (3.1%)	<b>15,124 (3.4%)</b>	−2.9	5.2
V Mental and behavioural disorders	65,105 (4.8%)	22,896 (5.5%)	<b>21,697 (4.4%)</b>	<b>20,512 (4.6%)</b>	−17.0	−16.8
VI Diseases of the nervous system and sensory organs	78,642 (5.8%)	26,120 (6.2%)	<b>27,508 (5.6%)</b>	<b>25,014 (5.5%)</b>	−19.6	−11.0
VII Diseases of the circulatory system	355,664 (26.1%)	116,615 (27.9%)	<b>119,853 (24.3%)</b>	<b>119,196 (26.4%)</b>	−10.7	−5.1
VIII Diseases of the respiratory system (+COVID-19)	308,983 (22.7%)	70,389 (16.8%)	<b>139,880 (28.3%)</b>	<b>98,714 (21.9%)</b>	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%)	<b>21,565 (4.4%)</b>	<b>22,563 (5.0%)</b>	−17.0	−4.9
X Diseases of the skin and subcutaneous tissue	5698 (0.4%)	1775 (0.4%)	<b>1902 (0.4%)</b>	2021 (0.4%)	−9.1	5.8
XI Diseases of the musculoskeletal system and connective tissues	15,500 (1.1%)	5162 (1.2%)	<b>5225 (1.1%)</b>	<b>5113 (1.1%)</b>	−14.2	−8.0
XII Diseases of the genitourinary system	91,206 (6.7%)	28,917 (6.9%)	<b>30,632 (6.2%)</b>	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	1630 (0.1%)	584 (0.1%)	<b>518 (0.1%)</b>	<b>528 (0.1%)</b>	−24.8	−16.0
XV Congenital malformations, deformities and chromosomal abnormalities	2471 (0.2%)	815 (0.2%)	<b>823 (0.2%)</b>	833 (0.2%)	−14.4	−5.1
XVI Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	28,810 (2.1%)	10,206 (2.4%)	<b>9475 (1.9%)</b>	<b>9129 (2.0%)</b>	−21.3	−16.9
XVII External causes of mortality	49,050 (3.6%)	16,141 (3.9%)	<b>16,078 (3.3%)</b>	<b>16,831 (3.7%)</b>	−15.5	−3.1

<sup>a</sup> Percentage of each cause of death compared to the total causes of death in 2019.<sup>b</sup> Percentage of each cause of death compared to the total causes of death in 2020.<sup>c</sup> Percentage of each cause of death compared to the total causes of death in 2021.<sup>d</sup> Significant differences ( $p < 0.01$ ) against causes of death in 2019 are indicated by bold text.**Fig. 1.** Proportionate mortality (%) due to diseases from the respiratory system, Spain, 2021.

**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) <sup>a</sup>	2020 (n = 493,776) <sup>b</sup>	2021 (n = 450,744) <sup>c</sup>	Change in % between 2020 vs. 2019	Change in % between 2021 vs. 2019
00A Covid-19 Virus identified	99,802 (7.3%)	–	<b>60,358 (12.2%)<sup>d</sup></b>	<b>39,444 (8.8%)</b>	–	–
00B Covid-19 Unidentified virus (suspected)	15,076 (1.1%)	–	<b>14,481 (2.9%)</b>	<b>595 (0.1%)</b>	–	–
00C Covid-19 associated multisystemic inflammatory syndrome COVID-19	44 (0.0%)	–	0 (0.0%)	<b>44 (0.0%)</b>	–	–
002 Tuberculosis and its late effects	589 (0.0%)	217 (0.1%)	<b>198 (0.0%)</b>	<b>174 (0.0%)</b>	–22.6%	–25.5%
018 Malignant tumour of the trachea, bronchi and lung	66,363 (4.9%)	22,007 (5.3%)	<b>21,918 (4.4%)</b>	<b>22,438 (5.0%)</b>	–15.6%	–5.3%
019 Other respiratory and intrathoracic malignancies	1462 (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)	2377 (0.2%)	1459 (0.3%)	<b>894 (0.2%)</b>	<b>24 (0.0%)</b>	–48.0%	–98.5%
063 Pneumonia	24,951 (1.8%)	9384 (2.2%)	<b>8768 (1.8%)</b>	<b>6799 (1.5%)</b>	–20.8%	–32.7%
064 Chronic lower respiratory tract diseases (except asthma)	35,095 (2.6%)	12,815 (3.1%)	<b>11,786 (2.4%)</b>	<b>10,494 (2.3%)</b>	–22.0%	–23.9%
065 Asthma	2742 (0.2%)	993 (0.2%)	<b>948 (0.2%)</b>	<b>801 (0.2%)</b>	–19.0%	–25.1%
066 Respiratory failure	6159 (0.5%)	2171 (0.5%)	<b>2039 (0.4%)</b>	<b>1949 (0.4%)</b>	–20.4%	–16.6%
067 Other diseases of the respiratory system	54,323 (4.0%)	20,859 (5.0%)	<b>17,988 (3.6%)</b>	<b>15,476 (3.4%)</b>	–26.9%	–31.1%
TOTAL "Causes of death of the respiratory system"	308,983 (22.7%)	70,389 (16.8%)	<b>139,880 (28.3%)</b>	<b>98,714 (21.9%)</b>	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%

<sup>a</sup> Percentage of each cause of death compared to the total causes of death in 2019.<sup>b</sup> Percentage of each cause of death compared to the total causes of death in 2020.<sup>c</sup> Percentage of each cause of death compared to the total causes of death in 2021.<sup>d</sup> Significant 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 <sup>a</sup>	2021 <sup>b</sup>	2019	2020	2021
00A Covid-19 virus identified	–	<b>32,498 (13.0%)<sup>c</sup></b>	<b>22,449 (9.7%)</b>	–	<b>27,860 (11.4%)</b>	<b>16,995 (7.7%)</b>
00B Covid-19 unidentified virus (suspected)	–	<b>6419 (2.6%)</b>	<b>309 (0.1%)</b>	–	<b>8062 (3.3%)</b>	<b>286 (0.1%)</b>
00C Covid-19 associated multisystemic inflammatory syndrome COVID-19	–	0 (0.0%)	<b>29 (0.0%)</b>	–	0 (0.0%)	<b>15 (0.0%)</b>
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%)	<b>16,615 (6.7%)</b>	<b>16,772 (7.2%)</b>	5072 (2.5%)	<b>5303 (2.2%)</b>	5666 (2.6%)
019 Other malignant tumours of the trachea, bronchi and lung	332 (0.2%)	359 (0.1%)	316 (0.1%)	152 (0.1%)	<b>143 (0.1%)</b>	160 (0.1%)
062 Influenza (includes influenza due to identified pandemic or zoonotic influenza viruses)	680 (0.3%)	<b>446 (0.2%)</b>	<b>14 (0.0%)</b>	779 (0.4%)	<b>448 (0.2%)</b>	<b>10 (0.0%)</b>
063 Pneumonia	4837 (2.3%)	<b>4704 (1.9%)</b>	<b>3831 (1.7%)</b>	4547 (2.2%)	<b>4064 (1.7%)</b>	<b>2968 (1.4%)</b>
064 Chronic lower respiratory tract diseases (except asthma)	9749 (4.6%)	<b>8832 (3.5%)</b>	<b>7925 (3.4%)</b>	3066 (1.5%)	<b>2954 (1.2%)</b>	<b>2569 (1.2%)</b>
065 Asthma	158 (0.1%)	212 (0.1%)	175 (0.1%)	835 (0.4%)	<b>736 (0.3%)</b>	<b>626 (0.3%)</b>
066 Respiratory failure	903 (0.4%)	<b>927 (0.4%)</b>	<b>824 (0.4%)</b>	1268 (0.6%)	<b>1112 (0.5%)</b>	<b>1125 (0.5%)</b>
067 Other diseases of the respiratory system	9983 (4.7%)	<b>8714 (3.5%)</b>	<b>7968 (3.4%)</b>	10,876 (5.3%)	<b>9274 (3.8%)</b>	<b>7508 (3.4%)</b>
TOTAL "Causes of death of the respiratory system"	43,711 (20.6%)	<b>79,850 (32.0%)</b>	<b>60,723 (26.2%)</b>	26,678 (12.9%)	<b>60,030 (24.6%)</b>	<b>37,991 (17.3%)</b>
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%)

<sup>a</sup> Percentage of each cause of death compared to the total causes of death for Men in its respective year.<sup>b</sup> Percentage of each cause of death compared to the total causes of death for Women in its respective year.<sup>c</sup> Significant differences ( $p < 0.01$ ) against 2019 causes are indicated by bold text.

**Table 4**

Crude and multivariate odds ratios for respiratory mortality (excluding COVID-19) in Spain in 2021.

Variable	Category	Crude		Multivariate	
		OR [95%CI]	p-Value <sup>a</sup>	OR [95%CI]	p-Value
Gender	Men	1.884 [1.850–1.918]	<b>&lt;0.001</b>	1.771 [1.738–1.804]	<b>&lt;0.001</b>
	Women	Ref	–	Ref	–
Autonomous communities	Andalucía	Ref	–	Ref	–
	Aragón	1.055 [1.000–1.113]	0.050	1.072 [1.015–1.132]	<b>0.012</b>
	Canarias	1.469 [1.404–1.537]	<b>&lt;0.001</b>	1.462 [1.396–1.530]	<b>&lt;0.001</b>
	Cantabria	1.175 [1.089–1.267]	<b>&lt;0.001</b>	1.199 [1.111–1.294]	<b>&lt;0.001</b>
	Castilla La Mancha	1.181 [1.129–1.235]	<b>&lt;0.001</b>	1.224 [1.169–1.281]	<b>&lt;0.001</b>
	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]	<b>0.033</b>	1.060 [1.027–1.094]	<b>&lt;0.001</b>
	Ceuta	1.284 [1.033–1.597]	<b>0.024</b>	1.304 [1.044–1.628]	<b>0.019</b>
	Valencia	0.984 [0.951–1.018]	0.353	0.992 [0.958–1.027]	0.650
	Extremadura	1.200 [1.136–1.268]	<b>&lt;0.001</b>	1.231 [1.163–1.302]	<b>&lt;0.001</b>
	Galicia	1.162 [1.119–1.207]	<b>&lt;0.001</b>	1.208 [1.162–1.255]	<b>&lt;0.001</b>
	Islas Baleares	1.074 [1.006–1.148]	<b>0.033</b>	1.087 [1.017–1.162]	<b>0.015</b>
	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]	<b>&lt;0.001</b>	1.400 [1.354–1.448]	<b>&lt;0.001</b>
	Melilla	1.309 [1.025–1.673]	<b>0.031</b>	1.392 [1.084–1.788]	<b>0.009</b>
	Navarra	1.074 [0.991–1.163]	0.080	1.105 [1.020–1.198]	<b>0.015</b>
	País Vasco	0.936 [0.894–0.980]	<b>0.005</b>	0.955 [0.912–1.001]	0.055
	Asturias	1.026 [0.970–1.084]	0.375	1.066 [1.007–1.128]	<b>0.028</b>
	Murcia	1.083 [1.024–1.146]	<b>0.005</b>	1.103 [1.042–1.168]	<b>&lt;0.001</b>
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]	<b>&lt;0.001</b>	2.687 [1.865–3.870]	<b>&lt;0.001</b>
	[40–49 years]	4.078 [2.906–5.722]	<b>&lt;0.001</b>	3.977 [2.832–5.582]	<b>&lt;0.001</b>
	[50–59 years]	7.417 [5.320–10.340]	<b>&lt;0.001</b>	7.105 [5.093–9.912]	<b>&lt;0.001</b>
	[60–69 years]	10.163 [7.298–14.153]	<b>&lt;0.001</b>	9.675 [6.943–13.482]	<b>&lt;0.001</b>
	[70–79 years]	8.203 [5.892–11.421]	<b>&lt;0.001</b>	7.970 [5.721–11.103]	<b>&lt;0.001</b>
	[80–89 years]	6.014 [4.321–8.372]	<b>&lt;0.001</b>	6.267 [4.500–8.730]	<b>&lt;0.001</b>
	[≥ 90 years]	4.993 [3.586–6.951]	<b>&lt;0.001</b>	5.649 [4.055–7.870]	<b>&lt;0.001</b>
Municipal residence size	Capital of province	Ref	–	–	–
	No information	0.549 [0.457–0.661]	<b>&lt;0.001</b>	0.579 [0.477–0.702]	<b>&lt;0.001</b>
	10,000 inhabitants or less	0.906 [0.885–0.928]	<b>&lt;0.001</b>	0.925 [0.902–0.947]	<b>&lt;0.001</b>
	10,001–20,000	0.914 [0.886–0.944]	<b>&lt;0.001</b>	0.932 [0.902–0.963]	<b>&lt;0.001</b>
	20,001–50,000	0.941 [0.915–0.967]	<b>&lt;0.001</b>	0.951 [0.924–0.978]	<b>&lt;0.001</b>
	50,001–100,000	0.968 [0.937–1.000]	<b>0.047</b>	0.956 [0.924–0.988]	<b>0.008</b>
	Greater than 100,000	0.995 [0.9627–1.028]	0.745	0.936 [0.905–0.968]	<b>&lt;0.001</b>
Country aggregations	Spain	Ref	–	–	–
	Africa	0.787 [0.678–0.913]	<b>0.002</b>	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]	<b>&lt;0.001</b>	0.760 [0.665–0.870]	<b>&lt;0.001</b>
	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]	<b>&lt;0.001</b>	0.859 [0.810–0.911]	<b>&lt;0.001</b>

CI: confidence interval.

<sup>a</sup> Significant differences ( $p < 0.05$ ) are indicated by bold text.

## Discussion

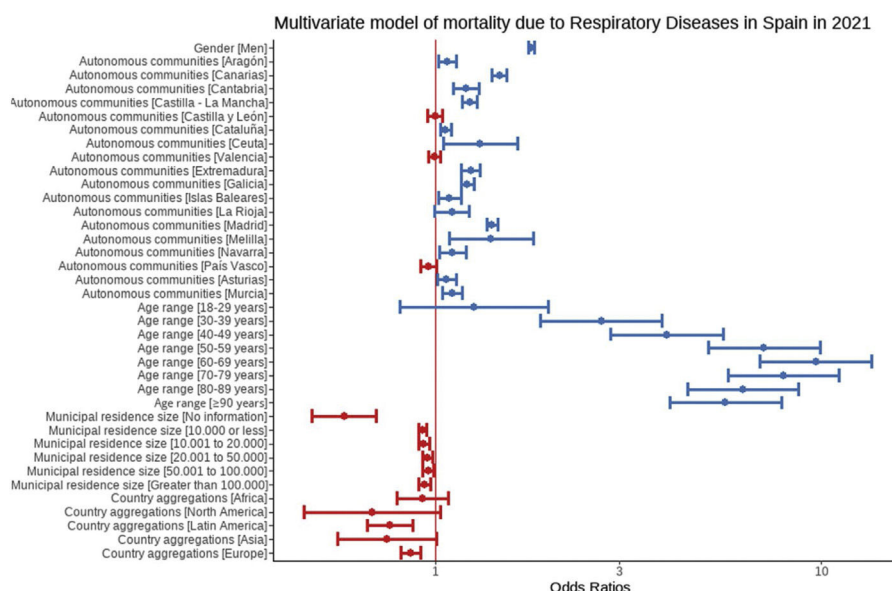
We report that the COVID-19 pandemic has had a lasting impact on both general and specific causes of death due to respiratory diseases in 2021 in Spain, and it has disproportionately affected certain regions, mainly Madrid and Catalunya. By accounting COVID-19, tuberculosis and lung cancer deaths within 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.<sup>12</sup> In Spain, with a relatively aged population and yet with alarming rates of smoking,<sup>13</sup> and of smoking-related deaths,<sup>14,15</sup> respiratory diseases also have a huge impact on individual and population health.<sup>16,17</sup> 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.<sup>18,19</sup>

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.<sup>20,21</sup> 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.<sup>22,23</sup> 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





**Fig. 2.** Forest plot of mortality predictors (odds ratios and 95% confidence intervals) for Respiratory Diseases excluding COVID-19 in Spain in 2021.

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.<sup>24</sup> 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.<sup>25,23</sup>

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.

### Ethical considerations

Not applicable as we only use administrative, anonymised official data.

### Funding

None.

### Conflict of interest

The authors declare there are no conflicts on interest to report related with this research.

### Acknowledgements

EF is partially funded by the Department of Research and Universities of the Generalitat de Catalunya [2021SGR00906]. EF thanks IDIBELL for the institutional support of the CERCA/Generalitat de Catalunya Program.

### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.medcli.2023.04.020>

## References

- Soriano JB, Peláez A, Fernández E, Moreno L, Ancochea J. The emergence of COVID-19 as a cause of death in 2020 and its effect on mortality by diseases of the respiratory system in Spain: trends and their determinants compared to 2019. *Arch Bronconeumol*. 2022;58:13–21. <http://dx.doi.org/10.1016/j.arbres.2022.03.001>. Epub 2022 Mar 21. PMID: 35340748.
- Sachs JD, Karim SSA, Akinin L, Allen J, Brosbøl K, Colombo F, et al. The Lancet Commission on lessons for the future from the COVID-19 pandemic. *Lancet*. 2022;400:1224–80. [http://dx.doi.org/10.1016/S0140-6736\(22\)01585-9](http://dx.doi.org/10.1016/S0140-6736(22)01585-9). Epub 2022 Sep 14. PMID: 36115368.
- García-Basteiro A, Alvarez-Dardet C, Arenas A, Bengoa R, Borrell C, Del Val M, et al. The need for an independent evaluation of the COVID-19 response in Spain. *Lancet*. 2020;396:529–30. [http://dx.doi.org/10.1016/S0140-6736\(20\)31713-X](http://dx.doi.org/10.1016/S0140-6736(20)31713-X). Epub 2020 Aug 6. PMID: 32771082.
- Soriano JB, Infante A. Aiming for the end of the COVID-19 pandemic: the what, how, who, where, and when. *Chin Med J (Engl)*. 2023. <http://dx.doi.org/10.1097/CM9.0000000000002149>. PMID: 36752803.
- STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidance for reporting observational research. Available from: <http://strobe-statement.org/index.php?id=strobe-home> [accessed 30.3.23].
- Instituto Nacional de Estadística (INE). Mortalidad por mes y causa de defunción [Mortality by month and cause of death]; 2021. Available from: <https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica.C&cid=1254736177009&menu=resultados&secc=1254736177011&idp=1254734710990> [accessed December 2022].
- Defunciones según la Causa de Muerte Año 2021 (datos definitivos) y primer semestre 2022 (datos provisionales). <https://www.ine.es/prensa/edcm.2021.pdf>. INE; Nota de prensa 19.12.22.
- Causa básica de defunción. INE. Available from: <https://www.ine.es/dynt3/inebase/es/index.htm?padre=8273&capsel=8275> [accessed 17.12.21].
- Wasserstein RL, Lazar NA. The ASA statement on *p*-values: context, process, and purpose. *Am Stat*. 2016;70:129–33. <http://dx.doi.org/10.1080/00031305.2016.1154108>. Published online:09 Jun.
- Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, et al. Statistical tests, *P* values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol*. 2016;31:337–50. <http://dx.doi.org/10.1007/s10654-016-0149-3>. Epub 2016 May 21. PMID: 27209009.
- Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature*. 2019;567:305–7. <http://dx.doi.org/10.1038/d41586-019-00857-9>. PMID: 30894741.
- GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med*. 2020;8:585–96. [http://dx.doi.org/10.1016/S2213-2600\(20\)30105-3](http://dx.doi.org/10.1016/S2213-2600(20)30105-3). PMID: 32526187.
- Gallus S, Lugo A, Liu X, Behrakis P, Boffi R, Bosetti C, et al. Who smokes in Europe? Data from 12 European countries in the TackSHS survey (2017–2018). *J Epidemiol*. 2021;31:145–51. <http://dx.doi.org/10.2188/jea.JE20190344>. Epub 2020 Apr 4.
- Rey-Brandariz J, Pérez-Ríos M, Santiago-Pérez MI, Galán I, Schiaffino A, Varela-Lema L, et al. Trends in smoking-attributable mortality in Spain: 1990–2018. *Eur J Public Health*. 2022;32:919–25. <http://dx.doi.org/10.1093/eurpub/ckac165>.
- Peruga A, Fernández E, Fernández R, Pérez-Ríos M, Rodríguez-Lozano F, Martínez C. Has the reduction in tobacco consumption in Spain stopped? No, but we have to speed it up. *Arch Bronconeumol*. 2023;16. <http://dx.doi.org/10.1016/j.arbres.2023.02.008>. S0300-2896(23)00035-2. Online ahead of print. PMID: 36863995.
- Soriano JB, Rojas-Rueda D, Alonso J, Antó JM, Cardona PJ, Fernández E, et al. The burden of disease in Spain: results from the Global Burden of Disease 2016. *Med Clin (Barc)*. 2018;151:171–90. <http://dx.doi.org/10.1016/j.medcli.2018.05.011>. PMID: 30037695.
- Lazarus JV, Ortiz A, Tyrovolas S, Fernández E, Guy D, White TM, et al. A GBD 2019 study of health and Sustainable Development Goal gains and forecasts to 2030 in Spain. *Sci Rep*. 2022;12:21154. <http://dx.doi.org/10.1038/s41598-022-24719-z>. PMID: 36477107.
- Libro Blanco: La Neumología en España. Dirección General: Pilar de Lucas Ramos. ISBN: 978-84-944106-2-8 Dep. Legal: B 15359-2015 Editado y coordinado por RESPIRA-Fundación Española del Pulmón-SEPAR. 2015.
- Lodenkemper R, Gibson CJ, Sibille Y. *European lung white book. The first comprehensive survey on respiratory health in Europe*. Lausanne: European Respiratory Society, European Lung Foundation; 2003.
- Schlager NW, Koppaka R. Lung disease in a global context. A call for public health action. *Ann Am Thorac Soc*. 2014;11:407–16. <http://dx.doi.org/10.1513/AnnalsATS.201312-420PS>. PMID: 24673697.
- Soriano JB, Soriano C, Fernández E. *Medicina respiratoria planetaria*. *Arch Bronconeumol*. 2017;53:297–9. <http://dx.doi.org/10.1016/j.arbres.2016.10.016>. Epub 2016 Dec 13. PMID: 27979636.
- Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur Respir J*. 2003;22:809–14. <http://dx.doi.org/10.1183/09031936.03.00031403>. PMID: 14621089.
- Burney P, Jarvis D, Perez-Padilla R. The global burden of chronic respiratory disease in adults. *Int J Tuberc Lung Dis*. 2015;19:10–20. <http://dx.doi.org/10.5588/ijtld.14.0446>. PMID: 25519785.
- Lista reducida de causas de muerte CIE-10 y su correspondencia con la CIE-9. INE. Available from: [https://www.ine.es/daco/daco42/sanitarias/lista\\_reducida\\_CIE10.pdf](https://www.ine.es/daco/daco42/sanitarias/lista_reducida_CIE10.pdf) [accessed 17.12.21].
- Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur Respir J*. 2003;22:809–14. <http://dx.doi.org/10.1183/09031936.03.00031403>. PMID: 14621089.