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Lifestyle Risk Factors, Inflammatory Mechanisms, and COVID-19 Hospitalization: A Community-Based Cohort Study of 387,109 Adults in UK

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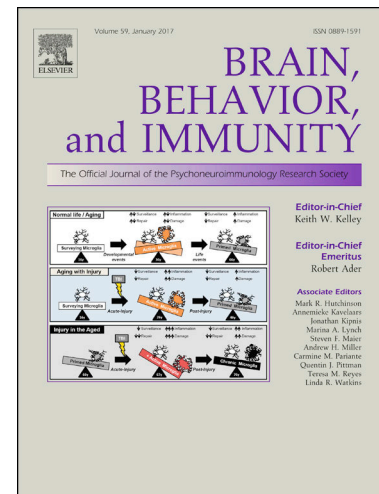
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**Lifestyle Risk Factors, Inflammatory Mechanisms, and COVID-19 Hospitalization: A Community-Based Cohort Study of 387,109 Adults in UK**

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**Abstract**

We conducted the first large-scale general population study on lifestyle risk factors (smoking, physical inactivity, obesity, and excessive alcohol intake) for COVID-19 using prospective cohort data with national registry linkage to hospitalisation. Participants were 387,109 men and women ( $56.4 \pm 8.8$  yr; 55.1% women) residing in England from UK Biobank study. Physical activity, smoking, and alcohol intake, were assessed by questionnaire at baseline (2006-2010). Body mass index, from measured height and weight, was used as an indicator of overall obesity. Outcome was cases of COVID-19 serious enough to warrant a hospital admission from 16-March-2020 to 26-April-2020. There were 760 COVID-19 cases. After adjustment for age, sex and mutually for each lifestyle factor, physical inactivity (Relative risk, 1.32, 95% confidence interval, 1.10, 1.58), smoking (1.42; 1.12, 1.79) and obesity (2.05 ; 1.68, 2.49) but not heavy alcohol consumption (1.12; 0.93, 1.35) were all related to COVID-19. We also found a dose-dependent increase in risk of COVID-19 with less favourable lifestyle scores, such that participants in the most adverse category had 4-fold higher risk (4.41; 2.52 – 7.71) compared to people with the most optimal lifestyle. C-reactive protein levels were associated with elevated risk of COVID-19 in a dose-dependent manner, and partly (10 – 16%) explained associations between adverse lifestyle and COVID-19. Based on UK risk factor prevalence estimates, unhealthy behaviours in combination accounted for up to 51% of the population attributable fraction of severe COVID-19. Our findings suggest that an unhealthy lifestyle synonymous with an elevated risk of non-communicable disease is also a risk factor for COVID-19 hospital admission, which might be partly explained by low grade inflammation. Adopting simple lifestyle changes could lower the risk of severe infection.

**KEY WORDS:** Physical activity, smoking, obesity, infection, coronavirus, C-reactive protein, population cohort

## 1. Introduction

For non-communicable disease outcomes, lifestyle risk factors have been consistently associated with morbidity, mortality and loss of disease-free years of life.<sup>1-4</sup> There are also population cohort data on possible adverse effects of poor lifestyle on serious respiratory infections. For example, physical inactivity and smoking appear to be independently associated with higher risk of community-acquired pneumonia and pneumonia mortality.<sup>5-9</sup> Evidence for alcohol intake and diet on risk of respiratory infection are less clear.<sup>8,9</sup>

A better understanding of the links between lifestyle risk factors and COVID-19 has obvious implications for prevention of severe outcomes and also in identifying characteristics of those people most at risk. We are, however, unaware of any existing data on the relation of lifestyle risk factors with COVID-19. Accordingly, we examined the association of lifestyle risk factors with new cases of COVID-19-hospitalisations in a general population-based cohort study.

## 2. Methods

### *2.1 Study Population*

We used data from UK Biobank, a prospective cohort study, the sampling and procedures of which have been well described.<sup>10</sup> Baseline data collection took place between 2006 and 2010 across twenty-two research assessment centres in the UK giving rise to a sample of 502,655 people aged 40 to 69 years (response rate 5.5%).<sup>10</sup> Ethical approval was received from the North-West Multi-centre Research Ethics Committee, and the research was carried out in accordance with the Declaration of Helsinki of the World Medical Association, and participants gave informed consent. No specific ethical approval was required for the present analyses of anonymised data.

### *2.2 Lifestyle Measures*

Physical activity, smoking, and alcohol consumption were assessed by questionnaire at baseline. These characteristics have demonstrated face validity in the UK Biobank sample through their associations with mortality and cardiovascular disease.<sup>11</sup> Participants were categorised into never, previous, and current smokers. From information on the weekly intake of beer and cider (1 pint = 2 units), wines (1 standard glass = 2 units) and spirits (1 shot = 1 unit), we aggregated units of alcohol intake per week. Heavy alcohol intake was defined as  $\geq 14$  units in women and  $\geq 21$  units in men.<sup>3</sup> Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) short form<sup>12</sup> that measures duration and frequency of moderate-to-vigorous physical activity (MVPA) from all domains in the last week. Meeting activity guidelines was defined as  $\geq 150$  min/week MVPA or  $\geq 75$  min/week vigorous PA.<sup>3</sup> Body weight was measured using Tanita BC418MA scales and standing height using a Seca height measure. Body mass index (BMI) was calculated [weight (kilograms)/height<sup>2</sup> (meters<sup>2</sup>) squared] and categorised into standard groups: healthy weight  $< 25$ ; overweight  $25 - < 30$ ; obese  $\geq 30$  kg/m<sup>2</sup>.

### 2.3 Covariates

During the clinic visit, data were collected via self-report for ethnicity (White, South Asian, Black, Chinese, other), educational attainment (college/degree; A-level; O-level; CSEs or equivalent; National Vocational Qualifications/ Higher National Diploma or equivalent; other professional qualification; none), and self-reported physician diagnosed cardiovascular diseases (heart attack, angina, stroke) and diabetes. Hypertension was defined as elevated measured blood pressure ( $\geq 140/90$  mmHg) and /or use of anti-hypertensive medication.

### 2.4 Ascertainment of Hospitalisation for COVID-19

Provided by Public Health England, data on COVID-19 status covered the period from 16<sup>th</sup> March 2020, after which testing was restricted to those with symptoms in hospital (<http://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=40100>). For the present analyses COVID-19 testing results up to 26<sup>th</sup> April 2020 were included. These data can be regarded as a proxy for hospitalisations for severe cases of the disease for England only; study members from Scotland and Wales were therefore omitted from our analytical sample. COVID-19 disease tests were performed on

samples from combined nose/throat swabs, using real time polymerase chain reaction (RT-PCR) in accredited laboratories.<sup>13</sup>

### 2.5 Statistical Analyses

Analyses were performed using SPSS Version 26. We assigned points to different levels of each lifestyle behaviour: smoking history (0=never; 1=past; 2=current), physical activity (0=meeting guidelines; 1= active but below guideline; 2=inactive), alcohol (0= moderate intake within guidelines; 1= never or very occasional; 2= heavy intake exceeding guidelines), obesity (0=healthy weight; 1=overweight; 2 = obese). Thus, scores ranged from 0 (optimal) to 8 (worst). We fitted regression models to estimate relative risk (RR) and 95% confidence intervals for associations between lifestyle scores and COVID-19. Relative risks were first adjusted for age and sex, followed by education, ethnicity, diabetes, hypertension, and cardiovascular diseases. We calculated Population Attributable Fraction (PAF) using our mutually-adjusted effect estimates on lifestyle factors and COVID-19 and lifestyle factor prevalence from Health Survey for England<sup>14,15</sup> (a representative, population-based survey of adults aged 16 and over living in private households in England) to evaluate the proportion of severe COVID-19 cases that could be avoided if high-risk people adopted a healthier lifestyle:

$$PAF \text{ in group } j = P_j (RR_j - 1) / [1 + \sum_{i=1}^K P_i (RR_i - 1)]$$

$$PAF = \sum_{j=1}^K PAF_j$$

where  $P_i$  = proportion of the population in group  $i$ ;  $RR_i$  = rate ratio in group  $i$ ;  $K$  = number of non-reference risk groups

## 3. Results

The analytical sample comprised 387,109 participants (56.2 ±8.0 years; 55.1% women) who were alive up to 5<sup>th</sup> March 2020, and had available data on lifestyle exposures and covariates. Participants were largely white British (94.5%). Of the lifestyle factors, 33.5% exceeded alcohol intake guidelines, 23.5% were obese, 9.7% smokers, 17.8% physically inactive, and 4.9% had a diabetes diagnosis, 56.1%

hypertension, and 5.2% cardiovascular disease. Around 0.2% (N=760) of the sample were hospitalized with a COVID-19 infection during the follow-up period, and their risk profile was characterized as being male, older age, smokers, physically inactive, less highly educated, non-white ethnicity, and higher prevalence of cardiometabolic comorbidity (Table 1).

### *3.1 Lifestyle and COVID-19*

There was a dose-dependent association between the risk of COVID-19 with worsening lifestyle scores, such that participants in the most unfavourable category had 4-fold higher risk (RR=4.41; 95% CI, 2.52, 7.71) (Table 2). These associations were little attenuated after adjustment for covariates. Risk ratios adjusted for age, sex and mutually for each lifestyle factor were raised for physical inactivity (1.32; 1.10, 1.58), smoking (1.42; 1.12, 1.79), obesity (2.05 ; 1.68, 2.49) but not for heavy alcohol consumption (1.12; 0.93, 1.35) in relation to COVID-19 compared to optimal reference categories.

### *3.2 Population attributable fraction*

Using the Health Survey for England prevalence estimates (17% for current smoking, 25% for ex-smoking, 27% for physical inactivity, 35% for overweight and 28% for obesity), the PAF for the three unhealthy lifestyle factors in combination was 51.4% (13.3% for smoking, 8.6% for physical inactivity, and 29.5% for overweight and obesity).

### *3.3 Inflammatory mechanisms*

We further explored potential mechanisms, specifically if low grade inflammation might partly explain associations between adverse lifestyle and risk of COVID-19. Data on high sensitivity C-reactive protein (hsCRP), measured at baseline at least 10 years before possible infection,<sup>16</sup> were available in a sub-sample of participants (n=363,263). We observed an association between adverse lifestyle score and higher hsCRP levels (B= 0.10, 95% CI, 0.09, 0.11) after adjustment for age, sex, education, ethnicity, diabetes, hypertension, cardiovascular disease. hsCRP levels were associated with elevated risk of COVID-19 in a dose-dependent manner (Table 3). When the association between lifestyle score and COVID-19 was adjusted for hsCRP, the effect estimates were attenuated by 10 – 16 % suggesting a possible mediating effect (Table 3).



#### 4. Discussion

The present study demonstrates associations between adverse lifestyle and higher risk of COVID-19 in a large community-dwelling cohort. The associations were not explained by taking into account covariates such as education, ethnicity and self-reported cardiometabolic diseases, although further adjustment for hsCRP did partially attenuate the association. Based on UK risk factor prevalence estimates, unhealthy behaviors in combination accounted for up to 51% of the population attributable fraction of severe COVID-19.

Physical activity has been previously shown to protect against serious community acquired infections in population cohort studies.<sup>5-9</sup> Other studies<sup>17-20</sup> in athletic populations have described a “J” shaped association between exercise volume and infection with optimal protection at moderate levels of activity. In the present study, protective associations of physical activity on COVID-19 were observed even at relatively low levels of activity below the current guidelines (i.e., < 150 min moderate to vigorous activity) and no dose-response effect was observed for higher levels. There are plausible biological mechanisms explaining the immunological benefits of exercise,<sup>17</sup> for example, anti-inflammatory effects and beneficial effects on adaptive immune responses.<sup>21</sup>

The existing evidence on obesity and infection have been mixed. Some data suggested BMI above 25 kg.m<sup>-2</sup> was protective against pneumonia mortality<sup>7,8</sup> whilst others have suggested that overweight and obesity was associated with higher risk of respiratory and skin infections whilst protective against viral and fungal infections.<sup>22</sup> In a large Norwegian cohort, overweight and obesity were associated with higher 30 day mortality risk after detection of blood borne bacterial infection.<sup>9</sup> Our results suggested both overweight and obesity were risk factors for severe COVID-19 infection, consistent with emerging data in small clinical studies.<sup>23</sup> The potential mechanisms have been linked to immune hyper-reactivity, impaired metabolic responses, and the adverse effects of obesity on lung function, diminishing forced expiratory volume and forced vital capacity.<sup>23</sup>

We found only weak evidence for a link between excessive alcohol intake and COVID-19, which was attenuated to the null in models mutually adjusted for other behavioral risk factors. This is largely consistent with our previous work on alcohol and infectious disease mortality.<sup>8</sup> Interestingly, ‘none drinkers’ were at greater risk of COVID-19, which is likely non-causal as this group have often stopped drinking due to prescribed medication and underlying health conditions.

The role of low-grade inflammation in susceptibility to severe COVID-19 infection remains poorly understood. Our data suggests low grade inflammation was a risk factor for severe COVID-19, and partially explained links between lifestyle behaviors and infection. C-reactive protein is known to play an important role in immune function<sup>24</sup> thus the findings are plausible.

There are several caveats to our work. Some cases of COVID-19 could have been captured in patients originally hospitalized for reasons other than the infection. We did not capture COVID-19 infections treated outside hospital settings; rather, our outcome was people with the infection of sufficient severity to warrant in-patient care. The response rate to the original baseline survey in UK Biobank was 5.5%. As such, this is a select group: relative to the general population, the study sample is healthier and better educated. While this means that estimates of the occurrence of disease, including COVID-19, have little utility, because exposures range is wide and the study sample is large, risk factors associations are not affected.<sup>25</sup> PAF reflects the prevalence of the risk factor in the population and the strength of its association with the outcome being considered; the core assumption is that the risk factor has a causal link to the outcome. As our results are based on observational data rather than an intervention, the present PAF-findings may overestimate of the proportion of COVID-19 hospitalisation that could be prevented by lifestyle change.

In conclusion, these data suggest that adopting simple lifestyle changes could lower the risk of severe COVID-19 infection.

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Contributions: MH and GDB generated the idea for the present paper, and with MK formulated an analytical plan; CRG prepared the data set; MH carried out all the data analyses and wrote the manuscript; All authors commented on an earlier version of the manuscript. MH will act as guarantors for this work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Table 1. Baseline characteristics of sample in relation to COVID-19**

	COVID-19 hospitalisation	
	No	Yes
Age (yrs)	56.4 ± 8.0	57.1 ± 9.0
Sex (% men)	44.8	55.3
Smokers	9.8	11.9
Physical inactivity	17.8	25.0
Moderate alcohol intake	36.2	28.6
Degree educated	32.8	26.7
White ethnicity	94.5	86.7
Diabetes	4.8	9.5
Hypertension	56.1	63.9
Cardiovascular disease	5.2	9.4
Body mass index (kg/m <sup>2</sup> )	27.3 ± 4.7	29.0 ± 5.4
Waist-Hip ratio	0.87 ± 0.1	0.91 ± 0.1
Total cholesterol (mmol/l)	5.7 ± 1.1	5.4 ± 1.2
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.3 ± 0.3
Glycated haemoglobin (mmol/mol)	35.9 ± 6.5	38.0 ± 8.8
C-reactive protein (log units)	0.98 ± 0.64	1.12 ± 0.68

Results are expressed as percentage or mean ± SD.

**Table 2. Combined and individual lifestyle behavioral risk factors in relation to COVID-19 hospitalisation (N=387,109)**

Total lifestyle score	CASES/N	Relative Risk (95% CI)	
		Model 1	Model 2
0 (optimal)	13 / 19,776	1.0 (ref)	1.0 (ref)
1	55 / 52,053	1.58 (0.86, 2.59)	1.48 (0.81, 2.71)
2	142/ 77,861	2.73 (1.55, 4.81)	2.43 (1.38, 4.29)
3	163/ 87,998	2.76 (1.57, 4.85)	2.41 (1.37, 4.25)
4	160/ 75,123	3.12 (1.77, 5.49)	2.70 (1.53, 4.75)
≥5 (worst)	227/74,298	4.41 (2.52, 7.71)	3.73 (2.12, 6.54)
p-trend		<0.001	<0.001
<b>Individual behaviours</b>			
<i>Smoking</i>			
Never	354/214,828	1.0 (ref)	1.0 (ref)
Past	313/134,855	1.34 (1.15, 1.56)	1.36 (1.15, 1.59)
Current	93/37,426	1.45 (1.16, 1.83)	1.36 (1.08, 1.71)
<i>Physical activity</i>			
Sufficient	382/209,489	1.0 (ref)	1.0 (ref)
Insufficient	192/ 108,707	0.98 (0.83, 1.17)	0.99 (0.84, 1.18)
None	186/68,913	1.51 (1.27, 1.81)	1.38 (1.15, 1.64)
<i>Alcohol consumption</i>			
Below guideline	216/140,908	1.0 (ref)	1.0 (ref)
Rarely/never	304/116,389	1.88 (1.55, 2.24)	1.57 (1.31, 1.88)
Above guideline	240/129,812	1.23 (1.00, 1.45)	1.24 (1.03, 1.50)
<i>Body mass index</i>			
Healthy weight	166/131,162	1.0 (ref)	1.0 (ref)
Overweight	317/165,052	1.41 (1.16, 1.70)	1.32 (1.09, 1.60)
Obesity	277/90,895	2.28 (1.88, 2.77)	1.97 (1.61, 2.42)

Model 1 adjusted for age and sex

Model 2 adjusted for age, sex, education, ethnicity, diabetes, hypertension, cardiovascular disease (heart attack, angina, or stroke)

**Table 3. Lifestyle risk factors, C-reactive protein, and Hospital Admission for COVID-19 in A Sub-sample with Available Biomarkers (N=363,263)**

Lifestyle score	Relative Risk (95% confidence interval)	
	Model 1 *	Model 2 †
0 (optimal)	1.0 (ref)	1.0 (ref)
1	1.46 (0.78, 2.74)	1.41 (0.75, 2.65)
2	2.44 (1.35, 4.40)	2.30 (1.27, 4.16)
3	2.44 (1.39, 4.39)	2.26 (1.25, 4.08)
4	2.77 (1.54, 5.00)	2.52 (1.39, 4.55)
≥5 (worst)	3.74 (2.09, 6.72)	3.30 (1.83, 5.95)
C-reactive protein quintile		
≤0.55 mg/L	-	1.0 (Ref)
0.56 – 1.02 mg/L	-	1.18 (0.90, 1.54)
1.03 – 1.75 mg/L	-	1.32 (1.01, 1.71)
1.76 – 3.33 mg/L	-	1.48 (1.15, 1.92)
> 3.33 mg/L	-	1.47 (1.13, 1.91)

\* Adjusted for age, sex, education, ethnicity, diabetes, hypertension, cardiovascular diseases.

† Additionally adjusted for high-sensitivity C-reactive protein.

### Highlights

- **The association between lifestyle factors and risk of COVID-19 hospitalisation is unknown.**
- **In this large community-based sample, poorer lifestyle habit and elevated C-reactive protein was associated with greater risk of COVID-19 hospitalisation.**
- **Unhealthy lifestyle behaviours in combination accounted for up to 51% of the population attributable fraction of severe COVID-19.**
- **Low grade inflammation may be an important mechanism.**
- **Adopting simple lifestyle changes could lower the risk of severe COVID-19 infection.**