Biological Psychiatry

Psychosocial Risk Factors, Noncommunicable Diseases, and Animal Models for COVID-19

To the Editor:

As summarized by several recent papers, numerous species can be infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), thus representing useful models for coronavirus disease 2019 (COVID-19) (1). While hamsters, ferrets, monkeys, and other species can be infected by SARS-CoV-2, mice cannot, emphasizing the utility of recently developed humanized mouse models, and viral vectors expressing human angiotensin-converting enzyme 2 (hACE2), the main target of SARS-CoV-2 (1,2). However, there are considerable limits if such approaches predominately utilize healthy young experimental subjects (1) or if viral infection is lethal in a high proportion of mice within a few days (2), a condition that is not observed in humans.

Nearly All Subjects With Severe Cases of COVID-19 Have Multiple Preexisting Noncommunicable Diseases

With most COVID-19 cases being asymptomatic, with no robust evidence that disease severity associates with genetic predisposition (3,4), and with aging being a well-documented risk factor, it is significant that 90% of individuals with severe cases requiring hospitalization have multiple preexisting noncommunicable diseases (NCDs). Common NCDs in COVID-19 patients are type 2 diabetes, hypertension, obesity, and chronic lung disease (Table 1).

Psychosocial Stress Increases Risk for Disease Susceptibility

Critically, several studies confirmed that severity of COVID-19 is disproportionately common in patients from low socioeconomic status (SES) groups and minorities experiencing multimorbidity and low life expectancy (5,6). The high susceptibility conferred by low SES can be explained in part by living in high-density housing, not having the option to comfortably quarantine, having unsafe working conditions, living with poor ventilation and air quality, and so forth. However, it has long been recognized that a gradient in the impact of SES on health exists in virtually any context in which this has been assessed, including in wealthier societies (5). Low SES strata are characterized by unpredictable and uncontrollable living conditions, high-stress biomarkers, and cumulative negative life events (7–9), and it is increasingly accepted that the risk conferred by low SES can be at least in part attributed to an underlying biology that is only recently starting to emerge and to be investigated at the physiological and molecular levels (5,8,10,11). Another indirect evidence that chronic stress can be involved in COVID-19 pathogenesis comes from the beneficial effect of dexamethasone for severe cases (12). Dexamethasone, in addition to limiting inflammation via glucocorticoid receptor–mediated activation, is well known to suppress the endogenous stress-related hypothalamic-pituitary-adrenocortical axis (13) and thus the endogenous secretion of adrenocorticotropic hormone and cortisol, two of the major stress hormones (14). Thus, it is reasonable to speculate that the inhibition of the endocrine stress response is among the benefits of short-term dexamethasone treatment in patients affected by COVID-19.

Overall, diseases exacerbating the COVID-19 prognosis appear to be highly sensitive to psychosocial risk factors. In particular, psychosocial stress mediates much of the link between low SES and high prevalence of NCDs (7,8); commensurate with that, NCDs and life-threatening COVID-19 outcomes disproportionately impact low SES communities and disadvantaged minorities (5,15).

Chronic Social Stress Animal Models Recapitulate the Multiple Comorbidities Increasing Risk for Severe COVID-19

These risk factors suggest that the conventional approach of cross-breeding humanized models of COVID-19 with monogenetic models of human disease, using pharmacological or surgical models (Table 1), or injecting viruses in mice expressing hACE2 in the same disease models, should not be the preferred approach, as it is unlikely to model the complexity of human risk factors. Consistent with this idea, SARS-CoV-2 injection in even healthy young mice engineered to express hACE2 rapidly resulted in death (2). Such risk factors suggest the importance of alternative approaches and the need to combine humanized mouse models of COVID-19 with models of multiple comorbid NCDs.

Here, we provide a rationale for the use of social and behavioral laboratory models of multiple comorbidities, including obesity, hypertension, cardiovascular disease, and accelerated senescence, in the study of COVID-19. Extensive research, including our own, has focused on models of chronic social stress that are contingent on negative social relationships built around uncontrollable and perceived potential life-threatening conditions (9,16,17). Such stress-based models can be ideal for studying the interactions between COVID-19 and NCDs. These are arguably the most potent and reliable (nongenetic and nonpharmacological) models to induce multiple comorbid disease observed in severe cases of COVID-19, such as obesity, type 2 diabetes, hypertension, a proinflammatory state, neurological and neuropsychiatric diseases, and accelerated aging, overall resulting in a shortened lifespan (18) (Table 1). Thus, we advocate for a research focus on 1) studies of humanized COVID-19 mice undergoing classic psychosocial stress models for worsening NCDs relevant to COVID-19 risk and 2) the use of hACE2 viral vectors coupled with such psychosocial stress models in wild-type animals, particularly old subjects. An interesting new opportunity provided by the selection of mutant SARS-CoV-2 viruses capable of infecting common laboratory strains of mice (19) is to pair the use of these viruses with chronic psychosocial stress paradigms in order to optimally model the human condition.

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Table 1. List of Preconditions Increasing Severe COVID-19 and Animal Models of Diseases

CDC List of Medical Conditions That Increase a Person's Risk of Severe Illness From COVID-19[a]			Laboratory Rodent Models for These Medical Conditions	
Level of Evidence	Condition	Evidence of Impact on COVID-19 Severity	Conventional Genetic, Pharmacological, or Surgical Models[b]	Disease Manifested by Laboratory Rodents Exposed to Chronic Social Stress
Strongest and Most Consistent Evidence	Cancer	Systematic review (21) Cohort study (22,23) Case series (24)	Cell line–derived xenograft; genetically engineered mouse cancer model (25,26)	Exacerbates the disease in genetic or xenograft inoculation models; spontaneous tumor development during aging (18,27)
	Chronic kidney disease	Case series (28–30) Cohort study (31–33)	Cisplatin injection; subtotal nephrectomy, DOCA-salt (34,35)	Exacerbates the disease in genetic models or vulnerable strains (27,36)
	COPD	Meta-analysis (37,38) Cohort study (32)	Elastase; chronic cigarette smoke exposure (39)	NA
	Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies	Cohort study (40,41) Meta-analysis (37,42) Case series (43)	Surgical pressure overload; ischemia-reperfusion injury; metabolic syndrome models (44)	Sustained tachycardia, arrhythmia; cardiac hypertrophy in some model; exacerbates cardiac disease in genetic models (45,46)
	Obesity (BMI ≥30 kg/m^2)	Cohort study (29,47–51) Cross-sectional study (52)	ob/ob; db/db; diet-induced obesity (53,54)	Causes hyperphagia and weight gain/obesity (model specific) (17)
	Severe obesity (BMI ≥40 kg/m^2)	Cohort study (55) Cross-sectional study (56) Meta-analysis (57)	ob/ob; db/db; diet-induced obesity (53,54)	No morbid obesity has been reported
Mixed Evidence	Type 2 diabetes mellitus	Case series (29) Longitudinal study (58) Cohort study (59,60) Meta-analysis (61) Cross-sectional study (62)	B6 ob/ob; BKS db/db; Zucker diabetic fatty; TALLYHO/JngJ (63)	Causes pre–type 2 diabetes and metabolic syndrome in WT; exacerbates diabetes in genetic strains (17,64)
	Asthma	Cohort study (32,64–68) Case series (68)	BALB/c injected with ovalbumin house dust mite (69)	Enhances allergen-induced airway inflammation (70)
	Cerebrovascular disease	Meta-analysis (71–74) Synthesis of evidence (75) Cohort study (40,41,76–78)	Intracarotid injection of occlusive microbeads/cholesterol crystals; carotid artery stenosis; BCAS mice (79,80)	Exacerbates stroke outcome and cerebrovascular disfunctions (81,82)
	Hypertension	Cohort study (32,40,41,83–85) Case series (86) Systematic review (87) Meta-analysis (37,42,88,89)	SHR rats; BPH mice; DOCA-salt; AngII injection (35)	Causes persistent increase in mean arterial pressure and heart rate (46,90)

AngII, angiotensin II; BCAS, bilateral common carotid artery stenosis; BMI, body mass index; CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease; db/db, diabetic mice; DOCA, deoxycorticosterone acetate; NA, not available; ob/ob, obese mice; SHR, spontaneously hypertensive rat; WT, wild-type.

[a]From (91).

[b]Only the most common models are described in this table: "strongest and most consistent evidence" = consistent evidence from multiple small studies or a strong association from a large study (CDC classification); "mixed evidence" = multiple studies that reached different conclusions about risk associated with a condition (CDC classification). The "limited evidence" category from the CDC website was omitted from this table. Additional references and preprints are available (91).

Conclusions

Mental stress has been advocated as a consequence of the COVID-19 pandemic, leading to negative long-term risk for psychopathologies (20). Here, we suggest that the reverse should also be considered. A direct causal effect of chronic stress mediators and underlying multiple comorbidities should be considered as a leading risk factor for this new disease. The catastrophic impact of SARS-CoV-2 is deeply intertwined with NCDs and psychosocial risk factors, and the use of naturalistic NCD models more closely reflecting the human disease seems essential.

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References

1. Muñoz-Fontela C, Dowling WE, Funnell SGP, Gsell P-S, Balta XR, Albrecht RA, *et al.* (2020): Animal models for COVID-19. Nature 586:509–515.
2. Zheng J, Wong LR, Li K, Verma AK, Ortiz ME, Wohlford-Lenane C, *et al.* (2021): COVID-19 treatments and pathogenesis including anosmia in K18-hACE2 mice. Nature 589:603–607.
3. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, *et al.* (2020): Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 370:eabd4570.
4. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, *et al.* (2020): Genomewide association study of severe Covid-19 with respiratory failure. N Engl J Med 383:1522–1534.
5. Marmot M (2020): Society and the slow burn of inequality. Lancet 395:1413–1414.
6. Stringhini S, Carmeli C, Jokela M, Avendaño M, Muennig P, Guida F, *et al.* (2017): Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: A multicohort study and meta-analysis of 1·7 million men and women. Lancet 389:1229–1237.
7. Marmot MG, Sapolsky R (2014): Of baboons and men: Social circumstances, biology, and the social gradient in health. In: Weinstein M, Lane MA, editors. Sociality, Hierarchy, Health: Comparative Biodemography: A Collection of Papers. Washington, DC: National Academies Press, 365–388.
8. Snyder-Mackler N, Burger JR, Gaydosh L, Belsky D, Noppert G, Campos FA, *et al.* (2020): Social determinants of health and survival in humans and other animals. Science 368:eaax9553.
9. Koolhaas JM, Bartolomucci A, Buwalda B, de Boer SF, Flügge G, Korte SM, *et al.* (2011): Stress revisited: A critical evaluation of the stress concept. Neurosci Biobehav Rev 35:1291–1301.
10. Sapolsky RM (2005): The influence of social hierarchy on primate health. Science 308:648–652.
11. Bartolomucci A (2007): Social stress, immune functions and disease in rodents. Front Neuroendocrinol 28:28–49.
12. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al.* (2021): Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 384:693–704.
13. Jacobson L, Sapolsky R (1991): The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. Endocr Rev 12:118–134.
14. Ferraù F, Ceccato F, Cannavò S, Scaroni C (2021): What we have to know about corticosteroids use during Sars-Cov-2 infection. J Endocrinol Invest 44:693–701.
15. Wiemers EE, Abrahams S, AlFakhri M, Hotz VJ, Schoeni RF, Seltzer JA (2020): Disparities in vulnerability to complications from COVID-19 arising from disparities in preexisting conditions in the United States. Res Soc Stratif Mobil 69:100553.
16. Takahashi A, Flanigan ME, McEwen BS, Russo SJ (2018): Aggression, social stress, and the immune system in humans and animal models. Front Behav Neurosci 12:56.
17. Razzoli M, Pearson C, Crow S, Bartolomucci A (2017): Stress, overeating, and obesity: Insights from human studies and preclinical models. Neurosci Biobehav Rev 76:154–162.
18. Razzoli M, Nyuyki-Dufe K, Gurney A, Erickson C, McCallum J, Spielman N, *et al.* (2018): Social stress shortens lifespan in mice. Aging Cell 17:e12778.
19. Leist SR, Dinnon KH, Schäfer A, Tse LV, Okuda K, Hou YJ, *et al.* (2020): A mouse-adapted SARS-CoV-2 induces acute lung injury and mortality in standard laboratory mice. Cell 183:1070–1085.e12.
20. Vinkers CH, van Amelsvoort T, Bisson JI, Branchi I, Cryan JF, Domschke K, *et al.* (2020): Stress resilience during the coronavirus pandemic. Eur Neuropsychopharmacol 35:12–16.
21. Fung M, Babik JM (2021): COVID-19 in immunocompromised hosts: What we know so far. Clin Infect Dis 72:340–350.
22. Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, *et al.* (2020): Determinants of COVID-19 disease severity in patients with cancer. Nat Med 26:1218–1223.
23. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, *et al.* (2020, March 1): Cancer patients in SARS-CoV-2 infection: A nationwide analysis in China. Lancet Oncol 21:335–337.
24. Zhang H, Wang L, Chen Y, Wu Q, Chen G, Shen X, *et al.* (2020): Outcomes of novel coronavirus disease 2019 (COVID-19) infection in 107 patients with cancer from Wuhan, China. Cancer 126: 4023–4031.
25. Day CP, Merlino G, Van Dyke T (2015): Preclinical mouse cancer models: A maze of opportunities and challenges. Cell 163:39–53.
26. Walrath JC, Hawes JJ, Van Dyke T, Reilly KM (2010): Genetically engineered mouse models in cancer research. Adv Cancer Res 106:113–164.
27. Schmidt D, Peterlik D, Reber SO, Lechner A, Männel DN (2016): Induction of suppressor cells and increased tumor growth following chronic psychosocial stress in male mice. PLoS One 11:e0159059.
28. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, *et al.* (2020): Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 — COVID-NET, 14 states, March 1–30, 2020. MMWR Morb Mortal Wkly Rep 69:458–464.
29. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al.* (2020): Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 323:2052–2059.
30. Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, *et al.* (2020): Covid-19 and kidney transplantation. N Engl J Med 382:2475–2477.
31. Myers LC, Parodi SM, Escobar GJ, Liu VX (2020): Characteristics of hospitalized adults with COVID-19 in an integrated health care system in california. JAMA 323:2195–2198.
32. Gold JAW, Wong KK, Szablewski CM, Patel PR, Rossow J, da Silva J, *et al.* (2020): Characteristics and clinical outcomes of adult patients hospitalized with COVID-19 — Georgia, March 2020. MMWR Morb Mortal Wkly Rep 69:545–550.

33. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, *et al.* (2020): Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 98:209–218.
34. Rabe M, Schaefer F (2016): Non-transgenic mouse models of kidney disease. Nephron 133:53–61.
35. Lerman LO, Kurtz TW, Touyz RM, Ellison DH, Chade AR, Crowley SD, *et al.* (2019): Animal models of hypertension: A Scientific Statement From the American Heart Association. Hypertension 73:e87–e120.
36. Bennett WM, Walker RG, Henry JP, Kincaid Smith P (1983): Chronic interstitial nephropathy in mice induced by psychosocial stress: Potentiation by caffeine. Nephron 34:110–113.
37. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, *et al.* (2020): Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. Int J Infect Dis 94:91–95.
38. Lippi G, Henry BM (2020): Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19): COPD and COVID-19. Respir Med 167:105941.
39. Serban KA, Petrache I (2018): Mouse models of COPD. Methods Mol Biol 1809:379–394.
40. Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T, *et al.* (2020): Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest 158:97–105.
41. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, *et al.* (2020): Factors associated with COVID-19-related death using OpenSAFELY. Nature 584:430–436.
42. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, *et al.* (2020): Risk factors of critical and mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect 81:e16–e25.
43. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, *et al.* (2020): Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 5:811–818.
44. Riehle C, Bauersachs J (2019): Small animal models of heart failure. Cardiovasc Res 115:1838–1849.
45. Sgoifo A, Carnevali L, Grippo AJ (2014): The socially stressed heart. Insights from studies in rodents. Neurosci Biobehav Rev 39:51–60.
46. Razzoli M, Lindsay A, Law ML, Chamberlain CM, Southern WM, Berg M, *et al.* (2020): Social stress is lethal in the mdx model of Duchenne muscular dystrophy. EBioMedicine 55:102700.
47. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, Stachel A (2020): Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. Clin Infect Dis 71:896–897.
48. Hur K, Price CPE, Gray EL, Gulati RK, Maksimoski M, Racette SD, *et al.* (2020): Factors associated with intubation and prolonged intubation in hospitalized patients with COVID-19. Otolaryngol Head Neck Surg 163:170–178.
49. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, *et al.* (2020): High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity 28:1195–1199.
50. Kalligeros M, Shehadeh F, Mylona EK, Benitez G, Beckwith CG, Chan PA, Mylonakis E (2020): Association of obesity with disease severity among patients with coronavirus disease 2019. Obesity 28:1200–1204.
51. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, *et al.* (2020): Severe obesity is associated with higher in-hospital mortality in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism 108:154262.
52. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, *et al.* (2020): Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. BMJ 369:m1966.
53. Barrett P, Mercer JG, Morgan PJ (2016): Preclinical models for obesity research. Dis Model Mech 9:1245–1255.
54. Brockmann GA, Bevova MR (2002): Using mouse models to dissect the genetics of obesity. Trends Genet 18:367–376.
55. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, *et al.* (2020): Obesity and mortality among patients diagnosed with COVID-19: Results from an integrated health care organization. Ann Intern Med 173:773–781.
56. Ko JY, Danielson ML, Town M, Derado G, Greenlund KJ, Daily Kirley P, *et al.* (2020): Risk factors for COVID-19-associated hospitalization: COVID-19–Associated Hospitalization Surveillance Network and Behavioral Risk Factor Surveillance System [published online ahead of print Sep 18]. Clin Infect Dis.
57. Bellino S, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, *et al.* (2020): COVID-19 disease severity risk factors for pediatric patients in Italy. Pediatrics 146:e2020009399.
58. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, *et al.* (2020): Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing Type 2 diabetes. Cell Metab 31:1068–1077.e3.
59. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, Klonoff DC (2020): Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol 14:813–821.
60. Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, *et al.* (2020): Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes Care 43:1399–1407.
61. Fadini GP, Morieri ML, Longato E, Avogaro A (2020): Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest 43:867–869.
62. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, *et al.* (2020): Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: A whole-population study. Lancet Diabetes Endocrinol 8:813–822.
63. Leiter EH (2009): Selecting the "right" mouse model for metabolic syndrome and type 2 diabetes research. Methods Mol Biol 560:1–17.
64. Razzoli M, McCallum J, Gurney A, Engeland WC, Bartolomucci A (2015): Chronic stress aggravates glucose intolerance in leptin receptor-deficient (db/db) mice. Genes Nutr 10:458.
65. Mahdavinia M, Foster KJ, Jauregui E, Moore D, Adnan D, Andy-Nweye AB, *et al.* (2020): Asthma prolongs intubation in COVID-19. J Allergy Clin Immunol Pract 8:2388–2391.
66. Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, *et al.* (2020): Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 at a tertiary care medical center in New York City. J Pediatr 223:14–19.e2.
67. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, *et al.* (2020): Severe coronavirus disease-2019 in children and young adults in the Washington, DC, Metropolitan Region. J Pediatr 223:199–203.e1.
68. Chow N, Fleming-Dutra K, Gierke R, Hall A, Hughes M, Pilishvili T, *et al.* (2020): Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 — United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 69:382–386.
69. Nials AT, Uddin S (2008): Mouse models of allergic asthma: Acute and chronic allergen challenge. Dis Model Mech 1:213–220.
70. Bailey MT, Kierstein S, Sharma S, Spaits M, Kinsey SG, Tliba O, *et al.* (2009): Social stress enhances allergen-induced airway inflammation in mice and inhibits corticosteroid responsiveness of cytokine production. J Immunol 182:7888–7896.
71. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J (2020): Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19–Systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis 29:104949.
72. Wang B, Li R, Lu Z, Huang Y (2020): Does comorbidity increase the risk of patients with covid-19: Evidence from meta-analysis. Aging (Albany NY) 12:6049–6057.
73. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM (2020): Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PLoS One 15:e0238215.
74. Khan MMA, Khan MN, Mustagir MG, Rana J, Islam MS, Kabir MI (2020): Effects of underlying morbidities on the occurrence of deaths in COVID-19 patients: A systematic review and meta-analysis. J Glob Health 10:020503.

75. Martins-Filho PR, Tavares CSS, Santos VS (2020): Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. Eur J Intern Med 76:97–99.
76. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, *et al.* (2020): Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 5:802–810.
77. Wang L, He W, Yu X, Hu D, Bao M, Liu H, *et al.* (2020): Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect 80:639–645.
78. Killerby ME, Link-Gelles R, Haight SC, Schrodt CA, England L, Gomes DJ, *et al.* (2020): Characteristics associated with hospitalization among patients with COVID-19 — Metropolitan Atlanta, Georgia, March–April 2020. MMWR Morb Mortal Wkly Rep 69:790–794.
79. Hainsworth AH, Allan SM, Boltze J, Cunningham C, Farris C, Head E, *et al.* (2017): Translational models for vascular cognitive impairment: A review including larger species. BMC Medicine 15:16.
80. Shih AY, Hyacinth I, Hartmann DA, Van Veluw SJ (2018): Rodent models of cerebral microinfarct and microhemorrhage. Stroke 49:803–810.
81. DeVries AC, Joh HD, Bernard O, Hattori K, Hurn PD, Traystman RJ, Alkayed NJ (2001): Social stress exacerbates stroke outcome by suppressing Bcl-2 expression. Proc Natl Acad Sci U S A 98:11824–11828.
82. Lehmann ML, Poffenberger CN, Elkahloun AG, Herkenham M (2020): Analysis of cerebrovascular dysfunction caused by chronic social defeat in mice. Brain Behav Immun 88:735–747.
83. Kim L, Garg S, O'Halloran A, Whitaker M, Pham H, Anderson EJ, *et al.* (2021): Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). Clin Infect Dis 72:e206–e214.
84. Ran J, Song Y, Zhuang Z, Han L, Zhao S, Cao P, *et al.* (2020): Blood pressure control and adverse outcomes of COVID-19 infection in patients with concomitant hypertension in Wuhan, China. Hypertens Res 43:1267–1276.
85. Yanover C, Mizrahi B, Kalkstein N, Marcus K, Akiva P, Barer Y, *et al.* (2020): What factors increase the risk of complications in SARS-CoV-2–infected patients? A cohort study in a Nationwide Israeli Health Organization. JMIR Public Heal Surveill 6:e20872.
86. Gottlieb M, Sansom S, Frankenberger C, Ward E, Hota B (2020): Clinical course and factors associated with hospitalization and critical illness among COVID-19 patients in Chicago, Illinois. Acad Emerg Med 27:963–973.
87. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA (2020): Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression. J Renin Angiotensin Aldosterone Syst 21: 1470320320926899.
88. Matsushita K, Ding N, Kou M, Hu X, Chen M, Gao Y, *et al.* (2020): The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis. Glob Heart 15:64.
89. Wu T, Zuo Z, Kang S, Jiang L, Luo X, Xia Z, *et al.* (2020): Multi-organ dysfunction in patients with COVID-19: A systematic review and meta-analysis. Aging Dis 11:874–894.
90. Finnell JE, Lombard CM, Padi AR, Moffitt CM, Wilson LB, Wood CS, Wood SK (2017): Physical versus psychological social stress in male rats reveals distinct cardiovascular, inflammatory and behavioral consequences. PLoS One 12:e0172868.
91. Centers for Disease Control and Prevention (2020): Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html. Accessed December 9, 2020.