

1 **RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM BLOCKERS ARE NOT ASSOCIATED**  
2 **WITH CORONAVIRUS DISEASE 2019 (COVID-19) HOSPITALISATION: STUDY OF 1439**  
3 **UK BIOBANK CASES**

4

5 **RUNNING TITLE: RENIN-ANGIOTENSIN SYSTEM BLOCKERS AND COVID-19**

6

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24 **ABSTRACT**

25 **Background:** Cardiometabolic morbidity and medications, specifically Angiotensin Converting  
26 Enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs), have been linked with adverse  
27 outcomes from coronavirus disease 2019 (COVID-19). This study aims to investigate, factors  
28 associated with COVID-19 positivity in hospital for 1,436 UK Biobank participants; compared with  
29 individuals who tested negative, and with the untested, presumed negative, rest of the cohort.

30

31 **Methods:** We studied 7,099 participants from the UK Biobank who had been tested for COVID-19 in  
32 hospital. We considered the following exposures: age, sex, ethnicity, body mass index (BMI), diabetes,  
33 hypertension, hypercholesterolaemia, ACEi/ARB use, prior myocardial infarction (MI), and smoking.  
34 We undertook comparisons between 1) COVID-19 positive and COVID-19 negative tested participants;  
35 and 2) COVID-19 tested positive and the remaining participants (tested negative plus untested,  
36 n=494,838). Logistic regression models were used to investigate univariate and mutually adjusted  
37 associations.

38

39 **Results:** Among participants tested for COVID-19, Black, Asian, and Minority ethnic (BAME)  
40 ethnicity, male sex, and higher BMI were independently associated with a positive result. BAME  
41 ethnicity, male sex, greater BMI, diabetes, hypertension, and smoking were independently associated  
42 with COVID-19 positivity compared to the remaining cohort (test negatives plus untested). However,  
43 similar associations were observed when comparing those who tested negative for COVID-19 with the  
44 untested cohort; suggesting that these factors associate with general hospitalisation rather than  
45 specifically with COVID-19.

46

47 **Conclusions:** Among participants tested for COVID-19 with presumed moderate to severe symptoms  
48 in a hospital setting, BAME ethnicity, male sex, and higher BMI are associated with a positive result.  
49 Other cardiometabolic morbidities confer increased risk of hospitalisation, without specificity for  
50 COVID-19. ACE/ARB use did not associate with COVID-19 status.

51

52 **Keywords:** coronavirus disease 2019; UK Biobank; ethnicity; sex; obesity; cardiometabolic disease;  
53 Angiotensin Converting Enzyme inhibitors; Angiotensin Receptor Blockers

54 **INTRODUCTION**

55 Coronavirus disease 2019 (COVID-19), the clinical illness caused by the severe acute respiratory  
56 syndrome coronavirus 2 (SARS-CoV-2), has reached pandemic levels. There has been growing  
57 recognition that patients with underlying cardiometabolic morbidities may be suffering higher rates of  
58 infection and a more severe disease course than the general population<sup>1-3</sup>. Debate has ensued regarding  
59 whether these observations relate to the conditions themselves or the medications with which they are  
60 treated. In particular, some have suggested a mechanistic role for Angiotensin Converting Enzyme  
61 inhibitors (ACEi) or Angiotensin Receptor Blockers (ARBs)<sup>4</sup>. However, recent reports have not  
62 produced convincing evidence for the specific association of ACEi/ARBs with poorer outcomes<sup>4-6</sup>.  
63 Cardiometabolic diseases are common and ACEi/ARBs are used by many vulnerable patients. It is  
64 therefore important to better understand the augmented risk associated with cardiometabolic factors and  
65 ACEi/ARB use with COVID-19, to inform clinical practice, and guidance to patients.

66

67 The UK Biobank (UKB) is a large cohort study comprising data from over 500,000 participants from  
68 across the UK, characterised in detail at baseline (2006-2010), and with linkages to Hospital Episode  
69 Statistic (HES) data. In response to the COVID-19 pandemic, the UKB facilitated rapid release of  
70 COVID-19 testing data for its participants through linkage with Public Health England<sup>7</sup>, providing a  
71 unique opportunity to study the effects of many well-defined exposures on COVID-19 status.

72

73 The aim of this study is to investigate the association of demographic factors (age, sex, ethnicity),  
74 cardiometabolic profile [body mass index (BMI), diabetes, hypertension, hypercholesterolaemia, prior  
75 myocardial infarction (MI), smoking], and ACEi/ARB use with COVID-19 positivity in hospital using  
76 data from UKB.

## 77 **METHODS**

### 78 **Setting and study population**

79 UKB is a prospective cohort study including over 500,000 participants from across the UK. Individuals  
80 aged 40-69 years old identified via National Health Service (NHS) registers were recruited over a four-  
81 year period between 2006-2010. Participants underwent detailed baseline assessment including  
82 characterisation of socio-demographics, lifestyle, medical history, and a series of physical measures.  
83 The protocol is publicly available<sup>8</sup>. Linkages with HES data permit longitudinal tracking of health  
84 outcomes for all participants with conditions recorded according to international classification of  
85 disease (ICD) codes. In addition, UKB has produced algorithmically defined outcome data for incidence  
86 of key illness, such as MI, through integration of data from multiple sources<sup>9</sup>. The latest data release  
87 (24<sup>th</sup> June 2020) includes test results from 16<sup>th</sup> March to 14<sup>th</sup> June. In the UK, until the 18<sup>th</sup> of May  
88 2020, testing was almost entirely limited to hospital settings, after this date, testing was extended to the  
89 community. Therefore, we consider a positive test performed up to the 18<sup>th</sup> of May as indicative of  
90 hospitalisation, beyond this date we required explicitly labelling of the sample as “inpatient”. Testing  
91 was based on a real-time polymerase chain reaction (RT-PCR) assay antigen test; for most participants  
92 the sample tested was from combined nose and throat swab; for patients in intensive care lower  
93 respiratory samples may have been used. Thus, we defined a cohort of participants who were tested for  
94 SARS-CoV-2 whilst admitted to hospital, and therefore are likely to have a relatively severe  
95 presentation.

96

### 97 **Ethics**

98 This study was covered by the ethics approval for UKB studies from the NHS National Research Ethics  
99 Service on 17th June 2011 (Ref 11/NW/0382) and extended on 10th May 2016 (Ref 16/NW/0274).

100

### 101 **Statistical analysis**

102 Statistical analysis was performed using R Version 3.6.2 [R Core Team (2019). R: A language and  
103 environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.  
104 URL <https://www.R-project.org/>], and RStudio Version 1.2.5019 [RStudio Team (2015). RStudio:  
105 Integrated Development for R. RStudio, Inc., Boston, MA URL <http://www.rstudio.com/>]. We  
106 considered the following exposures: age, sex, ethnicity, body mass index (BMI), diabetes, hypertension,  
107 high cholesterol, ACEi/ARB use, prevalent MI, and smoking. The cardiometabolic and demographic  
108 factors were selected based on existing reports of their potential association with COVID-19  
109 outcomes<sup>3,10,11</sup>. ACEi/ARBs were considered due to reports of potential mechanistic role of these  
110 medications in the clinical course of COVID-19<sup>4</sup>. We used age, sex, and ethnicity (White vs BAME)

111 as recorded at baseline. BMI was calculated from height and weight recorded at baseline. Smoking  
112 status was based on self-report. Hypertension, diabetes, and hypercholesterolaemia were defined  
113 through cross-checking across self-report and HES data. A list of ICD codes used is available in  
114 Supplementary Table 1. Information on prior MI was obtained from the UKB algorithmically defined  
115 health outcomes. ACEi/ARB use was determined from self-report (Supplementary Table 2). We  
116 considered the effect of ACEi and ARBs both separately and as an aggregate variable. We created three  
117 cohorts: test positives, test negatives, and the untested cohort (Figure 1). Individuals who were tested,  
118 but with unclear hospitalisation status were excluded from the analysis. We firstly compared the  
119 COVID-19 test positive cohort with the combined cohort of test negatives and the untested UKB  
120 population. In order to investigate possible bias relating to hospitalisation status, we also considered the  
121 importance of these exposure variables in two further comparisons: test positives vs test negatives and  
122 test negatives vs untested population. We used logistic regression models to elucidate univariate and  
123 then multivariate associations. There was no evidence of multicollinearity with inflation factor (VIF)  
124  $<2.0$  for all covariates. As the observed association with ethnicity was strong, we tested for potential  
125 interaction effects between ethnicity and all tested covariates in multivariate models. We present odds  
126 ratio (OR) for each exposure with the corresponding 95% confidence interval (CI) and p-value. Given  
127 the low background prevalence of COVID-19 positivity, the odds ratios can be interpreted as relative  
128 risks.

129 **RESULTS**

130 **Baseline characteristics**

131 Of the 7,668 UKB participants tested for COVID-19, 7,099 were likely in a hospital setting and are  
132 included in this analysis (Table 1, Figure 1), of these 1,439 tested positive and 5,660 tested negative.  
133 There was no record of testing for the remainder of the UKB cohort (n=494,838) (Figure 1).

134

135 In comparison to the untested cohort, the COVID-19 positive cohort were predominantly male (52.9%  
136 vs 45.5%), had a greater proportion of BAME individuals (12.9% vs 5.3%), and an all-round poorer  
137 cardiometabolic profile, with higher BMI, higher rates of smoking, prior MI, diabetes, hypertension,  
138 and high cholesterol; they also reported greater use of ACEi/ARB agents (21.8% vs 14.3%). However,  
139 comparing the COVID-19 positive cohort with the tested negative cohort (n=5,660), the differences  
140 were much less pronounced, as the test negative cohort also had a globally poorer cardiometabolic  
141 profile than the untested population.

142

143 **Association of exposures with COVID status**

144 *COVID-19 positive vs not COVID-19 positive (tested negative cohort plus untested cohort)*

145 We first tested whether there were univariate associations between exposures and COVID-19 positives  
146 (n=1,439) vs not COVID-19 positives (including tested negative and untested cohort, n=500,498).  
147 Univariate associations were significant for all covariates considered, except age. In multivariate  
148 models, the independent predictors of COVID-19 positivity were younger age, male sex, BAME  
149 ethnicity, greater BMI, diabetes, hypertension, and smoking (Table 2, Figure 2: Comparison 1).

150

151 *COVID-19 positive vs COVID-19 tested negative*

152 We next considered associations between exposures and COVID-19 positives (n=1,439) vs tested  
153 negative cohort (n=5,660). Within this sample, the univariate predictors of positivity were male sex,  
154 younger age, BAME ethnicity, greater BMI, and diabetes. These variables, with the exception of  
155 diabetes, remained statistically significant in the multivariate model with mutual adjustment for all other  
156 covariates (Table 2, Figure 2). The greatest magnitude of effect related to ethnicity; BAME individuals  
157 had almost twice the likelihood of a COVID-19 positive result compared to White ethnicities in the  
158 fully adjusted models [OR 1.95, 95% CI (1.60, 2.36)]. There was no evidence of interaction effect with  
159 ethnicity and any of the other covariates (Supplementary Table 3). Compared with women, men had  
160 22% greater odds of a COVID-19 positive test [OR 1.22, 95% CI (1.08, 1.38)]. For every 5kg/m<sup>2</sup>  
161 increase of BMI, there was 9% greater odds of COVID-19 positive status (Table 2, Figure 2:

162 Comparison 2). There was a negative association with age, this may reflect older age of participants  
163 admitted to hospital for reasons other than COVID-19; alternatively, it may be an artefact of the data  
164 related to the narrow age range in the sample. Notably, there was no significant association between  
165 ACEi/ARB use and COVID-19 status, which was consistent when testing effect of ACEi and ARBs  
166 separately (Supplementary Table 4).

167

168 *COVID-19 tested negatives vs untested population*

169 Finally, we investigated associations between the exposures with a negative test (n=5,660) vs untested  
170 UKB population (n=494,838). There were significant univariate associations for all covariates  
171 considered. In the multivariate model, BAME ethnicity, older age, higher BMI, diabetes, hypertension,  
172 high cholesterol, previous MI, and smoking were significant predictors of a having a negative test, and  
173 therefore of presenting to hospital, perhaps with respiratory symptoms, compared to not being tested  
174 (Table 2, Figure 2: Comparison 3).

## 175 **DISCUSSION**

### 176 **Summary of findings**

177 In this analysis of 7,099 UKB participants tested for COVID-19 in a hospital setting, BAME ethnicity,  
178 younger age, male sex, greater BMI, diabetes, hypertension, and smoking were independently  
179 associated with COVID-19 positive test in comparison to the rest of the cohort (tested negatives plus  
180 untested). However, within the tested sample, a positive result was more likely for men, BAME  
181 individuals, younger ages, and with greater BMI. Indeed, when compared with the background  
182 population, the pattern of associations between exposures and COVID-19 positive was similar to that  
183 for COVID-19 test negative. These findings suggest that BAME ethnicity, male sex, and higher BMI  
184 have specific relevance to COVID-19, whilst the other exposure associations between COVID-19  
185 positive and the remainder of the population reflect morbidities associated with general requirement for  
186 hospitalisation, without specificity to COVID-19. Furthermore, as testing was in a hospital setting, these  
187 associations relate specifically to the more severe end of the COVID-19 manifestations requiring  
188 hospitalisation. Notably, ACEi/ARB usage was not associated with COVID-19 status.

189

### 190 **Comparison with existing literature**

191 With the rapid global spread of COVID-19, understanding the determinants of infection risk and  
192 severity is a priority. Differences in ethnic background are known to contribute to differences in patterns  
193 of a number of diseases, including influenza<sup>12</sup>, due to different genetic susceptibilities and  
194 environmental exposures<sup>13</sup>. In the UK, national audit data demonstrates as many as one-third of  
195 COVID-19 patients admitted to intensive care are from BAME backgrounds; a rate which is  
196 disproportionate to their representation among the general UK population<sup>14</sup>. In our study, BAME  
197 ethnicity had specific association with higher risk of COVID-19 positive status that appeared  
198 independent from often-quoted confounders of cardiovascular and metabolic morbidity that are known  
199 to be higher in prevalence in BAME cohorts<sup>15</sup>. Having accounted for cardiometabolic morbidity, the  
200 possible explanations for this association remain numerous<sup>16</sup>, gravitating around both genetic and social  
201 factors; behavioural, cultural, and socioeconomic differences, including health-seeking behaviour and  
202 intergenerational cohabitation are all likely to play a role in the strong disparity observed in our study,  
203 providing key targets for both further research and public health policy. Initial studies, demonstrate  
204 complex interplay of biological and socio-economic factors and highlight need for urgent research in  
205 this area<sup>17</sup>.

206

207 Since the first reports emerging from China at the beginning of the outbreak, it has been widely  
208 recognized that males suffer higher rates of infection and poorer outcomes compared to females; with



209 reported distributions of approximately three-fifths men and two-fifths women<sup>18,19</sup>. The reasons for this  
210 are unclear. Animal studies demonstrate, that in mice infected with SARS-CoV, oestrogen-deplete  
211 status either due to male gender or ovariectomy is associated with higher risk of acute respiratory  
212 distress syndrome (ARDS), indicating a possible protective role of oestrogen signalling<sup>20</sup>. Men are  
213 known to have higher burden of cardiovascular disease than women up to the perimenopausal years;  
214 and thus, lower cardiometabolic morbidity among women in the younger cohort has been postulated to  
215 contribute to better outcomes. However, we demonstrate that in our study population, the association  
216 between male sex and higher infection rates was independent of cardiometabolic disease. Furthermore,  
217 male sex appears significant in our sample comprising an older cohort with almost all women being  
218 post-menopause, indicating that sex-differential disparities in COVID-19 disease severity relate to  
219 factors other than immediate-term oestrogen exposure. Thus, our findings suggest that the higher risk  
220 of COVID-19 in men is not sufficiently explained by the oestrogen pathway or greater burden of  
221 cardiometabolic disease.

222

223 Obesity is a global health issue, rising in prevalence and public health burden in both developed and  
224 developing countries. Patients who suffer from obesity are known to be at increased risk of a number  
225 of conditions, including cardiometabolic and respiratory disease, contributing to a poor physiological  
226 reserve. It is already known that patients with obesity have worse outcomes from influenza infection<sup>21,22</sup>.  
227 With the wealth of emerging research on COVID-19, concern has grown over the association between  
228 obesity and poor outcomes of infection<sup>23</sup>; with studies consistently demonstrating higher rates of critical  
229 or intensive care requirement among individuals with higher BMI<sup>24-26</sup>. Similar to ethnicity, the  
230 relationship between obesity and severe infection must be isolated from the confounding of obesity-  
231 related comorbidity. In our study, we demonstrate the distinct role of obesity from that of associated  
232 cardiometabolic diseases; with the major finding that obesity, and not its comorbidities, had  
233 independent and specific association with COVID-19 positivity. This is of important relevance, as  
234 mechanistic understanding of the reason behind this association may provide therapeutic insight. For  
235 example, obesity enhances risk of thrombosis, which has been a recent focus of interest given concern  
236 over a possible association between COVID-19 and prothrombotic intravascular coagulation<sup>27</sup>. The  
237 results of our study provide useful information for risk stratification of patients, highlight important  
238 avenues for further research, and emphasise the public health-level importance of continued targeting  
239 of obesity.

240

241 Several reports hypothesise potential mechanistic links between ACEi/ARB usage and adverse  
242 outcomes from COVID-19<sup>4</sup>. SARS-CoV-2 has been shown to exhibit specific tropism for the  
243 angiotensin-converting enzyme 2 (ACE2) receptor; by which means it enters the cells and establishes

244 itself in the host<sup>28</sup>. The expression of ACE2 receptors in epithelial cells of the lung, intestine, kidney  
245 and endothelium may be increased in those treated with ACEi/ARBs, thereby facilitating entry and  
246 multisystem manifestations of COVID-19<sup>29,30</sup>. The relationship between COVID19 infection risk and  
247 use of ACEi/ARBs has been a matter of debate since the early days of the outbreak, but recent studies  
248 have revealed a lack of independent association when morbidity variables, including atherosclerotic  
249 cardiovascular disease, heart failure and cardiometabolic diseases such as diabetes and hypertension  
250 were accounted for<sup>4,5</sup>. Furthermore, a recent study from Spain demonstrates no association between  
251 ACEi/ARB use and COVID-19 mortality or requirement for intensive care<sup>31</sup>. Findings from our sample  
252 are consistent with these reports, demonstrating univariate association with ACEi/ARB use which  
253 becomes non-significant after adjustment for cardiometabolic and demographic factors.

254

### 255 **Strengths and Limitations**

256 UKB is a comprehensive data source, incorporating a large sample with linkages to prospectively  
257 tracked health outcomes recorded in a standardised manner using ICD codes, enabling reliable and up-  
258 to-date definition of morbidities. The rapid release of COVID-19 testing data provides a huge  
259 opportunity to examine association of a large number of exposures with COVID-19 status and  
260 outcomes. Due to the observational study design, we cannot comment on causal relationships from the  
261 results, however, the prospective nature of the study ensures confident temporal separation of exposure  
262 and outcome. Whilst analyses using the whole UK Biobank cohort of over 500,000 people may detect  
263 very small associations which are unlikely to be clinically significant, we studied a subset of much more  
264 modest sample size, with exposures and covariates chosen on the basis of prior literature and biological  
265 plausibility with the magnitude of relationships observed likely to be clinically meaningful. Further  
266 research in different cohorts would be helpful in better understanding the impact of the exposures  
267 studied. Whilst we can be reasonably confident about hospitalisation status of the tested cohort in this  
268 study, there is uncertainty about the degree of symptoms. We acknowledge that there are local variations  
269 in testing approaches and that conclusions regarding disease severity drawn from hospitalisation status  
270 alone have limitations. Studies in cohorts with more granular outcome data are needed. Furthermore,  
271 our results cannot be generalisable to asymptomatic or mildly symptomatic patients.

272

### 273 **Conclusions**

274 This work highlights specific associations of BAME ethnicity, male sex, and higher BMI with COVID-  
275 19 positive status, which were independent of other demographic or cardiometabolic factors. More  
276 detailed characterisation of these associations in larger and more diverse cohorts is warranted,  
277 particularly with regards ethnicity. Investigation of potential biological pathways underlying these

278 observed associations may provide insight into the mechanisms by which SARS-CoV-2 causes disease  
279 enabling more informed pursuit of potential therapeutic targets.

280

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289

290

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294 **FIGURE LEGENDS**

295 **Figure 1 Title:** Summary of COVID-19 testing and results for UK Biobank participants

296 **Figure 1 legend:** Data includes COVID-19 test results from 16/03/2020 to 14/06/2020. During this  
297 time period, 7,688 participants, of the whole UK Biobank cohort (n=502,506) have been tested for  
298 COVID-19. 7,099 were likely in a hospital setting, of whom 1,439 participants had a positive result and  
299 5,660 tested negative. The remaining participants (n=494,838) have not been tested.

300

301 **Figure 2 Title:** Odds Ratios and 95% confidence intervals for each exposure from the multivariate  
302 logistic regression models in the three different comparisons\*

303 **Figure 2 legend:** \*Comparison 1: COVID-19 positive (n=1,439) vs not COVID-19 positive (tested  
304 negative plus untested cohort) (n=494,838); Comparison 2: COVID-19 positive (n=1,439) vs COVID-  
305 19 test negative (n=5,660); Comparison 3: COVID-19 test negative (n=5,660) vs untested population  
306 (n=494,838). Results are odds ratios with 95% confidence intervals. Dashed lines represent non-  
307 significant and solid lines statistically significant results, with threshold at  $p < 0.05$ .

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407 **Table 1 caption:** Data are n (%), mean (standard deviation), or median [interquartile range]. COVID-  
 408 19 data includes test results from 16/03/2020 to 14/06/2020 from hospital settings. \*We report age of  
 409 participants as of 01/04/2020. \*\* smoking includes current and previous smoking. †ACEi/ARB use is  
 410 defined as a binary measure, defined as true if record of any of medications in supplementary Table 2.  
 411 ACEi: Angiotensin Converting Enzyme inhibitor; ARB: Angiotensin Receptor Blocker; BAME: Black,  
 412 Asian, and Minority ethnic; BMI: body mass index; COVID-19: coronavirus 2019.

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**Table 1. Baseline participant characteristics**

	COVID-19 tested (n=7,099)	COVID-19 positive (n=1,439)	COVID-19 negative (n=5,660)	Untested population (n=494,838)
Sex (Male)	3,525 (49.7%)	761 (52.9%)	2,764 (48.8%)	225,352 (45.5%)
Age*	69.11 (± 8.65)	68.22 (± 9.19)	69.34 (± 8.49)	68.24 (± 8.10)
White ethnicity	6,498 (91.5%)	1,242 (86.3%)	5,256 (92.9%)	465,681 (94.1%)
BAME ethnicity	562 (7.9%)	185 (12.9%)	377 (6.7%)	26,429 (5.3%)
BMI (kg/m <sup>2</sup> )	27.66 [24.78, 31.13]	27.97 [25.18, 31.50]	27.58 [24.69, 31.02]	26.7 [± 24.13, 29.89]
Smoking**	3,663 (51.6%)	732 (50.9%)	2,931 (51.8%)	221,478 (44.8%)
Prior MI	557 (7.8%)	103 (7.2%)	454 (8.0%)	20,227 (4.1%)
Diabetes	1,029 (14.5%)	241 (16.7%)	788 (13.9%)	38,046 (7.7%)
Hypertension	3,338 (47.0%)	676 (47.0%)	2,662 (47.0%)	171,415 (34.6%)
High cholesterol	2,388 (33.6%)	477 (33.1%)	1,911 (33.8%)	115,133 (23.3%)
ACEi	1,117 (15.7%)	227 (15.8%)	890 (15.7%)	50,635 (10.2%)
ARB	418 (5.9%)	87 (6.0%)	331 (5.8%)	20,416 (4.1%)

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416 **Table 2 caption:** \*\* Comparison 1: COVID-19 positive (n=1,439) vs not COVID-19 positive (tested  
417 negative plus untested cohort) (n=494,838); Comparison 2: COVID-19 positive (n=1,439) vs COVID-  
418 19 test negative (n=5,660); Comparison 3: COVID-19 test negative (n=5,660) vs untested population  
419 (n=494,838). Results are odds ratio, 95% confidence interval, and p-value (from top to bottom) for  
420 each exposure. For continuous variables (age, BMI) coefficients refer to the effect on odds of the  
421 outcome per five unit increase in the exposures, i.e. 5-year increase in age and 5kg/m<sup>2</sup> increase in  
422 BMI. The remaining exposures are set as binary measures with results showing effect of change from  
423 non-disease to disease states, male sex vs female sex, BAME ethnicity vs White ethnicity; smoking  
424 history (current/previous) vs never smoked; ACEi/ARB use vs no ACEi/ARB use on odds of the  
425 outcome. \*indicates p-values <0.05. ACEi: Angiotensin Converting Enzyme inhibitor; ARB:  
426 Angiotensin Receptor Blocker; BMI: body mass index; coronavirus 2019: COVID-19; BAME: Black,  
427 Asian, and Minority ethnic; MI: myocardial infarction.

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**Table 2. Odds Ratios, 95% confidence intervals, and p-values for each exposure from univariate and multivariate logistic regression models in the**

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**three defined comparisons\*\***

Predictors	Comparison 1		Comparison 2		Comparison 3	
	Univariate Models	Multivariate Model	Univariate Models	Multivariate Model	Univariate Models	Multivariate Model
Male sex	1.34* [1.21, 1.49] 3.07×10 <sup>-8</sup>	1.19* [1.07, 1.32] 0.0017	1.18* [1.05, 1.32] 0.0061	1.22* [1.08, 1.38] 0.0012	1.14* [1.08, 1.20] 7.68×10 <sup>-7</sup>	1.00 [0.95, 1.06] 0.9759
Age (per 5 years)	1.00 [0.97, 1.03] 0.8620	0.96* [0.93, 1.00] 0.0316	0.93* [0.90, 0.96] 1.17×10 <sup>-5</sup>	0.94* [0.90, 0.97] 9.64×10 <sup>-4</sup>	1.09* [1.07, 1.11] 5.81×10 <sup>-24</sup>	1.03* [1.01, 1.05] 0.0013
BAME ethnicity	2.62* [2.23, 3.05] 4.58×10 <sup>-34</sup>	2.47* [2.10, 2.89] 5.58×10 <sup>-28</sup>	2.08* [1.72, 2.50] 1.59×10 <sup>-14</sup>	1.95* [1.60, 2.36] 2.07×10 <sup>-11</sup>	1.26* [1.14, 1.40] 1.29×10 <sup>-5</sup>	1.27* [1.14, 1.41] 1.70×10 <sup>-5</sup>
BMI (per 5kg/m2)	1.30* [1.24, 1.36] 2.19×10 <sup>-29</sup>	1.19* [1.13, 1.25] 7.63×10 <sup>-11</sup>	1.10* [1.04, 1.16] 3.62×10 <sup>-4</sup>	1.09* [1.03, 1.16] 0.0031	1.19* [1.16, 1.22] 4.47×10 <sup>-42</sup>	1.09* [1.06, 1.12] 3.78×10 <sup>-9</sup>
Diabetes	2.39* [2.08, 2.74] 7.39×10 <sup>-35</sup>	1.52* [1.29, 1.79] 3.72×10 <sup>-7</sup>	1.24* [1.06, 1.45] 0.0066	1.17 [0.98, 1.41] 0.0882	1.94* [1.80, 2.09] 1.05×10 <sup>-65</sup>	1.34* [1.23, 1.46] 2.80×10 <sup>-11</sup>
Hypertension	1.66* [1.50, 1.84] 8.27×10 <sup>-22</sup>	1.25* [1.09, 1.43] 0.0010	1.00 [0.89, 1.12] 0.9704	0.98 [0.84, 1.14] 0.7727	1.68* [1.59, 1.77] 1.27×10 <sup>-82</sup>	1.28* [1.20, 1.37] 5.90×10 <sup>-13</sup>
High cholesterol	1.62* [1.45, 1.81] 5.20×10 <sup>-18</sup>	1.12 [0.97, 1.28] 0.1234	0.97 [0.86, 1.10] 0.6592	0.95 [0.81, 1.11] 0.5006	1.68* [1.59, 1.78] 3.31×10 <sup>-75</sup>	1.19* [1.11, 1.27] 1.52×10 <sup>-6</sup>
ACEi/ARB	1.65* [1.45, 1.87] 7.54×10 <sup>-15</sup>	1.04 [0.89, 1.22] 0.5885	1.01 [0.88, 1.17] 0.8563	0.99 [0.83, 1.19] 0.9468	1.64* [1.54, 1.75] 2.31×10 <sup>-51</sup>	1.04 [0.96, 1.13] 0.3193
Prior MI	1.79* [1.45, 2.17] 1.41×10 <sup>-8</sup>	1.18 [0.94, 1.46] 0.1377	0.88 [0.70, 1.10] 0.2770	0.85 [0.66, 1.08] 0.1893	2.05* [1.85, 2.25] 1.70×10 <sup>-47</sup>	1.39* [1.25, 1.54] 1.02×10 <sup>-9</sup>
Smoking	1.27* [1.15, 1.41] 4.58×10 <sup>-6</sup>	1.26* [1.13, 1.40] 3.02×10 <sup>-5</sup>	0.96 [0.86, 1.08] 0.5348	1.02 [0.90, 1.15] 0.7369	1.33* [1.26, 1.40] 5.91×10 <sup>-26</sup>	1.24* [1.17, 1.31] 9.40×10 <sup>-15</sup>

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