

Journal Pre-proof

The Sexual Long COVID (SLC): erectile dysfunction as a biomarker of systemic complications for COVID-19 long haulers

Andrea Sansone MD, PhD , Daniele Mollaioli Psy D, PhD ,
Erika Limoncin PsyD, PhD , Giacomo Ciocca Psy D, PhD ,
Nguyễn Hoài Bắc MD, PhD , Thắng Nguyễn Cao MD ,
Guangdong Hou MD , Jianlin Yuan MD ,
Michael Zitzmann MD, PhD , Annamaria Giraldi MD, PhD ,
Emmanuele A. Jannini MD



PII: S2050-0521(21)00085-8
DOI: <https://doi.org/10.1016/j.sxmr.2021.11.001>
Reference: SXMR 389

To appear in: *Sexual Medicine Reviews*

Received date: 5 October 2021
Revised date: 30 October 2021
Accepted date: 9 November 2021

Please cite this article as: Andrea Sansone MD, PhD , Daniele Mollaioli Psy D, PhD ,
Erika Limoncin PsyD, PhD , Giacomo Ciocca Psy D, PhD , Nguyễn Hoài Bắc MD, PhD ,
Thắng Nguyễn Cao MD , Guangdong Hou MD , Jianlin Yuan MD , Michael Zitzmann MD, PhD ,
Annamaria Giraldi MD, PhD , Emmanuele A. Jannini MD , The Sexual Long COVID (SLC): erectile
dysfunction as a biomarker of systemic complications for COVID-19 long haulers, *Sexual Medicine
Reviews* (2021), doi: <https://doi.org/10.1016/j.sxmr.2021.11.001>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Copyright © 2021, International Society of Sexual Medicine. Published by Elsevier Inc. All rights reserved.

The Sexual Long COVID (SLC): erectile dysfunction as a biomarker of systemic complications for COVID-19 long haulers

Authors:

Andrea Sansone¹, MD, PhD; Daniele Mollaioli¹, Psy D, PhD; Erika Limoncin¹, PsyD, PhD; Giacomo Ciocca², Psy D, PhD; Nguyễn Hoài Bắc³, MD, PhD; Thắng Nguyễn Cao³, MD; Guangdong Hou⁴, MD; Jianlin Yuan⁴, MD; Michael Zitzmann⁵, MD, PhD; Annamaria Giraldi⁶, MD, PhD; and Emmanuele A. Jannini¹, MD

Affiliations:

¹Chair of Endocrinology and Medical Sexology (ENDOSEX), Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

²Department of Dynamic and Clinical Psychology, and Health Studies, "Sapienza" University of Rome, Rome, Italy

³Department of Andrology and Sexual Medicine, Hanoi Medical University's Hospital, Hanoi, Vietnam

⁴Department of Urology, Xijing Hospital, Fourth Military Medical University, Xi'an, China

⁵Center of Reproductive Medicine and Andrology, Institute of Reproductive and Regenerative Biology, Münster, Germany

⁶Sexological Clinic, Psychiatric Center Copenhagen, Rigshospitalet, Copenhagen, Denmark; Institute for Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.

Corresponding Author:

Emmanuele A. Jannini, MD

Chair of Endocrinology and Medical Sexology (ENDOSEX), Department of Systems Medicine, University of Rome Tor Vergata, via Montpellier 1, 00133 Rome, Italy; eajannini@gmail.com

Conflict of interests:

EAJ is or has been consultant and/or paid speaker for Bayer, Ibsa, Janssen, Lundbeck, Menarini, Otsuka, Pfizer, and Shionogi. The other Authors report no competing interests.

Acknowledgments:

AS and EAJ have been partially supported for this work by the Italian Ministry of University PRIN grant # 2017S9KTNE_002.

Introduction

COVID-19, the coronavirus disease caused by SARS-CoV-2, is an unprecedented issue for healthcare: the rapid spread of the different viral strains, the lack of universally viable treatments and the high prevalence of patients requiring intensive care contributed to a large number of casualties worldwide. As of September 30th, 2021, the World Health Organization has estimated over 4,7 million deaths for COVID-19 among more than 232 million cases [1]. This is largely suggestive of the largely variable clinical phenotype of the disease [2], with the vast majority of patients having contracted SARS-CoV-2 being asymptomatic, or having only mild symptoms [3,4] during the acute phase of the disease.

As new evidence started piling up, it became increasingly apparent that long-term chronic complications of COVID-19 were to be expected [5]. These complications, initially greeted with skepticism by many physicians, were defined as “long COVID” on social media [6], while from a more pathophysiological basis, they would more appropriately be defined as “post-acute” or “chronic”, according to the duration and onset [7]. At present, a growing body of evidence supports the notion that some patients might develop long-term, multiorgan complications of COVID-19 which may affect the patients’ quality of life and result in long-lasting disability, or increased vulnerability to other conditions. In fact, only some patients with COVID develop long-term complications, suggesting the idea that the presence of several risk factors, including demographic and life-style factors [8], the severity of the underlying infection and the resulting duration of in-patient stay, and prior health conditions could overexpress the effects of COVID infection for a longer period. Dyspnea, fatigue, and anxiety are among the chief complaints of COVID long-haulers; however, other residual effects of SARS-CoV-2 have been identified in more recent reports. This condition has been defined by the National Institute for Health and Care Excellence (NICE) as the persistence of symptoms occurring during or after SARS-CoV-2 infection in the absence of any other possible medical explanation [9], and by the NIH and CDC (National Institutes of Health and Centers for Disease Control, respectively) as all COVID-19 sequelae persisting beyond four weeks after the onset of disease [10].

COVID-19 affects many organs and systems, largely owing to the almost ubiquitous expression of the angiotensin-converting enzyme 2 (ACE2) receptor allowing internalization of the virus in target cells [11]. According to current evidence, SARS-CoV-2 invades endothelial cells through ACE2 and transmembrane protease serine 2 (TMPRSS2) [12], and the resulting endothelial damage has been investigated as one of the main features of the immunological hyper-response associated with worse outcomes for acute COVID-19 [13]. It is therefore largely expected that the same organs targeted by SARS-CoV-2 may be affected by long COVID [14], therefore providing a plausible explanation for its variable clinical phenotype.

This finding makes COVID-19 a relevant condition for sexual medicine experts, with the involvement of the endothelium in erectile function [15] being only the most obvious reason for concern [16]. Sexual function for patients with acute COVID-19 has barely been investigated, also owing to the disease severity; however, the persisting endothelial dysfunction occurring in long COVID might become a relevant issue for many individuals, made even more worrisome by the prevalence of the “post-acute COVID-19 syndrome” among younger individuals and by the possible interaction between different organic and non-organic mechanisms of action.

This review aims to investigate and highlight the mechanisms through which long-term consequences of COVID-19 can affect erectile function, also discussing the current evidence concerning the epidemiology of long COVID and the potential treatments, wherever available.

Materials and methods

We conducted a comprehensive literature search on PubMed, Scopus and Google Scholar through July 2021 using the following keywords with the AND/OR Boolean operators: SARS-CoV-2, Coronavirus, COVID, COVID-19, long-term, long covid, post acute covid, long haulers, erectile dysfunction, male sexual dysfunction. Results were then filtered for all papers published since the beginning of 2020. From the initial results of our search query, we also looked through citations and references of

relevant articles in order to retrieve additional resources. Results were limited to English, Italian and French only.

Results

Epidemiology of long COVID

Symptoms of “long COVID” were found to be quite consistent, although with varying prevalence in different studies, also owing to heterogeneous populations and to the different definitions used [14]. At present, the largest study on long COVID, performed in the United Kingdom on over 508,000 individuals and still only available as a pre-print [17], reports a 37.7% prevalence of at least one symptom at 12 weeks among more than 76,155 patients symptomatic for COVID. Many other studies have highlighted a worrying prevalence of symptoms persisting for several weeks, including an Italian study [5] on 143 hospitalized patients with a 84.7% prevalence in the post-acute phase and a Chinese study [18] on 1733 chronic patients, with symptoms occurring in up to 63% of patients at 6 months follow-up. A recent meta-analysis study pooling data from 15 studies, for a total of 47910 patients included in analysis, reported 80% of patients having at least one among more than 50 long-term complications of COVID-19 at two weeks following disease onset [19]. A systematic review on 45 studies published in May 2021 and accounting for 9751 patients reported that almost three out of four patients (72.5%) experienced at least one persistent symptom related to COVID-19, even at 6 months follow-up [20]. Another systematic review, including more than 250 000 COVID-19 survivors among 57 studies, reported a prevalence of long-COVID symptoms of 54.0%, 55.0%, and 54.0% at 1, 3, and 6 months, respectively [21]. On the other hand, some studies have reported only mild symptoms in a minority of patients, such as anosmia and ageusia in about 6-10% of patients [22–24] or abdominal pain and diarrhea in less than 5% of individuals [25,26]. Overall, these findings suggest that “long COVID” might be a systemic, long-lasting condition occurring in some patients with a previous history of SARS-CoV-2 infection, independently of the severity of the initial disease [27–29]. This can partly be due to the presence of microvascular involvement even in “silent” forms of COVID-19 [30–33], or to the presence of chronic low-grade inflammation which can trigger symptoms of long COVID [34,35]

even in asymptomatic patients. The presence of these combined factors can potentially increase the likelihood of developing erectile dysfunction (ED) in COVID-19 long haulers (figure 1).

Neuropsychiatric complications of long COVID

Pathophysiology and prevalence. Addressing the long-term complications of COVID-19 for neuropsychiatry is a daunting task, due to the involvement of the neurological system at many levels, from cognition to cerebrovascular events to sensory dysfunctions. Overall, this is further proof of the protean nature of COVID-19 and of its manifestations, with several pathogenetic mechanisms being involved.

The unfavorable chemokine profile featured in the “cytokine storm” [36] can promote neuroinflammation, endothelial dysfunction in brain vessels, vascular thrombosis and local hypoxia [36,37], and can also contribute to the onset of potential long-term neurological defects [38,39]. As SARS-CoV-2 has been identified in the cerebrospinal fluid [40,41], encephalitis following direct viral neuronal damage has been included among the complications of COVID-19. SARS-CoV-2 has also been proven able to infect brain endothelial cells, resulting in microvascular pathology occurring in brain vessels which can also influence the blood-brain barrier [42].

As previously reported, fatigue, headache and “brain fog” are undoubtedly the most common symptoms of long COVID, with an estimated prevalence 58%, 44%, and 27% prevalence [5,14,29,42]. Fatigue is more than a mere state of tiredness: it is a persistent state of weariness taking a heavy toll on physical and mental energy, often reported by patients for several weeks following the acute phase of COVID-19, independently of the severity of the disease [5,14,29,43]. Several pathogenetic mechanisms have been proposed for the onset of chronic fatigue following COVID-19: on top of psychological factors [44], several central and peripheral organic factors have been considered, including systemic low-grade inflammation [45,46], impaired cerebrospinal fluid drainage [47], and muscle damage [48]. Fatigue is not uncommon following viral infections [49], and some similarities

with chronic fatigue syndrome and myalgic encephalomyelitis have also been pointed out [50], as already occurred for SARS almost a decade ago [51].

“Brain fog”, is a colloquialism used to define the impairment in cognitive functions featuring confusion, sluggishness of thought and difficulties concentrating. Brain fog is not a defining condition of long COVID, being a neuropsychiatric complication of several other organic and non-organic conditions, including celiac disease [52,53], migraine [54], lupus [55] and myotonic dystrophy [56]. At present, the exact mechanisms leading to the development of brain fog are not fully understood; however, in long COVID, they are likely mild complications of COVID-related encephalitis [57], as also shown by the finding of abnormal neurologic exam [58], possibly associated with mast cells activation and release of proinflammatory cytokines [59]. The persistence of brain fog significantly worsens quality of life and cognition for affected patients. More severe forms of COVID-19 seemingly lead to worse cognitive impairment: however, similar neurological complications have also been reported in the past for patients requiring treatment in intensive care units (ICU) [60].

While these are the most common long-term neuropsychiatric complications, long COVID features other relevant symptoms. Olfactory and gustatory dysfunctions, which have been prominently reported in the acute phase of COVID-19, can persist for up to several months in a non-negligible percentage of affected individuals [61–63]: meta-analysis report that anosmia and ageusia are occurring in 21-23.6% and in 9-23% of COVID patients at follow-up [63–66]. Post-traumatic stress disorder, anxiety, depression and other psychiatric symptoms have also been reported in COVID-19 long haulers and to some extent, even in the general population [64–67]: this is likely a consequence of quarantine, lockdowns, isolation and health and economic concerns, which have contributed to worsen mental health [68], even more in individuals with underlying conditions such as dementia [69].

Relevance for erectile function. The cognitive defects and sleep disorders featured in long COVID [70] contribute to poorer sexual health [71–73]. Likewise, chronic fatigue has been associated with declining sexual functioning [74]. At present, no data on “brain fog” is available in regard to sexual health.

Isolation inevitably leads to reduced sexual intercourse frequency for non-cohabiting couples [75]. However, the long-term effects of lockdown and social isolation policies for mental health, mainly in regards to depression and anxiety, are still an open question. Currently available studies report a 15% prevalence of depressive symptoms [76] and a 19% prevalence of post-traumatic stress disorder (PTSD) (10.4% overt, 8.6% subclinical) [77] at three months post-discharge. At present it is expected that rates of PTSD, anxiety and depression will increase [78] for COVID long haulers, although symptoms are supposed to improve over time [78–85]. While anxiety, depression and PTSD have all been long considered risk factors for the development of sexual dysfunctions [79–86], the relation between sexual and mental health is bidirectional. Indeed, real-life data from Italy has identified a preventive effect of sexual activity concerning the risk of developing anxiety and depression during the first Italian lockdown [87]. Therefore, taking care of the sexual health of COVID-19 patients might be helpful in order to prevent the development of worse outcomes for mental health. The role of anxiety and depression in the development of sexual dysfunctions has also been hypothesized by a recent study comparing Chinese long COVID patients to healthy controls: prevalence of ED was significantly higher at the first follow-up visit, but this difference was no longer statistically significant at the second follow-up visit after three months, suggesting that sexual function improved as a result of better psychological status [88]. However, the small sample size (30 individuals at the second follow-up visit) might not be adequate to draw definite conclusions concerning the real extent of this issue [88]. Additionally, less investigated factors might contribute to the worsening of sexual function in long COVID patients, such as anosmia and ageusia: both conditions can negatively affect sexual behavior, owing to the “emotional” involvement of smell and taste in arousal and intimacy [89], and might persist for several months [28,29,89], blunting sexual interest. However, more studies on this topic are needed.

Respiratory complications of long COVID

Pathophysiology and prevalence. The respiratory system is undoubtedly the most vulnerable target for COVID-19, with a distinct involvement of the pulmonary tract, featuring dry cough, dyspnea,

hypoxemia, and abnormal imaging results. Dyspnea and shortness of breath are common long-term complaints for COVID-19 patients [28,29,90], and some data suggests that pulmonary function might require a long time to recover [91]. A meta-analysis study investigating the radiological and functional long-term complications on 3066 discharged COVID-19 patients reported a 44.3% prevalence of impaired lung function at three months after symptom onset or hospital discharge [92], highlighting the high relevance of long COVID for public health. Several pathogenetic mechanisms affecting the lung have been described [93], but whether the same mechanisms would apply for long-term consequences is a still open question [94]. The inflammatory response (particularly interleukin-6 [95], which is among the main drivers of inflammation for COVID-19 [96]) and the endothelial dysfunction occurring in the small vessels of the pulmonary circulation [36,97] induce pulmonary dysfunction, as also proven by the high prevalence of residual lung abnormalities at computed tomography (CT), such as ground glass opacity and signs of pulmonary fibrosis, occurring in 44.1% and 33.9% patients at three months according to the aforementioned meta-analysis study [92]. Fibrosis was more likely to occur in older patients with more severe forms of COVID-19 [98,99], and was proven to be found in COVID patients at 6 months follow-up [100]. Data from previous forms of acute respiratory distress syndrome (ARDS) suggest that pulmonary function might be impaired for several years [101,102], raising important concerns for the affected population.

Relevance for erectile function. Oxygen saturation decreases following pulmonary fibrosis [103], as also occurring in COVID-19 patients due to the combination of anemic and hypoxic hypoxia [104]. As oxygen is a necessary substrate for the production of nitric oxide (NO), pulmonary fibrosis negatively affects the erectile function [105]. In fact, sexual dysfunctions are known to occur in all conditions of impaired oxygen availability, including chronic obstructive pulmonary disease (COPD) [106] and interstitial lung disease [107]. The first line of treatment for ED involves the use of phosphodiesterase type 5 inhibitors (PDE5i), vasoactive agents which act downstream of NO synthesis; such drugs also improve pulmonary vasodilation [108], allowing for an increased alveolar gas exchange [109]. The benefits of these drugs do not end here: sildenafil, the first and most widely known PDE5i, also has anti-aggregation properties and inhibits neointimal hyperplasia through the cGMP-dependent protein

kinase (cGK) pathway, thus preventing further vascular injury and thrombosis [110], and has anti-inflammatory [111], anti-apoptotic [112] and anti-oxidant [113] properties which could improve inflammatory status in the lungs. Therefore, PDE5i can potentially be beneficial for both erectile and pulmonary function in long COVID patients, as currently investigated by dedicated trials [114–116].

Cardiovascular complications of long COVID

Pathophysiology and prevalence. COVID-19 has been identified as an independent risk factor for cardiovascular health, with significant data coming, among the others, from registry studies on over 86,700 individuals [117]. As endothelial cells express ACE2 and TMPRSS2, SARS-CoV-2 can invade them, resulting in a diffuse form of endotheliitis [32,118] which has been considered one of the main drivers of the microcirculatory dysfunction occurring in COVID-19 [118–120]. Unsurprisingly, patients with more severe forms of COVID-related vascular damage, including acute thrombotic events and pulmonary embolism, often also show more severe endothelial dysfunction [2,121]. The persistent endothelial dysfunction is, however, part of a more complex phenotype, supported by the unfavorable immune response and chemokine profile [121]: several mechanisms have been considered, including coagulopathy [122], chronic inflammation of cardiomyocytes, myocardial ischemia and local hypoxia [123], ultimately resulting in fibrotic changes occur in the heart [32,124]. Viral myocarditis, another possible consequence of SARS-CoV-2 infection, has been reported in autopsy findings [125] and in almost 80% of patients after more than two months from the onset of symptoms [126]. Following the onset or worsening of chest pain, tachycardia or dyspnea in the weeks after hospital discharge, a consultation with a cardiologist is warranted for COVID-19 patients in order to investigate possible long-term cardiovascular complications which might require additional work-up and/or treatment [123]. This is particularly relevant for younger individuals, especially athletes, who might also develop exercise-induced arrhythmias, including Postural Orthostatic Tachycardia Syndrome (POTS), due to involvement of the autonomic nervous system [127–129].

Relevance for erectile function. Erectile function is strictly dependent on the integrity of the endothelium [32,117]: endothelial dysfunction, such as occurring in long COVID, is therefore likely to

have negative repercussions on erection [32,118], which undoubtedly result in impaired sexual health and satisfaction [130]. Such effects have been shown to act regardless of anxiety and depression [131,132], suggesting that endothelial function might actually be an independent risk factor for the development of ED in affected patients. Additional support in these regards comes from the presence of SARS-CoV-2 particles and the reduced expression of endothelial NO synthase (eNOS) expression in the endothelium of COVID-19 patients [133]. The chemokine profile described in COVID-19 [134] can also contribute to the progression to more severe forms of erectile dysfunction [135]. As sexual activity can be considered a mild form of physical exercise, accounting for 3-5 metabolic equivalents [136], it can become somewhat hazardous in patients with myocarditis or with a sudden onset of chest pain - even more in case of pulmonary dysfunction. Likewise, patients with POTS might experience several debilitating symptoms, such as shortness of breath, sweating, and nausea [137], when changing position during sexual intercourse [138,139]. It is also worth mentioning that several drugs used in the clinical management of COVID-19 long term complications, including beta-blockers and diuretics [139], might have negative effects on erectile function [140].

Endocrine complications of long COVID

Pathophysiology and prevalence. Long-term complications of COVID-19 for endocrine function have not been investigated as thoroughly as cardiovascular or pulmonary systems. However, ACE2 is highly expressed by several cell types [141], including many highly relevant for the endocrine system such as pancreatic β -cells [142,143], hypothalamic and pituitary cells [144,145], and testicular Leydig and Sertoli cells [146,147]. Viral direct damage can therefore trigger endocrine complications. Testicular damage can potentially result in the development of subclinical hypogonadism [148,149], potentially influencing immune response [150], and can also potentially affect reproductive health [151,152], putting male fertility in jeopardy. Such effects, however, have not been studied at follow-up, and data concerning the prevalence of COVID-related hypogonadism (whether subclinical or overt) is at present unknown. Thyroid follicular and parafollicular epithelial cells also express ACE2, and several cases of thyrotoxicosis following SARS-CoV-2 infection have reported [153–155]: recent data show the

persistence of ultrasonographic alterations, possibly predisposing to late-onset thyroid dysfunction [156]. Prevalence of abnormal laboratory findings is widely variable across studies, with 15-56% and up to 8% of COVID-19 patients having low and high TSH levels, respectively. Pituitary apoplexy, an otherwise rare event, has been reported in several cases of COVID-19, often in association with a pre-existing pituitary adenoma [157], possibly secondary to endothelial dysfunction, coagulopathy and increased blood flow due to the underlying inflammatory condition [158]. COVID-19 can also lead to the onset of type 1 diabetes mellitus in predisposed individuals [159] following autoimmune reaction towards the β -cells [160], as well as to accelerated development of type 2 diabetes mellitus due to pancreatic inflammation, islet remodeling and progressive β -cell dysfunction [161]. Overall, these findings suggest that several endocrine and metabolic alterations can occur following COVID-19, potentially resulting in long-term dysfunctions requiring adequate management and treatment.

Relevance for erectile function. Endocrine disorders are known risk factors for the development and progression of sexual dysfunction in both men and women [162–165]. Reduced testosterone levels have been reported in long COVID patients, highlighting the risk of persistent hypogonadism following infection [166]. This finding is highly relevant, not only because of the fundamental role of androgens in sexual response [150], but also because of the worse outcomes being reported in patients with lower testosterone levels [149,167]. Besides testosterone, several other long-term endocrine complications of COVID-19 should be considered by sexual medicine experts: in particular, the progression towards overt diabetes might be the most worrisome item to be considered in long COVID. Indeed, diabetes is an independent risk factor for sexual dysfunctions [168], owing not only to the negative effects exerted on cardiovascular function, but also to other organic and non-organic factors, such as depression, weight gain and insulin resistance [169]. Additionally, such factors often interact: as an example, insulin resistance promotes weight gain, which in turn leads to the development of functional hypogonadotropic hypogonadism, resulting in worse lipid profile and quality of life which are partly restored by testosterone replacement therapy and weight loss [170,171]. It should be pointed out, however, that while obesity has marked effects on testosterone levels, the effect of androgens on adiposity is far more nuanced [172]. The effects of long COVID on

male fertility [151,152] might also contribute to worsen sexual health in affected couples [173], suggesting additional indirect effects which are so far underinvestigated.

Other long-term complications of COVID-19

As for many other chronic diseases, long COVID has important socio-economic consequences [174], resulting in, among the others, delayed medical care [175], xenophobia [176], and impaired education due to school closures [177]. Work disability has become an issue for many workers at high-risk of contracting COVID-19 [178], and the temporary lay-offs enacted during lockdowns have resulted in dramatic reduction in income. Even those who moved to remote working might have faced negative consequences for their own health, including exhaustion, more sedentary lifestyle, and mood disturbances [87,179,180]. Such consequences inevitably weigh on sexual function, by both increasing psychological distress and affecting general health. Patients with prolonged ICU stay might also develop unique complications, such as erosion of inflatable penile prosthesis due to catheterization [181]. Additionally, as medications used to treat ED are not covered by drug plans and can become an important cost, even more in times of economic hardships [182], the risk of neglecting sexual health treatments should be considered. Therefore, even if socio-economic consequences cannot be included into any of the former groups, they should be considered during any part of the clinical evaluation in sexual medicine.

Conclusions and future directions

COVID-19 is a typical viral, obviously transmissible disease where social behavior, i.e., lifestyle, plays a major role. In fact, the clinical impact of the COVID -19 is largely based on the age and on the presence of comorbidities with chronic, noncommunicable diseases (NCDs), which are also largely dependent on lifestyles. Finally, the seriousness of the long COVID itself is very frequently, but not always, proportional to the presence and to the severity of NCDs. These findings are highly relevant in the

context of sexual medicine, owing to the shared risk factors for sexual dysfunctions (particularly concerning ED) and COVID-19: several factors could contribute to the onset of sexual health issues in COVID patients, including endothelial dysfunction, prolonged hypoxia due to respiratory impairment, anxiety and depression, and endocrine disorders.

Taken together, all these aspects could be featured in a sexual long COVID (SLC) syndrome, which may not only have a pathophysiological and taxonomic value but could also act as a biomarker of the clinical impact of the “general” long COVID. As ED is a widely accepted clinical biomarker of cardiovascular and general health [183–185], it makes sense to hypothesize SLC as a clinical biomarker of long COVID, once again highlighting the relevance of sexual function outside the boundaries of sexual medicine. Plenty of evidence, in fact, clarifies how sexual health is lost at the earliest stages of chronic diseases and belatedly recovered in the process of complete healing. In this light, SLC might become the clinical biomarker of all systemic underlying factors featured in long COVID (figure 1): patients who develop symptoms of the SLC might indeed have worse risk profiles concerning all other complications of long COVID compared to those who maintain a good erectile function. Erectile disorders might therefore be a clinically tangible warning of the complex web of underlying vascular, endothelial, metabolic, neuropsychiatric and pulmonary risk factors [186]. This is also supported by the bidirectional relationship existing between COVID-19 and ED, suggesting not only that COVID-19 patients are more likely to develop ED, but also that, owing to the shared risk factors, odds ratio for developing COVID-19 is much higher in men having worse erectile function [186,187].

Another possible merit of the taxonomic introduction of the SLC could be educational. It is well known that arguments related to sexual health may have a much higher psychological impact on shifting from wrong behavioral habits to healthy lifestyles. This is particularly true for young people, a group peculiarly interested in sexual health and, unfortunately, still reluctant to vaccinate [187,188]. The ghost of SLC may help in the double effort to educate to get vaccinated and to improve healthy behaviors. “No vax, no sex” could become, on this light, a tremendously powerful motivational claim.

Hence, a flow such as that proposed in the figure 2 may highlight the mentioned relationships, which, once again, represent the role of lifestyles in the development of sexual dysfunctions dependent on both communicable (as COVID-19) and non-communicable diseases (as NCDs, increasing the COVID-19-related risks).

Future studies should be addressed at identifying the prevalence of ED among long COVID patients, using both validated questionnaires, such as the International Index of Erectile Function [189,190], and specific diagnostic tests, including dynamic duplex ultrasound of the penis [191]. These studies will provide the much-needed evidence concerning the extent to which erectile function is affected by long COVID and the exact mechanics behind this impairment. Additionally, more studies might be considered in order to measure whether patients developing SLC following the acute phase of the disease show worse outcomes for cardiovascular, respiratory, or neurologic function, compared to those who did not incur into any sexual dysfunction – once again suggesting a clinical phenotype in which erection is the “tip of the iceberg” of a more systemic dysfunction.

At present, despite the piling up evidence concerning the long-term complications of COVID-19, sexual health has drawn little attention from the medical community; however, as erectile function is among the most reliable mirrors of a man's overall health [184,185], also possibly predicting cardiovascular events [184,185], we strongly believe it is time to investigate more systematically the sexual function of COVID-19 long haulers.

References

- [1] Coronavirus disease (COVID-19) – World Health Organization n.d. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019> (accessed August 20, 2021).
- [2] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).
- [3] Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic : A Systematic Review. *Ann Intern Med* 2021;174:655–62. <https://doi.org/10.7326/M20-6976>.
- [4] Efrati S, Catalogna M, Abu Hamed R, Hadanny A, Bar-Chaim A, Benveniste-Levkovitz P, et al. Early and long term antibody kinetics of asymptomatic and mild disease COVID-19 patients. *Sci Rep* 2021;11:13780. <https://doi.org/10.1038/s41598-021-93175-y>.
- [5] Carfi A, Bernabei R, Landi F, Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA* 2020;324:603–5. <https://doi.org/10.1001/jama.2020.12603>.
- [6] Rubin R. As Their Numbers Grow, COVID-19 “Long Haulers” Stump Experts. *JAMA* 2020;324:1381–3. <https://doi.org/10.1001/jama.2020.17709>.
- [7] Baig AM. Chronic COVID syndrome: Need for an appropriate medical terminology for long-COVID and COVID long-haulers. *J Med Virol* 2021;93:2555–6. <https://doi.org/10.1002/jmv.26624>.
- [8] Mollaioli D, Ciocca G, Limoncin E, Di Sante S, Gravina GL, Carosa E, et al. Lifestyles and sexuality in men and women: the gender perspective in sexual medicine. *Reprod Biol Endocrinol* 2020;18:10. <https://doi.org/10.1186/s12958-019-0557-9>.
- [9] National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. London: National Institute for Health and Care Excellence (UK); 2021.
- [10] Datta SD, Talwar A, Lee JT. A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection: Illness Beyond Acute Infection and Public Health Implications. *JAMA* 2020;324:2251–2. <https://doi.org/10.1001/jama.2020.22717>.
- [11] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020;181:271-280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>.
- [12] Jin Y, Ji W, Yang H, Chen S, Zhang W, Duan G. Endothelial activation and dysfunction in COVID-19: from basic mechanisms to potential therapeutic approaches. *Signal Transduct Target Ther* 2020;5:293. <https://doi.org/10.1038/s41392-020-00454-7>.
- [13] Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol* 2021;17:46–64. <https://doi.org/10.1038/s41581-020-00357-4>.

- [14] Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. *BMJ* 2021;374:n1648. <https://doi.org/10.1136/bmj.n1648>.
- [15] Guay AT. ED2: erectile dysfunction = endothelial dysfunction. *Endocrinol Metab Clin North Am* 2007;36:453–63. <https://doi.org/10.1016/j.ecl.2007.03.007>.
- [16] Sansone A, Mollaioli D, Ciocca G, Limoncin E, Colonnello E, Vena W, et al. Addressing male sexual and reproductive health in the wake of COVID-19 outbreak. *J Endocrinol Invest* 2021;44:223–31. <https://doi.org/10.1007/s40618-020-01350-1>.
- [17] Whitaker M, Elliott J, Chadeau-Hyam M, Riley S, Darzi A, Cooke G, et al. Persistent symptoms following SARS-CoV-2 infection in a random community sample of 508,707 people. *BioRxiv* 2021. <https://doi.org/10.1101/2021.06.28.21259452>.
- [18] Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021;397:220–32. [https://doi.org/10.1016/S0140-6736\(20\)32656-8](https://doi.org/10.1016/S0140-6736(20)32656-8).
- [19] Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021;11:16144. <https://doi.org/10.1038/s41598-021-95565-8>.
- [20] Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Netw Open* 2021;4:e2111417. <https://doi.org/10.1001/jamanetworkopen.2021.11417>.
- [21] Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: A systematic review. *JAMA Netw Open* 2021;4:e2128568. <https://doi.org/10.1001/jamanetworkopen.2021.28568>.
- [22] Boscolo-Rizzo P, Borsetto D, Fabbris C, Spinato G, Frezza D, Menegaldo A, et al. Evolution of Altered Sense of Smell or Taste in Patients With Mildly Symptomatic COVID-19. *JAMA Otolaryngol Head Neck Surg* 2020;146:729–32. <https://doi.org/10.1001/jamaoto.2020.1379>.
- [23] Vaira LA, Hopkins C, Petrocelli M, Lechien JR, Chiesa-Estomba CM, Salzano G, et al. Smell and taste recovery in coronavirus disease 2019 patients: a 60-day objective and prospective study. *J Laryngol Otol* 2020;134:703–9. <https://doi.org/10.1017/S0022215120001826>.
- [24] Tomasoni D, Bai F, Castoldi R, Barbanotti D, Falcinella C, Mulè G, et al. Anxiety and depression symptoms after virological clearance of COVID-19: A cross-sectional study in Milan, Italy. *J Med Virol* 2021;93:1175–9. <https://doi.org/10.1002/jmv.26459>.
- [25] Eiros R, Barreiro-Perez M, Martin-Garcia A, Almeida J, Villacorta E, Perez-Pons A, et al. Pericarditis and myocarditis long after SARS-CoV-2 infection: a cross-sectional descriptive study in health-care workers. *BioRxiv* 2020. <https://doi.org/10.1101/2020.07.12.20151316>.
- [26] Landi F, Carfi A, Benvenuto F, Brandi V, Ciciarello F, Lo Monaco MR, et al. Predictive Factors for a New Positive Nasopharyngeal Swab Among Patients Recovered From COVID-19. *Am J Prev Med* 2021;60:13–9. <https://doi.org/10.1016/j.amepre.2020.08.014>.

- [27] Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 Symptom Burden: What is Long-COVID and How Should We Manage It? *Lung* 2021;199:113–9. <https://doi.org/10.1007/s00408-021-00423-z>.
- [28] Mandal S, Barnett J, Brill SE, Brown JS, Denny EK, Hare SS, et al. “Long-COVID”: a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2021;76:396–8. <https://doi.org/10.1136/thoraxjnl-2020-215818>.
- [29] Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2021;93:1013–22. <https://doi.org/10.1002/jmv.26368>.
- [30] Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection : A Narrative Review. *Ann Intern Med* 2020;173:362–7. <https://doi.org/10.7326/M20-3012>.
- [31] Long Q-X, Tang X-J, Shi Q-L, Li Q, Deng H-J, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020;26:1200–4. <https://doi.org/10.1038/s41591-020-0965-6>.
- [32] Liu PP, Blet A, Smyth D, Li H. The Science Underlying COVID-19: Implications for the Cardiovascular System. *Circulation* 2020;142:68–78. <https://doi.org/10.1161/CIRCULATIONAHA.120.047549>.
- [33] Vittori A, Lerman J, Cascella M, Gomez-Morad AD, Marchetti G, Marinangeli F, et al. COVID-19 Pandemic Acute Respiratory Distress Syndrome Survivors: Pain After the Storm? *Anesthesia & Analgesia* 2020;131:117–9. <https://doi.org/10.1213/ane.0000000000004914>.
- [34] Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: An overview. *Diabetes Metab Syndr* 2021;15:869–75. <https://doi.org/10.1016/j.dsx.2021.04.007>.
- [35] Suárez-Reyes A, Villegas-Valverde CA. Implications of Low-grade Inflammation in SARS-CoV-2 Immunopathology. *MEDICC Rev* 2021;23:42. <https://doi.org/10.37757/MR2021.V23.N2.4>.
- [36] Kempuraj D, Selvakumar GP, Ahmed ME, Raikwar SP, Thangavel R, Khan A, et al. COVID-19, Mast Cells, Cytokine Storm, Psychological Stress, and Neuroinflammation. *Neuroscientist* 2020;26:402–14. <https://doi.org/10.1177/1073858420941476>.
- [37] Yachou Y, El Idrissi A, Belapasov V, Ait Benali S. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. *Neurol Sci* 2020;41:2657–69. <https://doi.org/10.1007/s10072-020-04575-3>.
- [38] Pinna P, Grewal P, Hall JP, Tavares T, Dafer RM, Garg R, et al. Neurological manifestations and COVID-19: Experiences from a tertiary care center at the Frontline. *J Neurol Sci* 2020;415:116969. <https://doi.org/10.1016/j.jns.2020.116969>.
- [39] Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry* 2020;7:875–82. [https://doi.org/10.1016/S2215-0366\(20\)30287-X](https://doi.org/10.1016/S2215-0366(20)30287-X).
- [40] Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* 2020;94:55–8. <https://doi.org/10.1016/j.ijid.2020.03.062>.

- [41] Lu Y, Li X, Geng D, Mei N, Wu PY, Huang CC, et al. Cerebral micro-structural changes in COVID-19 patients-an MRI-based 3-month follow-up study. *EClinicalMedicine*. 2020; 25: 100484. *EClinicalMedicine* 2020;25:100484. <https://doi.org/10.1016/j.eclinm.2020.100484>.
- [42] Wenzel J, Lampe J, Müller-Fielitz H, Schuster R, Zille M, Müller K, et al. The SARS-CoV-2 main protease M_{pro} causes microvascular brain pathology by cleaving NEMO in brain endothelial cells. *Nat Neurosci* 2021. <https://doi.org/10.1038/s41593-021-00926-1>.
- [43] Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One* 2020;15:e0240784. <https://doi.org/10.1371/journal.pone.0240784>.
- [44] Morgul E, Bener A, Atak M, Akyel S, Aktaş S, Bhugra D, et al. COVID-19 pandemic and psychological fatigue in Turkey. *Int J Soc Psychiatry* 2021;67:128–35. <https://doi.org/10.1177/0020764020941889>.
- [45] Delorme C, Paccoud O, Kas A, Hesters A, Bombois S, Shambrook P, et al. COVID-19-related encephalopathy: a case series with brain FDG-positron-emission tomography/computed tomography findings. *Eur J Neurol* 2020;27:2651–7. <https://doi.org/10.1111/ene.14478>.
- [46] Guedj E, Million M, Dudouet P, Tissot-Dupont H, Bregeon F, Cammilleri S, et al. 18F-FDG brain PET hypometabolism in post-SARS-CoV-2 infection: substrate for persistent/delayed disorders? *Eur J Nucl Med Mol Imaging* 2021;48:592–5. <https://doi.org/10.1007/s00259-020-04973-x>.
- [47] Wostyn P. COVID-19 and chronic fatigue syndrome: Is the worst yet to come? *Med Hypotheses* 2021;146:110469. <https://doi.org/10.1016/j.mehy.2020.110469>.
- [48] Ferrandi PJ, Alway SE, Mohamed JS. The interaction between SARS-CoV-2 and ACE2 may have consequences for skeletal muscle viral susceptibility and myopathies. *J Appl Physiol* 2020;129:864–7. <https://doi.org/10.1152/jappphysiol.00321.2020>.
- [49] Islam MF, Cotler J, Jason LA. Post-viral fatigue and COVID-19: lessons from past epidemics. *Fatigue: Biomedicine, Health & Behavior* 2020;8:61–9. <https://doi.org/10.1080/21641846.2020.1778227>.
- [50] Perrin R, Riste L, Hann M, Walther A, Mukherjee A, Heald A. Into the looking glass: Post-viral syndrome post COVID-19. *Med Hypotheses* 2020;144:110055. <https://doi.org/10.1016/j.mehy.2020.110055>.
- [51] Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. *BMC Neurol* 2011;11:37. <https://doi.org/10.1186/1471-2377-11-37>.
- [52] Yelland GW. Gluten-induced cognitive impairment (“brain fog”) in coeliac disease. *J Gastroenterol Hepatol* 2017;32 Suppl 1:90–3. <https://doi.org/10.1111/jgh.13706>.
- [53] Trovato CM, Raucci U, Valitutti F, Montuori M, Villa MP, Cucchiara S, et al. Neuropsychiatric manifestations in celiac disease. *Epilepsy Behav* 2019;99:106393. <https://doi.org/10.1016/j.yebeh.2019.06.036>.

- [54] Conti P, D'Ovidio C, Conti C, Gallenga CE, Lauritano D, Caraffa A, et al. Progression in migraine: Role of mast cells and pro-inflammatory and anti-inflammatory cytokines. *Eur J Pharmacol* 2019;844:87–94. <https://doi.org/10.1016/j.ejphar.2018.12.004>.
- [55] Lynall M. Neuropsychiatric symptoms in lupus. *Lupus* 2018;27:18–20. <https://doi.org/10.1177/0961203318801672>.
- [56] White M. Patient Input to Inform the Development of Central Nervous System Outcome Measures in Myotonic Dystrophy. *Ther Innov Regul Sci* 2020;54:1010–7. <https://doi.org/10.1007/s43441-020-00117-3>.
- [57] Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann Clin Transl Neurol* 2020;7:2221–30. <https://doi.org/10.1002/acn3.51210>.
- [58] Graham EL, Clark JR, Orban ZS, Lim PH, Szymanski AL, Taylor C, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 “long haulers.” *Ann Clin Transl Neurol* 2021;8:1073–85. <https://doi.org/10.1002/acn3.51350>.
- [59] Theoharides TC, Conti P. COVID-19 and Multisystem Inflammatory Syndrome, or is it Mast Cell Activation Syndrome? *J Biol Regul Homeost Agents* 2020;34:1633–6. <https://doi.org/10.23812/20-EDIT3>.
- [60] Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–16. <https://doi.org/10.1056/NEJMoa1301372>.
- [61] Paderno A, Mattavelli D, Rampinelli V, Grammatica A, Raffetti E, Tomasoni M, et al. Olfactory and Gustatory Outcomes in COVID-19: A Prospective Evaluation in Nonhospitalized Subjects. *Otolaryngol Head Neck Surg* 2020;163:1144–9. <https://doi.org/10.1177/0194599820939538>.
- [62] Otte MS, Eckel HNC, Poluschkin L, Klussmann JP, Luers JC. Olfactory dysfunction in patients after recovering from COVID-19. *Acta Otolaryngol* 2020;140:1032–5. <https://doi.org/10.1080/00016489.2020.1811999>.
- [63] Lechien JR, Chiesa-Estomba CM, De Siaty DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020;277:2251–61. <https://doi.org/10.1007/s00405-020-05965-1>.
- [64] Dutheil F, Mondillon L, Navel V. PTSD as the second tsunami of the SARS-Cov-2 pandemic. *Psychol Med* 2021;51:1773–4. <https://doi.org/10.1017/S0033291720001336>.
- [65] Shuja KH, Aqeel M, Jaffar A, Ahmed A. COVID-19 Pandemic and Impending Global Mental Health Implications. *Psychiatr Danub* 2020;32:32–5. <https://doi.org/10.24869/psyd.2020.32>.
- [66] González-Sanguino C, Ausín B, Castellanos MÁ, Saiz J, López-Gómez A, Ugidos C, et al. Mental health consequences during the initial stage of the 2020 Coronavirus pandemic (COVID-19) in Spain. *Brain Behav Immun* 2020;87:172–6. <https://doi.org/10.1016/j.bbi.2020.05.040>.
- [67] Mazza C, Ricci E, Biondi S, Colasanti M, Ferracuti S, Napoli C, et al. A Nationwide Survey of Psychological Distress among Italian People during the COVID-19 Pandemic: Immediate

- Psychological Responses and Associated Factors. *Int J Environ Res Public Health* 2020;17. <https://doi.org/10.3390/ijerph17093165>.
- [68] Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet* 2020;395:912–20. [https://doi.org/10.1016/S0140-6736\(20\)30460-8](https://doi.org/10.1016/S0140-6736(20)30460-8).
- [69] Manca R, De Marco M, Venneri A. The Impact of COVID-19 Infection and Enforced Prolonged Social Isolation on Neuropsychiatric Symptoms in Older Adults With and Without Dementia: A Review. *Front Psychiatry* 2020;11:585540. <https://doi.org/10.3389/fpsy.2020.585540>.
- [70] Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review. *Brain Behav Immun* 2021. <https://doi.org/10.1016/j.bbi.2021.07.018>.
- [71] Momtaz YA, Hamid TA, Ibrahim R. The impact of mild cognitive impairment on sexual activity. *Am J Alzheimers Dis Other Demen* 2013;28:759–62. <https://doi.org/10.1177/1533317513504612>.
- [72] Freak-Poli R, Licher S, Ryan J, Arfan Ikram M, Tiemeier H. Cognitive Impairment, Sexual Activity and Physical Tenderness in Community-Dwelling Older Adults: A Cross-Sectional Exploration. *Gerontology* 2018;64:589–602. <https://doi.org/10.1159/000490560>.
- [73] Cho JW, Duffy JF. Sleep, Sleep Disorders, and Sexual Dysfunction. *World J Mens Health* 2019;37:261–75. <https://doi.org/10.5534/wjmh.180045>.
- [74] Chao C-H, Chen H-J, Wang H-Y, Li T-C, Kao C-H. Increased risk of organic erectile dysfunction in patients with chronic fatigue syndrome: a nationwide population-based cohort study. *Andrology* 2015;3:666–71. <https://doi.org/10.1111/andr.12052>.
- [75] Jacob L, Smith L, Butler L, Barnett Y, Grabovac I, McDermott D, et al. Challenges in the Practice of Sexual Medicine in the Time of COVID-19 in the United Kingdom. *J Sex Med* 2020;17:1229–36. <https://doi.org/10.1016/j.jsxm.2020.05.001>.
- [76] Vassalini P, Serra R, Tarsitani L, Koukopoulos AE, Borrazzo C, Alessi F, et al. Depressive symptoms among individuals hospitalized with COVID-19: Three-month follow-up. *Brain Sci* 2021;11:1175. <https://doi.org/10.3390/brainsci11091175>.
- [77] Tarsitani L, Vassalini P, Koukopoulos A, Borrazzo C, Alessi F, Di Nicolantonio C, et al. Post-traumatic stress disorder among COVID-19 survivors at 3-month follow-up after hospital discharge. *J Gen Intern Med* 2021;36:1702–7. <https://doi.org/10.1007/s11606-021-06731-7>.
- [78] Naidu SB, Shah AJ, Saigal A, Smith C, Brill SE, Goldring J, et al. The high mental health burden of “Long COVID” and its association with on-going physical and respiratory symptoms in all adults discharged from hospital. *Eur Respir J* 2021;57. <https://doi.org/10.1183/13993003.04364-2020>.
- [79] Corona G, Lee DM, Forti G, O’Connor DB, Maggi M, O’Neill TW, et al. Age-related changes in general and sexual health in middle-aged and older men: results from the European Male Ageing Study (EMAS). *J Sex Med* 2010;7:1362–80. <https://doi.org/10.1111/j.1743-6109.2009.01601.x>.
- [80] Jern P, Gunst A, Sandnabba K, Santtila P. Are early and current erectile problems associated with anxiety and depression in young men? A retrospective self-report study. *J Sex Marital Ther* 2012;38:349–64. <https://doi.org/10.1080/0092623X.2012.665818>.

- [81] Mitchell KR, Mercer CH, Ploubidis GB, Jones KG, Datta J, Field N, et al. Sexual function in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). *Lancet* 2013;382:1817–29. [https://doi.org/10.1016/S0140-6736\(13\)62366-1](https://doi.org/10.1016/S0140-6736(13)62366-1).
- [82] Carvalheira A, Traeen B, Štulhofer A. Correlates of men's sexual interest: a cross-cultural study. *J Sex Med* 2014;11:154–64. <https://doi.org/10.1111/jsm.12345>.
- [83] Piontek A, Szeja J, Błachut M, Badura-Brzoza K. SEXUAL PROBLEMS IN THE PATIENTS WITH PSYCHIATRIC DISORDERS. *Wiadomości Lekarskie* 2019;72. <https://doi.org/10.36740/wlek201910125>.
- [84] Pyke RE. Sexual Performance Anxiety. *Sex Med Rev* 2020;8:183–90. <https://doi.org/10.1016/j.sxmr.2019.07.001>.
- [85] Bird ER, Piccirillo M, Garcia N, Blais R, Campbell S. Relationship Between Posttraumatic Stress Disorder and Sexual Difficulties: A Systematic Review of Veterans and Military Personnel. *J Sex Med* 2021;18:1398–426. <https://doi.org/10.1016/j.jsxm.2021.05.011>.
- [86] Alidost F, Pakzad R, Dolatian M, Abdi F. Sexual dysfunction among women of reproductive age: A systematic review and meta-analysis. *Int J Reprod Biomed* 2021;19:421–32. <https://doi.org/10.18502/ijrm.v19i5.9251>.
- [87] Mollaioli D, Sansone A, Ciocca G, Limoncin E, Colonnello E, Di Lorenzo G, et al. Benefits of Sexual Activity on Psychological, Relational, and Sexual Health During the COVID-19 Breakout. *J Sex Med* 2021;18:35–49. <https://doi.org/10.1016/j.jsxm.2020.10.008>.
- [88] Hu B, Ruan Y, Liu K, Wei X, Wu Y, Feng H, et al. A Mid-to-Long Term Comprehensive Evaluation of Psychological Distress and Erectile Function in COVID-19 Recovered Patients. *J Sex Med* 2021. <https://doi.org/10.1016/j.jsxm.2021.08.010>.
- [89] Bertolo R, Cipriani C, Bove P. Anosmia and ageusia: a piece of the puzzle in the etiology of COVID-19-related transitory erectile dysfunction. *J Endocrinol Invest* 2021;44:1123–4. <https://doi.org/10.1007/s40618-021-01516-5>.
- [90] Liang L, Yang B, Jiang N, Fu W, He X, Zhou Y, et al. Three-month Follow-up Study of Survivors of Coronavirus Disease 2019 after Discharge. *J Korean Med Sci* 2020;35:e418. <https://doi.org/10.3346/jkms.2020.35.e418>.
- [91] Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J* 2020;55. <https://doi.org/10.1183/13993003.01217-2020>.
- [92] So M, Kabata H, Fukunaga K, Takagi H, Kuno T. Radiological and functional lung sequelae of COVID-19: a systematic review and meta-analysis. *BMC Pulm Med* 2021;21:97. <https://doi.org/10.1186/s12890-021-01463-0>.
- [93] Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. *J Med Virol* 2020;92:491–4. <https://doi.org/10.1002/jmv.25709>.

- [94] Blanco J-R, Cobos-Ceballos M-J, Navarro F, Sanjoaquin I, Arnaiz de Las Revillas F, Bernal E, et al. Pulmonary long-term consequences of COVID-19 infections after hospital discharge. *Clin Microbiol Infect* 2021;27:892–6. <https://doi.org/10.1016/j.cmi.2021.02.019>.
- [95] Moodley YP, Scaffidi AK, Misso NL, Keerthisingam C, McAnulty RJ, Laurent GJ, et al. Fibroblasts isolated from normal lungs and those with idiopathic pulmonary fibrosis differ in interleukin-6/gp130-mediated cell signaling and proliferation. *Am J Pathol* 2003;163:345–54. [https://doi.org/10.1016/S0002-9440\(10\)63658-9](https://doi.org/10.1016/S0002-9440(10)63658-9).
- [96] McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM, et al. Characterization of the Inflammatory Response to Severe COVID-19 Illness. *Am J Respir Crit Care Med* 2020;202:812–21. <https://doi.org/10.1164/rccm.202005-1583OC>.
- [97] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020;383:120–8. <https://doi.org/10.1056/NEJMoa2015432>.
- [98] Wei J, Yang H, Lei P, Fan B, Qiu Y, Zeng B, et al. Analysis of thin-section CT in patients with coronavirus disease (COVID-19) after hospital discharge. *J Xray Sci Technol* 2020;28:383–9. <https://doi.org/10.3233/XST-200685>.
- [99] Liu M, Lv F, Huang Y, Xiao K. Follow-Up Study of the Chest CT Characteristics of COVID-19 Survivors Seven Months After Recovery. *Front Med* 2021;8:636298. <https://doi.org/10.3389/fmed.2021.636298>.
- [100] Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. *Radiology* 2021;299:E177–86. <https://doi.org/10.1148/radiol.2021203153>.
- [101] Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293–304. <https://doi.org/10.1056/NEJMoa1011802>.
- [102] Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview. *Infez Med* 2020;28:174–84.
- [103] Graney BA, Wamboldt FS, Baird S, Churney T, Fier K, Korn M, et al. Looking ahead and behind at supplemental oxygen: A qualitative study of patients with pulmonary fibrosis. *Heart Lung* 2017;46:387–93. <https://doi.org/10.1016/j.hrtlng.2017.07.001>.
- [104] Cavezzi A, Troiani E, Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. *Clin Pract* 2020;10:1271. <https://doi.org/10.4081/cp.2020.1271>.
- [105] Verratti V, Di Giulio C, Berardinelli F, Pellicciotta M, Di Francesco S, Iantorno R, et al. The role of hypoxia in erectile dysfunction mechanisms. *Int J Impot Res* 2007;19:496–500. <https://doi.org/10.1038/sj.ijir.3901560>.
- [106] Turan O, Ure I, Turan PA. Erectile dysfunction in COPD patients. *Chron Respir Dis* 2016;13:5–12. <https://doi.org/10.1177/1479972315619382>.

- [107] Fløe A, Hilberg O, Wijsenbeek M, Bendstrup E. Erectile dysfunction is a common problem in interstitial lung diseases. *Sarcoidosis Vasc Diffuse Lung Dis* 2017;34:356–64. <https://doi.org/10.36141/svldd.v34i4.5692>.
- [108] Goldstein I, Burnett AL, Rosen RC, Park PW, Stecher VJ. The Serendipitous Story of Sildenafil: An Unexpected Oral Therapy for Erectile Dysfunction. *Sex Med Rev* 2019;7:115–28. <https://doi.org/10.1016/j.sxmr.2018.06.005>.
- [109] Schwarz ER, Kapur V, Rodriguez J, Rastogi S, Rosanio S. The effects of chronic phosphodiesterase-5 inhibitor use on different organ systems. *Int J Impot Res* 2007;19:139–48. <https://doi.org/10.1038/sj.ijir.3901491>.
- [110] Yang H-M, Jin S, Jang H, Kim J-Y, Lee J-E, Kim J, et al. Sildenafil Reduces Neointimal Hyperplasia after Angioplasty and Inhibits Platelet Aggregation via Activation of cGMP-dependent Protein Kinase. *Sci Rep* 2019;9:7769. <https://doi.org/10.1038/s41598-019-44190-7>.
- [111] Vlachopoulos C, Ioakeimidis N, Rokkas K, Angelis A, Terentes-Printzios D, Stefanadis C, et al. Acute effect of sildenafil on inflammatory markers/mediators in patients with vasculogenic erectile dysfunction. *Int J Cardiol* 2015;182:98–101. <https://doi.org/10.1016/j.ijcard.2014.12.072>.
- [112] Duarte-Silva E, Peixoto CA. Molecular Mechanisms of Phosphodiesterase-5 Inhibitors on Neuronal Apoptosis. *DNA Cell Biol* 2018;37:861–5. <https://doi.org/10.1089/dna.2018.4410>.
- [113] Perk H, Armagan A, Naziroğlu M, Soyupek S, Hoscan MB, Sütcü R, et al. Sildenafil citrate as a phosphodiesterase inhibitor has an antioxidant effect in the blood of men. *J Clin Pharm Ther* 2008;33:635–40. <https://doi.org/10.1111/j.1365-2710.2008.00962.x>.
- [114] Isidori AM, Giannetta E, Pofi R, Venneri MA, Gianfrilli D, Campolo F, et al. Targeting the NO-cGMP-PDE5 pathway in COVID-19 infection. The DEDALO project. *Andrology* 2021;9:33–8. <https://doi.org/10.1111/andr.12837>.
- [115] Menicagli R, Limodio M, Limodio M, Casotti MT, Menicagli L. Pulmonary Covid Fibrosis a New Pharmaceutical Approach. *Int J Prev Med* 2021;12:35. https://doi.org/10.4103/ijpvm.IJPVM_462_20.
- [116] Mostafa T. Could Oral Phosphodiesterase 5 Inhibitors Have a Potential Adjuvant Role in Combating COVID-19 Infection? *Sex Med Rev* 2021;9:15–22. <https://doi.org/10.1016/j.sxmr.2020.08.006>.
- [117] Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Fors Connolly A-M. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. *Lancet* 2021;398:599–607. [https://doi.org/10.1016/S0140-6736\(21\)00896-5](https://doi.org/10.1016/S0140-6736(21)00896-5).
- [118] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417–8. [https://doi.org/10.1016/S0140-6736\(20\)30937-5](https://doi.org/10.1016/S0140-6736(20)30937-5).
- [119] Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence. *J Clin Med Res* 2020;9. <https://doi.org/10.3390/jcm9051417>.

- [120] Jung F, Krüger-Genge A, Franke RP, Hufert F, Küpper J-H. COVID-19 and the endothelium. *Clin Hemorheol Microcirc* 2020;75:7–11. <https://doi.org/10.3233/CH-209007>.
- [121] Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. *Crit Care* 2020;24:353. <https://doi.org/10.1186/s13054-020-03062-7>.
- [122] Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020;8:e46–7. [https://doi.org/10.1016/S2213-2600\(20\)30216-2](https://doi.org/10.1016/S2213-2600(20)30216-2).
- [123] Paterson I, Ramanathan K, Aurora R, Bewick D, Chow C-M, Clarke B, et al. Long COVID-19: A Primer for Cardiovascular Health Professionals, on Behalf of the CCS Rapid Response Team. *Can J Cardiol* 2021. <https://doi.org/10.1016/j.cjca.2021.05.011>.
- [124] Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, et al. Autonomic dysfunction in “long COVID”: rationale, physiology and management strategies. *Clin Med* 2021;21:e63–7. <https://doi.org/10.7861/clinmed.2020-0896>.
- [125] Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, et al. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. *JAMA Cardiol* 2020;5:1281–5. <https://doi.org/10.1001/jamacardio.2020.3551>.
- [126] Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1265–73. <https://doi.org/10.1001/jamacardio.2020.3557>.
- [127] Shoenfeld Y, Ryabkova VA, Scheibenbogen C, Brinith L, Martinez-Lavin M, Ikeda S, et al. Complex syndromes of chronic pain, fatigue and cognitive impairment linked to autoimmune dysautonomia and small fiber neuropathy. *Clin Immunol* 2020;214:108384. <https://doi.org/10.1016/j.clim.2020.108384>.
- [128] Goldstein DS. The possible association between COVID-19 and postural tachycardia syndrome. *Heart Rhythm* 2021;18:508–9. <https://doi.org/10.1016/j.hrthm.2020.12.007>.
- [129] Buoite Stella A, Furlanis G, Frezza NA, Valentinotti R, Ajcevic M, Manganotti P. Autonomic dysfunction in post-COVID patients with and without neurological symptoms: a prospective multidomain observational study. *J Neurol* 2021. <https://doi.org/10.1007/s00415-021-10735-y>.
- [130] Colonnello E, Limoncin E, Ciocca G, Sansone A, Mollaioli D, Balercia G, et al. The Lost Penis Syndrome: A New Clinical Entity in Sexual Medicine. *Sex Med Rev* 2021. <https://doi.org/10.1016/j.sxmr.2021.08.001>.
- [131] Sansone A, Mollaioli D, Ciocca G, Colonnello E, Limoncin E, Balercia G, et al. “Mask up to keep it up”: Preliminary evidence of the association between erectile dysfunction and COVID-19. *Andrology* 2021;9:1053–9. <https://doi.org/10.1111/andr.13003>.
- [132] Sansone A, Jannini EA. COVID-19 and Erectile Dysfunction: Endothelial Dysfunction and Beyond. *World J Mens Health* 2021;39. <https://doi.org/10.5534/wjmh.210081>.

- [133] Kresch E, Achua J, Saltzman R, Khodamoradi K, Arora H, Ibrahim E, et al. COVID-19 Endothelial Dysfunction Can Cause Erectile Dysfunction: Histopathological, Immunohistochemical, and Ultrastructural Study of the Human Penis. *World J Mens Health* 2021;39:466–9. <https://doi.org/10.5534/wjmh.210055>.
- [134] Pedersen SF, Ho Y-C. SARS-CoV-2: a storm is raging. *J Clin Invest* 2020;130:2202–5. <https://doi.org/10.1172/JCI137647>.
- [135] Maiorino MI, Bellastella G, Giugliano D, Esposito K. From inflammation to sexual dysfunctions: a journey through diabetes, obesity, and metabolic syndrome. *J Endocrinol Invest* 2018;41:1249–58. <https://doi.org/10.1007/s40618-018-0872-6>.
- [136] Hellerstein HK, Friedman EH. Sexual activity and the postcoronary patient. *Arch Intern Med* 1970;125:987–99.
- [137] Grossman VGA, McGowan BA. Postural orthostatic tachycardia syndrome. *Am J Nurs* 2008;108:58–60. <https://doi.org/10.1097/01.NAJ.0000330266.83852.96>.
- [138] Benrud-Larson LM, Dewar MS, Sandroni P, Rummans TA, Haythornthwaite JA, Low PA. Quality of life in patients with postural tachycardia syndrome. *Mayo Clin Proc* 2002;77:531–7. <https://doi.org/10.4065/77.6.531>.
- [139] Benrud-Larson LM, Sandroni P, Haythornthwaite JA, Rummans TA, Low PA. Correlates of functional disability in patients with postural tachycardia syndrome: preliminary cross-sectional findings. *Health Psychol* 2003;22:643–8. <https://doi.org/10.1037/0278-6133.22.6.643>.
- [140] Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, et al. Erectile dysfunction. *Nat Rev Dis Primers* 2016;2:16003. <https://doi.org/10.1038/nrdp.2016.3>.
- [141] Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–7. <https://doi.org/10.1002/path.1570>.
- [142] Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* 2020;63:1500–15. <https://doi.org/10.1007/s00125-020-05180-x>.
- [143] Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020;8:782–92. [https://doi.org/10.1016/S2213-8587\(20\)30238-2](https://doi.org/10.1016/S2213-8587(20)30238-2).
- [144] Han T, Kang J, Li G, Ge J, Gu J. Analysis of 2019-nCoV receptor ACE2 expression in different tissues and its significance study. *Ann Transl Med* 2020;8:1077. <https://doi.org/10.21037/atm-20-4281>.
- [145] Frara S, Allora A, Castellino L, di Filippo L, Loli P, Giustina A. COVID-19 and the pituitary. *Pituitary* 2021;24:465–81. <https://doi.org/10.1007/s11102-021-01148-1>.
- [146] Douglas GC, O'Bryan MK, Hedger MP, Lee DKL, Yarski MA, Smith AI, et al. The novel angiotensin-converting enzyme (ACE) homolog, ACE2, is selectively expressed by adult Leydig cells of the testis. *Endocrinology* 2004;145:4703–11. <https://doi.org/10.1210/en.2004-0443>.

- [147] Wang Z, Xu X. scRNA-seq Profiling of Human Testes Reveals the Presence of the ACE2 Receptor, A Target for SARS-CoV-2 Infection in Spermatogonia, Leydig and Sertoli Cells. *Cells* 2020;9. <https://doi.org/10.3390/cells9040920>.
- [148] Yang M, Chen S, Huang B, Zhong J-M, Su H, Chen Y-J, et al. Pathological Findings in the Testes of COVID-19 Patients: Clinical Implications. *Eur Urol Focus* 2020;6:1124–9. <https://doi.org/10.1016/j.euf.2020.05.009>.
- [149] Rastrelli G, Di Stasi V, Inglese F, Beccaria M, Garuti M, Di Costanzo D, et al. Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. *Andrology* 2021;9:88–98. <https://doi.org/10.1111/andr.12821>.
- [150] Isidori AM, Buvat J, Corona G, Goldstein I, Jannini EA, Lenzi A, et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review. *Eur Urol* 2014;65:99–112. <https://doi.org/10.1016/j.eururo.2013.08.048>.
- [151] Corona G, Baldi E, Isidori AM, Paoli D, Pallotti F, De Santis L, et al. SARS-CoV-2 infection, male fertility and sperm cryopreservation: a position statement of the Italian Society of Andrology and Sexual Medicine (SIAMS) (Società Italiana di Andrologia e Medicina della Sessualità). *J Endocrinol Invest* 2020;43:1153–7. <https://doi.org/10.1007/s40618-020-01290-w>.
- [152] Paoli D, Pallotti F, Turriziani O, Mazzuti L, Antonelli G, Lenzi A, et al. SARS-CoV-2 presence in seminal fluid: Myth or reality. *Andrology* 2021;9:23–6. <https://doi.org/10.1111/andr.12825>.
- [153] Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, et al. SARS-CoV-2-related atypical thyroiditis. *Lancet Diabetes Endocrinol* 2020;8:739–41. [https://doi.org/10.1016/S2213-8587\(20\)30266-7](https://doi.org/10.1016/S2213-8587(20)30266-7).
- [154] Mattar SAM, Koh SJQ, Rama Chandran S, Cherng BPZ. Subacute thyroiditis associated with COVID-19. *BMJ Case Rep* 2020;13. <https://doi.org/10.1136/bcr-2020-237336>.
- [155] Ippolito S, Dentali F, Tanda ML. SARS-CoV-2: a potential trigger for subacute thyroiditis? Insights from a case report. *J Endocrinol Invest* 2020;43:1171–2. <https://doi.org/10.1007/s40618-020-01312-7>.
- [156] Pizzocaro A, Colombo P, Vena W, Ariano S, Magnoni P, Reggiani F, et al. Outcome of Sars-COV-2-related thyrotoxicosis in survivors of Covid-19: a prospective study. *Endocrine* 2021;73:255–60. <https://doi.org/10.1007/s12020-021-02758-2>.
- [157] Frara S, Loli P, Allora A, Santini C, di Filippo L, Mortini P, et al. COVID-19 and hypopituitarism. *Rev Endocr Metab Disord* 2021. <https://doi.org/10.1007/s11154-021-09672-y>.
- [158] Chigr F, Merzouki M, Najimi M. Autonomic Brain Centers and Pathophysiology of COVID-19. *ACS Chem Neurosci* 2020;11:1520–2. <https://doi.org/10.1021/acscchemneuro.0c00265>.
- [159] Marchand L, Pecquet M, Luyton C. Type 1 diabetes onset triggered by COVID-19. *Acta Diabetol* 2020;57:1265–6. <https://doi.org/10.1007/s00592-020-01570-0>.
- [160] Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. *Diabetes Metab Res Rev* 2020:e33213321. <https://doi.org/10.1002/dmrr.3321>.

- [161] Hayden MR. An Immediate and Long-Term Complication of COVID-19 May Be Type 2 Diabetes Mellitus: The Central Role of β -Cell Dysfunction, Apoptosis and Exploration of Possible Mechanisms. *Cells* 2020;9. <https://doi.org/10.3390/cells9112475>.
- [162] Sansone A, Romanelli F, Gianfrilli D, Lenzi A. Endocrine evaluation of erectile dysfunction. *Endocrine* 2014;46:423–30. <https://doi.org/10.1007/s12020-014-0254-6>.
- [163] Sansone A, Romanelli F, Jannini EA, Lenzi A. Hormonal correlations of premature ejaculation. *Endocrine* 2015;49:333–8. <https://doi.org/10.1007/s12020-014-0520-7>.
- [164] Carosa E, Sansone A, Jannini EA. MANAGEMENT OF ENDOCRINE DISEASE: Female sexual dysfunction for the endocrinologist. *Eur J Endocrinol* 2020;182:R101. <https://doi.org/10.1530/EJE-19-0903>.
- [165] Sansone A, Aversa A, Corona G, Fisher AD, Isidori AM, La Vignera S, et al. Management of premature ejaculation: a clinical guideline from the Italian Society of Andrology and Sexual Medicine (SIAMS). *J Endocrinol Invest* 2021;44:1103–18. <https://doi.org/10.1007/s40618-020-01458-4>.
- [166] Moreno-Perez O, Merino E, Alfayate R, Torregrosa ME, Andres M, Leon-Ramirez J-M, et al. Male pituitary-gonadal axis dysfunction in post-acute COVID-19 syndrome-Prevalence and associated factors: A Mediterranean case series. *Clin Endocrinol* 2021. <https://doi.org/10.1111/cen.14537>.
- [167] Dhindsa S, Zhang N, McPhaul MJ, Wu Z, Ghoshal AK, Erlich EC, et al. Association of Circulating Sex Hormones With Inflammation and Disease Severity in Patients With COVID-19. *JAMA Netw Open* 2021;4:e2111398. <https://doi.org/10.1001/jamanetworkopen.2021.11398>.
- [168] Shindel AW, Lue TF. Sexual Dysfunction in Diabetes. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al., editors. *Endotext*, South Dartmouth (MA): MDText.com, Inc.; 2021.
- [169] Sansone A, Mollaioli D, Ciocca G, Limoncin E, Colonnello E, Jannini EA. Sexual dysfunction in men and women with diabetes: a mirror of their complications? *Curr Diabetes Rev* 2021;17. <https://doi.org/10.2174/1573399817666210309104740>.
- [170] Allen MS, Walter EE. Health-Related Lifestyle Factors and Sexual Dysfunction: A Meta-Analysis of Population-Based Research. *J Sex Med* 2018;15:458–75. <https://doi.org/10.1016/j.jsxm.2018.02.008>.
- [171] Haider KS, Haider A, Saad F, Doros G, Hanefeld M, Dhindsa S, et al. Remission of type 2 diabetes following long-term treatment with injectable testosterone undecanoate in patients with hypogonadism and type 2 diabetes: 11-year data from a real-world registry study. *Diabetes Obes Metab* 2020. <https://doi.org/10.1111/dom.14122>.
- [172] Grossmann M. Hypogonadism and male obesity: Focus on unresolved questions. *Clin Endocrinol* 2018;89:11–21. <https://doi.org/10.1111/cen.13723>.
- [173] Luca G, Parrettini S, Sansone A, Calafiore R, Jannini EA. The Inferto-Sex Syndrome (ISS): sexual dysfunction in fertility care setting and assisted reproduction. *J Endocrinol Invest* 2021;44:2071–102. <https://doi.org/10.1007/s40618-021-01581-w>.

- [174] Nicola M, Alsafi Z, Sohrabi C, Kerwan A, Al-Jabir A, Iosifidis C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. *Int J Surg* 2020;78:185–93. <https://doi.org/10.1016/j.ijisu.2020.04.018>.
- [175] Czeisler MÉ, Marynak K, Clarke KEN, Salah Z, Shakya I, Thierry JM, et al. Delay or Avoidance of Medical Care Because of COVID-19-Related Concerns - United States, June 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1250–7. <https://doi.org/10.15585/mmwr.mm6936a4>.
- [176] Cheng SO. Xenophobia due to the coronavirus outbreak - A letter to the editor in response to “the socio-economic implications of the coronavirus pandemic (COVID-19): A review.” *Int J Surg* 2020;79:13–4. <https://doi.org/10.1016/j.ijisu.2020.05.017>.
- [177] UNESCO. Education: From disruption to recovery 2020. <https://en.unesco.org/covid19/educationresponse> (accessed September 6, 2021).
- [178] Burdorf A, Porru F, Rugulies R. The COVID-19 pandemic: one year later - an occupational perspective. *Scand J Work Environ Health* 2021;47:245–7. <https://doi.org/10.5271/sjweh.3956>.
- [179] Meyer B, Zill A, Dilba D, Gerlach R, Schumann S. Employee psychological well-being during the COVID-19 pandemic in Germany: A longitudinal study of demands, resources, and exhaustion. *Int J Psychol* 2021;56:532–50. <https://doi.org/10.1002/ijop.12743>.
- [180] Gibbs BB, Barone Gibbs B, Kline CE, Huber KA, Paley JL, Perera S. Covid-19 shelter-at-home and work, lifestyle and well-being in desk workers. *Occupational Medicine* 2021;71:86–94. <https://doi.org/10.1093/occmed/kqab011>.
- [181] Panuganti S, Dhanji S, Wang R. Erosion of inflatable penile prosthesis with prolonged Foley catheterization in the COVID-19 era. *Sex Med* 2021;9:100371. <https://doi.org/10.1016/j.esxm.2021.100371>.
- [182] Agochukwu-Mmonu N, Fendrick AM. The Economics of Viagra Revisited: The Price Is Right. *Urology* 2021. <https://doi.org/10.1016/j.urology.2021.05.037>.
- [183] Capogrosso P, Ventimiglia E, Boeri L, Capitanio U, Gandaglia G, Dehò F, et al. Sexual functioning mirrors overall men’s health status, even irrespective of cardiovascular risk factors. *Andrology* 2017;5:63–9. <https://doi.org/10.1111/andr.12299>.
- [184] Kloner RA. Erectile dysfunction as a predictor of cardiovascular disease. *Int J Impot Res* 2008;20:460–5. <https://doi.org/10.1038/ijir.2008.20>.
- [185] Dong J-Y, Zhang Y-H, Qin L-Q. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. *J Am Coll Cardiol* 2011;58:1378–85. <https://doi.org/10.1016/j.jacc.2011.06.024>.
- [186] Hsieh T-C, Edwards NC, Bhattacharyya SK, Nitschelm KD, Burnett AL. The epidemic of COVID-19-related erectile dysfunction: A scoping review and health care perspective. *Sex Med Rev* 2021. <https://doi.org/10.1016/j.sxmr.2021.09.002>.
- [187] Adams SH, Schaub JP, Nagata JM, Park MJ, Brindis CD, Irwin CE Jr. Young adult perspectives on COVID-19 vaccinations. *J Adolesc Health* 2021;69:511–4. <https://doi.org/10.1016/j.jadohealth.2021.06.003>.

- [188] Ainslie D, Ogwuru C, Sinclair R. Coronavirus and vaccine hesitancy, Great Britain - Office for National Statistics 2021. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandwellbeing/bulletins/coronavirusandvaccinehesitancygreatbritain/9august2021> (accessed October 4, 2021).
- [189] Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49:822–30. [https://doi.org/10.1016/s0090-4295\(97\)00238-0](https://doi.org/10.1016/s0090-4295(97)00238-0).
- [190] Corona G, Jannini EA, Maggi M. Inventories for male and female sexual dysfunctions. *Int J Impot Res* 2006;18:236–50. <https://doi.org/10.1038/sj.ijir.3901410>.
- [191] Salonia A, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC, et al. European Association of Urology Guidelines on Sexual and Reproductive Health-2021 Update: Male Sexual Dysfunction. *Eur Urol* 2021;80:333–57. <https://doi.org/10.1016/j.eururo.2021.06.007>.

Figure captions

Figure 1. The pathophysiology of erectile dysfunction in long COVID: mechanisms and progression.

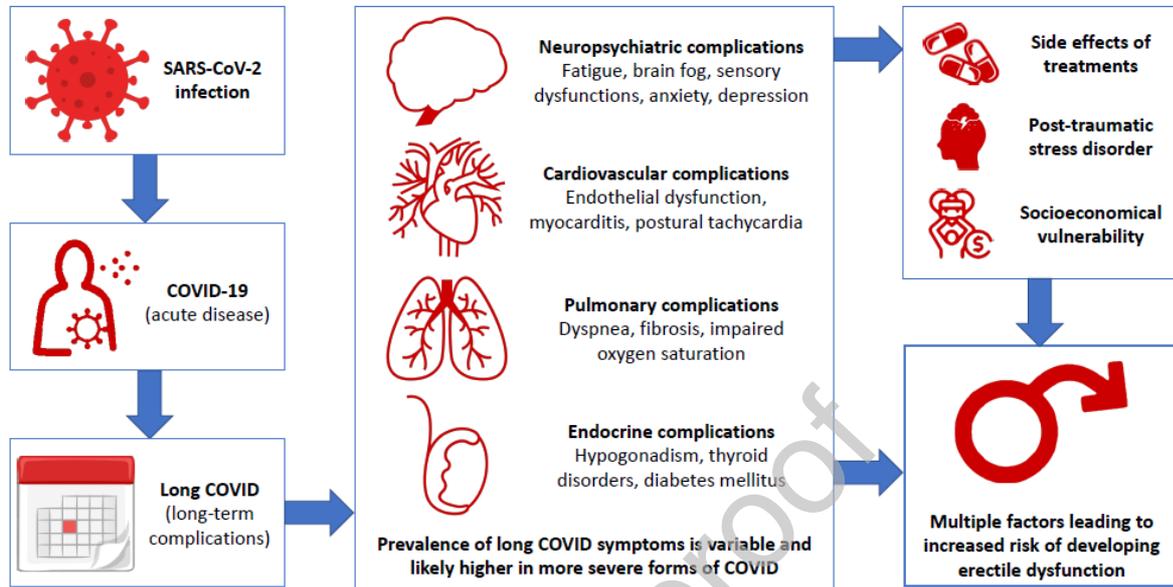


Figure 2. The Sexual Long COVID (SLC) as a clinical biomarker of complications of long COVID.

