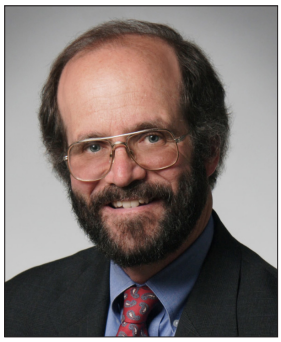
Sanjay Asthana, MD, FACP



Robert N. Golden, MD

Wisconsin Alzheimer's Disease Research Center—Notable Discoveries and Accomplishments in Dementia Research

Sanjay Asthana, MD, FACP; Robert N. Golden, MD

The population in the United States is aging rapidly. Currently, over 56 million Americans are older than 65, comprising 17% of the populace. By 2050, this number will increase to nearly 85 million. Much of this growth is due to the aging of Baby Boomers, who in 2030 will be aged 66 to 84—the "young old"—and will number 61 million people. At that time, those born prior to 1946—the "oldest old"—will amount to 9 million people. These individuals are vulnerable to multiple aging-associated diseases, including heart disease, cancer, stroke, dementia, and functional impairments that lead to higher morbidity and mortality compared to younger people. This will have a major impact on health care needs and expenditures.

Alzheimer's disease (AD) is the most common cause of dementia, afflicting more than 6.7 million Americans. The sixth leading cause of death in the nation, AD imposes devastating suffering and socioeconomic burdens on patients, their families, and society. The disease's neuropathologic hallmark is the deposition of amyloid and tau, two abnormally processed proteins that are deposited in parts of the brain and, over decades, lead to death of neurons and other pathologic changes that cause cognitive and functional deficits and eventual loss of life.

• • •

Author Affiliations: Sanjay Asthana, MD, FACP, is the associate dean for gerontology; the Duncan G. and Lottie H. Ballantine Professor of Geriatrics; head of the Division of Geriatrics and Gerontology, Department of Medicine; and director of the Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health. Robert N. Golden, MD, is dean of the UW School of Medicine and Public Health and vice chancellor for medical affairs at UW-Madison.

The Division of Geriatrics and Gerontology in the University of Wisconsin School of Medicine and Public Health's (SMPH) Department of Medicine is renowned internationally for its innovative programs in aging and dementia research. The division is one of the largest of its kind in the United States.

The SMPH supports the National Institutes of Health (NIH)-funded Wisconsin Alzheimer's Disease Research Center (ADRC), the first geriatrics-based center of excellence in dementia research in the country. Funded continuously since 2009, the ADRC conducts state-of-the-art research across the full continuum of AD pathophysiology, including its molecular biology, epidemiology, neuroimaging and fluid biomarkers, clinical phenotype, treatment, prevention, and community-engaged and dissemination and implementation research. The ADRC also supports several cohorts involving over 1100 participants with or without dementia, and it collaborates extensively with the NIH-funded Wisconsin Registry for Alzheimer's Prevention (WRAP). Led by Sterling Johnson, PhD, professor of medicine and associate director of the ADRC, WRAP coordinates a cohort of more than 1700 participants who were cognitively unimpaired and in their early- to mid-50s when recruited to study the natural progression of AD over 20 years ago. Together, the Wisconsin ADRC and WRAP provide access to two of the largest and longest-followed cohorts of well-characterized, diverse participants, as well as datasets for cutting-edge research across the pathobiology of AD and related dementias. Findings from ADRC- and WRAP-supported studies provide novel insights into molecular mechanisms underlying AD and related dementias. These findings are directly relevant to improving patient care, enhancing quality of life, reducing caregiver stress, and decreasing health care costs.

Studies show that AD pathology starts decades before the first symptoms of the disease. This provides a unique opportunity to diagnose the disease when a person is asymptomatic and initiate treatments or prevention strategies to slow or stop progression. The Wisconsin ADRC is among the first centers in the country to identify novel brain imaging, cerebrospinal fluid (CSF), and cognitive and blood-based biomarkers of preclinical AD that could diagnose the disease early; identify patients eligible to receive newly approved, disease-modifying treatments; and help with risk prediction. Recent breakthrough AD biomarker findings from the ADRC and WRAP indicate that:

- brain white matter undergoes degeneration during preclinical stages of AD and relates to cognitive decline;
- the age of onset and duration of amyloid deposition in the brain can be estimated from PET brain imaging and blood AD biomarkers;
- presence of both amyloid and tau in the brain is associated with faster cognitive decline;
- CSF markers of neurodegeneration, such as neurogranin and neurofilament light, increase with disease severity and predict worse cognitive performance; and

- plasma levels of phosphorylated tau-217, an abnormal epitope of tau, are strongly correlated with amyloid and tau PET scans, are associated with worse cognitive trajectories, and could serve as a marker of response to treatment with emerging new therapies for AD.

AD biomarker research findings from the Wisconsin ADRC and WRAP have attracted widespread attention and noteworthy funding from the NIH. The NIH recently awarded a $150 million grant to Dr Johnson entitled "ADRC Consortium for Clarity in AD and Related Dementias Research through Imaging (CLARiTI)." The grant's overarching scientific goal is to identify multiple etiologies that commonly coexist in patients with dementia. The project will involve all 37 ADRCs across the nation and collect longitudinal magnetic resonance imaging and amyloid and tau PET brain imaging, cognitive and blood-based AD biomarker data, and consent for brain autopsies in 2000 ethnoculturally diverse participants with or without dementia. CLARiTI will provide access to extensive, leading-edge neuroimaging and biomarker data collected through harmonized protocols across the country. This will generate information concerning the heterogeneity of clinical presentations and pathology, as well as the role of coexisting pathologies in AD and related dementias.

Convincing evidence shows that health inequities and health care discrimination lead to a delay in diagnosis and treatment of AD in millions of people from underserved, underrepresented groups across the nation. Under the guidance of Carey Gleason, PhD, leader of the Inclusion of Underrepresented Groups Core, the Wisconsin ADRC is examining AD disparities through the establishment of two of the largest cohorts of African American and Native American participants in the United States. Following more than a decade of prospective study, these cohorts provide substantial research data and blood and CSF samples for collaborative research worldwide. These biospecimens and data will help examine the potential effects of race and ethnicity on AD biomarkers, cognition, and transition from presymptomatic to symptomatic stages of the disease. Preliminary findings from a National Institute on Aging-funded study (principal investigator: Carey Gleason), entitled "African Americans Fighting Alzheimer's in Midlife (AA-FAiM)," suggest that a lower plasma ratio of two abnormal forms of amyloid in African Americans is associated with cognitive decline during preclinical stages of AD.

Systematic research has provided evidence that exposure to various sociocultural, biological, and environmental factors over the life course affects risk of and resilience to AD and related dementias. Under the leadership of Amy Kind, MD, PhD, the UW Center for Health Disparities Research is among the first centers to underscore the significance of examining the potential relationship between social determinants of health—encompassing economic stability, education quality, health care access and quality, neighborhood and built environments, and social and community context—and the pathobiology of AD and related dementias. In June 2018, Dr Kind and her team published a landmark paper in the New England Journal of Medicine identifying an Area Deprivation Index (ADI) as a marker of neighborhood disadvantage and a major contributor to health inequities in the United States, including those related to AD and related dementias. Wisconsin ADRC-supported studies employing ADI suggest that:

- living in most disadvantaged neighborhoods is associated with cognitive decline and accelerated neuronal death in areas of the brain specifically affected by AD pathology;
- neighborhood disadvantage is related to the development of amyloid plaques and neurofibrillary tangles; and
- residing in poor neighborhoods is linked with lower cerebral and hippocampal volume in cognitively unimpaired people.

In 2018, under the leadership of Dr Asthana, director of the Wisconsin ADRC, the NIH funded a study entitled "Wisconsin Longitudinal Study—Initial Lifetime Impact on Alzheimer's Disease (WLS-ILIAD)." The study involves over 6000 Wisconsin high school graduates from 1957 who have been followed by the UW Department of Sociology for more than 60 years. The study's goal is to examine the potential effects of lifelong exposure to various social determinants of health on risk of and resilience to dementia. In May 2023, the study was renewed with a $50 million NIH grant to collect blood samples from 5000 participants and evaluate the possible relationship between blood-based AD biomarkers and the diagnosis of dementia, markers of disease progression, and risk of or resilience to AD and related dementias. The renewed WLS-ILIAD study is the first to evaluate the association between social determinants of health and AD and related dementias in a population-based cohort.

The foundational principle of community-engaged research is the active engagement of members of communities facing health inequities and the incorporation of their input across all stages of a study, including its design, outcome measures, recruitment, data collection, analysis, implementation, and dissemination. Under the leadership of Dr Gleason and Dorothy Edwards, PhD, the ADRC has successfully recruited large numbers of participants from underrepresented groups, fostered by the center's commitment to the principles of community-engaged research. The ADRC supports several community advisory boards, which include leaders and research participants from communities with higher prevalence, burden, and suffering from dementia. This approach has helped the ADRC design studies of direct relevance and interest to marginalized communities in Wisconsin.

The Wisconsin ADRC and its multiple affiliated studies conduct cutting-edge, impactful research across the full continuum of AD and related dementias with direct relevance to enhanced patient care. Breakthrough research from the ADRC is generating information that will expand our understanding of the molecular pathobiology and early diagnosis, treatment, and prevention of AD and related dementias, as well as the sociocultural and environmental effects on these illnesses.

Breakthrough research from the ADRC is generating information that will expand our understanding of the molecular pathobiology and early diagnosis, treatment, and prevention of AD and related dementias, as well as the sociocultural and environmental effects on these illnesses.

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.