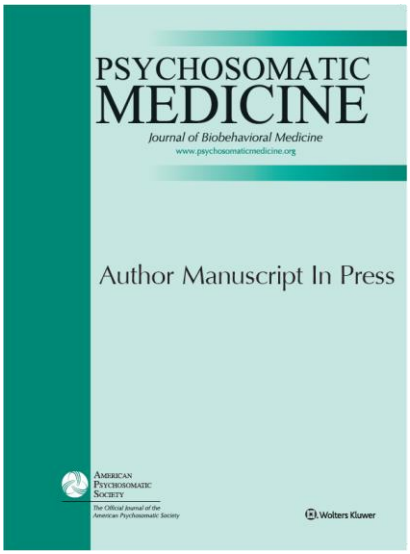

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Biobehavioral aspects of the COVID-19 pandemic: A review

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Abstract

Objectives: This review highlights the scope and significance of the COVID-19 pandemic with a focus on biobehavioral aspects, as well as critical avenues for research.

Methods: A narrative review of the published research literature was undertaken, highlighting major empirical findings emerging during the first and second wave of the COVID-19 pandemic.

Results: Interactions among biological, behavioral and societal processes are prominent across all regions of the globe during the first year of the COVID-19 emergency. Affective, cognitive, behavioral, socioeconomic and technological factors all play a significant role in the spread of infection, response precautions, and outcomes of mitigation measures. Affective disorders, suicidality and cognitive dysfunction have been widely reported consequences of both the infection, economic impact and the necessary public health mitigation measures themselves. The impact of COVID-19 may be especially serious for those living with severe mental illness and/or chronic medical diseases, given the confluence of several adverse factors in a manner that appears to have syndemic potential.

Conclusion: The COVID-19 pandemic has made clear that biological and behavioral factors interact with societal processes in the infectious disease context. Empirical research examining mechanistic pathways from infection, loss, and recovery to immunological, behavioral and emotional outcomes is critical. Examination of emotional and behavioral factors is critical to ongoing management of the current pandemic, as well as future major threats to global health.

Keywords: COVID-19; SARS-CoV-2; emotion; behavior; infection; pandemic

Key terms:

CDC: Centres for Disease Control (United States)

COVID-19: coronavirus disease 2019

MERS-Cov: Middle East Respiratory Syndrome coronavirus

SARS-Cov: severe acute respiratory syndrome coronavirus

SARS-Cov2: severe acute respiratory syndrome coronavirus 2

WHO: World Health Organization

The COVID-19 pandemic emerged rapidly during the first three months of 2020 following the identification of a cluster of 44 cases (11 severe) of atypical viral pneumonia of unknown cause in Wuhan, China on December 31, 2019. Some cases of the index cluster were vendors whom had a common link to a large wet market selling live seafood and wildlife (1). Despite early and extensive actions within China to prevent spread, by January 8, 2020 the first case outside of China was reported in Thailand (2), followed closely by subsequent large-scale outbreaks in Europe (particularly Italy and Spain), North America, South America and finally, Africa (Figures 1-3). The COVID-19 situation was declared a pandemic by the WHO on March 11, 2020 (3). Lockdowns and other mitigation measures were implemented around the world in a staged manner during this time, with significant evidence of success during the first wave (4,5). In the closing months of 2020, several candidate vaccines concluded phase 3 clinical trials, several of which emerged with high levels of demonstrated efficacy (6–10) setting the stage for the largest coordinated vaccination effort in world history.

A brief overview of COVID-19

COVID-19 is a respiratory illness caused by a novel variant of coronavirus, previously unknown to medical science. The coronavirus family of viruses (formally known as *Coronaviridae*) are so named based on the spike proteins (s-protein) around the outer surface of the virus giving the protein a distinct crown or 'corona'-like appearance (11,12). This family includes numerous viruses that naturally exist and reside within a variety of animal hosts (e.g., bats, pangolins, camels). Fortunately, only a small handful (n=7) of known coronaviruses have significant adverse effects on human beings. Of those known coronaviruses that infect humans, about half (NL63, 229E, OC43 and HKU1) cause a very mild or asymptomatic upper respiratory

tract illness in otherwise healthy individuals. The other species known to interact with humans cause more serious infections: SARS-CoV (Severe Acute Respiratory Syndrome coronavirus), MERS-CoV (Middle East Respiratory Syndrome coronavirus), and now SARS-CoV2 (SARS coronavirus 2). SARS-CoV and MERS-CoV have both caused epidemic outbreaks in recent decades, and significant fatalities within the geographical regions where these viruses initially emerged (13–16). SARS-CoV2 is the virus responsible for the current global pandemic as it causes COVID-19 (17–20). Despite being identified only in early 2020, SARS-CoV2 may have been responsible for isolated cases of human infection within rural regions of China in the months or even years prior to the current outbreak (21), and converging evidence suggests the possibility of limited circulation of the virus in human populations outside of China in late 2019 (22).

The Origins of the Pandemic

The ultimate origins of the COVID-19 pandemic may never be conclusively known, but the available evidence is consistent with a "spillover" event. Spillover events take place when viruses residing within their natural reservoirs intermittently come into contact with humans through a variety of interactions (e.g., hunting, animal husbandry or wet-markets). Over time, with repeated contact and interactions, the virus evolves and adapts to gain the ability to infect human cells. Available evidence has linked SARS-Cov2 to an initial bat host and a mammalian intermediary (possibly a pangolin, or other mammalian species) (21,23). Although its infection fatality ratio is significantly lower than SARS and MERS, its transmissibility is high, and coupled with the lack of population immunity (innate or acquired), the risk to the human population is substantial.

In the 2020 waves of COVID-19, strict social distancing interventions are estimated to have had a strong beneficial impact on disease spread among the general population, offsetting tens of millions of cases and millions of deaths around the world, based on analyses of predictive models (24). The long-term success of more circumscribed and sustainable public health measures to contain the spread of infection in the coming months and years may partially depend on the identification of high-risk groups (25). It is worth noting that even with strict population-wide physical distancing, protection of the most vulnerable (i.e., people with significant co-morbidities, over the age of 70), has been inadequate. For example, in the United States and Canada, those residing in long-term care facilities have faced disproportionate infection and mortality risk (26). Other high-risk groups include middle-aged to older adults with chronic lung disease or moderate-to-severe asthma, serious heart disease, compromised immune systems, obesity, diabetes mellitus, chronic renal disease, those undergoing dialysis, or those with liver disease (27). Recent work has also highlighted the excess risk of COVID-19, and a higher risk of experiencing more severe outcomes, in ethnoculturally diverse, urban neighborhoods, and among those generally subject to socioeconomic disadvantage (25,28).

Unique Features of COVID-19 Compared to Other Viral Epidemics

The novelty of SARS-CoV2 to the human species is a critical factor in understanding both the pathogenic variability and the public health response to this pandemic. Because SARS-CoV2 is a new virus, humans no specific immunological protection from prior population-level exposure. With exposure and recovery, there is evidence that antibodies are produced readily in response to SARS-CoV2 infection (21). There remains uncertainty about the specificity, strength, and longevity of immunological protection stemming from such exposure, although

some parameters of immune response appear to last between 3 and 5 months post-exposure (29,30).

In comparison to past pandemics, which includes the 2009 H1N1 pandemic (also known as "Swine Flu"), 1918 Flu pandemic (also known as the Spanish Flu), and the bubonic plague, COVID-19 differs along a number of dimensions. The mortality rate is lower than MERS (34%) (31), SARS (10%) (32), and the 1918 flu (1-3%) (33). The most recent seropositivity studies suggest an overall COVID-19 infection fatality rate below 1%, but highly age-stratified (34,35). Specifically, those over 80 years of age and/or with medical comorbidities have a substantially greater likelihood of dying from infection (up to 20%; (34,35). Children, in comparison, are overwhelmingly likely to have no symptoms or very mild symptoms, even when using patient data from clinical settings (36,37); there is also evidence that children may indeed be less susceptible to infection overall than adults (38). Age-related risk stratification was also evident in the 1918 flu, where mortality rates were lower for older versus younger adults, possibly due to prior exposure to a similar pathogen in the decades before the vulnerable younger generation was born (possibly the 1889 Russian flu pandemic; (39).

Affective Dynamics and the COVID-19 Epidemic

Predictably, fear has played a prominent role in responses to the COVID-19 pandemic, both in terms of the perspectives of political rhetoric and the experience of the individual member of the population. From the latter perspective, fear has an adaptive function as it serves to mobilize behavioral responses to immediately present threats of a physical nature (40,41), particularly those for threats that are evolutionarily significant (42). To the extent that humans

are evolutionarily primed to fear unfamiliar infectious pathogens, such a system ensures a robust response to such threats.

Self-protective responses comprise two separable response systems within the human brain: 1) a largely automated, subconscious system under the control of the amygdala and its sub-nuclei, and 2) a second conscious fear response of more neurophysiologically distributed origins within the neocortex, both of which are oriented to defensive threat preparedness in different ways (43,44). Under conditions of evolutionary preparedness, mobilized defensive responses—particularly the non-conscious variant linked to the amygdala—may be disproportionately stronger and/or more readily triggered by associated stimuli. This may be adaptive if it stimulates self-protective precautions on the individual and societal level, but may also misdirect responses in unproductive ways. The robust fear response to evolutionarily significant threats is in stark contrast to other threats that are very substantial, but either too familiar or of more recent evolutionary origins. For example, a robust and adaptive fear response is comparatively difficult to mobilize in response to the threat posed by familiar pathogens (e.g., mumps, rubella, influenza), chronic illness (e.g., diabetes mellitus and heart disease), and climate change, despite their being very substantial threats to humans individually and collectively as a species.

Even robust fear of infection may not motivate adaptive behaviors that reduce the probability of getting the SARS-Cov2 virus, however – for two reasons. First, SARS-Cov2 poses not only a physical threat of infection but also presents financial (e.g., job loss) and abstract threats (e.g., diminished freedom). Whereas fear of infection can in principle drive appropriate

precautionary behavior, the aforementioned symbolic threats may motivate *less* precautionary behavior in some circumstances (45). Second, decades of research indicate that fear can give rise to adaptive or maladaptive responses to threat depending upon coping appraisals (46–48). Coping appraisals refer to judgments of response efficacy, self-efficacy, and response costs. When people believe that recommended behaviors will reduce the threat of infection, are confident they can undertake recommended actions and see few costs in doing so, then fear promotes adaptive responses. However, when coping appraisal is low, fear engenders maladaptive responses, that is responses that do not in fact protect against the threat, or unwittingly amplify harm (47,49). Maladaptive responses to the COVID-19 threat have included accidental self-poisonings (50–52), xenophobia (53–55) and fatalism in response to the threat (47,49,56–58). Of equal concern may be hesitation to provide diagnosis and care for other life-threatening conditions (59,60), creating other types of mortality risk.

It is clear that affective dynamics of COVID-19 are complex. Fear of infection energizes precautionary behavior and this relationship is monotonic rather than curvilinear (41,57). However, according to prominent social psychological theories of precautionary behavior, arousing fear about infection by SARS-Cov2 will not, on its own, promote physical distancing and other precautionary behaviors. Adaptive responses to fear rely on beliefs about the efficacy, and personal and social costs, of precautionary behavior. Likewise, other motivating variables are important to consider beyond fear. For instance, geo-tracking data from 17 million US smartphone users indicate that sociocultural norms were much more powerful predictors of individual adherence to physical distancing than was the increase in rates of infection and death (as a proxy for life threat) from 9 March to 8 May, 2020 (61). From this perspective, social

norms—perceptions of others behavior and approval—might be a particularly important target for interventions and public communications in the specific case of COVID-19. A comprehensive review of normative influences and other social psychological factors can be found elsewhere (62).

Mental Health

The degree of threat posed by COVID-19, as well as the heavy and prolonged public health actions undertaken to mitigate its spread, both constitute significant stressors. Considerable disruption of worldview may occur for people previously viewing the world as a safe, predictable, and just place. Likewise, disruption of support networks, both personal and professional, have occurred for wide swaths of the population. These latter disruptions may be particularly serious for people who are most vulnerable to—or already suffering from—psychiatric illness prior to the onset of the pandemic; for example, those with a history of affective disorders, substance abuse issues, those with tenuous support networks, or those of lower socioeconomic status, particularly the homeless, those of African American and indigenous communities, and those affected by HIV/AIDS (63–65). Given the excess mortality from COVID-19 and other sources, more frequent instances of complicated bereavement may occur, particularly under circumstances where loved ones have not had an opportunity to adjust to the circumstance or say their goodbyes, and/or undertake their expected religious observances. Widespread unemployment may precipitate or exacerbate financial and other stressors, and in some cases, reduce access to quality mental health services. Any or all of these factors could contribute to a rise in psychiatric disorder within the world population in the wake of the COVID-19 pandemic.

Indeed, US population-level data from the Household Pulse Survey documented high levels of significant (i.e., present nearly every day or at least half the days in a week, and of a severity that would warrant clinical follow-up) depression and anxiety symptoms from April 23 to early 2021 (66); Figure 4 presents cumulative averages by age group. The mental health of young adults in the 18-29 year age range appears to be worst affected, with 51.5% reporting significant symptoms of depression or anxiety compared to the population-wide benchmark value of 11% from the 2019 National Health Interview Survey (NHIS) conducted a year earlier. Those in the highest age ranges (over 70 years) reported significant symptoms at less than half the prevalence of younger adults (approximately 25%), but rates were still more than double the 2019 population benchmark value. Cziesler and colleagues reported the findings from a representative panel survey conducted between June 24-30, 2020. In this survey, 40.9% of respondents reported at least one adverse emotional or behavioral symptom related to the COVID-19 public health emergency (i.e., anxiety, depression, stress/trauma, substance use for coping, or suicidal ideation; (67). The same age gradient was evident, but even more striking in that 74.9% of young adults (18-24 years) showed at least one mental or behavioral health symptom compared to 15.1% of those over the age of 65. This was also reflected in comparisons between those retired and those of working age (both employed and unemployed). Rates of reported symptoms of a depressive or anxiety disorder (30.9%), trauma / stress related disorder (26.3%), and substance use for coping with emotions (13.3%) were more than double the normative levels. Approximately one quarter of young adults (18-24 years; 25.5%) and unpaid caregivers for older adults (30.7%) reported having seriously considered suicide 30 days prior to the survey. Similarly, members of visible minorities (Hispanic (18.6%) and black (15.1%)) had significantly higher levels of such thoughts than the general population value of 10.7%.

A recent systematic review on the mental health impact of COVID-19 internationally has confirmed the above trends internationally, with high risk of mental disorder among young adults (<40 years of age), students, women, and those with high levels of exposure to COVID-19 media communications (68). With respect to the latter, in a Chinese sample, the mental health impact on children was particularly prominent among those with a high level of media exposure, via internet addiction or smart phone addiction (69). Further elucidation of social media as an amplifying and mitigating factor for psychological distress and disorder is an important avenue for research in the biobehavioral sphere.

The temporal patterning of psychological distress will be important to track in longitudinal studies. One such early study involving repeated longitudinal assessments in the UK showed increases followed by relative declines that nonetheless remained above expected levels (70).

A Syndemic Framework

The syndemic framework may be an appropriate lens through which to understand the interaction between psychiatric disorders, stress and behavioral factors in the COVID-19 context. A syndemic is a disproportionately increased disease burden resulting from a clustering of adverse factors; the interaction between the two or more factors is synergistic rather than additive (71). For example, severe psychiatric disorders interact directly with physiological vulnerability to COVID-19 and potentiate severe outcomes from it, and this may be further amplified by behavioral and emotional factors that each also confer their own vulnerability (e.g., smoking, stress; (72–77). The prevalence of smoking is much higher among those with severe mental

illness (particularly schizophrenia) than in the general population (53–56), and smoking also introduces physiological vulnerability to respiratory infection via structural and immunological mechanisms (57,58), making it likely that those with severe mental illness will experience more severe outcomes from COVID-19 than other people. The public health measures themselves may burden already taxed coping mechanisms and increased stress in this population, via behavioral and immunological mechanisms (78).

In support of the syndemic hypothesis, early data from a large retrospective cohort study (*N* = 7,348 consecutive adult patients, with laboratory confirmed COVID-19) in the United States found that a diagnosis of a schizophrenia spectrum disorder was associated with a 2.67 odds of mortality relative to patients without a psychiatric disorder (79). This finding is remarkable in part because a schizophrenia diagnosis adds an increment in mortality risk second only to age in magnitude, which is otherwise the strongest known risk factor for death following SARS-Cov2 infection. In the aforementioned study, those diagnosed with an anxiety or depressive disorder were not at enhanced mortality risk compared to patients without a psychiatric diagnosis, after adjustment for confounders (79).

In summary, the syndemic framework is a potentially useful framework with which to understand the multiple interacting vulnerabilities that are introduced by COVID-19 for psychiatric populations (71). At least one early study suggests that those living with schizophrenia spectrum disorder are one candidate group that warrant special attention in this respect (79).

Suicide

Though statistically rare, suicide is an important mental health outcome to monitor in the wake of COVID-19, equally as a function of psychiatric morbidities, economic situations, personal loss, stress, loneliness and social isolation (58,80–84). Prior pandemics have been associated with reliable increases in suicide rates, although the absolute number of suicides in such cases is a small fraction of those killed by the pandemic itself (85–87) highlighting the importance of interpreting both relative risk and absolute numbers (88). Early signs suggest the potential for increased suicide rates in the first wave of COVID-19 in North America, but the effects will take some time to become manifest in the published research literature. In one major Canadian city, the number of deaths by suicide on the main subway system—a relatively unambiguous instance intentional self-harm—was nearly double that of the running 10-year average, and the highest absolute level since such data was collected systematically (89). Likewise, significant increases in the prevalence of suicidal ideation have been documented in self-report surveys, particularly among young adults (67). Large-scale longitudinal analyses will assist in providing a clearer picture of the full range of impact of the pandemic in terms of ideation and self-harm, and should likely include consideration of passive forms of self-harm and so-called "deaths of despair" via substance abuse (90). The use of technology to reach and mitigate risk among those with psychiatric and substance abuse disorders will be critical for several years following the abatement of the pandemic itself (see "Technology and Behavior in the Pandemic Response" section of this article below).

Neurological Impacts

Viral infections can affect the central nervous system directly or via inflammatory processes arising from the activation of the body's defensive immune response. The latter inflammatory responses may affect membranes surrounding the brain (meningitis) or brain tissue itself (encephalitis). These inflammatory processes can trigger a number of cognitive symptoms and impairments, ranging from headache and pain, to difficulty concentrating and confusion, and even more severe clinical outcomes such as seizures, edema or death in extreme cases. A viral infection also contributes to one's infectious burden which is associated with cognitive decline (91,92).

One of the many unknowns about COVID-19 is the extent to which it impacts the brain (93,94). Other viral infections that can produce neurological or neuropsychiatric symptoms include influenza (95), MERS (96), Zika (97), herpes (98) and chickenpox (99). SARS-CoV-2 has a similar receptor binding domain structure to SARS-CoV and likely shares its neurotropism and neurotoxicity (100), and so we may expect COVID-19 to impact the brain similarly at least among those with severe infections. Current evidence suggests that SARS-CoV2 can induce endotheliitis (101). Thus, coagulopathy and vascular endothelial dysfunction are proposed as COVID-19 complications (102). Endothelial disfunction plays a critical role in the mechanisms leading to cerebral small vessel disease and related brain changes, such as white matter lesions and lacunar infarcts (103).

The high occurrence of cerebrovascular incidents among those hospitalized with COVID-19 suggests at least an indirect effect on the brain when the infection is severe; many other symptoms such as agnosia/ageusia, dizziness and confusion (widely reported among those who were or were not hospitalized) also suggest brain impacts of infection. Animal and human tissue research suggests that adverse consequences also exist from a mechanistic perspective (104). A recent surveillance study in the UK showed significant neurological manifestations of COVID-19 infection (105), as did a large retrospective cohort study in the United States involving 62,354 patients (106). The latter study found reciprocal relationships between COVID-19 risk and neuropsychiatric disorder, such that a pre-existing neuropsychiatric disorder amplified COVID-19 infection risk, and likewise, COVID-19 infection increased the risk of new onset psychiatric disorder or dementia (106).

Lifestyle Behaviors, Comorbidities, and Social Determinants

Primary demographic and disease-related risk factors for COVID-19 mortality are male sex, older age (over 65 years) (Figure 5) and the presence of underlying chronic medical conditions, such as hypertension, diabetes mellitus, chronic respiratory diseases (e.g., asthma), cardiovascular and cerebrovascular diseases. Behavioral risk factors are equally important and could include exercise as a protective factor vis-à-vis aerobic fitness, and smoking as a risk factor. Indeed, a systematic review of data from China suggests that smokers were more likely to suffer severe outcomes and hospitalizations. Early data from the CDC subsequently confirmed the same pattern among North American infections (27,107), and a more recent meta-analysis confirmed that smoking nearly doubles the chance of severe COVID-19 infection (77). A study at a major health system in New York revealed that among 5,700 patients presenting for hospital

treatment as a result of COVID-19 infection, the average age was 65, 60% were male, most had comorbidities, the most common being hypertension (56.6%), obesity (41.7%), and diabetes mellitus (33.8%) (108). In China, among 191 COVID-19 admissions to two major hospitals in Wuhan, 48% had comorbidities, of which hypertension was the most common (30%), followed by diabetes mellitus (19%) and heart disease (8%) (109). At least four studies have confirmed that those with evidence of cardiovascular disease are at increased risk of mortality with COVID-19 infection (110–112). Although data are not yet available for vaping as a risk factor for severe outcomes, the potential exists (113), and could explain some occurrence of severe outcomes in younger age groups. Indeed, COVID-19 related risks may be a compelling addition to anti-smoking and vaping communications (114). Other early life exposures that may confer risk include substance use (cocaine), anabolic steroid use, as well as some antidepressant medications (115–118). Careful research will be required to distinguish undiagnosed (or subclinical damage) from the effects of the virus itself.

Social determinants of health, such as poverty, race, physical environment, and homelessness appear to have a substantial impact on outcomes related to COVID-19 (25). Critical public health measures such as physical distancing are also more difficult for people/populations experiencing adverse social circumstances. Homelessness can contribute to overcrowding especially during lockdowns when public spaces are closed, which may increase the risk of infection (65). Similarly, food insecurity for children living in poverty who rely on school lunch programs may be increased during school closures. The resultant undernutrition or malnutrition contributes to lowered immunity, thereby increasing the risk of viral transmission (25). Social determinants can also interact with medical conditions in insidious ways. For

example, asthma morbidity is associated with poverty, exposure to smoke, and non-Hispanic black race (119), while asthma itself is a risk factor for COVID-19 morbidity (120). In the United States, several studies have found that those of African American descent are more likely to experience greater rates of infection and mortality from COVID-19 (121,122), an effect that could be attributable to higher likelihood of holding jobs that involve higher exposure to COVID-19, such as service positions and other front line positions, and less likely to be able to work from home.

Spatiotemporal analysis can play an essential role in the assessment of the associations between race or ethnicity, geographic and neighborhood inequities, and morbidity or mortality related to diseases (123,124). In this context, this analysis can be used to identify clusters or 'hot spots' of COVID-19 cases and detect spatial and temporal variations in racial and neighborhood disparities related to COVID-19, for targeted public health interventions (125). In effect, understanding where, when, and which group is disproportionately affected by COVID-19 can significantly enhance the public health response towards the disease.

Racism and Social Unrest

The COVID-19 pandemic has coincided with and contributed to various expressions of racism and social unrest. For example for Chinese Americans, racist tropes veiled under health-related fears (126,127), perceptions as "perpetual foreigners," (128) have been used to support the belief that they are threatening physical and cultural health of a white, Anglo-dominant U.S. society. Nearly half of both Chinese American parents and youth in one study reported being directly targeted by COVID-19 racial discrimination online and/or in person (129). Up to 91% of

parents and youth reported witnessing at least one incident of COVID-19 racial discrimination online and/or in person. In addition, the majority of parents and youth in the sample perceived collective racism in the forms of health-related Sinophobia, where the Chinese are considered a health threat to American society, and the media's role in perpetuating Sinophobia. These experiences of racism and racial discrimination were positively associated with poorer mental health and reduced psychological well-being in both parents and youth (129). Similar experiences have been reported by other Asian American communities during COVID-19 as spillover effects of anti-Chinese racism (130). Americans who were more fearful of COVID-19, had less accurate knowledge of the virus, more negative attitudes toward Asians, as well as those who had less trust in science and more trust in US political leadership reported being more likely to engage in discriminatory behavior toward people of Asian descent (131).

Technology and Behavior in the Pandemic Response

The role of technology during the COVID-19 epidemic has been prominent in a number of ways, both positive and negative. With respect to the former, technology continues to play a crucial role in efficiently and effectively conveying COVID-19 risk information and instructions for population-level response. Some countries are reliant on conventional text messaging (e.g., Vietnam), whereas others developed COVID-19 specific mobile phone applications (e.g., Canada, United States, UK) to provide up-to-date information to the public (132). However, despite the added features of apps, their passive nature makes them less preferable to active push notification systems, given the greater potential for information penetration and uniformity of messaging in the latter (133).

Several countries close to China were able to keep the COVID-19 cases and deaths very low because of their efficient use of technology, particularly South Korea and Vietnam. The extensive use of contact tracing apps (e.g., NCOVI, SmartCity in Vietnam) was a notable feature in their pandemic response (134). The use of such technology raises concerns over data privacy and the ethics of mass surveillance, likely contributing to their limited use in North America, the United Kingdom, and the European Union. A Bluetooth-based contact tracing app, developed by a joint initiative of Google and Apple, offers more data security for contact tracing and may deliver the desired security and information protection preferred by many western countries. However, more psychologically meaningful apps that engage self-regulatory mechanisms to promote active disease avoidance are important to explore (135).

Beyond loss of privacy, an additional dark role for technology is the viral spread of misinformation and rumors, particularly in social media (e.g., Facebook, Twitter) (136,137). Because of the ubiquitous nature of smartphones, people now have unrestricted access to this misinformation. Some rumors are potentially dangerous (e.g., consumption of methanol or disinfectant as a remedy of COVID-19) and can threaten human life (133). Furthermore, the use of social media and mobile apps (e.g., WhatsApp) to spread hatred and xenophobia was also widespread in the early days of the pandemic (138). Technology has also accelerated acceptance and integration of new routes accessing healthcare, including mental health service provision, with social distancing intact (e.g., telemedicine, for both physical and mental health contacts). Further technological progress—specifically in consumer-focused sphere—could bring a plethora of brain and body sensors to out-of-clinic and home settings, benefiting telemedicine, and urgent care and facilitating research in these contexts. There are already new dedicated

biomedical technologies announced that are intended for consumers to fight COVID-19, such as smart masks, disposable biosensors for continuous temperature and cardiac function monitoring. Utilizing such biomedical sensing and new mobile approaches stemming from uniquely capable and tightly integrated Artificial Intelligence could provide an in-depth and extensive healthcare, remotely.

Current Unknowns and Future Directions

Although scientific understanding of SARS-CoV-2 is growing steadily, there are still a number of unknowns about the virus itself, the illness that it causes in humans (COVID-19), and its biobehavioral impact on the population. Below are some of the critical questions for future biobehavioral research:

1. What are the psychological (e.g., stress, mood, social-cognition) and psychiatric (e.g., new occurrence of affective disorders, stress-related disorders, and/or exacerbation of existing conditions) impacts of COVID-19? How do these differ with respect to those who directly experienced infection, healthcare workers, and people in their wider social networks (family, friends)? What are the mechanisms by which such adverse impacts are generated (e.g., immunological, endocrinological, neurobiological, cognitive)? What factors predict resilience to adverse psychological and psychiatric effects of COVID-19?
2. What are the best ways to promote vaccine uptake and fidelity to precautionary behaviors as the pandemic persists? Perhaps more importantly, can biobehavioral research help to inform the communications strategies that might overcome vaccine hesitancy?
3. What are the effects of SARS-CoV-2 on the central nervous system, both in an acute sense (immediately following infection), in the short-term after recovery, and in the long-

term? Are there lasting impacts in some of those infected, and if so, what predicts these impacts? Does degree of impact of COVID-19 on the brain depend on exposure level or type of exposure?

4. Positive growth experiences have been reported anecdotally among some population members in industrialized nations during stay-at-home orders; plausible mechanisms might include reduced work stress, increased time with family, reduced exposure to advertising, reduced consumerism and re-evaluation of life situation. How common are such effects? What are the factors that predict personal growth during the pandemic? How lasting are such effects? What are the relevant mechanisms?
5. What are the psychological (cognitive, affective and attitudinal) predictors of receptivity to different kinds of mitigation measures, and/or the uptake of vaccine when available? Several studies have characterized those with low levels of trust in conventional authorities (e.g., physicians, public health officials) and associated communication sources as more likely to be hesitant about vaccination (139). In a large sample of 13,426 respondents from 19 countries in June, 2020, about 2 out of 3 respondents intended to take a vaccine if available, and those who were older, higher income, and with higher levels of trust were more likely to indicate strong intentions (140). Troublingly, vaccine hesitancy in the US appears to have increased from earlier to late in the pandemic (141). In a study involving Turkey and the UK, beliefs that COVID-19 was of natural origin were associated with less vaccine hesitancy (142). A recent meta-analysis of large sample studies revealed consistent effects of demographic variables as predictors of hesitancy, with female sex, lower income and ethnic minority status as predictors of higher hesitancy (143). Other individual differences are largely unexplored; it is possible for

instance that some cognitive styles and personality types might be more or less likely to endorse vaccination. Identification and tailoring of communications may be helpful in this respect.

6. What types of individual differences (i.e., cognitive, personality, attitudinal) predict adherence to social distancing and other COVID-19 mitigation measures? (144). Do these factors differ among the general population and health professionals in clinical settings?
7. What are the origins of the large age-related differences in psychiatric symptomology? What cohort-appropriate interventions might best be mobilized to assist those suffering from adverse mental health outcomes? Likewise, what psychological factors account for the relative resilience of older adults to such outcomes?

Conclusions

The COVID-19 pandemic has made clear that infectious disease continues to pose a major global threat, with virtually every country in the world profoundly affected by the virus itself and/or extreme mitigation measures intended to contain its spread. Throughout this historic event, interactions between biology and behavior have been prominent in the context of the substantial social and economic consequences of the COVID-19 pandemic. Important areas for continued investigation include affective responses to COVID-19, the neurobiological sequelae of the disease (both acute and long-term), and syndemic potentials involving psychopathology, substance use, and stress in the context of socioeconomic disadvantage. Interdisciplinary cooperation will enable the highest quality research to be conducted, ideally involving behavioral scientists, social scientists, epidemiologists, neuroscientists, technologists, biochemists and medical scientists working together to examine biobehavioral facets of the COVID-19 pandemic,

and its lasting effects on the world population. Many accounts suggest that the frequency of such spillover events are on the rise, due to a number of facets of globalization and human interference with wildlife; if true, it will mean that the templates that we establish for tracking and responding to these facets will be important to maintain and reflect upon long after the COVID-19 pandemic has fully abated.

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Figure captions

Figure 1.

COVID-19 deaths in each quarter of the 2020 calendar year. Data are in the public domain. Source: https://ourworldindata.org/coronavirus

Figure 2.

COVID-19 deaths by region for the 2020 calendar year. Data are in the public domain. Source: https://ourworldindata.org/coronavirus

Figure 3.

COVID-19 deaths by selected country for the 2020 calendar year, expressed in absolute numbers (panel A) and per capita (panel B). Data are in the public domain. Source: https://ourworldindata.org/coronavirus

Figure 4.

Mental health impacts of the COVID-19 pandemic as a function of age group. Data are from the Household PULSE Survey, Centres for Disease Control; bars represent average values collapsed across all panels of data collection between April 23, 2020 and February 1, 2021. For interpretive purposes, an all-ages reference value of 11% (anxiety or depressive symptoms; 6.5% for depression symptoms only; 8.2% for anxiety symptoms only) was found in the National Health Interview Survey (NHIS) conducted in the year prior to the pandemic. Measures are taken using a 2-item version of the Patient Health Questionnaire (PHQ-2) and a 2-item version of the Generalized Anxiety Disorder (GAD-2) scale, both adapted to a 7-day recall time frame. Data

are public domain. Source: Centres for Disease Control, https://www.cdc.gov/nchs/covid19/pulse/mental-health.htm.

Figure 5.

Age and sex distribution of COVID-19 deaths for the 2020 calendar year. Data are in public domain. Source: Centres for Disease Control, https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm.

Figure 1

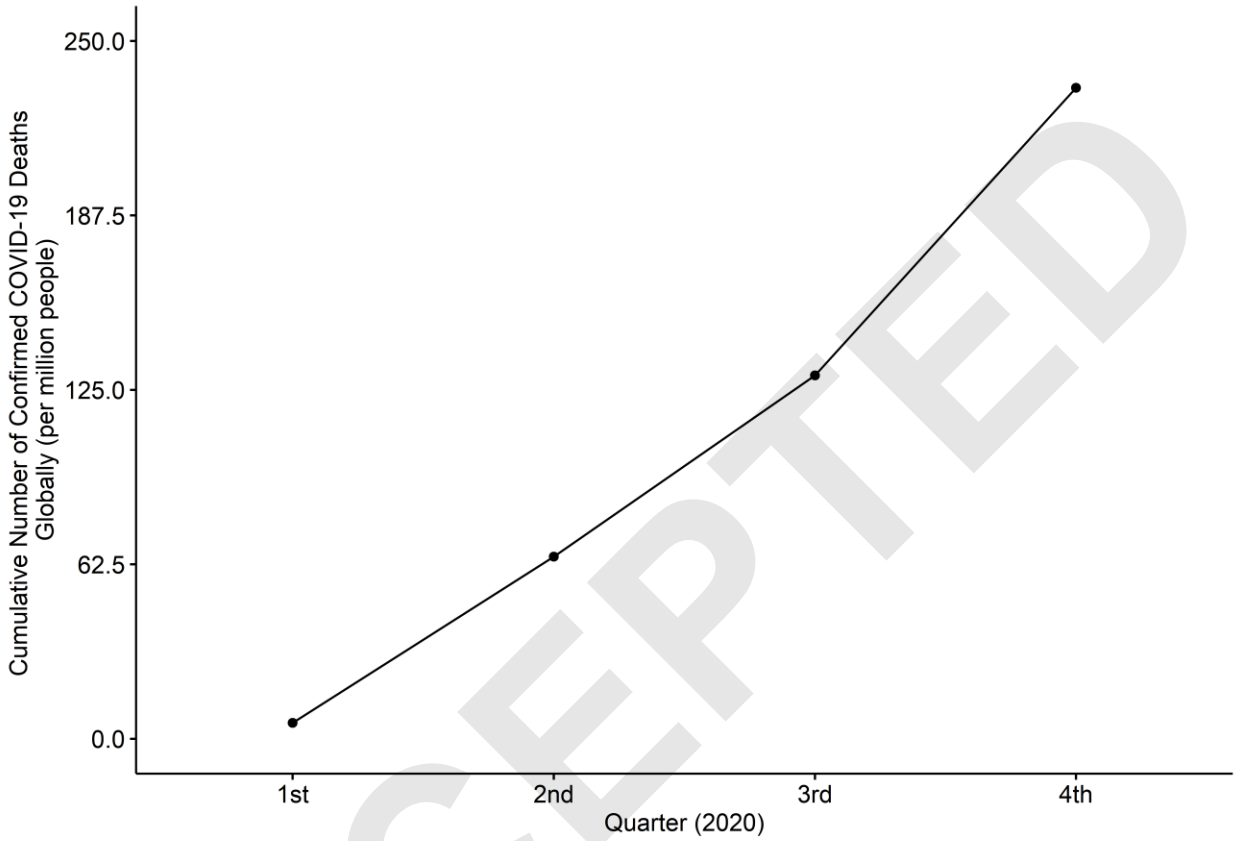

Figure 2

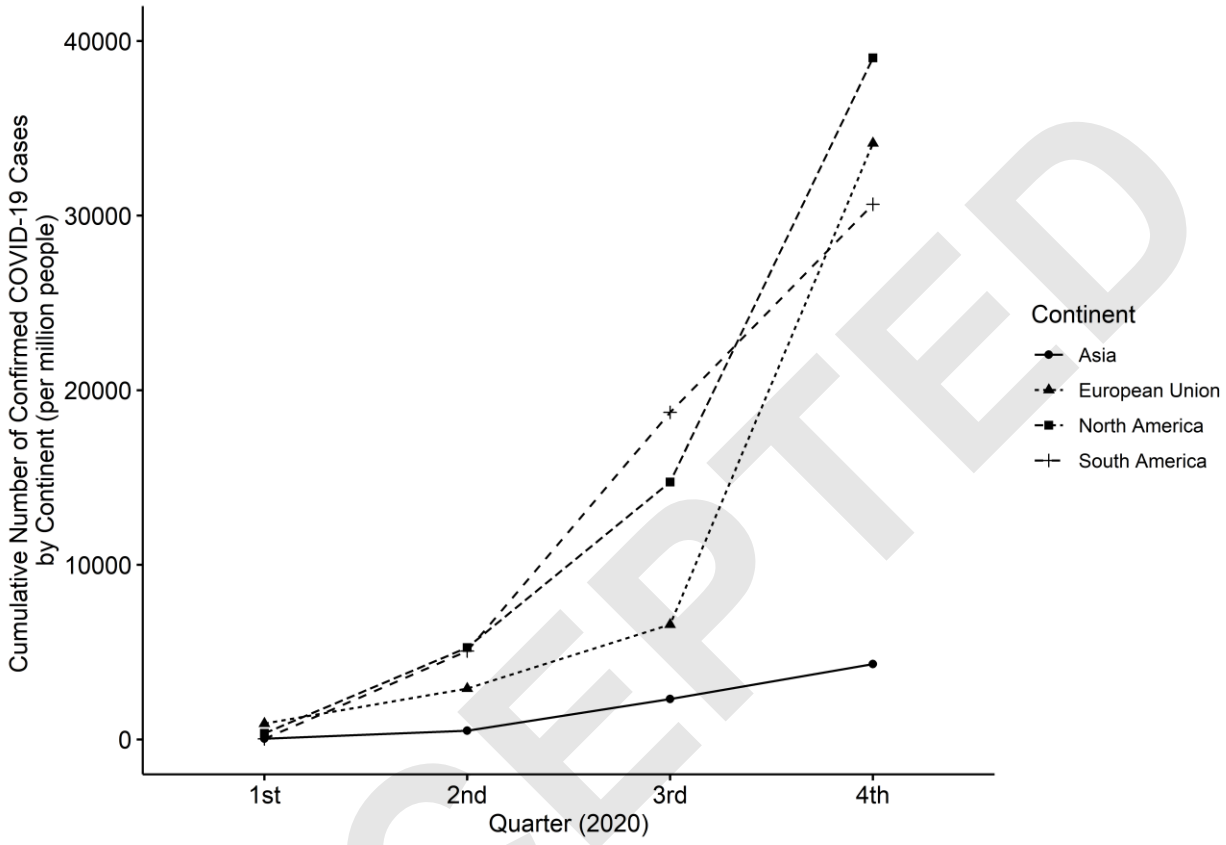

Figure 3

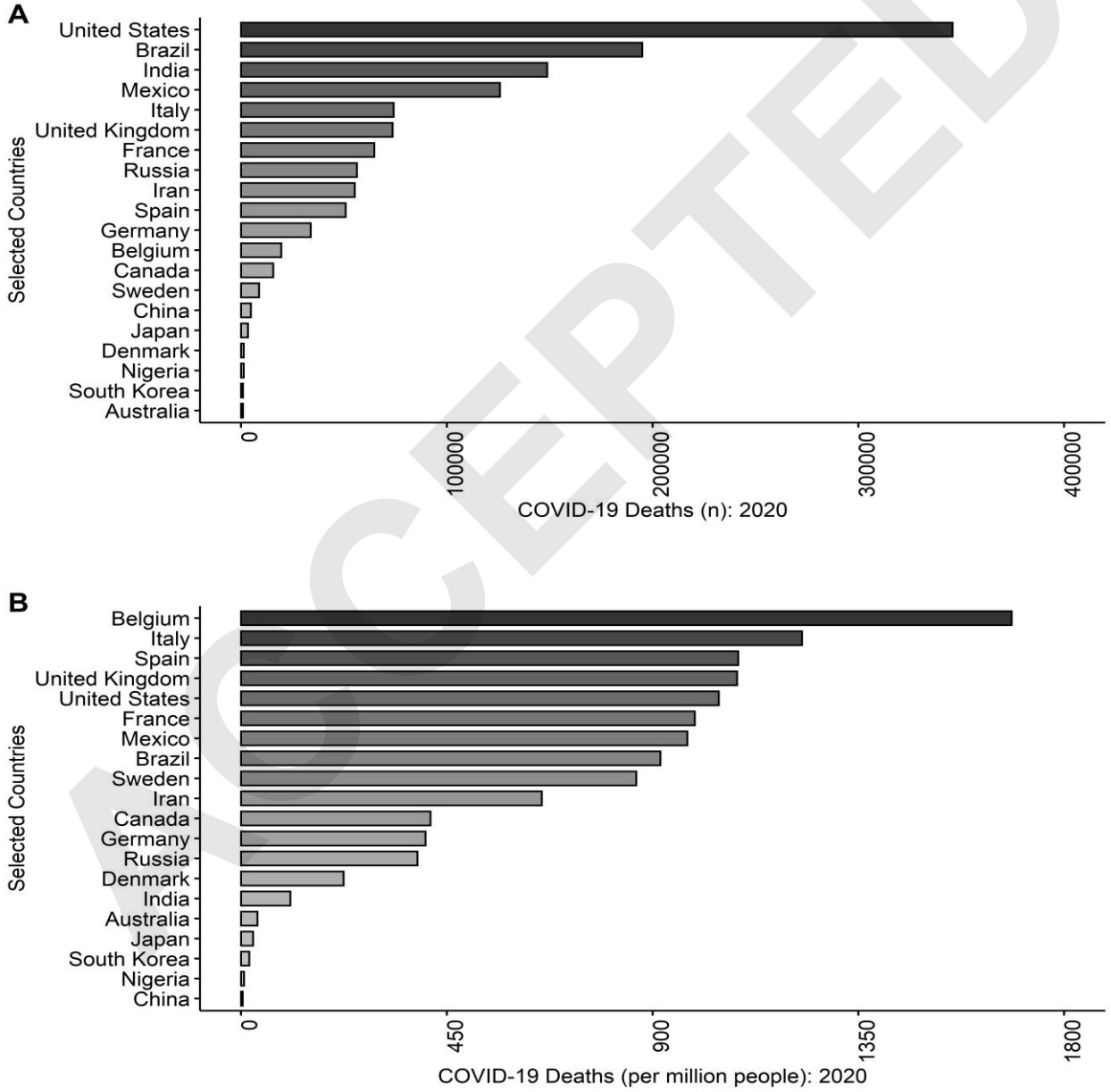

Figure 4

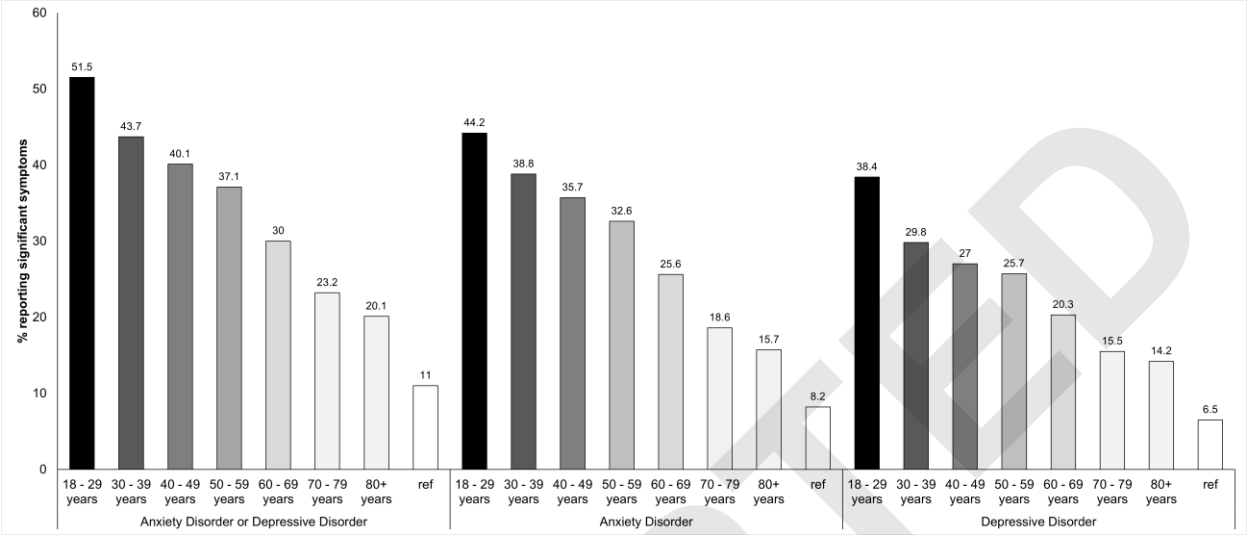

Figure 5