

# Mortality in COVID-19 among women on hormone replacement therapy: a retrospective cohort study

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**Background:** Limited recent observational data have suggested that there may be a protective effect of oestrogen on the severity of COVID-19 disease. Our aim was to investigate the association between hormone replacement therapy (HRT) or combined oral contraceptive pill (COCP) use and the likelihood of death in women with COVID-19.

**Methods:** We undertook a retrospective cohort study using routinely collected computerized medical records from the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) primary care database. We identified a cohort of 1,863,478 women over 18 years of age from 465 general practices in England. Mixed-effects logistic regression models were used to quantify the association between HRT or COCP use and all-cause mortality among women diagnosed with confirmed or suspected COVID-19 in unadjusted and adjusted models.

**Results:** There were 5,451 COVID-19 cases within the cohort. HRT was associated with a reduction in all-cause mortality in COVID-19 (adjusted OR 0.22, 95% CI 0.05 to 0.94). There were no reported events for all-cause mortality in women prescribed COCPs. This prevented further examination of the impact of COCP.

**Conclusions:** We found that HRT prescription within 6 months of a recorded diagnosis of COVID-19 infection was associated with a reduction in all-cause mortality. Further work is needed in larger cohorts to examine the association of COCP in COVID-19, and to further investigate the hypothesis that oestrogens may contribute a protective effect against COVID-19 severity.

**Key words:** combined oral contraceptive pill, COVID-19, HRT, mortality

## Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread globally with males and females equally susceptible to the infection. However, males experience greater severity of infection with higher rates of hospitalization and mortality.<sup>1</sup> A recent review of sex differences in COVID-19 including data from 38 countries reported mortality in males as 1.7 times higher than the average female.<sup>2</sup> Similar data have been observed in previous pandemics, including the SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus) outbreaks.<sup>3</sup> The reason for these sex differences is unclear. A range of hypotheses have been proposed from variations in patterned sex behaviours, such as smoking, co-morbidities, and sex-based immunological variations.<sup>2</sup> In particular, the role of oestrogen in female immune responses has received much attention.<sup>4,5</sup> Younger females or those with higher oestrogen levels are less likely to experience severe COVID-19 complications.<sup>4</sup> Earlier studies show that females mount faster and greater immune responses to viral infections through cellular and humoral immune responses.<sup>2</sup> Moreover, immune responses can be modulated by oestrogen through a reduction in T-cell exhaustion and suppression of IL-1 $\beta$  and IL-6 production.<sup>6</sup> This potentially limits the cytokine storm and subsequent respiratory

failure that is characteristically triggered by SARS-CoV-2. This may explain why fewer women compared to men have been hospitalized and admitted to ICU (Intensive Care Unit) or have died during the pandemic.<sup>1</sup>

To date, a limited number of studies have explored the association between oestrogen-containing products and COVID-19 outcomes. Recent observational data suggest that women aged 18–45 years taking the combined oral contraceptive pill (COCP) have a significantly lower risk of acquiring COVID-19 (odds ratios [OR] 0.87,  $P < 0.001$ ), as well as a reduction in hospital attendance (OR 0.79,  $P = 0.023$ ).<sup>7,8</sup> Evidence on hormone replacement therapy (HRT) has been less consistent. Increased rates of predicted (but not confirmed) COVID-19 were seen among HRT users in a recent large retrospective cohort study<sup>7</sup>; however, another recent cohort study demonstrated a significant reduction in mortality among women >50 years of age receiving oestradiol therapy (OR 0.33, 95% confidence interval [CI] 0.18 to 0.62).<sup>9</sup>

The potential protective effects of oestrogen on the severity of COVID-19 have important public health and clinical relevance. With the lack of curative treatment for the infection, repurposing of existing drugs including exogenous oestrogen products requires further investigation. Considering public and prescriber concern, it is necessary to better understand the potential impact of these drugs on women taking them.

## Key messages

- HRT prescription was associated with reduced all-cause mortality from COVID.
- These data suggest no evidence to discontinue HRT because of the pandemic.
- Research should explore the association between combined contraception and COVID outcomes.

In this study, we set out to quantify the association between COCP or HRT use, and the likelihood of mortality, among females with COVID-19 during the first 6 months of the pandemic.

## Methods

### Study design, data source, and population

In this retrospective cohort study, we used the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database of individual-level pseudonymized data that has been routinely collected from primary care records.<sup>10</sup> It includes continuous longitudinal data with sociodemographic information, prescribed medications, clinical diagnosis, symptoms, investigations, and results. The database includes 465 GP practices in both rural and urban areas of England covering a nationally representative population of 1.8 million women. Within the database, we identified a cohort of women registered on 1 January 2020 who were aged over 18 years with confirmed or probable COVID-19. Confirmed cases were defined as those with a positive RT-PCR assay for SARS-CoV-2 on a nasal or pharyngeal swab and probable cases were those diagnosed radiologically or clinically based on Public Health England's recommendations. Clinical symptoms included a new continuous cough, a fever ( $>37.8^{\circ}\text{C}$ ), or a loss/change in normal smell or taste. Data on the method of temperature measurement were not available.

The variability in the availability of RT-PCR testing during the pandemic meant that most recorded cases in the dataset were diagnosed as probable cases.<sup>11,12</sup> Our previous work shows that clinical and probable cases are similar in terms of outcomes; for mortality, the OR were 8.9 (95% CI 6.7 to 11.8,  $P < 0.0001$ ) and 9.7 (95% CI 7.1 to 13.2,  $P < 0.0001$ ) for RT-PCR confirmed and clinically diagnosed cases, respectively.<sup>13</sup>

### Exposure: HRT or COCP use

We defined the exposure as one or more HRT or COCP prescriptions within 6 months of a confirmed or suspected COVID-19 case. This had to be before case confirmation.

### Outcome: all-cause mortality

The primary outcome was all-cause mortality during the follow-up period from 1 January 2020 (index date) to 21 June 2020 (end date) as recorded in the electronic record.

### Covariables

We extracted data on age, ethnicity, and socioeconomic status. Ethnicity was self-reported in the records.<sup>14</sup> For socioeconomic status, the English Index of Multiple Deprivation (IMD) was used.<sup>15,16</sup> We combined IMD quintiles 1 and 2 because recent evidence shows that there is a low frequency of testing, leading to sparse data in the most deprived quintile.<sup>15</sup> We

included the most recently available data on the household size as this is important in acquiring COVID-19 infection.<sup>17</sup> For clinical variables, we considered body mass index (BMI) as the most recent recording within the 12 months before the study index date. Coding for co-morbidities was recorded as any history of hypertension, coronary heart disease, type 1 diabetes, type 2 diabetes, asthma, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) stage 3–5 before the study index date. Smoking status was categorized as non-smoker, active-smoker, or ex-smoker (the most recent coding within 12 months before the study index date). We also included prescriptions for prednisolone and/or disease-modifying anti-rheumatic drugs as a surrogate for immunosuppression. We used standardized coding required for NHS payment and administrative purposes to increase the consistency and quality of data included.

### Statistical analysis

Sociodemographic and clinical characteristics were summarized using descriptive statistics, and we compared the characteristics of those with and without missing data. Univariable logistic regression models were used to quantify the association between HRT and COCP (separately) in relation to all-cause mortality. For each, we then ran a single multivariable model fully adjusted for age, sex, ethnicity, index of multiple deprivation, household size, BMI, co-morbidities, and smoking status. Mixed-effects models were performed to account for practice clustering. We ran a complete case analysis, and as an additional sensitivity analysis, we ran a model using multiple imputation for missing data. Statistical analyses were performed using R (Version 3.5.3). The level of significance was set at 5%, and all statistical tests were two-tailed. Model parameters were reported using OR and 95% CI. Our findings are reported in line with the STROBE and RECORD guidelines for observational studies using routinely collected health data.

### Patient and public involvement

Patients and members of the public contributed to the research question, the outcome measures, and the dissemination of our findings.

## Results

### Participant characteristics

In this retrospective cohort study, the denominator population included 1,863,478 women across 465 general practices within the Oxford-RCGP RSC database during the first 6 months of the UK's COVID-19 pandemic. Within this sample, we identified a cohort of 5,451 women who had COVID-19. The mean follow-up period was 164.9 (SD 19.6) days. The mean age of the cohort was 59.0 years (SD 21.7); self-assigned ethnicity was predominantly White (64.8%). There were 235 women with HRT prescriptions and 171 with a prescription

**Table 1.** Baseline characteristics of women diagnosed with COVID-19 in the RCGP RSC database (from 1 January to 21 June 2020) presented by those on HRT, COCP, or neither drug

	Total (N = 5,451)	Neither drug (N = 5,045)	HRT (N = 235)	COCP (N = 171)
Sociodemographic				
Age (years) <sup>a</sup>	59.0 (21.7)	60.2 (21.7)	54.6 (9.4)	29.3 (7.4)
Ethnicity recorded	4,356 (79.9)	4,024 (79.8)	193 (82.1)	139 (81.3)
White	3,534 (64.8)	3,231 (64.0)	179 (76.2)	124 (72.5)
Asian	510 (9.4)	497 (9.9)	6 (2.6)	7 (4.1)
Black	211 (3.9)	203 (4.0)	4 (1.7)	4 (2.3)
Mixed and other	101 (1.9)	93 (1.8)	4 (1.7)	4 (2.3)
IMD quintile recorded	5,326 (97.7)	4,931 (97.7)	232 (98.7)	163 (95.3)
5 (least deprived)	1,136 (20.8)	1,018 (20.2)	74 (31.5)	44 (25.7)
4	1,088 (20.0)	999 (19.8)	58 (24.7)	31 (18.1)
3	1,054 (19.3)	986 (19.5)	36 (15.3)	32 (18.7)
1 and 2 (most deprived)	2,048 (37.6)	1,928 (38.2)	64 (27.2)	56 (32.7)
Settlement or population density	5,328 (97.7)	4,933 (97.8)	232 (98.7)	163 (95.3)
Rural	933 (17.1)	833 (16.5)	65 (27.7)	35 (20.5)
Urban	4,395 (80.6)	4,100 (81.3)	167 (71.1)	128 (74.9)
Clinical				
BMI recorded	5,122 (94.0)	4,724 (93.6)	231 (98.3)	167 (97.7)
BMI (kg/m <sup>2</sup> )	28.2 (7.3)	28.3 (7.3)	29.3 (6.4)	24.55 (4.5)
Smoking status recorded	5,328 (97.7)	4,928 (97.7)	233 (99.1)	167 (97.7)
Non-smoker	2,128 (39.0)	1,969 (39.0)	67 (28.5)	92 (53.8)
Active-smoker	486 (8.9)	447 (8.9)	28 (11.9)	11 (6.4)
Ex-smoker	2,714 (49.8)	2,512 (49.8)	138 (58.7)	64 (37.4)
Co-morbidity <sup>a</sup>	3,001 (55.1)	2,859 (56.7)	116 (49.4)	26 (15.2)
All medications <sup>b</sup>	2,452 (45.0)	2,333 (46.2)	100 (42.6)	19 (11.1)

<sup>a</sup>Includes hypertension, coronary heart disease, diabetes (type 1 or type 2), chronic kidney disease stage 3–5, asthma, COPD, immunocompromised.

<sup>b</sup>Includes antihypertensive medication, lipid-lowering medication, hypoglycaemic medication, inhalers, immunosuppressants.

for the COCP. [Table 1](#) summarizes sociodemographic and clinical characteristics in the whole cohort and separated as those on HRT or COCP. During the follow-up period, 664 (12.2%) women died. [Table 2](#) summarizes the characteristics of women who died; they were more likely to be older with multiple morbidities.

### HRT use and all-cause mortality in COVID-19

HRT use was associated with a lower likelihood of all-cause mortality in COVID-19 within unadjusted models (OR 0.15, 95% CI 0.06 to 0.37) and adjusted models (OR 0.22, 95% CI 0.05 to 0.94). We also observed that all-cause mortality risk was higher in COVID-19 among women who were older, underweight, from larger households, with hypertension, or on immunosuppressants. For those with asthma, however, we observed that being on HRT was associated with a significantly lower risk of mortality (OR 0.58, 95% CI 0.42 to 0.81). These results are shown in [Table 3](#).

An additional sensitivity analysis using multiple imputation for missing data found a non-significant reduction in all-cause mortality associated with HRT use (OR 0.47; 95% CI 0.18–1.23).

### COCP use and all-cause mortality in COVID-19

We had intended to examine COCP as an exposure but there were no reported events for the outcome of interest (all-cause mortality) in women prescribed COCPs. Accordingly, we were unable to examine COCP use.

## Discussion

### Main findings

In this cohort of 5,451 women with COVID-19 who were followed up in the first 6 months of the pandemic, HRT use was associated with a lower likelihood of all-cause mortality.

### Strengths and limitations

A major strength of this study is the use of a population-based cohort from 465 practices across England representing wide coverage with a denominator population of 3.6 million people. This included heterogeneity in sociodemographic and clinical variables. The data used are of high quality and completeness with twice-weekly updates that are also used by Public Health England to monitor the current and previous pandemics.<sup>10</sup> The availability of wide-ranging and precise data means that we were able to adjust for several confounders, although residual unmeasured confounding and risk of misclassification are still possible, as an inherent limitation of the retrospective cohort design. We considered both laboratory-confirmed and clinically probable cases as a single cohort due to the national inconsistency in testing availability at the time. Furthermore, data on the method of temperature measurement were not available. It is therefore plausible that not all those with clinically probable cases had SARS-CoV-2. Recent work from the Oxford-RCGP database, however, suggests that outcomes are similar in those with

**Table 2.** Baseline characteristics of women with COVID-19 who died during the follow-up period (1 January to 21 June 2020) in the Oxford-RCGP RSC database.

	Total (N = 5,451)	Non-decedent (N = 4,787)	Decedent (N = 664)
Age (years)	59.0 (21.7)	55.7 (20.8)	82.5 (11.3)
Ethnicity recorded	4,356 (79.9)	3,838 (80.2)	518 (78.0)
White	3,534 (64.8)	3,064 (64.0)	470 (70.8)
Asian	510 (9.4)	484 (10.1)	26 (3.9)
Black	211 (3.9)	200 (4.2)	11 (1.7)
Mixed other	101 (1.9)	90 (1.9)	11 (1.7)
IMD quintile recorded	5,326 (97.7)	4,671 (97.6)	655 (98.6)
5 (least deprived)	1,136 (20.8)	993 (20.7)	143 (21.5)
4	1,088 (20.0)	936 (19.6)	152 (22.9)
3	1,054 (19.3)	918 (19.2)	136 (20.5)
1 and 2 (most deprived)	2,048 (37.6)	1,824 (38.1)	224 (33.7)
Settlement or population density	5,328 (97.7)	4,671 (97.6)	657 (98.9)
Rural	933 (17.1)	816 (17.0)	117 (17.6)
Urban	4,395 (80.6)	3,855 (80.5)	540 (81.3)
BMI recorded	5,122 (94.0)		
BMI (kg/m <sup>2</sup> )	28.2 (7.3)	28.4 (7.3)	26.6 (7.1)
Smoking status recorded	5,328 (97.7)	4,684 (97.8)	26.6 (7.1)
Non-smoker	2,128 (39.0)	1,912 (39.9)	216 (32.5)
Active-smoker	486 (8.9)	446 (9.3)	40 (6.0)
Ex-smoker	2,714 (49.8)	2,326 (48.6)	388 (58.4)
Co-morbidity <sup>a</sup>	3,001 (55.1)	2,454 (51.3)	547 (82.4)
All medications <sup>b</sup>	2,452 (45.0)	1,980 (41.4)	472 (71.1)

<sup>a</sup>Includes hypertension, coronary heart disease, diabetes (type 1 or type 2), chronic kidney disease stage 3–5, asthma, COPD, immunocompromised.

<sup>b</sup>Includes antihypertensive medication, lipid-lowering medication, hypoglycaemic medication, inhalers, immunosuppressants.

clinically probable and laboratory-confirmed cases.<sup>13</sup> Our cohort is likely to reflect women with more severe COVID-19 symptoms who went for testing or made contact with a GP for review. If asymptomatic or with milder symptoms, they may not have sought health advice and will not be captured in this cohort.

In terms of the exposure, we examined medications based on prescriptions within the last 6 months rather than dispensed medications so there could be some over-ascertainment of exposure to HRT. Furthermore, as oestrogen was highlighted as having a role in COVID-19 reasonably early in the pandemic, it is possible that some women may have stopped taking their medications before contracting the infection. Our study did not examine the type of preparation or dose of HRT, as these data were not available from the database. Nor did we investigate the duration of medication use, and our follow-up period was short at less than 6 months. This might be important in oestrogen-related immune responses where longer exposures to hormones could be significant.<sup>2</sup> Age was included in the model as a categorical variable only, which may have limited our adjustment. This was done to reflect the much higher odds of all-cause mortality in the older age categories (compared to the <40-year reference category). We also used all-cause mortality as our outcome, and some deaths may therefore be unrelated to COVID-19. There was substantial confusion about the classification of COVID-19 mortality in the early part of the pandemic including changes in government guidance as the pandemic progressed. COVID-19-specific mortality was variable and as a new code, it may not have been widely used in primary care records. All-cause

mortality is likely to be a more reliable measure especially in the early part of the pandemic in which our study is set.

Finally, recent studies have identified a negative association between HRT prescription and socioeconomic status.<sup>18,19</sup> While we adjusted for socioeconomic status in our model (index of multiple deprivation), we cannot rule out residual confounding due to incomplete adjustment for this and/or incomplete or incorrect coding.

## Interpretation

Previous studies report lower rates of severe COVID-19 complications among women compared to men, and a number of published studies support the hypothesis that oestrogen may confer a protective effect against COVID-19.<sup>4,5,7–9</sup> This is consistent with the findings of the COVID Symptom Study, which (to our knowledge) is the largest observational study on this topic to date, including 152,637 women for menopause status.<sup>7</sup> Their findings across the cohort suggest that higher oestrogen levels may protect against COVID-19. The mechanism to explain this may be through increased cellular and humoral immune responses in females with higher oestrogen levels. Recent evidence suggests that females have a higher level and faster generation of serum SARS-CoV-2 IgG antibodies compared to males.<sup>20</sup> Higher oestrogen levels may also be able to better promote the direct anti-viral activity of T cells and modulate the uncontrolled immune response (cytokine storm) that has been observed in those with respiratory failure due to COVID-19.<sup>4,5</sup> Immune responses and oestrogen levels decrease with age which might

**Table 3.** Association between HRT use and the likelihood of death in women diagnosed with COVID-19 during the observation period (1 January to 21 June 2020;  $n = 5,451$ ).

	OR	95% CI		P-value
(i)Unadjusted models				
HRT use	0.15	0.061	0.366	0.000
(ii)Maximally adjusted models				
HRT use	0.22	0.05	0.94	0.041
Age 40–64 (years)	10.40	2.48	43.30	0.001
Age 65–74 (years)	58.90	14.00	249.00	0.000
Age over 75+ years	123.00	29.70	514.00	0.000
Ethnicity Asian	1.32	0.77	2.24	0.311
Ethnicity Black	0.87	0.42	1.81	0.710
Ethnicity Mixed and other	1.76	0.74	4.17	0.199
IMD quintile 1 and 2	0.81	0.58	1.13	0.221
IMD quintile 3	0.98	0.68	1.41	0.922
IMD quintile 4	0.80	0.56	1.15	0.233
Household size of 1	1.30	0.97	1.74	0.075
Household size of 5–8	1.35	0.84	2.18	0.220
Household size of >9	1.77	1.27	2.46	0.001
BMI categorized as obese	0.85	0.62	1.15	0.289
BMI categorized as overweight	0.87	0.66	1.16	0.350
BMI categorized as underweight	1.73	1.08	2.77	0.024
Active-smoker	1.92	1.15	3.20	0.013
Ex-smoker	1.21	0.94	1.56	0.144
Hypertension	1.65	1.26	2.16	0.000
Coronary heart disease	1.16	0.83	1.62	0.379
Type 1 diabetes	1.81	0.31	10.50	0.506
Type 2 diabetes	1.14	0.87	1.49	0.344
Chronic kidney disease stage 3–5	1.18	0.91	1.52	0.215
Asthma	0.58	0.42	0.81	0.001
COPD	1.13	0.76	1.68	0.552
Immunosuppressants	1.48	1.02	2.14	0.039

The following reference categories were used: White for ethnicity, Age band: 18–39 years, IMD: IMD quintile 5 (least deprived), Household size: 2–4, and BMI category: normal weight.

explain why previous studies and our results show a greater likelihood of worse outcomes in females with increasing age.<sup>17</sup> However, among women on HRT with exogenous oestrogen, the risk of all-cause mortality is reduced, but still does not reach that of younger females (presumably related to the direct effect of ageing on the immune system and the increased number of morbidities acquired with age).<sup>21</sup> In the COVID Symptom Study described earlier, the associations between HRT and COVID-19 in 17,798 women were not consistent.<sup>7</sup> Increased rates of predicted (but not confirmed) COVID-19 were seen among HRT users, however, there was no significant association between HRT and risk of hospitalization, and the authors did not report on mortality.<sup>7</sup> These differences might be explained by variations in HRT preparations, doses, and duration which were not examined and (as described above) may be important in oestrogen-led immune responses.<sup>2</sup> Other explanations may relate to differences in adjusted covariates which were limited to age, smoking, and BMI in their study. On the other hand, a recent large 64,466 case international retrospective cohort

study did demonstrate a significant reduction in mortality among women >50 years of age receiving oestradiol therapy (OR 0.33, 95% CI 0.18–0.62),<sup>9</sup> consistent with the findings of our study.

As the pandemic progresses and a greater understanding of the virus emerges, it is necessary to consider additional covariates such as household size and co-morbidities which we included.<sup>1</sup> Our results show that increased age, co-morbidities, extreme BMI, and immunosuppressants were all significantly associated with an increased likelihood of death among women with COVID-19; this is consistent with several recent reports.<sup>22,23</sup> There is some uncertainty in the literature about the role of asthma in the severity of COVID-19 outcome, but we observed that being on HRT was associated with a significantly lower risk of mortality (OR 0.58, 95% CI 0.42 to 0.81), suggesting that perhaps oestrogen is protective. However, these women with asthma are likely to also have been on asthma medication such as steroids which could contribute to some of the observed associations.<sup>24</sup>

## Conclusions

We found that HRT prescription within 6 months of a recorded diagnosis of COVID-19 infection was associated with a reduction in all-cause mortality. From these results, women should be reassured that there is no indication to discontinue HRT use because of the pandemic. Further work is needed to explore the effect of variations in HRT doses, preparations, and duration on COVID-19 complications. Additional research is also required in larger cohorts to examine the association between COCP and mortality in COVID-19.

## Supplementary material

Supplementary material is available at *Family Practice* online.

## Author contribution

HDM designed the study, wrote the first draft, and edited subsequent versions of the manuscript. WH contributed to the study design, led the data analysis, and revised the manuscript. MJ provided advice on statistical methods. MF, CRW, and Sdel contributed to the study design and revised the paper. Sdel also provided expertise on the RCGP RSC database.

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## Conflict of interest

The authors declare that no support from any organization and no financial relationships have influenced the submitted work. Sdel has had investigator-led funding from industry (all via his university), and is member of two advisory boards. No other authors have any competing interests to declare.

## Ethical approval

This study received approval from the Oxford-RCGP RSC study approval committee (RSC\_0920) and the University of Southampton Research Ethics committee (56309) on 6 May 2020.

## Data availability

Data from the Oxford-RCGP RSC database can be requested directly from: <https://www.rcgp.org.uk/clinical-and-research/our-programmes/research-and-surveillance-centre/supporting-research-teams/submit-a-data-request-online-form.asp>

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