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COVID's Impact on Non-communicable Diseases: What We Do Not Know May Hurt Us

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Abstract

Purpose ofReview In this review, we outline the impacts of the COVID-19 pandemic on non-communicable diseases around the world.

Recent Findings The mechanisms of COVID-19's impact on non-communicable diseases are both direct and indirect. The direct mechanisms include direct vascular and myocardial injury as well as pancreatic injury increasing incidence of new-onset diabetes. Indirect effects of the pandemic on non-communicable disease include delayed presentation for acute illness including STEMI and the impact of social distancing and quarantine policies on socialization, mental health, physical activity, and the downstream health impacts of inactivity and deconditioning.

Summary International focus has been on disease variants, infection control and management, healthcare system, and resource utilization and infection incidence. However, the impact of this pandemic on non-communicable diseases has been largely overlooked but will manifest itself in the coming years to decades.

Keywords COVID-19 · Coronavirus · Sars-CoV-2 · Pandemic · Non-communicable · Cardiac

Introduction

In December of 2019, initial reports emerged of a novel coronavirus outbreak in Wuhan, China, and declarations of public health emergency and pandemic were quickly issued by the WHO [1]. Since that time, the SARS-CoV-2 virus (COVID-19) has caused confirmed infections in over 296,496,809 people and is responsible for an estimated 5,462,631 deaths as of January 6, 2022 [2]. The virus has evolved rapidly since then with the emergence of multiple distinct variants which have posed novel diagnostic, clinical, and therapeutic challenges. The relatively accelerated evolutionary pattern may have occurred in response to incomplete vaccination uptake, with susceptible hosts providing a substrate for genetic adaptation. Regardless of the etiology, these variants have made the possibility of eradicating the virus altogether no longer a feasible goal. Instead, endemicity is much more likely the expected outcome of this pandemic. However, the effects of the COVID-19 pandemic and its endemicity are likely long-lasting with respect to non-communicable disease, even though the index illness was a communicable disease. The multiple curves of the pandemic, some of which are long-lasting and likely to manifest after years or decades, have been previously described [3]. As the shift occurs from pandemic to endemic, the next curve to flatten from an epidemiologic perspective will be the "neglected chronic conditions" curve, which comprises of cardiovascular co-morbidities such as hypertension, diabetes, obesity, sleep apnea, and hyperlipidemia but also non-cardiovascular conditions such as cancer screening and early diagnosis. Following this, the "mental health and economic burden" curves will manifest. The mechanisms of these long-lasting curves are a result of both direct and indirect

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effects and will be important to consider when formulating a plan to attenuate and flatten the peaks of these curves. Therefore, careful attention to "what we don't know" today is a critical component to address to minimize the collateral damage from the pandemic tomorrow and for decades to come.

Cardiovascular Comorbidities and Adverse Outcomes with COVID Infection

In the body of knowledge that has emerged since the onset of the COVID-19 pandemic, researchers have identified the characteristics and comorbidities associated with infection and poor outcomes. Meta-analyses have demonstrated significant increased risk of mortality (OR 3.36) in patients with hypertension compared to normotensive subjects [4]. Non-communicable diseases are associated with significantly poorer outcomes in the event of COVID-19 infection, marking those with pre-existing non-communicable diseases as particularly high risk from COVID-19 infection and as COVID-19 survivors. A case series of 5,700 patients found that hypertension (56.6%), obesity (41.7%), and diabetes (33.8%) were the most common comorbidities in patients with COVID-19 requiring hospitalization [5]. Not only do these patients with such pre-existing conditions do worse in the acute phase of the infection, their long-term outcomes will likely also be impacted through indirect mechanisms such as impaired chronic disease management and limited access to care during the pandemic.

Worldwide Impact on Non-communicable Cardiovascular Diseases

Heart Disease

The relationship between comorbid conditions and risk of COVID-19 infection as well as adverse outcomes in those with cardiovascular disease is clear. Cardiovascular diseases are the leading cause of death worldwide. According to the WHO, over 38% of premature deaths (defined as deaths under the age of 70 years) from non-communicable diseases were caused by cardiovascular diseases such as coronary artery disease, stroke, peripheral artery disease, congenital heart disease, and venous thromboembolic events [6].

Most cardiovascular disease, particularly coronary disease and stroke, are strongly impacted by behavioral and lifestyle risk factors, as well as comorbid conditions such as hypertension, diabetes mellitus, and obesity. The WHO estimates that 1.13 billion people worldwide have hypertension, 422 million people have diabetes, and 650 million people are obese [7–10]. An additional 1.9 billion people are overweight and at risk for excess weight-associated medical comorbidities [10]. This puts a large proportion of the global population at higher risk for COVID-19 with poorer prognosis, if infected. The impact of COVID-19 infection on the future prevalence of these conditions is something that only time will tell but by virtue of its mechanism of direct endothelial inflammation, COVID-19 infection may impose increased long-term atherosclerotic cardiovascular disease (ASCVD) risk in COVID survivors through the direct mechanisms of vascular and myocardial inflammation. A recent retrospective analysis by Xie et al. of 153,760 US veterans who survived the first 30 days of COVID-19 infection found that they had increased risk of stroke (HR 1.52), TIA (HR 1.49), and atrial fibrillation (HR 1.71), as well as other vascular and cardiac complications when compared to contemporary and historical cohorts who did not have COVID-19 [11].

COVID19: Mechanisms of Impact on Non-communicable Diseases in COVID-19 survivors

Vascular Inflammation

The COVID-19 virus utilizes the membrane-bound form of angiotensin-converting enzyme 2 (ACE2) to facilitate entry to host cells via the spike protein expressed in the viral coat [12, 13]. ACE2 is expressed in all tissues but is particularly upregulated on the surface of endothelial cells in the lung, heart (particularly cardiac pericytes), kidney, and intestine, putting these cells at highest risk from COVID-19 infection [12, 13]. Following infection with COVID-19 virus, endothelial cells become activated and dysfunctional leading to increased levels of pro-inflammatory cytokines, von Willebrand factor (vWF), clotting factor levels, and acute phase reactants including D-dimer, resulting in endotheliitis [14]. Retrospective data has shown that compared to cohorts who did not have COVID, even 30-day survivors of COVID had an increased risk of pulmonary embolism (HR 2.93) and deep vein thrombosis (HR 2.09) [11].

Myocardial Inflammation and Injury

Viral infections have long been known to be a leading cause of myocarditis. Since the onset of the COVID-19 pandemic, the virus association with myocardial inflammation and myocarditis has been readily observed. A systematic review including 374 patients demonstrated that compared to patients with non-severe COVID-19 infections, patients with severe COVID-19 had significantly higher cardiac troponin I levels (OR 25.6, 95% CI 6.8–44.5) [15]. Retrospective data published early in the pandemic in Wuhan, China, found that

high-sensitivity cardiac troponin I levels were elevated in over half of patients with acute COVID-19 that did not survive the infection [16]. A study of COVID-19 patients recovered from COVID-19 infection revealed persistent cardiac involvement at a median of 71 days after diagnosis in 78% of patient and ongoing myocardial inflammation in 60%, independent of co-morbidities, severity of index illness, and time from diagnosis [17]. The previously highlighted study of US veterans compared to contemporary and historical cohorts by Xie et al. found that COVID-19 was associated with a fivefold increased risk of myocarditis (HR 5.38) [11].

Even mild to moderate COVID-19 illness in non-hospitalized outpatients was associated with reduction in left and right ventricular systolic function and increases in troponin and natriuretic peptides, as well as aberration of physiology of multiple other organ systems. These included worsening respiratory mechanics (decreased lung volumes and increased airway resistance), decrements in glomerular filtration rate, and increase in deep venous thrombosis risk [18].

Despite the early identification of cardiac inflammation in patients with COVID-19, the mechanism of the inflammation as well as its impact on long-term prognosis and disease management remains controversial. Multiple mechanisms have been proposed, ranging from endotheliitis and microvascular disease leading to myocardial dysfunction to cytokine-induced myocarditis from diffuse cardiac inflammation. Regardless, however, the cardiovascular clinician may have to intensify efforts at clinical cardiovascular screening and risk assessment in COVID-19 survivors to diagnose and manage subclinical organ dysfunction in this patient population early.

Diabetes Control and Incidence

The association between diabetes mellitus and poorer outcomes following COVID-19 infection [19] has highlighted the impact on inpatient management of diabetes. However, on a population level, the impact of the pandemic, its associated lockdowns, and restrictions on diabetes are more complex. A recent meta-analysis found that glycemic control during the COVID-19 pandemic significantly improved in participants with type 1 diabetes with marginal improvement in A1c and time in goal glycemic range [20]. Alternatively, participants with type 2 diabetes had short-term worsening in glycemic control with a statistically significant increase in A1c (+0.14) [20]. There is even evidence of direct pancreatic injury in COVID-19 survivors [21]. Patients under the age of 18 years have been found more likely to be diagnosed with diabetes over 30 days after COVID-19 infection than patients without COVID-19 or participants with acute respiratory infections predating COVID-19 [21]. The long-term consequences of these observed impacts on glycemic control in type 2 diabetics and in survivors of COVID-19 increase the risk of hyperglycemia-associated morbidity. Further data is needed to guide the clinical management of diabetes control and secondary organ dysfunction during and following the pandemic.

Obesity

Emerging evidence that COVID triggers inflammation in adipose tissue may explain the adverse outcome observed with COVID-19 during acute infection but may also pose a higher risk of Long-COVID in patients who are obese [22], alerting the cardiovascular clinician to screen for and manage more aggressively for Long-COVID in this patient population. Whether weight loss is associated with a reversal of this increased risk remains to be seen.

Long-COVID

Throughout the COVID-19 pandemic, clinicians worldwide have noticed the emergence of a patient subset has persistent symptoms after their acute infection with the virus. A broad range of symptoms have been described in survivors and have involved several biologic systems including cardiopulmonary (e.g., chest pain, dyspnea, arrhythmias), neurologic, psychiatric, musculoskeletal (e.g., arthralgias and muscle weakness), and generalized symptoms such as fatigue [23••]. The names for this subset of patients have varied in scientific literature, convention, and social media, including "long-haulers," "post-COVID syndrome," and "Long-COVID" [24]. This has left the medical community without clear diagnostic criteria for diagnosis, monitoring, and management. The National Institute for Health and Care Excellence in the UK defines "Long COVID" as ongoing symptomatic COVID-19 with symptoms between 4 and 12 weeks and distinguishes it from post-COVID syndrome in which symptoms persist beyond 12 weeks [24]. Long COVID was solidified as a diagnosis with the issue of an ICD-10 code by the Centers for Disease Control and Prevention [25].

The mechanism for Long-COVID remains unclear, though it is thought to be multifactorial [23••]. Several studies following patients in the 2-to-6-month period following acute COVID-19 infection found the commonly reported symptom is dyspnea [26, 27, 28••, 29]. Chest pain is also reported in a significant subset of long-COVID patients, up to 18% of survivors at 30 days [29]; in a different study, chest pain was reported in 21% of survivors at 60 days post-diagnosis [28••]. It has been theorized that the etiology of long-COVID may be related to persistent inflammatory state [23••, 30] although exact pathophysiologic mechanisms are unknown. Therapies for long-COVID are also limited at this time. However, with an increasing proportion of the population testing positive and becoming COVID survivors,

especially in the wake of the recent Omicron variant, long-COVID may have a substantial public health impact.

Deconditioning Risk in COVID-19 Survivors

Patients infected with COVID-19 may also suffer loss of physical strength and independence. Prolonged periods of bed rest are associated with loss of lean leg mass suggesting that muscle disuse contributes to loss of muscle mass [31]. This risk is likely higher in patients requiring inpatient admission for COVID-19. Even if not critically ill, decreased mobility during inpatient hospitalization is associated with decline in activities of daily living, new institutionalization, and death in elderly patients [32]. Patients with communicable diseases are at particularly high risk due to isolation orders and movement restrictions to limit disease spread. Multiple mechanisms have been proposed for the development of acute illness-related sarcopenia including oxidative stress, muscle disuse, and elevated cortisol levels mediating protein catabolism [33, 34]. Regardless of the mechanism, patients hospitalized with COVID-19 who survive their hospitalization have low levels of physical functioning and impaired activity of daily living performance [35]. The therapies used to treat COVID-19 can also impact conditioning and increase the risk of severe muscle insufficiency, known as sarcopenia [36]. Dexamethasone was found to confer a survival benefit in COVID-19 in the RECOVERY trial; however, elevated iatrogenic hypercortisolism can further increase the risk of muscle loss with bedrest [37, 38].

Patients who suffer a significant functional decline often require transition to rehabilitation facilities to regain mobility and independence before they can return to their prior living situation. Long-term care facilities and nursing homes have been particularly impacted by the pandemic in part because patients at these facilities are often high risk due to age and comorbidities and due to physical proximity of staff and patients. It remains unclear how the pandemic has impacted the efficacy of the outpatient recovery process; however, social distancing recommendations limit group rehabilitation and exercise programs often utilized by these facilities.

COVID19: Mechanisms of Indirect Impact on Non-communicable Diseases in General Population (Non-survivors)

Hypertension Control

Primary hypertension was the leading cause of death and disability-adjusted life-years worldwide in 2010 [39]. Observational data has demonstrated that elevated blood pressure was associated with increased risk of cardiovascular disease, heart failure, stroke, and peripheral arterial disease [40]. A recent population study evaluating blood pressure control during the COVID-19 pandemic among 464,585 middle-aged participants in the USA demonstrated increased annual blood pressure from April to December 2020 compared to 2019 [41]. The same study demonstrated higher systolic and diastolic blood pressure elevations in women than in men. Older patients were found to have larger increases in systolic blood pressure, while younger participants had elevations in diastolic blood pressure [41]. While the elevations observed in this study were relatively small in magnitude with mean monthly changes in blood pressure ranging from 1.10 to 2.50 mmHg systolic and 0.14 to 0.53 mmHg diastolic, the long-term consequences of such a trend on the population could be significant. As noted by the authors, as little as a 2 mmHg elevation in systolic blood pressure has been associated with increased mortality from heart disease and stroke [42].

Stress-Induced Cardiomyopathy

As a result of the psychological, social, and economic stress during the early phases of the pandemic, there was a significant increase in incidence of stress cardiomyopathy observed during the COVID-19 pandemic to 7.8% compared with pre-pandemic levels of 1.5 to 1.8% from data published in July 2020 [43]. Although the prognosis of this condition is generally favorable with recovery of left ventricular function, the long-term impact on recurrence and future incidence of this condition could be lingering long after the acute infectious phase has resolved.

Inactivity and Deconditioning

Many nations had adopted social distancing recommendations and travel restrictions to limit population interaction and control viral spread. These isolation policies are not without unintended consequences, however, and led to unexpected impacts on socialization, emotional and mental health, and physical activity. The 2020 descriptive study by Tison et al. used data from a free smartphone app that tracked the daily step counts of over 450,000 unique users during the first 6 months of the COVID-19 pandemic [44]. Worldwide, they found that within 10 days of the pandemic declaration, mean daily steps decreased by 5.5%; within 30 days, daily steps had decreased 27%, though there were large differences between countries [44]. Elderly patients, who are the most vulnerable to these unintended consequences, were among those most impacted [45]. The positive effect of exercise on multiple cardiovascular risk factors and disease processes is well documented. Leisure running has been shown to reduce risk of all-cause and cardiovascular mortality [46]. In patients with stable coronary disease,

increased habitual exercise conferred a mortality decrease [47]. Exercise has even been demonstrated to attenuate disease progression in stable coronary disease [48]. The benefits of physical activity are not limited to coronary disease; individuals with increased level of physical activity had lower rates of hospitalization for heart failure [49]. Conversely, there is a deleterious association between sedentary lifestyles and morbidity and mortality from cardiovascular disease [50]. Considering these findings, the COVID-19 pandemic and the associated social distancing precautions on individual and population physical activity may have a profound impact on future incidence of cardiovascular diseases.

Social Isolation and Mental Health Impact

In addition to cardiovascular disease impact, social isolation can also affect mental well-being. Data from the United States Census Bureau's Household Pulse Survey demonstrated a 30% increase in prevalence of anxiety or depressive disorder symptoms from early-to-mid 2019 to January 2021, suggesting that one in four US adults has experienced symptoms of anxiety or depression during the pandemic [51]. In the USA, minority ethnic groups have been disproportionately impacted by the pandemic with up to 46% of Hispanic/Latino adults and 48% of non-Hispanic Black adults reporting symptoms of depression or anxiety when compared to non-Hispanic White adults (41%) [51]. Another group disproportionately impacted by the COVID-19 pandemic has been those designated "essential workers" who were 12% more likely than "non-essential workers" to report symptoms of anxiety or depression, 14% more likely to report suicidal thoughts, and 14% more likely to report increased or starting substance use [51].

Substance Use

These mental health and behavioral effects have further implications for mitigating the spread of the COVID-19 virus; clinical, psychosocial, and psychological factors make individuals with substance use disorders at higher risk for contracting viral infections [52]. The increased emotional stress related to the pandemic may also trigger substance use relapse [53]. Prior studies of treatment-engaged, abstinent alcohol-dependent patients compared to social drinkers demonstrated increased stress responses in alcohol-dependent patients following stress and alcohol cue exposure [54]. In the case of people who use illicit opioids, there is also evidence that they have a disproportionately increased burden of respiratory diseases [55], which could further increase their morbidity and mortality if infected with COVID-19. Populations with a high incidence of substance use such as incarcerated people, those suffering from homelessness or seeking treatment at addiction treatment facilities, may be limited in their ability to socially distance, putting them at increased risk of infection [53].

Dietary Habits and Food Access

Access to balanced food sources and non-processed foods is a component of cardiovascular health with higher consumption of ultra-processed foods being associated with higher risks of cardiovascular, coronary, and cerebrovascular disease [56]. Within urban areas in the USA, there are regions without access to stores providing fresh produce or unprocessed foodstuffs that asymmetrically impact low-income populations, the so-called "food deserts" [57]. In the USA, increased distance to grocery stores and food prices were positively associated with obesity [58]. Living in a food desert has also been linked to cardiovascular health problems, particularly among the lowest socioeconomic classes [59].

Access to vital goods can also be limited by financial barriers, a challenge being faced by many due to the economic impacts of the virus on global trade and various industries. In the developing world, these challenges can be exaggerated by limited governmental resources, supply chain interruptions, and markets remaining high traffic areas that can increase viral exposure. Social distancing and supply chain disruptions can have a profound impact on people's shopping habits and access to foods. Even in developed countries, COVID-19 lockdown measures have impacted dietary choices. In a study in the Netherlands, participants who were obese or overweight were more likely to eat less healthy foods than participants with a normal weight (OR 4.21, 95% CI 2.13–8.32 and OR 2.26, 95% CI 1.24–4.11, respectively) [60]. While the study found that overall, daily dietary routines persisted despite lockdown measures and social distancing, socio-demographic differences were observed in participants who reported significant changes to their diet [60]. Similar studies have been performed in the USA where several groups found that participants reported low levels of food security early in the pandemic, with as many as 44% of low-income US adults reporting food insecurity [61, 62]. A study by Bin Zarah et al. observed participants reporting high food security despite COVID-19's impact on job loss and the rise in the consumer price index of food [63]. While the long-term impact of the pandemic on food security, eating habits, and downstream health effects may not be known, it is clear that COVID-19 may be contributing to widening health disparities.

Healthcare Access and Delivery

Healthcare delivery systems have had to adapt to the various stresses that the COVID-19 pandemic has placed on

national health centers and healthcare systems. Several variables have contributed to care delivery challenges including social distancing guidelines, patient illness and quarantine, limited hospital resources, missed appointments, and staffing shortages within health systems due to burnout, illness, or post-exposure quarantine. One advent of these limitations has been the adoption of telehealth visits for outpatient care. Some institutions have gone further, incorporating telehealth for inpatient and ICU care to minimize staff exposure. Despite the readily available technology for telehealth in developed countries, its utilization has historically been slow in the USA, likely because of billing and reimbursement barriers. The increased adoption of telehealth has the potential to close gaps in healthcare disparities both during the pandemic and beyond. Unfortunately, given the need for internet access and often high-speed internet for video telehealth, the increased adoption of telehealth has the potential to widen healthcare disparities as well. A recent study by Jain et al. looked at data from 2016 to 2017 CDC survey data and found that the prevalence of internet use was 84% in the studied population but only 72% among those with hypertension or diabetes [64]. They also found that frequent internet users were more likely to be educated, younger, employed, have health care coverage, and White compared to survey respondents that did not use internet in the preceding 30 days [64]. The potential benefits, and drawbacks, of contemporary telehealth were recently highlighted in a review by Mahtta et al. where the authors further explore how the indiscriminate use of telehealth may widen disparities among minority groups [65].

The pandemic's impact on care delivery was also observed in more acute care settings. Despite the association of COVID-19 with myocardial injury, the pandemic's impact on acute MI (AMI) incidence remains to be seen but the pandemic's influence of presentation and management is apparent. In a single-center prospective study ($n = 26$) from Milan, Italy, investigators found a higher proportion of patients presented with late presentation STEMI in 2020 (50%) compared to the historical cohort (4.8%) [66•]. A retrospective, single-center study in Japan found an statistically significantly increased incidence of delayed STEMI presentation (26.5%) compared to the prior year (12.1%), with similarly prolonged onset-to-door times during the pandemic [67]. Other studies have demonstrated similarly delayed presentations during acute myocardial infarction, with a center in Lithuania finding 80% of NSTEMI patients presenting 12 h after pain onset compared to 42% in the pre-pandemic cohort [68]. Invasive management of MI has also been impacted; one single-center retrospective study found that the median door-to-balloon time in STEMI was delayed from 60 min pre-pandemic to 72 min during the COVID-19 pandemic [67]. The cause of treatment delays was likely multifactorial; however, prolonged triage times, COVID-19 testing, staffing shortages due to redistribution, or illness may all have been contributing.

Medication Access and Adherence

The prolonged and recurrent surges of the pandemic have also caused significant public anxiety. The impact of mental health on medication adherence has been previously documented: in one study of hypertensive patients, stress increased the likelihood of medication non-adherence (OR 2.42, 95% CI 1.06–5.5) [69]. COVID-19 has also impacted medication prescribing and adherence directly. Early in the pandemic, it was found that ACE2 was involved in viral infectivity [70]. This fueled the global concern for angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) increasing personal risk of infection, which may have impacted medication compliance. This fear was shared by patients and providers alike, and the European Society of Cardiology and the American College of Cardiology promptly released position statements to address this concern [71, 72]. Decreased adherence to medications and medical recommendations will certainly exacerbate the strain on healthcare systems and have long-term implications for chronic disease management.

Impacts on Clinical Research

Clinical trial research has not been spared consequences from the pandemic. Clinical trials bound by adherence to study protocols planned well in advanced and subject to institutional and regulatory oversight. Many trials approved or initiated prior to the pandemic faced significant challenges in adapting their study design to social distancing restrictions, public response to COVID-19, and the sequela of viral infection in study populations.

One illustrative example of a trial whose findings highlight the impact of COVID-19 on clinical research is the GUIDE-HF trial [73]. The study investigated the CardioMEMS implantable pulmonary artery pressure monitoring system and its impact on heart failure events and mortality [73]. The primary endpoint event rate had to change during the pandemic phase of the trial, leading the authors to have to perform a pre-COVID-19 impact analysis. Overall, the primary endpoint was not statistically significant; however, subsequent analysis of COVID-19 impact demonstrated a statistically significant 28% reduction in heart failure hospitalizations and a reduction in the cumulative incidence of heart failure events using hemodynamic-guided management (HR 0.76, 95% CI 0.61–0.95) [73].

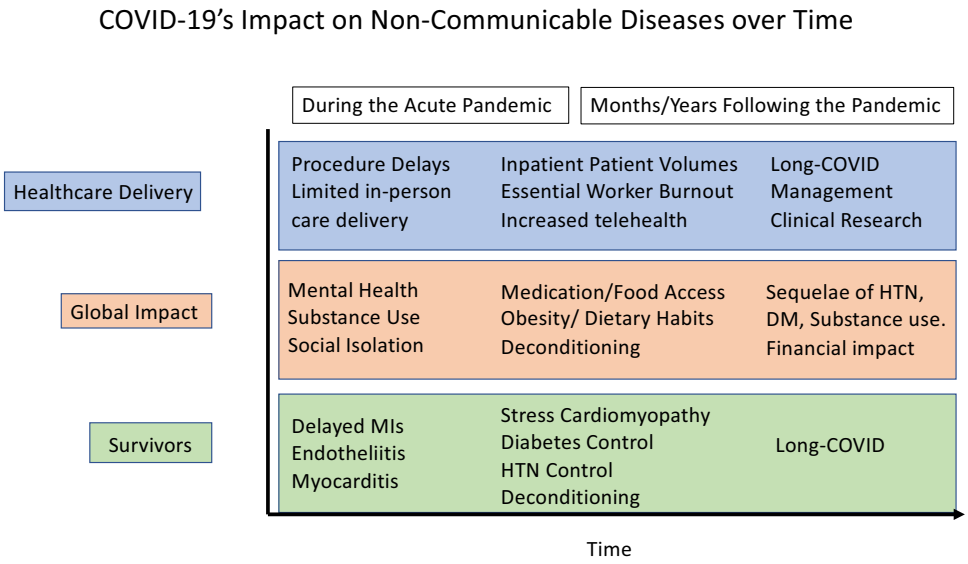

Fig. 1 Impact of COVID-19 pandemic on non-communicable diseases on the level of individual survivors, the global community, and healthcare delivery

Clinical trials enrolling during the pandemic have faced similar issues, and the long-term impact of the pandemic on ethical clinical study design and research protocol remains an area of concern and potential innovation for the international medical community.

Conclusion

The COVID-19 pandemic has impacted international relations, immigration, healthcare policy, global economies, and the day-to-day lives of people around the world. As healthcare providers, it is our responsibility to care for patients, educate the public, and monitor the health sequelae of this pandemic. Unfortunately, the impact of the pandemic on non-communicable diseases and chronic disease management will not be readily apparent. The effect of a more sedentary lifestyle and the associated risks of weight gain, deconditioning, diastolic dysfunction, and heart failure and arrhythmia, potentially compounded by limited access to medical care, may not become evident for years, even decades.

Declarations

Conflict of Interest Karl Gordon Patti: No disclosures. Payal Kohli: Speaker's Bureau: Boston Scientific, Amarin, Esperion, AstraZeneca, Merck, Advisory Board: Amgen, Boston Scientific, Novartis, Esperion, Doximity, DocWire/MashUP MD, Honoraria: ACC/ABIM Question Writing, Current Atherosclerosis Reports Section Editor ($400), Amgen, Consultant: Grand Rounds, American College of Cardiology, Grand Rounds, 2nd MD, Writing/Editorial Board: Healthline, GE/SkyWord, American College of Cardiology.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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