

# BMJ Open Does comorbidity burden explain the higher COVID-19 mortality risk among men? A retrospective cross-sectional analysis of a well-defined cohort of patients in Bronx, New York

Aastha Vasa <sup>1</sup>, Maya Kini,<sup>2</sup> Joel Neugarten,<sup>1</sup> Eran Bellin,<sup>3</sup> Ladan Golestaneh <sup>1</sup>

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<sup>1</sup>Department of Medicine, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York, USA

<sup>2</sup>Rye Country Day School, Rye, New York, USA

<sup>3</sup>Epidemiology and Population Health, Montefiore Medical Center, Yonkers, New York, USA

## Correspondence to

Aastha Vasa;  
[aastha.vasa@einsteinmed.edu](mailto:aastha.vasa@einsteinmed.edu)

## ABSTRACT

**Objectives** Men have a higher mortality rate and more severe COVID-19 infection than women. The mechanism for this is unclear. We hypothesise that innate sex differences, rather than comorbidity burden, drive higher male mortality.

**Design** Retrospective cohort.

**Setting** Montefiore Health System (MHS) in Bronx, New York, USA.

**Participants** A cohort population of 364 992 patients at MHS between 1 January 2018 and 1 January 2020 was defined, from which individuals hospitalised during the pre-COVID period (1 January 2020–15 February 2020) (n=5856) and individuals hospitalised during the COVID-19 surge (1 March 2020–15 April 2020) (n=4793) were examined for outcomes. A subcohort with confirmed COVID-19+ hospitalisation was also examined (n=1742).

## Primary and secondary outcome measures

Hospitalisation and in-hospital mortality.

**Results** Men were older, had more comorbidities, lower body mass index and were more likely to smoke. Unadjusted logistic regression showed a higher odds of death in hospitalised men than women during both the pre-COVID-19 and COVID-19 periods (pre-COVID-19, OR: 1.66 vs COVID-19 OR: 1.98). After adjustment for relevant clinical and demographic factors, the higher risk of male death attenuated towards the null in the pre-COVID-19 period (OR 1.36, 95% CI 1.05 to 1.76) but remained significantly higher in the COVID-19 period (OR 2.02; 95% CI 1.73 to 2.34).

In the subcohort of COVID-19+ hospitalised patients, men had 1.37 higher odds of in-hospital death (95% CI 1.09 to 1.72), which was not altered by adjustment for comorbidity (OR remained at 1.38 (95% CI 1.08 to 1.76)) but was attenuated with addition of initial pulse oximetry on presentation (OR 1.26, 95% CI 0.99 to 1.62).

**Conclusions** Higher male mortality risk during the COVID-19 period despite adjustment for comorbidity supports the role of innate physiological susceptibility to COVID-19 death. Attenuation of higher male risk towards the null after adjustment for severity of lung disease in hospitalised COVID-19+ patients further supports the role of higher severity of COVID-19 pneumonia in men.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Using Looking Glass, we built a database of patients (n=364 992) who received outpatient care between 1 January 2018 and 1 January 2020 and was defined as the denominator patient population.
- ⇒ Those patient with hospitalisations and in-hospital deaths during the pre-COVID-19 and COVID-19 periods were examined as a proportion of the denominator population allowing for a robust assessment of risk.
- ⇒ To elucidate the role of baseline comorbidity in higher risk of COVID-19 mortality in men, we used mixed-effects logistic regression to examine the association between sex and hospitalisation/death (outcomes) with and without adjustment for patient comorbidity.
- ⇒ The analysis did not include outpatient deaths which limited the scalability of the findings and introduced sampling bias.

## INTRODUCTION

Numerous studies have shown that men have a higher risk of COVID-19-related death as compared with women.<sup>1–14</sup> Men also have a more severe disease course, with higher odds of in-hospital adverse outcomes such as ICU admission, need for ventilatory support, and higher odds of acute kidney and cardiac injury.<sup>3</sup> Mediators of the risk difference between the sexes have been attributed to differences in comorbidities, risk behaviours (such as smoking and not seeking preventive healthcare), exposure rate (more men work in occupations that force them to leave their homes and have contact with other people) and biological differences in susceptibility.<sup>2,8</sup> For example, preliminary data from Gebhard *et al* describe an association between comorbidities, risk behaviours (ie, smoking) and COVID-19 disease severity.<sup>11</sup> Another study from a cohort of patients in Bronx, New

York, showed that obesity, male sex and older age were associated with greater in-hospital mortality.<sup>15</sup> Other researchers argue that inherent biological differences in ACE expression, androgen-mediated regulation of transmembrane serine protease 2 (TMPRSS2), as well as sex differences in immune responses, are the actual mediators.<sup>5 7-9 16 17</sup>

To address the question of what is mediating the higher male risk for COVID-19-related mortality, cohort studies should adjust for comorbidity and viral exposure to test the strength of association between male sex and COVID-19 outcome, with the understanding that a demonstration of the attenuation of this strength supports the role of these explanatory variables in imparting higher male risk. In this study, we first establish the disproportionate higher risk of in-hospital male death in one large health system in the Bronx during a period impacted by the COVID-19 surge of 2020 as compared with a pre-COVID time period. Because of the comprehensive nature of our clinical database and because this was still a period where vaccinations were not available, we are uniquely able to evaluate the role of comorbidity and smoking behaviour as an explanation for the higher risk of in-hospital COVID-19-related death in men. We then examine the role of severity of SARS-CoV-2-related pneumonia as a plausible explanation for any higher male risk found in a subcohort of patients hospitalised with confirmed COVID-19 illness.

## MATERIALS AND METHODS

To test the association of sex with COVID-19-related outcomes, we: (1) test the relative risk of male hospitalisation and in-hospital mortality, as compared with female, during the initial COVID-19 surge of New York (1 March 2020–15 April 2020) and compare this risk to a pre-COVID-19 time period (1 January 2020–15 February 2020)<sup>18</sup>; (2) then compare the odds of male versus female death in a subset of patients hospitalised with a confirmed positive COVID-19 test during the COVID-19 surge time period and (3) provide a descriptive analysis of the city/state and national level impact of COVID-19 death by sex using Vital Statistics/Centers for Disease Control and Prevention (CDC) data.<sup>19 20</sup>

### Study populations

1. To minimise sampling bias, a baseline population of 364 992 Bronx addressed adult patients (>18 years) receiving care at Bronx Montefiore Health System (BMHS) between 1 January 2018 and 1 January 2020 was defined. From this population, we extracted variables and outcomes data on individuals hospitalised during the pre-COVID-19 period (1 January 2020–15 February 2020) and during the COVID-19 surge (1 March 2020–15 April 2020). Clinical Looking Glass (CLG),<sup>21</sup> Montefiore's clinical/claims database, was used to collect individual demographic and co-morbidity data: including sex, age (categorised by deciles), race/ethnicity (self-identified and categorised into racial/

ethnic categories), diabetes mellitus status (based on International Classification of Diseases (ICD) coding and/or evidence for Hemoglobin A1c (HgbA1c) level >6.5 within 2 years prior to entry into cohort), hypertension (based on ICD coding and/or evidence for systolic blood pressure > 150 mm Hg within 2 years prior to entry into cohort), asthma (based on ICD coding), Charlson score (comorbidity score calculated by CLG based on ICD-10 coding for diagnoses required for calculation of the score within 6 months prior to entry into cohort<sup>22 23</sup>), any history of smoking and body mass index (BMI, based on latest BMI recorded at any type of clinical visit at Montefiore). Individual addresses were linked to the American Community Survey<sup>24</sup> to define census tract level sociodemographic variables (% of households living under the poverty line, completed high school, had health insurance, used public transportation to commute to work and had access to internet). We also defined mean household size by census tract.

2. The subset of patients, drawn from the baseline population (see above), who were hospitalised during the COVID-19 period (n=1742) with evidence for COVID-19 testing and a positivity of COVID-19 test was analysed separately.
3. Finally, to test the generalisability of the findings of our cohort to a larger city, state and national population, the New York Department of Health's Vital Statistics registry was accessed for total population and death estimates to build proportions of all-cause male/female death rates in four time periods (2015–2018).<sup>19</sup> The time periods include 4 years of data prior to the COVID-19 surge, and proportion of city-wide death during COVID-19, were similarly reported. Using 2020 Census data to derive baseline breakdown of sex in the denominator population, proportions were calculated to determine the rates of COVID-19 cases, admissions and hospitalisations for men versus women.<sup>25</sup> Furthermore, CDC data were accessed to evaluate the proportion of COVID-19-related as compared with COVID-19-unrelated deaths by sex in New York State and across the country as of 29 March 2022.

### Outcome variable

Proportion of patients who had an in-hospital death in either time period.

### Exposure variable

Patient sex.

### Statistical analysis

Stata V.15.0 was used for analyses. Bivariate analysis was done to compare distribution between male and female of demographic (race and age), clinical risk (history of diabetes, hypertension, asthma, smoking status, Charlson Comorbidity Score and BMI) and community-level variables using t-test for normally distributed variables and Wilcoxon rank-sum test for non-normally distributed

variables. In the subset of hospitalised COVID+patients, initial respiratory rate, white cell count, systolic blood pressure, respiratory rate and pulseoximetry at initial hospital encounter were also included in sex-category-based bivariate analyses.

Mixed effects logit modelling (random effects presented by individual patients in duplicated baseline populations, each representing a different time period) tested the probability of male versus female hospitalisation rate and death in and between the pre-COVID-19 and COVID-19 time periods, while adjusting for all demographic and clinical risk variables that were significantly different by

sex in bivariate analyses.<sup>26</sup> Interaction between sex and COVID-19 versus pre-COVID-19 time period with respect to hospitalisation and mortality outcome was tested as an additive 'lincom' postestimation test.<sup>27</sup> We then stratified logistic regression models by time period while adjusting for similar confounding variables.

For the hospitalised COVID+ subpopulation, logistic regression modelling, using stepwise forward addition techniques (at a significance for inclusion of  $p<0.05$ ), tested the association of sex and mortality while adjusting for demographic and comorbid confounding variables, and those clinical variables on presentation to the hospital.

**Table 1** Bivariate comparison of demographic, clinical and community-level variables in men versus women

N=364 992	Men (n=133 300; 36.5%)	Women (n=231 692; 63.5%)	P value
Age (years) (mean ( $\pm$ SD))	50.0 (18.9)	49.9 (19.0)	0.001
Age (median; 25–75% IQR)	52 (34–64)	50 (33–64)	<0.001
Race/ethnicity (n; %)			<0.001
Non-Hispanic white	12 295 (9.2)	16 344 (7.1)	
Non-Hispanic black	36 147 (27.1)	67 928 (29.3)	
Hispanic	47 887 (35.9)	89 948 (38.8)	
Other	36 971 (27.7)	57 472 (24.8)	
Charlson score (median; 25–75% IQR)	1 (0–2)	1 (0–2)	<0.001
Charlson score category			<0.001
1 (<1)	60 041 (45.0)	109 448 (47.3)	
2 (1–2)	46 473 (34.9)	77 715 (33.5)	
3 (>2)	26 786 (20.1)	44 489 (19.2)	
Diabetes (n, %)			<0.001
Yes	23 759 (17.8)	36 120 (15.6)	
No	109 541 (82.2)	195 572 (84.4)	
Hypertension (n, %)			<0.001
Yes	62 906 (47.2)	100 892 (43.6)	
No	70 394 (52.8)	130 800 (56.5)	
Asthma (n, %)			<0.001
Yes	11 146 (8.4)	32 036 (13.8)	
No	122 154 (91.6)	199 656 (86.2)	
Smoker (n, %)			<0.001
Yes	48 495 (36.4)	55 644 (24.0)	
No	70 781 (53.1)	156 233 (67.4)	
BMI (median; 25–75% IQR) (n=639 506)	28.0 (24.6–32.0)	29.2 (25.2–34.0)	<0.001
Community-level social determinants (mean ( $\pm$ SD))			
Average household size	2.8 (0.4)	2.8 (0.4)	0.1
% completed high school	28.1 (5.3)	28.1 (5.2)	0.9
% with active internet subscription	73.2 (7.9)	72.8 (7.9)	<0.001
% with health insurance	9.1 (4.3)	9.1 (4.2)	<0.05
% of households living under the poverty line	23.5 (13.2)	24.2 (13.3)	<0.001
% using public transportation to commute to work	59.1 (13.0)	59.7 (12.6)	<0.001

BMI, body mass index.

**Table 2** Odds of male hospitalisation and death during the pre-COVID-19 and COVID-19 time period

N=364 992	Male as compared with female Model 1 (95% CI)	Male as compared with female Model 2 (95% CI)
OR for hospitalisation during pre-COVID-19 period	1.07 (1.02 to 1.14)	1.04 (0.98 to 1.10)
OR for hospitalisation during COVID-19 period	1.22 (1.15 to 1.30)	1.25 (1.18 to 1.33)
OR for death during pre-COVID-19 period	1.66 (1.30 to 2.12)	1.36 (1.05 to 1.76)
OR for death during COVID-19 period	1.98 (1.71 to 2.28)	2.02 (1.73 to 2.34)

Model 1: unadjusted; model 2: model 1+adjustment for race/ethnicity, age, diabetes (y/n), hypertension (y/n), asthma (y/n), smoking status (yes or former/no) and for every one point increase in Charlson score.

Simple proportions were used to test the sex-based all-cause mortality differences between sexes of data from New York City during the 2015–2018 and the city-wide mortality during the COVID-19 surge.

### Sensitivity analysis

The BMI variable had ~18% missing observations and was excluded from both regression models. In sensitivity analyses, we included BMI into the multivariate adjusted models to examine any difference in the coefficient of interest with and without its inclusion, and any change in the accuracy of the drawn inferences.

Because of the inherent difficulty with interpreting differences in community-level attributes between men and woman (units in census data defined as households and not individuals), they were left out of the final regression models. In sensitivity analyses, we included community level attributes (in bulk, see [table 1](#)) and examined any difference in coefficient of interest with and without their inclusion.

### Patient and public involvement

Patients and the public were not involved in the design, conduct, outcome measures or recruitment of this study.

## RESULTS

The mean age of the baseline population was 49.9 years old, 7.8% were white, 28.5% were black and 37.8% were Hispanic. 36.5% of the baseline population was male, with 16.4% diagnosed with diabetes, 44.9% with hypertension and 11.8% with asthma ([table 1](#)).

Men were slightly older (mean age of 50.0 years for men vs 49.9 years for women;  $p=0.001$ ), had more comorbidities (20.1% men had a  $>3$  Charlson score vs 19.2% women;  $p<0.001$ ), more had diabetes (17.8% vs 16.5%;  $p<0.001$ ) and hypertension (47.2% vs 43.6%;  $p<0.001$ ) and had a lower BMI than women (median of 28.0 for men vs median of 29.2 for women;  $p<0.001$ ). More men smoked than women (36.4% vs 24.0%;  $p<0.001$ ), but a lower proportion had asthma (8.4% vs 13.8%;  $p<0.001$ ). There was no difference between men and women with respect to census tract average household size or percentage of households that completed high school. More men had an active internet subscription (mean of 73.2% for men vs 72.8% for women;  $p<0.001$ ), fewer men came from

households that lived under the poverty line (mean of 23.5% for men vs 24.2% for women;  $p<0.001$ ) and fewer men used public transportation to commute to work (mean of 59.1% men vs 59.7% women;  $p<0.001$ ) ([table 1](#)).

During the pre-COVID-19 period, 5856/364 992 individuals were hospitalised (1.6%), while during the COVID-19 period 4793/364 992 (1.3%) were hospitalised. In unadjusted and adjusted models, men had a higher odds of hospitalisation in both time periods ([table 2](#)). The interaction between male sex and time period with respect to odds of hospitalisation was statistically significant ( $p<0.001$ ) suggesting a higher risk of male hospitalisations during COVID-19 as compared with pre-COVID-19 time period. Furthermore, the odds of pre-COVID-19 male hospitalisation attenuated towards the null after adjustment for relevant comorbidities including Charlson Comorbidity Score, but remained robust without any attenuation during the COVID-19 period ([table 2](#)).

Two hundred and fifty-four individuals from the pre-COVID-19 time period and 748 individuals from the COVID-19 period had an in-hospital death event. During the pre-COVID-19 time period, men had greater in-hospital deaths, with a 0.03% difference in proportion who died between men and women. During the COVID-19 time period, the difference between male and female proportions of in-hospital deaths was 0.15%. Stratified analyses showed men were had a positive and significant odds of death during both pre-COVID-19 and COVID-19 time periods (OR pre-COVID 1.66 (95% CI 1.30 to 2.12) vs OR COVID-19 1.98 (95% CI 1.71 to 2.28)) as compared with women. Addition of confounding demographic and clinical variables attenuated the odds of male death in the pre-COVID-19 period but not in the COVID-19 period ([table 2](#)).

Sensitivity analysis showed that addition of BMI to the logit model altered the adjusted OR of male death in the pre-COVID-19 (from OR 1.37 (95% CI 1.05 to 1.77) to OR 1.29 (95% CI 0.99 to 1.67); LR test of model with BMI nested vs without:  $p<0.001$ ;  $n=3\,19\,753$ ) and in the COVID-19 (from OR 1.99 (95% CI 1.71 to 2.31) to OR 1.99 (95% CI 1.71 to 2.31); LR test  $p=0.94$ ). The addition of BMI to the logit model testing for interaction showed no change in the  $p$  value for interaction between sex and time period with respect to mortality ( $p$  for interaction

0.24 with vs 0.25 without BMI in the model; LR test  $p=0.6$ ) Addition of community-level variables including percentage of households with high school education, living under poverty line, using public transport to commute to work, access to internet and mean household size, did not alter the OR of male death in the pre-COVID-19 period (OR 1.35 (95% CI 1.04 to 1.77) and in the COVID-19 period (OR 1.99 (95% CI 1.7 to 2.32)) significantly.

In the sample of patients who tested positive for COVID-19 and were hospitalised ( $n=1742/364\ 992$ ; 0.48%), 849 were male (48.7%), median age was 64.9 years, median Charlson score was 3 (IQR 1–4) with 737 individuals (42.3%) diagnosed with diabetes, 1467 (84.2%) diagnosed with hypertension and 398 (22.8%) diagnosed with asthma. Mean BMI was 30.2 ( $\pm 7.5$ ) among patients in the sample. Men had higher comorbidity with 464 (53.7%), as compared with 436 (48.8%), categorised in the highest Charlson score category (table 2). Men also had higher rates of smoking than women (table 3). Men had 1.37 odds of in-hospital death (95% CI 1.09 to 1.72) as compared with women after adjusting for race/ethnicity and age, which was not altered by the addition of clinical comorbidity (OR remained at 1.38 (95% CI 1.08 to 1.76)). However, addition of pulse oximetry on presentation to the hospital attenuated the odds of male death towards the null (1.26 (95% CI 0.99 to 1.62)).

City-wide male versus female death rates showed a difference of 0.02% between male and female mortality for 2015 and a 0.04% difference in 2016, 2017 and 2018 (online supplemental table 1). City-wide data from the department of health on COVID-19 cases, hospitalisations and deaths from 29 February 2020–1 June 2020 was analysed.<sup>28</sup> As shown in online supplemental table 2, there were 0.4% more men who tested positive, 0.2% more men who were hospitalised and 0.11% more men who died from COVID-19 than women. This suggests a relative increase of male mortality during COVID-19 as compared with prior years, portraying the differential impact of COVID-19 on men at a population level.

State-wide and national CDC data on COVID-19 and all-cause deaths for people  $\geq 18$  years old and people  $\geq 65$  years old was analysed.<sup>20</sup> In New York State and nationally, more men died from COVID-19 than women. This difference was greater than the sex differences in all-cause mortality suggesting an even greater male vulnerability to COVID-19 (online supplemental table 3).

## DISCUSSION

In this analysis of an ambulatory population of the BMHS we showed a higher proportion of men than women were hospitalised during both pre-COVID-19 and COVID-19 time periods. The higher male risk for hospitalisation was driven by higher comorbidity in the pre-COVID-19 period but not during the COVID-19 period. Men were also at disproportionately higher risk of death during both time periods, and even though

their greater risk of death attenuated towards the null in the pre-COVID-19 time period with adjustment for relevant comorbidities it remained significantly elevated compared with females during the COVID-19 period. These data show that the higher comorbidity burden and higher prevalence of smoking among males does not explain the higher risk of COVID-19-related mortality in men. Thus, even though comorbidity at least partially explains the higher male risk for death in the general population, it fails to do so during the COVID-19 surge of 2020. This suggests the unique vulnerability of men to the virus. In our subgroup analysis of those hospitalised patients with an established positive COVID-19 test, we showed that the higher risk of male death was attenuated towards the null only when adjusting for pulseoximetry readings on hospitalisation, suggesting that men were more critically ill with COVID-19 pneumonia than women and this may have been an explanation for their higher death rate.

Using city-wide data from the department of health, and state-wide and national data from the CDC, a higher risk of male COVID-19 cases, hospitalisations and deaths was also observed.<sup>19 20</sup> The greater ARDS and respiratory failure rates in males were attributed to a dysregulated immune response in other studies.<sup>8</sup> Furthermore, the higher male risk for mortality may be related to sexual dimorphism in ACE2 and TMPRSS2 expression and regulation.<sup>8 16 29</sup> To enter a host cell, SARS-CoV-2 binds to the ACE2 surface receptor via its spike protein. Androgen mediated upregulation of TMPRSS2 has been hypothesised to contribute to increased male disease severity with COVID-19.<sup>7–9 16</sup> In fact, men on androgen deprivation therapy for prostate cancer have a significant reduction in COVID-19 infection compared with men with prostate cancer not on this therapy.<sup>7</sup> Sex-based differences in immune responses have been theorised as another explanation for the increased male mortality with COVID-19. Sex hormones and the X chromosome (which encodes for various immune regulatory genes) have a significant influence on the immune response.<sup>9</sup> Kelada *et al* report that female sex hormones are immunostimulatory.<sup>5</sup> Oestrogen contributes to B cell development and induces production of cytokines in response to viral entry while facilitating reduction of viral load.<sup>5</sup> High levels of oestrogen and progesterone in females have been shown to suppress pro-inflammatory cytokine production, and stimulate cell-mediated immunity and antibody production all of which contribute to faster viral clearance.<sup>1</sup> When hormone replacement therapy was given to postmenopausal women, a decreased mortality from COVID-19 was observed.<sup>30</sup> Animal studies demonstrated greater disease severity in female mice after a ovariectomy or administration of an oestrogen receptor antagonist.<sup>31</sup> These findings suggest a protective effect of female sex that is not explained by comorbidities.<sup>1</sup> Sex differences in vaccine responses have also been demonstrated, with women mounting stronger responses.<sup>17</sup> However, our data predate COVID-19 vaccines so that vaccine

**Table 3** Demographic and clinical variables by sex among those hospitalised with a positive COVID-19 test

N=1742	Men	Women	P value
	N=849 (48.7%)	N=893 (51.3%)	
Age (years) (mean;±SD)	65.4 (14.6)	64.4 (15.9)	0.2
Race/ethnicity sum (n; %)			
Non-Hispanic white	74 (8.7)	45 (5.0)	<0.001
Non-Hispanic black	322 (37.9)	392 (43.9)	
Hispanic	289 (34.0)	323 (36.2)	
Other	164 (19.3)	133 (14.9)	
Charlson score (median; 25–75% IQR)	3 (1–4)	2 (1–4)	<0.05
Charlson score category			
1 (<1)	92 (10.8)	132 (14.8)	<0.05
2 (1–2)	293 (34.5)	325 (36.4)	
3 (>2)	464 (54.7)	436 (48.8)	
Diabetes (n, %)			0.3
Yes	349 (41.1)	388 (43.5)	
No	500 (58.9)	505 (56.6)	
Hypertension (n, %)			0.1
Yes	726 (85.5)	741 (83.0)	
No	123 (14.5)	152 (17.0)	
Asthma (n, %)			<0.001
Yes	125 (14.7)	273 (30.6)	
No	724 (85.3)	620 (69.4)	
Smoker (n, %)			<0.001
Yes	369 (43.5)	301 (33.7)	
No	463 (54.5)	585 (65.5)	
BMI (median; 25–75% IQR)	27.7 (24.0–31.8)	30.6 (26.5–35.6)	<0.001
Albumin (g/dL) (mean; SD)	3.7 (0.5)	3.8 (0.5)	0.3
WBC count (K/uL) (median; IQR) (n=1707)	6.8 (5.2–9.7)	7.0 (5.2–9.4)	0.7
Total bilirubin (mg/dL) (median; IQR) n=1587	0.5 (0.4–0.7)	0.4 (0.3–0.6)	<0.001
C reactive protein (mg/L) (median; IQR) n=676	13.1 (6.1–20.3)	9.0 (4.5–16.3)	<0.001
Lymphocyte count (K/uL) (median; IQR) n=1707	0.8 (0.6–1.2)	1.1 (0.7–1.1)	<0.001
Temperature (median; IQR) n=1732	99.0 (98.3–100.1)	99.0 (98.3–100.1)	0.5
SBP (median; IQR) n=1737	132 (117–149)	130 (114–145)	0.01
Pulse rate (beats/minute) (median; IQR)	97 (83–111)	95 (83–110)	0.3
Pulse oximetry (% O <sub>2</sub> ) (mean; SD) n=1735	92.1 (9.1)	93.4 (7.6)	0.002
Respiratory rate (respirations/minute) (mean; SD)	21.2 (5.5)	20.7 (4.6)	0.08

SBP, Systolic Blood Pressure; WBC, White Blood Cell.

responsiveness and or vaccine seeking behaviours do not contribute to our findings.

Higher exposure to virus is another potential explanation for the higher male risks observed. Men are more likely to break social distancing rules and less likely to wear masks or perform proper hand hygiene than women.<sup>2 5</sup> Also, men smoke more than women which has clear implications on cardiovascular and pulmonary health.<sup>32</sup> Such differences in health behaviour may be a

result of cultural and societal constructs of what ‘masculine’ behaviour entails.<sup>2</sup> To examine the potential role of men’s social behaviour in putting them at risk of higher exposure to, and of a higher inoculum dose when exposed, examining outcomes in a controlled environment, such as nursing homes, where male and female residents have similar exposures, may be instructive. Nursing home data show that male residents die at a greater rate than female residents from COVID-19.<sup>33–37</sup> Heras *et al*

reported the mortality rate for COVID-positive nursing home male residents was 42% compared with 12.9% for COVID-19-positive female residents.<sup>35</sup> Another study from an Italian nursing home found that the male COVID-19 mortality rate was 46%, while for females, it was 41%, a significant difference.<sup>37</sup> Similar findings were present in another study from multiple US nursing homes, where the male COVID-19 mortality rate was also reported as being higher.<sup>36</sup> Thus, the role of exposure to virus as an explanation for why men have worse COVID-19 outcomes than women is not compelling.

Limitations of this study include lack of data on deaths occurring outside of the hospital in the pre COVID-19 and COVID-19 time periods, which would shed light on the role of differential self-referrals to the hospital in the observed outcomes. Furthermore, hospital and population data may provide incomplete documentation of clinical and demographic variables. Unfortunately, New York City's Office of Vital Statistics has not yet completed death data for 2020, which would have provided total death counts in the city by sex. Moreover, our study was an observational analysis and as such any inference is not conclusive. Residual confounding is also a limitation as there are factors that we did not adjust for (eg, environmental factors). Although our database lacked data on male vs female exposures to the virus, we have used the nursing home data in the previous paragraph to illustrate how exposure rates are playing a lesser role than once thought. Lastly, our data may not apply to the current wave of the pandemic. A review of the literature found that reduction in death with newer variants of the COVID-19 virus, and with the protective effects of vaccination and boosters seemed to favour men more than women. Notwithstanding the enhanced mortality benefit of late among men, they remained at higher risk of mortality than women in most reports.<sup>38–40</sup>

In conclusion, we showed that comorbidity burden and risk behaviours (smoking) are not the main drivers of the higher risk of adverse COVID-19 outcomes in men, but severity of COVID-19 related pneumonia is likely a significant driver. Future studies should look more closely at sex-based differences in physiologic, hormonal and immune mediators in response to COVID-19 infection.

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#### ORCID iDs

Aastha Vasa <http://orcid.org/0000-0002-2092-0029>

Ladan Golestaneh <http://orcid.org/0000-0003-1848-582X>

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1     **Supplementary Table 1:** All-cause mortality stratified by age and gender in NYC from 2015-2018.

	Female	Male		Female	Male
2015					
Total Population	4,468,694	4,081,711	Total population ≥ 65 y/o	667,759	459,256
All-cause mortality	27,646 (0.62%)	26,140 (0.64%)	All-cause mortality ≥65 y/o	22,143 (3.3%)	17,495 (3.8%)
2016					
Total Population	4,462,674	4,074,999	Total population ≥ 65 y/o	682,766	472,309
All-cause mortality	27,365 (0.61%)	26,526 (0.65%)	All-cause mortality ≥65 y/o	21,732 (3.2%)	17,602 (3.7%)
2017					
Total Population	4,509,363	4,113,335	Total population ≥ 65 y/o	728,204	506,817
All-cause mortality	27,280 (0.60%)	26,525 (0.64%)	All-cause mortality ≥65 y/o	21,942 (3.0%)	17,780 (3.5%)
2018					
Total Population	4,392,779	4,005,969	Total population ≥ 65 y/o	733,294	512,799
All-cause mortality	27,713 (0.63%)	26,702 (0.67%)	All-cause mortality ≥65 y/o	22,428 (3.1%)	18,087 (3.5%)

2  
3     **Supplementary Table 2:** Rates of city-wide COVID-19 cases, hospitalizations and deaths from  
4     February 29-June 1, 2020 for men vs women

	Female	Male
Total population of NYC in 2020	4,604,591	4,199,598
COVID cases	98,992 (2.1%)	104,675 (2.5%)
Hospitalizations	23,612 (0.5%)	30,589 (0.7%)
Deaths	7,494 (0.16%)	11,183 (0.27%)

16     **Supplementary Table 3:** COVID deaths and all-cause deaths for New York State and United States  
17     stratified by age and gender.

	New York State (≥18 years old)	New York State (≥65 years old)		United States (≥18 years old)	United States (≥65 years old)
COVID deaths (men: women)	18,616 / 16,681= 1.12	14,340 / 14,318 = 1.00	COVID deaths (men: women)	539,109/ 434,210 = 1.24	384,144/ 340,914 = 1.13
All-cause deaths (men: women)	130,982 / 127,508= 1.02	96,151 / 107,640= 0.89	All-cause deaths (men: women)	3,920,042/ 3,526,332 = 1.11	2,692,587/ 2,819,106 = 0.96

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40 Sensitivity analyses using continuous and categorical variables for age and Charlson score in the  
41 stratified regression models found the following (of note, all of these models adjusted for race  
42 (non-Hispanic White, non-Hispanic Black, Hispanic and Other) as a categorical variable, diabetes  
43 (yes or no) as a categorical variable, hypertension (yes or no) as a categorical variable, asthma  
44 (yes or no) as a categorical variable and smoking (no, former and current) as a categorical  
45 variable):

46 When age decile and Charlson score as a continuous variable were used in the multivariate  
47 models, the point estimates for odds of male death during pre-covid and covid were: 1.35  
48 (1.04-1.75) and 2.02 (1.74-2.35). When age as a continuous variable and Charlson score as a  
49 continuous variable were used in the multivariate models, the point estimates for odds of male  
50 death during pre-covid and covid were: 1.37 (1.06-1.77) and 2.05 (1.77-2.39) respectively.  
51 When age decile and Charlson score as a categorical variable (see Table 1 on page 9) were used  
52 in the multivariate models, the point estimates for odds of male death during pre-covid and  
53 covid were 1.49(1.16-1.93) and 2.07(1.78-2.41) respectively.

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