

**National Institute on Aging
Division of Behavioral and Social Research**

**Aging Research on COVID-19:
A NIA Investigators' Workshop**

JUNE 17-18, 2021

Draft July 30, 2021



This meeting summary was prepared by Rose Li and Associates, Inc., under contract to the National Institute on Aging (NIA) Division of Behavioral and Social Research (BSR). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of NIA. Contributions to this summary by the following individuals are gratefully acknowledged: Caroline Sferrazza, Shadya Sanders, Dana Carluccio, Elizabeth A. Finch, Bethany Stokes, and Nancy Tuveesson.

Table of Contents

Acronym Definitions.....	iii
Executive Summary	1
Meeting Summary	4
Opening Remarks, Day 1	4
Session 1: Peripheral and Neurological Sequelae of COVID-19 Infection	4
Impact of Lung Injury on Neuroinflammation and Brain Functioning	4
Age-associated Changes in SARS-CoV-2 Infected Non-human Primate Species.....	5
Kynurenic Acid Blockade of NMDA Receptors in Primate Prefrontal Cortex—Contribution to Long- COVID-19 Symptoms of “Brain Fog”	7
Brain Histopathology in Subjects with COVID-19 Disease	8
Mapping of SARS-CoV-2 Brain Invasion in COVID-19 Disease.....	9
A Multipronged Interrogation of Large-scale Omics Data to Reveal COVID-19 Pathways	10
General Discussion	11
Session 2: Aging-related Risk Factors in COVID-19 Vulnerability	11
The Telomeres COVID-19 Lymphopenia Nexus.....	11
Short Telomeres and T-Cell Shortfall in COVID-19: The Aging Effect.....	13
Plasma Proteomics of COVID Infection with Cardiac Involvement.....	13
Specific Risk Factors Associated with COVID-19 Severe Outcomes for Older Patients	14
General Discussion	16
Session 3: Dementia Care, Caregiving, and Psychosocial Outcomes During the Pandemic.....	16
COVID-19 and U.S. Nursing Homes: Implications for the Future.....	16
The Effects of the COVID-19 Pandemic on the Lived Experience of Diverse Older Adults Living Alone with Cognitive Impairment.....	17
Clinical Features and Outcomes of Patients with Dementia Compared to an Aging Cohort Hospitalized During the Initial New York City COVID-19 Wave.....	18
Disruptions and Adaptations to Care for Homebound Patients with Dementia and Other Serious Illnesses in the Context of COVID-19.....	19
Decreased In-person Social Contact During the Pandemic Is Associated with Worsening Mental Health Despite Increased Remote Contact Frequency	20
General Discussion	21
Session 4: Efforts to Develop Therapies	22
Drug Repurposing for COVID-19 Using Graph Neural Network with Genetic, Mechanistic, and Epidemiological Validation	22
Searching for Invariants in the Dynamic Fitness Landscapes of SARS-CoV-2 and Humans	23
COVID-19, Cellular Senescence, and Senolytic Agents: The Path to Translation.....	24
Developing Therapies to Improve Antiviral Immunity in Older Adults	26
Intravenous Guanfacine for Critical Illness Brain Dysfunction During COVID-19 Pandemic.....	27
Opening Remarks, Day 2	28
Session 5: Factors Affecting Risk and Resilience	29
High Prevalence of COVID-19 with Low Case Fatality Rates Among Tsimane and Moseten Native South Americans	29
COVID-19 Stress and Cognitive Health Disparities.....	30
Factors Predicting Self-Efficacy for Enacting COVID Prevention Actions in Older Sexual Minority Men with HIV.....	32
Impact of COVID-19 on Stress and Loneliness in an ADRC Cohort.....	33

ACP COVID: Communicating with Outpatients for Vital Informed Decisions	34
Session 6: Developing Tools and Models for Coping with a Pandemic	35
Daily Stress Reactivity and Resilience Resources Assessed Multiple Times During the Pandemic....	35
Outpatient Care Delivery and Telemedicine During the COVID-19 Pandemic.....	36
The Caregiver Resource Room: Development of an Online Assessment and Referral Platform for Family Caregivers	37
Web-based Evaluations of Cognitive Aging in the Time of COVID	38
A Spatial Model of the Spread of COVID-19 and Economic Conditions	39
General Discussion	40
Session 7: Epidemiology	40
Understanding Coronavirus in America	40
Following the Pandemic in Real Time: The 2020 Wave of the Health and Retirement Study	41
COVID-19, Finances, and Cognitive Impairment: New Data from High School & Beyond	42
COVID-19 and Alzheimer’s Disease: Analyses of Risk, Disparity, and Outcomes from Electronic Health Records in the U.S.	42
Excess Mortality During the COVID-19 Pandemic for People with Alzheimer’s Disease	43
General Discussion	44
Appendix A: Agenda	45
Appendix B: Workshop Attendees	49

Acronym Definitions

ACP	advance care planning
AD	Alzheimer's disease
ADRC	Alzheimer's Disease Research Center
ADRD	Alzheimer's disease and related dementias
AI	artificial intelligence
APP	amyloid precursor protein
BAL	bronchoalveolar lavage
BBB	blood-brain barrier
C4R	Collaborative Cohort of Cohorts for COVID-19 Research
COVID-19	corona virus disease 2019
CNS	central nervous system
CSF	cerebrospinal fluid
CTRA	conserved transcriptional response to adversity
DAB	Division of Aging Biology
DBSR	Division of Behavioral and Social Research
DGCG	Division of Geriatrics and Clinical Gerontology
dIPFC	dorsolateral prefrontal cortex
DN	Division of Neuroscience
EHR	electronic health record
ET	evolutionary trace
FDA	U.S. Food and Drug Administration
FOA	funding opportunity announcement
FSTL3	follistatin-like 3
GOC	goals of care
GWAS	genome-wide association study
HFRS	Hospital Frailty Risk Score
ICD	International Classification of Diseases
ICU	intensive care unit
IFN	interferon
IHC	immunohistochemistry
IL-2	interleukin 2
IL-10	interleukin 10
IV	intravenous
KAT II	kynurenic aminotransferase
KYNA	kynurenic acid
LCS	limited clone size
LPS	lipopolysaccharide
MCA	middle cerebral artery
MCI	mild cognitive impairment
MCS	maximum clone size
MENA	Middle Eastern/Arab Americans

MENDING	Maximizing Treatment of Neurological Dysfunction using Intravenous Guanfacine
MINDDS	Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep
MGH	Massachusetts General Hospital
MIP	mixed-integer linear program
MSVD	Mount Sinai Visiting Doctors Program
NDHWB	Notre Dame Study of Health and Well-being
NIA	National Institute on Aging
NINDS	National Institute of Neurological Disorders and Stroke
NHLBI	National Heart, Lung, and Blood Institute
NHP	non-human primate
nic- α 7Rs	nicotinic α 7 receptor
NLP	natural language processing
NMDA	N-Methyl D-aspartic acid
NMDAR	NMDA receptor
NSHAP	National Social Life, Health, and Aging Project
nsp	nonstructural protein
NVU	neurovascular unit
NYC H+H	NYC Health + Hospitals
ORF	open reading frame
PAMP	pathogen-associated molecular pattern
PASC	post-acute sequelae of SARS-CoV-2 infection
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PFC	prefrontal cortex
PI3K	phosphatidylinositol 3-kinase
PPE	personal protective equipment
PTSD	post-traumatic stress disorder
RdRp	RNA-dependent reverse transcriptase
RTI	respiratory tract infection
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SASP	senescence-associated secretory phenotype
SCAP	senescent cell anti-apoptotic pathway
SES	socioeconomic status
SMM	sexual minority men
TeSLA	telomere shortest length assay
TL ₀	telomere length onset
vWF	von Willebrand factor
WUSTL	Washington University in St. Louis

Executive Summary

On June 17-18, 2021, the National Institute on Aging (NIA) convened Aging Research on COVID-19: A NIA Investigators' Workshop. The virtual workshop showcased COVID-19 research supported by NIA administrative supplements issued following the start of the COVID-19 pandemic.

Older adults are among the most susceptible to adverse outcomes from COVID-19 infection. Much of the COVID-19 research supported by these supplements investigates the impact of known aging processes on the immune response to COVID-19. Research is also focused on the effects of severe infection on aging trajectories in light of reports that COVID-19 can produce neurological and neuropsychiatric symptoms that may exacerbate age-related cognitive decline and the development of Alzheimer's disease and related dementias. These projects may help to identify factors that affect risk and resilience for age- and infection-related outcomes alike, including for conditions beyond the scope of the COVID-19 pandemic.

In addition to exploring the effects of COVID-19, NIA also supports research on intervention strategies. Many efforts to develop therapeutic agents that can treat COVID-19 and reduce the incidence of severe infection in older adults are under way. Many behavioral approaches to combat the spread of COVID-19 have also been developed and implemented. The socio-behavioral factors that influence individual- and community-level uptake of COVID-19 mitigation strategies are another focus of NIA-supported research. The effects of these interventions on existing health disparities and vulnerable populations are emphasized throughout this line of research.

The presentations were organized into seven broad subject areas: peripheral and neurological sequelae of COVID-19 infection; aging-related risk factors in COVID-19 vulnerability; dementia care, caregiving, and psychosocial outcomes during the pandemic; efforts to develop therapies; factors affecting risk and resilience; developing tools and models for coping with a pandemic; and epidemiology.

Session 1: Peripheral and Neurological Sequelae of COVID-19 Infection

Session Chair Dr. Luci Roberts moderated presentations and discussion on research related to the neurological impact of COVID-19 infection. Dr. Niccolò Terrando presented first on a model of the effects of lung injury on the central nervous system. Dr. Joanne Turner gave the second presentation on age-associated changes in SARS-CoV-2 infection with evidence from multiple non-human primate models. Dr. Amy F.T. Arnsten delivered the third presentation on the effects of kynurenic acid on NMDA receptors in the prefrontal cortex and the implications of this mechanism for the cognitive effects of COVID-19 infection. Dr. Thomas G. Beach presented fourth on human postmortem evidence of brain histopathology specifically associated with SARS-CoV-2 infection. Dr. Geidy E. Serrano, a colleague of Dr. Beach, then presented details about an ongoing effort to map the spread of SARS-CoV-2 in the human brain. Dr. Sharlee Climer delivered the final presentation on a multipronged approach to analyzing large-scale omics data that can be applied to clinically heterogeneous conditions, including COVID-19, to

identify patterns of plasma analytes and associated outcomes. Dr. Roberts moderated questions for speakers throughout the session, including a general discussion of sex differences that have been observed in the various studies presented during the session.

Session 2: Aging-related Risk Factors in COVID-19 Vulnerability

Session Chair Dr. Max Guo moderated presentations and discussion on research related to aging-related risk factors for COVID-19 vulnerability. Dr. Abraham Aviv presented first on the relationship between telomere length and T-cell lymphopenia, a hallmark of COVID-19 infection. Dr. James J. Anderson then presented a model that was developed in collaboration with Dr. Aviv and describes T-cell clonal expansion as exhibiting threshold-like behavior that is controlled by telomere length. Dr. Anthony Rosenzweig delivered the third presentation on a proteomic analysis of COVID-19 infection with cardiac involvement, which has been associated with adverse outcomes and increased mortality. Dr. Judy Zhong gave the final presentation on an electronic health record–based analysis of the age-specific risk factors that are associated with severe outcomes in older COVID-19 patients. Dr. Guo moderated questions for speakers throughout the session, including a general discussion of potential intersections across the studies presented during the session.

Session 3: Dementia Care, Caregiving, and Psychosocial Outcomes During the Pandemic

Session Chair Dr. Elena Fazio moderated presentations and discussion on COVID-19 research related to dementia care, caregiving, and psychosocial outcomes. Dr. Vince Mor presented first on the impacts of COVID-19 on U.S. nursing homes and implications for the future of long-term residential care. Dr. Elena Portacolone gave the second presentation on the unique vulnerabilities faced by older adults with cognitive impairments who live alone that were exacerbated during the pandemic, with an emphasis on older adults of color. Dr. James M. Noble delivered the third presentation on the clinical features and outcomes of COVID-19 patients with dementia. Dr. Katherine Ornstein gave the fourth presentation on how COVID-19 has affected homebound patients with dementia. Dr. Louise Hawkey delivered the final presentation on the impact of social relationships on physical and mental health in the context of COVID-19.

Session 4: Efforts to Develop Therapies

Session Chair Dr. Jean Yuan moderated presentations and discussion on ongoing efforts to develop therapies for COVID-19. Dr. Xiaoqian Jian presented first on a machine learning-based approach to drug repurposing that could greatly reduce the time and cost of developing new therapies for COVID-19 as well as other illnesses. Dr. Olivier Lichtarge then described an evolutionary trace method for the identification of variationally constrained protein residues that may represent drug targets that are less likely to escape drugs and vaccines. Dr. James Kirkland delivered the third presentation on the potential for senolytic drugs to treat multiple conditions that are impacted by fundamental aging processes. Dr. Joan Mannick gave the fourth presentation on clinical trials of mTOR inhibitors that may improve interferon-induced antiviral immunity in older adults. Dr. Christopher G. Hughes delivered the final presentation on efforts to develop treatments for delirium, including ongoing studies of intravenous guanfacine and dexmedetomidine.

Session 5: Factors Affecting Risk and Resilience

Session Chair Dr. Dallas Anderson moderated presentations and discussion on factors affecting risk and resilience for COVID-19. Dr. Hillard Kaplan presented first on two native South American populations, the Tsimane and Mosesten, who have experienced very low mortality from COVID-19 despite high rates of infection. Dr. Kristine J. Ajrouch then presented on a study of COVID-19 stress and cognitive health disparities among three prominent racial/ethnic groups in the metro-Detroit area. Dr. Brett M. Millar delivered the third presentation on the factors that predict self-efficacy for COVID-19 preventive actions in older sexual minority men living with HIV. Dr. Trey Bateman gave the fourth presentation on an ongoing study of the impact of stress and loneliness due to the pandemic in a cohort from the Wake Forest Alzheimer's Disease Research Center. Drs. James A. Tulsky and Angelo Volandes delivered the final presentation on the development of a rapidly implemented advance care planning telehealth program specific to COVID-19.

Session 6: Developing Tools and Models for Coping with a Pandemic

Session Chair Dr. Marcel Salive moderated presentations and discussion on the development of tools and models for coping with a pandemic. Dr. Cindy Bergeman presented first on a study of reactivity and resilience to stress during the pandemic. Dr. Michael Lawrence Barnett then presented on outpatient care delivery and telemedicine in the context of COVID-19. Dr. Francesca Falzarano delivered the third presentation on the development of an online assessment and referral platform for family caregivers of people living with dementia. Dr. Lee Ryan gave the fourth presentation on an ongoing internet-based study of cognitive aging. Dr. Bruce Weinberg delivered the final presentation on the co-evolution of infections and the economy during the pandemic.

Session 7: Epidemiology

Session Chair Dr. John Phillips moderated presentations and discussion on COVID-19 epidemiology research. Dr. Arie Kapteyn presented first on a study of pandemic effects on American households. Dr. David Weir gave the second presentation about how COVID-19 affected the 2020 wave of the Health and Retirement Study. Drs. John Robert Warren and Chandra Muller delivered the third presentation on how the pandemic has affected finances and cognitive impairment. Dr. Rong Xu gave the fourth presentation on research that leveraged electronic health records to analyze risks, disparities, and outcomes related to COVID-19 and Alzheimer's disease. The final presentation by Dr. Lauren Gilstrap examined excess mortality among Medicare enrollees with Alzheimer's disease during the pandemic.

Meeting Summary

Opening Remarks, Day 1

Ron Kohanski, PhD, Director, National Institute on Aging (NIA)/Division of Aging Biology (DAB); and Lis Nielsen, PhD, Director, NIA/Division of Behavioral and Social Research (BSR)

Dr. Kohanski began by describing the biological processes that occur across an individual's lifecourse as the hallmarks of aging. These hallmarks increase with age; exacerbating a hallmark accelerates the effects of aging, while reductions ameliorate the rate of aging. Aging and aging hallmarks contribute to how people respond to infectious diseases such as COVID-19. Many of the research projects in the upcoming presentations represent various hallmarks of aging as well as relationships between these hallmarks.

Dr. Nielsen noted that many efforts to deal with the pandemic were behavioral in nature, with profound social and economic impacts on individuals. Several mitigation strategies compounded existing disparities, particularly for vulnerable populations, such as nursing home residents, socially isolated older adults, and individuals with dementia. Forthcoming presentations described many of the socio-behavioral factors that can influence individual- and community-level uptake of mitigation strategies. Dr. Nielsen noted and commended collaborations between researchers and the utilization of shared toolkits and platforms (e.g., PhenX toolkit, Disaster Research Response, or DR2 program). Future research will likely leverage the work presented herein to prepare vulnerable communities for future pandemics.

Session 1: Peripheral and Neurological Sequelae of COVID-19 Infection

Moderator: Luci Roberts, PhD, NIA/Division of Neuroscience (DN)

Impact of Lung Injury on Neuroinflammation and Brain Functioning

Niccolò Terrando, PhD, Duke University

The systemic impact of inflammation on the neurovascular unit (NVU) is particularly severe in the context of pre-existing neurodegeneration. In addition to exacerbating neurovascular dysfunction and microglial activation, systemic inflammation induces behavioral features similar to delirium in mouse models of Alzheimer's disease (AD). Given that delirium is a well-established risk factor for dementia and that as many as 20-30 percent of all COVID-19 patients develop delirium during hospitalization, COVID-19 infection may accelerate the progression and emergence of AD and related dementias (ADRD). Dr. Terrando and colleagues developed a model to evaluate the effects of lung injury on the central nervous system (CNS). Intranasal administration of lipopolysaccharide (LPS) triggers robust lung injury pathology at a range of doses and exposure regimens, although 3 days of repetitive LPS exposure are required to reliably trigger microglial activation in the brain. Moreover, genes related to neutrophil activity and pro-inflammatory cytokines are significantly upregulated in the CNS after 3-day exposure to LPS. Neutrophil invasion through the NVU may be a key mediator of early changes in neuroinflammation and delirium onset. As early as 6 hours after the last dose of LPS in the 3-day exposure model, significant neutrophil infiltration in the brain parenchyma as well as

neurovascular and endothelial dysfunction can be observed. Similarly, this LPS exposure paradigm induces distinct patterns of blood–brain barrier (BBB) dysfunction and opening that resemble the effects of orthopedic surgery. Compared to other effects of inflammation, the effects of this lung injury model on synaptic structure appear to be more sustained and show no signs of rescue as late as 72 hours after the last dose of LPS. Dr. Terrando and colleagues plan to establish a lung injury model that entails intranasal administration of SARS-CoV-2 spike protein and/or LPS to study the effects of systemic COVID-19 infection on the CNS. This model will be studied in the context of neurodegeneration by leveraging mouse models of AD. Therapeutic interventions will also be implemented in an effort to protect the CNS from further degeneration in this SARS-CoV-2 lung injury model.

Discussion

Dr. Terrando emphasized the importance of repetitive daily exposure to LPS for priming the immune response. Single exposures fail to produce effects in the CNS even at higher doses or later timepoints; however, single doses are sufficient to induce lung injury. Notably, systemic administration of LPS triggers neuroinflammation faster than lung exposure. Initial work with SARS-CoV-2 spike protein in this model have also underscored the necessity of repetitive exposure for producing effects in CNS. Work with the spike protein does not require BSL3 facilities and therefore presents an opportunity to model hallmarks of COVID-19 infection with minimal exposure hazards.

Openings in the BBB may be a gateway through which neutrophils enter the brain, and Dr. Terrando plans to investigate this possibility in real time using 2-photon imaging. Dr. Terrando noted that BBB dysfunction is evident at 6, 24, and 72 hours after LPS exposure; this dysfunction can be visualized by fibrinogen deposition in the brain parenchyma and with endothelial markers.

Age-associated Changes in SARS-CoV-2 Infected Non-human Primate Species

Joanne Turner, PhD, Texas Biomedical Research Institute

Dr. Turner and colleagues are studying the effects of COVID-19 infection in three non-human primate (NHP) models: rhesus macaques, baboons, and marmosets. The NHPs are monitored for 2 weeks following ocular, intratracheal, or intranasal infection with the USA-WA1/2020 strain of SARS-CoV-2; both pre- and postmortem samples are banked for analysis. Pilot studies showed that while all three NHP species can be infected by SARS-CoV-2, marmosets exhibit only mild illness while both rhesus macaques and baboons exhibit moderate illness. The rhesus macaque has become the gold standard NHP species for studying vaccines and therapies for SARS-CoV-2.

Early reports during the pandemic indicated that the elderly are more susceptible to SARS-CoV-2 infection. Thus, Dr. Turner and colleagues are examining age-associated changes in SARS-CoV-2 infected NHPs. In both young and old rhesus macaques, type II pneumocytes are predominantly infected by SARS-CoV-2 in the lung. However, a greater proportion of pneumocytes are infected in older macaques at 3 days post-infection than in younger macaques, and levels of SARS-CoV-2 infected pneumocytes decrease more slowly as older

macaques recover compared to younger macaques. The adaptive immune responses of younger and older baboons appear to be more similar to each other, although some age-associated differences are present. Neutralizing antibodies were undetectable until day 14 post-infection in both younger and older baboons, and levels of these neutralizing antibodies were not significantly different between age groups. In general, T-cell responses were similar or slightly lower in older baboons compared to younger baboons. Levels of interferon gamma (IFN γ) are lower in older baboons at day 14 post-infection; levels of type I interferon alpha (IFN- α) and interleukin 10 (IL-10) may also be lower in older baboons, although more analysis is needed to confirm this result. The observation of lower IFN γ levels in baboons somewhat parallels observations of reduced interleukin 2 (IL-2) produced in rhesus macaques in response to antigen. These age-associated differences in T cell responses may explain why older animals experience an extended period of SARS-CoV-2 infection.

Dr. Turner and colleagues plan to continue this line of research by identifying early antigen-specific T- and B-cell responses as well as SARS-CoV-2 variant-specific responses across NHP species and conducting in-depth analyses of peripheral and brain tissues after SARS-CoV-2 infection; SARS-CoV-2 can be detected in the brains of multiple species, including rhesus macaques and mouse models (e.g., hACE2 transgenic mice). Dr. Turner will also continue an ongoing proteomic analysis of bronchoalveolar lavage (BAL) fluid in the lung and a phenotypic analysis of alveolar macrophages that will help to define how cellular influx in the lung during acute COVID-19 infection promotes robust inflammation; age-associated shifts in macrophage expression phenotypes have already been observed in mice, humans, and baboons.

Discussion

Dr. Turner noted that the course of infection in NHPs is relatively fast and resolves by day 5-6 post-infection in both younger and older animals. Dr. Turner added that although it is too early to draw conclusions about mediators of infection (e.g., lipid mediators, resolvins, anti-inflammatory pathways) in these NHP samples, these mediators can be investigated in future studies, particularly if those studies focus at the peak of infection (around day 3).

Dr. Turner clarified that presence of SARS-CoV-2 in the brains of NHPs was not confirmed by polymerase chain reaction (PCR) as part of this research but has been published in other NHP studies. Typically, SARS-CoV-2 RNA is detectable late in the course of infection around week 2 or 3. Dr. Turner added that these reports parallel data from rodents, in which peak levels of viral RNA were present in the lung at day 3 but were not detectable in the brain until several days later. Thus, SARS-CoV-2 appears to be present in the brain at later timepoints than other tissues of interest.

Kynurenic Acid Blockade of NMDA Receptors in Primate Prefrontal Cortex— Contribution to Long-COVID-19 Symptoms of “Brain Fog”

Amy F.T. Arnsten, PhD; Shengtao Yang, PhD; Dibyadeep Datta, PhD; and Min Wang, PhD, Yale Medical School

Many COVID-19 patients have residual cognitive deficits, with impairments in working memory, attention regulation, long-term memory, and executive functions being most prominent. These cognitive abilities are carried out by the prefrontal cortex (PFC), a brain region that is also impacted by age. The cognitive operations subserved by the PFC depend on recurrent excitatory synapses in the dorsolateral prefrontal cortex (dlPFC) that can sustain neuronal firing without sensory stimulation. These synapses are characterized by unique NMDA receptor (NMDAR) and nicotinic $\alpha 7$ receptor (nic- $\alpha 7$ R) neurotransmission. Kynurenic acid (KYNA), which is produced under inflammatory conditions including COVID-19 infection, blocks NMDARs and nic- $\alpha 7$ Rs and may therefore interfere with synaptic function in the PFC.

KYNA is naturally expressed in aged rhesus macaques, likely as a result of increased inflammation with age. Preliminary data from these aged NHPs showed that both endogenous and exogenous KYNA reduced the firing rate of delay cells in the dlPFC by blocking NMDARs and nic- $\alpha 7$ Rs. Moreover, higher levels of KYNA were associated with impaired performance on a working memory task. Application of D-serine, which acts as an agonist at the same glycine site where KYNA blocks NMDARs, stimulated neuronal firing and blocked the effects of KYNA on these receptors. Similar results have been demonstrated with galantamine, which blocks the effects of KYNA on nic- $\alpha 7$ Rs. Notably, galantamine is a cholinesterase inhibitor that has been approved for the treatment of AD.

Dr. Arnsten and colleagues investigated whether systemic administration of an inhibitor of kynurenic aminotransferase (KAT II), which produces KYNA from kynurenine, could improve working memory performance in aged monkeys with naturally occurring cognitive deficits. Preliminary behavioral data demonstrate a positive correlation in which the oldest animals exhibit the greatest enhancement of cognitive performance following KAT II inhibitor administration, likely because the oldest animals may have the highest levels of KYNA. Dr. Arnsten noted that one KAT II inhibitor—N-acetylcysteine—is already available for use in humans. In addition to inhibiting KAT II, inhibition of tryptophan metabolism (which occurs upstream of KYNA production) may be a helpful strategy for helping COVID-19 patients with residual cognitive deficits, particularly at older ages.

Discussion

Dr. Arnsten explained that these cells and circuits in the dlPFC are among the most vulnerable to tau pathology and degeneration in AD and aging. Thus, the added insult of NMDAR and nic- $\alpha 7$ R blockade resulting from inflammation-induced KYNA production could further weaken these circuits and exacerbate the effects of neurodegenerative diseases or aging processes.

Dr. Arnsten clarified that preliminary data have not demonstrated clear preferential binding of KYNA to NMDARs versus nic- $\alpha 7$ Rs (or vice versa). Asked whether these data may be indicative

of an adaptive response to inflammation, Dr. Arnsten speculated that because these circuits are so energy intensive, inhibition of NMDAR activity could represent an adaptive strategy to save energy and help the body fight infection.

Dr. Arnsten stated that galantamine may have a unique response to KYNA relative to other acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine) because of its activity at nic- α 7Rs, although the enhancement of endogenous cholinergic stimulation provided by all such inhibitors may be clinically useful to some degree. Dr. Arnsten noted that the NMDAR blockade would remain in place following galantamine administration, and therefore a KAT II inhibitor or agent that prevents the metabolism of tryptophan may be more neuroprotective than a cholinesterase inhibitor.

Dr. Arnsten suggested that kynurenin dysregulation early in life, as with other inflammatory signaling factors, could sensitize the brain for inflammatory responses later in life to smaller stressors or inflammatory events. Thus, tryptophan inhibition or similar mechanisms that could maintain a more typical kynurenin environment may be neuroprotective at early ages.

Brain Histopathology in Subjects with COVID-19 Disease

Thomas G. Beach, MD, PhD, Banner Sun Health Research Institute

Prior reports of COVID-19-associated brain histopathology describe a broad range of conditions; however, it is unclear how many of these conditions differ from those found in other types of critical illness resulting in death and whether the changes were due to direct invasion of the brain by SARS-CoV-2 or indirect effects of systemic reactions. Dr. Beach and colleagues have examined brain histopathology in autopsy subjects with COVID-19 to elucidate the neuropathological effects of the illness. Approximately one-third of the autopsies conducted by the team between March 2020 and May 2021 tested positive for COVID-19 by nasopharyngeal swab. Of the initial 20 cases studied, only 2 exhibited histopathology that was unequivocally related to COVID-19. In one case, the subject had encephalitis with acute hemorrhages, fibrinoid vascular necrosis, edema, and transtentorial uncal herniation. Hemorrhages in this case were present in the medial temporal lobe (including amygdala), thalamus, and basal pons. This case was also COVID-19 positive by RT-PCR in the entorhinal cortex. In the other case, the subject had a large acute middle cerebral artery (MCA) ischemic and hemorrhagic infarction. This case was negative for COVID-19 in all brain regions, suggesting that the histopathology resulted from systemic effects of coagulopathy.

Common additional findings in these initial 20 cases included patchy amyloid precursor protein (APP) immunoreactivity in white matter (11 cases) and sparse perivascular mononuclear cell cuffing (9 cases); the latter is a typical viral histopathological change. To determine the degree of the observed brain histopathology that was due to the effects of the virus itself versus nonspecific effects of critical illness, Dr. Beach and colleagues examined control subjects for comparison; notably, very few studies of COVID-19 autopsies to date have included control brains. Control cases included 10 subjects with non-COVID, autopsy-proven, acute bronchopneumonia and 10 subjects without any pneumonia. APP staining was present in 4 non-pneumonia cases and 8 pneumonia cases, and all cases had sparse perivascular

mononuclear cell cuffing. Therefore, neither APP immunoreactivity in white matter nor sparse perivascular mononuclear cell cuffing appear to be specific effects of COVID-19. In a follow-up study, Dr. Beach observed similar rates of acute or subacute infarction or ischemic changes in both non-COVID, autopsy-proven, acute bronchopneumonia and cases without any pneumonia, suggesting that pneumonia is not associated with an increased rate of acute brain infarction or hemorrhage; these rates are comparable to reports on COVID-19 pneumonia.

The rate of histopathology that is unequivocally due to SARS-CoV-2 in the brains of people dying with COVID-19 appears to be very low. Further comparative studies that include non-COVID brains are needed. Dr. Beach and colleagues plan to repeat these studies with additional COVID-19 brains and survey for microglial activation across brain regions, as well as perform transcriptomic analysis of COVID versus non-COVID brains. They also plan to leverage additional RT-PCR methods to achieve more sensitive viral detection and check for signs of replication-competent SARS-CoV-2 virus.

Discussion

Dr. Beach noted that the subjects examined in these autopsies were critically ill to the point that measuring some other conditions of interest, such as delirium, was prohibitively difficult. He and his colleagues plan to examine whether a synergistic effect on the degree of neuroinflammation exists in cases with COVID-19 and AD neuropathology.

Although the BBB was not examined directly in autopsies of COVID-19 patients, Dr. Beach noted that sparse perivascular mononuclear inflammatory cells were present in the brain at levels that were no more prevalent than any other autopsy, indicating that no large-scale inflammatory cell invasion of the brain had occurred in these cases. Dr. Beach and colleagues plan to conduct protein assays for panels of cytokines in addition to transcriptomic analyses and potentially immunohistochemistry (IHC) for vascular markers.

Mapping of SARS-CoV-2 Brain Invasion in COVID-19 Disease

Geidy E. Serrano, PhD, Banner Sun Health Research Institute

Although many clinical and autopsy reports describe a broad range of neurological conditions associated with SARS-CoV-2, it is unclear which conditions are due to direct CNS invasion by SARS-CoV-2 as opposed to the indirect effects of systemic reactions to critical illness. To date, 21 previous studies have investigated the CNS presence of SARS-CoV-2, only 13 of which reported detection of the virus in brain tissue; the mean detection rate of SARS-CoV-2 in brain tissue was 24 percent. However, these studies only assessed a few brain regions; the most comprehensive of these studies screened 10 brain regions total. In addition, only 1 out of a total of 5 studies has reported detection of SARS-CoV-2 in cerebrospinal fluid (CSF). Dr. Serrano presented additional data from an extensive neuroanatomical survey conducted with Dr. Beach and colleagues to address this knowledge gap. The survey included 20 subjects who were all clinically considered to have died from COVID-19 disease. All subjects had one or more pre-existing risk conditions for COVID-19, and all subjects had age-related neurodegenerative or cerebrovascular disease. As presented by Dr. Beach, only 2 of these subjects exhibited histopathology that was unequivocally related to COVID-19.

Researchers can leverage multiple methods to directly assess the presence of SARS-CoV-2 in brain tissue, including IHC, in situ hybridization, and RT-qPCR. Target regions for RT-qPCR methods include open reading frame (ORF) 1ab, RNA-dependent reverse transcriptase (RdRp), and genes for the spike protein, envelope protein, or nucleocapsid protein. Dr. Serrano and colleagues utilized RT-qPCR with primers for the envelope gene to assess 16 brain regions from the 20 subjects in their survey; CSF and cardiac blood serum were also tested. SARS-CoV-2 RNA was detected in 4 subjects for one or more brain regions, including the olfactory bulb, amygdala, entorhinal cortex, temporal and frontal neocortex, dorsal medulla, and leptomeninges. This detection rate (20 percent) is consistent with previous studies. In general, the number of viral copies in brain tissue appears to be lower than in positive control tissue (i.e., COVID-19 lung tissue in this study). Like other human coronaviruses, SARS-CoV-2 can invade the brain in susceptible patients, although many gaps in knowledge remain, including what viral and host factors influence SARS-CoV-2 brain invasion and whether the virus is cleared from the brain following acute illness. Dr. Serrano and colleagues plan to repeat this survey with additional COVID-19 brains, as well as with other RT-qPCR primers for the nucleocapsid gene and RdRp.

Discussion

Dr. Serrano clarified that although they have not collected samples from the vagus nerve, the dorsal motor nucleus, trigeminal nerve nucleus, and the femoral nerve have been surveyed; SARS-CoV-2 was detected in one dorsal motor nucleus sample and four femoral nerve samples to date.

A Multipronged Interrogation of Large-scale Omics Data to Reveal COVID-19 Pathways

Carlos Cruchaga, PhD, Washington University in St. Louis; and Sharlee Climer, PhD, University of Missouri-St. Louis

COVID-19 patients present with a high degree of clinical heterogeneity. Drs. Climer and Cruchaga aim to identify patterns of analytes in plasma that are associated with the wide range of COVID-19 outcomes to enable tailored treatment specific to outcome subtype and facilitate early interventions. Their study cohort includes 289 individuals hospitalized for COVID-19 and 150 controls that were ascertained pre-pandemic and matched on the basis of ancestry, age, and sex. Deep clinical records, including electronic health records (EHRs), were obtained for study subjects, which captured 32 comorbidities and 16 neurological outcomes. Using SomaLogic proteomics, 7,000 proteins were quantified from at least one plasma sample per individuals; more than 800 of these proteins are involved in the inflammatory response. With this platform, modified single-stranded DNA aptamers are used to bind specific protein targets that are then quantified by a DNA microarray. Quality control is currently being performed on the data, which will be made available to the research community as soon as the data are cleaned. The study represents a pioneering multi-omic characterization of COVID-19 infection and outcome.

The Climer (University of Missouri), Cruchaga (Washington University in St. Louis), and Jacobson (Oak Ridge National Laboratory) labs have leveraged their diverse expertise to pursue multi-

pronged analytical approaches with the goal of discerning intricate patterns in data. Their methods include network modeling, Mendelian randomization, explainable artificial intelligence (AI), deep learning, and an exact approach that lies at the intersection of AI and linear programming. This exact approach identifies all optimal and near-optimal solutions in a dataset, and although it is computationally demanding, the team is increasing scalability by utilizing an alternative search strategy and massive parallelization. The approach can be used to identify analyte patterns with the highest differences in frequencies between two sets of individuals. This problem can be cast as a mixed-integer linear program (MIP) that the team aims to solve using a cut-and-solve iterative search strategy; this strategy has outperformed IBM's Cplex in more than 12 publications from other labs, requires minimal memory, and is suitable for massive parallelization. The team developed and optimized Sync—which can process more than 700 analytes for pattern sizes of up to seven proteins using a local computer cluster—and has utilized it to analyze proteomic data from CSF samples collected from 199 people with late-onset AD and 579 controls. The Sync analysis identified five patterns of seven proteins each that largely overlapped and exhibited clear associations with phenotype. Moreover, all identified proteins are prominent features of the PI3K/Akt pathway, which has previously been associated with AD. This approach provides an agile model for evaluating the landscape of heterogeneous diseases.

Discussion

Drs. Climer and Cruchaga clarified that the study has recruited sufficient sample size to assess whether differences in protein profiles exist between Blacks/African Americans and Caucasians, although these data are not yet available.

General Discussion

Sex Differences

Multiple presenters are investigating the presence of sex differences in their studies. Dr. Beach noted that COVID-19 is clinically more severe in men than women and confirmed that more males than females are affected by non-COVID pneumonia in their autopsy program. Dr. Arnsten cited an ongoing study at Yale that has evidence of higher kynurenine levels in plasma samples from males compared to females. Dr. Turner noted subtle sex differences, particularly in the brain, in studies of K18-hACE2 transgenic mice. In contrast, Dr. Terrando has not observed any sex differences in their neutrophil transfer reporter data.

Session 2: Aging-related Risk Factors in COVID-19 Vulnerability

Moderator: Max Guo, PhD, Chief, Genetics and Cell Biology Branch, NIA/DAB

The Telomeres COVID-19 Lymphopenia Nexus

Abraham Aviv, MD, Rutgers University

T-cell lymphopenia (i.e., low T-cell count) is a hallmark of COVID-19 infection. Although the underlying mechanism of T-cell lymphopenia in COVID-19 is not understood, data from intensive care unit (ICU) admissions indicate that individuals with a lower T-cell count are at

higher risk of developing severe COVID-19. Severe COVID-19 infection and post-COVID-19 pulmonary fibrosis have also been associated with shorter leukocyte telomeres. While B-cell telomeres elongate upon transition from naïve to memory cells, T-cell telomeres shorten during this transition. Telomere length is a limiting factor in the replicative capacity of T-cells, such that T-cell clonal expansion may stall in individuals with shorter telomeres, including many older adults and some young adults. During COVID-19 infection, the demand for clonal expansion may outpace replicative capacity particularly if telomeres are short, suggesting that individuals with shorter telomeres may be at higher risk for T-cell lymphopenia and more severe disease. Dr. Aviv and colleagues tested the hypothesis that telomere lengths are associated with T-cell lymphopenia in COVID-19 by performing the telomere shortest length assay (TeSLA) in peripheral blood mononuclear cells (PBMCs). The proportion of telomeres shorter than 2 kilobases was higher in elderly (i.e., mean age 86 years) COVID-19 patients with lower lymphocyte counts, and a higher mean telomere length was associated with higher lymphocyte counts. A similar pattern was observed in a younger (i.e., 60-69 years) cohort of adults, in which shorter T-cell telomeres were associated with fewer T-cells.

In a generic infection, the innate immune response is triggered quickly and followed by the adaptive immune response, including T-cell clonal expansion and antibody production. In cases of mild SARS-CoV-2 infection, the innate immune response is somewhat delayed and viral load rises, but the adaptive immune response eventually catches up and clears the virus. In severe COVID-19, however, the innate immune response is even more delayed and the subsequent T-cell response is insufficient to clear the virus or attenuate the innate immune response, which can result in cytokine storm. This crosstalk between the innate and adaptive immune responses may be mediated by the contribution of telomere length to T-cell lymphopenia, wherein individuals with inherently short telomeres may fail to mount an optimal adaptive immune response to SARS-CoV-2 and ultimately develop severe COVID-19.

Discussion

Dr. Aviv clarified that because an individual's telomere length is established prior to infection, the role of telomere length in the immune response is not necessarily specific to COVID-19. Similar associations between telomere length and immune responses have been documented for influenza and cold viruses.

Dr. Aviv noted that the results presented were part of a pilot study and must be replicated on a larger scale. The final study must also account for a range of factors known to influence telomere length (e.g., age, sex, cardiovascular disease, obesity).

Dr. Aviv explained that the telomere lengthening that occurs when B-cells undergo clonal expansion is unusual for somatic tissues; while robust telomerase activity promotes telomere lengthening in the germline, the same is not generally true for somatic cells. Dr. Aviv added that COVID-19 patients rarely present with B-cell lymphopenia.

Short Telomeres and T-Cell Shortfall in COVID-19: The Aging Effect*James J. Anderson, PhD, University of Washington*

Dr. Anderson presented a model, developed in collaboration with Dr. Aviv, in which telomere length controls T-cell clonal expansion in response to infection. Upon infection, the degree of T-cell clonal expansion is determined by immune system processes. However, as telomere length in naïve T-cells declines with age, the maximum capacity for T-cell clonal expansion also declines. Therefore, T-cell expansion in response to infection at older ages is limited by telomere length. The point at which telomeres have shortened enough to limit T-cell clonal expansion is denoted by telomere length onset (TL_0). In this model, clonal expansion exhibits threshold-like behavior; prior to TL_0 , clone size remains constant at a maximum size while telomere length decreases with age, whereas after TL_0 , clones will become exponentially smaller with increasing age while telomere length remains constant.

The chronological age that corresponds to TL_0 varies across individuals. Because telomere length decreases linearly with age in this model, individuals with longer telomere lengths early in life will reach TL_0 later in life than individuals with shorter early-life telomere length. At the population level, the distribution of individuals above and below the TL_0 threshold is approximately equal at age 50; most individuals will be above the TL_0 threshold (i.e., capable of producing maximum clone size [MCS]) before this age and will have fallen below the TL_0 threshold (i.e., capable of producing only limited clone size [LCS]) by age 70. The proportion of individuals susceptible to COVID-19 mortality increases with age due to the population shift across the TL_0 threshold. The hazards ratio for susceptibility to COVID-19 mortality dramatically increases and diverges from susceptibility to all-cause mortality around age 50 or when the mean clone size of the LCS group has diminished to 15 percent of MCS and the immune system is no longer able to clear the virus. Therefore, this model may explain the high mortality in older COVID-19 patients and suggests that elements of immune system aging may exhibit threshold-like behavior, with age of onset dependent on early-life telomere length. Such thresholds of aging, if significant and predictable at an early age, could have implications for multiple fields.

Plasma Proteomics of COVID Infection with Cardiac Involvement*Anthony Rosenzweig, MD, Massachusetts General Hospital*

Cardiac involvement is associated with adverse outcomes in COVID-19, including increased mortality; however, the mechanisms driving cardiac complications in COVID-19 are not clear. Dr. Rosenzweig and colleagues performed plasma proteomics with a discovery cohort of 80 COVID-19 patients ($n=54$) and controls ($n=26$) who were grouped according to disease severity and cardiac involvement. In addition, results from this cohort were validated in 305 independent COVID-19 patients and further investigated in a Syrian hamster model of severe COVID-19. The proteomic analysis identified senescence-associated secretory phenotype (SASP) proteins—known markers of biological aging—as strongly associated with disease severity and cardiac involvement even in age-matched cohorts, suggesting that biological aging may play a larger role in these phenotypes than chronological aging. Infection of young hamster models

with SARS-CoV-2 recapitulated SASP enrichment in lung mRNA profiles, which may indicate that viral infection can induce these markers of senescence.

COVID-19 infection and disease severity were associated with a strong downregulation of ADAMTS13, a von Willebrand factor (vWF)-cleaving protease whose loss-of-function causes microvascular thrombosis. Furthermore, levels of ADAMTS13 can be used to distinguish groups of patients according to COVID-19 severity (i.e., lower levels of ADAMTS13 are associated with more severe COVID-19). In addition, lower ADAMTS13 levels were associated with markers of thrombosis and myocardial injury, and a Mendelian randomization analysis using the UK Biobank supported a causal role for ADAMTS13 in myocardial injury. Expression of ADAMTS13 also decreased after SARS-CoV-2 infection in hamster models. Targeted ADAMTS13 repletion strategies may be effective for COVID-19 patients with low levels of ADAMTS13.

The heart failure biomarker NTproBNP was associated with a dramatic increase in follistatin-like 3 (FSTL3), indicative of increased activin/TGF β signaling in COVID-related heart failure. Increased FSTL3 was strongly associated with cardiac involvement in COVID-19 and correlated with both heart failure and myocardial injury. These results are consistent with prior work suggesting a role for FSTL3 in multiple heart failure models; previous studies have shown that FSTL3 increases with age and in proportion to the severity of heart failure, and FSTL3 has been found both necessary and sufficient to induce heart failure in three animal models. Inhibitors of FSTL3 have been approved by the U.S. Food and Drug Administration (FDA) for other indications and may be a viable option to support COVID-19 patients with evidence of heart failure.

Discussion

Dr. Rosenzweig clarified that this plasma proteomic analysis does not identify the cell types responsible for the protein changes described. Dr. Aviv added that SASP is associated with shorter telomeres in multiple somatic cell types.

Specific Risk Factors Associated with COVID-19 Severe Outcomes for Older Patients

Judy Zhong, PhD, New York University Medical Center

The high rates of morbidity and mortality due to COVID-19 among older adults in nursing homes has been widely reported; yet the impact of COVID-19 on community-dwelling older adults has been less studied. Moreover, the previous ambulatory care experience of community-dwelling older adults has rarely been considered in studies of COVID-19 risks and outcomes. Dr. Zhong and colleagues investigated the specific risk factors for community-dwelling older adults (i.e., 75 years and older) that are associated with hospitalization and severe outcomes of COVID-19 by leveraging two EHR networks in New York City: INSIGHT and NYC Health + Hospitals (NYC H+H). The networks included 119,000 COVID-19-positive patients over age 50 during the study period, approximately 60 percent of whom had EHR data (i.e., ambulatory visit history with any of the EHR network-associated hospitals) prior to their COVID-19 diagnosis.

Dr. Zhong and colleagues found that risk factors for severe outcomes of COVID-19 in this study were age-specific. Among individuals with an ambulatory care history, for example, males were at higher risk than females for severe outcomes among 50–64-year-olds, but sex was no longer found to be a risk factor for the oldest age group (i.e., 75 years and older). Notably, the odds ratio for many of the established demographic and comorbidity risk factors decreased with advancing age, indicating a weaker association between these risk factors and severe outcomes at older ages. Interestingly, this decreasing association with age was observed despite the risk factors being more prevalent in the oldest adults. The attributable risk fraction considers both the prevalence and odds ratio of a risk factor. Dr. Zhong and colleagues have found that the adjusted attributable fraction of many risk factors (e.g., sex, race/ethnicity) indicated a much smaller attributable risk for the oldest age group. Notably, dementia is the only comorbidity risk factor that was associated with higher attributable risk in this group. Frailty was identified as the biggest factor with the highest attributable risk in the oldest adults. The analysis also revealed differences in outcomes between individuals with and without ambulatory care history. The overall adjusted odds ratio for hospitalization between these groups demonstrated that individuals without an ambulatory care history were nearly 50 percent more likely to be hospitalized. Moreover, this odds ratio increased for the oldest patients without ambulatory records.

Discussion

Dr. Zhong clarified that although the prevalence of comorbidities increased among older patients in this analysis, the odds ratio for those comorbidity risk factors generally decreased. Dr. Zhong added that comorbidity factors were ascertained solely from ambulatory care visit records and that no biological samples were collected in this study.

Dr. Zhong noted that the transition to the current EPIC EHR system differed across hospitals in New York City, which could have resulted in record history gaps for this study. Dr. Zhong confirmed that this transition was completed for the hospitals within NYC H+H by March 2020.

Dr. Zhong explained that frailty was estimated based on the Hospital Frailty Risk Score (HFRS), which utilizes *International Classification of Diseases* (ICD) codes from EHRs to classify patients according to relative level of frailty. That HFRS was not compared to other related metrics is a limitation of this study, however Dr. Zhong remarked that frailty was consistently identified as the largest attributable risk factor using multiple modeling approaches.

Dr. Aviv noted that the disappearance of sex effects as risk factors at older ages could potentially be attributed to the fact that females typically live longer than men, and as such the healthiest men survive to older ages. Dr. Zhong plans to investigate whether men in older cohorts are healthier overall than men in younger cohorts as well as the impact that this bias may have on the risk factor analysis.

General Discussion

Approaches to Research on COVID-19 Effects on Aging Trajectories

Dr. Rosenzweig noted that studies conducted early in the pandemic, including some of the work presented at this meeting, were often limited to samples that were easily available and less able to adopt multimodal approaches (e.g., proteomic and epigenetic analysis on the same cohort) that would be valuable for the study of aging and COVID-19. Dr. Rosenzweig added that the Massachusetts Consortium on Pathogen Readiness has collected samples that would be appropriate for such composite studies. Similar large-scale efforts to bank samples and clinical data (e.g., at Massachusetts General Hospital) could also be leveraged to support future research on the long-term consequences of COVID-19 infection, including hypotheses that COVID-19 may accelerate trajectories of aging. Dr. Rosenzweig's observations that SARS-CoV-2 may induce senescence factors suggests that COVID-19 may trigger accelerated aging phenotypes. Dr. Aviv suggested that cardiovascular disease will become an increasingly important focus of COVID-19 research in the context of aging, noting that monocytes become highly pro-inflammatory as telomeres shorten and that cardiovascular disease following other infections (e.g., influenza) is well-documented.

Session 3: Dementia Care, Caregiving, and Psychosocial Outcomes During the Pandemic

Moderator: Elena Fazio, PhD, NIA/BSR

COVID-19 and U.S. Nursing Homes: Implications for the Future

Vince Mor, PhD, Brown University

The earliest instances of COVID-19 deaths occurred within nursing homes; however, the majority of resources went to hospitals. The responsibility for the increased number of COVID-19 fatalities within nursing homes is complex and could be described by dueling narratives: one narrative places blame on nursing homes for having poor standards of care, and the other insists that excess fatalities were caused by an inadequate public health response, characterized by insufficient support, inadequate personal protective equipment (PPE), and a lack of federal guidance geared toward protecting nursing home residents. Dr. Mor explored the factors that influence nursing home policy, risk factors for symptomatic and asymptomatic infections of COVID-19, and adverse events due to vaccination against SARS-CoV-2.

By tracking mortality across 351 nursing homes in the U.S. over time, Dr. Mor found that the risk of contracting SARS-CoV-2 among nursing home residents is most directly associated with community rates of infection. The 30-day COVID-19 mortality rate declined before vaccinations began, for both symptomatic and asymptomatic individuals, regardless of frailty. This decline in fatality persisted while infection rates increased, with age and cognitive impairment being the most significant predictor of mortality risk.

Once vaccinations began, Dr. Mor's team partnered with the Centers for Disease Control and Prevention (CDC) to study vaccine-related adverse events. To determine whether the vaccine

led to any adverse reactions among nursing home residents, he compared early vaccinated nursing home residents to later-vaccinated nursing home residents. Dr. Mor and colleagues found vaccine administration had no adverse effect or excess mortality. Although some nursing home residents died after receiving the vaccine, the mortality rate was not different for early vs. late vaccinated cases, and the majority of these cases were considered to be “old and frail.”

Dr. Mor concluded by describing how COVID-19 has amplified long-standing challenges of nursing homes. Nursing homes provide both social and medical care and both are connected to historical financial strategies that may no longer fit modern needs. He thus suggested that some structural change may be needed, such as separating post-acute care from long-term residential care. Dr. Mor emphasized that aging research should continue to study nursing homes because of their critical role in serving a vulnerable population.

Discussion

Dr. Mor clarified that his research also considered the practice of nurses commuting between nursing home facilities, which is a potential—but difficult to investigate—source of COVID-19 transmission. He added that a small but inconsistent effect of cross-nursing home transmission is seen in nursing homes with higher percentages of contract staff. Nonetheless, nursing home infection rates are more consistently related to community infection rather than cross-nursing home infection.

Dr. Elena Fazio asked whether nursing homes are assessing how their procedures, particularly for testing and vaccination, may change to prepare for future pandemics based on their experiences with COVID-19. After confirming that nursing homes are looking ahead to future potential pandemics, Dr. Mor reminded attendees that most nursing homes did not have access to rapid testing until September 2020. Unfortunately, many state policies continued the use of the slower, individual PCR testing rather than implement rapid sweep-style antigen testing, which could have benefited nursing homes because they frequently lacked sufficient PPE.

The Effects of the COVID-19 Pandemic on the Lived Experience of Diverse Older Adults Living Alone with Cognitive Impairment

Elena Portacolone, PhD, MBA, MPH, University of California, San Francisco

Living alone in old age is common across all racial and ethnic groups. Approximately 4.3 million older adults with cognitive impairment live alone; however, data for this population are sparse. Dr. Portacolone investigated whether racially and ethnically diverse older adults with cognitive impairment who live alone experienced exacerbated precarity, defined in this research by insecurity, uncertainty, and limited access to appropriate services due to the pandemic.

Dr. Portacolone and her team of bilingual and bicultural researchers recruited a sample of 59 adults over age 55 living alone, conducted interviews (April-July 2020), and performed a content analysis. Dr. Portacolone identified five themes among her sample population: (1) a distinct fear of death, mostly triggered by news media coverage of the pandemic and prevalence of comorbidities; (2) feelings of extreme isolation or being trapped because of mitigation practices; (3) beliefs in misinformation; (4) coping mechanisms, which ranged from

taking precautions such as mask-wearing to exercising indoors; and (5) the importance of accessing essential resources such as food and access to home care aides. Sample participants described limited access to desired healthcare services, as well as mental health care. Two participants with reported suicidal ideations prior the pandemic did not access mental health services.

Dr. Portacolone's research highlights the unique vulnerabilities faced by older adults with cognitive impairments who live alone, particularly during a public health crisis, as well as the essential instrumental, emotional, and mental health support provided by home care aids to this population.

Discussion

Dr. Portacolone noted the importance of the population of older adults who have a cognitive impairment and are living alone for the research community. All responsibilities fall to older adults living alone themselves, yet they are reluctant to share any concerns with those around them, which may lead to changes in their current lifestyle or a loss of independence. Further, many older adults living alone may not realize that they have a cognitive impairment.

Clinical Features and Outcomes of Patients with Dementia Compared to an Aging Cohort Hospitalized During the Initial New York City COVID-19 Wave

James M. Noble, MD, Columbia University Irving Medical Center

During the initial impact of COVID-19, clinicians at the Alzheimer's Disease Research Center (ADRC) of the Columbia University Irving Medical Center (CUIMC) received two prominent types of calls: first, calls about the presentation of delirium in patients with COVID-19 related symptoms and second, calls about increased stress on caregivers for patients with ADRC. Dr. Noble's research investigates whether delirium is an unrecognized symptom of COVID-19, particularly for patients with dementia.

Using retrospective symptom data for patients with COVID-19, Dr. Noble found that compared to patients without known dementia, patients with dementia were three times more likely to present with delirium, and less likely to present with other commonly known COVID-19 symptoms (e.g., fever, cough, chest pain). He noted that the prevalence of delirium remained after controlling for age, sex, and other symptoms. Further, individuals with dementia had higher COVID-19 fatality rates, although the association was moderated by age and comorbidities. He also noted that as care delivery pivoted from in-person to virtual care, dementia patients and their caretakers encountered multiple pandemic-related stressors.

Although this research was conducted in a single center and in a cohort hospitalized during the first wave of COVID-19 to hit New York City, its identification of an association between a dementia diagnosis and higher COVID-19 mortality deserves further attention. Moreover, the potential importance of delirium as a COVID-19 symptom in patients with dementia puts added pressure on the fact that dementia is frequently underrepresented in medical records overall.

Discussion

When asked about future waves of the pandemic, Dr. Noble noted that his research was limited to the first wave of COVID-19, but added that, over the course of the pandemic, hospitals have become better equipped to handle increased infection rates and have reported reduced mortality rates. In addition, he noted that the study results may be biased because many individuals avoided going into the hospital during the pandemic.

Disruptions and Adaptations to Care for Homebound Patients with Dementia and Other Serious Illnesses in the Context of COVID-19

Katherine Ornstein, PhD, Mount Sinai School of Medicine

Although the nursing home population has been a frequent topic of discussion during the COVID-19 pandemic, the homebound population is actually larger. This population is often overlooked by the research community and general public, despite high levels of caregiver burden, social isolation, and difficulty in accessing and financing appropriate care. All of these challenges have worsened during the pandemic.

Dr. Ornstein and colleagues conducted a retrospective, qualitative chart review combined with electronic medical record (EMR) data extraction to better understand the end-of-life experience among homebound people who died during the first surge of COVID-19 infections in New York City. She leveraged the Mount Sinai Visiting Doctors Program (MSVD)—a large academic, home-based, primary and palliative care program—for this research because it provides multidisciplinary care for a homebound population of 1,300 patients, the majority of whom live with dementia. During the peak of the COVID-19 pandemic, many MSVD staff who provided primary care were re-assigned to hospitals, thereby halting critical in-home care for the homebound.

Of MSVD patients who died between March 1 and June 30, 2020, 25 percent experienced a disruption in care. Disruptions and adaptations were documented for, but not limited to, hospice services, medical supplies, and home health aide support. Dr. Ornstein highlighted that home health aides often called out of shifts, because of fears of contracting SARS-CoV-2. Among patients with family caregivers, nearly half experienced disruptions in an aspect of care (e.g., medical supplies, symptom management, or hospice services).

However, Dr. Ornstein also found that MSVD program participants did receive care and services despite major disruptions during the pandemic. The MSVD program maintained the trust of patients and families by increasing team coordination and supporting home care aides as COVID fatality rates increased. Dr. Ornstein's research also revealed the importance of providing emotional support to caregivers who were dealing with high mortality rates and modifications to the ways they provide care.

Dr. Ornstein's team concluded that leveraging telehealth among homebound older adults is a difficult proposition, and nearly all patients required additional in-person assistance to participate in telehealth appointments. Patients with cognitive or sensory impairments demonstrated an inability to use telehealth devices.

Discussion

When asked about differences between patients who were homebound and lived alone versus those who lived with others, Dr. Ornstein stated that the majority of homebound patients living alone are more reliant on paid caregivers. Unfortunately, during the pandemic, disruptions to paid care caused homebound patients to experience a loss of support.

Decreased In-person Social Contact During the Pandemic Is Associated with Worsening Mental Health Despite Increased Remote Contact Frequency

Louise Hawkley, PhD, and Linda Waite, PhD, NORC at the University of Chicago

Using data from the National Social Life, Health, and Aging Project (NSHAP) COVID Study, Dr. Hawkley described the relationship between social contact and physical and mental health. Her research investigated the extent to which older adults engaged in in-person and remote (e.g., phone calls, messaging, video chat) modes of contact and the effect that in-person versus remote contact may have had on their happiness, feelings of depression, and perceived loneliness. NSHAP is a longitudinal, population-based study that began in 2005, with a second cohort with community-dwelling adults over the age of 50 added in 2015. Dr. Hawkley focused on data collected from 2,672 participant surveys between September 2020 and January 2021.

Results indicate that approximately 63 percent of participants had in-person contact with family living outside of their home less than once per week through the testing period. Nearly 17 percent described their pandemic in-person contact as a little less often, and about 21 percent a lot less often, than before the pandemic. The majority (55-70 percent based on contact mode) of participants described no change in the frequency of each mode of contact since the start of the pandemic (e.g., if in person contact was low prior to the pandemic, it generally remained low). Less than 10 percent of the cohort noted increased in-person contact with family or friends through the testing period. Most participants noted that their contact with family and friends who live outside of the home occurred through phone calls or text messaging. Nearly one-quarter of participants increased their use of at least one remote contact modes.

After weighting and adjusting for demographic factors and survey mode, Dr. Hawkley found that decreases in in-person contact with family and friends are associated with a statistically significant increase in loneliness. Dr. Hawkley's research suggests that participants who decreased their contact with family and friends during the pandemic became less happy and more depressed and experienced more loneliness compared to pre-pandemic results collected in 2015. Further, increases in remote modes of communication are not associated with any impact on mental health. It remains unclear whether rates of use of remote methods could have impacted these results, because the increases in remote contact were small. Dr. Hawkley added that only one aspect of loneliness, that is, isolation, was associated with a negative impact on mental health. Compared to isolation, *feeling left out or lacking companionship* had weak associations with social contact.

Discussion

Dr. Hawkey explained that several factors can explain the lower uptake of remote modes of communication by older adults, including limited knowledge of and access to devices and high-speed internet, which are known issues within the United States. For the small number of people who increased their in-person contact during the pandemic, these individuals may have had a greater need for in-person support (e.g., household support).

General Discussion***Shifts in Care Narratives***

Ongoing research aims to better understand the evolving narrative around nursing homes and the prediction of COVID-19 outcomes. The impact of the pandemic varies both geographically and temporally, and at the onset of the pandemic nursing homes were poorly integrated into the broader public health infrastructure. Previous measures of quality in nursing homes were also not good predictors of success during the pandemic, which forced the field to learn more about nursing home facilities and how the implementation of testing protocols and staffing could affect infection and mortality rates.

Home-based care has always been a critical service, particularly for people with dementia. The pandemic has highlighted the need to seek better ways to deliver this type of care, which must consider the needs of family members and paid caregivers. Much knowledge has been gained regarding telehealth, including that it is helpful for some patients but not all. The pandemic also increased awareness of, and appreciation for, the substantial contributions of essential workers toward public health.

Dr. Noble added that many caregivers, facilities, and front-line staff have not been able to describe their experiences throughout this pandemic. In addition to caregivers, survivors of COVID-19 have also had various experiences depending on symptoms, severity, and burden. For example, older adults within the community typically fared well and the majority of the caregiving and mitigation burden was placed on younger adults.

COVID-19 Registry Development

When asked about the potential for a registry that could be used to generate predictions of hospitalization, survivorship, or dementia risks and their relationship to COVID-19, Dr. Ornstein stated that the MSVD is maintaining such a registry and is conducting ongoing research about COVID-19 survivors. Dr. Noble added that such a registry would also be used to investigate relationships between COVID-19 exposures and ADRD outcomes. Dr. White noted that Brown University is building a national repository of EHR data across nursing homes.

Telehealth and Telemedicine

Throughout the meeting multiple researchers described the challenges older adults face while attempting to leverage technology for telemedicine or increased communication. However, they also described successes in the uptake of telehealth services, when paired with assistance. For caregivers of homebound patients, the addition of telehealth has eliminated scheduling burdens and has enabled the inclusion of additional family members during doctor's

appointments. Although use of telemedicine is overall lower for older adults, compared to those under age 65, many homebound older adults learned how to use the technology, which opened opportunities not only for the use of telemedicine, but also for increased communication and remote work opportunities.

Impact of Dementia

Presenters were asked whether cognitive and physiological changes associated with dementia are accounted for during their analyses and whether they contribute to effect sizes. Dr. Mor noted that both his research on U.S. nursing homes and international research suggest that the effects of dementia and levels of cognitive impairment were significant even when accounting for age. Unfortunately, the mechanism that would explain the relationship between dementia and cognitive impairment is not well understood. Dr. Portacolone noted that participants in her sample experienced a significant drop in mental stimulation, which she attributed to limited social interaction and pandemic-related stress.

Cultural Barriers to Telehealth

Based on comments from participants, Dr. Hawkley noted that cultural barriers to telehealth could affect its use, because some patients may not believe that virtual care can adequately assess symptoms. Dr. Ornstein added that more research is needed to understand the barriers of telehealth, such as high levels of mistrust.

Session 4: Efforts to Develop Therapies

Moderator: Jean Yuan, MD, PhD, NIA/DN

Drug Repurposing for COVID-19 Using Graph Neural Network with Genetic, Mechanistic, and Epidemiological Validation

Xiaoqian Jiang, PhD, University of Texas Health Science Center at Houston

Drug development often requires many years of effort; however, drug repurposing can save a significant amount of time by reducing the safety and pharmacokinetic uncertainty of the process. Numerous methods for drug repurposing exist, including bioinformatic analysis of genetic associations, molecular docking, and pathway mapping; retrospective analysis of real-world data; and high-throughput phenotypic screens with *in vitro* and *in vivo* models. Dr. Jiang presented a harmonized machine learning approach to drug repurposing that leverages each of these methods to generate a more robust and reliable drug repurposing model that can be used to combat COVID-19. This approach utilizes knowledge graph neural representation and weak supervision to draw connections across existing biological knowledge (i.e., gene-gene interactions, drug-target interactions, gene expression, and pathway information) and real-world data (i.e., *in vivo* and *in vitro* efficacy, clinical trial effectiveness, and real-world side effects) to rank drug candidates for repurposing.

The first step of this machine learning-based approach is to derive a drug's embedding in relation to SARS-CoV-2 using neural graph representation. This SARS-CoV-2 knowledge graph is informed by biological knowledge and real-world data about interactions among virus baits,

host genes, pathways, drugs, targets, and phenotypes. A deep graph neural network approach was used to derive quantitative drug representations that reflect both local interaction and global topology. This model is similar to convolutional neural networks in that it is restricted to neighborhood nodes. Because collective knowledge about COVID-19 is still evolving, Dr. Jiang and colleagues adopted a Bayesian approach to avoid overfitting the model to current data and thus represent node embedding as a probability. Furthermore, universal knowledge was incorporated in the model via pre-trained node embedding. The next step of the approach is to rank and validate candidate drugs. Drugs are prioritized based on their relationship to real-world evidence as well as their similarity to drugs currently being tested in clinical trials. High-ranking candidate drugs are externally validated based on gene profiles, *in vitro* drug screening results, and calculated average treatment effects for currently used drugs from EHR data on hospitalized COVID-19 patients. Finally, drugs are reranked using a weak supervision aggregation method to synthesize all available information. This harmonized drug repurposing approach is generalizable to other illnesses. In addition, Dr. Jiang and colleagues plan to incorporate ongoing *in vitro* experiments to validate drug combinations.

Discussion

Dr. Jiang clarified that the candidate drug ranking and validation process utilizes ICD codes from EHR data on hospitalized COVID-19 patients to determine which patients have been using various FDA-approved drugs and to calculate average treatment effects for those drugs; the approach does not currently leverage unstructured EHR notes.

Dr. Jiang noted that each source of data that informs this approach has inherent bias. Moreover, coverage for any one data source may be insufficient because the number of patients was only in the thousands at the time data were collected for this study. Although it is difficult to assert a threshold value for recall or precision at this time, Dr. Jiang suggested that recall greater than 0.6 would be promising.

Searching for Invariants in the Dynamic Fitness Landscapes of SARS-CoV-2 and Humans

Olivier Lichtarge, MD, PhD, Baylor College of Medicine

Dr. Lichtarge and colleagues applied the evolutionary trace (ET) method to systematically interrogate the evolutionary fitness landscape of the entire coronavirus family across the SARS-CoV-2 proteome, which encodes 29 proteins. ET performs alanine scanning mutagenesis *in silico* to map functional sites on protein structures. The result depicts a gradient of the fitness landscape at any position on the protein structure, which represents the evolutionary force exerted at a particular residue by constraints from natural selection. This information enables identification of variationally constrained or evolutionarily fixed target sites that may be less likely to escape drugs and vaccines. ET can also be used on a large scale to compare all known structures at sites with similar evolutionary signals to allow inference of proteins that perform the same function and prediction of ligands. Although ET has been used extensively in eukaryotes and some prokaryotes, the application of ET to SARS-CoV-2 structural proteome represents the first use of this method in viruses.

Using ET, Dr. Lichtarge and colleagues identified functional sites in SARS-CoV-2 that fulfilled the criteria for ET success: the sites were non-random and overlapped with known functional sites as well as sites already known to interact with drugs (e.g., remdesivir). The identified sites were also cross-referenced with documented mutation rates to find surface clusters that are functionally important across the coronavirus family and less likely to mutate in SARS-CoV-2. These sites represent promising target sites for new drugs; for example, these data have been used to recognize a candidate target site in the nonstructural protein (nsp) hydrolase domain that is homologous with a human hydrolase, enabling refinement of an inhibitor that binds to the nsp3 macrodomain structure. ET can also be used to identify pan-coronavirus epitopes that would broadly confer cross-immunity in a vaccine. Cross-reactive and non-cross-reactive epitopes can be distinguished by using ET to derive a new score that evaluates cross-reactivity more significantly than was possible using sequence identity. The single most likely cross-reactive SARS-CoV-2 epitope in this study was independently verified in work recently published in *Science* by Elledge and colleagues. Dr. Lichtarge noted that when more whole genome/exome sequencing data are available for COVID-19 patients, ET could also be used to stratify severity of COVID-19 infection in humans based on genes linked to mild versus severe infection.

Discussion

Dr. Lichtarge remarked that these data allow researchers to assess genotype-phenotype associations in the context of massive amounts of new data on mutations and functional divergences during evolution. Ideally, these insights will translate into greater power to resolve genome-wide association studies (GWAS) and similar research. Results from GWAS and pharmacogenomic studies could then be used to associate drug responsiveness with differences in individual genomes and inform hypotheses for clinical trials. Insufficient amounts of high-quality data from exomes and genomes of COVID-19 patients hinder current studies, although this challenge should be overcome as more data are generated.

COVID-19, Cellular Senescence, and Senolytic Agents: The Path to Translation

James Kirkland, MD, PhD, Mayo Clinic

Cellular senescence is a cell fate that can be induced by a variety of cell stressors. Approximately 30 to 70 percent of senescent cells develop SASP, a tissue-damaging phenotype that promotes inflammation and spread of senescence. Pathogen-associated molecular patterns (PAMPs) can amplify key SASP factors in senescent cells, which may represent one mechanism by which elderly individuals or people with chronic diseases who have increased senescent cell burden become more inflamed and more susceptible to damage and disability from infections. Dr. Kirkland and colleagues confirmed that antigens associated with SARS-CoV-2 can exacerbate SASP in cultures of human senescent preadipocytes in a dose-dependent manner. Furthermore, SASP factors produced by senescent cells can upregulate viral entry proteins that are involved in coronavirus uptake (e.g., ACE2, TMPRSS2) in non-senescent human lung epithelial cells. SASP factors can also inhibit levels of interferon-induced transmembrane proteins—an innate antiviral defense mechanism—in non-senescent cells; antibodies against combinations of SASP factors can partially prevent this inhibition.

Dr. Kirkland and colleagues have developed senolytic agents that kill senescent cells using an approach driven by two core hypotheses: first, senescent cells can kill nearby cells through apoptosis while they themselves resist death, implying increased pro-survival and anti-apoptotic defenses; and second, senescent cells, like cancer cells, exhibit apoptotic resistance and metabolic shifts. These hypotheses informed a bioinformatics-based proteomic analysis that identified senescent cell anti-apoptotic pathways (SCAPs), which confer apoptotic resistance in senescent cells. Senolytic drugs transiently disable key nodes in SCAP networks, effectively disabling a senescent cell's defense against its own pro-apoptotic SASP. Fisetin, a natural product flavonoid, is one such senolytic drug that utilizes this transient mechanism to selectively induce apoptosis in senescent but not non-senescent cells. Emerging evidence supports the benefits of senolytics for multiple conditions, consistent with the geroscience hypothesis that fundamental aging processes may be root cause contributors to aging phenotypes, geriatric syndromes, chronic diseases, and age-related loss of resilience. Moreover, preclinical evidence suggests that clearing senescent cells reduces mortality among older model animals exposed to common pathogens. Multiple human trials are currently testing the use of senolytics, including fisetin, in COVID-19 cases for hospitalized and nursing home populations. If clinical trials are successful, senolytic drugs may be promising treatments beyond acute COVID-19 infection, including for the long-term complications of COVID-19 as well as other non-COVID infections or conditions.

Discussion

Dr. Kirkland cautioned that senolytic drugs should not yet be taken outside the context of carefully controlled clinical trials, because the potential side effects are unknown at this time. Nonetheless, one advantage of senolytic drugs is the ability to administer them intermittently to obtain transient effects; only brief exposure to senolytic agents is required to initiate apoptosis in senescent cells, which should reduce potential side effects compared to drugs that require continuous administration. Dr. Kirkland added that the senolytic drugs currently in trials have established side effect profiles and track records or are high doses of natural products.

Dr. Kirkland confirmed that changes in circulating SASP proteins can be detected as a response to senolytic treatment in both animal models and preliminary clinical studies. These changes predict treatment response in animal models, although it is too early to determine whether the changes predict clinical response in humans. Dr. Kirkland added that senolytic treatment in older mice can greatly attenuate cytokine storm and improve antibody responses.

Dr. Kirkland noted that sex differences in senescent cell accumulation are consistently observed across species, such that accumulation tends to be steady throughout the lives of male animals but delayed and more pronounced later in the lives of female animals. Whether these sex differences will impact senolytic treatment responses is not yet clear.

Dr. Kirkland clarified that senolytic agents are not inherently anti-inflammatory, but rather kill a cell type (i.e., senescent cells) that contributes to aberrant inflammation. Dr. Kirkland added that senolytic drugs exert their effects through multiple mechanisms related to the pillars of aging, including by affecting IFN production, viral entry, and levels of T lymphocyte

sequestration, which may improve the likelihood that drug efficacy will successfully translate to humans.

Developing Therapies to Improve Antiviral Immunity in Older Adults

Joan Mannick, MD, Life Biosciences

The COVID-19 pandemic has highlighted the dysfunction of the aging immune system, an aging-related condition often ignored by drug developers. A key element of immune dysfunction in older adults is deficient type I IFN responses to viral infection, which may help to explain why COVID-19 is so severe in that population. Published data have shown that more severe COVID-19 is associated with deficient IFN- α production and IFN-induced gene expression. Furthermore, a significant percentage of patients with life-threatening COVID-19 pneumonia have genetic mutations in the type I IFN pathway or auto-antibodies against type I IFN. One approach that may improve immune function including the deficient type 1 INF response in older adults is to target biological mechanisms that underlie aging, such as the activity of mTOR. Evidence from humans and animal models suggests that mTOR inhibitors improve influenza vaccination response in older individuals. Notable, non-hypothesis-driven RNAseq of whole blood samples from older adults treated with mTOR inhibitors revealed that mTOR inhibition upregulated the type I IFN response.

Dr. Mannick and colleagues investigated whether the mTOR inhibitor RTB101 could improve type 1 IFN-induced antiviral immunity in older adults. Low doses of RTB101 were well-tolerated in older adults and enhanced serum IFN- α levels only in the context of a respiratory tract infection (RTI), which may be safer than therapies that continuously upregulate IFN levels. RTB101 also significantly upregulated IFN-induced antiviral gene expression in whole blood samples compared to placebo. *Ex vivo* experiments demonstrated that RTB101 upregulated IFN production in plasmacytoid dendritic cells that were isolated from the blood of older adults, but this upregulation only occurs in the presence of a viral mimetic. Thus, both clinical and *ex vivo* evidence showed that RTB101 does not induce IFN- α production on its own but rather enhances the IFN response to viruses or viral mimetics. Likewise, the results of large Phase IIb and Phase III trials in which RTB101 was administered once daily for 16 weeks during winter cold and flu season supported that RTB101 may have particular benefit for reducing severity of RTIs as opposed to overall incidence. In a subsequent pilot trial of RTB101 as prophylaxis to decrease the severity of COVID-19 in nursing homes during an outbreak, none of the subjects who received RTB101 developed progressive COVID-19 (compared to 23 percent in the placebo arm). Although these results must be replicated in larger trials, current data suggest that mTOR inhibitors may reduce the severity of viral RTIs, including COVID-19, in older adults by boosting IFN-induced antiviral responses to viral infections.

Discussion

Dr. Mannick acknowledged that the differences in significance between the Phase IIb and Phase III could be due in part to the different trial populations. The Phase IIb trial, which showed a significant effect of RTB101, enrolled a sicker population than the Phase III trial, which showed only a trend toward a significant effect. In addition, the effects of RTB101 were stronger in

Phase III subjects aged 75 and older than in younger subjects from the same trial. Similarly, the highest responders in the Phase IIb trial were aged 85 and older. Dr. Mannick suggested that the oldest adults may have a more homogenous deficiency in immune function and that a more targeted trial population may reveal a stronger treatment effect.

Dr. Mannick noted that RTB101 generally reduced levels of inflammatory markers while IFN responses increases, suggesting that the mTOR inhibitor may suppress virus-induced inflammation.

Intravenous Guanfacine for Critical Illness Brain Dysfunction During COVID-19 Pandemic

Oluwaseun Johnson-Akeju, MD, MGH; and Christopher G. Hughes, MD, Vanderbilt University

Brain dysfunction, including delirium and coma, is very common in ICU patients. Light sedation is typically administered to ICU patients to keep them alert and interactive, but despite this sedation approximately 25 to 75 percent of ICU patients will develop delirium, with hypoactive delirium being the most common subtype. In contrast, COVID-19 ICU patients most commonly receive deep sedation due to high mechanical ventilation requirements and exhibit a 55 percent incidence of delirium overall, with much higher rates of agitation and hyperactive delirium. Thus, deeper sedation and treatment with benzodiazepines or antipsychotics are used for COVID-19 ICU patients to control symptoms of hyperactive delirium, despite a lack of evidence that these drugs successfully treat delirium.

Cognitive impairment is common after critical illness and sepsis. Notably, similar rates of cognitive impairment (e.g., brain fog) have been documented following COVID-19 infection. Delirium is likely the most modifiable risk factor for cognitive impairment following critical illness. However, a lack of prophylactic or initial therapies to treat delirium poses a challenge for targeting delirium to improve acute brain function and long-term cognitive outcomes. The most evidence-based treatment for delirium is currently dexmedetomidine, an α_2 adrenergic receptor agonist that requires intravenous (IV) infusion and ICU admission due to its short half-life and potential to cause bradycardia and hypotension. Dexmedetomidine is hypothesized to treat delirium by improving CNS inflammation, microcirculatory blood flow, and sleep, and is currently being evaluated in the Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) study.

Guanfacine is another α_2 adrenergic receptor agonist with higher selectivity for the α_{2A} receptor in the CNS, which should mitigate the potential for bradycardia and hypotension. An oral formulation of guanfacine is currently available, although oral formulations are difficult to administer to acutely agitated and delirious patients. The Maximizing trEatment of Neurological Dysfunction using INtravenous Guanfacine (MENDING) study is a Phase II trial of IV guanfacine for treatment of delirium that leverages the α_2 agonist mechanistic work and cognitive assessments from the MINDDS study. The specific aims of the MENDING study are to determine the effects of IV guanfacine on (1) acute brain dysfunction (i.e., delirium and coma), (2) mechanical ventilation and hospital course, and (3) global cognition up to 12 months after

hospital discharge following critical illness and diagnosis of delirium. The MENDING study is currently enrolling subjects.

Discussion

Dr. Hughes explained that although incidence of post-traumatic stress disorder (PTSD) attributed to ICU stays is generally tracked in larger studies, PTSD will not be assessed in the MENDING study because rates are generally too low to sufficiently evaluate in a small sample size.

Dr. Hughes hypothesized that COVID-19 ICU patients may experience higher rates of hyperactive delirium for a variety of reasons. For example, these patients are kept on higher ventilator settings and tend to exhibit asynchrony with the ventilator. COVID-19 patients also experience bouts of hypoxia, leading to feelings of shortness of breath and agitation. In addition, COVID-19 patients are more frequently treated with heavy sedation and benzodiazepines, which initially leads to hypoactive delirium but can have the opposite effect upon emergence from sedation. Finally, the lack of family presence can also exacerbate agitation.

Dr. Arnsten commented that guanfacine's ability to support synaptic connectivity in PFC may contribute to reductions in active delirium.

Opening Remarks, Day 2

Eliezer Masliah, MD, Director, NIA/DN; and Basil Eldadah, MD, PhD, Chief, Geriatrics Branch, NIA/Division of Geriatrics and Clinical Gerontology (DGCG)

Multiple pathways—including aging processes, genetics, and environmental influences—contribute to the pathogenesis of AD/ADRD. Dr. Masliah emphasized that research on aging and neurodegeneration must embrace and integrate these pathways to achieve a therapeutic intervention for AD/ADRD by 2025, the aspirational deadline implemented by the National Plan to address AD. The research presented on Day 1 of this meeting highlighted each of these pathways, with a particular emphasis on the environmental contributions to AD/ADRD pathogenesis that include infectious disorders such as COVID-19. NIA has recently issued multiple new funding opportunity announcements (FOAs) for research investigating the relationships among inflammation, pathogens, and AD/ADRD, including FOAs related to the infectious etiology of AD/ADRD, the pathogenesis of HIV-related neurodegeneration, the role of the microbiome in the aging brain and AD/ADRD, and the study of neurological and neurocognitive sequelae associated with COVID-19. NIA has also joined the National Institute of Neurological Disorders and Stroke (NINDS) and the National Heart, Lung, and Blood Institute (NHLBI) to fund the Collaborative Cohort of Cohorts for COVID-19 Research (C4R) to rapidly carry out observational research on the involvement of pulmonary, cardiovascular, hematologic, and neurocognitive disorders in COVID-19. In addition to these NIA efforts, Congress recently passed a special appropriation of \$1.15 billion for the study of post-acute sequelae of SARS-CoV-2 infection (PASC). Given the gravity of the neurological and neuropsychiatric effects of COVID-19, NIA will co-host a workshop in July 2021 on the

Neurological and Psychiatric Effects of SARS-CoV-2 in conjunction with NINDS and the National Institute of Mental Health (NIMH).

Dr. Eldadah highlighted NIA DGCG's support for a variety of research in older populations, including multiple chronic conditions, polypharmacy and e-prescribing, frailty and falls, functional outcomes, palliative care, and resilience. In addition, DGCG promotes initiatives focused on aging research at the intersection of medical and surgical specialties as well as research on aging processes across the lifespan, including menopause and exceptional longevity. Dr. Eldadah acknowledged that COVID-19 has underscored ongoing health disparities related to aging and multiple morbidities as well as racial and ethnic disparities and expressed hopeful optimism that the fast pace of research on COVID-19 over the past year may lead to new scientific knowledge that can reduce mortality and suffering and promote health equity when the next pandemic surfaces.

Session 5: Factors Affecting Risk and Resilience

Moderator: Dallas Anderson, PhD, MPH, NIA/DN

High Prevalence of COVID-19 with Low Case Fatality Rates Among Tsimane and Mosenen Native South Americans

Hillard Kaplan, PhD, Chapman University

The Tsimane and Mosenen are native South American populations whose exposomes are very different from those of many westernized populations. These populations engage in high rates of physical activity throughout life and are estimated to be twice as active as the typical American. The Tsimane and Mosenen also experience high rates of untreated infectious diseases, including intestinal parasites and respiratory diseases. In contrast, these populations experience a virtual absence of cardiovascular disease even at advanced ages.

The Tsimane and Mosenen experienced a dramatic spike in COVID-19 infections in the summer of 2020; case numbers have since tapered off, and no cases have been documented since November 2020. The infection rate was very high: SARS-CoV-2 infected 73 percent of the adult population. Similar infection rates were observed across all ages and sexes, and slightly higher rates of infection were reported among the Tsimane compared to the Mosenen. The prevalence of neutralizing antibodies among infected individuals was also notably high, indicative of a vigorous immune response; whereas 33 percent of German COVID-19 survivors had neutralizing antibodies, 83 percent of infected individuals in these native populations had neutralizing antibodies. The presence of neutralizing antibodies was associated with symptomatic illness, and only 18 percent of infected individuals were asymptomatic. Approximately 19 percent of infected individuals reported being sick for more than 3 weeks, and both binding and neutralizing antibodies increased with the duration of impairment.

Despite the high rates of infection and symptomatic illness, fatality rates among both populations were very low; for example, the Tsimane reported only one death due to COVID-19, while 45 deaths would have been expected if the Tsimane died at the same rate as New

Yorkers of the same age. Dr. Kaplan offered some hypotheses to explain the “Tsimane paradox.” First, the communal subsistence lifestyle of the Tsimane people entails significant food sharing and visitation between households; however, these encounters generally occur in outdoor environments, which could have resulted in high transmission of SARS-CoV-2, but at low doses. Second, the low prevalence of obesity, diabetes, and hypertension may have reduced mortality. Third, the high pathogen burden may have increased immune responsiveness but also have resulted in a more balanced immunomodulation that could have blunted fatal cytokine storms. For example, eosinophils—a white blood cell response to parasites—are elevated throughout life among the Tsimane and are associated with a reduced pro-inflammatory response to H1N1. Finally, the Tsimane and Moseten may benefit from currently undiscovered protective genes.

Discussion

Dr. Kaplan clarified that the Tsimane participate in a mixture of hunting, fishing, and horticulture and utilize very little technology. In contrast, the Moseten are more dedicated farmers and participate in markets where they can buy and sell crops, resulting in a somewhat more Westernized diet. Nonetheless, the Moseten are still very physically active, and Dr. Kaplan added that the Tsimane and Moseten themselves hypothesize that their high rates of physical activity contribute to their low mortality rates. Both populations experience high rates of pathogen burden, although the Moseten have greater access to medical care.

Dr. Kaplan remarked that although exposure to COVID-19 still occurs among the Tsimane and Moseten, the lack of new cases since November 2020 suggests that these groups may have achieved herd immunity. However, SARS-CoV-2 variants may still pose a threat for reinfection, and efforts to encourage vaccination among the Tsimane and Moseten are ongoing.

Dr. Aviv suggested that one potential innate mechanism for low mortality among the Tsimane and Moseten could be longer telomeres, and cited evidence from sub-Saharan African populations that are more resistant to severe COVID-19 infection and have telomeres that are considerably longer than those of Whites with European ancestry. Dr. Kaplan confirmed that unpublished telomere data have been collected from the Tsimane and Moseten as part of this research, and that preliminary analysis suggests a slower rate of telomere shortening with age in these populations.

Dr. Kaplan noted that major impacts of delirium or changes in mental status were not reported during the COVID-19 pandemic among these populations. Dr. Kaplan also clarified that the few Tsimane and Moseten who did die of COVID-19 may have had some typical risk factors for COVID-19 and, in one case, may have actually died of hunger and thirst after the rest of the village evacuated the area as a precautionary measure.

COVID-19 Stress and Cognitive Health Disparities

Kristine J. Ajrouch, PhD, University of Michigan

The AD Risk and Ethnic Factors: The Case of Arab Americans study is the first of its kind to focus on AD health disparities in Middle Eastern/Arab Americans (MENA) aged 65 and older living in

the largest and most visible MENA community in the United States. The opportunity to compare MENA to other racial/ethnic groups is not always available, in part because MENA are treated as White according to the Office of Management and Budget standards for reporting on race and ethnicity. Furthermore, more than half of the MENA individuals living in this metro-Detroit area community are considered linguistically isolated. Dr. Ajrouch described a COVID-19 supplement study that leveraged the bilingual resources of the parent AD study to conduct telephone interviews to address three primary aims: (1) to characterize the prevalence of COVID-19 stress types and cognitive health among three prominent racial/ethnic groups in metro-Detroit (i.e., MENA, Black, White), (2) to identify aspects of social relations that buffer links between COVID-19 stress and cognitive health, and (3) to determine the role of pre-existing social resources of COVID-19 stress and cognitive health.

Dr. Ajrouch and colleagues have collected 316 telephone interviews thus far and aim to collect a total of 200 interviews from each group. Demographics are important covariates for this study, and patterns have begun to emerge with regard to the gender, education, and marital status of respondents. Notably, MENA respondents include fewer females and tend to have lower levels of education than Black or White respondents. In addition, approximately 76 percent of MENA respondents are married, whereas 56 and 36 percent of White and Black respondents are married, respectively. Preliminary data suggest that older MENA adults show vulnerabilities in areas of COVID-19 stress, because they report the highest COVID-19-related stress levels. After adjusting for covariates, being MENA was associated with various COVID-19 stressors—including experiencing symptoms of COVID-19, knowing someone who died of COVID-19, and losing income during the pandemic—when compared to White respondents, but no difference in COVID-19 stress associations were found when MENA were compared to Black respondents. MENA also have unique social relationship patterns compared to other groups in the metro-Detroit area. MENA reported the highest in-person and video chat contact frequency with friends and family, as well as the lowest contact frequency with text, email, or social media. These patterns differ significantly from White respondents, who reported the highest use of text, email, or social media. Greater use of texting was also associated with a higher likelihood of knowing someone who died of COVID-19 among Black respondents, which could signify that texting is an important source of contact for older Black individuals. Finally, MENA also show vulnerabilities pertaining to cognitive health. MENA scored the lowest on one measure of cognitive health (digit span), indicating the lowest levels of cognitive health; no racial or ethnic differences were detected on the other cognitive measures. Next steps for this study are to complete data collection, investigate the links between pandemic stress and cognitive health, and explore other aspects of social relations and their influence on both COVID-19 stress and cognitive health. Data from this supplement and the parent study will broaden collective understanding of health disparities.

Discussion

Dr. Ajrouch clarified that data are collected from multiple counties in the metro-Detroit area, beyond the large MENA enclave with individuals who are considered linguistically isolated. As such, the full population represented within the total dataset is very heterogeneous. Dr.

Ajrouch noted that MENA populations are bifurcated in terms of socioeconomic status (SES), with equal proportions of MENA individuals reporting either high or low SES.

Factors Predicting Self-Efficacy for Enacting COVID Prevention Actions in Older Sexual Minority Men with HIV

Brett M. Millar, PhD, Hunter College, CUNY

The COVID-19 pandemic compounded the physical, mental, and social health challenges as well as sociostructural challenges that are faced regularly by older adults living with HIV. Dr. Millar and colleagues surveyed a highly engaged population of racially diverse, older sexual minority men (SMM) living with HIV whose age, race/ethnicity, and HIV status place them at higher risk for social isolation and adverse outcomes related to COVID-19. Respondents rated their confidence in their ability to engage in four domains of self-efficacy related to COVID-19 prevention: social distancing, utilizing recommended preventive measures (e.g., handwashing), avoiding exposure, and taking steps to prevent others from contracting COVID-19. Respondents also completed measures of self-compassion, depression, and insomnia.

Higher scores on the 12-item Self-Compassion Scale were positively associated with self-efficacy in each of the four COVID-19 prevention domains. These associations remained significant when adjusted for age, income, and depression. This finding highlights the beneficial effects of self-compassion on self-efficacy for engaging in and maintaining protective behaviors during the pandemic among a sample of SMM living with HIV in New York City. Dr. Millar underscored that the care for oneself involved in self-compassion also extended to self-efficacy for acting to prevent others from contracting COVID-19. Additional findings include negative associations between insomnia symptoms and self-efficacy for social distancing and other preventive measures, and between depression and self-efficacy for engaging in preventive measures. Dr. Millar plans to investigate the sleep-related findings further, as well as qualitative data from interviews regarding telehealth delivery and medication access.

Discussion

Dr. Millar clarified that the respondents included both individuals with detectable and undetectable HIV, as well as some individuals with and without histories of AIDS diagnoses. As such, the relative risk for adverse outcomes from COVID-19 varied throughout the study cohort. Dr. Millar added that respondents were generally highly engaged with their medical care, perhaps due to shifting attitudes that emphasize managing HIV as a chronic condition and adhering to medication regimens.

Dr. Millar noted that although there are additional recommended precautions for people living with HIV to stay healthy during the pandemic, the vaccine guidance for people living with HIV is the same as for the general population.

Impact of COVID-19 on Stress and Loneliness in an ADRC Cohort

Suzanne Craft, PhD; and Trey Bateman, PhD, Wake Forest University

The direct and indirect harms caused by COVID-19 have had disproportionately large impacts on the health of older adults. One of these harms, loneliness (i.e., a mismatch between a person's preferred and actual social relations), has increased considerably since the start of the pandemic; while only 27 percent of older adults reported feeling isolated before the pandemic, more than half of older adults reported feeling isolated during the first months of the pandemic. Adverse environmental or social exposures, including loneliness, are perceived by the CNS as a threat and trigger physiological changes, including the conserved transcriptional response to adversity (CTRA)—a module of gene expression changes that include an increase in pro-inflammatory genes and a decrease in cell-based immunity, IFN, and antibody synthesis-related genes. CTRA, which may lead to an increase in inflammatory-related disease risk, was first described in studies of loneliness in humans and has since been observed in conditions of chronic stress, poverty, bereavement, and PTSD.

Drs. Bateman, Craft, and colleagues are examining the relationship of COVID-19 with loneliness and stress in a well-characterized cohort for cognitive aging at the Wake Forest AD Research Center (ADRC). The study includes an assessment of CTRA as a marker of the physiologic embodiment of chronic stress, how certain behaviors and exposures moderate CTRA, and whether CTRA differs by cognitive or biomarker status. Measures include telephone-based questionnaires as well as remote collection of dried blood spots (DBS) for transcriptional analysis, which will produce a single CTRA contrast score that can be then modeled for associations with variables of interest. To date, 190 out of an anticipated 400 individuals have been recruited for the study. Dr. Bateman noted that one challenge for recruitment is the difficulty of administering remote assessments to individuals with mild cognitive impairment (MCI). Preliminary data show that loneliness and perceived stress are well-correlated across diagnostic groups. In addition, individuals with MCI appear to experience significantly more loneliness than cognitively normal individuals; Dr. Bateman noted that a formal interaction between race and cognition may be present, but the study is currently underpowered to draw a conclusion at this point in the study. No effects of neighborhood deprivation on loneliness have been observed to date.

Discussion

Dr. Bateman acknowledged that ADRC cohorts are often not representative of communities' demographic qualities, and that the current study faces difficulties recruiting individuals with lower SES or less formal education. The Wake Forest ADRC is committed to improving inclusion of underrepresented minorities in studies of cognitive aging, including through various outreach efforts to share cognitive aging knowledge with the broader community in the Winston-Salem area.

ACP COVID: Communicating with Outpatients for Vital Informed Decisions

James A. Tulsky, MD; and Angelo Volandes, MD, Dana-Farber Cancer Institute, MGH

The COVID-19 pandemic has highlighted the importance of advance care planning (ACP) for the most at-risk patients, including older adults. Many of these patients, especially from underrepresented communities, had no documented ACP conversations prior to hospital admission for COVID-19, and clinicians often found themselves unprepared to guide these conversations. Ideally, conversations about ACP and goals of care (GOC) would not occur in an inpatient setting during acute illness but rather in the outpatient setting. To address this need, Drs. Tulsky and Volandes are conducting an intervention trial to assess the efficacy of a rapidly implemented COVID-19-specific ACP/GOC telehealth program that combines ACP video decision aids with communication skills training on ACP documentation in the EHR for older patients in the outpatient setting as well as to address racial and ethnic disparities in ACP. The intervention is being implemented throughout Northwell Health, the largest health care system in New York State. Notably, half of all outpatients in Northwell Health are from underrepresented communities. The trial compares ACP documentation during three time periods: 6 months prior to the COVID-19 pandemic (i.e., October 2019-March 2020), during the COVID-19 surge in New York (i.e., April 2020-September 2020), and during the intervention period (i.e., January 2021-June 2021).

The intervention includes ACP video decision aids with content specific to COVID-19 that are watched by clinicians and patients during clinic visits and are sent to patients for viewing at home. Video narrators and B-roll footage represent the community being served (i.e., racial/ethnic groups, age groups) and are available in Spanish. Two weeks prior to clinic visits, patients participate in a telehealth visit with a nurse or social worker to begin the ACP conversation. To prepare clinicians to have high-quality conversations about GOC, the intervention also includes a series of training sessions for clinicians to practice their skills, including conversational approaches specific to COVID-19. These skills are designed to help clinicians empower patients to make a plan according to their values and avoid presenting patients with a list of difficult GOC choices. To date, 185 clinicians from six Northwell Health sites have undergone the training; 82 percent would recommend the course, and 74 percent reported that they were likely to use these skills in clinical practice. These clinicians have reached more than 16,000 unique patients.

The sample for this pre-post open cohort pragmatic trial includes 7,800 patients and 150 clinicians. The outcome of the trial is an ACP composite that includes recognition in the EHR of either GOC discussions, life-sustaining treatment limitations, COVID-19 health care proxy identification, or hospice referral. These items were identified using natural language processing (NLP) of EHRs, which reduces the time required to review an EHR from 2 hours to 5 minutes each. The analysis will include a comparison of changes from control to intervention between White and non-White subjects as well as Medicaid and non-Medicaid patients.

Discussion

Dr. Tulskey explained that a more general ACP approach, as opposed to a COVID-19-specific approach, would not have been ideal for this study because these patients were high-risk for adverse outcomes from COVID-19 but had not actually contracted COVID-19. As such, ACP conversations were predicated on a hypothetical situation that could occur in the future, as opposed to a chronic condition that would generally trigger late GOC conversations under more typical circumstances.

Dr. Volandes noted that this study is a supplement to a larger study that uses NLP and a similar intervention in the context of cancer. Dr. Volandes also emphasized that a key contribution of this work to the field is the use of NLP to analyze EHR notes, which often contain more detailed and more accurate information about a patient's ACP/GOC wishes than the more structured advanced directives EHR tab. Dr. Tulskey added that another important component of this intervention is simply the act of having ACP/GOC conversations before major decisions of care need to be made, which prepares patients and family members to make better decisions in real time.

Session 6: Developing Tools and Models for Coping with a Pandemic

Moderator: Marcel Salive, MD, MPD, NIA/DGCG

Daily Stress Reactivity and Resilience Resources Assessed Multiple Times During the Pandemic

Cindy Bergeman, PhD, University of Notre Dame

The Notre Dame Study of Health and Well-being (NDHWB) aims to understand stress and resilience of everyday life. Stressors can include emotional and physiological responses that, when left untreated or increase, can become precursors to disease and result in health outcomes that impact an individuals' physical health, functional ability, and psychological well-being. Resilience against these stressors can depend on internal psychological sources (e.g., sense of control, self-esteem, optimism) or external social supportive sources (e.g., friends and family support, community resources).

This study investigated the impact of COVID-19 as a global stressor. Participants had an initial assessment, answered questionnaires, logged diary entries, provided saliva samples, and underwent an experimental stress manipulation (to understand real-time stress responses) to understand the impact of COVID-19 as a chronic stressor and the extent to which an individual's stress impacts their negative emotionality, or their stress reactivity.

Dr. Bergeman found that pandemic-related worries exacerbated stress reactivity, compounding negative affect—such as anger, fear, anxiety, and depression—that an individual may experience. Positive emotions and expressions, known as positive affect, were found to be a coping strategy and opportunity for growth in the face of pandemic-related challenges.

Older adults, in general, had less stress reactivity than younger adults. Older adults expressed concern about social isolation and fears of contracting diseases, while younger adults were also

concerned about navigating multiple roles (e.g., working from home, losing childcare, and assuming additional responsibilities). In addition, when worry levels were highest during the early waves of the pandemic, the role of positive affect was not as strong. Dr. Bergeman found that younger adults strengthened their ability to deal with stress through positive emotions as time progressed. Future research will include health, cognitive, and stress data to understand the pandemic's longer-term consequences on individuals.

Discussion

Dr. Bergeman explained that other data about participants, such as employment, sleep, alcohol use, or other coping strategies, have not been analyzed yet.

The study includes multiple measures of resilience, most of which address the extent to which individuals can reduce their stress reactivity and increase their resilience. In addition, Dr. Bergeman's team is investigating the impact of positive emotions and their use to undo the effects of stress.

Outpatient Care Delivery and Telemedicine During the COVID-19 Pandemic

Michael Lawrence Barnett, MD, Harvard T.H. Chan School of Public Health

Although telemedicine was relatively rare before the pandemic, its use had already begun to accelerate quickly. During the pandemic, the federal government waived restrictions and regulations that limited reimbursement of care providers for telemedicine services. Dr. Barnett investigated national trends and changes in care delivery during the pandemic, with an emphasis on telemedicine for the aging population, because they are vulnerable to severe COVID-19 and face barriers to access and successful use of novel technologies. The aging population also has a greater need for continuous health care contact.

In a cohort of commercially insured patients and Medicare Advantage members, Dr. Barnett found that in-person care visits declined by 46 percent between March and June 2020; however, telemedicine visits offset a portion of this decline. Overall, the combination of telemedicine and in-person outpatient visits decreased by 24 percent. Regardless of geography or socioeconomic status, adults aged 65 and older experienced a larger decline (40 percent) in outpatient care visits, while those under age 65 averaged a 29 percent reduction.

Dr. Barnett also found that medical specialties with traditionally high telemedicine use maintained their total visit volume. Psychiatry and endocrinology represented the bulk of telemedicine visits, while ophthalmology and optometry had the lowest number of telemedicine visits. Further, the use and volume of telemedicine varied widely based on visit diagnosis. For example, visits for behavioral health diagnoses were the most likely to occur via telemedicine, while upper respiratory infections were less likely to have telehealth appointments but also fell substantially in overall visit volume.

This research may not be generalizable to all populations, such as Medicaid patients, and does not capture changes in delivery of care after June 2020. Dr. Barnett noted that he could not distinguish between care visits conducted via audio only and those conducted with both audio

and video, and that evaluation of this dimension could generate further information about the quality of care and inequities based on access. Telemedicine is likely a permanent fixture for health care, and forthcoming policies should support its use.

Discussion

Dr. Barnett noted that recent data suggest that total outpatient visit volume has returned to pre-pandemic levels, with the exception of pediatric patients, and up to 20 percent of visits are being conducted virtually. He clarified that among older adults with chronic conditions, , medical care appointments changed at the same rate throughout the study period as for older adults without chronic conditions. For individuals with complex conditions, like diabetes, no signal for negative outcomes was found, and glycemic control remained stable as telemedicine use increased.

Although telemedicine was available before the pandemic, and was sometimes covered through health insurance, Dr. Barnett believes its increased use will persist, adding that the observed changes are not caused by a change in awareness of telehealth options or measurement.

The Caregiver Resource Room: Development of an Online Assessment and Referral Platform for Family Caregivers

Francesca Falzarano, PhD, Cornell University

Of the nearly 6 million individuals living with dementia, 83 percent receive care at home from a family member, who is often unpaid. More than half of these caregivers report high emotional stress, clinically significant levels of anxiety and depression, and anticipatory grief. Caregiver needs vary based on the patient's disease severity and the caregiver's competing responsibilities (e.g., work or childcare). When their responsibilities are high, many caregivers tend to neglect their own needs, resulting in poor caregiver wellbeing and early long-term care placement for the individual receiving care. Further, the accumulation of stress related to care can lead to poor care outcomes.

Dr. Falzarano described her concept of a Caregiver Resource Room program, which would apply the Stress Process Model to provide personalized recommendations to caregivers about available support resources and potentially help to increase utilization of these resources. The ultimate goal is to increase caregiver self-efficacy, alleviate feelings of burden, and reduce clinically relevant mental health issues.

Inefficiencies and barriers to access have been observed in current systems intended to support caregivers, and Dr. Falzarano believes that machine learning technology can be leveraged to create better systems. Her conceptual Caregiver Resource Room would provide caregivers with targeted services in a completely virtual platform and would avoid common barriers to utilization (e.g., cost, fear, guilt, stigma, lack of respite care). Based on the care needs of the person with dementia, caregivers will enter personalized care preferences and background information, and the algorithm will produce a personalized list of support options for both the caregiver and the person receiving care.

Discussion

Dr. Falzarano noted that her tool is intended for use by caregivers, but will also benefit those receiving care. An additional study has been conducted specifically to evaluate individuals with MCI, which found that a generalized adoption of technology is successful when these individuals have support in technology use. Cornell University can provide remote training to caregivers on how to use the tool.

Dr. Falzarano noted that pilot testing of the Caregiver Resource Room has focused on resources available within the tri-state area (i.e., New York, New Jersey, and Connecticut) to build a test set for the machine learning algorithm. Researchers manually update the algorithms to reflect the availability of each resource so that users receive relevant information.

Web-based Evaluations of Cognitive Aging in the Time of COVID

Lee Ryan, PhD, University of Arizona

Although the majority of older adults will not develop dementia within their lifetime, many will experience a range of cognitive impairments that lead to significant health consequences. Age-related cognitive impairment is complex, and Dr. Ryan and colleagues have emphasized the need for an individualized approach to understanding and treating the effects of cognitive aging. One example of such an approach is *Mindcrowd*, a dual-phase, internet-based study of cognitive aging that includes a questionnaire, a memory and reaction time test, and collection of biological samples (dried blood spots) from participants.

Mindcrowd recruits participants who are demographically representative of the United States population. *Mindcrowd* data suggested that a compiled score of common comorbidities (e.g., hypertension, heart disease, obesity, smoking, and diabetes) could be used to predict associative memory performance. In October 2020, additional questions were added to assess the cognitive impacts of SARS-CoV-2 infection. An assessment of data from biological samples taken during the pandemic also showed that individuals who experienced COVID-19 symptoms, and the 12 percent of patients who tested positive for COVID-19 antibodies, were significantly more likely to have a medical history of asthma, smoking, acid reflux, and ulcers.

A second wave of surveys has been distributed to expand the study; this wave includes additional cognitive testing and more questionnaire fields about COVID-19 vaccination status and viral exposures.

In addition to yielding insights about cognitive aging, this study has shown that many individuals are willing to engage in web-based studies and provide biological samples.

Discussion

Dr. Ryan explained that the *Mindcrowd* questionnaire leverages cross-validated scales, and she expressed confidence that the current measures are appropriate for demographically diverse groups within the United States. She added that samples from individuals from diverse backgrounds can be compared through paired associations tests to understand differences in subpopulations within the larger cohort.

Dr. Ryan confirmed that blood samples are used not only for genetic testing, but also to conduct inflammatory panels and to test the impact of viral exposure on cognitive function.

A Spatial Model of the Spread of COVID-19 and Economic Conditions

Bruce Weinberg, PhD, Ohio State University

Dr. Weinberg described the bidirectional relationship between physical and mental health and economic outcomes within the context of geosocial spread that characterizes a pandemic. Dr. Weinberg analyzed this relationship during the COVID-19 pandemic by using the health-economic outcomes frontier, a model that depicts how different policies impact economic losses and the source of those losses. This model can be used to identify optimal health and economic policies. Dr. Weinberg found that the policies implemented by the U.S. government, did not match the health-economic outcomes frontier, and led to poorer outcomes for both the economy and for public health.

To understand the differences between optimal government policies and the actual policies implemented on local and federal scales, Dr. Weinberg collected data from 369 of the largest counties in the U.S., which account for 70 percent of the U.S. population. These data included COVID-19 infection rates, mortality rates, seasonally adjusted consumption, COVID mitigation policies, medical capacities, and economic measures. Data analyses revealed that early decisions generate persistent outcomes. For example, if a location experiences a 1 percent increase in infections during one period, that location will also experience an increase in infections—albeit one that is slightly lower (0.66 percent)—during the next period. Because of these dynamics, if poor policy decisions are made early, their health and economic effects are difficult to overcome.

Infection rates are traditionally inversely correlated with economic consumption (i.e., as infection rates increase, consumption decreases). Because of this relationship, there are limitations to prioritizing the economy over public health. Through model simulations, however, Dr. Weinberg found that an optimal policy included mask mandates and moderate lockdowns, resulting in both lower infection rates *and* increased economic consumption. Unfortunately, actual outcomes for the United States were worse than expected. Dr. Weinberg described two potential explanations for the poor outcomes. First, policies to improve economic outcomes worsened health outcomes over time, and second, COVID-19 infections spread more rapidly during the initial reopening phase. Due to poor policy decisions in the early phases of the pandemic, health outcomes worsened even when optimal policies were enacted. Future research will include vaccination measures and will investigate asymptomatic cases and disparities associated with infection.

Discussion

Dr. Weinberg clarified that the health-economic outcomes frontier model uses data on unemployment insurance and economic stimulus payments to assess policy effects on consumption. Additional variables within the model range from medical demand indices through weather variables (i.e., temperature and precipitation).

To differentiate various levels of COVID-mitigation policies (e.g., mask requirements, indoor capacity) within the model, Dr. Weinberg's research team used a coding system developed by *The New York Times* to categorize industries' response to COVID-19.

General Discussion

Collaborative Care

As a primary care physician, Dr. Barnett noted a strong preference for using telemedicine to connect physicians who care for patients with comorbidities. However, he added that the complexity and multifactorial nature of collaborative care makes it difficult to prove a demonstrable benefit to patients.

Efficacy of Online Cognitive Testing/Risks of Cheating on Cognitive Tasks

Because of the potential for coaching on cognitive tasks conducted remotely, Dr. Ryan collects data on each *Mindcrowd* participant's keystrokes and timing. She has also observed instances of participants receiving assistance during in-person testing.

Optimal Lockdown Timing

Dr. Weinberg noted that the current application of the health-economic outcomes frontier model is near its computational capacity. However, conceptually this model should be able to provide optimal lockdown timing for localities, much as precision medicine can be used to tailor care for individual patients. He added that the current model shows that initial lockdown measures in the United States were too restrictive, and that optimal mitigation is more modest and focused on mask mandates.

Lifestyle Factors/Predictors for Cognitive Aging

Dr. Ryan's second phase survey collects data to evaluate lifestyle factors, such as diet and the quality of social interactions. She found that older adults are significantly impacted by social isolation and that the degree and quality of social interactions impact the adult lifespan.

Session 7: Epidemiology

Moderator: John Phillips, PhD, Chief, Population and Social Processes Branch, NIA/BSR

Understanding Coronavirus in America

Arie Kapteyn, PhD, University of Southern California

The Understanding America Study has regularly collected economic, attitudinal, and health data on nearly 10,000 individuals every 2 weeks since 2014. With each data collection wave, a harmonized longitudinal file and individual wave file are made publicly available for download, which have been leveraged by more than 350 research groups. The study encompasses physical and mental health aspects, as well as economic aspects, that have affected individuals and families throughout the pandemic beginning in March 2020.

Dr. Kapteyn found that psychological distress among adults peaked in April 2020, with significant disparities between men and women. Women with children reported the highest

levels of psychological distress, whereas men with children reported the lowest; these differences are attributed to how childcare responsibilities fall primarily to women. He also found that alcohol use was directly related to psychological distress. Disparities in economic standing, particularly savings rates, were also observed between individuals who kept their jobs and grew their savings and those who lost their jobs and used their savings.

Dr. Kapteyn noted a specific interest in investigating patterns among people working from home, mental and physical health status, labor markets, and the status of families with children.

Discussion

Dr. Kapteyn confirmed that response rates throughout the pandemic remained relatively stable over time, which was attributed to participant compensation.

Following the Pandemic in Real Time: The 2020 Wave of the Health and Retirement Study

David Weir, PhD, University of Michigan

The Health and Retirement Study (HRS) is a helpful resource for studying the effects of the COVID-19 pandemic. This longitudinal study, which began data collection in 1992, implements a multi-disciplinary design to cover health, cognition, psychological behavior, well-being, and economic factors. Core data collection in 2020 coincided with the onset of the pandemic, and modifications were made to appropriately collect needed data. Additional data were collected to analyze experiences during the pandemic's peak.

When participants reflected on the pandemic and mitigation efforts, the majority (69.8 percent) noted no delays in receiving health care. Dr. Weir noted a persistent level of vaccine hesitancy and stated that individuals who were disinterested in receiving a SARS-CoV-2 vaccine were also unwilling to receive an influenza vaccine.

The HRS used self-administered antibody testing, prior to the vaccine rollout, to understand the breadth of asymptomatic cases, as well as the prevalence of long-COVID cases. Preliminary results using enzyme-linked immunosorbent assay (ELISA) showed that 5.6 percent of participants reported a positive PCR test result, but 21.3 percent tested positive for antibodies. Further, the within-household partners of people with a positive PCR test were also likely to have a positive PCR test, but a positive antibody test was not associated with antibody status in the partner. Dr. Weir noted that symptomatic people with no positive PCR test, and asymptomatic individuals with a positive test, were more likely to participate in this voluntary study. The transition to include COVID-19-relevant data into the HRS demonstrated the potential for integrating participant-collected biological samples into future studies.

Discussion

Dr. Weir noted that despite significant recruitment efforts, participation in the HRS among Black adults is lower than that of White participants, which may generate a weighting issue during analysis.

COVID-19, Finances, and Cognitive Impairment: New Data from High School and Beyond

John Robert Warren, PhD, University of Minnesota; and Chandra Muller, PhD, University of Texas at Austin

Dr. Warren described a proposed COVID-19 supplement to the 2021-2022 follow-up of the High School and Beyond longitudinal study. High School and Beyond focuses on how early-life inequalities affect the body and lead to disparities in cognitive impairment. Lifecourse factors such as structural racism and educational structures can influence cognitive functioning through both social and biological pathways (genetics also plays a role in cognitive impairment). COVID-19 may affect cognitive functioning through the same pathways, including through its financial impacts. By measuring COVID-19 impacts, the proposed supplement will thus help improve models of cognitive impairment and understanding of the pathways through which education and early life experiences increase risk of impairment decades later.

The High School and Beyond study sampled high school sophomores and seniors, measuring their educational opportunities and collecting their transcripts every 2 years between 1980 and 1986. Racial and ethnic minorities were randomly oversampled in certain locations. To understand basic outcomes at mid-life, a 2014-2015 follow-up was conducted through telephone and web-based surveys, in-home health visits, and administrative linkages. Dr. Warren noted that the web-based survey was used as a screening tool for cognitive impairment, and if participants showed signs of impairment, they were encouraged to complete their survey over the phone.

The COVID-19 supplement to the 2021-22 follow-up will include questions about participants' health status, vaccination status, and levels of social interaction as well as their experiences of the pandemic's financial consequences. Final measures to prepare this study for dissemination include linking collected data to Experian Credit Bureau records.

Discussion

Dr. Warren clarified that certain attributes of an individual's high school yearbook (e.g., extracurricular activities, social linkages, and attractiveness) are being tested to understand their association with later life outcomes.

COVID-19 and Alzheimer's Disease: Analyses of Risk, Disparity, and Outcomes from Electronic Health Records in the U.S.

Rong Xu, PhD, Case Western Reserve University

This study examined three facets of COVID-19: the risk of contraction among individuals with AD, disparities in risk of contraction and outcomes across race and gender, and outcomes among patients with AD. Dr. Xu hypothesized that patients with AD have a higher risk of contracting COVID-19 because they are likely to have comorbidities and a damaged blood-brain barrier and live in congregate situations. She further hypothesized that COVID-19 can

exacerbate existing racial and gender disparities and emphasized that the risk of contracting COVID-19 among patients with AD will be highest among Black and African American women.

After adjusting for demographics, comorbidities, and living conditions, Dr. Xu found that each hypothesis was correct. Individuals with AD had a higher risk of contracting COVID-19, and this risk was higher for Black and African Americans, compared to Whites, and for women compared to men. Risks of hospitalization and death were highest among Black and African Americans with AD. She added that the increased risk of COVID-19 was associated only with AD and not related dementias.

This study was limited to the earliest stages of the pandemic and uses patient EHR data. Unfortunately, many socio-economic and lifestyle factors were not considered in this study. Future research will address how the risk of contracting COVID-19 evolves over time for patients with AD, whether a SARS-CoV-2 infection could trigger AD onset, and how long-COVID may affect individuals who survived the initial infection stage. Researchers intend to investigate existing medications that could be used to treat persistent COVID-19 symptoms.

Discussion

Dr. Xu clarified that her sample included individuals as young as age 18 to identify any cases of early onset dementia or post-traumatic dementia. She added that the EHR data used in this study come from the Clinical Terms of the International Health Terminology Standards Development Organization (SNOMED CT) and the less frequently used ICD-10.

Excess Mortality During the COVID-19 Pandemic for People with Alzheimer's Disease

Lauren Gilstrap, MD, Dartmouth College

Dr. Gilstrap's research uses a measure to better understand the total impact of excess mortality (i.e., deaths that are directly or indirectly associated with COVID-19) on the population during the pandemic. Her study includes individuals who were diagnosed with COVID-19, those who were undiagnosed, and those whose deaths were caused by changes in the health care system.

Overall, Dr. Gilstrap found that excess deaths were higher among older individuals but were highest among Black and Hispanic individuals. In addition, between May and July 2020, the number of deaths among individuals with ADRD increased by 10 percent compared to 2019 among individuals living both within the community and within nursing homes. However, among individuals with ADRD living in nursing homes, Dr. Gilstrap found that there were 24 percent more deaths in 2020, compared to 2019. Further, in areas where infection rates were high, nursing home residents with ADRD experienced 20 percent more excess deaths than nursing home residents without ADRD.

Individuals with ADRD had higher mortality rates overall, but the difference between ADRD and non-ADRD mortality was larger in areas with higher rates of COVID-19. For individuals without ADRD, excess mortality was not seen in communities with low rates of COVID-19 infection. In the same communities, however, risk of excess death increased for all ADRD patients, and

further increased for nursing home residents with ADRD. Future research will consider later waves of the pandemic and will include data from August to December of 2020.

Discussion

Dr. Gilstrap noted that although the current sample consists of Medicare patients using fee-for-service methods, she does not expect that results would differ for individuals with Medicare Advantage. With current Medicare data, cause of death must be inferred. According to data from researchers at the Virginia Commonwealth University, it is estimated that roughly two-thirds of excess deaths in 2020 are due to COVID-19.

Dr. Gilstrap added that additional research could help researchers understand how COVID-19 may impact patients with ADRD and other chronic diseases. She added that she will study later waves of the pandemic to understand whether nursing homes have learned best practices and whether excess deaths differ between waves.

General Discussion

Survey Research

To quickly disseminate an augmented version of the UAS study during the height of pandemic mitigation efforts, investigators used common variables and measures. For the High School and Beyond Study, several measures were updated, and time to extensively pilot test these updated measures was limited. As the impacts and knowledge of the pandemic changed, the measures were again updated to capture the availability of vaccines and medications.

Comorbidities Effect on Excess Deaths

Dr. Gilstrap noted that determining the cause of excess deaths is important to prevent additional deaths. As a heart failure physician, she noted that heart disease, a common comorbidity, traditionally contributes to a large portion of excess deaths. However, due to lifestyle changes from COVID-mitigation, many cardiologists noted that incidence of heart attacks suddenly declined at the onset of the pandemic. Understanding the cause of negative outcomes is critical for researchers to prevent excess deaths.

Seroneutralization Antibody Assays

Dr. Weir noted that his research tests antibodies in saliva samples, and it is unclear whether seroneutralization assays can be conducted using such samples. Dr. Muller noted that for whole blood samples, her research group is using a test that can differentiate between individuals who previously had the virus and those who have been vaccinated, but individuals who had both an infection and the vaccination currently will present as vaccinated.

Appendix A: Agenda

Day 1: June 17, 2021

- 10:00 am Opening Remarks
Ron Kohanski, PhD, National Institute on Aging (NIA)/Division of Aging Biology (DAB); and Lis Nielsen, PhD, Director, NIA/Division of Behavioral and Social Research (BSR)
- 10:15 am ***Session 1: Peripheral and Neurological Sequelae of COVID-19 Infection***
Moderator: Luci Roberts, PhD, NIA/Division of Neuroscience (DN)
- Impact of Lung Injury on Neuroinflammation and Brain Functioning
Niccolò Terrando, PhD, Duke University
- Age-associated Changes in SARS-CoV-2 Infected Non-human Primate Species
Joanne Turner, PhD, Texas Biomedical Research Institute
- Kynurenic Acid Blockade of NMDA Receptors in Primate Prefrontal Cortex – Contribution to Long-COVID-19 Symptoms of “Brain Fog”
Amy F.T. Arnsten, PhD; Shengtao Yang, PhD; Dibyadeep Datta, PhD; and Min Wang, PhD, Yale Medical School
- Brain Histopathology in Subjects with COVID-19 Disease
Thomas G. Beach, MD, PhD, Banner Sun Health Research Institute
- Mapping of SARS-CoV-2 Brain Invasion in COVID-19 Disease
Geidy E. Serrano, PhD, Banner Sun Health Research Institute
- A Multipronged Interrogation of Large-scale Omics Data to Reveal COVID-19 Pathways
Carlos Cruchaga, PhD, Washington University in St. Louis (WUSTL); and Sharlee Climer, PhD, University of Missouri-St. Louis
- 12:00 pm Break
- 12:15 pm ***Session 2: Aging-related Risk Factors in COVID-19 Vulnerability***
Moderator: Max Guo, PhD, Chief, Genetics and Cell Biology Branch, NIA/DAB
- The Telomeres COVID-19 Lymphopenia Nexus
Abraham Aviv, MD, Rutgers University
- Short Telomeres and T-Cell Shortfall in COVID-19: The Aging Effect
James J. Anderson, PhD, University of Washington

Plasma Proteomics of COVID Infection with Cardiac Involvement
Anthony Rosenzweig, MD, Massachusetts General Hospital (MGH)

Specific Risk Factors Associated with COVID-19 Severe Outcomes for Older Patients
Judy Zhong, PhD, New York University Medical Center

1:30 pm Break

2:00 pm ***Session 3: Dementia Care, Caregiving, and Psychosocial Outcomes During the Pandemic***

Moderator: Elena Fazio, PhD, NIA/BSR

COVID-19 and U.S. Nursing Homes: Implications for the Future
Vince Mor, PhD, Brown University

The Effects of the COVID-19 Pandemic on the Lived Experience of Diverse Older Adults Living Alone with Cognitive Impairment
Elena Portacolone, PhD, University of California, San Francisco

Clinical Features and Outcomes of Patients with Dementia Compared to an Aging Cohort Hospitalized During the Initial New York City COVID-19 Wave
James M. Noble, MD, Columbia University

Disruptions and Adaptations to Care for Homebound Patients with Dementia and Other Serious Illnesses in the Context of COVID-19
Katherine Ornstein, PhD, Mount Sinai School of Medicine

Decreased In-person Social Contact During the Pandemic is Associated with Worsening Mental Health Despite Increased Remote Contact Frequency
Louise Hawkey, PhD; and Linda Waite, PhD, NORC at the University of Chicago

3:30 pm Break

3:45 pm ***Session 4: Efforts to Develop Therapies***

Moderator: Jean Yuan, MD, PhD, NIA/DN

Drug Repurposing for COVID-19 Using Graph Neural Network with Genetic, Mechanistic, and Epidemiological Validation
Xiaoqian Jiang, PhD, University of Texas Health Science Center at Houston

Searching for Invariants in the Dynamic Fitness Landscapes of SARS-CoV-2 and Humans
Olivier Lichtarge, MD, PhD, Baylor College of Medicine

COVID-19, Cellular Senescence, and Senolytic Agents: The Path to Translation

James Kirkland, MD, PhD, Mayo Clinic

Developing Therapies to Improve Antiviral Immunity in Older Adults

Joan Mannick, MD, Life Biosciences

Intravenous Guanfacine for Critical Illness Brain Dysfunction During COVID-19 Pandemic

Oluwaseun Johnson-Akeju, MD, MGH; and Christopher G. Hughes, MD, Vanderbilt University

5:15 pm Adjourn for Day

Day 2: June 18, 2021

10:00 am Opening Remarks

Eliezer Masliah, MD, Director, NIA/DN; and Basil Eldadah, MD, PhD, Chief, Geriatrics Branch, NIA/Division of Geriatrics and Clinical Gerontology (DGCG)

10:15 am **Session 5: Factors Affecting Risk and Resilience**

Moderator: Dallas Anderson, PhD, MPH, NIA/DN

High Prevalence of COVID-19 with Low Case Fatality Rates Among Tsimane and Mosesten Native South Americans

Hillard Kaplan, PhD, Chapman University

COVID-19 Stress and Cognitive Health Disparities

Kristine J. Ajrouch, PhD, University of Michigan

Factors Predicting Self-Efficacy for Enacting COVID Prevention Actions in Older Sexual Minority Men with HIV

Brett M. Millar, PhD, Hunter College, CUNY

Impact of COVID-19 on Stress and Loneliness in an ADRC Cohort

Suzanne Craft, PhD; and Trey Bateman, PhD, Wake Forest University

ACP COVID: Communicating with Outpatients for Vital Informed Decisions

James A. Tulsky, MD; and Angelo Volandes, MD, Dana-Farber Cancer Institute, MGH

11:45 am Break

12:00 pm **Session 6: Developing Tools and Models for Coping with a Pandemic**

Moderator: Marcel Salive, MD, MPD, NIA/DGCG

Daily Stress Reactivity and Resilience Resources Assessed Multiple Times During the Pandemic

Cindy Bergeman, PhD, University of Notre Dame

Outpatient Care Delivery and Telemedicine During the COVID-19 Pandemic

Michael Lawrence Barnett, MD, Harvard T.H. Chan School of Public Health

The Caregiver Resource Room: Development of an Online Assessment and Referral Platform for Family Caregivers

Francesca Falzarano, PhD, Cornell University

Web-based Evaluations of Cognitive Aging in the Time of COVID

Lee Ryan, PhD, University of Arizona

Co-evolution of Infections and the Economy During the COVID-19 Pandemic

Bruce Weinberg, PhD, Ohio State University

1:30 pm Break

2:00 pm **Session 7: Epidemiology**

Moderator: John Phillips, PhD, Chief, Population and Social Processes Branch, NIA/BSR

Tracking the Pandemic Effects on American Households

Arie Kapteyn, PhD, University of Southern California

Following the Pandemic in Real Time: The 2020 Wave of the Health and Retirement Study

David Weir, PhD, University of Michigan

COVID-19, Finances, and Cognitive Impairment: New Data from High School & Beyond

John Robert Warren, PhD, University of Minnesota; and Chandra Muller, PhD, University of Texas at Austin

COVID-19 and Alzheimer's Disease: Analyses of Risk, Disparity, and Outcomes from Electronic Health Records in the U.S.

Rong Xu, PhD, Case Western Reserve University

Excess Mortality During the COVID-19 Pandemic Among Medicare Enrollees with Alzheimer's Disease

Lauren Gilstrap, MD, Dartmouth College

3:30 pm Adjourn

Appendix B: Workshop Attendees

Kristine Ajrouch, PhD
University of Michigan

Amy FT Arnsten, PhD
Yale University

Michael Lawrence Barnett, MD
Harvard T.H. Chan School of Public Health

Cindy Bergeman, PhD
University of Notre Dame

Carlos Cruchaga, PhD
Washington University, St. Louis

Lauren Gilstrap, MD, MPH
Dartmouth College

Xiaoqian Jiang, PhD
University of Texas Health Science Center

Hillard Kaplan, PhD
Chapman University

James Kirkland, MD, PhD
Mayo Clinic

Olivier Lichtarge, MD, PhD
Baylor College of Medicine

Brett Millar, PhD
Hunter College, CUNY

James M. Noble, MD
Columbia University

Elena Portacolone, PhD
University of California, San Francisco

Lee Ryan, PhD
University of Arizona, Translational Genomics Institute

James A. Tulsky, MD
Cancer Institute; Advance Care Planning Decisions

James Anderson, PhD
University of Washington

Abraham Aviv, MD
Rutgers University

Thomas G. Beach, MD, PhD
Banner Sun Health Research Institute

Suzanne Craft, PhD
Wake Forest University

Francesca Falzarano, PhD
Cornell University

Louise Hawkley, PhD
NORC at the University of Chicago

Christopher G. Hughes, MD, MS, FCCM
Vanderbilt University

Arie Kapteyn, PhD
University of Southern California

Morgan Levine, PhD
Yale University

Joan Mannick, MD
Life Biosciences

Vince Mor, PhD
Brown University

Katherine Ornstein, PhD
Icahn School of Medicine at Mount Sinai

Anthony Rosenzweig, MD
Massachusetts General Hospital

Niccolo Terrando, PhD
Duke University

Joanne Turner, PhD
Texas Biomedical Research Institute

John Robert Warren, PhD
University of Minnesota

Bruce Weinberg, PhD
Ohio State University

David Weir, PhD
University of Michigan

Rong Xu, PhD
Case Western Reserve University

Judy Zhong, PhD
New York University Medical Center