Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Sex Differences in Mortality Rates and Underlying Conditions for COVID-19 Deaths in England and Wales

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Abstract

Objective: To address the issue of limited national data on the prevalence and distribution of underlying conditions among COVID-19 deaths between sexes and across age groups.

Patients and Methods: All adult (≥18 years) deaths recorded in England and Wales (March 1, 2020, to May 12, 2020) were analyzed retrospectively. We compared the prevalence of underlying health conditions between COVID and non−COVID-related deaths during the COVID-19 pandemic and the age-standardized mortality rate (ASMR) of COVID-19 compared with other primary causes of death, stratified by sex and age group.

Results: Of 144,279 adult deaths recorded during the study period, 36,438 (25.3%) were confirmed COVID deaths. Women represented 43.2% (n=15,731) of COVID deaths compared with 51.9% (n=55,980) in non-COVID deaths. Overall, COVID deaths were younger than non-COVID deaths (82 vs 83 years). ASMR of COVID-19 was higher than all other common primary causes of death, across age groups and sexes, except for cancers in women between the ages of 30 and 79 years. A linear relationship was observed between ASMR and age among COVID-19 deaths, with persistently higher rates in men than women across all age groups. The most prevalent reported conditions were hypertension, dementia, chronic lung disease, and diabetes, and these were higher among COVID deaths. Pre-existing ischemic heart disease was similar in COVID (11.4%) and non-COVID (12%) deaths.

Conclusion: In a nationwide analysis, COVID-19 infection was associated with higher age-standardized mortality than other primary causes of death, except cancer in women of select age groups. COVID-19 mortality was persistently higher in men and increased with advanced age.

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More than 12 million patients worldwide have been infected with the severe acute respiratory syndrome coronavirus (SARS-CoV-2), resulting in the illness referred to as COVID-19.[1] The United Kingdom has the second highest recorded number of deaths in the world after the US, with 39,728 deaths recorded as of June 6, 2020.[2,3]

Age and comorbidities such as hypertension, diabetes, and ischemic heart disease (IHD) are strong predictors of adverse outcomes and mortality in people infected with COVID-19.[4-6] Furthermore, differences in COVID-19 survival have been observed between sexes, with female patients shown to have better outcomes. Several hypotheses have been proposed as an explanation of the latter, including biological (genetic and hormonal) differences between sexes as well as lower burden of comorbidity in female patients.[4-8] Detailed data concerning underlying

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conditions are limited, with data from New York State reporting that 89.7% of patients with fatalities attributed to COVID-19 had at least 1 comorbidity, most commonly hypertension, diabetes, and hyperlipidemia.[9] In the United Kingdom, 91% of patients who died of COVID-19 in March 2020 had at least 1 pre-existing condition, with ischemic heart disease the most common (14%).[10] There is inconclusive evidence, however, on how the distribution of underlying conditions varies by sex and age in those who have died of COVID-19.[11-13] Furthermore, it is unclear as to how the underlying conditions in COVID-19 deaths differ from those in similar age and sex groups who have died of non–COVID-related causes.

Therefore, we investigated the pre-existing conditions in adults (≥18 years) who had died of COVID-19 in England and Wales between March 1, 2020 and May12, 2020, stratified by sex and age group, and compared this with patients whose deaths were not attributed to COVID-19.

METHODS

Data Source, Study Design, and Population

This cross-sectional study included records of all adult (aged ≥18 years) deaths between March 1, 2020, and May12, 2020, in England and Wales that were collected from the Office for National Statistics (ONS) Civil Registrations of Death dataset and stratified according to COVID-19 status.[2] Children and adolescents aged below 18 years were excluded for the purpose of this analysis, as their susceptibility to death of COVID-19 is significantly lower than that of adults, and the pattern of their causes of death vary from those in adults.[14] The process of death certification and registration is a legal requirement in the United Kingdom, where a physician who has seen the deceased within the last 14 days of his or her life must complete a Medical Cause of Death Certificate unless a postmortem examination is planned. During the COVID-19 pandemic, the 14-day requirement was temporarily extended to 28 days, allowing for the exceptional circumstances. The ONS dataset includes information concerning the deceased's age, sex, registration office (town or city), primary cause of death, as well as up to 15 supplementary codes for their underlying conditions. A total of 900 patients younger than 18 years of age were excluded. There were no other inclusion or exclusion criteria. The International Classification of Diseases 10th revision (ICD-10) codes were used to extract data on COVID-19 (as the primary cause of death), pulmonary embolism, pre-existing IHD, heart failure, dementia, chronic kidney disease (CKD), hypertension, chronic lung disease, diabetes, liver disease, peripheral vascular disease (PVD), valvular heart disease, major bleeding, cancers, stroke (ischemic and hemorrhagic), acute coronary syndrome (ACS), and infective endocarditis. A full list of diagnosis codes used in the study is provided in Supplemental Table 1 (available online at www.mayoclinicproceedings.org).

Statistical Analyses

We compared the reported underlying acute and chronic conditions between patients with and without confirmed COVID-19 as the underlying primary contributory cause, stratified according to sex and age band (18 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, 80 to 89, and ≥90 years). Age was not normally distributed and therefore summarized using median and interquartile range (IQR) and compared using the Kruskal-Wallis test. Categorical variables were summarized as percentages and analyzed using the χ^2 test or Fisher's exact test, as appropriate. Age-standardized mortality rates (ASMR), expressed as rates per 100,000 capita, were calculated for each age band based on the mid-2019 population census for England and Wales.[15] Statistical analyses were performed using Stata 16 MP (StataCorp, College Station, Texas).

Ethical Approval

This work was endorsed by the Scientific Advisory Group for Emergencies (SAGE), the body responsible for ensuring timely and coordinated scientific advice is made available to UK government decision makers. SAGE supports UK cross-government

TABLE 1. Crude and Age-Standardized Mortality Rates[a] Between March 1 and May 12, 2020, Depending on COVID-19 Status and Sex

	COVID-negative									COVID-positive								
	Men (n=51,879)			Women (n=55,980)			Total (n=107,859)			Men (n=20,707)			Women (n=15,731)			Total (n=36,438)		
	n	Crude %	ASMR	n	Crude %	ASMR	n	Crude %	ASMR	n	Crude %	ASMR	n	Crude %	ASMR	n	Crude %	ASMR
Age Groups, years																		
18-29	126	0.2%	2.7	85	0.2%	1.9	211	0.2%	2.3	37	0.2%	0.8	25	0.2%	0.6	62	0.2%	0.7
30-39	297	0.6%	7.6	261	0.5%	6.6	558	0.5%	7.1	103	0.5%	2.6	72	0.5%	1.8	175	0.5%	2.2
40-49	965	1.9%	25.7	774	1.4%	20.3	1739	1.6%	23	342	1.7%	9.1	195	1.2%	5.1	537	1.5%	7.1
50-59	3005	5.8%	76.9	2158	3.9%	53.7	5163	4.8%	65.2	1204	5.8%	30.8	621	3.9%	15.5	1825	5.0%	23
60-69	6321	12.2%	207.8	4446	7.9%	139.0	10,767	10.0%	172.5	2555	12.3%	84	1275	8.1%	39.9	3830	10.5%	61.4
70-79	13,298	25.6%	576.1	10,326	18.4%	400.7	23,624	21.9%	483.6	5427	26.2%	235.1	3127	19.9%	121.3	8554	23.5%	175.1
80-89	18,867	36.4%	1853.9	20,233	36.1%	1452.9	39,100	36.3%	1622.2	7942	38.4%	780.4	6247	39.7%	448.6	14189	38.9%	588.7
90+	9000	17.3%	5388.9	17,696	31.6%	4889.3	26,696	24.8%	5047.1	3097	15.0%	1854.4	4169	26.5%	1151.8	7266	19.9%	1373.6

[a]ASMR per 100,000 population.

ASMR = age-standardized mortality rates.

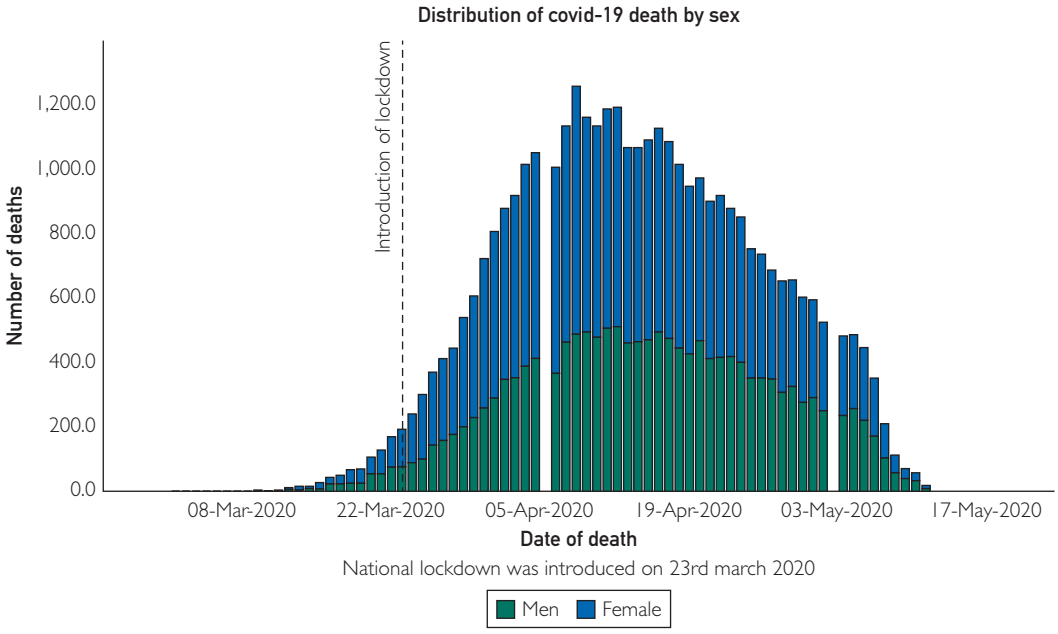

FIGURE 1. Distribution of COVID-19 deaths in England and Wales from the start of the pandemic through May12, 2020, according to sex.

decisions in the Cabinet Office Briefing Room (COBR) and by National Health Service (NHS) England, which overseas commissioning decisions in the NHS and NHS Improvement, which is responsible for overseeing quality of care in NHS hospitals.

RESULTS

A total of 36,438 adult COVID-19 deaths were recorded in England and Wales between March 1 and May 12, 2020, of which 20,707 (56.8%) were in men and 15,731 (43.2%) in women. The first death due to COVID-19 infection in the United Kingdom was recorded on March 2, 2020. Over the same period, a total of 107,859 non−COVID-related deaths were recorded, including 51,879 (48.1%) in men and 55,980 (51.9%) in women. The median age of COVID-19 deaths was lower than that in non−COVID-related deaths (82 [73,88] vs 83 [74, 89] years). Overall, women were older in the COVID and non-COVID groups (84 [76, 90] vs 80 [72, 87] years, $P<.001$).

The majority of deaths were observed among people aged 80 to 89 years (COVID: 38.9%; non-COVID: 36.4%; Table 1). ASMR increased with age in both groups and were consistently higher for all age bands for non-COVID compared with COVID deaths. The ASMR was 61.4 per 100,000 population in the 60 to 69 age group for COVID deaths and 172.5 per 100,000 population for non-COVID deaths. The absolute number of COVID-19 deaths was higher for men than women throughout the study period (Figure 1), with peak mortality observed between the April 4 and April 20, 2020. The ASMR was approximately 2-fold higher in men compared with women across all age groups for COVID-19−related deaths. (Table 1, Figure 2) A similar pattern was observed in the non-COVID group, albeit with less pronounced sex differences in ASMR. Overall, the most common cause of death in younger age groups (<60 years) was cancer, whereas the most common causes of death in older age groups (>80 years) were dementia, cancer, and old age (Table 2). However, ASMR of COVID-19 was higher than all other primary causes of death for people without COVID-19, across

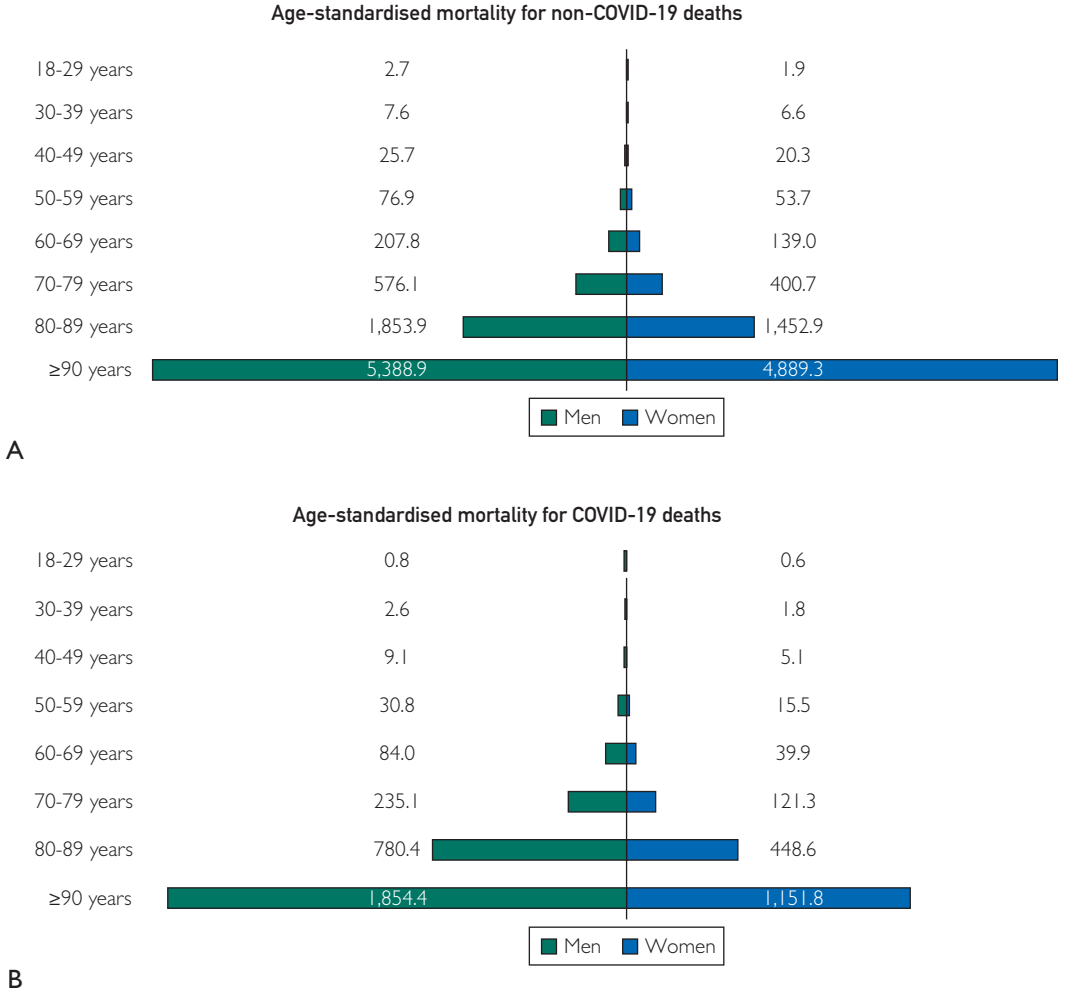

FIGURE 2. Age standardized mortality rate according to COVID status (per 100,000 population).

all age groups and sexes, with the exception of cancer deaths for women aged 30 to 79 years. The highest number of COVID-19 deaths was in London (total male, female: 7510, 4519, 2991) (Supplemental Table 2, Supplemental Figure 1, available online at www.mayoclinicproceedings.org)

Approximately one-third of patients had no underlying chronic conditions in the non-COVID (29.9%) and COVID groups (31.8%), and close to 1 in 10 patients with COVID-19 and non−COVID-19 deaths had 3 or more underlying conditions (10.4% vs 9%) (Table 3, Figure 3) The rate of reported underlying chronic conditions was generally higher in COVID than non-COVID deaths, with the most prevalent reported conditions being hypertension (COVID vs non-COVID: 19.0% and 11.2%), dementia (COVID vs non-COVID: 18.8% vs 15.9%), chronic lung disease (COVID vs non-COVID: 15.6% vs 11.4%) and diabetes (COVID vs non-COVID: 15.2% vs 8.1%). The rates of pre-existing IHD were similar in COVID (11.4%) and non-COVID (12%) deaths, although lower reported rates of cancers (7.8% vs 23.4%) were observed among patients with reported COVID deaths (Table 3). The prevalence of pre-existing IHD appeared to be significantly lower in men in the COVID-19 vs the non−COVID-19 deaths among those aged <60 years but was similar for all other age groups (Supplemental

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TABLE 2. Frequencies and Age-Standardized Mortality Rates of Primary Causes of Deaths

Primary cause of death, n (ASMR[a])	Age group (years)							
	18-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
COVID-19								
Men	37 (0.8)	103 (2.6)	342 (9.1)	1204 (30.8)	2555 (84)	5427 (235.1)	7942 (780.4)	3097 (1854.4)
Women	25 (0.6)	72 (1.8)	195 (5.1)	621 (15.5)	1275 (39.9)	3127 (121.3)	6247 (448.6)	4169 (1151.8)
Total	62 (0.7)	175 (2.2)	537 (7.1)	1825 (23)	3830 (61.4)	8554 (175.1)	14189 (588.7)	7266 (1373.6)
AKI								
Men	1 (0)	0 (0)	1 (0)	8 (0.2)	23 (0.8)	63 (2.7)	108 (10.6)	36 (21.6)
Women	0 (0)	0 (0)	1 (0)	10 (0.2)	30 (0.9)	47 (1.8)	101 (7.3)	54 (14.9)
Total	1 (0)	0 (0)	2 (0)	18 (0.2)	53 (0.8)	110 (2.3)	209 (8.7)	90 (17)
PE								
Men	1 (0)	17 (0.4)	23 (0.6)	73 (1.9)	135 (4.4)	149 (6.5)	98 (9.6)	20 (12)
Women	5 (0.1)	15 (0.4)	22 (0.6)	38 (0.9)	89 (2.8)	153 (5.9)	160 (11.5)	59 (16.3)
Total	6 (0.1)	32 (0.4)	45 (0.6)	111 (1.4)	224 (3.6)	302 (6.2)	258 (10.7)	79 (14.9)
Stroke								
Men	6 (0.1)	10 (0.3)	42 (1.1)	103 (2.6)	198 (6.5)	388 (16.8)	514 (50.5)	201 (120.4)
Women	1 (0)	9 (0.2)	38 (1)	81 (2)	166 (5.2)	454 (17.6)	849 (61)	594 (164.1)
Total	7 (0.1)	19 (0.2)	80 (1.1)	184 (2.3)	364 (5.8)	842 (17.2)	1363 (56.6)	795 (150.3)
ACS								
Men	0 (0)	10 (0.3)	66 (1.8)	187 (4.8)	348 (11.4)	532 (23)	486 (47.8)	127 (76)
Women	2 (0)	4 (0.1)	14 (0.4)	36 (0.9)	102 (3.2)	254 (9.9)	356 (25.6)	197 (54.4)
Total	2 (0)	14 (0.2)	80 (1.1)	223 (2.8)	450 (7.2)	786 (16.1)	842 (34.9)	324 (61.3)
Acute respiratory failure								
Men	2 (0)	5 (0.1)	8 (0.2)	41 (1)	78 (2.6)	152 (6.6)	124 (12.2)	33 (19.8)
Women	3 (0.1)	5 (0.1)	11 (0.3)	31 (0.8)	74 (2.3)	162 (6.3)	141 (10.1)	47 (13)
Total	5 (0.1)	10 (0.1)	19 (0.3)	72 (0.9)	152 (2.4)	314 (6.4)	265 (11)	80 (15.1)
Respiratory infections								
Men	23 (0.5)	24 (0.6)	82 (2.2)	258 (6.6)	733 (24.1)	2181 (94.5)	3841 (377.4)	2035 (1218.5)
Women	7 (0.2)	24 (0.6)	61 (1.6)	209 (5.2)	539 (16.8)	1523 (59.1)	3508 (251.9)	3054 (843.8)
Total	30 (0.3)	48 (0.6)	143 (1.9)	467 (5.9)	1272 (20.4)	3704 (75.8)	7349 (304.9)	5089 (962.1)
Other infections								
Men	7 (0.2)	9 (0.2)	26 (0.7)	77 (2)	170 (5.6)	491 (21.3)	814 (80)	346 (207.2)
Women	5 (0.1)	11 (0.3)	26 (0.7)	61 (1.5)	145 (4.5)	381 (14.8)	829 (59.5)	584 (161.3)
Total	12 (0.1)	20 (0.3)	52 (0.7)	138 (1.7)	315 (5)	872 (17.8)	1643 (68.2)	930 (175.8)
Chronic lung disease								
Men	0 (0)	0 (0)	8 (0.2)	41 (1)	151 (5)	373 (16.2)	284 (27.9)	67 (40.1)
Women	0 (0)	0 (0)	6 (0.2)	38 (0.9)	139 (4.3)	346 (13.4)	283 (20.3)	92 (25.4)
Total	0 (0)	0 (0)	14 (0.2)	79 (1)	290 (4.6)	719 (14.7)	567 (23.5)	159 (30.1)
Old age (senility)								
Men	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	27 (1.2)	906 (89)	1224 (732.9)
Women	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	36 (1.4)	1440 (103.4)	3288 (908.4)
Total	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	63 (1.3)	2346 (97.3)	4512 (853)
Dementia								
Men	0 (0)	0 (0)	0 (0)	7 (0.2)	70 (2.3)	543 (23.5)	1589 (156.1)	710 (425.1)
Women	0 (0)	0 (0)	1 (0)	17 (0.4)	94 (2.9)	710 (27.6)	2736 (196.5)	2383 (658.4)
Total	0 (0)	0 (0)	1 (0)	24 (0.3)	164 (2.6)	1253 (25.6)	4325 (179.4)	3093 (584.7)
Heart failure								
Men	2 (0)	8 (0.2)	38 (1)	119 (3)	285 (9.4)	646 (28)	1023 (100.5)	471 (282)
Women	1 (0)	4 (0.1)	17 (0.4)	43 (1.1)	98 (3.1)	408 (15.8)	884 (63.5)	628 (173.5)
Total	3 (0)	12 (0.2)	55 (0.7)	162 (2)	383 (6.1)	1054 (21.6)	1907 (79.1)	1099 (207.8)

Continued on next page

TABLE 2. Continued

Primary cause of death, n (ASMR[a])	Age group (years)							
	18-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
CKD								
Men	0 (0)	0 (0)	2 (0.1)	18 (0.5)	38 (1.2)	72 (3.1)	128 (12.6)	46 (27.5)
Women	1 (0)	1 (0)	0 (0)	6 (0.1)	25 (0.8)	45 (1.7)	104 (7.5)	22 (6.1)
Total	1 (0)	1 (0)	2 (0)	24 (0.3)	63 (1)	117 (2.4)	232 (9.6)	68 (12.9)
Cancers								
Men	11 (0.2)	82 (2.1)	254 (6.8)	962 (24.6)	2086 (68.6)	3724 (161.3)	3393 (333.4)	862 (516.1)
Women	14 (0.3)	103 (2.6)	321 (8.4)	970 (24.2)	1815 (56.7)	3175 (123.2)	3011 (216.2)	906 (250.3)
Total	25 (0.3)	185 (2.3)	575 (7.6)	1932 (24.4)	3901 (62.5)	6899 (141.2)	6404 (265.7)	1768 (334.2)
Other causes								
Men	73 (1.6)	132 (3.4)	415 (11.1)	1111 (28.4)	2005 (65.9)	3957 (171.4)	5559 (546.2)	2822 (1689.7)
Women	46 (1)	85 (2.1)	256 (6.7)	618 (15.4)	1130 (35.3)	2632 (102.1)	5831 (418.7)	5788 (1599.1)
Total	119 (1.3)	217 (2.8)	671 (8.9)	1729 (21.8)	3135 (50.2)	6589 (134.9)	11,390 (472.6)	8610 (1627.7)

[a]ASMR per 100,000 population

ACS, acute coronary syndrome; AKI, acute kidney injury; ASMR = age standardized mortality rates; CKD = chronic kidney disease; PE = pulmonary embolism.

Table 3A and 3B, available online at www.mayoclinicproceedings.org).

Overall, women were more likely to have no underlying chronic conditions compared with men in both COVID and non-COVID groups (COVID: 33.6% vs 30.5%, non-COVID: 31.1% vs 28.6%; Table 3, Figures 3 and 4). Among COVID-19 deaths, women had higher rates of dementia (21.2% vs 17%, $P<.001$) as underlying conditions compared with men, whereas men had higher rates of pre-existing IHD (14.1% vs 7.9%), CKD (11.4% vs 9.5%), hypertension (20.1% vs 17.4%), and diabetes (17.1% vs 12.8%) compared with women ($P<.001$ for all). There was no difference in the rates of underlying cancer, liver disease, pulmonary embolism, and valvular heart disease between sexes. Although this pattern was generally consistent across the age groups, the rates of certain underlying conditions were higher for the younger age bands (Supplemental Table 3A and 3B, available online at www.mayoclinicproceedings.org, Figure 4) Pulmonary embolism was more frequently reported in <60 and 60 to 69 age deciles, more so in men than women (<60 years: 3.0% vs 2.6%, 60 to 69 years: 2.9% vs 1.8%, $P<.001$ for both). Patients in the younger age deciles were also more likely to have cancer, with higher rates observed in women compared with men (<60 years: 12.5% vs 7.4%, 60 to 69 years: 14% vs 10%, $P<.001$ for both).

DISCUSSION

This national study is the first to report detailed, patient-level data about the prevalence of underlying conditions according to COVID-19 status in England and Wales during the COVID-19 pandemic. We found that the age-standardized mortality rate for COVID-19 was higher than that from all common primary causes of death in non-COVID patients across all age groups and sexes, except for cancers in women between the ages of 30 and 79 years. Second, we show that age standardized mortality was consistently higher for men than women for COVID-19 deaths by a factor of almost 2 across age groups. Finally, we provide a contrast of the distribution of underlying acute and chronic conditions between COVID and non−COVID-related deaths, and report that hypertension, chronic lung diseases, and diabetes were more commonly observed in COVID-19 deaths, whereas cancers where more commonly observed in non-COVID deaths.

The greatest proportion of COVID deaths in England and Wales were observed in the 70 to 79 and 80 to 89 age groups, with the median age being 82 years. The median

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TABLE 3. Characteristics and Underlying Conditions of Reported Deaths According to COVID Status and Sex

	COVID-negative				COVID-positive			
	Men (n=51,879)	Women (n=55,980)	Total (n=107,859)	*P* value	Men (n=20,707)	Women (n=15,731)	Total (n=36,438)	*P* value
Age, median (IQR)	81 (72, 87)	85 (76, 91)	83 (74, 89)	<.001	80 (72, 87)	84 (76, 90)	82 (73, 88)	<.001
Month of death, n (row %)				<.001				<.001
March	23,564 (49.9)	23,649 (50.1)	47,213		2804 (61.7)	1739 (38.3)	4543	
April	23,591 (46.9)	26,687 (53.1)	50,278		16,221 (56.8)	12,335 (43.2)	28,556	
May[a]	4724 (45.6)	5644 (54.4)	10,368		1682 (50.4)	1657 (49.6)	3339	
Number of reported chronic underlying conditions				<.001				<.001
0	14,821 (28.6)	17,388 (31.1)	32,209 (29.9)		6318 (30.5)	5287 (33.6)	11,605 (31.8)	
1	21,904 (42.2)	25,225 (45.1)	47,129 (43.7)		7501 (36.2)	6028 (38.3)	13,529 (37.1)	
2	9729 (18.8)	9071 (16.2)	18,800 (17.4)		4537 (21.9)	2965 (18.8)	7502 (20.6)	
≥3	5425 (10.5)	4296 (7.7)	9721 (9)		2351 (11.4)	1451 (9.2)	3802 (10.4)	
Chronic conditions								
Pre-existing ischemic heart disease, n (%)	8114 (15.6)	4799 (8.6)	12,913 (12)	<.001	2918 (14.1)	1235 (7.9)	4153 (11.4)	<.001
Heart failure, n (%)	5907 (11.4)	5312 (9.5)	11,219 (10.4)	<.001	1609 (7.8)	1301 (8.3)	2910 (8)	.08
Dementia, n (%)	6620 (12.8)	10,490 (18.7)	17,110 (15.9)	<.001	3523 (17)	3328 (21.2)	6851 (18.8)	<.001
Chronic kidney disease, n (%)	4173 (8)	4099 (7.3)	8272 (7.7)	<.001	2354 (11.4)	1500 (9.5)	3854 (10.6)	<.001
Hypertension, n (%)	5655 (10.9)	6407 (11.4)	12,062 (11.2)	.005	4171 (20.1)	2740 (17.4)	6911 (19.0)	<.001
Chronic lung disease, n (%)	6550 (12.6)	5755 (10.3)	12,305 (11.4)	<.001	3125 (15.1)	2559 (16.3)	5684 (15.6)	.002
Diabetes, n (%)	4833 (9.3)	3937 (7)	8770 (8.1)	<.001	3531 (17.1)	2020 (12.8)	5551 (15.2)	<.001
Liver disease, n (%)	1516 (2.9)	895 (1.6)	2411 (2.2)	<.001	278 (1.3)	182 (1.2)	460 (1.3)	.12
Peripheral vascular disease, n (%)	1189 (2.3)	854 (1.5)	2043 (1.9)	<.001	357 (1.7)	130 (0.8)	487 (1.3)	<.001
Valvular heart disease, n (%)	1019 (2)	881 (1.6)	1900 (1.8)	<.001	273 (1.3)	202 (1.3)	475 (1.3)	.78
Cancers, n (%)	12,475 (24)	12,745 (22.8)	25,220 (23.4)	<.001	1615 (7.8)	1216 (7.7)	2831 (7.8)	.81
Acute conditions								
Stroke[b], n (%)	3620 (7)	4309 (7.7)	7929 (7.4)	<.001	1287 (6.2)	839 (5.3)	2126 (5.8)	<.001
Major bleeding, n (%)	1585 (3.1)	1575 (2.8)	3160 (2.9)	.02	218 (1.1)	120 (0.8)	338 (0.9)	.004
Pulmonary embolism, n (%)	932 (1.8)	1027 (1.8)	1959 (1.8)	.64	280 (1.4)	181 (1.2)	461 (1.3)	.09
Acute coronary syndrome, n (%)	2614 (5)	1529 (2.7)	4143 (3.8)	<.001	307 (1.5)	137 (0.9)	444 (1.2)	<.001
Infective endocarditis, n (%)	390 (0.8)	343 (0.6)	733 (0.7)	.005	85 (0.4)	80 (0.5)	165 (0.5)	.17

[a]Correct as of May 12, 2020.
[b]Includes bleeding and ischemic strokes.
IQR = interquartile range.

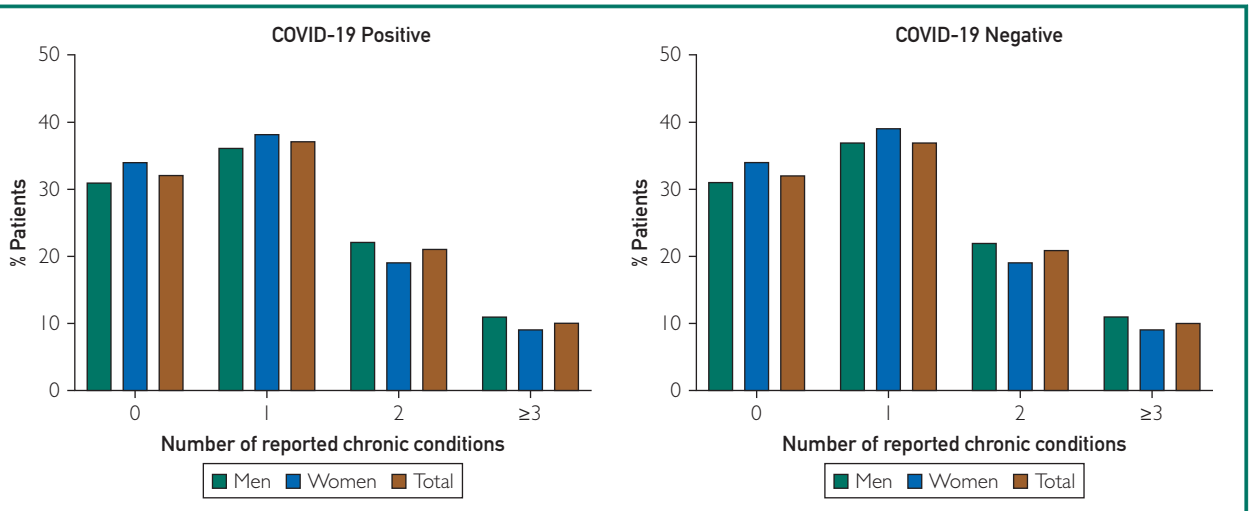

FIGURE 3. Number of reported underlying chronic conditions in the overall cohort and according to COVID status and sex.

age of death in Italy was 81 years, based on 31,096 deaths (as of May 21, 2020), which is similar to our findings. Their report demonstrates that the highest number of deaths was observed in the 80 to 89 years of age group (n=12,729/31,096), followed by 70 to 79 years (n=8466) and ≥90 years (n=5227); however, ASMRs were not presented, which makes interpretation of data difficult, particularly when comparing with non-COVID deaths or data derived from other countries.[16] Similarly, data from the National Center for Health Statistics (NCHS) as of May 13, 2020, demonstrates that mortality was highest in the 75 to 84 and ≥85-year groups (27.2% and 31.8%, respectively) in the United States but, again, they do not present age-adjusted figures.[17]

The majority of recent studies have focused on the crude mortality or case-fatality rates of COVID-19.[18-21] The latter is a proportion of the cumulative reported number of deaths by the cumulative number of reported cases and can be misleading, as there is often a lag in the manifestation of symptoms, testing for disease, and reporting of the number of cases, meaning that the true case-fatality rate is often underestimated, as demonstrated with previous epidemics.[22,23] ASMRs take into account differences in the age structure of a population and allow a more direct comparison of underlying conditions, especially when these vary by age. Although there have been several reports about mortality during the COVID-19 pandemic, these have either not been derived from national populations or have not compared mortality rates with other causes of death within the population.[17,19,24-27] Our analysis, which provides full population coverage of all deaths in England and Wales, is the first to demonstrate that the ASMR of COVID is significantly higher than that of any other primary cause of death in non-COVID subjects throughout the same period. This finding was consistent across all age groups and in both sexes, with the exception of women between 30 and 79 years of age, whose mortality from cancer was comparable with that of COVID.

Our findings suggest that ASMRs in men were almost double compared with that of women across all age groups, despite crude death rates suggesting a significantly higher proportion of women ≥90 years dying of COVID-19 compared with men. Our crude findings are consistent with reports in the United States, which show that 41.7% of female deaths were among those 85 years and older compared with only 23.9% in men, with higher mortality in younger male age

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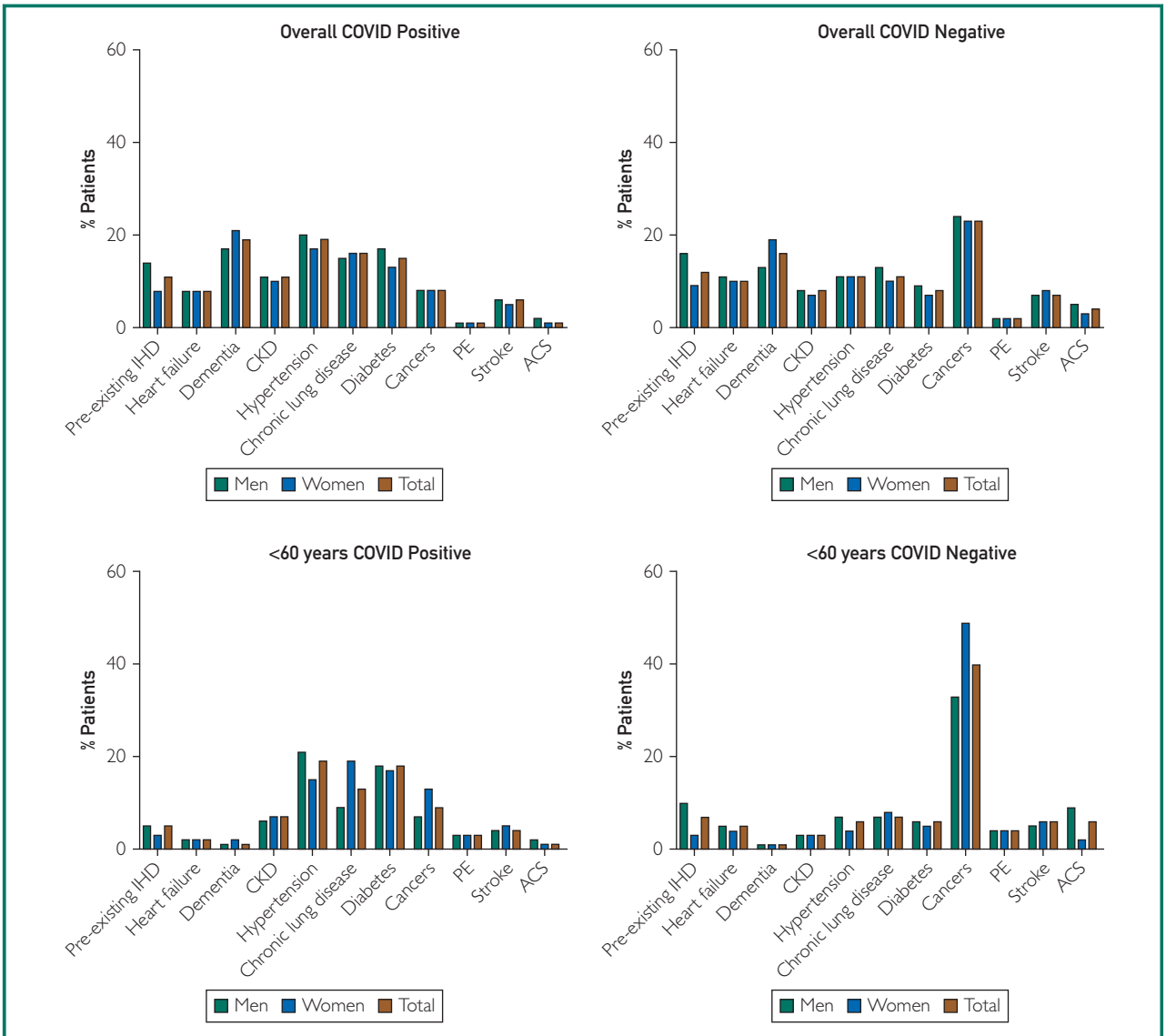

FIGURE 4. Top reported conditions associated with COVID and non-COVID deaths in England and Wales in overall cohort and according to sex and age group. ACS = acute coronary syndrome; CKD = chronic kidney disease: IHD = ischemic heart disease; PE = pulmonary embolism. *Figure continued on next page.*

groups compared with women.[17] Similarly, data on COVID-related deaths in Italy (n=31,096) demonstrates higher mortality in men than women across all age deciles except ≥90 years, in which mortality was higher than in women.[16] However, neither analyses provided an adjustment for age, which makes comparisons between sexes challenging.

Differences in outcomes between sexes could be explained by the greater number of reported underlying conditions in men compared with women, as demonstrated in our analysis. Another proposed hypothesis relates to the circulating level of angio tensin-converting enzyme 2 (ACE2), the main host cell receptor toward which SARS-CoV-2 has been shown to have significantly high affinity, which has been shown to be greater in men than women and in adults compared with children.[5,28,29] Furthermore, women are believed to have better immune

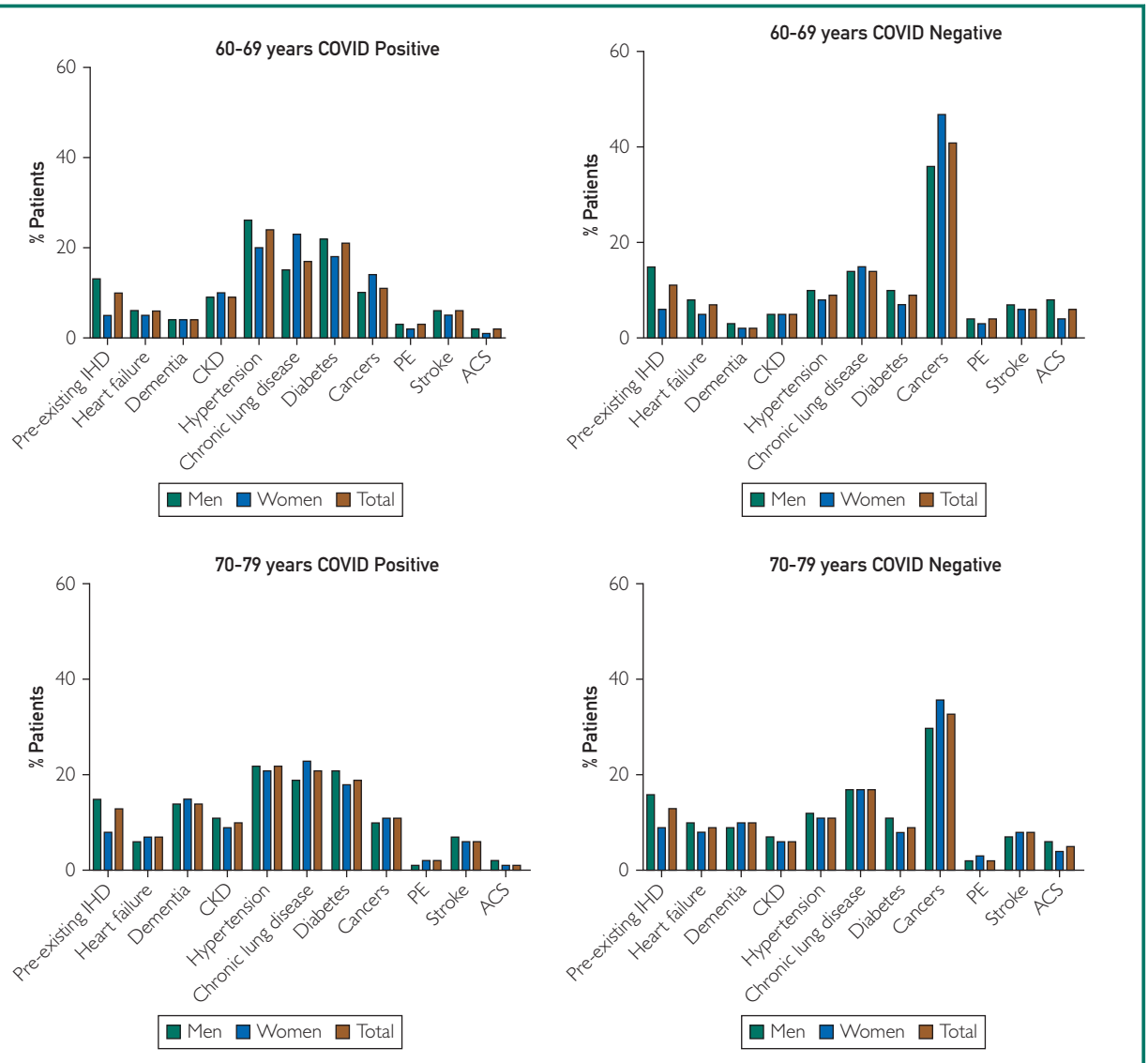

FIGURE 4. (Continued).

response against viral infections compared with men, primarily because of higher levels of estrogen, which is also believed to directly suppress viral replication.[7,8,13] The decline in levels of estrogen with advanced age, albeit with higher level in women throughout, could also explain the higher rate of mortality in elderly subjects.[6]

Our analysis suggests that a small proportion of COVID-19 deaths experienced acute events such ACS, acute stroke, and pulmonary embolism, and these were lower than in non-COVID deaths. It is difficult to compare these findings with other studies owing to limited data on the acute conditions reported in COVID deaths from other countries or whether there may have been an element of reporting bias, in which acute events were reported as COVID deaths. Previous studies have suggested a high prevalence of certain comorbidities, such as hypertension and IHD, in patients who died of COVID-19.[20,24,25,30] However, these have been mostly limited by their small sample size or analysis of selected cohorts (eg, intensive care admission only). In our analysis we find that one-third

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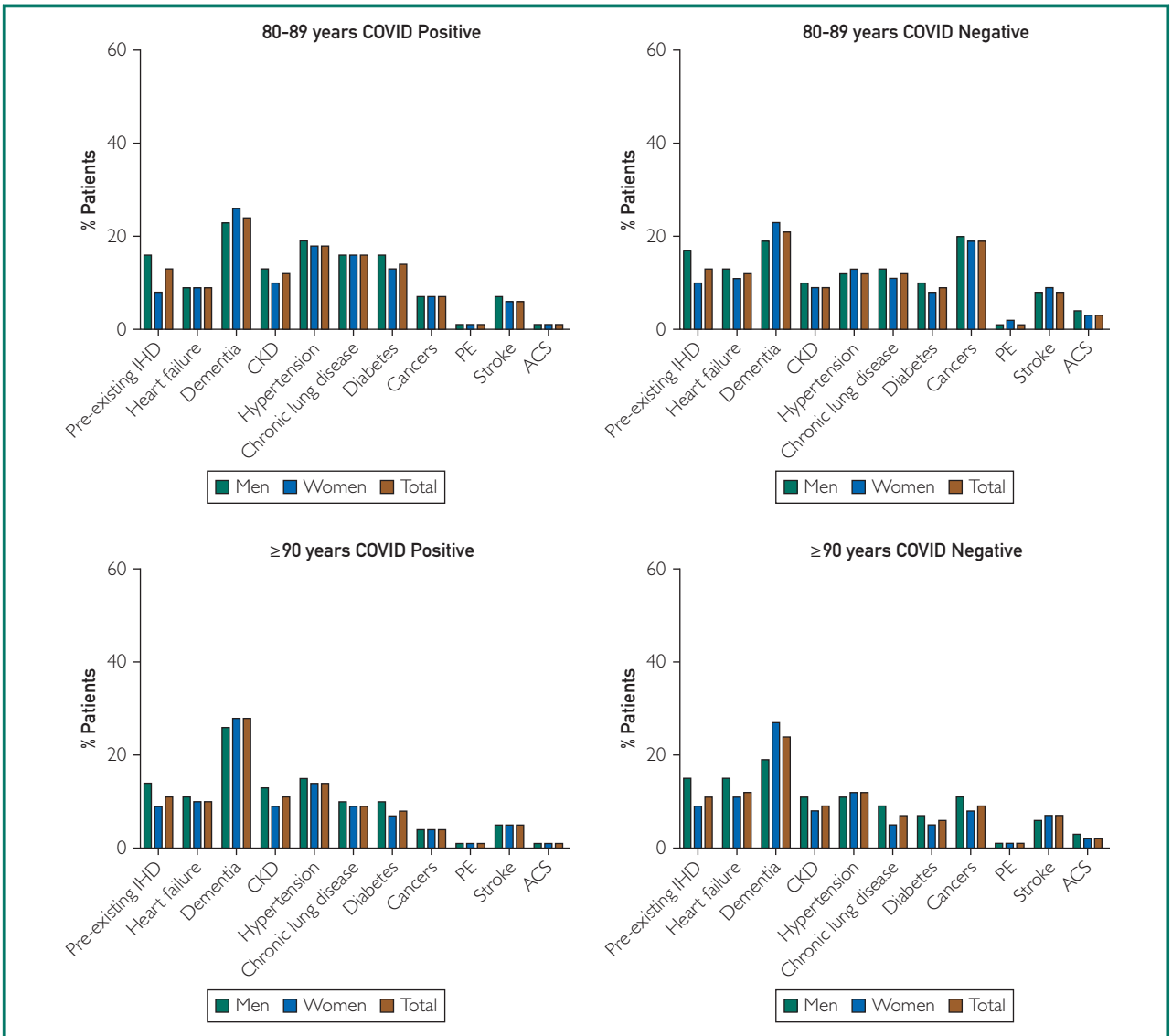

FIGURE 4. (Continued).

of patients who died had no underlying chronic conditions, but there were more chronic conditions in COVID than non-COVID deaths, with the most prevalent reported being hypertension, dementia, chronic lung disease, and diabetes in both groups.

Of note, we find that the prevalence of IHD in COVID-19–related deaths is similar to that observed in non COVID-19 deaths, apart from in younger men (<60 years old), in which, paradoxically, the prevalence is double that in patients who died non-COVID deaths. Reports from several studies have demonstrated a high prevalence of cardiovascular disease (CVD) in patients with COVID-19.[24,25,31] Although the underlying mechanisms are unclear, patients with CVD are more likely to develop severe COVID infection, which is attributed to multiple factors including advanced age, lower ACE2 levels, and impaired immunity.[32] It is also possible that pharmacological treatment administered for COVID infection provokes fatal arrhythmias, to which CVD patients appear to be more susceptible.[33] In a meta-analysis of 1576 COVID-infected patients,

the most prevalent comorbidities were hypertension (21.1%), diabetes (9.7%), and CVD (8.4%). Their analysis showed that the odds ratios (ORs) of hypertension and CVD were significantly higher in patients with severe than nonsevere COVID (OR, 2.36; 95% confidence interval [CI], 1.46-3.83) and 3.42 (95% CI, 1.88-6.22), respectively).[34] However, these data may not hold true in patients who die of COVID, who may have greater baseline comorbidity. In a report from the Italian Instituto Superiore Di Sanita, the prevalence of hypertension (68.3%) and IHD (28.3%) was significantly higher in COVID deaths (n=31.096).[16] Differences between countries may reflect differences in reporting methods or sociodemographic and genetic differences.

Among COVID deaths, acute conditions were observed to be either similar between sexes (pulmonary embolism) or more prevalent in men (ACS and acute stroke). In terms of chronic conditions, women had higher rates of dementia, heart failure, and chronic lung disease compared with men, whereas men had higher rates of pre-existing IHD, CKD, hypertension, and diabetes. Notably, there was no difference in the rates of underlying cancer between sexes. Although the pattern of findings was consistent across age groups, certain differences in underlying conditions were noted. Pulmonary embolism was more frequently reported in <60 and 60 to 69 age deciles among COVID deaths, more so in men than women, whereas cancer rates were higher in younger age groups, especially in women compared with men. Data on 31.096 COVID deaths from Italy shows that men had a higher prevalence of IHD (31.7% vs 21.3%), diabetes (30.8% vs 28.8%), and chronic renal failure (21.5% vs 18.2%) and lower prevalence of heart failure (14.6% vs 18.1%) compared with women and that there was no difference in the rates of active cancer between sexes (men: 15.9% vs women: 15.6%), all of which is in line with our findings.[16] However, their report did not compare these conditions among age groups.

The current findings have several important implications from a national and international perspective. Our comprehensive analysis adds to the body of literature on sex and age differences in patterns of death from a national perspective in a population with a high mortality rank. Furthermore, our report of underlying medical conditions in the overall population of COVID-19 deaths, as well as in both sexes, may help inform stakeholders' and governments' policies by identifying high-risk groups that could benefit from prolonged shielding, especially in the event of a second peak or vaccination priority in the future.

Limitations

Although our study provides insights into the patterns of age and sex differences in COVID-19—related deaths and reported underlying medical conditions in a full nationwide cohort from England and Wales, there are a number of limitations. First, only conditions that were thought to contribute to the death are entered on the death certificate, rather than a list of all comorbid conditions that a patient may have. Our analysis therefore provides an overview of comorbid conditions that were judged by clinicians completing the death certificate to have contributed to death, without any external auditing, rather than a description of all prevalent comorbid conditions. Second, we did not have access to ethnic data, which may have confounded our analyses, particularly given that the mortality rate from COVID-19 in black, Asian, and minority ethnic people have been reported as up to 3 times greater.[35]

CONCLUSION

In this nationwide analysis of deaths in England and Wales between March 1 and May 12, 2020, we demonstrate that the age-adjusted mortality of COVID-19 was higher than that of other primary causes of death across all age groups and in both sexes, with the exception of cancer mortality in women between ages 30 and 79 years, whose adjusted-mortality was higher than COVID-19. Our findings also suggest persistently higher age-adjusted mortality in men compared with women across all age groups throughout the study period. Our report of underlying medical conditions in the overall population of COVID-19 deaths, as well as in

both sexes, may help inform stakeholder and government body policies by identifying high-risk groups.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility of all data.

Abbreviations and Acronyms: **ACS** = acute coronary syndrome; **ASMR** = age standardized mortality rate; **CVD** = cardiovascular disease; **IHD** = ischemic heart disease; **ONS** = Office for National Statistics

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