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Original Research

Trends in prevalence and the effects on hospital outcomes of dementia in patients hospitalized with acute COPD exacerbation

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ABSTRACT

Aims: To assess changes in prevalence and the effects on hospital outcomes of dementia among patients hospitalized with an acute exacerbation of chronic obstructive pulmonary disease (AE-COPD); and to evaluate sex-differences, as well as the impact of COVID-19 pandemic in this relationship.
Methods: We used a nationwide discharge database to select patients admitted with AE-COPD in Spain from 2011 to 2020. We identified those with any type of dementia, vascular dementia (VaD) or Alzheimer's disease (AD).
Results: We identified 658,429 hospitalizations with AE-COPD (4.45% had any type of dementia, 0.79% VaD and 1.57% AD). The presence of any type of dementia remained stable from 2011 to 2015, and increased significantly between 2016 and 2020. For VaD, the time trend showed no change until 2020, when a significant increment was found. The probability of AD decreased significantly overtime. The in-hospital mortality (IHM) among patients with any type of dementia remained stable overtime until 2020, when it increased significantly. Older age, higher comorbidity, COVID-19, and use of mechanical ventilation were variables associated to IHM. Women had lower risk of dying in the hospital than men in all subgroups.
Conclusions: After a previous period of stability, the prevalence of any type of dementia increased over the last 5 years of the study, although we identified different trends depending on the specific cause of dementia. The IHM remained stable overtime until 2020, when it increased, probably related to the COVID-19 pandemic. It is remarkable the protective effect of female sex for IHM.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a condition characterized by progressive decline in pulmonary function and periods of exacerbation, both of which may impact on morbidity and mortality of patients with this disease worldwide [1]. On the other hand, it is frequently associated with a wide group of comorbidities that also contribute substantially to its poor outcome [2]. Among the most frequent reported comorbidities are cardiovascular diseases, endocrine and metabolic disorders, anemia, neoplasms, gastrointestinal diseases, and neuropsychiatric diseases, conditions often linked with smoking, systemic inflammation, airflow limitation, and aging [3].

Cognitive impairment is common in people with COPD. Among the mechanisms proposed for the association of COPD with cognitive impairment are oxidative stress, tissue hypoxemia, inactive state, and systemic inflammatory state [4,5]. COPD patients with comorbid cognitive impairment are more likely to suffer from adverse factors such as difficulties with daily functioning and increased risk of dementia [6].

Abbreviations: AE-COPD, acute exacerbation of COPD; CCI, Charlson comorbidity index; COPD, Chronic obstructive pulmonary disease; ICD9, International Classification of Disease 9th version; ICD10, International Classification of Disease 10th version; IHM, in-hospital mortality; SNHDD, Spanish National Hospital Discharge Database.

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Furthermore, longitudinal studies suggest greater risk of developing this comorbidity in COPD patients diagnosed in midlife, and associate COPD with the development of dementia [7,8].

To date, few studies has investigated a direct relationship between COPD and dementia [9,10]. In addition, some of them have even revealed inconsistent conclusions [11,12], which justifies the realization of new studies in this field. In a recent systematic review and meta-analysis of three cohort studies, Wang et al. revealed that that the risk of dementia was higher among COPD patients than in those without COPD [13]. In addition, it has been described that the relationship between COPD and dementia persists even after accounting for the presence of vascular disease, suggesting that COPD is an independent predictor of dementia [14]. However, previous studies do not provide information on specific types of dementia, such as Alzheimer's or vascular dementia, so it is impossible to distinguish the different effects of COPD on specific types of dementia [10].

Dementia and COPD are frequent conditions in hospitalized elderly patients, but data regarding the time trends in the incidence and the demographic and medical history of inpatients suffering these two diseases concomitantly are scare in Spain. Furthermore, information on the potential effects of dementia on the risks of in-hospital mortality (IHM), specifically among patients hospitalized with acute exacerbation of COPD (AE-COPD), is limited.

In this investigation we aimed: 1) to assess changes in the prevalence of dementia divided in "any type of dementia", "vascular dementia", and "Alzheimer's disease" among patients hospitalized with an acute exacerbation of COPD (AE-COPD) in Spain from year 2011 to year 2020; 2) to evaluate the existence of sex differences in the prevalence, clinical support, and the in-hospital mortality (IHM) among AE-COPD patients with dementia; 3) to analyze which study variables were associated to the in hospital-mortality (IHM) among patients with AE-COPD and dementia; and 4) to investigate if the COVID-19 pandemic has affected the prevalence of dementia and the IHM in patients with AE-COPD.

2. Material and methods

2.1. Study design and data source

We have conducted an epidemiological retrospective study. The data source is the Spanish National Hospital Discharge Database (SNHDD). Details on the database characteristics are available online [15,16]. Briefly, the SNHDD is an administrative database that includes all hospital discharges from Spanish hospitals (public and private) with over 4 million records every year. The variables included were sex, age, dates of hospital admission and hospital discharge, patient destination after discharge (home, died in the hospital, voluntary discharge, or to a social institution), medical diagnosis present at admission or detected during the hospitalization and diagnostic or therapeutic procedures conducted in the hospital.

Before year 2016 the SNHDD used the International Classification of Disease 9th version, (ICD9) for coding and, from 2016 onward, the International Classification of Disease 10th version (ICD10) [15,16].

2.2. Study population and study variables

The study population included all patients aged ≥40 years with a code for AE-COPD recorded in the SNHDD and admitted to the hospital from January 1, 2011, to December 31, 2020. An acute exacerbation was defined as an episode of hospitalization with COPD as the primary (most responsible) diagnostic code using the international classification for disease codes ICD9 (491, 492, 493.2x, 496) or ICD10 (J41, J42, J43, and J44) as suggested by Sadatsafavi et al. [17]. We excluded all patients with missing data for age, sex, dates of admission or discharge or discharge destination.

Among those with AE-COPD we identified those with an ICD code, in any diagnosis position, for any type of dementia and those with specific codes for vascular dementia or Alzheimer's disease. The ICD9 and ICD10 codes for these diseases are shown in Supplementary Table 1.

To analyze the comorbidity, we estimated the Charlson comorbidity index (CCI), for each patient, as proposed by Sundararajan et al. [18], and the presence of a COVID-19 infection (Supplementary Table 1).

The use of invasive and non-invasive mechanical ventilation during the hospital admission was assessed with the corresponding codes recorded in any procedures fields of the SNHDD (Supplementary Table 1).

The hospital outcomes included the IHM, defined as the percentage of patients that died in the hospital after being admitted for AE-COPD.

2.3. Statistical analysis

All analyses were stratified according to sex. For each year, the prevalence of any type of dementia, vascular dementia, and Alzheimer's disease was calculated among AE-COPD hospitalized patients. The distribution according to study variables was estimated for each subgroup of patients.

The descriptive statistical analysis included total frequencies and percentages for categorical variables and means with standard deviations (SD) for continuous variables.

The analysis of temporal trends in the prevalence and distribution of categorical variables was conducted with the Cochran-Mantel-Haenszel statistic or the Cochran-Armitage test and for continuous variables with the linear regression *t*-test.

Fisher exact test was applied to compare categorical variables and the *t*-test or the Wilcoxon rank sum test for continuous variables, as required.

We used multivariable logistic regression to assess factors associated with the presence of any type of dementia, vascular dementia, and Alzheimer's disease after adjusting by age, CCI, and COVID-19, the models were constructed for women and men separately and joined together to evaluate the effect of sex. This same statistical method and variables were used to identify those factors independently associated with the IHM in men and women with AE-COPD and any type of dementia, vascular dementia, and Alzheimer's disease. Model construction was done following Hosmer et al. recommendations [19]. The results were shown with the odds ratio (OR) and 95% confidence intervals (CI).

Statistical software used was Stata 14 (Stata, College Station, TX, USA).

2.4. Ethics statement

The Spanish Ministry of Health provided us with the required SNHDD databases after evaluating the objectives and ethical aspects of our investigation. As this study was conducted with an administrative, anonymous database it was not necessary to request the informed consent of the patients. The SNHDD can be asked for to the Spanish Ministry of Health filling and application form available online [20].

3. Results

From year 2011 to year 2020 there were 658,429 hospitalizations in Spain of patients aged 40 years or over with a diagnosis of AE-COPD, of them 81.03% were men. A remarkable decrement was observed in year 2020 (51,396 hospitalizations), when compared with the previous three years (>74.000 hospitalizations per year).

Among all patients with AE-COPD hospitalized from 2011 to 2020, 29,386 (4.45%) had a code for any type of dementia, 5221 had a code for vascular dementia (0.79%) and 10,327 had a code for Alzheimer's disease (1.57%).

3.1. Temporal trends in the prevalence of any type of dementia, vascular dementia and Alzheimer's disease among patients with AE-COPD

As can be seen in Table 1, the prevalence of any type of dementia among patients hospitalized with AE-COPD increased significantly from 3.38% in year 2011 to 6.45% in year 2020 ($p < 0.001$). Likewise, the prevalence of vascular dementia rose from 0.71% to 0.92% ($p < 0.001$). Alzheimer's disease was codified in a lower proportion in year 2020 (1.50%) when compared to year 2011 (1.93%; $p < 0.001$).

In patients presenting with any type of dementia, vascular dementia and Alzheimer's disease the mean number of comorbid conditions, measured with the CCI, increased significantly overtime (all $p < 0.001$). COVID-19 was diagnosed in 406 (12.25%), 48 (10.15%) and 93 (12.09%) patients hospitalized in year 2020 for AE-COPD who also suffered any type of dementia, vascular dementia and Alzheimer's disease, respectively.

The use of invasive mechanical ventilation and non-invasive mechanical ventilation, showed a small, but significant increment, only among those patients with any type of dementia (Table 1).

In patients with any type of dementia the IHM increased from 10.05% in year 2011 to 11.82% in 2019, showing a marked increment to 16.51% in 2020 (Table 1). The IHM for vascular dementia and Alzheimer's disease remained stable from 2011 to 2019 increasing by 4.45%, for vascular dementia, and by 4.78% for Alzheimer's disease in

Table 1
Characteristics of the patients hospitalized from 2011 to 2020 in Spain with an acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) and concomitantly having a diagnosis code for any type of dementia, vascular dementia, and Alzheimer disease.

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	p-value trend
Hospitalizations with AE-COPD, N	59737	61856	59295	60385	64752	69954	74224	79791	77039	51396	NA
Any type of dementia, n (prevalence %)	2020 (3.38)	2124 (3.43)	1972 (3.33)	2008 (3.33)	2127 (3.28)	3364 (4.81)	3811 (5.13)	4316 (5.41)	4330 (5.62)	3314 (6.45)	<0.001
Men, n (%)	1602 (79.31)	1648 (77.59)	1539 (78.04)	1555 (77.44)	1697 (79.78)	2694 (80.08)	3017 (79.17)	3450 (79.94)	3434 (79.31)	2686 (81.05)	0.058
Women, n(%)	418 (20.69)	476 (22.41)	433 (21.96)	453 (22.56)	430 (20.22)	670 (19.92)	794 (20.83)	866 (20.06)	896 (20.69)	628 (18.95)	
Age, mean (SD)	82.84 (6.56)	83(6.43)	82.98 (6.45)	82.98 (6.74)	82.63 (7.04)	82.51 (7.7)	83.01 (7.45)	82.76 (7.72)	82.64 (8.26)	82.49 (8.06)	0.117
CCI, mean (SD)	0.92(0.9)	0.92 (0.92)	0.97 (0.92)	1(0.94)	1(0.95)	1.14 (1.06)	1.16 (1.05)	1.2(1.06)	1.27 (1.11)	1.26 (1.08)	<0.001
COVID-19-19, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	406 (12.25)	NA
Invasive mechanical ventilation, n(%)	7(0.35)	8(0.38)	6(0.3)	1(0.05)	0(0)	28(0.83)	38(1)	47(1.09)	47(1.09)	49(1.48)	<0.001
Non-Invasive mechanical ventilation, n(%)	64(3.17)	76(3.58)	69(3.5)	79(3.93)	100(4.7)	80(2.38)	110 (2.89)	166 (3.85)	176 (4.06)	160 (4.83)	<0.001
IHM, n(%)	203 (10.05)	214 (10.08)	190 (9.63)	179 (8.91)	221 (10.39)	367 (10.91)	454 (11.91)	514 (11.91)	512 (11.82)	547 (16.51)	<0.001
Vascular dementia, n (prevalence %)	423 (0.71)	464 (0.75)	426 (0.72)	419 (0.69)	480 (0.74)	571 (0.82)	608 (0.82)	674 (0.84)	683 (0.89)	473 (0.92)	<0.001
Men, n (%)	363 (85.82)	390 (84.05)	344 (80.75)	346 (82.58)	413 (86.04)	471 (82.49)	497 (81.74)	569 (84.42)	569 (83.31)	397 (83.93)	0.449
Women, n(%)	60 (14.18)	74 (15.95)	82 (19.25)	73 (17.42)	67 (13.96)	100 (17.51)	111 (18.26)	105 (15.58)	114 (16.69)	76 (16.07)	
Age, mean (SD)	82.19 (7.25)	82.77 (6.31)	82.66 (6.78)	82.36 (6.33)	82.14 (6.94)	82.44 (7.15)	83.25 (6.92)	82.65 (6.89)	82.54 (7.54)	83.02 (7.34)	0.240
CCI, mean (SD)	1.27 (0.96)	1.31 (0.99)	1.35 (0.96)	1.34 (1.04)	1.38 (0.97)	1.51 (1.13)	1.47(1.1)	1.53 (1.05)	1.61 (1.14)	1.58 (1.13)	<0.001
COVID-19, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	48 (10.15)	NA
Invasive mechanical ventilation, n(%)	3(0.71)	2(0.43)	2(0.47)	0(0)	0(0)	1(0.18)	3(0.49)	0(0)	3(0.44)	0(0)	0.227
Non-Invasive mechanical ventilation, n(%)	14(3.31)	13(2.8)	17(3.99)	12(2.86)	22(4.58)	10(1.75)	10(1.64)	17(2.52)	17(2.49)	13(2.75)	0.120
IHM, n(%)	41(9.69)	42(9.05)	38(8.92)	39(9.31)	45(9.38)	63 (11.03)	58(9.54)	64(9.5)	72 (10.54)	71 (15.01)	0.081
Alzheimer's disease, n (prevalence %)	1153 (1.93)	1189 (1.92)	1079 (1.82)	1030 (1.71)	1092 (1.69)	879 (1.26)	961 (1.29)	1122 (1.41)	1053 (1.37)	769(1.5)	<0.001
Men, n (%)	894 (77.54)	881 (74.1)	815 (75.53)	767 (74.47)	824 (75.46)	679 (77.25)	755 (78.56)	888 (79.14)	798 (75.78)	583 (75.81)	0.083
Women, n(%)	259 (22.46)	308 (25.9)	264 (24.47)	263 (25.53)	268 (24.54)	200 (22.75)	206 (21.44)	234 (20.86)	255 (24.22)	186 (24.19)	
Age, mean (SD)	83.35 (5.83)	83.55 (5.95)	83.58 (5.87)	83.31 (6.71)	83.34 (6.56)	83.02 (6.25)	83.23 (6.24)	83.52 (5.99)	83.44 (6.33)	83.44 (6.26)	0.689
CCI, mean (SD)	0.81 (0.87)	0.78 (0.87)	0.79 (0.85)	0.88 (0.88)	0.86(0.9)	0.92 (0.94)	0.92 (0.97)	0.96 (0.97)	1.02 (1.04)	1.03 (1.02)	<0.001
COVID-19, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	93 (12.09)	NA
Invasive mechanical ventilation, n(%)	3(0.26)	3(0.25)	3(0.28)	1(0.1)	0(0)	1(0.11)	2(0.21)	3(0.27)	1(0.09)	1(0.13)	0.805
Non-Invasive mechanical ventilation, n(%)	37(3.21)	45(3.78)	30(2.78)	44(4.27)	50(4.58)	10(1.14)	18(1.87)	18(1.6)	26(2.47)	24(3.12)	0.52
IHM, n(%)	126 (10.93)	126 (10.6)	109 (10.1)	87(8.45)	122 (11.17)	66(7.51)	108 (11.24)	116 (10.34)	103 (9.78)	112 (14.56)	0.001

CCI: Charlson Comorbidity Index. IHM: in-hospital mortality. NA: Not applicable.

year 2020 when compared to the previous year.

3.2. Sex differences in prevalence and characteristics of any type of dementia, vascular dementia and Alzheimer's disease among patients hospitalized with AE-COPD

As can be seen in Table 2, the prevalence of any type of dementia was significantly higher among women than men with AE-COPD until year 2017, when it became more prevalent among men. Over the entire time period women had slightly higher values, 4.86% versus 4.37%, than men ($p < 0.001$).

The mean age of women showed a significant decrease overtime from 85.54 to 82.7 years ($p < 0.001$), with no change being observed among men. In the last years the mean age of men and women has become very similar, around 82 years.

For both sexes the mean CCI significantly rose from 2011 to 2020, overall men had a higher CCI (1.18) than women (0.99; $p < 0.001$).

The IHM increased overtime for men and women reaching the highest proportions on year 2020 (17.16% and 13.69% respectively). Over the entire time period the crude IHM among men was 11.94% versus 10.17% for women ($p < 0.001$).

Regarding vascular dementia (Table 3), the overall prevalence was higher among men than women (0.82% vs. 0.69%: $p < 0.001$), increasing significantly overtime only among men. Comorbidity, measured with the CCI, rose for men and women over the study period with higher mean values for men every year and in the entire period (1.52 vs. 1.34: $p < 0.001$).

The total IHM among men and women with vascular dementia hospitalized for AE-COPD were 10.62% vs. 8.12% respectively ($p = 0.031$), remaining stable overtime for both sexes.

Shown in Table 4 are the results for Alzheimer's disease according to sex. From 2011 to 2020, 7884 (1.48%) men and 2443 (1.96%) women hospitalized with AE-COPD, had a code for Alzheimer's disease ($p < 0.001$). The prevalence of Alzheimer's disease decreased significantly between 2011 and 2020 in both men and women ($p < 0.001$), being higher in women in all study years.

Between 2011 and 2020, in both sexes, the mean CCI in AE-COPD-patients with Alzheimer's disease increased significantly ($p > 0.001$), being higher among men than women (0.98 vs. 0.90: $p < 0.001$). Overall, the IHM was very similar among men and women (10.40% and 10.44%) and increased overtime only among men.

3.3. Multivariable analysis of factors associated with the presence of any type of dementia, vascular dementia and Alzheimer's disease among patients hospitalized with AE-COPD

As can be seen in Table S2 the presence of any type of dementia remained stable until year 2015, when compared with reference year

Table 2
Sex differences in the prevalence and characteristics of the patients hospitalized from 2011 to 2020 in Spain with an acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) and concomitantly having a diagnosis code for any type of dementia.

		2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	p-value trend
Men	N, prevalence	1602 (3.18)	1648 (3.17)	1539 (3.11)	1555 (3.1)	1697 (3.19)	2694 (4.8)	3017 (5.13)	3450 (5.48)	3434 (5.72)	2686 (6.65)	<0.001
	Age, mean(SD)	82.13 (6.47)	82.48 (6.22)	82.38 (6.27)	82.57 (6.67)	82.29 (6.72)	82.17 (7.45)	82.77(7)	82.58 (7.58)	82.55 (7.83)	82.44 (7.72)	0.057
	40–64 year, n (%)	17(1.06)	20(1.21)	18(1.17)	23(1.48)	18(1.06)	70(2.6)	42(1.39)	78(2.26)	88(2.56)	71(2.64)	<0.001
	65–79 year, n (%)	467 (29.15)	452 (27.43)	408 (26.51)	422 (27.14)	470 (27.7)	713 (26.47)	747 (24.76)	871 (25.25)	959 (27.93)	709 (26.4)	
	≥80 year, n (%)	1118 (69.79)	1176 (71.36)	1113 (72.32)	1110 (71.38)	1209 (71.24)	1911 (70.94)	2228 (73.85)	2501 (72.49)	2387 (69.51)	1906 (70.96)	
	CCI, mean (SD)	0.94 (0.91)	0.94 (0.93)	0.97 (0.92)	1.02 (0.95)	1.02 (0.97)	1.18 (1.08)	1.19 (1.07)	1.25 (1.07)	1.32 (1.13)	1.31 (1.1)	<0.001
	COVID-19, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	334 (12.43)	NA
	Invasive mechanical ventilation, n(%)	6(0.37)	7(0.42)	5(0.32)	0(0)	0(0)	21(0.78)	28(0.93)	39(1.13)	35(1.02)	42(1.56)	<0.001
	Non-Invasive mechanical ventilation, n(%)	56(3.5)	63(3.82)	51(3.31)	61(3.92)	83(4.89)	63(2.34)	81(2.68)	132 (3.83)	138 (4.02)	112 (4.17)	<0.001
	IHM, n(%)	166 (10.36)	169 (10.25)	160 (10.4)	142 (9.13)	175 (10.31)	296 (10.99)	360 (11.93)	432 (12.52)	423 (12.32)	461 (17.16)	<0.001
Women	N, prevalence	418 (4.47)	476 (4.81)	433 (4.41)	453 (4.44)	430 (3.72)	670 (4.85)	794 (5.14)	866 (5.16)	896 (5.26)	628(5.7)	<0.001
	Age, mean (SD)	85.54 (6.19)	84.81 (6.83)	85.13 (6.63)	84.41 (6.78)	84(8.04)	83.88 (8.51)	83.91 (8.88)	83.45 (8.22)	82.99 (9.75)	82.71 (9.38)	<0.001
	40–64 year, n (%)	1(0.24)	4(0.84)	6(1.39)	7(1.55)	15(3.49)	30(4.48)	34(4.28)	26(3)	43(4.8)	30(4.78)	<0.001
	65–79 year, n (%)	56(13.4)	82 (17.23)	65 (15.01)	82(18.1)	81 (18.84)	110 (16.42)	153 (19.27)	193 (22.29)	206 (22.99)	163 (25.96)	
	≥80 year, n (%)	361 (86.36)	390 (81.93)	362 (83.6)	364 (80.35)	334 (77.67)	530 (79.1)	607 (76.45)	647 (74.71)	647 (72.21)	435 (69.27)	
	CCI, mean (SD)	0.82 (0.84)	0.85 (0.87)	0.98 (0.91)	0.94 (0.91)	0.91 (0.89)	0.98 (0.96)	1.04 (0.97)	1(0.98)	1.06(1)	1.07 (0.98)	<0.001
	COVID-19, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	72 (11.46)	NA
	Invasive mechanical ventilation, n(%)	1(0.24)	1(0.21)	1(0.23)	1(0.22)	0(0)	7(1.04)	10(1.26)	8(0.92)	12(1.34)	7(1.11)	<0.001
	Non-Invasive mechanical ventilation, n(%)	8(1.91)	13(2.73)	18(4.16)	18(3.97)	17(3.95)	17(2.54)	29(3.65)	34(3.93)	38(4.24)	48(7.64)	0.036
	IHM, n(%)	37(8.85)	45(9.45)	30(6.93)	37(8.17)	46(10.7)	71(10.6)	94 (11.84)	82(9.47)	89(9.93)	86 (13.69)	0.019

Prevalence of any type of dementia among patients hospitalized with an AE-COPD exacerbation. CCI: Charlson Comorbidity Index. IHM: in-hospital mortality. NA: Not applicable.

Table 3
Sex differences in the prevalence and characteristics of the patients hospitalized from 2011 to 2020 in Spain with an acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) and concomitantly having a diagnosis code for **vascular dementia**.

		2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	p-value trend
Men	N, prevalence	363 (0.72)	390 (0.75)	344(0.7)	346 (0.69)	413 (0.78)	471 (0.84)	497 (0.85)	569 (0.90)	569 (0.95)	397 (0.98)	<0.001
	Age, mean(SD)	81.83 (7.37)	82.35 (6.16)	82.43 (6.34)	81.84 (6.25)	81.83 (6.9)	82.18 (7.02)	83.09 (6.23)	82.42 (6.89)	82.32 (7.59)	82.56 (7.26)	0.169
	40–64 year, n (%)	8(2.2)	5(1.28)	6(1.74)	6(1.73)	7(1.69)	9(1.91)	2(0.4)	13(2.28)	16(2.81)	11(2.77)	0.406
	65–79 year, n (%)	105 (28.93)	109 (27.95)	90 (26.16)	110 (31.79)	116 (28.09)	134 (28.45)	121 (24.35)	149 (26.19)	173 (30.4)	105 (26.45)	
	≥80 year, n (%)	250 (68.87)	276 (70.77)	248 (72.09)	230 (66.47)	290 (70.22)	328 (69.64)	374 (75.25)	407 (71.53)	380 (66.78)	281 (70.78)	
	CCI, mean (SD)	1.29 (0.98)	1.31(1)	1.34 (0.94)	1.37 (1.04)	1.39 (0.99)	1.56 (1.14)	1.49 (1.1)	1.56 (1.06)	1.66 (1.16)	1.62 (1.12)	<0.001
	COVID-19, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	39(9.82)	<0.001
	Invasive mechanical ventilation, n(%)	3(0.83)	1(0.26)	1(0.29)	0(0)	0(0)	1(0.21)	3(0.6)	0(0)	3(0.53)	0(0)	0.207
	Non-Invasive mechanical ventilation, n(%)	12(3.31)	11(2.82)	12(3.49)	8(2.31)	21(5.08)	9(1.91)	5(1.01)	14(2.46)	12(2.11)	9(2.27)	0.028
	IHM, n(%)	35(9.64)	34(8.72)	32(9.3)	34(9.83)	40(9.69)	50 (10.62)	54 (10.87)	59 (10.37)	63 (11.07)	62 (15.62)	0.132
Women	N, prevalence	60(0.64)	74(0.75)	82(0.83)	73(0.72)	67(0.58)	100 (0.72)	111 (0.72)	105 (0.63)	114 (0.67)	76(0.69)	0.587
	Age, mean (SD)	84.38 (6.04)	85(6.63)	83.63 (8.38)	84.82 (6.17)	84.09 (6.92)	83.67 (7.66)	83.95 (9.42)	83.85 (6.76)	83.67 (7.19)	85.39 (7.35)	0.808
	40–64 year, n (%)	0(0)	2(2.7)	3(3.66)	1(1.37)	0(0)	2(2)	6(5.41)	1(0.95)	1(0.88)	0(0)	0.459
	65–79 year, n (%)	11 (18.33)	15 (20.27)	16 (19.51)	9(12.33)	13(19.4)	21(21)	22 (19.82)	22 (20.95)	25 (21.93)	17 (22.37)	
	≥80 year, n (%)	49 (81.67)	57 (77.03)	63 (76.83)	63(86.3)	54(80.6)	77(77)	83 (74.77)	82(78.1)	88 (77.19)	59 (77.63)	
	CCI, mean (SD)	1.17 (0.83)	1.36 (0.99)	1.4 (1.05)	1.21 (0.99)	1.33 (0.82)	1.27 (1.06)	1.39 (1.11)	1.32 (1.01)	1.36 (1.03)	1.39 (1.2)	0.900
	COVID-19, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	9(11.84)	<0.001
	Invasive mechanical ventilation, n(%)	0(0)	1(1.35)	1(1.22)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0.428
	Non-Invasive mechanical ventilation, n(%)	2(3.33)	2(2.7)	5(6.1)	4(5.48)	1(1.49)	1(1)	5(4.5)	3(2.86)	5(4.39)	4(5.26)	0.717
	IHM, n(%)	6(10)	8(10.81)	6(7.32)	5(6.85)	5(7.46)	13(13)	4(3.6)	5(4.76)	9(7.89)	9(11.84)	0.311

Prevalence: Prevalence of vascular dementia among patients hospitalized with a COPD exacerbation. CCI: Charlson Comorbidity Index. IHM: in-hospital mortality. NA: Not applicable.

2011, and then increased significantly from year 2016 to year 2020, This was seen in men, women and both sexes and the highest OR's appeared in year 2020. Higher age and CCI were also associated to higher probability of having a code for any type of dementia beside sex. As can be seen in Table S2, a diagnosis of COVID-19 was associated to a 56% higher prevalence of any type of dementia among men (OR 1.56, 95%CI 1.38–1.77) and 62% among women (OR 1.62; 95%CI 1.24–2.12) hospitalized with AE-COPD. After adjusting for all covariates, being a woman was associated to the presence of any type of dementia among patients with AE-COPD (OR 1.29; 95% CI 1.26–1.33)

The adjusted time trend for vascular dementia showed no change until year 2020, when a significant increment was found among men, women and both sexes. Higher age and CCI were associated to more vascular dementia in all sexes (Table S2).

Unlike vascular dementia and any type of dementia, the probability of having a code for Alzheimer's disease decreased significantly from year 2011–2020 among men and women hospitalized with AE-COPD. Older age, COVID-19 and being a woman (OR 1.56; 95% CI 1.49–1.63) showed a significant association with the presence of Alzheimer's disease.

Shown in Table S3 are the results of the multivariable analysis of the factors associated with the IHM among men and women hospitalized with an AE-COPD and concomitantly suffering any type of dementia, vascular dementia, and Alzheimer's disease.

Among men and women hospitalized with AE-COPD, who also suffered any type of dementia, the IHM remained stable overtime until year 2020, when it showed a significant increase. Older age, higher CCI, a code for COVID-19, and the use of non-invasive mechanical ventilation or invasive mechanical ventilation were variables associated to the IHM. Women had lower risk of dying in the hospital than men in the fully adjusted model (OR 0.84; 95%CI 0.77–0.93).

The same predictors were associated with increased risk of IHM in patients with AE-COPD and vascular dementia and Alzheimer's disease (Table S3). Remarkable the protective effect of female sex for vascular dementia (OR 0.72; 95% CI 0.55–0.93) and Alzheimer's disease (OR 0.78; 95%CI 0.64–0.98).

4. Discussion

To the best of our knowledge, this is the first large-sample, nationwide population-based study, to evaluate the trends in prevalence of dementia (any type of dementia, vascular dementia and Alzheimer's disease) in patients admitted for AE-COPD. We found that the prevalence of any type of dementia remained stable from 2011 to 2015, and then increased significantly from year 2016 to year 2020. The aging of population may affect this trend, as well as the increase of comorbidity [21]. Puteikis et al. also observed that the prevalence of dementia increased with age in patients with COPD [22]. In addition, comorbidity has also been identified as a good predictor of dementia, with the risk increasing along with the number of comorbidities [23]. After adjusting for all covariates in our study, being a woman was associated to the presence of any type of dementia among patients with AE-COPD. In a

Table 4
Sex differences in the prevalence and characteristics of the patients hospitalized from 2011 to 2020 in Spain with an acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) and concomitantly having a diagnosis code for Alzheimer's. disease.

		2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	p-value trend
Men	N, prevalence	894 (1.77)	881(1.7)	815 (1.65)	767 (1.53)	824 (1.55)	679 (1.21)	755 (1.28)	888 (1.40)	798 (1.33)	583 (1.44)	<0.001
	Age, mean(SD)	82.7 (5.62)	82.98 (5.81)	82.8 (5.72)	83(6.5)	82.96 (6.36)	82.63 (6.14)	82.97 (5.87)	83.34 (5.84)	83.02 (6.21)	83.37 (6.03)	0.294
	40–64 year, n (%)	3(0.34)	5(0.57)	3(0.37)	6(0.78)	5(0.61)	3(0.44)	4(0.53)	5(0.56)	3(0.38)	1(0.17)	0.406
	65–79 year, n (%)	234 (26.17)	221 (25.09)	205 (25.15)	188 (24.51)	204 (24.76)	173 (25.48)	163 (21.59)	179 (20.16)	200 (25.06)	135 (23.16)	
	≥80 year, n (%)	657 (73.49)	655 (74.35)	607 (74.48)	573 (74.71)	615 (74.64)	503 (74.08)	588 (77.88)	704 (79.28)	595 (74.56)	447 (76.67)	
	CCI, mean (SD)	0.84 (0.88)	0.81 (0.89)	0.78 (0.85)	0.88 (0.88)	0.87 (0.9)	0.93 (0.94)	0.94 (0.98)	0.99 (0.99)	1.04 (1.05)	1.07 (1.04)	<0.001
	COVID-19, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	66 (11.32)	NA
	Invasive mechanical ventilation, n(%)	2(0.22)	3(0.34)	3(0.37)	0(0)	0(0)	1(0.15)	1(0.13)	3(0.34)	0(0)	0(0)	0.314
	Non-Invasive mechanical ventilation, n(%)	31(3.47)	36(4.09)	24(2.94)	33(4.3)	39(4.73)	5(0.74)	15(1.99)	15(1.69)	19(2.38)	11(1.89)	0.061
	IHM, n(%)	102 (11.41)	96(10.9)	87 (10.67)	62(8.08)	87 (10.56)	50(7.36)	84 (11.13)	97 (10.92)	73(9.15)	82 (14.07)	0.007
Women	N, prevalence	259 (2.77)	308 (3.11)	264 (2.69)	263 (2.58)	268 (2.32)	200 (1.45)	206 (1.33)	234 (1.41)	255(1.5)	186 (1.69)	<0.001
	Age, mean (SD)	85.62 (6.01)	85.21 (6.07)	86(5.66)	84.21 (7.22)	84.5 (7.03)	84.36 (6.44)	84.19 (7.39)	84.21 (6.49)	84.74 (6.52)	83.66 (6.94)	0.052
	40–64 year, n (%)	1(0.39)	0(0)	1(0.38)	6(2.28)	6(2.24)	2(1)	2(0.97)	0(0)	0(0)	2(1.08)	0.001
	65–79 year, n (%)	32 (12.36)	47 (15.26)	36 (13.64)	49 (18.63)	51 (19.03)	30(15)	44 (21.36)	51 (21.79)	50 (19.61)	45 (24.19)	
	≥80 year, n (%)	226 (87.26)	261 (84.74)	227 (85.98)	208 (79.09)	211 (78.73)	168(84)	160 (77.67)	183 (78.21)	205 (80.39)	139 (74.73)	
	CCI, mean (SD)	0.69 (0.80)	0.69 (0.80)	0.83 (0.83)	0.88 (0.88)	0.83 (0.89)	0.87 (0.94)	0.85 (0.92)	0.85 (0.92)	0.96 (0.99)	0.91 (0.94)	0.009
	COVID-19, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	27 (14.52)	NA
	Invasive mechanical ventilation, n(%)	1(0.39)	0(0)	0(0)	1(0.38)	0(0)	0(0)	1(0.49)	0(0)	1(0.39)	1(0.54)	0.772
	Non-Invasive mechanical ventilation, n(%)	6(2.32)	9(2.92)	6(2.27)	11(4.18)	11(4.1)	5(2.5)	3(1.46)	3(1.28)	7(2.75)	13(6.99)	0.140
	IHM, n(%)	24(9.27)	30(9.74)	22(8.33)	25(9.51)	35 (13.06)	16(8)	24 (11.65)	19(8.12)	30 (11.76)	30 (16.13)	0.127

Prevalence: Prevalence of Alzheimer's disease among patients hospitalized with a COPD exacerbation. CCI: Charlson Comorbidity Index. IHM: in-hospital mortality. NA: Not applicable.

recent meta-analysis, Wang et al. [8] showed a significant increase in the risk of dementia or cognitive impairment among patients with COPD but, unlike our results, they found that this risk was not affected by gender, although it was affected by age. However, they found that this risk was more pronounced in patients younger than 65 years. They suggested that exposure to COPD-related risk factors affects the age of onset, and has a greater impact on young people, leading to a higher risk of dementia. It must be taken into account that only two studies were included in the subgroup analysis, both being from the same region, which may reduce statistical efficiency [8].

When we analysed the types of dementia, we did not find changes in the prevalence of vascular dementia until the year 2020, when a significant increase was observed in both sexes. However, the prevalence was clearly higher in men than in women. These results are noteworthy since, in the general population, no sex differences have been found in the prevalence of vascular dementia [24,25]. On the other hand, the probability of having a code for Alzheimer's disease decreased significantly from 2011 to 2020 among men and women hospitalized with AE-COPD. To our knowledge, there are no previous epidemiological studies evaluating the trends in incidence and prevalence of these specific types of dementia in populations of patients with COPD. However, Wolters et al. analysed aggregated data from individuals >65 years of age in 7 population-based cohort studies in the United States and Europe from the Alzheimer Cohort Consortium finding that he incidence of Alzheimer's disease decreases significantly (HR 0.84 95%CI 0.76–0.92) from 1988 to 2015 [26]. In any case, changes in dementia prevalence trends obtained in our study could be attributed to various interventions, including improved education as well as more effective treatment for vascular risk factors [26–29].

The comparison of the prevalence of any type of dementia, vascular dementia and Alzheimer's disease obtained in patients admitted for AE-COPD in our study with that existing in the general population is difficult to carry out, since there are few studies in the general population that have been carried out with a methodology similar to ours. In addition, it has been shown that the prevalence of dementia varies greatly between them [30,31]. In any case, Liao et al. demonstrated that COPD is associated with a higher subsequent risk of dementia after adjusting for comorbidities [32]. Specifically, the association between COPD and dementia is greater in patients with more frequent episodes of acute exacerbation of COPD.

In our study, the marked decrease in year 2020 in the number of hospitalizations for AE-COPD is striking. Our results are consistent with those described in other studies, which showed a significant reduction in admissions for COPD exacerbations during the onset of the COVID-19 pandemic compared to pre-pandemic times, coinciding with the introduction of public health measures, including social distancing and universal masking [33–35]. Although some studies, particularly those early in the pandemic, found a lower prevalence of COPD among hospitalized

patients with COVID-19 than would be expected from population prevalence [36], more recent studies have shown that having COPD is an independent risk factor for hospital admission with COVID-19, although the risk is modest [37].

We observed that a diagnosis of COVID-19 increased the prevalence of any type of dementia among patients hospitalized with AE-COPD. In our opinion a possible reason for this association is that patients with COVID-19 and AE-COPD who also suffered dementia were hospitalized more than those without dementia due to the difficulties of isolation for dementia patients in their houses. However, this hypothesis should be confirmed in studies with clinical histories.

The use of invasive mechanical ventilation and non-invasive mechanical ventilation, showed a small, but significant increment, but only among those patients with any type of dementia. In our opinion, and agreeing with other authors, more than a greater need for mechanical ventilation in patients with dementia, increased use of mechanical ventilation in these patients has been linked to increased availability of intensive care unit beds [38,39]. Sharma et al. also found a substantial increase in the use of invasive mechanical ventilation in patients with advanced dementia [40]. In the same way, Sullivan et al. found that the use of non-invasive ventilation rapidly increased from 2000 through 2017 among Medicare beneficiaries at the end of life, especially among persons with cancer and dementia, without reciprocal decreases in invasive mechanical ventilation [41]. This is worrisome given that the presence of dementia is one of the variables that negatively influences the success of non-invasive ventilation in COPD patients ventilated for an episode of hypercapnic respiratory failure. In fact, in a previous study, it has been observed that dementia increased the chance of non-invasive ventilation failure about 20 times [42]. It is also necessary to take into account the absence of evidence to support its use as palliative ventilatory support in these patients [43].

Previous studies have reported an increased risk of IHM in patients admitted to hospital who had a diagnosis of COPD and dementia [44]. Our study showed that, among men and women hospitalized with AE-COPD who suffered any type of dementia, the IHM remained stable overtime until year 2020, when it showed a significant increase. This increase coincides with the appearance of COVID pandemic. In fact, COVID-19 was a factor associated to the IHM in these patients, in addition to others, such as older age, higher CCI, and the use of mechanical ventilation. The same predictors were associated with increased risk of IHM in patients with AE-COPD and vascular dementia and Alzheimer's disease. Although there are no similar studies published in COPD hospitalized patients with dementia, a meta-analysis of 24 studies involving 46,391 patients also showed an enhanced risk of severity and mortality from COVID-19 infection in patients with dementia [45]. In addition, Pisaturo et al. suggested that the increased mortality in this meta-analysis could be related to the presence of multiple comorbidities and the negative impact of age [46]. As in other studies [47], the need for mechanical ventilation during admission also increased the risk of IHM in our study population. It is also important to note that withholding invasive life support measures in patients with physiological decompensation, particularly if it is not clinically appropriate, may also contribute to IHM [48].

Women had lower risk of dying in the hospital than men. It has been previously described that sex plays an important role in determining hospital related outcomes in COPD patients, such that being a man was associated with a poorer outcome [49]. This is possibly due to differences in disease severity, healthcare utilization behaviors and response to treatment [50]. Similarly, sex disparities have also been reported among patients with dementia [51]. So, male sex has also been associated with increased mortality in people with dementia in previous studies [52].

The observed increase in the prevalence of any type of dementia in patients admitted for AE-COPD found in our investigation has several practical implications. It is expected that the improvements in the treatment of chronic diseases and improvement in the survival of the population will lead to more people with surviving into old age and developing dementia [53], including patients with COPD, therefore making necessary that effective interventions are implemented. According to the latest version of the Lancet Commission on Dementia Prevention, based on results from large cohort studies, up to 40% of dementia cases could be prevented by modifying several risk factors, including smoking and air pollution [54], which are also known risk factors for the development of COPD. Population-based approaches are likely to be the most impactful, cost-effective, and meaningful to reduce the global burden of dementia. Public health campaigns are needed to raise awareness about the link between COPD, and the other mentioned risk factors, with dementia. Campaigns must encourage lifestyle changes, which could reduce the incidence of COPD and mitigate dementia risk [54,55].

The strength of our study is the use of population-based data that are highly representative of the general population. However, certain limitations to our findings should be considered. Firstly, we used te ICD-9 and ICD-10 codes to identify patients with AE-COPD and dementia, which may lead to misidentification of some cases. Furthermore, changes in coding practices overtime could partially explain variations in the time trends. However, the use of hospital discharge records and administrative databases for the diagnosis of dementia, has been shown to be sufficiently sensitive and specific for epidemiological investigations [56,57]. Secondly, some of the known prognostic factors of COPD, including smoking history, lung function and severity of COPD or dementia were not available in our database so baseline sex differences could not be assessed. Third, we lacked information on the treatment and control of COPD and dementia. Fourth, COVID pandemic started in Spain in March 2020, so the study only included the beginning of the pandemic. In addition, it was not designed to establish the impact of COVID, and causality could not be established. Finally, it was only possible to assess IHM, since we did not have information on the patients once they were discharged.

5. Conclusions

In conclusion, in this large-sample study we found that, among patients admitted with AE-COPD, the prevalence of any type of dementia remained stable from 2011 to 2015, and then increased significantly from year 2016 to year 2020, although we identified variations in these trends depending on the specific cause of dementia. The IHM remained stable overtime until year 2020, when it showed a significant increase, probably related to the COVID-19 pandemic. It is remarkable the protective effect of female sex for IHM, both for any type of dementia and for the specific types evaluated. Clinicians should pay attention to the relationship between AE-COPD and dementia, to avoid worse outcomes and reduce the burden of both diseases. Future research should deepen the study of the mechanisms that relate both processes.

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CRediT authorship contribution statement

Javier de Miguel-Diez: Conceptualization, Validation, Writing – original draft, Writing – review & editing. **Ana Lopez-de-Andres:** Conceptualization, Validation, Writing – original draft, Writing – review & editing. **Rodrigo Jimenez-Garcia:** Data curation, Writing – original draft, Writing – review & editing. **Valentin Hernández-Barrera:** Data curation, Writing – review & editing. **David Carabantes-Alarcon:** Writing – original draft, Writing – review & editing. **Jose J. Zamorano-Leon:** Software, Writing – review & editing. **Ricardo Omaña-Palanco:** Validation, Writing – review & editing. **Francisco Javier González-Barcala:** Validation, Writing – review & editing. **Natividad Cuadrado-Corrales:** Conceptualization, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

All authors declare that they have none Conflict of Interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107223.

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