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Vascular dementia in the Spanish elderly population according to type 2 diabetes status: trends in incidence, characteristics and outcomes (2004-2013)

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Key Words: Type 2 diabetes; Vascular dementia; Hospitalization; In-hospital mortality

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ABSTRACT

Objectives: To examine trends in the incidence and outcomes of vascular dementia (VaD) hospitalizations in elderly patients with and without type 2 diabetes (T2DM) in Spain, 2004-2013.

Design: Retrospective study.

Setting: Spain.

Participants: We used national hospital discharge data to select all patients aged ≥70 discharged from a hospital with VaD as a primary diagnosis.

Main outcome measures: Overall incidence was calculated and stratified by diabetes status (T2DM or non-diabetic) and age groups. We analyzed diagnostic and therapeutic procedures, patient comorbidities, infectious complications, length of hospital stays and in-hospital mortality (IHM).

Results: We identified a total of 170,607 admissions for VaD (34.3% with T2DM). The adjusted incidence was higher among people with T2DM over the study period. We found a higher incidence in men than women in all years studied. T2DM was positively associated with VaD hospitalization (IRR 2.14, 95%CI 2.11-1.16). The mean age at admission was higher than 80 years for all groups and more than 70% had a Charlson Comorbidity Index value ≥2. Pneumonia was significantly associated with a higher mortality (OR 2.59, 95%CI 2.52 -2.67). We found that percutaneous endoscopic gastrostomy was associated with lower IHM (OR 0.37, 95%CI 0.31-0.45), while parenteral nutrition had the opposite effect (OR 1.29, 95%CI 1.18-1.41). Diabetes was not associated with higher IHM (OR 0.99, 95%CI 0.93–1.06). For the entire sample, time-trend analyses showed a significant decrease in mortality in patients admitted for VaD (OR 0.98, 95%CI 0.97–0.99).

Conclusions: Incidence rates for VaD hospitalizations were twice as high in diabetic patients compared to non-diabetics. Men had significantly higher incidence rates than women,

regardless of diabetes status. In both groups studied, pneumonia and parenteral nutrition were associated with mortality while percutaneous endoscopic gastrostomy was associated with survival. The presence of diabetes was not associated with higher IHM during hospitalization with VaD.

Strengths and limitations of this study

- The strength of our investigation lies in its large sample size, the 10-year follow-up period, and the standardized methodology.
- A limitation is the lack of information on VaD or T2DM duration, treatments for this last condition or sociodemographic characteristic.
- Another limitation is the lack of specificity of clinically defined VaD.

INTRODUCTION

Dementia has become a significant global economic, social, and public health burden. [1,2] The most common types of dementia are vascular dementia (VaD) and Alzheimer's disease (AD), which together account for more than 90% of all cases. [1]

Several epidemiological studies have also demonstrated that diabetic patients are at an increased risk for stroke, lacunar infarcts, AD and VaD [3-5] through Aβ/tau-dependent and independent mechanisms. [3]

Type 2 diabetes mellitus (T2DM), which affects more than 300 million people worldwide, [6] increases the risk of macrovascular and microvascular complications, and it is also an independent risk factor for vascular dementia [7,8] and AD. [9] It has recently been published that diabetic patients have a 60% greater risk for the development of dementia. [10] Factors reportedly linked with dementia include age, smoking, hypertension and diabetes, therefore it is only to be expected that hospitalization for VaD will increase in the coming years. [11,12] For this reason, it seems necessary to analyze the evolution of VaD over time and to evaluate which factors and procedures may increase in-hospital mortality (IHM).

In this study, we used national hospital discharge data to examine trends in the incidence of VaD among hospitalized men and women with and without T2DM between 2004 and 2013 in Spain. In particular, we analyzed trends in the use of diagnostic and therapeutic procedures, patient comorbidities, common infectious and medical complications and in-hospital outcomes such as length of hospital stay (LOHS), readmission rates and IHM.

METHODS

This retrospective, observational study was conducted using the Spanish National Hospital Database (CMBD, *Conjunto Minimo Básico de Datos*). [13] We selected all patients aged ≥70 years hospitalized for VaD (ICD-9-CM codes: 290.40, 290.41, 290.42, 290.43) as the primary diagnosis between January 1, 2004 and December 31, 2013.

Discharges were grouped by diabetes status as follows: T2DM (codes: 250.x0; 250.x2) and no diabetes.

We calculated the adjusted incidence of discharge rates after VaD for men and women with and without T2DM per 100,000 inhabitants, as described in detail in the Supplementary Methods.

Clinical characteristics included information on overall comorbidity at the time of diagnosis, which was assessed by calculating the Charlson Comorbidity Index (CCI) [14] as described in detail in the Supplementary Methods.

We analyzed the presence of hypertension (codes: 401, 401.0, 401.1, 401.9) and atrial fibrillation (code: 427.31) in any diagnosis position during vascular dementia hospitalization. We also identified common infectious complications such as pneumonia (codes: 480-488, 507.0-507.8) and urinary tract infection (codes: 590.0, 590.9, 595.0, 595.9, 597.80, 599.0). We analyzed other medical complications, specifically agitation (code: 307.9) and malnutrition (code: 263.9).

We identified the following diagnostic and therapeutic procedures: magnetic resonance (code: 88.91), computed tomography angiography (CAT) (code: 87.03), percutaneous endoscopic gastrostomy (PEG) (code: 43.11), mechanical ventilation (codes: 96.7; 96.70; 96.71; 96.72), parenteral nutrition (codes: 99.15) and bladder catheterization (code: 57.94).

Patient readmissions were defined as inpatient re-hospitalization within 30 days of discharge (30-day readmission). The mean LOHS and the proportion of patients who died during the hospital admission, IHM, were also estimated for each year studied.

Statistical analysis is described in the Supplementary Methods.

RESULTS

We identified a total of 170,607 discharges of patients (78,499 men and 92,108 women) admitted with VaD as the primary diagnosis. Patients with T2DM accounted for 34.3% of the

total. The prevalence of T2DM in men with VaD increased significantly during the study period, from 28.94% in 2004 to 34.58% in 2013 (p<0.01). The prevalence of diabetes in women with VaD increased from 34.13% to 35.37% (p<0.01).

The overall adjusted incidence of admissions for VaD was higher among the oldest subgroup (≥85 years), both in men and women, diabetic and non-diabetic. In T2DM patients older than 85 years, we found that incidence rates were 1,369.63 per 100,000 inhabitants in women and 1,308.71 per 100,000 inhabitants in men. In the non-diabetic group, incidence rates for men and women were 776.52 and 824.15 per 100.000 inhabitants, respectively (Supplementary Table).

The adjusted incidence rate of admissions for VaD increased significantly in men with T2DM aged ≥85 years old (1,191.79 cases per 100,000 inhabitants in 2004 to 1,393.17 cases in 2013). However, there were no significant changes in the incidence of diagnosis of VaD in T2DM-women aged ≥85 years (Supplementary Table).

As can be seen in Table 1, the mean age was 80.72 years (SD, 5.65 years) in diabetic men and 82.4 years (SD,5.93 years) in men without diabetes. According to the CCI, 40.86% of men with T2DM had three or more coexisting conditions; in men without diabetes this figure was 39.3%. The percentage of men with T2DM who have two or more coexisting conditions is slightly higher than that of non-diabetic men (81% vs. 79.71%)

Table 1. Characteristic, Charlson Comorbidity Index and clinical conditions among men with and without type 2 diabetes hospitalized with vascular dementia. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value
No Diabetes												
N	4185	4511	4697	4889	5152	5346	5705	5892	5877	6083	52337	<0.001
Incidence	255.04	256.93	251.11	261.37	280.32	296.14	316.02	325.64	324.81	335.44	290.47	
Age, mean (SD)	81.28(6.01)	81.32(5.82)	81.64(5.92)	82(6.06)	81.9(5.95)	82.61(5.95)	82.78(5.83)	83.01(5.71)	83.15(5.88)	83.41(5.76)	82.4(5.93)	<0.001
70-74 years old, n (%)	626(14.96)	610(13.52)	572(12.18)	597(12.21)	630(12.23)	509(9.52)	513(8.99)	426(7.23)	491(8.35)	461(7.58)	5435(10.38)	0,000
75-79 years old, n (%)	1053(25.16)	1154(25.58)	1173(24.97)	1132(23.15)	1215(23.58)	1167(21.83)	1162(20.37)	1223(20.76)	1071(18.22)	1075(17.67)	11425(21.83)	
80-84 years old, n (%)	1247(29.8)	1413(31.32)	1493(31.79)	1490(30.48)	1541(29.91)	1556(29.11)	1760(30.85)	1839(31.21)	1808(30.76)	1878(30.87)	16025(30.62)	
≥85 years old, n(%)	1259(30.08)	1334(29.57)	1459(31.06)	1670(34.16)	1766(34.28)	2114(39.54)	2270(39.79)	2404(40.8)	2507(42.66)	2669(43.88)	19452(37.17)	
Charlson Comorbidity Index1, n (%)	934(22.32)	962(21.33)	1019(21.69)	1015(20.76)	1119(21.72)	1124(21.03)	1119(19.61)	1113(18.89)	1091(18.56)	1126(18.51)	10622(20.3)	0,000
Charlson Comorbidity Index2, n (%)	1748(41.77)	1968(43.63)	1927(41.03)	2048(41.89)	2072(40.22)	2195(41.06)	2281(39.98)	2330(39.55)	2219(37.76)	2359(38.78)	21147(40.41)	
Charlson Comorbidity Index≥3, n (%)	1503(35.91)	1581(35.05)	1751(37.28)	1826(37.35)	1961(38.06)	2027(37.92)	2305(40.4)	2449(41.56)	2567(43.68)	2598(42.71)	20568(39.3)	
Atrial fibrillation, n (%)	830(19.83)	907(20.11)	1030(21.93)	1095(22.4)	1155(22.42)	1270(23.76)	1397(24.49)	1452(24.64)	1488(25.32)	1493(24.54)	12117(23.15)	<0.001
Hypertension, n (%)	1398(33.41)	1537(34.07)	1707(36.34)	1745(35.69)	1883(36.55)	2004(37.49)	2196(38.49)	2288(38.83)	2349(39.97)	2420(39.78)	19527(37.31)	<0.001
Malnutrition, n (%)	104(2.49)	177(3.92)	185(3.94)	231(4.72)	243(4.72)	274(5.13)	251(4.4)	308(5.23)	280(4.76)	339(5.57)	2392(4.57)	<0.001
Pneumonia, n (%)	1028(24.56)	1180(26.16)	1136(24.19)	1260(25.77)	1303(25.29)	1448(27.09)	1526(26.75)	1594(27.05)	1603(27.28)	1638(26.93)	13716(26.21)	<0.001
Urinary tract infection, n (%)	682(16.3)	743(16.47)	790(16.82)	808(16.53)	881(17.1)	963(18.01)	992(17.39)	1079(18.31)	1108(18.85)	1150(18.91)	9196(17.57)	0.001
Agitation, n (%)	16(0.38)	16(0.35)	16(0.34)	24(0.49)	22(0.43)	31(0.58)	36(0.63)	34(0.58)	32(0.54)	39(0.64)	266(0.51)	0.225
Diabetes												
N	1703	2000	2297	2376	2578	2735	2887	3057	3313	3216	26162	<0.001
Incidence	450.73	501.91	548.05	566.9	578.82	579.89	612.11	591.26	640.77	571.82	568.77	
Age, mean (SD)	79.6(5.59)	79.74(5.58)	79.84(5.57)	80.2(5.6)	80.43(5.6)	80.51(5.65)	81.01(5.46)	81.37(5.62)	81.49(5.65)	81.71(5.66)	80.72(5.65)	<0.001
70-74 years old, n (%)	342(20.08)	393(19.65)	438(19.07)	400(16.84)	413(16.02)	426(15.58)	376(13.02)	388(12.69)	392(11.83)	352(10.95)	3920(14.98)	0,000
75-79 years old, n (%)	540(31.71)	621(31.05)	683(29.73)	752(31.65)	767(29.75)	791(28.92)	759(26.29)	789(25.81)	855(25.81)	811(25.22)	7368(28.16)	
80-84 years old, n (%)	487(28.6)	599(29.95)	728(31.69)	669(28.16)	786(30.49)	855(31.26)	959(33.22)	939(30.72)	1048(31.63)	1019(31.69)	8089(30.92)	
≥85 years old, n(%)	334(19.61)	387(19.35)	448(19.5)	555(23.36)	612(23.74)	663(24.24)	793(27.47)	941(30.78)	1018(30.73)	1034(32.15)	6785(25.93)	
Charlson Comorbidity Index1, n (%)	348(20.43)	398(19.9)	490(21.33)	508(21.38)	509(19.74)	494(18.06)	513(17.77)	558(18.25)	594(17.93)	559(17.38)	4971(19)	0,000
Charlson Comorbidity Index2, n (%)	710(41.69)	784(39.2)	925(40.27)	942(39.65)	1079(41.85)	1095(40.04)	1191(41.25)	1200(39.25)	1341(40.48)	1234(38.37)	10501(40.14)	
Charlson Comorbidity Index≥3, n (%)	645(37.87)	818(40.9)	882(38.4)	926(38.97)	990(38.4)	1146(41.9)	1183(40.98)	1299(42.49)	1378(41.59)	1423(44.25)	10690(40.86)	
Atrial fibrillation, n (%)	319(18.73)	409(20.45)	443(19.29)	454(19.11)	521(20.21)	574(20.99)	591(20.47)	639(20.9)	700(21.13)	678(21.08)	5328(20.37)	0.331
Hypertension, n (%)	780(45.8)	945(47.25)	1087(47.32)	1201(50.55)	1303(50.54)	1410(51.55)	1456(50.43)	1517(49.62)	1653(49.89)	1647(51.21)	12999(49.69)	0.001
Malnutrition, n (%)	41(2.41)	58(2.9)	85(3.7)	73(3.07)	81(3.14)	110(4.02)	127(4.4)	121(3.96)	127(3.83)	117(3.64)	940(3.59)	0.010
Pneumonia, n (%)	390(22.9)	431(21.55)	490(21.33)	536(22.56)	599(23.24)	651(23.8)	706(24.45)	768(25.12)	804(24.27)	763(23.73)	6138(23.46)	0.024
Urinary tract infection, n (%)	299(17.56)	335(16.75)	351(15.28)	392(16.5)	449(17.42)	500(18.28)	520(18.01)	578(18.91)	580(17.51)	573(17.82)	4577(17.49)	0.059
Agitation, n (%)	6(0.35)	6(0.3)	6(0.26)	4(0.17)	10(0.39)	14(0.51)	13(0.45)	13(0.43)	20(0.6)	19(0.59)	111(0.42)	0.254

N: Number of discharges; Incidence: per 100,000 inhabitants; Comorbidities included in the Charlson comorbidity index, except diabetes and dementia. P value for comparison by year. Poisson regression model for incidence rates, ANOVA for means, Pearson´s chi-square for proportions.

Hypertension was significantly more prevalent in diabetic men than in those without diabetes (49.69% and 37.31%, respectively), but atrial fibrillation, malnutrition, pneumonia and agitation were more frequent in non-diabetic men (Table 1).

The estimated adjusted incidence of discharges due to VaD in men with diabetes increased significantly from 450.73 cases in 2004 to 571.82 cases per 100,000 diabetic men in 2013. In the men without diabetes, the incidence rate increased significantly from 255.04 cases in 2004 to 335.44 cases per 100,000 non-diabetic patients in 2013. The incidences were higher among men with diabetes than those without diabetes in all the years studied (Table 1).

As can be seen in Table 1, for both groups studied, a significant increase in the mean age, higher values of CCI and an increase in the prevalence of hypertension were observed over the study period.

We found that the proportion of patients with malnutrition has significantly increased over time, ranging from 2.49% in 2004 to 5.57% in 2013 in men without T2DM, and from 2.41% to 3.64% in those with diabetes over the study period ($p<0.05$). In both diabetic and non-diabetic men, we found that pneumonia increased significantly over time. In non-diabetic men, urinary tract infections increased from 16.3% to 18.91% ($p<00.5$); however, in diabetic men this infectious complication remained stable. Agitation has remained stable over time in both groups (Table 1).

Over the study period, 54% of all VaD hospitalizations were women. The mean age for women with T2DM was significantly lower than in those without diabetes (83.17 years vs. 85.01 years). Women with T2DM had higher CCI values compared to those without diabetes (29.21% and 26.8% with three or more coexisting conditions, respectively) (Table 2).

Table 2. Characteristic, Charlson Comorbidity Index and clinical conditions among women with and without type 2 diabetes hospitalized with vascular dementia. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value
No Diabetes												
N	4489	5089	5018	5313	6007	6066	6448	6881	7167	7124	59602	<0.001
Incidence	192.92	210.3	199.7	211.44	234.61	232.59	247.23	260.71	271.55	266.76	233.75	
Age, mean (SD)	83.93(6.01)	84.19(5.99)	84.27(6.07)	84.59(5.94)	84.76(5.95)	85.16(5.88)	85.24(5.87)	85.54(5.75)	85.65(5.69)	85.88(5.79)	85.01(5.91)	<0.001
70-74 years old, n (%)	340(7.57)	310(6.09)	328(6.54)	293(5.51)	289(4.81)	266(4.39)	260(4.03)	220(3.2)	246(3.43)	214(3)	2766(4,64)	<0.001
75-79 years old, n (%)	693(15.44)	813(15.98)	770(15.34)	761(14.32)	879(14.63)	782(12.89)	844(13.09)	854(12.41)	787(10.98)	794(11.15)	7977(13,38)	
80-84 years old, n (%)	1337(29.78)	1486(29.2)	1465(29.19)	1544(29.06)	1669(27.78)	1609(26.52)	1657(25.7)	1718(24.97)	1861(25.97)	1758(24.68)	16104(27,02)	
≥85 years old, n(%)	2119(47.2)	2480(48.73)	2455(48.92)	2715(51.1)	3170(52.77)	3409(56.2)	3687(57.18)	4089(59.42)	4273(59.62)	4358(61.17)	32755(54,96)	
Charlson Comorbidity Index1, n (%)	1346(29.98)	1640(32.23)	1565(31.19)	1615(30.4)	1849(30.78)	1746(28.78)	1736(26.92)	1808(26.28)	1913(26.69)	1772(24.87)	16990(28,51)	<0.001
Charlson Comorbidity Index2, n (%)	2065(46)	2264(44.49)	2242(44.68)	2382(44.83)	2656(44.22)	2734(45.07)	2957(45.86)	3093(44.95)	3112(43.42)	3131(43.95)	26636(44,69)	
Charlson Comorbidity Index≥3, n (%)	1078(24.01)	1185(23.29)	1211(24.13)	1316(24.77)	1502(25)	1586(26.15)	1755(27.22)	1980(28.77)	2142(29.89)	2221(31.18)	15976(26,8)	
Atrial fibrillation, n (%)	1185(26.4)	1311(25.76)	1368(27.26)	1447(27.24)	1645(27.38)	1634(26.94)	1799(27.9)	2015(29.28)	2068(28.85)	2021(28.37)	16493(27.67)	<0.001
Hypertension, n (%)	1889(42.08)	2160(42.44)	2196(43.76)	2461(46.32)	2759(45.93)	2945(48.55)	2988(46.34)	3197(46.46)	3409(47.57)	3441(48.3)	27445(46.05)	<0.001
Malnutrition, n (%)	152(3.39)	205(4.03)	231(4.6)	231(4.35)	301(5.01)	317(5.23)	352(5.46)	381(5.54)	365(5.09)	406(5.7)	2941(4.93)	<0.001
Pneumonia, n (%)	783(17.44)	988(19.41)	898(17.9)	916(17.24)	1162(19.34)	1180(19.45)	1252(19.42)	1299(18.88)	1442(20.12)	1350(18.95)	11270(18.91)	<0.001
Urinary tract infection, n (%)	871(19.4)	999(19.63)	1077(21.46)	1070(20.14)	1308(21.77)	1394(22.98)	1475(22.88)	1634(23.75)	1565(21.84)	1681(23.6)	13074(21.94)	<0.001
Agitation, n (%)	13(0.29)	18(0.35)	19(0.38)	15(0.28)	27(0.45)	20(0.33)	21(0.33)	41(0.6)	21(0.29)	31(0.44)	226(0.38)	0.103
Diabetes												
N	2326	2553	2852	2920	3192	3525	3546	3841	3852	3899	32506	<0.001
Incidence	410.63	457.16	518.13	530.48	533.07	544.7	547.95	524.92	526.42	477.63	508.01	
Age, mean (SD)	82.01(5.83)	82.21(6.07)	82.43(6.06)	82.75(6)	83.12(6)	83.16(5.85)	83.35(5.75)	83.72(5.87)	83.68(5.78)	84.15(5.77)	83.17(5.92)	<0.001
70-74 years old, n (%)	270(11.61)	287(11.24)	297(10.41)	292(10)	279(8.74)	298(8.45)	242(6.82)	243(6.33)	254(6.59)	220(5.64)	2682(8,25)	<0.001
75-79 years old, n (%)	530(22.79)	584(22.88)	634(22.23)	582(19.93)	645(20.21)	667(18.92)	692(19.51)	710(18.48)	669(17.37)	600(15.39)	6313(19,42)	
80-84 years old, n (%)	742(31.9)	775(30.36)	862(30.22)	879(30.1)	911(28.54)	1063(30.16)	1093(30.82)	1144(29.78)	1165(30.24)	1179(30.24)	9813(30,19)	
≥85 years old, n(%)	784(33.71)	907(35.53)	1059(37.13)	1167(39.97)	1357(42.51)	1497(42.47)	1519(42.84)	1744(45.4)	1764(45.79)	1900(48.73)	13698(42,14)	
Charlson Comorbidity Index1, n (%)	638(27.43)	694(27.18)	776(27.21)	809(27.71)	854(26.75)	971(27.55)	934(26.34)	949(24.71)	998(25.91)	931(23.88)	8554(26,32)	<0.001
Charlson Comorbidity Index2, n (%)	1064(45.74)	1180(46.22)	1269(44.5)	1307(44.76)	1434(44.92)	1610(45.67)	1599(45.09)	1701(44.29)	1632(42.37)	1660(42.58)	14456(44,47)	
Charlson Comorbidity Index≥3, n (%)	624(26.83)	679(26.6)	807(28.3)	804(27.53)	904(28.32)	944(26.78)	1013(28.57)	1191(31.01)	1222(31.72)	1308(33.55)	9496(29,21)	
Atrial fibrillation, n (%)	594(25.54)	671(26.28)	747(26.19)	798(27.33)	880(27.57)	932(26.44)	920(25.94)	977(25.44)	1059(27.49)	1118(28.67)	8696(26.75)	0,045
Hypertension, n (%)	1237(53.18)	1429(55.97)	1643(57.61)	1672(57.26)	1871(58.62)	2106(59.74)	2077(58.57)	2159(56.21)	2180(56.59)	2177(55.83)	18551(57.07)	0,000
Malnutrition, n (%)	41(1.76)	82(3.21)	105(3.68)	107(3.66)	123(3.85)	163(4.62)	126(3.55)	173(4.5)	167(4.34)	162(4.15)	1249(3.84)	0,000
Pneumonia, n (%)	342(14.7)	385(15.08)	420(14.73)	457(15.65)	529(16.57)	634(17.99)	584(16.47)	607(15.8)	631(16.38)	650(16.67)	5239(16.12)	0,011
Urinary tract infection, n (%)	518(22.27)	592(23.19)	720(25.25)	703(24.08)	814(25.5)	920(26.1)	879(24.79)	966(25.15)	971(25.21)	962(24.67)	8045(24.75)	0,044
Agitation, n (%)	4(0.17)	8(0.31)	4(0.14)	7(0.24)	12(0.38)	6(0.17)	9(0.25)	16(0.42)	9(0.23)	16(0.41)	91(0.28)	0,266

N: Number of discharges; Incidence: per 100,000 inhabitants; Comorbidities included in the Charlson comorbidity index, except diabetes and dementia. P value for comparison by year. Poisson regression model for incidence rates, ANOVA for means, Pearson´s chi-square for proportions.

Hypertension was more frequent in women with diabetes than in women without T2DM (57.07% vs. 46.05%). However, the prevalence of atrial fibrillation was slightly higher in non-diabetic women than in diabetic ones (27.67% vs. 26.75%) (Table 2).

As can be seen in Table 2, the incidence rate of hospitalization among women with T2DM increased significantly, from 410.63 cases per 100,000 diabetic women in 2004 to 477.63 cases in 2013. Incidence rates also increased from 192.92 cases per 100,000 in 2003 to 266.76 cases in 2013 ($p<0.05$) among non-diabetic women. As seen with men, rates were consistently higher in diabetic women.

A significant increase in the mean age, comorbidity, hypertension and in the prevalence of atrial fibrillation was observed in women with and without diabetes over the study period. We found an increase in the prevalence of malnutrition, pneumonia and urinary tract infections during hospitalization in both diabetic and non-diabetic women (Table 2).

If we compare diabetic men with diabetic women, we find that men have a higher adjusted incidence rate than women in all years analyzed. Diabetic men are significantly younger (80.72 vs. 83.17 years) and have a CCI ≥3, (40.86% vs. 29.21%) in greater proportion than women over the study period. On the other hand, diabetic women showed more atrial fibrillation (26.75% vs. 20.37%) and hypertension (57.07% vs. 49.69%) than diabetic men.

The IHM among men with or without T2DM did not change significantly over the period of study, ranging from 16.62% to 14.49% in diabetic patients and from 17.08% to 16.29% in non-diabetic patients (Table 3).

Table 3. Hospitalizations outcomes, diagnosis and therapeutic procedures among men with and without type 2 diabetes hospitalized with vascular dementia. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value
No Diabetes												
In hospital mortality, n (%)	715(17.08)	770(17.07)	787(16.76)	817(16.71)	834(16.19)	847(15.84)	902(15.81)	974(16.53)	1024(17.42)	991(16.29)	8661(16.55)	0.334
LOHS, median (IQR)	9(9)	8(10)	8(9)	8(9)	8(9)	8(9)	8(9)	8(9)	7(8)	7(8)	8(9)	<0.001
Readmission, n (%)	589(14.07)	654(14.5)	725(15.44)	767(15.69)	824(15.99)	875(16.37)	896(15.71)	975(16.55)	899(15.3)	891(14.65)	8095(15.47)	0.007
CAT, n (%)	1097(26.21)	1061(23.52)	1089(23.19)	1135(23.22)	1189(23.08)	1251(23.4)	1283(22.49)	1330(22.57)	1250(21.27)	1298(21.34)	11983(22.9)	<0.001
Magnetic Resonance, n (%)	135(3.23)	146(3.24)	128(2.73)	164(3.35)	193(3.75)	178(3.33)	208(3.65)	193(3.28)	179(3.05)	179(2.94)	1703(3.25)	0.127
PEG, n (%)	36(0.86)	42(0.93)	38(0.81)	35(0.72)	43(0.83)	61(1.14)	65(1.14)	50(0.85)	50(0.85)	55(0.9)	475(0.91)	0.348
Parenteral nutrition, n (%)	71(1.7)	79(1.75)	81(1.72)	79(1.62)	98(1.9)	86(1.61)	99(1.74)	100(1.7)	94(1.6)	121(1.99)	908(1.73)	0.853
Mechanical ventilation, n (%)	32(0.76)	28(0.62)	39(0.83)	42(0.86)	50(0.97)	52(0.97)	81(1.42)	93(1.58)	129(2.19)	105(1.73)	651(1.24)	<0.001
Bladder Catheterization, n (%)	145(3.46)	147(3.26)	174(3.7)	195(3.99)	242(4.7)	273(5.11)	267(4.68)	295(5.01)	327(5.56)	338(5.56)	2403(4.59)	<0.001
Diabetes												
In hospital mortality, n (%)	283(16.62)	327(16.35)	369(16.06)	373(15.7)	373(14.47)	419(15.32)	447(15.48)	469(15.34)	476(14.37)	466(14.49)	4002(15.3)	0.303
LOHS, median (IQR)	8(9)	9(9)	8(9)	8(9)	8(9)	8(9)	8(9)	7(8)	7(8)	7(8)	8(9)	<0.001
Readmission, n (%)	288(16.91)	358(17.9)	407(17.72)	416(17.51)	433(16.8)	481(17.59)	493(17.08)	555(18.16)	556(16.78)	518(16.11)	4505(17.22)	0.633
CAT, n (%)	433(25.43)	518(25.9)	568(24.73)	538(22.64)	603(23.39)	665(24.31)	673(23.31)	732(23.95)	756(22.82)	775(24.1)	6261(23.93)	0.169
Magnetic Resonance, n (%)	60(3.52)	81(4.05)	96(4.18)	81(3.41)	105(4.07)	107(3.91)	117(4.05)	114(3.73)	108(3.26)	109(3.39)	978(3.74)	0.561
PEG, n (%)	9(0.53)	16(0.8)	15(0.65)	11(0.46)	21(0.81)	24(0.88)	14(0.48)	29(0.95)	28(0.85)	38(1.18)	205(0.78)	0.057
Parenteral nutrition, n (%)	31(1.82)	29(1.45)	33(1.44)	37(1.56)	30(1.16)	44(1.61)	55(1.91)	31(1.01)	51(1.54)	59(1.83)	400(1.53)	0.134
Mechanical ventilation, n (%)	7(0.41)	14(0.7)	20(0.87)	17(0.72)	28(1.09)	31(1.13)	33(1.14)	46(1.5)	63(1.9)	40(1.24)	299(1.14)	<0.001
Bladder Catheterization, n (%)	48(2.82)	77(3.85)	68(2.96)	110(4.63)	88(3.41)	117(4.28)	132(4.57)	168(5.5)	156(4.71)	183(5.69)	1147(4.38)	<0.001

LOHS: length of hospital stay; CAT: Computed tomography angiography; PEG: Percutaneous Endoscopic Gastrostomy. P value for comparison by year: Binary logistic regression for incidence, Kruskal-Wallis for medians, Pearson´s chi-square for proportions.

The mean LOHS decreased significantly from 9 days in 2004 to 7 days in 2013 in non-diabetic men and from 8 to 7 days in diabetic men ($p<0.05$). Readmissions remained stable approximately 17% over time for diabetic patients, while they slightly increased in non-diabetic men ranging from 14.07% in 2004 to 14.65% in 2013 ($p<0.05$).

As can be seen in Table 3, a significant increase in the use of bladder catheterization was found in diabetic men, raising from 2.82% in 2004 to 5.69% in 2013, and from 3.46% to 5.56% in the same period among those without the disease. The use of PEG has remained stable at approximately 1% of hospitalizations due to VaD, both in diabetic and non-diabetic patients. However, there has been a significant increase in the use of mechanical ventilation in diabetic and non-diabetic men, ranging from 0.41% and 0.76% in 2004 to 1.24% and 1.73% in 2013, respectively.

Of the diagnostic procedures analyzed, the most commonly used was CAT (22.9% in non-diabetic men and 23.93% in diabetic ones) followed by magnetic resonance (3.25% and 3.74%, respectively). The use of CAT in non-diabetic men has significantly decreased, while it has remained stable in diabetic men over the study period.

The IHM among diabetic women with a VaD discharge did not change significantly over the study period, as can be seen in Table 4. However, in women without diabetes the IHM decreased significantly from 16.08% in 2004 to 14.42% in 2013. Over the 10-year study period, the LOHS in women with and without diabetes decreased significantly ($p<0.05$). We found that readmissions significantly increased in non-diabetic women, ranging from 11.63% in 2004 to 13.64% in 2013, while it remained stable over time for diabetic women.

Table 4. Hospitalizations outcomes, diagnosis and therapeutic procedures among women with and without type 2 diabetes hospitalized with vascular dementia. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value
No Diabetes												
In hospital mortality, n (%)	722(16.08)	846(16.62)	747(14.89)	772(14.53)	947(15.76)	928(15.3)	920(14.27)	1042(15.14)	1085(15.14)	1027(14.42)	9036(15.16)	0.008
LOHS, median (IQR)	8(9)	8(9)	8(9)	8(9)	8(9)	8(9)	7(9)	7(8)	7(7)	7(7)	8(9)	<0.001
Readmission, n (%)	522(11.63)	591(11.61)	641(12.77)	686(12.91)	779(12.97)	769(12.68)	910(14.11)	963(14)	1026(14.32)	972(13.64)	7859(13.19)	<0.001
CAT, n (%)	1109(24.7)	1182(23.23)	1214(24.19)	1280(24.09)	1364(22.71)	1338(22.06)	1503(23.31)	1525(22.16)	1497(20.89)	1570(22.04)	13582(22.79)	<0.001
Magnetic Resonance, n (%)	118(2.63)	120(2.36)	120(2.39)	136(2.56)	178(2.96)	165(2.72)	150(2.33)	202(2.94)	147(2.05)	181(2.54)	1517(2.55)	0.027
PEG, n (%)	47(1.05)	45(0.88)	48(0.96)	54(1.02)	57(0.95)	67(1.1)	77(1.19)	64(0.93)	93(1.3)	51(0.72)	603(1.01)	0.058
Parenteral nutrition, n (%)	76(1.69)	105(2.06)	116(2.31)	106(2)	110(1.83)	134(2.21)	133(2.06)	133(1.93)	134(1.87)	126(1.77)	1173(1.97)	0.378
Mechanical ventilation, n (%)	30(0.67)	20(0.39)	27(0.54)	23(0.43)	35(0.58)	43(0.71)	51(0.79)	91(1.32)	106(1.48)	96(1.35)	522(0.88)	<0.001
Bladder Catheterization, n (%)	79(1.76)	97(1.91)	126(2.51)	147(2.77)	168(2.8)	192(3.17)	229(3.55)	241(3.5)	222(3.1)	275(3.86)	1776(2.98)	<0.001
Diabetes												
In hospital mortality, n (%)	343(14.75)	383(15)	408(14.31)	447(15.31)	452(14.16)	516(14.64)	484(13.65)	530(13.8)	562(14.59)	541(13.88)	4666(14.35)	0.641
LOHS, median (IQR)	8(9)	8(9)	8(9)	8(9)	8(9)	8(8)	7(9)	7(8)	7(7)	7(7)	8(9)	<0.001
Readmission, n (%)	314(13.5)	370(14.49)	433(15.18)	452(15.48)	503(15.76)	594(16.85)	548(15.45)	625(16.27)	612(15.89)	594(15.23)	5045(15.52)	0.641
CAT, n (%)	625(26.87)	650(25.46)	737(25.84)	728(24.93)	802(25.13)	838(23.77)	819(23.1)	955(24.86)	805(20.9)	869(22.29)	7828(24.08)	<0.001
Magnetic Resonance, n (%)	49(2.11)	52(2.04)	81(2.84)	55(1.88)	86(2.69)	97(2.75)	101(2.85)	118(3.07)	98(2.54)	91(2.33)	828(2.55)	0.037
PEG, n (%)	22(0.95)	22(0.86)	20(0.7)	32(1.1)	31(0.97)	37(1.05)	43(1.21)	34(0.89)	39(1.01)	24(0.62)	304(0.94)	0.290
Parenteral nutrition, n (%)	63(2.71)	63(2.47)	72(2.52)	43(1.47)	66(2.07)	79(2.24)	59(1.66)	81(2.11)	60(1.56)	65(1.67)	651(2)	0.002
Mechanical ventilation, n (%)	9(0.39)	12(0.47)	17(0.6)	14(0.48)	21(0.66)	28(0.79)	41(1.16)	63(1.64)	54(1.4)	41(1.05)	300(0.92)	<0.001
Bladder Catheterization, n (%)	58(2.49)	58(2.27)	71(2.49)	90(3.08)	87(2.73)	105(2.98)	106(2.99)	139(3.62)	138(3.58)	163(4.18)	1015(3.12)	<0.001

LOHS: length of hospital stay; CAT: Computed tomography angiography; PEG: Percutaneous Endoscopic Gastrostomy. P value for comparison by year: Binary logistic regression for incidence, Kruskal-Wallis for medians, Pearson´s chi-square for proportions.

As observed for men, we found a significant increase in the use of mechanical ventilation, from 0.39% to 1.05% in diabetic women and from 0.67% to 1.35% in non-diabetic women with VaD over the study period. The most commonly used diagnostic procedure was CAT for both groups of women. However, it was used in a higher proportion among those women with rather than without diabetes in all the years studied. The use of magnetic resonance has increased in diabetic women over time.

When we compared hospitalization outcomes between diabetic men and women, we found higher crude IHM among men than women in the total study population (15.3% vs. 14.35%), in all the years studied. Readmission rates were also significantly higher among men than women (17.22% vs. 15.52%). The use of magnetic resonance was used in a significantly higher proportion of diabetic men than diabetic women (3.74% vs. 2.55%), and PEG was more frequently used among diabetic women (0.94% vs. 0.78%).

The Poisson regression models conducted to assess the effect of the disease on the incidence of VaD hospitalizations from 2004 to 2013 in Spain, yielded an IRR for men with T2DM of 2.14 (95% CI 2.11-1.16). This means that, after adjusting for possible confounders, the incidence among diabetic men was 2-fold higher than among non-diabetic men. The corresponding figure for women was 0.75 (95% CI 0.74-0.76).

As can be seen in Table 5, among men and women with diabetes, IHM was significantly greater in older subjects (OR 1.48; 95% CI 1.38-1.59 and OR 1.54; 95% CI 1.40-1.69 in ≥85 aged group compared with reference category of 70-74 years, respectively). IHM was significantly higher in diabetic men and women with more comorbidities (OR 1.35; 95% CI, 1.27-1.42 and OR 1.62; 95% CI, 1.54-1.70 for those men and women with ≥3 comorbidities). IHM was also significantly higher in those men and women with pneumonia (OR 2.5; 95% CI, 2.44-2.65 and OR 2.64; 95% CI, 2.53-2.75) and in those with atrial fibrillation (OR 1.15; 95% CI, 1.09-1.20 and OR 1.21; 95% CI 1.16-1.26, respectively).

Table 5. Factors associated to in hospital mortality among men and women with and without type 2 diabetes hospitalized with vascular dementia. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

		Men	Woman	BOTH
		OR (95CI%)	OR (95CI%)	OR (95CI%)
Sex	Men	NA	NA	1.01(0.98-1.04)
Age group	70-74 years	1	1	1
	75-79 years	1.07(0.99-1.15)	1.11(1.01-1.23)	1.08(1.052-1.15)
	80-84 years	1.24(1.15-1.33)	1.24(1.13-1.37)	1.24(1.17-1.31)
	≥85 years	1.48(1.38-1.59)	1.54(1.40-1.69)	1.51(1.42-1.60)
Charlson Comorbidity Index	One	1	1	1
	Two	1.11(1.05-1.17)	1.23(1.17-1.29)	1.18(1.13-1.22)
	Three o over	1.35(1.27-1.42)	1.62(1.54-1.70)	1.49(1.43-1.54)
Atrial fibrillation		1.15(1.09-1.20)	1.21(1.16-1.26)	1.18(1.15-1.22)
Hypertension		0.83(0.80-0.87)	0.87(0.84-0.90)	0.85(0.83-0.87)
Malnutrition		0.91(0.83-1.00)	0.91(0.83-0.99)	0.91(0.85-0.97)
Pneumonia		2.55(2.44-2.65)	2.64(2.53-2.75)	2.59(2.52-2.67)
Urinary tract infection		0.85(0.81-0.90)	0.79(0.75-0.83)	0.82(0.79-0.85)
LOHS (days)		0.98(0.97-0.99)	0.98(0.97-0.99)	0.98(0.97-0.99)
Readmission		1.45(1.38-1.52)	1.38(1.31-1.44)	1.41(1.36-1.46)
CAT		0.69(0.66-0.73)	0.67(0.64-0.71)	0.68(0.66-0.71)
Magnetic Resonance		0.37(0.31-0.45)	0.25(0.20-0.32)	0.32(0.27-0.37)
PEG		0.44(0.34-0.57)	0.32(0.24-0.42)	0.37(0.31-0.45)
Parenteral nutrition		1.45(1.27-1.66)	1.17(1.03-1.32)	1.29(1.18-1.41)
Mechanical ventilation		2.98(2.59-3.43)	2.67(2.29-3.11)	2.83(2.55-3.14)
Type 2 Diabetes		0.99(0.95-1.04)	1.01(0.97-1.05)	1.00(0.98-1.03)
Year		0.97(0.96-0.98)	0.97(0.96-0.98)	0.97(0.96-0.98)

LOHS: length of hospital stay; CAT: Computed tomography angiography; PEG: Percutaneous Endoscopic Gastrostomy

The diabetic men and women who received mechanical ventilation had a higher probability of dying (2.98-fold and 2.67-fold, respectively) during their hospital stay than those who did not undergo this procedure. The use of PEG was associated with a reduced IHM among both diabetic men and women admitted for VaD (OR 0.44; 95% CI, 0.34-0.45 and OR 0.32; 95% CI, 0.24-0.42, respectively). In contrast, patients who received parenteral nutrition were more

likely to die during their stay (OR 1.45; 95% CI, 1.27-1.66 and OR 1.17; 95% CI, 1.03-1.32, respectively).

Time-trend analysis showed a significant decrease in IHM from 2004 to 2013 in diabetic men and women (OR 0.97; 95% CI 0.96-0.98). When we analyzed the entire database, and after adjusting for all covariates, suffering from diabetes was not associated with a higher IHM in either men or women (OR 0.99; 95% CI, 0.95-1.04 and OR 1.01; 95% CI 0.97-1.05).

DISCUSSION

In this study of more than 170,000 admissions for VaD, we found that the prevalence of T2DM among men and women hospitalized has increased over time in all age groups. This finding is not surprising because the prevalence of diabetes and dementia are both rapidly increasing. [2,6]

The association between diabetes and the risk of dementia has received much attention in epidemiological studies. Ohara et al. reported an increase in the prevalence of all-cause dementia in the Japanese population, [16] and diabetes was also identified as a significant risk factor. Growing evidence in support of a biological relationship between diabetes and VaD suggests a multifactorial pathogenesis that involves insulin metabolism, hyperglycemic toxicity, chronic inflammation and vascular changes. [16,17] Diabetes is a known risk factor for microvascular and macrovascular complications including stroke; [18] this suggests that the relationship between diabetes and VaD is robust and not only driven by confounding. In our study, age was the most strongly associated factor for VaD, and diabetic patients were significantly younger than non-diabetic ones. Previous research has shown that patients with both VaD and T2DM have a significantly earlier onset of VaD, a faster rate of cognitive decline and a greater prevalence of neuropsychiatric symptoms than patients with VaD alone. [19] In our study we found, as expected, a higher prevalence of hypertension among diabetic patients compared to non-diabetics. It has been reported that arterial stiffness and small vessel

disease can predict future cognitive decline in elderly people with T2DM. [20]Over time, we observed that people admitted to the hospital due to VaD were progressively older, with increasing comorbid conditions and more hospital readmissions, which highlight the increasing frailty of these patients. A link between comorbidity and the risk of dementia in diabetic patients has also been published. [21]To further decrease the medical and social economic burden associated with dementia, it seems necessary to focus on chronic disease prevention.

Infections, diabetes or their complications have been highlighted as common reasons for hospital admission in patients with dementia. [22] In our study, pneumonia and urinary tract infections significantly increased over the study period. The use of bladder catheterization has significantly increased over time, which can contribute to the higher observed prevalence of urinary tract infections, but they are not associated with higher mortality. However, pneumonia is one of the infectious complications that has significantly increased over the study period and is also associated with a worse prognosis. The use of mechanical ventilation has also significantly increased, and it is also associated with higher IHM. This finding is relevant because it seems to be a bidirectional relationship: hospitalization with pneumonia has been associated with dementia and persistent cognitive dysfunction with severe infections. [23] On the other hand, dysphagia occurs frequently in patients with dementia and is related to aspiration pneumonia. Interestingly, we have found lower mortality in patients fed by PEG. This protective effect could be associated with a better nutritional and hydration status and potentially lower rates of aspiration pneumonia, but this is only a hypothesis because our study was not designed to evaluate the association between PEG and pneumonia. Furthermore, there is controversial evidence on this issue. Finucane et al. found no data to suggest that tube feeding of patients with advanced dementia prevented aspiration pneumonia, prolonged survival or provided palliation, [24] while Nakajoh et al. showed that

the incidence of pneumonia was significantly higher in stroke patients with dysphagia who were fed orally compared to those who received tube feeding (54.3 vs. 13.2%,p<0.001). [25]

As has been described previously for ischemic and hemorrhagic stroke, we have not found an increased IHM due to VaD in patients with diabetes compared to those without. [18,26] Despite the fact that obesity is recognized as a major risk factor in the development of cardiovascular diseases and diabetes, a higher BMI may be associated with a lower mortality and a better outcome in several chronic diseases. [27-29] During the past decade, there has been increasing evidence that patients, especially the elderly, with several chronic diseases and elevated BMI may demonstrate lower all-cause and cardiovascular mortality compared with patients of normal weight. [27] This observation has been referred to as “the obesity paradox”. [28,29] The protective effect of nutritional status in overweight and obese elderly individuals, and the health-deteriorating effects of undernutrition in non-overweight subjects, probably contribute to this paradox. Although unfortunately in our study the BMI of patients admitted for VaD was not registered, this could be a possible explanation. This hypothesis concerning a better nutritional status is consistent with the better outcomes described above in those patients undergoing PEG.

The strength of our investigation lies in its large sample size, its 10-year follow-up period and its standardized methodology. [30] Nevertheless, our study is subject to a series of limitations. CMBD contains administrative discharge data for hospitalizations and uses information that physician included in the discharge report. Therefore, we lack information on relevant variables that may act as confounders, such as VaD or T2DM duration, treatments for this last condition or sociodemographic characteristics, among others.

Another important limitation is the lack of specificity of clinically defined VaD. The cognitive impairment observed in VaD and AD plus atherosclerosis might overlap extensively. We are aware that considering other databases, such as mortality registries, in

addition to discharge data would be advisable in order to detect patients with VaD dying outside of a hospital, especially at nursing homes. Unfortunately, in Spain this process is still unavailable for us.

CONCLUSIONS

Our national data show that the incidence of VaD increased significantly during the period of study. People with T2DM have more than double the risk of VaD after adjusting for other risk factors. Patients admitted with VaD were progressively older and had multiple comorbidities. Pneumonia was associated with poorer prognosis, and the use of PEG was associated with reduced mortality. Diabetes was not associated with IHM, and the time-trends show that mortality is decreasing over time.

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CONTRIBUTIONS

NMR, RJG and ALdA researched data, contributed to the discussion, wrote the manuscript, and reviewed/edited the manuscript. VHB researched data and reviewed/edited the manuscript. NMR-MMB-JMdMY-JdMD-RJG-ALdA contributed to the discussion and reviewed/edited the manuscript.

All authors reviewed and gave their final approval of the version to be submitted.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

"No additional data available"

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SUPPLEMENTARY METHODS

We calculated the adjusted incidence of discharge rates after vascular dementia (VaD) for men and women with and without type 2 diabetes (T2DM) per 100,000 inhabitants. We calculated yearly diabetes-specific incidence rates dividing the number of cases per year, sex, and age group by the corresponding number of people in that population group, using age- and sex-adjusted estimated prevalence of diabetes obtained from National Health Surveys (NHS) conducted in 2003/4, 2006/7, 2009/10 and 2011/12 and data from Di@bet.es Study. [1,2] From 2001 till 2010, Spanish NHS has been published every two or three years. So diabetic population for the missing years was estimated assuming that growth rate was the same thorough the period 2004-2013. We estimated rate fitting a linear regression model with population from years when NHS was available and we used this model to impute population for 2005, 2008 and 2013. We also calculated the yearly age- and sex-specific incidence rates for non-diabetic patients dividing the number of cases per year, sex, and age group by the corresponding number of people in that population group (excluding those with T2DM), according to data from the Spanish National Institute of Statistics, as reported on December 31 of each year. [3] All incidences were adjusted to the year 2013 population.

Clinical characteristics included information on overall comorbidity at the time of diagnosis, which was assessed by calculating the Charlson Comorbidity Index (CCI). [4] The index applies to 17 disease categories, the scores of which are added to obtain an overall score for each patient. We divided patients into three categories: low index, which corresponds to patients with no previously recorded disease or with one disease category; medium index, patients with two categories; and high index, patients with three or more disease categories.

To calculate the CCI we used 15 disease categories, excluding diabetes and dementia as described by Thomsen et al. [5]

Statistical analysis

A descriptive statistical analysis was performed for all continuous variables and categories by stratifying discharges for vascular dementia according to diabetes status and sex. Variables are shown as proportions, means with standard deviations or medians with interquartile ranges (LOHS). Bivariate analyses of variables according to year was using $\chi 2$ linear trend analysis (proportions), ANOVA (means) and Kruskall-Wallis test (medians), as appropriate. To assess differences between those men and women with and without T2DM, for each year and for the total sample, the statistical tests conducted for continuous variables were the T test for normal distributions and the Mann–Whitney test for non-normal distributions and categorical variables were compared using the Chi-square test.

In order to test the time trend in the incidence due to VaD, we fitted separate Poisson regression models for men and women with and without T2DM, using year of discharge, age, CCI, hypertension, atrial fibrillation, infectious complications, malnutrition, agitation, diagnostic and therapeutic procedures and readmission as independent variables. So that estimates correspond to Incidence Rate Ratio (IRR) with their 95% confidence intervals. The inclusion of year of discharge allow us to estimate the average yearly rate of change.

For IHM, logistic regression analyses were performed for men and women with mortality as a binary outcome for those with and without diabetes and for the entire population to assess the influence of diabetes on IHM. The independent variables included in the model were those that showed a significant association in the bivariate analysis or considered relevant in the medical literature.

Statistical analyses were performed using Stata version 10.1 (Stata, College Station, Texas, USA). Statistical significance was set at $p<0.05$ (2-tailed).

Ethics

Data confidentiality was maintained at all times in accordance with Spanish legislation. Patient identifiers were deleted before the database was provided to the authors in order to maintain patient anonymity. It is not possible to identify patients on individual levels, either in this article or in the database. Given the anonymous and mandatory nature of the dataset, it was not necessary to obtain informed consent. The study protocol was approved by the ethics committee of the Universidad Rey Juan Carlos.

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Supplementary Table. Incidence of hospitalizations with vascular dementia among people with and without type 2 diabetes according to sex and age groups. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

Rate* 100.000/Inh	Diabetes	Age group	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value
Men	No	70-74	94.44	89.32	81.36	84.92	95.68	82.91	83.57	68.93	79.45	74.1	83.66	<0.001
		75-79	210.88	211.6	198.33	191.4	208.25	202.8	201.93	247.69	216.9	260.87	213.09	<0.001
		80-84	436.5	423.05	390.5	389.72	413.81	429.29	485.58	437.61	430.23	392.87	421.69	0.372
		≥85	652.21	689.83	753.13	862.05	789.82	834.04	895.58	866.84	903.98	886.14	824.15	<0.001
	Yes	70-74	220.31	245.77	266.13	243.04	247.71	252.27	222.66	237.99	240.44	223.93	240.19	0.341
		75-79	437.4	496.19	538.43	592.83	527.72	482.81	463.28	434.65	471.01	407.09	479.19	<0.001
		80-84	684.81	788.86	901.56	828.49	945.7	1000.27	1121.94	864.39	964.72	773.21	887.28	0.001
		≥85	1191.79	1032.39	954.29	1182.21	1218.95	1239.99	1483.13	1473.93	1594.54	1393.17	1308.71	<0.001
	Both	70-74	118.32	119.00	116.41	114.92	126.4	119.45	113.57	104.22	113.05	104.32	115.09	0.001
		75-79	255.79	264.71	258.39	262.29	271.96	264.86	259.85	297.95	285.21	308.52	272.4	<0.001
		80-84	485.99	490.81	479.62	466.23	510.86	538.25	607.01	525.27	540.02	475.06	511.78	<0.001
		≥85	720.61	745.45	792.37	924.5	868.51	904.76	997.94	980.44	1033.2	986.38	911.42	<0.001
Women	No	70-74	37.79	34.39	36.32	32.45	33.88	33.13	32.38	28.49	31.86	28.86	33.12	<0.001
		75-79	109.37	115.35	99.22	98.06	112.88	100.08	108.01	108.95	100.4	100.98	105.16	0.118
		80-84	301.13	309.31	283.44	298.72	313.54	293.75	302.52	298.33	323.16	291.05	301.48	0.593
		≥85	606.23	744.35	774.9	856.96	799.7	716.21	774.61	805.93	842.19	808.91	776.52	<0.001
	Yes	70-74	125.2	148.93	174.96	172.02	157.77	162.02	131.58	107.16	112.02	81.61	133.06	<0.001
		75-79	277.62	303.68	327.3	300.46	315.38	309.76	321.37	327.01	308.12	274.08	306.61	0.894
		80-84	877.79	782.59	759.27	774.24	699.39	723.21	743.62	719.43	732.64	689.29	741.21	<0.001
		≥85	1040.53	1219.07	1441.66	1588.68	1556.53	1483.56	1505.36	1353.57	1369.1	1211.87	1369.63	0.660
	Both	70-74	54.69	54.57	58.26	54.53	55.15	57.15	50.87	46.35	50.05	42.92	52.55	<0.001
		75-79	148.33	155.72	144.78	138.49	155	145.38	154.11	156.25	145.46	138.68	148.16	0.375
		80-84	393.36	390.19	369.13	384.36	389.4	384.61	395.84	389.45	411.76	378.94	388.82	0.246
		≥85	683.25	831.01	900.4	994.69	936.14	850.43	902.43	916.84	948.9	899.74	890.19	<0.001

Adjusted incidence per 100,000 inhabitants. P value for time trend using Poisson regression

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4,5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	Supplementary methods
Study size	10	Explain how the study size was arrived at	4,5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Supplementary methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Supplementary methods
		(*b*) Describe any methods used to examine subgroups and interactions	Supplementary methods
		(*c*) Explain how missing data were addressed	Supplementary

			methods
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-16
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-16
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	5-16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-16
		(*b*) Report category boundaries when continuous variables were categorized	5-16
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Observational study of vascular dementia in the Spanish elderly population according to type 2 diabetes status: trends in incidence, characteristics and outcomes (2004-2013)

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Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Type 2 diabetes, Vascular dementia, Hospitalization, In-hospital mortality

Observational study of vascular dementia in the Spanish elderly population according to type 2 diabetes status: trends in incidence, characteristics and outcomes (2004-2013)

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Key Words: Type 2 diabetes; Vascular dementia; Hospitalization; In-hospital mortality

Word count: 3,536

ABSTRACT

Objectives: To examine trends in the incidence and outcomes of vascular dementia (VaD) hospitalizations in elderly patients with and without type 2 diabetes (T2DM) in Spain, 2004-2013.

Design: Retrospective study.

Setting: Spain.

Participants: We used national hospital discharge data to select all patients aged ≥70 discharged from a hospital with VaD as a primary diagnosis.

Main outcome measures: Overall incidence, diagnostic and therapeutic procedures, patient comorbidities, infectious complications, length of hospital stays and in-hospital mortality (IHM).

Results: We identified a total of 170,607 admissions for VaD (34.3% with T2DM). We found a significant upward linear trend in the incidence of VaD for men and women with and without diabetes from 2004 to 2013.The adjusted incidence was higher among people with T2DM over the study period. We found a higher incidence in men than women in all years studied. T2DM was positively associated with VaD hospitalization among men (IRR 2.14, 95%CI 2.11-2.16) and for women (IRR 2.22; 95% CI 2.19-2.25).

Pneumonia was significantly associated with a higher mortality (OR 2.59, 95%CI 2.52 -2.67). We found that percutaneous endoscopic gastrostomy was associated with lower IHM (OR 0.37, 95%CI 0.31-0.45), while parenteral nutrition had the opposite effect (OR 1.29, 95%CI 1.18-1.41). Diabetes was not associated with higher IHM (OR 0.99, 95%CI 0.93–1.06). For the entire sample, time-trend analyses showed a significant decrease in mortality in patients admitted for VaD (OR 0.98, 95%CI 0.97–0.99).

Conclusions: Incidence rates for VaD hospitalizations were twice as high in diabetic patients compared to non-diabetics. Men had significantly higher incidence rates than women,

regardless of diabetes status. In both groups studied, pneumonia and parenteral nutrition were associated with mortality while percutaneous endoscopic gastrostomy was associated with survival. The presence of diabetes was not associated with higher IHM during hospitalization with VaD.

Strengths and limitations of this study

- The strength of our investigation lies in its large sample size, the 10-year follow-up period, and the standardized methodology.
- A limitation is the lack of information on VaD or T2DM duration, treatments for this last condition or sociodemographic characteristic.
- Another limitation is the lack of specificity of clinically defined VaD.

INTRODUCTION

Dementia has become a significant global economic, social, and public health burden. [1,2] The most common types of dementia are vascular dementia (VaD) and Alzheimer's disease (AD), which together account for more than 90% of all cases. [1]

Several epidemiological studies have also demonstrated that diabetic patients are at an increased risk for stroke, lacunar infarcts, AD and VaD [3-5] through Aβ/tau-dependent and independent mechanisms. [3]

Type 2 diabetes mellitus (T2DM), which affects more than 300 million people worldwide, [6] increases the risk of macrovascular and microvascular complications, and it is also an independent risk factor for vascular dementia [7,8] and AD. [9] It has recently been published that diabetic patients have a 60% greater risk for the development of dementia. [10] Factors reportedly linked with dementia include age, smoking, hypertension and diabetes, therefore it is only to be expected that hospitalization for VaD will increase in the coming years. [11,12] For this reason, it seems necessary to analyze the evolution of VaD over time and to evaluate which factors and procedures may increase in-hospital mortality (IHM).

In this study, we used national hospital discharge data to examine linear trends in the incidence of VaD among hospitalized men and women with and without T2DM between 2004 and 2013 in Spain. In particular, we analyzed linear trends in the use of diagnostic and therapeutic procedures, patient comorbidities, common infectious and medical complications and in-hospital outcomes such as length of hospital stay (LOHS), readmission rates and IHM.

METHODS

This retrospective, observational study was conducted using the Spanish National Hospital Database (CMBD, *Conjunto Minimo Básico de Datos*). [13] We selected all patients aged ≥70 years hospitalized for VaD (ICD-9-CM codes: 290.40, 290.41, 290.42, 290.43) as the primary diagnosis between January 1, 2004 and December 31, 2013.

Discharges were grouped by diabetes status as follows: T2DM (codes: 250.x0; 250.x2) and no diabetes.

We calculated the adjusted incidence of discharge rates after VaD for men and women with and without T2DM per 100,000 inhabitants, as described in detail in the Supplementary Methods.

Clinical characteristics included information on overall comorbidity at the time of diagnosis, which was assessed by calculating the Charlson Comorbidity Index (CCI) [14] as described in detail in the Supplementary Methods.

We specifically analyzed the presence of previous stroke (ICD 9MD codes 430.x, 431.x, 433.x1, 434.x1, 435.x, 436, and 362.3), hypertension (codes: 401, 401.0, 401.1, 401.9) and atrial fibrillation (code: 427.31) in any diagnosis position during vascular dementia hospitalization. We also identified common infectious complications such as pneumonia (codes: 480-488, 507.0-507.8) and urinary tract infection (codes: 590.0, 590.9, 595.0, 595.9, 597.80, 599.0). We analyzed other medical complications, specifically agitation (code: 307.9) and malnutrition (code: 263.9).

We identified the following diagnostic and therapeutic procedures: magnetic resonance (code: 88.91), computed tomography angiography (CAT) (code: 87.03), percutaneous endoscopic gastrostomy (PEG) (code: 43.11), mechanical ventilation (codes: 96.7; 96.70; 96.71; 96.72), parenteral nutrition (codes: 99.15) and bladder catheterization (code: 57.94).

Patient readmissions were defined as inpatient re-hospitalization within 30 days of discharge (30-day readmission). The mean LOHS and the proportion of patients who died during the hospital admission, IHM, were also estimated for each year studied.

Statistical analysis is described in the Supplementary Methods.

ETHICS

Data confidentiality was maintained at all times in accordance with Spanish legislation.

Patient identifiers were deleted before the database was provided to the authors in order to maintain patient anonymity. It is not possible to identify patients on individual levels, either in this article or in the database. Given the anonymous and mandatory nature of the dataset, it was not necessary to obtain informed consent according to the Spanish legislation. The study protocol was approved by the ethics committee of the Universidad Rey Juan Carlos.

RESULTS

We identified a total of 170,607 discharges of patients (78,499 men and 92,108 women) admitted with VaD as the primary diagnosis. Patients with T2DM accounted for 34.3% of the total. The prevalence of T2DM in men with VaD increased significantly during the study period, from 28.94% in 2004 to 34.58% in 2013 ($p<0.01$). The prevalence of diabetes in women with VaD increased from 34.13% to 35.37% ($p<0.01$).

The overall adjusted incidence of admissions for VaD was higher among the oldest subgroup (≥85 years), both in men and women, diabetic and non-diabetic. In T2DM patients older than 85 years, we found that incidence rates were 1,369.63 per 100,000 inhabitants in women and 1,308.71 per 100,000 inhabitants in men. In the non-diabetic group, incidence rates for men and women were 776.52 and 824.15 per 100.000 inhabitants, respectively (Supplementary Table).

The adjusted incidence rate of admissions for VaD increased significantly in men with T2DM aged ≥85 years old (1,191.79 cases per 100,000 inhabitants in 2004 to 1,393.17 cases in 2013). However, there were no significant changes in the incidence of diagnosis of VaD in T2DM-women aged ≥85 years (Supplementary Table).

As can be seen in Table 1, the mean age was 80.72 years (SD, 5.65 years) in diabetic men and 82.4 years (SD,5.93 years) in men without diabetes. According to the CCI, 40.86% of men with T2DM had three or more coexisting conditions; in men without diabetes this figure was

39.3%. The percentage of men with T2DM who have two or more coexisting conditions is slightly higher than that of non-diabetic men (81% vs. 79.71%)

Table 1. Characteristic, Charlson Comorbidity Index and clinical conditions among men with and without type 2 diabetes hospitalized with vascular dementia. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value
No Diabetes												
N	4185	4511	4697	4889	5152	5346	5705	5892	5877	6083	52337	<0.001
Incidence	255.04	256.93	251.11	261.37	280.32	296.14	316.02	325.64	324.81	335.44	290.47	
Age, mean (SD)	81.28(6.01)	81.32(5.82)	81.64(5.92)	82(6.06)	81.9(5.95)	82.61(5.95)	82.78(5.83)	83.01(5.71)	83.15(5.88)	83.41(5.76)	82.4(5.93)	<0.001
70-74 years old, n (%)	626(14.96)	610(13.52)	572(12.18)	597(12.21)	630(12.23)	509(9.52)	513(8.99)	426(7.23)	491(8.35)	461(7.58)	5435(10.38)	0.000
75-79 years old, n (%)	1053(25.16)	1154(25.58)	1173(24.97)	1132(23.15)	1215(23.58)	1167(21.83)	1162(20.37)	1223(20.76)	1071(18.22)	1075(17.67)	11425(21.83)	
80-84 years old, n (%)	1247(29.8)	1413(31.32)	1493(31.79)	1490(30.48)	1541(29.91)	1556(29.11)	1760(30.85)	1839(31.21)	1808(30.76)	1878(30.87)	16025(30.62)	
≥85 years old, n(%)	1259(30.08)	1334(29.57)	1459(31.06)	1670(34.16)	1766(34.28)	2114(39.54)	2270(39.79)	2404(40.8)	2507(42.66)	2669(43.88)	19452(37.17)	
Charlson Comorbidity Index1, n (%)	934(22.32)	962(21.33)	1019(21.69)	1015(20.76)	1119(21.72)	1124(21.03)	1119(19.61)	1113(18.89)	1091(18.56)	1126(18.51)	10622(20.3)	0.000
Charlson Comorbidity Index2, n (%)	1748(41.77)	1968(43.63)	1927(41.03)	2048(41.89)	2072(40.22)	2195(41.06)	2281(39.98)	2330(39.55)	2219(37.76)	2359(38.78)	21147(40.41)	
Charlson Comorbidity Index≥3, n (%)	1503(35.91)	1581(35.05)	1751(37.28)	1826(37.35)	1961(38.06)	2027(37.92)	2305(40.4)	2449(41.56)	2567(43.68)	2598(42.71)	20568(39.3)	
Previous sroke	1963(46.91)	2114(46.86)	2320(49.39)	2305(47.15)	2528(49.07)	2649(49.55)	2949(51.69)	2976(50.51)	3059(52.05)	3148(51.75)	26011(49.70)	<0.001
Atrial fibrillation, n (%)	830(19.83)	907(20.11)	1030(21.93)	1095(22.4)	1155(22.42)	1270(23.76)	1397(24.49)	1452(24.64)	1488(25.32)	1493(24.54)	12117(23.15)	<0.001
Hypertension, n (%)	1398(33.41)	1537(34.07)	1707(36.34)	1745(35.69)	1883(36.55)	2004(37.49)	2196(38.49)	2288(38.83)	2349(39.97)	2420(39.78)	19527(37.31)	<0.001
Malnutrition, n (%)	104(2.49)	177(3.92)	185(3.94)	231(4.72)	243(4.72)	274(5.13)	251(4.4)	308(5.23)	280(4.76)	339(5.57)	2392(4.57)	<0.001
Pneumonia, n (%)	1028(24.56)	1180(26.16)	1136(24.19)	1260(25.77)	1303(25.29)	1448(27.09)	1526(26.75)	1594(27.05)	1603(27.28)	1638(26.93)	13716(26.21)	<0.001
Urinary tract infection, n (%)	682(16.3)	743(16.47)	790(16.82)	808(16.53)	881(17.1)	963(18.01)	992(17.39)	1079(18.31)	1108(18.85)	1150(18.91)	9196(17.57)	0.001
Agitation, n (%)	16(0.38)	16(0.35)	16(0.34)	24(0.49)	22(0.43)	31(0.58)	36(0.63)	34(0.58)	32(0.54)	39(0.64)	266(0.51)	0.225
Diabetes												
N	1703	2000	2297	2376	2578	2735	2887	3057	3313	3216	26162	<0.001
Incidence	450.73	501.91	548.05	566.9	578.82	579.89	612.11	591.26	640.77	571.82	568.77	
Age, mean (SD)	79.6(5.59)	79.74(5.58)	79.84(5.57)	80.2(5.6)	80.43(5.6)	80.51(5.65)	81.01(5.46)	81.37(5.62)	81.49(5.65)	81.71(5.66)	80.72(5.65)	<0.001
70-74 years old, n (%)	342(20.08)	393(19.65)	438(19.07)	400(16.84)	413(16.02)	426(15.58)	376(13.02)	388(12.69)	392(11.83)	352(10.95)	3920(14.98)	0.000
75-79 years old, n (%)	540(31.71)	621(31.05)	683(29.73)	752(31.65)	767(29.75)	791(28.92)	759(26.29)	789(25.81)	855(25.81)	811(25.22)	7368(28.16)	
80-84 years old, n (%)	487(28.6)	599(29.95)	728(31.69)	669(28.16)	786(30.49)	855(31.26)	959(33.22)	939(30.72)	1048(31.63)	1019(31.69)	8089(30.92)	
≥85 years old, n(%)	334(19.61)	387(19.35)	448(19.5)	555(23.36)	612(23.74)	663(24.24)	793(27.47)	941(30.78)	1018(30.73)	1034(32.15)	6785(25.93)	
Charlson Comorbidity Index1, n (%)	348(20.43)	398(19.9)	490(21.33)	508(21.38)	509(19.74)	494(18.06)	513(17.77)	558(18.25)	594(17.93)	559(17.38)	4971(19)	0.000
Charlson Comorbidity Index2, n (%)	710(41.69)	784(39.2)	925(40.27)	942(39.65)	1079(41.85)	1095(40.04)	1191(41.25)	1200(39.25)	1341(40.48)	1234(38.37)	10501(40.14)	
Charlson Comorbidity Index≥3, n (%)	645(37.87)	818(40.9)	882(38.4)	926(38.97)	990(38.4)	1146(41.9)	1183(40.98)	1299(42.49)	1378(41.59)	1423(44.25)	10690(40.86)	
Previous sroke	791(46.45)	992(49.6)	1071(46.63)	1099(46.25)	1267(49.15)	1437(52.54)	1476(51.13)	1517(49.62)	1660(50.11)	1695(52.71)	13005(49.71)	<0.001
Atrial fibrillation, n (%)	319(18.73)	409(20.45)	443(19.29)	454(19.11)	521(20.21)	574(20.99)	591(20.47)	639(20.9)	700(21.13)	678(21.08)	5328(20.37)	0.331
Hypertension, n (%)	780(45.8)	945(47.25)	1087(47.32)	1201(50.55)	1303(50.54)	1410(51.55)	1456(50.43)	1517(49.62)	1653(49.89)	1647(51.21)	12999(49.69)	0.001
Malnutrition, n (%)	41(2.41)	58(2.9)	85(3.7)	73(3.07)	81(3.14)	110(4.02)	127(4.4)	121(3.96)	127(3.83)	117(3.64)	940(3.59)	0.010
Pneumonia, n (%)	390(22.9)	431(21.55)	490(21.33)	536(22.56)	599(23.24)	651(23.8)	706(24.45)	768(25.12)	804(24.27)	763(23.73)	6138(23.46)	0.024
Urinary tract infection, n (%)	299(17.56)	335(16.75)	351(15.28)	392(16.5)	449(17.42)	500(18.28)	520(18.01)	578(18.91)	580(17.51)	573(17.82)	4577(17.49)	0.059
Agitation, n (%)	6(0.35)	6(0.3)	6(0.26)	4(0.17)	10(0.39)	14(0.51)	13(0.45)	13(0.43)	20(0.6)	19(0.59)	111(0.42)	0.254

N: Number of discharges; Incidence: per 100,000 inhabitants; Comorbidities included in the Charlson comorbidity index, except diabetes and dementia. P value for comparison by year. Poisson regression model for incidence rates, ANOVA for means, Pearson´s chi-square for proportions.

The prevalence of previous stroke was similar and near to 50% among men with and without diabetes in all years studied and rose significantly over time ($p<0.001$) from around 46% to 52% in both groups of patients. Hypertension was significantly more prevalent in diabetic men than in those without diabetes (49.69% and 37.31%, respectively), but atrial fibrillation, malnutrition, pneumonia and agitation were more frequent in non-diabetic men (Table 1).

The estimated adjusted incidence of discharges due to VaD in men with diabetes increased significantly from 450.73 cases in 2004 to 571.82 cases per 100,000 diabetic men in 2013. In the men without diabetes, the incidence rate increased significantly from 255.04 cases in 2004 to 335.44 cases per 100,000 non-diabetic patients in 2013. The incidences were higher among men with diabetes than those without diabetes in all the years studied (Table 1).

As can be seen in Table 1, for both groups studied, a significant increase in the mean age, higher values of CCI and an increase in the prevalence of hypertension were observed over the study period.

We found that the proportion of patients with malnutrition has significantly increased over time, ranging from 2.49% in 2004 to 5.57% in 2013 in men without T2DM, and from 2.41% to 3.64% in those with diabetes over the study period ($p<0.05$). In both diabetic and non-diabetic men, we found that pneumonia increased significantly over time. In non-diabetic men, urinary tract infections increased from 16.3% to 18.91% ($p<00.5$); however, in diabetic men this infectious complication remained stable. Agitation has remained stable over time in both groups (Table 1).

Over the study period, 54% of all VaD hospitalizations were women. The mean age for women with T2DM was significantly lower than in those without diabetes (83.17 years vs. 85.01 years). Women with T2DM had higher CCI values compared to those without diabetes (29.21% and 26.8% with three or more coexisting conditions, respectively) (Table 2).

Table 2. Characteristic, Charlson Comorbidity Index and clinical conditions among women with and without type 2 diabetes hospitalized with vascular dementia. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value
No Diabetes												
N	4489	5089	5018	5313	6007	6066	6448	6881	7167	7124	59602	
Incidence	192.92	210.3	199.7	211.44	234.61	232.59	247.23	260.71	271.55	266.76	233.75	<0.001
Age, mean (SD)	83.93(6.01)	84.19(5.99)	84.27(6.07)	84.59(5.94)	84.76(5.95)	85.16(5.88)	85.24(5.87)	85.54(5.75)	85.65(5.69)	85.88(5.79)	85.01(5.91)	<0.001
70-74 years old, n (%)	340(7.57)	310(6.09)	328(6.54)	293(5.51)	289(4.81)	266(4.39)	260(4.03)	220(3.2)	246(3.43)	214(3)	2766(4.64)	<0.001
75-79 years old, n (%)	693(15.44)	813(15.98)	770(15.34)	761(14.32)	879(14.63)	782(12.89)	844(13.09)	854(12.41)	787(10.98)	794(11.15)	7977(13.38)	
80-84 years old, n (%)	1337(29.78)	1486(29.2)	1465(29.19)	1544(29.06)	1669(27.78)	1609(26.52)	1657(25.7)	1718(24.97)	1861(25.97)	1758(24.68)	16104(27.02)	
≥85 years old, n(%)	2119(47.2)	2480(48.73)	2455(48.92)	2715(51.1)	3170(52.77)	3409(56.2)	3687(57.18)	4089(59.42)	4273(59.62)	4358(61.17)	32755(54.96)	
Charlson Comorbidity Index1, n (%)	1346(29.98)	1640(32.23)	1565(31.19)	1615(30.4)	1849(30.78)	1746(28.78)	1736(26.92)	1808(26.28)	1913(26.69)	1772(24.87)	16990(28.51)	<0.001
Charlson Comorbidity Index2, n (%)	2065(46)	2264(44.49)	2242(44.68)	2382(44.83)	2656(44.22)	2734(45.07)	2957(45.86)	3093(44.95)	3112(43.42)	3131(43.95)	26636(44.69)	
Charlson Comorbidity Index≥3, n (%)	1078(24.01)	1185(23.29)	1211(24.13)	1316(24.77)	1502(25)	1586(26.15)	1755(27.22)	1980(28.77)	2142(29.89)	2221(31.18)	15976(26.8)	
Previous sroke	2048(45.62)	2333(45.84)	2357(46.97)	2406(45.29)	2747(45.73)	2906(47.91)	3185(49.4)	3427(49.8)	3478(48.53)	3552(49.86)	28439(47.71)	<0.001
Atrial fibrillation, n (%)	1185(26.4)	1311(25.76)	1368(27.26)	1447(27.24)	1645(27.38)	1634(26.94)	1799(27.9)	2015(29.28)	2068(28.85)	2021(28.37)	16493(27.67)	<0.001
Hypertension, n (%)	1889(42.08)	2160(42.44)	2196(43.76)	2461(46.32)	2759(45.93)	2945(48.55)	2988(46.34)	3197(46.46)	3409(47.57)	3441(48.3)	27445(46.05)	<0.001
Malnutrition, n (%)	152(3.39)	205(4.03)	231(4.6)	231(4.35)	301(5.01)	317(5.23)	352(5.46)	381(5.54)	365(5.09)	406(5.7)	2941(4.93)	<0.001
Pneumonia, n (%)	783(17.44)	988(19.41)	898(17.9)	916(17.24)	1162(19.34)	1180(19.45)	1252(19.42)	1299(18.88)	1442(20.12)	1350(18.95)	11270(18.91)	<0.001
Urinary tract infection, n (%)	871(19.4)	999(19.63)	1077(21.46)	1070(20.14)	1308(21.77)	1394(22.98)	1475(22.88)	1634(23.75)	1565(21.84)	1681(23.6)	13074(21.94)	<0.001
Agitation, n (%)	13(0.29)	18(0.35)	19(0.38)	15(0.28)	27(0.45)	20(0.33)	21(0.33)	41(0.6)	21(0.29)	31(0.44)	226(0.38)	0.103
Diabetes												
N	2326	2553	2852	2920	3192	3525	3546	3841	3852	3899	32506	
Incidence	410.63	457.16	518.13	530.48	533.07	544.7	547.95	524.92	526.42	477.63	508.01	<0.001
Age, mean (SD)	82.01(5.83)	82.21(6.07)	82.43(6.06)	82.75(6)	83.12(6)	83.16(5.85)	83.35(5.75)	83.72(5.87)	83.68(5.78)	84.15(5.77)	83.17(5.92)	<0.001
70-74 years old, n (%)	270(11.61)	287(11.24)	297(10.41)	292(10)	279(8.74)	298(8.45)	242(6.82)	243(6.33)	254(6.59)	220(5.64)	2682(8.25)	<0.001
75-79 years old, n (%)	530(22.79)	584(22.88)	634(22.23)	582(19.93)	645(20.21)	667(18.92)	692(19.51)	710(18.48)	669(17.37)	600(15.39)	6313(19.42)	
80-84 years old, n (%)	742(31.9)	775(30.36)	862(30.22)	879(30.1)	911(28.54)	1063(30.16)	1093(30.82)	1144(29.78)	1165(30.24)	1179(30.24)	9813(30.19)	
≥85 years old, n(%)	784(33.71)	907(35.53)	1059(37.13)	1167(39.97)	1357(42.51)	1497(42.47)	1519(42.84)	1744(45.4)	1764(45.79)	1900(48.73)	13698(42.14)	
Charlson Comorbidity Index1, n (%)	638(27.43)	694(27.18)	776(27.21)	809(27.71)	854(26.75)	971(27.55)	934(26.34)	949(24.71)	998(25.91)	931(23.88)	8554(26.32)	<0.001
Charlson Comorbidity Index2, n (%)	1064(45.74)	1180(46.22)	1269(44.5)	1307(44.76)	1434(44.92)	1610(45.67)	1599(45.09)	1701(44.29)	1632(42.37)	1660(42.58)	14456(44.47)	
Charlson Comorbidity Index≥3, n (%)	624(26.83)	679(26.6)	807(28.3)	804(27.53)	904(28.32)	944(26.78)	1013(28.57)	1191(31.01)	1222(31.72)	1308(33.55)	9496(29.21)	
Previous sroke	1138(48.93)	1265(49.55)	1413(49.54)	1347(46.13)	1587(49.72)	1740(49.36)	1749(49.32)	1921(50.01)	1872(48.6)	1934(49.6)	15966(49.12)	0.142
Atrial fibrillation, n (%)	594(25.54)	671(26.28)	747(26.19)	798(27.33)	880(27.57)	932(26.44)	920(25.94)	977(25.44)	1059(27.49)	1118(28.67)	8696(26.75)	0.045
Hypertension, n (%)	1237(53.18)	1429(55.97)	1643(57.61)	1672(57.26)	1871(58.62)	2106(59.74)	2077(58.57)	2159(56.21)	2180(56.59)	2177(55.83)	18551(57.07)	0.000
Malnutrition, n (%)	41(1.76)	82(3.21)	105(3.68)	107(3.66)	123(3.85)	163(4.62)	126(3.55)	173(4.5)	167(4.34)	162(4.15)	1249(3.84)	0.000
Pneumonia, n (%)	342(14.7)	385(15.08)	420(14.73)	457(15.65)	529(16.57)	634(17.99)	584(16.47)	607(15.8)	631(16.38)	650(16.67)	5239(16.12)	0.011
Urinary tract infection, n (%)	518(22.27)	592(23.19)	720(25.25)	703(24.08)	814(25.5)	920(26.1)	879(24.79)	966(25.15)	971(25.21)	962(24.67)	8045(24.75)	0.044
Agitation, n (%)	4(0.17)	8(0.31)	4(0.14)	7(0.24)	12(0.38)	6(0.17)	9(0.25)	16(0.42)	9(0.23)	16(0.41)	91(0.28)	0.266

N: Number of discharges; Incidence: per 100,000 inhabitants; Comorbidities included in the Charlson comorbidity index, except diabetes and dementia. P value for comparison by year. Poisson regression model for incidence rates, ANOVA for means, Pearson´s chi-square for proportions.

Among women, the overall prevalence of previous stroke was significantly higher for diabetic than non-diabetics (49.12% vs. 47.71%). Only among women without diabetes a significant increase was found from 2004 to 2013. Hypertension was more frequent in women with diabetes than in women without T2DM (57.07% vs. 46.05%). However, the prevalence of atrial fibrillation was slightly higher in non-diabetic women than in diabetic ones (27.67% vs. 26.75%) (Table 2).

As can be seen in Table 2, the incidence rate of hospitalization among women with T2DM increased significantly, from 410.63 cases per 100,000 diabetic women in 2004 to 477.63 cases in 2013. Incidence rates also increased from 192.92 cases per 100,000 in 2003 to 266.76 cases in 2013 ($p<0.05$) among non-diabetic women. As seen with men, rates were consistently higher in diabetic women.

A significant increase in the mean age, comorbidity, hypertension and in the prevalence of atrial fibrillation was observed in women with and without diabetes over the study period. We found an increase in the prevalence of malnutrition, pneumonia and urinary tract infections during hospitalization in both diabetic and non-diabetic women (Table 2).

If we compare diabetic men with diabetic women, we find that men have a higher adjusted incidence rate than women in all years analyzed. Diabetic men are significantly younger (80.72 vs. 83.17 years) and have a CCI ≥3, (40.86% vs. 29.21%) in greater proportion than women over the study period. On the other hand, diabetic women showed more atrial fibrillation (26.75% vs. 20.37%) and hypertension (57.07% vs. 49.69%) than diabetic men.

The IHM among men with or without T2DM did not change significantly over the period of study, ranging from 16.62% to 14.49% in diabetic patients and from 17.08% to 16.29% in non-diabetic patients (Table 3).

Table 3. Hospitalizations outcomes, diagnosis and therapeutic procedures among men with and without type 2 diabetes hospitalized with vascular dementia. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value
No Diabetes												
In hospital mortality, n (%)	715(17.08)	770(17.07)	787(16.76)	817(16.71)	834(16.19)	847(15.84)	902(15.81)	974(16.53)	1024(17.42)	991(16.29)	8661(16.55)	0.334
LOHS, median (IQR)	9(9)	8(10)	8(9)	8(9)	8(9)	8(9)	8(9)	8(9)	7(8)	7(8)	8(9)	<0.001
Readmission, n (%)	589(14.07)	654(14.5)	725(15.44)	767(15.69)	824(15.99)	875(16.37)	896(15.71)	975(16.55)	899(15.3)	891(14.65)	8095(15.47)	0.007
CAT, n (%)	1097(26.21)	1061(23.52)	1089(23.19)	1135(23.22)	1189(23.08)	1251(23.4)	1283(22.49)	1330(22.57)	1250(21.27)	1298(21.34)	11983(22.9)	<0.001
Magnetic Resonance, n (%)	135(3.23)	146(3.24)	128(2.73)	164(3.35)	193(3.75)	178(3.33)	208(3.65)	193(3.28)	179(3.05)	179(2.94)	1703(3.25)	0.127
PEG, n (%)	36(0.86)	42(0.93)	38(0.81)	35(0.72)	43(0.83)	61(1.14)	65(1.14)	50(0.85)	50(0.85)	55(0.9)	475(0.91)	0.348
Parenteral nutrition, n (%)	71(1.7)	79(1.75)	81(1.72)	79(1.62)	98(1.9)	86(1.61)	99(1.74)	100(1.7)	94(1.6)	121(1.99)	908(1.73)	0.853
Mechanical ventilation, n (%)	32(0.76)	28(0.62)	39(0.83)	42(0.86)	50(0.97)	52(0.97)	81(1.42)	93(1.58)	129(2.19)	105(1.73)	651(1.24)	<0.001
Bladder Catheterization, n (%)	145(3.46)	147(3.26)	174(3.7)	195(3.99)	242(4.7)	273(5.11)	267(4.68)	295(5.01)	327(5.56)	338(5.56)	2403(4.59)	<0.001
Diabetes												
In hospital mortality, n (%)	283(16.62)	327(16.35)	369(16.06)	373(15.7)	373(14.47)	419(15.32)	447(15.48)	469(15.34)	476(14.37)	466(14.49)	4002(15.3)	0.303
LOHS, median (IQR)	8(9)	9(9)	8(9)	8(9)	8(9)	8(9)	8(9)	7(8)	7(8)	7(8)	8(9)	<0.001
Readmission, n (%)	288(16.91)	358(17.9)	407(17.72)	416(17.51)	433(16.8)	481(17.59)	493(17.08)	555(18.16)	556(16.78)	518(16.11)	4505(17.22)	0.633
CAT, n (%)	433(25.43)	518(25.9)	568(24.73)	538(22.64)	603(23.39)	665(24.31)	673(23.31)	732(23.95)	756(22.82)	775(24.1)	6261(23.93)	0.169
Magnetic Resonance, n (%)	60(3.52)	81(4.05)	96(4.18)	81(3.41)	105(4.07)	107(3.91)	117(4.05)	114(3.73)	108(3.26)	109(3.39)	978(3.74)	0.561
PEG, n (%)	9(0.53)	16(0.8)	15(0.65)	11(0.46)	21(0.81)	24(0.88)	14(0.48)	29(0.95)	28(0.85)	38(1.18)	205(0.78)	0.057
Parenteral nutrition, n (%)	31(1.82)	29(1.45)	33(1.44)	37(1.56)	30(1.16)	44(1.61)	55(1.91)	31(1.01)	51(1.54)	59(1.83)	400(1.53)	0.134
Mechanical ventilation, n (%)	7(0.41)	14(0.7)	20(0.87)	17(0.72)	28(1.09)	31(1.13)	33(1.14)	46(1.5)	63(1.9)	40(1.24)	299(1.14)	<0.001
Bladder Catheterization, n (%)	48(2.82)	77(3.85)	68(2.96)	110(4.63)	88(3.41)	117(4.28)	132(4.57)	168(5.5)	156(4.71)	183(5.69)	1147(4.38)	<0.001

LOHS: length of hospital stay; CAT: Computed tomography angiography; PEG: Percutaneous Endoscopic Gastrostomy. P value for comparison by year: Binary logistic regression for incidence, Kruskal-Wallis for medians, Pearson´s chi-square for proportions.

The mean LOHS decreased significantly from 9 days in 2004 to 7 days in 2013 in non-diabetic men and from 8 to 7 days in diabetic men ($p<0.05$). Readmissions remained stable approximately 17% over time for diabetic patients, while they slightly increased in non-diabetic men ranging from 14.07% in 2004 to 14.65% in 2013 ($p<0.05$).

As can be seen in Table 3, a significant increase in the use of bladder catheterization was found in diabetic men, raising from 2.82% in 2004 to 5.69% in 2013, and from 3.46% to 5.56% in the same period among those without the disease. The use of PEG has remained stable at approximately 1% of hospitalizations due to VaD, both in diabetic and non-diabetic patients. However, there has been a significant increase in the use of mechanical ventilation in diabetic and non-diabetic men, ranging from 0.41% and 0.76% in 2004 to 1.24% and 1.73% in 2013, respectively.

Of the diagnostic procedures analyzed, the most commonly used was CAT (22.9% in non-diabetic men and 23.93% in diabetic ones) followed by magnetic resonance (3.25% and 3.74%, respectively). The use of CAT in non-diabetic men has significantly decreased, while it has remained stable in diabetic men over the study period.

The IHM among diabetic women with a VaD discharge did not change significantly over the study period, as can be seen in Table 4. However, in women without diabetes the IHM decreased significantly from 16.08% in 2004 to 14.42% in 2013. Over the 10-year study period, the LOHS in women with and without diabetes decreased significantly ($p<0.05$). We found that readmissions significantly increased in non-diabetic women, ranging from 11.63% in 2004 to 13.64% in 2013, while it remained stable over time for diabetic women.

Table 4. Hospitalizations outcomes, diagnosis and therapeutic procedures among women with and without type 2 diabetes hospitalized with vascular dementia. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value
No Diabetes												
In hospital mortality, n (%)	722(16.08)	846(16.62)	747(14.89)	772(14.53)	947(15.76)	928(15.3)	920(14.27)	1042(15.14)	1085(15.14)	1027(14.42)	9036(15.16)	0.008
LOHS, median (IQR)	8(9)	8(9)	8(9)	8(9)	8(9)	8(9)	7(9)	7(8)	7(7)	7(7)	8(9)	<0.001
Readmission, n (%)	522(11.63)	591(11.61)	641(12.77)	686(12.91)	779(12.97)	769(12.68)	910(14.11)	963(14)	1026(14.32)	972(13.64)	7859(13.19)	<0.001
CAT, n (%)	1109(24.7)	1182(23.23)	1214(24.19)	1280(24.09)	1364(22.71)	1338(22.06)	1503(23.31)	1525(22.16)	1497(20.89)	1570(22.04)	13582(22.79)	<0.001
Magnetic Resonance, n (%)	118(2.63)	120(2.36)	120(2.39)	136(2.56)	178(2.96)	165(2.72)	150(2.33)	202(2.94)	147(2.05)	181(2.54)	1517(2.55)	0.027
PEG, n (%)	47(1.05)	45(0.88)	48(0.96)	54(1.02)	57(0.95)	67(1.1)	77(1.19)	64(0.93)	93(1.3)	51(0.72)	603(1.01)	0.058
Parenteral nutrition, n (%)	76(1.69)	105(2.06)	116(2.31)	106(2)	110(1.83)	134(2.21)	133(2.06)	133(1.93)	134(1.87)	126(1.77)	1173(1.97)	0.378
Mechanical ventilation, n (%)	30(0.67)	20(0.39)	27(0.54)	23(0.43)	35(0.58)	43(0.71)	51(0.79)	91(1.32)	106(1.48)	96(1.35)	522(0.88)	<0.001
Bladder Catheterization, n (%)	79(1.76)	97(1.91)	126(2.51)	147(2.77)	168(2.8)	192(3.17)	229(3.55)	241(3.5)	222(3.1)	275(3.86)	1776(2.98)	<0.001
Diabetes												
In hospital mortality, n (%)	343(14.75)	383(15)	408(14.31)	447(15.31)	452(14.16)	516(14.64)	484(13.65)	530(13.8)	562(14.59)	541(13.88)	4666(14.35)	0.641
LOHS, median (IQR)	8(9)	8(9)	8(9)	8(9)	8(9)	8(8)	7(9)	7(8)	7(7)	7(7)	8(9)	<0.001
Readmission, n (%)	314(13.5)	370(14.49)	433(15.18)	452(15.48)	503(15.76)	594(16.85)	548(15.45)	625(16.27)	612(15.89)	594(15.23)	5045(15.52)	0.641
CAT, n (%)	625(26.87)	650(25.46)	737(25.84)	728(24.93)	802(25.13)	838(23.77)	819(23.1)	955(24.86)	805(20.9)	869(22.29)	7828(24.08)	<0.001
Magnetic Resonance, n (%)	49(2.11)	52(2.04)	81(2.84)	55(1.88)	86(2.69)	97(2.75)	101(2.85)	118(3.07)	98(2.54)	91(2.33)	828(2.55)	0.037
PEG, n (%)	22(0.95)	22(0.86)	20(0.7)	32(1.1)	31(0.97)	37(1.05)	43(1.21)	34(0.89)	39(1.01)	24(0.62)	304(0.94)	0.290
Parenteral nutrition, n (%)	63(2.71)	63(2.47)	72(2.52)	43(1.47)	66(2.07)	79(2.24)	59(1.66)	81(2.11)	60(1.56)	65(1.67)	651(2)	0.002
Mechanical ventilation, n (%)	9(0.39)	12(0.47)	17(0.6)	14(0.48)	21(0.66)	28(0.79)	41(1.16)	63(1.64)	54(1.4)	41(1.05)	300(0.92)	<0.001
Bladder Catheterization, n (%)	58(2.49)	58(2.27)	71(2.49)	90(3.08)	87(2.73)	105(2.98)	106(2.99)	139(3.62)	138(3.58)	163(4.18)	1015(3.12)	<0.001

LOHS: length of hospital stay; CAT: Computed tomography angiography; PEG: Percutaneous Endoscopic Gastrostomy. P value for comparison by year: Binary logistic regression for incidence, Kruskal-Wallis for medians, Pearson´s chi-square for proportions.

As observed for men, we found a significant increase in the use of mechanical ventilation, from 0.39% to 1.05% in diabetic women and from 0.67% to 1.35% in non-diabetic women with VaD over the study period. The most commonly used diagnostic procedure was CAT for both groups of women. However, it was used in a higher proportion among those women with rather than without diabetes in all the years studied. The use of magnetic resonance has increased in diabetic women over time.

When we compared hospitalization outcomes between diabetic men and women, we found higher crude IHM among men than women in the total study population (15.3% vs. 14.35%), in all the years studied. Readmission rates were also significantly higher among men than women (17.22% vs. 15.52%). The use of magnetic resonance was used in a significantly higher proportion of diabetic men than diabetic women (3.74% vs. 2.55%), and PEG was more frequently used among diabetic women (0.94% vs. 0.78%).

The Poisson regression models conducted to assess the effect of the disease on the incidence of VaD hospitalizations from 2004 to 2013 in Spain, yielded an IRR for men with T2DM of 2.14 (95% CI 2.11-2.16). This means that, after adjusting for possible confounders, the incidence among diabetic men was 2-fold higher than among non-diabetic men. The corresponding figure for women was 2.22 (95% CI 2.19-2.25).

As can be seen in Table 5, among men and women with diabetes, IHM was significantly greater in older subjects (OR 1.48; 95% CI 1.38-1.59 and OR 1.54; 95% CI 1.40-1.69 in ≥85 aged group compared with reference category of 70-74 years, respectively). IHM was significantly higher in diabetic men and women with more comorbidities (OR 1.35; 95% CI, 1.27-1.42 and OR 1.62; 95% CI, 1.54-1.70 for those men and women with ≥3 comorbidities). IHM was also significantly higher in those men and women with pneumonia (OR 2.5; 95% CI, 2.44-2.65 and OR 2.64; 95% CI, 2.53-2.75) and in those with atrial fibrillation (OR 1.15; 95% CI, 1.09-1.20 and OR 1.21; 95% CI 1.16-1.26, respectively).

Table 5. Factors associated to in hospital mortality among men and women with and without type 2 diabetes hospitalized with vascular dementia. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

		Men	Woman	BOTH
		OR (95CI%)	OR (95CI%)	OR (95CI%)
Sex	Men	NA	NA	1.01(0.98-1.04)
Age group	70-74 years	1	1	1
	75-79 years	1.07(0.99-1.15)	1.11(1.01-1.23)	1.08(1.052-1.15)
	80-84 years	1.24(1.15-1.33)	1.24(1.13-1.37)	1.24(1.17-1.31)
	≥85 years	1.48(1.38-1.59)	1.54(1.40-1.69)	1.51(1.42-1.60)
Charlson Comorbidity Index	One	1	1	1
	Two	1.11(1.05-1.17)	1.23(1.17-1.29)	1.18(1.13-1.22)
	Three o over	1.35(1.27-1.42)	1.62(1.54-1.70)	1.49(1.43-1.54)
Atrial fibrillation		1.15(1.09-1.20)	1.21(1.16-1.26)	1.18(1.15-1.22)
Hypertension		0.83(0.80-0.87)	0.87(0.84-0.90)	0.85(0.83-0.87)
Malnutrition		0.91(0.83-1.00)	0.91(0.83-0.99)	0.91(0.85-0.97)
Pneumonia		2.55(2.44-2.65)	2.64(2.53-2.75)	2.59(2.52-2.67)
Urinary tract infection		0.85(0.81-0.90)	0.79(0.75-0.83)	0.82(0.79-0.85)
LOHS (days)		0.98(0.97-0.99)	0.98(0.97-0.99)	0.98(0.97-0.99)
Readmission		1.45(1.38-1.52)	1.38(1.31-1.44)	1.41(1.36-1.46)
CAT		0.69(0.66-0.73)	0.67(0.64-0.71)	0.68(0.66-0.71)
Magnetic Resonance		0.37(0.31-0.45)	0.25(0.20-0.32)	0.32(0.27-0.37)
PEG		0.44(0.34-0.57)	0.32(0.24-0.42)	0.37(0.31-0.45)
Parenteral nutrition		1.45(1.27-1.66)	1.17(1.03-1.32)	1.29(1.18-1.41)
Mechanical ventilation		2.98(2.59-3.43)	2.67(2.29-3.11)	2.83(2.55-3.14)
Type 2 Diabetes		0.99(0.95-1.04)	1.01(0.97-1.05)	1.00(0.98-1.03)
Year		0.97(0.96-0.98)	0.97(0.96-0.98)	0.97(0.96-0.98)

LOHS: length of hospital stay; CAT: Computed tomography angiography; PEG: Percutaneous Endoscopic Gastrostomy

The diabetic men and women who received mechanical ventilation had a higher probability of dying (2.98-fold and 2.67-fold, respectively) during their hospital stay than those who did not undergo this procedure. The use of PEG was associated with a reduced IHM among both diabetic men and women admitted for VaD (OR 0.44; 95% CI, 0.34-0.45 and OR 0.32; 95% CI, 0.24-0.42, respectively). In contrast, patients who received parenteral nutrition were more

likely to die during their stay (OR 1.45; 95% CI, 1.27-1.66 and OR 1.17; 95% CI, 1.03-1.32, respectively).

Time-trend analysis showed a significant decrease in IHM from 2004 to 2013 in diabetic men and women (OR 0.97; 95% CI 0.96-0.98). When we analyzed the entire database, and after adjusting for all covariates, suffering from diabetes was not associated with a higher IHM in either men or women (OR 0.99; 95% CI, 0.95-1.04 and OR 1.01; 95% CI 0.97-1.05).

DISCUSSION

In this study of more than 170,000 admissions for VaD, we found that the prevalence of T2DM among men and women hospitalized has increased over time in all age groups. This finding is not surprising because the prevalence of diabetes and dementia are both rapidly increasing. [2,6]

The association between diabetes and the risk of dementia has received much attention in epidemiological studies. [15] Ohara et al. reported an increase in the prevalence of all-cause dementia in the Japanese population, [16] and diabetes was also identified as a significant risk factor. Growing evidence in support of a biological relationship between diabetes and VaD suggests a multifactorial pathogenesis that involves insulin metabolism, hyperglycemic toxicity, chronic inflammation and vascular changes. [16,17] Diabetes is a known risk factor for microvascular and macrovascular complications including stroke; [18] this suggests that the relationship between diabetes and VaD is robust and not only driven by confounding. In our study, age was the most strongly associated factor for VaD, and diabetic patients were significantly younger than non-diabetic ones. Previous research has shown that patients with both VaD and T2DM have a significantly earlier onset of VaD, a faster rate of cognitive decline and a greater prevalence of neuropsychiatric symptoms than patients with VaD alone. [19] In our study we found, as expected, a higher prevalence of hypertension among diabetic patients compared to non-diabetics. It has been reported that arterial stiffness and small vessel

disease can predict future cognitive decline in elderly people with T2DM. [20]Over time, we observed that people admitted to the hospital due to VaD were progressively older, with increasing comorbid conditions and more hospital readmissions, which highlight the increasing frailty of these patients. A link between comorbidity and the risk of dementia in diabetic patients has also been published. [21]To further decrease the medical and social economic burden associated with dementia, it seems necessary to focus on chronic disease prevention.

Infections, diabetes or their complications have been highlighted as common reasons for hospital admission in patients with dementia. [22] In our study, pneumonia and urinary tract infections significantly increased over the study period. The use of bladder catheterization has significantly increased over time, which can contribute to the higher observed prevalence of urinary tract infections, but they are not associated with higher mortality. However, pneumonia is one of the infectious complications that has significantly increased over the study period and is also associated with a worse prognosis. The use of mechanical ventilation has also significantly increased, and it is also associated with higher IHM. This finding is relevant because it seems to be a bidirectional relationship: hospitalization with pneumonia has been associated with dementia and persistent cognitive dysfunction with severe infections. [23] On the other hand, dysphagia occurs frequently in patients with dementia and is related to aspiration pneumonia. Interestingly, we have found lower mortality in patients fed by PEG. This protective effect could be associated with a better nutritional and hydration status and potentially lower rates of aspiration pneumonia, but this is only a hypothesis because our study was not designed to evaluate the association between PEG and pneumonia. Furthermore, there is controversial evidence on this issue. Finucane et al. found no data to suggest that tube feeding of patients with advanced dementia prevented aspiration pneumonia, prolonged survival or provided palliation, [24] while Nakajoh et al. showed that

the incidence of pneumonia was significantly higher in stroke patients with dysphagia who were fed orally compared to those who received tube feeding (54.3 vs. 13.2%,p<0.001). [25]

As has been described previously for ischemic and hemorrhagic stroke, we have not found an increased IHM due to VaD in patients with diabetes compared to those without. [18,26] Despite the fact that obesity is recognized as a major risk factor in the development of cardiovascular diseases and diabetes, a higher BMI may be associated with a lower mortality and a better outcome in several chronic diseases. [27-29] During the past decade, there has been increasing evidence that patients, especially the elderly, with several chronic diseases and elevated BMI may demonstrate lower all-cause and cardiovascular mortality compared with patients of normal weight. [27] This observation has been referred to as "the obesity paradox". [28,29] The protective effect of nutritional status in overweight and obese elderly individuals, and the health-deteriorating effects of undernutrition in non-overweight subjects, probably contribute to this paradox. Although unfortunately in our study the BMI of patients admitted for VaD was not registered, this could be a possible explanation. This hypothesis concerning a better nutritional status is consistent with the better outcomes described above in those patients undergoing PEG.

The strength of our investigation lies in its large sample size, its 10-year follow-up period and its standardized methodology. [30] Nevertheless, our study is subject to a series of limitations. CMBD contains administrative discharge data for hospitalizations and uses information that physician included in the discharge report. Therefore, we lack information on relevant variables that may act as confounders, such as VaD or T2DM duration or treatments for this last condition, among others. Calculation of incidence on the basis of a database without any access to socio-demographic variables is another limitation.

Another important limitation is the lack of specificity of clinically defined VaD. The cognitive impairment observed in VaD and AD plus atherosclerosis might overlap

extensively. We are aware that considering other databases, such as mortality registries, in addition to discharge data would be advisable in order to detect patients with VaD dying outside of a hospital, especially at nursing homes. Unfortunately, in Spain this process is still unavailable for us.

Finally, as we state in the ethics section patient identifiers were deleted before the database was provided to us in order to maintain patient anonymity and it is not possible to identify patients on individual levels, either in this article or in the database. Therefore it is impossible for us to select a sample of study participant and to identify their medical records in order to validate the VaD and T2DM diagnosis because we don't know in which hospital the participant was admitted.

Van de Vorst et al assessed the validity of the Dutch Hospital Discharge Register (HDR) for vascular dementia by comparing the ICD 9 MD codes with medical records. These authors concluded that the validity of using HDR codes to identify patients with dementia is high. For VaD the positive predictive Value (PPV) was of 91.3% (95% CI 72.0-98.8%) and there were no significant differences in PPV according to age, gender, setting of diagnosis, and comorbidity.[31]

Regarding the validity of diabetes diagnosis a recent review and meta-analysis found that a commonly-used administrative database definition for diabetes (2 physician outpatient billings and/or one hospitalization with a diabetes record on the discharge abstract summary within a two-year period) has a pooled sensitivity of 82.3% (95%CI 75.8, 87.4) and specificity of 97.9% (95%CI 96.5, 98.8%), based on the findings of six studies with complete data available. [32]

In Canada, Kokotailo et al found that, among patients with stroke, when compared with hospital medical record the ICD 9 MD diagnosis of DM in the discharge report had a sensitivity of 94% (95%CI 69–99) and an specificity of 98% (95%CI 91–99). [33]

CONCLUSIONS

Our national data show that the incidence of VaD increased significantly during the period of study. Men and women with T2DM have more than double the risk of VaD admissions after adjusting for other risk factors. Patients admitted with VaD were progressively older and had multiple comorbidities. Pneumonia was associated with poorer prognosis, and the use of PEG was associated with reduced mortality. Diabetes was not associated with IHM, and the time-trends show that mortality is decreasing over time.

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CONTRIBUTIONS

NMR, RJG and ALdA researched data, contributed to the discussion, wrote the manuscript, and reviewed/edited the manuscript. VHB researched data and reviewed/edited the manuscript. NMR-MMB-JMdMY-JdMD-RJG-ALdA contributed to the discussion and reviewed/edited the manuscript.

All authors reviewed and gave their final approval of the version to be submitted.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

"No additional data available"

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Supplementary Table. Incidence of hospitalizations with vascular dementia among people with and without type 2 diabetes according to sex and age groups. Analysis of the Spanish National Hospital Discharge Database from 2004 to 2013.

Rate* 100.000/Inh	Diabetes	Age group	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value
Men	No	70-74	94.44	89.32	81.36	84.92	95.68	82.91	83.57	68.93	79.45	74.1	83.66	<0.001
		75-79	210.88	211.6	198.33	191.4	208.25	202.8	201.93	247.69	216.9	260.87	213.09	<0.001
		80-84	436.5	423.05	390.5	389.72	413.81	429.29	485.58	437.61	430.23	392.87	421.69	0.372
		≥85	652.21	689.83	753.13	862.05	789.82	834.04	895.58	866.84	903.98	886.14	824.15	<0.001
	Yes	70-74	220.31	245.77	266.13	243.04	247.71	252.27	222.66	237.99	240.44	223.93	240.19	0.341
		75-79	437.4	496.19	538.43	592.83	527.72	482.81	463.28	434.65	471.01	407.09	479.19	<0.001
		80-84	684.81	788.86	901.56	828.49	945.7	1000.27	1121.94	864.39	964.72	773.21	887.28	0.001
		≥85	1191.79	1032.39	954.29	1182.21	1218.95	1239.99	1483.13	1473.93	1594.54	1393.17	1308.71	<0.001
	Both	70-74	118.32	119.00	116.41	114.92	126.4	119.45	113.57	104.22	113.05	104.32	115.09	0.001
		75-79	255.79	264.71	258.39	262.29	271.96	264.86	259.85	297.95	285.21	308.52	272.4	<0.001
		80-84	485.99	490.81	479.62	466.23	510.86	538.25	607.01	525.27	540.02	475.06	511.78	<0.001
		≥85	720.61	745.45	792.37	924.5	868.51	904.76	997.94	980.44	1033.2	986.38	911.42	<0.001
Women	No	70-74	37.79	34.39	36.32	32.45	33.88	33.13	32.38	28.49	31.86	28.86	33.12	<0.001
		75-79	109.37	115.35	99.22	98.06	112.88	100.08	108.01	108.95	100.4	100.98	105.16	0.118
		80-84	301.13	309.31	283.44	298.72	313.54	293.75	302.52	298.33	323.16	291.05	301.48	0.593
		≥85	606.23	744.35	774.9	856.96	799.7	716.21	774.61	805.93	842.19	808.91	776.52	<0.001
	Yes	70-74	125.2	148.93	174.96	172.02	157.77	162.02	131.58	107.16	112.02	81.61	133.06	<0.001
		75-79	277.62	303.68	327.3	300.46	315.38	309.76	321.37	327.01	308.12	274.08	306.61	0.894
		80-84	877.79	782.59	759.27	774.24	699.39	723.21	743.62	719.43	732.64	689.29	741.21	<0.001
		≥85	1040.53	1219.07	1441.66	1588.68	1556.53	1483.56	1505.36	1353.57	1369.1	1211.87	1369.63	0.660
	Both	70-74	54.69	54.57	58.26	54.53	55.15	57.15	50.87	46.35	50.05	42.92	52.55	<0.001
		75-79	148.33	155.72	144.78	138.49	155	145.38	154.11	156.25	145.46	138.68	148.16	0.375
		80-84	393.36	390.19	369.13	384.36	389.4	384.61	395.84	389.45	411.76	378.94	388.82	0.246
		≥85	683.25	831.01	900.4	994.69	936.14	850.43	902.43	916.84	948.9	899.74	890.19	<0.001

Adjusted incidence per 100,000 inhabitants. P value for time trend using Poisson regression

SUPPLEMENTARY METHODS

We calculated the adjusted incidence of discharge rates after vascular dementia (VaD) for men and women with and without type 2 diabetes (T2DM) per 100,000 inhabitants by age groups and overall. To do so we used the Spanish populations for each year studied according to the Spanish National Statistics Institute as reported on December 31 of each year. [1]. To stratify the population according to diabetes status we used data obtained from National Health Surveys (NHS) conducted in 2003/4, 2006/7, 2009/10 and 2011/12 and data from Di@bet.es Study.[2, 3] All these surveys allow us to have an accurate prevalence estimation of diabetes by sex and age groups.[4] Then we multiply the prevalence of diabetes for each sex- age group and year by the Spanish population that same year to obtain the people with and without diabetes.

From 2001 till 2012, Spanish NHS has been done every two or three years. We estimated a rate fitting model using linear regression with prevalences of diabetes from years 2003/4, 2006/7, 2009/10 and 2011/12 when NHS was available. Then we used this model to impute prevalences and to estimate the population suffering diabetes by sex and age groups for those years when NHS was not conducted, those are years 2005, 2008 and 2013.

Once this was done we used the direct standardization method to calculate the adjusted incidences for each diabetes status stratified by age groups and sex using the Spanish population for year 2013 as standard.

We only use standardization methods for incidences. The proportions of clinical conditions and diagnosis and therapeutic procedures are not adjusted. The values shown in the results are the observed prevalence, calculated by dividing the number of subject with these conditions or procedures by the number of observed vascular dementia admission for the year studied.

Clinical characteristics included information on overall comorbidity at the time of diagnosis, which was assessed by calculating the Charlson Comorbidity Index (CCI). [5] The index applies to 17 disease categories, the scores of which are added to obtain an overall score for each patient. We divided patients into three categories: low index, which corresponds to patients with no previously recorded disease or with one disease category; medium index, patients with two categories; and high index, patients with three or more disease categories.

To calculate the CCI we used 15 disease categories, excluding diabetes and dementia as described by Thomsen et al. [6]

Statistical analysis

A descriptive statistical analysis was performed for all continuous variables and categories by stratifying discharges for vascular dementia according to diabetes status and sex. Variables are shown as proportions, means with standard deviations or medians with interquartile ranges (LOHS). Bivariate analyses of variables according to year was using $\chi 2$ linear trend analysis (proportions), ANOVA (means) and Kruskall-Wallis test (medians), as appropriate. To assess differences between those men and women with and without T2DM, for each year and for the total sample, the statistical tests conducted for continuous variables were the T test for normal distributions and the Mann–Whitney test for non-normal distributions and categorical variables were compared using the linear Chi-square test.

In order to test the linear time trend in the incidence due to VaD, we fitted separate Poisson regression models for men and women with and without T2DM, using year of discharge, age, CCI, hypertension, atrial fibrillation, infectious complications, malnutrition, agitation, diagnostic and therapeutic procedures and readmission as independent variables. So that estimates correspond to Incidence Rate Ratio (IRR) with

their 95% confidence intervals. The inclusion of year of discharge allow us to estimate the average yearly rate of change.

For IHM, logistic regression analyses were performed for men and women with mortality as a binary outcome for those with and without diabetes and for the entire population to assess the influence of diabetes on IHM. The independent variables included in the model were those that showed a significant association in the bivariate analysis or considered relevant in the medical literature.

Statistical analyses were performed using Stata version 10.1 (Stata, College Station, Texas, USA). Statistical significance was set at $p<0.05$ (2-tailed).

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4,5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	Supplementary methods
Study size	10	Explain how the study size was arrived at	4,5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Supplementary methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Supplementary methods
		(*b*) Describe any methods used to examine subgroups and interactions	Supplementary methods
		(*c*) Explain how missing data were addressed	Supplementary

			methods
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-16
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-16
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	5-16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-16
		(*b*) Report category boundaries when continuous variables were categorized	5-16
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.