Sex-differences in mortality rates and underlying conditions for COVID-19 deaths in England and Wales

Running title: Underlying conditions in COVID-19 deaths

Mohamed O. Mohamed, MRCP(UK)[1,2], Chris P. Gale, PhD FRCP[3,4,5], Evangelos Kontopantelis, PhD[6], Tim Doran, MD[7], Mark de Belder, MD FRCP[8], Miqdad Asaria, PhD[9], Thomas Luscher, MD FRCP[10], Jianhua Wu, PhD[3], Muhammad Rashid, PhD[1,2], Courtney Stephenson, BSc[11], Tom Denwood, MSc[11], Chris Roebuck, MSc[11], John Deanfield, FRCP[12], Mamas A. Mamas, DPhil[1,2]

1. Keele Cardiovascular Research Group, Centre for Prognosis Research, Institutes of Applied Clinical Science and Primary Care and Health Sciences, Keele University, United Kingdom
2. Department of Cardiology, Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom
3. Leeds Institute for Data analytics, University of Leeds, Leeds, UK
4. Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
5. Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
6. Division of Informatics, Imaging and Data Science, University of Manchester, Manchester, UK.
7. Department of Health Sciences, University of York, York, UK.
8. National Institute for Cardiovascular Outcomes Research, Barts Health NHS Trust, UK
9. London School of Economics, London, UK
10. Royal Brompton and Harefield NHS Foundation Trust, London, UK
11. NHS Digital
12. University College London, London, UK

Correspondence to:

Mamas A. Mamas
Professor of Cardiology
Keele Cardiovascular Research Group,
Centre for Prognosis Research,
Institute for Primary Care and Health Sciences,
Keele University, UK
mamasmamas1@yahoo.co.uk

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Abbreviations

ACS	Acute coronary syndrome
ASMR	Age standardized mortality rate
CVD	Cardiovascular disease
IHD	Ischemic heart disease
ONS	Office for National Statistics

Abstract

Background: Limited national data exists on the prevalence and distribution of underlying conditions among COVID-19 deaths between sexes and across age groups.

Methods: All adult (≥18 years) deaths recorded in England and Wales (1st March 2020 to 12th May 2020) were retrospectively analyzed. We compared 1) the prevalence of underlying health conditions between COVID and non-COVID related deaths during the COVID-19 pandemic and 2) 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 cases. Women represented 43.2% (n=15,731) of COVID deaths compared to 51.9% (n=55,980) in non-COVID deaths. Overall, COVID deaths were younger 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 30-79 years. A linear relationship was observed between ASMR and age amongst 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 amongst COVID deaths. Pre-existing ischemic heart disease was similar in COVID (11.4%) and non-COVID (12%) deaths.

Conclusions: 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.

Introduction

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 (UK) has the second highest recorded number of deaths in the world after the US, with 39,728 deaths recorded as of 6th June 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 5 6] Furthermore, differences in COVID-19 survival has been observed between sexes, with females 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 females.[4-8] Detailed data concerning underlying conditions is limited, with data from New York state reporting that 89.7% of fatalities attributed to COVID-19 had at least one comorbidity, most commonly hypertension, diabetes and hyperlipidemia.[9] In the UK 91% of COVID-19 deaths in March 2020 had at least one 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 that have died from COVID-19. [11-13] Furthermore, it is unclear as to how the underlying conditions in COVID-19 deaths differ from those in similar age/sex groups that have died from non-COVID related causes.

Therefore, we investigated the pre-existing conditions in adults (≥18 years) who had died from COVID-19 in England and Wales between 1st March 2020 and 12th May 2020, stratified by sex and age group, and compare this with patients whose death was 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 1st March 2020 and 12th May 2020 in England and Wales 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 since their susceptibility to death from COVID-19 is significantly lower than adults, and the pattern of their causes of death vary to those in adults. [14] The process of death certification and registration is a legal requirement in the United Kingdom where a doctor who has seen the deceased within the last 14 days of life must complete a Medical Cause of Death Certificate unless a post-mortem 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, tenth 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, 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 **Supplementary Table S1**.

Statistical Analysis

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 (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89 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 chi squared (X^2) test or Fisher's exact test, where 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 (College Station, TX).

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 decisions in the Cabinet Office Briefing Room (COBR)) and by 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 1st March and 12th May 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 2nd March 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<0.001).

The majority of death were observed among people aged 80-89 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 60-69 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 4th and 20th April 2020. The ASMR was approximately two-fold higher in men compared to 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 all age groups and sexes, with the exception of cancer deaths for women aged 30-79 years. The highest number of COVID-19 deaths was in London (total/male/female: 7,510, 4,519, 2,991). (**Table S2, Figure S1**)

Approximately a third of individuals had no underlying chronic conditions in the non-COVID (29.9%) and COVID groups (31.8%), and close to one in ten patients with COVID-19 and non-COVID-19 deaths had three 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 amongst 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. (**Supplementary Tables S3A and S3B**)

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**). Amongst COVID-19 deaths, women had higher rates of dementia (21.2% vs. 17%, $p<.001$) as underlying conditions compared with men whilst 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%), 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. While this pattern was generally consistent across the age groups, the rates of certain underlying conditions were higher for the younger age bands (**Table S3A and S3B, Figure 4**) Pulmonary embolism was more frequently reported in <60 and 60-69 age deciles, more so in men than women (<60 years: 3.0% vs. 2.6%, 60-69 years: 2.9% vs. 1.8%, $p<.001$ for both). Individuals in the younger age deciles were also more likely to have cancer with higher rates observed in women compared to men (<60 years: 12.5% vs. 7.4%, 60-69 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 & 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 30-79 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 70-79 and 80-89 age groups, with the median age being 82 years. The median age of death in Italy was 81 years, based on 31,096 deaths (as of May 21st, 2020), which is similar to our findings. Their report demonstrates that the highest number of deaths was observed in the 80-89 years group (n=12,729/31, 096), followed by 70-79 years (n=8466) and ≥90 years (n=5227), however age standardized mortality rates 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 13th May 2020 demonstrates that mortality was highest in the 75-84 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 since 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] Age-standardized mortality rates take in to account differences in the age structure of a population and allow a more direct comparison of underlying

conditions especially when these vary by age. Whilst 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 age standardized mortality rate 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 30-79 years whose mortality from cancer was comparable to that from COVID.

Our findings suggest that age-standardized mortality in men was almost double compared to that of women across all age groups, despite crude death rates suggesting a significantly higher proportion of women ≥90 years dying from COVID-19 compared with men. Our crude findings are consistent with reports in the US, which show 41.7% of female deaths were amongst those 85 years and older compared to only 23.9% in men, with higher mortality in younger male age groups compared to 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 where 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 to women as demonstrated in our analysis. Another proposed hypothesis relates to the circulating level of angiotensin-converting enzyme 2 (ACE2), the main host cell receptor towards 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 to children. [28 5, 29] Furthermore, women are believed to have a better

immune response against viral infections compared with men, primarily due to 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 females throughout, could also explain the higher rate of mortality elder 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 to other studies due 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, where acute events were reported as COVID deaths. Previous studies have suggested a high prevalence of certain comorbidities such as hypertension and ischemic heart disease in patients who died from COVID-19. [20 24, 25 30] However, these have been mostly limited by their small sample size or analysis of selected cohorts (e.g. intensive care admission only). In our analysis we find that a third of individuals 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.

Interestingly, we find that the prevalence of ischemic heart disease in COVID-19 related deaths is similar to that observed in non COVID-19 deaths, apart from in younger men (<60 years old) where paradoxically the prevalence is double that in patients that died non-COVID deaths. Reports from several studies have demonstrated a high prevalence of cardiovascular disease (CVD) in patients with COVID-19. [25 24 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 (OR) of hypertension and CVD were significantly higher in patients with severe than non-severe 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 from COVID, who may have greater baseline comorbidity. In a report from the Italian Instituto Superiore Di Sanita the prevalence of hypertension (68.3%) and ischemic heart disease (28.3%) was significantly higher in COVID deaths (n=31.096). [35] Differences between countries may reflect differences in reporting methods, or sociodemographic and genetic differences.

Amongst 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 to men, whilst 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 60-69 age deciles amongst COVID deaths, more so in men than women, whereas cancer rates were higher in younger age groups, especially in women compared to 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 to 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 are in line with our findings. [35] However, their report did not compare these conditions between age groups.

The present 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 who could benefit from prolonged shielding, especially in the event of a second peak, and/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, that may confound our analyses, particularly given that the mortality rate from COVID-19 in Black, Asian and minority ethnic people have been reported as up to three times greater.[36]

Conclusions

In this nationwide analysis of deaths in England and Wales between 1st March and 12th May 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 30-79 years, whose adjusted-mortality was

higher than COVID-19. Our findings also suggest persistently higher age-adjusted mortality in men compared to 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 stakeholders' and government body policies by identifying high-risk groups.

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Figures captions and legends:

Figure 1. Distribution of Covid-19 deaths in England and Wales from the start of the pandemic through 12th May 2020 according to sex

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

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

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

Legend: ACS: acute coronary syndrome; CKD: chronic kidney disease: IHD: ischaemic heart disease; PE: pulmonary embolism

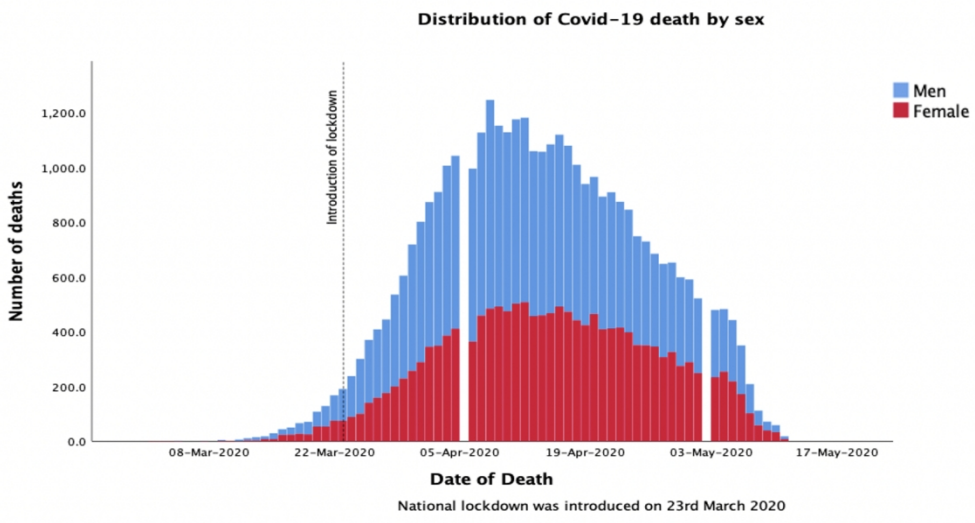

Figure 1.

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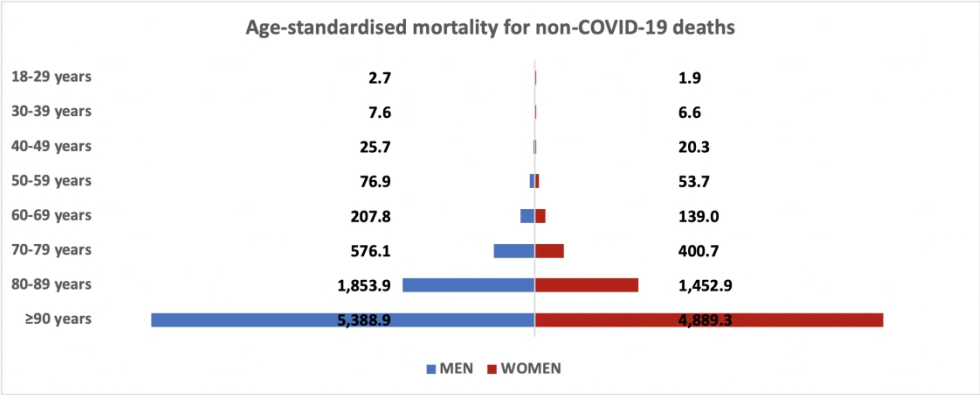

Figure 2A.

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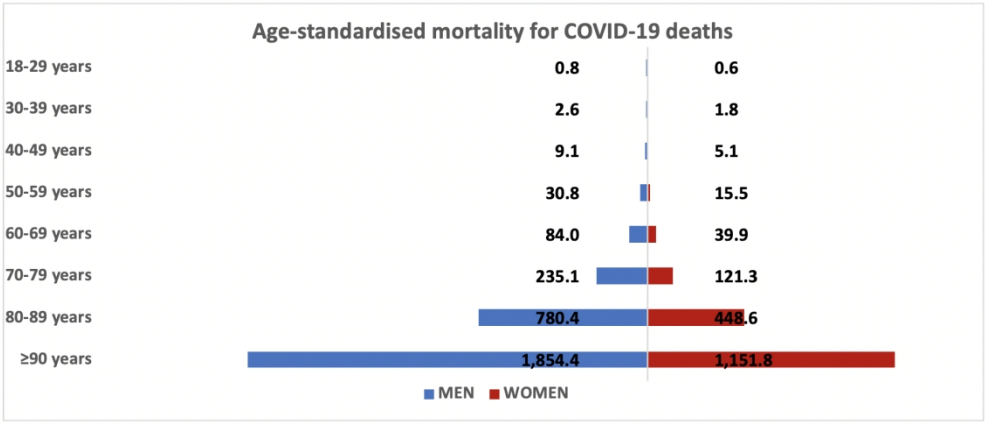

Figure 2B.

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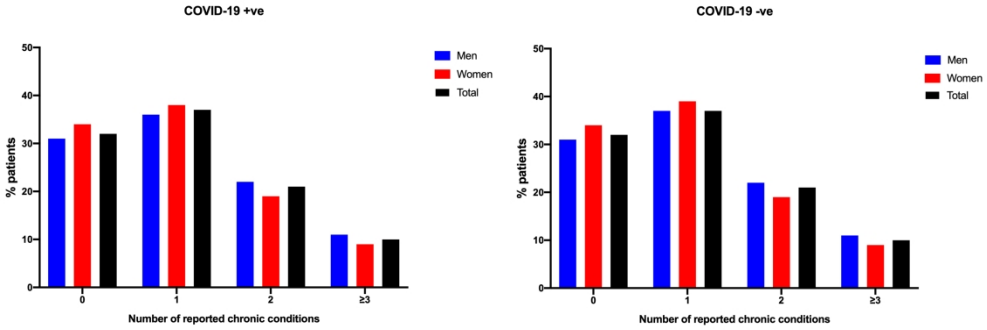

Figure 3.

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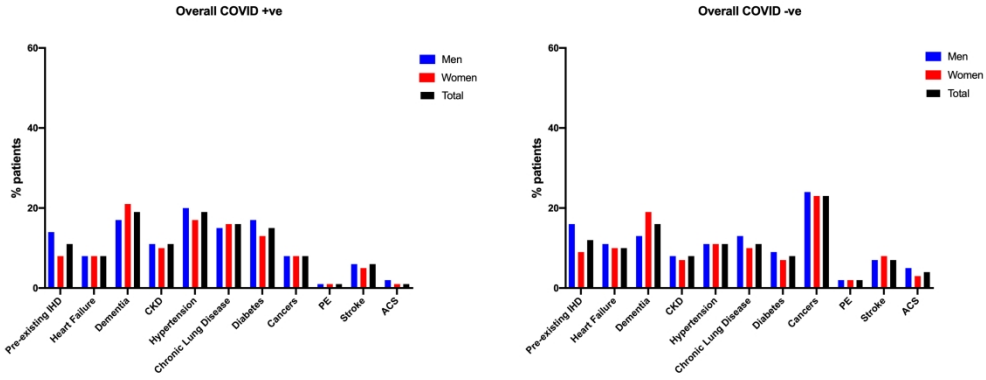

Figure 4A

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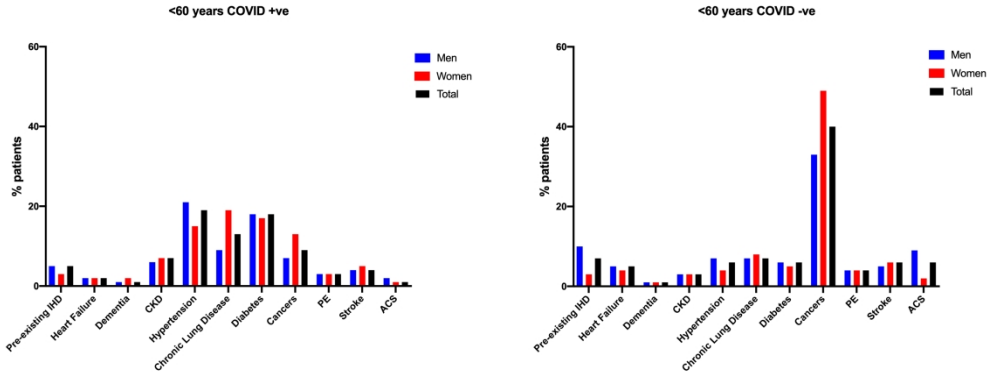


Figure 4B

259x101mm (300 x 300 DPI)

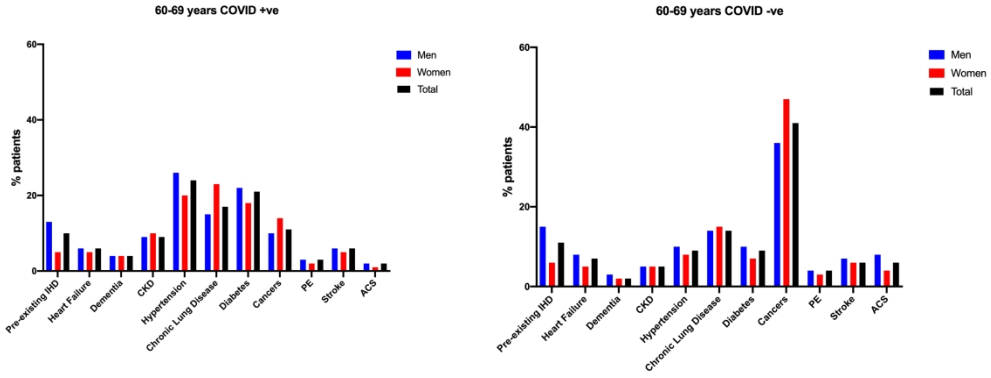


Figure 4C

273x106mm (300 x 300 DPI)

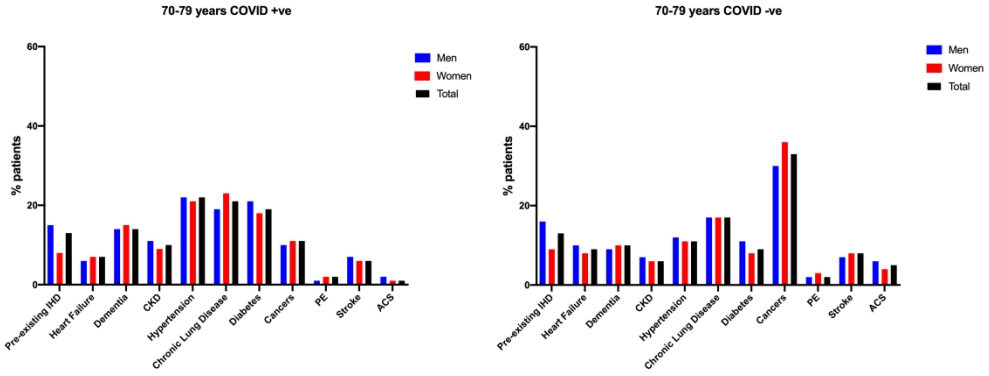


Figure 4D

278x107mm (300 x 300 DPI)

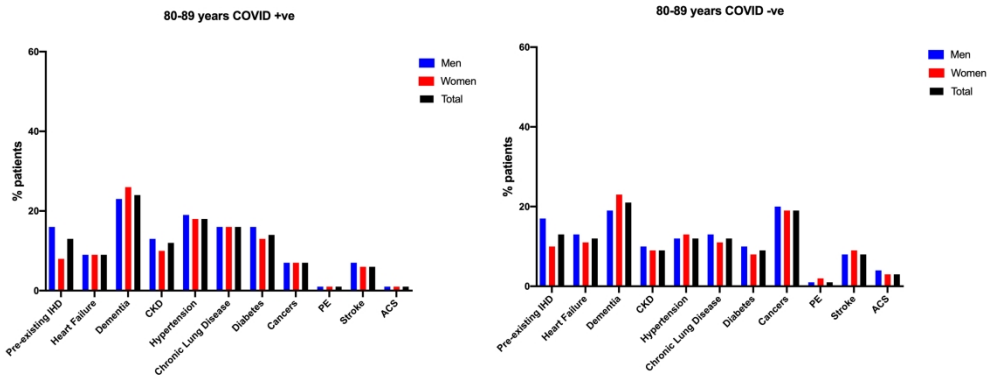


Figure 4E

276x109mm (300 x 300 DPI)

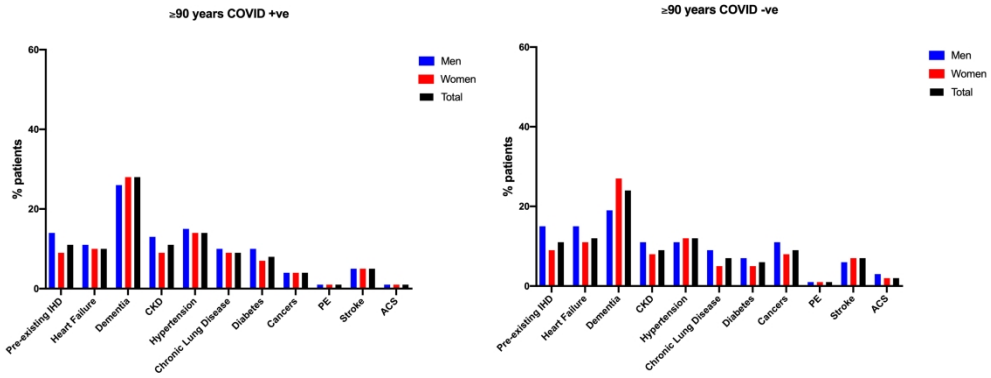


Figure 4F

276x109mm (300 x 300 DPI)

Table 1. Crude and Age-standardised mortality rates (ASMR)[a] between 1st March and 12th May 2020 depending on COVID-19 status and sex

	COVID-negative									COVID-positive								
	Men (n=51879)			Women (n=55980)			Total (n=107859)			Men (n=20707)			Women (n=15731)			Total (n=36438)		
	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	10767	10.0%	172.5	2555	12.3%	84	1275	8.1%	39.9	3830	10.5%	61.4
70-79	13298	25.6%	576.1	10326	18.4%	400.7	23624	21.9%	483.6	5427	26.2%	235.1	3127	19.9%	121.3	8554	23.5%	175.1
80-89	18867	36.4%	1853.9	20233	36.1%	1452.9	39100	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	17696	31.6%	4889.3	26696	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

Table 2. Frequencies and age-standardised mortality rates (ASMR) of primary causes of deaths

	Age group (years)							
Primary cause of death, n (ASMR[a])	**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)
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)	11390 (472.6)	8610 (1627.7)

[a] ASMR: per 100,000 population

Table 3. Characteristics and underlying conditions of reported deaths according to COVID status and sex

	COVID-negative				COVID-positive			
	Men (n=51879)	**Women (n=55980)**	**Total (n=107859)**	**p-value**	**Men (n=20707)**	**Women (n=15731)**	**Total (n=36438)**	**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	23564 (49.9)	23649 (50.1)	47213		2804 (61.7)	1739 (38.3)	4543	
April	23591 (46.9)	26687 (53.1)	50278		16221 (56.8)	12335 (43.2)	28556	
May[a]	4724 (45.6)	5644 (54.4)	10368		1682 (50.4)	1657 (49.6)	3339	
Number of reported chronic underlying conditions				<.001				<.001
0	14821 (28.6)	17388 (31.1)	32209 (29.9)		6318 (30.5)	5287 (33.6)	11605 (31.8)	
1	21904 (42.2)	25225 (45.1)	47129 (43.7)		7501 (36.2)	6028 (38.3)	13529 (37.1)	
2	9729 (18.8)	9071 (16.2)	18800 (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 Ischaemic Heart Disease, n (%)	8114 (15.6)	4799 (8.6)	12913 (12)	<.001	2918 (14.1)	1235 (7.9)	4153 (11.4)	<.001
Heart Failure, n (%)	5907 (11.4)	5312 (9.5)	11219 (10.4)	<.001	1609 (7.8)	1301 (8.3)	2910 (8)	.08
Dementia, n (%)	6620 (12.8)	10490 (18.7)	17110 (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)	12062 (11.2)	.005	4171 (20.1)	2740 (17.4)	6911 (19.0)	<.001
Chronic Lung Disease, n (%)	6550 (12.6)	5755 (10.3)	12305 (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 (%)	12475 (24)	12745 (22.8)	25220 (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 12th May 2020

[b] Includes bleeding and ischaemic strokes

IQR: interquartile range

Sex-based Differences in Reported Underlying Conditions and Rates of COVID-19 Deaths in England and Wales

Online Supplementary Material

- **Table S1.** List of ICD-10 CM diagnosis codes used in the study
- **Table S2**. Rates of COVID-19 deaths per county region according to sex
- **Table S3.** Characteristics and reported underlying conditions of deceased patients A) without and B) with COVID -19 according to sex and age group
- **Figure S1.** Distribution of Covid-19 deaths in England and Wales according to sex

Table S1. List of ICD-10 CM* diagnosis codes used in the study

Diagnosis	Codes
COVID-19	U07.1
Pre-existing Ischaemic Heart Disease	I25.2, I25.6, Z98.61, I25.10, I25.110, I25.111, I25.118, I25.119, I25.7*, I25.8*, I25.9*, Z95.1
Heart Failure	I50*, I42*, I25.5
Dementia	F01*, F02*, F03*
Chronic Kidney Disease	N18*
Hypertension	I10*
Chronic Lung Disease	J41*, J42*, J43*, J44*, J45*, J47*
Diabetes	E08*, E09*, E10*, E11*, E13*
Liver Disease	K70*, K72.1*, K72.9*, K73*, K74*, K75*, K76*, K77*
Peripheral Vascular Disease	I70*, I73*
Valvular Heart Disease	I34*, I35*, I36*, I37*
Cancers	C00-C96*
Stroke	G46.3, G46.4, G46.5, G46.6, G46.7, I60*, I61*, I62*, I63*, I64*
Major Bleeding	I60*, I61*, I62*, R58, K92.0, K92.1, K92.2, K25.0, K25.1, K25.2, K25.4, K25.5, K25.6, K26.0, K26.1, K26.2, K26.4, K26.5, K266, K27.0, K27.1, K27.2, K27.4, K27.5, K27.6, K28.0, K28.1, K28.2, K28.4, K28.5, K28.6
Pulmonary embolism	I26*
Acute Coronary Syndrome	I20*, I21*, I22*
Infective Endocarditis	I33*, I38*, I39*

*International Classification of Diseases, tenth revision (ICD-10)

Table S2. Rates of COVID-19 deaths per county region according to sex

County	Men	Women	Total
Bedfordshire	267 (1.3%)	168 (1.1%)	435 (1.2%)
Berkshire	298 (1.4%)	271 (1.7%)	569 (1.6%)
Bristol	152 (0.7%)	114 (0.7%)	266 (0.7%)
Buckinghamshire	204 (1%)	190 (1.2%)	394 (1.1%)
Cambridgeshire	201 (1%)	141 (0.9%)	342 (0.9%)
Cheshire	422 (2.1%)	341 (2.2%)	763 (2.1%)
Cornwall	91 (0.4%)	46 (0.3%)	137 (0.4%)
Cumbria	191 (0.9%)	165 (1.1%)	356 (1%)
Derbyshire	337 (1.6%)	270 (1.7%)	607 (1.7%)
Devon	166 (0.8%)	128 (0.8%)	294 (0.8%)
Dorset	54 (0.3%)	39 (0.2%)	93 (0.3%)
Durham	317 (1.5%)	302 (1.9%)	619 (1.7%)
East Sussex	161 (0.8%)	127 (0.8%)	288 (0.8%)
East York	146 (0.7%)	78 (0.5%)	224 (0.6%)
Essex	745 (3.6%)	505 (3.2%)	1250 (3.5%)
Gloucestershire	269 (1.3%)	235 (1.5%)	504 (1.4%)
Hampshire	493 (2.4%)	364 (2.3%)	857 (2.4%)
Hertfordshire	452 (2.2%)	364 (2.3%)	816 (2.3%)
Isle of Wight	21 (0.1%)	22 (0.1%)	43 (0.1%)
Kent	535 (2.6%)	407 (2.6%)	942 (2.6%)
Lancashire	275 (1.3%)	182 (1.2%)	457 (1.3%)
Lancashire	174 (0.8%)	139 (0.9%)	313 (0.9%)
Leicestershire	257 (1.3%)	211 (1.4%)	468 (1.3%)
Lincolnshire	154 (0.7%)	113 (0.7%)	267 (0.7%)
London	4519 (22%)	2991 (19.1%)	7510 (20.8%)
Manchester	1256 (6.1%)	1023 (6.5%)	2279 (6.3%)
Merseyside	752 (3.7%)	578 (3.7%)	1330 (3.7%)
Norfolk	235 (1.1%)	149 (1%)	384 (1.1%)
North Yorkshire	370 (1.8%)	297 (1.9%)	667 (1.8%)
Northampton	216 (1.1%)	176 (1.1%)	392 (1.1%)
Northumberland	118 (0.6%)	97 (0.6%)	215 (0.6%)
Nottinghamshire	367 (1.8%)	311 (2%)	678 (1.9%)
Oxfordshire	221 (1.1%)	183 (1.2%)	404 (1.1%)
Rutland	<15 (0%)*	<15 (0%)*	<15 (0%)*
Shropshire	117 (0.6%)	95 (0.6%)	212 (0.6%)
Somerset	102 (0.5%)	62 (0.4%)	164 (0.5%)
South Yorkshire	460 (2.2%)	430 (2.8%)	890 (2.5%)
Stafford	336 (1.6%)	276 (1.8%)	612 (1.7%)
Suffolk	184 (0.9%)	140 (0.9%)	324 (0.9%)
Surrey	547 (2.7%)	436 (2.8%)	983 (2.7%)

Tyne & Wear	432 (2.1%)	426 (2.7%)	858 (2.4%)
Wales	810 (3.9%)	638 (4.1%)	1448 (4%)
Warwick	213 (1%)	161 (1%)	374 (1%)
West Midlands	1543 (7.5%)	1113 (7.1%)	2656 (7.3%)
West Sussex	176 (0.9%)	144 (0.9%)	320 (0.9%)
West Yorkshire	795 (3.9%)	614 (3.9%)	1409 (3.9%)
Wiltshire	194 (0.9%)	168 (1.1%)	362 (1%)
Worcestershire	211 (1%)	196 (1.3%)	407 (1.1%)

*Exact number not revealed for confidentiality purposes

Table S3A. Characteristics and reported underlying conditions of deceased patients without COVID -19 according to sex and age group

Age Group (Sex)/Condition	<60 years (n=7671)			60-69 years (n=10767)			70-79 years (n=23624)			80-89 years (n=39100)			>90 years (n=26696)		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
Number of reported chronic underlying conditions															
0	1312 (29.9)	791 (24.1)	2103 (27.4)	1543 (24.4)	975 (21.9)	2518 (23.4)	3353 (25.2)	2483 (24)	5836 (24.7)	5322 (28.2)	6061 (30)	11383 (29.1)	3291 (36.6)	7078 (40)	10369 (38.8)
1	2378 (54.1)	2098 (64)	4476 (58.3)	3077 (48.7)	2550 (57.4)	5627 (52.3)	5766 (43.4)	5188 (50.2)	10954 (46.4)	7486 (39.7)	8589 (42.5)	16075 (41.1)	3197 (35.5)	6800 (38.4)	9997 (37.4)
2	518 (11.8)	304 (9.3)	822 (10.7)	1133 (17.9)	654 (14.7)	1787 (16.6)	2619 (19.7)	1781 (17.2)	4400 (18.6)	3789 (20.1)	3710 (18.3)	7499 (19.2)	1670 (18.6)	2622 (14.8)	4292 (16.1)
≥3	185 (4.2)	85 (2.6)	270 (3.5)	568 (9)	267 (6)	835 (7.8)	1560 (11.7)	874 (8.5)	2434 (10.3)	2270 (12)	1873 (9.3)	4143 (10.6)	842 (9.4)	1197 (6.8)	2039 (7.6)
Chronic conditions															
Pre-existing Ischaemic Heart Disease, n (%)	456 (10.4)	95 (2.9)	551 (7.2)	929 (14.7)	280 (6.3)	1209 (11.2)	2173 (16.3)	888 (8.6)	3061 (13)	3199 (17)	1994 (9.9)	5193 (13.3)	1357 (15.1)	1542 (8.7)	2899 (10.9)
Heart Failure, n (%)	239 (5.4)	127 (3.9)	366 (4.8)	527 (8.3)	233 (5.2)	760 (7.1)	1332 (10)	859 (8.3)	2191 (9.3)	2491 (13.2)	2237 (11.1)	4728 (12.1)	1318 (14.6)	1856 (10.5)	3174 (11.9)
Dementia, n (%)	20 (0.5)	23 (0.7)	43 (0.6)	156 (2.5)	105 (2.4)	261 (2.4)	1197 (9)	1036 (10)	2233 (9.5)	3511 (18.6)	4569 (22.6)	8080 (20.7)	1736 (19.3)	4757 (26.9)	6493 (24.3)
Chronic Kidney Disease, n (%)	146 (3.3)	97 (3)	243 (3.2)	287 (4.5)	199 (4.5)	486 (4.5)	935 (7)	588 (5.7)	1523 (6.4)	1814 (9.6)	1727 (8.5)	3541 (9.1)	991 (11)	1488 (8.4)	2479 (9.3)

Hypertension, n (%)	293 (6.7)	137 (4.2)	430 (5.6)	631 (10)	367 (8.3)	998 (9.3)	1541 (11.6)	1101 (10.7)	2642 (11.2)	2212 (11.7)	2611 (12.9)	4823 (12.3)	978 (10.9)	2191 (12.4)	3169 (11.9)
Chronic Lung Disease, n (%)	289 (6.6)	249 (7.6)	538 (7)	882 (14)	646 (14.5)	1528 (14.2)	2205 (16.6)	1756 (17)	3961 (16.8)	2378 (12.6)	2170 (10.7)	4548 (11.6)	796 (8.8)	934 (5.3)	1730 (6.5)
Diabetes, n (%)	280 (6.4)	149 (4.5)	429 (5.6)	608 (9.6)	330 (7.4)	938 (8.7)	1403 (10.6)	821 (8)	2224 (9.4)	1915 (10.1)	1689 (8.3)	3604 (9.2)	627 (7)	948 (5.4)	1575 (5.9)
Liver Disease, n (%)	532 (12.1)	316 (9.6)	848 (11.1)	396 (6.3)	199 (4.5)	595 (5.5)	379 (2.9)	222 (2.1)	601 (2.5)	177 (0.9)	132 (0.7)	309 (0.8)	32 (0.4)	26 (0.1)	58 (0.2)
Peripheral Vascular Disease, n (%)	59 (1.3)	21 (0.6)	80 (1)	164 (2.6)	73 (1.6)	237 (2.2)	362 (2.7)	174 (1.7)	536 (2.3)	463 (2.5)	352 (1.7)	815 (2.1)	141 (1.6)	234 (1.3)	375 (1.4)
Valvular Heart Disease, n (%)	39 (0.9)	18 (0.5)	57 (0.7)	79 (1.2)	34 (0.8)	113 (1)	216 (1.6)	134 (1.3)	350 (1.5)	446 (2.4)	403 (2)	849 (2.2)	239 (2.7)	292 (1.6)	531 (2)
Cancers, n (%)	1457 (33.2)	1614 (49.2)	3071 (40)	2288 (36.2)	2095 (47.1)	4383 (40.7)	4045 (30.4)	3719 (36)	7764 (32.9)	3683 (19.5)	3861 (19.1)	7544 (19.3)	1002 (11.1)	1456 (8.2)	2458 (9.2)
Acute conditions															
Stroke[a], n (%)	239 (5.4)	200 (6.1)	439 (5.7)	414 (6.5)	275 (6.2)	689 (6.4)	934 (7)	850 (8.2)	1784 (7.6)	1459 (7.7)	1727 (8.5)	3186 (8.1)	574 (6.4)	1257 (7.1)	1831 (6.9)
Major Bleeding, n (%)	258 (5.9)	162 (4.9)	420 (5.5)	271 (4.3)	184 (4.1)	455 (4.2)	389 (2.9)	388 (3.8)	777 (3.3)	488 (2.6)	546 (2.7)	1034 (2.6)	179 (2)	295 (1.7)	474 (1.8)
Pulmonary embolism, n (%)	164 (3.7)	131 (4)	295 (3.8)	226 (3.6)	152 (3.4)	378 (3.5)	255 (1.9)	278 (2.7)	533 (2.3)	227 (1.2)	335 (1.7)	562 (1.4)	60 (0.7)	131 (0.7)	191 (0.7)
Acute Coronary Syndrome, n (%)	372 (8.5)	80 (2.4)	452 (5.9)	476 (7.5)	169 (3.8)	645 (6)	788 (5.9)	395 (3.8)	1183 (5)	748 (4)	583 (2.9)	1331 (3.4)	230 (2.6)	302 (1.7)	532 (2)
Infective Endocarditis, n (%)	43 (1)	22 (0.7)	65 (0.8)	43 (0.7)	22 (0.5)	65 (0.6)	119 (0.9)	78 (0.8)	197 (0.8)	139 (0.7)	141 (0.7)	280 (0.7)	46 (0.5)	80 (0.5)	126 (0.5)

n=number of cases

[a] Includes bleeding and ischaemic strokes

Table S3B. Characteristics and underlying conditions of deceased patients with COVID-19 according to sex and age group

Age Group (Sex)/Condition	<60 years (n=2599)			60-69 years (n=3830)			70-79 years (n=8554)			80-89 years (n=14189)			>90 years (n=7266)		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
Number of reported chronic underlying conditions															
0	753 (44.7)	343 (37.6)	1096 (42.2)	788 (30.8)	402 (31.5)	1190 (31.1)	1455 (26.8)	897 (28.7)	2352 (27.5)	2260 (28.5)	1972 (31.6)	4232 (29.8)	1062 (34.3)	1673 (40.1)	2735 (37.6)
1	594 (35.2)	392 (42.9)	986 (37.9)	940 (36.8)	512 (40.2)	1452 (37.9)	1995 (36.8)	1212 (38.8)	3207 (37.5)	2855 (35.9)	2368 (37.9)	5223 (36.8)	1117 (36.1)	1544 (37)	2661 (36.6)
2	248 (14.7)	132 (14.5)	380 (14.6)	547 (21.4)	250 (19.6)	797 (20.8)	1271 (23.4)	650 (20.8)	1921 (22.5)	1850 (23.3)	1273 (20.4)	3123 (22)	621 (20.1)	660 (15.8)	1281 (17.6)
≥3	91 (5.4)	46 (5)	137 (5.3)	280 (11)	111 (8.7)	391 (10.2)	706 (13)	368 (11.8)	1074 (12.6)	977 (12.3)	634 (10.1)	1611 (11.4)	297 (9.6)	292 (7)	589 (8.1)
Chronic conditions															
Pre-existing Ischaemic Heart Disease, n (%)	88 (5.2)	31 (3.4)	119 (4.6)	327 (12.8)	68 (5.3)	395 (10.3)	826 (15.2)	252 (8.1)	1078 (12.6)	1245 (15.7)	525 (8.4)	1770 (12.5)	432 (13.9)	359 (8.6)	791 (10.9)
Heart Failure, n (%)	37 (2.2)	20 (2.2)	57 (2.2)	143 (5.6)	67 (5.3)	210 (5.5)	349 (6.4)	229 (7.3)	578 (6.8)	744 (9.4)	578 (9.3)	1322 (9.3)	336 (10.8)	407 (9.8)	743 (10.2)
Dementia, n (%)	16 (0.9)	14 (1.5)	30 (1.2)	89 (3.5)	48 (3.8)	137 (3.6)	756 (13.9)	472 (15.1)	1228 (14.4)	1846 (23.2)	1608 (25.7)	3454 (24.3)	816 (26.3)	1186 (28.4)	2002 (27.6)
Chronic Kidney Disease, n (%)	106 (6.3)	67 (7.3)	173 (6.7)	232 (9.1)	122 (9.6)	354 (9.2)	591 (10.9)	294 (9.4)	885 (10.3)	1033 (13)	646 (10.3)	1679 (11.8)	392 (12.7)	371 (8.9)	763 (10.5)
Hypertension, n (%)	357 (21.2)	133 (14.6)	490 (18.9)	659 (25.8)	254 (19.9)	913 (23.8)	1204 (22.2)	647 (20.7)	1851 (21.6)	1479 (18.6)	1138 (18.2)	2617 (18.4)	472 (15.2)	568 (13.6)	1040 (14.3)

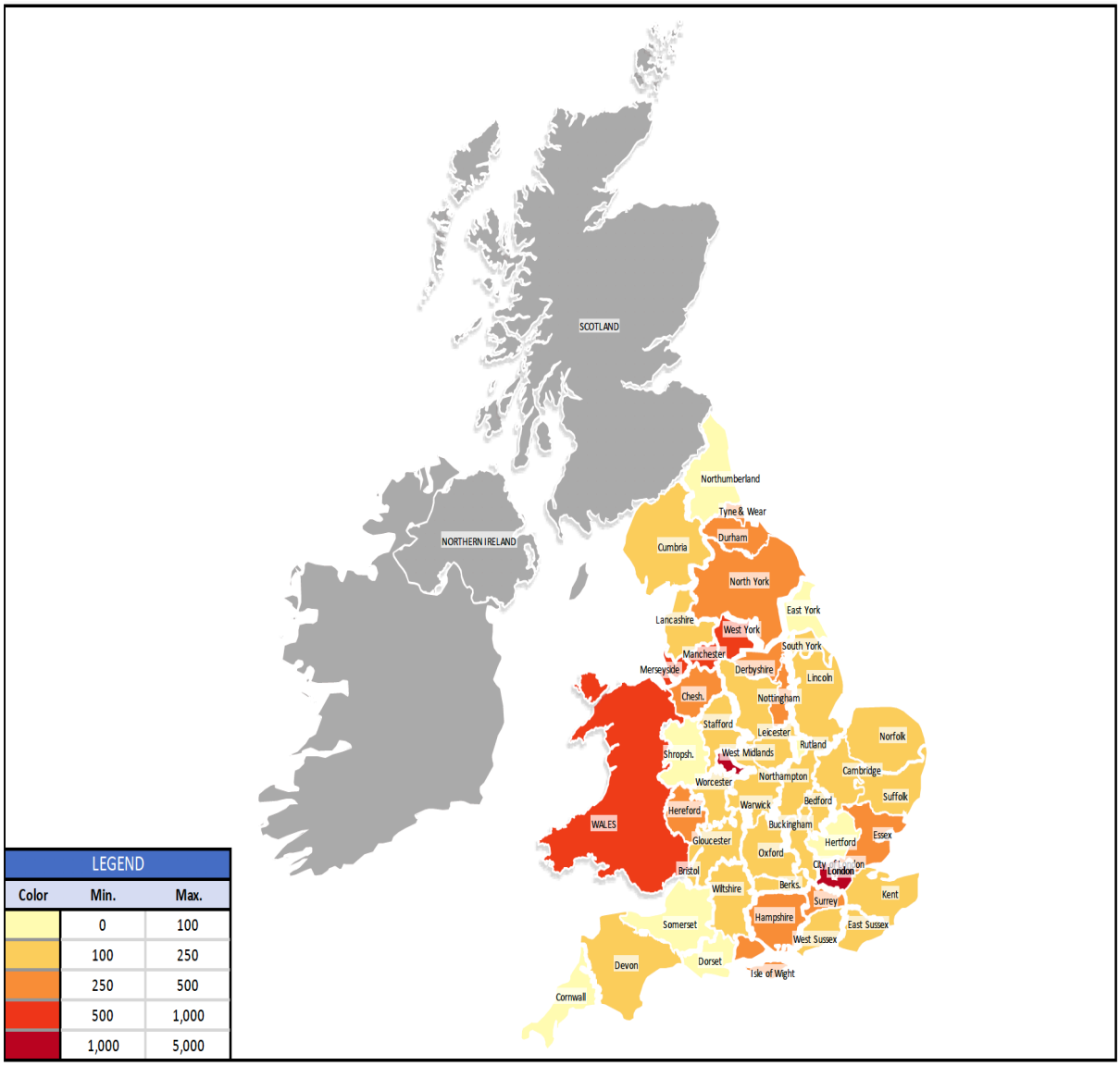
Chronic Lung Disease, n (%)	157 (9.3)	172 (18.8)	329 (12.7)	374 (14.6)	290 (22.7)	664 (17.3)	1040 (19.2)	733 (23.4)	1773 (20.7)	1233 (15.5)	1010 (16.2)	2243 (15.8)	321 (10.4)	354 (8.5)	675 (9.3)
Diabetes, n (%)	311 (18.4)	151 (16.5)	462 (17.8)	573 (22.4)	233 (18.3)	806 (21)	1112 (20.5)	547 (17.5)	1659 (19.4)	1231 (15.5)	802 (12.8)	2033 (14.3)	304 (9.8)	287 (6.9)	591 (8.1)
Liver Disease, n (%)	87 (5.2)	56 (6.1)	143 (5.5)	80 (3.1)	47 (3.7)	127 (3.3)	66 (1.2)	46 (1.5)	112 (1.3)	40 (0.5)	30 (0.5)	70 (0.5)	5 (0.2)	3 (0.1)	8 (0.1)
Peripheral Vascular Disease, n (%)	13 (0.8)	5 (0.5)	18 (0.7)	53 (2.1)	14 (1.1)	67 (1.7)	136 (2.5)	33 (1.1)	169 (2)	122 (1.5)	53 (0.8)	175 (1.2)	33 (1.1)	25 (0.6)	58 (0.8)
Valvular Heart Disease, n (%)	4 (0.2)	4 (0.4)	8 (0.3)	17 (0.7)	9 (0.7)	26 (0.7)	69 (1.3)	25 (0.8)	94 (1.1)	125 (1.6)	109 (1.7)	234 (1.6)	58 (1.9)	55 (1.3)	113 (1.6)
Cancers, n (%)	125 (7.4)	114 (12.5)	239 (9.2)	256 (10)	178 (14)	434 (11.3)	555 (10.2)	358 (11.4)	913 (10.7)	550 (6.9)	408 (6.5)	958 (6.8)	129 (4.2)	158 (3.8)	287 (3.9)
Acute conditions															
Stroke[a], n (%)	66 (3.9)	45 (4.9)	111 (4.3)	150 (5.9)	68 (5.3)	218 (5.7)	365 (6.7)	179 (5.7)	544 (6.4)	547 (6.9)	356 (5.7)	903 (6.4)	159 (5.1)	191 (4.6)	350 (4.8)
Major Bleeding, n (%)	35 (2.1)	23 (2.5)	58 (2.2)	41 (1.6)	15 (1.2)	56 (1.5)	39 (0.7)	30 (1)	69 (0.8)	80 (1)	38 (0.6)	118 (0.8)	23 (0.7)	14 (0.3)	37 (0.5)
Pulmonary embolism, n (%)	51 (3)	24 (2.6)	75 (2.9)	73 (2.9)	23 (1.8)	96 (2.5)	77 (1.4)	53 (1.7)	130 (1.5)	65 (0.8)	62 (1)	127 (0.9)	14 (0.5)	19 (0.5)	33 (0.5)
Acute Coronary Syndrome, n (%)	26 (1.5)	7 (0.8)	33 (1.3)	45 (1.8)	12 (0.9)	57 (1.5)	92 (1.7)	30 (1)	122 (1.4)	112 (1.4)	57 (0.9)	169 (1.2)	32 (1)	31 (0.7)	63 (0.9)
Infective Endocarditis, n (%)	6 (0.4)	5 (0.5)	11 (0.4)	7 (0.3)	7 (0.5)	14 (0.4)	25 (0.5)	16 (0.5)	41 (0.5)	38 (0.5)	38 (0.6)	76 (0.5)	9 (0.3)	14 (0.3)	23 (0.3)

n=number of cases

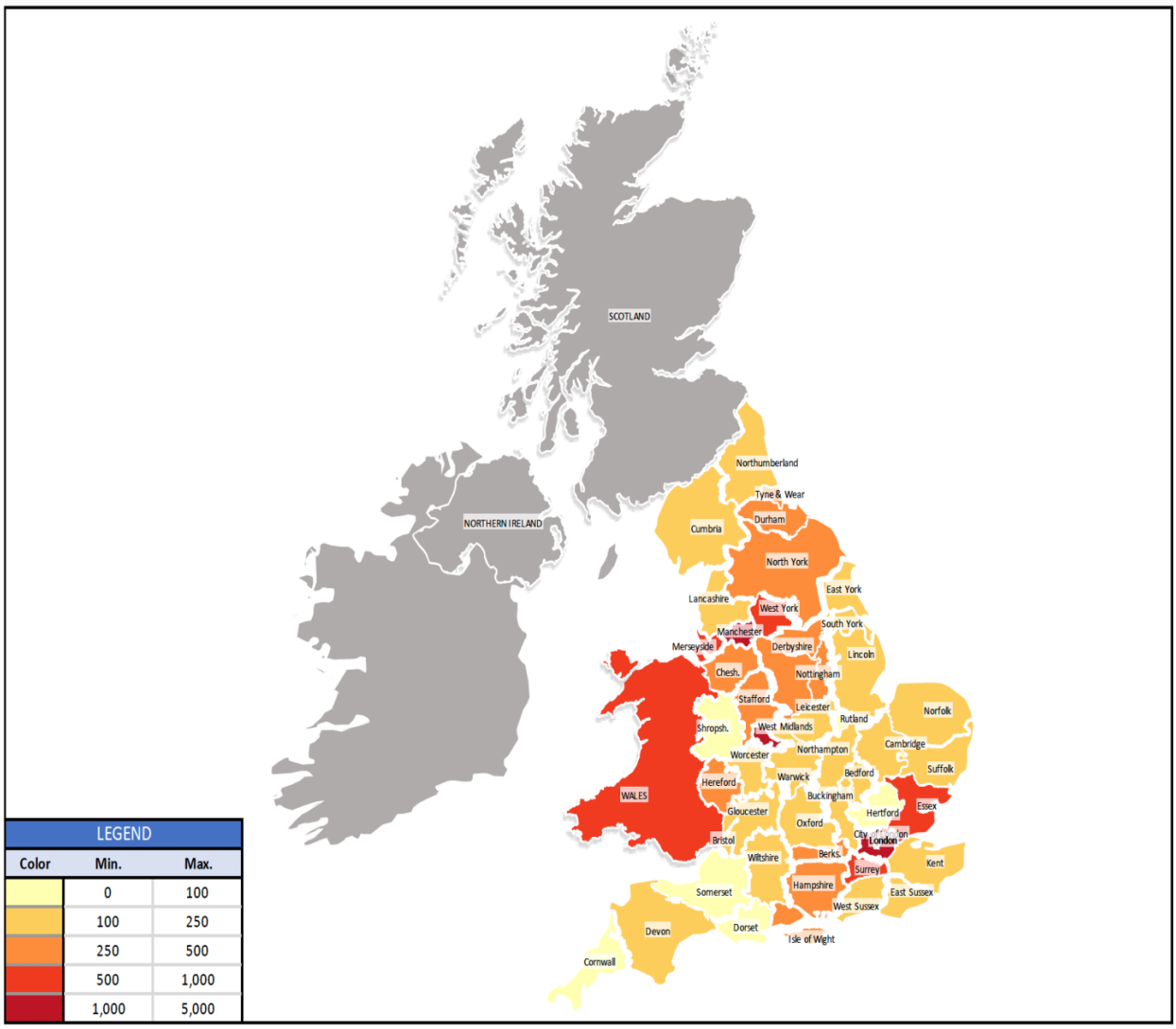
[a] Includes bleeding and ischaemic strokes

Figure S1. Distribution of Covid-19 deaths in England and Wales in A) Men and B) Women*

A)



B)



*Start of pandemic through 12th May 2020

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Manuscript No.: 2020-1269

Manuscript Title: Sex-differences in mortality rates and underlying conditions for COVID-19 deaths in England and Wales

Date Submitted: 15-Jun-2020

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4. Expert testimony	✓			
5. Grants/grants pending	✓			Amgen, AstraZeneca, Ablative Solutions
6. Payment for lectures including service on speakers bureaus	✓			Bayer Healthcare, Amgen, Novo Nordisk, Pfizer
7. Payment for manuscript preparation	✓			
8. Patents (planned, pending or issued)	✓			
9. Royalties	✓			
10. Payment for development of educational presentations			✓	Amgen, Bayer, Boehringer Ingelheim, Daichi Sankyo, Novartis, Servier, Sanofi
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Mayo Clinic Proceedings
Underlying Conditions in COVID-19 Deaths

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

Mohamed O. Mohamed, MRCP(UK)[1,2], Chris P. Gale, PhD FRCP[3,4,5], Evangelos Kontopantelis, PhD[6], Tim Doran, MD[7], Mark de Belder, MD FRCP[8], Miqdad Asaria, PhD[9], Thomas Luscher, MD FRCP[10], Jianhua Wu, PhD[3], Muhammad Rashid, PhD[1,2], Courtney Stephenson, BSc[11], Tom Denwood, MSc[11], Chris Roebuck, MSc[11], John Deanfield, FRCP[12], Mamas A. Mamas, DPhil[1,2]

1. Keele Cardiovascular Research Group, Centre for Prognosis Research, Institutes of Applied Clinical Science and Primary Care and Health Sciences, Keele University, United Kingdom
2. Department of Cardiology, Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom
3. Leeds Institute for Data analytics, University of Leeds, Leeds, UK
4. Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
5. Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
6. Division of Informatics, Imaging and Data Science, University of Manchester, Manchester, UK.
7. Department of Health Sciences, University of York, York, UK.
8. National Institute for Cardiovascular Outcomes Research, Barts Health NHS Trust, UK
9. London School of Economics, London, UK
10. Royal Brompton and Harefield NHS Foundation Trust, London, UK
11. NHS Digital
12. University College London, London, UK

Correspondence to:

Mamas A. Mamas
Professor of Cardiology
Keele Cardiovascular Research Group,
Centre for Prognosis Research,
Institute for Primary Care and Health Sciences,
Keele University, UK
mamasmamas1@yahoo.co.uk

Key Words: COVID-19; deaths; England; United Kingdom; outcomes; sex differences

Abbreviations

ACS	Acute coronary syndrome
ASMR	Age standardized mortality rate
CVD	Cardiovascular disease
IHD	Ischemic heart disease
ONS	Office for National Statistics

Abstract

Background: Limited national data exists on the prevalence and distribution of underlying conditions among COVID-19 deaths between sexes and across age groups.

Methods: All adult (≥18 years) deaths recorded in England and Wales (1st March 2020 to 12th May 2020) were retrospectively analyzed. We compared 1) the prevalence of underlying health conditions between COVID and non-COVID related deaths during the COVID-19 pandemic and 2) 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 cases. Women represented 43.2% (n=15,731) of COVID deaths compared to 51.9% (n=55,980) in non-COVID deaths. Overall, COVID deaths were younger 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 30-79 years. A linear relationship was observed between ASMR and age amongst 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 amongst COVID deaths. Pre-existing ischemic heart disease was similar in COVID (11.4%) and non-COVID (12%) deaths.

Conclusions: 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.

Introduction

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 (UK) has the second highest recorded number of deaths in the world after the US, with 39,728 deaths recorded as of 6th June 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 5 6] Furthermore, differences in COVID-19 survival has been observed between sexes, with females 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 females.[4-8] Detailed data concerning underlying conditions is limited, with data from New York state reporting that 89.7% of fatalities attributed to COVID-19 had at least one comorbidity, most commonly hypertension, diabetes and hyperlipidemia.[9] In the UK 91% of COVID-19 deaths in March 2020 had at least one 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 that have died from COVID-19. [11-13] Furthermore, it is unclear as to how the underlying conditions in COVID-19 deaths differ from those in similar age/sex groups that have died from non-COVID related causes.

Therefore, we investigated the pre-existing conditions in adults (≥18 years) who had died from COVID-19 in England and Wales between 1st March 2020 and 12th May 2020, stratified by sex and age group, and compare this with patients whose death was 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 1st March 2020 and 12th May 2020 in England and Wales 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 since their susceptibility to death from COVID-19 is significantly lower than adults, and the pattern of their causes of death vary to those in adults. [14] The process of death certification and registration is a legal requirement in the United Kingdom where a doctor who has seen the deceased within the last 14 days of life must complete a Medical Cause of Death Certificate unless a post-mortem 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, tenth 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, 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 **Supplementary Table S1**.

Statistical Analysis

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 (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89 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 chi squared (X^2) test or Fisher's exact test, where 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 (College Station, TX).

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 decisions in the Cabinet Office Briefing Room (COBR)) and by 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 1st March and 12th May 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 2nd March 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<0.001).

The majority of death were observed among people aged 80-89 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 60-69 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 4th and 20th April 2020. The ASMR was approximately two-fold higher in men compared to 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 all age groups and sexes, with the exception of cancer deaths for women aged 30-79 years. The highest number of COVID-19 deaths was in London (total/male/female: 7,510, 4,519, 2,991). (**Table S2, Figure S1**)

Approximately a third of individuals had no underlying chronic conditions in the non-COVID (29.9%) and COVID groups (31.8%), and close to one in ten patients with COVID-19 and non-COVID-19 deaths had three 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 amongst 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. (**Supplementary Tables S3A and S3B**)

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**). Amongst COVID-19 deaths, women had higher rates of dementia (21.2% vs. 17%, $p<.001$) as underlying conditions compared with men whilst 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%), 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. While this pattern was generally consistent across the age groups, the rates of certain underlying conditions were higher for the younger age bands (**Table S3A and S3B, Figure 4**) Pulmonary embolism was more frequently reported in <60 and 60-69 age deciles, more so in men than women (<60 years: 3.0% vs. 2.6%, 60-69 years: 2.9% vs. 1.8%, $p<.001$ for both). Individuals in the younger age deciles were also more likely to have cancer with higher rates observed in women compared to men (<60 years: 12.5% vs. 7.4%, 60-69 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 & 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 30-79 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 70-79 and 80-89 age groups, with the median age being 82 years. The median age of death in Italy was 81 years, based on 31,096 deaths (as of May 21st, 2020), which is similar to our findings. Their report demonstrates that the highest number of deaths was observed in the 80-89 years group (n=12,729/31, 096), followed by 70-79 years (n=8466) and ≥90 years (n=5227), however age standardized mortality rates 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 13th May 2020 demonstrates that mortality was highest in the 75-84 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 since 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] Age-standardized mortality rates take in to account differences in the age structure of a population and allow a more direct comparison of underlying conditions especially when these vary by age. Whilst 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 age standardized mortality rate 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 30-79 years whose mortality from cancer was comparable to that from COVID.

Our findings suggest that age-standardized mortality in men was almost double compared to that of women across all age groups, despite crude death rates suggesting a significantly higher proportion of women ≥90 years dying from COVID-19 compared with men. Our crude findings are consistent with reports in the US, which show 41.7% of female deaths were amongst those 85 years and older compared to only 23.9% in men, with higher mortality in younger male age groups compared to 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 where 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 to women as demonstrated in our analysis. Another proposed hypothesis relates to the circulating level of angiotensin-converting enzyme 2 (ACE2), the main host cell receptor towards 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 to children. [28] [5, 29] Furthermore, women are believed to have a better immune response against viral infections compared with men, primarily due to 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 females throughout, could also explain the higher rate of mortality elder 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 to other studies due 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, where acute events were reported as COVID deaths. Previous studies have suggested a high prevalence of certain comorbidities such as hypertension and ischemic heart disease in patients who died from COVID-19. [20] [24, 25] [30] However, these have been mostly limited by their small sample size or analysis of selected cohorts (e.g. intensive care admission only). In our analysis we find that a third of individuals 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.

Interestingly, we find that the prevalence of ischemic heart disease in COVID-19 related deaths is similar to that observed in non COVID-19 deaths, apart from in younger men (<60 years old) where paradoxically the prevalence is double that in patients that died non-COVID deaths. Reports from several studies have demonstrated a high prevalence of cardiovascular disease (CVD) in patients with COVID-19. [25] [24] [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 (OR) of hypertension and CVD were significantly higher in patients with severe than non-severe 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 from COVID, who may have greater baseline comorbidity. In a report from the Italian Instituto Superiore Di Sanita the prevalence of hypertension (68.3%) and ischemic heart disease (28.3%) was significantly higher in COVID deaths (n=31.096). [35] Differences between countries may reflect differences in reporting methods, or sociodemographic and genetic differences.

Amongst 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 to men, whilst 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 60-69 age deciles amongst COVID deaths, more so in men than women, whereas cancer rates were higher in younger age groups, especially in women compared to 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 to 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 are in line with our findings. [35] However, their report did not compare these conditions between age groups.

The present 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 who could benefit from prolonged shielding, especially in the event of a second peak, and/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, that may confound our analyses, particularly given that the mortality rate from COVID-19 in Black, Asian and minority ethnic people have been reported as up to three times greater.[36]

Conclusions

In this nationwide analysis of deaths in England and Wales between 1st March and 12th May 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 30-79 years, whose adjusted-mortality was higher than COVID-19. Our findings also suggest persistently higher age-adjusted mortality in men compared to 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 stakeholders' and government body policies by identifying high-risk groups.

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Table 1. Crude and age-standardised mortality rates (ASMR)[a] between 1st March and 12th May 2020 depending on COVID-19 status and sex

	COVID-negative									COVID-positive								
	Men (n=51879)			Women (n=55980)			Total (n=107859)			Men (n=20707)			Women (n=15731)			Total (n=36438)		
	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	10767	10.0%	172.5	2555	12.3%	84	1275	8.1%	39.9	3830	10.5%	61.4
70-79	13298	25.6%	576.1	10326	18.4%	400.7	23624	21.9%	483.6	5427	26.2%	235.1	3127	19.9%	121.3	8554	23.5%	175.1
80-89	18867	36.4%	1853.9	20233	36.1%	1452.9	39100	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	17696	31.6%	4889.3	26696	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

Table 2. Frequencies and age-standardised mortality rates (ASMR) of primary causes of deaths ([a] ASMR: per 100,000 population).

	Age group (years)							
Primary cause of death, n (ASMR[a])	**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)
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)	11390 (472.6)	8610 (1627.7)

Table 3. Characteristics and underlying conditions of reported deaths according to COVID status and sex

	COVID-negative				COVID-positive			
	Men (n=51879)	**Women (n=55980)**	**Total (n=107859)**	**p-value**	**Men (n=20707)**	**Women (n=15731)**	**Total (n=36438)**	**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	23564 (49.9)	23649 (50.1)	47213		2804 (61.7)	1739 (38.3)	4543	
April	23591 (46.9)	26687 (53.1)	50278		16221 (56.8)	12335 (43.2)	28556	
May[a]	4724 (45.6)	5644 (54.4)	10368		1682 (50.4)	1657 (49.6)	3339	
Number of reported chronic underlying conditions				<.001				<.001
0	14821 (28.6)	17388 (31.1)	32209 (29.9)		6318 (30.5)	5287 (33.6)	11605 (31.8)	
1	21904 (42.2)	25225 (45.1)	47129 (43.7)		7501 (36.2)	6028 (38.3)	13529 (37.1)	
2	9729 (18.8)	9071 (16.2)	18800 (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 Ischaemic Heart Disease, n (%)	8114 (15.6)	4799 (8.6)	12913 (12)	<.001	2918 (14.1)	1235 (7.9)	4153 (11.4)	<.001
Heart Failure, n (%)	5907 (11.4)	5312 (9.5)	11219 (10.4)	<.001	1609 (7.8)	1301 (8.3)	2910 (8)	.08
Dementia, n (%)	6620 (12.8)	10490 (18.7)	17110 (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)	12062 (11.2)	.005	4171 (20.1)	2740 (17.4)	6911 (19.0)	<.001
Chronic Lung Disease, n (%)	6550 (12.6)	5755 (10.3)	12305 (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 (%)	12475 (24)	12745 (22.8)	25220 (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 12th May 2020

[b] Includes bleeding and ischaemic strokes

IQR: interquartile range

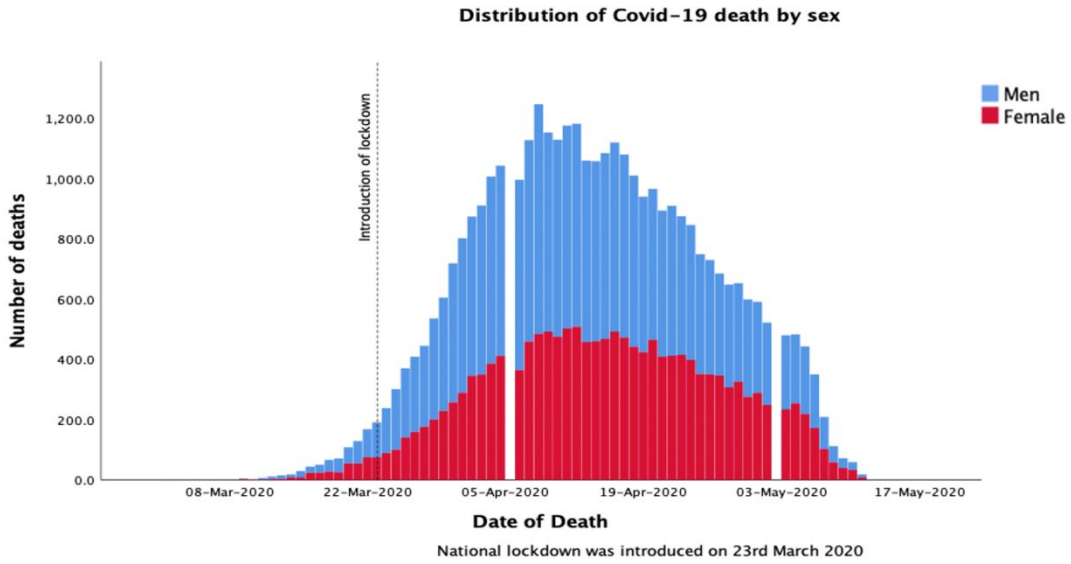
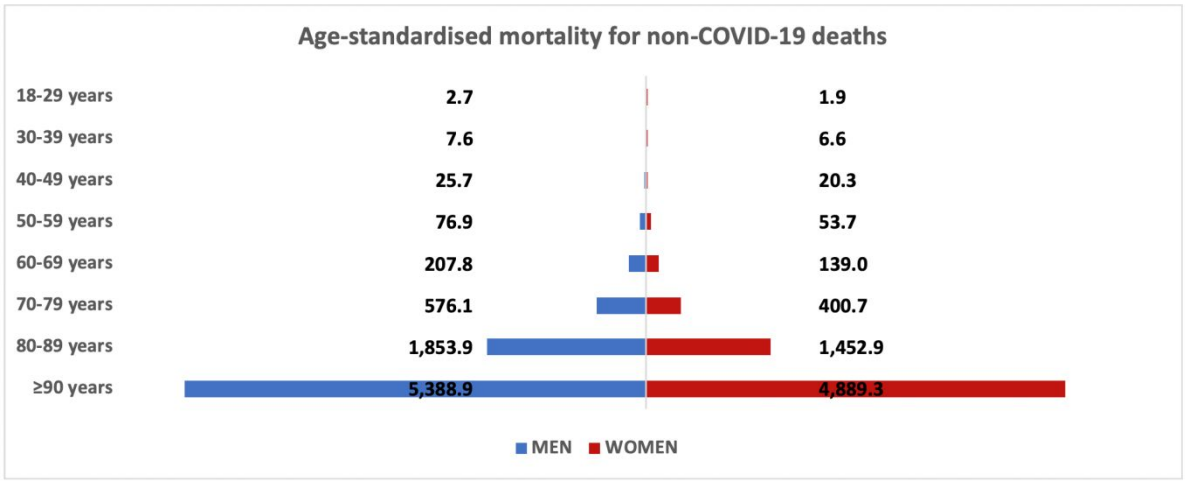


Figure 1. Distribution of Covid-19 deaths in England and Wales from the start of the pandemic through 12th May 2020 according to sex. ACS: acute coronary syndrome; CKD: chronic kidney disease: IHD: ischaemic heart disease; PE: pulmonary embolism.

2A



2B

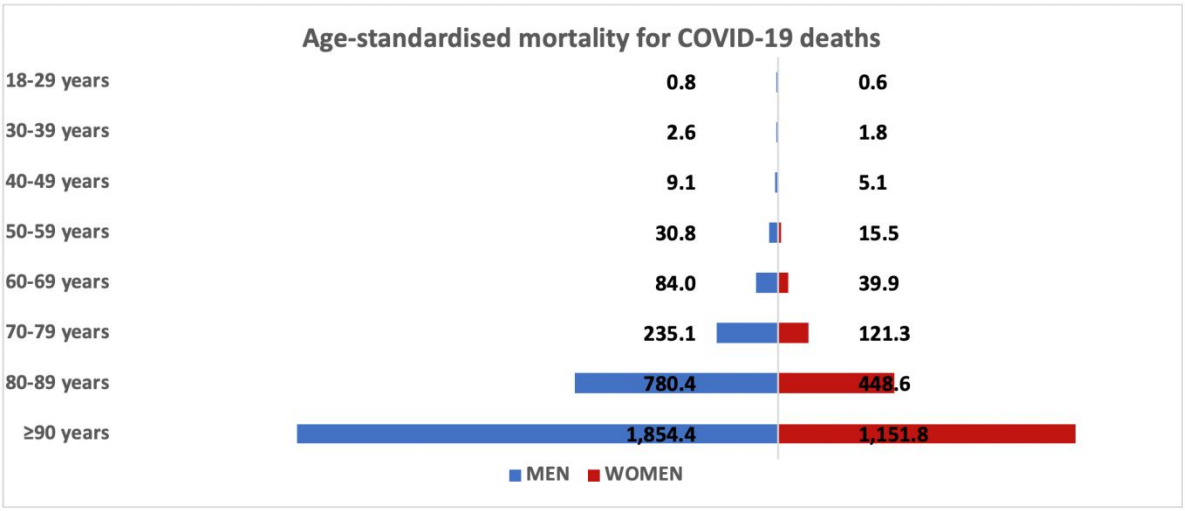


Figure 2. Age standardized mortality rate according to COVID status (per 100,000 population). ACS: acute coronary syndrome; CKD: chronic kidney disease: IHD: ischaemic heart disease; PE: pulmonary embolism.

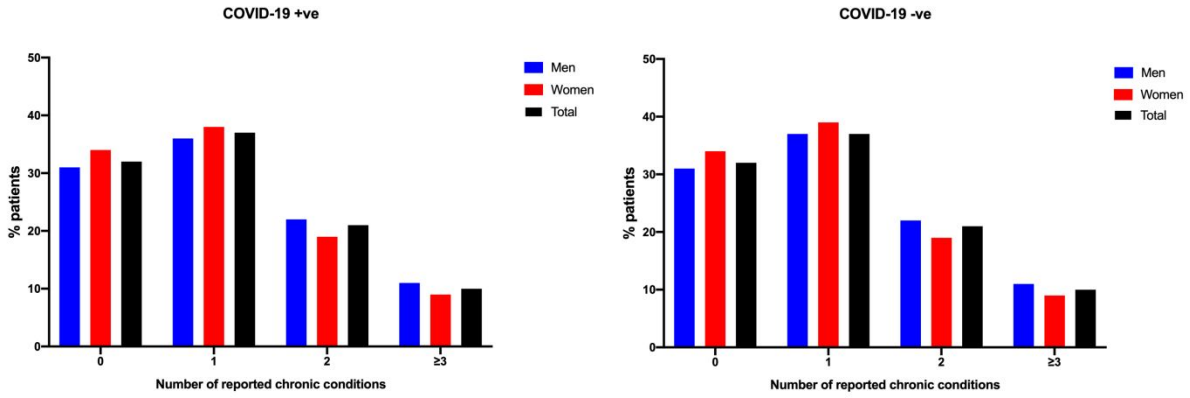
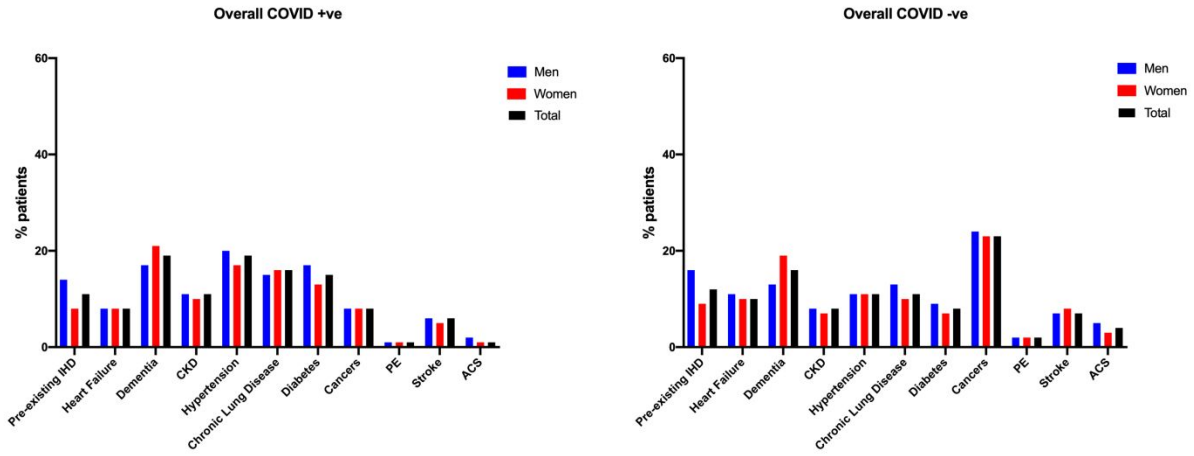
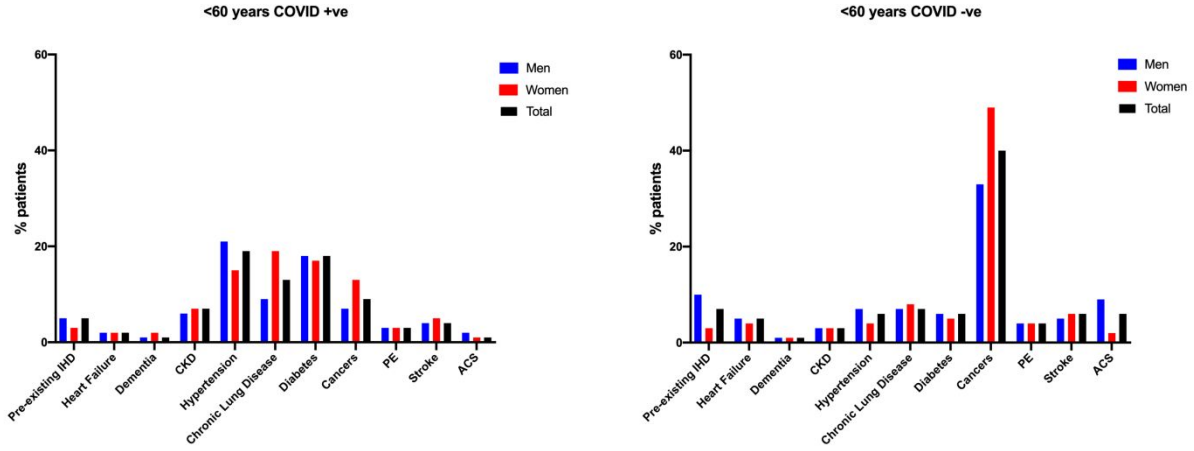


Figure 3. Number of reported underlying chronic conditions in the overall cohort and according to COVID status and sex. ACS: acute coronary syndrome; CKD: chronic kidney disease: IHD: ischaemic heart disease; PE: pulmonary embolism.

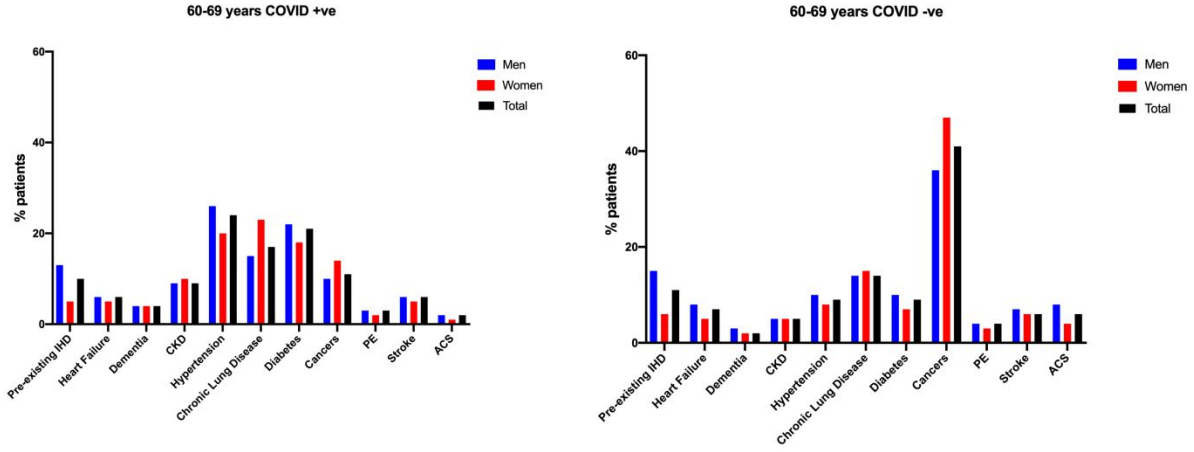
4A


Overall COVID +ve
Overall COVID -ve
Men
Women
Total
% patients
0
20
40
60
Pre-existing IHD
Heart Failure
Dementia
CKD
Hypertension
Chronic Lung Disease
Diabetes
Cancers
PE
Stroke
ACS

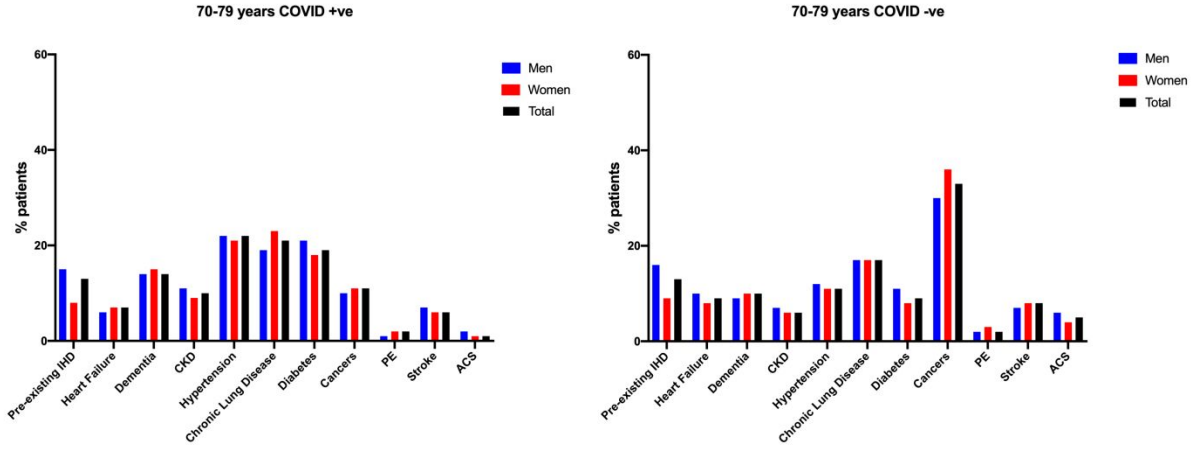
4B


<60 years COVID +ve
<60 years COVID -ve
Men
Women
Total
% patients
0
20
40
60
Pre-existing IHD
Heart Failure
Dementia
CKD
Hypertension
Chronic Lung Disease
Diabetes
Cancers
PE
Stroke
ACS

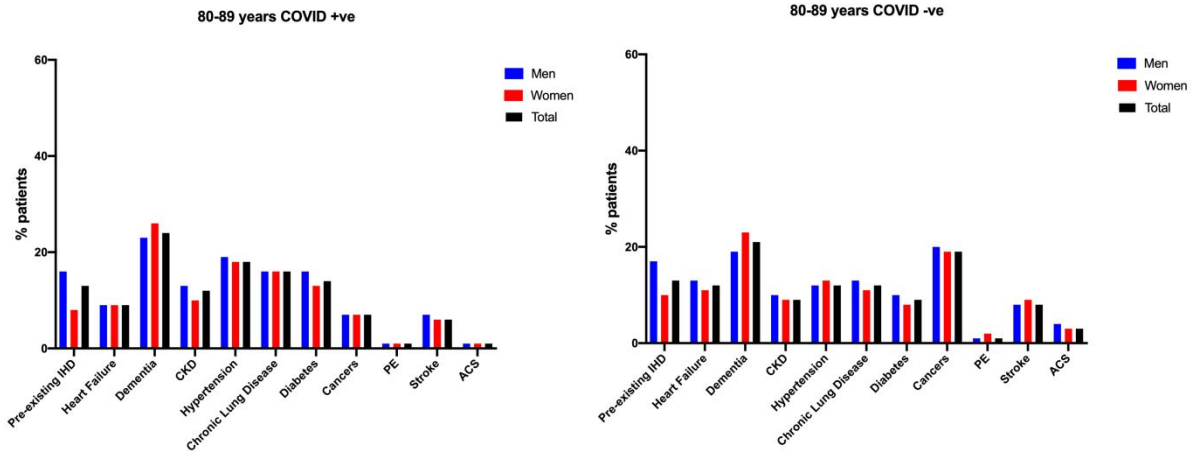
4C


60-69 years COVID +ve
60-69 years COVID -ve
Men
Women
Total
% patients
0
20
40
60
Pre-existing IHD
Heart Failure
Dementia
CKD
Hypertension
Chronic Lung Disease
Diabetes
Cancers
PE
Stroke
ACS

4D



4E



4F

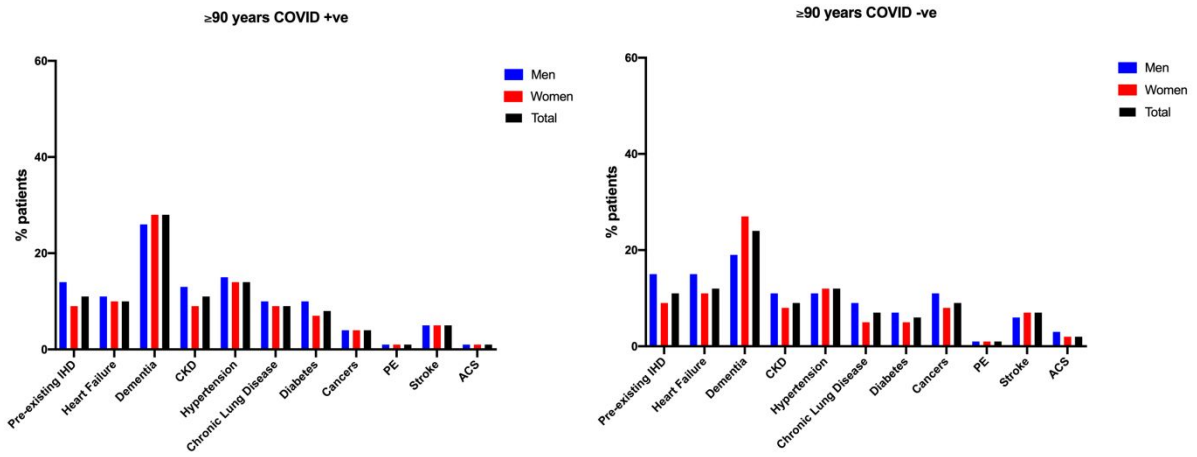


Figure 4. Top reported conditions associated with COVID and non-COVID deaths in England and Wales in overall cohort and according to sex and age group. ACS: acute coronary syndrome; CKD: chronic kidney disease: IHD: ischaemic heart disease; PE: pulmonary embolism.

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

Online Supplementary Material

- **Table S1.** List of ICD-10 CM diagnosis codes used in the study

- **Table S2**. Rates of COVID-19 deaths per county region according to sex

- **Table S3.** Characteristics and reported underlying conditions of deceased patients A) without and B) with COVID -19 according to sex and age group

- **Figure S1.** Distribution of Covid-19 deaths in England and Wales according to sex

Table S1. List of ICD-10 CM* diagnosis codes used in the study

Diagnosis	Codes
COVID-19	U07.1
Pre-existing Ischaemic Heart Disease	I25.2, I25.6, Z98.61, I25.10, I25.110, I25.111, I25.118, I25.119, I25.7*, I25.8*, I25.9*, Z95.1
Heart Failure	I50*, I42*, I25.5
Dementia	F01*, F02*, F03*
Chronic Kidney Disease	N18*
Hypertension	I10*
Chronic Lung Disease	J41*, J42*, J43*, J44*, J45*, J47*
Diabetes	E08*, E09*, E10*, E11*, E13*
Liver Disease	K70*, K72.1*, K72.9*, K73*, K74*, K75*, K76*, K77*
Peripheral Vascular Disease	I70*, I73*
Valvular Heart Disease	I34*, I35*, I36*, I37*
Cancers	C00-C96*
Stroke	G46.3, G46.4, G46.5, G46.6, G46.7, I60*, I61*, I62*, I63*, I64*
Major Bleeding	I60*, I61*, I62*, R58, K92.0, K92.1, K92.2, K25.0, K25.1, K25.2, K25.4, K25.5, K25.6, K26.0, K26.1, K26.2, K26.4, K26.5, K266, K27.0, K27.1, K27.2, K27.4, K27.5, K27.6, K28.0, K28.1, K28.2, K28.4, K28.5, K28.6
Pulmonary embolism	I26*
Acute Coronary Syndrome	I20*, I21*, I22*
Infective Endocarditis	I33*, I38*, I39*

*International Classification of Diseases, tenth revision (ICD-10)

Table S2. Rates of COVID-19 deaths per county region according to sex

County	Men	Women	Total
Bedfordshire	267 (1.3%)	168 (1.1%)	435 (1.2%)
Berkshire	298 (1.4%)	271 (1.7%)	569 (1.6%)
Bristol	152 (0.7%)	114 (0.7%)	266 (0.7%)
Buckinghamshire	204 (1%)	190 (1.2%)	394 (1.1%)
Cambridgeshire	201 (1%)	141 (0.9%)	342 (0.9%)
Cheshire	422 (2.1%)	341 (2.2%)	763 (2.1%)
Cornwall	91 (0.4%)	46 (0.3%)	137 (0.4%)
Cumbria	191 (0.9%)	165 (1.1%)	356 (1%)
Derbyshire	337 (1.6%)	270 (1.7%)	607 (1.7%)
Devon	166 (0.8%)	128 (0.8%)	294 (0.8%)
Dorset	54 (0.3%)	39 (0.2%)	93 (0.3%)
Durham	317 (1.5%)	302 (1.9%)	619 (1.7%)
East Sussex	161 (0.8%)	127 (0.8%)	288 (0.8%)
East York	146 (0.7%)	78 (0.5%)	224 (0.6%)
Essex	745 (3.6%)	505 (3.2%)	1250 (3.5%)
Gloucestershire	269 (1.3%)	235 (1.5%)	504 (1.4%)
Hampshire	493 (2.4%)	364 (2.3%)	857 (2.4%)
Hertfordshire	452 (2.2%)	364 (2.3%)	816 (2.3%)
Isle of Wight	21 (0.1%)	22 (0.1%)	43 (0.1%)
Kent	535 (2.6%)	407 (2.6%)	942 (2.6%)
Lancashire	275 (1.3%)	182 (1.2%)	457 (1.3%)
Lancashire	174 (0.8%)	139 (0.9%)	313 (0.9%)
Leicestershire	257 (1.3%)	211 (1.4%)	468 (1.3%)
Lincolnshire	154 (0.7%)	113 (0.7%)	267 (0.7%)
London	4519 (22%)	2991 (19.1%)	7510 (20.8%)
Manchester	1256 (6.1%)	1023 (6.5%)	2279 (6.3%)
Merseyside	752 (3.7%)	578 (3.7%)	1330 (3.7%)
Norfolk	235 (1.1%)	149 (1%)	384 (1.1%)
North Yorkshire	370 (1.8%)	297 (1.9%)	667 (1.8%)

Northampton	216 (1.1%)	176 (1.1%)	392 (1.1%)
Northumberland	118 (0.6%)	97 (0.6%)	215 (0.6%)
Nottinghamshire	367 (1.8%)	311 (2%)	678 (1.9%)
Oxfordshire	221 (1.1%)	183 (1.2%)	404 (1.1%)
Rutland	<15 (0%)*	<15 (0%)*	<15 (0%)*
Shropshire	117 (0.6%)	95 (0.6%)	212 (0.6%)
Somerset	102 (0.5%)	62 (0.4%)	164 (0.5%)
South Yorkshire	460 (2.2%)	430 (2.8%)	890 (2.5%)
Stafford	336 (1.6%)	276 (1.8%)	612 (1.7%)
Suffolk	184 (0.9%)	140 (0.9%)	324 (0.9%)
Surrey	547 (2.7%)	436 (2.8%)	983 (2.7%)
Tyne & Wear	432 (2.1%)	426 (2.7%)	858 (2.4%)
Wales	810 (3.9%)	638 (4.1%)	1448 (4%)
Warwick	213 (1%)	161 (1%)	374 (1%)
West Midlands	1543 (7.5%)	1113 (7.1%)	2656 (7.3%)
West Sussex	176 (0.9%)	144 (0.9%)	320 (0.9%)
West Yorkshire	795 (3.9%)	614 (3.9%)	1409 (3.9%)
Wiltshire	194 (0.9%)	168 (1.1%)	362 (1%)
Worcestershire	211 (1%)	196 (1.3%)	407 (1.1%)

*Exact number not revealed for confidentiality purposes

Table S3A. Characteristics and reported underlying conditions of deceased patients without COVID -19 according to sex and age group

Age Group (Sex)/Condition	<60 years (n=7671)			60-69 years (n=10767)			70-79 years (n=23624)			80-89 years (n=39100)			>90 years (n=26696)		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
Number of reported chronic underlying conditions															
0	1312 (29.9)	791 (24.1)	2103 (27.4)	1543 (24.4)	975 (21.9)	2518 (23.4)	3353 (25.2)	2483 (24)	5836 (24.7)	5322 (28.2)	6061 (30)	11383 (29.1)	3291 (36.6)	7078 (40)	10369 (38.8)
1	2378 (54.1)	2098 (64)	4476 (58.3)	3077 (48.7)	2550 (57.4)	5627 (52.3)	5766 (43.4)	5188 (50.2)	10954 (46.4)	7486 (39.7)	8589 (42.5)	16075 (41.1)	3197 (35.5)	6800 (38.4)	9997 (37.4)
2	518 (11.8)	304 (9.3)	822 (10.7)	1133 (17.9)	654 (14.7)	1787 (16.6)	2619 (19.7)	1781 (17.2)	4400 (18.6)	3789 (20.1)	3710 (18.3)	7499 (19.2)	1670 (18.6)	2622 (14.8)	4292 (16.1)
≥3	185 (4.2)	85 (2.6)	270 (3.5)	568 (9)	267 (6)	835 (7.8)	1560 (11.7)	874 (8.5)	2434 (10.3)	2270 (12)	1873 (9.3)	4143 (10.6)	842 (9.4)	1197 (6.8)	2039 (7.6)
Chronic conditions															
Pre-existing Ischaemic Heart Disease, n (%)	456 (10.4)	95 (2.9)	551 (7.2)	929 (14.7)	280 (6.3)	1209 (11.2)	2173 (16.3)	888 (8.6)	3061 (13)	3199 (17)	1994 (9.9)	5193 (13.3)	1357 (15.1)	1542 (8.7)	2899 (10.9)
Heart Failure, n (%)	239 (5.4)	127 (3.9)	366 (4.8)	527 (8.3)	233 (5.2)	760 (7.1)	1332 (10)	859 (8.3)	2191 (9.3)	2491 (13.2)	2237 (11.1)	4728 (12.1)	1318 (14.6)	1856 (10.5)	3174 (11.9)
Dementia, n (%)	20 (0.5)	23 (0.7)	43 (0.6)	156 (2.5)	105 (2.4)	261 (2.4)	1197 (9)	1036 (10)	2233 (9.5)	3511 (18.6)	4569 (22.6)	8080 (20.7)	1736 (19.3)	4757 (26.9)	6493 (24.3)

Chronic Kidney Disease, n (%)	146 (3.3)	97 (3)	243 (3.2)	287 (4.5)	199 (4.5)	486 (4.5)	935 (7)	588 (5.7)	1523 (6.4)	1814 (9.6)	1727 (8.5)	3541 (9.1)	991 (11)	1488 (8.4)	2479 (9.3)
Hypertension, n (%)	293 (6.7)	137 (4.2)	430 (5.6)	631 (10)	367 (8.3)	998 (9.3)	1541 (11.6)	1101 (10.7)	2642 (11.2)	2212 (11.7)	2611 (12.9)	4823 (12.3)	978 (10.9)	2191 (12.4)	3169 (11.9)
Chronic Lung Disease, n (%)	289 (6.6)	249 (7.6)	538 (7)	882 (14)	646 (14.5)	1528 (14.2)	2205 (16.6)	1756 (17)	3961 (16.8)	2378 (12.6)	2170 (10.7)	4548 (11.6)	796 (8.8)	934 (5.3)	1730 (6.5)
Diabetes, n (%)	280 (6.4)	149 (4.5)	429 (5.6)	608 (9.6)	330 (7.4)	938 (8.7)	1403 (10.6)	821 (8)	2224 (9.4)	1915 (10.1)	1689 (8.3)	3604 (9.2)	627 (7)	948 (5.4)	1575 (5.9)
Liver Disease, n (%)	532 (12.1)	316 (9.6)	848 (11.1)	396 (6.3)	199 (4.5)	595 (5.5)	379 (2.9)	222 (2.1)	601 (2.5)	177 (0.9)	132 (0.7)	309 (0.8)	32 (0.4)	26 (0.1)	58 (0.2)
Peripheral Vascular Disease, n (%)	59 (1.3)	21 (0.6)	80 (1)	164 (2.6)	73 (1.6)	237 (2.2)	362 (2.7)	174 (1.7)	536 (2.3)	463 (2.5)	352 (1.7)	815 (2.1)	141 (1.6)	234 (1.3)	375 (1.4)
Valvular Heart Disease, n (%)	39 (0.9)	18 (0.5)	57 (0.7)	79 (1.2)	34 (0.8)	113 (1)	216 (1.6)	134 (1.3)	350 (1.5)	446 (2.4)	403 (2)	849 (2.2)	239 (2.7)	292 (1.6)	531 (2)
Cancers, n (%)	1457 (33.2)	1614 (49.2)	3071 (40)	2288 (36.2)	2095 (47.1)	4383 (40.7)	4045 (30.4)	3719 (36)	7764 (32.9)	3683 (19.5)	3861 (19.1)	7544 (19.3)	1002 (11.1)	1456 (8.2)	2458 (9.2)
Acute conditions															
Stroke[a], n (%)	239 (5.4)	200 (6.1)	439 (5.7)	414 (6.5)	275 (6.2)	689 (6.4)	934 (7)	850 (8.2)	1784 (7.6)	1459 (7.7)	1727 (8.5)	3186 (8.1)	574 (6.4)	1257 (7.1)	1831 (6.9)
Major Bleeding, n (%)	258 (5.9)	162 (4.9)	420 (5.5)	271 (4.3)	184 (4.1)	455 (4.2)	389 (2.9)	388 (3.8)	777 (3.3)	488 (2.6)	546 (2.7)	1034 (2.6)	179 (2)	295 (1.7)	474 (1.8)
Pulmonary embolism, n (%)	164 (3.7)	131 (4)	295 (3.8)	226 (3.6)	152 (3.4)	378 (3.5)	255 (1.9)	278 (2.7)	533 (2.3)	227 (1.2)	335 (1.7)	562 (1.4)	60 (0.7)	131 (0.7)	191 (0.7)

Acute Coronary Syndrome, n (%)	372 (8.5)	80 (2.4)	452 (5.9)	476 (7.5)	169 (3.8)	645 (6)	788 (5.9)	395 (3.8)	1183 (5)	748 (4)	583 (2.9)	1331 (3.4)	230 (2.6)	302 (1.7)	532 (2)
Infective Endocarditis, n (%)	43 (1)	22 (0.7)	65 (0.8)	43 (0.7)	22 (0.5)	65 (0.6)	119 (0.9)	78 (0.8)	197 (0.8)	139 (0.7)	141 (0.7)	280 (0.7)	46 (0.5)	80 (0.5)	126 (0.5)

n=number of cases

[a] Includes bleeding and ischaemic strokes

Table S3B. Characteristics and underlying conditions of deceased patients with COVID-19 according to sex and age group

Age Group (Sex)/Condition	<60 years (n=2599)			60-69 years (n=3830)			70-79 years (n=8554)			80-89 years (n=14189)			>90 years (n=7266)		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
Number of reported chronic underlying conditions															
0	753 (44.7)	343 (37.6)	1096 (42.2)	788 (30.8)	402 (31.5)	1190 (31.1)	1455 (26.8)	897 (28.7)	2352 (27.5)	2260 (28.5)	1972 (31.6)	4232 (29.8)	1062 (34.3)	1673 (40.1)	2735 (37.6)
1	594 (35.2)	392 (42.9)	986 (37.9)	940 (36.8)	512 (40.2)	1452 (37.9)	1995 (36.8)	1212 (38.8)	3207 (37.5)	2855 (35.9)	2368 (37.9)	5223 (36.8)	1117 (36.1)	1544 (37)	2661 (36.6)
2	248 (14.7)	132 (14.5)	380 (14.6)	547 (21.4)	250 (19.6)	797 (20.8)	1271 (23.4)	650 (20.8)	1921 (22.5)	1850 (23.3)	1273 (20.4)	3123 (22)	621 (20.1)	660 (15.8)	1281 (17.6)
≥3	91 (5.4)	46 (5)	137 (5.3)	280 (11)	111 (8.7)	391 (10.2)	706 (13)	368 (11.8)	1074 (12.6)	977 (12.3)	634 (10.1)	1611 (11.4)	297 (9.6)	292 (7)	589 (8.1)
Chronic conditions															
Pre-existing Ischaemic Heart Disease, n (%)	88 (5.2)	31 (3.4)	119 (4.6)	327 (12.8)	68 (5.3)	395 (10.3)	826 (15.2)	252 (8.1)	1078 (12.6)	1245 (15.7)	525 (8.4)	1770 (12.5)	432 (13.9)	359 (8.6)	791 (10.9)
Heart Failure, n (%)	37 (2.2)	20 (2.2)	57 (2.2)	143 (5.6)	67 (5.3)	210 (5.5)	349 (6.4)	229 (7.3)	578 (6.8)	744 (9.4)	578 (9.3)	1322 (9.3)	336 (10.8)	407 (9.8)	743 (10.2)
Dementia, n (%)	16 (0.9)	14 (1.5)	30 (1.2)	89 (3.5)	48 (3.8)	137 (3.6)	756 (13.9)	472 (15.1)	1228 (14.4)	1846 (23.2)	1608 (25.7)	3454 (24.3)	816 (26.3)	1186 (28.4)	2002 (27.6)

Chronic Kidney Disease, n (%)	106 (6.3)	67 (7.3)	173 (6.7)	232 (9.1)	122 (9.6)	354 (9.2)	591 (10.9)	294 (9.4)	885 (10.3)	1033 (13)	646 (10.3)	1679 (11.8)	392 (12.7)	371 (8.9)	763 (10.5)
Hypertension, n (%)	357 (21.2)	133 (14.6)	490 (18.9)	659 (25.8)	254 (19.9)	913 (23.8)	1204 (22.2)	647 (20.7)	1851 (21.6)	1479 (18.6)	1138 (18.2)	2617 (18.4)	472 (15.2)	568 (13.6)	1040 (14.3)
Chronic Lung Disease, n (%)	157 (9.3)	172 (18.8)	329 (12.7)	374 (14.6)	290 (22.7)	664 (17.3)	1040 (19.2)	733 (23.4)	1773 (20.7)	1233 (15.5)	1010 (16.2)	2243 (15.8)	321 (10.4)	354 (8.5)	675 (9.3)
Diabetes, n (%)	311 (18.4)	151 (16.5)	462 (17.8)	573 (22.4)	233 (18.3)	806 (21)	1112 (20.5)	547 (17.5)	1659 (19.4)	1231 (15.5)	802 (12.8)	2033 (14.3)	304 (9.8)	287 (6.9)	591 (8.1)
Liver Disease, n (%)	87 (5.2)	56 (6.1)	143 (5.5)	80 (3.1)	47 (3.7)	127 (3.3)	66 (1.2)	46 (1.5)	112 (1.3)	40 (0.5)	30 (0.5)	70 (0.5)	5 (0.2)	3 (0.1)	8 (0.1)
Peripheral Vascular Disease, n (%)	13 (0.8)	5 (0.5)	18 (0.7)	53 (2.1)	14 (1.1)	67 (1.7)	136 (2.5)	33 (1.1)	169 (2)	122 (1.5)	53 (0.8)	175 (1.2)	33 (1.1)	25 (0.6)	58 (0.8)
Valvular Heart Disease, n (%)	4 (0.2)	4 (0.4)	8 (0.3)	17 (0.7)	9 (0.7)	26 (0.7)	69 (1.3)	25 (0.8)	94 (1.1)	125 (1.6)	109 (1.7)	234 (1.6)	58 (1.9)	55 (1.3)	113 (1.6)
Cancers, n (%)	125 (7.4)	114 (12.5)	239 (9.2)	256 (10)	178 (14)	434 (11.3)	555 (10.2)	358 (11.4)	913 (10.7)	550 (6.9)	408 (6.5)	958 (6.8)	129 (4.2)	158 (3.8)	287 (3.9)
Acute conditions															
Stroke[a], n (%)	66 (3.9)	45 (4.9)	111 (4.3)	150 (5.9)	68 (5.3)	218 (5.7)	365 (6.7)	179 (5.7)	544 (6.4)	547 (6.9)	356 (5.7)	903 (6.4)	159 (5.1)	191 (4.6)	350 (4.8)
Major Bleeding, n (%)	35 (2.1)	23 (2.5)	58 (2.2)	41 (1.6)	15 (1.2)	56 (1.5)	39 (0.7)	30 (1)	69 (0.8)	80 (1)	38 (0.6)	118 (0.8)	23 (0.7)	14 (0.3)	37 (0.5)
Pulmonary embolism, n (%)	51 (3)	24 (2.6)	75 (2.9)	73 (2.9)	23 (1.8)	96 (2.5)	77 (1.4)	53 (1.7)	130 (1.5)	65 (0.8)	62 (1)	127 (0.9)	14 (0.5)	19 (0.5)	33 (0.5)

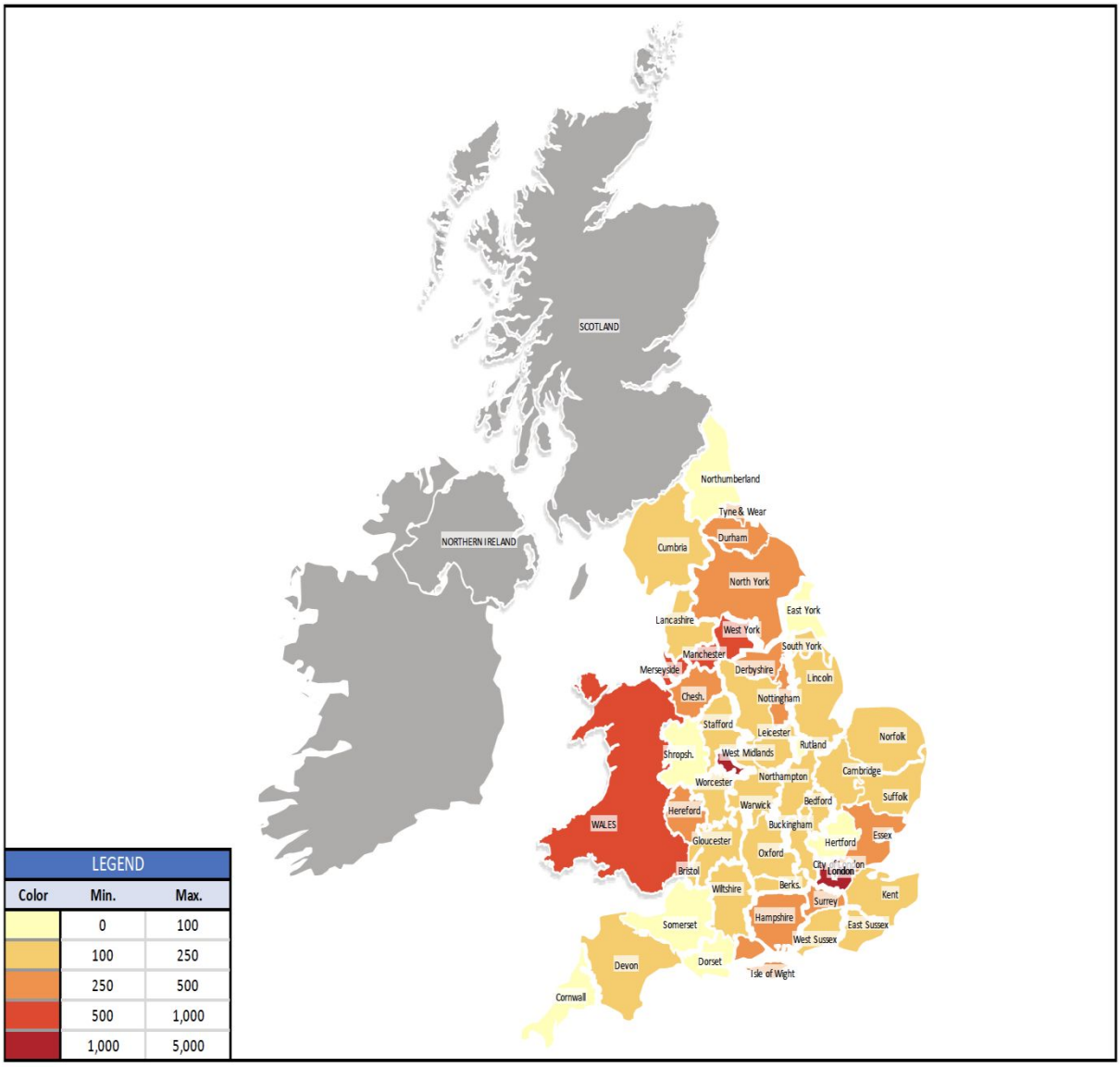
Acute Coronary Syndrome, n (%)	26 (1.5)	7 (0.8)	33 (1.3)	45 (1.8)	12 (0.9)	57 (1.5)	92 (1.7)	30 (1)	122 (1.4)	112 (1.4)	57 (0.9)	169 (1.2)	32 (1)	31 (0.7)	63 (0.9)
Infective Endocarditis, n (%)	6 (0.4)	5 (0.5)	11 (0.4)	7 (0.3)	7 (0.5)	14 (0.4)	25 (0.5)	16 (0.5)	41 (0.5)	38 (0.5)	38 (0.6)	76 (0.5)	9 (0.3)	14 (0.3)	23 (0.3)

n=number of cases

[a] Includes bleeding and ischaemic strokes

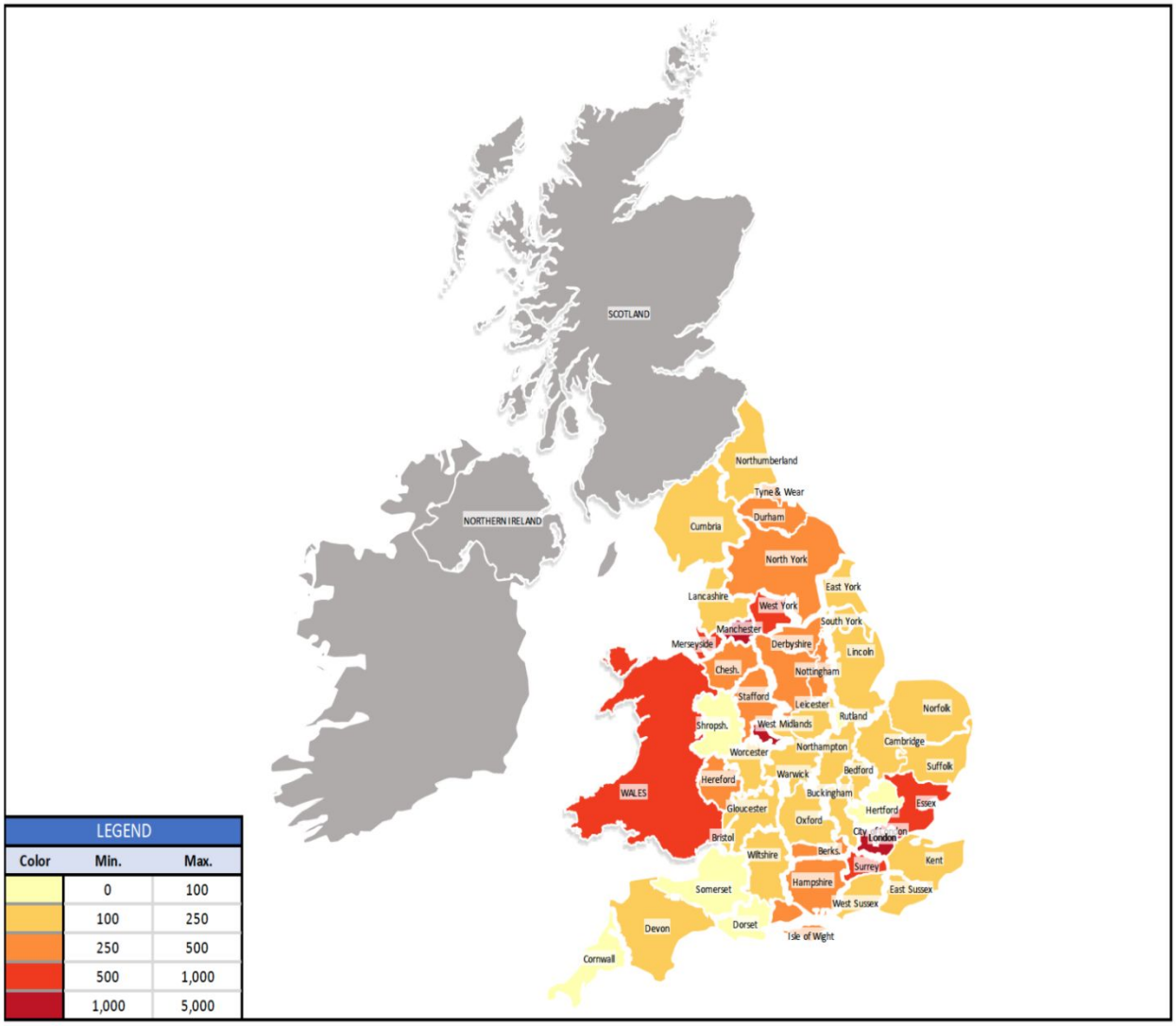
Figure S1. Distribution of Covid-19 deaths in England and Wales in A) Men and B) Women*

A)



LEGEND		
Color	Min.	Max.
	0	100
	100	250
	250	500
	500	1,000
	1,000	5,000

B)



*Start of pandemic through 12th May 2020