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Chairman Casey, Ranking Member Scott, and members of the Special Committee on Aging, thank you for providing me this opportunity to present my perspective on the exciting approaches that are available today supporting the goal to take aim at Alzheimer's Disease and Related Dementias (ADRD). I am a board-certified geriatrician at the University of Utah School of Medicine where I am Professor and Chief of the Geriatrics Division and Executive Director for the University of Utah Center on Aging. I have provided primary care for older adults for the past 30 plus years. In my primary care geriatrics medical home clinic, with the support of an interprofessional team of providers, I evaluate patients who present with cognitive concerns, diagnose and treat ADRD, and provide ongoing longitudinal care for these patients, and their families and caregivers. I provide whole-person centered care – not limited to just their cognitive concerns. In this regard, I should disclose that I do not consider myself to be an Alzheimer's Disease expert. However, I do have expertise in caring for persons who have dementia, and often many other chronic medical conditions. My research expertise is focused on mechanisms of vascular aging and the age-related increase in blood pressure, also known as geriatric hypertension. I will discuss how vascular aging and hypertension have emerged as key actors in the ADRD story – particularly with the good news that there are effective approaches to prevent cognitive impairment. I am an investigator with two clinical trials that are evaluating vascular risk factors for ADRD – SPRINT MIND and PREVENTABLE. In addition, I am a member of the Research Roundtable for the Alzheimer's Association's Centers for Disease Control and Prevention: BOLD Public Health Center of Excellence on Dementia Risk Reduction supported by the "Building Our Largest Dementia (BOLD) Infrastructure for Alzheimer's Act" – PL115-406. Finally, I am a member of the American Geriatrics Society Board of Directors.

Definitions, the Grand Challenge and Grand Opportunity

Cognitive impairment is not normal aging. Rather, memory loss and limitations in other cognitive abilities develop as part of a disease process. The continuum of cognitive decline from mild cognitive impairment (MCI) to progressively more severe levels of dementia is shown in **Figure 1**. MCI is a discrete clinical condition diagnosed when there are limitations in memory or another cognitive ability, but the individual remains able to perform her or his daily activities. It is an obligatory precursor that in many individuals progresses to dementia, defined by the point when impairments in daily activities develop. Dementia should be thought of as a syndrome, not a cause. Alzheimer's Disease is a common, but only one of a host of conditions that cause dementia. It is of critical importance to evaluate an individual with a dementia syndrome diagnosis so that its cause may be identified. It is also important to understand that ADRD does not present in isolation, but is more often the dominant comorbidity among many other chronic medical conditions and medications that an older adult may be managing. Hence, the need for comprehensive, person-centered care.

ADRD is a "Grand Challenge" facing our society and medical science in the 21st century. Statistics from the Alzheimer's Association are that an estimated 6 million Americans are living with ADRD in 2021, and 11 million Americans are providing unpaid care for persons with ADRD. Alzheimer's Disease is the only one of the top ten leading causes of death in the United States that is increasing in prevalence. In the last 10 years, heart disease deaths have decreased by 7.3% while deaths from AD have increased by 145%. The estimated costs of health care, long-term care and hospice for ADRD in the US is estimated to be $355 billion currently and expected to grow to $1.1 trillion by 2050.

Addressing ADRD is a significant and important undertaking in Utah where the ADRD statistics are even more sobering. Driven by the aging demographic trends in Utah, demographic projections estimate that the number of people with AD in Utah will increase from the current 34,000 to 42,000 – a 24% increase – by 2025. The Utah Department of Health has created a state plan for Alzheimer's Disease and Related Dementias 2018-2022 which is currently being implemented.

ADRD also is a "Grand Opportunity" for academic research. Scientific advances in neuroscience, genetics, informatics, and imaging provide new abilities to probe disease mechanisms and inform practical solutions for diagnosis and management. These research advances open the door to investigations into mechanisms of cognitive resilience and characterize resiliency factors as moderators between neuropathology and dementia in ADRD. The National Institutes of Health AD Research Summit in 2015 identified "Understand all aspects of healthy brain aging and *cognitive resilience* to inform strategies for

AD prevention" as one of the transformative concepts that summit participants agreed was critical to the future of AD research. NIA has developed the AD+ADRD Research Implementation Milestones to represent a research framework detailing specific steps and success criteria towards achieving the goal of the National Plan to Address Alzheimer's Disease to treat and prevent AD and ADRDs by 2025.

Effective strategies to prevent and treat MCI and ADRD are available

There is not yet a proven, safe, disease-modifying treatment for individuals diagnosed with Alzheimer's Disease. Several promising approaches – antibody therapies that are directed to reduce the levels of the abnormal ß-amyloid protein in the brain that are believed to cause damage to brain cells – are currently under investigation. There is much hope that one or more of these amyloid immunotherapies will become available to prevent AD progression early in the disease course.

There is a growing body of evidence that effective strategies to prevent and treat MCI and ADRD are available today. The 2020 dementia prevention, intervention, and care report from the Lancet Commission concluded, "Together the 12 modifiable risk factors account for around 40% of worldwide dementias, which consequently could theoretically be prevented or delayed. The potential for prevention is high and might be higher in low-income and middle-income countries (LMIC) where more dementias occur."[1] **Figure 2**, taken from the Commission's report, illustrates the relative contributions across the life span for each of these *modifiable* risk factors – less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, infrequent social contact, excessive alcohol consumption, head injury, and air pollution.

The age-related vascular contributions to ADRD have been the focus of my own research interest. These mechanisms are illustrated in **Figure 3**.[2] I am an investigator with the Systolic Blood Pressure Intervention Trial (SPRINT) Memory and Cognition in Decreased Hypertension (MIND) clinical trial funded by the National Institutes of Health (ClinicalTrials.gov, NCT01206062). This study demonstrated that among those with hypertension, intensive management of systolic blood pressure (SBP) to a treatment goal of 120 mm Hg reduced the development of mild cognitive impairment (MCI) by 19% [3] and slowed the accumulation of white matter hyperintensities in the brain [4]. This landmark study offers hope that a new paradigm is needed to develop strategies that may delay MCI and AD. In her editorial to the SPRINT-MIND publication, Dr. Yaffe stated, "*Indeed, the timing is right to investigate multidomain risk reduction strategies personalized for older adults and their individual risk profiles. Eventually this modifiable risk factor approach could be combined with disease-modifying*

drugs so that one day, it will be possible to identify persons at risk of AD and related dementia (either by biomarkers, genetics, or cognitive symptoms) and offer an effective strategy for prevention of cognitive impairment."[5] The PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr adults (PREVENTABLE) (ClinicalTrials.gov NCT04262206) is a pragmatic clinical trial currently being conducted in 20,000 adults age 75 years and older that is evaluating whether a commonly used heart medication – a statin – will be beneficial in preventing MCI and dementia.

In parallel with efforts to provide disease modifying treatments for AD, the importance of implementing existing preventive strategies cannot be overstated. The most effective way to decrease ADRD prevalence is to postpone its onset. A two-year delay in dementia onset would translate to 2.2 million fewer Americans developing dementia in 2040 – a 20% reduction [6] (**Figure 4**).

There are effective, evidenced-based, dementia care programs that could be implemented today. The Care Ecosystem pragmatic clinical trial of people with dementia and their caregivers evaluated a telephone-based care delivery approach using a care team navigator supported by a team of dementia specialists (advanced practice nurse, social worker and pharmacist). There were significant improvements in caregiver quality of life, depression and burden, and a reduction in emergency room utilization.[7] Another innovative program is "Community Aging in Place—Advancing Better Living for Elders (CAPABLE; ClinicalTrials.gov NCT01743495)" that targets supporting low-income older adults to age in place. Its approach teams a nurse, an occupational therapist and a handy worker to address the home environment and to improve safety and independence. The study demonstrated lower likelihood of inpatient and long-term service use and lower over-all Medicaid spending.[8]

Recommendations:

These recent advances in strategies to prevent cognitive impairment and to provide effective dementia management services lead me to conclude with the following recommendations:

1. Promote Prevention Strategies

Promoting cognitive screening is an important precursor to implementing prevention strategies. Creating a dementia aware society where cognitive screening is normalized will help to reduce the stigma that often accompanies a dementia diagnosis. The need for early detection of cognitive impairment is all the more relevant today so that preventive strategies and treatments may be initiated early. Requiring validated, objective, screening tests of memory and

cognition in the Medicare Annual Medicare Wellness visit is one strategy to accomplish this.

Implementing public health strategies that target modifiable dementia risk factors that will be recommended as an outcome from the CDC BOLD Infrastructure programs will be critically important. Many of these modifiable risk factors disproportionally impact underserved populations with adverse social determinants of health. Mitigating the impact of these health disparities is urgently needed.

2. Develop a Dementia-competent workforce

Most dementia care is provided by primary care health professionals. All members of the health care team will require education and training to competently evaluate and manage patients with cognitive impairment and dementia. In parallel, there is a need to expand the number of geriatrics health care professionals, including geriatricians and cognitive specialists, to meet the demands for appropriate diagnosis of patients with dementia.

There is a special need to support hands-on caregivers and the direct care worker (in home and in long term care settings) workforce to equip them to care for persons with dementia. This support should include ensuring living wages, benefits and paid family leave.

3. Support Dementia Management Programs and Family Caregivers

There is a pressing need to provide options so persons with dementia and their families and caregivers can access the right care, in the right setting, at the right time. Efforts to expand home and community-based services (HCBS) and making evidence-based programs like the Care Ecosystem and CAPABLE more broadly available will help decrease excess health care system utilization and avoid premature placements in skilled nursing facilities. The recently introduced bipartisan "Comprehensive Care for Alzheimer's Act" is designed to support the development and evaluate dementia care management programs like these. At the same time, we must work to improve nursing home care so that this setting is available to families who can no longer support their loved one at home.

4. Continue to invest in ADRD Research

The recent infusion of ADRD research support has already begun to yield important results such as those I have cited. Ensuring that more ADRD clinical trials appropriately include participants across the lifespan without upper age limits[9], include appropriate racial, ethnic, and gender diversity,[10,11] and incorporate geriatrics relevant outcomes such as cognitive function (as is being done in the PREVENTABLE study) is important in this regard, especially when FDA approval of new therapies is being considered. Future research is sorely needed

to identify mechanisms for cognitive resilience, promoting cultural awareness, and addressing the disproportionate impact of health disparities in developing cognitive impairment.

Thank you for giving me the opportunity to share my perspective with you today. I look forward to addressing your questions and comments.

Figures

Figure 1: The cognitive impairment continuum.

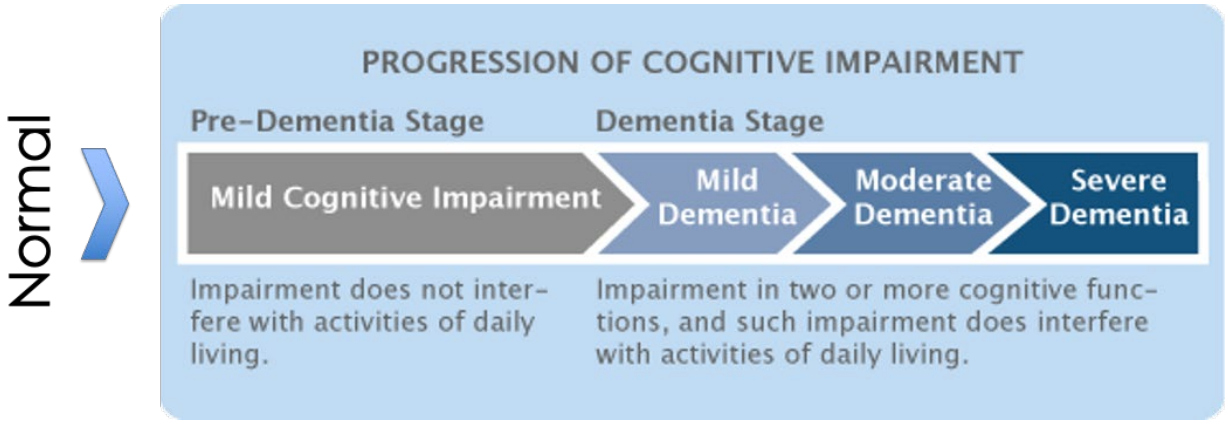


Figure 2. Population attributable fraction of potentially modifiable risk factors for dementia. [1]

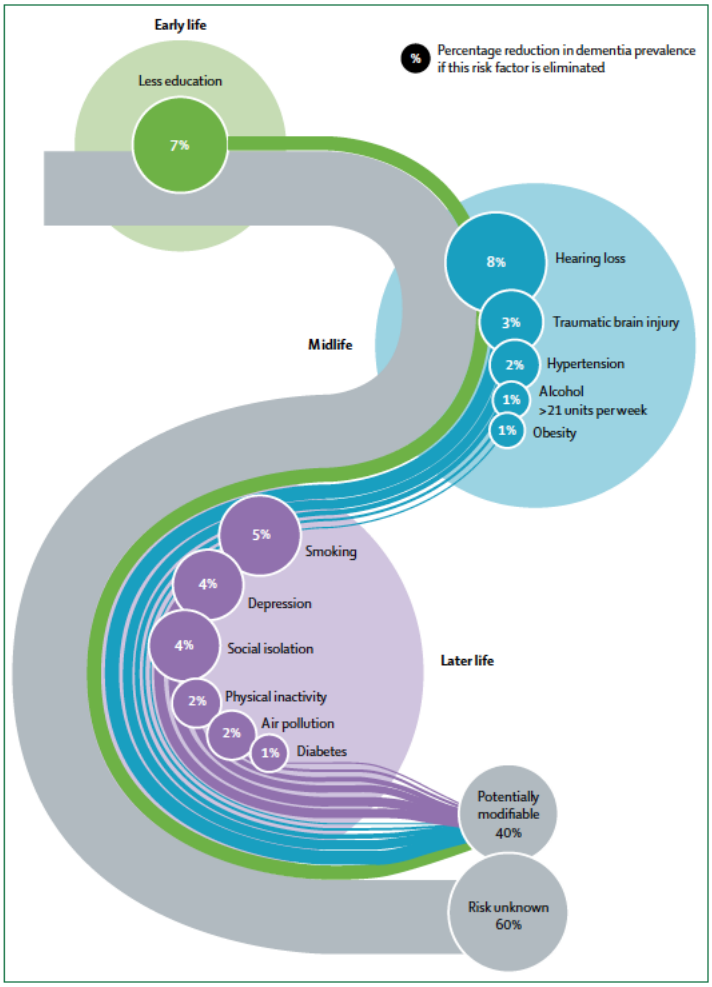


Figure 3: Putative pathways for hypertension to increase risk for cognitive decline in aging and neurodegenerative disease [2]

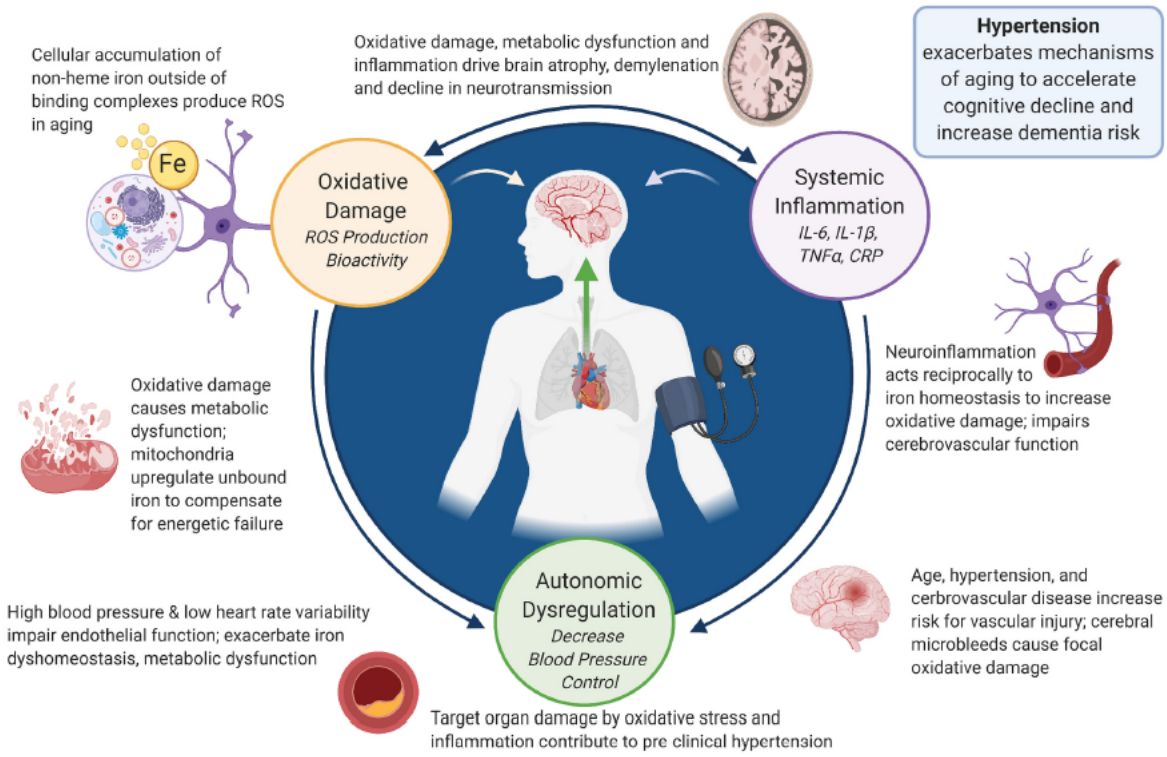
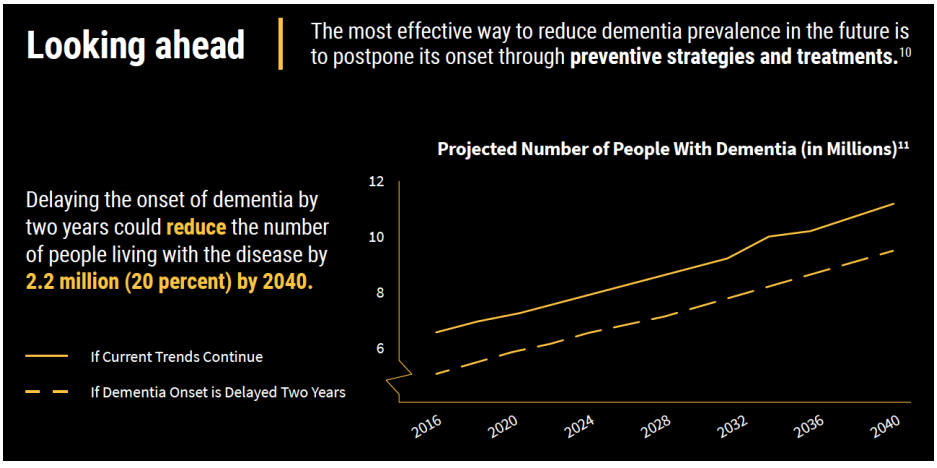


Fig. 1. A summary figure describing putative pathways for hypertension to increase risk for cognitive decline in aging and neurodegenerative disease. Midlife hypertension accelerates neurodegeneration and cognitive decline in aging, and increases the risk for Alzheimer's disease and related dementia (ADRD). Although hypertension is a modifiable risk factor, successful blood pressure control with antihypertensive treatment does not reduce the risk for ADRD. This suggests hypertension may act upon antecedents of age-related neurodegeneration. The three pathways reviewed were (1) oxidative damage and metabolic dysfunction; (2) systemic inflammation; and (3) autonomic control and heart rate variability. The pathways reflect cumulative and progressive changes in nervous system function and health that are typical in aging, contribute to the development of hypertension and drive neural and cognitive decline, which chronic high blood pressure further exacerbates. The pathways interact to create a self-propagating cascade that subsequent blood pressure control may slow, but not halt, to account for dementia risk. Abbreviations: ROS—reactive oxygen species; IL-6 and IL-1β—interleukin-6 and − 1β; TNFα—tumor necrosis factor alpha; CRP—C-reactive protein. Figure created with BioRender.com.

Figure 4: Impact of ADRD Preventive Strategies [6]



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2. Daugherty AM. Hypertension-related risk for dementia: A summary review with future directions. Seminars in Cell & Developmental Biology 2021.

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Additional Resources:

2020 Update of the National Plan to Address Alzheimer's Disease https://aspe.hhs.gov/pdf-report/national-plan-address-alzheimers-disease-2020-update

National Data: https://www.alz.org/media/Documents/alzheimers-facts-and-figures-infographic.pdf

Utah Data: https://www.alz.org/media/Documents/utah-alzheimers-facts-figures-2021.pdf

Utah Alzheimer's Disease State Plan: Utah's State Plan for Alzheimer's Disease and Related Dementias 2018-2022. Version 1.0. (2017) Salt Lake City, Utah: Utah Department of Health https://livingwell.utah.gov/docs/Alzheimers_StatePlan.pdf

Alzheimer's Association Trajectory Report: https://www.alz.org/media/Documents/trajectory-report-infographic.pdf

CDC BOLD Initiative: https://www.cdc.gov/aging/bold/index.html