

Closing the gap in Alzheimer's disease research through the Sex | Gender in Neurodegeneration Consortium



Alzheimer's disease research has reached an inflection point. Over the past two decades, evidence for sex and gender differences in Alzheimer's disease and related dementias (AD/ADRD) has expanded substantially, yielding a more comprehensive understanding of how neurodegeneration unfolds across the life course^{1,2}. Yet these discoveries have accumulated faster than our ability to integrate them into study design, analytical frameworks and translation. Recent investments in women's health and aging (<https://wellcomeleap.org/>, <https://arpa-h.gov/explore-funding/initiatives-and-sprints/sprint-for-womens-health>, <https://www.nuttallwomenshealth.org/>) have greatly

expanded opportunities to investigate sex- and gender-related mechanisms in neurodegeneration. As a result, it is increasingly recognized that sex and gender influence AD/ADRD risk, biology, diagnosis, pathophysiology, treatment and clinical outcomes in meaningful ways. However, sex and gender remain inconsistently integrated into study design, data standards, analytical frameworks and results interpretations, limiting the ability to translate accumulating knowledge into mechanistic insight and clinical application^{2,3}.

Addressing these challenges will require coordinated, large-scale approaches that integrate data, standardize measurement and enable cross-cohort analysis. The Sex | Gender in Neurodegeneration (S|GN) Consortium

(<https://www.sgnconsortium.org/>) was established to provide the infrastructure needed to advance the field from fragmented observations to coordinated, life-course investigation of sex and gender in AD/ADRD (Fig. 1). Rather than creating a new cohort, the consortium connects complementary longitudinal studies spanning reproductive aging, cognitive aging, biomarkers and neurodegeneration. Progress will depend less on generating additional isolated datasets than on harmonizing existing resources into integrated scientific frameworks capable of addressing overarching scientific questions at scale. Inconsistent definitions of menopause, hormone therapy and gender-related variables, together with incomplete reporting of sex-disaggregated

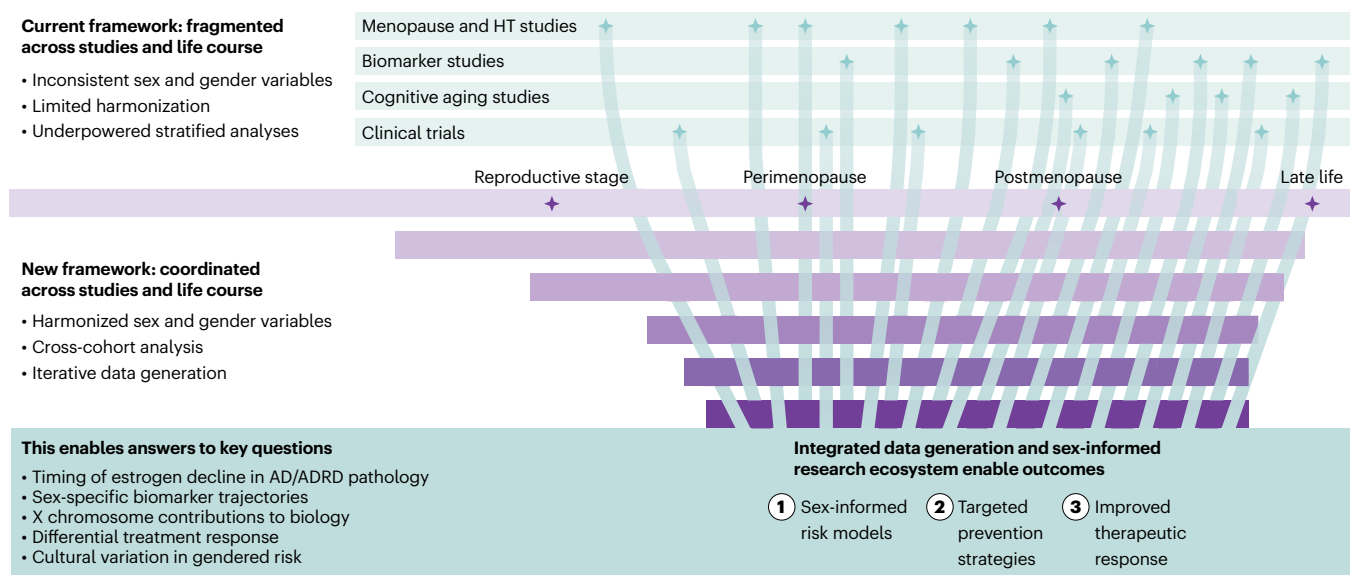


Fig. 1 | Research in AD/ADRD. Current approaches to studying sex and gender in Alzheimer's disease and related dementias (AD/ADRD) are fragmented across the life course, with studies of reproductive transitions, aging, biomarkers and clinical outcomes often conducted in isolation. As a result, key questions such as the timing of hormonal effects on pathology, sex-specific biomarker trajectories and differential treatment responses span life stages but cannot be resolved within existing datasets. A coordinated, life-course framework is needed to integrate these domains. The Sex | Gender in Neurodegeneration (S|GN) Consortium represents one approach to enabling this integration through harmonization of sex- and gender-related variables, cross-cohort analyses

and iterative data generation. Such efforts aim to support the development of sex-informed risk models, prevention strategies and therapeutic approaches in AD/ADRD. This initiative advances understanding of sex differences in AD/ADRD by integrating datasets on reproductive transitions, aging, cognitive decline and related biomarkers. The initial phase focuses on harmonizing and analyzing existing data to identify key research priorities and knowledge gaps. These insights will guide future data generation and prospective collection while continued expansion of participating cohorts will support increasingly comprehensive and globally representative analyses. HT, hormone therapy.

results, hinder harmonization, meta-analysis and reproducibility. Unified definitions for sex, gender, reproductive history, hormone exposure and related variables, together with interoperable informatics platforms and transparent reporting standards, will enable the field to move from isolated observations toward cumulative, reproducible science.

The consortium's phased approach begins with harmonizing existing datasets and generating targeted endocrine measurements from banked biospecimens, followed by coordinated cross-cohort analyses, expansion of international cohort participation, and development of thematic scientific working groups. Near-term milestones include publication of foundational position papers, establishment of working groups, and public release of harmonized resources following an initial consortium embargo. Through the Alzheimer's Disease Data Initiative, analysis-ready datasets and shared analytical standards will support reproducible discovery while informing future prospective studies and data generation⁴. Working groups will focus on priority scientific themes spanning endocrine biology, biomarkers, genetics, neuroinflammation, prevention and therapeutic response, with cross-working-group collaborations taking place as opportunities arise.

Beyond scientific analyses, the consortium is designed to coordinate complementary efforts already underway across regions. Many countries and funding organizations are investing in women's health, healthy aging, dementia prevention, precision medicine and biomedical data infrastructure. Rather than duplicating existing investments, the consortium seeks to connect these national and international initiatives. Coordinated networks can reduce duplication, accelerate validation across diverse populations, and enable funders to invest strategically in questions that require global rather than local solutions. By aligning scientific priorities with regional strengths, the consortium aims to maximize the value of existing investments while accelerating translation into policy and clinical practice.

Advancing our field requires moving beyond descriptive findings toward routine, structured integration of sex and gender analyses and interpretation across research. This goal is accomplished by establishing expectations that results be consistently stratified by sex, biomarker assessments be interpreted within sex-specific contexts, and therapeutic strategies be evaluated with attention to sex-specific effects⁵. Equally important

and insufficiently interrogated is the role of hormonal and reproductive factors as components of disease etiology, rather than as secondary or exploratory variables^{6–8}.

Despite substantial progress, the field now faces a different challenge: connecting disparate observations into a coherent understanding of how sex and gender shape neurodegeneration across the life course. The next phase of research should focus on resolving three overarching scientific questions that require harmonized, multidisciplinary investigation.

How do hormonal and life-course exposures shape disease? Although reproductive aging, endogenous and exogenous hormone exposure, and life-course experiences have all been associated with AD/ADRD risk, how these factors influence disease initiation, progression, and resilience remains insufficiently characterized^{2,9}. Resolving these questions will require longitudinal datasets spanning midlife through late life and including diverse populations.

Which biological mechanisms underlie sex-specific vulnerability? Evidence consistently demonstrates sex differences across genetics, biomarkers, immune function and disease progression, yet the mechanisms responsible for these observations have yet to be fully elucidated². Critical questions include whether biomarker thresholds should be interpreted differently by sex; how endocrine, immune, vascular and genetic pathways interact throughout aging; and whether reproducible sex-specific molecular signatures can be identified across diverse ancestral populations. Resolving these questions will require integrated analyses that combine clinical phenotypes with multimodal biomarker and multi-omic data rather than studying each modality in isolation.

How should these discoveries transform clinical practice? Whether prevention strategies, biomarker interpretation or therapeutic approaches should differ by sex remains uncertain. Sex-disaggregated clinical trial results continue to be inconsistently reported, limiting understanding of treatment response and safety. Likewise, gendered social and structural factors – including caregiving roles, healthcare access and diagnostic bias – are rarely incorporated into analytical frameworks despite their potential influence on disease trajectories and health equity. Integrating biological and gender-related determinants into translational research will be critical for developing more precise and equitable approaches to dementia prevention and care.

The next advances in sex- and gender-informed AD research will come not from larger individual studies, but from coordinated infrastructure that enables harmonized analyses across populations, disciplines and health systems. Global investment should prioritize field-defining questions spanning mechanistic biology, longitudinal observational studies, secondary analyses and targeted data generation where evidence gaps persist. At the same time, policy must evolve alongside science by supporting equitable participant recruitment, strengthening infrastructure for women's and men's brain health, and establishing evidence-based guidance for reproductive health, hormone therapy and cognitive aging. Building the required infrastructure through efforts such as SIGN to align scientific, funding and policy communities around shared priorities may facilitate the translation of decades of fragmented observations into more precise and equitable approaches to prevention, diagnosis and treatment.

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Published online: 28 August 2026

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Acknowledgements

This work was conducted through the AD Data Initiative. CPM, MHSC and NB are employees of Gates Ventures,

whose time was contributed in kind to support the AD Data Initiative. R.F.B. is supported by National Institute on Aging (R01AG079142, DP2AG082342), Wellcome Leap CARE and the Cure Alzheimer's Fund. J. P. is supported by the National Institute on Aging (RF1AG088811), Alzheimer's Association SAGA, Wellcome Leap CARE and an anonymous foundation. S.S. is supported by a Wellcome Leap CARE award, Alzheimerfonden and Forte (The Swedish Research Council for Health, Working Life and Welfare). M.K. is supported by funding from the Innovative Health Initiative Joint Undertaking (JU)-PROMINENT under grant agreement 101112145; the EU Innovative Health Initiative Joint Undertaking (IHI JU) AD-RIDDLE under grant agreement 101132933; a Region Stockholm research

grant (ALF, Sweden); the Center for Innovative Medicine (CIMED) at Region Stockholm (Sweden); Stiftelsen Stockholms sjukhem (Sweden); the Swedish Research Council for Health, Working Life and Welfare (FORTE); and Hjärnfonden (Sweden).

Competing interests

T.J.H. serves on the scientific advisory board for Circular Genomics, serves as deputy editor for *Alzheimer's and Dementia: TRCI* and served as section editor for *Alzheimer's and Dementia*. M.K. serves on the advisory boards for Eisai, Bioarctic, Eli Lilly, Roche, Combinostics and Nestlé (personal compensation). C.P.M., R.F.B., M.H.S.C., J.P., S.S. and N.B. declare no competing interests.