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

Running title: Sex differences in underlying conditions of COVID-19 deaths

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Introduction

More than 4 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 more than 37,837 deaths recorded as of 28th May 2020.[2 3]

Age, male sex and the presence of comorbidities are strong predictors of adverse outcomes and mortality in people infected with COVID-19. [4 5] 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.[6] 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%).[7] It is not clear, however, how the distribution of underlying conditions varies by sex and age in those that have died from COVID-19, and how the distribution of underlying conditions differs from those in similar age / sex groups that have died from non-COVID related causes.

Therefore, we investigated the pre-existing conditions in adults 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

Records of 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] 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. 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 ischaemic heart disease (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 (ischaemic and haemorrhagic), 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 COVID-19 as the underlying primary contributory cause, stratified according to sex, and age band (states the bands here). 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 analysed using the chi squared (X^2) test or Fisher's exact test, where appropriate. Age-standardised 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. 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 for men and 15,731 (43.2%) for women. The first death due to COVID-19 infection 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 males and 55,980 (51.9%) in females. 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, females 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 withCOVID 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 males than females 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 males compared to females across all age groups. (**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), followed by the West Midlands (total/male/female: 2,656, 1,543, 1,113), Manchester (total/male/female: 2,279, 1,256, 1,023) and Wales (total/male/female: 1,448, 810, 638). (**Table S2, Figures 3A and 3B**)

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 4**) 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 ischemic heart disease 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 underlying ischemic heart disease appeared to be significantly lower in men in the COVID-19 vs the non COVID-19 deaths particularly in the among those aged <60 years, but was similar for all other age groups. (**Supplementary Tables S3A and S3B**)

Overall, females were more likely to have no underlying chronic conditions compared with males in both COVID and non-COVID groups (COVID: 33.6% vs. 30.5%, non-COVID: 31.1% vs. 28.6%, **Table 3**). **Figures 4, 5**)Amongst COVID-19 deaths, females had higher rates of dementia (21.2% vs. 17%, $p<0.001$) as underlying conditions compared with males whilst males 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 females (p<0.001 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 5**) Pulmonary embolism was more frequently reported in <60 and 60-69 age deciles, more so in males than females (<60 years: 3.0% vs. 2.6%, 60-69 years: 2.9% vs. 1.8%, p<0.001 for both). Individuals in the younger age deciles were also more likely to have cancer with higher rates observed in females compared to males (<60 years: 12.5% vs. 7.4%, 60-69 years: 14% vs. 10%, p<0.001 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 pandemicWe 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 females between the ages of 30-79 years. Second, we show that age standardised mortality was consistently higher for males than females 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 in keeping with 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 standardised mortality rates were not presented which makes interpretation of data difficult, particularly when comparing with non-COVID deaths. [8] 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. [9]

The majority of recent studies have focused on the crude mortality or case-fatality rates of COVID-19. [10 11,12] 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. [13,14] 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. [9,11,15-18] Our analysis, which provides full population coverage of all deaths in England and Wales, is the first to demonstrate that the age standardised 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 females between 30-79 years whose mortality from cancer was comparable to that from COVID.

Our findings suggest that age-standardised mortality in males was almost double compared to that of females across all age groups, despite crude death rates suggesting a significantly higher proportion of females ≥90 years dying from COVID-19 compared with males. 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 males, with higher

mortality in younger male age groups compared to females. [9] Similarly, data on COVID-related deaths in Italy (n=31,096) demonstrates higher mortality in males than females across all age deciles except ≥90 years where mortality was higher than in females. [8] 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 males compared to females 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 males than females, and in adults compared to children. [19 5,20]

. 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. [12 15,16 21] 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. [16] [15] [22] 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. [23] It is also possible that pharmacological treatment administered for COVID infection provokes fatal arrhythmias, to which CVD patients appear to be more susceptible. [24] 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). [25] 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 ischaemic heart disease (28.3%) was significantly higher in COVID deaths (n=31.096). [26] 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 males (ACS and acute stroke). In terms of chronic conditions, females had higher rates of dementia, heart failure and chronic lung disease compared to males, whilst males 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 males than females, whereas cancer

rates were higher in younger age groups, especially in females compared to males. Data on 31.096 COVID deaths from Italy shows that males 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 females, and that there was no difference in the rates of active cancer between sexes (males: 15.9% vs. females: 15.6%), all of which are in line with our findings. [26] 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 government body policies by identifying high-risk groups who could benefit from prolonged shielding 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, it is unclear what proportion of the deaths reported as COVID deaths had a positive PCR test for the SARS-CoV-2 virus, and how many were clinically diagnosed based on the clinical presentation and diagnostic findings such as chest x-ray abnormalities. This may introduce case ascertainment bias. Second, 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, rather than a description of all prevalent comorbid conditions. Third, 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.[27]

Conclusions

In thisnationwide 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 females between 30-79 years, whose adjusted-mortality was higher than COVID-19. Our findings also suggest persistently higher age-adjusted mortality in males compared to females 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. Distribution of Covid-19 deaths in England and Wales in A) Males and B) Females*

Legend: *start of pandemic through 12th May

Figure 4. Number of reported underlying chronic conditions in the overall cohort and according to COVID status and sex

Figure 5. 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