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Association among Lifestyle and Risk Factors with SARS-CoV-2 Infection

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Yi Ko, M.D.[1], Zi-Ni Ngai, B.Med.Sc.[2], Rhun-Yian Koh, Ph.D.[3] and Soi-Moi Chye, Ph.D.[3]

[1]Department of Cardiology, Blackpool Victoria Hospital, Blackpool, UK, [2]School of Health Science, International Medical University, Kuala Lumpur, [3]Division of Applied Biomedical Science and Biotechnology, School of Health Science, International Medical University, Kuala Lumpur, Malaysia

Address for correspondence
Soi-Moi Chye, Ph.D.
Division of Applied Biomedical Science and Biotechnology, School of Health Science, International Medical University, No. 126, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia
Phone 60-3-27317220
Fax 60-3-86567229
E-mail chye_soimoi@imu.edu.my

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Abstract

Coronavirus disease 2019 (COVID-19) has become a major health burden worldwide, with over 600 million confirmed cases and 6 million deaths by 15 December 2022. Although the acute phase of COVID-19 management has been established, the long-term clinical course and complications due to the relatively short outbreak is yet to be assessed. The current COVID-19 pandemic is causing significant morbidity and mortality around the world. Interestingly, epidemiological studies have shown that fatality rates vary considerably across different countries, and men and elderly patients are at higher risk of developing severe diseases. There is increasing evidence that COVID-19 infection causes neurological deficits in a substantial proportion to patients suffering from acute respiratory distress syndrome. Furthermore, lack of physical activity and smoking are associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) susceptibility. We should therefore explore why lack of physical activity, smoking, etc causing a population more susceptible to SARS-CoV-2 infection, and mechanism involved. Thus, in this review article, we summarize epidemiological evidence related to risk factors and lifestyle that affect COVID-19 severity and the mechanism involved. These risk factors or lifestyle interventions include smoking, cardiovascular health, obesity, exercise, environmental pollution, psychosocial social stress, and diet.

Keywords: COVID-19; Lifestyle Intervention; Risk Factors

Introduction

The year 2020 was devastating for global health. In February 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19) a “Public Health Emergency of International Concern” after it emerged in Wuhan, Hubei Province in December of 2019. Over 228 countries have been affected by the pandemic and over 600 million COVID-19 cases have been confirmed worldwide, resulting in over 6 million deaths as of 15 December 2022. There is an overall mortality rate of 5% for COVID-19 (95% confidence interval [CI], 0.01 to 0.11) which affects not only the health but also the economy and quality of life of communities[1].

This infection causes asymptomatic or mild to moderate symptoms and clinical manifestations, ranging from fever, dry cough, and shortness of breath to acute respiratory distress syndrome (ARDS) and interstitial pneumonia[2]. While life-threatening complications such as cytokine storm and ARDS could arise in severe COVID-19. Most of the patients (80.9%) were either asymptomatic or presented with only mild pneumonia[3]. Currently, the most effective prevention strategies against COVID-19 remain to be public health measures such as social distancing and optimum use of face masks. During the pandemic, China and other countries promoted social distancing, canceled public gatherings, closed schools, quarantined, and imposed lockdowns. These measures all contribute to physical inactivity. A lack of physical activity has significant con-

sequences for physical and mental health, including anxiety, stress, an increased risk of chronic diseases, and a worsening of chronic conditions[4]. Moreover, epidemiological studies have shown that fatality rates vary considerably across different countries, and men and elderly patients are at higher risk of developing severe diseases. There is increasing evidence that COVID-19 infection causes neurological deficits in a substantial proportion to patients suffering from ARDS. Furthermore, lack of physical activity and smoking are associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) susceptibility[5]. We should therefore explore why lack of physical activity, smoking etc causing a population more susceptible to SARS-CoV-2 infection, and the mechanism involved. Thus, in this review article, we summarize epidemiological evidence related to risk factors and lifestyle that affect COVID-19 severity and the mechanism involved.

Smoking

Smoking increases the severity of COVID-19. It has been proved that current smokers were 1.45 times (95% CI, 1.03 to 2.04) more likely to have severe complications compared to former and non-smokers[6]. Simons et al.[7] also demonstrated that current (relative risk [RR], 1.70; 95% CI, 1.14 to 2.55; p=0.01; I^2=29%) and former (RR, 2.00; 95% CI, 1.57 to 2.55; p<0.001; I^2=0%) smokers had a higher in-hospital mortality from COVID-19 compared with non-smokers. Structurally, smoking affects airway defense by impairing muco-ciliary clearance, causing peri-bronchiolar inflammation and fibrosis (airway remodeling), making the lung more susceptible to infection. Smoking also causes oxidative stress and inflammatory activities in the lung, affecting airway permeability (leaky lung) and angiotensin-converting enzyme 2 (ACE2) expression[8]. The ACE2 receptor is the site of SARS-CoV2 virus entry into the host cell since the S2 domain of the viral spiked envelope has a high affinity for the receptor. It is shown that smoking up-regulates the ACE2 receptor in the lung epithelium[9]. Moreover, studies show that smoking increased the level of SARS-CoV-2 entry-associated protease (transmembrane serine protease 2 [TMPRSS2]), cathepsin B, serpins, and furin and these proteases activate the viral particle facilitate the viral engulfment and increase cell-cell transmission[10,11].

Research have shown that chronic smoking significantly increased the production of pro-inflammatory cytokines interleukin 6 (IL-6), monocyte chemotactic protein-1 (MCP-1), keratinocyte-derived chemokine (KC), tumor necrosis factor-alpha (TNF-α), aggravation of neutrophils and macrophages, and goblet cell metaplasia in the airway. All these results in chronic lung inflammation, ARDS, and neutrophilia[12,13]. Apart from that, the production of interferon gamma-induced protein 10 (IP-10), MCP-3, hepatocyte growth factor (HGF), monokine induced by gamma interferon (MIG), macrophage inflammatory protein 1α (MIP-1α), IL-6, TNF-α, interferon gamma (IFN-γ), IL-2, IL-7, and granulocyte-macrophage colony-stimulating factor (GM-CSF) also induced cytokine storm and result in ARDS[14]. Additionally, Blanco-Melo et al.[15] proved that reduced innate antiviral defenses, low levels of type I and III interferons, increased chemokines, and IL-6 production could increase SARS-CoV-2 replication. In COVID-19 lung autopsy patients also found neutrophil infiltration in pulmonary capillaries with fibrin deposition, extravasation of neutrophils into the alveolar space and neutrophilic mucositis. Furthermore, excessive activation of neutrophil extracellular traps leads to tissue damage, micro thrombosis, and permanent damage to the pulmonary, cardiovascular, and renal systems, resulting in severe COVID-19 and death[14,15].

Archie and Cucullo[16] demonstrated that smoking could be related to neurological and cerebrovascular complications of COVID-19. COVID-19 patients have exhibited neurological symptoms such as headache, altered consciousness, sudden loss of taste and smell, paresthesia, and stroke[17]. This is because smoking disrupts the blood-brain barrier (BBB), increases BBB permeability and facilitates virus entering into brain parenchyma. Moreover, smoking also induces oxidative stress and alters immune responses[18]. In addition, *in vitro* study suggested that nicotine might upregulate alpha-7 nicotinic receptor (α7-nAChR), a receptor that could promote cellular uptake of the SARS-CoV-2 virus. As α7-nAChR is present both in neuronal and non-neuronal cells, it could be suggested chronic smokers might have a role in promoting brain infection as well as other organ damage[19]. Respiratory symptoms of COVID-19 could cause hypoxia in the central nervous system (CNS). Anaerobic metabolism of the brain cells produces acidic metabolites which trigger cerebral vasodilation. This leads to brain cells swelling, interstitial edema, and blockage of cerebral blood flow and finally encompasses acute ischemic stroke[20]. Apart from that, epidemiological studies show that smoking also increases the circulatory level of pro-coagulant factor, von Willebrand factor and down-regulates anticoagulation factor, thrombomodulin. All these results in forming of microthrombi and intravascular coagulation in CNS and causing neurological complications[21].

In summary, smoking increases morbidity and the

mortality of COVID-19 by causing structural airway changes, inducing local inflammation, altering the coagulation cascade, and upregulating the ACE2 receptor.

Cardiovascular Disease

Evidence suggested that COVID-19 is also closely associated with cardiovascular system (CVS) pathology. COVID-19 patients have been shown to develop fatal cardiac complications such as heart failure, arrhythmias, myocarditis, and acute coronary syndrome. These cardiac complications have caused a significant portion of mortality among COVID-19 patients[22]. The development of cardiovascular complications is linked to a higher risk for adverse outcomes including higher rates of intensive care unit admissions and death[23]. Cardiac-specific biomarkers such as troponin T and N-terminal pro b-type natriuretic peptide (NT-proBNP) have also been shown to be with important prognostic value for COVID-19 patients, with elevation linked to increased incidence of mortality. Although cardiac complications could arise from previously healthy patients or due to side effects of antivirals given, it has been shown that having cardiovascular comorbidities such as hypertension and diabetes significantly increases the risk of developing cardiovascular complications[22,24].

CVS-related comorbidities increase morbidity and mortality of COVID-19 significantly. In fact, the analysis of data acquired from the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (2020) reported a rise in fatality rate to 10.5% for cardiovascular disease (CVD), 7.3% for diabetes, and 6.0% for hypertension among COVID-19 patients, while the overall case-fatality rate was only 0.3%[25]. The rate of hypertension and diabetes mellitus appears to be higher among those with worse outcomes from COVID-19. However, CVS risk factors do not seem to increase COVID-19 susceptibility. There are multiple theories on how CVS increases morbidity and mortality[26]. Zheng et al.[27] suggests that patient with CVS comorbidities had reduced cardiac functional reserve and therefore making the patient more susceptible to sudden deterioration of COVID-19. Liu et al.[28] pointed out the up-regulation of ACE2 in failing hearts might increase the infectivity and mortality in COVID-19 patients. Poor control of blood pressure may also cause dysregulation of the immune system, worsening the complications of COVID-19[29]. Hypertension affects lymphocyte count and causes CD8+ T cell dysfunction. This not only decreases the immunity against the virus but also causes the overproduction of cytokines[30]. Although anti-hypertensives such as ACE inhibitors and angiotensin receptor blockers upregulate the ACE2 receptor and therefore might theoretically increase the susceptibility and severity of COVID-19, there were debates on whether these medications were causing harm and thus should be discontinued[31].

In summary, the presence of cardiovascular risk factors is associated with worse outcomes of COVID-19. Cardiovascular complications not only decrease the patient's overall fitness but also affect the ACE2 receptor activity in the body.

Obesity

Obesity is believed to be a major risk factor for COVID-19. Epidemiological studies showed a correlation between obesity and COVID-19. Meta-analysis of Yang et al.[32] showed that patients with obesity were at risk of a more severe form of COVID-19 (odds ratio [OR], 2.31; 95% CI, 1.3 to 4.12). The outcome of COVID-19 also tends to be worse in obese patients (OR, 2.31; 95% CI, 1.3 to 4.12)[32]. Another meta-analysis carried out by Singh et al.[33] also found that normal weight is protective to COVID-19 disease severity compare to overweight (body mass index [BMI] 25–29.9 kg/m^2) (RR, 0.75; 95% CI, 0.69–0.82; p≤0.001; I^2=88%), Class 1 and Class 2 obesity (BMI of 30–39.99 kg/m^2) (RR, 0.67; 95% CI, 0.60–0.74; p≤0.001; I^2=94%) and Class 3 obesity (BMI >40 kg/m^2) (RR, 0.77; 95% CI, 0.68–0.88; p≤0.001; I^2=89%).

It is known that obesity causes an immune system defect. The effect of immunization is shown to be weakened in obese patients. Obesity had also been identified as a risk factor for viral infections[34]. Body of obese patients is in a state of constant chronic inflammation, with increased concentrations of chemokines, adipokines, and pro-inflammatory cytokines. Chronic inflammation results in decreased macrophage activity and impaired immune memory during acute infection[35]. The action of dendritic cells and T cell response to stimulus are also decreased. The cells' response to cytokines in obese patients is altered, resulting in decreased cytotoxic cell response during viral infection. The balance of endocrine hormones, such as leptin, is also disrupted in obese patients, affecting the interaction between the metabolic and immune systems. Adipokines released by adipose tissue generate an environment that is favorable for immune-related diseases[36].

Obesity is related to metabolic syndrome and comorbidities such as diabetes, hypertension, and CVD, which were all shown to increase the severity and death rate of COVID-19[37]. It is also shown that ACE2

receptors could be found abundantly in adipose tissue, with a higher level than in lung tissue[38]. Apart from that, obesity also affects respiratory mechanics, with decreased lung volume, pulmonary function, and chest expansion. This might explain the increased requirement for respiratory support in obese COVID-19 patients[39].

In summary, obesity is shown to be associated with increased severity and worse outcome of COVID-19. Obesity also increases the work of breathing; excessive adipose tissue also causes constant chronic inflammation that weakens the innate immune response. The presence of metabolic syndrome also worsens the disease prognosis.

Exercise

Exercise is shown to be a protective factor for COVID-19. An epidemiological study found an association between physical inactivity and hospital admission due to COVID-19 (RR, 1.32; 95% CI, 1.10 to 1.58)[40]. Evidence suggested that moderate-intensity exercise is beneficial to the immune system. Regular bout of short-lasting exercise (moderate-to-vigorous intensity aerobic exercise, <60 minutes) is shown to enhance the recirculation and activity of immunoglobulins, anti-inflammatory cytokines, neutrophils, natural killer cells, cytotoxic T cells, and immature B cells[41]. A similar effect is also observed after moderate-intensity exercise. Moderate-intensity exercise was shown to down-regulate excessive inflammation within the respiratory tract[42]. Routine daily exercise is associated with enhanced immune activity, improve immune regulation and improve metabolic health[41]. Regular exercise for >6 months has been shown to not only prevent age-related immune dysfunction but also improve the effectiveness of flu vaccination in elderly populations. This is important as elderlies are shown to be more vulnerable to COVID-19[43]. Additionally, exercise could relieve stress and anxiety caused by isolation and psychosocial factor, which is associated with reduced immune function[44]. The effect of sudden exercise cessation on health is extensively reviewed by Charansonney. It is shown that many beneficial effects of physical exercise on metabolic and cardiovascular health can be lost with only two weeks of inactivity, resulting in increased blood pressure and impaired aerobic capacity. Sudden cessation of exercise is related to the rapid onset of insulin resistance in muscle tissue, along with muscle atrophy. The excessive metabolites were reallocated to the liver, resulting in the release of atherogenic lipoproteins, accelerating atherosclerotic disease. Abrupt cessation of physical activity is also related to reducing venous return and decreased coronary perfusion, predisposing patient to collapse when resuming exercise. It is also observed that the resting heart rate increases after exercise cessation, resulting in a higher risk of cardiovascular motility and mortality[45].

In summary, regular, moderate-intensity exercise is protective against COVID-19, while sudden cessation of exercise is believed to be harmful. Exercise not only improves immune function but also reduces anxiety levels and improves psychological well-being.

Environmental Factor

A study from SIMA (Società Italiana di Medicina Ambientale) showed a correlation between higher COVID-19 spread in Northern Italy with more severe air pollution and higher local relative humidity, while a hot climate is associated with lower infectivity[45]. Li et al.[46] further proved that lower temperature is related to higher COVID-19 incidence ($p<0.05$). Bashir et al.[47] showed that an increase in air pollutants such as particulate matter (PM) 10 ($p=0.05$), PM 2.5 ($p=0.1$), SO_2 ($p=0.1$), CO ($p=0.05$), lead ($p=0.05$), and nitrogen dioxide (NO_2; $p=0.1$) were associated with significantly higher cases and deaths in California. Another nationwide, cross-sectional study in the US found that an increase of 1 $\mu g/m^3$ in PM 2.5 is associated with an 8% increase in the COVID-19 death rate (95% CI, 2% to 15%)[48].

Atmospheric particulate matter (PM 2.5, PM 10) is proven to be associated with more severe COVID-19. It is hypothesized that in the damaged lung, the SARS virus uses air pollutant particles as fertile "territory" which allows the virus to survive longer and become more aggressive[49]. PM also damages the human respiratory barrier integrity[50]. Long-term exposure to PM also adversely affects the respiratory and CVS, increasing the severity of COVID-19[51]. NO_2 also increases the fatality of COVID-19[52], it is shown that NO_2 induces airway inflammation, characterized by up-regulation of pro-inflammatory cytokines (IL-1β, IL-6, and intercellular adhesion molecule-1) and the imbalance of Th1/Th2 ratio[53].

Moreover, the immune function might be suppressed at lower temperatures[54]. *In vitro* study showed a decrease in phagocytic activity of pulmonary alveolar macrophages under low temperatures[55]. Inhaling cold air could also cause bronchial constriction, making the lung more susceptible to infection[56].

In summary, environmental factors such as cold weather, air pollution, and exposure to pollutants are associated with an increased COVID-19 death rate. It

is believed that these factors are related to suppressed immune systems and reduced pulmonary health.

Socioeconomic Status and Psychosocial Stress

There could be a link between socioeconomic status, psychosocial stress, and COVID-19. A study from the UK Biobank showed an association between elevated risk of COVID-19 and disadvantaged levels of education (OR, 2.05; 95% CI, 1.70 to 2.47), income (OR, 2.00; 95% CI, 1.63 to 2,47), area deprivation (OR, 2.20; 95% CI, 1.86 to 2.59), occupation (OR, 1.39; 95% CI, 1.14 to 1.69), psychological distress (OR, 1.58; 95% CI, 1.32 to 1.89), mental health (OR, 1.50; 95% CI, 1.25 to 1.79), neuroticism (OR, 1.19; 95% CI, 1.00 to 1.42), and performance on two tests of cognitive function: verbal and numerical reasoning (OR, 2.66; 95% CI, 2.06 to 3.34) and reaction speed (OR, 1.27; 95% CI, 1.08 to 1.51)[57]. Studies from New York across five boroughs showed that Bronx, the least socioeconomically advantaged borough, had the highest rate of hospitalization (634 per 100,000 population) and death rate (224 per 100,000) of COVID-19 patients. While Manhattan, the most socioeconomically advantaged borough, had the lowest rate of hospitalization (331 per 100,000 population) and death rate (122 per 100,000) of COVID-19 patients[58]. Report from the Office for National Statistics in the UK also showed an association between deprivation (income, employment, health, education, crime, the living environment and access to housing) and increased COVID-19 mortality[59]. Furthermore, it is noted that black, Asian, and minority ethnic (BAME) groups had a higher risk of severe COVID-19 and death[60]. A similar trend is also being recorded from the healthcare workers from National Health Service[61].

Several theories have been proposed regarding socioeconomic status and COVID-19. People with lower socioeconomic status and BAME groups are more likely to live in overcrowded environments, making social distancing more difficult[62]. Lower socioeconomic status is related to comorbidities such as obesity and CVS[63,64]. It is also hypostatized that people with a higher burden of psychological distress were likely to be more concerned about COVID-19, therefore having a lower threshold of visiting the hospital when symptoms arise, thus the higher hospital admission rate[57].

In summary, psychosocial factors such as level of education, income, and housing condition are associated with COVID-19 severity. It is believed that these factors are associated with overcrowding, poorer self-care, and reduced health.

Diet and Nutrients

A cross-sectional study carried out by Li et al.[65] noted a high prevalence of malnutrition (52.7% malnourished, 27.5% at risk of malnutrition) among elderly COVID-19 patients admitted to the hospital. Bousquet et al.[66] demonstrated that there is a difference in regional diet (high in fermented milk, uncooked/fermented cabbage) in low death rates countries such as Germany, Korea, and Taiwan compared to other high death rates countries. Butler and Barrientos[67] also proved that a Western diet, characterized by high saturated fats, sugars and refined carbohydrates, and low in fibre, unsaturated fat and antioxidants is related to a higher death rate of COVID-19. Moreover, Carpagnano et al.[68] showed that there is a high prevalence of vitamin D insufficiency among severe COVID-19 patients. Rhodes et al.[69] also proved that there is an association between vitamin D deficiency, altitude and ultraviolet light exposure with COVID-19 mortality.

It is known that balanced diet and optimal nutrition are crucial for maintaining optimal immune function. Malnutrition is associated with deterioration of immune function and a decrease in immune cell and cytokine production[70]. Low protein status is associated with low antibody production. Low micronutrient status is also associated with impaired immune cell activity, reduced cytokine production, and low antibody production[71]. Excessive consumption of Western diet and high-fat diet were known to be associated with comorbidities such as hypertension, diabetes, and obesity which were related to severe COVID-19. A diet high in saturated fatty acids is associated with chronic activation of the innate immune system and inhibition of the adaptive immune system[72]. Animal study also shows that a high-fat diet increases the circulating monocytes and alveolar macrophage in the lung, causing airway inflammation[73]. High-fat diet also causes oxidative stress, impairing T cell and B cell proliferation and maturation, making patient more susceptible to viral infection[74].

Healthy diet was shown to be associated with a lower risk of severe COVID-19. A diet rich in fish and plant-based food consisting of omega-3 fatty acids[75], vitamin A[76], vitamin C[77], polyphenols[78], and carotenoids[79] were shown to exhibit anti-inflammatory and antioxidant effects, lowering oxidative stress and chronic non-specific inflammation in the body. Intake of fermented milk, dietary fiber[80], and phytochemicals (polyphenols)[81] were associated with healthy gut microbiota, which reduces the risk of severe COVID-19 as well. Several food sources such as fish, meat, plant, and fermented milk were shown to exhibit anti-ACE properties[82,83]. It is also

shown that food intake affects ACE levels in the blood significantly. This could have a significant effect on the susceptibility to severe COVID-19[84].

The role of vitamin D in the immune system and lung health has been reviewed extensively[85]. It is known that patients with vitamin D deficiency were at higher risk of developing ARDS[86]. Vitamin D receptor is expressed at the surface of respiratory epithelial cells and alveolar macrophage. Vitamin D metabolism-related enzymes such as 1α-hydroxylase could also be found at the surface of respiratory epithelial cells[87]. *In vitro* studies show that vitamin D3 (1,25(OH)2D3) increases macrophage production of catelicidin (LL-37), which plays a vital role in the prevention of viral infection against human cell[88]. 1,25(OH)2D3 is also shown to regulate inflammatory activities through the modulation of nuclear factor-κB activity[89,90].

In summary, malnutrition, including under and overnutrition, is shown to be associated with worse COVID-19 outcomes. Optimum nutrition is important in maintaining a healthy immune system. Several nutrients also exhibit anti-inflammatory and antioxidant effects. Vitamin D is proven to be protective against COVID-19 infection through multiple mechanisms.

Conclusion

In conclusion, although evidence regarding COVID-19-related epidemiological data remains relatively new and rapidly updating, current evidence suggested that there are associations among smoking, cardiovascular health, obesity, exercise, environmental pollution psychosocial stress, and diet with COVID-19 severity and mortality and mechanism involved. Thus, this article suggested that lifestyle intervention could be applied, in addition to current social isolation measures, to control of current COVID-19 pandemic.

Authors' Contributions

Conceptualization: Ko Y, Chye SM. Methodology: Ngai ZN, Koh RY. Investigation: Ko Y, Ngai ZN. Writing - original draft preparation: Ko Y, Ngai ZN. Writing - review and editing: Koh RY, Chye SM. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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