NATIONAL ACADEMIES Sciences Engineering Medicine

Preventing and Treating Dementia

Research Priorities to Accelerate Progress

Committee on Research Priorities for Preventing and Treating Alzheimer's Disease and Related Dementias

JANUARY 15, 2025

Study Origin

- The NIH invested billions of dollars in the last decade to support research on detecting, understanding, and developing interventions for Alzheimer's disease and related dementias (AD/ADRD).
- Those investments have led to many scientific advances, but there remains a growing urgency for interventions to prevent or cure AD/ADRD and reduce their societal costs.
- At the direction of the U.S. Congress, the National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke (NINDS) asked the National Academies of Sciences, Engineering, and Medicine to convene an expert committee to examine and assess the current state of biomedical research and to recommend research priorities to advance the prevention and treatment of AD/ADRD.

Statement of Task Summary

- Examine and assess the current state of biomedical research aimed at preventing and effectively treating AD/ADRD
- Assess the evidence on nonpharmacological interventions aimed at preventing and treating AD/ADRD
- Identify key barriers to advancing AD/ADRD prevention and treatment and opportunities to address these key barriers and catalyze advances across the field
- Review and synthesize the most promising areas of research into preventing and treating AD/ADRD

The committee was also tasked with identifying specific **near- and medium-term scientific questions** (i.e., in a 3-to-10-year period) that may be addressed through NIH funding.

Study Scope

- Alzheimer's disease and other common causes of clinical dementia, including frontotemporal dementia, Lewy body dementia, vascular dementia, and mixed etiology dementia, fell within the study scope.
- Excluded from the scope were nonneurodegenerative causes of clinical dementia, such as acquired immunodeficiency syndrome and traumatic brain injury, as well as clinical dementia arising acutely following incident stroke.
- Also excluded from the study scope was
  - Research on dementia care and caregiving interventions, including care models (e.g., care coordination)
  - Recommendations related to the implementation and scaling of tools and interventions in clinical practice and community settings

Study Terminology

- *AD/ADRD* – refers to the causes of dementia within the study scope.
- *Dementia* – also refers to this group of neurodegenerative diseases.
- *Related dementias* – include frontotemporal dementia, Lewy body dementia, vascular dementia, limbic-predominant age-related TDP-43 encephalopathy, and mixed etiology dementia, in this report.
- *Clinical dementia* – refers to impairment that meets the clinical criteria for a diagnosis of dementia, in this report.

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Why is This Study Important Now?

- AD/ADRD research is at an inflection point:
  - Cutting-edge tools and technologies (e.g., fluid and digital biomarkers, multiomics approaches, and AI) are poised to radically change the research and clinical landscape.
  - Investments have produced the first treatments for slowing the progression of Alzheimer's disease in some individuals; a significant expansion of the therapeutic pipeline with promising interventions that are not specific to any single dementia type; an uncovering of shared molecular pathways contributing to AD/ADRD and resilience factors; and a growing understanding of the contribution of mixed pathologies.

However, scientific gaps and barriers remain that impede the development of effective interventions to significantly improve the lives of individuals living with dementia and prevent its development.

Information Gathering Process

Five public meetings, including a public workshop held in January 2024

Scoping review of published systematic reviews

Additional reviews of peer-reviewed literature

Commissioned paper on sex and gender differences in AD/ADRD

Review of additional written comments and materials received throughout the study

Research Priorities

Key Scientific Gaps

- Lack of rigorous evidence for effective public health strategies to prevent AD/ADRD.
- Incomplete understanding of the biology and multiple etiologies underlying cognitive decline and dementia, as well as mechanisms of resilience, which impedes drug discovery and the development of effective preventive and therapeutic interventions.
- Lack of effective, validated, and accessible tools and methods (e.g., novel biomarker tests, digital assessment technologies) for detecting early changes in brain health and accurately diagnosing, subtyping, and monitoring AD/ADRD in diverse populations. Importantly, there has been insufficient progress made in the development of tools for causes of dementia other than AD.

Research Priorities

The committee developed **11 research priorities** (Recommendation 1) and scientific questions, for NIH to address in the near and mid-term, to accelerate the translation of discoveries into effective interventions.

Research Priority Categories

The research priorities relate to **three main categories:**

Quantify brain health across the life course and accurately predict risk of, screen for, diagnose, and monitor AD/ADRD

Build a more comprehensive and integrated understanding of the disease biology and mechanistic pathways that contribute to AD/ADRD development and resilience over the life course

Catalyze advances in interventions for the prevention and treatment of AD/ADRD spanning from precision medicine to public health strategies

These recommended research priorities emphasize opportunities that are applicable across all dementia types, including mixed pathologies, and advance the committee's broader goal of optimizing brain health across the life course.

Recommendation 1: Research priorities to catalyze advances in prevention and treatment

- Develop better tools, including novel biomarker tests and digital assessment technologies, to monitor brain health across the life course and screen, predict, and diagnose AD/ADRD at scale (**Research Priority 2-1**)
- Implement advances in clinical research methods and tools to generate data from real-world clinical practice settings that can inform future research (**Research Priority 2-2**)

Recommendation 1 Continued

- Identify factors driving AD/ADRD risk in diverse populations, particularly understudied and disproportionately affected groups, to better understand disease heterogeneity—including molecular subtypes and disparities in environmental exposures—and to identify prevention opportunities and advance health research equity (**Research Priority 3-1**)
- Characterize the exposome and gene–environment interactions across the life course to gain insights into biological mechanisms and identify opportunities to reduce AD/ADRD risk and increase resilience (**Research Priority 3-2**)
- Elucidate the genetic and other biological mechanisms underlying resilience and resistance to identify novel targets and effective strategies for AD/ADRD prevention and treatment (**Research Priority 3-3**)
- Develop integrated molecular and cellular causal models to guide the identification of common mechanisms underlying AD/ADRD and their validation as novel targets for prevention and treatment (**Research Priority 3-4**)

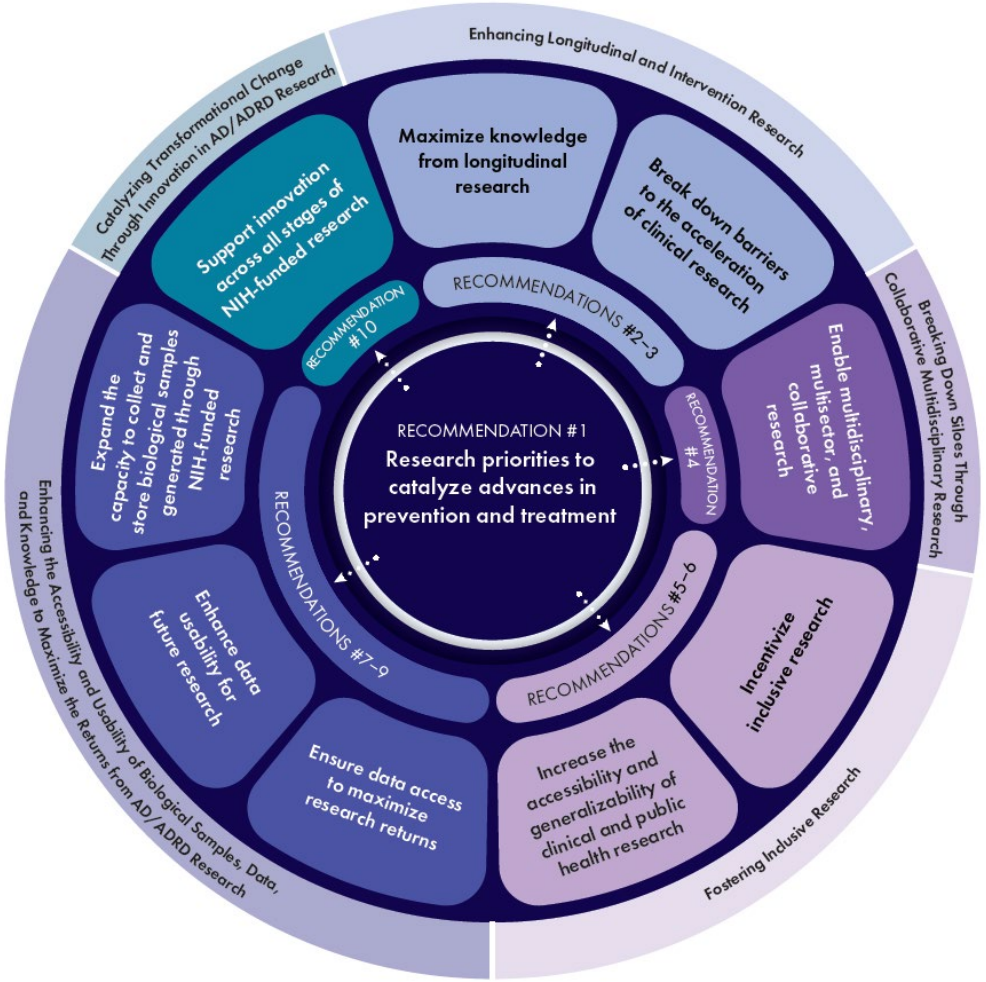
Recommendation 1 Continued

- Integrate innovative approaches and novel tools into the planning, design, and execution of studies to accelerate the identification of effective interventions (**Research Priority 4-1**)
- Advance the development and evaluation of combination therapies (including pharmacological and nonpharmacological approaches) to better address the multifactorial nature of AD/ADRD (**Research Priority 4-2**)
- Evaluate precision medicine approaches for the prevention and treatment of AD/ADRD to better identify interventions likely to benefit specific groups of individuals (**Research Priority 4-3**)
- Advance the adoption of standardized outcomes for assessing interventions that are sensitive, person-centered, clinically meaningful, and reflect the priorities of those at risk for or living with AD/ADRD (**Research Priority 4-4**)
- Evaluate the effects of public health approaches on dementia incidence, including in understudied/ disproportionately affected populations (**Research Priority 4-5**)

NIH Investment

NIH has invested in each of these research priority areas to varying degrees. Going forward, significant, continued investment in the priority research areas must address the knowledge gaps laid out in this report. Success in tackling these research priorities requires an expansion of research efforts beyond AD and the inclusion of diverse and understudied and/or disproportionately affected populations.

Committee recommendations for advancing the prevention and treatment of AD/ADRD



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Recommendation Area: Enhancing Longitudinal and Intervention Research

- NIH has made significant investments to expand and leverage longitudinal research related to aging, resilience, and AD/ADRD.
- Opportunities exist to expand these existing efforts and to maximize what can be learned from ongoing and future longitudinal and intervention research.

Recommendation 2: Maximize knowledge from longitudinal research

NIH should prioritize investments in longitudinal research to address existing knowledge gaps regarding factors that influence brain health over the life course.

- Invest in data infrastructure, data harmonization, and the cultivation of specialized expertise to enable the collection of data and conduct of analyses within and across existing cohorts
- Create new, multidimensionally diverse cohorts
- Strategically add data points important to assessing brain health into existing cohorts constituted for research on other health conditions
- Routinely collect early and midlife exposure data (e.g., residential and work history, environmental toxicants, nutrition, education) from cohort study participants
- Ensure that the data generated from shared biological samples is stored, searchable, and sharable

Note: This recommendation text has been abridged for this presentation.

Recommendation 3: Break down barriers to the acceleration of clinical research

The NIH should lead efforts across relevant entities to accelerate movement of promising interventions into clinical trials and expand use of innovative approaches to improve the efficiency of clinical trials.

- Organize NIH investments in basic and translational research on potential molecular targets to create a pipeline of validated targets
- Expand the use of innovative trial designs and increase investment in early phase, proof-of-concept, and later stage pragmatic trials
- Identify and promulgate best practices for decreasing the barriers to the clinical trial start-up phase
- Continue investing in innovative funding models that support the progression of candidate interventions across the early-stage clinical research pipeline
- Maximize coordination between NIH-funded AD/ADRD clinical trial programs and NIH-funded AD/ADRD centers and evaluate these centers for representative participant clinical trial enrollment

Note: This recommendation text has been abridged for this presentation.

Recommendation Area: Breaking Down Silos Through Collaborative, Multidisciplinary Research

- Funding strategies have historically favored AD and fail to address the reality of mixed pathologies that contribute to dementia.
- Innovative funding strategies and other incentives that encourage collaboration will be needed to address the current siloing of research and accelerate the development of interventions for preventing and treating AD/ADRD.
- Other strategies include multi-institute research consortia, public–private partnerships, challenge programs, and CBPR approaches.

Recommendation 4: Enable multidisciplinary, multisector, and collaborative research

The NIH should expand mechanisms and leverage existing resources to break down silos and encourage multidisciplinary and integrative AD/ADRD research efforts, including the following:

- Expand trans-NIH initiatives and co-funded projects focused on healthy aging and neurodegenerative diseases to reduce the siloing of research, better cross-link and use existing resources, and address inconsistencies in NIH data sharing policies.
- Prioritize research funding for projects with multidisciplinary research teams that address community-informed research questions.
- Expand collaborations globally, including in low- and middle-income countries, for both longitudinal research and clinical trials to better understand the biology of AD/ADRD and enhance the generalizability of findings to diverse populations.
- NIA and NINDS should collaborate with the National Center for Advancing Translational Sciences and others to speed up the translation of research advances to clinical and public health practice and expand research inquiries through the collection of real-world evidence.

Recommendation Area: Fostering Inclusive Research

- Populations that are disproportionately affected by dementia (e.g., certain ethnic/racial groups, people with low socioeconomic status or educational attainment) are persistently underrepresented in AD/ADRD research
- Achieving greater inclusivity and accessibility in AD/ADRD research requires a multipronged approach, which should include:
  - community engagement, recruitment, and the development of culturally appropriate research tools
  - addressing attrition at the screening stage, particularly for members of underrepresented groups
  - regular analysis of recruitment, enrollment, and retainment outcomes
  - building a diverse research workforce at all levels

Recommendation 5: Incentivize inclusive research

The **NIH** should incentivize and guide the use of inclusive research practices to increase the accessibility of research and ensure that study populations are representative of populations at risk for and living with AD/ADRD.

- Strengthen requirements for the recruitment of diverse populations before initiating data collection
- Support research to further understand participant and institutional barriers to involvement
- Develop social determinants of health metrics to be used as measures of diversity
- Incentivize the incorporation of standardized benchmark measurements to evaluate and correct selection bias into new and ongoing research studies
- Work with the CMS to explore Medicare and Medicaid enrollment as opportunities for data collection
- Support initiatives to identify and overcome barriers to entry and continued professional advancement for a diverse clinical research workforce

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Recommendation 6: Increase the accessibility and generalizability of clinical and public health research

Investigators supported by the NIH should adopt inclusive research practices to increase the accessibility of research and ensure that study populations are representative of populations at risk for and living AD/ADRD. NIH-supported investigators should:

- Reduce barriers to research participation
- Eliminate unnecessarily restrictive exclusion criteria that screen out diversity in the study population
- Invest in the development of long-term, mutually beneficial relationships between research institutions and communities, and embed trials sites in communities with underrepresented populations
- Meaningfully engage and incorporate the perspectives of research participants and their communities throughout the research design and execution process

Note: This recommendation text has been abridged for this presentation.

Recommendation Area: Enhancing the Accessibility and Usability of Biological Samples, Data, and Knowledge

- Ensure that biological samples, data, and findings are accessible and useful to the scientific community.
- NIH has funded a range of platforms and repositories to support storage and accessibility of diverse data types.
- A key challenge before NIH is linking its major data hubs into an agile, integrated data ecosystem while preserving the autonomy of the individual platforms.

Recommendation 7: Ensure data access to maximize research returns

NIH should convene a workgroup to work with NIH-funded investigators to identify and implement solutions to barriers that impede access to data from AD/ADRD research.

- the need for a centralized and continuously updated NIH-managed system for existing NIH data sources
- provision of incentives and clear procedures for ensuring compliance with the DMSP;
- approaches to maximize access to data from initiatives funded by multiple NIH institutes and centers;
- incentivization of transparent reporting and the synthesis of findings from negative studies;
- provision of project-specific supplemental funding;
- formulation of guidance for subsets of data to be categorized into access levels based on the access controls needed to protect sensitive data;
- return of derived data and analysis code from data users to the parent study;
- approaches to facilitate access to data from international collaborations; and
- expansion of capacity for storing raw digital data.

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Recommendation 8: Enhance data usability for future research

To enable the usability of data generated by NIH-funded AD/ADRD research, NIH should:

- Invest in data harmonization and interoperability efforts (e.g., use of common data elements) across data platforms and through collaborations across institutions and organizations
- Set requirements for user-intuitive data dictionaries
- Explore new approaches, such as natural language processing, to automate the integration of different data types (e.g., clinical phenotype, multiomics data, exposure data)
- Fund the development and dissemination of novel open-source tools and analytic methods (e.g., large language models and other AI/ML methods, statistical transport methods, data fusion approaches, and synthetic data) to collect, link, explore, and query existing data and support efficient analyses when data privacy rules create barriers
- Provide dedicated grants for investigators working in settings with proprietary data that are difficult to share (e.g., major clinical datasets)

Note: This recommendation text has been abridged for this presentation.

Recommendation 9: Expand the capacity to collect and store biological samples generated through NIH-funded research

The NIA and NINDS, should expand support for the collection and storage of biological samples from NIH-funded AD/ADRD research to maximize opportunities for future use.

- Provide supplements to researchers that meet the actual cost of storing and sharing samples
- Expand support for the collection and storage of highly characterized biological samples (e.g., antemortem and postmortem blood and cerebrospinal fluid, donated brains) from participants of any longitudinal research studies and clinical trials, and from the public
- Use standardized sample collection, assessment, and storage practices with careful consideration of the implications of different storage approaches for future value
- Facilitate access to biological samples from international collaborations
- Support digitized neuropathology to enable quantitative analysis using artificial intelligence and other computational methods

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Recommendation Area: Catalyzing Transformational Change Through Innovation in AD/ADRD Research

- Basic research: developing and applying novel models and tools, seeking commonalities with related fields
- Translational research: increasing the viability of innovative research targets and approaches
- Clinical research: adopting innovative trial designs and participant recruitment and engagement mechanisms
- Population research: identifying and integrating novel data sources that can be used to evaluate population-level strategies and effects on inequalities.

Recommendation 10: Support innovation across all stages of NIH-funded research

The NIH should use existing funding structures and other incentives to stimulate innovation in AD/ADRD research.

- Implement advances and tools generated by ARPA-H and others into NIH-funded AD/ADRD research
- Field a program-wide review of the opportunities and barriers to interdisciplinary and transformational research at NIH-funded AD/ADRD centers and infrastructure programs
- Capitalize on practices and technologies of other fields that may address AD/ADRD research needs
- Prioritize support for research inquiries that have clear potential for future scalability and uptake
- Build partnerships with foundations and other research funders to coordinate seamless funding pathways for fast-tracked phase 1–2 high-risk research opportunities
- Identify and provide short-term funding for specific, highly innovative components of otherwise unsuccessful new and competing award applications
- Identify past projects in the NIH portfolio that have progressed to real-world clinical implementation and adapt the grant review process to include criteria that promotes real-world clinical implementation

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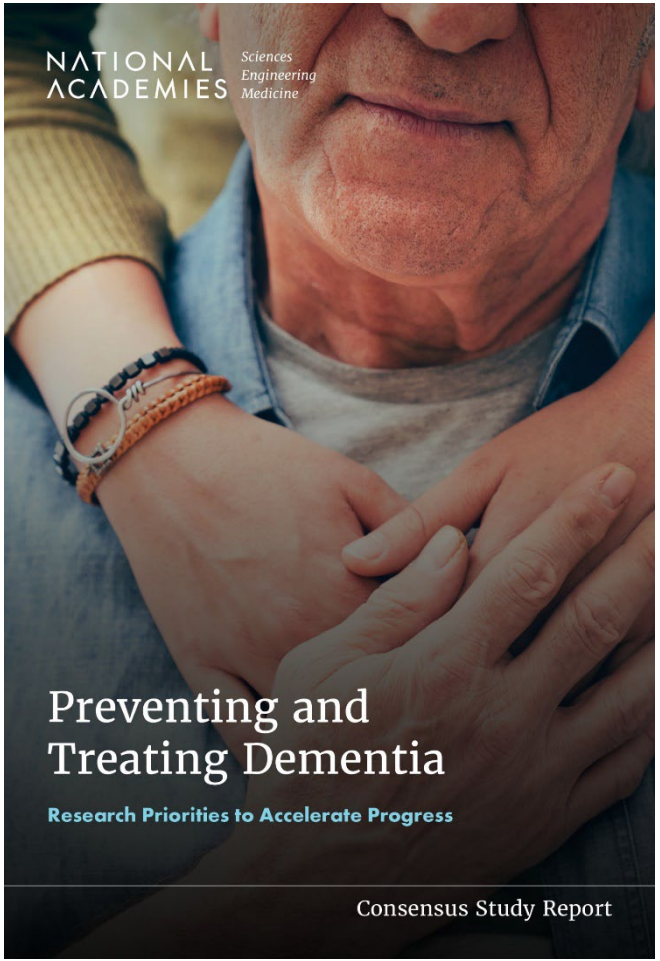
Concluding Remarks

The last decade of research has brought real progress. With the continued strategic research investments outlined by the committee, along with the collaborative efforts of NIH, academic researchers, private industry, health care professionals, funders, policy makers, advocates, and people living with AD/ADRD, it is possible to envision a future where dementia is preventable and treatable.

The full report is available for free download on the study webpage.

Other materials will be available through the study page, including:

- Report Highlights
- Listing of Report Recommendations
- Proceedings of a Workshop—In Brief
- Commissioned Paper on Sex and Gender Differences in AD/ADRD
- Public Release Webinar Recording



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Questions about the Study?

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More information available at www.nationalacademies.org/dementia-research

Thank You!

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