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Depression pandemic and cardiovascular risk in the COVID-19 era and long COVID syndrome: gender makes a difference

Valentina Bucciarelli , Milena Nasi , Francesco Bianco , Jelena Seferovic , Vladimir Ivkovic , Sabina Gallina , Anna Vittoria Mattioli

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Depression pandemic and cardiovascular risk in the COVID-19 era and long COVID syndrome: gender makes a difference

Short title: depression and cardiovascular risk in women during COVID-19 pandemic

Valentina Bucciarelli[1], Milena Nasi[2], Francesco Bianco[1], Jelena Seferovic[3], Vladimir Ivkovic[4], Sabina Gallina[5], Anna Vittoria Mattioli[2]

[1] Department of Pediatrics and Congenital Cardiac Surgery and Cardiology, Ospedali Riuniti, Ancona, Italy

[2] Department of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy; National Institute for Cardiovascular Research - INRC, Bologna, Italy

[3] Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

[4] Neural Systems Group, Department of Psychiatry, Massachusetts General Hospital & Harvard Medical School

[5] Department of Neuroscience, Imaging and Clinical Sciences, "G. D'Annunzio" University, Chieti, Italy

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Correspondence:
Valentina Bucciarelli, M.D., Ph.D.
Department of Pediatric and Congenital Cardiology and Cardiac Surgery
c/o Azienda Ospedaliero-Universitaria “Ospedali Riuniti” – Ancona
Via Conca, 71

60123, Ancona (AN)

Italy

Tel. +39 071 596 5316

Fax: +39 071 596 5360

E-mail: valentina.bucciarelli@ospedaliriuniti.marche.it

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ABSTRACT

The ongoing COVID-19 pandemic highlighted a significant interplay between cardiovascular disease (CVD), COVID-19 related inflammatory status, and depression. Cardiovascular (CV) injury is responsible for a substantial percentage of COVID-19 deaths while COVID-19 social restrictions emerged as a non-negligible risk factor for CVD as well as a variety of mental health issues, and in particular, depression. Inflammation seems to be a shared condition between these two disorders. Gender represents a potential modifying factor both in CVD and depression, as well as in COVID-19 short- and long-term outcomes, particularly in cases involving long-term COVID complications. Results from emerging studies indicate that COVID-19 pandemic affected male and female populations in different ways. Women seem to experience less severe short-term complications but suffer worse long-term COVID complications, including depression, reduced physical activity, and deteriorating lifestyle habits, all of which may impact CV risk. Here, we summarize the current state of knowledge about the interplay between COVID-19, depression, and CV risk in women.

Keywords: Gender medicine; COVID-19; long COVID; depression; cardiovascular disease; inflammation.

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Introduction

Cardiovascular (CV) injury is associated with a significant proportion of COVID-19 deaths and a preexisting cardiovascular disease (CVD) is one of the most common risk factors for hospitalization and death in COVID-19 patients. (1) On the other hand, the health policy reactions to the COVID-19 pandemic, with lockdown and significant movement restriction, have already been proven to determine widespread effects on CV risk, affecting both the general population and the survivors of COVID-19. The significant limitation of economic and social activities has led to unemployment, increased sedentary time, social isolation, and worsening of consequent increased incidence of mental health issues, all of which are well-recognized risk factors for CVD and associated with worsening CV outcomes. Moreover, it seems that patients with chronic CVD experienced worsening of health-related quality of life during the COVID-19 pandemic, despite stability of their CVD. (2)

Thus, a dangerous link exists between CVD, depression and COVID-19, as these three conditions may co-exist and deleteriously affect each other, having a common, noteworthy risk factor, namely inflammation. Furthermore, gender has already been highlighted as a potential and relevant modifying factor both for CVD and depressive disorders (DD) as well as for COVID-19 short- and long-term outcomes. In particular, depression is still an under-recognized and under-treated risk factor for CVD, particularly in women, and COVID-19 pandemic is exacerbating gender-linked mental health challenges. (3, 4)

Thus, the aim of this review is to provide a comprehensive analysis about the interplay between gender, depression, CVD and COVID-19, with a special focus on long COVID status.

In this regard, we narratively reviewed the published literature (including searches in the MEDLINE [via PubMed] database) through March 2020. Articles were retrieved using keywords and medical subject heading terms related to COVID-19, SARS-CoV-2, depression, cardiovascular disease, and gender medicine.

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COVID-19 and depression in general population and in women

Depression is a psychiatric condition characterized by alterations in regulators of mood, behavior and affection and represents one of the most common causes of disability in high-income countries, being associated with high societal and healthcare costs, both in terms of direct medical expenses and reduced work productivity associated with functional impairment.

It is more prevalent in women than men, with a doubled worldwide chance of suffering from depression, especially during the mid-puberty and later life. About 20-25% of women go through depression during their life and depression symptoms have been considered a relevant emergent non-traditional risk factors for CVD in the female population. Moreover, patients with CVD suffer from depression more than the general population and people with depression are more prone to develop CVD, as they commonly adopt habits that overlap with CV risk factors. (4)

A growing body of evidence is emerging about the effects of COVID-19 pandemic on mental health in the general population, resulting in identification of a number of clinical and demographical factors that predict the risk of depression. A meta-analysis of community-based studies about the prevalence of depression during COVID-19 pandemic, including a total of 12 studies, highlighted a pooled prevalence of depression of 25% (95% CI: 18%-33%), with significant heterogeneity between studies. (5) Moreover, symptoms of depressive disorder increased considerably in the United States during April–June of 2020, compared with the same period in 2019. (6)

Female gender firstly emerged as a significant risk for worsening health status and higher self-reported depression symptoms, as women seem to have both a higher prevalence of risk factors known to intensify during a pandemic, including preexisting depressive and anxiety disorder, chronic environmental strain and domestic violence. Moreover, they experience pandemic-related stressors specific to reproductive functioning and stages, i.e. fertility issues, pregnancy, miscarriage, postpartum depression, intimate partner violence. (3)

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A recent survey study by Perlis et al., including a total of 3904 individuals, investigated whether acute COVID-19 symptoms are associated with the probability of subsequent depressive symptoms. 52.4% of patients met criteria for moderate or greater symptoms of major depression; at the regression analysis, these symptoms were more likely among younger individuals, men and among those with greater self-reported overall COVID-19 severity. (7)

In particular, female gender, younger age, student and unemployment status, specific physical symptoms (i.e., myalgia, dizziness), and poor self-rated health status were firstly significantly associated with a greater psychological impact of the outbreak and higher levels of stress, anxiety, and depression. (8) Analogous data were described for the female health care workers. (9)

Besides the short-term interaction between COVID-19 and depression, a considerable risk for psychiatric and neurological morbidity in the 6 months after COVID-19 infection exists, especially in patients who had severe COVID-19. (10, 11)

Moreover, psychiatric morbidity at follow-up appears to be associated with persistent physical symptoms such as breathlessness and myalgia, the latter being associated with impaired quality of life, both in adults and young people. (12)

Middle aged women, under the age of 50, seem to have a greater chance of suffering a variety of devastating ongoing symptoms, due to the presence of a persistent inflammatory burden, such as fatigue, breathlessness, muscle pain, anxiety, depression, and “brain fog” after hospital treatment for COVID-19 (Table 1). (13)

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COVID-19, inflammation and cardiovascular disease in general population and in women

Acute inflammation is a protective, time-limited, innate response that could be localized or systemic. When the threat that has triggered the inflammation has passed, the process resolves and the contraction of the immune response restores the initial homeostasis. An excessive acute response or the persistence of the systemic inflammation, and as a consequence of the immune

activation, is linked to several cardiovascular, neurodegenerative, and metabolic diseases, cancers, pathologies of the musculoskeletal system, and depression. (14)

An overreaction of the innate response is one of the major drivers of the severe forms of COVID-19 whose pathogenesis could be divided into three phases: (1) pulmonary, (2) inflammatory, and (3) prothrombotic. The pulmonary phase begins when the virus enters the respiratory system of the host and infects target cells. Binging and internalization of the infected target cells leads to a decrease in angiotensin-converting enzyme 2 (ACE2), and to a perturbation of the renin-angiotensin system (RAS), which damages the respiratory system. (15) In the inflammatory phase, the infection induces target and immune cells to produce a large amount of circulating proinflammatory cytokines and inflammatory markers—the so-called cytokine storm responsible for the acute lung injury in the severe forms of the disease. In the subsequent prothrombic phase, the systemic inflammatory response could trigger coagulopathy and multi-organ failure. (16) Hyperinflammation has been proposed as underlying mechanism predisposing patients with CVD for severe COVID-19. (17)

Thus, COVID-19 can induce profound alterations in the immune response that are influenced by the sex of the patients. First of all, in the general population, several sex differences exist in immunological parameters: males and females show differences in white cell count, neutrophil to lymphocyte ratio, and toll-like receptors, which are involved in the recognition of and response to microbial infections. (18) Moreover, males are overrepresented among patients with higher levels of pro-inflammatory markers, including C-reactive protein considered a marker of disease severity, associated with a subsequent higher risk of lung damage. (19) Compared to females, males with COVID-19 showed a higher plasmatic concentration of several proinflammatory cytokines and chemokines (IL-2, TNFα, IL-7, IL-18, CCL14, and CCL23). The fact that also anti-inflammatory cytokines such as IL-10 have been higher in males could be a mechanism to contain inflammation and tissue damages. (20) Furthermore, in males, higher expression of androgen could lead to enhanced expression of the transmembrane serine protease 2 (TMPRSS2), that is involved in the

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process of priming of spike protein during SARS-COV2 infection, and this might be a potential reason for greater predisposition of males for COVID-19 infection. (21)

These differences could influence the inflammation process, which resolves more rapidly in women than in men, probably due to the anti-inflammatory effects of estrogen. (22) It is not surprising, then, that sex differences influence not only the immune response to SARS-COV-2 but also the outcome of COVID-19, as well as drug absorption, metabolism and tolerance and, thus, COVID-19 treatment efficacy. (21) Lastly, it seems that significant sex differences exist in long-term CV outcomes after COVID-19. (1, 23) Thus, the differences in the inflammatory burden between male and female population may explain the gender-related disparities both in COVID-19 clinical manifestations and in CV outcomes after COVID-19.

The above-mentioned mechanisms may also be involved in the pathophysiology of long COVID, a condition wherein the affected individuals do not recover for several weeks or months following the onset of symptoms suggestive of COVID-19. In general, women appear to be twice as likely to develop long COVID as men, but only until around age 60, when the risk level becomes similar. The cause for the symptoms of long COVID may be an extreme inflammatory response triggered by the virus, but also an autoimmune reaction "unveiled" by the virus itself, possibly due to molecular mimicry with some components of our body. The autoimmune hypothesis could justify the higher incidence of this condition in women. (24)

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The potential relationship between COVID-19, depression and CVD

What has happened in the last year as a result of the pandemic that has hit the whole world?

An important increase in depression and stress was detected in different countries and affected all age groups, from children to the elderly. Although the methods adopted by countries to reduce the impact of the COVID-19 pandemic varied dramatically, the most common epidemiologic mitigation strategy throughout the world has been seen to impose quarantine and isolation at home. (25)

Although most publications explore the effects of COVID-19 on depression and stress in the general population or in population groups, little has been investigated on its effects on women. (26) Erving and coworkers examined whether stress exposures experienced within and across various life domains are predictors of depression among Afro–Caribbean women, a specific ethnic group within the black female population of the United States of America (USA). They specifically analyzed the relationship between 5 stress exposures and depression: major discrimination, everyday discrimination, past-month chronic stress, financial strain, and negative interactions with family. Of these five stress exposures, chronic stress and financial strain were associated with increased risk for depression. (27) During the pandemic, economic tension and chronic stress increased enormously, especially in the low-income segments of the population and in vulnerable individuals.

Women have been strongly affected by quarantine for many reasons. The first reason is social; the woman has often primary roles as caregivers within families. The additional care burden associated with childcare and home education during blockages and caring for sick family members can lead to significant psychological distress leading to depression. Stay-at-home measures along with financial and security concerns can put a strain on families, which in some situations can lead to high stress levels in women. In addition, having less time for education, work, and career advancement, women can experience increased social inequality. Furthermore, in the case of women who live alone, isolation and the reduction of social relations together with the fear of the economic crisis favor the appearance of depression. (28)

Several studies indicate that the COVID-19 pandemic has a disproportionately large economic effect on women because it affects the sectors in which they are most active. The manufacturing-and-retail industry has experienced large fallbacks in export and sales because of lockdown and distancing measures. The World Trade Organization (WTO) reports that female employees make up 80% of the workforce in manufacturing ready-made garments in Bangladesh, where industry orders fell by 81% in April 2020 alone. In addition, a greater proportion of women than men work in

tourism and business travel, which are severely disturbed by travel restrictions and will require a long recovery period. Furthermore, women are more frequently frontline health workers, thus potentially making them more susceptible to virus infection. (29) In this way, the pandemic has exacerbated financial entanglement, which represents a critical factor in intimate partner violence (IPV), along with social isolation and substance abuse (SU). IPV and SU share a multidirectional relationship that abruptly strengthened during COVID-19. Firstly, perpetrators of SU may enhance aggression and coercive behaviors and, thus, IPV; secondly, women who survive to IPV may themselves use substances to cope. Both SU and IPV significantly increased during COVID-19 pandemic, with severe short and long-term mental health issues such as depression, a so-called "pandemic within a pandemic". (30)

Wellbeing is a complex status that includes different features, such as health, emotions, relationships, and other quality-of-life dimensions. Stevenson and Wolfers observed a 'paradox': despite improvement in their lives on many objective measures, women's happiness in the USA declined between 1972 and 2006. (31) There are several plausible explanations for this decline – for example, women may be held to higher expectations that are more difficult to meet. Stress and depression induced changes in lifestyle, promoting unhealthy diet, sedentary behavior and eat-drink for cope with stress. These changes in lifestyle seem to affect men and women in a different way. Women were more likely to develop food craving to cope with stress. Food craving is characterized by a high intake of fat- and sugar-rich foods leading to obesity. Obesity is a well-known risk factor for COVID-19 and is associated with high levels of inflammation. (32)

Several studies have suggested that a higher body mass index (BMI) or obesity are risk factors for complications arising from COVID-19 infection. (32) This may be due to several reasons: a higher prevalence of pulmonary problems in obese populations and a higher level of chronic inflammation and the adverse effect of obesity on diabetes. Again, a recent study showed that higher BMI was associated with a stronger risk of COVID-19 related mortality in women than in men. (33) Some evidence suggests that dietary patterns and individual nutrients can influence systemic markers of

immune functions. However, the complexity of the interaction (nutrition and immunology) necessitates further research. The Mediterranean diet is widely recognized to have anti-inflammatory properties due to relatively high dietary intake of antioxidants and anti-inflammatory foods (vegetables, legumes, olive oil, whole grains, nuts, and monounsaturated fats). Moreover, several studies showed that adherence to a healthy dietary pattern, such as Mediterranean diet, is inversely associated with depression. (34)

The association between diet and depression is independent from other confounding factors, such as body mass index, health behaviors, education and cultures. In turn, depression itself could affect eating habits leading to overeating and gain weight. Due to the restrictions imposed by the governments to stay at home, boredom and stress induced an increase in food consumption, which can lead to people inadvertently seeking comfort during times of stress. During the COVID-19 pandemic, a change in food choices has been reported suggesting a switch to unhealthy diet. An increase in the consumption of comfort food, such as chocolate, candies, chips and fast food take-outs was reported in several countries. Moreover, due to change in social habits, the sales of coffee (15.2%), snacks and aperitifs have also increased. (35) On the other hand, the intake of fruits and vegetables was reduced.

COVID-19 lockdown has further led to an increase in smoking due to time spent at home, mental distress and potential post-traumatic stress disorder (PTSD). It is well known that smoking habit in women leads to a significant early increase of CV risk and CVD. Cardio-metabolic health is strictly connected to sedentary behavior and physical activity. This has substantial immune and metabolic implications, especially in those at risk or with metabolic diseases including individuals with obesity and Type 2 diabetes. Furthermore, it is well known that women of all ages are less active than men.

Although physical activity (PhA) plays a paramount role in reducing CVD-related incidents, recent data from clinical trials suggest that activity alone is not enough to reduce the risk of CVD in older adults. Both physical inactivity (PhI), defined as insufficient PhA level to meet present PhA

recommendations for age, and sedentary behavior (SedB), defined as any waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture, have been recently identified as having negative impacts on health status in older adults. (36)

A recent systematic review of 66 studies demonstrated that PhA significantly declined and SedB increased during the COVID-19 pandemic lockdown, regardless of the subpopulation or the methodology used. (37) Limited physical activity, increased sitting and screen time as a consequence of collective quarantine, may be associated with several metabolic effects that would increase the CV risk, especially in CVD patients, and the risk of severe COVID-19 outcomes as well. (38) It has also been established that many beneficial metabolic and CV adjustment in response to physical exercise can be lost in just two weeks of inactivity, impairing aerobic capacity, and/or increasing blood pressure. Again, physical inactivity and sedentary behavior are positively related to depression and reduction mental health. (39)

COVID-19 related lockdowns have affected physical activity and sedentary behavior in both sex. However, during pandemic period, mental health was both a motivator and a barrier to PhA and women engaged in less PhA due to COVID-19 reported significantly lower mental health scores, lower social, emotional and psychological well being. (40) On the other hand, maintaining and enhancing physical activity participation showed to mitigate the mental health consequences of COVID-19. (41) Thus, given the several physical and mental benefits of increased PhA and decreased SedB, public health strategies should include the creation and implementation of interventions that promote safe PhA and reduce SedB (Table 2). Supervised long-term cardiac rehabilitation programs have been shown to be safe and effective during COVID-19 pandemic. (42)

In summary, during COVID-19 and its aftermath it is imperative to consider the effects of the pandemic and social isolation on women's health, both in terms of CV and mental issues.

Recent data showed that as the outbreak of COVID-19 has developed, referral rates to mental health and psychology services have significantly dropped, especially in female population, despite a

likely increase in psychological distress, IPV and SU. (43) Thus, healthcare providers' training must be enhanced to understand the additional burdens of depression and CVD and to increase help seeking in the context of COVID-19. A comprehensive action supporting physical activity and healthy diet is mandatory to encourage women to keep up an adequate lifestyle in order to manage both depression and CV risk factors.

Conclusions

The impact of depression on healthcare and social costs is crucial. The latter acts as a relevant modifiable CV risk factor and as one of the primary determinants of quality of life for cardiac patients. Moreover, depression has been identified as a significant short-term and long-term related complication of COVID-19 infection, with a remarkable impact on work productivity and disability. In particular, COVID-19 related depression might lead to a substantial increase in sedentary time, smoking habit and negative dietary behavior, which in turn are able to worsen CV outcomes.

Furthermore, inflammation acts as the common pathophysiologic substrate both for COVID-19 and CV outcomes. Women seem to be less prone to COVID-19 infection and, thanks to the anti-inflammatory effects of estrogens, experience a more rapid recovery from COVID-19. On the other hand, they undergo a disproportionately large economic and psychological effect during COVID-19 pandemic, with an increased risk to develop mental health issues both on short and long term after COVID-19 infection, the latter being associated with a worsening of negative dietary and behavioral habits potentially related to CV risk. Moreover, middle-aged women appear to be twice as likely to develop long COVID as men, with a further negative effect both on mental disability and social and working concerns.

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Thus, healthcare providers are strongly encouraged to inquire for depression among patients with ongoing or previous COVID-19 infection, and gender-specific issues must be taken into account to provide specific answers to male and female patients. In this view, specific protocols should be adopted in order to support and promote healthy lifestyle and adequate physical activity after COVID-19 infection.

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Table 1. Relevant clinical trials that explored the epidemiology of depression and mental health issues in COVID-19 and long COVID syndrome.

References	Total pts (n), % women (%)	Population	Aim	Results
Perlis R.et al (7)	3904 (44.3%)	US adult participants in 8 waves of an internet-based nonprobability survey conducted by Qualtrics with multiple panels of respondents	Association between acute COVID-19 symptoms and the probability of subsequent depressive symptoms.	52.4% of participants met the criteria for symptoms of major depressive disorder. Presence of headache was associated with greater probability of moderate or greater depression symptoms (adjusted odds ratio [OR], 1.33; 95%CI, 1.10-1.62). Women were less likely to have symptoms than men (adjusted OR, 0.72; 95%CI, 0.61-0.84).
Taquet M.et al (10)	236 379 (55.6%)	Retrospective cohort study from the TriNetX electronic health records network	Incidence rates and relative risks of neurological and psychiatric diagnoses in patients in the 6 months following a COVID-19 diagnosis.	The estimated incidence of a neurological or psychiatric diagnosis in the following 6 months was 33.62% (95% CI 33.17–34.07); the incidence of mood disorder was 13.66% (13.35-13.99%) in the whole population and increased in patients with hospitalization and with intensive therapy unit admission.
Huang C.et al (11)	1733 (48%)	Patients with confirmed COVID-19 who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7, 2020, and May 29, 2020	Describe the long-term health consequences of patients with COVID-19 who have been discharged from hospital and investigate the associated risk factors.	Anxiety or depression was reported among 23% (367 of 1617) of patients.
Naidu SB. et al (12)	946 (39.8%)	Adults discharged from hospital with a clinical diagnosis of COVID-19	Evaluation of the mental health burden in adults discharged from hospital with COVID-19 and exploration of the factors that contribute to this.	13.8% of adults screened was positive for depression. Adults with positive PHQ-2 and TSQ were significantly more likely to experience persistent symptoms (PHQ2 80.0% vs. 41.8%, TSQ 88.8% vs. 42.9%; both p<0.001) and they were also less likely to have returned to work (PHQ2 36.0% vs. 57.6%, p=0.004; TSQ 37.5% vs. 56.5%, p=0.01).
Torjesen I. (13)	1077 (36%)	Adults discharged from hospital with a clinical diagnosis of COVID-19 involving an assessment between two- and seven-months later	Impact of COVID-19 on health and employment, to identify factors associated with recovery and to describe recovery phenotypes.	At follow-up only 29% felt fully recovered, 20% had a new disability, and 19% experienced a health- related change in occupation. Factors associated with failure to recover were female, middle- age, white ethnicity, two or more co-morbidities, and more severe acute illness.

List of abbreviations: CVD, cardiovascular disease; Pts, patients; OR, odds ratio; AE, adverse events; DM, diabetes mellitus; PhA, physical activity; AMI, acute myocardial infarction; PHQ-9, Patient Health Questionnaire-9; CAG, coronary angiography; AF, atrial fibrillation; MSIMI, mental stress-induced myocardial.

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Table 2. Practical suggestions for lifestyle and behavior activity in managing depression after pandemic COVID-19

Contact friends and family
Go outside, take short walk, and change your daily itinerary to avoid monotony
Expose yourself to the sun
Reduce sitting time (i.e., watching TV)
Contact psychological support

Legend: TV, television.

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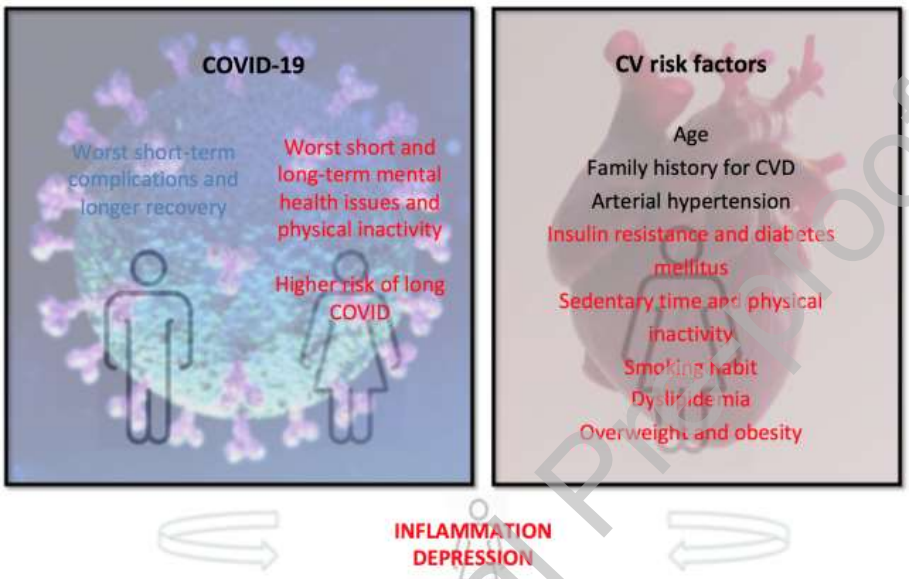


Figure 1.

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