**Mortality in COVID-19 amongst women on Hormone Replacement Therapy: A retrospective cohort study**

**Short title: COCP/HRT use in COVID-19 and mortality**

**Article type: epidemiology**

Hajira Dambha-Miller1, William Hinton2, Christopher R Wilcox1, Mark Joy2, Michael Feher2 and Simon de Lusignan2,3

1. Primary Care Research Centre, University of Southampton
2. Nuffield Department of Primary Care Health Sciences, University of Oxford
3. Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), London, UK

**Correspondence:** Dr Christopher Wilcox, Primary Care and Population Health, University of Southampton, Southampton, SO16 5ST, Email: Christopher.wilcox@soton.ac.uk

**Number of tables:** 3

**Number of figures:** Nil

**Keywords:** HRT, Combined Oral Contraception, COVID-19, mortality

KEY MESSAGES

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

**ABSTRACT**

**Background**

Limited recent observational data has suggested 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 Contraception (COCP) use, and the likelihood of death in women with COVID-19.

**Methods**

We undertook a retrospective cohort study using routinely-collected computerised 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 Hormone Replacement Therapy (HRT) or Combined Oral Contraceptive Pill (COCP) use, and all-cause mortality among women diagnosed with confirmed- or suspected COVID 19 in unadjusted and adjusted models.

**Results**

There were 5451 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 six 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.

**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 hospitalisation and mortality.[1] 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. [2] Similar data have been observed in previous pandemics including the SARS-CoV (Severe Acute Respiratory Syndrome Corona Virus) and MERS-CoV (Middle East Respiratory Syndrome Corona Virus) outbreaks.[3] 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.[2] In particular, the role of oestrogen in female immune responses has received much attention.[4,5] Younger females or those with higher oestrogen levels are less likely to experience severe COVID-19 complications.[4] Earlier studies show that females mount faster and greater immune responses to viral infections through cellular and humoral immune responses.[2] Moreover, immune responses can be modulated by oestrogen through a reduction in T-cell exhaustion and suppression of IL-1β and IL-6 production.[6] 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 hospitalised, admitted to ITU or have died during the pandemic. [1]

To-date, a limited number of studies have explored the association between oestrogen-containing products and COVID-19 outcomes. Recent observational data suggests that women aged 18-45 years taking the Combined Oral Contraceptive Pill (COCP) have a significantly lower risk of acquiring COVID-19 (OR 0.87, p<0.001) , as well as a reduction in hospital attendance (OR 0.79, p=0.023) [7,8]. Evidence on Hormone Replacement Therapy (HRT) has been less consistent. Increased rates of predicted (but not confirmed) COVID-19 were seen amongst HRT users in a recent large retrospective cohort study [7], however another recent cohort study demonstrated a significant reduction in mortality amongst women >50 years-of-age receiving estradiol therapy (OR 0.33, 95% CI 0.18-0.62) [9].

The potential protective effects of oestrogen on the severity of COVID-19 has 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 for women taking them.

In this study, we set out to quantify the association between COCP or HRT use, and the likelihood of mortality, amongst females with COVID-19 during the first six 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 pseudonymised data that has been routinely collected from primary care records.[10] 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 the 1st 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 Public Health England’s recommendations. Clinical symptoms included a new continuous cough, a fever >37.8 degrees or a loss/change in normal smell or taste. Data on the method of temperature measurement was 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. [11,12] Our previous work shows that clinical and probable cases are similar in terms of outcomes; for mortality, the odds ratios 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. [13]

*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 1st January 2020 (index date) to 21st 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.[14] For socioeconomic status, the English Index of Multiple Deprivation was used. [15,16] 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.[15] We included the most recently available data on the household size as this is important in acquiring COVID-19 infection.[17] 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 were 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 categorised 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 standardised coding required for NHS payment and administrative purposes to increase consistency and quality of data included.

*Statistical Analysis*

Sociodemographic and clinical characteristics were summarised 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, comorbidities, 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 2-tailed. Model parameters were reported using odds ratios (ORs) and 95% confidence intervals. 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 setting the research question, the outcome measures and the dissemination of our findings.

*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)

**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 six months of the UK’s COVID-19 pandemic. Within this sample, we identified a cohort of 5451 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 for the COCP. Table 1 summarises 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 summarises 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 amongst 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 below.

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 as 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 5451 women with COVID-19 who were followed up in the first six 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 is of high quality and completeness with twice-weekly updates that are also used by Public Health England to monitor the current and previous pandemics.[10] 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 is 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 was 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 clinically probable and laboratory-confirmed cases.[18] 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 this data was not available from the database. Nor did we investigate the duration of medication use, and our follow-up period was short at less than six months. This might be important in oestrogen related immune responses where longer exposures to hormones could be significant.[2] 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 years 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 [19,20]. Whilst 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 amongst women compared to men, and a number of published studies support the hypothesis that oestrogen may confer a protective effect against COVID-19 [4,5,7–9]. 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. [7] Their findings across the cohort suggests 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 antibody compared to males.[21] Higher oestrogen levels may also be able to better promote 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. [4,5] Immune responses and oestrogen level decrease with age which might explain why previous studies and our results show a greater likelihood of worse outcomes in females with increasing age.[1,7] However, amongst women on HRT with exogenous oestrogen the risk of all-cause mortality are reduced but still do 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.[22] In the COVID Symptom Study described earlier, the associations between HRT and COVID-19 in 17,798 women were not consistent. [7] Increased rates of predicted (but not confirmed) COVID-19 were seen amongst HRT users, however there was no significant association between HRT and risk of hospitalisation, and the authors did not report on mortality. [7] 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.[2] 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 amongst women >50 years-of-age receiving estradiol therapy (OR 0.33, 95% CI 0.18-0.62) [9], 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.[1] Our results show that increased age, co-morbidities, extreme BMI and immunosuppressants were all significantly associated with an increased likelihood of death amongst women with COVID-19; this is consistent with several recent reports.[23,24] 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. [25]

**Conclusions**

We found that HRT prescription within six 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 been COCP and mortality in COVID-19.

**FUNDING:**

HDM is a National Institute for Health Research (NIHR) funded Academic Clinical Lecturer and has received NIHR SPCR funding for this project (SPCR2014-10043), and also acknowledges receipt of MRC funding for her COVID research (MR/V027778/1). CW is a NIHR-funded Academic Clinical Fellow. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the UK National Institute for Health Research (NIHR) or the Department of Health and Social Care.

**AUTHOR CONTRIBUTION:**

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

**CONFLICT OF INTEREST STATEMENT:**

The authors declare that no support from any organisation and no financial relationships have influenced the submitted work. SdeL has had investigator-led funding from industry, and is member of two advisory boards, all funding are via his University. 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 the 6th May 2020.

**DATA AVAILABILITY:**

Data from the Oxford- RCGP RSC database can 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.aspx>

**LIST OF TABLE LEGENDS:**

Table 1: Baseline characteristics of women with COVID-19 in the RCGP RSC database presented by those on HRT, COCP or neither drug

Table 2: Baseline characteristics of women with COVID-19 who died during the follow-up period in the Oxford-RCGP RSC database

Table 3: Association between HRT use and the likelihood of death in women with COVID-19 (n= 5451)

**REFERENCES:**

1 Williamson EJ, Walker AJ, Bhaskaran K, *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**. doi:10.1038/s41586-020-2521-4

2 Scully EP, Haverfield J, Ursin RL, *et al.* Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat Rev Immunol* 2020;**20**. doi:10.1038/s41577-020-0348-8

3 Karlberg J, Chong DSY, Lai WYY. Do Men Have a Higher Case Fatality Rate of Severe Acute Respiratory Syndrome than Women Do? *Am J Epidemiol* 2004;**159**:229–31. doi:10.1093/aje/kwh056

4 Al-Lami RA, Urban RJ, Volpi E, *et al.* Sex Hormones and Novel Corona Virus Infectious Disease (COVID-19). Mayo Clin. Proc. 2020;**95**. doi:10.1016/j.mayocp.2020.05.013

5 Shabbir S, Hafeez A, Rafiq MA, *et al.* Estrogen shields women from COVID-19 complications by reducing ER stress. *Med Hypotheses* 2020;**143**. doi:10.1016/j.mehy.2020.110148

6 Vaninov N. In the eye of the COVID-19 cytokine storm. *Nat Rev Immunol* 2020;**20**. doi:10.1038/s41577-020-0305-6

7 Costeira R, Lee KA, Murray B, *et al.* Estrogen and COVID-19 symptoms: Associations in women from the COVID Symptom Study. *PLoS One* 2021;**16**:e0257051. doi:10.1371/journal.pone.0257051

8 Schroeder M, Jarczak D, Nierhaus A, *et al.* The majority of male patients with COVID-19 present low testosterone levels on admission to Intensive Care in Hamburg, Germany: a retrospective cohort study. doi:10.1101/2020.05.07.20073817

9 Seeland U, Coluzzi F, Simmaco M, *et al.* Evidence for treatment with estradiol for women with SARS-CoV-2 infection. *BMC Med* 2020;**18**:369. doi:10.1186/s12916-020-01851-z

10 De Lusignan S, Correa A, Smith GE, *et al.* RCGP Research and Surveillance Centre: 50 years’ surveillance of influenza, infections, and respiratory conditions. Br. J. Gen. Pract. 2017;**67**:440–1. doi:10.3399/bjgp17X692645

11 Dambha-Miller H, Griffin SJ, Young D, *et al.* Posted on Annals of Family Medicine COVID-19 Collection, courtesy of Hajira Dambha-Miller. 2020.

12 de Lusignan S, Lopez Bernal J, Zambon M, *et al.* Emergence of a Novel Coronavirus (COVID-19): A Protocol for Extending Surveillance Used by the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) and Public Health England (PHE) (Preprint). *JMIR Public Heal Surveill* 2020;**6**:e18606. doi:10.2196/18606

13 Joy M, Hobbs FR, Bernal JL, *et al.* Excess mortality in the first COVID pandemic peak: cross-sectional analyses of the impact of age, sex, ethnicity, household size, and long-term conditions in people of known SARS-Cov-2 status in England. *Br J Gen Pract* Published Online First: October 2020. doi:10.3399/bjgp20X713393

14 Hippisley-Cox J, Coupland C, Vinogradova Y, *et al.* Predicting cardiovascular risk in England and Wales: Prospective derivation and validation of QRISK2. *BMJ* 2008;**336**:1475–82. doi:10.1136/bmj.39609.449676.25

15 Government D for C and L. The English Index of Multiple Deprivation (IMD) 2015—Guidance.

16 Tippu Z, Correa A, Liyanage H, *et al.* Ethnicity recording in primary care computerised medical record systems: an ontological approach. *J Innov Heal Informatics* 2017;**23**. doi:10.14236/jhi.v23i4.920

17 Martin CA, Jenkins DR, Minhas JS, *et al.* Socio-demographic heterogeneity in the prevalence of COVID-19 during lockdown is associated with ethnicity and household size: Results from an observational cohort study. *EClinicalMedicine* 2020;**25**. doi:10.1016/j.eclinm.2020.100466

18 Joy M, Hobbs FR, Bernal JL, *et al.* Excess mortality in the first COVID pandemic peak: cross-sectional analyses of the impact of age, sex, ethnicity, household size, and long-term conditions in people of known SARS-Cov-2 status in England. *Br J Gen Pract* 2020;**70**:bjgp20X713393. doi:10.3399/bjgp20x713393

19 Hillman S, Shantikumar S, Ridha A, *et al.* Socioeconomic status and HRT prescribing: a study of practice-level data in England. *Br J Gen Pract* 2020;**70**:e772–7. doi:10.3399/bjgp20X713045

20 Lawlor DA, Davey Smith G, Ebrahim S. Socioeconomic Position and Hormone Replacement Therapy Use: Explaining the Discrepancy in Evidence From Observational and Randomized Controlled Trials. *Am J Public Health* 2004;**94**:2149–54. doi:10.2105/AJPH.94.12.2149

21 Zeng F, Dai C, Cai P, *et al.* A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: A possible reason underlying different outcome between sex. *J Med Virol* 2020;**92**. doi:10.1002/jmv.25989

22 Koff WC, Williams MA. Covid-19 and Immunity in Aging Populations — A New Research Agenda. *N Engl J Med* 2020;**383**:804–5. doi:10.1056/nejmp2006761

23 OpenSAFELY Collaborative T, Williamson E, Walker AJ, *et al.* OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. doi:10.1101/2020.05.06.20092999

24 Holman N, Knighton P, Kar P, *et al.* Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020;**8**:823–33. doi:10.1016/S2213-8587(20)30271-0

25 Schultze A, Walker AJ, MacKenna B, *et al.* Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. *Lancet Respir Med* 2020;**8**:1106–20. doi:10.1016/S2213-2600(20)30415-X

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total**  (N= 5451) | **Neither drug**  (N = 5045) | **HRT**  (N = 235) | **COCP**  (N = 171) |
| ***Sociodemographic*** | | | | |
| Age (years) \* | 59.0 (21.7) | 60.2 (21.7) | 54.6 (9.4) | 29.3 (7.4) |
| Ethnicity recorded | 4356 (79.9) | 4024 (79.8) | 193 (82.1) | 139 (81.3) |
| White | 3534 (64.8) | 3231 (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 & other | 101 (1.9) | 93 (1.8) | 4 (1.7) | 4 (2.3) |
| IMD Quintile recorded | 5326 (97.7) | 4931 (97.7) | 232 (98.7) | 163 (95.3) |
| 5 (Least deprived) | 1136 (20.8) | 1018 (20.2) | 74 (31.5) | 44 (25.7) |
| 4 | 1088 (20.0) | 999 (19.8) | 58 (24.7) | 31 (18.1) |
| 3 | 1054 (19.3) | 986 (19.5) | 36 (15.3) | 32 (18.7) |
| 1&2 (Most deprived) | 2048 (37.6) | 1928 (38.2) | 64 (27.2) | 56 (32.7) |
| Settlement or population density | 5328 (97.7) | 4933 (97.8) | 232 (98.7) | 163 (95.3) |
| Rural | 933 (17.1) | 833 (16.5) | 65 (27.7) | 35 (20.5) |
| Urban | 4395 (80.6) | 4100 (81.3) | 167 (71.1) | 128 (74.9) |
| ***Clinical*** | | | | |
| BMI recorded | 5122 (94.0) | 4724 (93.6) | 231 (98.3) | 167 (97.7) |
| BMI (kg/m2) | 28.2 (7.3) | 28.3 (7.3) | 29.3 (6.4) | 24.55 (4.5) |
| Smoking status recorded | 5328 (97.7) | 4928 (97.7) | 233 (99.1) | 167 (97.7) |
| Non-smoker | 2128 (39.0) | 1969 (39.0) | 67 (28.5) | 92 (53.8) |
| Active-smoker | 486 (8.9) | 447 (8.9) | 28 (11.9) | 11 (6.4) |
| Ex-smoker | 2714 (49.8) | 2512 (49.8) | 138 (58.7) | 64 (37.4) |
| Co-morbidity\* | 3001 (55.1) | 2859 (56.7) | 116 (49.4) | 26 (15.2) |
| All medications\*\* | 2452 (45.0) | 2333 (46.2) | 100 (42.6) | 19 (11.1) |

\* Includes hypertension, coronary heart disease, diabetes (type 1 or type 2), chronic kidney disease stage 3-5, asthma, COPD, immunocompromised

\*\* Includes antihypertensive medication, lipid-lowering medication, hypoglycaemic medication, inhalers, immunosuppressants

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

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Total**  N= 5451 | **Non-decedent**  N=4787 | **Decedent**  N=664 |
| Age (years) | 59.0 (21.7) | 55.7 (20.8) | 82.5 (11.3) |
| Ethnicity recorded | 4356 (79.9) | 3838 (80.2) | 518 (78.0) |
| White | 3534 (64.8) | 3064 (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 | 5326 (97.7) | 4671 (97.6) | 655 (98.6) |
| 5 (Least deprived) | 1136 (20.8) | 993 (20.7) | 143 (21.5) |
| 4 | 1088 (20.0) | 936 (19.6) | 152 (22.9) |
| 3 | 1054 (19.3) | 918 (19.2) | 136 (20.5) |
| 1&2 (Most deprived) | 2048 (37.6) | 1824 (38.1) | 224 (33.7) |
| Settlement or population density | 5328 (97.7) | 4671 (97.6) | 657 (98.9) |
| Rural | 933 (17.1) | 816 (17.0) | 117 (17.6) |
| Urban | 4395 (80.6) | 3855 (80.5) | 540 (81.3) |
| BMI recorded | 5122 (94.0) |  |  |
| BMI (kg/m2) | 28.2 (7.3) | 28.4 (7.3) | 26.6 (7.1) |
| Smoking status recorded | 5328 (97.7) | 4684 (97.8) | 26.6 (7.1) |
| Non-smoker | 2128 (39.0) | 1912 (39.9) | 216 (32.5) |
| Active-smoker | 486 (8.9) | 446 (9.3) | 40 (6.0) |
| Ex-smoker | 2714 (49.8) | 2326 (48.6) | 388 (58.4) |
| Co-morbidity \* | 3001 (55.1) | 2454 (51.3) | 547 (82.4) |
| All medications \*\* | 2452 (45.0) | 1980 (41.4) | 472 (71.1) |

\* Includes hypertension, coronary heart disease, diabetes (type 1 or type 2), chronic kidney disease stage 3-5, asthma, COPD, immunocompromised

\*\* Includes antihypertensive medication, lipid lowering medication, hypoglycaemic medication, inhalers, immunosuppressants

**Table 3: Association between HRT use and the likelihood of death in women diagnosed with COVID-19 during the observation period (1st January to 21st June 2020), n= 5451)**

1. *Unadjusted models*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | OR | 95% CI | | p-value |
| HRT use | 0.15 | 0.061 | 0.366 | 0.000 |

1. *Maximally adjusted models*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | OR | 95% CI | | p-value |
| 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+ | 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 & 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 Categorised as obese | 0.85 | 0.62 | 1.15 | 0.289 |
| BMI Categorised as overweight | 0.87 | 0.66 | 1.16 | 0.350 |
| BMI Categorised 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 to 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 for BMI category: Normal weight