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Perspective

COVID-19 and metabolic diseases: a heightened awareness of health inequities and a renewed focus for research priorities

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SUMMARY

Chronic metabolic disorders such as diabetes and obesity are major public health issues in the United States. However, significant disparities in their prevalence and incidence place a greater burden on US racial and ethnic minority groups, contributing to worse COVID-19 outcomes in many. Improving treatment and prevention of diabetes and obesity is critical to the NIDDK. In this Perspective, we will review the burden of metabolic diseases in the United States, the observed disparities for metabolic diseases in relation to COVID-19, and research opportunities to address underlying causes of metabolic diseases, their associated health disparities, and COVID-19.

BURDEN OF METABOLIC DISEASES

Diabetes and obesity remain among the most common and important public health conditions in the world today. The International Diabetes Foundation has reported that 463 million people in the world were living with diabetes in 2019, and that number was projected to increase by 51% to 700 million by the year 2045 (https://www.diabetesatlas.org/en/resources/). They also reported that one in two of those with diabetes (232 million) were undiagnosed and that one of every five people in the world (20%) aged >65 years old had diabetes. In the United States, it is estimated that 34.2 million people have diabetes, and that another 88 million have pre-diabetes; 90%–95% of the US diabetes burden is due to type 2 diabetes (https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf). Diabetes can result in significant long-term complications (e.g., retinopathy, nephropathy, and neuropathy) in addition to other major comorbid conditions, such as cardiovascular disease (CVD), stroke, Alzheimer's disease, and chronic obstructive pulmonary disease. The World Health Organization has reported that between 2000 and 2016 there was a 5% increase in premature mortality from diabetes (https://www.who.int/news-room/fact-sheets/detail/diabetes). Still, there has been some positive news. For example, it has been reported that US rates of diabetes-related complications declined substantially in the two decades from 1990 to 2010 (Gregg et al., 2014). The authors suggest that the findings may reflect a combination of many factors, including significant advances in acute clinical care and improvements in the performance of the health care system as well as enhanced management of risk factors such as blood pressure, lipid levels, and smoking. Other recent reports suggest that between 2007 and 2017, global death rates from type 2 diabetes fell at an annualized rate of 0.58% (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2017; Williams et al., 2019). However, the United States remained one of the top five countries in the world with the highest death rates from type 2 diabetes. Taken together, these observations suggest that, despite biomedical research advances that have reduced the rates of diabetes-related complications, a large burden of disease persists because of the increased prevalence of diabetes. This large burden of disease has also been shown to disproportionately affect racial and ethnic minority groups and, as outlined in this Perspective, has now been recognized as a major contributor to the disparities observed in COVID-19 severity.

In addition to the personal costs to individuals—including reduced quality of life, lost productivity, and premature mortality—diabetes and its complications pose an unsustainable financial cost to our society. Globally, it has been estimated that diabetes accounts for 10% of health expenditures (760 billion USD) (https://www.diabetesatlas.org/en/resources/). Domestically, the total cost of diagnosed diabetes in the United States during 2017 was estimated at $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity—an increase of 26% since 2012. Of total health care expenditures, about 24% (one in every four health care dollars) is incurred by people with diabetes (American Diabetes Association, 2018). Therefore, to address this burden, we must continue to support innovative research and successfully translate effective management strategies for diabetes and its complications.

It is also imperative that we have a renewed focus on obesity prevention and treatment, given the well-documented contribution of obesity to type 2 diabetes etiology. Most keenly illustrating this relationship, it has been estimated that among US adults aged 18 years or older with diagnosed diabetes in 2013–2016, 89.0% had overweight or obesity, defined as a

body mass index (BMI) of 25 kg/m^2 or higher (https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf). Global obesity prevalence has increased in boys and girls from <1% in 1975 to 6%–8% in 2016 (Jaacks et al., 2019). Over the same time period, there has been a global increase in prevalence for both men (3%–11%) and women (6%–15%) (Jaacks et al., 2019). Alarmingly, data indicate that an estimated 42.4% of US adults had obesity (defined as BMI of 30 kg/m^2 or higher) in 2017–2018 (https://www.cdc.gov/nchs/products/databriefs/db360.htm). Increasing obesity rates are a significant domestic and global health concern as individuals with obesity are at increased risk not only for type 2 diabetes, but also other serious chronic diseases, such as CVD and hypertension, as well as premature death. Indeed, one study found that of 84 behavioral, environmental, occupational, and metabolic risks evaluated, high BMI ranked as the fourth highest in attributable deaths and disability-adjusted life-years (Jaacks et al., 2019; GBD 2017 Risk Factor Collaborators, 2018). Clearly, addressing the diabetes burden will require our society to focus on obesity prevention and treatment; as elegantly summarized in a 2018 Endocrine Society Statement, ''control of obesity is the most important public health strategy for the prevention of diabetes and its devastating consequences'' (Bray et al., 2018).

DISPARITIES AND METABOLIC DISEASE

When evaluating the burden of metabolic diseases in the United States, significant disparities exist in prevalence, incidence, and mortality among racial and ethnic minority groups (Clements et al., 2020; Thornton et al., 2020). Specifically, compared to non-Hispanic Whites, American Indian, Native Hawaiian and Pacific Islander, Alaska Native, Hispanic, and non-Hispanic Black adults are disproportionately affected by type 2 diabetes and obesity (Thornton et al., 2020). For example, Black adults have a prevalence rate for type 2 diabetes nearly double that of non-Hispanic Whites, and this gap in prevalence and incidence seems only to have been on the increase over a 30-year span (Bancks et al., 2017; Menke et al., 2015). In 2017–2018, the prevalence of obesity for non-Hispanic Whites was 42.2% compared with 44.8% in Hispanics; non-Hispanic Black adults had the highest prevalence of obesity—49.6%—compared with all other race and Hispanic-origin groups (https://www.cdc.gov/nchs/products/databriefs/db360.htm).

Unfortunately, disparities are also increasingly observed for metabolic disease in our youth. The SEARCH study has reported that youth and adolescents who develop type 2 diabetes and are primarily obese disproportionately represent US racial and ethnic minority groups. The study reported that between 2002 and 2015, the incidence of type 2 diabetes increased among youth (10–19 years old) in all age, sex, and race/ethnicity groups, with the exception of non-Hispanic Whites (https://www.cdc.gov/mmwr/volumes/69/wr/mm6906a3.htm). The steepest increase was seen among Asians/Pacific Islanders (7.7% per year), whereas Hispanics, non-Hispanic Blacks, and American Indians had reported rates of 6.5%, 6.0%, and 3.7%, respectively (https://www.cdc.gov/mmwr/volumes/69/wr/mm6906a3.htm).

Increasing cases of youth-onset type 2 diabetes associated with obesity is a concerning trend given that type 2 diabetes in youth and adolescents is considered a more aggressive disease. Data indicate that it may exhibit more rapid progression of heart, eye, and kidney disease; appears to be less responsive to medication; and has a markedly different pathophysiology than in adults (Nadeau et al., 2016). It is sobering to read reports projecting that adolescents with type 2 diabetes may lose approximately 15 years of life expectancy and may also have a reduced quality of life due to the development of chronic diabetes complications in mid-life (Rhodes et al., 2012).

The existing disparities in type 2 diabetes and obesity prevalence and outcomes for both youth and adults should raise significant concern outside the context of a pandemic. But given the stark reality that diabetes and obesity and their associated comorbidities markedly increase COVID-19 severity and can increase hospitalization and mortality by over 2-fold, there is a greatly heightened awareness of disparities in metabolic disease from a public health perspective (Apicella et al., 2020).

DISPARITIES IN COVID-19 SEVERITY AND MORTALITY

Since the onset of the COVID-19 pandemic and with the prolonged course and surge in new cases, we have learned a great deal about major risk factors, management strategies, and innovative therapeutics for COVID-19 illness. It has become clear that increasing age, certain comorbidities (diabetes, obesity, CVD, and chronic kidney disease), and gender are strongly associated with COVID-19 severity and mortality (Apicella et al., 2020; Mauvais-Jarvis, 2020; Muniyappa and Gubbi, 2020) (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). Whereas the mechanisms by which these conditions predispose to severity are not precisely known, it is postulated that these risk factors and conditions lead to tissue and cellular interactions with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the causative agent of COVID-19—that contribute greatly to the cytokine storm characteristic of more serious disease (Mauvais-Jarvis, 2020). There is ample evidence to show that obesity as assessed by BMI is associated with increased mortality and greater likelihood of mechanical ventilation (Simonnet et al., 2020; Tartof et al., 2020). Population-based cohort studies have reported increased mortality in people with either type 1 or type 2 diabetes who develop COVID-19, and that age increases this risk in those with either type of diabetes (Holman et al., 2020; Barron et al., 2020). Increased COVID-19-related mortality in people with diabetes has also been associated with BMI, cardiovascular and renal complications, and glycemic control as assessed by HbA1c (Holman et al., 2020; Barron et al., 2020). Moreover, better glycemic control in those with type 2 diabetes has been associated with lower mortality compared with poor glycemic control (Zhu et al., 2020). Taken together, the studies to date confirm that having obesity or diabetes confers a significantly greater risk of disease severity or death from COVID-19.

As the pandemic unfolded, it also became very clear that US racial and minority populations are disproportionately affected, with the observations that non-Hispanic Black, Native American, and Latinx populations bear the greatest burden. Conducting a cross-sectional study using publicly reported COVID-19 mortality data available at the time, Gross et al. (2020) showed a mortality ratio of 3.57 when comparing Black with White populations,

and 1.88 when comparing Latinx with White populations. More recent reports continue to show that Black and Hispanic populations are much more highly represented among COVID-19-related deaths than each of these groups is represented percentage-wise in the general population, and that racial and ethnic disparities among COVID-19 decedents have persisted over the course of the pandemic—and, if anything, may be increasing among Hispanics (https://www.cdc.gov/mmwr/volumes/69/wr/mm6942e1.htm#:~:text=Analysis%20of%20114%2C411%20COVID%2D19,%25%20were%20non%2DHispanic%20Black).

The question remains as to what factors are responsible for the racial and ethnic differences in COVID-19 morbidity and mortality. Recently, a review on the topic suggested that there are no differences in genetic or immune disposition by race or ethnicity, and that racial and ethnic differences cannot be accounted for by ABO blood groups or by use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) (Carethers, 2020). However, it was suggested by the authors that the observed disparity in COVID-19 outcomes experienced by multiple racial and ethnic minority groups in the United States and the United Kingdom may "have its origins in systemic structural disadvantages for this population which set up the development of co-morbidities, with this population ultimately disproportionately acquiring high risk factors for COVID-19" (Carethers, 2020). Thus, there is heightened awareness of the important role that environmental, economic, and social disadvantages play in promoting development of metabolic diseases, prompting a renewed focus on social determinants of health as central to the etiology of the disparities we are witnessing for metabolic diseases and COVID-19 (Butler, 2017). Social determinants of health (SDOH) have been defined as "the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks" (https://www.cdc.gov/socialdeterminants/index.htm). SDOH have been grouped into five domains: economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context (https://www.cdc.gov/socialdeterminants/index.htm). Thus, examples of "structural disadvantages" that were recently reported and that may be playing a role in COVID-19 disparities and applicable to SDOH domains may include (1) lower college attainment, (2) greater representation in jobs that are less likely to allow work at home (e.g., food and transportation industry occupations) and therefore limit ability to adhere to social distancing guidelines, (3) disadvantages in housing (i.e., large number in household for house size) and low income neighborhood location, and (4) lower household income (Carethers, 2020).

The concepts outlined above suggest that environmental, economic, and social disadvantages may be major contributing factors for the increased severity of disease and mortality from COVID-19 for certain racial and ethnic minority groups in the United States (Figure 1). Thus, it is of great interest that several reports suggest that adjustment for these conditions greatly reduces the observed mortality rate. For example, in a retrospective cohort study in Louisiana, Price-Haywood et al. (2020) analyzed data from 3,481 patients. Although Blacks represented only 31% of the health system's population, they represented 70.4% of the COVID-19 patients and had greater prevalence of metabolic diseases (obesity, diabetes, hypertension, and chronic kidney diseases) than White patients. Black race, increasing age, greater burden of disease (Charlson Comorbidity Index), having public insurance, living in a low-income area, and obesity were all associated with increased chance for hospitalization. However, after adjustment for differences in sociodemographic and clinical characteristics on admission, the authors reported that Black race was not associated with higher mortality in the hospital than White race (Price-Haywood et al., 2020). Yehia et al. (2020) evaluated the association of race with mortality in patients hospitalized with COVID-19 at 92 hospitals. They also reported in their study that Black patients had higher prevalence of diabetes, hypertension, and chronic kidney disease. However, after adjusting for sociodemographic factors and comorbidities, there was no statistical difference in all-cause, in-hospital mortality between Blacks and Whites. These studies do confirm the observations that certain racial and ethnic groups have a higher risk for COVID-19 illness, but also provide evidence that the observed disparities appear to be present at diagnosis and prior to hospitalization, as mortality did not differ based on race for those able to access the hospital (Yehia et al., 2020). Given the evidence from the reports cited above, and as outlined by the Centers for Disease Control and Prevention, race and ethnicity can be considered as "risk markers for other underlying conditions that impact health," which include sociodemographic factors, health care access, increased risk of COVID-19 exposure due to one's occupation, etc. (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html). With this concept in mind, Belanger et al. (2020), in an elegant perspective on the topic, proposed SDOH (including racism, access to healthy foods, and health care) as the "root cause" of racial and ethnic health disparities from COVID-19 and, more specifically, identified long-standing disparities in nutrition and obesity (and the resulting obesity-related complications of diabetes, hypertension, and CVD) in the United States as playing "a crucial role in the health inequities unfolding during the pandemic."

RESEARCH GAPS IN COVID-19 AND METABOLIC DISEASES

Our scientific and medical community has never before witnessed such a health and humanitarian crisis as we are seeing today with the COVID-19 pandemic. Despite the many challenges, we have already learned a great deal about the mode of entry for SARS-CoV-2, the resulting pathophysiology, associated risk factors, and the importance of simple public health measures of social distancing, wearing masks, and washing hands to prevent contracting the virus and developing COVID-19 illness. The National Institutes of Health has been part of a coordinated effort to tackle the COVID-19 crisis, developing and funding many research opportunities related to therapeutics, diagnostic testing, and other critical issues (https://grants.nih.gov/grants/guide/COVID-Related.

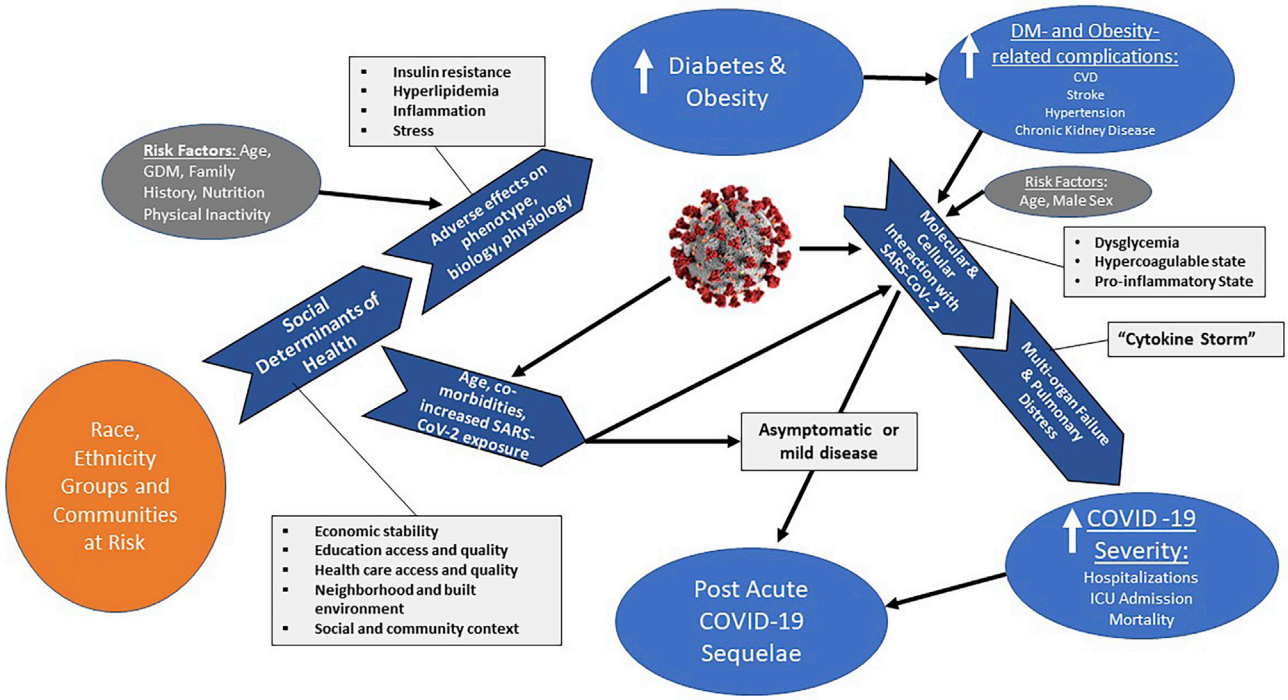

Figure 1. Interaction of environmental, economic, and social disadvantages to metabolic diseases and COVID-19 infection and severity

Environmental, economic, and social disadvantages as assessed from social determinants of health domains may contribute greatly to increased prevalence of the metabolic diseases (obesity and diabetes) and to greater disease burden with COVID-19. As outlined, certain racial and ethnic minority groups have higher rates of obesity and diabetes, due in part to SDOH. Upon SARS-CoV-2 infection, the adverse metabolic conditions (i.e., pro-inflammatory, pro-coagulable state, dysglycemia) present in those with metabolic diseases (such as diabetes and obesity) may predispose to molecular and tissue interactions that lead to a cytokine storm and increased severity of COVID-19 disease and mortality in those individuals at high risk, whereas others remain asymptomatic or with mild disease. In addition, even in the absence of co-morbid conditions such as diabetes and obesity, some racial and ethnic groups are at increased risk for SARS-CoV-2 exposure and therefore also at risk for its acute and post-acute sequalae. DM, diabetes mellitus; GDM, gestational diabetes mellitus. Adapted from concepts presented in Muniyappa and Gubbi (2020); Carethers (2020); Butler (2017); Mauvais-Jarvis (2020).

cfm). Based on the new research efforts, we have noted incredible and rapid progress with the development of novel therapeutics and have seen at least two vaccines move from clinical trials to become part of nationwide vaccination programs in less than a year. However, we are still on a steep learning curve with this pandemic; for example, as we detail below, there are growing concerns regarding post-acute COVID-19 sequelae (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/late-sequelae.html). As we learn even more about the virus and COVID-19 illness, research opportunities will continue to emerge. But based on the evidence to date specifically for metabolic disease and COVID-19, there are a number of observations that represent important research opportunities:

- Obesity and obesity-related conditions are major risk factors for COVID-19 severity.
- Diabetes is associated with a greater than 2-fold increased risk of death and other adverse outcomes from COVID-19.
- Obesity and type 2 diabetes disproportionally affect people from minority racial and ethnic populations in the United States and people in lower socio-economic status groups, which appears to be the case with COVID-19 illness as well, suggesting that SDOHs are playing a major role in observed COVID-19 disparities.
- There appear to be associations between hyperglycemia and poor outcomes in patients with diabetes hospitalized with COVID-19, and glycemic management has not been adequately studied.
- Cellular mechanisms explaining the increased morbidity and mortality in individuals with diabetes and obesity are postulated, but still not precisely known, and if known, could greatly inform development of effective interventions.
- Finally, of great importance is the putative role COVID-19 plays in unmasking diabetes or inducing new cases.

Given the observations reported above, and the fact that diabetes and obesity are diseases of great interest to our institute, the NIDDK has already responded with research funding opportunities for COVID-19. In April 2020, the NIDDK published a notice alerting our scientific community to the urgent need for research on COVID-19 related to the mission of NIDDK, through which we provided supplemental funding awards to grantees who revised the scope of ongoing projects to focus on questions regarding the direct action of SARS-CoV-2 on kidney, gastrointestinal tract function, and the endocrine/metabolic system, as well as the collection of biosamples that could help inform the understanding of renal, gastrointestinal, and endocrine/metabolic sequelae of viral infection (https://grants.nih.gov/grants/

guide/notice-files/NOT-DK-20-018.html). More recently, the NIDDK published a funding opportunity announcement through which we expect to support new, mechanistic-oriented research projects in 2021 that will investigate the pathways responsible for increased adverse outcomes in COVID-19—either due to diseases of interest to NIDDK or that result in damage to organs of interest to NIDDK—in cells, tissues, animal models, and human subjects (https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-021.html). Specific study questions of interest for diabetes, obesity and nutrition, and metabolic and endocrine diseases include:

- Exploring the mechanisms for any increased susceptibility or altered course of COVID-19 due to type 1 or type 2 diabetes or diabetic complications;
- Identifying the roles of dysregulated glycemia, insulin resistance, insulin secretion, etc., in severity of response to COVID-19;
- Exploring mechanisms whereby COVID-19 results in acute or chronic metabolic dysfunction, or the onset of diabetes or other endocrine diseases;
- Identifying mechanisms involved in alterations in the course of existing type 1 or type 2 diabetes or the complications of diabetes following COVID-19;
- Identifying the specific tissues, biological systems, and pathways that explain the increased susceptibility, greater severity, or diminished response to treatment for COVID-19 in patients with obesity;
- Elucidating the aspects of adipose tissue biology that could play a key role in regulating or modulating the severity of COVID-19, disease course, response to treatment, and outcomes in the obese state;
- Determining the mechanisms by which differences in nutritional status, including micronutrient status and metabolism, impact observed variability and disparities in COVID-19 susceptibility, course, and response to treatment; and
- Determining the mechanisms by which diet-host-microbiome interactions impact the course of COVID-19 and/or are affected by COVID-19.

In addition to our interest in the mechanisms outlined above, we now recognize that many individuals experience persistent symptoms (e.g., fatigue, respiratory issues, inability to concentrate) after recovering from their initial illness that may be considered manifestations of post-acute COVID-19 syndrome, or PACS. (Huang et al., 2021). At this time, the etiology of PACS is not precisely known, and as such, we lack effective therapies to address it. However, the same factors leading to higher prevalence of COVID-19 disease in certain racial and ethnic groups will likely have equal significance for PACS. Given the enormous number of COVID-19 cases in the United States, even if only a small percentage of individuals develop PACS, this post-acute condition will have a significant and adverse impact on the public health and welfare, particularly combined with the pre-existing burden of diabetes, obesity, kidney diseases, and other noncommunicable chronic diseases.

While we are now at a place and time that the mechanistic studies and questions outlined above are critical to understanding the clinical and physiologic effect of COVID-19 in individuals with metabolic disease, we also understand that it is equally important that we address the underlying conditions predisposing to COVID-19 severity. Thus, there is a need to focus on SDOH and truly understand how these factors contribute to human phenotype, biology, and physiology in ways that adversely affect an individual's health and contribute to increasing prevalence of metabolic diseases. We recognize that certain racial and ethnic groups bear a disproportionate burden of the metabolic diseases of interest to the NIDDK and that these diseases are major risk factors for COVID-19 illness. Thus, we remain committed to research programs aimed at reducing COVID-19 disparities.

Recently, we described major avenues that the NIDDK is pursuing to alleviate health disparities in its mission diseases. These include identifying the causes of health disparities and supporting clinical research to test viable hypotheses (Roberts and Rodgers, 2020). We have long recognized that disparities in NIDDK mission diseases may stem partly from biological differences, but now we have a heightened awareness, due to what we are witnessing form the pandemic, that disparities stem from systemic differences in access to care, environmental exposures, and other external factors. These factors remain of equal interest and, thus, we confirm our commitment to support research on social determinants of health. Research in this direction will not only help increase our understanding of diseases of interest to NIDDK during the pandemic, but can also greatly inform post-pandemic research. We previously stated that SDOH "is crucial for lighting a path toward health equity and a vital complement to studying the biological etiology of disparities" (Roberts and Rodgers, 2020). Given the public health crisis brought on by COVID-19, this stands out for the NIDDK as a significant research need.

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AUTHOR CONTRIBUTIONS

W.T.C. and G.P.R. wrote and edited this work. Both authors reviewed and edited final content.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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